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HABILITATION

The complex syndrome of functional neurological disorder: Clinical manifestations and neural correlates of motor and non-motor symptoms

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This work is dedicated to people with functional neurological disorder.

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Abbreviations

DSM-5 Diagnostic and Statistical Manual of Mental Disorders 5th Edition

FMD functional movement disorders

HRQoL health-related quality of life

ICD-10 International Classification of Diseases, 10th Edition

MRI magnetic resonance imaging

RLS restless legs syndrome

TPJ the temporoparietal junction

Introduction

Functional neurological disorders also referred to as conversion disorder or dissociative disorders are frequent conditions in neurology settings (Stone *et al.*, 2012). Motor subtype of functional neurological disorder also referred to as functional movement disorders (FMD) are characterized by abnormal motor control with abnormal movements or weakness that are significantly altered by distraction, beliefs and expectation, and which are clinically incongruent/incompatible with movement disorders known to be caused by neurological disease (Espay *et al.*, 2018a). FMD are associated with disability and impaired quality of life similar to that seen in people with multiple sclerosis and Parkinson's disease (Gendre *et al.*, 2019). Long term prognosis is very poor with most people remaining with disabling symptoms in the long term (Gelauff *et al.*, 2014).

Despite being a prevalent and costly condition, FMD have been unprecedently neglected and marginalized by the clinical and research community for most of the 20th century (Stephen *et al.*, 2021). The traditional psychological explanations assuming a causal role of psychological stressors in the development of FMD have prevailed without being challenged by neurobiologically informed models until recently (Edwards *et al.*, 2012).

Over the last two decades, there has been significant progress in our understanding of the brain mechanisms underlying FMD, updates in terminology and classification, improvements in diagnosis and treatment (Espay *et al.*, 2009). However, these advances seem to be rather restricted to the functional neurological disorder community and both the clinicians and patients struggle with multiple barriers and unmet needs in this field at the intersection between neurology and psychiatry (LaFaver *et al.*, 2020; Di Vico *et al.*, 2021). The long diagnostic journey most of the patients undergo before obtaining the right diagnosis is an eloquent indicator of excessive health care resourse consumption (Tinazzi *et al.*, 2020).

Terminology and nosological Classification

The term *functional* was introduced to reduce the stigma associated with emphasizing the psychological causes that are unproven and tightly associated with the old labels such as psychogenic, conversion or dissociative (Stone *et al.*, 2002; Edwards *et al.*, 2014; Jankovic, 2014; Begue *et al.*, 2019). However, FMD is not an official label in current classification systems. FMD is classified as "motor dissociative (conversion) disorder" (F.44.4) in the Psychiatry Section in the ICD-10 (International Classification of Diseases, 10th Edition) (WHO, 2004) and as "motor conversion disorder/functional neurological symptom disorder" in the chapter Somatic Symptom and Related Disorder in the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5)(APA, 2013).

Epidemiology

Functional disorders are very common in neurology, they represent the second most common reason to see a neurologist after headache (Stone *et al.*, 2010a). Based on a community registry, Functional neurological disorders have an incidence of 4-12/100 000 population/year and a prevalence of 50 per 100 000 population. FMD have incidence 4-5/100 000 and account for up to 20% of patients referred to movement disorders clinics (Carson and Lehn, 2016). Women are more frequently affected and represent 73% of FMD patients. The mean age at onset is 40 years (Lidstone *et al.*, 2022).

Diagnosis of FMD

The diagnosis of FMD is a "rule in" clinical diagnosis. It should be based on positive signs of inconsistency of abnormal movement control and evidence of features that are incongruent/incompatible with an organic disease (Gupta and Lang, 2009). Various general techniques and phenotype-specific tests can demonstrate signs of inconsistency and incongruence with the organic disease (Espay and Lang, 2015). Twenty-two studies reported 37 bedside clinical tests or combinations of these tests for the diagnosis of FMD including weakness, which had some form of validation (controlled designs to test for specificity and sensitivity

and/or provided data on inter-rater reliability) (Daum *et al.*, 2014; Daum *et al.*, 2015; Aybek and Perez, 2022). However, only a limited number of tests have been validated in larger samples, and numerous tests provided only low sensitivity.

The positive diagnosis is based on findings of inconsistency and incongruence with an organic disease in both the history and the neurological examination. When both inconsistency and incongruence are present, the diagnosis of clinically definite FMD can be made (Gupta and Lang, 2009). Similarly, the diagnosis of conversion disorder according to the DSM-5 criteria no longer requires the identification of an associated psychological stressor (APA, 2013). Importantly the presence or absence of psychiatric comorbidities, psychological factors such as traumatic life events, acute or chronic psychological stress, litigation and a secondary gain should not bias the diagnostic process as they can also be present in organic diseases (Stone *et al.*, 2013).

Inconsistency is characterized by variability of motor symptoms over time, selective disability, and alteration by distraction, expectations or illness beliefs. Typically, motor symptoms are suppressed when the attention is drawn away (distractibility), or they get worse when attention is drawn to the body during examination. Changes by non-physiological manoeuvres (suggestibility) such as triggering motor symptoms by application of a vibrating tuning fork to the limb are also a manifestation of inconsistency. Regardless of motor phenotype, competitive, complex tasks, either motor or cognitive (e.g. using mental arithmetic) can be used to divert attention away from the affected body part. Besides suppression or disappearance of functional motor symptoms during correct task performance, a poor task performance with persisting abnormal movements is also suggestive of functional etiology. In some cases, the abnormal movement may persist even with the attention diverted away (e.g. in cases of non-distractible functional tremor or dystonia). Sometimes, the appearance or worsening of an abnormal movement in a distant body part occurs when the ongoing abnormal movement is suppressed by holding it down (Park *et al.*, 2015).

In the clinical assessment, careful observation over long periods of time and during the performance of multiple tasks may be necessary to detect signs of distractibility, variability, and selectivity of motor symptoms. Characteristic for FMD also is impairment of explicit motor control during the examination while automatic/spontaneous movements during transfers in the room, getting dressed/undressed etc., are normal (Parees *et al.*, 2013; Araujo *et al.*, 2019). Other examples of inconsistency are variability of movement pattern (change in phenotype) or severity in time and selectivity of impairment which can also present as a mismatch between the objectively observed impairment and the self-reported limitations during activities of daily living.(Hayes *et al.*, 1999)

Incongruence involves a combination of symptoms and signs that are not seen in other neurological disorders; the pattern itself is incompatible with the functioning of the nervous system and does not respect the anatomical and physiological rules. FMD often present with bizarre, mixed movements, difficult to classify and precipitated paroxysms. However, to be certain that abnormal movement patterns do not present or progress according to the wide phenotypic range of known organic movement disorders requires extensive expertise in movement disorder (Espay and Lang, 2015).

