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Type II thyroplasty changes cortical activation in patients with spasmodic dysphonia

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ABSTRACT

Objective: Spasmodic dysphonia (SD) is a complex neurological communication disorder characterized by a choked, strain-strangled vocal quality with voice stoppages in phonation. Its symptoms are exacerbated by situations where communication failures are anticipated, and reduced when talking with animals or small children. Symptoms are also reduced following selected forms of treatment. It is reasonable to assume that surgical alteration reducing symptoms would also alter brain activity, though demonstration of such a phenomenon has not been documented. The objective of this study is to reveal brain activity of SD patients before and after surgical treatment.
Methods: We performed lateralization thyroplasties on three adductor SD patients and compared pre- and post-operative positron emission tomography recordings made during vocalization.
Results: Pre-operatively, cordal supplementary motor area (SMA), bilateral auditory association areas, and thalamus were activated while reading aloud. Such activity was not observed in normal subjects. Type II thyroplasty was performed according to Isshiki's method and the strained voice was significantly reduced or eliminated in all three patients. Post-operative PET showed normal brain activation pattern with a significant decrease in cordal SMA, bilateral auditory association areas and thalamus, and a significant increase in rostral SMA compared with pre-operative recordings.
Conclusion: This is the first report showing that treatment to a peripheral organ, which reverses voice symptoms, also reverses dysfunctional patterns of the central nervous system in patients with SD.

1. Introduction

Adductor spasmodic dysphonia is an irregular hyperadduction of the vocal folds occurring during phonation secondary to inappropriate intrinsic laryngeal muscle activity [1]. Patients with adductor SD exhibit a choked, strained-strangled voice quality with abrupt initiation and termination of voicing resulting in short breaks in phonation [2]. This involuntary movement disease affecting the vocal folds is classified as an idiopathic focal dystonia variably affecting laryngeal muscle control during speech [3]. However, the pathophysiology of SD is not well understood.

Literature in other areas of idiopathic focal dystonia (e.g., writer's cramp) have implicated central and basal ganglia involvement as the cause [4]. Radionuclide imaging studies have reported structural alterations in the lentiform nucleus in patients with idiopathic focal dystonia [5,6]. It has also been suggested that disinhibition and overexcitation of the motor cortex in basal ganglia pathology leads to co-contractions and dystonic postures [7]. Positron emission tomography (PET) studies enable one to observe abnormal brain activation, even in patients without evidence of an organic lesion. PET studies in patients with writer's cramp reveal abnormal activation in basal ganglia, thalamus, and supplementary motor area (SMA) [8,9].

Similarly in SD, while the vast majority have no obvious lesions, we have learned from some that the basal ganglia and thalamus

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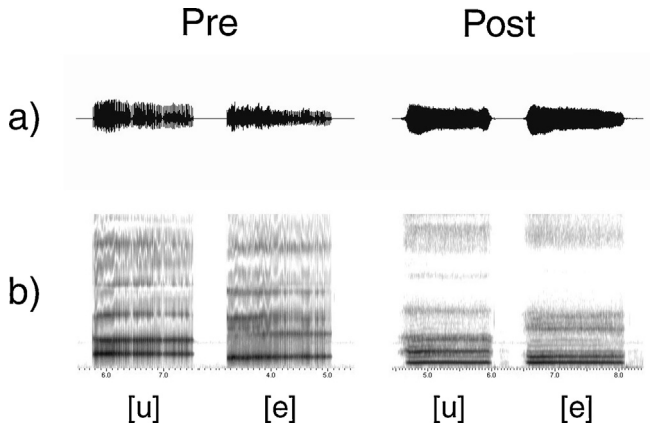

Fig. 1. Sound wave and spectrogram of the subject 1. Sound wave (a) and spectrogram (b) of [u] and [e]. Before operation, the voice has irregular intensity and interruption with distorted formant. After operation, the voice has improved with regular intensity and smooth pitch.

appear to be related to the etiology [10]. Whether or not they have similar involvement of the basal ganglia and thalamus is unknown, though an earlier SD patient case report using PET reported inactivation of SMA while reading aloud [11]. One interpretation of this finding is that the SD may be related to interference with motor programming. We reasoned that treatment reducing the spasmodic condition might also modify the pattern of cortical activation and in so doing provide further explanation of this puzzling disease.

