

Clinical and neural responses to cognitive behavioral therapy for functional tremor

Alberto J. Espay, MD, MSc, Scott Ries, LISW, Thomas Maloney, MS, Jennifer Vannest, PhD, Erin Neefus, BS, CCRP, Alok K. Dwivedi, PhD, Jane B. Allendorfer, PhD, Lawson R. Wulsin, MD, W. Curt LaFrance, Jr, MD, MPH, Anthony E. Lang, MD, FRCP, and Jerzy P. Szaflarski, MD, PhD

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Correspondence

Dr. Espay
alberto.espay@uc.edu

Abstract

Objectives

To evaluate changes in tremor severity and motor/emotion-processing circuits in response to cognitive behavioral therapy (CBT) delivered as treatment for functional tremor (FT), the most common functional movement disorder in adults.

Methods

Fifteen patients with FT underwent fMRI with motor, basic-emotion, and intense-emotion tasks before and after 12 weeks of CBT. Baseline fMRI was compared to those of 25 healthy controls (HCs). The main clinical endpoint was the tremor score (sum of severity, duration, and incapacitation subscores) adapted from the Rating Scale for Psychogenic Movement Disorders (PMDRS) assessed by a blinded clinician. CBT responders were defined as those with PMDRS score reduction >75%. Anatomic and functional brain images were obtained with a 4T MRI system. Generalized linear model and region-of-interest analyses were used to evaluate before-versus-after treatment-related changes in brain activation.

Results

CBT markedly reduced tremor severity ($p < 0.01$) with remission/near remission achieved in 73.3% of the cohort. Compared to HCs, in those with FT, a functionally defined fMRI region of interest in the anterior cingulate/paracingulate cortex showed increased activation at baseline and decreased activation after CBT during basic-emotion processing ($p = 0.012$ for CBT responders). Among CBT responders, the change in anterior cingulate/paracingulate was more significant in those with more severe baseline depression ($r = 0.75$, $p < 0.01$).

Conclusions

Tremor severity improved significantly after CBT. The improvement was associated with changes in the anterior cingulate/paracingulate activity, which may represent a marker of emotional dysregulation in FT and a predictor of treatment response.

Classification of evidence

This study provides Class III evidence that CBT significantly improves tremor severity in patients with functional tremor.

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From the Gardner Family Center for Parkinson's Disease and Movement Disorders (A.J.E., E.N.); Mood Disorders Center (S.R., L.R.W.), University of Cincinnati Gardner Neuroscience Institute; Pediatric Neuroimaging Research Consortium (T.M., J.V.), Cincinnati Children's Hospital; Department of Pediatrics (J.V.), University of Cincinnati College of Medicine, OH; Department of Biomedical Sciences (A.K.D.), Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso; Department of Neurology (J.B.A., J.P.S.), University of Alabama at Birmingham; Division of Neuropsychiatry and Behavioral Neurology (W.C.L.), Rhode Island Hospital, Providence; and Edmond J. Safra Program in Parkinson's Disease and Morton and Gloria Shulman Movement Disorders Clinic (A.E.L.), Toronto Western Hospital, University of Toronto, Ontario, Canada.

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Glossary

AFNI = Analysis of Functional Neuroimages; **CBT** = cognitive behavioral therapy; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **FSL** = FMRIB Software Library; **FT** = functional tremor; **HAM-A** = Hamilton Anxiety Scale; **HAM-D** = Hamilton Depression Scale; **HC** = healthy control; **ICD-10** = *International Classification of Diseases, 10th revision*; **MINI** = Mini International Neuropsychiatric Interview; **PMDRS** = Rating Scale for Psychogenic Movement Disorders; **PNES** = psychogenic nonepileptic seizures; **ROI** = region of interest; **TFCE** = threshold-free cluster enhancement.

A phenotype-specific diagnosis of functional (psychogenic) tremor (FT) is achieved with clinically definite certainty when a tremor exhibits all of the following characteristics: (1) entrainment or full suppressibility; (2) distractibility; (3) tonic coactivation at tremor onset; (4) pause of tremor during contralateral ballistic movements; and (5) variability in frequency, axis, or distribution.¹ Although FT is the most common functional movement disorder in adults, its pathophysiologic underpinnings remain poorly understood. Recent therapeutic studies have focused on motor rehabilitation (specialist physiotherapy in a cohort of functional motor disorders, including 17% patients with FT² and tremor retraining/biofeedback in 10 patients³) but not on cognitive or behavioral interventions tailored to its neurobiology. There is no specific biomarker to help in the selection of patients for physical or psychological interventions, and the long-term prognosis of patients with FT remains poor.⁴

Cognitive behavioral therapy (CBT) is increasingly used to treat FT given the emergent evidence of efficacy in other functional neurologic disorders.⁵ CBT is a structured, time-limited therapy that helps patients identify how thinking affects emotional states or specific behaviors with an aim of inducing change in cognitions and behaviors around movements and interpersonal functioning. While typically manualized,⁵ this treatment can be tailored to individual patients on the basis of their experiences and cognitive frameworks.

