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Functional neurological disorder, physical activity and exercise: What we know and what we can learn from comorbid disorders

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ABSTRACT

Functional neurological disorder (FND) is a common neurologic disorder associated with many comorbid symptoms including fatigue, pain, headache, and orthostasis. These concurrent symptoms lead patients to accumulate multiple diagnoses comorbid with FND, including fibromyalgia, chronic fatigue syndrome, postural orthostatic tachycardia syndrome, persistent post-concussive symptoms, and chronic pain. The role of physical activity and exercise has not been evaluated in FND populations, though has been studied in certain comorbid conditions. In this traditional narrative literature review, we highlight some existing literature on physical activity in FND, then look to comorbid disorders to highlight the therapeutic potential of physical activity. We then consider abnormalities in the autonomic nervous system (ANS) as a potential pathophysiological explanation for symptoms in FND and comorbid disorders and postulate how physical activity and exercise may provide benefit via autonomic regulation.

Functional neurological disorder (FND) is a common, often chronic neurologic disorder associated with significant distress and disability [1]. The clinical presentation spans a variety of neurologic symptoms, including seizures, weakness and movement difficulties, sensory disturbances, dizziness, and cognitive concerns. With an estimated prevalence of 50 per 100,000, FND is one of the most common diagnoses seen in neurology [2,3]. FND subtypes tend to co-occur, with many patients with functional seizures also exhibiting motor FND [4]. Common FND-related symptoms include fatigue, pain, headache, and orthostasis [5,6]. These concurrent symptoms lead patients to accumulate multiple comorbid disorders, including fibromyalgia, chronic fatigue syndrome, and postural orthostatic tachycardia syndrome.

Despite the prevalence, treatment of FND remains an under-researched area. The most highly studied treatments for FND are psychological and physical therapies, but given that a substantial portion of patients are treatment-refractory or cannot access recommended resources, other treatment modalities should naturally be explored. The role of physical activity, exercise, and sports has not been studied in FND populations, although therapeutic use of physical activity has been studied in other neurological disorders and comorbid disorders. There is significant overlap in the symptoms described in FND and comorbid disorders, suggesting potential shared underlying mechanisms; for example, patients with functional seizures report fatigue similar to those with chronic fatigue syndrome, and both patients with FND and fibromyalgia often report pain as a debilitating symptom [5,7]. In this review, we highlight existing literature on physical activity in FND, then look at comorbid disorders, including fibromyalgia, chronic fatigue syndrome, postural orthostatic tachycardia syndrome, persistent post-concussive symptoms, and chronic pain to explore the therapeutic potential of physical activity [5]. We then consider abnormalities in the autonomic nervous system (ANS) as a potential pathophysiological mechanism for symptoms in FND and comorbid disorders and postulate how physical activity and exercise may provide benefit via autonomic regulation.

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Methods

This is a traditional narrative literature review. PubMed was used to find articles from 2017 to 2023 on functional disorders/FND, fibromyalgia, chronic fatigue syndrome, postural orthostatic tachycardia syndrome, physical activity, exercise, and sports. Keyword terms for FND included, "conversion disorder," "functional neurologic*," "medically unexplained illness, "medically unexplained symptoms." This yielded 1,459 articles; 63 relevant articles were included in the review. Articles were excluded if deviating from primary topic of interest. Mention of ANS and related measurements were searched for in this subset of conditions; initial search yielded 59 results, and 41 relevant articles were used for this review. Exact search is listed below. Articles were collected, reviewed, and summarized by primary author (KAB).

PubMed Search Terms:

- ((conversion disorder OR "functional neurologic*" OR "medically unexplained illness" OR medically unexplained symptoms OR fibromyalgia OR POTS[tiab] OR "chronic fatigue"[tiab] OR chronic fatigue syndrome OR Postural Orthostatic Tachycardia Syndrome)) AND (("physical activity" OR exercise OR sport*[tiab] OR walking OR running OR dancing[tiab] OR exercise therapy)) AND (2017:2023[pdat])
- ("Autonomic Nervous System"[Mesh] AND ("Actigraphy"[Mesh] OR "Electroencephalography"[Mesh] OR "Surveys and Questionnaires"[Mesh] OR electrodermal OR Compass-31)) AND (((conversion disorder OR "functional neurologic*" OR "medically unexplained illness" OR medically unexplained symptoms OR fibromyalgia OR POTS[tiab] OR "chronic fatigue"[tiab] OR chronic fatigue syndrome OR Postural Orthostatic Tachycardia Syndrome))

Physical activity in FND and comorbid disorders

Defining physical activity, exercise, and sports

Physical activity is defined as any bodily movement that requires energy expenditure, which is in contrast to sedentary activity. Exercise is planned, structured, and repetitive physical activity for the purpose of attaining physical fitness [8]. Sports are a subset of exercise that can be undertaken individually or as part of a team, and involve many neuropsychological stimuli, such as executive functioning, reaction times, decision making, and social interaction [9]. Physical therapy (physiotherapy, or PT) is a form of rehabilitative physical activity prescribed by health care providers with the goal of improving physical and psychological wellbeing.

Physical activity and brain health in neurologic conditions

Physical activity has been shown to promote brain health. Exercise promotes neuroplasticity and long-term potentiation, which is needed for memory formation [10]. In both human and animal models, physical activity improves cognition and prevents neurodegeneration [11]. Meta-analyses of longitudinal observational studies show aerobic and other forms of exercise to be associated with reduced risk of dementia, and may even have an effect in preventing dementia in adults with normal cognition and mild cognitive impairment [12]. To date, physical activity is the only disease-modifying intervention for idiopathic Parkinson's disease, with evidence for improving both motor and executive function [13,14]. Exercise has been shown to alleviate depressive symptoms, likely by promoting neurotrophic factors [15]. Benefits of physical activity in epilepsy have recently been studied at length, and include improved quality of life metrics and even decreased seizure frequency in some studies [16]. With this context in mind, one can imagine that there may be similar benefit in FND, thus prompting this deeper look at published literature on physical activity and exercise in comorbid conditions (Table 1).

Physical activity in FND

Most literature on FND and physical activity looks to PT as treatment for FND. PT has been utilized to successfully treat motor FND. In a 2013 systematic review of available literature, more that 50 % of patients improved with PT [17,18]. One small study evaluated the effectiveness of a 12-week progressive walking exercise intervention among individuals with motor FND, reporting benefits in functional symptoms, depression and anxiety scores, as well as $VO_{2\ max}$ [19].

As per the 2015 physiotherapy consensus recommendations, motor FND is conceptualized as an "involuntary but learnt habitual movement pattern driven by abnormal self-directed attention" [20]. As such, PT for FND focuses on moving attention away from the functional deficit and toward activation of complex, often automatic movements. In a study of children with FND, dance and exercise were used to promote distraction, thus empowering patients to use alternative motor programs, resulting in FND symptom resolution for 85–95 % of the patients [21]. Another case report cited improvement in functional gait disorder in a woman who used a form of neurologic music therapy during her physical therapy sessions, which may have served to break the pattern of self-directed attention [22].

Table 1
FND Comorbid disorders, known activity patterns in these disorders, and evidence of therapeutic use of physical activity and exercise. GET: Graded Exercise Therapy; CBT: Cognitive Behavioral Therapy.

FND Comorbid Disorder	Activity Patterns	Evidence for therapeutic use of Physical activity and Exercise	References
Fibromyalgia	Less physical activity compared to controls Lack of regular exercise Kinesiophobia	*Aerobic Exercise (sustained increased heart rate, ex: treadmill, walking, Zumba, water aerobics)*: decreased pain, reduced symptom severity, decreased pain catastrophizing *Strength/Resistance training (contracting muscles against resistance, ex: weight lifting, body weight)*: decreased pain perception, improved quality of life *Combined Programs (aerobic + stretching + resistance training)*: reduced pain intensity, improved quality of life, physical functioning, and psychological functioning, decreased depression, improved cognition	[31,32,33,37,40,41,44,46,48]
Chronic fatigue syndrome	40 % reduction in activity compared to controls	*GET + CBT*: reduced fatigue and improved physical function at 1 year *Pacing*: use remains controversial	[52,53]
Persistent post-concussion symptoms	Decreased activity compared to MSK injury controls	*Aerobic Exercise*: improved severity and number of symptoms, decreased kinesiophobia, decreased anxiety, decreased fatigue, improved quality of life	[66,67,69]
Postural orthostatic tachycardia syndrome	Inability to tolerate >30 min of exercise Kinesiophobia and postural intolerance	*Aerobic Exercise*: resolution of diagnosis, improved overall well-being and quality of life *Horizontal exercises (ex: rowing, swimming, recumbent bike)*: improved tolerance of exercise regimens	[70,71]
Chronic Pain	Decreased activity	*Aerobic Exercise (treadmill, walking, dance)*: improved functional status, well-being, pain acceptance *Attention-shifting exercises (exercising unaffected muscles)*: decreased pain	[75,76,77]

Physical rehabilitation has also been used in conjunction with psychotherapy to examine relationships between physical symptoms and thoughts. In their review on models of care for FND, Saxena and colleagues proposed that patients with functional seizures in particular may benefit from physiotherapy after engagement with psychotherapy, using it as a means to become more aware of warning signs for events [17,23]. In a study of multidisciplinary rehabilitation for acute FND (including physical therapy and other rehabilitation therapies), comorbid depression, anxiety, and post-traumatic stress disorder did not interfere with improved self-care and mobility outcomes [24]. Of note, in a small randomized control trial (RCT) of cognitive behavioral therapy (CBT) versus CBT with adjunctive PT for motor FND, there was no added clinical benefit of PT; the sample heavily included patients with functional tremor, thus perhaps not representing the breadth of FND phenotypes [25]. Chronicity of disease matters, with worse outcomes associated with longer duration of FND [26].