Distractibility or improvement of the abnormal motor function when the patient is volitionally performing a competitive motor or cognitive task is a sign of both inconsistency and incongruency in most phenotypes. The exception is tics, which also change over time and are suppressible with complex tasks (Espay and Lang, 2015) and pain associated with weakness, which can also be distractible (Stone and Aybek, 2016).

Several historical features and examination findings are commonly present in patients with FMD regardless of movement phenomenology. These features are not diagnostic of FMD but can be helpful as a part of the diagnostic process (Gupta and Lang, 2009). Patients often describe the sudden onset and rapid progression, which might be triggered by a physical event (Parees *et al.*, 2014b). Unlike the slowly progressive course of most movement disorders, the progression can be rapid to become severe. The phenomenology of the movement type may shift over time. Patients also may report marked variability in symptom severity often

associated with fatigue and pain in day-to-day performance and complete remissions and sudden recurrences. Remittance to placebo or suggestion has become a part of the diagnostic criteria for a documented FMD (Fahn and Williams, 1988; Gupta and Lang, 2009). However, a recent study did not find stronger placebo responses in FMD patients than healthy controls. It has been argued that occasional dramatic placebo responses may occur because functional symptoms are inherently more changeable than those due to organic disease (Huys *et al.*, 2021).

In the diagnostic process laboratory and imaging examinations are of limited value. Electrophysiological studies can help to characterize features of FMD that can be useful for the diagnosis (Hallett, 2010). Specifically, electrophysiological assessment of tremor and myoclonus can provide a valuable information that is not possible to obtain from the physical examination (Gupta and Lang, 2009). Electrophysiological recordings of electromyographic activity and movement using accelerometers can demonstrate inconsistency in parameters that are difficult to tell by the naked eye such as latencies, variability or change in frequency. Electrophysiological characteristics of functional tremor involve, presence of coactivation of agonist and antagonist muscles, coherence of tremor in different body parts which is not present in organic tremors.

Electrophysiology can also document incongruencies, i.e., the "unobservable" phenomena that are present in functional but not in organic disorders such as the premotor potential also called the Bereitschaftspotenzial which is preceding functional myoclonic jerks obtained using the electroencephalography back-averaging technique or coherence of tremor in different body parts. The fact that the electrophysiological characterization of tremor and myoclonus can provide a valuable information that is not possible to obtain from the physical examination has been reflected in the revised diagnostic criteria for FMD by Gupta and Lang in 2009 who introduced a new category of laboratory i.e. electrophysiologically supported definite FMD (Gupta and Lang, 2009; Schwingenschuh *et al.*, 2011b; Schwingenschuh *et al.*, 2016).

FMD phenotypes

The clinical presentation of FMD is very heterogeneous. FMD may present with any type of movement disorder, often with mixed manifestations combining abnormal movements of different types and functional weakness. Mixed FMD (23.1%), tremor (21.6%) and weakness (18.1%) were the most common phenotypes in a recent meta-analysis including a large population of FMD patients (n=4905) (Lidstone *et al.*, 2022). Increased startle or startle-like movements and precipitated paroxysmal movements are frequent in patients with FMD.

Functional weakness

Functional weakness represents a common motor phenotype of FMD. Up to 10% of strokes mimics are due to functional weakness (B *et al.*, 2021). Functional weakness is characterized by variability in severity over time and discordant performance in different tasks during one examination session (Stone *et al.*, 2010b; Stone and Aybek, 2016; Gelauff *et al.*, 2019). Functional weakness often presents with a non-pyramidal distribution and/or as collapsing or give-way weakness (Daum *et al.*, 2015). In the lower limb, a reliable sign of functional weakness is Hoover's sign demonstrating that hip extension returns transiently to normal during contralateral hip flexion against resistance (Ziv *et al.*, 1998; McWhirter *et al.*, 2011). Similarly, the hip abduction returns to normal during contralateral hip abduction against resistance in functional weakness (Sonoo, 2004). In the upper limb a reliable sign is the drift without pronation during the arm stabilization test (Daum and Aybek, 2013).

Functional tremor

Functional tremor is the most common manifestation of FMD, presenting with abnormal movements accounting for up to 30 % of FMD (Tinazzi *et al.*, 2020; Lidstone *et al.*, 2022). Variability of frequency, characteristic response to externally cued rhythmic movements (entrain to the cued frequency), and distractibility are the key features that distinguish functional tremor from organic tremor, which presents

with a stable frequency, and is not distractible by competitive motor or cognitive tasks (Deuschl *et al.*, 1998; Roper *et al.*, 2013; van der Stouwe *et al.*, 2016). In another dual-task interference test, a competitive ballistic movement with the less affected hand is accompanied by an interruption of the tremor in the contralateral hand (Kumru *et al.*, 2004; Kumru *et al.*, 2007).

Functional dystonia

Functional dystonia is the second most abnormal movement type in patients with FMD (Tinazzi *et al.*, 2020; Lidstone *et al.*, 2022). While organic dystonia is typically mobile and tends to be action induced, patients with functional dystonia typically present with fixed abnormal postures (Schrag *et al.*, 2004). Functional dystonia is often less distractible than other functional abnormal movements; sometimes a brief give way of muscle activity during distraction can be observed (Frucht *et al.*, 2020). Functional dystonia is commonly accompanied by severe pain, and there is an overlap with complex regional pain syndrome type 1 (Popkirov *et al.*, 2018). There is no specific diagnostic test for functional dystonia (Aybek and Perez, 2022).

Functional myoclonus

Myoclonus should be a simple, sudden brief movement/jerk caused by involuntary muscle activity (Tinazzi *et al.*, 2020; Lidstone *et al.*, 2022). Functional myoclonus is usually variable in duration and distribution of jerks, often with multiple components over time (Hallett, 2016). Functional myoclonus may be suppressed with competitive complex tasks or and it may also entrain to externally cued rhythmic movements (Dreissen *et al.*, 2016). Functional stimulus sensitive reflex myoclonus is characterized by latencies that are variable and similar to voluntary reaction time (Hallett, 2016). Palatal myoclonus and the so-called propriospinal myoclonus characterized by repetitive, usually arrhythmic fixed pattern flexion movements of the trunk, hips, and knees are often of functional origin (Stamelou *et al.*, 2012; van der Salm *et al.*, 2014).

