RESEARCH ARTICLE

Prepulse Inhibition of the Blink Reflex Is Abnormal in Functional Movement Disorders

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ABSTRACT: Background: Patients with functional movement disorders also typically have functional somatic symptoms, including pain, fatigue, and sensory disturbance. A potentially unifying mechanism for such symptoms is a failure in processing of sensory inputs. Prepulse inhibition is a neurophysiological method that allows for the study of preconscious somatosensory processing.
Objective: The objective of this study was to assess prepulse inhibition in patients with functional movement disorders and healthy control subjects.
Methods: We analyzed the effect of a weak electrical stimulus to the index finger (prepulse) on the magnitude of the R2 response of the blink reflex induced by electrical stimuli delivered to the supraorbital nerve in 22 patients with clinically established functional movement disorders and 22 matched controls. Pain, depression, anxiety, and obsessive-compulsive symptoms were assessed using self-rated questionnaires. In addition, in patients we assessed motor symptom severity.
Results: Prepulses suppressed the R2 response of the blink reflex in both groups, by 36.4% (standard deviation: 25.6) in patients and by 67.3% (standard deviation: 16.4) in controls. This difference was significant ($P < 0.001$). There was no significant correlation between motor and non-motor symptom measures and prepulse inhibition size.
Conclusions: Impaired prepulse inhibition of the blink reflex suggests an abnormal preconscious processing of somatosensory inputs, which can be interpreted within predictive coding accounts of both functional movement disorders and functional somatic syndromes. Our results, along with previous findings of a reduced prepulse inhibition in fibromyalgia syndrome, support a possible unified pathophysiology across functional neurological and somatic syndromes with noteworthy implications for diagnostic classification and development of novel biomarkers and treatments. © 2019 International Parkinson and Movement Disorder Society

Key Words: attention; blink reflex; functional movement disorders; prepulse inhibition; sensory integration

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Functional movement disorders (FMDs) are commonly observed in neurological practice. Clinically, FMDs are characterized by variability of signs (e.g., changes in character or fluctuation in their form of presentation), alleviation by distraction, and incongruence with movement disorders caused by a known neurological disease.[1] The positive diagnostic features of FMD indicate the ability for normal function to occur (e.g., cessation of functional tremor with distraction), but the apparent inability of the person to access this normal function when they wish to.

In patients who present primarily with FMDs, multiple other functional somatic symptoms are almost always

present, especially pain, fatigue, and cognitive difficulties.[2] Likewise, patients presenting primarily with chronic pain syndromes, such as complex regional pain syndrome type I, commonly also have functional motor symptoms.[3] Patients with fibromyalgia present with a high rate of motor symptoms in the absence of another condition that could explain the symptoms.[4] Recently, neurobiological models of functional symptoms based on, or strongly influenced by, predictive coding accounts of perception and movement control have been proposed.[5,6] 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. A key feature of this proposed mechanism is that the same basic computational phenomenon can account for functional symptoms across motor, sensory, and interoceptive domains. It is therefore likely that there could be biomarkers of this proposed underlying dysfunction which would be common across functional motor and somatic syndromes.

Prepulse Inhibition (PPI) is a neurophysiological phenomenon in which a weak sensory event, subthreshold for eliciting any reflex response (prepulse), leads to reduction in magnitude of the reflex response that would be otherwise elicited by a reflex-eliciting stimulus presented 30 to 500 ms later. The inhibitory effect of a prepulse is considered to be related to the attentional shift toward the sensory input brought about by the prepulse.[7,8] PPI reflects an early stage of attentional processes involved in information selection processing that operates at the subcortical level,[9-11] outside of conscious awareness. Reduction in PPI is one of the most robust biomarkers of schizophrenia and has also been found to be abnormal in numerous other neuropsychiatric conditions, including obsessive-compulsive disorder (OCD) and panic disorder.[12-14] In a recent study, patients with fibromyalgia syndrome, which is one of the most common causes of chronic widespread pain, showed reduced PPI, which was interpreted as indicating altered sensory perception and processing in fibromyalgia.[15]

Our aim was to evaluate PPI of the R2 response of the blink reflex in patients with clinically established FMD and sex-/age-matched healthy control subjects. Furthermore, we assessed the relationship of PPI with self-reported measures of pain. We also assessed the influence of factors previously associated with PPI, such as anxiety, and obsessive-compulsive features.[12,13]

Subjects and Methods

We studied 22 patients (18 females; mean age: 44.7 [standard deviation {SD} 12.1] years; mean disease duration: 6.5 [SD, 5.7] years) with clinically definite FMD from the specialized outpatient service for FMD at the Neurology Department of Charles University in Prague, 1st Faculty of Medicine and General University Hospital.

Twenty-two unrelated sex- and age-matched control subjects (18 females; mean age: 44.8 [SD, 12.8] years) were recruited. The diagnosis of FMD, according to Gupta and Lang criteria,[17] was established following detailed clinical interview and examination by an experienced movement disorders specialist (T.S.) based on positive signs of functional weakness and/or abnormal movements inconsistent and incongruent with known movement disorders. In all controls, a complete medical history was obtained, and full neurological examination was performed. Only controls without neurological symptoms or signs of nervous system disorder were included in the study. The study was approved by the ethics committee of *General University Hospital* (identification number: 614/18S-IV), and all participants gave their written informed consent to participate in the study.

In each FMD patient, we evaluated and phenomenologically classified motor symptoms as functional weakness, tremor, dystonia/spasm, myoclonus, gait disorder, or speech disturbance. We recorded the predominant motor symptom type and all additional motor symptoms. The Simplified Functional Movement Disorders Rating Scale (s-FMDRS) was used to assess functional motor disorder severity of both abnormal movements and weakness.[18] Seventeen patients reported presence of sensory symptoms (hyperesthesia, dysesthesia, or paresthesia) in some body part; however, no patient had sensory deficits (hypoesthesia) in the right upper limb where the prepulse stimulus was applied.

Exclusion criteria were the presence of comorbidities known to affect PPI, such as definite or suspected diagnosis of schizophrenia-spectrum disorders, Tourette's syndrome, temporal lobe epilepsy with psychosis, OCD,[19] and panic disorder,[13] and administration of medication known to affect PPI, such as dopamine receptor antagonists.[16,20] Similarly, we did not include any patients with a previously diagnosed fibromyalgia or patients reporting a widespread musculoskeletal or myofascial pain suggestive of fibromyalgia.

A structured interview was completed in order to detect medical comorbidities and to obtain family history, current medication (including hormonal contraceptives) and drugs of abuse, habits of smoking and consumption of caffeinated beverages, and handedness in all subjects. All participants were asked to refrain from smoking and drinking caffeinated beverages within 3 to 4 hours of the study.[20] Information about menstrual cycle phase and hormonal contraceptive use was recorded in female participants.[21]

Four FMD and 2 control subjects were on serotonin reuptake inhibitors or on serotonin and norepinephrine reuptake inhibitors. Six patients and 4 healthy volunteers were on medications not thought to affect PPI, such as

blood pressure medication, statins, levothyroxine, oral antihistamines, or proton pump inhibitors; 1 patient was on corticosteroid medication.

All subjects completed the following questionnaires: State-Trait Anxiety Inventory (STAI X-1) for assessment of anxiety; Beck Depression Inventory (BDI-II)[23] to measure depressive symptomatology; PainDETECT[24] for assessment of intensity of current, average, and maximal pain during the last 4 weeks preceding the examination; and Obsessive-Compulsive Inventory Revised (OCI-R), an 18-item self-report measure with high specificity for symptoms of OCD.

Neurophysiological Investigation

All neurophysiological examinations were carried out in a moderately lit and quiet room with participants sitting on a chair in a comfortable position. Subjects were thoroughly informed about the different types of stimuli they would receive, but the investigator and the equipment were out of their view, for them not to see the timing and type of stimulation. Recordings were performed with routine electrodiagnostic equipment (Synergy, CareFusion, London, UK). Band-pass frequency filters for electromyography (EMG) was 30 to 3,000 Hz. The sampling rate for signal storage was 2,000 Hz.

Paradigm

The non-rectified EMG activity of the orbicularis oculi muscles was recorded bilaterally with 10-mm surface gold electrodes attached to the skin using conductive electrode gel. The active electrode was placed over the middle portion of the muscle below each eye and the reference electrode 2 cm lateral to the outer canthus of each eye. Each blink reflex was evoked by an electrical stimulus (a constant current rectangular pulse of 0.5-ms duration) delivered to the right supraorbital nerve with a surface electrode, cathode over the supraorbital notch, and anode 3 cm above along the course of the nerve on the forehead. We used a stimulus intensity 10 times sensory threshold, defined as the minimum intensity that subjects would perceive in at least four of eight stimulations.

Prepulse modulation was assessed by applying a prepulse stimulus 100 ms before the supraorbital nerve stimulation. Prepulse stimuli (constant current rectangular pulses of 0.2-ms duration) were delivered through ring electrodes attached to the right index finger at the middle and distal phalanges with the cathode proximal at 2 times the subject's sensory threshold intensity. Care was taken to choose a prepulse stimulus intensity subthreshold for any reflex response (approximately 1.5 times sensory threshold). We obtained eight blink reflex responses for each experimental condition, that is, a supraorbital nerve stimulus alone (baseline) or a supraorbital nerve stimulus preceded by the index finger stimulus (prepulse). Baseline and prepulse trials were intermingled at random, with always an interval of at least 10 seconds separating two consecutive trials.

Rating of Discomfort

The level of discomfort associated with stimulation was rated with a numeric rating scale (NRS; 0 = no discomfort, 10 = unbearable).

Statistical Analysis

EMG recordings were rectified and analysed offline. Trials containing artefacts or spontaneous blinks were excluded (approximately 1% of trials). In each trial, we identified the early ipsilateral R1 and the late ipsilateral (R2) and the contralateral (R2c) blink reflex components.

