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ORIGINAL COMMUNICATION

Identifying diagnostic biomarkers in functional motor disorders through multimodal behavioral, neurophysiological, and imaging assessment using explainable machine learning

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Abstract

Background Functional motor disorders (FMDs) represent a frequent and disabling neurological condition. The lack of reliable diagnostic biomarkers and their heterogeneity might affect diagnosis. We identified multimodal biomarkers distinguishing FMDs from healthy controls (HCs) using machine-learning approaches.

Methods In this multicenter cross-sectional study, consecutive adults with a clinically established FMDs diagnosis ($n=75$, 74.7% female; mean age 44.20 ± 12.92) and age- and sex-matched HCs ($n=75$; 58.6% female; 48.42 ± 11.67) were recruited. All participants underwent standardized behavioral, neurophysiological, and brain MRI assessment exploring motor, exteroceptive, and interoceptive domains. A Random Forest (RF) classifier combined with repeated stratified k-fold cross-validation was trained on the collected features. Predictive performance was evaluated using accuracy, sensitivity, specificity, precision, F1-score, and AUC-ROC. SHapley Additive exPlanations interpreted feature importance.

Results The strongest diagnostic biomarkers were lower dual-task effect scores for postural sway area under eyes-closed motor and cognitive conditions, and gait speed during the motor dual-task, followed by increased vDMN and basal ganglia networks functional connectivity, reduced baseline ipsilateral–contralateral R2 blink reflex area, and higher DNIC-to-baseline N2P2 amplitude ratios for the lower limb. The RF classifier achieved robust performance (accuracy 85.0%, sensitivity 83.9%, specificity 86.1%, F1-score 85.7%, AUC-ROC 0.921).

Conclusions Motor, functional neuroimaging, and neurophysiological markers demonstrated diagnostic value in distinguishing FMDs from healthy controls, addressing the current lack of objective tools and supporting more confident and accurate diagnosis of these heterogeneous conditions.

Trial Registration Trial registration number NCT06328790. Registered on 26 March 2024.

Keywords Gait disorders · Postural balance · Pain · Functional neuroimaging · Biomarkers · Machine learning

Introduction

Functional motor disorders (FMDs) are among the most common forms of functional neurological disorders. They present with movement abnormalities that are incongruent with recognized neurological disease and frequently improve when attention is diverted (inconsistency). FMDs account for over half of functional neurological cases, with an estimated incidence of 4–12 per 100,000 individuals per year and a prevalence of about 50 per 100,000 [1, 2].

They can manifest as hypokinetic movement (weakness, bradykinesia) or as hyperkinetic movement (tremor, dystonia) involving different body regions, including the face and head, limbs, and trunk, as well as gait disorders [3, 4]. Patients with FMDs commonly experience a range of nonmotor symptoms, including fatigue, pain, anxiety, and depression, which are known to adversely affect quality of life (QoL) and increase the overall burden of the condition [5].

The pathophysiology of FMDs remains incompletely understood [2]. Neurobiological models highlight disrupted self-agency, abnormal attentional focus

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on movement, and altered expectations or beliefs about bodily function, which are shared mechanisms among the different subtype manifestations [2, 6]. From this view, symptoms may arise from altered top–down predictions that outweigh sensory evidence. It results in internally generated perceptions, which are experienced as involuntary and incongruent with intended actions [7]. This model supports the role of dysfunction in networks integrating interoception, exteroception, and motor control to drive symptom development and persistence [7].

The use of positive clinical signs, such as Hoover's sign and entrainment, has improved the diagnosis of FMDs. However, diagnostic uncertainty may last, especially when organic disease coexists. It underscores the need for objective diagnostic tools [8–10] to identify biomarkers that may support diagnosis, stratification, and treatment monitoring and then help elucidate disease mechanisms [11].

The biomarker field in FMDs remains fragmented [11]. Identifying biomarkers in FMDs may provide clinicians with objective, potentially disease-specific indicators of underlying biological dysfunction, supporting earlier diagnosis and increasing diagnostic confidence, as complementary tools alongside positive clinical signs. A recent systematic review found that although neurophysiological markers for functional myoclonus and tremor are promising, most candidate biomarkers lack validation and generalizability across phenotypes [11]. Evidence in patients with functional weakness, gait, and balance impairment is still preliminary. Reliable markers for other phenotypes, such as functional dystonia and tics, are lacking [11]. In addition, most studies involve small samples, particularly those involving neuroimaging, and use single-domain approaches, limiting reproducibility and comparability [11]. Finally, advanced computational methods, including multimodal machine-learning approaches, have rarely been applied [11, 12].

To address these limitations, studies are needed that examine large, well-characterized cohorts using comprehensive motor neurophysiological and imaging measures that capture motor, interoceptive, and exteroceptive functions. Integrating these data using modern analytical approaches may help identify reliable mechanistic signatures and accelerate translation into clinical practice.

The objective of this study was to develop a biomarker-informed diagnostic algorithm for FMDs by integrating motor, neurophysiological, and MRI measures. We hypothesized that integrating motor, neurophysiological, and neuroimaging biomarkers through machine-learning methods can reliably distinguish FMDs from healthy controls, addressing the need for objective, mechanistic, and informed diagnostic tools.

Methods

A multicenter cross-sectional study was performed. Participants were recruited from three tertiary Movement Disorders Centers in Italy: the Neurological Unit B of the AOUI (Verona), the Neurological Clinic of AOU San Giovanni di Dio e Ruggi d'Aragona (Salerno), and the Neuroimaging Research Unit of the Division of Neuroscience at IRCCS San Raffaele Scientific Institute (Milan). The study was supported by the European Union–Next Generation EU–NRRP M6C2–Investment 2.1 Enhancement and strengthening of biomedical research in the NHS (PNRR-MAD-2022-12376826; CUP Master: E33C22001030006) [13].

Study participants

Adults with a clinically definite diagnosis of FMDs, established according to the Gupta and Lang diagnostic criteria [14] and healthy controls (HCs) were recruited at the Neurological Unit B of the AOUI (Verona) and at the Neurological Clinic, AOU San Giovanni di Dio e Ruggi d'Aragona (Salerno) between March 2023 and November 2024. Shared eligibility criteria across the participating centers were adopted [13]. All participants were required to be at least 18 years old and to have a Mini-Mental State Examination score of 24/30 or higher. Exclusion criteria were the presence of physical conditions preventing the informed consent provision, certified neurological or psychiatric comorbidities (e.g., neuropathy, seizures, or major depression, autism, ADHD), and contraindications to 3 T MRI scanning.

Clinical assessment

Demographic and clinical information, including age and gender, disease duration, and symptom phenotype, were prospectively collected according to the study protocol [13] following the General Data Protection Regulation. In the FMDs' group, motor symptom severity was rated using the Simplified Functional Movement Disorders Rating Scale (S-FMDRS, score range 0–54, higher scores indicate greater motor impairment) [15]. Non-motor symptoms were assessed through validated assessments in all participants. Fatigue was scored using the Multidimensional Fatigue Inventory (MFI-20), with subscale scores ranging from 4 to 20; higher scores indicate greater fatigue. Pain was evaluated with the Brief Pain Inventory (BPI; severity and interference subscales, each ranging from 0 to 10, with higher values indicating greater pain burden). Psychological symptoms assessment included the Beck Anxiety Inventory (BAI), which ranges from 0 to 63, and the Beck Depression

Inventory (BDI-II), which ranges from 0 to 63 (higher scores indicating more severe symptoms). Alexithymia was assessed using the Toronto Alexithymia Scale (TAS-20; range 20–100), with higher scores indicating greater impairment in identifying and describing emotions. Health-related quality of life was assessed with the 12-item Short-Form Health Survey (SF-12), which provides mental and physical health component scores ranging from 0 to 60, with higher scores indicating better perceived health status [16–21]. A detailed description of the collected demographic and clinical variables is provided in the study protocol [13]. Participants underwent a comprehensive instrumental evaluation, including motor, neurophysiological, and MRI assessments to explore motor, exteroceptive, and interoceptive functions. The same standardized procedures were applied across all participating centers, as detailed below.

