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ORIGINAL ARTICLE

Aberrant Cerebello-Cortical Connectivity in Pianists With Focal Task-Specific Dystonia

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Abstract

Musician's dystonia is a type of focal task-specific dystonia (FTSD) characterized by abnormal muscle hypercontraction and loss of fine motor control specifically during instrument playing. Although the neuropathophysiology of musician's dystonia remains unclear, it has been suggested that maladaptive functional abnormalities in subcortical and cortical regions may be involved. Here, we hypothesized that aberrant effective connectivity between the cerebellum (subcortical) and motor/somatosensory cortex may underlie the neuropathophysiology of musician's dystonia. Using functional magnetic resonance imaging, we measured the brain activity of 30 pianists with or without FTSD as they played a magnetic resonance imaging-compatible piano-like keyboard, which elicited dystonic symptoms in many but not all pianists with FTSD. Pianists with FTSD showed greater activation of the right cerebellum during the task than healthy pianists. Furthermore, patients who reported dystonic symptoms during the task demonstrated greater cerebellar activation than those who did not, establishing a link between cerebellar activity and overt dystonic symptoms. Using multivoxel pattern analysis, moreover, we found that dystonic and healthy pianists differed in the task-related effective connectivity between the right cerebellum and left premotor/somatosensory cortex. The present study indicates that abnormal cerebellar activity and cerebello-cortical connectivity may underlie the pathophysiology of FTSD in musicians.

Key words: effective connectivity, focal task-specific dystonia, functional MRI, musician's dystonia

Introduction

Dystonia is a movement disorder defined as "sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both" (Albanese et al. 2013). Focal task-specific dystonia (FTSD) is a type of dystonia that affects a single part of the body (i.e., focal) primarily during overtrained motor actions such as writing and instrument playing (Cohen and Hallett 1988; Furuya and Altenmüller 2013) but not during other motor activities (i.e., task specific) (Hofmann et al. 2015). Importantly, FTSD often has a disproportionate impact on those relying on skilled motor control in their professional careers (Altenmüller et al. 2012; Furuya and Hanakawa 2016); for example, hand dystonia impairs musicians' ability to execute the individuated finger movements required for playing instruments, thereby threatening their livelihood (Furuya et al. 2015).

The pathophysiological mechanisms of FTSD are not yet entirely clear. One hypothesis is that FTSD is caused by maladaptive neural changes (Hallett 2011; Furuya and Hanakawa 2016) that arise from interactions between extensive motor practice and predisposing factors such as genetics (Schmidt et al. 2006), mental traits (Ioannou and Altenmüller 2014), and biomechanical characteristics of the body (Leijnse et al. 2015). Empirical evidence indicates that such maladaptive changes may occur in the somatosensory/motor cortices as well as subcortical areas (Furuya and Hanakawa 2016). Transcranial magnetic stimulation (TMS) studies have suggested that FTSD may arise from a loss of inhibition in the primary motor cortex (M1) (Rosenkranz et al. 2005; Furuya et al. 2018). Task functional magnetic resonance imaging (fMRI) studies have demonstrated hyperactivation of cortical motor areas, including M1, in musician's dystonia of the hand (Pujol et al. 2000) and orofacial "embouchure" (Haslinger et al. 2010). Somatosensory cortex is also disorganized: previous studies have demonstrated altered representations of the affected body part (Elbert et al. 1998; Uehara et al. 2019), abnormal functional connectivity (FC) with the motor cortex (Rosenkranz et al. 2005), and structural enlargement (Garraux et al. 2004).

Compared with these brain regions, less is known about the cerebellum's role in the pathophysiology of FTSD. Classically, the cerebellum has not been implicated in dystonia. Nevertheless, several neuroimaging studies have reported altered cerebellar activations in FTSD (Odergren et al. 1998; Preibisch et al. 2001; Lerner et al. 2004; Kadota et al. 2010; Wu et al. 2010; Moore et al. 2012). However, it remains unclear how cerebellar abnormalities are associated with dystonic symptoms as cerebellar activity does not directly trigger muscle contractions. The task-specific nature of FTSD suggests that the motor cortex itself is not functionally altered, but instead an input from some subcortical area may be affecting the somatosensory/motor cortices' functionality. For example, the cerebellum may be altering motor cortical excitability via cerebro-cerebellar connectivity. The efficacy of stereotactic ventro-oral thalamotomy for FTSD supports this hypothesis (Horisawa et al. 2019). Moreover, although Uehara and colleagues found no significant differences in cortical activity between wind instrumentalists with and without FTSD, they found an association between dystonic behaviors and a combination of primary motor, somatosensory, cerebellar, and putaminal activity (Uehara et al. 2019). This suggests that functional abnormalities in not just a single but multiple brain regions (or their associated networks) might be responsible for FTSD. Additionally, patients with writer's cramp showed strongly negative FC between the cerebellum and sensorimotor regions at resting state (Dresel et al. 2014). To our knowledge, however, no previous studies address how tasks that might cause dystonic symptoms modulate the connectivity between the cerebellum and somatosensory/motor cortices in FTSD.

In this study, we asked pianists with and without FTSD to play an MRI-compatible piano-like keyboard during fMRI scanning and to report their dystonic symptoms during the task. We hypothesized that: (1) M1 and cerebellar activity might be modulated by the presence of dystonia and (2) abnormal task-related modulation of connectivity between the cerebellum and sensorimotor regions might underlie musician's dystonia. To test these hypotheses, we analyzed not only task-related neural activity, but also the effective connectivity between the cerebellum and the somatosensory/motor cortices using both traditional univariate analysis and multivoxel pattern analysis (MVPA).

