Impaired self-agency in functional movement disorders

A resting-state fMRI study

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ABSTRACT

Objective: To investigate the neural mechanisms underlying impaired self-agency in patients with functional movement disorders using resting-state functional MRI (fMRI).

Methods: We obtained resting-state fMRI on 35 patients with clinically definite functional movement disorders and 35 age- and sex-matched healthy controls. Between-group differences in functional connectivity from the right temporo-parietal junction (TPJ), a region previously demonstrated to play a critical role in self-agency by comparing internal predictions of movement with actual external events, were assessed using *t* tests. All participants were screened for psychiatric diagnoses using a structured clinical interview and completed the Beck Depression Inventory and Childhood Trauma Questionnaire.

Results: Compared to the healthy controls, patients with functional movement disorders showed decreased functional connectivity between the right TPJ and the right sensorimotor cortex, cerebellar vermis, bilateral supplementary motor area, and right insula. These findings were independent of depression, anxiety, and childhood trauma scores included in our assessment as covariates.

Conclusions: The decreased functional connectivity between the right TPJ and bilateral sensorimotor regions observed in patients with functional movement disorders supports a model whereby impaired motor feed-forward together with altered sensory feedback from sensorimotor regions and areas of sensorimotor integration to the right TPJ contributes to patients' impaired sense of self-agency. ***Neurology*® 2016;87:564–570**

GLOSSARY

AFNI = Analysis of Functional Neuroimages; **ALFF** = amplitude of low-frequency fluctuation; **BDI** = Beck Depression Inventory; **BOLD** = blood oxygenation level-dependent; **CTQ** = Childhood Trauma Questionnaire; **FC** = functional connectivity; **FMD** = functional movement disorders; **fMRI** = functional MRI; **FoV** = field of view; **HAM-A** = Hamilton Anxiety Rating Scale; **HAM-D** = Hamilton Rating Scale for Depression; **HC** = healthy control; **ME-ICA** = multi-echo independent component analysis; **MEMPRAGE** = multi-echo magnetization-prepared rapid gradient echo; **MNI** = Montreal Neurological Institute; **rTPJ** = right temporo-parietal junction; **SCID** = Structured Clinical Interview for DSM-IV-TR, Patient Edition; **SMA** = supplementary motor area; **TE** = echo time; **TR** = repetition time.

Patients with functional movement disorders (FMD) comprise roughly half of patients with functional neurologic symptoms, and represent one of the more common disorders referred to the modern neurology clinic.[1] Despite its prevalence, the mechanisms underlying FMD remain poorly understood.

Impairment in self-agency, the sense that one is controlling one's own actions, is a characteristic feature of FMD,[2] with patients reporting lack of voluntary control over their abnormal movements despite physiologic evidence demonstrating that these movements use voluntary motor pathways. According to the influential comparator model, the sense of self-agency relies upon a constant monitoring of whether an action's consequences occur as predicted.[3] In this model, the right temporo-parietal junction (rTPJ) plays the critical role of mismatch detector, comparing internal predictions of movement with feedback from actual external events.[4,5] Previous task-based functional neuroimaging has demonstrated hypoactivity and impaired

Editorial, page 554

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From the Human Motor Control Section, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke (C.W.M., K.L., M.H., S.G.H.), and Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health (R.A.), National Institutes of Health, Bethesda, MD; Department of Neurology (K.L.), University of Louisville, KY; and Department of Psychiatry (S.A.E.), Georgetown University, Washington, DC.

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functional connectivity (FC) of the rTPJ during functional tremor,[6] suggesting that altered connectivity of the rTPJ may contribute to impaired self-agency in patients with FMD.

Resting-state MRI provides an approach to examining functional neural networks in the absence of any explicit task. Functional neural networks are identified by correlations of spontaneous fluctuations in blood oxygen levels (blood oxygenation level–dependent [BOLD]).[7,8] In this study, we sought to investigate the neural mechanisms contributing to impaired self-agency in patients with FMD by exploring group differences in resting-state FC from the rTPJ between patients with FMD and age- and sex-matched healthy controls (HCs).

