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Abnormalities in grey matter structure in embouchure dystonia

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ABSTRACT

Introduction: Embouchure dystonia (ED) is a debilitating movement disorder in professional brass players leading to involuntary muscle contractions/spasms during play. To date, activity changes in sensorimotor cortices during motor tasks and tactile processing, as well as connectivity changes at rest in sensorimotor and auditory brain networks have been described in the disease.

Objective: To characterize differences in grey matter volume and asymmetry between brass musicians suffering from ED, healthy brass musicians and healthy nonmusicians.

Methods: High-resolution structural magnetic resonance imaging was obtained from 24 brass musicians with ED, 23 healthy brass musicians and 24 healthy nonmusicians. Whole-brain voxel-wise morphometry and asymmetry analyses, as well as region-of-interest-based volumetry analysis were performed on the subjects' images and compared between groups. Further, correlations with clinical parameters were investigated.

Results: ED patients showed increased grey matter volume in the primary sensorimotor cortex in relation to both healthy brass players and nonmusicians. Both healthy and diseased musicians showed increased thalamic symmetry in relation to nonmusicians; diseased brass musicians additionally showed increased basal ganglia symmetry compared to nonmusicians. There was an inverse correlation of disease duration with both mean putaminal volume and the extent of basal ganglia asymmetry.

Conclusion: This work provides first evidence for structural abnormalities in task-specific orofacial (musician's) dystonia. Somatotopy-related structural primary sensorimotor cortex changes underlying previously observed functional abnormalities underscore the role of maladaptive plasticity in the disease. The study further shows subcortical brain (a)symmetry changes in healthy brass players and hints at a possible role of such changes in focal dystonia.

1. Introduction

Focal dystonia (FD) is characterized by involuntary activity of agonist and antagonist muscles in the affected body region, leading to loss of fine motor control. In embouchure dystonia (ED), those involuntary movements affect the orofacial muscles of professional brass musicians specifically during play (task-specific focal dystonia, TSFD), most often marking the end of their professional career [1]. Functional neuroimaging in ED showed increased activity in primary and higher-order sensorimotor cortices, cerebellum and/or basal ganglia (BG),

either during dystonic/nondystonic motor tasks or tactile stimulation of dystonic/nondystonic body parts [2,3]. Further, abnormal resting-state functional connectivity within sensorimotor, cerebellar and auditory networks was seen [4]. While grey matter (GM) structure has mostly been investigated for FD of hand and neck describing abnormality in sensorimotor cortices, BG and cerebellum, it has not yet been characterized in TSFD of the orofacial muscles [5]. Furthermore, healthy professional musicians themselves also display both structural and functional changes in the sensorimotor and cerebellar cortices [6] including changes in brain symmetry [7]. Besides possible

Abbreviations: ADDS, arm dystonia disability scale; AI, asymmetry index; BG, basal ganglia; CON, healthy nonmusicians; ED, embouchure dystonia; FD, focal dystonia; FWHM, full width at half maximum; GM, grey matter; GMV, grey matter volume; MuCON, healthy professional brass players; PAT, brass players with embouchure dystonia; ROI, region of interest; TIV, total intracranial volume; TSFD, task-specific focal dystonia

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endophenotypic traits advantageous for acquisition of highly-skilled movements, these changes are largely assumed to occur in response to intensive instrumental practice, and possible instrument-specific characteristics have been proposed [8]. Yet, neuroimaging literature is sparse regarding wind instruments in healthy subjects [9]. This study hence aimed at characterizing the abnormalities in GM structure and (a)symmetry between professional brass players suffering from the task-specific orofacial ED, healthy brass playing professionals and healthy nonmusicians.