Biomarker development in the motor domain

The motor domain was investigated through assessment of blink reflex responses along with instrumental analyses of gait and postural stability.

Blink Reflex was evaluated through the supraorbital branch of the trigeminal nerve, using electrical stimulation by surface electrodes on the supraorbital notch. Rectified electromyographic (EMG) activity was bilaterally recorded from the orbicularis oculi muscles. Electrical stimuli were provided by square-wave pulses (duration: 0.2 ms; intensity: supramaximal). Inter-stimulus intervals varied randomly to reduce habituation effects. For each trial, the R2 component was identified, and the area under the ipsilateral response curve was calculated and averaged across repetitions. Baseline R2 areas were measured for both the ipsilateral and contralateral responses. A single summary index was then obtained by averaging the two values, as previously described in the literature [22]

$$\text{Average} = \frac{\text{Area ipsilateral} + \text{Area controlateral}}{2}.$$

Gait and postural control were assessed under both single-task and dual-task conditions using an electronic spatiotemporal gait analysis system and stabilometric platform [23, 24]. During the motor dual-task, participants performed repetitive pronation–supination movements with the dominant hand. In the cognitive dual-task condition, they were asked to perform serial subtractions of 7 starting from 100. During the visual dual-task, participants maintained fixation on a target positioned at eye level. Spatial–temporal gait analysis consisted of walking at the self-selected speed for 10 m using instrumental gait analysis.

Postural control testing was conducted, while participants stood on a firm surface without upper-limb support. Foot position was standardized as described in the study protocol [23]. Postural measurements were performed under single-task, motor dual-task, and cognitive dual-task conditions as above mentioned, both with eyes-open (EO) and eyes-closed (EC) [23]. The primary stabilometric parameters included sway area (mm2) and center-of-pressure (CoP) sway perimeter (mm), which represent quantitative indicators of postural stability.

For gait analysis, the parameters of interest included step length and walking speed as spatial and temporal gait performance, and stride time variability as an indicator of gait automaticity [24].

To quantify the impact of dual-tasking, the Dual-Task Effect (DTE) was calculated as the percentage change between dual-task and single-task performance using the following formula [25]:

$$\text{DTE}(\%) = \frac{\text{Dual task performance} - \text{Single task performance}}{\text{Single task performance}} \times 100.$$

Biomarker development in the exteroceptive domain

Exteroceptive processing was investigated using sensory attenuation (SA), tonic vibration reflex (TVR), and laser-evoked potentials (LEPs) [26–29].

SA, reflecting predictive sensorimotor integration during voluntary action, was quantified as the ratio of the participant's matched force to the externally applied target force. This ratio was used as a behavioral biomarker of sensorimotor predictive control [13].

Proprioceptive perception was evaluated using the tonic vibration reflex (TVR) protocol. The angular displacement of the vibrated arm, representing the magnitude of the reflex-induced movement, and the angular position of the contralateral tracking arm, reflecting the participant's conscious perception of limb position, were derived as behavioral indices [27].

Proprioceptive accuracy was estimated by calculating the average angular difference between the vibrated arm and the tracking arm across trials, defined as the proprioceptive error [13].

Nociceptive processing was evaluated using laser-evoked potentials (LEPs), which provide a non-invasive measure of cortical responses to nociceptive stimulation [29, 30]. LEPs were recorded, while participants directed their attention either toward or away from the stimulated hand during a conditioned pain modulation paradigm designed to investigate the diffuse noxious inhibitory control (DNIC) system [29].

Noxious stimuli were delivered using a Nd:YAP laser stimulator (wavelength 1.34 μm, beam diameter 5 mm, pulse duration 5 ms) to the dorsum of the right hand and foot. After each pulse, the stimulation site was slightly moved

to avoid nociceptor sensitization or fatigue. Stimulus intensity was personalized to the participant's pain threshold, set at 4 on an 11-point numerical rating scale (0 = no pain; 10 = worst imaginable pain). During the recordings, the individual's pain threshold remained constant throughout the session, with stimulation intensity set at 1.5 times the individual's pain threshold. A total of 25–30 stimuli were delivered with inter-stimulus intervals ranging from 20 to 30 s. Electroencephalographic (EEG) signals were recorded using Ag/AgCl surface electrodes positioned at Cz and Fz (referenced to the nose) and at T3 referenced to Fz according to the international 10–20 system. LEPs components were identified based on polarity and latency, focusing on the vertex N2–P2 complex and the lateralized N1 component [29].

Recording was obtained in three experimental conditions: baseline, during heterotopic noxious conditioning stimulation (DNIC), and after the DNIC protocol [29]. During the DNIC condition, participants immersed their left foot distal to the ankle joint into an ice-water bath at approximately 0 °C. The N2/P2 amplitude was used as the primary biomarker [13, 29]. To evaluate modulation relative to baseline, ratios between experimental conditions and baseline were calculated separately for upper and lower limbs [29] according to the following formula:

$$\text{Ratio} = \frac{\text{Specific condition}}{\text{Baseline condition}}.$$

Biomarker development in the interoceptive domain

Interoceptive processing was assessed using the Heartbeat Perception Task (HPT), which evaluates the ability to detect internal bodily signals generated by the Central Nervous System [31]. This paradigm provides an indirect measure of the accuracy with which individuals perceive their own heartbeats. Within the predictive-processing framework, we hypothesized that individuals with FMDs might show a mismatch between objectively recorded heart rate and the subjectively perceived heartbeat count. Accordingly, the ratio between objective and perceived heart rate was calculated and used as a biomarker reflecting interoceptive processing accuracy [13].

Biomarker in the cerebral domain

Brain MRI examination was performed using a 3 Tesla scanner, including structural and functional sequences.

Structural imaging included T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences to exclude relevant CNS lesions, and a three-dimensional (3D) T1-weighted acquisition for morphometric analysis of gray matter volumes. Resting-state functional MRI (Rs-fMRI) investigated functional connectivity (FC) within sensorimotor and non-motor brain networks [1–3, 32–34]. Established neuroimaging pipelines were used for image preprocessing and analysis. Resting-state functional connectivity (RS-FC) was evaluated using independent component analysis (MELODIC; Multivariate Exploratory Linear Optimized Decomposition into Independent Components) within the FMRIB Software Library (FSL, version 5.0). Regional gray matter volumes were evaluated using FMRIB's Integrated Registration and Segmentation Tool in FSL. The following deep gray matter structures were included in the analysis: nucleus caudate, globus pallidus, putamen, thalamus, nucleus accumbens, amygdala, and hippocampus bilaterally. In addition, cerebellar gray matter volumes were assessed using the SUIT toolbox in SPM12 (http://www.fil.ion.ucl.ac.uk/spm, Wellcome Trust Center for Neuroimaging, London).