Materials and Methods

Participants

Fifteen healthy pianists (all right-handed; 4 males and 11 females; mean age 27.5 years old, range 20–54 years old; mean starting age of playing piano, 7.2 years old, range 5–21 years old; mean amount of daily practice, 3.3 hours, range 1–6 hours) and 15 pianists with FTSD (13 right-handed; 6 males and 9 females; mean age 40.3 years old, range 21–57 years old; mean starting age of playing piano 5.0 years old, range 3–10 years old; mean amount of daily practice, 4.1 hours, range 1.5–10 hours; mean period affected by FTSD 3.0 years, range 1–15 years) participated in this study (Tables 1 and 2). All participants learned to play the piano at private piano schools and/or music colleges. Pianists with FTSD were recruited at the Department of Neurology of the National Center of Neurology and Psychiatry (NCNP) Hospital. Pianists with FTSD were diagnosed by a board-certified neurologist with expertise in movement disorders. Informed consent was obtained from all participants according to the experimental protocol approved by the NCNP's Ethical Committee. All participants in the patient group had no neurological abnormalities and reported no history of neuropsychiatric disorders except for FTSD. All FTSD patients suffered from dystonic symptoms in either the right or both hands. The duration of the disorder ranged from 1 to 15 years (mean duration $\pm$ standard deviation $= 4.9 \pm 5.1$ years) at the time of participation. Two patients had previously received an injection of botulinum-toxin A; however, the injection was performed at least 3 months prior to the study. One patient had undergone stereotactic ventro-oral thalamotomy for dystonic symptoms of the left hand; this patient developed FTSD of the right hand 1 year after the surgery. The dystonic symptoms in this patient appeared only in the right hand at the time of the study.

Experimental Design

During the experiment, participants laid supine on a scanner bed with an MRI compatible piano keyboard placed on their lower abdomen. Participants were comfortably able to play the keyboard. We asked all participants to perform sequential finger movements on the piano keyboard involving all digits of the right hand. The sequence of keyboard presses was the repetition of the first 5 notes in the C major scale: thumb, index finger, middle finger, ring finger, little finger, ring finger, middle finger, index finger, and so on. The task was paced at 5 Hz by playing

Table 1 Characteristics of pianists with FTSD

Patient ID	Gender	Age, years	Affected hand	Affected finger	Age when starting the piano, years	Amount of daily practice, hours	Period affected by FTSD, years	BTX injection (years before experiment)
1	M	23	LR	3, 4(L); 5(R)	7	10	5	No
2	M	36	R	3	13	2.5	3	No
3	M	21	R	4, 5	5	5	2	No
4	F	57	R	4	5	2	9	No
5	F	36	R	1	6	3.5	2	No
6	F	50	R	1–5	7	2	3	No
7	F	43	R	4	5	10	3	No
8	M	38	LR	4(L); 4(R)	6	4.5	15	No
9	F	44	R	3, 4	6	1.5	1	No
10	F	48	R	4	4	3	2	No
11	M	43	R	3	6	1.5	1	No
12	F	47	R	3	6	4	6	No
13	F	48	R	3	6	3.5	1	No
14	M	35	R	4, 5	5	5	9	Yes (7)
15	F	37	R	3	21	4	2	Yes (0.5)
Mean (range)	6 M; 9 F	40.3 (21–57)			7.2 (5–21)	4.1 (1.5–10)	4.3 (1–15)	

Note: BTX, botulinum-toxin A; F, female; M, male.

Table 2 Characteristics of healthy pianists

Healthy pianist ID	Gender	Age, years	Age when starting the piano, years	Amount of daily practice, hours
1	M	25	5	6
2	F	29	3	6
3	F	28	9	6
4	M	32	5	1.5
5	F	36	3	1
6	M	23	10	3
7	F	54	8	3
8	F	24	3	1.75
9	F	20	4	3
10	F	19	3	1
11	F	20	4	1
12	F	20	7	5
13	F	37	4	3
14	F	22	4	2
15	M	24	3	6
Mean (range)	4 M; 11 F	27.5 (20–54)	5.0 (3–10)	3.3 (1–6)

notes to the participant through an MRI-compatible headset. The notes that we delivered through the headset were the same notes that we asked participants to play on the keyboard. The participants viewed a computer monitor, which displayed "GO" during the task period and "REST" during the rest period. They were not able to see nor receive auditory feedback from the keyboard but received tactile and proprioceptive feedback about the key presses through their fingers and hand. Previous work has shown that dystonic symptoms are not changed due to the presence of auditory feedback (Cheng et al. 2013). One fMRI run consisted of 15 task blocks for 12 s alternating with a baseline period of a semirandomly selected duration (3, 6, or 9 s) in which the same auditory stimuli as the task period were provided. Each fMRI run lasted for 5.14 minutes. Each participant underwent 2 fMRI runs along with whole-brain high-resolution 3D T_1-weighted anatomical scan. Pianists with FTSD were divided into 2 subgroups based on whether they did or did not experience dystonic symptoms during the task, as assayed using self-reports. The participants were also required to play a piano keyboard outside of MRI to test their piano skill and/or the severity of their dystonic symptoms (Supplementary 1) (Furuya et al. 2018).