METHODS

Participants. Thirty-five patients with clinically definite FMD,[9] as diagnosed by at least 2 movement disorders specialists (including M.H.), were recruited from the Human Motor Control clinic at the NIH between October 2011 and November 2014. Thirty-five 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 not dealing with neuroimaging.[10] Exclusion criteria for all participants included (1) comorbid neurologic disease; (2) psychotic disorder, bipolar disorder, current substance abuse, or current depressive episode; (3) history of traumatic brain injury with loss of consciousness; (4) active autoimmune disorder; (5) current suicidal ideation; (6) disease severity requiring inpatient treatment; (7) use of tricyclic antidepressants or antiepileptic medication; (8) contraindication for MRI; and (9) pregnancy. To help ensure recruitment of a healthy control population currently free of psychiatric disease, HCs were additionally excluded for use of any antidepressant medication within the prior 6 months. Of note, none of our HCs was currently taking any type of CNS-acting medications (table 1). Participants were continued on any preexisting medications throughout the study.

Standard protocol approvals, registrations, and participant consents. All participants provided written informed consent. The NIH Institutional Review Board approved the study.

Neuropsychological measurements. All participants met with an experienced clinical psychologist (R.A.), who administered the Hamilton Anxiety Rating Scale (HAM-A)[11] and Hamilton Rating Scale for Depression (HAM-D),[12] and screened participants for psychiatric diagnoses using the Structured Clinical Interview for DSM-IV-TR, Patient Edition (SCID).[13] Participants also completed the Beck Depression Inventory (BDI)[14] and Childhood Trauma Questionnaire (CTQ).[15]

Imaging acquisition. Structural and functional 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 T1-weighted anatomical MRI (multi-echo magnetization-prepared rapid gradient echo [MEMPRAGE], voxel size 1 × 1 × 1 mm; repetition time [TR] 400 ms; echo time [TE] 1.69 ms; echo spacing 9.8 ms; number of echoes 4; bandwidth 650 Hz/Px; inversion time 1,100 ms; flip angle 7°; acceleration factor 2; matrix size 176 × 256 × 256; field of view [FoV] 256 mm, acquisition time: 6 minutes 2 seconds). Functional images were collected using a T2-weighted multi-echoplanar imaging sequence (voxel size 3 × 3 × 3 mm; TR 2,000 ms; TE 11/22/33 ms; flip angle 70°; FoV 210 mm, phase FoV 87.5%, acceleration factor 3, number of slices 34; interleaved, bandwidth 2,552 Hz/Px; repetitions: 180) for 6 minutes. Two runs were collected per participant. During acquisition of functional MRI (fMRI), participants were instructed to remain as still as possible, close their eyes, remain awake, and not think of anything in particular.

Data preprocessing. The MEMPRAGE images were averaged across echoes, and used for registration. fMRI image processing and analysis were performed using the Analysis of Functional Neuroimages (AFNI) software.[16] The AFNI tool meica.py, a technique demonstrated to remove complex artifacts such as motion by using TE dependence as a measure of BOLD signal, was used for preprocessing as previously described.[17] We normalized the echoplanar imaging volumes to the MNI_caez_N27 template, and smoothed them with a 4.5-mm full-width-half-maximum Gaussian kernel. The 2 runs were concatenated before TE

Table 1 Demographic and clinical characteristics

	Patients with FMD (n = 35)	Healthy controls (n = 35)
Age, y	43.6 ± 10.6 (26-62)	40.6 ± 9.9 (24-61)
Sex, F/M	28/7	25/10
Taking CNS-acting medication, n[a]	20	0
Disease duration, y	4.9 ± 5.1 (0.4-19)	—
HAM-A	13.6 ± 7.7[b] (0-34)	2.7 ± 2.5 (0-8)
HAM-D	9.9 ± 6.1[b] (0-26)	2.1 ± 1.5 (0-5)
BDI	8.4 ± 7.2[b] (0-31)	3.2 ± 4.4 (0-19)