For the RS-FC analysis, regions of interest from the Automated Anatomical Labeling (AAL) atlas overlapping with clusters showing significant group differences were identified (Fig. 1A). Mean functional connectivity values from these regions were subsequently extracted and included in the machine-learning analysis's feature selection step. The MRI acquisition parameters and preprocessing details are in the Supplementary material.

Statistical analysis

Conventional statistical methods were used as initial analyses to examine differences between FMDs vs HCs in demographic and clinical data, as well as in behavioral, neurophysiological, and imaging variables. Analysis of covariance (ANCOVA), with age and gender as covariates, was used to analyze continuous variables between groups. Categorical variables differences were compared using the Chi-square (χ^2) test. The effect size for group comparisons was quantified using Cohen's d (Software statistics SPSS—v.30).

Artificial intelligence analysis

Machine Learning (ML) methods identified potential biomarkers to distinguish patients with FMDs from HCs. The ML workflow included gait-related and postural dual-task effects, FC parameters, mean proprioceptive error, neurophysiological indices, and the average ipsi-contralateral R2 area from the blink reflex.

Classification was implemented by using a Random Forest (RF) [35] classifier. To ensure balanced class distribution within folds and to obtain robust estimates of generalization performance, model performance was evaluated using a repeated stratified k-fold cross-validation ($k = 5$, repeated five times). This method splits the dataset into k subsets (folds) with balanced class proportions (stratification). The training

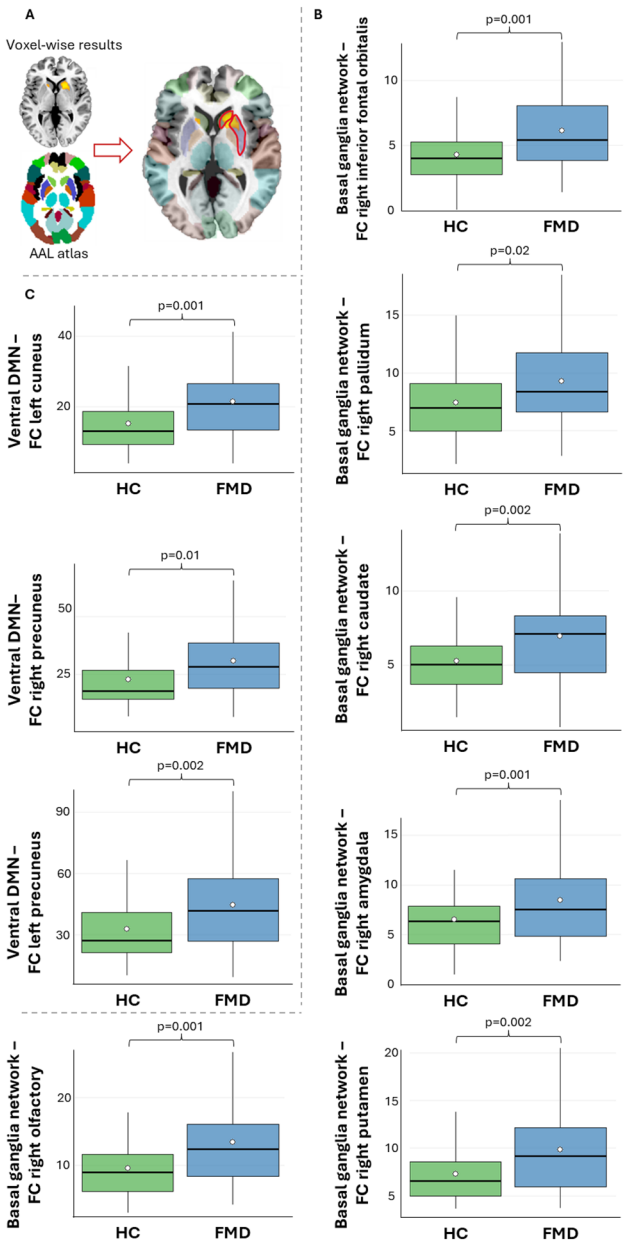

Fig. 1 Resting-state fMRI analysis and results. **A** Spatial overlap between clusters identified by the voxel-wise analysis and regions from the AAL atlas used for feature extraction. **B** Regions showing increased FC within the basal ganglia network in patients with FMDs relative to HCs. **C** regions exhibiting increased FC within the ventral default mode network in the FMDs group relative to HCs. *p* values were derived from ANCOVA models adjusted for age and gender. *FC* functional connectivity, *FMDs* functional movement disorder, *HCs* healthy controls, *DMN* default mode network

and testing process was repeated many times with different fold combinations (repetition) to reduce variability caused by data partitioning and provide more reliable estimates of the model's generalization ability [36]. Sensitivity, specificity, precision, accuracy, balanced accuracy, F1-score, and the area under the receiver-operating characteristic curve (AUC-ROC) were used to evaluate model performance [37]. In particular, the AUC-ROC provides a qualitative indicator for binary classification (score range: 0–1), with a score of 0.5 indicating classification no better than random guessing. Sensitivity and specificity, respectively, quantified the model's ability to predict positive classifications correctly. The overall proportion of correct predictions was reflected by accuracy. The following formulas were used:

Specificity:

$$Sp = \frac{\mathrm{TN}}{\mathrm{TN}+\mathrm{FP}}(\%).$$

Sensitivity:

$$Se = \frac{\mathrm{TP}}{\mathrm{TP}+\mathrm{FN}}(\%).$$

Precision:

$$Pr = \frac{\mathrm{TP}}{\mathrm{TP}+\mathrm{FP}}(\%).$$

Accuracy:

$$Ac = \frac{\mathrm{TP}+\mathrm{TN}}{\mathrm{TN}+\mathrm{FP}+\mathrm{FN}+\mathrm{TP}}(\%).$$

Balanced accuracy:

$$Ac = \frac{1}{2}\left(\frac{\mathrm{TP}}{\mathrm{TP}+\mathrm{FN}}+\frac{\mathrm{TN}}{\mathrm{TN}+\mathrm{FP}}\right)(\%).$$

TP, TN, FN, and FP identify true positives, true negatives, false positives, and false negatives, respectively.

A feature selection procedure was incorporated within the cross-validation framework to identify the subset of variables that best improved model accuracy and to prevent information leakage between training and test sets. Hyperparameter tuning was also performed within the cross-validation framework to optimize model performance and mitigate risks of underfitting or overfitting.

To improve the interpretability of the model, explainable artificial intelligence (XAI) techniques were applied using SHapley Additive exPlanations (SHAP). SHAP values were used to quantify the contribution of individual biomarkers to the classification output, allowing identification of the most informative biomarkers and their directional influence on the classification of FMDs versus HCs. Both global (overall feature importance) and local (sample-specific) interpretability were generated.

Results

Study participants

The study included 150 participants, divided into 75 FMDs and 75 HCs. Of 75 FMDs, 56 [74.7%] were female; mean age 44.5 ± 12.87 years; 19 [25.3%] were male; mean age 43.6 ± 13.4 years). Among 75 HCs, 44 [58.6%] were female; mean age 48.62 ± 10.99 years; 31 [41.3%] were male; mean age 48.13 ± 12.80 years). No between-group significant differences were observed for age ($p = 0.078$) and gender ($p = 0.058$). The phenotypic distribution of the FMDs cohort is reported in Supplementary Table 1.