Physical activity in fibromyalgia

Fibromyalgia (FBM) is a disorder of widespread pain, and much like FND, it often involves concurrent physical and psychological features [27]. In an outpatient cohort of patients with widespread pain and/or FBM, 53 % had comorbid FND [28].

FBM is one of the main FND-comorbid disorders in which physical activity and exercise has been rigorously and extensively studied. Despite this, patients with FBM report significantly less recreational, transportation-related, and total physical activity compared to healthy controls [29,30]. As a needs-assessment, Sieczkowska and colleagues looked at exercise practices of patients with FBM, and found that most patients did not exercise regularly, with 65.7 % of 304 patients stating they did not exercise at all; notably, patients who did exercise reported overall superior quality of life [27]. Many patients with FBM do not believe that physical activity will improve their symptoms, thus hindering widespread recommendation [30,31]. In fact, 38 % of patients with FBM report kinesiophobia, or an enhanced fear of movement [30–32]. Exercise should therefore be used thoughtfully to be therapeutic for patients with FBM.

Many meta-analyses have determined the benefit of exercise, with aerobic exercise being the most robustly studied. Sosa-Reina and colleagues in a 2017 systematic review found strong evidence that aerobic exercise decreases the pain and severity of FBM symptoms, while other types of combined exercise including aerobic, stretching exercises and muscle strengthening were most effective in reducing comorbid depression [32,33]. Both supervised aerobic and resistance-training programs reduced pain intensity and improved quality of life, physical functioning, and psychological functioning in a study of women with FBM [30,31]. Albuquerque and colleagues proposed in their meta-analysis that aerobic training and combined modality exercise programs lasting 13–24 weeks with activity sessions between 30–60 minutes showed the best outcomes for FBM impact and pain [33,34].

Pain is a tremendous barrier to participation in physical activity. Patients with FBM also often have amplification of their perceived exertion [30]. This is in part due to pain catastrophizing, the phenomena in which fear and rumination about pain results in amplification of perceived pain. Pain catastrophizing is inversely related to muscular endurance, portending physical limitations as a result of psychological perceptions [35]. Masquelier and colleagues proposed that the intensity of aerobic exercise should be between 40-80 % of the maximum heart rate *or* at a perceived exertion level of 9–15 (maximum 20) on the Borg scale in order to avoid pain catastrophizing [31]; starting with low intensity physical activity reduces pain catastrophizing [35–37]. In a study of women with FBM and high levels of pain, those who walked *despite* pain reported less impact of FBM symptoms, anxiety, depression, and cognitive issues. Regular walking behavior was associated with less pain catastrophizing, suggesting that optimizing engagement with exercise may improve symptoms even when patients themselves perceive harm from engagement [37]. This balanced approach requires patients to have trust in their provider and for providers to honor individual patient differences. Non-responders to physical activity and exercise often have higher levels of depression, thus poorly-controlled psychiatric co-morbidities may need to be addressed in tandem with physical activity interventions [38].

Given the significant symptom burden, pain catastrophizing, and kinesiophobia of patients with FBM, physical activity should be individualized to promote adherence. As such, a variety of intensities and types of activity has been evaluated, nearly all of which have yielded positive results [33,38–40]. Andrade and colleagues skillfully investigated this notion of physical activity agency by allowing patients to choose their preferred exercise regimen among the options of walking, resistance training, or stretching. All groups had significant improvement in quality of life, reduction in depression, and improved cognitive outcomes [41]. Both highly regulated aerobic exercise, such as Norouzi and colleague's treadmill walking for 12 consecutive weeks with standardized time and maximum heart rate targets, and less regulated triweekly Zumba classes were effective at reducing depressive symptoms, allowing for diversity in exercise regimen with retained benefit; of note, there was no clinically meaningful improvement in motor functioning in either group (as measured via a timed walking test) [42]. Strength training programs have shown FBM symptom reduction as stand-alone treatment or in combination with aerobic exercise in many studies. Most importantly, strength training was shown to have a high mean compliance rate of 84 % [31]; though the literature may show that certain regimens of aerobic exercise or multimodal therapies provide the most overall symptom reduction, the program in which a patient feels they will adhere will ultimately be the best choice. Similarly, meditative movement therapy such as yoga and tai-chi have shown the most benefit for pain reduction and thus may be good options for patients who struggle with adherence to higher levels of physical exertion [31,43]. Aquatic based activities have recently been systematically evaluated and likely also have similar benefit to more highly studied aerobic activity for FBM [40,44,45]. Even short duration regimens have been found to be effective, validating that any amount of participation in physical activity may be helpful for patients with FBM [39,44].

Attentional diversion through exercise, much like in FND, has been proposed to be driving some of the efficacy of physical activity for FBM; by focusing on what is working, there is less perceived pain and better functionality. Strength training decreases pain perception and improves quality of life in multiple review studies [31,33,46–48]. In a crossover study of low- versus high-level resistance training, women with FBM preferred heavy load resistance for symptom reduction; despite the objective increase in difficulty, there was reduction of symptoms when there was a more substantial stimulus to divert attention [49].

The recent controversies in chronic fatigue syndrome literature (discussed below) warrants investigation into any potential harm of physical activity and exercise in FBM. The most reported exercise-related adverse event is muscle pain, which as discussed is likely amplified given the prevalence of pain catastrophizing. The incidence of exercise-related adverse events is low, with no serious adverse events reported in clinical studies [31]. This indicates that the benefits of exercise in treating symptoms of FBM far outweigh any potential harm.

All in all, multiple types of physical activity have demonstrated significant improvement for FBM symptoms. Patients do best when prescribed a regimen directly by their doctor, and these regimens should thoughtfully recognize the patient's physical activity preferences and predominant symptoms in order to maximize benefit and adherence [50].

Physical activity in chronic fatigue syndrome

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), is an incompletely understood illness manifested by post-exertional fatigue, cognitive issues, sleep disturbances, and/or chronic

pain. According to the Centers for Disease Control (CDC), CFS affects up to 2.5 million Americans [51]. Patients with CFS exhibit a 40 % reduction in activity as measured on natural history actigraphy [52]. Specialty clinics for CFS have reported that 84 % of patients over time develop at least one comorbid functional or psychiatric condition [17,51,52].

The best available research on treatment for CFS comes from the 2011 Pacing, graded Activity, and Cognitive behavioral therapy (PACE) trial, a RCT that showed that individualized graded exercise therapy (GET) in conjunction with CBT was most effective at reducing fatigue and improving physical function after one year [53]. GET uses principals of starting with low-intensity activity and gradually increasing based on patient tolerance, as was shown to be effective in FBM. Since the 2011 trial, many other studies have shown that graded exercise therapy improves quality of life, ability to work, physical functioning, anxiety, and depression [54,55]. Synthesis of the Physiotherapy Evidence Database (PEDro) showed that there is moderate evidence that exercise can improve fatigue, sleep, physical functioning, and overall health in patients with CFS who are well enough to attend an outpatient clinic, irrespective of type of exercise [51,55].

Importantly, the PACE trial showed that GET was more effective than adaptive pacing therapy (APT, or pacing). Pacing is promoted as an energy conservation strategy of restricting exposures to post-exertional malaise-inducing stimuli and reducing daily activities [51,53]. In 2021, the United Kingdom's National Institute for Health and Care Excellence (NICE) published new CFS treatment guidelines, which favors pacing over GET and CBT. FND and CFS experts have published their serious concerns with the new NICE guidelines, arguing that pacing may actually be harmful to CFS care [56,57]. All in all, though it remains controversial in light of the new guidelines, the most effective and studied treatment for CFS appears to be GET and CBT, and their success in CFS should prompt application in patients with FND.

