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# Impaired resting vagal tone in patients with functional movement disorders

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ABSTRACT

*Introduction:* The autonomic nervous system plays an integral role in the maintenance of homeostasis during times of stress. The functioning of the autonomic nervous system in patients with functional movement disorders (FMD) is of particular interest given the hypothesis that converted psychological stress plays a critical role in FMD disease pathogenesis. We sought to investigate autonomic nervous system activity in FMD patients by examining heart rate variability (HRV), a quantitative marker of autonomic function.

*Methods:* 35 clinically definite FMD patients and 38 age- and sex-matched healthy controls were hospitalized overnight for continuous electrocardiogram recording. Standard time and frequency domain measures of HRV were calculated in the awake and asleep stages. All participants underwent a thorough neuropsychological battery, including the Hamilton Anxiety and Depression scales and the Beck Depression Inventory.

*Results:* Compared to controls, patients with FMD exhibited decreased root mean square of successive differences between adjacent NN intervals (RMSSD) ($p = 0.02$), a marker of parasympathetic activity, as well as increased mean heart rate ($p = 0.03$). These measures did not correlate with the depression and anxiety scores included in our assessment as potential covariates.

*Conclusion:* In this exploratory study, patients with FMD showed evidence of impaired resting state vagal tone, as demonstrated by reduced RMSSD. This decreased vagal tone may reflect increased stress vulnerability in patients with FMD.

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## 1. Introduction

Accounting for up to 20% of patients evaluated at specialized movement disorders neurology clinics, patients with functional movement disorders (FMD) are often among the most disabled [1] and the most refractory to treatment. The underlying pathogenesis of the disorder remains poorly understood. Many neurologists consider elevated stress levels to be a universal feature of patients with FMD [2], and increased stress is hypothesized to contribute to disease pathogenesis. Evaluating autonomic nervous system (ANS) activity in patients with FMD is therefore of particular interest given the role of the ANS in the maintenance of homeostasis during times of stress.

Heart rate variability (HRV), reflecting the oscillation in the inter-beat interval (normal-to-normal (NN) interval), provides a quantitative assessment of autonomic function. In addition to acting as a predictor of cardiovascular morbidity and mortality [3], HRV is also considered to serve as a marker of psychological well-being [4,5]. Among healthy adults, resting-state HRV has been

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demonstrated to correlate with socially adaptive coping strategies [6]. Vagal tone in particular has been proposed to serve as a physiological marker of stress vulnerability [7], with impaired vagal tone reflecting impaired ability to react to external stressors. Decreased HRV has been demonstrated in a variety of neuropsychiatric disorders, including psychogenic non-epileptic seizures (PNES) [8–10], major depressive disorder [11], and generalized anxiety disorder [12]. To date, HRV has not been examined in patients with FMD.

In this exploratory study, we investigated whether FMD patients exhibit impairments in ANS function by comparing standard measures of HRV derived from continuous ECG recordings collected during awake and asleep epochs in FMD patients and their age- and sex-matched healthy controls (HCs).

## 2. Methods

### 2.1. Participants

Thirty-five patients with a diagnosis of "clinically definite" FMD [13] were recruited from the Human Motor Control clinic at the National Institutes of Health (NIH) between October 2011 and March 2015. Thirty-eight age- and sex-matched HCs were recruited from the NIH Clinical Research Volunteer Program database. Participants partially overlap with those reported in a previous manuscript exploring the hypothalamic-pituitary-adrenal axis in FMD [14]. Exclusion criteria for all participants included: a) history of cardiac disease; b) use of heart-rate altering medication; c) comorbid neurological disease; d) comorbid psychotic disorder, bipolar disorder, current substance abuse or current depressive episode; e) history of traumatic brain injury with loss of consciousness; f) active autoimmune disorder; g) current suicidal ideation; h) disease severity requiring inpatient treatment; and i) use of tricyclic antidepressants or antiepileptic medication. HCs were additionally excluded for use of any antidepressant medication within the last six months. The NIH institutional review board approved the study. All participants provided written informed consent.