Recently, Isshiki et al. [12] reported type II thyroplasty for the treatment of SD. In this surgery, the thyroid cartilage is incised at midline and pulled apart to mechanically reduce the excessive contraction of the vocal folds during phonation. This being the case, thyroplasty treatment appears to be an ideal means of make pre- and post-treatment recordings of cortical activity in order to gain information on whether the activated areas are part of the primary pathology or not. In this study, we used PET studies to reveal brain activity of three SD patients before and after completion of type II thyroplasty.

2. Subjects and methods

2.1. Subjects and clinical course

Three right-handed Japanese subjects with adductor type SD served as subjects for this study (29-year-old male, 32-year-old female and 14-year-old female). All subjects were diagnosed with adductor SD based on flexible laryngoscopy laryngeal findings and voice symptoms as described by Brin et al. [2]. Fiberoptic laryngoscopy was performed to confirm irregular hyperadduction of the vocal folds, tremor, and dystonic movements during speech. Patients showed no other signs of neurological abnormality, no gastroesophageal reflux, no dystonic movements in the larynx while at rest, a negative history for usage of neuroleptic medication and exhibited normal MRIs. Voice breaks were observed in all three patients. Subjective and objective examination of voice symptoms were performed pre- and post-operatively. Voice symptoms were evaluated by a speech-language pathologist using the GRBAS scale [13] and the percent of normal function (PNF), which is a global visual analog scale where 100% is a normal voice and 0% is an inability to phonate [2]. For objective examinations, sound spectrogram (Fig. 1b), maximum phonation time, mean air flow, AC/DC [14], intensity of voice, fundamental pitch, voice range, and jitter (%) were used (Table 1).

Type II thyroplasties were performed for all patients following Isshiki's procedure [12]. In brief, the thyroid cartilage surrounding the vocal fold was incised at midline pulled apart approximately 4 mm. Silicone was inserted and sutured between the edges to maintain a gap (Fig. 2a andb).

2.2. PET activation study

Regional cerebral blood flow (rCBF) was measured to assess the cortical activation during vocalization pre-operatively and 3 months post-operatively. Written informed consent was obtained from each patient after providing him or her with a detailed explanation of the study. This study was performed in accordance with the guidelines of the Declaration of Helsinki and was approved by the Committee of Medical Ethics, Graduate School of Medicine, Kyoto University, Japan.

Patients' brains were scanned using a General Electric Advance tomography (GE Medical Systems, Milwaukee, WI, USA) following injection of ^{15}O-labeled water. Two different conditions were applied during the scan: (1) resting with neither phonatory nor articulatory movement, and (2) reading aloud commonly used sentences from a cardboard placed 50 cm in front of the patient. Each session lasted 1.5 min starting 30 s prior to intravenous injection of $H_2{}^{15}O$, with an interval of 10 min between sessions. Each session was repeated four times. Images were reconstructed with the Kinahan–Rogers reconstruction algorithm. Hanning filters were used and yielded transaxial and axial resolutions of 6 mm and 10 mm (full-width at half-maximum, FWHM), respectively. The field of view and pixel size of the reconstructed images were 256 mm and 2 mm × 2 mm × 4.75 mm, respectively. The rCBF measurements were adjusted to a global mean of 50 ml/100 ml/min. The data acquired were analyzed with the Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK) software implemented in MATLAB (Version 6.1 Release 12, The Mathworks Inc., MA, USA). Scans for each patient were realigned to the first scanned image and all images were transformed into a standard three-dimensional coordinate space of Talairach and Tournoux [15] using MNI templates of SPM in order to normalize image data. Each image

Table 1
Objective and subjective examination of vocal symptom of each patient before and after operation.