Physical activity in persistent post-concussive symptoms

Traumatic brain injury (TBI) is an umbrella term that includes all injury to the brain via an external force. About 85 % of TBIs are diagnosed as mild (mTBI), with concussion being the mildest and most prevalent form. In adults, symptoms following a concussion are expected to resolve within 10–14 days after the injury. Up to 15 % of individuals continue to have symptoms, and if ongoing for at least one month after injury, symptoms are referred to as persistent post-concussion symptoms (PPCS, previously known as post-concussive syndrome) [58–60]. Studies have shown that mild head injuries are the precipitating factor for the onset of approximately 16–84 % of functional seizures [61]. Functional stuttering and dizziness have also been reported after concussion, as have presentations of functional weakness, tremor, gait disorders, oculomotor, and vision disorders [62,61]. As such, some PPCS may be a subtype of FND, especially when acquired outside of sport settings [63,64].

PPCS is specifically defined as three or more symptoms of headache, dizziness, fatigue, irritability, difficulty with concentration and mental tasks, memory impairment, sleep disturbances, heightened emotional responses, and poor stress tolerance that interfere with daily life [65]. Exercise is thought to improve post-concussive symptoms through improved cerebral blood flow and enhanced neuroplasticity contributing to restoration of integrity of brain networks, as shown in functional magnetic resonance imaging (fMRI) studies of patients with PPCS who exercised daily on a treadmill compared to non-exercising PPCS controls [66]. However, patients with PPCS tend to be less active [67]. As such, many small trials have focused on exercise in this activity-deficient group. An 8-week remotely delivered (via Fitbit actigraphy) progressive walking intervention improved severity of post-concussive symptoms, kinesiophobia, anxiety, fatigue, and quality of life [68]. Patients with PPCS who engaged in aerobic activity were more likely to have fewer post-concussive symptoms compared to stretching alone in two RCTs, though there are too few studies to conclude that aerobic exercise is the only activity that should be encouraged in recovery [66,69]. Much like other FND comorbid conditions, physical activity prescriptions should focus on efficacy and optimization of participation.

Physical activity in postural orthostatic tachycardia syndrome

Postural orthostatic tachycardia syndrome (POTS) is a disorder of orthostatic intolerance without hypotension, which is often premorbid to the diagnosis of FND [5]. In POTS, exercise intolerance directly correlates with reduced functionality, with 61 % of patients reporting the inability to tolerate more than thirty minutes of exercise [70]. Physical reconditioning with exercise training is an important component of treatment. Like other conditions discussed, patients may report kinesiophobia due to worry of exacerbating symptoms, thus physical activity should be individually graded and patient-focused. Many protocols use horizontal exercise (rowing, swimming, recumbent bike, etc.) on initiation, allowing patients to exercise while avoiding the upright posture that elicits POTS symptoms until patients can gradually tolerate other means of aerobics [71]. Exercise training has been shown to improve overall well-being and quality of life for patients with POTS, so much so that in an aggregate of multiple studies of a 3-month aerobic exercise program, 53–71 % of participants no longer met physiologic criteria for POTS [71].

Physical activity in chronic pain

Chronic pain is a very common symptom in people with FND, and can impede recovery [72]. A recent systematic review and meta-analysis found that 55 % of patients with FND reported pain [73]. In one outpatient pain management cohort of patients with primary chronic pain, 88 % had comorbid FND [28]. The presence of chronic pain has been incorporated into a validated tool to differentiate between functional seizures and epilepsy [74].

In chronic low-back pain, different types of exercise, including aerobic exercise, walking, tai chi, and Pilates, improve functional status when compared to no exercise [75,76]. Much like in FND, therapeutic exercise for chronic pain emphasizes attentional shifts to modify rather than eliminate pain. Exercising a non-painful part of the body can have analgesic effects on the painful part, highlighting the importance of engaging in activity even if there are initial physical limitations. Chronic neck pain was reduced equally by direct neck motor control exercises and non-neck-specific muscle strengthening, possibly suggesting that attentional shifts can improve perceived symptoms, though improvement may also be related to the benefit of global reconditioning [77]. In a study of dance for chronic pain, many participants noted no decreased pain but rather improved acceptance of pain and improved mental and emotional well-being [78]. Similarly, studies using PT protocols for FND have not shown reduction in comorbid chronic pain, but did show improvements in social and physical function [79,80].

FND and comorbid conditions and the autonomic nervous system

Physical activity and the ANS

The autonomic nervous systemic (ANS) is the branch of the nervous system that controls a variety of involuntary physiologic processes. During moderate-to high-intensity aerobic exercise, the sympathetic branch of the ANS raises heart rate, skin temperature, and sweat secretion [81]. After consistent exercise, there are positive adaptations of ANS activity, such as declines in diastolic blood pressure and heart rate, consistent with parasympathetic modulation [82]. Vasodilation occurs in the extremities during exercise; in physical inactivity, deconditioning favors sympathetic vasoconstriction, causing pain [81]. Through its sympathetic and parasympathetic branches, the ANS can control and modulate the activity of each organ individually. During

exhaustive exercise, individual organ control is replaced by a more generalized stimulation or inhibition of organ activity, but after metabolic regeneration from acute exercise, the individual control is reestablished. Intact functioning of central ANS control is associated with antagonistic behavior of sympathetic and parasympathetic activity. In conditions impairing the integrity of the central autonomic network, there is breakdown of expected antagonism between sympathetic and parasympathetic branches, which can lead to aberrant double stimulation or inhibition of the two ANS branches [83].

Certain parameters induced by exercise correlate with different parts of the ANS (Table 2). Isolated sympathetic functioning at the skin can be measured via electrodermal activity (EDA); increased conductance suggests increased sweat, and as such increased sympathetic activity [84]. Isolated parasympathetic functioning at the sinus node can be measured via proxies for heart rate variability (HRV). HRV is based on the principle that heart rate changes from beat to beat [85]. Variability can be measured via time domain (time period between heartbeats) or frequency domain (frequency of changes in heart rate). Increased root mean square of successive R-R interval differences (rMSSD, time domain) and high frequency oscillations (HF, frequency domain) reflect greater parasympathetic influence [84]. It is noteworthy that studies of HRV in ANS literature at large is of questionable quality due to lack of rigorous standardized measurements [86]. $VO_{2\ max}$ or $VO_{2\ peak}$ reflect the maximum amount of oxygen that an individual can use during exercise, signifying endurance capacity [87]. The Composite Autonomic Symptom Score-31 (COMPASS-31) is a validated clinical questionnaire organized into six domains to assess subjective function of the ANS (orthostatic intolerance, vasomotor, secretomotor, pupillomotor, gastrointestinal transit, and bladder control) [88].

It is important to recognize that measures of the ANS are organ-specific; for example, elevated EDA suggests increased sympathetic activity *at the skin*, and it is impossible to make body-level, and thus disease-level, conclusions about ANS functioning without comprehensive measurements. Additionally, the ANS does not necessarily function in a linear manner, nor are measurements universally consistent even among healthy controls, thus isolated measurement of autonomic parameters must be interpreted with caution [16,89].

Autonomic nervous system in FND

There is evidence to suggest that the ANS may be dysregulated in FND. Across several studies, patients with functional seizures have significant elevation of baseline heart rate and reduced measures of heart rate variability (rMSSD and HF), suggesting some basal level of adrenergic stimulation and decreased parasympathetic regulation, respectively, though this is not consistent across all studies, and may be most pronounced in pediatric populations [90–92]. Compared to healthy controls, patients with FND report heightened functional symptoms after viewing negative images, and demonstrate physiologic activation of the ANS through increased heart rate and skin conductance [93]. However, similarly valent images did not cause increased pupillary dilation (another marker of sympathetic functioning) in a study of motor FND, thus there is likely unexplored nuance to the degree of autonomic activation and organ-level differences in functioning [94]. As such, conclusions cannot yet be made regarding true differences in autonomic functioning in FND [95].

Multiple studies have looked specifically at measures of the ANS to better differentiate between functional and epileptic seizures. Compared to patients with epileptic convulsions, patients with functional seizures have unpredictable changes in EDA, whereas ictally, those with epileptic etiology had a strong adrenergic surge as measured by EDA and ictal tachycardia [96]. Of note, there is a high rate of ictal tachycardia in patients with functional seizures, thus tachycardia should be used with caution as a differentiating factor [92]. Patients with functional seizures have significant pre-ictal increase in heart rate followed by post-ictal decrease in heart rate compared to focal impaired awareness seizures [92]. This may suggest central ANS and/or hypothalamic-pituitary-adrenal (HPA) axis hyperactivity prior to a functional seizure at the level of the sinus node.