MRI Data Acquisition

Imaging was conducted on a 3-T MRI scanner (Siemens Verio) with a 32-channel phased array receiver coil. We acquired gradient echo-planar images sensitive to T_2* decay using the following parameters: repetition time (TR) = 3000 ms, echo time (TE) = 40 ms, flip angle = 90 degrees, with 45 transaxial slices, slice thickness = 3.5 mm without an interslice gap, matrix size = 64 × 64, field of view (FOV) = 192 × 192 mm, 3.0 × 3.0 × 3.5 mm voxel size. 3D T_1-weighted anatomical MRIs were obtained with a magnetization-prepared rapid gradient echo sequence as follows: TR = 1900 ms, TE = 2.52 ms, inversion time (TI) = 900 ms, flip angle = 9 degrees, matrix size = 256 × 256,

FOV = 250 × 250 mm^2, ~1 mm^3 cubic voxels. All image data were converted to the Neuroimaging Informatics Technology Initiative format before further processing.

Data Analysis

Preprocessing

All functional MRI data were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) on MATLAB R2014a (Mathworks). Five volumes were removed from the analysis to allow for T_1 equilibrium effects. We then performed slice timing correction, realignment, spatial normalization into Montreal Neurological Institute (MNI) space with a resolution of 2 × 2 × 2 mm, and smoothing with an 8-mm full-width at half-maximum Gaussian kernel.

fMRI Image Analysis of Brain Activity

Task-related fMRI signal changes were modeled for the rest and task phases as boxcar functions convolved with a canonical hemodynamic response function in a general linear model (GLM) analysis. The head motion parameters were included in the GLM model, yielding weighted contrast (c*beta) images for each individual. The contrast images, defined as the t-contrast of "task > rest," were computed for all participants and were submitted to the second-level group statistical analysis. The group analysis consisted of 2 comparison levels; 1-sample *t*-tests to compare task-related activation in each group and also the 2 groups combined and a 2-sample *t*-test to investigate differences in the task-related activation between the groups.

Effective Connectivity Analysis

Effective connectivity refers explicitly to the influence that one neural system exerts over another, either at a synaptic or population level (Friston 2011). Here we conducted effective connectivity analysis to understand the dynamic modulation of FC between the cerebellum and the other brain regions. To calculate effective connectivity, we used a psychophysiological interaction (PPI) analysis developed in SPM8. PPI is an analytic method that explores task-dependent changes in the connectivity between seed volumes of interests (VOIs) and each voxel within target VOIs (Friston et al. 1997; Gitelman et al. 2003; Davis et al. 2014). We set a seed VOI in the right cerebellum where the activation in patients was significantly greater than that in healthy pianists (cluster-level $P < 0.05$ corrected for family-wise error (FWE), see Results). In each voxel in the whole brain, we then computed the degree to which FC with the cerebellar VOI was modulated with the keypresses task in comparison with the baseline, yielding contrast images. In univariate voxel-wise analysis, contrast images reflecting task-related modulation of the connectivity at the individual level were submitted to a group analysis to look into the difference of effective between the groups.

MVPA of Cortical Activity and Effective Connectivity

We applied MVPA to the keyboard playing-related cortical activity and effective connectivity. MVPA is a technique that detects differences between conditions or groups with higher sensitivity than conventional univariate analysis by comparing distributed patterns of neural activity. In this multivariate approach, data from individual voxels within a region are jointly analyzed to infer the functional role of brain areas and networks (Haxby et al. 2001; Cox and Savoy 2003; Kamitani and Tong 2005; Haynes and Rees 2006; Norman et al. 2006).

Previous evidence indicates that patients with FTSD may have somatotopic disorganization (Elbert et al. 1998; Bara-Jimenez et al. 2000; Nelson et al. 2010). We thus hypothesized that abnormal activity signifying dystonia could be distributed as a pattern spanning across voxels because of the potentially disorganized somatotopy of fingers in pianists with FTSD. We set anatomical masks for the premotor cortex (Brodmann area [BA] 6), primary motor cortex (BA4), and somatosensory cortices (BA1–3), according to the Wake Forest University PickAtlas Version 3.0.5 (Maldjian et al. 2003). The number of voxels included in the VOI masks varied between from 900 to 4265. From each mask, we retrieved a multivoxel activation pattern in which a value in each voxel reflected the keyboard playing task-related activity relative to the baseline activity. For MVPA we used a machine learning technique (Cox and Savoy 2003; Kamitani and Tong 2005; De Martino et al. 2008) to classify pianists with FTSD from healthy pianists. Specifically, support vector machine (SVM) (Cortes and Vapnik 1995) was used from the R libSVM package (SVM-Type: C-classification, SVM-Kernel: radial, cost: 1) (Chang and Lin 2011). For each VOI mask, 30-fold, leave-one-out cross-validation was performed as we had 30 participants. At each fold, multivoxel brain activity patterns in the VOI mask from 29 participants were used to train the SVM classifier, which, at the test phase, classified the remaining participant as either a healthy pianist or a pianist with FTSD, according to his/her multivoxel brain activity pattern in the same VOI mask.

Using MPVA, we tested a second hypothesis that effective connectivity between the cerebellum and the cortical motor and somatosensory areas might carry information that can classify healthy pianists from those with dystonia. We set a seed VOI in the right cerebellum, which was the same location as that in the univariate effective connectivity analysis above. To examine modulation of the effective connectivity during the keyboard playing task relative to baseline, we computed the effective connectivity between the cerebellar seed VOI and each voxel within the anatomical masks of motor and somatosensory areas (the premotor [BA6], motor [BA4], and somatosensory [BA1–3] cortices), which were used also for the MVPA of the brain activity. After retrieving multivoxel patterns of the effective connectivity, the same machine learning method and statistics as were used for analyzing brain activity were applied. If effective connectivity could discriminate between pianists with and without FTSD, this would suggest that those connectivity patterns contain specific information about FTSD.