	Subject 1		Subject 2		Subject 3	
	Pre	Post	Pre	Post	Pre	Post
GRBAS scale	G3R1B0A0S3	G1R1B1A0S1	G2R1B0A0S2	G1R1B0A0S1	G2R1B0A0S2	G1R1B0A0S0
Maximum phonation time	20	13	26	35	9	13
Mean air flow	32	180	84	71	21	70
AC/DC	41	39	34	45	26	34
Intensity	69	72	74	75	75	79
Fundamental frequency	133	262	143	151	–	354
Voice range (Hz)	101–244	214–337	115–283	100–305	–	285–414
Jitter (%)	11.98	2.43	2.57	1.45	8.00	0.79
Percent of normal function	10	80	35	75	60	75

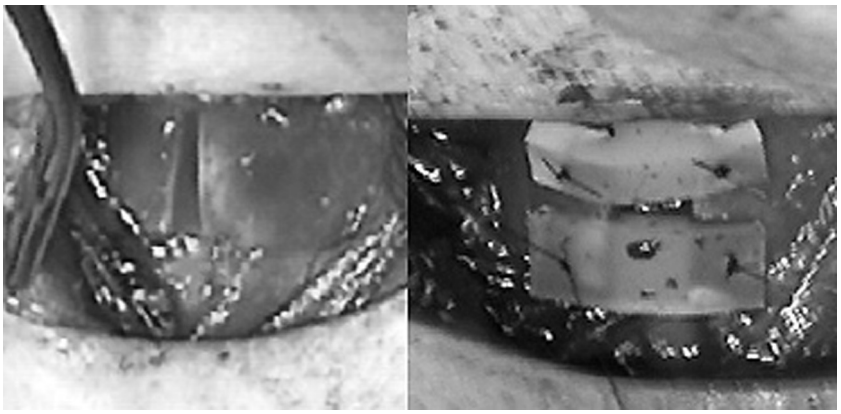

Fig. 2. Operative procedure of type II thyroplasty. Thyloid cartilage was incised at the midline (a) and a silicon was inserted between the gap (b).

was smoothed using a Gaussian filter of 14 mm (FWHM) in the *x*-, *y*- and *z*-axes to improve signal-to-noise ratio. ANCOVA (analysis of covariance), using global activity as a confounding covariate, was performed on a pixel-to-pixel basis to adjust each scan data. Contrasts between tasks were evaluated with *t*-tests and then converted to *z*-values. We evaluated the activation by comparing the resting state (condition 1) with vocalization (condition 2) of pre- and post-operative experiments, respectively. We also directly compared the activated areas during phonation between pre- and post-operation by comparing the activated regions during phonation (condition 2-1) in the pre-operative study with those in the post-operative study. The threshold was set at $P < 0.001$ (uncorrected for multiple comparisons) for comparison between phonation versus resting state, and at $P < 0.05$ for comparison between pre- and post-operative study. Significant activations were reported for cluster size greater than 10 voxels.

All post-operative examinations were performed 3 months post-thyroplasty.

3. Results

3.1. Voice symptoms

Pre-operative sound spectrograms revealed irregular and distorted pitch and interrupted phonation in all three patients (Fig. 1a and b). The GRBAS scale was G3R1B0A0S3 in patient 1, G2R1B0A0S2 in patient 2, and G2R1B0A0S2 in patient 3, while PNF was 10%, 35%, and 60%, respectively. Jitter (%) was 11.98%, 2.57%, and 8.00%, in each patient. Patients showed no response to voice therapy employing the muscular relaxation procedures of Roy et al. [16] and the administration of minor tranquilizers.

Strained voice quality was significantly reduced or eliminated in all patients, following surgery. GRBAS scale and PNF showed improvement in all patients with scores of G1R1B1A0S1, G1R1B0A0S1, G1R1B0A0S0, 80%, 75% and 75%, respectively. Patients 2 and 3 showed improvement in maximum phonation time and AC/DC. Patient 1 showed marked increase in airflow volume and fundamental frequency with little decrease of AC/DC. Post-operative jitter (%) showed improvement in all patients with a value of 2.43%, 1.45%, and 0.79%, respectively. Sound spectrograms also documented voice improvements with regular intensity and no voice interruptions characteristic of SD (Fig. 1a and b).