Abbreviations: FMD = functional movement disorders; BDI = Beck Depression Inventory; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression.
Data are presented as the mean ± SD (range) unless otherwise indicated.
[a] CNS-acting medications included clonazepam (n = 7), alprazolam (n = 2), trihexyphenidyl (n = 2), gabapentin (n = 4), baclofen (n = 1), sertraline (n = 2), citalopram (n = 1), escitalopram (n = 2), duloxetine (n = 1), desvenlafaxine (n = 1), venlafaxine (n = 1), Adderall (n = 1), acetazolamide (n = 2), carbidopa/levodopa (n = 1), and ropinirole (n = 1).
[b] $p < 0.001$.

dependence analysis. Denoised time courses were bandpass filtered ($0.01 < f < 0.1$ Hz) in AFNI to obtain the resting state fluctuations of the BOLD signal.

FC and statistical analysis. The rTPJ was defined as the seed, using average coordinates derived from a meta-analysis of 15 imaging studies investigating the role of the rTPJ in the sense of self-agency (Montreal Neurological Institute [MNI] 51, −46, 31).[5] Groupwise comparison between patients and HCs was performed using the AFNI tool 3dGroupInstaCorr. Between-group 2-sample *t* tests were performed, with age, sex, HAM-D score, HAM-A score, BDI score, and scores on CTQ as covariates, to detect significant differences between groups (voxel-level p value <0.02; cluster size >28 voxels; determined by a Monte-Carlo simulation resulted in a cluster-level significance threshold of $p < 0.05$).

To confirm that the differences in FC do not exist throughout the brain in patients with FMD compared to HCs, we also performed groupwise comparison of FC using the right posterior cingulate (MNI −10, 54, 14), a central component of the default mode network,[18] as a control seed.

To rule out differences due to hypoactivity in the rTPJ seed region, we compared spontaneous neuronal activity in the rTPJ in patients and HCs. To accomplish this, we performed between-group 2-sample *t* tests of the amplitude of low-frequency fluctuation (ALFF).[19]

Motion within the scanner might also potentially confound between-group differences in FC. To control for possible differences, we compared the mean and SD of resting-state BOLD time courses extracted from the right and left precentral gyri, computed for each participant. We also compared the number of TE-dependent components detected for each group.

To confirm that participants in both groups maintained their eyes closed during acquisition of resting-state fMRI sequences, we examined V1 connectivity using Brodmann area 17 (MNI −4, −93, 9) as our seed. Previous studies have demonstrated increased coherence of the visual cortex during the eyes closed relative to the eyes open with visual fixation condition.[20] Given evidence demonstrating that spontaneous BOLD signal fluctuations in the visual cortex increase during sleep,[21] we additionally compared the SD of resting-state BOLD time courses extracted from V1, computed for each participant.

Group differences in use of CNS-acting medication might also confound between-group differences in FC. To address this, we compared the FC correlation maps for medicated vs nonmedicated patients.

Two-sided Student *t* tests were used to evaluate for statistically significant differences between groups. Significance threshold was set at $p < 0.05$.

To test for correlation between rTPJ FC and levels of childhood trauma, we performed linear regression analysis of mean z connectivity to CTQ subscore. Outliers in FC were removed using Prism 6.0 (ROUT method, Q = 1%). To examine the relationship between disease duration and rTPJ FC, we calculated Pearson correlation coefficients.

Table 2 Quantification of childhood trauma

	Patients with FMD	Healthy controls	*p* Value
Emotional	9.8 ± 5.7	7.8 ± 3.3	0.08
Physical	7.7 ± 3.6	6.7 ± 2.2	0.17
Sexual	7.1 ± 4.5	6.4 ± 4.0	0.47
Emotional neglect	9.1 ± 4.7	10.0 ± 4.6	0.44
Physical neglect	6.3 ± 1.8	6.5 ± 3.0	0.74

Abbreviation: FMD = functional movement disorders.
Data are presented as mean ± SD. Childhood trauma quantified using Childhood Trauma Questionnaire.