Functional gait disorders

Gait disorders are another frequent presentation of FMD (Tinazzi *et al.*, 2020; Lidstone *et al.*, 2022). Most functional gait disorders look bizarre and incongruent with known gait disorders (Fung, 2016). Balance during examination is often better than the claim, and compensatory strategies sometimes tend to be contra-productive. Several gait patterns have been identified as common and typical for functional etiology (Daum *et al.*, 2014). These include dragging of a leg behind the body, excessive slowness with an exaggerated delay in gait initiation, walking on ice pattern with decreased stride length and height and stiff knees and ankles, gait with uneconomic postures, gait with sudden knee buckling, or unsteady gait characterized by crossed legs and sudden side steps or veering (Lempert *et al.*, 1991; Baik and Lang, 2007; Jordbru *et al.*, 2012). However, for a clinically established diagnosis, multiple tests including straight walking, performing a dual-task, running or walking backwards, walking with eyes closes are usually needed to identify improvement or marked change in gait pattern i.e., positive signs of distractibility/inconsistency and incongruence) (Nonnekes *et al.*, 2020).

Other phenotypes

Functional facial and eye movement abnormalities are also common (Fekete *et al.*, 2012; Kaski *et al.*, 2015; Baizabal-Carvallo and Jankovic, 2016; Kaski and Bronstein, 2016; Baizabal-Carvallo and Jankovic, 2017a, b; Teodoro *et al.*, 2019). Functional tic-like movements can manifest either alone or in overlap with tic disorder. Given their similarities such as action monitoring, attentional allocation the diagnosis is often challenging (Ganos *et al.*, 2014; Demartini *et al.*, 2015; Ganos *et al.*, 2019).

Comorbid conditions

Patients with FMD almost always have multiple additional symptoms (e.g. sensory symptoms and pain, often in multiple body regions including headache, fatigue, cognitive complaints, anxiety and depression, seizures, bladder and bowel problems). A vast majority of FMD patients fulfil clinical criteria for other

functional somatic syndromes/somatic symptom disorders (i.e. chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome) (Wessely *et al.*, 1999). Poor concentration, memory problems and other cognitive complaints can also cause distress and functional impairment (Teodoro *et al.*, 2018).

Patients with FMD may also suffer from other co-occurring functional neurological disorders, such as functional sensory symptoms or non-epileptic seizures/dissociative seizures (Erro *et al.*, 2016). Psychiatric comorbidities such as mood and anxiety disorders, post-traumatic stress disorder, personality disorder and dissociation are also commonly reported in patients with FMD (Feinstein *et al.*, 2001; Gelauff *et al.*, 2014). However, psychiatric comorbidities are also frequent in organic disorders (Zutt *et al.*, 2017). Therefore, their presence or absence does not help to determine the etiology. Various personality disorders including dependent, antisocial, and borderline personality disorder, have been reported inconsistently, mostly from small samples (Feinstein *et al.*, 2001; Kranick *et al.*, 2011; Gelauff *et al.*, 2014). Recently, obsessive-compulsive personality disorder has been reported (Demartini *et al.*, 2014).

Functional and organic disorders are often coexistent. Functional symptoms are present in up to 12 % of other neurological disorders across neurological subspecialties (Stone *et al.*, 2012). Recent studies reported frequent functional symptoms in Parkinson's disease (including the prodromal phase) and Multiple Sclerosis may also be associated with functional symptoms (Wissel *et al.*, 2018; Onofrj *et al.*, 2022; Walzl *et al.*, 2022).

Pathophysiology

FMD is a complex condition with a multifactorial and heterogeneous etiology. There is a growing understanding of the biological, psychological and social factors that seem to be involved in the pathophysiology, but the picture is still very incomplete.

FMD has been traditionally related to psychological factors. However, a history of childhood trauma and negative life events preceding symptom onset has been found inconsistently; life stressors are not apparent

in many patients and are present in many people without FMD (Ludwig *et al.*, 2018). Although life adversities and other psychological factors are not considered to be causal but rather predisposing, precipitating or perpetuating factors, they have still remained a target of interest in the neurobiologically oriented research, in particular in neuroimaging studies (Perez *et al.*, 2021b). In contrast to this, biological factors such as genetic differences, neurotransmitter alterations and neuroimmune changes, which are commonly studied in other neurological and psychiatric disorders, have been addressed only marginally and in small samples (Apazoglou *et al.*, 2018; Demartini *et al.*, 2019; van der Feltz-Cornelis *et al.*, 2021).

Neurobiological model – theoretical framework

Recently neurobiological models of functional symptoms based on predictive coding accounts of brain function have been proposed (Edwards *et al.*, 2012; Van den Bergh *et al.*, 2017).

Predictive coding account of the brain function postulates that the brain's network architecture is an active inference generator that operates according to the Bayesian approach to probability via a multilevel neuronal cascade (Friston, 2010). Learned beliefs about the world and about oneself work like top-down predictions explaining sensory signals that transmit prediction errors up the neuronal hierarchy (Friston, 2010). A key feature of this proposed mechanism is that the same basic computational phenomenon can account for functional symptoms across the motor, sensory and interoceptive domains. These models suggest that functional symptoms arise from the development of abnormal “priors” or predictions, the expression of which is driven by an abnormal allocation of attention (Edwards *et al.*, 2012). The neural correlates of abnormal predictions in FMD are not known. According to this model, proprioceptive predictions related to the dynamics of movement are formed within an intermediate motor area (e.g., the supplementary motor area) and are afforded too much precision via misdirected attentional gain from higher hierarchical levels. The prediction signal is propagated down the motor hierarchy, producing a proprioceptive prediction error peripherally that is fulfilled by a generation of an abnormal movement or a lack of movement in functional weakness. Prediction errors reporting unpredicted content in the motor

domain to higher cortical areas (e.g., pre-supplementary motor area) are explained in terms of a symptomatic interpretation as involuntary movements or as failure to realize the movement that was intended in FW (Edwards *et al.*, 2012).

Since the proposal of the predictive coding account on FMD (and functional neurological symptoms in general) by Edwards et al., 2012, the evidence for the role of regions associated with generative processes supporting predictions, attention and conceptualization has been accumulated in pathophysiological research in this area (Baizabal-Carvallo *et al.*, 2019; Perez *et al.*, 2021b).

Mechanisms underlying FMD

Electrophysiological studies

FMD use the same neural pathways as those for voluntary movements and electrophysiological studies consistently find normal activation of primary motor and sensory pathways and the presence of Bereitschaftspotenzial, which is associated with voluntary movements (Hallett, 2010). Abnormal function of the brain at different levels has been reported inconsistently in FMD. Some abnormalities that are present in organic dystonia were not found in cases with functional dystonia. In one study using paired associative stimulation, abnormally high plasticity was found only in the organic group (Quartarone *et al.*, 2009). In other studies, only patients with organic but not patients with functional blepharospasm had abnormal blink reflex recovery curve (Schwingenschuh *et al.*, 2011a) or temporal discrimination (Katschnig *et al.*, 2010). However, various other electrophysiological studies found abnormalities such as the impaired the short interval intracortical inhibition (Espay *et al.*, 2006; Avanzino *et al.*, 2008) and impaired temporal discrimination (Morgante *et al.*, 2011) in FMD. These abnormalities have also been associated with a wide range of other neuropsychiatric disorders including movement disorders such as Parkinson's disease and dystonia (Udupa and Chen, 2019) and many mental disorders and other somatic symptom disorders. Therefore, these findings challenge the categorical distinction between "functional" and "organic"

disorders. Importantly, these abnormalities cannot be fabricated voluntarily and provide evidence that FMD are genuine disorders of the brain.

