Gray matter differences in patients with functional movement disorders

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Abstract

Objective

To explore alterations in gray matter volume in patients with functional movement disorders.

Methods

We obtained T1-weighted MRI on 48 patients with clinically definite functional movement disorders, a subset of functional neurologic symptom disorder characterized by abnormal involuntary movements, and on 55 age- and sex-matched healthy controls. We compared between-group differences in gray matter volume using voxel-based morphometry across the whole brain. All participants in addition underwent a thorough neuropsychological battery, including the Hamilton Anxiety and Depression Scales and the Childhood Trauma Questionnaire. To determine whether confounding factors such as comorbid depression, anxiety, or childhood trauma exposure contributed to the observed structural changes, nonparametric correlation analysis was performed.

Results

Patients with functional movement disorders exhibited increased volume of the left amygdala, left striatum, left cerebellum, left fusiform gyrus, and bilateral thalamus, and decreased volume of the left sensorimotor cortex (whole-brain corrected $p \leq 0.05$). Volumetric differences did not correlate with measures of disease duration or patient-rated disease severity.

Conclusion

This study demonstrates that patients with functional movement disorders exhibit structural gray matter abnormalities in critical components of the limbic and sensorimotor circuitry. These abnormalities may represent a premorbid trait rendering patients more susceptible to disease, the disease itself, or a compensatory response to disease.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CTQ = Childhood Trauma Questionnaire; **FMD** = functional movement disorder; **FND** = functional neurologic symptom disorder; **GLM** = general linear model; **GM** = gray matter; **GMV** = gray matter volume; **HAM-A** = Hamilton Anxiety Rating Scale; **HAM-D** = Hamilton Rating Scale for Depression; **HC** = healthy control; **MEMPRAGE** = multiecho magnetization-prepared rapid gradient echo; **VBM** = voxel-based morphometry.

Functional neurologic symptom disorder (FND) is one of the most common diagnoses seen in the modern neurology clinic.¹ Despite its prevalence, our understanding of the underlying neurobiology of FND remains incomplete.

Functional neuroimaging studies have implicated abnormalities in several neural networks in patients with FND.² Increased amygdalar activation to arousing stimuli has been detected,^{3,4} along with altered functional connectivity between the amygdala and regions involved in motor planning.³ Altered striatal and thalamic activation has been demonstrated,^{5,6} as well as abnormal functional connectivity between brain regions involved in sensorimotor integration and those involved in self-agency.^{7,8}

While functional neuroimaging studies have demonstrated numerous alterations in limbic and sensorimotor networks in patients with FND, studies examining structural brain alterations in this population are sparse. Only a handful of studies have explored structural alterations in patients with FND,^{9–14} with conflicting results. These prior studies have been limited by small sample sizes, ranging from 10 to 26 patients. Furthermore, it remains unclear whether confounding psychiatric comorbidities play a role in mediating these structural changes.

To shed further light on possible neuroanatomical differences in patients with FND, we recruited 48 patients with functional movement disorders (FMD), a subset of FND characterized by abnormal involuntary movements, and 55 matched healthy controls (HCs) as part of an observational study including neuroimaging. We hypothesized that patients with FMD would exhibit altered gray matter volume (GMV) when compared with HCs, as has been demonstrated in patients with other FNDs.^{9–13} Given the scarcity of studies examining GMV in the FMD patient population, we chose to perform voxel-based morphometry (VBM) across the whole brain to investigate these differences in GMV between patients with FMD and HCs. We subsequently assessed whether within-group differences in GMV correlate with comorbid anxiety and depressive symptoms, childhood trauma exposure, or disease characteristics including duration and severity.

Methods

Participants

Sixty-four patients with clinically definite FMD,¹⁵ as diagnosed by at least 2 movement disorders specialists (M.H., C.W.M., K.L.), were recruited from the Human Motor Control Clinic at

the NIH between October 2011 and December 2016. Sixty-four age- and sex-matched HCs (± 3 years) were recruited from the NIH Clinical Research Volunteer Program database. Participants partially overlap with those reported in previous articles.^{8,16–18} Exclusion criteria included comorbid neurologic disease; psychosis, bipolar disorder, or current substance abuse; history of traumatic brain injury; active autoimmune disorder; current suicidality; disease severity requiring hospitalization; use of tricyclic antidepressants or antiepileptic medication; contraindication for MRI; abnormal clinical MRI brain; and pregnancy. HCs were excluded for use of antidepressant medication within the last 6 months. Participants were continued on any preexisting medications.