RESULTS

Demographic and clinical characteristics. Seventy participants, consisting of 35 patients with FMD and an equal number of age- and sex-matched HCs, were included in the analysis. Groups did not differ in terms of demographic data (table 1). Patients scored considerably higher than the HCs on various assessments of anxiety and depression (table 1). There were no between-group differences in terms of exposure to childhood trauma (table 2). Clinically, patients reported average disease duration of 4.9 years (SD 5.1). Patients self-reported a range of involuntary movements, including tremor (74%), other jerking movements (63%), abnormal gait and/or balance (63%), abnormal speech (46%), abnormal posturing/dystonia (43%), and paresis (31%).

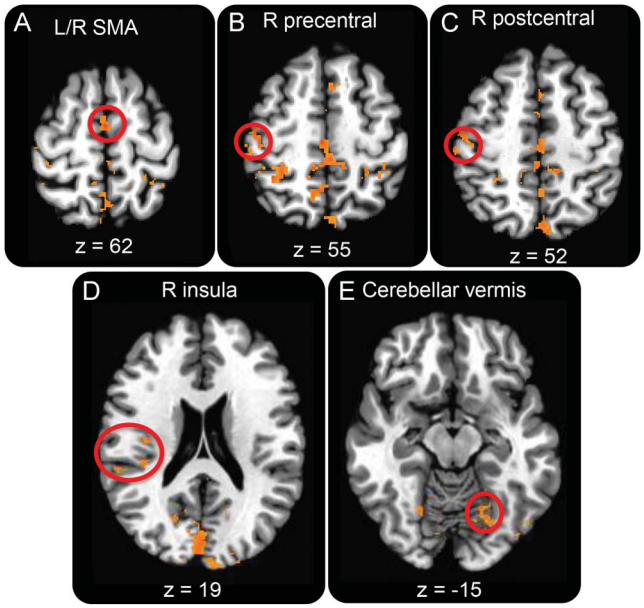
Image preprocessing. As quality control, we confirmed that the number of BOLD components derived from multi-echo independent component analysis (ME-ICA) preprocessing did not differ between the 2 groups (mean BOLD components: 22.8 for HCs, 22.9 for patients, $p = 0.96$).

To test for differences in overall motion, we calculated the mean and SD of the resting-state BOLD time courses extracted from the right and left precentral gyri, and found that these values did not differ between patients and HCs (right precentral gyrus: p for mean and SD = 0.96 and 0.62, respectively; left precentral gyrus: p for mean and SD = 0.77 and 0.47, respectively). We confirmed that both groups exhibited a pattern of FC from V1 consistent with the eyes-closed condition (figure e-1 on the *Neurology*® Web site at Neurology.org).[20] In addition, the SD of the resting-state BOLD time courses extracted from V1 did not differ between patients and HCs ($p = 0.25$), suggesting that the level of alertness did not vary between groups.

As an additional control, we verified that the spontaneous neural activity in the rTPJ did not vary between patients and HCs by comparing the ALFF between the 2 groups (data not shown, $p > 0.05$).

Differences in resting-state FC between patients with FMD and HCs. Compared to the HCs, patients with FMD exhibited decreased rTPJ resting-state FC with bilateral sensorimotor regions: notably right sensorimotor cortex, cerebellar vermis, bilateral supplementary motor area (SMA), and right insula (figure 1). A complete list of regions is presented in table 3. There were no group differences in the

Figure 1 **Decreased functional connectivity (FC) between the right temporoparietal junction (rTPJ) and bilateral sensorimotor regions in patients with functional movement disorders (FMD)**



Maps demonstrate group differences in rTPJ resting-state FC between patients with FMD and healthy controls. Images show decreased FC in patients with FMD between the rTPJ (seed) and the (A) bilateral supplementary motor area (SMA) (circled), (B) right precentral gyrus (circled), (C) right postcentral gyrus (circled), (D) right insula (circled), and (E) cerebellar vermis (circled). The threshold for display was set at $p < 0.02$; cluster size >28 voxels.

correlation between rTPJ FC and age, sex, anxiety, or depression scores. Disease duration did not correlate with FC from the rTPJ (table e-1). Additionally, there were no differences in resting-state FC between patients with FMD and HCs for the right posterior cingulate seed.

