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ORIGINAL ARTICLE

Positive signs from the history as an aid for early diagnosis in functional movement disorders: The prospective TASMAN study

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Abstract

Background and purpose: There has been a concerted move in recent times to shift from an exclusionary to a positive diagnosis of functional movement disorders (FMDs). To date, most of the focus has been on defining positive physical signs. Here the focus was on the diagnostic specificity of specific symptoms and patient characteristics.

Methods: For this prospective cohort study, newly referred patients in the Netherlands and Australia were recruited before their first neurology appointment. Participants completed questionnaires within 2 months prior to their visit at one of the six different clinics. Directly following the first consultation, physicians received a questionnaire about their diagnostic process. Patients were excluded if the diagnosis was not a movement disorder. Univariate and multivariate regression analyses were conducted to identify predictors of FMDs. Subsequently, a predictive model was constructed and assessed using the area under the receiver operating curve.

Results: Between 1 March 2021 and 1 March 2023, 465 patients were eligible for inclusion, of whom 171 (37%) had an FMD and 294 (63%) a non-FMD. Distinguishing factors amongst these groups included age at onset, gender, history or family history of a functional and psychiatric disorder, sudden onset, specific triggers, fluctuation patterns throughout the day and over an extended period, pain, fatigue, depression, anxiety and dissociation. Using these, a predictive model was developed, yielding a discriminative accuracy of 88%.

Conclusion: Specific symptoms and patient characteristics have high diagnostic discriminative value between FMDs and non-FMDs, providing an additional tool in positive diagnosis.

KEYWORDS
associated features, clinical characteristics, diagnosis, functional movement disorders

Lucille Dorresteijn, Teus van Laar, Tom van Mierlo, David Palmer, Jeroen van Vugt, Brian Wood are collaborators.

INTRODUCTION

Functional movement disorders (FMDs) are complex conditions at the interface of neurology and psychiatry. As the motor-dominant subtype within the spectrum of functional neurological disorders, their presentation is characterized by abnormal movements, including tremors, dystonia, myoclonus and weakness [1].

According to the current criteria, a diagnosis of FMD should be based on positive signs detected mainly during examination, like internal inconsistency, effects of distraction and variability, although evidence of distractibility and variability of the movement disorder can also be gleaned from the history [2, 3]. Examples include Hoover's sign in functional paresis (positive when there is a lack of strength in voluntary hip extension whilst normal involuntary hip extension occurs during contralateral hip flexion against resistance) or entrainment in functional tremors (positive when a tremor synchronizes with the frequency of voluntary tapping of another body part) [4, 5]. These positive signs demonstrate that movements temporarily improve when attention is focused on a different body part, disappear during distraction, or change in frequency and amplitude whilst a patient is performing another rhythmical movement [6].

In contrast to positive findings on neurological investigation, specific positive features from the history have remained relatively understudied, despite them potentially adding significant value to the diagnostic process. Several potentially useful historical features have been noted in patients with FMDs (regardless of the movement disorder phenomenology), but data on their sensitivity and specificity are lacking [7, 8]. In an earlier retrospective study in a large consecutive cohort of patients from a tertiary referral clinic specialized in hyperkinetic movement disorders, our study group has shown that some of these clinical characteristics and associated features are frequently reported and might be discriminative between FMDs and non-FMDs [9]. These factors included age, sex, history of a psychiatric disorder, positive family history, abrupt onset, a fluctuating disease course and the presence of pain and fatigue. These findings are in concordance with the literature, in which female gender, a relatively young age of onset [10], psychiatric comorbidities [11], precipitating physical events [12], marked variability in symptom severity (including complete remissions and sudden recurrences) [13] and high levels of pain and fatigue [14, 15] appear to be more commonly reported in those with FMD.

A prospective study was therefore established to assess a wide range of clinical characteristics and associated features in a variety of movement disorder clinics, including academic and non-academic hospital settings with diverse populations of movement disorder patients.

Through this work the aim was to provide clinicians with unbiased information on the diagnostic value of these historical and patient characteristics to increase the confidence with which they could reach an early correct diagnosis of FMD.

METHODS

Study design and procedures

The study design was an international multicentre prospective observational cohort study. Participants were recruited prospectively and consecutively from four different movement disorder clinics in the Netherlands (one academic medical centre, three non-academic hospitals) and two in Australia (one quaternary level teaching hospital and one private practice with special interest in FMDs). Between March 2021 and October 2022, all newly referred movement disorder patients were informed about the study by email or post. After giving consent, they completed the study questionnaires within 2 months prior to their outpatient clinic visit. Directly following the first appointment, the responsible movement disorder specialist received an online questionnaire about the diagnostic process, which was completed within 4 weeks, prior to any additional information being gathered.

The TASMAN study was performed in accordance with the ethical and legal guidelines of the University Medical Centre Groningen in the Netherlands (METc 2021/049, 202000821) and the Metro South Health Human Research Ethics Committee in Australia (HREC/2021/QMS/77349). All participants gave written or electronic consent.

Participants

For inclusion in the study, all participants were over the age of 16, able to read Dutch or English, and had been referred to a movement disorder clinic. Patients with functional paresis were included because, although not a movement disorder phenotype in the strict sense, they are described as such in the literature. Patients with a diagnosis which was not a movement disorder (e.g., primary psychiatric disorder or neuromuscular disorder), patients who had no clinically confirmed diagnosis after the first visit with their physician (missing data) and patients who were unable to provide informed consent were excluded. Patients with comorbid (neurological) disease were not excluded from the study.

Patient information

Patients filled in questionnaires online prior to the initial consultation about demographics, temporal dynamics of symptoms, non-motor symptoms, patient-rated symptom severity and disability, quality of life, and occupational functioning. Parameter selection was based on data from our retrospective study and related literature [9, 16]. An overview of patient questionnaires was added (Appendix A).

