Biomarker-Based Diagnostic Algorithm for Functional Motor Disorders: Investigating Motor, Exteroceptive, and Interoceptive Domains Through Artificial Intelligence Analysis

Tinazzi M.[1,2], Gandolfi M.[1,2], Sandri A.[1], Sarasso E.[7,8,12], Gardoni A.[7,8], Basaia S.[7], Barone P.[3], Pellecchia M.T.[3], Erro R.[3], Cuoco S.[3], Carotenuto I.[3], Russo M.[3], Vinciguerra C.[3], Botto A.[4], Amboni M.[3], Di Vico I.A.[1], Fiorio M.[2], Pedrotti G.[2], Paolicelli A.[1], Mansueto G.[1,5], Pizzini F. B.[1,5], Barillari M.[1,5], Lauriola M.F.[1], Tozzi M.C.[1], Rusciano F.[1], Geroin C.[6], Fasoli M.[2], Marotta A.[2], Pizzolla E.[2], Salaorni F.[2], Lozzi I.[2], Squintani G.M.[1], Mariotto S.[1], Tamburin S.[1,2], Paio F.[2], De Biasi G.[3], Piscosquito G.[3], Zenere L.[1,7], Sibilla E.[7], Canu E.[7,9], Filippi M.[7,8,9,10,11], Agosta F.[7,8,9].

[1] Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy; [2] Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy; [3] Neurological Clinic, AOU San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy; [4] Department of Neuroradiology, AOU San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy; [5] Department of Engineering for Innovation Medicine (DIMI), Verona University, Verona, Italy; [6] Department of Surgery, Dentistry, Paediatrics and Gynecology, University of Verona, 37134 Verona, Italy; [7] Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy; [8] Vita-Salute San Raffaele University, Milan, Italy; [9] Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; [10] Neurorehabilitation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; [11] Neurophysiology service, IRCCS San Raffaele Scientific Institute, Milan, Italy; [12] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal Child Health, University of Genoa, Genoa, Italy.

Contacts: michele.tinazzi@univr.it; marialuisa.gandolfi@univr.it; angela.sandri_01@univr.it

INTRODUCTION

Functional motor disorders (FMD) are disabling neurological conditions marked by involuntary but learned movement patterns [1,2]. They are often poorly understood, diagnosed late, and inadequately treated, leading to disability, reduced quality of life, and increasing social and economic costs [2,3]. Beyond abnormal attentional focus, maladaptive beliefs and expectations, and an altered sense of agency, symptoms may arise from dysfunction in neural systems integrating motor, exteroceptive, and interoceptive domains. Such disruption may drive both motor and non-motor symptoms. Identifying validated diagnostic and prognostic biomarkers is crucial for early detection, tailored treatments, and rehabilitation [4]. **Funding statement:** This project is funded by the European Union (Next Generation EU – NRRP M6C2, Investment 2.1, PNRR-MAD-2022-12376826, aimed at enhancing biomedical research within the Italian National Health System (SSN).

OBJECTIVES

To develop diagnostic and prognostic biomarker algorithms for FMD across the motor, exteroceptive, and interoceptive domains, supported by advanced behavioural, neurophysiological, and MRI assessments combined with explainable artificial intelligence (XAI).

RESEARCH METHODS

Study design: Cross-sectional evaluating FMD (n=75) vs HC (n=75);

Assessments

- Clinical & PROs: S-FMDRS, fatigue (MFI-20), pain, anxiety (BAI), depression (BDI-II), alexithymia (TAS-20), QoL (SF-12)
- Multidomain: Behavioural, neurophysiological & MRI (motor, exteroceptive, interoceptive, cerebral) as reported in Table 1 [5].

RESULTS

Subjects: 75 patients with definite FMD (mean age: 44.20 years; 56 females) and 75 HC (mean age: 48.42 years; 44 females).

Clinical/Behavioral: Higher levels of depression, anxiety, alexithymia, pain, and fatigue in FMD vs HC (all $p<0.05$), and lower quality of life in FMD ($p<0.05$).

Diagnostic Algorithm: The model identified key features from motor, cognitive, and neuroimaging domains that improved diagnostic accuracy in distinguishing FMD from HC. The most important features included motor and cognitive dual task postural and gait performance, followed by functional connectivity within the default mode and basal ganglia networks. SHAP value analysis showed that higher values of these features predicted FMD classification, while lower values predicted HC.

DISCUSSION

A multidimensional profile characterizes FMD (behavioral, motor, neurophysiological, imaging), providing multimodal biomarkers that may support personalized diagnostic strategies.

While additional validation is required, these findings support a multidimensional view of the pathophysiology of FMD and highlight the potential of integrated biomarkers to inform more personalized diagnostic strategies.

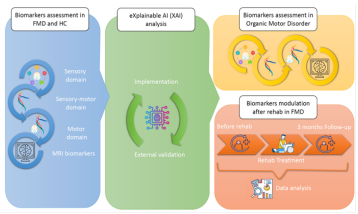

Figure 1. Study overview

FMD, Functional Motor Disorder; HC, Healthy Control; MRI, Magnetic Resonance Imaging; XAI, eXplainable Artificial Intelligence.

Domain	Tests	Main Biomarkers
Motor	PPI (blink reflex)	R2 magnitude
	Gait analysis	Gait speed, stride length, variability, swing time, double support
	Stabilometry	Sway area, CoP displacement & velocity
Exteroceptive	Sensory attenuation	Force ratio (matched vs target)
	TVR	Arm angle for vibration/tracking
	SEP	Late SEP amplitude
	LEP	N2/P2 amplitude
Interoceptive	HPT	Objective/subjective HR ratio
Cerebral	MRI (T2-FLAIR)	Excluding CNS lesions
	MRI (3D T1)	Cortical thickness, GM volumes (sensory, motor, executive, SoA)
	Resting-state fMRI	Connectivity (sensorimotor, executive, SoA)

Table 1. Study Biomarkers

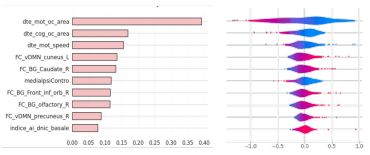

Figure 2. Features most frequently selected by the model to improve accuracy

The features most frequently selected by the model to improve accuracy are represented. The left plot shows the average feature importance within the model.
The right plot represents the distribution of SHAP values for each feature. Each dot corresponds to a sample, with color indicating the feature's value (blue for low, red for high). The horizontal position indicates the impact of that value on the model's prediction: positive SHAP values push the prediction toward the FMD class, while negative values push it toward healthy controls (HC).

[1] Tinazzi M et al., 2020 Mov Disord Clin Pract; 7(8):920-929. [2] Hallett M et al., 2022 Lancet Neurol; 21:537-550. [3] Tinazzi M et al., 2024 Neurol Sci; 2024 Nov 13. [4] Thomsen BLC, et al. J Neurol Neurosurg Psychiatry. 2020;91(12):1261-1269. [5] Gandolfi M et al., 2024 PLoS One; 19(9):e0309408.