Neuroimaging studies

Abnormalities in both brain function and structure in FMD have been shown in studies using task-based and resting-state functional neuroimaging, structural MRI, and multimodal techniques (Voon *et al.*, 2016; Perez *et al.*, 2021b). Different aspects of motor control, sense of agency, emotional processing, and more recently treatment effects, the gene-environment-brain interactions have been addressed. One line of work searched for neural correlates of abnormal motor control in FMD. Most of this work has been done in patients with functional weakness using different motor tasks (Marshall *et al.*, 1997; Spence *et al.*, 2000; Burgmer *et al.*, 2006; Cojan *et al.*, 2009). Patients were compared to both normally moving healthy controls and to controls feigning paresis. Those studies identified different patterns of altered brain activity related to motor planning, intention, movement initiation, execution, and inhibition. However, some recent studies did not find between-group differences during motor tasks. Although no clear pattern was found across studies comparing functional weakness to simulated weakness, all studies reported a different activation pattern during movement execution in the affected limb in patients compared to feigners.

The fact that the FMD have the characteristics of voluntary movements (such as distractibility and presence of pre-movement potential) but are perceived by patients as involuntary suggests that an abnormal sense of agency may be a part of the disorder (Hallett, 2007, 2010). Agency is the experience of being the cause of our own actions. According to the current view, self-generated movements are accompanied by a sensory prediction of the motor outcome. This feedforward signal is compared to sensory feedback. When the prediction matches the sensory outcome, it gives rise to a sense of self-agency; conversely a mismatch gives rise to the sensation that we are not in control of our movements (Haggard, 2008; Nahab *et al.*, 2011). Abnormal activity of the right temporoparietal junction (TPJ), which has been implicated in comparing the feedforward and the feedback signal, has been identified in an early study comparing brain activity during

the functional tremor with voluntary mimicked tremor (Voon *et al.*, 2010b). The involvement of TPJ in FMD was confirmed by several subsequent studies that used different paradigms such as virtual reality manipulation of the self-agency or Libet's clock to study intention awareness (Voon *et al.*, 2010b; Maurer *et al.*, 2016; Baek *et al.*, 2017; Nahab *et al.*, 2017).

Emotional processing in FMD has been addressed by several studies using an emotion-task-based fMRI study design (Voon *et al.*, 2010a; Aybek *et al.*, 2015; Espay *et al.*, 2018b). Abnormalities found involved the abnormal activity of brain regions involved in emotional processing (the amygdala) and their connectivity with involved motor processing (the supplementary motor area), suggesting abnormal limbic-motor interactions (Voon *et al.*, 2010a).

Several resting-state fMRI studies which used different analytical approaches have also identified various abnormalities at the level of cortical and subcortical regions and whole-brain networks that differentiated patients from healthy controls.

Over the past decade, an increasing number of studies reported structural alterations in individuals with functional disorders including FMD, which have been found in the sensorimotor, prefrontal, striatal-thalamic, paralimbic, and limbic regions (Begue *et al.*, 2019). However, inconsistencies in findings and a lack of group-level differences have also been described. Further studies reported brain changes following treatment, suggesting that both cognitive behavioral therapy and motor retraining may reorganize activity and connectivity in emotion processing and motor control networks in FMD (Espay *et al.*, 2019; Faul *et al.*, 2020).

Two recent multimodal studies investigated the genes-environment-brain interaction. One study identified brain areas impacted by childhood trauma and their overlap with regional gene expression profile. Implicated genes are involved in stress-related neuroplasticity, neurodevelopment, and locomotory behavior, suggesting these genes may be important in promoting brain reorganization following childhood

trauma in this population (Diez *et al.*, 2020). A different study investigated the contribution of variants in selected stress-related genes (18 SNPs) to clinical manifestations and circuit-level phenotypes either directly or in interaction with childhood trauma. Among the 18 SNPs that were analyzed, a tryptophan hydroxylase 2 gene polymorphism showed a relationship to age of onset and amygdala–frontal connectivity suggesting serotonin levels may be a potential molecular mechanism modulating FMD phenotype (Spagnolo *et al.*, 2020).

In summary, the major lines of evidence suggested disorders in networks involved in volition, emotion and motor control (Baizabal-Carvallo *et al.*, 2019). Findings from more recent and larger studies also pointed towards the role of cingulo-insular alterations may contribute to impaired multimodal integration of affective and bodily related information, which could help explain the multiplicity of sensorimotor, affective and cognitive symptoms in some patients with FND and somatic symptom disorder (Ospina *et al.*, 2019).

At the network level, the regions that have been associated with FMD (even if considering only the rs-studies) are from across multiple networks of the brain (Yeo *et al.*, 2011). In FMD, beside the sensorimotor and the limbic networks, other major networks have been implicated such as the default network involved in conceptualization, the executive control network and the ventral attention network/salience network, which are linked to body-oriented attention. This is in line with the cognitive perspective on FMD (Edwards *et al.*, 2012). The involvement of multiple brain networks also parallels the finding that supported the current view on emotions as cognitive processes that are actively built by the brain using a set of interacting brain regions commonly involved in basic psychological operations (Lindquist *et al.*, 2012).

Behavioral studies

Self-agency, attention, and attention-motor control interaction in FMD have been addressed using behavioral paradigms. Abnormal action-binding effect (Kranick *et al.*, 2013) and the loss of sensory attenuation (Parees *et al.*, 2014a; Macerollo *et al.*, 2015) have been correlated with the loss of sense of

agency, along with findings from neuroimaging studies may help to explain why patients report that they do not experience the abnormal movement as voluntary. Impaired motor control in FMD was experimentally found in situations where movements were highly predictable, and there was an opportunity for explicit control while unpredictable movements occurring in an implicit fashion were normal (Parees *et al.*, 2013).

Several studies assessed performance in different tasks requiring attentional resources with contradictory findings (Roelofs *et al.*, 2003; Heintz *et al.*, 2013; Voon *et al.*, 2013; Huys *et al.*, 2020; de Vroege *et al.*, 2021). Recently, in the attention network test, the alerting and orienting effects of presented cues were normal, but executive control of attention under conflict was abnormal in patients with FMD compared to patients with an organic movement disorder and healthy controls (Huys *et al.*, 2020).

Executive dysfunction seems to be an important secondary feature of FMD due to the overutilization of attentional resources for explicit movement control.