Proposed diagnostic biomarkers

Statistical analysis results

Preliminary analyses excluded stride time variability due to high variability across participants and the SA ratio due to missing data in more than 10% of patients. The baseline R2 area of the blink reflex was retained, as post-stimulation values differed substantially between the two laboratories, precluding valid inter-site comparisons.

Table 1 shows the statistical analysis results. FMDs were characterized by a mean S-FMDRS score of 17.21 ± 9.24. Compared to HCs, FMDs exhibited greater psychological distress and reduced QoL. They had higher TAS-20 Total Score (48.41 ± 15.09 vs. 39.99 ± 9.73; $p = 0.001$; $d = 0.65$), higher anxiety levels on the BAI Total Score (19.85 ± 10.02 vs. 8.36 ± 7.44; $p < 0.001$; $d > 1$), and higher depressive symptoms assessed on the BDI-II Total Score (12.62 ± 9.64 vs. 5.91 ± 5.56; $p < 0.001$; $d = 0.85$). QoL was lower in FMDs in both the physical component (33.09 ± 9.39 vs. 51.54 ± 8.79; $p < 0.001$; $d > 1$) and the mental component (43.39 ± 12.01 vs. 48.51 ± 9.65; $p = 0.017$; $d = 0.5$). Fatigue levels were also higher in FMDs, as shown by the MFI Total Score, than in HCs (64.14 ± 16.67 vs. 43.73 ± 14.38; $p < 0.001$; $d > 1$). Moreover, pain levels were higher in FMDs, as shown by BPI subscores higher than those of HCs ($p < 0.001$, $d > 0.8$).

Proprioceptive performance was impaired in FMDs, who showed a higher mean proprioceptive error than HCs (1.84 ± 6.74 vs –0.13 ± 5.54; $p = 0.030$; $d \approx 0.5$). Interoceptive functioning did not differ between groups.

Reduced brainstem excitability in the FMDs group was revealed by Blink Reflex analysis. Significantly lower ipsilateral (1.10 ± 0.57 vs 1.27 ± 0.51; $p = 0.002$) and contralateral (0.93 ± 0.50 vs 1.07 ± 0.52; $p = 0.042$) baseline R2 areas were found in FMDs compared to HCs. In the FMDs group, a reduction of the averaged R2 area across both sides was measured (1.02 ± 0.53 vs 1.17 ± 0.51; $p = 0.006$; $d \approx 0.4$) [22].

LEPs showed no between-group differences in baseline or modulation amplitudes (during and post-protocol) for either limb in laser-evoked N2P2 potentials. However, FMDs showed a higher DNIC/Baseline N2P2 ratio in the lower limb, compared to HCs (0.93 ± 0.27 vs 0.84 ± 0.16; $p = 0.010$; $d \approx 0.4$).

Gait performance was poorer in the FMDs group across all experimental conditions than in HCs. In the single-task, FMDs showed reduced step length and slower gait speed (both $p < 0.001$). During the motor dual-task, these deficits further increased ($p < 0.001$). In contrast, a more negative dual-task effect (DTEs) for step length (–5.22 ± 2.23% vs –2.38 ± 1.76%) and speed (–12.30 ± 2.09% vs –3.60 ± 1.60%; both $p < 0.001$) was measured in FMDs, demonstrating a higher dual-tasking interference effect in FMDs than HCs.

Similarly, during the cognitive dual-task, gait impairments deteriorated in FMDs, but the DTE effect (step length DTE –6.08 ± 2.32%; speed DTE –16.40 ± 2.26%) was more negative in FMDs than in HCs.

In the visual dual-task, gait parameters remained significantly lower in FMDs than HCs ($p < 0.001$), with DTE values for step length (2.17 ± 2.10%) and gait speed (1.06 ± 2.71%) closer to zero, possibly reflecting reliance on visual cues.

This pattern may indicate that the visual task imposed a lower cognitive load, possibly due to an external attentional focus that enhanced gait performance and partially mitigated performance decrements. The magnitude of the group differences was consistent with moderate-to-large effects, as indicated by Cohen's d values ≥ 0.5.

Postural control was also impaired in FMDs. Under the single-task condition, sway was greater in FMDs than HCs in both eyes-open (EO: area 285.83 ± 179.04 vs 201.10 ± 130.36 mm^2, $p < 0.001$; perimeter 349.06 ± 199.28 vs 284.99 ± 113.25 mm, $p = 0.005$) and eyes-closed (EC: area 1039.72 ± 829.45 vs 415.04 ± 278.18 mm^2, $p < 0.001$; perimeter 663.00 ± 351.00 vs 491.19 ± 197.54 mm, $p < 0.001$) conditions.

Under the motor dual-task, FMDs had a larger sway area than HCs, both with EO (FMDs: 306.59 ± 147.39 mm^2; HCs: 248.67 ± 119.53 mm^2; $p = 0.004$) and EC (FMDs: 783.71 ± 562.18 mm^2; HCs: 472.16 ± 256.39 mm^2; $p < 0.001$). Under the cognitive dual-task condition, they continued to exhibit poorer postural stability. During EO, the area was higher in FMDs (322.42 ± 163.22 mm^2) than in controls (256.79 ± 210.50 mm^2, $p < 0.001$), and the perimeter was also increased (434.87 ± 162.62 mm vs. 346.02 ± 129.84 mm, $p < 0.001$). Likewise, EC area (492.78 ± 290.45 mm^2 vs. 354.95 ± 269.60 mm^2, $p < 0.001$) and perimeter (565.54 ± 217.25 mm vs. 450.31 ± 158.43 mm, $p < 0.001$) were significantly larger

Table 1 Comparison between individuals with functional movement disorder (FMDs) and healthy controls (HCs)

