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SPASMODIC DYSPHONIA PRIMARY DYSTONIA IS ASSOCIATED WITH CORTICAL AND SUBCORTICAL ALTERATIONS: A MULTIMODAL IMAGING STUDY

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BACKGROUND AND OBJECTIVES

The pathophysiology of spasmodic dysphonia (SD) is still not fully understood. Several functional neuroimaging studies during voice and narrative speech production in SD patients found activation changes in the laryngeal/orofacial sensorimotor cortex and basal ganglia.[1-3] Furthermore, structural neuroimaging studies showed altered white matter (WM) integrity of the internal capsule as well as increased grey matter (GM) volume of the laryngeal sensorimotor cortex in SD patients.[4,5] Additional studies are needed to confirm such structural changes associated with the disease. This study aims to evaluate patterns of cortical morphology, basal ganglia, and white matter (WM) microstructural alterations in patients with SD relative to healthy controls. (HC).

METHODS

Table 1. Demographic, clinical, cognitive characteristics of the sample. We recruited 13 SD patients and 30 sex and age matched healthy controls.

	Patients with spasmodic dysphonia	Healthy controls	p
Number	13	30	-
Sex [men:women]	6:7	15:15	0.82
Age [years]	57.8±14 (36-78)	58.1±11 (36-77)	0.98
Education [years]	12.2±3.1 (4-16)	13.8±2.4 (8-16)	0.15
Disease duration [years]	9.1±7.3 (2-27)	-	-
Positive family history [yes:no]	1:13	-	-
Ever treated with botulinum toxin [yes:no]	7:6	-	-
BFMS total score, 0-120	4.4± 2.0 (1-6)	-	-
UDRS total score, 0-44	4.9±1.4 (3-7)	-	-
MMSE	29.5 ± 1.0 (27-30)	29.8 ± 0.5 (28-30)	0.17
WMH load [ml]	0.24±0.31 (0-1.0)	0.46±1.09 (0-4.0)	0.29

Values are means ± standard deviations (range) or numbers of patients. P values refer to Fisher exact test or Mann-Whitney U-test as appropriate. Abbreviations: BFMS, Burke Fahn Marsden Scale; MMSE, Mini-mental State Examination; UDRS, Unified Dystonia Rating Scale; WMH, white matter hyperintensities.

MRI ACQUISITION and ANALYSIS

1.5 T (Philips Medical Systems, Achieva): dual-echo turbo spin-echo (SE), 3D T1-weighted Transient Field Echo (TFE), and pulsed gradient SE single shot echo-planar (diffusion-encoding gradients applied in 65 non-collinear directions) sequences were obtained.

- **GM cortical analysis**: estimation of cortical thickness, area and volume were performed on the 3D T1-weighted TFE images using the FreeSurfer image analysis suite, version 5.3. The cerebral cortex was parcellated into 34 regions per hemisphere (Desikan atlas).
- **GM subcortical analysis**: Basal ganglia segmentation on 3D T1-weighted scans was performed using FIRST (FSL) and volumes of basal ganglia were normalized to the total intracranial volume; basal ganglia maps were then transformed to the DT MRI space, and average fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AxD), and radial diffusivity (RadD) were measured for each GM nucleus.
- **WM analysis**: Tract-based spatial statistics (TBSS) in FSL to assess FA and MD, permutation-based inference tool for nonparametric statistical thresholding ("randomise"; 5000 permutations).

RESULTS

Figure 1. Vertex-by-vertex analysis shows regional differences in cortical surface areas between patients with spasmodic dysphonia and healthy control subjects represented on an averaged brain map (p<0.01, number of vertex>100). Regions of increased cortical surface area in patients relative to controls are shown in red/yellow, while regions of decreased cortical surface area are shown in blue/cyan. Colored bar represents t values. L= left, R= right.