The magnitude of the ipsi- and contralateral R2 responses were measured as the area under the curve (henceforth R2 area and R2c area, respectively). The R1 component of the response was used as a marker that the afferent volley generated by prepulse stimuli had effectively reached the brainstem.[29]

The R3 response,[27,28] which was observed in some patients, particularly in the initial recordings, was not included in our calculations because it was not part of the planned study protocol.

To evaluate PPI we calculated the average of R2 and R2c areas as "blink reflex magnitude" for each trial. For each individual, we calculated the square root of individual blink reflex magnitudes to stabilize their variances, computed the mean of the resulting values over the eight trials obtained per condition (baseline and prepulse), and squared the means back to the original numerical scale. For normalization of data among subjects, we expressed the change in the blink reflex magnitude in prepulse trials relatively to baseline trials as the percentage of the baseline trials (%PPI; %PPI = mean blink reflex magnitude in prepulse trials/mean blink reflex magnitude in baseline trials × 100). The size of the PPI effect (PPI size), which was the primary outcome, was calculated for each individual as the difference in blink reflex magnitude between the prepulse (%PPI) and the baseline trials (100%).

The statistical comparison of patient and control groups was performed using Student's t test for numeric outcomes and using Fisher's exact test for categorical outcomes. A linear model was used to adjust the group comparison for BDI-II, STAI X-1, and PainDETECT scores (which were summed when entering the model to cope with their correlation and to reduce the number of covariates given the limited sample size). Holm's correction for multiple comparisons was used to correct the family-wise error of the 12 intergroup tests of neurophysiological and questionnaires data, four within-group tests of neurophysiological and NRS data, and of six correlation tests. P values <0.05 after correction

were considered significant. Uncorrected P values are reported for descriptive purposes, unless stated otherwise. Statistical analyses were performed in R statistical software (R Foundation for Statistical Computing, Vienna, Austria).[30]

Results

FMD patients and control subjects were not significantly different in smoking habit (11 FMD patients vs. 8 control subjects; P = 0.36 uncorr.) or regular caffeine intake (18 FMD patients vs. 19 control subjects; P = 1.00 uncorr.).

Motor symptom characteristics are presented in Table 1. The majority of patients had a mixed phenotype. Mean s-FMDRS (range, 0–54) was 9.0 (SD, 5.1).

Results from the neurophysiological analysis are shown in Table 2. Examples of blink reflex responses without and with prepulse stimulation in a patient and a healthy control subject are shown in Figure 1. Baseline blink reflex characteristics did not differ significantly between the groups. Prepulses significantly suppressed the blink reflex magnitude in both groups of subjects (t_{21} = –4.768; P = 0.0001 corr. in FMD patients; t_{21} = –6.13; P < 0.0001 corr. in controls). The PPI was 36.4% (SD, 25.6) in FMD patients and 67.3% (SD, 16.4) in controls. This difference was significant ($t_{35.7}$ = 4.78; P = 0.0003 corr.; Table 2; Fig. 2).

No difference was found between patients and control subjects in sensory thresholds for both the supraorbital nerve stimulation ($t_{41.0}$ = –0.13; P = 0.8960 uncorr.) and the prepulse stimulus to the index fingers ($t_{37.9}$ = –1.41; P = 0.1668 uncorr.). Prepulses significantly reduced the level of discomfort resulting from the applied stimuli as measured on the NRS in both groups (t_{21} = 5.26; P < 0.0001 corr. in FMD patients; t_{21} = 6.32; P < 0.0001 corr. in control subjects). This reduction in discomfort did not differ between groups ($t_{38.4}$ = 0.53; P = 0.5984 uncorr.).

Results of self-reported measures are shown in Table 3. Patients reported a higher level of pain and depression compared to controls. The OCI-R score was missing in 1 patient. There was no significant between-group difference in anxiety and obsessive-compulsive symptoms. When adjusting for these factors using a linear model, the between-group difference in PPI size remained significant ($F_{1,37}$ = 6.95; P = 0.0122).

Data on menstrual cycle phase and hormonal contraceptives use are presented in Supporting Information Table S1. No between-group difference was found in frequencies of different menstrual cycle phases, menopause, and hormonal contraceptives (Fisher's exact test, P = 0.6287).

PPI size did not correlate with the severity of depression, anxiety, pain, motor symptoms, obsessive-compulsive symptoms, or disease duration (the smallest, P = 0.2969 uncorr.).

We performed the above presented analyses with similar results in a subgroup of subjects free of medication with known effects on the central nervous system and in a subgroup of patients who had no motor symptoms in the right upper limb where the prepulse was applied. Details are presented in the Supporting Information.

TABLE 1. Motor symptoms in FMD patients

Motor symptom	Predominant (n)	Additional (n)
Tremor	7	4
Gait disorder	7	6
Dystonia or spasms	4	1
Weakness	4	12
Myoclonus	0	2
Parkinsonism	0	1

Predominant indicates number of patients (n) in whom given motor symptom was present as predominant phenotype. Additional indicates number of patients (n) in whom given motor symptom was present as additional phenotype.

Discussion

Here, we have explored the physiological phenomenon of PPI in FMD. We found that patients with FMD have reduced PPI compared to control subjects.

It is commonly proposed that impaired PPI reflects impaired sensory-motor gating.[32] In normal environmental conditions, multiple stimuli may adopt the role of prepulse stimuli and cause PPI of undesired motor reactions, which would otherwise interfere with sensory processing of relevant inputs.[10,33] Stimulus-triggered effects in the central nervous system, such as arousal or

TABLE 2. Neurophysiological measures of unconditioned blink reflex (baseline) and prepulse inhibition (prepulse) in FMD patients and in control subjects

	R1 Amplitude [mV]			R2 Magnitude [ms × mV]		
	FMD Patients	Control Subjects	*P* Value	FMD Patients	Control Subjects	*P* Value
Baseline	440.4 (156.7)	423.4 (192.7)	0.7510	4.74 (2.49)	3.73 (2.35)	0.1750
Prepulse	535.0 (195.0)	484.9 (232.8)	0.4439	2.91 (1.98)	1.12 (0.75)	0.0005**

Mean values (SD) are presented. Uncorrected *P* values are based on Student's *t* test.
Asterisks indicate *P* values significant after correction for multiple testing (**P < 0.01).

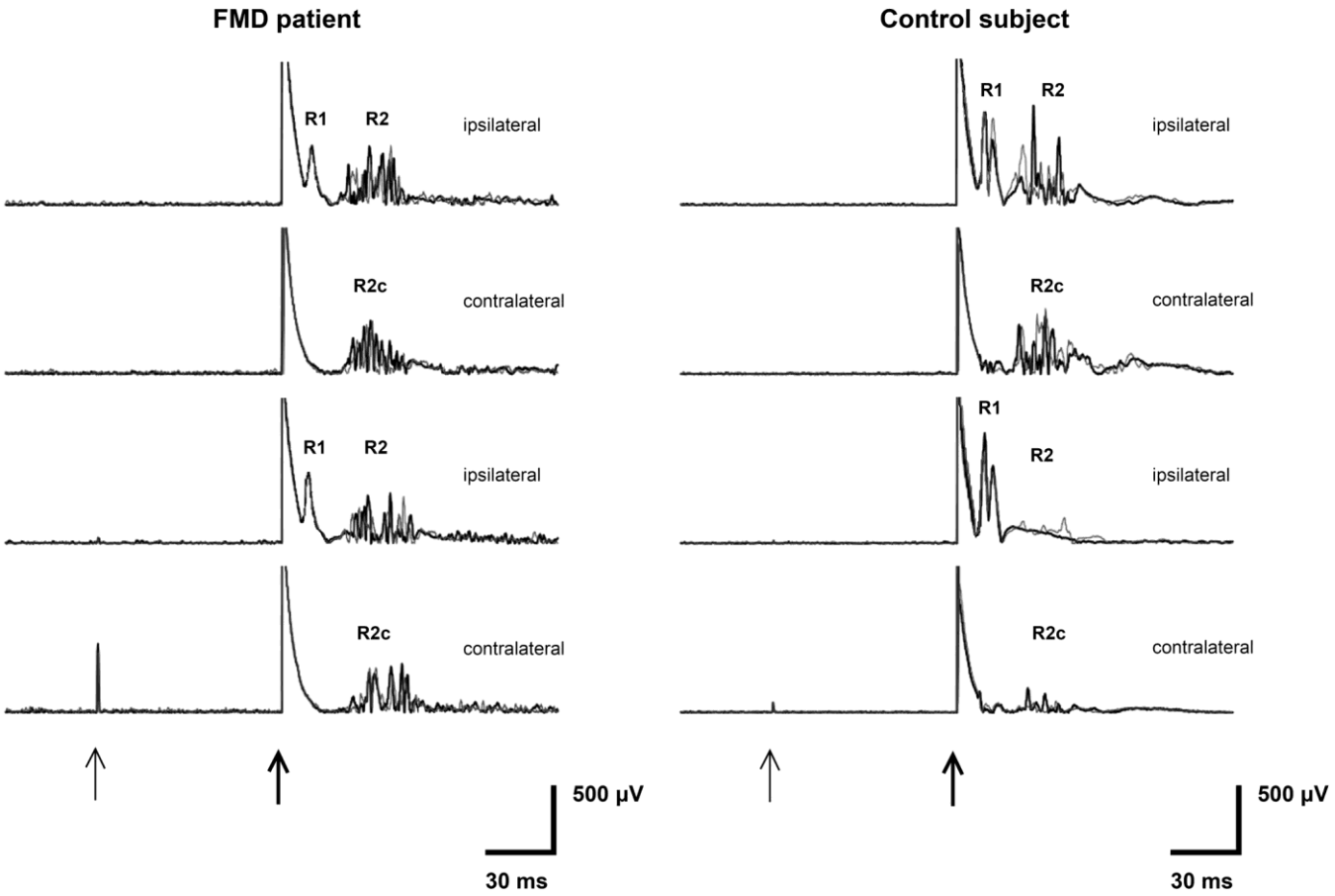

FIG. 1. Representative examples of blink reflexes without (upper two traces) and with prepulse stimulation (lower two traces) in a patient with functional movement disorder (FMD patient, left) and in a healthy control subject (right). Each trace represents two superimposed rectified recordings. Thick arrows indicate stimuli applied to the right supraorbital nerve; thin arrows indicate prepulse stimuli delivered to the right index finger. Early ipsilateral R1, late ipsilateral (R2), and late contralateral (R2c) blink reflex components are labeled. Note that the R2 and R2c area in prepulse trials was markedly larger (i.e., there was less prepulse inhibition) in the patient than in the control subject.