Variables	FMDs ($n=75$)	HCs ($n=75$)	p value
Clinical–demographical			
Age (years)	44.20 ± 12.92	48.42 ± 11.67	0.078
Gender (F/M)	56/19	44/31	0.057
TAS-20	48.41 ± 15.09	39.99 ± 9.73	0.001*
BAI	19.85 ± 10.02	8.36 ± 7.44	< 0.001*
BDI	12.62 ± 9.64	5.91 ± 5.56	< 0.001*
SF-12 physical	33.09 ± 9.39	51.54 ± 8.79	< 0.001*
SF-12 mental	43.39 ± 12.01	48.51 ± 9.65	0.017*
MFI-total score	64.14 ± 16.67	43.73 ± 14.38	< 0.001*
BPI worse pain	5.65 ± 3.80	1.49 ± 2.66	< 0.001*
BPI slight pain	2.43 ± 2.96	0.65 ± 1.42	< 0.001*
BPI mean pain	4.19 ± 3.25	1.19 ± 2.28	< 0.001*
BPI now pain	3.49 ± 3.36	0.65 ± 1.55	< 0.001*
BPI interference general	4.27 ± 3.83	1.00 ± 2.33	< 0.001*
BPI interference mood	3.08 ± 3.60	1.12 ± 2.50	< 0.001*
BPI interference walking ability	4.07 ± 3.80	0.78 ± 2.09	< 0.001*
BPI interference work	3.92 ± 3.72	0.70 ± 1.92	< 0.001*
BPI interference relations with other people	2.35 ± 3.28	0.40 ± 1.44	< 0.001*
BPI interference sleep	3.33 ± 3.81	0.75 ± 2.09	< 0.001*
BPI interference enjoyment of life	2.41 ± 3.51	0.55 ± 1.55	< 0.001*
Mean interference BPI	3.35 ± 2.89	0.75 ± 1.72	< 0.001*
S-FMDRS total score	17.21 ± 9.24	–	Not Applicable
Interoception			
Accuracy mean	0.43 ± 0.29	0.45 ± 0.29	0.854
Confidence mean	5.59 ± 2.55	5.49 ± 2.47	0.768
Ratio accuracy/confidence mean	13.00 ± 8.79	12.2 ± 8.52	0.786
Exteroception			
Mean proprioceptive error	1.84 ± 6.74	−0.13 ± 5.54	0.030*
Motor			
Blink reflex			
Ipsilateral baseline R2 area	1.10 ± 0.57	1.27 ± 0.51	0.002*
Contralateral baseline R2 area	0.93 ± 0.50	1.07 ± 0.52	0.042*
Average ipsi-contralateral R2 area	1.02 ± 0.53	1.17 ± 0.51	0.006*
Laser evocated potential			
Upper limb baseline amp N2P2	35.52 ± 14.60	28.09 ± 9.82	0.067
Upper limb DNIC amp N2P2	27.32 ± 14.14	23.30 ± 9.82	0.157
Upper limb post amp N2P2	29.94 ± 9.49	27.24 ± 9.42	0.485
Ratio DNIC/baseline amp N2P2	0.86 ± 0.26	0.85 ± 0.21	0.350
Ratio post-DNIC/baseline amp N2P2	0.95 ± 0.32	0.99 ± 0.21	0.321
Lower limb baseline amp N2P2	28.29 ± 12.35	26.54 ± 10.24	0.316
Lower limb DNIC amp N2P2	24.47 ± 12.69	22.20 ± 11.50	0.165
Lower limb post-DNIC amp N2P2	25.42 ± 10.12	24.83 ± 7.70	0.810
Ratio DNIC/baseline amp N2P2	0.93 ± 0.27	0.84 ± 0.16	0.010*
Ratio post-DNIC/baseline amp N2P2	0.92 ± 0.16	0.95 ± 0.15	0.113
Gait analysis			
Single task			
Step length (m)	1.15 ± 0.26	1.26 ± 0.13	< 0.001*
Speed (m/s)	0.94 ± 0.27	1.10 ± 0.15	< 0.001*
Motor dual-task			
Step length (m)	1.09 ± 0.24	1.23 ± 0.12	< 0.001*

Table 1 (continued)

Variables	FMDs ($n=75$)	HCs ($n=75$)	p value
Speed (m/s)	0.83 ± 0.24	1.07 ± 0.14	< 0.001*
DTE step length (%)	−5.22 (2.23)	−2.38 (1.76)	< 0.001*
DTE speed (%)	−12.30 (2.09)	−3.60 (1.60)	< 0.001*
Cognitive dual-task			
Step length (m)	1.08 ± 0.27	1.20 ± 0.12	< 0.001*
Speed (m/s)	0.79 ± 0.22	0.99 ± 0.15	< 0.001*
DTE step length (%)	−6.08 (2.32)	−4.76 (1.11)	< 0.001*
DTE speed (%)	−16.4 (2.26)	−9.92 (1.41)	< 0.001*
Visual dual-task			
Step length (m)	1.14 ± 0.22	1.31 ± 0.11	< 0.001*
Speed (m/s)	0.93 ± 0.24	1.19 ± 0.15	< 0.001*
DTE step length (%)	2.17 (2.10)	3.96 (2.61)	< 0.001*
DTE speed (%)	1.06 (2.71)	2.90 (2.56)	< 0.001*
Postural control			
Single task			
EO area (mm^2)	285.83 ± 179.04	201.10 ± 130.36	< 0.001*
EO perimeter (mm)	349.06 ± 199.28	284.99 ± 113.25	0.005*
EC area (mm^2)	1039.72 ± 829.45	415.04 ± 278.18	< 0.001*
EC perimeter (mm)	663.00 ± 351.00	491.19 ± 197.54	< 0.001*
Motor dual-task			
EO area (mm^2)	306.59 ± 147.39	248.67 ± 119.53	0.004*
EO perimeter (mm)	547.81 ± 235.39	518.60 ± 190.79	0.875
EC area (mm^2)	783.71 ± 562.18	472.16 ± 256.39	< 0.001*
EC perimeter (mm)	846.82 ± 445.93	705.44 ± 281.79	0.010*
DTE EO area	15.17 (4.88)	18.65 (4.37)	0.687
DTE EO perimeter	56.04 (3.82)	73.62 (6.04)	0.985
DTE EC area	−16.67 (3.82)	16.92 (4.21)	< 0.001
DTE EC perimeter	28.38 (3.75)	43.36 (4.67)	0.875
Cognitive dual-task			
EO area (mm^2)	322.42 ± 163.22	256.79 ± 210.50	< 0.001*
EO perimeter (mm)	434.87 ± 182.62	346.02 ± 129.84	< 0.001*
EC area (mm^2)	492.78 ± 290.45	354.95 ± 269.60	< 0.001*
EC perimeter (mm)	565.54 ± 217.25	450.31 ± 158.43	< 0.001*
DTE EO area	14.76 (5.73)	15.73 (5.74)	0.654
DTE EO perimeter	25.71 (3.29)	21.42 (3.05)	0.367
DTE EC area	−34.02 (4.82)	−21.10 (3.60)	< 0.001*
DTE EC perimeter	−6.01 (3.87)	−2.87 (2.74)	0.957

F female, *M* male, *S-FMDRS* Simplified Functional Movement Disorders Rating Scale, *MFI-20* Multidimensional Fatigue Inventory scale, *BPI* Brief Pain Inventory, *SF-12* 12-Item Short-Form Health survey, *BAI* Beck Anxiety Inventory, *BDI-II* Beck Depression Inventory-II, *TAS-20* Toronto Alexithymia Scale, *Amp* amplitude, *DTE* dual-task effect, *EO* eyes-open condition, *EC* eyes-closed condition

[a]Statistical significance

in FMDs. Overall, these between-group differences were associated with moderate-to-large effect sizes ($d \geq 0.5$).

In the motor dual-task condition, no differences emerged in the DTE-EO area, the DTE-EO perimeter, or the DTE-EC perimeter. However, the DTE-EC area was significantly lower in FMDs (–16.67 ± 3.82% vs 16.92 ± 4.21%; $p < 0.001$), as was the cognitive DTE (–34.02 ± 4.82% vs –21.10 ± 3.60%; $p < 0.001$).

Exploratory subgroup analyses comparing gait and stabilometric parameters between HCs and FMDs patients without a gait phenotype, as well as between FMDs patients with and without a gait phenotype, are reported in

Supplementary Tables 2–5 to examine whether gait abnormalities were also present in patients without a clinically defined gait phenotype. Objective gait and stabilometric abnormalities were present in FMDs patients, even in the absence of a clinically defined gait phenotype, though more pronounced in those with overt gait disorders.

Structural MRI analyses indicated higher cerebellar volumes (mm^3) in FMDs compared to HCs, involving the following areas: vermis Crus II (531.76 ± 57.69 vs. 504.36 ± 56.21, $p = 0.019$), left lobule VIIIa (7601.63 ± 719.04 vs. 7188.28 ± 850.92, $p = 0.014$), vermis VIIIa (1670.84 ± 164.57 vs. 1579.86 ± 176.00, $p = 0.018$), left lobule VIIIb (6135.44 ± 567.58 vs. 5798.72 ± 667.10, $p = 0.011$), and vermis VIIIb (809.08 ± 52.82 vs. 771.43 ± 66.81, $p = 0.018$) (Supplementary Fig. 1). No significant group differences emerged in the volumes of deep gray matter structures.