Increased attention to movements has been described in FMD. However, it has been found that any kind movement disorder (i.e. functional or organic), induces increased attention to one's movement. This increase in conscious motor processing may be adaptive and necessary for safe and efficient movements.

Management

Previously, patients were usually told their condition was psychogenic or stress-related, and they were encouraged to search for psychological treatment. Over the past decade, the shift in the theoretical frame of FMD has been paralleled by changes in the approach to management.

The first step after establishing a positive diagnosis is an explanation that helps the patient understand that FMD is a genuine disorder, which is common, with the potential for reversibility. Most of the evidence supporting the positive impacts of a diagnostic explanation comes from studies on dissociative seizures

(Perez and LaFrance, 2016). Diagnosis delivery should follow the normal rules of explanation without unnecessary overemphasizing the role of psychological stressors as causative factors. The explanation should start with explaining the mechanism, i.e. malfunctioning of the brain, in preference to explaining the etiology, which is unclear, complex and probably very heterogeneous in FMD. It is useful to demonstrate to patients the positive signs, e.g. Hoover's sign, distractibility of tremor and explain the impact of abnormal attention (Stone and Edwards, 2012; Carson *et al.*, 2016). Providing additional explanation (e.g., www.neurosymptoms.org) and education for patients and their relatives does not substitute a therapeutic intervention (Gelauff *et al.*, 2020). However, it can improve understanding and acceptance of an FMD diagnosis and improve readiness for further treatment (Cope *et al.*, 2021).

Physiotherapy has a key role in the multidisciplinary management of FMD. Two randomized controlled trials (RCT) using physical therapy and more observational trials and cohort studies reported a good outcome in 50-70% of patients from moderate to large size effect with a sustained benefit at follow-ups (Jordbru *et al.*, 2013; Nielsen *et al.*, 2017). Consensus recommendations based on the evidence and expert opinion provide a description of the general approach and specific strategies for different motor phenotypes (Nielsen *et al.*, 2015). The general approach consists of education with the demonstration that normal movement can occur and an explanation of the impacts of abnormal attention, movement retraining and self-management strategies. Movement retraining consists in building up the components of the movement using automatic symptom-free movements re-emerging with diverted attention. Another key component is changing maladaptive behaviors related to symptoms (Nielsen *et al.*, 2019). More recently, recommendations for occupational therapy in functional neurological disorders have been published (Nicholson *et al.*, 2020a).

Psychological interventions have traditionally been considered the treatment of choice for functional neurological disorders and are often recommended to people with FMD. However, the high-quality studies with long-term follow-up are lacking (Gutkin *et al.*, 2020). In FMD, promising results have been found in

studies using the cognitive-behavioral approach and psychodynamic psychotherapy (Sharpe *et al.*, 2011; Kompoliti *et al.*, 2014; Hubschmid *et al.*, 2015; Dallocchio *et al.*, 2016). A psychiatrist familiar with the FMD should assess and treat psychiatric comorbidity. There is also some evidence from RCT and from observational studies for the efficacy of multidisciplinary treatment (Jordbru *et al.*, 2013).

Evidence from RCTs suggested the efficacy of other techniques such as neuromodulation (e.g. transcranial magnetic stimulation- TMS) (Oriuwa *et al.*, 2022) and hypnosis (Moene *et al.*, 2002, 2003; Vizcarra *et al.*, 2019). However, single-pulse TMS paradigms used in several studies were unlikely to cause neuromodulator changes in the brain and rather a cognitive-behavioral effect can be assumed (Garcin *et al.*, 2017). We still lack reliable evidence for a clear neuroanatomical target from imaging studies such as the left DLPF in depression, where TMS became an established technique (Lefaucheur *et al.*, 2020). RCTs examining botulinum toxin in FMD treatment have not provided evidence for its efficacy (Dreissen *et al.*, 2019; Vizcarra *et al.*, 2019). Other techniques that will require further evidence are therapeutic sedation (Stone *et al.*, 2014) and approaches using virtual reality (Bullock *et al.*, 2020).

It also is essential to detect and treat comorbid conditions, whether psychiatric or neurological, during the initial examination and follow-up (Gelauff *et al.*, 2020; Perez *et al.*, 2021a).

Prognosis, disability

FMD is associated with disability and impaired quality of life similar to that seen in people with organic movement disorders (Gendre *et al.*, 2019). Non-motor symptoms such as fatigue, anxiety, and cognitive complaints are important predictors of impaired quality of life (Gelauff *et al.*, 2018; Vechetova *et al.*, 2018). The prognosis is very poor, with most people remaining with disabling symptoms in the long term (Gelauff and Stone, 2016). Levels of physical disability and psychological comorbidity at follow-up were high. The mean percentage of patients same or worse at follow-up for all studies was 60% (Gelauff *et al.*, 2014). Consistent negative prognostic predictors include long duration of symptoms before diagnosis and personality disorders, whereas good outcomes are associated with young age and early diagnosis.

Investigations should be performed as quickly as possible, as protracted testing may delay or disrupt positive management (Gelauff *et al.*, 2014).

Gaps and unmet needs

Classification

In Czechia, the valid diagnostic code is motor dissociative (conversion) disorder in the ICD 10th revision (WHO, 2004). ICD-10 categorizes FMD under the Psychiatric section, thus perpetuating patients' and physicians' confusion and barriers to adequate management. The ICD-11 included functional disorders also within the neurology section for the first time (WHO, 2018). However, only several phenotypes (functional tremor, parkinsonism and dystonia) have been included in the Neurology section, while other motor phenotypes such as myoclonus, and gait disorders can be classified only under the Psychiatry section. Furthermore, the current classification systems disregard a common clinical experience of multiple motor and non-motor symptoms coexisting in one individual and an increasing body of evidence supporting the same underlying mechanism across symptom domains (Edwards *et al.*, 2012; Van den Bergh *et al.*, 2017). Pain, fatigue and other symptoms in people with FMD are currently classified separately in ICD-10 where there is one diagnostic category for the dissociative motor disorder (F44.4) and another for persistent *somatoform pain* disorder (F45.4) (WHO, 2018). A similar diagnostic division is present or DSM-5, where associated pain is labelled as somatic symptom disorder (e.g. with predominant pain), but only if psychological distress regarding symptoms accompanied by thoughts and behaviors are judged to be "excessive" by the clinician (APA, 2013). Thus, patients are given several diagnoses such as motor conversion disorder and chronic somatoform pain. This situation highlights the need for a detailed characterization of the relationship between numerous symptoms coexisting in one individual which would inform further classification revisions.