Standard protocol approvals, registrations, and patient consents

The study was approved by the NIH Institutional Review Board. Written informed consent was obtained from all participants prior to study participation.

Neuropsychological assessment

All participants met with an experienced clinical psychologist (R.A., S.S.), who administered the Hamilton Anxiety Rating Scale (HAM-A)¹⁹ and Hamilton Rating Scale for Depression (HAM-D),²⁰ and screened participants for psychiatric diagnoses using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Version IV-TR, Patient Edition.²¹ Participants completed the Beck Depression Inventory,²² State Trait Anxiety Inventory,²³ and Childhood Trauma Questionnaire (CTQ).²⁴ Patients with FMD self-rated disease severity over the last 7 days on a scale from 1 to 5 (1 = least severe, 5 = most severe).

Structural MRI acquisition

Structural images were acquired with a 3T Siemens (Munich, Germany) Skyra scanner using a 32-channel head coil. Participants lay supine with their head fixed using foam pads. Axial anatomical images were acquired using a T1-weighted anatomical MRI (multiecho magnetization-prepared rapid gradient echo [MEMPRAGE], voxel size $1 \times 1 \times 1$ mm; repetition time 400 ms; echo time 1.69 ms; echo spacing 9.8 ms; number of echos 4; bandwidth 650 Hz/Px; inversion time 1,100 ms; flip angle 7 degrees; acceleration factor 2; matrix size $176 \times 256 \times 256$; field of view 256 mm; acquisition time 6 minutes 2 seconds).

Imaging processing

The MEMPRAGE images were averaged across echoes. Structural data were analyzed with FSL-VBM²⁵ (fsl.fmrib.ox.ac.uk/

fsl/fslwiki/FSLVBM), an optimized VBM protocol²⁶ carried out with FSL tools.²⁷ Briefly, brain extraction and gray matter (GM) segmentation was performed prior to registering structural images in native space into the Montreal Neurological Institute 152 standard space template using nonlinear registration. Images from an equal number of patients and HCs were averaged and flipped along the x-axis to create a left–right symmetric, study-specific GM template. The use of a study-specific custom template minimizes the amount of deformation required for each participant during nonlinear registration, and has been demonstrated to improve the plausibility of between-group comparisons.²⁸ All native GM images were nonlinearly registered to the study-specific template. GM segments were modulated to correct for local expansion or contraction due to the nonlinear component of the spatial transformation. The modulated GM images were smoothed with an isotropic Gaussian kernel with a sigma of 2 mm. To correct for multiple comparisons across space, voxel-wise statistical testing was performed using the general linear model (GLM), including permutation-based nonparametric testing ($n = 5,000$ iterations).²⁹ Age and total intracranial volume were included as covariates. Threshold-free cluster enhancement–based analysis was used to identify cluster-like structures that were displayed at $p \leq 0.05$ (whole-brain corrected).

Total intracranial volume, total GMV, and total white matter volume were estimated using Freesurfer image analysis software (surfer.nmr.mgh.harvard.edu/).

To address group differences in the use of CNS-acting medications, we performed voxel-wise GLM on a subset of non-medicated participants, including 22 patients with FMD and an equal number of age- and sex-matched HCs. To address the possible role of sex, we performed voxel-wise GLM on 38 female patients with FMD and an equal number of age-matched female HCs.

Statistical analysis

Categorical variables were analyzed using χ^2 analysis; continuous variables were analyzed using the Mann-Whitney U test. We evaluated the association between volumetric differences and well-validated scales of anxiety, depression, and childhood trauma using bivariate 2-tailed nonparametric correlation procedures; similar methods were used to evaluate the association between volumetric differences and disease duration/severity. Given significant between-group differences in HAM-A and HAM-D scores, the FMD and HC populations were considered separately for these variables. The α error was set at 0.05. Given the exploratory nature of the correlation analysis, correction for multiple comparisons was not performed. Statistical analyses were conducted using the Statistical Package for Social Sciences, version 24.0 (IBM SPSS [Chicago, IL] Statistics for Macintosh).

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator if approved by our Research Ethics Board.