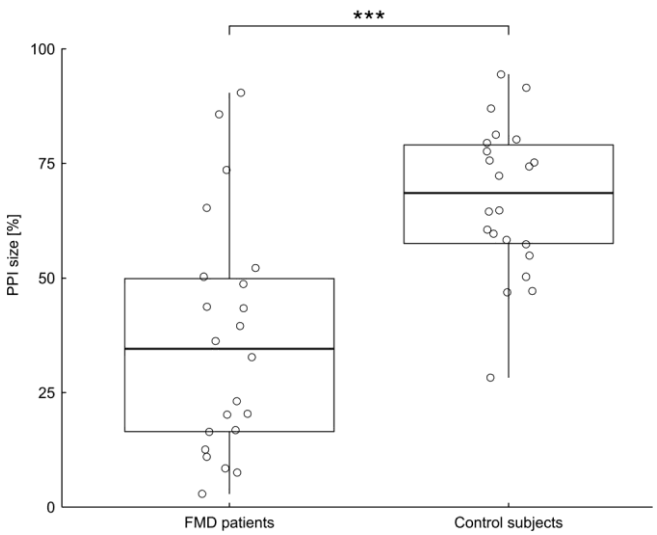

FIG. 2. PPI size in FMD patients and control subjects. PPI size (i.e., the difference between mean blink reflex magnitude in baseline trials and in trials with prepulse, expressed in %) was smaller in FMD patients as compared to control subjects (P = 0.0003 corr.). ***Denotes $P < 0.001$.

TABLE 3. Self-reported measures of depression, anxiety, obsessive-compulsive features, and pain in FMD patients and control subjects

	FMD Patients	Control Subjects	*P* Value
BDI- II	15.5 (9.7)	5.1 (5.7)	0.0001**
STAI X-1	43.2 (9.4)	36.5 (10.4)	0.0296
OCI-R	13.8 (12.9)	13.0 (11.0)	0.8171
Pain actual	5.0 (2.9)	0.1 (0.3)	<0.0001***
Pain maximal	7.6 (2.4)	1.9 (2.0)	<0.0001***
Pain average	6.3 (2.4)	1.0 (1.1)	<0.0001***

Pain actual/average/maximal = the PainDETECT scale items.
Mean values (SD) are presented; uncorrected *P* values are based on Student's *t* test.
Asterisks indicate *P* values significant after correction for multiple testing (**$P < 0.01$; ***$P < 0.001$).

attention reorienting, likely depend on stimulus salience.[34] Internal or top-down signals guide perception through a dynamic interaction with sensory and bottom-up processes.[35] The PPI may be a by-product of such processes, reflecting subcortical integration.[36,37]

PPI is regulated by specific neurochemical and anatomical substrates within the prefrontal cortex, thalamus, amygdala, hippocampus, striatum, pallidum, and the pedunculopontine nucleus, with a central role of the ventral striatum/nucleus accumbens.[32,38-40] Lack of differences between FMD patients and controls in the unconditioned blink reflex suggest that there is normal integrity of brainstem circuits. Abnormal top-down regulatory mechanisms mediating PPI through projections from forebrain structures to pontine reflex circuity may be the most likely network underlying abnormal PPI. Given that PPI is a subcortical automatic phenomenon and occurs before conscious perception of the stimulus,[37] our results are in line with the differentiation of functional movement disorders from feigned or malingered phenomena.[5]

PPI is known to be modulated by higher-order cognitive processes (e.g., attentional modulation and conditional modulation).[32] Volitional attentional influences seem to occur more consistently at longer interstimulus intervals; however, there is some evidence that PPI may be modulated by attentional processing even at a short interstimulus interval of 120 ms.[41,42] At early stages of sensory information processing, the level of impact of the prepulse may vary as a function of prepulse saliency.[42] Therefore, reduction in PPI may reflect not only an impaired nonselective attention allocation or attention reorienting and protection of early-stage processing, but also the outcome of preattentive processing in terms of an early evaluation of the significance of the prepulse. In FMD patients, functional imaging studies have shown dysfunction of the brain regions involved in the salience network, including ventral striatum and amygdala.[43-45] Dysfunction of the right temporoparietal junction in FMD has been linked to abnormal self-agency[46,56]; however, this region is also associated with attention reorienting, that is, redirecting attention from one object to another or switching between networks.[35,47] These changes could be relevant in PPI dysregulation in FMD.

Abnormal PPI is one of the most robust and reproducible markers of schizophrenia and is considered to be a highly heritable phenotypic measure.[48] In patients with schizophrenia, the loss of PPI has been related to the "abnormal salience" theory of schizophrenia.[49,50] This relates to a fundamental difficulty in filtering salient information from the environment, which, in turn, is thought to drive abnormal perceptual inferences and therefore hallucinations and delusions.[51]

In patients with schizophrenia, the inability to detect salient events was demonstrated by abnormal mismatch negativity, a neurophysiological event-related potential that is recorded when an unexpected event occurs.[51,52] In schizophrenia, one could hypothesize that unconstrained sensory input prevents differentiation of salient events, such as the prepulse stimulus from other stimuli, and hence it fails to influence other sensorimotor activity such as the blink reflex (abnormal somatosensory gating).

Pathophysiological theories of schizophrenia and functional symptoms are fundamentally different, making it appear difficult to reconcile the presence of abnormal PPI in both disorders. In contrast to abnormal salience, it has been proposed that in FMD there is relative insensitivity to extero- and interoceptive input attributed to abnormally strong high-level priors. However, this abnormality would also be predicted to cause abnormal PPI given that the resulting insensitivity to salient events occurring in the sensorium would be predicted to lead to downweighting of the influence of the prepulse on other sensorimotor activity (e.g., the blink reflex). Comparative studies between FMD, "organic" movement disorders, and schizophrenia would be useful to provide further evidence for these hypothesized mechanisms of impaired PPI and other inhibitory mechanisms.

There are findings from imaging, electrophysiological, and psychophysical studies in FMD which align with this proposal. We have previously reported abnormal sensory attenuation in patients with FMDs.[53,54] This phenomenon has also been reported in patients with schizophrenia, but as with our finding of reduced PPI, we have proposed that the mechanism for abnormal sensory attenuation in schizophrenia is likely to be different than in patients with functional symptoms.[55]

Beside schizophrenia,[48] PPI disturbances are associated with a wide range of neuropsychiatric disorders with an established dysfunction of corticobasal ganglia circuits, including movement disorders such as Huntington's disease,[62] Parkinson's disease,[63] and dystonia.[64] However, a reduced PPI does not necessarily indicate circuit or clinical dysfunction as documented by a wide range of basal levels of PPI in healthy subjects and studies on sex differences and menstrual cyclicity of PPI in healthy humans.[21,65] Importantly, an intact PPI was found in other serious brain disorders such as bipolar disorder[66] or major depressive disorder.[67,71]

Whereas previous studies across many different clinical entities, including functional dystonia, revealed reduced short interval intracortical inhibition suggestive of impairment in gamma-aminobutyric acid–mediated cortical inhibition,[68,69] reduced PPI indicates impairment in a subcortical inhibitory mechanism at the preattentive stage. These findings challenge the categorical distinction between functional and "nonfunctional"/"organic" disorders. Rather, there may well be many routes to the development of abnormal PPI, given the range of disorders affecting movement, mental state, and pain sensation that are associated with abnormal PPI.

The lack of a definite correlation between PPI size and motor symptom severity or disease duration does not allow us to conclude that it plays a mechanistic role in generation of motor symptoms in FMD. Interestingly, in organic dystonia patients with sensory trick, PPI was less

impaired. It was suggested that a dysfunction in the processing of sensory input contributes to the maintenance of dystonic spasms.[64] Relationship of PPI size to motor symptom persistency should be possibly studied in FMD. Abnormal PPI may represent a premorbid trait rendering patients more susceptible to disease (as suggested in schizophrenia)[48,59] or it may be a consequence of, or a compensatory phenomenon related to the disease.

There were no between-group differences in sensory thresholds nor in the effect of the prepulse on intensity of discomfort resulting from application of the electrical stimuli. This contrasts with the finding of a reduced effect of prepulses on pain in fibromyalgia patients compared to control subjects. In line with previous studies, patients with FMD reported higher levels of depression and pain than control subjects.[70] However, these factors do not seem to systematically affect the impairment in PPI in FMD patients: When adjusting for these factors, the difference in PPI size remained highly significant.

In accord with findings in larger cohorts of FMD patients,[73,74] functional weakness and hyperkinetic phenotypes coexisted in a large proportion of our patients, and deficits in PPI were present regardless of motor symptom type. Such observations favor lumping these clinical populations together in future studies on FMD biomarkers.