Pathophysiology

Despite significant advances in our understanding of the mechanism underlying FMD, in particular, due to neuroimaging and electrophysiological studies, our knowledge of pathophysiology is still limited, and nurmerous methodological issues have been raised. The abnormities found in electrophysiology and imaging studies have been found in small samples and lack reproduction. Numerous abnormalities found in FMD and have been reported in many other conditions, including different functional neurological disorders, somatic symptom disorders, neurological and psychiatric conditions. These abnormalities may be disease-related, compensatory and/or they may also be the consequence of shared predisposing vulnerabilities and comorbidities. However, characterization of predisposing vulnerabilities, organic and functional comorbidities, symptom severity, disease duration, and other confounders has usually been limited. Another under-researched area are neural differences between various subtypes of functional neurological disorders. A recent review on neuroimaging in functional neurological symptoms highlighted the need for multicentric longitudinal studies(Perez *et al.*, 2021b). Only studies with a greater number of independent samples are able to address patient heterogeneity concerns with complementary between-group analyses with stratified sub-group and within-group analyses (i.e. patients with weakness vs patients with hyperkinetic FMD) based on clinically relevant characteristics (i.e. symptom severity, psychiatric comorbidities etc.).

Diagnosis and treatment

An early diagnosis, with subsequent treatment involving rehabilitative and/or psychological treatments, can promote recovery. However, there are no diagnostic and treatment guidelines. Most of the diagnostic tests have been studied in very small samples without proper validation (Daum *et al.*, 2014; Daum *et al.*, 2015; Aybek and Perez, 2022). Up to date, there is no disorder-specific outcome measure covering the complex nature of the functional neurological disorder (Pick *et al.*, 2020).

Similarly, support from evidence-based medicine regarding FMD specific treatments is still limited, and there is a lack of predictors of specific treatment outcomes and prognosis (Aybek and Perez, 2022). Medical professionals must still rely on expert recommendations and clinical experience. Even movement disorders experts often feel a lack of sufficient knowledge in FMD and are reluctant to engage in taking care of these patients (LaFaver *et al.*, 2020). The lack of effectiveness of conventional symptomatic medical therapy is another source of frustration for clinicians and patients with chronic debilitating symptoms (Wessely *et al.*, 1999).

Access to adequate treatment and disability benefits

A high standard of care for FMD patients should ideally involve a multidisciplinary team comprising neurologists, psychiatrists, physical medicine and rehabilitation doctors, physiotherapists and psychotherapists. Multidisciplinary and specialized clinics are insufficient with regard to the number of patients. Despite the high prevalence, persistency of FMD, high disability rate and poor health related quality of life of people with FMD, and socioeconomic consequencies, the national healthcare systems developing and implementing policies fail to integrate FMDs among healthcare and research priorities (Carson *et al.*, 2011). Besides facing numerous barriers to adequate care, FMD patients do not benefit from appropriate legal rights, social support and social protection including an adequate disability-related financial support.

Distinction from malingering

Despite the evidence from studies in FMD that demonstrated an abnormal sense of agency and other changes in brain function that cannot be voluntarily fabricated and differ from patterns found in people faking abnormal motor control, many physicians still tend to suspect deliberate production of motor symptoms. Up to date, no clinical or laboratory tests have been developed to distinguish FMD from malingering of factitious disorder and protect patients from the doubts of simulation. This situation is unfortunate, given that malingering is supposed to be relatively rare in the clinical context. Patients' stigma

is also associated with a low prestige of functional symptoms compared to those with a well-defined anatomical basis which are considered more serious (Album and Westin, 2008).

Conclusion

Functional neurological disorder is one of the commonest conditions that neurologists encounter in clinical practice, making up 10-15% of general neurology outpatient clinics and 10% of admissions to hyperacute stroke services. FMD is often persistent and associated with significant disability and health care resources consumption. Neurologists often report finding interactions with such patients difficult, and specific services that can help with treatment are poorly developed, commonly falling between neurology and psychiatry services.

Despite great progress that has been made in increasing awareness and interest amongst neurologists and psychiatrists, with important developments in pathophysiological understanding, diagnosis, diagnostic explanation, and treatment, including multicenter randomized trials of psychological therapy and physiotherapy, there are still numerous gaps in knowledge and unmet needs in the research are and the clinical practice for both the patients and the clinicians. As research expands, subsequent adequate education of professionals across disciplines and the development of healthcare facilities are critical steps towards the improvement of the patients' outcomes through an early and correct diagnosis and disease-specific and evidence-based multidisciplinary management of FMD.

Main aims of the current work

The clinical presentation of FMD is heterogeneous and patients with FMD almost always have multiple additional psychological and somatic symptoms (e.g. anxiety and depression, cognitive complaints, sensory symptoms and pain, fatigue) that can result from comorbid psychiatric, other neurological disorders (i.e. “organic”) or that may be functional symptoms.

Different comorbid conditions may share pathophysiological mechanisms and risk factors / predisposing vulnerabilities that can play a role in development and/or maintenance of FMD. A thorough multidimensional mapping of comorbid symptoms and conditions/disorders can help to understand their mutual relationship and clinical relevance. Identifying and managing treatable comorbid conditions may lessen the burden and improve HRQoL of patients with FMD.

The aim of the current work was to address the complex relationship between motor and non-motor symptoms in FMD, their neurophysiological correlates and clinical significance. The motor and non-motor symptoms in our FMD cohort have been assessed across different constructs (i.e. from a perspective of behavioral elements, processes, mechanisms, and responses) that comprise different aspects of the overall range of human functioning (i.e. from normal to abnormal). Measurement of constructs can occur using different methods (units of analysis). In our work, neurocircuit, behavioral, and self-report assessment were used.

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Study 1. Motor and non-motor symptoms in FMD, their impact on HRQoL

Věchetová G, Slovák M, Kemlink D, Hanzlíková Z, Dušek P, Nikolai T, Růžička E, Edwards MJ, Serranová T. The impact of non-motor symptoms on the health-related quality of life in patients with functional movement disorders. J Psychosom Res. 2018 Dec; 115:32-37.
doi: 10.1016/j.jpsychores.2018.10.001.

Evidence from other neurological disorders (e.g., in Parkinson's disease or Multiple Sclerosis) with abnormal motor control suggests that non-motor symptoms such as fatigue, pain, cognitive and psychological symptoms may be associated with significant disability and impairment of HRQoL over and above that caused by the motor symptoms. Excepting co-morbid affective disorders, non-motor symptoms and their impact on HRQoL have not been systematically studied in FMD.

In a cross-sectional study we aimed to assess the impact of non-motor symptoms including anxiety, depression, subjective cognitive complaints, fatigue and excessive daytime sleepiness, pain, and apathy on HRQoL in a consecutive sample of FMD patients. Non-motor symptoms and HRQoL / disability were also recorded from healthy control subjects. As hypothesized, patient self-reported severity of non-motor symptoms but not objectively assessed motor symptom severity by clinician was found to be a significant determinant of HRQoL in FMD patients. These results provided an important input to the FND Core Outcome Measure group working on a Functional neurological disorders specific Core Outcome Set development are reflected the review of the theoretical challenges specific to functional neurological disorder and the systematic review of the literature assessing the different outcomes and measurement instruments used to date in clinical trials and other research completed by an 'interim' consensus Core Outcome Set development (Nicholson *et al.*, 2020b; Pick *et al.*, 2020).