Results

Demographic and clinical characteristics

Sixty-four patients with FMD and 64 HCs were initially recruited; due to screening failures, dropouts, and acquisition failures, GMV analyses were restricted to 48 patients with FMD and 55 HCs. We did not detect between-group differences in terms of age, sex, education level, or handedness (table 1). As expected given prior studies,^{8,17,18} patients scored considerably higher than HCs on scales of depression and anxiety (table 1). There were no significant between-group differences on the CTQ. Patients reported average disease duration of 5.9 years. Patients' self-reported abnormal movements included tremor (75%), jerking movements (65%), abnormal gait/balance (71%), abnormal speech (50%), abnormal posturing/dystonia (35%), and paresis (35%). Seventy-seven percent of patients had bilateral or nonlateralizing symptoms; 17% had right-lateralizing symptoms, and 6% had left-lateralizing symptoms. In terms of family history, 52% of patients with FMD reported family history of neurologic disease, compared to 36% of HCs. Thirty-one percent of patients with FMD reported family history of psychiatric disease, compared to 24% of HCs.

GM differences associated with FMD

As illustrated in figure 1 and table 2, patients with FMD exhibited greater GMV compared to HCs in the left amygdala, left putamen, left caudate, left cerebellum, left parahippocampal gyrus, left fusiform gyrus, and bilateral thalami, including the medial dorsal and ventral lateral nuclei. Patients with FMD had reduced GMV of the left precentral and postcentral gyri. We did not detect between-group differences in total GM or white matter volume.

Group differences in GMV might be confounded by group differences in the use of CNS-acting medications (table 1). To investigate this possibility, we analyzed group differences in GMV in nonmedicated participants, including 22 patients with FMD and 22 matched HCs. Abnormal movements in the patient subgroup were comparable to that of the larger group, and included tremor (71%), jerking movements (62%), abnormal gait/balance (62%), abnormal speech (43%), abnormal posturing/dystonia (33%), and paresis (33%). Sixty-four percent of patients had bilateral or nonlateralizing symptoms; 23% had right-lateralizing symptoms, and 13% had left-lateralizing symptoms. Between-group differences in this subset of nonmedicated participants were comparable to those observed in the larger sample, with patients with FMD exhibiting greater GMV in the left amygdala, left putamen, left caudate, and left thalamus, and reduced GMV in the left precentral and postcentral gyri (table 2).

Table 1 Clinical and demographic characteristics of study cohorts

	FMD patients (n = 48)	HCs (n = 55)	p Value
Age, y	44.6 ± 11.6 (21–67)	45 ± 12 (24–69)	0.90
Sex, F/M	38/10	40/15	0.447
Handedness, R/L	43/5	53/2	0.173
Education, some college or greater, n	44	47	0.327
Taking CNS-acting medication, n ^a	26	—	—
Disease duration, y	5.9 ± 6.7 (0.4–35)	—	—
HAM-A	13.5 ± 8.0 (0–34)	2 ± 2 (0–8)	6.2 × 10 ^{−16}
HAM-D	9.7 ± 6.0 (0–26)	2 ± 1 (0–5)	1.7 × 10 ^{−18}
BDI	8.9 ± 7.8 (0–31)	2 ± 4 (0–19)	4.9 × 10 ^{−9}
STAI-S	41.6 ± 11.9 (20–66)	33 ± 9 (20–51)	6.6 × 10 ^{−5}
STAI-T	56.9 ± 12.2 (36–89)	47 ± 10 (25–71)	1.8 × 10 ^{−4}
CTQ (total)	41.4 ± 17.2 (25–92)	35.9 ± 12.5 (25–78)	0.146

Abbreviations: BDI = Beck Depression Inventory; CTQ = Childhood Trauma Questionnaire; FMD = functional movement disorders; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression; HC = healthy controls; STAI-S = State Trait Anxiety Inventory (state); STAI-T = State Trait Anxiety Inventory (trait).

Values are expressed as mean ± SD (range), unless otherwise indicated.

^a CNS-acting medications included clonazepam (n = 8), gabapentin (n = 6), alprazolam (n = 4), escitalopram (n = 3), carbidopa/levodopa (n = 2), sertraline (n = 2), trihexyphenidyl (n = 2), acetazolamide (n = 2), trazodone (n = 1), aripiprazole (n = 1), fluoxetine (n = 1), venlafaxine (n = 1), desvenlafaxine (n = 1), lorazepam (n = 1), ropinirole (n = 1), citalopram (n = 1), entacapone (n = 1), amphetamine/dextroamphetamine (n = 1), baclofen (n = 1), and duloxetine (n = 1).