Multiple-choice questions were used to ask about comorbid conditions in the participants and their first-degree relatives, including a variety of neurological, psychiatric and functional disorders (e.g.,

fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome). Mode of onset and temporal course were assessed asking questions about the speed of symptom development (sudden or gradual) and progression over short and long term (symptoms have remained stable, worsened, improved, fluctuated). Furthermore, participants were asked about specific triggers that preceded their motor symptoms (e.g., trauma, infection, general anaesthesia, medication, vaccination) and if they could remember and describe the exact start of their symptoms. This was the only open question. In addition, the total word count of the description was calculated.

Non-motor symptoms, that is, pain, fatigue, dissociation, depression and anxiety, were scored using validated questionnaires. Pain was assessed using the subscale of the SF-36/RAND36 (36-item Short Form Health Survey, with a maximum score of 100 which stands for low pain) [17]. The fatigue severity domain of the Checklist Individual Strength (CIS) was used to measure fatigue [18]. This subscale consists of eight items evaluating how participants' fatigue felt during the last 2 weeks and has a score range from 8 to 56. Severe fatigue is defined as a score of 35 or more on this subdomain. The CIS has been well validated amongst chronic fatigue syndrome patients. The five-item Somatoform Dissociation Questionnaire (SDQ-5) was used to measure dissociation, with scores ranging from 5 to 25 [19, 20]. The SDQ-5 has been validated to discriminate patients with or without dissociative disorders in psychiatry, with scores over 8 indicating significant somatoform dissociation. The Patient Health Questionnaire 9 (PHQ-9) was used to objectify the severity of depressive symptoms [21]. Anxiety was assessed using the Generalized Anxiety Disorder seven-item scale (GAD-7) [22]. Both scales instruct participants to indicate how often they have been bothered by each symptom over the last 2 weeks using a 4-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). Possible scores on the PHQ-9 range from 0 to 27, and on the GAD-7 from 0 to 21, with higher scores indicating higher levels of depression and anxiety. Both scales use cut-off points to categorize these levels.

Patient-rated severity and disability, quality of life and occupational functioning were also scored online. Overall severity and disability of symptoms was measured using modifications of the Clinical Global Impressions Scale, asking the patient themselves on a 7-point Likert scale: how would you rate the overall severity or disability of your current movement disorder? [23]. Quality of life was measured with a single question from the World Health Organization Quality of Life questionnaire: How would you rate your quality of life on a 5-point Likert scale? [24]. Patients were also asked to report on their profession and working status, and whether they received financial support for health-related reasons by means of several multiple-choice questions.

Diagnosis

Directly after the first visit, attending physicians received an online questionnaire about their diagnosis and diagnostic certainty on a scale from 0 to 100. Physicians were tasked with discriminating between FMDs and non-FMDs, and specifying their exact diagnosis, including any functional components if present, in an unrestricted format. They were asked to determine the dominant motor phenotype (e.g., tremor, myoclonus, tic disorder) and the presence of other motor symptoms. All records were reviewed after 6 months' follow-up by the researchers and, when the diagnosis had changed, the final diagnosis was used for analysis. Specifically, physicians were also questioned about the presence of positive symptoms on neurological examination. An overview of a physician's questionnaire was added (Appendix B).

Power analysis

Based on previous studies it was expected that a maximum of 12 variables would be included in the multivariate logistic regression prediction model to distinguish patients with FMDs from patients with non-FMDs. With the expected maximum of 12 degrees of freedom that is needed to develop the model the aim was for a sample consisting of $12^2 = 144$ patients in both groups. The expected ratio of patients with FMDs and patients with non-FMDs (based on our retrospective study) is 1 versus 2, which leads to the inclusion of a total of 432 patients with movement disorders. Assuming 90% of new patients in a movement disorder clinic receive a final diagnosis of a movement disorder (either FMD or non-FMD), this results in a sample size of 476 subjects, which was rounded to 500 patients. After the first 200 patients an interim analysis was performed on these expected ratios.

Statistical analyses

Baseline continuous characteristics were reported as mean ± SD for continuous variables or if not normally distributed as median with range. Categorical variables were reported as numbers with corresponding percentages. Independent *t* tests or Mann–Whitney *U* tests (as appropriate) were used to test which continuous variables were univariately associated with a diagnosis of FMD. Chi-squared tests were used for categorical variables. Clinical variables that were univariately associated ($p < 0.05$) with a diagnosis of FMD were entered in a multivariate logistic regression analysis after checking for multicollinearity. In the case of multicollinearity between variables, the variable that produced the best model fit (based on −2 log likelihood) was included in the model. After entering the variables into the multivariate model, variables with the highest *p* values were eliminated step-by-step (backward method) until the fit of the model decreased significantly (again based on the −2 log likelihood). This analysis was based on clinical variables only.

Sensitivity, specificity and positive and negative prediction values (PPV and NPV) of the multivariate model were calculated. The ability of our model to identify patients with FMDs was quantified as the area under the receiver operating characteristic curve (AUC). The standard threshold value of the predicted probability for

patients used to calculate the AUC is 0.5 (so patients have a 50% chance of having FMD). To optimize the metrics (sensitivity, specificity, PPV and NPV), various cut-off values of the predicted values were analysed. The multivariate regression model was internally validated by 1000 iterations of bootstrap. The adequacy of the fitted model was tested using the Hosmer and Lemeshow goodness-of-fit statistic. All statistical tests were two-sided with a significance level at 0.05. SPSS version 27.0 (IBM, Armonk, NY, USA) was used to perform statistical mathematics.

RESULTS

Clinical characteristics and diagnosis

Based on the results of our interim analysis which showed that 15% of patients were not diagnosed with a movement disorder, 529 patients were recruited in this study in the period March 2021–March 2023 (higher than the aim of 500 patients). Fifteen patients were unable to give informed consent. Ten cases were excluded from the study due to lack of a clinical diagnosis from the physician after first consultation and in 39 cases the final diagnosis was not a movement disorder (e.g., polyneuropathy, nine; mononeuropathy, five; lumbar spinal stenosis, four). A total of 465 patients were eligible for inclusion in the study, of whom 171 (37%) had an FMD and 294 (63%) were diagnosed with a non-FMD. The most common diagnoses in this last group were Parkinson's disease (26%), idiopathic focal dystonia (14%) and essential tremor (13%). A complete list of non-FMD diagnoses is provided in Table S1.