Functional neuroimaging studies have suggested that functional neurologic disorders are network disorders and that the symptoms associated with the disruption of various parts of the networks may explain the observed variation in clinical symptoms.⁶ The neurobiological basis of FT has been examined only in small heterogeneous cohorts, largely in the resting state.^{7,8} In a recent fMRI study, we showed, using a basic-emotion task comparing FT with healthy controls (HCs), that FT is associated with alterations in several brain regions, including the anterior cingulate/paracingulate cortex.⁹ In that study, in response to emotional stimuli, patients with FT demonstrated alterations in functional connectivity in networks involved in emotion processing and theory of mind.⁹ However, it is unclear whether these alterations in fMRI signals or connectivity could constitute a biomarker of treatment response or normalize after a successful therapeutic intervention.¹⁰

In this prospective study of CBT, we sought to obtain data on the feasibility and efficacy of CBT for patients with clinically definite FT using cognitive elements from the model for intervening in psychogenic nonepileptic seizures (PNES)⁵ and to determine the extent to which neuronal circuits associated with emotion processing change in response to CBT in patients with FT. We hypothesized that CBT would reduce the tremor burden in at least half of the participants with FT and that activations in brain regions in response to emotional stimuli would change among those benefiting from treatment and possibly normalize or return to the level observed in HCs. Thus, the primary behavioral outcome measure was reduction in tremor, and the primary imaging outcome measure was reduction of activation in response to therapy in the a priori anterior cingulate/paracingulate region of interest (ROI). Although the network involved in the generation and maintenance of functional neurologic disorders is large,⁶ the anterior cingulate/paracingulate region was selected because of its known role in emotion processing, in theory of mind, and in the hyperactivity in FT vs HCs shown previously (from a study admittedly designed concurrently).⁹

Methods

Participants

We prospectively recruited 15 consecutively consenting patients over a 2-year period with clinically definite unilateral or asymmetric FT affecting the upper limbs according to established clinical criteria.¹ We chose this number of participants on the basis of prior sample size calculations suggesting that for a liberal significance threshold of 0.05, a minimum of 12 participants is required to achieve 80% power at the single-voxel level for typical activations while accounting for intraparticipant and interparticipant variability.¹¹ Tremor needed to be absent or minimal at rest to avoid interference with the scanning procedure. Patients were excluded if they did not understand and accept the FT diagnosis, had any comorbid functional movement or neurologic disorder, or were on benzodiazepines and were unable to discontinue them at the time of fMRI scanning. We also prospectively recruited 25 age- and sex-matched HCs with no history of neurologic or medical disorders. Patients with FT were consented for participation into a 12-week CBT program and an fMRI protocol before and after treatment. HCs underwent fMRI only once and were not subjected to the intervention. This study was approved by the local institutional review board, and all participants provided informed consent.

To reach the recruitment goal, we screened 22 patients with FT, of whom 7 were not recruited for the following reasons: 1 malingering (rather than conversion), 1 not meeting criteria for FT, 1 unwilling to provide consent, 1 unacceptance of diagnosis, 1 unable to undergo MRI due to prior neurosurgical procedure, and 2 (excluded after providing consent) with excessive tremor during scanning and inability to get comfortable in the scanner. Data excluded from final analyses due to noncompletion of the task or for data-quality issues were for basic-emotion processing task (1 HC) and intense-emotion processing task (1 FT, 1 HC).

Clinical measurements

The primary clinical endpoint for CBT was the tremor score (sum of severity, duration, and incapacitation subscores) adapted from the Rating Scale for Psychogenic Movement Disorders (PMDRS; range 0–128 [higher is worse])¹² through an offline video-based rating by a clinician blinded to treatment timing. Both participants with FT and HCs underwent a 15-minute structured diagnostic interview based on the Mini International Neuropsychiatric Interview (MINI)¹³ to screen for axis I DSM-IV and ICD-10 psychiatric disorders.¹⁴ We also administered the 17-item Hamilton Depression Scale (HAM-D)¹⁵ and the 14-item Hamilton Anxiety Scale (HAM-A)¹⁶ to evaluate for psychic and somatic anxiety. These scales were administered as part of a structured interview.

Cognitive behavioral therapy

CBT is a structured, time-limited therapy administered to help patients identify how thinking affects emotional states that express clinically as either physical symptoms or behaviors. On the basis of preliminary experience by the authors,⁵ patients with FT received 12 weekly CBT outpatient sessions with the following characteristics: structured 1-hour sessions were led by a social worker with 25 years of experience with CBT delivery (S.R.) with a preset agenda at the onset of each session; the therapist undertook an active and engaged stance, applying Socratic questioning (thoughtful inquiring by the therapist to elicit engaged dialog to examine underlying thoughts); and each session was followed by a specific homework assignment, building on the gains from the session. The primary structure used was consistent with Aaron Beck's model of cognitive therapy, making extensive use of thought monitoring, identification of cognitive distortions, and thought restructuring. The CBT sessions were adapted from the protocol developed previously for the management of PNES⁵ and included the same elements that were tailored to individual patients on the basis of the results of clinical interview performed before initiation of the intervention. Emphasis was placed on periods of tremor exacerbation between research visits, using these as opportunities to capture related automatic thoughts (thought monitoring) and to examine potential cognitive distortions that may have preceded them. The anxiety and depression scales were separately collected by the principal investigator (A.J.E.), but all patients received an initial orientation to the treatment process and the

intervention, as well as education on relapse prevention (techniques to manage reemergence of symptoms after completion of treatment) in combined sessions with the principal investigator and CBT provider. We defined responders as patients with complete remission or >75% reduction in PMDRS scores and partial responders as those with less benefit than responders.

fMRI procedure: tasks

The finger-tapping motor task

The finger-tapping motor task was made up of a 30-second block of right-only finger tapping, followed by a 30-second block of left-only tapping, followed by a 30-second block of inactivity (rest), all repeated in the same sequence 4 times. A visual prompt was presented every second, and participants were instructed to move a lever using their right or left index finger, according to whether the R or L was flashing, at the once-per-second rate. Compliance with tapping procedure was monitored visually by study personnel. The total task duration was 6 minutes; right and left tapping conditions were modeled separately with the blocks of inactivity (rest) treated as baseline in the analyses. This task was designed to assess and monitor the integrity of the motor system, hypothesized to be unaffected.