Given between-group differences in the use of CNS-acting medication (table 1), we assessed the effect of medication use by comparing FC from the rTPJ in medicated vs nonmedicated patients. With the exception of FC to the left superior frontal gyrus, the use of CNS-acting medication did not affect FC from the rTPJ (table e-2).

Although childhood trauma scores did not vary between groups (table 2), exposure to childhood emotional abuse was found to differentially influence rTPJ FC. Compared to HCs, patients exhibited increased FC between the rTPJ and the left insula with increasing levels of childhood emotional abuse (figure 2). There were no group differences in correlations between rTPJ FC and childhood sexual abuse, physical abuse, physical neglect, or emotional neglect scores.

DISCUSSION Impaired self-agency is a key feature of patients with FMD. It is readily evident on patients' self-reports of their involuntary movements, and supported by performance on indirect assessments of self-agency, including intentional binding and sensory attenuation paradigms.[22–24] In this study, we examined the mechanism underlying impaired self-agency in patients with FMD using resting-state functional MRI. We demonstrated decreased FC in patients with FMD between the rTPJ, a region known to play a critical role in the self-agency network, and bilateral sensorimotor regions, including right sensorimotor cortex, bilateral cerebellum, bilateral SMA, and right insula.

This resting-state fMRI analysis provides important evidence supporting organic abnormalities in FC in patients with FMD. This is particularly relevant given the persistent false belief among many neurologists that functional neurologic symptoms are commonly feigned, and that many patients are malingering.[25,26]

Furthermore, our work provides evidence for a model underlying impaired self-agency in patients with FMD. Numerous studies have implicated the rTPJ as playing a critical role in the self-agency network,[4,5,27,28] acting as a mismatch detector by processing discrepancies between motor intentions and motor consequences.[4,5] We propose that the impaired FC found in patients with FMD in our study between the rTPJ and right sensorimotor cortex and bilateral cerebellum reflects impaired motor feed-forward and sensory feedback signaling to the rTPJ. The SMA, also demonstrated to exhibit decreased FC to the rTPJ in our patient population, has been demonstrated to contribute to the phenomenon of intentional binding,[29] whereby motor intention is temporally matched with sensory feedback. The impaired FC between the rTPJ and this area of sensorimotor integration may also contribute to the impaired sense of self-agency in patients with FMD.

Our results are consistent with findings from a task-based, within-subject fMRI study of 8 patients with functional tremor. This study detected hypoactivity of the rTPJ during functional vs mimicked tremor. Furthermore, the authors demonstrated altered task-related FC between the rTPJ and bilateral sensorimotor cortex, cerebellar vermis/declive, right cuneus, and bilateral anterior cingulate,[6] many of the same regions that we have identified in our resting-state analysis. While the previously performed study was limited to patients with functional tremor, our study included patients with a variety of functional movements, suggesting greater generalizability of our model for impaired self-agency in patients with conversion motor symptoms. Additional studies could explore whether a similar mechanism is applicable to other disorders characterized by impaired self-agency.

Several of the regions identified in our study, including the right insula, left SMA, right inferior parietal, left cerebellum, right middle temporal, right precuneus, and right superior temporal regions, have been previously identified as being functionally connected,