Subgroup Analysis

We conducted subgroup analysis for both brain activity and effective connectivity in pianists with FTSD. For brain activity, we extracted c*beta values from the clusters of voxels of the right cerebellum and the left M1 according to the group-level *t*-map of task-related activity from all participants. For effective connectivity, we calculated the mean of the effective connectivity values (c*beta values) in cerebellar-BA3/6 connectivity (BA3/6 were chosen because these regions exhibited a difference in effective connectivity between healthy pianists and pianists with FTSD, see Results). Then we performed a subgroup analysis to compare the brain activity and effective connectivity between pianists with FTSD who showed dystonic symptoms and those who did not during fMRI acquisition.

Table 3 Brain areas showing significant activation: All activations survived a threshold of voxel-level uncorrected $P < 0.001$ with $P < 0.05$ for family-wise error corrected at the cluster level

Cluster No.	Anatomical region (BA)	MNI coordinates			Peak z-score	Number of voxels	Effect size
		x	y	z			
	Healthy pianists						
1	Left precentral gyrus	−40	−18	60	5.72	1120	2.06
1	Left postcentral gyrus (1)	−54	−20	48	4.39		1.37
1	Left precentral gyrus (3a)	−32	−24	42	3.71		1.10
2	Right cerebellum, lobule VI	20	−52	−24	3.99	313	1.21
	Pianists with FTSD						
1	Left postcentral gyrus (4a)	−38	−24	54	5.78	2484	2.10
1	Left postcentral gyrus (3b)	−42	−34	60	5.56		1.96
1	Left precentral gyrus (4a)	−36	−26	66	5.35		1.84
2	Right cerebellum, lobule V	10	−54	−18	6.16	1753	2.35
2	Right cerebellum, lobule V	16	−48	−24	6.10		2.31
	Pianists with FTSD > healthy pianists						
1	Right cerebellum, lobule V	2	−58	−20	3.95	231	1.68
1	Right cerebellum, lobule V	14	−44	−24	3.59		1.49
1	Right cerebellum, lobule V	2	−54	−4	3.39		1.39

Statistics

In all imaging analyses with SPM, statistical significance was set at an extent threshold of $P < 0.05$ (FWE corrected) with a height threshold at uncorrected $P < 0.001$. Anatomical labels were assigned using the Anatomy toolbox for SPM (Eickhoff et al. 2005). We used Cohen's d as an index of effect size. The effect size of Cohen's d was considered as small, medium, or large if it fell into the following ranges: ≥0.2, ≥0.5, or ≥0.8, respectively (Lakens 2013). In MVPA, a binomial test was used to determine the significance of the classification accuracy ($P < 0.05$). In the subgroup analysis, the c∗beta values were compared using Welch's 2-sample t-test. Differences were considered statistically significant at $P < 0.05$. Statistical analyses were carried out using R (http://www.r-project.org/).

Results

Analysis of the Participants' Profiles

The healthy pianists were younger than the pianists with FTSD ($t_{28} = 3.66$, $P = 0.001$, $d = 1.33$). Although overtraining and the starting age of piano training have been suggested to play a key role in the development of FTSD (Furuya and Hanakawa 2016), the 2 groups showed no difference in starting age ($t_{28} = 1.73$, $P = 0.10$, $d = 0.63$). The amount of daily practice of healthy pianists and that of patients with FTSD before disease onset was not significantly different either ($t_{28} = 0.99$, $P = 0.33$).

Brain Activity During Keyboard Playing Movement

During the keyboard playing task, relative to the resting condition, both the pianists with FTSD and healthy pianists showed significantly larger activations ($P < 0.05$ FWE corrected at the cluster level) only in the sensorimotor areas contralateral to the moving hand and the ipsilateral cerebellum (Fig. 1, Table 3). The group comparison of the task-related activity showed that right cerebellar activity (lobule V) was significantly greater in pianists with FTSD than in healthy pianists (Fig. 2, Table 3). We failed to find differences in somatosensory/motor cortical activation between pianists with FTSD and healthy pianists using this traditional univariate analysis.

No significant correlation was found between the measure of the piano skill level/severity of dystonic symptoms and the cerebellar activity in either the healthy pianists or the pianists with FTSD (Supplementary 1). Since the healthy pianists were younger than the pianists with FTSD, a potential concern is that the age difference may affect the group-wise differences in the imaging results. However, there was no correlation between the age and cerebellar activity in either the healthy pianists ($r = 0.03$, $P = 0.92$) or the pianists with FTSD ($r = -0.25$, $P = 0.37$).

Effective Connectivity in the Motor and Sensorimotor Area

A voxel-by-voxel univariate PPI analysis failed to find a difference in effective connectivity between the cerebellar motor and somatosensory areas when comparing the 2 groups at the predetermined threshold for significance ($P < 0.05$, FWE corrected).

MVPA Analysis in the Motor and Sensorimotor Area

MVPA failed to discriminate between pianists with FTSD and healthy pianists while using the keyboard playing-related brain activity in the motor/sensorimotor areas (BA1–3, 4, 6) (Table 4, Fig. 3). We then tested if MVPA of the effective connectivity between the cerebellum and motor/somatosensory areas could discriminate between the 2 groups. Effective connectivity between the cerebellum and the premotor cortex (BA6) and that between the cerebellum and the fundus of the somatosensory cortex (BA3) allowed us to discriminate pianists with FTSD from healthy pianists with 70% accuracy (binomial test, $P = 0.04$; Table 4).