In FMD patients, the mean diagnostic certainty scored by physicians after the first consultation was 95% compared to 88% in the non-functional group. In 158 (92%) of FMD patients, physicians reported positive symptoms at neurological examination (distractibility, entrainment, motor inconsistency and/or incongruence). Interestingly, positive symptoms were also scored in 43 patients with a non-FMD (15%). Two patients (1%) initially diagnosed with FMD turned out to have a non-FMD after 6 months' review (one orthostatic tremor, one choreatic movements secondary to thalamic infarction), whilst in five patients from the non-functional group the diagnosis was changed to FMD (2%).

Demographics and temporal dynamics of symptoms

The mean age at onset was younger in patients with FMD compared to non-FMD (43 vs. 60 years) with a significant female predominance. The median duration of symptoms was relatively shorter in the FMD cohort (38 vs. 49 months). Patients with FMD were significantly more likely to have another functional disorder or psychiatric disorder in their medical history. Also, these disorders were more frequently seen in their first-degree relatives compared to patients with non-FMD. There were no significant differences in family history of non-functional neurological disorders between the two groups. Acute onset and fluctuation over time, both short term and long term, were significantly more frequently noted by the FMD group. The commonest specific triggers at onset were injury, infection and life events for patients with FMDs, whilst in non-FMD patients medication and general anaesthesia were more often reported (Table S2). Other specific triggers in FMDs included sleep paralysis, COVID vaccinations and vascular events, and chiropractic treatment in the non-FMD cohort. Interestingly, 55% of the patients with FMD could describe the start of their symptoms compared to 21% of the non-FMD group. In these descriptions the mean number of words used was 40 in the FMD cohort (SD 35.7) and 23 (SD 17.6) in patients with other movement disorders.

Non-motor symptoms

Functional movement disorder patients scored significantly higher on all non-motor symptoms compared to the non-FMD group (Table 1). The presence of bodily pain (a score of <50 on the RAND36, lower pain scores represent more pain) was reported by 82% of the FMD patients and by 54% of the non-FMD group (median 33 vs. 49, $p < 0.001$). Severe fatigue (a score of 35 or more on the CIS) was present in 86% of the FMD versus 59% of the non-FMD patients (median 44 vs. 38, $p < 0.001$). Depressive symptoms and anxiety (a score of 5 or more on the PHQ-9 and GAD-7) were also more frequent in the FMD group compared to the non-FMD group, 87% versus 59% (median 10 vs. 6, $p < 0.001$) and 66% versus 43% (median 7 vs. 4, $p < 0.001$). Patients with FMD reported also more dissociative symptoms (a score of 8 or more on the SDQ-5) than patients from the non-FMD group, 63% versus 26% (median 9 vs. 6, $p < 0.001$).

Quality of life, severity, physical and occupational impairment

In both groups, quality of life scores were low (3 out of 5) on the WHO ladder in the majority of patients. Severity and physical impairment were significantly different, with higher scores (representing worse outcome) in patients with FMDs. Proportions of patients in study or work did not differ between the two cohorts; however, FMD patients worked significantly less than before and stopped working more often because of their movement disorders compared to non-FMD patients. More than one in 10 participants in both groups had a profession in healthcare (12% vs. 14%).

Multivariate logistic regression

Significant variables from Table 1 were added to a multivariate model. Due to multicollinearity between movement disorder severity and physical impairment, only one of these two variables could be included in the multivariate model, which was physical impairment (best model fit). Logistic regression analysis showed that age,

TABLE 1 Clinical characteristics and associated features in patients with FMD versus non-FMD.

Variable	Functional, $N = 171$	Non-functional, $N = 294$	p value
Demographics			
Age at onset in years (mean, SD, min–max)	43 ± 18.2 (12–83)	60 ± 16.3 (15–90)	<0.001
Sex (*n*, % female)	124 (72.5%)	137 (46.6%)	<0.001
Duration of symptoms in months (median, IQR)	38 (16–77)	49 (17–143)	0.062
Key motor phenotype	Paresis 26%	Tremor 59%	
	Tremor 22%	Dystonia 16%	
	Myoclonus 13%	Ataxia 5%	
	Dystonia 12%	Chorea 4%	
Key motor phenotype	Gait disorder 11%	Paresis 4%	
Secondary motor phenotype	82 (48%)	116 (39%)	0.080
Academic hospital	68 (40%)	161 (55%)	
Non-academic hospital	31 (18%)	105 (36%)	
Specialized FMD clinic	69 (40%	12 (4%)	
Specialized Parkinson clinic	3 (2%)	16 (5%)	
History			
History of a functional (neurological) disorder	84 (49%)	57 (19%)	<0.001
History of a psychiatric disorder	82 (48%)	49 (17%)	<0.001
Family history of a functional disorder	51 (30%)	39 (13%)	<0.001
Family history of a non-functional neurological disorder	77 (45%)	146 (50%)	0.335
Family history of a psychiatric disorder	82 (48%)	61 (21%)	<0.001
Mode of onset and temporal course			
Acute onset (*n*, %)	98 (57%)	45 (15%)	<0.001
Specific trigger (*n*, %)	87 (51%)	73 (25%)	<0.001
Fluctuations short term (*n*, %)	91 (53%)	79 (27%)	<0.001
Fluctuations long term (*n*, %)	90 (53%)	62 (21%)	<0.001
Non-motor symptoms			
Pain, RAND36 (median, IQR) Pain scores <50	33 (22–44)	49 (33–60)	<0.001
Fatigue, CIS (median, IQR) Fatigue scores ≥35	44 (39–50)	38 (31–46)	<0.001
Depression, PHQ-9 (median, IQR) Depression scores ≥5	10 (6–16)	6 (3–10)	<0.001
Anxiety, GAD-7 (median, IQR) Anxiety scores ≥5	7 (3–13)	4 (1–7)	<0.001
Dissociation, SDQ-5 (median, IQR) Dissociation scores ≥8	9 (6–13)	6 (5–8)	<0.001
Quality of life, severity, physical and occupational impairment			
WHO-QoL, range 1–5 (median, IQR)	3 (2–4)	3 (3–4)	<0.001
Severity, range 1–7 (median, IQR)	5 (4–6)	4 (3–5)	<0.001
Physical impairment, range 1–7 (median, IQR)	5 (4–6)	4 (3–5)	<0.001
In work/studying (*n*, %) - less than before (*n*, %) - hours (median, IQR)	68 (40%) 43 (63%) 29 (15–38)	99 (34%) 20 (20%) 32 (20–39)	0.194 <0.001