Given a previously demonstrated effect of sex on volumetric associations,³⁰ we also investigated between-group differences in GMV of 38 female patients with FMD and 38 matched HCs. Between-group differences in this subset of participants

were comparable to those observed in the larger sample, with female patients with FMD exhibiting greater GMV in the left amygdala, left putamen, and left thalamus, and reduced GMV in the left precentral and postcentral gyri (figure 2).

Figure 1 Gray matter differences associated with functional movement disorders (FMDs)

Table 2 Gray matter abnormalities associated with functional movement disorders (FMDs)

Entire cohort	Region	BA	Size	x	y	z
FMD > HC						
1	R thalamus, L thalamus	—	908	−12	−10	10
2	L putamen, L amygdala, L parahippocampal gyrus	—	591	−20	10	−14
3	L caudate	—	227	−12	12	12
4	L fusiform gyrus	36	161	−52	−42	−24
5	L cerebellar tonsil	—	97	−36	−54	−42
6	L culmen	—	64	−38	−44	−30
HC > FMD						
1	L precentral, postcentral	1, 3, 4	103	−50	−14	40
2	L precentral	4, 6	37	−40	−22	62
Nonmedicated cohort						
FMD > HC						
1	L putamen, inferior frontal gyrus	—	237	−20	10	−14
2	L posterior cingulate	31	136	−20	−67	16
3	L amygdala	—	89	−30	−1	−17
4	L caudate	—	51	−8	16	14
5	L thalamus	—	22	−10	−11	10
6	L hippocampus	—	21	−30	−14	−8
7	L lingual gyrus	19	16	−14	−56	−1
HC > FMD						
1	L precentral, postcentral	4, 6	33	−46	−14	54
2	L precentral	6	37	−46	−8	50

Abbreviations: BA = Brodmann area; HC = healthy control.

Sample referred to as entire cohort includes patients with FMD (n = 48) and matched HCs (n = 55). Sample referred to as nonmedicated cohort includes patients with FMD (n = 22) and matched HCs (n = 22) who were not on any CNS-acting medication. Clusters surviving whole brain multiple comparisons correction (general linear model) at $p \leq 0.05$ are listed in order of descending size. Coordinates refer to the voxel with the peak t value in the cluster.

Lateralization of patient symptoms might also potentially contribute to the observed volumetric differences. To address this, we compared the 37 patients with nonlateralizing symptoms to the 11 patients with lateralizing symptoms. The small number of patients with lateralizing symptoms (n = 3 patients with left-lateralizing symptoms, n = 8 patients with right-lateralizing symptoms) precludes formal statistical comparison of these groups. We instead examined volumetric differences in individual patients, and found considerable overlap between patients with nonlateralizing, left-lateralizing, and right-lateralizing symptoms, without evidence of between-group differences (figure 3).

Prior studies have demonstrated that patients with functional paresis exhibit increased volume of the premotor cortex¹¹ and decreased thalamic volume.¹² We sought to determine whether the volumetric differences in our patients who exhibited both

functional paresis as well as functional hyperkinetic movements differed from the volumetric differences detected in patients with only functional hyperkinetic movements. We compared volumetric differences in the 17 patients with functional paresis to those in the 31 patients exhibiting only hyperkinetic movements, and did not find evidence for between-group differences ($p > 0.05$; data not shown).

Participants with higher childhood trauma scores exhibited larger volume of the left caudate ($p = 0.016$) and left cerebellar tonsil ($p = 0.0003$) in our post hoc analysis (table 3). Patients with higher anxiety scores exhibited smaller volume of the left fusiform gyrus ($p = 0.035$), whereas patients with higher depression scores exhibited larger volume of the left cerebellar tonsil ($p = 0.014$; table 3). Among patients, disease duration and patient-rated measures of disease severity did not correlate with volumetric differences (table 4).

Figure 2 Gray matter differences associated with functional movement disorders (FMDs), female-only cohort

Panels show T1-weighted axial images illustrating regions of increased (A) and decreased (B) gray matter volume in female patients with FMD as compared to healthy controls. Group differences are adjusted for differences in age and intracranial volume. $p < 0.05$, whole brain corrected. Image left is brain right; z coordinates indicated in upper left.