Brain Activity/Effective Connectivity and Dystonic Symptoms During fMRI

Based on the self-reports, 10 pianists with FTSD experienced dystonic symptoms (mean age 37.3 years old, range 21–57 years old, FTSD+ group) during fMRI measurement whereas 5 pianists with FTSD did not (mean age 46.2 years old, range 38–50 years

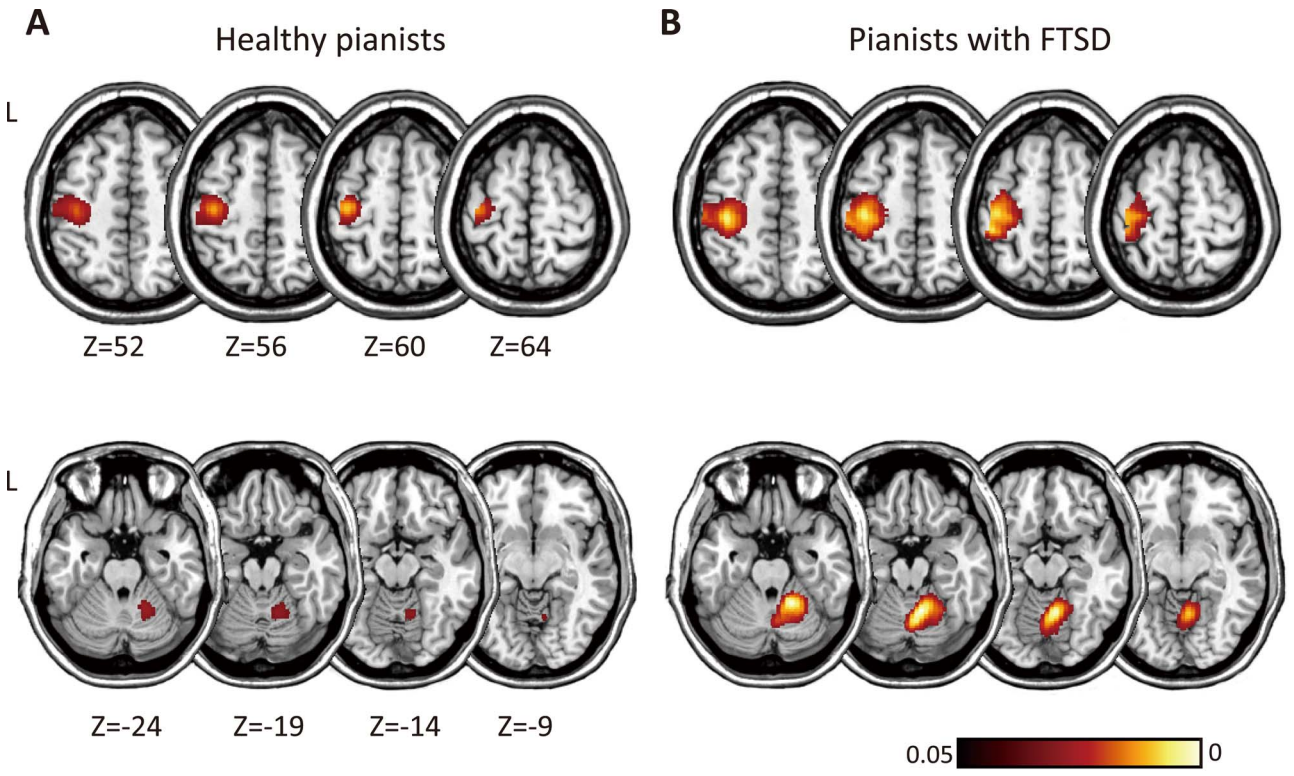

Figure 1. Significant brain activation during the keyboard playing task in healthy pianists (A) and pianists with FTSD (B). All results are displayed at $P < 0.05$ for FWE corrected at the cluster level.

old, FTSD− group). There was no significant age difference between the FTSD+ and FTSD− groups ($t_{13} = 1.79$, $P = 0.097$, $d = 0.98$). We performed VOI-based comparisons of activity and effective connectivity between the FTDS+ group and FTDS− group. The FTDS+ group showed greater activity in the cerebellum ($t_{13} = 3.55$, $P = 0.004$, $d = 1.94$, Fig. 4A) but not in the motor cortex ($t_{13} = 1.39$, $P = 0.189$, $d = 0.76$, Fig. 4A) than the FTDS− group. We tested if the presence of dystonic symptoms during fMRI scanning was associated with cerebello-BA6/-BA3 connectivity as detected by the MVPA analysis. The FTDS+ group showed higher effective connectivity between the cerebellum and the premotor cortex (BA6) than the FTDS− group ($t_{13} = 2.53$, $P = 0.025$, $d = 1.38$, Fig. 4B). However, we failed to find any difference in cerebello-BA3 effective connectivity between the FTDS+ group and FTDS− group ($t_{13} = 1.57$, $P = 0.141$, $d = 0.86$, Fig. 4B).

Discussion

We examined the brain activity and effective connectivity of patients with musician's dystonia while they performed a keyboard playing task, which induced dystonic symptoms in many but not all participants. We found pianists with FTSD exhibited increased cerebellar activity compared with healthy pianists during the keyboard playing task. This suggests that cerebellar overactivity may be linked to the presence of dystonic symptoms while patients are performing a task. Moreover, we found that multivoxel patterns of effective connectivity between the cerebellum and premotor/primary somatosensory areas contained information that could discriminate pianists with FTSD from healthy pianists. To our knowledge, this is the first study to demonstrate that task-related modulation of cerebello-somatosensory/motor area connectivity is associated with the pathophysiology of FTSD.

The healthy pianists and the pianists with FTSD did not differ in terms of the starting age of piano training or the amount of practice. Regrettably, it was difficult to recruit age-matched healthy pianists as controls in the present study; resultantly, the healthy pianists were younger than the pianists with FTSD. However, we would like to emphasize that the age difference could not explain the main findings: the main findings, cerebellar overactivity, and cerebello-BA6 connectivity, were not correlated with age. Additionally, although the mean age of the FTSD+ group tended to be younger than that of the FTSD− group, the FTSD+ group showed greater cerebellar activity and cerebello-BA6 connectivity than the FTSD− group. These results from the subgroup analysis argue against the possibility that cerebellar overactivity and altered cerebello-cortical connectivity reflected the age differences rather than the pathophysiology of FTSD.