Study 2. Motor and non-motor symptoms, a correlation and cluster analysis

Forejtová Z, Serranová T, Sieger T, Slovák M, Nováková L, Věchetová G,
Růžička E, Edwards MJ. The complex syndrome of functional neurological disorder.
Psychol Med. 2022 Jan 7:1-11. doi: 10.1017/S0033291721005225.

Increasing evidence supporting a unified neurobiological model for all functional symptoms across different domains (i.e. the same underlying mechanism can account for motor, sensory, cognitive and interoceptive phenomena) (Edwards *et al.*, 2012; Van den Bergh *et al.*, 2017) is contrast with current classification systems the DSM-5 and ICD-10 (and the upcoming ICD-11) that preserve a diagnostic division between different symptoms that co-occur in one person. In both systems, in particular pain, fatigue and other symptoms in people with functional neurological disorder are currently classified separately/with another label (APA, 2013; WHO, 2018). Up to date, no studies addressed data-driven identification of specific clusters of patients based on specific symptoms, supporting the current symptom-based diagnostic classification schemes.

To provide evidence that might shed light on this complex and unsatisfactory situation, we performed a correlation and cluster analysis regarding specific motor and non-motor symptoms, quality of life and disability in a large cohort of consecutive patients with motor functional neurological disorders. Using hierarchical cluster analysis supplemented with gap statistics, we found a lack of distinctive subtypes along with a high degree of correlation between all subjective and objective measures of motor and non-motor symptoms. This finding further supports the current neurobiological models proposing unified pathophysiology for all functional symptoms and has major implication for future revisions of the disease classifications. as it supports development of a single diagnostic category encompassing patients with functional neurological disorder and other functional somatic symptoms. I addition, it has important implications for research and specialized services development.

Study 3. Identifying FMD mimics – prevalence of restless legs syndrome in FMD

Serranová T, Slovák M, Kemlink D, Šonka K, Hallett M, Růžička E. Prevalence of restless legs syndrome in functional movement disorders: a case-control study from the Czech Republic. BMJ Open. 2019 Jan 21;9(1):e024236. doi: 10.1136/bmjopen-2018-024236.

Frequent complaints of patients with FMD include variable sensory symptoms and pain in multiple body regions, mood disorders, fatigue and sleep problems. (Factor *et al.*, 1995; Gelauff *et al.*, 2014). As some of these symptoms could be due to comorbid restless legs syndrome (RLS) which is defined by an urge to move a body part (usually the lower limbs) typically accompanied by a wide range of sensory symptoms (Allen *et al.*, 2014). Clinical diagnosis of RLS can be supported by actigraphic measurement of periodic leg movements, which are considered a biomarker of RLS (Montplaisir *et al.*, 1997; Kemlink *et al.*, 2008; Allen *et al.*, 2014; Plante, 2014). While some evidence has been provided on increased prevalence of RLS in other conditions frequently associated with FMD such as migraine or fibromyalgia, no studies targeted RLS prevalence in FMD patients (Trenkwalder *et al.*, 2016).

In a case-control study in a consecutive sample of patients with FMD and a matched control group we found an increased prevalence of RLS according to the current diagnostic criteria in FMD group. Such a high prevalence of clinically diagnosed RLS in FMD (43.8% vs 7.9% in controls) may have been biased by suggestibility or overreporting, however, we found a clinically diagnosed RLS along with actigraphic finding of clinically relevant periodic limb movements in a significant proportion of FMD patients (21.2% vs 2.6% of controls). Functional motor and sensory symptoms may mimic RSL which may be underdiagnosed in FMD patients. RLS is a treatable condition, this finding has clinical implications for the management of FMD as well for further research of pathophysiological mechanisms and shared risk factors including genetic vulnerability underlying both conditions.

Study 4. Subcortical processing of somatosensory inputs in FMD – a neurophysiological study

Hanzlíková Z, Kofler M, Slovák M, Věchetová G, Fečíková A, Kemlink D, Sieger T, Růžička E, Valls-Solé J, Edwards MJ, Serranová T. Prepulse inhibition of the blink reflex is abnormal in functional movement disorders. Mov Disord. 2019 Jul;34(7):1022-1030. doi: 10.1002/mds.27706.

A potentially unifying mechanism for multiple motor and non-motor symptoms such as pain, fatigue or sensory disturbances that co-occur in FMD patients is a failure in processing of sensory inputs. Prepulse inhibition is a neurophysiological method that allows for the study of pre-conscious somatosensory processing. Prepulse inhibition is a physiological phenomenon which serves to protect the early processing of a stimulus (the prepulse) at the subcortical level within a very short time interval form undesired motor reflex reaction. The prepulse is a weak stimulus (such as light electrical stimulus to the finger) and which inhibits the reflex response to a subsequent strong stimulus eliciting blink reflex.

In a case-control study we found an impaired prepulse inhibition of the blink reflex indicating an abnormal early-stage processing of somatosensory inputs at subcortical level in FMD. This finding is not specific to FMD, along with previous findings of a reduced prepulse inhibition in fibromyalgia syndrome, or functional cystitis, it supports a possible unified pathophysiology across functional neurological and somatic syndromes proposed by current neurobiological mode with noteworthy implications for diagnostic classification and development of novel biomarkers and treatments.

Prepulse inhibition is a subcortical automatic phenomenon and occurs before conscious perception of the stimulus. (Correa *et al.*, 2018) Our results are therefore relevant for understanding that despite their characteristics of voluntary movements, FMD are genuine disorders of brain function with abnormalities which cannot be fabricated voluntarily (Edwards *et al.*, 2012).

Study 5. Neurocognitive aspects of motor control in FMD - a video-oculographic study

Slovák M, Sieger T, Bonnet C, Ulmanová O, Hanuška J, Růžička E, Serranová T. Antisaccades and vergence abnormalities in functional movement disorders: A video-oculographic study. Mov Disord. 2016 Jul;31(7):1072-3. doi: 10.1002/mds.26641

Attention plays an important role in the theoretical framework and in the clinical settings. Numerous neurophysiological and behavioral tests can be used to assessed different aspects of attentional processing. Video-oculographic saccadic eye movements measures can be used to evaluate automatic and volitional eye movements control and some neurocognitive aspects of motor control (Hutton and Ettinger, 2006).