2. Methods

2.1. Participants

We compared 24 professional brass players with ED (PAT; m/f = 21/3, age = 43.5 ± 11.2 years) recruited from the institute for music physiology and musicians medicine in Hanover with 23 professional healthy brass musicians (MuCON; m/f = 22/1, age = 42.4 ± 11.2 years) from local professional orchestras/conservatories and 24 healthy nonmusician controls (CON; m/f = 18/6, age = 42.7 ± 11.9 years; inclusion criteria see supplement). The university ethics board approved the study and all participants gave their informed consent according to the Declaration of Helsinki. For clinical rating of dystonia severity, all healthy/diseased brass musicians performed a videotaped standardized play as performed in previous studies [2–4]. As sensitive and established scales for rating of ED are yet lacking (i.e. ratings such as the Burke-Fahn-Marsden/Tubiana-Chamagne score are not sensitive for ED-specific symptoms such as deterioration of sound, attack of the tongue etc.) [10], the play was blindly rated by an expert in ED (E.A.) according to an ordinal scale specifically tailored for ED (Table 1) as previously performed [2–4]. To take possible coincidence of writer's cramp in ED into account, we screened PAT with the arm dystonia disability scale (ADDS). Between-group differences in age, sex, total intracranial volume (TIV) as well as (for musicians) age at start of play, duration of active period, daily musical practice at time of the study, and ED score were tested for using parametric/nonparametric tests in SPSS25 wherever appropriate.

2.2. Data acquisition

Anatomic high-resolution MRI scans were acquired on one Philips Achieva 3.0 T scanner (Philips, Amsterdam, The Netherlands) equipped with an 8-channel head coil using a magnetization-prepared rapid-acquisition gradient-echo sequence (repetition/echo/inversion time 9/4/780 ms, field-of-view 240 × 240mm², 170 slices, voxel size 1 × 1 × 1mm³, scan time 6min).

Table 1
Clinical and demographic data.

	brass musicians with ED	healthy brass musicians	healthy non-musicians
Age, y (mean, SD)	43.5, 11.2	42.4, 11.2	42.7, 11.9
Sex (m/f)	23/3	22/1	18/6
TIV, cm ³ (mean, SD)	1602.6, 126.1	1582.4, 135.2	1527.9, 156.0
instrument (horn/trumpet/trombone)	9/7/8	12/5/6	NA
Age at start of play, y (mean, SD)	10.5, 2.5	10.7, 3.8	NA
Daily play, h (median, IQR)	3.8, 1.3	2.5, 1.13	NA
		with ED	
		1.0, 2.0	
ED score (median, IQR) ^a	3, 1.25	1, 1.0	NA

SD = standard deviation; IQR = interquartile range; y = years; h = hours; TIV = total intracranial volume; m = male; f = female; NA = not applicable. 1 = normal play, 2 = nearly normal play, not distinctly dystonic; 3–5 = abnormal playing with evidence of dystonic orofacial movements (minor/medium/severe degree).

^a Embouchure dystonia score (dystonic symptom rating during performance of standardized sequences).

2.3. Voxel-based morphometry (VBM) analysis

Morphometric analysis was performed with the CAT12 toolbox (<http://dbm.neuro.uni-jena.de/cat/>) for SPM12b (<http://www.fil.ion.ucl.ac.uk/spm/>) and Matlab16b (The MathWorks Inc., Natick, USA) using standard parameters. After denoising, inhomogeneity correction and affine registration, the skull-stripped anatomical scans were tissue-segmented followed by diffeomorphic anatomical registration using lie algebra (DARTEL) to the default DARTEL_IXI555 Montreal Neurological Institute (MNI) space template with a final voxel size of 1 mm³. Modulation of GM segments was performed by multiplication with the Jacobian determinant. Normalized data were smoothed with a 10 mm full-width-at-half-maximum (FWHM) Gaussian kernel. Between-group comparison was performed by implementing a full factorial random effects model adjusted for sex, age and TIV with absolute threshold masking of 0.1. Results of the whole-brain analysis at a cluster-forming (peak-level) threshold of p < 0.001 were family-wise error (FWE)-corrected for multiple comparisons at the cluster level (p_{FWEc} < 0.05).