Cerebellar Overactivity and FTSD

We found greater activation of the right cerebellum in pianists with FTSD. This cerebellar overactivity was primarily exhibited by patients who experienced dystonic symptoms during the task. This finding is consistent with several previous studies (Odergren et al. 1998; Preibisch et al. 2001; Lerner et al. 2004), which found increased cerebellar activity mainly during writing in patients with writer's cramp. The present study extended these studies by showing cerebellar overactivity when

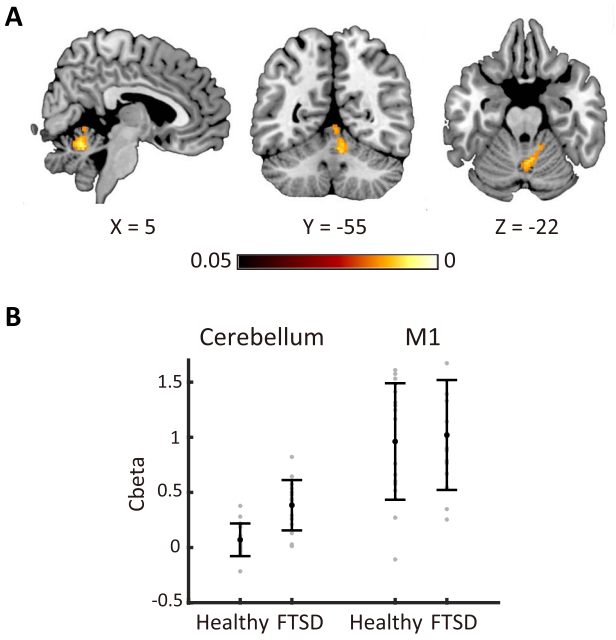

Figure 2. (*A*) Differences in brain activation between pianists with FTSD and healthy pianists. All results are displayed at $P < 0.05$ FWE corrected at the cluster level. (*B*) c∗beta values within the cluster in right cerebellum (MNI coordinate = 2, −58, −20; cluster size = 231), which is shown in (*A*) and the activated cluster within the left M1 in the group *t*-map of all participants (MNI coordinate = −40, −20, 60; cluster size = 3273 voxels). ∗$P < 0.01$. c∗beta values within the same clusters of healthy pianists are shown as a reference. Healthy, FTSD: healthy pianists and pianists with FTSD, respectively.

Table 4 Classification accuracy

	S1			M1	Premotor
	BA1	BA2	BA3	BA4	BA6
Connectivity	40.0%	50.0%	70.0%*	66.7%	70.0%*
Activity	56.7%	53.5%	63.3%	53.5%	50%

Note: *$P < 0.05$ (binomial test).

patients with musician's dystonia had dystonic symptoms. However, our results are inconsistent with other studies, which showed decreased cerebellar activation during dexterous finger movements (e.g., tapping task with one finger) in patients with musician's dystonia and writer's cramp (Kadota et al. 2010; Wu et al. 2010; Moore et al. 2012). No dystonic postures were observed or reported in these studies. An overview of those previous studies suggests that in FTSD, cerebellar activities are exaggerated during tasks that evoke dystonic symptoms, for example, writing in writer's cramp and a keyboard playing task in pianist's dystonia. In contrast, cerebellar activity may be decreased when patients perform tasks that do not evoke dystonic symptoms, for example, one finger tapping task in writer's cramp or musician's dystonia. We propose that cerebellar activity in FTSD may be either increased or decreased in a motor task, depending upon the relationship between the tasks employed during fMRI and the task specificity of FTSD.

An interesting question is how the cerebellar function relates to the emergence of task-specific motor abnormality. The relationship between (over)training and development of FTSD has long been known (Furuya and Hanakawa 2016), and it is widely accepted that the cerebellum is involved in motor learning (Doya 2000). Previous imaging studies have found that cerebellar activity increases when beginning to learn a new motor task (Friston et al. 1992; Grafton et al. 1994; Seitz et al. 1994; Flament et al. 1996). Such cerebellar activity may reflect the formation of a neural circuit for feedforward motor control (i.e., an internal model) (Imamizu et al. 2000). Cerebellar overactivity in FTSD may reflect the disruption of cerebellar circuits related to feedforward motor control acquired through learning.

Activity in Motor and Somatosensory Areas

In pianists with FTSD, neither the univariate analysis nor the MVPA analysis found abnormal activity in the somatosensory/-motor areas. In pianists, FTSD affects the muscles responsible for fine movement of the hand and forearm. It is therefore reasonable to assume that FTSD would cause abnormal motor area activity during a hand motor task. But while some previous studies found abnormal motor and sensorimotor activity in FTSD (Preibisch et al. 2001; Oga et al. 2002; Hu et al. 2006; Islam et al. 2009; Kadota et al. 2010; Wu et al. 2010), some studies did not (Blood et al. 2004; Delmaire et al. 2005). Furthermore, both increases (Preibisch et al. 2001; Hu et al. 2006; Kadota et al. 2010) and decreases (Oga et al. 2002; Islam et al. 2009; Wu et al. 2010) in activity have been reported when comparing patients with FTSD and healthy controls. The reasons behind this discrepancy are unknown but may include the type of FTSD under consideration, inhomogeneous and relatively small numbers of participants in some studies, and methodological differences in tasks, data acquisition, and analyses. In the present study, rather surprisingly, even patients experiencing dystonic symptoms during fMRI did not reveal abnormal activity in the motor area. However, abnormal activity in motor-related areas may not be a prerequisite of dystonic symptoms. Indeed, in a recent study, a combination of activity from several areas was correlated with dystonic symptoms in embouchure dystonia, although each area did not show significant group-wise differences (Uehara et al. 2019).