Discussion

We report abnormalities in brain morphometry associated with FMD, a type of FND characterized by abnormal involuntary movements. Specifically, we found that patients

with FMD, as compared to HCs, exhibited altered GMV in critical components of the limbic and motor circuitry, with greater GMV of the left amygdala, left caudate, left putamen, left cerebellum, left fusiform gyrus, and bilateral thalami, and reduced GMV of the left sensorimotor cortex. These findings

Figure 3 No effect of laterality of patient symptoms on volumetric findings

(A–H) Dotplot illustrates lack of between-group differences in gray matter volume among patients with functional movement disorders with bilateral, left-lateralizing, and right-lateralizing symptoms.

Table 3 Correlations between gray matter volumetric differences and scores on psychometric scales

Cluster	HAM-A		HAM-D		CTQ
	FMD	HC	FMD	HC	FMD + HC
R/L thalamus	0.01	-0.01	0.06	-0.02	0.08
L putamen, amygdala	0.16	0.15	0.13	0.15	0.15
L caudate	-0.01	0.08	0.04	-0.01	0.24 ^a
L fusiform gyrus	-0.31 ^b	0.07	-0.22	0	-0.04
L cerebellar tonsil	0.27	-0.07	0.35 ^c	-0.2	0.35 ^d
L culmen	0.02	0.06	-0.02	0.05	0.08
L precentral, postcentral	0.07	-0.03	-0.09	-0.002	-0.02
L precentral	-0.09	-0.03	-0.05	-0.15	0.02

Abbreviations: CTQ = Childhood Trauma Questionnaire; FMD = functional movement disorders; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression; HC = healthy control.

Sample includes patients with FMD (n = 48) and matched HCs (n = 55). Values given are Spearman *r* for correlation between gray matter volumetric differences and scores on scales of anxiety, depression, and childhood trauma. Given significant between-group differences in anxiety and depression scales, the FMD and HC populations were considered separately in correlations including these scales.

^a*p* = 0.016.

^b*p* = 0.035.

^c*p* = 0.014.

^d*p* = 0.0003.

are noteworthy as they provide important evidence that patients with FMD possess not only altered functional brain connectivity, as previously described, but also structural alterations that are not readily identifiable on routine clinical MRI brain.

Several observations bolster our confidence in these findings. First, clusters were significant after multiple comparison correction at the whole brain level. Importantly, the whole-brain approach used in our analysis eliminates a priori bias in interpretation of our findings. Second, similar findings were obtained when performing analysis in a subset of non-medicated patients with FMD and their matched HCs, as well

as in a subset of female participants. Third, volumetric differences in most of the regions identified in our analysis did not correlate with anxiety or depression symptoms, suggesting that the findings may be specific to FMD.

Our study is the largest to date examining GM structural changes in patients with FMD, and the only study specifically examining these changes in patients with hyperkinetic FMD. Several of our observations are consistent with structural neuroimaging studies in patients with other functional neurologic symptoms. Reduced GMV in the bilateral precentral and postcentral gyri has also been described in patients with psychogenic nonepileptic seizures.⁹ In contrast, increased volume of the bilateral premotor cortex¹¹ and reduced volume of the left thalamus¹² have been reported in patients with functional paresis. Differences between studies may in part reflect differences in methodology, given that VBM, used in our study, reflects both cortical surface area as well as GMV, whereas voxel-based cortical thickness, used to analyze the cohort with functional paresis,¹¹ directly measures cortical ribbon thickness. The disparity between studies may also stem from differences between patient populations, and reflect differing underlying brain structure in patients with hyperkinetic vs hypokinetic functional motor symptoms. While our study was not sufficiently powered to examine the effect of different types of functional motor symptoms (e.g., tremor, dystonia, paresis) on brain structure, this merits further exploration in future studies.

Our findings reinforce a growing body of research implicating abnormalities in limbic and sensorimotor networks in patients with FMD. It is intriguing that many of the brain regions

Table 4 Correlations between gray matter volumetric differences and disease measures

Cluster	Duration	Severity
L putamen, amygdala	-0.16	0.05
R thalamus	0.14	-0.03
L thalamus	-0.06	0.03
L caudate	0.13	0.07
R thalamus	0.14	0.04
L precentral, postcentral	0.04	-0.08
L postcentral	0.16	-0.13

Sample includes patients with functional movement disorders (n = 48). Values given are Spearman *r* for correlation between gray matter volumetric differences and measures of disease duration or severity.