(Continues)

TABLE 1 (Continued)

Variable	Functional, $N = 171$	Non-functional, $N = 294$	p value
Not in work (n, %)	103 (60%)	195 (66%)	<0.001
- related to symptoms	59 (57%)	44 (23%)	
- for other reasons	44 (43%)	151 (77%)	
Profession in healthcare	21 (12%)	41 (14%)	0.673

Note: Higher scores represent good outcome in RAND36 and WHO-QoL; higher scores represent bad outcome in CIS, PHQ, GAD, SDQ, Severity and Physical impairment.

Abbreviations: CIS, Checklist Individual Strength; GAD-7, Generalized Anxiety Disorder; IQR, interquartile range; PHQ-9, Patient Health Questionnaire 9, RAND36, Dutch equivalent of SF-36 Short Form Health Survey; SD, standard deviation; SDQ-5, Somatoform Dissociation Questionnaire; WHO-QoL, a single question from the World Health Organization Quality of Life questionnaire.

TABLE 2 Multivariate regression analysis of features independently related to FMD.

Variable	Regression coefficient	OR (95% CI)	Bootstrap (95% CI)
Intercept (α)	−1.007		
Age	−0.038	0.963 (0.949–0.977)	(−0.057 to −0.023)
History of a functional disorder	0.717	2.048 (1.151–3.644)	(0.157–1.357)
History of a psychiatric disorder	0.885	2.423 (1.350–4.349)	(0.244–1.607)
Acute onset	1.657	5.245 (3.020–9.110)	(1.137–2.295)
Fluctuations long term	0.940	2.561 (1.480–4.432)	(0.398–1.546)
Pain	−0.026	0.975 (0.957–0.993)	(−0.046 to −0.007)
Fatigue	0.050	1.051 (1.020–1.083)	(0.019–0.087)

Abbreviations: CI, confidence interval; FMD, functional movement disorder; OR, odds ratio.

history of a functional or psychiatric disorder, family history of a non-functional neurological disorder, acute onset, specific trigger, fluctuations over long term and the presence of pain or fatigue remained significantly predictive for the presence of an FMD (Table 2).

The multivariate logistic regression analysis based on clinical variables only showed a sensitivity of 70.8%, a specificity of 90.1%, a PPV of 80.7% and an NPV of 84.1% when a cut-off of 0.5 was used for the predicted value (standard threshold). The model's performance was evaluated using the receiver operating characteristic curve, depicted by the blue line in Figure 1. The area under the curve (AUC) was 88% (95% confidence interval 85.1%–91.5%), indicating a strong ability to discriminate between FMDs and non-FMDs.

Next to the threshold value of 0.5 (standard threshold) also other thresholds of predicted probability were investigated, to ensure high sensitivity and high NPV. Using a threshold of 0.2 (so patients with a 20% chance of having FMD were classified as FMD), the analysis showed a sensitivity of 89.5%, a specificity of 66.3%, and a PPV and NPV of 60.7% and 91.5%, respectively. The bootstrap analysis for internal validation showed similar regression coefficients compared to our original model showing robustness of the model. In addition, the Hosmer and Lemeshow goodness of fit test was non-significant ($p = 0.650$), implying that the model's estimates fitted the data at an acceptable level.

DISCUSSION

In this study, the aim was to assess the discriminative value of specific historical features and patient characteristics that can help to distinguish patients with FMDs from other movement disorders. Uniquely, it was conducted prospectively before patients were interacting with any physician, which minimizes bias and ensures that the data collected are not overly influenced by the clinician's perspective. The data collected in this study came exclusively from the questionnaires. Previous prediction models have shown clinical value in diagnosing FMDs; however, these were all done retrospectively based on documentation and information from clinicians [9, 25].

Based on individual clinical data from 465 patients from various movement disorder clinics in the Netherlands and Australia, a novel diagnostic prediction model was developed. The final model yielded an estimated absolute probability of FMD based on self-reported information from seven objective clinical features. Overall, this model had high diagnostic accuracy, expressed as an AUC curve of 88% (95% confidence interval 85.1–91.5) demonstrating the positive diagnostic value of specific historical and patient characteristics, and therefore clinicians with additional evidence-based tools for diagnosis.