Reduced PPI has been previously demonstrated in patients with fibromyalgia syndrome and interstitial cystitis/bladder pain syndrome.[15,75] In our sample of FMD patients, the magnitude of PPI was not related to the reported severity of pain and nor was it linked to a specific motor phenotype. The unified mechanism of functional symptoms presenting in motor, sensory, interoceptive, or cognitive domains proposed by neurobiological models is in line with clinical overlap of symptom domains and of risk factors such as trauma and recent health events.[76-78] However, diagnostic classification systems have persistently sought to create a diagnostic divide between (often polysymptomatic) people with predominant pain and fatigue from those with typical "conversion disorder." This distinction has been maintained in the latest edition of Diagnostic and Statistical Manual of Mental Disorders (DSM) with separate categories of conversion disorder/functional neurological symptom disorder (which would include people with FMD) and somatic symptom disorder (which would include people with functional pain and fatigue syndromes). The PPI finding we report is therefore another piece of evidence that this diagnostic distinction is not likely to be correct. Further research in this area should systematically test whether there are indeed trans-syndromic biomarkers in those with functional symptoms, taking care of course to deal with the potentially confounding effects of shared comorbidities such as depression and anxiety. Finally, the utility and treatment consequences of a diagnostic category that includes both functional neurological disorders and somatic symptom disorder criteria (i.e., the somatization disorder diagnosis from DSM-IV with updated "rule in" criteria for functional neurological disorders components of the diagnosis) could be assessed, although this would require a reassessment of the necessity or otherwise of including psychological and/or behavioral factors as of diagnostic importance, which were dropped from DSM-5 criteria for functional neurological disorders.

Our study has limitations. It is not known whether there is an interference of voluntary or functional movements on PPI. However, an electrical stimulus to a tremulous index finger may have a gating effect over the sensory stimulus coming from the moving finger. We did not find a difference in PPI size with prepulses applied to the right upper limb with and without abnormal movements. However, a possible interaction between the site of motor symptom and PPI, which might provide important insights into the sensorimotor gating and the pathophysiology of FMD, might not have been detected because of a small sample size. Another limitation of the study is that we did not perform a structured psychiatric interview for psychiatric comorbidities, which may be more sensitive to the detection of abnormalities compared to our questionnaire methods. Additionally, the relationship between deficits in PPI and attentional and cognitive factors should be analyzed in the future.

In conclusion, this is the first study demonstrating abnormal PPI in patients with FMD. Integration of this novel finding with previous PPI data in people with chronic pain and previous pathophysiological findings in FMD gives support for a trans-syndromic view of functional symptoms. Here, a common abnormality in past expectancies and attentional allocation to these priors could produce perceptual and/or motor control distortions, which could be reflected in markers of sensorimotor integration such as PPI. This has implications for the structure of our current diagnostic criteria and for the search for biomarkers and novel therapies in these common and disabling disorders. ■

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Supporting Data

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The complex syndrome of functional neurological disorder

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Abstract

Background. Patients with functional neurological disorders (FND) often present with multiple motor, sensory, psychological and cognitive symptoms. In order to explore the relationship between these common symptoms, we performed a detailed clinical assessment of motor, non-motor symptoms, health-related quality of life (HRQoL) and disability in a large cohort of patients with motor FND. To understand the clinical heterogeneity, cluster analysis was used to search for subgroups within the cohort.

Methods. One hundred fifty-two patients with a clinically established diagnosis of motor FND were assessed for motor symptom severity using the Simplified Functional Movement Disorder Rating Scale (S-FMDRS), the number of different motor phenotypes (i.e. tremor, dystonia, gait disorder, myoclonus, and weakness), gait severity and postural instability. All patients then evaluated each motor symptom type severity on a Likert scale and completed questionnaires for depression, anxiety, pain, fatigue, cognitive complaints and HRQoL.

Results. Significant correlations were found among the self-reported and all objective motor symptoms severity measures. All self-reported measures including HRQoL correlated strongly with each other. S-FMDRS weakly correlated with HRQoL. Hierarchical cluster analysis supplemented with gap statistics revealed a homogenous patient sample which could not be separated into subgroups.

Conclusions. We interpret the lack of evidence of clusters along with a high degree of correlation between all self-reported and objective measures of motor or non-motor symptoms and HRQoL within current neurobiological models as evidence to support a unified pathophysiology of 'functional' symptoms. Our results support the unification of functional and somatic syndromes in classification schemes and for future mechanistic and therapeutic research.

Introduction

Medically unexplained symptoms (MUS) are hugely common across the medical practice. They are often chronic, disabling, associated with very high health and social care expenditure, and have major personal and family impact in terms of quality of life and financial security (Creed & Barsky, 2004). Traditionally the diagnosis of MUS has adopted an exclusionary approach (tests are normal, therefore it is MUS) and pathophysiological understanding has focused on psychological causation, in particular, the idea that physical symptoms are an expression of underlying anxiety. This has informed treatment approaches which rely strongly on reassurance regarding the lack of serious underlying physical illness, the reattribution of physical symptoms to psychological causes, and the psychological and pharmacological treatment of anxiety/depression. The diagnosis is heavily stigmatised with many healthcare professionals viewing such patients as not genuinely ill, alongside general negative societal attitudes to psychological *v.* physical illnesses.

In contrast, the last 15–20 years have seen a resurgence of scientific, clinical and service development interest in functional neurological disorder (FND) (Espay et al., 2018). This work has confirmed FND to be a very common diagnosis in modern neurological practice (about 16% of new neurology outpatient attendances, about 10% of admissions to hyperacute stroke services) (Stone et al., 2010), that it is associated with low rates of misdiagnosis, and that long-term prognosis with regard to disability and quality of life is poor, similar to that seen in multiple sclerosis and Parkinson's disease (Anderson et al., 2007; Gendre et al., 2019; Stone, Sharpe, Rothwell, & Warlow, 2003). Major efforts have been made to change the diagnostic approach from an exclusionary one to a positive one based on specific symptoms and signs, and for this to be reflected in diagnostic explanation (APA, 2013). Rather than suggesting it is 'unexplained', the modern diagnosis of FND emphasises that it is a specific diagnosis

which has an underlying mechanism. Here much work has been undertaken to provide a neurobiological dimension to pathophysiological explanations (Baizabal-Carvallo, Hallett, & Jankovic, 2019; Edwards, Adams, Brown, Parees, & Friston, 2012). This does not seek to ignore or downgrade a psychological level explanation, but rather to explain the brain basis of symptoms in addition. There has been a consequent rebalancing of predisposing factors in FND (e.g. past trauma) to consider them as risk factors that may or may not be relevant to symptom development (Ludwig et al., 2018). This allows a more bespoke approach to diagnostic explanation, formulation and treatment, reflected in the development of specific psychological and physical rehabilitation techniques that do not depend on Freudian notions of repressed trauma and the catharsis of psychoanalytical exploration (Espay et al., 2018).

These developments have resulted in somewhat of a disconnect between diagnostic classification and current scientific evidence for those diagnosed with functional neurological symptoms and for those with 'MUS' in general. This disconnect reflects a long-standing division in (psychiatric) classification schemes between conversion disorder and somatisation disorder. In the latest iteration of the Diagnostic and Statistical Manual of Mental Illness (DSM 5), Conversion Disorder was moved from the Dissociative disorders category to Somatic symptom disorder category and relabelled as Functional Neurological Symptom Disorder/Conversion disorder. The diagnostic emphasis switched to positive neurological symptoms and signs, and that the diagnosis did not depend on the identification of conflicts or other stressors though it is acknowledged that these might often be present and might be relevant (APA, 2013). However, this diagnosis only covers functional motor symptoms, symptoms of sensory loss/disturbance (but not pain), and non-epileptic attacks. This restrictive definition is in direct opposition to the very common presence of non-motor symptoms in those with functional motor symptoms, in particular pain, fatigue and cognitive symptoms such as cognitive 'fog'. In previous work by ourselves and others, such symptoms in addition to depression and anxiety correlated with health-related quality of life (HRQoL), but not with an objective rating of motor symptom severity (Vechetova et al., 2018). Neurobiological models for the FND are in fact agnostic to the nature of the symptom – the same underlying mechanism can account for motor, sensory, cognitive and interoceptive phenomena (Edwards et al., 2012; Van den Bergh, Witthoft, Petersen, & Brown, 2017). Despite this clinical and scientific background, pain, fatigue and other symptoms in people with FND are currently classified separately in DSM-5, for example as somatic symptom disorder (e.g. with predominant pain), but only if psychological distress regarding symptoms is judged to be 'excessive', or with another label such as chronic pain syndrome (APA, 2013). A similar diagnostic division is present in the International Statistical Classification of Diseases and Related Health (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).

Here we sought to provide evidence that might shed light on this complex and unsatisfactory situation. We performed a detailed clinical assessment of symptoms, quality of life and disability in a large cohort of patients with a motor FND. We specifically wished to determine the presence and nature of correlations between specific symptoms (motor, non-motor, psychological) and quality of life/disability. Also, we wished to determine if there were specific clusters of patients based on specific symptoms, supporting the current symptom-based diagnostic classification schemes.

Materials and methods

One hundred and ninety-five consecutive patients diagnosed with clinically definite motor FND according to Gupta and Lang criteria [141 females, mean age 46.3 (standard deviation, S.D.= 12.1, range 19–81) years; mean disease duration: 7.3 (SD 7.0) years] in the specialised outpatient service for motor FND at the Neurology Department of Charles University in Prague, 1st Faculty of Medicine and General University Hospital (Gupta & Lang, 2009) from January 2017 to March 2020 (until the beginning of the coronavirus pandemic) were included in the study. Patients who visited after the beginning of the coronavirus pandemic (i.e. from 4/2020 later) were not included as there could be multiple biases.