The fMRI literature highlights overlapping activation in FND within areas known to be involved in autonomic regulation. The amygdala is involved in emotional salience, and projects to the hypothalamus and brainstem to trigger autonomic responses to stimuli [97]. In patients with motor FND, there is amygdala hypersensitization, demonstrating unchecked autonomic overactivation [98]. fMRI in FND has also shown increased coupling between the insula and anterior cingulate cortex. The anterior cingulate functions to integrate autonomic responses from the insula and amygdala, and thus aberrant overconnectivity may result in cardiac autonomic dysregulation in patients with FND [97].

Table 2
Validated measurements of Autonomic Nervous System (ANS) functioning.

Measurement	ANS Function Reflected by Measurement
Skin temperature	Sympathetic activity at the skin, also modulated by thermoregulatory system
Electrodermal activity (EDA)	Sympathetic activity at the skin (sweat)
Heart rate variability (HRV)	Parasympathetic activity at the sinus node, measured via time or frequency domain: *Root mean square of successive R-R interval differences (rMSSD):* time period between heartbeats *High frequency oscillations (HF):* frequency of changes in heart rate
$VO_{2\ max}$ or $VO_{2\ peak}$	Maximum amount of oxygen that an individual can use during exercise, endurance capacity
Composite Autonomic Symptom Score-31 (COMPASS-31)	Validated clinical questionnaire of subjective function of the ANS

Autonomic nervous system in FBM

There is abundant literature on autonomic functioning in FBM, with publications dating back to the 1970s. Autonomic symptom burden via COMPASS-31 strongly correlates with severity metrics in FBM, suggesting that subjective reports of autonomic symptoms relate to symptom burden [99–102]. COMPASS-31 scores in FBM are not only higher compared to healthy controls, but also in comparison to rheumatoid arthritis, highlighting that dysautonomia may distinguish FBM from other conditions [100].

Patients with FBM have an overrepresentation of adrenergic activity based on self-report and organ-specific summation. In a study of twenty-five patients with FBM, direct recording of the post-ganglionic muscle sympathetic neural activity (MSNA) from the peroneal nerve showed higher sympathetic drive at the muscle compared to controls, and correlated with perceived pain [103]. Patients appear to have decreased resting and nighttime markers of HRV (correlating with decreased parasympathetic regulation at the sinus node), as well as decreased skin conductance with stressors (correlating with decreased sympathetic activity at the skin), demonstrating atypical double inhibition of ANS branches [104–106]. When presented with objectively safe stimuli, patients with FBM plus temporomandibular joint (TMJ) disorders have greater reduction in parasympathetic markers (as measured by decreased respiratory sinus arrythmia) when compared to TMJ alone, resulting in disproportionate sympathetic activity and possibly demonstrating an aberrant readiness to perceive danger in safe environments [107]. Diminished autonomic regulation in FBM may reduce the ability to cope with environmental demands, thus propagating increases in stress and pain levels.

Most studies of cardiopulmonary fitness in FBM show significantly lower peak oxygen uptake ($VO_{2\ peak}$) during treadmill aerobic exercise compared with controls, which may lead to exercise intolerance [108]. Sympathetic skin responses, which are mediated by postganglionic, unmyelinated sympathetic fibers, are decreased in patients with FBM; the clinical significance of this is not clear, but may further suggest

underlying dysautonomia [106].

Because FBM has been extensively studied, there is literature on the therapeutic potential of physical activity in FBM that uses improvement in autonomic functioning as an outcome measure. A systematic review of different exercise modalities shows that moderate-to-high intensity aerobic exercise increases markers of HRV and $VO_{2\ max}$, thus promoting regulation of the ANS [109,110]. There have not yet been studies of improved autonomic functioning in strength training regimens, and there are inconsistent results in resistance training regimens [109,111]. The deconditioning model of pain in FBM (either as a precipitating or perpetuating factor) suggests that decreased activity leads to high sympathetic tone in the limbs, resulting in pain. Exercise causes vasodilation, which improves pain; this is also the mechanism by which amitriptyline acts on α1-adrenoceptors, providing validation for its use to reduce FBM-related pain [99].

Autonomic nervous system in CFS

The ANS is likely implicated in CFS. fMRI studies frequently show differences in CFS patients in the cingulate region, which is integral to autonomic regulation and emotional processing [112]. Patients with CFS have been evaluated via COMPASS-31, in which 50 % of patients report significant signs of autonomic dysfunction [113].

When undergoing physical activity and exercise, patients with CFS show differences in autonomic functioning. After three months of daily walking, as tracked by an actigraphy wearable technology, those who reported non-improvement had significantly reduced rMSSD, a HRV marker indicating decreased parasympathetic activity at the sinus node [113]. Patients with CFS exhibit significant exercise intolerance as part of their disease. Joseph and colleagues used invasive cardiopulmonary exercise testing (iCPET) to show that CFS patients have low VO_{2peak}, suggesting impaired systemic oxygen extraction, and that a significant portion (31 %) of patients with CFS have small fiber autonomic neuropathy. The authors propose that the lack of sympathetic tone from the microvasculature may cause decreased oxygen arrival in the periphery [87]. This, in conjunction with deconditioning-induced vasoconstriction, may contribute to exertional fatigue and exercise intolerance. Patients with post-acute sequelae of SARS-CoV-2 have similarly low $VO_{2\ peak}$, suggesting that "long COVID" also has significant autonomic disruption as part of its pathophysiology [114].

Autonomic nervous system in POTS

POTS, of all the disorders related to FND, is likely the most directly interrelated to dysautonomia. Patients with POTS demonstrate an exaggerated submaximal exercise heart rate, meaning there is disproportionate tachycardia related to the metabolic equivalent of task (MET) [115]. Fifty percent of individuals with POTS experience a partial sympathetic denervation of blood vessels in the lower extremities, resulting in reduced vasoconstriction during upright posture, worsening postural orthostasis [65]. A study by Rea and colleagues showed equally elevated COMPASS-31 scores in POTS as in patients with autonomic failure (parkinsonism, diabetes neuropathy, and non-diabetic autonomic neuropathy), further highlighting the underlying dysautonomia [116].

Autonomic nervous system in PPCS

Acutely after mTBI, there is evidence of dysautonomia [61,65]. It has not been studied whether individuals who develop PPCS have higher levels of early autonomic dysregulation, but certainly there is evidence of dysautonomia in both acute mTBI and PPCS. Patients with persistent post-traumatic headache have higher COMPASS-31 scores in comparison to migraine patients and healthy controls [117]. Development of POTS after concussion delays recovery, suggesting broader dysautonomia [65].

Autonomic nervous system in psychiatric symptoms and disorders

Psychiatric symptoms and disorders are often co-occurrent with FND and considered risk factors [118]. Psychiatric disorders have characteristic autonomic patterns. Hypervigilance of post-traumatic stress disorder (PTSD) correlates with increased EDA, decreased markers of HRV, and increased pupillary dilation, suggesting sympathetic predominance [92,119]. Anhedonia accompanying depression correlates with decreased markers of HRV (via rMSSD), and EDA, suggesting widespread autonomic hypoactivation [92,96,120]. Heightened arousal of anxiety correlates with higher resting EDA and lower markers of HRV (measured via frequency of changes in RR intervals on telemetry), suggesting dysregulated sympathetic activity [121]. COMPASS-31 is elevated in all these conditions [122]. These disorder-specific ANS conclusions are likely oversimplifications, and there is significant variability in studies and between individuals. It is unlikely that there is a consistent, linear pattern of autonomic function (or dysfunction) in any disorder, but rather a pattern of disturbed equilibrium of the sympathetic and parasympathetic systems. Psychiatric symptoms are highly comorbid with functional disorders and may help explain some of the variability in results when testing for dysautonomia. It is important that when attempting to use exercise therapeutically in FND and other functional disorders, we account for differences in baseline comorbidities and how they may relate to autonomic and performance outcomes.

Conclusion

Physical activity and exercise appear to be largely beneficial for treatment and symptom reduction in FND and comorbid disorders. As discussed, physical activity and exercise are important for brain health in many conditions, and thus are likely beneficial in FND. Intentional physical activity and exercise may activate alternative motor pathways and increase sense of agency, therefore improving FND symptoms. Given that inactivity, exercise intolerance, fatigue, and pain are common in FND and other comorbid disorders, physical activity prescriptions should be tailored to optimize individual participation and symptom relief. Questions regarding optimal type of physical activity, natural history of physical activity in FND, and possible interactions of prior exposure to exercise on the development of FND remain unanswered, which makes this an untapped area for patient-centered research on treatment development. In addition, the effects of sports are almost completely unstudied, and may have distinct effects compared to other physical activity literature given its added layer of neuropsychological and social components.