It was found that more than one out of three referrals had FMD (171 patients), which is higher than reported in previous studies on this topic [26]. Although this study was conducted across various clinics, two of the centres were specialized FMD centres, which may have contributed to the elevated numbers. Compared to non-FMD patients, FMD patients tended to be younger and had a female predominance. Tremor was by far the most dominant motor symptom in non-functional patients (59%), which might be due to the relatively high number of patients with Parkinson's disease

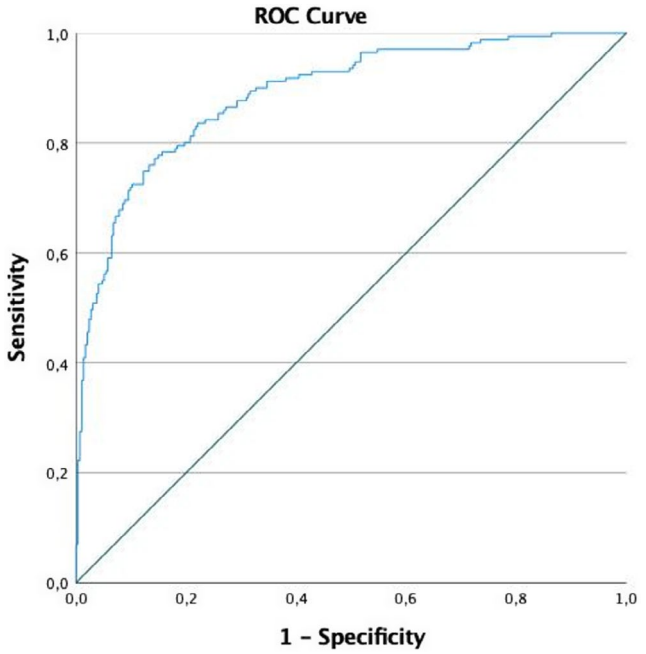

FIGURE 1 Area under the receiving operating characteristic curve (AUC). The blue line depicts the AUC of the multivariate logistic regression model and the grey line depicts the result of chance.

($n = 76$) and essential tremor ($n = 37$). In the functional group there was considerable variation in key movement phenotype, and almost half of the patients had more than one motor phenotype (48%). This could be due to the difficulty physicians face in phenotyping FMDs, given that they are by definition incongruent with a recognized neurological disease. Another explanation for the large amount of overlap could be a suspected shared pathophysiology between different FMDs, which has been hypothesized in the literature [27, 28].

Although earlier studies suggested otherwise [29, 30], a comparable number of patients with more than one phenotype in the non-functional group (39%) was found, so this overlap is not unique to FMDs.

Historical data from our study support the biopsychosocial complexity in functional disorders. Psychiatric and other functional comorbidities were more frequent in FMD patients, which substantiates preliminary findings in the literature [31, 32] and highlights the role of psychological factors in functional neurological disorder. Moreover, patients with FMDs were also more likely to report a positive family history of a functional or psychiatric disorder, which contributes to a biological view on functional disorders. A family history of another neurological condition was common but not discriminative between the two groups and might be seen as a risk factor for an FMD as well as a non-FMD [33, 34].

In line with previous studies [12, 35], patients with FMDs were more likely (51% vs. 25%) to have an acute onset and/or specific trigger that preceded symptoms, for example traumatic injury, new medication. For a long time the emphasis of a diagnosis of a functional disorder was on psychological stressors. Our data confirm studies by Pareés et al. that non-psychological triggers are equally important to the development of FMDs [36]. More than half of the FMD patients (55%) versus only 21% of non-functional patients could describe the onset of their symptoms in detail. This may reflect that precipitating events occurring at the initial onset of the disorder not only possibly contribute to disrupted attentional focus and changes in predictive processing but also have significant impact on patient's recall accuracy. For the descriptions, this group used almost twice as many words as patients with other movement disorders. This finding is remarkably similar to findings in patients with functional cognitive symptoms (another subgroup of functional disorders) [37], who provide a more detailed personal history with explicit examples in comparison to people with neurodegenerative disorders (e.g., dementia). This further supports overlap, not only between different functional motor phenotypes, but also between different subtypes of functional disorders in general.

Not surprisingly, inconsistency over time (which is a hallmark feature for FMDs) as captured by the variables fluctuation over long term and short term, also showed discriminative value.

The non-motor variables depression, anxiety, dissociation, pain and fatigue were prevalent in both groups. The elevated ratings across all patients emphasize the increasing awareness that non-motor symptoms play a crucial role in both FMDs and non-FMDs and should be acknowledged when determining treatment strategies [38, 39]. Although at a group level all non-motor features were discriminative between our cohorts, only pain and fatigue remained in our model as most discriminating factors for the individual patient.

Our results highlight that patients with FMDs are as disabled and have as impaired quality of life as patients with other movement disorders [40]. Quality of life and physical functioning were highly impaired in both patient groups, supporting earlier studies [41]. No significant difference in healthcare employment between our two groups was found, which is in contrast to a recent Swiss study [42]. Although FMD patients exhibited significantly higher rates of health-related unemployment, in the majority of individuals their disorder did not prevent them from working. This is comparable to earlier data and contradicts anecdotal suggestions that functional symptoms are perpetuated by work avoidance [43]. In fact, the relationship between reduced quality of life and health-related unemployment in FMD patients might reflect the crucial role of social factors. Since work provides structure, purpose, social interaction and a sense of identity, being unable to work can lead to financial stress, social isolation and a loss of self-worth, all of which can negatively impact overall well-being.

Our newly developed algorithm can potentially assist clinicians in diagnosing FMD. This would not only create more awareness and confidence for clinicians not diagnosing movement disorder patients on a regular basis, but also early diagnosis and (hopefully) earlier management and treatment for FMD. This in turn may result in better outcomes, as long symptom duration is the worst prognostic factor in this patient group [44]. Whilst most clinicians rely on examination findings to rule-in a diagnosis of FMD, the predictive tool could also be beneficial for general neurologists, who may have

less time or expertise in this field. The historical features and patient characteristics found to be discriminative between people with FMDs and non-FMDs are likely to generalize to other functional syndromes based on existing clinical data [37, 45], and further prospective studies would be useful in this regard.