Exclusion criteria included age <18 years old, MRI abnormality, intellectual disability, major neurological conditions affecting the central nervous system and/or interfering with motor function (e.g. Parkinson's disease, multiple sclerosis, stroke), psychotic spectrum disorders, bipolar disorder and substance use disorder. The diagnosis of motor FND was based on detailed clinical interviews and examination by an experienced movement disorders specialist based on positive signs of functional weakness or abnormal movements inconsistent and incongruent with known movement disorders (Espay et al., 2018; Gupta & Lang, 2009). The study was approved by the local ethics committee and all participants gave their written consent to take part in the study.

Objective assessment of motor symptoms

The motor symptoms were classified as functional weakness, tremor, dystonia, myoclonus, gait disorder, or speech disorder.

Dominant (most severe and/or most frequent motor symptom) and additional motor symptom types (i.e. tremor, dystonia, gait disorder, myoclonus and weakness) were identified and the number of different motor symptoms in each patient was used as a proxy measure for motor disorder complexity.

The severity of the motor disorder was assessed using The Simplified FMD Rating Scale (S-FMDRS) (Nielsen et al., 2017). The presence or absence of abnormal movement at each of seven body regions (face and tongue, head and neck, left upper limb and shoulder girdle, right upper limb and shoulder girdle, trunk and abdomen, left lower limb, right lower limb) was recorded and rated according to symptom severity and duration (maximum score: 54).

Gait aid score (10 m minimal distance) was evaluated as normal gait = 0, abnormal gait no need for assistance or walking aids = 1, assistance or walker or crutches needed = 2, wheelchair dependent = 3). The criteria for classifying patients as wheelchair dependent were based on the objective gait assessment and only those patients who were completely unable to walk (with or without assistance/support) were classified as wheelchair dependent. Patients using a wheelchair for transportation (some of them for excessive pain, fatigue or low tolerance of exercise rather than motor disorder) but able to walk a short distance (10 m) during the examination were assigned to other groups.

Objective assessment of gait function (S-FMDRS gait subscore = sum of severity and duration of gait disorder, range 0–6) was also used for analysis (Nielsen et al., 2017). The presence of instability during the neurological examination was recorded (present = 0,

absent = 1). Postural instability was classified as present if the patient was not able to stand/walk without support. Positive functional Romberg or pull test backwards were also considered a sign of postural instability. History of falls or instability was not taken into account.

Subjective assessment of motor and non-motor symptoms

All patients evaluated their own motor symptom severity on a 3-point Likert scale (not bothered at all = 0, bothered a little = 1, bothered a lot = 2) according to the *Patient-Health-Questionnaire* (PHQ-15). The scale considered 5 motor symptoms categories. In addition to PHQ-15 items assessing motor function including weakness (1), motor coordination impairment (2) and gait disorder (3), we added one item assessing tremor and jerks, i.e. merging tremor and myoclonus together (4) and one item assessing abnormal postures or spasms (5). The total score (subjective motor symptoms severity, SMSS, range 0–10) was calculated.

Additionally, all patients completed questionnaires for depression, anxiety, fatigue, pain, cognitive complaints and HRQoL.

To measure depressive symptomatology *the Beck Depression Inventory* (BDI-II) was used, consisting of 21 items with a total score 0–63 (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961).

To measure levels of anxiety we used the *State-Trait Anxiety Inventory* (STAI X-1, STAI X-2), a measure of state (20 item STAI X-1) and trait anxiety (20 items STAI X-2) with the range 20–80 for each part (Spielberger, 1983).

Fatigue was assessed using *the Fatigue Severity Scale* (FSS), a 9-item scale with the range 1–7 focusing on a functional impact and severity of physical and mental fatigue (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989).

To assess pain, we used the *PainDetect* visual analogue scale (VAS) with the range 0–10 for each subscale (VAS, 0 = no pain, 10 = maximum pain) scales for evaluation of current pain intensity, the average pain and the maximal pain in last 4 weeks. The average of these values (the current, the average and the maximal pain intensity = Pain composite score, total score 0–30) for each subject was used for analyses (Freynhagen, Baron, Gockel, & Tolle, 2006).

Subjective cognitive complaints were measured using the Czech validated version of the *Cognitive Complaints Questionnaire* (Le questionnaire de plainte cognitive, QPC), based on an original French 10- item dichotomous (yes/no) questionnaire assessing the presence of cognitive difficulties in the last 6 months with the range 0–10 (Markova et al., 2017). The first two items inquire about general memory abilities, while the remaining eight items inquire about more particular cognitive complaints including difficulties with spatial orientation, language, instrumental activities and personality change.

HRQoL was assessed using the *12-Item Short-Form Health Survey* (SF-12) (Ware, Kosinski, & Keller, 1996). Physical Functioning, Role Limitations (both Physical and Emotional), Social Functioning, Pain, Mental Health, Vitality and General Health are domains of HRQoL that are reflected in SF-12 (total score 12–44, higher scores associated with better HRQoL). In order to control for possible autocorrelation bias from the partial overlap of several SF-12 items with measures of anxiety, depression, fatigue and pain we calculated the *SF-12 general health subscore* including only items regarding the impact of general health state (i.e. SF-12 items 1, 2, 3, 4, 5, 9, 12; total score 7–25) while excluding items related to mental health, mood and emotional problems, bodily pain and fatigue.

To measure a health state to complement the HRQoL, *the EuroQoL 5-dimension 3-level instrument* (*EQ-5D-3L*) *descriptive part* (EQ-5D, range 5–15) and *visual analogue scale* (EQ-VAS, range 0–100%, with 100% being the best imaginable state of health) were used. Five dimensions are reflected in EQ-5D: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with three response categories each (no problems, some problems and severe problems) (Rabin, Gudex, Selai, & Herdman, 2014).

Statistical analysis

Pearson's correlation coefficient was computed to explore the bivariate relations between variables. Lasso regression with 10-fold cross-validation was used to identify variables affecting the HRQoL measures to later enter a multiple linear model (Friedman et al. 2010). Candidate covariates entering the Lasso model were: age, sex, disease duration, subjective motor symptoms severity, S-FMDRS total score, motor phenotype complexity (number of motor symptoms), S-FMDRS gait subscore, presence of gait abnormality and instability, gait aid score, STAI X-2, BDI-II, QPC, FSS and Pain composite score.

Complete hierarchical clustering using Euclidean distance was used to find putative clusters in data. In particular, we aimed to identify subgroups of patients, where patients in one group had similar characteristics, but different from the patients in other groups. We considered three sets of data when finding clustering: (i) all variables entering the Lasso model, (ii) all variables entering the Lasso model plus the indicators of primary and secondary motor symptoms, and (iii) non-motor variables only (STAI X-1 and STAI X-2, BDI- II, QPC, FSS, and Pain composite score). The data were standardised using the z-score transformation to balance the influence of individual variables, whose original scales could differ by an order of magnitude. Highly correlated variables of STAI X-1, STAI X-2, and BDI-II were decorrelated (replaced by principal components). The significance of putative clustering found was assessed using the gap statistics (Tibshirani, Walther, & Hastie, 2001).

Statistical analyses were carried out in R (R Core Team, 2020) using glmnet package for Lasso modelling (Friedman et al., 2010), cluster package for gap statistics calculation (Maechler, Rousseeuw, Struyf, Hubert, & Hornik, 2021), and idendro package for interactive dendrogram exploration (Sieger, Hurley, Fišer, & Beleites, 2017). Corrections for multiple testing were intentionally not performed in order to enable inspection of raw p values, e.g. those of correlations between selected pairs of variables of interest.

Results

All consecutive 195 patients with motor FND fulfilling inclusion criteria underwent a full clinical assessment and agreed to fill the questionnaires, however, 17 patients did not return the questionnaires and 26 patients did not complete all questionnaires. All subjects with missing data were excluded from the analysis.

Complete dataset was obtained from 152 patients with clinically definite motor FND (109 females) with mean age 46.0 (SD 12.2) years, mean disease duration was 6.6 years, median 5 years.

Forty-three patients were excluded from the analysis because of missing data [32 females, mean age 47.5 (SD 11.7) years, mean disease duration: 10.0 (SD 7.0) years, median 8 years]. A significantly earlier motor FND onset and longer disease duration

Table 1. Objective characteristics of motor symptoms - dominant and additional motor phenotype

		Percentage of patients with a given additional motor phenotype out of patients with the given primary phenotype (%)[c]						
n (152)[a]	Dominant motor symptoms (%)[b]	Gait disorder	Weakness	Tremor	Dystonia	Myoclonus	Speech disorder	Postural instability (%)[d]
Gait disorder	32	–	62	42	0	4	17	67
Weakness	24	72	–	22	6	0	11	31
Tremor	19	31	34	–	0	7	7	10
Dystonia	16	64	36	48	–	12	12	8
Myoclonus	8	33	17	17	8	–	0	17
Speech dis.	1	0	0	0	0	0	–	0

[a]Number of patients.
[b]Numbers give percentages (%) in whom given motor symptom was present as dominant phenotype.
[c]e.g. 42% of patients with primary gait disorder suffered from secondary tremor.
[d]Percentages of patients reporting postural instability out of the total number of patients in whom given motor symptom was present as dominant phenotype e.g. 67% of patients with primarily gait disability reported postural instability.

($p < 0.001$) than in the analysed sample could partially explain lower compliance in this group. In most of these patients, FND had started before a specialised service for FND patients was established in 2015. Chronic course with exposure to numerous diagnostic procedures and a lack of effective treatments might have affected the willingness to collaborate on research. No significant differences were found between the groups in either of the motor domains.

Objective motor symptom characteristics are presented in Table 1.

In our cohort, 29% had a monosymptomatic motor presentation, 41% presented with two different types of motor symptoms. Only 3% of patients showed more than 4 phenotypes.