2.4. Voxel-based asymmetry (VBA) analysis

Asymmetry analysis was performed based on a voxel-wise approach outlined by Kurth and colleagues [11]. To achieve the required accurate correspondence for voxel-wise comparisons (as the same brain structures can differ in spatial location between hemispheres), the structural MRI scans were first segmented and affine registered to a symmetric tissue probability map provided by Kurth and coworkers [11]. The resulting grey and white matter segments were then flipped at the midline. Subsequently, both flipped and non-flipped (original) segments were nonlinearly warped to a custom symmetric DARTEL_IXI555 MNI space template (previously created from segmented, flipped and non-flipped grey and white matter segments from 555 subjects of the publicly available IXI dataset (<https://brain-development.org>) using CAT12 default parameters) using DARTEL. Normalized data were modulated by multiplication with the Jacobian determinant. Next, voxel-wise asymmetry indices (AIs) were calculated from each subject's flipped and non-flipped modulated normalized GM segments ($AI = \frac{(original - flipped)}{0.5 \times (original + flipped)}$) so that in the right hemisphere positive AI values indicated rightward, and negative values indicate leftward asymmetry (in the left hemisphere vice versa). To eliminate redundant information, the left hemisphere was discarded through multiplication with a right-hemispheric mask. AI maps were smoothed with a 10 mm FWHM Gaussian kernel. Between-group comparisons were performed with a full factorial random effects model adjusted for sex and age at voxels with a mean GM value > 0.1 [11]. Results were corrected for multiple comparisons at the cluster level (p_{FWEc} < 0.05) at a peak-level threshold of p < 0.001 uncorrected. As results from voxel-wise group

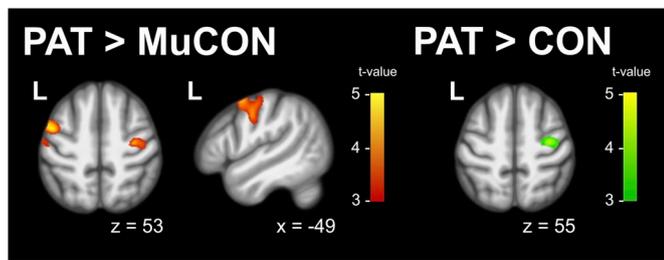


Fig. 1. Areas with significant increase in GM volume in PAT compared to MuCON (in red) and CON (in green), projected on the averaged anatomical scan from all 71 participants. Overlaid statistical parametric maps were thresholded at the cluster level ($p_{FWEC} < 0.05$). Slice position is given in MNI space in millimeters relative to the anterior commissure. PAT, patients with embouchure dystonia, MuCON, healthy brass players, CON, healthy nonmusicians. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

analysis cannot directly be interpreted unequivocally (e.g. a significant cluster in a positive contrast can indicate less negative or more positive AI values), the cluster-specific i) mean AIs and ii) mean left- and right-hemispheric GM volumes (GMVs) were extracted for significant clusters in each subject for post-hoc evaluation to determine i) the directionality of asymmetry, and ii) if the altered (a)symmetry was driven by focal GM changes in one hemisphere. To exclude bias by global hemispheric asymmetry, the hemispheric GMVs were calculated and compared between groups.

2.5. Atlas-based volumetry (ABV) analysis

To compensate possible method-related sensitivity/spatial specificity limitations of VBM, we additionally analyzed the mean GMV in macroanatomical atlas-defined regions of interest (ROIs) with putative role in idiopathic FD. To ensure unbiased ROI selection, respective brain areas were identified through activation likelihood estimation meta-analysis of existing VBM studies in FD (selection criteria see supplement) using the revised algorithm by Turkeltaub and colleagues (GingerALEv2.3.6, <http://brainmap.org/ale/>) [12]. This approach models entered activation foci from the literature as centroids of 3D Gaussian probability distributions, accounting for spatial uncertainty of neuroimaging data. The null distribution of cluster excursions for cluster threshold generation was established by calculating 5000 permutations of random distributions of activation foci throughout the brain using the toolbox-implemented nonparametric Monte Carlo method. Correction was performed at the cluster-level ($p_{FWEC} < 0.05$) at a cluster-forming threshold of $p < 0.001$ uncorrected [13]. Based on the meta-analysis results, we selected anatomical bilateral ROIs from the Harvard Oxford atlas (who showed good fit in all investigated regions verified by visual inspection; figure s-2) for brain regions within ± 9 mm (average smoothing kernel of all included studies) of the meta-analysis clusters' peak location to take the spatial uncertainty induced by smoothing into account. Next, mean GMV in each ROI were extracted from each subjects' unsmoothed segmented, normalized modulated GM images and statistically compared between-groups in SPSS25 in an analysis of variance adjusted for age, sex and TIV ($p < 0.05$) with a Bonferroni-adjusted post-hoc analysis.