FC analyses showed greater connectivity in individuals with FMDs within the basal ganglia (BG) network. In particular, increased FC was detected in the anterior part of right amygdala ($p = 0.023$), right caudate nucleus ($p = 0.002$), right pallidum ($p = 0.018$), the mesial part of right inferior frontal gyrus (pars orbitalis; $p < 0.001$), the right olfactory cortex ($p = 0.001$), and the right putamen ($p = 0.002$) compared to HCs (Fig. 1B).

Within the default mode network (DMN), patients with FMDs also showed higher connectivity than HCs in the left cuneus ($p = 0.001$), left precuneus ($p = 0.002$), and right precuneus ($p = 0.008$) (Fig. 1C). The magnitude of these group differences corresponded to moderate-to-large effect sizes (Cohen's $d \geq 0.6$).

Model performance and explainable AI analysis

The most informative predictors were the DTE × sway area under EC motor and cognitive tasks; the DTE × gait speed in the motor task; FC parameters within the vDMN (left cuneus and right precuneus) and the BG network (right caudate nucleus, right inferior frontal gyrus–orbital part, and right olfactory cortex), the lower limb DNIC and baseline N2P2 amplitude ratio, and the average ipsilateral–contralateral R2 area.

Using a balanced dataset (75 FMDs vs 75 HCs), the RF classifier demonstrated robust discrimination between FMDs and HCs (Table 2), with cross-validation to ensure generalizability. The model achieved an average standard of 85.0% (SD = 0.08) and a balanced accuracy of 84.8% (SD = 0.10). This indicates that the classifier correctly identifies class labels in most cases. Comparable values were found for specificity (86.1%, SD = 0.12) and sensitivity (83.9%, SD = 0.12), indicating balanced ability to identify both FMDs and HCs correctly. The lack of overfitting toward one class (e.g., favoring controls) is particularly relevant in clinical applications, as it could lead to misleading diagnostic conclusions. The F1-score (85.7%, SD = 0.08) confirmed stable predictive performance.

Table 2 Metrics evaluation of the classifier

Evaluation metric (%)	Mean (SD) on all folders
Accuracy (%)	85.0 (0.08)
Balanced accuracy (%)	84.8 (0.10)
Specificity (%)	86.1 (0.12)
Sensitivity (%)	83.9 (0.12)
F1-score (%)	85.7 (0.08)
AUC-ROC	0.921

% percentage, *SD* standard deviation, *AUC-ROC area under the receiver-operating characteristic curve*

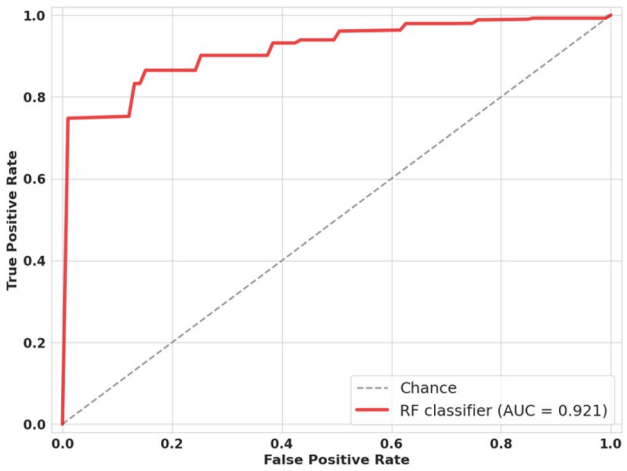

Fig. 2 Performance of the Random Forest (RF) classifier in discriminating patients with functional movement disorders (FMDs) from healthy controls (HCs). *RF* Random Forest, *AUC-ROC* area under the receiver-operating characteristic curve

The model achieved an AUC-ROC of 0.921 (Fig. 2), indicating excellent discriminative performance. This result implies that, in 92.1% of cases, the classifier assigns a higher probability of belonging to the FMD group to a randomly selected patient than to a randomly selected HC. These findings confirm that the extracted features and the model jointly capture discriminant patterns to differentiate between FMDs and HCs.

The SHAP bar plot (Fig. 3) displays the relative importance of each feature, ordered by the mean absolute SHAP value reflecting its influence on the model's predictive output.

Figure 4 presents the SHAP summary plot (Fig. 4), highlighting the influence of each feature on the model output. Higher (positive) SHAP values (red) increased the likelihood of FMDs classification, while lower (blue)

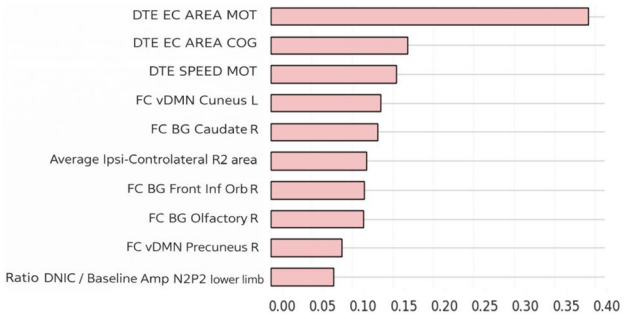

Fig. 3 Top ten features contributing to the classification model. The bar plot shows the relative importance of each feature in distinguishing between groups, as determined by the model. *DTE* dual-task effect, *EC* eyes-closed condition, *MOT* motor condition, *COG* cognitive condition, *FC* functional connectivity, vDMN ventral default mode network, BG basal ganglia, *Front Inf Orb* orbital part of inferior frontal gyrus, *DNIC* diffuse noxious inhibitory system, *Amp* amplitude, *L* left, *R* right

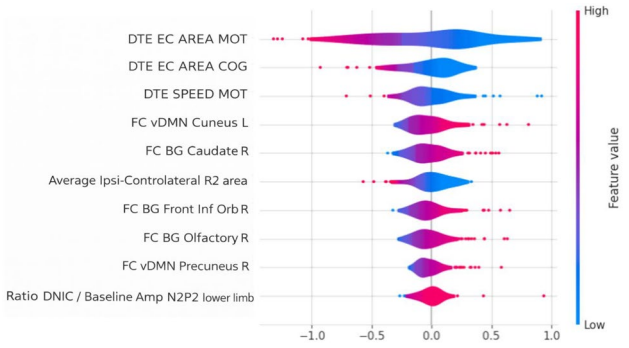

Fig. 4 SHAP summary plot showing the contribution of the top ten features to the model output. Each dot represents an individual sample, color-coded by feature values (red/blue). Positive SHAP values increase the likelihood of FMDs classification, and negative values increase the likelihood of HCs classification. *DTE* dual-task effect, *EC* eyes-closed condition, *MOT* motor condition, *COG* cognitive condition, *FC* functional connectivity, *vDMN* ventral default mode network, *BG* basal ganglia, *Front Inf Orb* orbital part of inferior frontal gyrus, *DNIC* diffuse noxious inhibitory system, *Amp* amplitude, *L* left, *R* right; red color indicates higher values; blue color indicates low values

values favor classification as HCs. Lower DTE × sway area values under eyes-closed motor and cognitive conditions, lower DTE × gait speed values during the motor task, increased FC within the vDMN and basal ganglia networks, lower baseline ipsilateral–contralateral R2 area values, higher functional connectivity within frontal and olfactory basal ganglia regions, and a higher DNIC-to-baseline N2P2 amplitude ratio for the lower limb were all associated with a greater likelihood of classification as FMDs relative to healthy controls.