The basic-emotion face recognition task

The basic-emotion face recognition task presented participants with 120 different faces over 14 minutes, corresponding to unique (nonrepeating) facial identities depicting a particular emotion (sadness, happiness, or fear) or a neutral expression.¹⁷ This task was designed to assess response to basic-emotional stimuli. The processing of emotional expressions is thought to occur subliminally and automatically. However, it is dependent on attention to the task,¹⁸ which is engaged by asking participants to decide the sex of each face by pressing 1 of 2 buttons with the right thumb. Thirty prototypically happy, 30 sad, 30 fearful, and 30 neutral expressions were selected from the NimStim set of facial expressions¹⁹ and presented in random order. Each stimulus was presented for 2 seconds with variable interstimulus interval of 3.9 ± 2.4 seconds, during which a fixation cross appeared. The event-related design with variable interstimulus delay (jitter) was used to minimize habituation of activation, which may occur in block designs with highly repetitive and predictable stimulus presentation.²⁰ It is well recognized that activation by faces in some brain areas is strongly affected by attentional condition, while in other brain areas, it is not (e.g., amygdala response to fearful stimuli).²¹

The intense-emotion task

The intense-emotion task (continuous performance task with emotional and neutral distracters) used a series of offensive or disgusting images to engage intense-emotional circuitry.²² A visual oddball paradigm was constructed for this task in which 70% of the cues were squares, 10% were circles (targets), 10% were emotionally unpleasant pictures, and 10% were emotionally neutral pictures. Pictures originated from the

International Affective Picture System (University of Florida, Gainesville) and were selected according to previously used criteria.²³ Participants used the same response buttons as for the basic-emotion task and were asked to press with the right thumb a 2 for circles and 1 for all other images. There were 158 total items with a constant display time of 2.75 seconds and a 0.25-second interval with fixation cross. Items were split over 2 runs of the task in the imaging session with the content of each run being the same.

The behavioral experiments were programmed in E-Prime (version 1; pstnet.com). Stimuli were presented via magnetic resonance-compatible VGA goggles and headphones (Resonance Technologies, Inc, Los Angeles, CA). In each scanning session, echo-planar imaging was acquired during behavioral paradigms with a T2*-weighted gradient-echo planar imaging pulse sequence (repetition/echo time 3000/29 milliseconds, field of view 256 × 256 mm, matrix 64 × 64, slice thickness 4 mm, flip angle 75° with the behavioral paradigms precisely timed to image acquisition). To correct for geometric distortion and Nyquist ghost artifacts, a multi-echo reference scan was performed. A T1-weighted 3-D anatomic high-resolution scan using modified equilibrium Fourier transform sequence (repetition/echo time 13/6 milliseconds, T[MD] 1.1 seconds, field of view 192 × 256 × 256 mm, matrix 192 × 256 × 265, slice thickness 1 mm, flip angle 20°) was acquired.

Anatomic data

We used `fslreorient2std` from the FMRIB Software Library (FSL) to rotate data to standard orientation. Next, we performed bias correction and brain extraction on T1 anatomic scans using FSL's `FAST`²⁴ and `BET`,²⁵ respectively. Images were spatially normalized with FSL's `FLIRT`²⁶ to the 2-mm isotropic Montreal Neurological Institute ICBM 152 nonlinear sixth-generation template.²⁷ Subcortical segmentation was performed with FSL's `FIRST`.²⁸

Functional data

For each fMRI task data, typical preprocessing steps, including reorientation, slice timing correction, and brain extraction, were carried out with FSL's `fslreorient2std`, `slicetimer`, and `BET`,²⁵ respectively. We detected outlying functional volumes based on motion and intensity using FSL's `fsl_motion_outliers`. Motion correction of the blood oxygenation level-dependent time series was carried out next with `FLIRT`.²⁶ The functional file was interpolated to 2 × 2 × 2-mm voxel size and aligned to the Montreal Neurological Institute template²⁷ by coregistering it with the participant's T1 using FSL's `FLIRT`.^{26,29} Next, the motion related artifacts were regressed from the data by setting up a general linear model design using 24 motion parameters (6 motion parameters, the 6 motion parameters squared, a first-order autoregressive model of the 6 motion parameters, and a first-order autoregressive model of the 6 motion parameters squared) plus an additional parameter for each detected outlier.³⁰ A `CompCor` regression was also implemented using

the eigenvectors from the first 5 of 10 principal components within a white matter and CSF mask, respectively.³¹

Image processing and statistical analysis

Reconstruction of the raw data was performed with 3D Hamming filter using in-house software developed in IDL (`ittvis.com`). First-level fMRI data processing was carried out using functions from FSL and from Analysis of Functional Neuroimages (AFNI) with the most recent updates incorporated to minimize the chance of false positives.³² For the finger-tapping task, right tapping > inactivity (rest) and left tapping > inactivity (rest) were used to model motor-related activity. In the basic-emotion task, activation related to face processing was assessed via the comparison between all faces of any emotional valence compared to the neutral expression that served as a baseline. In addition, happy, sad, and fearful faces were each contrasted with neutral expression to assess regions of activation associated with visual processing of each type of emotional expression. In the intense-emotion task (continuous performance task with emotional and neutral distracters), emotional pictures were compared to neutral pictures, as well as to the baseline of solid squares, to identify regions of activation associated with intense-emotion processing. The residuals from the general linear model were high-pass filtered in accordance with the task timing, 0.008 Hz for finger tapping and 0.04 Hz for the basic-emotion and intense-emotion tasks, and smoothed with a 6-mm full-width half-maximum filter with AFNI's `3dBandpass`. For the finger-tapping task, we assessed group differences between pre-CBT fMRI in FT and the baseline HC fMRI (2-sample *t* test) and pre-/post-CBT fMRI (paired *t* test) in patients with FT. All group results were corrected for multiple comparisons at the whole-brain level with FSL's threshold-free cluster enhancement (TFCE),³³ a nonparametric permutation test, with 5,000 permutations.