2.6. Regression analyses

Possible linear correlations of “dystonia severity defined by ED score” and “disease duration (years)” with voxel-wise GM values (VBM analysis), volumetry-based mean GMVs (ABV analysis) and voxel-wise AI values (VBA analysis) in PAT were investigated using regression analyses in SPM12b and SPSS25 respectively. Nuisance regressors/correction for multiple comparisons were set as for between-group

analyses, with additional Bonferroni-correction for two investigated covariates of interest. For voxel-wise analyses, voxels showing a significant main effect in the between-group comparisons were a-priori defined as volume of interest and small volume correction was applied.

3. Results

Statistical analysis did not show significant difference in brain volumes/demographic characteristics between-groups ($p_s > 0.05$). There was no significant difference in average daily instrument play between MuCON and PAT before disease onset. After disease onset, daily practice abated ($z = -3.83, p < 0.001$), also compared to their healthy colleagues ($W_s = 411.5, z = -3.52, p < 0.001$). Mean disease duration was 7.2 ± 6.7 years and was not associated with years of musical practice ($r = -0.04, p = 0.84$). PAT screening by ADDS showed no signs of hand dystonia ($99.6 \pm 1.4\%$). PAT video ED rating scores were significantly higher than in MuCON ($W_s = 338.5, z = -4.87, p < 0.001$). A rating of three in one single healthy player was attributed to the setting of videotaped scoring, as the subject did not suffer from dystonic symptoms/impairment in clinical exam and history.

3.1. VBM analysis

Between-group contrasts revealed significantly increased GMV in the precentral gyrus (PreCG) and sulcus and the postcentral gyrus (PoCG) in the left, and the PreCG in the right hemisphere in PAT compared to MuCON. Compared to CON, GMV in PAT was increased in

Table 2

A. Changes of local grey matter volume between groups. B. Changes of local grey matter asymmetry between groups.

A.					
Effect of group					
Region	peak coordinate			extent (voxel)	F score
	x	y	z		
R precentral gyrus (BA4)	36	-14	56	2485	14.88
R precentral gyrus (BA4)	40	-18	60		12.89
PAT > MuCON					
Region	x	y	z	extent (voxel)	t score
L precentral sulcus (BA6)	-44	0	54	5063	4.86
L precentral gyrus (BA4)	-52	-8	40		4.33
L postcentral gyrus (BA1)	-52	-14	54		3.45
R precentral gyrus (BA4)	36	-14	56	3427	4.97
PAT > CON					
Region	x	y	z	extent (voxel)	t score
R precentral gyrus (BA6)	34	-12	56	3974	4.42
R precentral gyrus (BA6)	32	-8	64		4.09
R postcentral gyrus (BA3)	18	-34	62		4.01

B.					
Effect of group					
Region	peak coordinate			extent (voxel)	F score
	x	y	z		
Thalamus	16	-21	13	5390	25.46
Putamen	31	-6	1		12.20
PAT vs. CON					
Region	x	y	z	extent (voxel)	t score
Thalamus	16	-21	13	9431	7.13
Putamen	31	-5	1		4.91
Insula	43	-9	2		3.71
MuCON vs. CON					
Region	x	y	z	extent (voxel)	t score
Thalamus	23	-15	13	2196	5.03

Coordinates (mm) in the Montreal Neurological Institute space. Displayed grey matter volume/asymmetry index differences significant at $p_{FWEC} < 0.05$. PAT = brass players with ED; MuCON = healthy brass players; CON = healthy non-musicians. R = right hemisphere; L = left hemisphere.