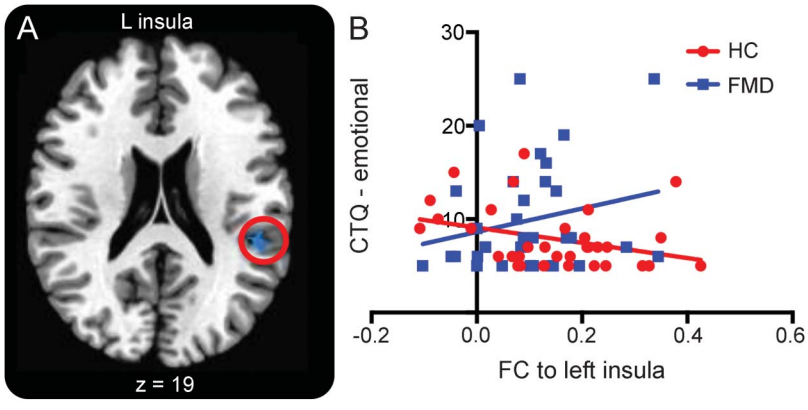
Table 3 Statistically significant differences in right temporo-parietal junction (rTPJ) functional connectivity (FC) between healthy controls and patients with functional movement disorders

			Montreal Neurologic Institute coordinates			
Brain region	L/R	Cluster size, mm^3	x	y	z	Z score
Posterior cingulate	L/R	1,347	−6	64	7	4.67
Precuneus	L/R	383	−3	52	58	3.82
Middle temporal gyrus	R	126	−68	34	−10	3.91
Middle temporal gyrus	L	28	45	65	5	4.61
Insula	R	106	−56	34	19	3.93
Middle cingulate gyrus	L	99	3	−19	37	4.17
Inferior parietal lobule	R	95	−36	38	43	3.89
SMA	L/R	74	0	8	61	4.06
Middle occipital gyrus	L	62	45	80	−13	3.50
Precentral gyrus	R	59	−48	17	55	3.54
Postcentral gyrus	R	54	−56	23	52	4.02
Declive (vermis)	L	42	36	65	−19	4.05
Superior frontal gyrus	L	38	0	−57	31	4.13
Superior frontal gyrus	L	30	15	−60	31	3.37
Middle frontal gyrus	L	29	56	−19	34	3.62

Abbreviation: SMA = supplementary motor area.
A corrected threshold of $p < 0.05$ corrected by Monte Carlo was used; 2-sample *t* tests were performed with age, sex, Beck Depression Inventory score, and Childhood Trauma scores as covariates to test the group difference in FC from the rTPJ.

and playing a role in the leading network of self-agency.[30] This leading network, which also includes the rTPJ, is speculated to be involved in the process of mismatch detection. In this model, activation of the leading network is subsequently followed by lagging network activation, which is proposed to bring self-agency information to conscious awareness. Our analysis does not address potential impairments in this lagging network, which may also contribute to impaired self-agency in patients with FMD.

Figure 2 Childhood emotional trauma differentially affects right temporo-parietal junction (rTPJ) functional connectivity (FC) in patients with functional movement disorders (FMD)



Connectivity map and scatterplot demonstrate group differences in correlation between rTPJ resting-state FC to left insula and levels of childhood emotional trauma. Connectivity map (A) and adjacent scatterplot (B) demonstrate rTPJ FC in patients with FMD compared to healthy controls (HCs) with increasing levels of childhood emotional abuse. Scatterplot shows the relationship between mean *z* connectivity values and Childhood Trauma Questionnaire emotional abuse subscore for patients and HCs.

Strengths of our study include the relatively large sample size and the participants' extensive psychometric characterization. Importantly, the comprehensive psychometric characterization of both patients and HCs allowed us to control for comorbidities including depression, anxiety, and childhood trauma exposure. While our patient population scored higher on scales rating anxiety and depression, scores did overlap between the 2 groups. In addition, a considerable fraction of our HCs had a history of mood or anxiety disorder based on the results of the SCID (7/35 HCs with history of depression and 10/35 HCs with history of anxiety disorder), making them more appropriate controls than a cohort without any history of mental illness. Our extensive psychometric characterization allowed us to assess for group differences in rTPJ FC as they correlated to measures of depression, anxiety, and childhood trauma. No group differences were detected in terms of correlation between rTPJ FC and indices of depression, anxiety, childhood sexual abuse, physical abuse, physical neglect, or emotional neglect. We did detect group differences in correlation between rTPJ FC and childhood emotional abuse, with patients exhibiting increased FC between the rTPJ and the left insula

with increasing levels of childhood emotional abuse. Although the exact implication of this finding remains unclear, it is intriguing given previous studies demonstrating the adaptability of FC of the left insula in response to childhood trauma.[31]