Small volume correction

Given the hypothesized involvement of the anterior cingulate/paracingulate, a small volume correction was implemented over these regions to correct the fMRI task-based statistical results for multiple comparisons. The small volume mask was defined anatomically with the Harvard-Oxford Cortical Atlas. FSL's `randomize` was used to implement small volume correction with the nonparametric TFCE method with 5,000 permutations.

ROI analysis

An ROI analysis was conducted to examine the change in activation associated with CBT in regions that were maximally different between HCs and patients with FT before CBT in our previous study.⁹ The larger sample size in this previous cross-sectional nonintervention study allowed us to select ROIs on the basis of results corrected for multiple comparisons. Specifically, for each task contrast, ROIs were selected from the group-level contrast using a *z* threshold of 2.3 and *p* < 0.05 corrected (using FSL's nonparametric TFCE method). These ROIs were in the right cerebellum for the motor task; in the anterior cingulate/paracingulate

cortex, left Heschl gyrus, and left precentral gyrus for the basic-emotion task; and in the parahippocampal gyrus, brainstem, and anterior cingulate/paracingulate cortex for the intense-emotion task.⁹ Mean activation values were extracted from these functionally defined ROIs, and then *t* tests were performed to determine pre-to post-CBT changes in activation. The HAM-D scores were then correlated with the difference in activation (post-CBT activation minus pre-CBT activation). These results were not subject to small volume correction.

Clinical data statistical analysis

Quantitative data were expressed as mean \pm SD and median and categorical data as frequency and proportion as appropriate. The sample characteristics were compared between FT and HCs using either the unpaired *t* test or Fisher exact test. The effect of CBT on PMDRS was evaluated with paired *t* test with effect size summarized using mean change along with 95% confidence interval and percent relative change with SD. The Shapiro-Wilk test was used to assess gaussian distributions. All results based on parametric analyses were validated with nonparametric analyses using Wilcoxon signed-rank tests. Spearman rank correlation analysis was used to examine correlations of change in PMDRS with baseline characteristics. The change in PMDRS (pre-post CBT) was also compared according to dichotomized age, sex, disease duration, affected body region and movement type, MINI, HAM-A, and HAM-D using a 2 sided Student *t* test. Values of $p \leq 5\%$ level of significance were considered statistically significant. To visually summarize the treatment effects and the distribution of before-versus-after change in PMDRS, box-whisker plots and bar plots were constructed.

Results

Population characteristics

We included 15 patients with FT (age 50.5 ± 14.2 years, 12 women) and 25 HCs (43.6 ± 14.6 years, 21 women). With 1 exception (recorded as unknown), all participants were right-handed. Average disease duration in the FT cohort was 2.3 ± 1.6 (range, 1–4) years (table 1). Age and sex were not statistically different between the groups.

Psychiatric features

Depression (HAM-D score 14.9 ± 11.8 vs 0.76 ± 1.4 , $p < 0.001$) and anxiety (HAM-A score 16.9 ± 13.9 vs 0.76 ± 2.0 , $p < 0.001$) scores were higher in the FT group compared to HCs. Major depression was ascertained in 5 of 15 patients with FT and posttraumatic stress disorder in 4 of 15 per MINI screen. HAM-D and HAM-A scores were highly correlated (Pearson $r = 0.9498$).

Clinical changes

The change in PMDRS score was normally distributed (Shapiro-Wilk test, $p = 0.16$). CBT reduced the PMDRS score from 34.3 ± 17.1 to 7.4 ± 10.8 ($78.7 \pm 33.8\%$, mean change 26.87 ; 95% confidence interval 16.6 – 37.2 , $p < 0.001$) with 9 of

15 patients experiencing complete resolution of their tremor and 2 of 15 experiencing near-complete ($>75\%$) resolution at study endpoint (figure 1). The effect of CBT on PMDRS score was not influenced by any baseline variable except for age (correlation = -0.5 , $p = 0.06$), with greater improvement in patients below the mean age (<50 years; 35.4 ± 19.6 vs 17.1 ± 12.4 , $p = 0.05$) compared to those ≥ 50 years of age. Neither disease duration nor any other clinical variable, including depression or anxiety scores, predicted changes in PMDRS score (table 2). The results remained unchanged for each outcome after the data were analyzed with nonparametric tests.

Finger-tapping fMRI task

As expected, there were no significant differences in pre- vs post-CBT activation between participants with FT and HCs after adjustment for multiple comparisons at the whole-brain level.

Basic-emotion fMRI task

In general, compared to HCs, the anterior cingulate/paracingulate cortex showed increased activation at baseline and decreased activation after CBT during basic-emotion processing ($p = 0.012$ for CBT responders). At baseline, small volume correction applied to the cingulate/paracingulate region revealed greater activation in the FT group compared to HCs in the right cingulate/paracingulate gyri for the emotional faces $>$ neutral faces contrast. For the sad faces $>$ neutral faces contrast, small volume correction showed greater activation in the FT group in the anterior cingulate and left and right paracingulate regions (figure 2, top, and table 3). For the pre- vs post-CBT activation, small volume correction revealed a reduction in activation in the right paracingulate gyrus for both the sad faces $>$ neutral faces contrast and the emotional faces $>$ neutral faces contrast (figure 2, bottom, and table 3).

Intense-emotion fMRI task

The planned analysis in the cingulate/paracingulate ROI with small volume correction applied revealed greater activation for the emotional images $>$ neutral images contrast in HCs compared to those with FT (figure 3 and table 3).

ROI results (mean activation, without small volume correction)

The ROI in the anterior cingulate/paracingulate cortex showed a significant decrease in activation from before to after CBT during the basic-emotion task ($p = 0.05$ corrected). Among CBT responders, a greater change in the anterior cingulate/paracingulate activation pattern from before to after CBT was associated with higher pre-CBT depression scores (greater HAM-D score) ($r^2 = 0.7556$, $p = 0.008$) (figure 4).