There is evidence corroborating modulation of autonomic functioning through physical activity and exercise. As such, there is hope for the therapeutic use of physical activity and exercise to improve outcomes in patients with FND and comorbid disorders, possibly by counteracting dysautonomia. While the causal relationship between autonomic dysfunction and functional disorders remains unclear, targeting the ANS therapeutically is justified given that the ANS likely plays a role in precipitating and/or perpetuating functional symptoms [95]. Given evidence presented about the changes in the ANS in FND and comorbid disorders with physical activity and exercise, one could postulate that physical activity may lead to FND symptom reduction (Figure 1). Future studies must be rigorous and intentional in what measures of the ANS are used; multi-organ system physiologic and self-reported validated metrics must be used, such as combining EDA, metrics of HRV, body temperature, COMPASS-31, and central measurements in order to avoid making premature disease-specific conclusions about overall ANS functioning.

This is a traditional narrative literature review, thus the level of bias and rigor of each study included has not been systematically assessed. Other limitations include performance bias; patients in intervention groups may be more likely to improve simply because they underwent an intervention. This may be why most evaluated studies favored the

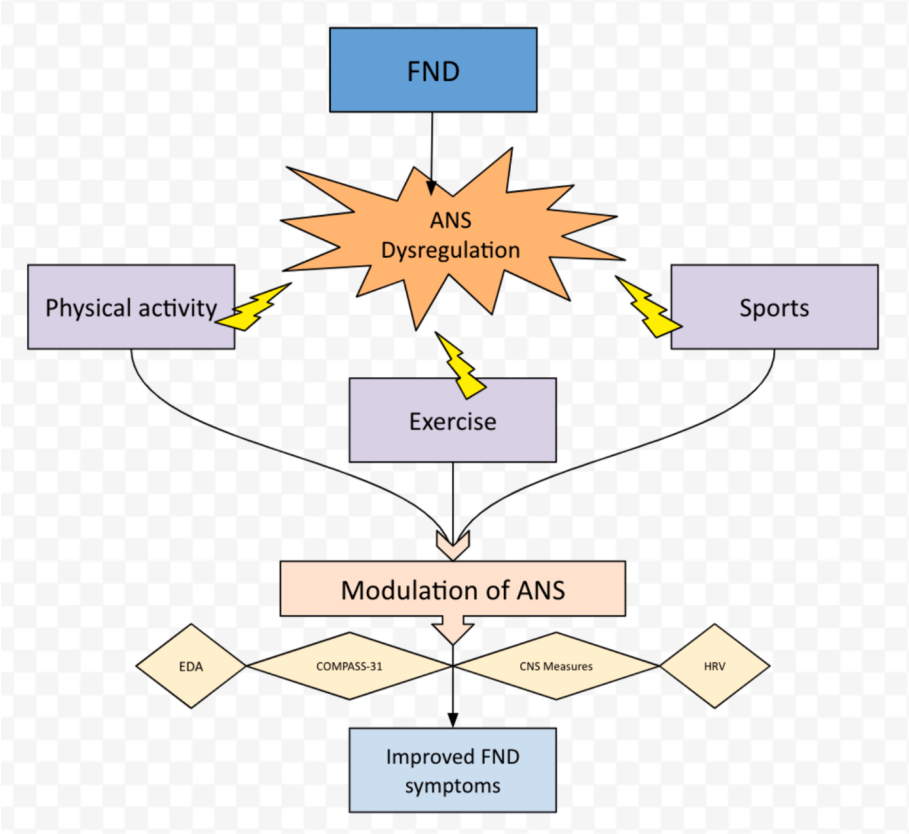

Fig. 1. Hypothetical Framework for the effect of physical activity, exercise, and sports on Functional Neurological Disorder (FND). In FND, there is suspected dysregulation of the autonomic nervous system (ANS). We propose that physical activity, exercise, and sports may be used therapeutically to alter ANS functioning, as can be measured through electrodermal activity (EDA), heart rate variability (HRV), Composite Autonomic Symptom Score (COMPASS-31), and via a variety of central nervous system (CNS) metrics.

intervention group. Relatedly, there is likely publication bias, or a tendency to publish significant results. Given the expansive variety of physical activity interventions that improved mood and quality of life in FND-comorbid disorders, it is possible that behavioral activation, or engagement in enjoyable activities leading to psychological betterment, is the cause of post-intervention improvement possibly in addition to the physiological benefit of physical activity itself [123]. Confirmation and selection bias may also play a role, given the authors' general belief that physical activity is beneficial in these disorders and that the ANS is a logical branch of the nervous system to mediate pathology and response to physical activity interventions. As mentioned above, ANS measurements remain poorly standardized across studies, and measurements are not universally consistent even among healthy controls, thus isolated measurement of autonomic parameters must be interpreted with caution.

Though there is still much to be learned regarding the role of the ANS in FND, there is reason to believe that physical activity and exercise, likely though regulation of the ANS, may be beneficial in treatment. As such, this serves as a call to action for rigorous study.

Ethical statement

No ethical concerns to declare for authors involved in this review. Sex and gender were used correctly throughout review. The human subject research reviewed in this publication were vetted by corresponding institutions' IRB.

CRediT authorship contribution statement

Kelly A. Boylan: Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Barbara A. Dworetzky:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization. **Gaston Baslet:** Writing – review & editing, Resources. **Ginger Polich:** Writing – review & editing, Resources. **M. Angela O'Neal:** Writing – review & editing, Resources. **Claus Reinsberger:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Cope SR, Smith JG, Edwards MJ, Holt K, Agrawal N. Enhancing the communication of functional neurological disorder diagnosis: A multidisciplinary education session. Eur J Neurol 2020.
[2] Stone J, Carson A, Duncan R, Roberts R, Warlow C, Hibberd C, et al. Who is referred to neurology clinics?–the diagnoses made in 3781 new patients. Clin Neurol Neurosurg 2010;112(9):747–51.
[3] Aiarzaguena JM, Gaminde I, Grandes G, Salazar A, Alonso I, Sanchez A. Somatisation in primary care: experiences of primary care physicians involved in a training program and in a randomised controlled trial. BMC Fam Pract 2009;10:73.
[4] Rather MA, Cavanna AE. Nonepileptic attack disorder and functional movement disorder: A clinical continuum? Epilepsy Behav 2020;106:107028.
[5] Ducroizet A, Zimianti I, Golder D, Hearne K, Edwards M, Nielsen G, et al. Functional neurological disorder: Clinical manifestations and comorbidities; an online survey. J Clin Neurosci 2023;110:116–25.