Together with the exaggerated cerebellar but normal motor/sensorimotor activity in patients who showed dystonic symptom, abnormal cerebellar activity might affect M1 and cause dystonic symptom at muscles through connectivity with premotor, which has projections to M1.

Cerebello-Cortical Connectivity

Although the pianists with FTSD did not exhibit any abnormalities in M1 activity during our study, dystonic symptoms must arise from altered M1 output as this region directly sends commands to muscles. This raises the possibility that dystonic symptoms arise from abnormal connectivity between motor cortex and other brain regions. We found that the task-related modulation of cerebello-cortical connectivity contained sufficient information to discriminate musicians with FTSD from healthy musicians, providing novel evidence for the involvement of the cerebello-cortical communication systems (Allen and Tsukahara 1974) in FTSD. Given that M1 is disinhibited in FTSD, we suggest that abnormal cerebello-cortical connectivity relates to abnormal cortical excitability, which has also been previously suggested by TMS studies of FTSD (Furuya et al. 2018).

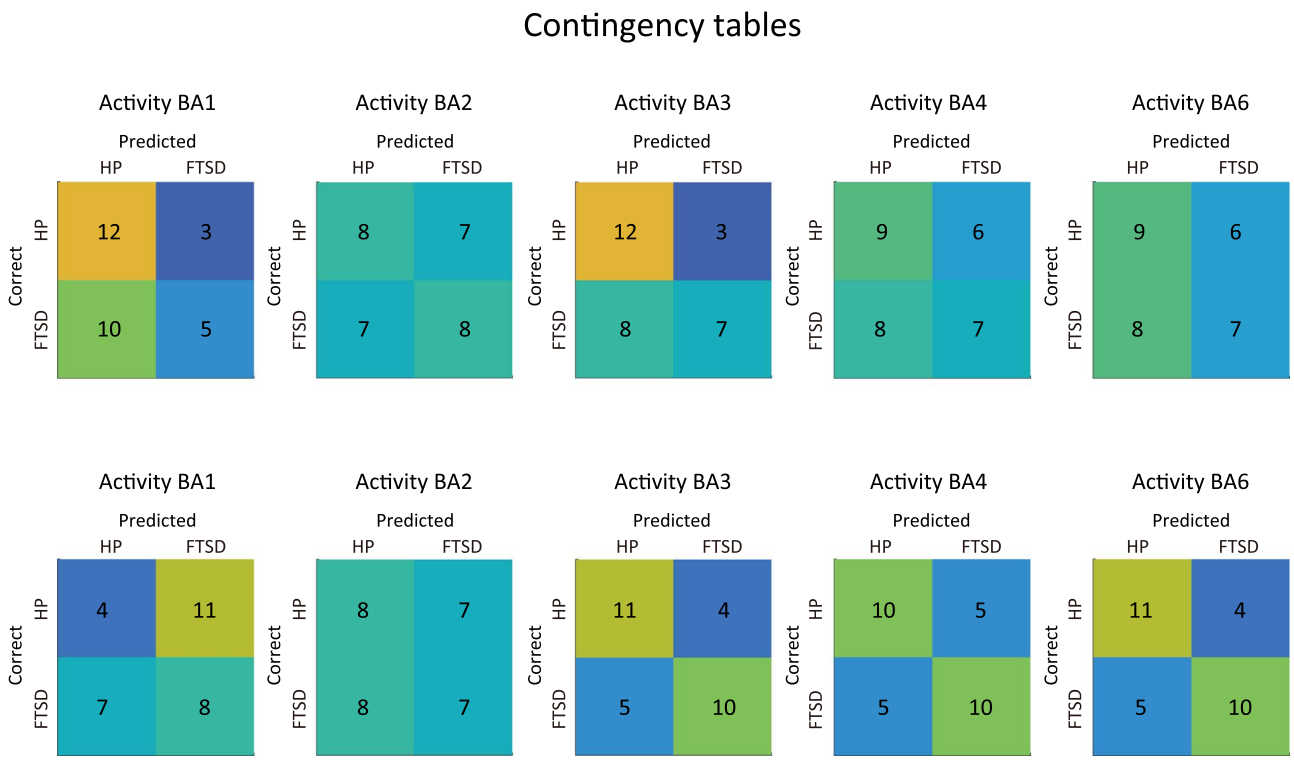

Figure 3. The contingency tables report the number of healthy pianists and pianists with FTSD who were correctly or incorrectly classified by SVM based on keyboard playing-related brain activity of the motor/sensorimotor areas and effective connectivity with the cerebellum (BA1–3, 4, 6). HP: healthy pianists, FTSD: pianists with FTSD.