3.2. Brain activations

Pre-operatively, bilateral superior and middle temporal gyri (auditory association area), bilateral transverse temporal gyri (primary auditory area), Broca's area, bilateral sensorimotor cortex (SMC), bilateral visual cortices, cordal SMA, cerebellum, right thalamus and left putamen were significantly activated while reading aloud (Fig. 3). There was no activation in the rostral supplementary motor area, which is activated in normal subjects while reading aloud.

Post-operatively, the right superior temporal gyrus, bilateral primary auditory areas, bilateral SMC, bilateral visual cortices, rostral SMA and cerebellum were activated during phonation, which is similar to the activated areas during phonation in normal

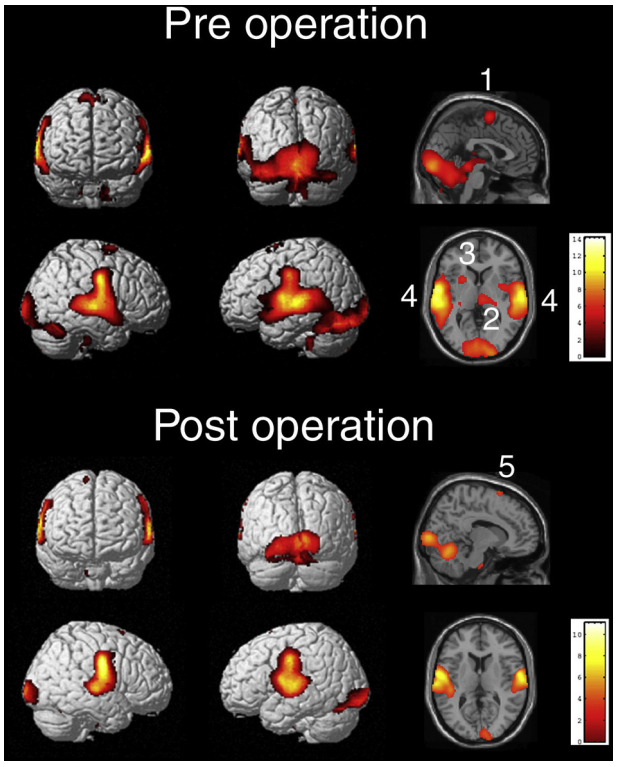

Fig. 3. Brain activation during reading aloud in pre- and post-operation. Areas of significant brain activation during reading aloud rendered onto the lateral surface of a standard brain using SPM 99 (voxel level: $P < 0.001$, uncorrected). In pre-operation, cordal SMA, bilateral auditory association cortex, right thalamus, and left putamen were significantly activated in addition to Broca's area, bilateral sensorimotor cortex, bilateral visual cortices, and cerebellum. In post-operation, rostral SMA, smaller area of auditory association cortex showed significant activation, whereas cordal SMA, right thalamus, and left putamen showed no significant activation (1: cordal SMA, 2: right thalamus, 3: left putamen, 4: auditory association cortex, 5: rostral SMA). Color scale indicates degree of significance.