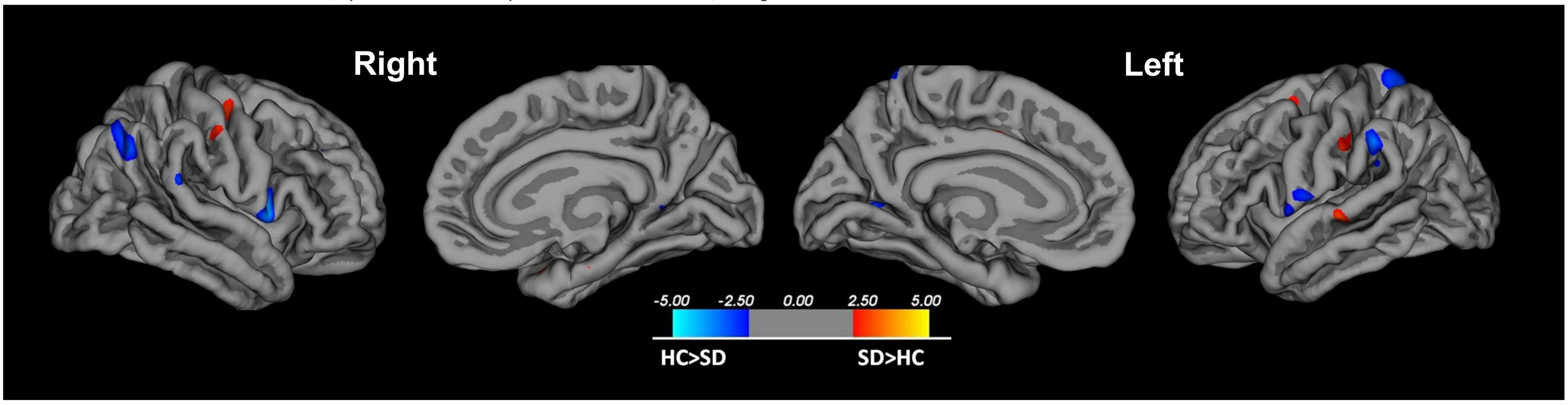
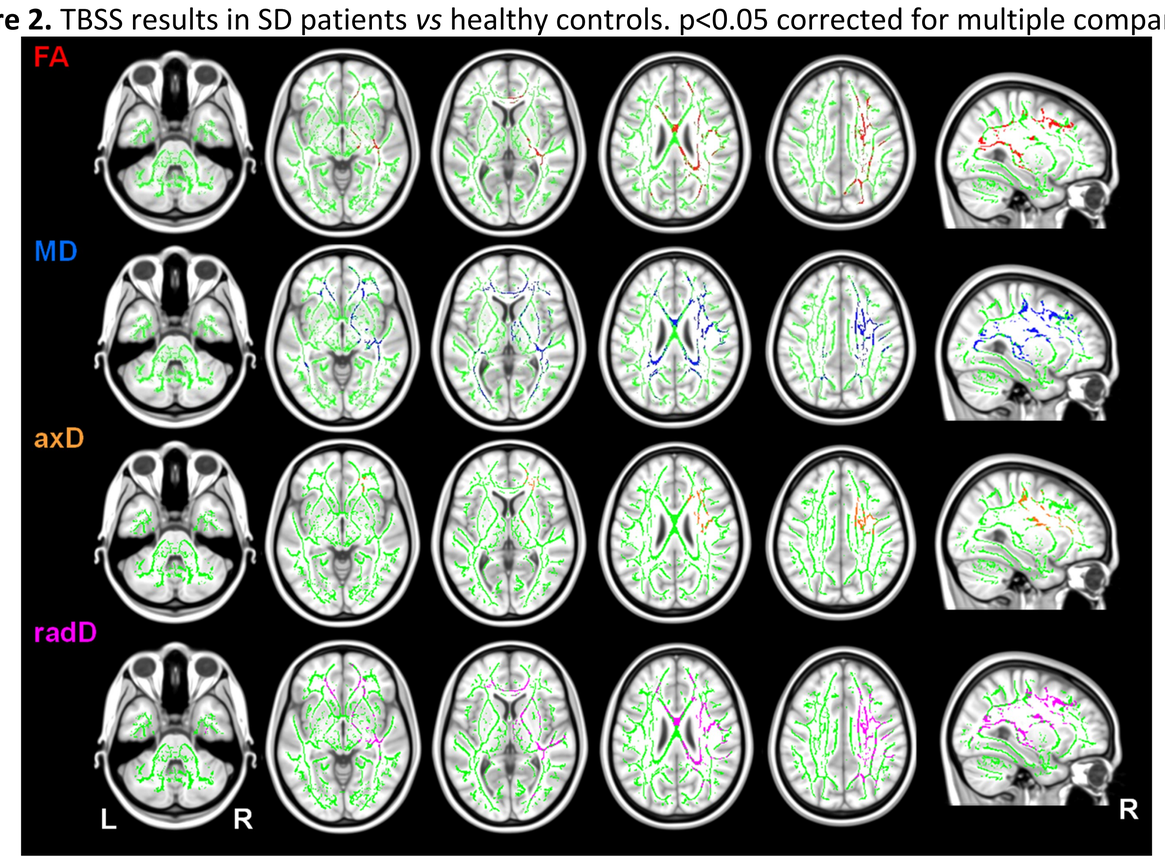


Table 2. Basal ganglia normalized volumes and mean DT MRI metrics.