[6] Gilmour GS, Nielsen G, Teodoro T, Yogarajah M, Coebergh JA, Dilley MD, et al. Management of functional neurological disorder. J Neurol 2020;267:2164–72.
[7] Teodoro T, Edwards MJ, Isaacs JD. A unifying theory for cognitive abnormalities in functional neurological disorders, fibromyalgia and chronic fatigue syndrome: systematic review. J Neurol Neurosurg Psychiatry 2018;89(12):1308–19.
[8] Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 1985;100(2):126.
[9] Jacobson J, Matthaeus L. Athletics and executive functioning: How athletic participation and sport type correlate with cognitive performance. Psychol Sport Exerc 2014;15(5):521–7.
[10] Radahmadi M, Hosseini N, Alaei H. Effect of exercise, exercise withdrawal, and continued regular exercise on excitability and long-term potentiation in the dentate gyrus of hippocampus. Brain Res 2016;1653:8–13.
[11] Cabral DF, Rice J, Morris TP, Rundek T, Pascual-Leone A, Gomes-Osman J. Exercise for brain health: an investigation into the underlying mechanisms guided by dose. Neurotherapeutics 2019;16:580–99.
[12] Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396(10248):413–46.
[13] Garcia Ruiz PJ, Luquin Piudo R, Martinez Castrillo JC. On disease modifying and neuroprotective treatments for parkinson's disease: physical exercise. Front Neurol 2022;13:938686.
[14] Cammisuli DM, Bonuccelli U, Daniele S, Martini C, Fusi J, Franzoni F. Aerobic exercise and healthy nutrition as neuroprotective agents for brain health in patients with Parkinson's disease: A critical review of the literature. Antioxidants 2020;9(5):380.
[15] Zhao JL, Jiang WT, Wang X, Cai ZD, Liu ZH, Liu GR. Exercise, brain plasticity, and depression. CNS Neurosci Ther 2020;26(9):885–95.
[16] van den Bongard F, Hamer HM, Sassen R, Reinsberger C. Sport and physical activity in epilepsy: A systematic review. Dtsch Arztebl Int 2020;117(1–2):1.
[17] Saxena A, Godena E, Maggio J, Perez DL. Towards an outpatient model of care for motor functional neurological disorders: a neuropsychiatric perspective. Neuropsychiatr Dis Treat 2020:2119–34.
[18] Nielsen G, Stone J, Edwards MJ. Physiotherapy for functional (psychogenic) motor symptoms: a systematic review. J Psychosom Res 2013;75(2):93–102.
[19] Dallocchio C, Arbasino C, Klersy C, Marchioni E. The effects of physical activity on psychogenic movement disorders. Mov Disord 2010;25(4):421–5.
[20] Nielsen G, Stone J, Matthews A, Brown M, Sparkes C, Farmer R, et al. Physiotherapy for functional motor disorders: a consensus recommendation. J Neurol Neurosurg Psychiatry 2015;86(10):1113–9.
[21] Kim Y-N, Gray N, Jones A, Scher S, Kozlowska K, editors. The role of physiotherapy in the management of functional neurological disorder in children and adolescents. Semin. Pediatr. Neurol.; 2022: Elsevier.
[22] Hebb C, Raynor G, Perez DL, Nappi-Kaehler J, Polich G. The use of rhythmic auditory stimulation for functional gait disorder: A case report. NeuroRehabilitation 2022;50(2):219–29.
[23] Barbey A, Pjanic I, Studer H, Bischoff N, Bassetti CLA, Aybek S. Management of functional neurological disorders (FND): experience from a Swiss FND clinic. Clin Trans Neurosci 2022;6(1):2.
[24] Polich G, Zalanowski S, Lewis JM, Sugarman S, Christopulos K, Hebb C, et al. Inpatient rehabilitation for acute presentations of motor functional neurological disorder (FND): A retrospective cohort study. Am J Phys Med Rehabil 2023;10:1097.
[25] Dallocchio C, Tinazzi M, Bombieri F, Arnó N, Erro R. Cognitive behavioural therapy and adjunctive physical activity for functional movement disorders (conversion disorder): a pilot, single-blinded, randomized study. Psychother Psychosom 2016;85(6):381–3.
[26] Kasia K, Nicola G, Stephen S, Blanche S. Psychologically informed physiotherapy as part of a multidisciplinary rehabilitation program for children and adolescents with functional neurological disorder: physical and mental health outcomes. J Paediatr Child Health 2021;57(1):73–9.
[27] Sieczkowska SM, Vilarino GT, de Souza LC, Andrade A. Does physical exercise improve quality of life in patients with fibromyalgia? Ir J Med Sci 2020;189(1971):341–7.
[28] Mason I, Renée J, Marples I, McWhirter L, Carson A, Stone J, et al. Functional neurological disorder is common in patients attending chronic pain clinics. Eur J Neurol 2023.
[29] Vancampfort D, Van Damme T, McGrath RL, Machado VA, Schuch F. Physical activity levels among people with fibromyalgia: A systematic review and meta-analysis. Musculoskeletal Care 2023.
[30] Akdoğan MR, DoĞAnci EB, Tüzün Z, Arslan S, Melikoğlu MA. Does fibromyalgia affect physical activity due to pain? Agri: Agri (Algoloji) Dernegi'nin Yayin Organidir= The Journal of the Turkish Society of Algology 2023;35(2):63–7.
[31] Masquelier E, D'haeyere J. Physical activity in the treatment of fibromyalgia. Joint Bone Spine 2021;88(5):105202.
[32] Karacay BC, Sahbaz T, Ceylan CM. The vicious cycle of physical inactivity, fatigue and kinesiophobia in patients with fibromyalgia syndrome. Reumatismo 2022;74(4).
[33] Sosa-Reina MD, Nunez-Nagy S, Gallego-Izquierdo T, Pecos-Martín D, Monserrat J, Álvarez-Mon M. Effectiveness of therapeutic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomized clinical trials. Biomed Res Int 2017;2017.
[34] Albuquerque MLL, Monteiro D, Marinho DA, Vilarino GT, Andrade A, Neiva HP. Effects of different protocols of physical exercise on fibromyalgia syndrome treatment: Systematic review and meta-analysis of randomized controlled trials. Rheumatol Int 2022;42(11):1893–908.
[35] Izquierdo-Alventosa R, Inglés M, Cortés-Amador S, Gimeno-Mallench L, Chirivella-Garrido J, Kropotov J, et al. Low-intensity physical exercise improves pain catastrophizing and other psychological and physical aspects in women with fibromyalgia: A randomized controlled trial. Int J Environ Res Public Health 2020;17(10):3634.
[36] López-Gómez I, Velasco L, Gutiérrez L, Écija C, Catalá P, Peñacoba C. Symptoms in women with fibromyalgia after performing physical activity: the role of pain catastrophizing and disease impact. Clin Rheumatol 2023;42(1):225–32.
[37] Catala P, Lopez-Roig S, Ecija C, Suso-Ribera C, Peñacoba PC. Why do some people with severe chronic pain adhere to walking prescriptions whilst others won't? A cross-sectional study exploring clinical and psychosocial predictors in women with fibromyalgia. Rheumatol Int 2021;41(8):1479–84.
[38] Serrat M, Sanabria-Mazo JP, Almirall M, Musté M, Feliu-Soler A, Méndez-Ulrich JL, et al. Effectiveness of a multicomponent treatment based on pain neuroscience education, therapeutic exercise, cognitive behavioral therapy, and mindfulness in patients with fibromyalgia (FIBROWALK study): a randomized controlled trial. Phys Ther 2021;101(12):pzab200.
[39] Couto N, Monteiro D, Cid L, Bento T. Effect of different types of exercise in adult subjects with fibromyalgia: a systematic review and meta-analysis of randomised clinical trials. Sci Rep 2022;12(1):10391.
[40] Andrade A, Dominski FH, Sieczkowska SM, editors. What we already know about the effects of exercise in patients with fibromyalgia: An umbrella review. Semin. Arthritis Rheumat. 2020: Elsevier.
[41] Andrade A, Steffens RAK, Vilarino GT, Miranda R, Benetti M, Coimbra DR. Preferred exercise and mental health of the patients with fibromyalgia syndrome. Complement Ther Clin Pract 2020;40:101195.
[42] Norouzi E, Hosseini F, Vaezmosavi M, Gerber M, Pühse U, Brand S. Zumba dancing and aerobic exercise can improve working memory, motor function, and depressive symptoms in female patients with fibromyalgia. Eur J Sport Sci 2020;20(7):981–91.
[43] Bravo Navarro C, Skjaerven LH, Guitard Sein-Echaluce ML, Catalan-Matamoros D. Effectiveness of movement and body awareness therapies in patients with fibromyalgia: a systematic review and meta-analysis. Eur. J. Phys. Rehab. Med., 2019, 55, 5, p646-657. 2019.
[44] Faíl LB, Marinho DA, Marques EA, Costa MJ, Santos CC, Marques MC, et al. Benefits of aquatic exercise in adults with and without chronic disease—a systematic review with meta-analysis. Scand J Med Sci Sports 2022;32(3):465–86.
[45] Ma J, Zhang T, Li X, Chen X, Zhao Q. Effects of aquatic physical therapy on clinical symptoms, physical function, and quality of life in patients with fibromyalgia: A systematic review and meta-analysis. Physiother Theory Pract 2024;40(2):205–23.
[46] Park H-K, Song M-K, Kim D-J, Choi I-S, Han J-Y. Comparison of core muscle strengthening exercise and stretching exercise in middle-aged women with fibromyalgia: A randomized, single-blind, controlled study. Medicine 2021;100(50).
[47] Kundakci B, Kaur J, Goh SL, Hall M, Doherty M, Zhang W, et al. Efficacy of nonpharmacological interventions for individual features of fibromyalgia: A systematic review and meta-analysis of randomised controlled trials. Pain 2022;163(8):1432–45.
[48] Maestre-Cascales C, Castillo-Paredes A, Romero-Parra N, Adsuar JC, Carlos-Vivas J. Gradual strength training improves sleep quality, physical function and pain in women with fibromyalgia. Int J Environ Res Public Health 2022;19(23):15662.
[49] Andersson UM, Åberg AC, von Koch L, Palstam A. Women with fibromyalgia prefer resistance exercise with heavy loads—A randomized crossover pilot study. Int J Environ Res Public Health 2021;18(12):6276.
[50] Sanz-Banos Y, Pastor-Mira M-A, Lledo A, Lopez-Roig S, Penacoba C, Sanchez-Meca J. Do women with fibromyalgia adhere to walking for exercise programs to improve their health? Systematic review and meta-analysis. Disabil Rehabil 2018;40(21):2475–87.
[51] Bateman L, Bested AC, Bonilla HF, Chheda BV, Chu L, Curtin JM, et al., editors. Myalgic encephalomyelitis/chronic fatigue syndrome: essentials of diagnosis and management. Mayo Clinic Proceed.; 2021: Elsevier.
[52] King E, Beynon M, Chalder T, Sharpe M, White PD. Patterns of daytime physical activity in patients with chronic fatigue syndrome. J Psychosom Res 2020;135:110154.
[53] White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet 2011;377(9768):823–36.
[54] Smakowski A, Adamson J, Turner T, Chalder T. Graded exercise therapy for patients with chronic fatigue syndrome in secondary care–a benchmarking study. Disabil Rehabil 2022;44(20):5878–86.
[55] Dannaway J, New CC, New CH, Maher CG. Exercise therapy is a beneficial intervention for chronic fatigue syndrome (PEDro synthesis). Br J Sports Med 2018;52(8):542–3.
[56] White P, Abbey S, Angus B, Ball HA, Buchwald DS, Burness C, et al. Anomalies in the review process and interpretation of the evidence in the NICE guideline for chronic fatigue syndrome and myalgic encephalomyelitis. J Neurol Neurosurg Psychiatry 2023;94(12):1056–63.
[57] Sanal-Hayes NEM, McLaughlin M, Hayes LD, Mair JL, Ormerod J, Carless D, et al. A scoping review of 'Pacing' for management of Myalgic Encephalomyelitis/