There are some limitations to this study. Clinicians were asked to choose only between a functional or non-functional diagnosis, not allowing dual diagnosis for the analysis. However, when asked, in 41 patients with a non-FMD, clinicians answered that there was also a functional component to the symptom presentation. Possibly, this might have led to an underestimation of our model. Another is the limitation of possible covariance between our positive clinical variables and the final diagnosis by the movement disorder specialist. Although the gold standard for the diagnosis of FMD is to base it on findings in neurological examination, and in our study in 92% of patients it was reported that these were in place, it cannot be ruled out that in some cases features from the history were used in making the diagnosis. Interestingly, positive symptoms from the examination were also reported by clinicians in 43 patients from the non-FMD group. This could reflect the limitation that clinicians were not allowed to make a dual diagnosis, but also highlights that positive signs should be used judiciously. These signs should be weighed carefully in the context of an individual patient's presentation and are often not as sensitive or specific as is commonly believed [46]. The fact that patient outcome data were based on self-reported online questionnaires has disadvantages. This sort of study design is prone to recall bias and may have led to an overestimation of some variables, for example symptom severity. Also, there was a high number of tremor patients in the non-functional group, which is probably due to this study having been conducted in movement disorder centres where Parkinson's disease is commonly seen. In this specific group there might be less doubt about the diagnosis for clinicians compared to patients with dystonia or tic disorders. Finally, although data have been collected from various clinics, these were all patients referred to a movement disorder specialist.

CONCLUSION

In this study positive clinical features from the history of movement disorder patients that discriminate between FMDs and non-FMDs were determined. Combined in a prediction algorithm, seven of these features predict FMD to a high degree of certainty. Whilst clinicians are always urged to be careful and holistic in their consideration of the full range of clinical evidence when making a diagnosis of FMD or a non-FMD, it is believed that these findings can support clinicians in their diagnostic process, which might lead to earlier diagnoses and thereby potential improve patient outcomes. This study supports that FMD is a distinct condition with its own consistent clinical characteristics and ongoing research will further support this classification.

AUTHOR CONTRIBUTIONS

Tjerk J. Lagrand: Conceptualization; investigation; writing – original draft; writing – review and editing; data curation; formal analysis. **Jeannette M. Gelauff:** Conceptualization; investigation; writing – review and editing; data curation. **Marjolein Brusse-Keizer:** Formal analysis; methodology; conceptualization; writing – review and editing. **Alexander C. Lehn:** Conceptualization; investigation; writing – review and editing. **Marina A. J. Tijssen:** Conceptualization; investigation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors disclose no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

Dear participant,

Thank you very much for taking part in the TASMAN-study.

We would kindly ask you to fill in this questionnaire, **before your visit to the neurologist.**

About the questionnaire:

We would like to ask you to always give an answer, even if you are not sure about it. The point is that you think a particular answer is the best of the options given, and not that it is a perfect answer for you.

At the end there is opportunity for comments. If you would like to comment on certain questions, you can do so then.

Thank you!

Yours sincerely,

Tjerk Lagrand, Neurologist, Clinical Research Fellow Movement Disorders

Department of Neurology, Princess Alexandra Hospital, Brisbane

Demographics

1. Date of filling in this questionnaire?

……(DD/MM/YYYY)

2. What is your sex?

◯ Male

◯ Female

3. What is your age (in years)?
In numbers

……

Education & Work Status

4. What is the highest grade or level of school that you have completed?

◯ 8th grade or less
◯ Some high school, did not graduate
◯ High school graduate, diploma or the equivalent
◯ Some college credit, no diploma
◯ Trade/technical/vocational training
◯ Associate or Bachelor's Degree
◯ Master's Degree
◯ Professional or Doctorate Degree

5. Are you currently studying/working?

◯ Yes

◯ No

5a1 What is your field of study/ current profession?

……

5a2 How many hours a week do you study or work?
In numbers

…… hours

5a3 Are you studying/working less than usual because of your current complaints?

◯ Yes

◯ No

5a4 How many hours a week are you studying/working less than usual because of your current complaints?
In numbers

…… hours

5b

5b1 When did you stop studying/working?
Please fill in a date. If you don't know the exact date, please fill in an approximate date.

…… (DD/MM/YYYY)

5b2 Are your current complaints the reason that you had to stop studying/working?

◯ Yes

◯ No

5b3 If you have worked previously, what was your last profession?

……

Past Medical History

6. Do you, or have you had, any of the following conditions/diagnoses?
Please select all that apply.

☐ Cardiovascular Disease (e.g., heart attack, hypertension, arrhythmia)
☐ Diabetes
☐ Thyroid Disease
☐ Pulmonary Disorders (e.g., asthma, COPD)
☐ Osteoporosis
☐ Fibromyalgia
☐ Transient Ischemic Attack/Stroke/Brain Infarction/Brain Hemorrhage
☐ Epilepsy
☐ Psychogenic Non-Epileptic Seizures (PNES)
☐ Depressive Disorder
☐ Hyperventilation Syndrome
☐ Anxiety Disorder
☐ Attention Deficit Hyperactivity Disorder (ADHD)/Autism Spectrum disorder (ASD)
☐ Kidney Disease
☐ Anaemia
☐ Malignancy (e.g., cancer, leukaemia)
☐ Irritable Bowel Syndrome (IBS)
☐ Inflammatory Bowel Disease (e.g., Crohn's disease, ulcerative colitis)
☐ Complex (Regional) Pain Syndrome
☐ Chronic Fatigue Syndrome (CFS)/Myalgic Encephalomyelitis (ME)
☐ Dementia
☐ Medically Unexplained Symptoms
☐ No, none of the conditions mentioned above

Family history

7. Have any of your first-degree relatives (i.e., parents, siblings, children) ever had the following conditions/diagnoses?
Please select all that apply.