identified in our volumetric study have been previously demonstrated to exhibit altered activity and functional connectivity in patients with FMD. Heightened activity in response to valenced stimuli has been demonstrated in both the right³ and left amygdalae.^{4,31} Altered functional activation has also been described in a number of subcortical structures, with increased functional activity in the basal ganglia and cerebellum of functional dystonia patients⁶ and decreased functional activity in the basal ganglia and thalamus of functional paresis patients.⁵ Altered functional connectivity between the left amygdala and the supplementary motor area has been demonstrated in patients with FND while performing a combined emotional-sensorimotor task, potentially suggesting a link between the circuitries involved in dysregulated emotional processing and motor control.³¹ While the similarity in affected regions across functional and structural neuroimaging studies is thought-provoking, it remains difficult to ascertain whether differences in functional activation and connectivity contribute to structural alterations, or whether the converse is true. Future studies should investigate whether structural connectivity, in particular white matter tracts originating from regions identified in this study, also differs in patients with FMD.

The lateralization of our imaging findings to the left side of the brain is quite striking. We did not observe between-group differences in handedness or a significant effect of symptom lateralization on volumetric differences, suggesting that these potential sources of bias do not contribute to our findings. Prior work from functional neuroimaging studies and lesion studies provides evidence for lateralization of amygdala function, with studies suggesting that emotional stimuli enhanced by verbal or conscious processing preferentially activate the left amygdala,^{32,33} and enhanced perception of aversive words depends specifically on the left amygdala.³³ Left lateralized abnormalities in emotion processing have also been previously demonstrated in patients with FMD, including hypoactivation in the left motor and insular cortices in response to intense emotional stimuli³⁴ and hyperactivation of the left amygdala during simultaneous negative emotional stimulation and passive movement of the symptomatic hand.³¹ Further studies are needed to further probe the relationship between these lateralized abnormalities in emotional processing and the structural abnormalities we describe here.

Strengths of our study include the large sample size and the extensive psychometric characterization of patients and HCs. Given the high comorbidity of mood and anxiety disorders among patients with FMD, the history of mood or anxiety disorder in a considerable fraction of our HCs (12/55 HCs with history of anxiety and 10/55 HCs with history of depression) rendered our HCs a more appropriate control group than a cohort without history of mental illness.

Our extensive psychometric characterization allowed us to assess correlations between volumetric differences and psychiatric comorbidities, including depression, anxiety, and

childhood trauma exposure. With the exception of 2 weak correlations between volumetric differences and psychometric scores, our analysis failed to detect significant associations between anxious or depressive symptoms and alterations in GMV, suggesting that the differences in GMV detected in this study are independent of these comorbidities. Participants with increased childhood trauma exposure exhibited larger volume of the left caudate and left cerebellar tonsil. These data contrast with prior studies demonstrating that individuals with greater early life stress, both healthy controls^{35,36} as well as depressed patients,³⁷ exhibit decreased right caudate volume. However, GM vulnerabilities may depend not only on total childhood maltreatment, but also on maltreatment subtype,³⁸ presence of recent stressors,³⁹ and gene by environment interactions.⁴⁰ Differences in these variables may account in part for the inconsistency between our findings and that of other groups.

Our analysis did not show significant correlation between volumetric differences and measures of disease duration and severity. Using a self-reported scale of functional neurologic symptoms, another group similarly failed to find an association between symptom severity and cingulo-insular volume in an FND patient cohort.³⁰ When using a stratified group-level analysis, this same group demonstrated that patients with FND with high self-reported impairments in physical and mental health exhibited structural differences when compared to HCs while those with low self-reported impairments did not, suggesting that symptom burden may in fact correlate with GM differences in those patients with a high symptom burden.¹⁴ The presence or absence of a correlation between volumetric differences and disease severity must, however, be considered cautiously given the lack of a well-validated clinical rating scale for objective, standardized FMD symptom assessment. Our study and those cited above highlight the need for a standardized battery of tools for accurate and objective assessment of FMD symptom severity in future studies.

Our study has several limitations. First, the lack of a well-validated clinical rating scale for FMD limits our ability to detect a meaningful relationship between disease severity and structural changes. Second, over half of our patients with FMD were taking CNS-acting medications, which may affect GMV. However, our volumetric analysis of a subset of non-medicated participants produced similar results to those observed with the larger cohort, suggesting that our findings are independent of medication effect. As an additional limitation, correction for multiple comparisons was not performed for the post hoc correlation analysis given the exploratory nature of this part of the investigation. However, this limitation does not influence our important finding that volumetric changes in patients with FMD were independent of anxiety and depression scores.