Mean S-FMDRS was 11.3 (SD 8.0, range 0–39). The mean S-FMDRS gait subscore was 2.8 (SD 2.2, range 0–6). Instability during the neurological examination was present in 33% of subjects.

Normal gait was present in 36% of patients, 44% of patients had gait disorder without the need for assistance or walking aids, 16% of patients needed assistance, walker or crutches. Only 4% of patients were wheelchair dependent.

Data from questionnaires on non-motor symptoms, self-reported severity of motor symptoms and HRQoL in patients are shown in Fig. 1.

Correlation analysis

Correlation analysis evaluated the relation between the following domains: age, age of motor FND onset (FMD onset), disease duration, number of motor phenotypes, S-FMDRS total score, S-FMDRS gait subscore, gait aid score, SMSS score and non-motor domains (BDI-II, STAI X-1,2, FSS, QPC and Pain composite score) including HRQoL (SF-12 score, SF-12: general health subscore, EQ-5D, EQ-VAS score).

The main correlation analysis results are shown in Fig. 2, additional/complementary correlation analyses are reported in the following summary of the results. The complete set of correlation analysis results is presented in Online Supplementary Fig. S1.

Age was positively correlated to subjective cognitive complaints (QPC scores) ($p < 0.001$), trait anxiety (STAI X-2 score) ($p < 0.01$) and negatively to the quality of life (SF-12) ($p < 0.01$), the general health subscore of SF-12 ($p < 0.001$) and EQ-VAS score ($p < 0.01$).

A weak positive correlation ($p < 0.05$) was revealed for state anxiety (STAI X-1 score), BDI-II and S-FMDRS gait subscore.

There was found a significant positive correlation between disease duration and fatigue ($p < 0.001$). Disease duration negatively correlated with gait aid score ($p < 0.01$), and weakly with S-FMDRS gait subscores ($p < 0.05$).

All objective measures of motor symptom severity and complexity (number of motor phenotypes, S-FMDRS total score, S-FMDRS gait subscore, gait aid score) correlated with each other ($p < 0.001$). The S-FMDRS total score significantly correlated with all non-motor symptoms measures (BDI-II, STAI X-1,2, QPC, FSS, pain score). On the other hand, the number of motor phenotypes correlated only with subjective cognitive complaints score (QPC) and EQ5D score ($p < 0.001$), and weakly with pain and SF-12 scores.

S-FMDRS gait subscore correlated with other objective measures of motor symptom severity (number of motor phenotypes, S-FMDRS total scores) ($p < 0.001$), but also with all HRQoL measures ($p < 0.01$) and all non-motor scores ($p < 0.05$) (Fig. 2).

The subjective motor symptoms severity score significantly correlated with objective measures of motor symptom severity assessed using the S-FMDRS total scores (including S-FMDRS gait subscore, $p < 0.001$), and all non-motor and QoL scores ($p < 0.001$) (Fig. 2).

All non-motor measures (BDI-II, STAI X-1,2, FSS, Pain composite score, QPC) correlated strongly with each other and with the SMSS score. The strongest correlation was observed between depression (BDI-II score) and anxiety (STAI X-1,2 score) and cognitive complaints (QPC score).

Both measures of motor symptom severity, the subjective and objective (SMSS, Number of motor phenotypes, S-FMDRS scores, S-FMDRS gait subscores) correlated with HRQoL measures (SF-12 and EQ-5D-3L). SF-12 score and SF-12: general health subscore correlated equally with most measurements.

Although no differences in SF-12 and EQ-5D-3L scores (EQ-5D and EQ-VAS, respectively) were found between patients with dominant gait disorder and patients with other dominant phenotypes ($p = 0.63$, $p = 0.58$, respectively), the presence of postural instability was associated with worse scores of SF-12 and EQ-5D-3L (both $p < 0.001$). Similarly, more severe impairment in gait as measured by the use of walking aids (gait aid score

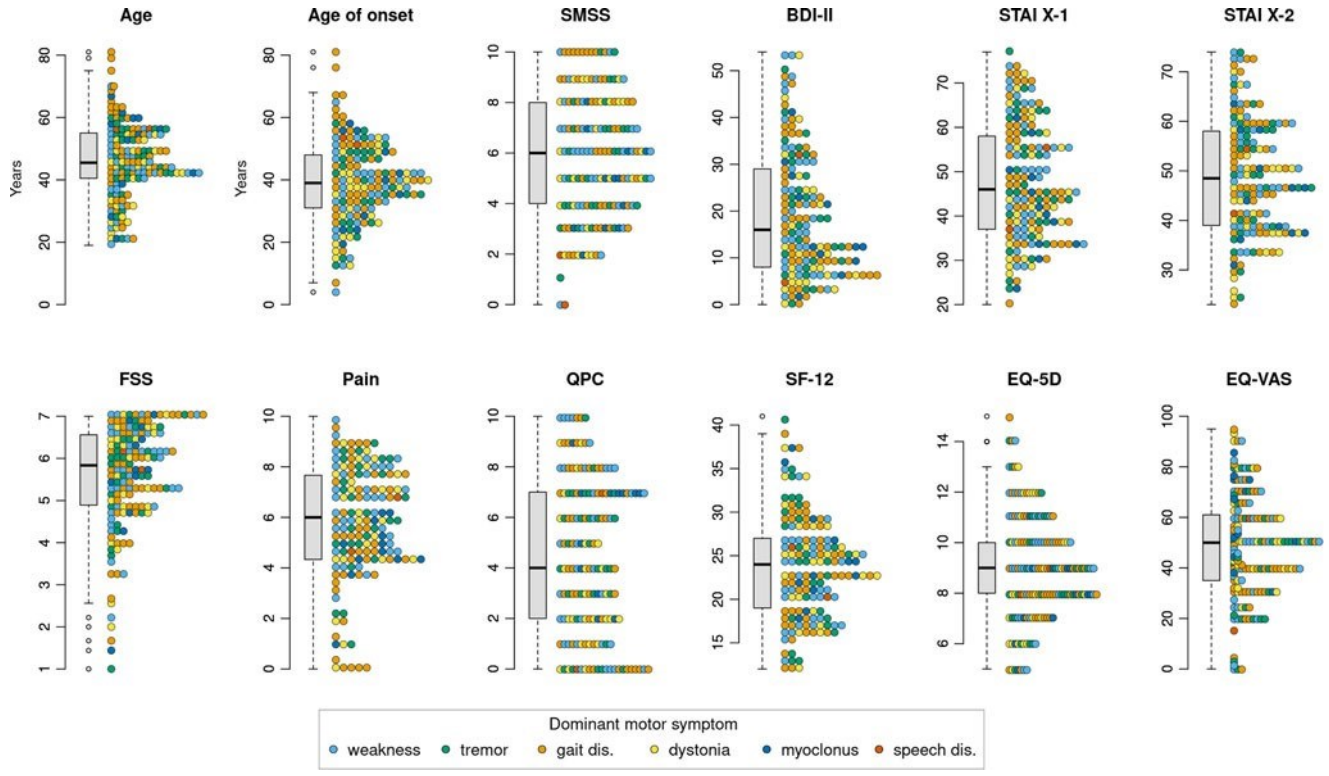

Fig. 1. Self-reported/subjective measures of motor and non-motor symptom severity and HRQoL. Boxplots and histograms of age, motor and non-motor symptom severity, and HRQoL. Colour dots represent individual patients (n = 152) with their primary motor phenotype. BDI-II = The Beck Depression Inventory II; EQ-5D descriptive part of EQ-5D-3L; EQ-VAS = EQ visual analogue scale, part of EQ-5D-3L; EQ-5D-3L = EuroQoL 5-dimension 3-level instrument; FSS = The Fatigue Severity Scale; Pain = The PainDetect scale items -mean from three values the current/average/maximal pain intensity; QPC = The Cognitive Complaints Questionnaire; SD = standard deviation; SF-12 = The 12-Item Short Form Health Survey; SMSS = subjective motor symptoms severity, STAI X-1/STAI X-2 = The State/Trait Anxiety Inventory.

up to the value of 2) was associated with worse scores of SF-12 and EQ-5D-3L (both $p < 0.001$). Nevertheless, wheelchair dependent patients reported only worse EQ-5D ($p < 0.001$) and general health subscore of SF-12 ($p = 0.01$), but not SF-12 ($p = 0.19$) or EQ-VAS score ($p = 0.32$) compared to patients without gait problems.

Age of motor FND onset correlated significantly only with S-FMDR gait subscore and gait aid score (shown in the Online Supplementary Fig. S1).

No significant correlations were found between disease duration and SF-12 and EQ-5D-3L scores.

All non-motor measures strongly correlated with HRQoL measures (SF-12 and EQ-5D-3L).

Predictors of HRQoL

Multiple linear regression revealed BDI-II ($p < 0.001$), Pain composite score ($p < 0.001$), SMSS score ($p = 0.008$), STAI-X2 ($p = 0.010$), and FSS ($p = 0.03$) were the factors affecting jointly the HRQoL (the SF-12 score).

Similarly, the multiple linear regression model of the subscore of SF-12 related to general health revealed that FSS ($p < 0.001$), BDI-II ($p < 0.001$), Pain composite score ($p = 0.010$), age ($p = 0.008$) and Subjective motor symptoms severity ($p = 0.047$) were the factors affecting jointly the HRQoL.

The current health status (EQ-5D measures) was strongly affected by BDI-II scores ($p < 0.001$), need for use gait aids (Gait aid score) ($p < 0.001$), acute pain scores ($p = 0.002$) and S-FMDRS ($p = 0.009$). The health status measured using EQ-VAS was affected by Pain composite score ($p < 0.001$), STAI-X2 ($p = 0.002$), SMSS ($p = 0.003$) and age ($p = 0.003$). The effect of S-FMDRS on SF-12 and EQ-VAS was not significant when adjusting for the other factors in the multiple linear model, it only affected the EQ-5D.