### 2.2. Heart rate collection and analysis

Participants were hospitalized overnight for continuous Holter monitoring ranging from 14 to 24 h total duration. Holter data were analyzed using Impresario software. All recordings were visually inspected and manually edited to identify and remove artifacts and non-beats. Data were subsequently split into awake and asleep epochs and imported into Matlab for calculation of standard HRV time and frequency domain measures recommended by the task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [15]. Five time domain measures of HRV were calculated: RMSSD (root mean square of successive differences between adjacent NN intervals); SDNN (standard deviation of NN intervals); SDANN (standard deviation of the averages of NN intervals calculated over all 5 min segments); NN50 (the number of pairs of adjacent NN intervals differing by more than 50 ms); and pNN50 (the NN50 count divided by the total number of NN intervals). RMSSD reflects the beat-to-beat variation in heart rate, and is the primary time domain measure used to assess parasympathetic sources of HRV. NN50 and pNN50 also estimate high frequency variation, and are highly correlated with RMSSD, although RMSSD is thought to possess superior statistical properties. SDNN and SDANN are used as estimates of overall HRV, and do not distinguish between sympathetic or parasympathetic sources of variability [15]. Frequency domain measures included: total power (TP); power in high frequency (HF) (0.15–0.4 Hz), low frequency (LF) (0.04–0.15 Hz), and very low frequency (VLF) (<0.04 Hz) ranges; LF and HF in normalized units (LFn and HFn); and the ratio of LF to HF (LF/HF). HF power is predominantly mediated by the parasympathetic nervous system, whereas LF power reflects both sympathetic and parasympathetic activity [15]. Mean heart rate (HR) was also assessed.

### 2.3. Neuropsychological assessment

All participants met with a clinical psychologist (R.A.), who administered the Hamilton Anxiety Rating Scale (HAM-A) [16] and the Hamilton Rating Scale for Depression (HAM-D) [17]. Participants also completed the Beck Depression Inventory (BDI) [18].

### 2.4. Statistical analysis

Box-Cox transformation was applied to HRV measures to achieve approximately normal distributions. To investigate possible group effects on HRV measures, repeated measures analysis of covariance (rm-ANCOVA) was performed with time (awake/asleep epochs) as within-subject variable, group (FMD, HC) as between-subject variable, and age and sex as covariates. To determine whether to include scales of depression and anxiety in our statistical model as covariates, we evaluated the association between HRV parameters and well-validated scales of anxiety and depression (HAM-A and HAM-D, respectively) using rm-ANCOVA. Given the absence of significant association between HAM-A score and any of the HRV parameters on rm-ANCOVA, this scale was not included as a covariate in our final model. A significant interaction between group and HAM-D score was detected, thus rm-ANCOVA evaluating the association between HRV and HAM-D score was performed separately for the two groups (FMD, HC). In the FMD group, we did not detect a significant association between HAM-D score and any of the HRV parameters. The HAM-D score among all participants in the HC group was in the normal range (Table 1), and therefore any potential association between HAM-D score and HRV parameter was not deemed meaningful. Given these findings, HAM-D was not included as a covariate in our final model.

To explore a possible relationship between disease duration and HRV, linear correlations between disease duration and measures of HRV were assessed by calculating Pearson's correlation coefficients.

Group differences in HRV might be confounded by group differences in the use of CNS-acting medications, specifically the use of SSRI and SNRI anti-depressants [19]. To address this potential confounder, we performed additional rm-ANCOVA analysis excluding the seven patients who were taking SSRIs or SNRIs. We also compared the means of the relevant HRV parameters in medicated versus non-medicated patients using two-sample student's *t*-tests. Significance threshold was set at $p < 0.05$. Given the exploratory nature of the study, correction for multiple comparisons was not performed.

## 3. Results

### 3.1. Demographic and clinical characteristics

35 FMD patients and 38 age- and sex-matched HCs were included in the analysis. Groups did not differ significantly in terms of demographic data (Table 1). Patients scored significantly higher than HCs on anxiety and depression rating scales (Table 1). Clinically, patients reported an average disease duration of 5.6 years (SD 5.3). Patients self-reported a range of involuntary movements, including tremor (71%), other jerking movements (63%), abnormal gait and/or balance (63%), abnormal speech (43%), abnormal posturing/dystonia (40%), and paresis (31%).