Our results demonstrate abnormalities in GMV in critical components of the limbic and motor circuitry in patients with FMD. It remains unclear whether these structural findings are

a cause or consequence of the disorder; these structural abnormalities could represent a premorbid trait predisposing patients to disease, the disease itself, or an adaptive response to disease. The recent finding that children with FND also exhibit volumetric differences, in the absence of the psychiatric comorbidities and long history of medication use often seen in adult cohorts, supports the idea that abnormalities in brain structure in FND may be intrinsic to the disease or experience-dependent plasticity inherent to the disease.¹³ Longitudinal studies tracking patients' symptoms in addition to structural and functional neuroimaging data, both over time as well as in response to successful treatment regimens, may help to address this important question.

Author contributions

C.W. Maurer: drafting initial manuscript, manuscript revision, study design, data acquisition, data analysis. K. LaFaver: manuscript revision, study design, data acquisition, data analysis. G.S. Limachia: data analysis, manuscript revision. G. Capitan: data analysis, manuscript revision. R. Ameli: manuscript revision, data acquisition. S. Sinclair: manuscript revision, data acquisition. S.A. Epstein: manuscript revision, study design, data acquisition, data analysis. M. Hallett: manuscript revision, study design, data acquisition, data analysis. S.G. Horovitz: manuscript revision, study design, data acquisition, data analysis.

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Disclosure

C.W. Maurer has performed consulting work for the Gerson Lehrman Group. K. LaFaver is performing contracted work for Pfizer and is a consultant for the Gerson Lehrman Group. G.S. Limachia, G. Capitan, R. Ameli, S. Sinclair, and S.A. Epstein report no disclosures relevant to the manuscript. M. Hallett serves as Chair of the Medical Advisory Board for and may receive honoraria and funding for travel from the Neurotoxin Institute. He may accrue revenue on US Patent #6,780,413 B2 (issued August 24, 2004): Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders and US Patent #7,407,478 (issued August 5, 2008): Coil for Magnetic Stimulation and methods for using the same (H-coil); in relation to the latter, he has received license fee payments from the NIH (from Brainsway) for licensing of this patent. He is on the Editorial Board of approximately 20 journals, and received royalties and/or honoraria from publishing from Cambridge University Press, Oxford University Press, and Elsevier. Dr. Hallett's research at the NIH is largely supported by the NIH Intramural Program. Supplemental research funds have been granted by UniQure for a clinical trial of AAV2-GDNF for Parkinson Disease, Merz for treatment studies of focal hand