Discussion

This pilot clinical and fMRI study revealed 2 important findings: (1) CBT led to remission or near remission in almost 75% of this cohort of patients with FT, an impressive

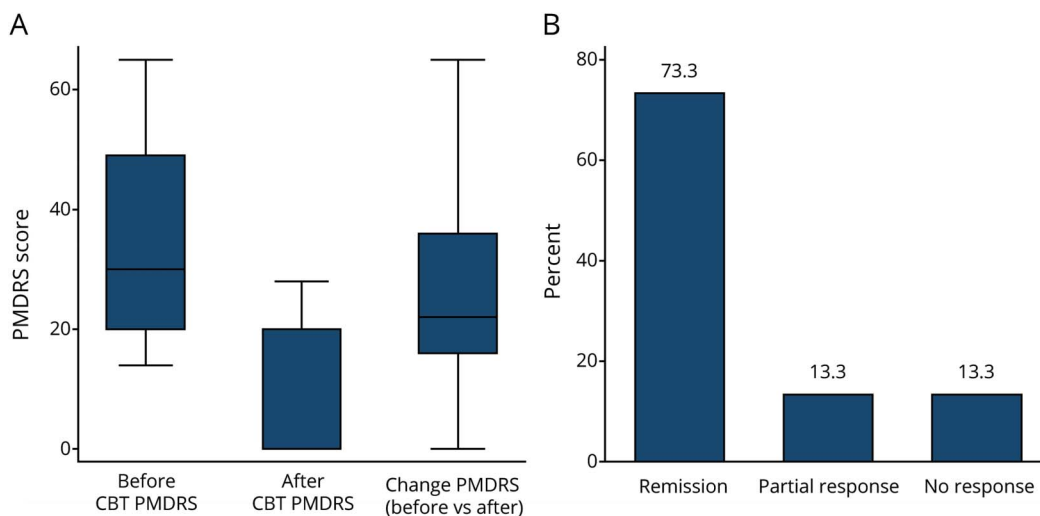
Table 1 FT Cohort

Patient	Age, y	Sex	Duration, mo	Tremor topography	Centrally acting medications	FMD type	HAM-A score	HAM-D score	MINI score	PMDRS score before	PMDRS score after	Outcome
1	63	F	42	Trunk, BLE	None	Chronic	1	3	None	36	0	Responder
2	45	F	12	BUE	None	Chronic	3	5	None	25	0	Responder
3	58	F	24	RUE, stutter	Citalopram, quetiapine, clonazepam, lamotrigine, sertraline	Chronic	28	20	MDD, PD, PTSD	30	25	Nonresponder
4	38	F	48	RUE, RLE, and R face	Citalopram, diazepam, propranolol, topiramate	Chronic	7	10	None	20	0	Responder
5	38	F	48	BUE, head	Cyclobenzaprine, duloxetine	Paroxysmal	28	26	MDD, PD, GAD	52	20	Partial responder
6	30	F	14	RUE	Clonazepam	Chronic	3	3	None	22	0	Responder
7	43	F	72	Generalized, speech	Paroxetine	Paroxysmal	46	43	MDD, GAD, PD, PTSD, possible BD	63	0	Responder
8	27	M	12	RUE	Amitriptyline	Chronic	0	0	None	65	0	Responder
9	44	M	42	Generalized	Gabapentin, fluoxetine, clonazepam, baclofen	Chronic	24	18	PD, PTSD	49	7	Responder
10	66	F	12	LUE, BLE	None	Paroxysmal	22	11	None	17	0	Responder
11	65	M	16	Head, RUE, > LUE	None	Chronic	5	7	None	23	23	Nonresponder
12	49	F	12	BUE	Clonazepam, diazepam, venlafaxine	Paroxysmal	27	29	MDD, PD-A, PTSD	14	0	Responder
13	75	F	12	RUE, RLE	Escitalopram	Chronic	13	10	None	36	8	Responder
14	63	F	30	RUE, RLE	None	Paroxysmal	14	15	PD-A, OCD	16	0	Responder
15	53	F	12	BUE, BLE	Clonazepam, desvenlafaxine, lamotrigine, lithium carbonate	Chronic	32	23	MDD, PD, SP, AD, PsyD	46	28	Partial Responder

Characteristics and clinical outcome before and after CBT.

Abbreviations: AD = alcohol dependence; BD = bipolar disorder; BLE = bilateral lower extremities; BUE = bilateral upper extremities; CBT = cognitive behavioral therapy; FMD = fibromuscular dysplasia; FT = functional tremor; GAD = generalized anxiety disorder; HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Scale; LUE = left arm; MDD = major depressive disorder; MINI = Mini International Neuropsychiatric Interview; OCD = obsessive-compulsive disorder; PD = panic disorder; PD-A = panic disorder with agoraphobia; PMDRS = Rating Scale for Psychogenic Movement Disorders; PsyD = psychotic disorder; PTSD = posttraumatic stress disorder; RUE = right arm; SP = social phobia.

Figure 1 Clinical changes after CBT.



(A) Box-whisker plots visually summarize the distribution of responses before and after cognitive behavioral therapy (CBT). (B) Distribution of response categories based on change in Rating Scale for Psychogenic Movement Disorders (PMDRS) score after CBT.

magnitude of benefit for a chronic condition with progressive disability and no proven available treatment; and (2) the CBT-mediated improvement was associated with a large difference in the fMRI activity of the anterior cingulate/paracingulate region, with the magnitude of change being higher among those with more severe baseline depression. The absence of functional changes in motor regions despite the marked reduction of tremor severity after CBT indicates that the motor system itself is unaffected in FT. These findings suggest that CBT may be a promising therapeutic intervention for FT (and plausibly a range of other functional movement disorders) and that the anterior cingulate/paracingulate region is an important node in the emotion-processing network associated with FT. Furthermore, normalization of medial frontal overactivity may represent a mechanism of action for CBT, perhaps playing a greater role among those with depression.