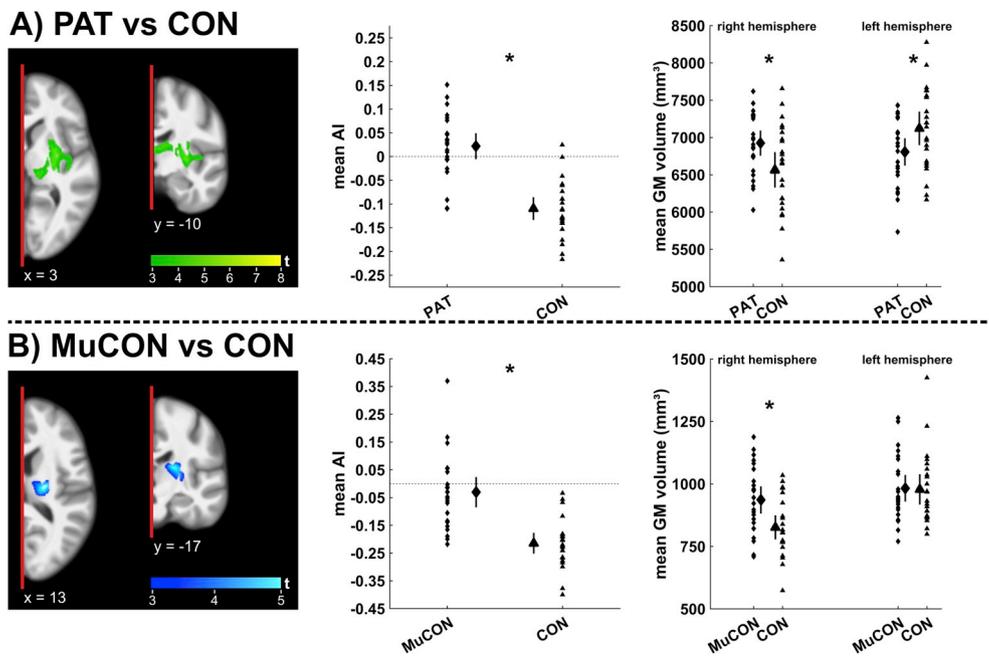


Fig. 2. Areas with significantly altered grey matter asymmetry in (A) PAT and (B) MuCON compared to CON. Left column: Areas with significantly higher asymmetry indices in patients (in green)/healthy brass players (in blue) projected on the right hemisphere of the averaged anatomical scan of all participants. Overlaid statistical parametric maps were thresholded at the cluster level $p_{FWEC} < 0.05$. Slice position is given in MNI space in millimeters relative to the anterior commissure. Middle column: Dot plot of cluster-specific mean AIs in each group. Right column: Dot plot of cluster-specific grey matter volumes in the right and left hemisphere in both groups. Error bars depict the double standard error of mean. Asterisks depict significant differences ($p < 0.05$) during exploratory analysis. AI, asymmetry index, GM, grey matter; CON, healthy nonmusicians (triangles); MuCON, healthy brass players (diamonds); PAT, patients with embouchure dystonia (circles). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the right PreCG and PoCG (Fig. 1, Table 2). There was no significant difference between MuCON and CON.

3.2. VBA analysis

Compared with CON, MuCON showed significantly different (more positive) AI values in the thalamus, and PAT showed significantly different (more positive) AI values in a cluster encompassing the thalamus, putamen and insula (Fig. 2). There was no significant difference between PAT and MuCON.

Exploratory analysis of the cluster's mean AIs revealed that this was due to reduced leftward lateralization (= increasing symmetry) in the thalamus in MuCON compared to CON ($t_{46} = 7.24$, $p < 0.001$, $r = 0.73$). In PAT compared to CON, loss of left-hemispheric lateralization extended beyond the thalamus to the putamen and the insula and was more pronounced (a slight rightward lateralization was seen ($t_{45} = 4.81$, $p < 0.001$, $r = 0.58$)). Exploratory analysis of cluster mean GMVs indicated that this effect was on one side owed to a significantly increased right-hemispheric cluster-specific GMV in both PAT ($t_{46} = 2.45$, $p = 0.018$, $r = 0.34$) and MuCON ($t_{45} = 2.53$, $p = 0.015$, $r = 0.35$) compared to CON, but in PAT left-hemispheric cluster-specific GMV was additionally significantly reduced compared to CON ($t_{46} = -2.17$, $p = 0.035$, $r = 0.31$).

3.3. ABV analysis

Literature search identified 17 studies comprising in total 19 experiments and 93 experimental foci fulfilling the inclusion criteria (table s-1). GingerALE meta-analysis revealed significant clusters extending over the left primary sensorimotor cortex and at the border between putamen and pallidum in both hemispheres (figure s-1). Based on these results, we investigated the mean GMV in the PreCG, PoCG, putamen and pallidum in each hemisphere. Both hemispheres were investigated, as lateralization effects in the meta-analysis may be owed to the focus on the right hand in focal hand dystonia studies.