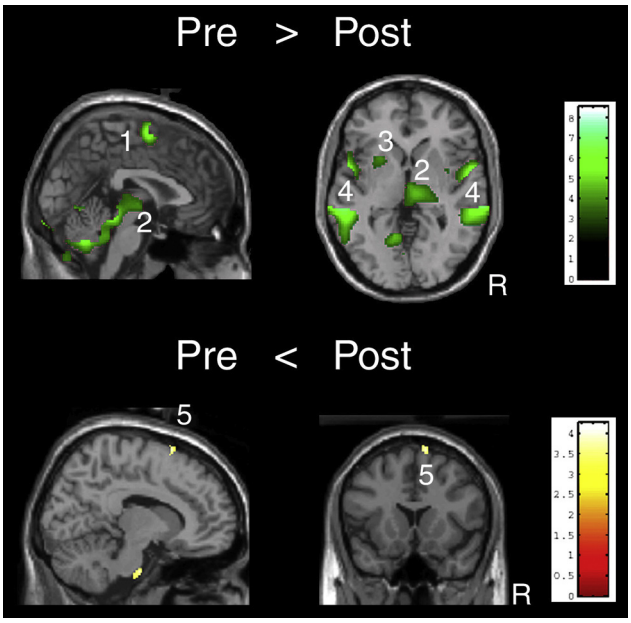

Fig. 4. Comparison of brain activation during reading aloud between pre- and post-operation. Areas of significant decreased activation post-operatively compared with pre-operative data are seen in the upper row (cold colors). Areas of significant increased activation post-operatively compared with pre-operative data are seen in the lower row (warm colors). Post-operatively, cordal SMA, right thalamus, left putamen, bilateral auditory association cortex showed a significant decrease in activation compared with preoperative. While post-operatively, rostral SMA showed a significant increase in activation compared with preoperative (1: cordal SMA, 2: right thalamus, 3: left putamen, 4: auditory association cortex, 5: rostral SMA, voxel level: $P < 0.05$). Color scale indicates degree of significance.

subjects (Fig. 3). Activation of bilateral auditory association areas, cordal SMA, thalamus, and cerebellum were reduced or nearly absent post-operatively.

Next, areas activated during vocalization were directly compared pre- and post-operatively (Fig. 4). Compared to pre-operation, bilateral auditory association areas, right thalamus, left putamen and cordal SMA showed significantly decreased activation post-operatively, whereas rostral SMA revealed a significant increase.

Peak *t*-values and *x*-, *y*-, *z*-coordinates of activated regions under each stimulated condition are presented in Table 2, while regions of the rCBF, of which exhibited significant difference between pre- and post-operation, are presented in Table 3.

4. Discussion

4.1. Activation in SMA

SMA is located on Brodmann's area (BA) 6 in the frontal lobe and the function of SMA is thought to be motor planning and programming [17]. Neuronal recordings in monkeys revealed that there is functional subdivision of SMA and it can be divided into rostral and caudal SMA [18]. Rostral SMA is reported to be activated during preparatory periods before performance of prelearned movement [19], whereas direct movement-related activity is more prominent in caudal SMA [18]. Functional imaging studies in humans also confirmed the concept of a subdivision of SMA into functionally distinct parts [20]. It has been considered that a functional subdivision between caudal and rostral (pre) SMA occurs at the level of the ventral anterior commissure (VAC) line [20,21]. A greater degree of activation in the rostral SMA has been shown with self-paced movement compared to externally triggered movement, with no significant difference in the degree of activation in the caudal SMA [22].

Several investigators have reported abnormal activation of SMA in focal dystonia; however, activation patterns in subdivisions of SMA are still in discussion. Ibanez et al. [9] reported less activation in rostral SMA during writing in writer's cramp compared with control subjects. Baumann et al. reported that "paced joystick movements in freely selected directions with the right hand"[8] and "writing 'dog'" [23] in writer's cramp induced increased activation in rostral SMA and decreased activation in caudal SMA, which was contrary to the report of Ibanez et al. [9]. It has been reported that rCBF in the rostral SMA is positively correlated with increasing sequence complexity of overlearned movements [24] and the differences in task complexity may reflect different activation patterns in subdivisions of SMA.

Activation of SMA has also been reported during vocalization [25,26], and lesions in the SMA are known to cause inabilities of voluntary utterance [27]. For example, Penfield and Jasper [28] reported that spontaneous speech is arrested by electric stimulation of SMA. Although there are few reports focusing on the subdivision of SMA during vocalization, activated areas in SMA were rostral to VAC line [25,26,29], suggesting that rostral SMA is activated during vocalization. Vocalization is a prelearned movement for normal adults and the activation of rostral SMA

Table 2
Peak *t*-values and *x*-, *y*-, *z*-coordinates of activated regions under each stimulation condition.