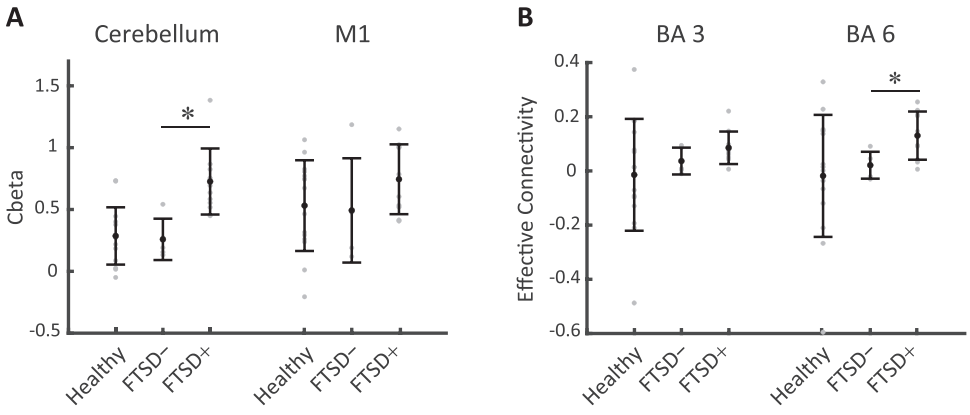

Figure 4. Results of subgroup analysis. (*A*) c∗beta values within the VOIs in the right cerebellum and M1 area. The values were retrieved from functional VOIs, which were the clusters of task-induced activation in the right cerebellum (MNI coordinate = 16, −48, −24; cluster size = 1584) and left M1 (MNI coordinate = −40, −20, 60; cluster size = 3273 voxels) according to the *t*-map derived from all participants. (*B*) Mean effective connective value (c∗beta) between cerebellum and motor/somatosensory area (BA3, 6), with the results of healthy participants shown as a reference. Healthy: healthy pianists. FTSD+/−: pianists with FTSD who did (+) or did not (−) experience dystonic symptoms while playing a simple melody. $^*P < 0.01$.

Additionally, we found that pianists with FTSD exhibited changes of cerebello-somatosensory/motor connectivity without accompanying abnormal activity in the somatosensory/motor cortical areas. The pattern of effective connectivity between the cerebellum and the premotor/somatosensory areas discriminated between the pianists with FTSD and those without. Moreover, the patients who experienced dystonic symptoms during scanning (FTDS+ group) exhibited higher effective connectivity between the cerebellum and premotor areas (BA6) than those did not (FTDS− group). Premotor areas project to M1 and have been shown to be involved in the pathophysiology of FTSD in many studies (Pujol et al. 2000; Haslinger et al. 2010; Kadota et al. 2010; Delnooz et al. 2013). For instance, repetitive TMS over the premotor area, but not M1, improves writing ability in writer's cramp patients (Murase et al. 2005). Moreover, the somatosensory area receives afferents from muscles (Yamada et al. 2016) and projects to M1 (Zarzecki et al. 1978). Although the premotor and somatosensory cortices have direct connections with the spinal cord, these areas likely affect muscle activity through M1. Hence, abnormality of M1 activity in FTSD, such as

cortical disinhibition (Furuya et al. 2018), might be influenced by abnormal inputs from the premotor areas.

Although we did not find altered brain activity or connectivity in the basal ganglia, basal ganglia malfunction has been implicated as a possible pathophysiological mechanism for various forms of FTSD (Neychev et al. 2011; Quartarone and Hallett 2013; Kita et al. 2018). Anatomical connections between the basal ganglia and cerebellum have been identified in both rodents (Ichinohe et al. 2000) and nonhuman primates (Hoshi et al. 2005). Basal ganglia and cerebellar thalamo-cortical channels project to the same regions, yet different layers, of motor cortex in rodents (Kuramoto et al. 2009, 2011). Recent MRI-based tractography studies support the existence of a direct pathway between the basal ganglia and the cerebellum in humans (Milardi et al. 2016; Cacciola et al. 2017; Quartarone et al. 2020). Thus, the basal ganglia and the cerebellum are likely to interact each other.

How the cerebellum is involved in dystonia is still an unresolved question. Based solely on neuroimaging studies, it is difficult to tell whether cerebellar activation causes dystonia symptoms or is a compensatory mechanism to mitigate these symptoms. In the subgroup analysis of brain activity, the FTSD+ group showed higher cerebellar activity than the FTSD− group. If the cerebellar activity played a compensatory role in masking symptoms, this activity should have been higher in the FTSD− group than the FTSD+ group. If the cerebellar activity resulted from excessive proprioceptive inputs from somatosensory areas due to muscle cramps, we would expect abnormal cerebello-BA3 connectivity rather than cerebello-BA6 connectivity since BA3 is the cortical source of proprioceptive afferents. Given the role of cerebello-premotor connectivity in motor planning/preparation (Hua and Houk 1997; Bostan et al. 2013), the present result suggests that abnormal cerebellar activity and cerebello-premotor connectivity may cause muscle cramps, but again, we cannot rule out the possibility that the cerebellum plays a more compensatory role in dystonia. Previous studies also support a causal role of the cerebellum in dystonia. Microinjection of low doses of the excitatory amino acid agonist (kainate) into the cerebellar vermis of normal mice evoked reliable and reproducible dystonic postures of the trunk and limbs (Pizoli et al. 2002). The severity of dystonia increased linearly with the dose of kainate. In humans, surgeons have noted dystonic movements in humans following stimulation of the dentate nucleus (Nashold and Slaughter 1969) or that of the cerebellar receiving area of the thalamus (Lenz et al. 1990). In addition, dystonia could be associated with structural lesions of the brainstem (medulla, pons) and/or cerebellum (LeDoux and Brady 2003). These findings lead to the hypothesis that increases in neuronal activity in the cerebellum, rather than a reduction of activity, may induce dystonia.

In conclusion, we for the first time showed that the cerebellum was involved in the pathophysiology of FTSD via task-related cerebellar overactivity and cerebello-somatosensory/motor area connectivity. The cerebellar overactivity and the cerebello-motor area connectivity were obvious when symptoms appeared in the dystonic patients. The cerebellum may potentially play a general role in the production of involuntary movements.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

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