ABV revealed a significant main effect of group for each the right and left PreCG (R/L $F_{2,68} = 5.69/5.28$, $p = 0.005/0.008$, $\eta_p^2 = 0.15/0.14$) and each the right and left PoCG (R/L $F_{2,68} = 5.41/3.66$, $p = 0.007/0.031$, $\eta_p^2 = 0.10/0.14$; figure s-3). Bonferroni-corrected post-hoc analysis revealed a significantly increased mean GMV again in

both the left and right PreCG in PAT compared to both MuCON (R/L $p = 0.021/0.015$) and CON (R/L $p = 0.011/0.027$). For the right PoCG, post-hoc contrasts indicated an increased GMV in PAT compared to CON ($p = 0.008$). For the left-hemispheric PoCG, no significant differences in the post-hoc between-group comparisons were seen after correction for multiple comparisons.

3.4. Regression analysis

ABV analysis: Multiple regression was significant for each the left and right putaminal ROI (R/L $F_{4,19} = 8.41/9.67$, $p < 0.001$; $R^2 = 0.64/0.67$), with disease duration being significantly explanatory of relatively lower mean putaminal GMV (R/L $\beta = -0.49/-0.42$, $p = 0.006/0.013$).

VBA analysis: Regression analysis with voxel-wise AI indices showed a significant association of GM asymmetry in the volume of interest with disease duration in the putamen ($x|y|z = 29|-10|1$, $t = 5.52$, $k = 368$, $p_{FWESVC} = 0.003$), extending to the lateral pallidum ($x|y|z = 24|-12|3$, $t = 4.13$, $p_{FWESVC} = 0.035$; figure s-4). Exploration of cluster-specific mean AI showed increasing disease duration significantly explaining rightward (loss of leftward) asymmetry ($\beta = 0.74$, $p < 0.001$; $R^2 = 0.55$). Evaluation of the cluster-specific GMV indicated that while volume decreased in both hemispheres with increasing disease duration, the change in brain symmetry was rather explained by a significant loss of left-hemispheric GMV ($\beta = -0.43$, $p = 0.013$) in the cluster.

There were no significant associations of disease duration with VBM data, and no associations with ED score in any analysis.

4. Discussion

4.1. Primary sensorimotor cortices

Increased primary sensorimotor cortex GMV was complementarily observed in hypothesis-supported ROI-based and assumption-free voxel-wise approaches, in the latter localizing to the face/lip representation. While earlier work in hand musician's dystonia did not report primary sensorimotor changes [14], studies of hand TSFD made such observations with conflicting directionality [5], for which methodological aspects, inter-study differences (e.g. mixed focal hand TSFD

collectives) or (partly) small sample sizes may be discussed [15]. The somatotopic character of changes in this first orofacial musician's TSFD study amends observations in hand TSFD. Studies at cellular level suggest that morphometric GM changes may be interpreted as correlate of altered (trans)neuronal organization (i.e. plasticity) [16], and healthy volunteers have accordingly shown such changes after motor training/repetitive transcranial magnetic stimulation [16]. In monkeys, dystonia-like symptoms induced by repetitive motor training were accompanied by disorganized primary somatosensory cortex somatotopy as a sign of dysfunctional neuronal plasticity [17]. Deranged right-hemispheric functional primary somatosensory somatotopy demonstrated in ED during task and somatosensory stimulation [3,18] may be mirrored by some cranial shift of right-compared to left-hemispheric findings. Electrophysiological studies in FD made corresponding observations for the motor cortex including nonsymptomatic muscle representations, pointing to accompanying failure of inhibitory mechanisms [19]. Consistent with loss of inhibition, task-related fMRI has shown primary sensorimotor overactivity in ED [2].

Though mean GMV of the pre-/postcentral gyrus in healthy brass players was in between the magnitudes in ED patients and nonmusicians (figure s-3), direct comparison to nonmusicians did not show significant differences. While the overall literature, performed almost exclusively in pianists/string players, provides evidence for primary sensorimotor changes in instrumentalists, describing (among others) greater topographic representations, altered central sulcus length and correlation with increasing professionalism [8], the extent and character of the primary sensorimotor VBM findings has been varying. Among others positive GM density correlations with musical professionalism, reduced GMV, or no abnormalities have been observed [8,20,21]. The only study looking into structural changes in wind players analyzing cortical thickness observed concurrently a thickness increase in the anterior, and a reduction in the posterior right postcentral gyrus and no change in the precentral cortex [9]. It is hence conceivable that methodological constraints (e.g. reduced sensitivity due to limited localization accuracy and fine facial sensorimotor representations) and methodological differences to previous studies (e.g. statistical control for brain size, modulation) might have played a role [22]. Giving special consideration to a certain sex frequency variation across groups, we did not see significant GMV sex effects, and no sex-associated voxel-level trends in sensorimotor cortices at uncorrected peak-level.