Cortical areas	Pre-operation			*T* value	Post-operation			*T* value
	x	*y*	*z*		*x*	*y*	*z*	
Rostral supplementary motor area		–			10	10	62	3.95
Cordal supplementary motor area	4	−5	58	6.74		–		
Right middle temporal gyrus	57	−27	−3	8.59		–		
Left middle temporal gyrus	−48	−63	−7	3.69		–		
Right superior temporal gyrus	57	−21	7	10.29	48	−23	2	6.57
Left superior temporal gyrus	−54	−7	6	12.68	−57	−21	6	7.51
Right transverse temporal gyrus	48	−19	9	5.87	52	−15	11	7.58
Left transverse temporal gyrus	−45	−15	10	7.63	−55	−7	10	8.92
Broca's area	−48	18	9	4.27	−50	1	14	6.06
Right thalamus	8	−23	−1	4.78		–		
Left putamen	−20	8	4	4.50		–		
Right sensorimotor cortex	45	−15	31	13.35	47	−15	31	11.05
Left sensorimotor cortex	−47	−15	31	10.16	−45	−15	31	9.10
Right visual cortex	17	−100	−5	7.20	8	−95	−3	6.41
Left visual cortex	−11	−100	−5	6.01	−17	−98	−11	5.08
Right cerebellum	6	−69	−25	8.67	10	−65	−19	5.95
Left cerebellum	−13	−63	−25	7.89	−18	−69	−21	5.21

Table 3
Regions of the rCBF of which exhibited significant difference between pre- and post-operation.

	Cortical areas	*x*	*y*	*z*	*T* value
Pre > post (conjunction)	Thalamus	8	−23	−1	4.78
	Cordal supplementary motor area	1	−7	56	6.38
	Broca's area	−48	16	11	4.24
	Right middle temporal gyrus	50	−3	−4	7.13
	Right superior temporal gyrus	48	−40	5	7.02
	Left middle temporal gyrus	−48	−1	−7	8.50
	Left superior temporal gyrus	−50	−36	14	6.22
	Right cerebellum	3	−63	−33	6.50
	Left cerebellum	−25	−86	−26	5.37
Pre < post (conjunction)	Rostral supplementary motor area	10	12	62	3.86
	Left sensorimotor cortex	−55	−23	41	4.24

is consistent with suggestions that rostral SMA is related to prelearned movement. In this study, SD patients revealed activation in caudal SMA and lack of activation in rostral SMA. These results are interpreted to suggest that vocalization for SD patients characterized by voice breaks and a strain-strangled quality is not a prelearned movement, but a movement which is done with an external cue feedback from their own voice or laryngeal muscle movements.

4.2. Activation of basal ganglia and thalamus

The basal ganglia and the thalamus are well known to play important roles during movement. Organic lesions of the basal ganglia in acquired dystonia have led to the notion that the basal ganglia is critically involved in causing idiopathic dystonia [7] and structural change of lentiform nucleus in idiopathic focal dystonia [5], suggesting that a disinhibition and overexpression of the motor cortex based on a basal ganglia pathology leads to co-contractions and dystonic postures [7]. The thalamus is also thought to be involved in causing idiopathic dystonia, since thalamic necrosis is known to cause significant dystonia affecting speech and upper limb motor function [30]. In SD patients, Schaefer et al. [10] reported that 6 of 19 patients had abnormal spin-echo MRI findings, ranging from infarcts within the basal ganglia to demyelinating lesions within the supralateral angles of the lateral ventricles. Organic change was also reported in the thalamus in a patient with pharyngeal and laryngeal dystonia that showed symptoms similar to SD [31]. Thus, basal ganglia and thalamus are thought to be related to SD.

Functional brain imaging studies have also revealed abnormality of central processing of movement in patients with dystonia [7,9]. Writing in normal subjects induces a rCBF increase in the contralateral SMC, SMA and ipsilateral cerebellum, with no rCBF increase in basal ganglia and thalamus [7]. Peribisch et al. [7] reported the activation of the contralateral thalamus, in addition to extensive activation of the primary sensorimotor cortex and significant activation of the ipsilateral cerebellum in patients with writer's cramp. Odergren et al. [32] described an increased activity of the thalamus and cerebellum and an increased activation of putamen during writing in writer's cramp [9]. In normal subjects, no significant activation occurs during vocalization in the basal ganglia and the thalamus [25,26]. Our results showed significant activation in the right thalamus and left putamen during vocalization in subjects with SD, which is similar to what has been reported in writer's cramp.