The anterior cingulate and paracingulate regions may be important for the generation of FT and the prediction of CBT response. We recently showed that this region had increased activity in patients with FT compared to HCs during emotional faces processing after controlling for depression scores and correcting for multiple comparisons,⁹ which is consistent with our current results. Both small volume correction analysis and ROI analysis show that CBT elicits a normalizing effect by reducing this anterior cingulate/paracingulate activity during emotion processing. Significant activation in the cingulate/paracingulate region after emotional stimuli has been correlated with alexithymia (the inability to identify and describe emotions)³⁴ and may represent a common psychopathologic mechanism in functional motor disorders.³⁵ In addition, the anterior cingulate region plays a role in cognitive processing related to attention (because abnormal attention to symptoms

seems key in functional motor symptoms), as explained under bayesian models of brain function.³⁶ It is possible that changes in attention may provide a mechanism for an intervention such as CBT to exert its benefit. Furthermore, the anterior paracingulate cortex is considered a key prefrontal region subserving the theory of mind, the ability to represent mental states, which is important for the understanding of the intentions of people involved in social interactions and in predicting future intentional social interactions.³⁷ The impaired reasoning about our own and other people's mental states has already been identified in another functional neurologic disorder, PNES.³⁸ Theory of mind can unify functional neurologic disorders by reconciling the perception of the internal states of the body, or interoception, across a variety of emotional states.³⁹ In the setting of altered emotion processing, the ability to predict future events is eroded.⁴⁰ This impaired bayesian prediction may explain the ostensible contradictions between voluntary and unconscious motor control in functional motor disorders, resulting in abnormal predictive beliefs about movements, which are therefore experienced as involuntary, that is, without a sense of agency.⁴¹

This is the first study that measured longitudinally the neural correlates of a response to an intervention in a functional movement disorder. Prior studies on the neurobiology of FT have focused largely on cross-sectional imaging of patients in the resting state. These fMRI studies showed decreased functional connectivity between the right temporoparietal junction and bilateral sensorimotor regions, which is considered to underlie the impairment of sensory motor integration and patients' impaired self-agency, the sense of control of one's own actions.^{7,8} The demonstration of hypermetabolism in the medial posterior parietal lobes bilaterally by PET with ¹⁸F-deoxyglucose in the resting state of a single participant also

Table 2 Clinical variables and correlation with post-CBT PMDRS in the FT cohort

	Mean (SD), median	Correlation with PMDRS change (Spearman <i>r</i>)	<i>p</i> Value
Age, y	50.5 (14.2), 49	-0.50	0.06
Duration, y	2.3 (1.6), 1.5	0.26	0.35
HAM-A	16.9 (13.9), 14	-0.17	0.54
HAM-D	14.9 (11.8), 11	-0.17	0.54
PMDRS score change after CBT according to baseline characteristics		No. (%)	PMDRS score change mean (SD)
Age, y			
<50		8 (53.3)	35.4 (19.6)
≥50		7 (46.7)	17.1 (12.4)
Duration, y			
<1.5		7 (46.7)	27.0 (17.4)
≥1.5		8 (53.3)	26.8 (20.7)
Sex			
Male		3 (20)	35.7 (33.0)
Female		12 (80)	24.7 (14.7)
Affected body parts			
Single		5 (33.3)	33.6 (20.3)
Multiple		10 (66.7)	23.5 (17.8)
FMD type			
Persistent		10 (66.7)	26.1 (18.6)
Paroxysmal		5 (33.3)	28.4 (20.6)
MINI score			
Absent		8 (53.3)	26.6 (18.6)
Present		7 (46.7)	27.1 (20.0)
HAM-A score			
<14		8 (53.3)	26.5 (18.7)
≥14		7 (46.7)	27.3 (7.5)
HAM-D score			
<10		7 (46.7)	28.0 (19.7)
≥10		8 (53.3)	25.9 (18.9)

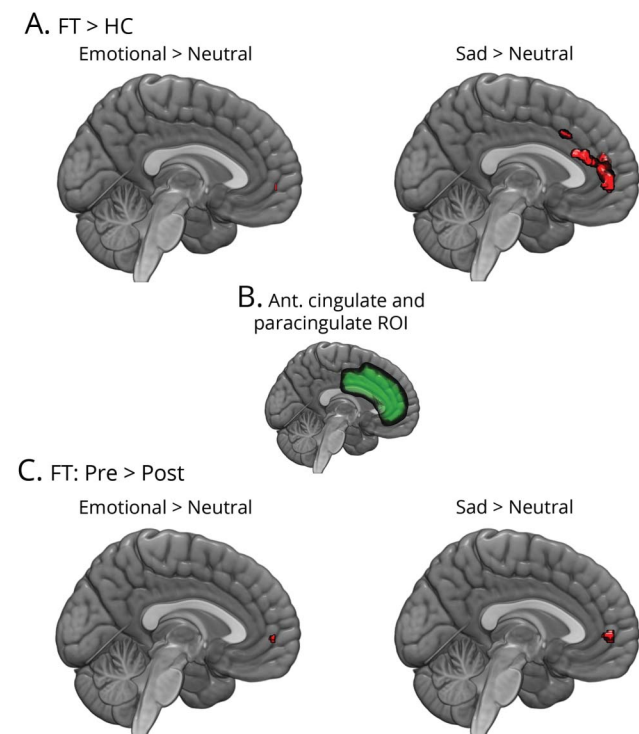
Abbreviations: CBT = cognitive behavioral therapy; FMD = functional movement disorder; FT = functional tremor; HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Scale; MINI = Mini International Neuropsychiatric Interview (outcome: absent and present psychiatric disorder as per MINI structured interview); PMDRS = Rating Scale for Psychogenic Movement Disorders.

supports an impairment of sensorimotor integration.⁴² In contrast to a previous resting-state study (which demonstrated temporoparietal junction hypofunction⁸), our fMRI protocol focused on motor and emotion-processing tasks, with particular attention to pre- versus post-CBT changes.