Discussion

This study identified a multimodal set of motor, neurophysiological, and connectivity biomarkers that distinguishes individuals with FMDs from HCs. Gait and postural dual-task measures emerged as the strongest diagnostic biomarkers, with lower dual-task interference effects (DTE) for sway area under eyes-closed motor and cognitive conditions, and lower DTE values for gait speed during the motor dual-task. These results indicate that in FMDs, the performance improvements occur when attentional demands are diverted away from motor control [23, 24, 38]. At the network level, greater FC within the vDMN and basal ganglia networks, enhanced connectivity in frontal and orbitofrontal regions, and added discriminative power to the model [39]. Neurophysiological biomarkers included reduced blink reflex excitability and impaired nociceptive modulation at the spinal level, as evidenced by reduced baseline ipsilateral-contralateral R2 blink reflexes and higher DNIC-to-baseline N2P2 amplitude ratios (in the lower limb), respectively [40].

This panel of multimodal diagnostic biomarkers is consistent with the neurobiological framework of FMDs' pathogenesis, in which top–down regulation is disrupted, and thus provides a unifying explanation for impaired motor automaticity, abnormal reflex modulation, and altered sensory–motor integration [2, 41].

DTE measures emerged as the primary diagnostic component of clinical motor assessment, extending previous literature on the role of both motor and cognitive dual-tasking in postural control and visual fixation during gait in a larger sample using robust analytic methods [23, 24, 38].

Initial evidence for the relevance of dual-task paradigms in functional gait disorders was provided by an early cross-sectional study involving 29 individuals that examined the impact of dual-tasking on selected spatiotemporal gait measures. The analyzed measures included gait speed and stride length, reflecting overall gait performance, and stride time variability, considered an indicator of gait automaticity [24]. Compared with HCs, patients with FMDs demonstrated lower gait speed and shorter stride length, along with greater stride time variability. A significant main effect and a group-by-task interaction were found for gait speed and stride length, but no interaction was observed for stride time variability. These findings suggested that dual-task conditions primarily affected gait performance while leaving gait automaticity relatively preserved. Overall, the findings pointed to alterations in higher-level mechanisms involved in gait control and proposed that stride time variability is a potential marker with diagnostic relevance.

A later cross-sectional study expanded the sample to 87 individuals with FMDs. It adopted a broader set of gait

measures with ROC-based analyses across motor, cognitive, and visual dual-task conditions [38]. Several gait variables, including gait speed, stride length, double support, and swing time percentage, distinguished patients with FMDs from HCs with excellent accuracy (AUC > 0.90) in both single- and dual-task settings. In contrast, stride time variability and related indices showed lower discriminative performance (AUC < 0.80). These results confirmed earlier findings and are consistent with the present study, which extends them to a larger cohort using a multimodal machine-learning approach.

Evidence on postural control in FMDs remains limited. A posturographic study in 30 patients with FMDs [23] showed improved postural stability during motor dual-tasking under eyes-closed conditions, with sway area decreasing in FMDs (–1%) and increasing in HCs (+70.4%). No differences were observed during cognitive dual-tasking. These results support the role of motor and cognitive dual-tasking in improving postural control by redirecting attention toward external focus [42]. The improvement in gait during visual cues likely reflects a compensatory mechanism, consistent with the clinical benefit of external focus strategies [24].

The prominence of gait- and postural-related features as top predictors may be considered relevant independently of the presence of a clinically defined gait phenotype. Although this finding should be interpreted cautiously, as it is based on exploratory supplementary analyses conducted in a subgroup of participants (Supplementary Tables 2–5), these measures may reflect shared mechanisms across different FMDs phenotypes rather than the contribution of a specific subgroup. Non-motor symptoms, such as anxiety and depression, may also influence these findings. Previous evidence suggests that these conditions are associated with alterations in gait and postural control [43, 44].

Findings from motor and neurophysiological assessments support these abnormal top–down modulations of both motor and nociceptive pathways, as reflected by increased proprioceptive error and elevated DNIC ratios, respectively [27, 29]. These results point to altered integration of body-related sensory information, in line with models proposing disrupted internal signal processing in FMDs. While tonic vibration reflex alterations have previously been reported only in patients with functional weakness [27], our findings suggest that impaired integration of proprioceptive signals may be shared across FMDs phenotypes. Moreover, the reduced R2 blink reflex area builds on prior neurophysiological work demonstrating altered baseline brainstem excitability, without the need for modulatory paradigms [22].

Neuroimaging findings reveal increased FC in regions belonging to both the DMN and the basal ganglia-limbic network. This pattern of multi-network involvement corroborates the previous evidence of increased DMN connectivity and supports disruptions of large-scale networks involved in self-monitoring, salience attribution, and sensorimotor integration [39, 45, 46]. The DMN comprises medial posterior and ventral midline areas, including the precuneus, posterior cingulate cortex, cuneus, and ventromedial prefrontal cortex. These regions play a key role in self-referential processing, internally directed attention, and the examination of bodily and emotional states [47]. Abnormal DMN connectivity has been described in several conditions characterized by heightened self-focus and impaired regulation of internal representations. These include neurological disorders such as multiple sclerosis, Parkinson's disease, and epilepsy, as well as chronic pain, mood disorders (including depression and anxiety), autism spectrum disorders [48, 49], and in FMDs [39].

In this context, particular attention should be given to the role of the precuneus and cuneus in distinguishing FMDs patients from healthy controls. According to the previous studies, increased connectivity within these key DMN nodes may reflect a failure of DMN suppression during motor preparation and execution [46, 50–52]. This, in turn, supports their involvement in altered self-referential and agency processing, as well as in the abnormal integration of exteroceptive and interoceptive signals in these patients. Furthermore, the increased FC within the basal ganglia network (including limbic regions) may reflect altered interactions between emotion and motor control [45, 53–55]. The merging of these abnormalities across domains strengthens the fact that FMDs might be considered a disorder of sensorimotor integration and predictive control, rather than being limited to the motor network. However, nonmotor symptoms that are part of the FMDs profile and are difficult to disentangle in these patients, such as anxiety and depression, may have influenced these findings. Previous neuroimaging studies have shown that these conditions are associated with alterations in large-scale brain networks, including the default mode network, limbic circuits, and prefrontal regions involved in self-referential processing and emotional regulation [56–58]. In addition, anxiety levels have been specifically linked to disrupted functional connectivity between limbic structures and executive control networks [56, 57]. Therefore, the contribution of these symptoms should be considered when interpreting neuroimaging biomarkers in FMDs.

Recent evidence also suggests that structural alterations in the basal ganglia, cerebellum, and prefrontal cortex may play a role in FND, although studies are currently sparse and yield heterogeneous findings [12]. In our study, we observed only cerebellar volume differences in FMDs; however, these features did not survive feature selection in the multimodal machine-learning pipeline. This suggests that, although structural MRI changes might be detectable in FMDs, arguing against a strict functional/structural dichotomy [45], they may be less discriminative than functional MRI,

neurophysiological, and behavioral markers when evaluated together.