☐ Transient Ischemic Attack/Stroke/Brain Infarction/Brain Hemorrhage
☐ Parkinson's disease
☐ Multiple Sclerosis (MS)
☐ Epilepsy
☐ Psychogenic Non-Epileptic Seizures (PNES)
☐ Depressive Disorder
☐ Hyperventilation Syndrome
☐ Anxiety Disorder
☐ Attention Deficit Hyperactivity Disorder (ADHD)/Autism Spectrum disorder (ASD)
☐ Essential Tremor
☐ Torticollis/Dystonia
☐ Fibromyalgia
☐ Irritable Bowel Syndrome (IBS)
☐ Huntington's Disease
☐ Functional Movement Disorder
☐ Complex (Regional) Pain Syndrome
☐ Chronic Fatigue Syndrome (CFS)/Myalgic Encephalomyelitis (ME)
☐ Dementia
☐ Medically Unexplained Symptoms
☐ Another Neurological Disorder, namely:

☐ No, none of the conditions mentioned above runs in my family

Onset & Temporal Course

*You are participating in this study because you will soon visit a neurologist for your problems with movement(s). You may also have other complaints, however, the questions below are **about your movement problems only**.*

8. What is the date your symptoms began (approximate)?

……(DD/MM/YYYY)

9a How did your symptoms start?

- ◯ Suddenly
- ◯ Gradually

9b. Was there a specific trigger that preceded your symptoms?

- ◯ No
- ◯ Yes, the symptoms started just after a trauma (e.g., fall, car-accident)
- ◯ Yes, the symptoms started just after an infection (e.g., flu, urinary tract infection)
- ◯ Yes, the symptoms started just after a new medicine
- ◯ Yes, the symptoms started just after anaesthesia/surgery
- ◯ Yes, the symptoms started just after a major life-event (e.g., losing a job, a death of someone close)
- ◯ Yes, the symptoms started just after a trigger that is not mentioned above, namely:

9c. Do you remember the exact moment when your symptoms first started?

- ◯ Yes
- ◯ No

9d. If yes, could you explain in your own words how your symptoms started and where you were at the time?
(150 words maximum)

10. How have your complaints progressed over time?

- ◯ The complaints have remained stable
- ◯ The complaints are getting worse
- ◯ The complaints are getting better
- ◯ The complaints fluctuate; sometimes they are there, sometimes they are not

11. How have your complaints been over the last week?

- ◯ The complaints were relatively stable
- ◯ The complaints were variable

Other Symptoms

12a. How much physical pain have you experienced during the past 4 weeks?

- ◯ None
- ◯ Very mild
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Very severe

12b. During the past 4 weeks, how much has pain interfered with your normal work (including both work outside the home and housework)?

- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Quite a bit
- ◯ Extremely

13.

Below you find 8 statements.

With these statements we hope to get a sense of how you have felt **during the last two weeks**.

13a. I feel tired.

Yes, that is true 1 2 3 4 5 6 7 No that is not true

13b.I feel physically exhausted

Yes, that is true 1 2 3 4 5 6 7 No that is not true

13c. I feel fit

Yes, that is true 1 2 3 4 5 6 7 No that is not true

13d. I feel weak

Yes, that is true 1 2 3 4 5 6 7 No that is not true

13e. I feel rested

Yes, that is true 1 2 3 4 5 6 7 No that is not true

13f. I am in bad shape

Yes, that is true 1 2 3 4 5 6 7 No that is not true

13g. I tire easily

Yes, that is true 1 2 3 4 5 6 7 No that is not true

13h. I am in good shape

Yes, that is true 1 2 3 4 5 6 7 No that is not true

14. The following questions refer to different physical symptoms or body experiences, which you may have had either briefly or over a longer period of time.

Please indicate to what extent these experiences apply to you over **the past year.** For each statement, please circle the possibility that best applies to YOU.

Sometimes:

14a. I have pain while urinating	1	2	3	4	5
14b. My body, or a part of it, is insensitive to pain	1	2	3	4	5
14c. I see things around me differently than usual (for example as if looking through a tunnel, or seeing merely a part of an object)	1	2	3	4	5
14d. It is as if my body, or a part of it, has disappeared	1	2	3	4	5
14e. I cannot speak (or only with great effort) or I can only whisper	1	2	3	4	5

15. The following questions refer to different feelings and symptoms, which you may have experienced either briefly or over a longer period of time.

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
15a. Little interest or pleasure in doing things	O	O	O	O
15b. Feeling down, depressed, or hopeless	O	O	O	O
15c. Trouble falling or staying asleep, or sleeping too much	O	O	O	O
15d. Feeling tired or having little energy	O	O	O	O
15e. Poor appetite or overeating	O	O	O	O
15f. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	O	O	O	O
15g. Trouble concentrating on things, such as reading the newspaper or watching television	O	O	O	O
15h. Moving or speaking so slowly that other people could have noticed. Or the opposite- being fidgety or restless	O	O	O	O
15i. Thoughts that you would be better off dead, or of hurting yourself in some way	O	O	O	O

16. Over the last 2 weeks, how often have you been bothered by the following problems?	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
16a. Feeling nervous, anxious or on edge	O	O	O	O
16b. Not being able to stop or control worrying	O	O	O	O
16c. Worrying too much about different things	O	O	O	O
16d. Trouble relaxing	O	O	O	O
16e. Being so restless that it is hard to sit still	O	O	O	O
16f. Becoming easily annoyed or irritable	O	O	O	O
16g. Feeling afraid as if something awful might happen	O	O	O	O

General condition

17. How would you rate the overall severity of your current movement problems?

- ◯ No problem
- ◯ Minor problem
- ◯ Mild problem
- ◯ Moderate problem
- ◯ Moderately severe problem
- ◯ Severe problem
- ◯ Very severe problem

18. How would you rate the overall disability that is caused by your problems?

- ◯ Not at all
- ◯ A little bit
- ◯ Mildly
- ◯ Moderate
- ◯ Quite a bit
- ◯ Markedly
- ◯ Extremely

19. How would you rate your quality of life?

- ◯ Very poor
- ◯ Poor
- ◯ Neither poor nor good
- ◯ Good
- ◯ Very good

Final Questions

20. Have you been seen by a neurologist in the past because of your current movement problems?

◯ Yes

◯ No

20a.
If yes, what diagnosis have you been given?
If you do not remember the name(s) of a specific diagnosis, you can also write down what the neurologist said, what he/she thought was the cause of your symptoms.