It has previously been postulated that patients with FT exhibit abnormalities in subcortical processing similar to those found in other functional neurologic disorders.⁴³ One study in

patients with unilateral paralysis and hemianesthesia documented a decrease in regional cerebral blood flow to passive vibratory stimulation in the thalamus and basal ganglia using single photon emission CT with (99m)Tc-ethyl cysteinate dimer after an intervention.⁴³ Together, compared to HCs, the data suggest that abnormal processing of emotional information is associated with limbic activation via changes in connectivity between basal ganglia and thalamocortical circuits and results in a deficit in sensory or motor processing.⁴⁴

Figure 2 Differences in fMRI activation for the basic-emotion task after small volume correction.



(A) Differences between participants with functional tremor (FT) and healthy controls (HCs). Regions in red showed greater activation in FT. (B) Region over which small volume correction was implemented. (C) Changes from before cognitive behavioral therapy (CBT) to after CBT in patients with FT. Regions in red showed greater activation before CBT that decreased after CBT. ROI = region of interest.

Alternatively, simple emotional stimuli may instead lead to functional deafferentation due to active inhibition of somatosensory processing by limbic areas concerned with emotion and attention,⁴⁵ thus resulting in the overall decreased fMRI responses to the emotion-processing paradigm. The extent to which these changes in patients with FT apply to other functional movement disorders remains unclear.

Finally, the issue of asymmetry is worth briefly highlighting because, in the basic-emotion task, the activation was greater in the right cingulate/paracingulate cortex in the FT group. Asymmetry is often observed in studies of patients with functional neurologic disorders and is not necessarily always present in the same hemisphere.⁶ One study argued that emotional disturbances related to right hemispheric abnormalities may be the etiology of emotional disturbances that result, as an end effect, in PNES (a functional neurologic disorder), and another study documented aberrant right uncinata fasciculus (connection between amygdala and medial frontal regions, including cingulate); this was not confirmed by other studies.

Limitations

Our study has limitations. As an open-label study, comparisons were performed before and after CBT rather than in an

ideal parallel design with patients having received a placebo intervention. Because of the limited sample size, we were unable to determine the effects, if any, of symptom duration >4 years and other clinical variables, including severe and continuous resting tremor (these patients had to be excluded in order to be scanned). In addition, we used a nonmanualized form of CBT, inducing a source of variability; however, it was important to tailor the therapy to individual patients. As a result of this adjustment, it may be difficult to reproduce our findings in other settings, including clinical trials. The fMRI paradigms used in the current study have not been studied for intraindividual consistency over time, and changes in cortical activation may be altered without implying true biological changes. Furthermore, we did not measure anxiety and depression at follow up, preventing us from measuring the extent to which some of the fMRI changes may have been explained by changes in mood states.⁴⁶ This concern has become especially warranted with the increasing recognition that fMRI processing may result in false positives or confounded data,⁴⁷ and the technical updates we incorporated³² may not have entirely eliminated this potential shortcoming. Finally, it is also possible that at least some of the differences in activation in participants with FT may relate to their psychiatric comorbid condition and be a sign of maladaptive cognitive interpretations of emotions.⁴⁸ Attenuating the potential for a direct effect of psychiatric comorbid conditions in our ROI, fluorodeoxyglucose-PET studies in patients with major depression have shown that interpersonal psychotherapy reduces glucose metabolism of the left middle anterior cingulate cortex,⁴⁹ while CBT increases glucose metabolism in the dorsal anterior cingulate cortex.⁵⁰

CBT significantly improved FT in this open-label study, with nearly 75% remission or near remission. Improvements were associated with decreased overactivity in the anterior cingulate/paracingulate region, especially prominent in those with greater depression at baseline. Because it is possible that changes in emotion-processing networks/anterior cingulate region may be related to changes in associated psychiatric comorbid conditions rather than changes in the severity of the movement disorder, a randomized controlled trial will need to include a control arm (such as psychoeducation) ideally matched for associated psychiatric comorbidities. Future studies should be aimed at ascertaining the long-term duration of benefits and the extent to which adjuvant interventions such as physical therapy may yield synergistic effects. If confirmed, changes in the anterior cingulate/paracingulate region may represent a marker of FT and predict CBT response.

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Table 3 Regions of difference in fMRI task activation using a small volume correction over the anterior cingulate/paracingulate ROI

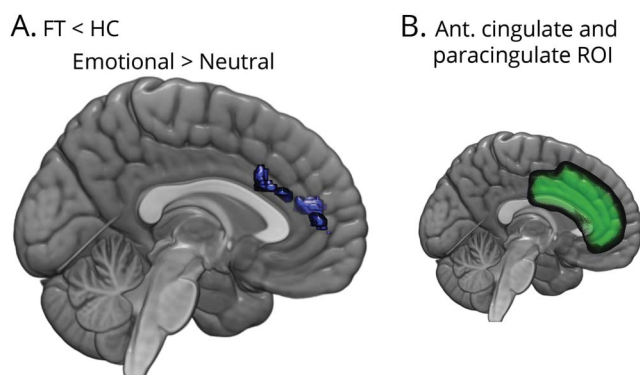
Task	First-level contrast	Second-level contrast	Voxel count	Maximum z	Minimum corrected p value	COG x, mm	COG y, mm	COG z, mm	Atlas region
Basic-emotion task	Emotional faces > neutral faces	FT > HC	6	2.87	0.045	3	54	-1.99	Right paracingulate gyrus
		FT pre-CBT > FT post-CBT	13	2.46	0.033	4.16	53.1	0.159	Right paracingulate gyrus
	Sad faces > neutral faces	FT > HC	425	3.1	0.006	2.25	45.2	10.3	Right anterior cingulate gyrus
			56	2.67	0.024	0.25	18.5	36.3	Anterior cingulate gyrus
Intense-emotion task	Emotional images > neutral images	HC > FT	75	2.99	0.015	5.35	51.6	1.95	Right paracingulate gyrus
			102	3.13	0.011	-13.8	45.3	14.5	Left paracingulate gyrus
			42	2.6	0.027	2.15	48.4	7.57	Right paracingulate gyrus