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References

- Stone J, Carson A, Duncan R, et al. Who is referred to neurology clinics? The diagnoses made in 3781 new patients. *Clin Neurol Neurosurg* 2010;112:747–751.
- Aybek S, Vuilleumier P. Imaging studies of functional neurologic disorders. *Handb Clin Neurol* 2016;139:73–84.
- Voon V, Brezing C, Gallea C, et al. Emotional stimuli and motor conversion disorder. *Brain* 2010;133:1526–1536.
- Aybek S, Nicholson TR, O'Daly O, Zelaya F, Kanaan RA, David AS. Emotion-motion interactions in conversion disorder: an fMRI study. *PLoS One* 2015;10:e0123273.
- Vuilleumier P, Chicherio C, Assal F, Schwartz S, Slosman D, Landis T. Functional neuroanatomical correlates of hysterical sensorimotor loss. *Brain* 2001;124:1077–1090.
- Schrag AE, Mehta AR, Bhatia KP, et al. The functional neuroimaging correlates of psychogenic versus organic dystonia. *Brain* 2013;136:770–781.
- Voon V, Gallea C, Hattori N, Bruno M, Ekanayake V, Hallett M. The involuntary nature of conversion disorder. *Neurology* 2010;74:223–228.
- Maurer CW, LaFaver K, Ameli R, Epstein SA, Hallett M, Horovitz SG. Impaired self-agency in functional movement disorders: a resting-state fMRI study. *Neurology* 2016;87:564–570.
- Labate A, Cerasa A, Mula M, et al. Neuroanatomic correlates of psychogenic non-epileptic seizures: a cortical thickness and VBM study. *Epilepsia* 2012;53:377–385.
- Atmaca M, Aydin A, Tezcan E, Poyraz AK, Kara B. Volumetric investigation of brain regions in patients with conversion disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30:708–713.
- Aybek S, Nicholson TR, Draganski B, et al. Grey matter changes in motor conversion disorder. *J Neurol Neurosurg Psychiatry* 2014;85:236–238.
- Nicholson TR, Aybek S, Kempton MJ, et al. A structural MRI study of motor conversion disorder: evidence of reduction in thalamic volume. *J Neurol Neurosurg Psychiatry* 2014;85:227–229.
- Kozłowska K, Griffiths KR, Foster SL, Linton J, Williams LM, Korgaonkar MS. Grey matter abnormalities in children and adolescents with functional neurological symptom disorder. *Neuroimage Clin* 2017;15:306–314.
- Perez DL, Williams B, Matin N, et al. Corticolimbic structural alterations linked to health status and trait anxiety in functional neurological disorder. *J Neurol Neurosurg Psychiatry* 2017;88:1052–1059.
- Williams DT, Ford B, Fahn S. Phenomenology and psychopathology related to psychogenic movement disorders. *Adv Neurol* 1995;65:231–257.
- Epstein SA, Maurer CW, LaFaver K, Ameli R, Sinclair S, Hallett M. Insights into chronic functional movement disorders: the value of qualitative psychiatric interviews. *Psychosomatics* 2016;57:566–575.
- Maurer CW, LaFaver K, Ameli R, Toledo R, Hallett M. A biological measure of stress levels in patients with functional movement disorders. *Parkinson Relat Disord* 2015;21:1072–1075.
- Maurer CW, Liu VD, LaFaver K, et al. Impaired resting vagal tone in patients with functional movement disorders. *Parkinson Relat Disord* 2016;30:18–22.
- Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;32:50–55.
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62.
- First MB, Spitzer RL, Gibbon M, Williams J. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (SCID-I/P, 1/2007 Revision): Biometrics Res [online]. New York: NYSPI; 2002.
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–571.
- Spielberger CD, Gorsuch RL, Lushene RE, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. Palo Alto: Consult Psychol Press; 1983.
- Bernstein DP, Fink L, Handelsman L, et al. Initial reliability and validity of a new retrospective measure of child abuse and neglect. *Am J Psychiatry* 1994;151:1132–1136.
- Douaud G, Smith S, Jenkinson M, et al. Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. *Brain* 2007;130:2375–2386.
- Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 2001;14:21–36.
- Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004;23(suppl 1):S208–S219.
- Senjem ML, Gunter JL, Shiung MM, Petersen RC, Jack CR Jr. Comparison of different methodological implementations of voxel-based morphometry in neurodegenerative disease. *Neuroimage* 2005;26:600–608.
- Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. *Neuroimage* 2014;92:381–397.

30. Perez DL, Matin N, Barsky A, et al. Cingulo-insular structural alterations associated with psychogenic symptoms, childhood abuse and PTSD in functional neurological disorders. *J Neurol Neurosurg Psychiatry* 2017;88:491–497.
31. Hassa T, Sebastian A, Liepert J, Weiller C, Schmidt R, Tuscher O. Symptom-specific amygdala hyperactivity modulates motor control network in conversion disorder. *Neuroimage Clin* 2017;15:143–150.
32. Morris JS, Ohman A, Dolan RJ. Conscious and unconscious emotional learning in the human amygdala. *Nature* 1998;393:467–470.
33. Anderson AK, Phelps EA. Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature* 2001;411:305–309.
34. Espay AJ, Maloney T, Vannest J, et al. Dysfunction in emotion processing underlies functional (psychogenic) dystonia. *Mov Disord* 2018;33:136–145.
35. Cohen RA, Grieve S, Hoth KF, et al. Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. *Biol Psychiatry* 2006;59:975–982.
36. Dannlowski U, Stuhrmann A, Beutelmann V, et al. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biol Psychiatry* 2012;71:286–293.
37. Saleh A, Potter GG, McQuoid DR, et al. Effects of early life stress on depression, cognitive performance and brain morphology. *Psychol Med* 2017;47:171–181.
38. Edmiston EE, Wang F, Mazure CM, et al. Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. *Arch Pediatr Adolesc Med* 2011;165:1069–1077.
39. Paquola C, Bennett MR, Hatton SN, Hermens DF, Lagopoulos J. Utility of the cumulative stress and mismatch hypotheses in understanding the neurobiological impacts of childhood abuse and recent stress in youth with emerging mental disorder. *Hum Brain Mapp* 2017;38:2709–2721.
40. Frodl T, Reinhold E, Koutsouleris N, et al. Childhood stress, serotonin transporter gene and brain structures in major depression. *Neuropsychopharmacology* 2010;35:1383–1390.