You will soon visit the neurologist who will ask and examine your complaints extensively to try to make a diagnosis.

Nevertheless, we as researchers are curious whether you already have an idea what the cause of your movement complaints could be, for example, because you know people with similar complaints or from searching the internet.

Therefore, this final question:

21. What do you think is the cause of your movement complaints, and can you explain why you think so?
Even if you are not sure, we are curious about your thoughts.
If you have no idea, you can leave this field open.

This was the last question.

Thank you for completing this survey.

If you have any additional comments, please add them here.

1. Is your 'probable diagnosis' a movement disorder?

◯ Yes

◯ No, namely:

If 'No, namely', the questionnaire stops automatically.

2. What was the key movement disorder phenotype?

◯ Tremor
◯ Myoclonus
◯ Dystonia
◯ Chorea (including ballismus)
◯ Tics
◯ Ataxia
◯ Paresis/Spasticity
◯ Hypokinetic-rigid syndrome
◯ Gait disorder (which is not better described by any of the other options)
◯ Other, namely:

3. Were there any other movement disorder phenotypes?

◯ Yes

◯ No

If yes, please specify:

☐ Tremor
☐ Myoclonus
☐ Dystonia
☐ Chorea (including ballismus)
☐ Tics
☐ Ataxia
☐ Paresis/Spasticity
☐ Hypokinetic-rigid syndrome
☐ Gait disorder (which is not better described by any of the other options)
☐ Other, namely:

4. What was your 'probable diagnosis' after the first visit?
If there was more than one diagnosis or a combination of diagnoses, please tick the most prominent diagnosis.

◯ Functional Movement Disorder

◯ Non-Functional Movement Disorder, namely:

.....

5. How confident were you in your diagnosis after the first visit?
Scale 0-100%

0% |----------|---------- **100%**

APPENDIX B

Dear colleague,

Thank you for participating in the TASMAN Study.

This is a short questionnaire about the diagnosis and the diagnostic process after the patient's first visit to your outpatient clinic.

We would like to ask you to always answer the question, even if you are not sure about it. The point is that you think a particular answer is the best of the given options, and not that it is a perfect answer for you. At the end there is opportunity for comments.

Thank you for your time and effort.

6a. Can you indicate whether the following patient factors were 'present', 'not present' or 'not asked / unknown'?

	Present	Not present	Not asked / Unknown
History of a Functional Neurological Disorder (e.g., PNES, fibromyalgia)	O	O	O
History of a Non-Functional Neurological Disorder (e.g., Parkinson's disease, stroke)	O	O	O
First-degree relative with a Functional Neurological Disorder	O	O	O
First-degree relative with a Non-Functional Neurological Disorder	O	O	O
Profession in Health Care	O	O	O
Profession in Agricultural Sector	O	O	O
Acute onset	O	O	O
Gradually onset	O	O	O
Fluctuating disease course	O	O	O
Progressive disease course	O	O	O
Cognitive symptoms	O	O	O
Depressive complaints	O	O	O
Anxiety complaints	O	O	O
Loss of sense of smell	O	O	O
Sleeping problems	O	O	O
Dissociative symptoms	O	O	O
Gastro-intestinal problems	O	O	O
Pain	O	O	O
Fatigue	O	O	O
Disability in daily functioning	O	O	O

6b. Can you indicate which of the following examination findings were 'present', 'not present' or 'not tested'

Examination	Present	Not present	Not tested
Lack of facial expression	O	O	O
Problems with saccades and pursuit	O	O	O
Hypokinesia	O	O	O
Rigidity	O	O	O
Distractibility	O	O	O
Entrainment	O	O	O
Variable resistance during manipulation ('Gegenhalten')	O	O	O
Sensory trick	O	O	O
Stimulus sensitivity	O	O	O
Sensory problems	O	O	O
Reflex problems	O	O	O
Gait disturbances	O	O	O
Incongruity with 'organic' neurological disease	O	O	O

7. In your opinion, was there, in addition to your diagnosis of a non-functional movement disorder, also a significant functional component?

◯ Yes

◯ No

7a. If yes, please specify this functional component

8. Have you requested additional tests since the patient's visit?

◯ Yes

◯ No

If yes, please specify:

☐ Laboratory investigations
☐ CT
☐ MRI
☐ Nuclear imaging
☐ Lumbar puncture
☐ EMG
☐ EEG
☐ Electrophysiological study of tremor/myoclonus
☐ Genetic testing
☐ Neuropsychological testing
☐ Other, namely

9. What did your advice and / or initiated treatment consist of?

☐ Expectative management
☐ Medication

- ☐ Botulin toxin
- ☐ Advanced therapy (e.g., DBS)
- ☐ Referral physiotherapist
- ☐ Referral psychologist
- ☐ Referral rehabilitation center
- ☐ Referral specialized center for functional neurological disorders
- ☐ Referral medical specialist, other than neurologist
- ☐ Referral to another neurologist (including second opinion)
- ☐ Other, namely: ☐

10. Considering your total clinical experience, how ill is the patient at this time?

- ◯ Normal, not at all ill
- ◯ Borderline ill
- ◯ Mildly ill
- ◯ Moderately ill
- ◯ Markedly ill
- ◯ Severely ill
- ◯ Among the most extremely ill patients

11. Considering your total clinical experience, how would you rate the patient's overall disability?

- ◯ Not at all
- ◯ A little bit
- ◯ Mildly
- ◯ Moderate
- ◯ Quite a bit
- ◯ Severely
- ◯ Extremely

12. Compared to the patient's condition at baseline, how do you estimate this patient's condition after one year?

- ◯ Very much improved
- ◯ Much improved
- ◯ Minimally improved
- ◯ No change
- ◯ Minimally worse
- ◯ Much worse
- ◯ Very much worse

This was the last question

Thank you for taking part in this survey.

If you have any additional comments, please add them here.