4.2. Abnormal symmetry in thalamus and basal ganglia

Healthy and diseased brass players both showed increased thalamic symmetry compared to nonmusicians, that showed left-hemispheric thalamic lateralization in line with previous data in the healthy [23]. As observed in both, this may mostly be attributable to musical practice. Prompt integration of multimodal sensorimotor information requires conjunct activity in a fronto-parieto-temporal network involving the pre- and supplementary motor, inferior frontal, superior temporal and supramarginal cortex [24], and the thalamus herein has been suggested an important relay, with (cortico-)thalamo-cortical loops guiding multimodal sensory processing (e.g. tone, rhythm) [25], and (cortico-)thalamo-basal-ganglia- and cerebello-cortical loops involved in motor learning/sensorimotor integration (e.g. motor sequencing, adaption) [6]. Increased thalamic symmetry may thus mirror an adaption to intensive, bilateral orofacial (and bimanual) coordinative sensorimotor training in brass playing, in which a musician's nondominant hemisphere seems to undergo stronger plastic reorganization [8]. This is the first description of voxel-wise thalamic changes in healthy brass musicians. Earlier studies investigating cerebral asymmetry in musicians focused on the absolute pitch subgroup, describing mainly leftward planum temporale asymmetry [7,8]. Seminal work in a mixed keyboard/string player group described left-hemispheric thalamic lateralization within-group, but did not conduct a comparison against nonmusicians [7].

The subcortical increase in symmetry/rightward tendency compared to nonmusicians was more pronounced in ED, comprising putaminal peaks not seen in the comparison involving healthy players, and was driven not only by locally increased right-hemispheric but also diminished left-hemispheric GMV. Thalamo-cerebellar and -basal ganglia loops described in the musical context seem also important in FD pathogenesis [5]. Interestingly, abnormal cerebellar structure has been reported quite regularly in nonmusician TSFDs, while BG structure change alone is reported more frequently in non-TSFDs compared to TSFDs [5], a discrepancy whose origins remains yet unknown. The BG's assumed important role in dystonia is deduced from their key position in motor learning by filtering relevant sensory input to the motor system, movement selection and cortical plasticity/excitability modulation [19]. In already highly-trained individuals, sensorimotor processes are greatly automatized and seem to require less BG involvement [26], mirrored by abating BG volume in high motor-proficiency professionals [27] (contrasting cortical-level findings [16]). Granert and colleagues observed increased putaminal GMV in dystonic vs. healthy pianists, but at the same time an overall association of lower BG volumes with higher temporal piano key stroke precision (a measure of motor skill) [14]. Nonsymptomatic DYT1 mutation carriers show higher BG volume than diseased individuals [28]. Hence, alternatively to a correlate of symptom production in FD, increased BG volume has been discussed as possible correlate of compensatory effort. Our regression analyses suggested that i) the mean putaminal volume was negatively correlated with disease duration and ii) that this affected the left putamen more relative to the right in the voxel-wise approach. This is in line with findings in writer's cramp, where relative reduction of increased striatal GMV and abating somatosensory BG overactivity during tactile stimulation have been shown with increasing disease duration [29,30]. Considering the outline above, one might speculate if relative putaminal GMV reduction with disease duration in ED might be a correlate of adaptive processes leading to altered BG involvement, or sign of degradation of compensatory efforts with time [29,30] (as symptom severity increase/spread to other activities are seen in some in the first years [1]). As morphometry does not allow inferring if our observations are primary or compensatory, longitudinal research, yet sparse in FD, may be needed to further elucidate this phenomenon.

5. Conclusion

The present study provides robust first-time evidence for cortical and subcortical GM abnormalities in ED, investigating the largest patient sample in this rare disease to date. Further, the study provides evidence for brain (a)symmetry changes in healthy brass players and points to a possible role of such changes not only in musical professionalism [8] but also in dystonia. The good concordance of ROI- and voxel-based results underlines the relevance of meta-analyses for characterization of central disease-related changes.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2019.05.008>.

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