Abbreviations: CBT = cognitive behavioral therapy; FT = functional tremor; HC = healthy control; ROI = region of interest. Clusters are defined at a threshold of $z > 2.3$, a corrected $p < 0.05$, and voxel size > 5 voxels.

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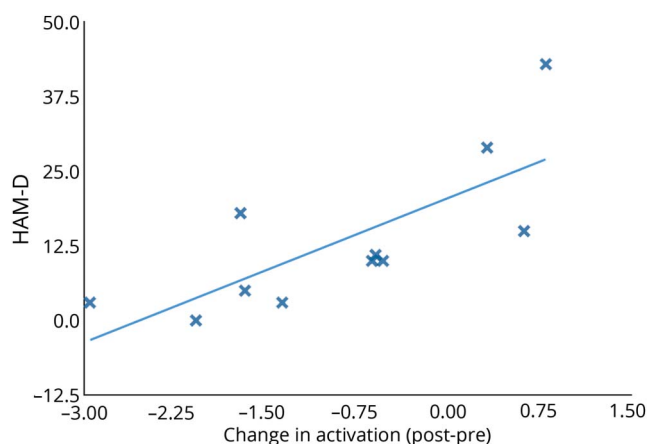
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Figure 3 Differences in fMRI activation for the intense-emotion task after small volume correction.



(A) Differences between participants with functional tremor (FT) and healthy controls (HCs). Regions in blue showed greater activation in HCs. (B) Region over which small volume correction was implemented.

Figure 4 Changes in activation and depression scores.



A strong correlation was found between Hamilton Depression Scale (HAM-D) scores and changes in activation, before cognitive behavioral therapy to after CBT, in the anterior cingulate/paracingulate region ($r^2 = 0.56$, $p = 0.008$) among those patients with FT who responded to CBT therapy.

Defense (W81XWH-17- 1-0619 [principal investigator]); serves on the Epilepsy Foundation Professional Advisory Board; has received honoraria for the American Academy of Neurology Annual Course; has served as a clinic development consultant at University of Colorado Denver, Cleveland Clinic, Spectrum Health, and Emory University; and has provided medico-legal expert testimony. A. Lang has served as an advisor for AbbVie, Allon Therapeutics, Avanir Pharmaceuticals, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Ceregene, Cipla, InteKrin, Lilly, Medtronic, Merck, Novartis, NeuroPhage Pharmaceuticals, Teva, and UCB; received honoraria from Medtronic, Teva, UCB, and AbbVie; received grants from Brain Canada, the Canadian Institutes of Health Research, the Edmond J. Safra Philanthropic Foundation, the Michael J. Fox Foundation, the Ontario Brain Institute, National Parkinson Foundation, Parkinson Society Canada, Physicians Services Inc, Tourette Syndrome Association, and W. Garfield Weston Foundation; received publishing royalties from Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press; and has served as an expert witness in cases related to the welding industry. J. Szaflarski has received research funding from NIH, Shor Foundation for Epilepsy Research, Eisai, Epilepsy Foundation of America, Food and Drug Administration, Compumedics Neuroscan, Inc, Department of Defense, state of Alabama, and University of Alabama at Birmingham. While this research was conducted, he was supported by NIH K23 NS052468. He serves as an associate editor of *Restorative Neurology and Neuroscience* and *Journal of Epileptology* and on editorial boards of the journals *Epilepsy & Behavior*, *Folia Medica Copernicana*, and *Journal of Medical Science*. Go to Neurology.org/N for full disclosures.

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Appendix Authors

Name	Location	Role	Contribution
Alberto J. Espay, MD, MSc	University of Cincinnati, OH	Corresponding Author	Conception of research project, literature search, writing of the first manuscript draft
Scott Ries, LISW	University of Cincinnati, OH	Author	CBT provider, review and critique of the manuscript
Thomas Maloney, MS	Cincinnati Children's Hospital, OH	Author	fMRI data analysis, review and critique of the manuscript
Jennifer Vannest, PhD	Cincinnati Children's Hospital, OH	Author	fMRI data analysis, review and critique of the manuscript
Erin Neefus, BS, CCRP	University of Cincinnati, OH	Author	fMRI data collection, data manager, review and critique of the manuscript.
Alok K. Dwivedi, PhD	Texas Tech University Health Sciences Center, El Paso	Author	Biostatistician, clinical data analysis, review and critique of the manuscript
Jane B. Allendorfer, PhD	University of Alabama at Birmingham	Author	fMRI data analysis, review and critique of the manuscript
Lawson R. Wulsin, MD	University of Cincinnati, OH	Author	Review and critique of the manuscript
W. Curt LaFrance, MD, MPH	Rhode Island Hospital, Providence	Author	Review and critique of the manuscript
Anthony E. Lang, MD, FRCP	University of Toronto, Ontario, Canada.	Author	Review and critique of the manuscript
Jerzy P. Szaflarski, MD, PhD	University of Alabama at Birmingham.	Author	Overall supervision of the study, Review and critique of the manuscript

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