In a case-control video-oculography study we found eye movement abnormalities that resembled the typical clinical findings in FMD: reflexive or automated movements to "exogenous" cues (i.e. prosaccades) were not altered while the attention demanding volitional movements (antisaccade and vergence movements) were disturbed (Parees *et al.*, 2013). This finding further extended published data on impaired response inhibition in FMD (Roelofs *et al.*, 2003; Voon *et al.*, 2013).

In contrast to earlier published data, we found rather low incidence of a clinically overt convergence spasm in our FMD group (Fekete *et al.*, 2012), a low prevalence of convergence spasm was later confirmed by a study conducted in larger group of FMD patients (Teodoro *et al.*, 2019). Subclinical abnormalities in vergence movements in FMD patients with FMD seem to reflect difficulties in voluntary motor performance of an effort and attention demanding motor task typical for FMD patients (Parees *et al.*, 2013).

Study 6. Identifying phenotype specific alterations in brain connectivity in FMD – a neuroimaging study

Mueller K, Růžička F, Slovák M, Forejtová Z, Dušek P, Dušek P, Jech R, Serranová T. Symptom-severity-related brain connectivity alterations in functional movement disorders. Neuroimage Clin. 2022 Mar 3;34:102981. doi: 10.1016/j.nicl.2022.102981

Addressing the underlying mechanisms related to brain function and connectivity that are specific to different motor phenotypes of FMD has been defined as an unmet need in the research agenda(Perez *et al.*, 2021b). Formation of abnormal predictions is thought to be one of the key pathophysiological mechanisms in FMD. It has been suggested that top-down dynamics of generative models of the brain i.e., is closely related to the spontaneous activity in brain networks during resting state associated with activity withing the default mode network (Friston, 2010; Pezzulo *et al.*, 2021; Yeshurun *et al.*, 2021).

To identify brain connectivity alterations related to functional weakness we assessed network centrality changes in a group of patients with heterogeneous motor manifestations and healthy controls using task-free functional MRI in combination with different network centrality approaches. Presence of functional weakness was associated with increased centrality in the left TPJ and the precuneus when comparing patients with and without functional weakness, and when comparing patients with functional weakness with healthy controls. The role of the left TPJ and the precuneus as key regions involved in brain connectivity alterations related to functional weakness was further supported by a positive correlation between motor symptom severity and network centrality in these regions, which was shown to be specific to functional weakness. In this recent work, we proposed that both regions that are key regions in self-referential processes and important hubs within the default mode network may be promising targets for phenotype-specific non-invasive brain stimulation. Specifically, based on our results the effects of inhibitory protocols using cathodal transcranial direct current stimulation (Inukai *et al.*, 2016) or lower frequency repetitive transcranial magnetic stimulation (Chen *et al.*, 1997) should be addressed in patients with functional weakness.

Study 7. Bridging structural and functional biomarkers in functional movement disorder using network mapping

Sojka P, Slovák M, Věchetová G, Jech R, Perez DL, Serranová T. Bridging structural and functional biomarkers in functional movement disorder using network mapping. Brain Behav. 2022 Apr 16:e2576. doi: 10.1002/brb3.2576.

Biomarkers of FMD symptom severity are poorly understood, which is a factor that negatively impacts the development of biologically informed treatments. In a neuroimaging study, we investigated gray matter volumetric profiles in FMD, and related findings to resting-state functional connectivity profiles using Human Connectome Project data.

We did not find any volumetric differences in FMD cohort compared to controls. However, individual differences in FMD symptom severity as measured using the Simplified FMD rating scale negatively correlated with volumetric profiles in the temporoparietal junction– specifically the right supramarginal and bilateral superior temporal gyri. These findings remained significant adjusting for FMD subtype or antidepressant use but did not remain statistically significant adjusting for depression and anxiety scores.

Atrophy network mapping was also used to probe whether FMD-related structural alterations preferentially impacted brain areas with dense resting-state functional connectivity. Symptom severity-related structural alterations mapped onto regions with dense resting-state functional connectivity -identifying several disease epicenters in default mode, ventral attention, and salience networks. FMD-related structural alteration preferentially impacted higher-order brain areas exhibiting increased resting state functional connectivity influence (degree centrality) based on the healthy human functional connectome.

This study further supported current view of FMD as a multinetwork disorder with an important role for the temporoparietal junction and its related connectivity in the pathophysiology of this condition. More research will be needed to explore the intersection of functional neurological symptoms and mood.

Future directions

Despite important advances in the field, we are still far from a complete understanding of the pathophysiology of FMD. FMD is a highly heterogenous disorder, and there is growing recognition that the development of FMD likely depends on varying combinations of biological, psychological and social etiological factors both in populations and within a given individual. Genetic, neuroimaging, neurophysiology and behavioral variables could represent useful biomarkers for identifying patients with FMD, FMD subtypes, and monitoring tools response to an intervention in FMD clinical trials. Various candidate biomarkers have emerged including stress/HPA axis response markers, neurophysiology and neuroimaging variables that could inform diagnosis (including subtyping) and prognosis (via treatment response) as well as end points or core outcome assessment in FMD clinical trials. (Thomsen *et al.*, 2020; Perez *et al.*, 2021b; Aybek and Perez, 2022) Positive clinical findings, supported by laboratory or ancillary investigations, can be used to develop a diagnostic outcome measure to assess severity and disability of FND patients, and to anchor the development of biomarkers of treatment response. However, there is an urgent need for unbiased data driven research involving genetic and other laboratory biomarkers from large well characterized samples ideally assessed with a disease-specific set of measures capturing the broad range of motor and non-motor symptoms that are associated with FMD as well as other comorbidities and risk factors.

A recent analysis of the genome-wide association summary statistic data from consortia of 25 brain disorders from large samples (but not including conversion disorder/FMD patients), found that psychiatric disorders broadly share a considerable portion of their common variant genetic risk, and provided evidence that their current clinical boundaries do not reflect distinct underlying pathogenic processes, at least on the genetic level (Brainstorm *et al.*, 2018).

As already proposed for neurodegenerative disorders, a need for a phenotype agnostic data driven subtyping based on neuroimaging, genetics and omics biomarkers in disorders of the brain with heterogeneous clinical

manifestations and multiple comorbidities might shed light on shared vs distinctive pathophysiological mechanisms in these heterogeneous conditions (Sturchio *et al.*, 2020) and to provide basis for future biosubtype-specific disease-modifying therapeutic efforts.

Future multi-site clinical, imaging, and with biospecimen data collection to identify and validate biomarkers and facilitate cluster and other analytic techniques to identify homogeneous subgroups of FMD patients, with differential response to psychoactive medications (e.g., antidepressants), and identification of novel biological targets for future therapeutic endeavors. Validated FMD-specific clinical outcome measure and a fit-for-purpose patient-rated clinical scale will help to quantify the severity and disability of FMD patients. Discovery of biomarkers and biological signatures of FMD will expand and complement the psychosocial model of FMD and help launch a future of precision medicine for these patients.

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