Among the neurophysiological variables examined, only a limited number showed potential diagnostic relevance. Notably, individuals with FMDs exhibited significantly reduced baseline brainstem excitability compared with HCs. Evidence from previous research also supports alterations in blink reflex modulation. A cross-sectional study including 22 patients with clinically established FMDs and 22 matched HCs evaluated the R2 component of the blink reflex induced by electrical stimulation using a prepulse inhibition (PPI) paradigm [22]. In that study, prepulse stimuli reduced the R2 response in both groups; however, the magnitude of inhibition was smaller in patients (36.4%, SD 25.6) than in HCs (67.3%, SD 16.4), resulting in a significant between-group difference. No associations were detected between the degree of the PPI and the severity of motor or non-motor symptoms. Reduced PPI has been interpreted as reflecting alterations in the preconscious processing of somatosensory information, in line with predictive coding models proposed for FMDs and related functional somatic syndromes. However, that study did not identify differences in baseline R2 amplitudes, whereas the present findings did[22].

Our findings on impaired descending nociceptive inhibition in FMDs replicated previous evidence [29]. However, the high levels of pain observed in the FMDs group, together with the well-established presence of pain in this population, may represent a clinically relevant factor contributing to impaired nociceptive modulation at the spinal level. In contrast, findings on the blink reflex could not be compared with the previous literature and should be considered novel [59]. As previously noted, we did not assess PPI, because stimulation procedures differed between centers, precluding reliable cross-site comparison. However, our findings suggest that, even in the absence of PPI paradigms, the ipsilateral–contralateral R2 blink reflex area may represent a clinically meaningful diagnostic biomarker reflecting basal alterations in top–down modulation of brainstem reflex circuits. We hypothesize that blink reflex and DNIC abnormalities may represent complementary manifestations of the same top–down dysregulation identified in our connectivity analyses. It suggests a hierarchical influence descending from cortical systems to brainstem reflex circuits, and then to spinal nociceptive pathways. Our functional connectivity findings support this view, showing hyperconnectivity within networks implicated in self-referential processing, cognitive control, and action selection. Excessive engagement of these higher-order regulatory systems may suppress brainstem excitability and disrupt motor automaticity.

Brief mention should also be made of previous literature on neurophysiological and behavioral features, previously reported in single-domain studies. Although tonic vibration reflex measures and heartbeat detection (indices of exteroceptive and interoceptive processing) did not survive feature selection in our multimodal analysis, we cannot exclude their potential contribution to characterizing FMDs neurobiology. Rather, when evaluated alongside more discriminative behavioral, connectivity, and neurophysiological markers, their relative diagnostic weight appeared lower.

As this is the first study to evaluate multimodal biomarkers within the same cohort of individuals with FMDs, comparison with prior literature is limited. The main reason is that the previous studies examined single biomarkers independently and often in small samples [12, 22, 26, 27, 40]. In addition, differences in experimental protocols, cohort phenotype composition, and the isolated assessment of some physiological domains may explain discrepancies across studies. Nonetheless, our findings, using the same experimental protocols reported in the literature, largely confirm and extend existing evidence by demonstrating the added value of evaluating motor, neurophysiological, and imaging markers simultaneously in a large cohort of FMD patients [12, 22, 26, 27, 40]. Thus, this study advances the field [11] by identifying clinically interpretable biomarkers, which pave the way for early identification, patient stratification, and the development of mechanism-informed rehabilitation strategies. In practical terms, these markers could increase diagnostic confidence, particularly in complex cases, as complementary tools alongside established positive clinical signs rather than as standalone diagnostic criteria. Gait and stabilometric assessments under dual-task conditions appear readily applicable in routine practice, whereas MRI and neurophysiological measures may be better considered as complementary tools for selected cases or specialized settings. These results support the development of future precision-medicine approaches and technology-enabled diagnostic tools in FMDs.

We sought to address key limitations of prior work by integrating multimodal data and accounting for clinical heterogeneity. However, the cross-sectional design of our study limits inference on causality and prognostic relevance. In addition, we excluded the presence of neurodevelopmental conditions, such as ADHD or autism spectrum disorders, which are relatively common in FND, and we did not collect information on childhood trauma, which may also influence biomarker profiles [60]. Therefore, future studies should validate these biomarkers in independent cohorts using longitudinal designs, while also incorporating these additional variables. Their integration into clinical practice and the examination of how they can distinguish across different FMD subtypes and mixed functional–organic presentations should be further investigated. Generalizability and scalability of the predictive AI model may be further enhanced by larger multicenter datasets and multitask learning approaches. An important next step toward clinical translation will also be the validation of these findings

in patient-versus-patient designs, particularly through comparisons with individuals affected by organic movement disorders.

In summary, this study shows that it is possible explore the multidimensional neurobiological framework in FMDs investigating dysfunction across motor, attentional, and pain-modulatory circuits by behavioral, neurophysiology, and neuroimaging assessment within an explainable machine-learning framework. The development of objective biomarkers that complement established clinical examination may enhance diagnostic confidence and ultimately support more effective and efficient care for individuals with FMDs.

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Author contributions All authors whose names appear on the submission made substantial contribution to the conception and design of the work (MT, MTP, FA, ES, MG, MF, PB), to the acquisition, analysis, or interpretation of data (AG, SB, SC, IC, CR, FA, CV, AB, MA, DR, IADV, MF, GP, AP, MC, FBP, MB, MFL, MT, FR, CG, MF, AM, FS, GMS, SM, ST, FP, GDB, GP, LZ, EC); drafted the work (MTP, MT, AS, MG, MR, ES, SB, AG); or revised it critically for important intellectual content (RE, AF, GM, FBP, MT, FA). All authors approved the final version for publication and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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data availability The data analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of interest E. Sarasso, S. Basaia, and E. Canu have received research support from the Italian Ministry of Health. M. Filippi is the Editor-in-Chief of the Journal of Neurology, Associate Editor of Human Brain Mapping, Neurological Sciences, and Radiology; received compensation for consulting services from Alexion, Almirall, Biogen, Merck, Novartis, Roche, and Sanofi; speaking activities from Bayer, Biogen, Celgene, Chiesi Italia SpA, Eli Lilly, Genzyme, Janssen, Merck-Serono, Neopharmed Gentili, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, and TEVA; participation in Advisory Boards for Alexion, Biogen, Bristol-Myers Squibb, Merck, Novartis, Roche, Sanofi, Sanofi-Aventis, Sanofi-Genzyme, Takeda, scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol-Myers Squibb, Lilly, Novartis, and Sanofi-Genzyme; he receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Italian Ministry of Health, the Italian Ministry of University and Research, and Fondazione Italiana Sclerosi Multipla. F. Agosta is Associate Editor of NeuroImage: Clinical, has received speaker honoraria from Biogen Idec, Italfarmaco, Roche, Zambon, and Ely Lilli, and receives or has received research supports from the Italian Ministry of Health, the Italian Ministry of University and Research, AriSLA (Fondazione Italiana di Ricerca per la SLA), the European Research Council, the EU Joint Programme–Neurodegenerative Disease Research (JPND), and Foundation Research on Alzheimer Disease (France). The other authors have declared that they have no competing interests. M. Gandolfi has received research support from Fondazione Italiana Sclerosi Multipla. M.T. Pellecchia has received research support from the Italian Ministry of Health and the Italian Ministry of University. M. Tinazzi has received research support from the Italian Ministry of Health. A. Fratucello received compensation for consulting services from Novartis.

Ethical approval Ethics approval was obtained from the respective committees (4201CESC-PNRR-MAD-2022-12376826). The trial was registered in clinicaltrials.gov (NCT06328790).

Informed consent All patients provided written informed consent. The study adhered to the ethical standards for research involving human participants as outlined in the Declaration of Helsinki.

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