Cluster analysis

The cluster analysis revealed that the patients could not be reliably separated into several subgroups: the gap statistic insinuated that the patients formed a relatively homogeneous cluster. This result was found for each of the three data sets considered.

Discussion

Correlation and cluster analyses of self-evaluated and objectively assessed motor symptoms, self-evaluated non-motor symptoms severity and quality of life in a relatively large cohort of patients with heterogeneous motor manifestations including functional weakness provided the following findings.

(1) Objectively assessed motor symptom severity including scales for gait impairment and FND phenotypic complexity correlated with subjectively reported motor symptoms severity. The objectively assessed motor symptom severity using S-FMDRS correlated with all self-reported non-motor symptoms severity scores.

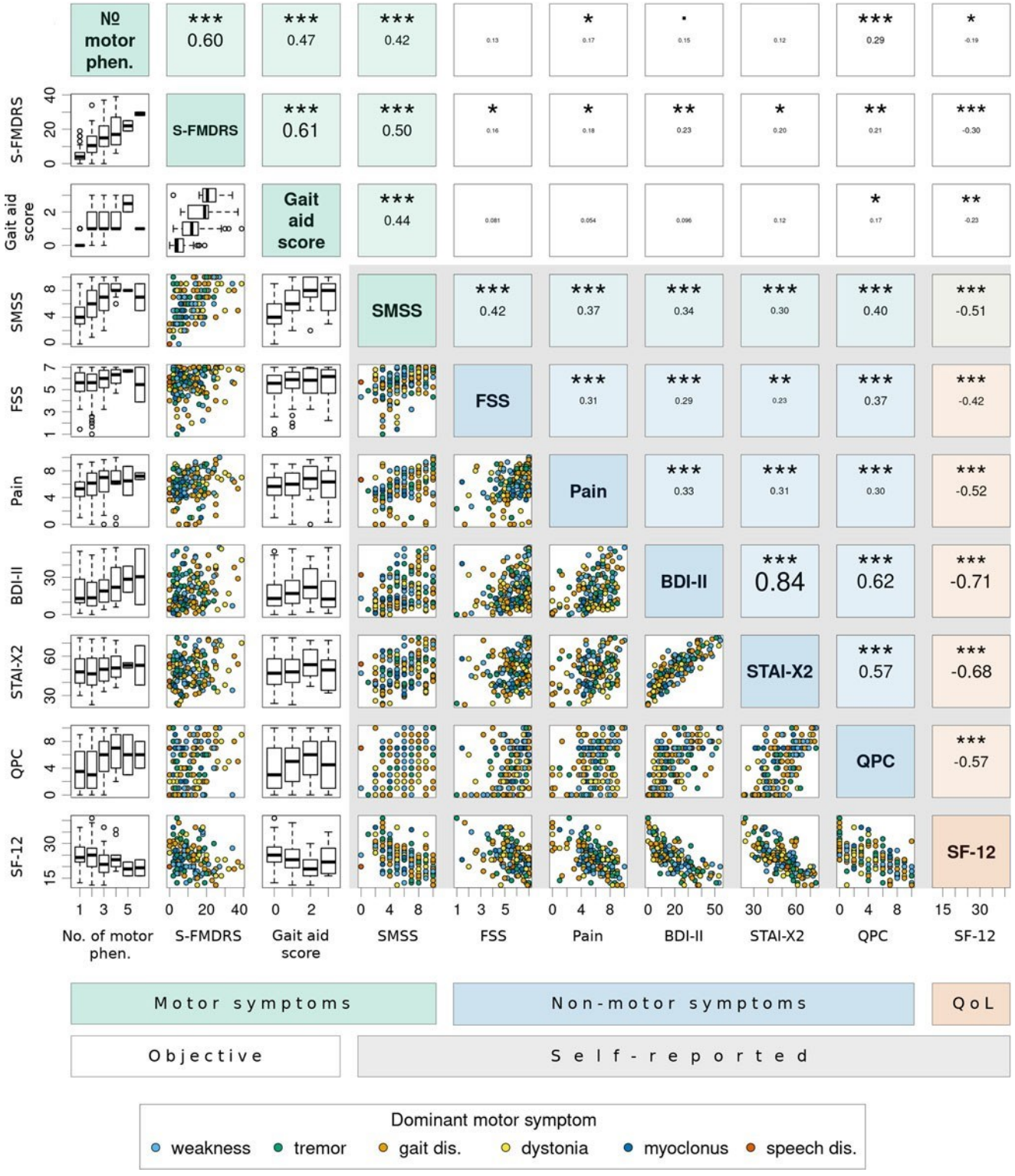

Fig. 2. Correlations between main objective and subjective domains and SF-12. Bivariate scatter plots and boxplots are shown below the diagonal. Note the absence of diverse clusters in the data. Above the diagonal, there are Pearson's correlations coefficients and their significance shown. Note the high correlations within the block of motor symptoms (green), and within the block of non-motor symptoms (blue) and QoL (yellow). The Subjective motor symptoms severity (SMSS) correlated with all other domains. Each measure (e.g. number of motor phenotypes, S-FMDRS etc) is projected on *x*-axis beneath its corresponding label on the diagonal and on the *y*-axis to the left of the label. BDI-II = the Beck Depression Inventory II; FSS = the Fatigue Severity Scale; Gait aid score (0 = normal gait, 1 = abnormal gait no need for assistance or walking aids, 2 = assistance or walker or crutches needed, 3 = wheelchair dependent); Pain = the PainDetect scale items-mean from three values the current/average/maximal pain intensity; QPC = the Cognitive Complaints Questionnaire; SF-12 = the 12-Item Short-Form Health Survey (total score 12–44, higher scores associated with better HRQoL); S-FMDRS = the Simplified FMD Rating Scale (0 – … most severe motor symptoms); SMSS = Subjective motor symptoms severity; STAI X-2 = the State/Trait Anxiety Inventory. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

(2) There was a significant mutual correlation between all subjectively reported motor and non-motor symptom measures.
(3) Both the subjective and objective motor symptoms measures showed a significant correlation with HRQoL measures, however, the subjectively reported severity of motor symptoms along with fatigue, pain, depression and anxiety were the main drivers of HRQoL. The objective motor symptoms only partially affected the current health status.
(4) Cluster analysis revealed that the patient sample was relatively homogenous and could not be separated into subgroups based on specific/discrete motor and non-motor features.

These findings suggest that regardless of motor phenotype, there is a continuum in disease severity across multiple domains where patients with mild motor symptom severity reported less severe non-motor symptoms and more severely affected patients reported more severe non-motor symptoms along with worse HRQoL.

Relationship between motor and non-motor symptoms

Consistent with previously reported relationships between multiple non-motor symptoms, (Gelauff et al., 2018; Gendre et al., 2019; Vechetova et al., 2018) here we also found relationships between the self-evaluated motor symptom severity and several objective measures of motor impairment. Motor symptom severity assessed using S-FMDRS also correlated with depression, anxiety, fatigue and pain scales. Rather against expectations, no correlation was found between the gait scales and pain.

Interestingly, out of the non-motor symptoms, the subjective cognitive complaint severity was the only measure that correlated with all other subjective and objective motor and non-motor measures which may reflect the role of attentional processes in the development of FND and the importance of the cognitive symptoms (Edwards et al., 2012; Sadnicka, Daum, Meppelink, Manohar, & Edwards, 2020; Teodoro, Edwards, & Isaacs, 2018).

The distribution of the data from subjective and objective assessment suggests that patients with objectively less severe motor impairment report having a less subjective motor impairment and less severe non-motor symptoms, i.e. they are not 'over-reporting' severity of their motor and systematically presenting maximal values.

A significant correlation between objective motor symptom severity and psychological symptom severity (anxiety, depression) has previously been reported in patients with functional myoclonus while it was absent in the organic myoclonus control group (Zutt et al., 2017).

Further studies are needed to show whether the pattern of multiple motor and non-motor correlations and a lack of clusters is specific to motor FND or also other FND. Despite the expectation that motor symptoms generally associate with psychological or non-motor symptoms, the literature across different neurological disorders has provided inconsistent results with a large number of studies reporting a lack of correlations in Multiple Sclerosis (Braga, Prado, Bichueti, & Oliveira, 2016) (Arnett, Higginson, Voss, Randolph, & Grandey, 2002; Bakshi, 2003; Brassington & Marsh, 1998; Krupp, Alvarez, LaRocca, & Scheinberg, 1988; Krupp et al., 1989; Schreurs, de Ridder, & Bensing, 2002; Vercoulen et al., 1996), Myasthenia gravis (Bartel & Lotz, 1995; Chen, Chang, Chiu, & Yeh, 2011; Doering, Henze, & Schussler, 1993; Tennant, Wilby, & Nicholson, 1986), adult spinal muscular atrophy (Gunther et al., 2019) and Parkinson's disease (Park et al., 2018).

Impact of motor and non-motor symptoms on HRQoL

The analysis of the impact of motor and non-motor symptoms on HRQoL revealed a negative correlation between all non-motor scales, motor symptom severity, disability measures and HRQoL measures. Nevertheless, the subjectively reported motor symptom severity rather than S-FMDRS could explain HRQoL, together with depression, pain, anxiety and fatigue. This result extends findings from our previous study conducted in a smaller cohort of motor FND patients which, however, did not consider the self-reported severity of motor symptoms and thus only highlighted the contribution of non-motor symptoms to HRQoL (Vechetova et al., 2018).