One major limitation of our study is that over half of our patients were taking CNS-acting medications. However, we found that the FC values between the rTPJ and the bilateral sensorimotor regions identified in our study were similar between medicated and nonmedicated patients, and therefore independent of medication effect. We did detect a moderate difference in FC between the rTPJ and left anteromedial superior frontal gyrus between medicated and nonmedicated patients with FMD ($p = 0.02$). The anteromedial superior frontal gyrus has been demonstrated to be involved in the cognitive control and default mode networks,[32] which are known to be affected by CNS-acting medications.[33] However, the exact mechanism for how medication use affects FC between the rTPJ and the superior frontal gyrus remains unclear, and would merit further study.

Potential between-group differences in motion also represent a possible confounder. To minimize biases due to differences in head movement, we employed ME-ICA, a technique demonstrated to remove complex artifacts such as motion from resting-state data in an operator-independent manner[17] by acquiring data at multiple echo times, and using TE dependence as a measure of BOLD signal. In addition, we ruled out differences in overall movement and level of alertness between groups by examining resting-state BOLD time courses extracted from the right/left precentral gyri and V1, respectively.

Our patient group is also biased towards patients who are sufficiently accepting of a diagnosis of functional neurologic disorder that they are willing to participate in a study involving several days of inpatient evaluation. While in this respect study participants may not be entirely representative of the clinical population with this disorder, the consistency of our findings with previous work[6] suggests that our findings are likely representative of patients with clinically definite FMD.

While our work supports a functional disruption in self-agency in patients with FMD, it remains uncertain whether this disruption is a cause or consequence of the disorder. We have shown that impairments in rTPJ FC do not worsen with increasing disease duration; however, further studies would be necessary to explicitly prove that impairments in the self-agency network produce the symptoms characteristic of FMD. Exploring the changes to the self-agency network before and after successful treatment regimens, such as those advocating greater accountability and reinforcement of normal motor patterns,[34,35] might shed further light on this question.

Our results demonstrate deficits in resting-state FC between the rTPJ and regions involved in bilateral sensorimotor processing and integration in patients with FMD. Given the well-recognized role of the rTPJ in sense of self-agency, we propose that the deficits identified in our study contribute to the impaired self-agency that is characteristic of patients with FMD. Our findings may have important implications with respect to how neurologists, psychiatrists, patients, and their families conceptualize this often debilitating disorder.

AUTHOR CONTRIBUTIONS

C.W.M.: drafting initial manuscript, study design, data acquisition, data analysis. K.L.: manuscript revision, study design, data acquisition, data analysis. R.A.: manuscript revision, data acquisition. S.E.: manuscript revision, study design, data acquisition, data analysis. M.H.: manuscript revision, study design, data acquisition, data analysis. S.G.H.: manuscript revision, study design, data acquisition, data analysis.

STUDY FUNDING

Supported by the National Institute of Neurological Disorders and Stroke Intramural Research Program.

DISCLOSURE

C. Maurer reports no disclosures relevant to the manuscript. K. LaFaver has provided consulting services for US World Meds. R. Ameli and S. Epstein report no disclosures relevant to the manuscript. M. Hallett serves as Chair of the Medical Advisory Board for and receives honoraria and funding for travel from the Neurotoxin Institute. He may accrue revenue on US Patent: Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders, and US Patent: 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. Dr. Hallett's research at the NIH is largely supported by the NIH Intramural Program. Supplemental research funds have been granted by BCN Peptides, S.A., for treatment studies of blepharospasm; Medtronics, Inc., for studies of deep brain stimulation; UniQure for a clinical trial of AAV2-GDNF for Parkinson Disease; Merz for treatment studies of focal hand dystonia; and Allergan for studies of methods to inject botulinum toxins. S. Horovitz reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received October 15, 2015. Accepted in final form March 25, 2016.

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