Chronic Fatigue Syndrome (ME/CFS): lessons learned for the long COVID pandemic. J Transl Med 2023;21(1):720.
[58] Alarie C, Gagnon I, Quilico E, Teel E, Swaine B. Physical activity interventions for individuals with a mild traumatic brain injury: A scoping review. J Head Trauma Rehabil 2021;36(3):205–23.
[59] Patricios JS, Schneider KJ, Dvorak J, Ahmed OH, Blauwet C, Cantu RC, et al. Consensus statement on concussion in sport: the 6th International Conference on Concussion in Sport–Amsterdam, October 2022. British journal of sports medicine. 2023;57(11):695-711.
[60] Leddy JJ, Haider MN, Noble JM, Rieger B, Flanagan S, McPherson JI, et al. Clinical assessment of concussion and persistent post-concussive symptoms for neurologists. Curr Neurol Neurosci Rep 2021;21:1–14.
[61] Popkirov S, Carson AJ, Stone J. Scared or scarred: Could 'dissociogenic'lesions predispose to nonepileptic seizures after head trauma? Seizure 2018;58:127–32.
[62] Roth CR, Cornis-Pop M, Beach WA. Examination of validity in spoken language evaluations: Adult onset stuttering following mild traumatic brain injury 1. NeuroRehabilitation 2015;36(4):415–26.
[63] Stone J. Post-Concussion Syndrome.
[64] Mavroudis I, Chatzikonstantinou S, Petridis F, Palade OD, Ciobica A, Balmus I-M. Functional overlay model of persistent post-concussion syndrome. Brain Sci 2023;13(7):1028.
[65] Miranda NA, Boris JR, Kouvel KM, Stiles L. Activity and exercise intolerance after concussion: identification and management of postural orthostatic tachycardia syndrome. J Neurol Phys Ther 2018;42(3):163.
[66] Leddy JJ, Cox JL, Baker JG, Wack DS, Pendergast DR, Zivadinov R, et al. Exercise treatment for postconcussion syndrome: a pilot study of changes in functional magnetic resonance imaging activation, physiology, and symptoms. J Head Trauma Rehabil 2013;28(4):241–9.
[67] van Markus-Doornbosch F, Peeters E, Volker G, van der Pas S, Vlieland TV, Meesters J. Physical activity, fatigue and sleep quality at least 6 months after mild traumatic brain injury in adolescents and young adults: a comparison with orthopedic injury controls. Eur J Paediatr Neurol 2019;23(5):707–15.
[68] Alarie C, Gagnon I, Guise Ed, McKerral M, Kersalé M, Swaine B. A remotely delivered progressive walking intervention for adults with persistent symptoms of a mild traumatic brain injury: feasibility and exploration of its impact. Frontiers in rehabilitation sciences. 2022;3:898804.
[69] Kurowski BG, Hugentobler J, Quatman-Yates C, Taylor J, Gubanich PJ, Altaye M, et al. Aerobic exercise for adolescents with prolonged symptoms after mild traumatic brain injury: an exploratory randomized clinical trial. J Head Trauma Rehabil 2017;32(2):79.
[70] Vas A, Rich E, Wang W, Patterson M, Parsons T. Daily functionality in adults with POTS: predictive factors. Occup Ther Health Care 2022;36(3):237–52.
[71] Fu Q, Levine BD. Exercise and non-pharmacological treatment of POTS. Auton Neurosci 2018;215:20–7.
[72] Stone J, Hoeritzauer I, Gelauff J, Lehn A, Gardiner P, van Gils A, et al. Functional Disorders in Neurology. Neurol Clin 2016;34(3):667–81.
[73] Steinruecke M, Mason I, Keen M, McWhirter L, Carson AJ, Stone J, et al. Pain and functional neurological disorder: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2024.
[74] Kerr WT, Janio EA, Braesch CT, Le JM, Hori JM, Patel AB, et al. Identifying psychogenic seizures through comorbidities and medication history. Epilepsia 2017;58(11):1852–60.
[75] Chou R, Deyo R, Friedly J, Skelly A, Hashimoto R, Weimer M, et al. Nonpharmacologic therapies for low back pain: a systematic review for an American College of Physicians clinical practice guideline. Ann Intern Med 2017;166(7):493–505.
[76] Borisovskaya A, Chmelik E, Karnik A. Exercise and chronic pain. physical exercise for human. Health 2020:233–53.
[77] Ferro Moura Franco K, Lenoir D, dos Santos Franco YR, Jandre Reis FJ, Nunes Cabral CM, Meeus M. Prescription of exercises for the treatment of chronic pain along the continuum of nociplastic pain: A systematic review with meta-analysis. Eur J Pain 2021;25(1):51–70.
[78] Hickman B, Pourkazemi F, Pebdani RN, Hiller CE, Fong YA. Dance for chronic pain conditions: A Systematic Review. Pain Med 2022;23(12):2022–41.
[79] Nielsen G, Buszewicz M, Stevenson F, Hunter R, Holt K, Dudziec M, et al. Randomised feasibility study of physiotherapy for patients with functional motor symptoms. J Neurol Neurosurg Psychiatry 2017;88(6):484–90.
[80] Reuber M, Burness C, Howlett S, Brazier J, Grünewald R. Tailored psychotherapy for patients with functional neurological symptoms: a pilot study. J Psychosom Res 2007;63(6):625–32.
[81] Vieluf S, Hasija T, Jakobsmeyer R, Schreier PJ, Reinsberger C. Exercise-induced changes of multimodal interactions within the autonomic nervous network. Front Physiol 2019;10:240.
[82] Gupt AM, Kumar M, Sharma RK, Misra R, Gupt A. Effect of moderate aerobic exercise training on autonomic functions and its correlation with the antioxidant status. Indian J Physiol Pharmacol 2015;59(2):162–9.
[83] Tulppo MP, Kiviniemi AM, Hautala AJ, Kallio M, Seppänen T, Tiinanen S, et al. Sympatho-vagal interaction in the recovery phase of exercise. Clin Physiol Funct Imaging 2011;31(4):272–81.
[84] Sarkis RA, Thome-Souza S, Poh M-Z, Llewellyn N, Klehm J, Madsen JR, et al. Autonomic changes following generalized tonic clonic seizures: an analysis of adult and pediatric patients with epilepsy. Epilepsy Res 2015;115:113–8.
[85] Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Front Public Health 2017;258.
[86] Tak LM, Riese H, de Bock GH, Manoharan A, Kok IC, Rosmalen JGM. As good as it gets? A meta-analysis and systematic review of methodological quality of heart rate variability studies in functional somatic disorders. Biol Psychol 2009;82(2):101–10.
[87] Joseph P, Arevalo C, Oliveira RKF, Faria-Urbina M, Felsenstein D, Oaklander AL, et al. Insights from invasive cardiopulmonary exercise testing of patients with myalgic encephalomyelitis/chronic fatigue syndrome. Chest 2021;160(2):642–51.
[88] Compass. 31: A refined and abbreviated composite autonomic symptom score. Mayo Clin Proc 2012;87(12).
[89] Lerma C, Martinez-Martinez LA, Ruiz N, Vargas A, Infante O, Martinez-Lavin M. Fibromyalgia beyond reductionism. Heart rhythm fractal analysis to assess autonomic nervous system resilience. Scand J Rheumatol 2016;45(2):151–7.
[90] Radmanesh M, Jalili M, Kozlowska K. Activation of functional brain networks in children with psychogenic non-epileptic seizures. Front Hum Neurosci 2020;14:339.
[91] Paredes-Echeverri S, Maggio J, Bègue I, Pick S, Nicholson TR, Perez DL. Autonomic, endocrine, and inflammation profiles in functional neurological disorder: A systematic review and meta-analysis. J Neuropsychiatry Clin Neurosci 2022;34(1):30–43.
[92] Reinsberger C, Perez DL, Murphy MM, Dworetzky BA. Pre-and postictal, not ictal, heart rate distinguishes complex partial and psychogenic nonepileptic seizures. Epilepsy Behav 2012;23(1):68–70.
[93] Pick S, Millman LSM, Ward E, Short E, Stanton B, Reinders AATS, et al. Unravelling the influence of affective stimulation on functional neurological symptoms: A pilot experiment examining potential mechanisms. J Neurol Neurosurg Psychiatry 2023.
[94] Slovák M, Anýž J, Erlebach J, Sieger T, Forejtová Z, Fabián V, et al. Emotional arousal in patients with functional movement disorders: A pupillometry study. J Psychosom Res 2022;162:111043.
[95] Van den Bergh O, Witthöft M, Petersen S, Brown RJ. Symptoms and the body: taking the inferential leap. Neurosci Biobehav Rev 2017;74:185–203.
[96] Reinsberger C, Sarkis R, Papadelis C, Doshi C, Perez DL, Baslet G, et al. Autonomic changes in psychogenic nonepileptic seizures: toward a potential diagnostic biomarker? Clin EEG Neurosci 2015;46(1):16–25.
[97] Palma J-A, Benarroch EE. Neural control of the heart: recent concepts and clinical correlations. Neurology 2014;83(3):261–71.
[98] Perez DL, Nicholson TR, Asadi-Pooya AA, Bègue I, Butler M, Carson AJ, et al. Neuroimaging in functional neurological disorder: state of the field and research agenda. NeuroImage: Clinical 2021;30:102623.
[99] Kulshreshtha P, Deepak KK. Autonomic nervous system profile in fibromyalgia patients and its modulation by exercise: a mini review. Clin Physiol Funct Imaging 2013;33(2):83–91.
[100] Solano C, Martinez A, Becerril L, Vargas A, Figueroa J, Navarro C, et al. Autonomic dysfunction in fibromyalgia assessed by the Composite Autonomic Symptoms Scale (COMPASS). JCR. J Clin Rheumatol 2009;15(4):172–6.
[101] Puri BK, Lee GS. Clinical assessment of autonomic function in fibromyalgia by the refined and abbreviated composite autonomic symptom score (COMPASS 31): A case-controlled study. Rev Recent Clin Trials 2022;17(1):53–7.
[102] Vincent A, McAllister SJ, Singer W, Toussaint LL, Sletten DM, Whipple MO, et al. A report of the autonomic symptom profile in patients with fibromyalgia. JCR. J Clin Rheumatol 2014;20(2):106–8.
[103] Zamunér AR, Barbic F, Dipaola F, Bulgheroni M, Diana A, Atzeni F, et al. Relationship between sympathetic activity and pain intensity in fibromyalgia. Clin Exp Rheumatol 2015;33(1 Suppl 88):S53–7.
[104] Furlan R, Colombo S, Perego F, Atzeni F, Diana A, Barbic F, et al. Abnormalities of cardiovascular neural control and reduced orthostatic tolerance in patients with primary fibromyalgia. J Rheumatol 2005;32(9):1787–93.
[105] Lerma C, Martinez A, Ruiz N, Vargas A, Infante O, Martinez-Lavin M. Nocturnal heart rate variability parameters as potential fibromyalgia biomarker: correlation with symptoms severity. Arthritis Res Ther 2011;13(6):1–9.
[106] Reyes del Paso GA, de la Coba P. Reduced activity, reactivity and functionality of the sympathetic nervous system in fibromyalgia: An electrodermal study. PLoS One 2020;15(10):e0241154.
[107] Eisenlohr-Moul TA, Crofford LJ, Howard TW, Yepes JF, Carlson CR, de Leeuw R. Parasympathetic reactivity in fibromyalgia and temporomandibular disorder: associations with sleep problems, symptom severity, and functional impairment. J Pain 2015;16(3):247–57.
[108] Gaudreault N, Boulay P. Cardiorespiratory fitness among adults with fibromyalgia. Breathe 2018;14(2):e25–33.
[109] Andrade A, Vilarino GT, Serafim TT, Pereira Junior AA, de Souza CA, Sieczkowska SM. Modulation of autonomic function by physical exercise in patients with fibromyalgia syndrome: A systematic review. Pm&r 2019;11(10):1121–31.
[110] Sañudo Corrales FdB, Carrasco Páez L, Hoyo Lora Md, Figueroa A, Saxton JM. Vagal modulation and symptomatology following a 6-month aerobic exercise programme for women with Fibromyalgia. Clin Exp Rheumatol, 1-5. 2015.
[111] Kingsley JD, McMillan V, Figueroa A. The effects of 12 weeks of resistance exercise training on disease severity and autonomic modulation at rest and after acute leg resistance exercise in women with fibromyalgia. Arch Phys Med Rehabil 2010;91(10):1551–7.
[112] Murga Gandasegui I, Aranburu Laka L, Gargiulo P-Á, Gómez-Esteban J-C, Lafuente Sánchez J-V. Myalgic encephalomyelitis/chronic fatigue syndrome: a neurological entity? Medicina 2021;57(10):1030.
[113] Friedberg F, Adamowicz JL, Bruckenthal P, Milazzo M, Ramjan S, Quintana D. Non-improvement in chronic fatigue syndrome: relation to activity patterns, uplifts and hassles, and autonomic dysfunction. Psychosom Med 2022;84(6):669.