GM nuclei		Healthy controls					Patients with spasmodic dysphonia				
		FA	MD	axD	radD	Volume	FA	MD	axD	radD	Volume
Caudate	L	0.25 ± 0.02	0.77 ± 0.03	0.97 ± 0.04	0.67 ± 0.03	3370.9 ± 467.6	0.26 ± 0.02	0.78 ± 0.03	0.99 ± 0.04	0.7 ± 0.02	3286.3 ± 456.1
	R	0.23 ± 0.02	0.77 ± 0.03	0.95 ± 0.03	0.67 ± 0.03	3456.5 ± 387.9	0.23 ± 0.02	0.80 ± 0.04*	0.99 ± 0.05*	0.7 ± 0.03*	3367.2 ± 436.2
Globus pallidus	L	0.34 ± 0.03	0.8 ± 0.06	1.08 ± 0.06	0.65 ± 0.05	1811.0 ± 245.4	0.33 ± 0.04	0.8 ± 0.06	1.08 ± 0.07	0.66 ± 0.06	1784.1 ± 189.4
	R	0.37 ± 0.03	0.79 ± 0.06	1.11 ± 0.07	0.64 ± 0.06	1772.8 ± 378.2	0.37 ± 0.03	0.83 ± 0.09	1.16 ± 0.11	0.67 ± 0.08	1770.8 ± 181.1
Putamen	L	0.26 ± 0.03	0.76 ± 0.03	0.96 ± 0.03	0.66 ± 0.03	4843.3 ± 585.1	0.26 ± 0.03	0.76 ± 0.02	0.97 ± 0.03	0.66 ± 0.02	4797 ± 643.1
	R	0.25 ± 0.02	0.76 ± 0.03	0.95 ± 0.03	0.66 ± 0.02	4761 ± 518.4	0.24 ± 0.02	0.79 ± 0.04*	0.98 ± 0.05	0.69 ± 0.03*	4730.6 ± 617.1
Thalamus	L	0.36 ± 0.018	0.79 ± 0.03	1.11 ± 0.03	0.65 ± 0.03	7340.1 ± 1030.6	0.37 ± 0.02	0.79 ± 0.02	1.11 ± 0.03	0.63 ± 0.03	7521.2 ± 736.8
	R	0.35 ± 0.02	0.81 ± 0.04	1.1 ± 0.04	0.66 ± 0.04	7079.2 ± 755.4	0.35 ± 0.02	0.82 ± 0.05	1.12 ± 0.06	0.67 ± 0.04	7293.5 ± 761.2

Values are means ± standard deviations. *p<0.05 between patients and controls. Abbreviations: L:left; R:right; FA: fractional anisotropy, MD: mean diffusivity; AxD: axial diffusivity; RadD: radial diffusivity. Volume values are in mm^3.

Figure 2. TBSS results in SD patients *vs* healthy controls. p<0.05 corrected for multiple comparisons.



Correlations between WM metrics and clinical variables (p<0.05 FWE):

No significant correlation among DT-MRI metrics and clinical scales (BFMS, UDRS, and disease duration) was found in the patients group

CONCLUSIONS

- ✓ SD is associated with cortical morphological changes in regions involved in the sensorimotor processing and speech controlling networks, as well as in areas responsible for auditory monitoring, language and visual perception.
- ✓ Increased MD and radD and decreased FA were detected in the corpus callosum and in major WM tracts of the right hemisphere in patients with SD when compared to controls.
- ✓ Microstructural abnormalities of the caudate and putamen nuclei with no volumetric change were also detected in SD patients.
- ✓ Taken together, our findings point to SD as a network disorder supporting a view that multi-level alterations in voice-controlling networks, that included regions devoted not only to sensorimotor integration, motor preparation and motor execution, but also processing of auditory and visual information during speech.
- ✓ Such alterations might have a role in the pathophysiology of SD, contributing to the clinical manifestations of this condition.

References: 1. Kiyuna et al., Auris Nasus Larynx 2014; 2. Haslinger et al., Neurol 2005; 3. Ali et al., J Speech Lang Hear Res 2006; 4. Simonyan et al., Brain 2008; 5. Simonyan et al., Cer Cortex 2012.