The correlation between non-motor measures and HRQoL could result from a significant overlap between the non-motor symptoms measures and several items from the SF-12. To control for this autocorrelation bias between the SF-12 and measures of anxiety, depression, fatigue and pain we performed an analysis with scores only from SF-12 items on general health with the same results.

None of the predominant motor phenotypes was associated with worse HRQoL, nevertheless, patients with the presence of gait impairment (alone or as an accompanying symptom) had worse HRQoL as compared to patients without gait disorder. We also found a relationship between objectively assessed gait severity and the presence of postural instability and impaired HRQoL. These results are similar to those found in disorders such as Parkinson's Disease where postural instability and gait disorder are associated with and impaired HRQoL (Muslimovic et al., 2008).

Older age was associated with more severe cognitive impairment and anxiety, more severe gait abnormality and poorer quality of life. Longer disease duration and later disease onset were associated with more severe gait performance and a more frequent need to use gait aids. Interestingly, longer disease duration was not associated with higher non-motor symptoms severity except for fatigue or a higher number of phenotypes (i.e. more complex phenotype).

This pattern is rather against expectations and also differs from most progressive neurodegenerative or neuroinflammatory diseases where long-duration predicts worsening of symptoms and increase in non-motor symptoms frequency and severity across different domains which was documented for example in Motor Neuron Disease (Gunther et al., 2016) or in Parkinson's Disease (Antonini et al., 2012).

Cluster analysis

Patients with motor FND are usually classified according to the dominant motor phenotype they present with (e.g. functional tremor, functional weakness). This is useful when considering differential diagnosis and targeted investigations, and also in physiotherapy management where specific techniques exist for the treatment of specific motor difficulties (Espay & Lang, 2015; Nielsen et al., 2015). Identifying and addressing non-motor symptoms (somatic and psychological) is an additional key part of diagnosis and management (Feinstein, Stergiopoulos, Fine, & Lang, 2001; Garcin et al., 2017; Gelauff, Stone, Edwards, & Carson, 2014; Jacob, Kaelin, Roach, Ziegler, & LaFaver, 2018;

Maggio et al., 2020; Nielsen, 2016; Nielsen et al., 2019). We felt it was important, therefore, to analyse whether different combinations of comorbid non-motor symptoms can define more homogeneous/unique subgroups or are associated with specific motor characteristics.

A recent study found no differences in selected characteristics such as demographics, mode of onset and severity of depression, anxiety, pain and fatigue between predefined groups of patients with the different dominant phenotypes (Gelauff, Rosmalen, Gardien, Stone, & Tijssen, 2020). Here we used a data-driven approach to search for motor FND subtypes with cluster analysis techniques in an unbiased fashion. Despite a relatively large sample of patients, we failed to identify subtypes based on multiple motor features including motor symptom severity and commonly co-morbid non-motor symptoms in this sample of patients.

In contrast to the lack of clusters in our motor FND group of patients, previous high-quality studies using the same methodology (gap statistics) reported homogeneous clusters including drug-naive parkinsonism (Jain, Park, & Comer, 2015), comorbidities associated with obesity (Reategui, Ratte, Bautista-Valarezo, & Duque, 2019), breast cancer progression data (Alexe, Dalgin, Ganesan, Delisi, & Bhanot, 2007). However, most cluster analysis studies in neurological conditions with motor symptoms such as Parkinson's disease (Ba, Obaid, Wieler, Camicioli, & Martin, 2016; Mu et al., 2017; Yang, Kim, Yun, Kim, & Jeon, 2014) or fibromyalgia (Yim et al., 2017) suffered from important methodological problems which could have led to false-positive cluster identification. Therefore, making inferences about the specificity of our findings is not possible and further studies are needed.

Interpretation

Our finding of a significant relationship between subjective measures of motor and/or non-motor symptoms and measures of HRQoL may be affected by content overlap across questionnaires. For example, HRQoL questionnaires address the impact of impaired mobility, mood, fatigue on QoL; the BDI scale for depression assessment includes several items on somatic symptoms.

However, the lack of evidence of clusters along with a high correlation between all self-reported measures of motor and non-motor symptoms and HRQoL is entirely consistent with the predictions of predictive coding/active inference accounts of FND. These models suggest that symptoms are perceptions of the state of the body. The symptoms are generated by neural processes that actively sample information from the body and process this information in the context of prior predictions or expectations into conscious perceptions (i.e. symptoms = percepts) (Edwards et al., 2012; Van den Bergh et al., 2017).

Crucially, these models are agnostic to the content of the percept. It is proposed that in people with FND an abnormal prior expectancy regarding a particular symptom is enhanced in its strength (precision), and this overwhelms incoming sensory data that would indicate a normal state of the body. In this way an abnormal percept results which is experienced spontaneously and involuntarily, without a sense of control or agency over what has been experienced. This same dysfunction can affect motor, interoceptive and exteroceptive control. Therefore, a high degree of cross-correlation could reflect a common dysfunction that underpins motor and non-motor symptoms (Edwards et al., 2012; Van den Bergh et al., 2017).

This is consistent not only with our data, but also consistent with clinical experience. In patients with functional motor symptoms, multiple somatic symptoms are commonly seen. In some patients the severity of symptoms wax and wane with, for example, the pain becoming more prominent while motor symptoms might improve slightly. Some patients start with chronic pain or fatigue and then later develop functional motor symptoms and vice versa. These phenotypic observations are entirely consistent with a single pathophysiological process which can affect multiple input streams and the sensorimotor control of movement.

Although the applicability of our results to other groups of somatic symptom disorder is hypothetical and needs to be supported by further studies, this idea is also consistent with recent proposals for the pathophysiology of chronic pain. Here, active inference models of chronic pain have been proposed that largely mirror those that have been proposed for FND (Hechler, Endres, & Thorwart, 2016; Seymour, 2019). The widely used concept of 'central sensitisation' in chronic pain, is entirely compatible with the computational process of abnormal high-level priors relating to pain, which then distort pain perception. Though the word 'sensitisation' suggests abnormal sensitivity to incoming sensory/nociceptive input, recent computational models of chronic pain as well as experimental data showing, for example, ***higher*** pain thresholds to electrically induced peripheral pain in people with chronic pain, propose a systematic ***down-weighting*** of peripheral sensory input and therefore a percept driven by the abnormal high level prior (Hechler et al., 2016). This is identical to what is proposed in models of FND (Edwards et al., 2012; Van den Bergh et al., 2017). Similarly, anxiety and depression also fit in the predictive coding model. The role of active inference and predictive coding in emotion processing and depression has already been postulated (Barrett, Quigley, & Hamilton, 2016; Lindquist & Barrett, 2012). According to a Dual system fear and anxiety theory, subcortical changes in the brain and body physiology can be modulated by anxiolytics or antidepressants while different cortical networks generating conscious feeling states reflected in self-reports of fear and anxiety can be targeted by psychotherapeutic approaches (LeDoux & Pine, 2016).

Clinical implications

What are the clinical implications of the absence of clusters and finding of such a strong intercorrelation of motor and non-motor symptoms severity?

First, it suggests that mechanistic and therapeutic advances in the field of FND, chronic pain and other somatic symptoms may be able to be usefully combined with insights from one symptom type likely to be informative for others.

Second, future revisions of DMS-5 and ICD-11 should consider developing a single diagnostic category covering the full spectrum of 'functional' symptoms including pain, fatigue or cognitive complaints. For ICD-11 this should ideally be within both the 'physical' and 'mental' parts of the classification system, or perhaps more radically within a single 'brain' section rather than perpetuating a scientifically and clinically indefensible dualism between brain and mind. This does not imply that neurological and psychiatric illnesses are all best understood at a neurobiological level of understanding, but simply that the brain (and wider nervous system) is the key biological substrate from which neurological, cognitive, emotional and behavioural dysfunction arises.

Third, clinical services might benefit from a degree of unification too. Currently, it is common for services to operate in a

rather atomised fashion with chronic pain, chronic fatigue, persistent physical symptoms and FND services working in isolation, alongside multiple speciality-specific services such as functional breathing disorders services in respiratory medicine departments and functional gastrointestinal disorders services within gastroenterology departments. There clearly remains a role for organ-specific specialism in diagnosis and some aspects of treatment. Overlap between functional and organ-specific disease/illness is quite common, meaning that diagnostic expertise within particular medical sub-specialities remains very important (Stone et al., 2012). However, there are also many areas of overlap where scientific and clinical skills and knowledge can be pooled. Crucially, rather than considering this as an isolated sub-specialism (such as psychosomatic medicine), such services need to be fully integrated into regular medical practice, which includes the integration of psychiatry and psychology too.

Limitations

Our cluster analysis study should be considered as preliminary, for a more definite conclusion on motor FND subtypes large, multicentre, international and well-characterised cohorts of patients should be performed. A limitation of this study was the lack of a disease-specific tool for the assessment of subjective motor symptom severity. We used a non-validated simple Likert scale questionnaire tool which may have led to overvaluation of subjective severity in the context of multiple mild symptoms and undervaluation of severely bothersome monosymptomatic manifestations (the more symptoms you are present the higher the score).

Finally, selected measures targeted some of the most common symptoms, however, other important symptoms or aspects of motor FND (e.g. alexithymia, bladder and bowel symptoms etc., dissociative symptoms, sleep disorders) could have been omitted.

Conclusions

This is the first cluster analysis-based study of motor and non-motor symptoms from a relatively large cohort of patients with motor FND. Lack of distinctive subtypes along with a high degree of correlation between all subjective and objective measures of motor, non-motor symptoms and quality of life can be interpreted within the current neurobiological models suggesting unified pathophysiology of the full range of functional symptoms. Our results should inform future revisions of the disease classifications and support the development of a single diagnostic category encompassing patients with FND and other functional somatic symptoms which has important implications for research and service development.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721005225.

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Conflict of interest. None declared.

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