[114] Joseph P, Singh I, Oliveira R, Capone CA, Mullen MP, Cook DB, et al. Exercise pathophysiology in myalgic encephalomyelitis/chronic fatigue syndrome and post-acute sequelae of SARS-CoV-2: more in common than not? Chest 2023.
[115] Van Iterson EH, Laffin LJ, Mayuga KA, Centeno EH, Ahmed T, Cho L, et al. High Submaximal exercise heart rate impacts exercise intolerance in the postural orthostatic tachycardia syndrome. J Cardiopulm Rehabil Prev 2020;40(3): 195–201.
[116] Rea NA, Campbell CL, Cortez MM. Quantitative assessment of autonomic symptom burden in Postural tachycardia syndrome (POTS). J Neurol Sci 2017; 377:35–41.
[117] Howard L, Dumkrieger G, Chong CD, Ross K, Berisha V, Schwedt TJ. Symptoms of autonomic dysfunction among those with persistent posttraumatic headache attributed to mild traumatic brain injury: a comparison to migraine and healthy controls. Headache: The Journal of Head and Face Pain 2018;58(9):1397–407.
[118] Myers L, Sarudiansky M, Korman G, Baslet G. Using evidence-based psychotherapy to tailor treatment for patients with functional neurological disorders. Epilepsy Behav Rep 2021;16:100478.
[119] Mestanikova A, Ondrejka I, Mestanik M, Hrtanek I, Snircova E, Tonhajzerova I. Electrodermal activity in adolescent depression. Pulm Infect Inflamm 2016:83–8.
[120] Ginton LM, Vuong E, Lake MT, Nhapi RT, Zar HJ, Yrttiaho S, et al. Investigating pupillometry to detect emotional regulation difficulties in post-traumatic stress disorder. World J Biol Psychiatry 2022;23(2):127–35.
[121] Dieleman GC, Huizink AC, Tulen JHM, Utens EMWJ, Creemers HE, van der Ende J, et al. Alterations in HPA-axis and autonomic nervous system functioning in childhood anxiety disorders point to a chronic stress hypothesis. Psychoneuroendocrinology 2015;51:135–50.
[122] Junaković A, Skočić Hanžek M, Adamec I, Krbot Skorić M, Habek M. A complex interplay between autonomic symptoms and symptoms of depression, anxiety, and stress. Neurol Sci 2023;1–11.
[123] Jacobson NS, Dobson KS, Truax PA, Addis ME, Koerner K, Gollan JK, et al. A component analysis of cognitive–behavioral treatment for depression. 2000.