4.3. Auditory verbal feedback processing

When normal subjects read aloud, significant activity is observed in the primary auditory cortex in addition to Broca's area, motor area, SMA, and cerebellum, whereas no significant activity is observed in the auditory association area [25,29,33]. It is well known that striking changes occur in speech when air-conducted auditory feedback is delayed [34]. Hirano et al. [33] reported significant activation of the auditory association area and no activation of the SMA when subjects heard their own voices under delayed auditory feedback. Based on these findings, Hirano et al. [33] proposed two different methods of speech processing for vocalization, the programmed system mediated by the SMA, and the auditory verbal feedback system with participation of the auditory association cortex. They speculated that distorted voice needed auditory feedback, which is related to the activation of the auditory association cortex [33]. In our study with SD patients, rostral SMA showed no significant activation, whereas cordal SMA and bilateral auditory association areas showed significant activation, which is consistent with what we have reported previously [11]. As aforementioned, rostral SMA is related to programming of prelearned movements and cordal SMA is related to direct movement activities [18]. Our results suggest that SD patients process their distorted speech using an auditory verbal feedback system without programmed system mediation by the rostral SMA.

4.4. Brain activation of SD patients and post-operative changes

With vocal improvement following treatment, activation patterns in the SMA and auditory association areas during vocalization showed similar patterns to that of normal subjects. They exhibited a significant decrease in caudal SMA and bilateral auditory association areas and a significant increase in rostral SMA compared with that shown pre-operatively. This is the first report to show that treatment to a peripheral organ, which reverses voice symptoms, also reverses dysfunctional patterns of the central nervous system in patients with SD. The abnormal activation of the basal ganglia, SMA, and thalamus in our study, and the existence of organic lesions in these areas which have been reported in SD [10] or SD-like [31] patients in other studies suggest that normal pattern of activation in these areas are required for normal speech. Reversed dysfunctional brain activity in patients with reversed symptoms supports this notion.

5. Conclusions

In patients with SD, abnormal activation was observed in cordal SMA, bilateral auditory association areas, putamen, and thalamus during vocalizations prior to treatment. No activation was observed in rostral SMA, which is related to programming of prelearned movement. We hypothesize that SD patients process distorted speech with an auditory verbal feedback system. Interestingly, with an improvement in symptoms following

surgery, abnormal activation disappeared and PET results showed normal brain activation patterns with a significant decrease in cordal SMA, bilateral A2, and thalamus, and a significant increase in rostral SMA compared with pre-operative recordings. This indicates that people generally speak according to a prelearned speech production program without hearing their own voice well. When their vocal output becomes distorted from the expected motor program they initiate a monitoring mode and use the auditory association area to hear their voice. Finally, we believe these results are the first to demonstrate that treatment of a peripheral organ can change the abnormal brain activation in patients with SD as evidenced by PET.

Conflict of interest

All authors have not been received any financial support or relationship that may pose a conflict of interest.

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References

[1] Rodriquez AA, Ford CN, Bless DM, Harmon RL. Electromyographic assessment of spasmodic dysphonia patients prior to botulinum toxin injection. Electromyogr Clin Neurophysiol 1994;34:403–7.
[2] Brin MF, Blitzer A, Stewart C. Laryngeal dystonia (spasmodic dysphonia): observations of 901 patients and treatment with botulinum toxin. Adv Neurol 1998;78:237–52.
[3] Ludlow CL, Schulz GM, Yamashita T, Deleyiannis FW. Abnormalities in long latency responses to superior laryngeal nerve stimulation in adductor spasmodic dysphonia. Ann Otol Rhinol Laryngol 1995;104:928–35.
[4] Marsden CD, Obeso JA, Zarranz JJ, Lang AE. The anatomical basis of symptomatic hemidystonia. Brain 1985;108(Pt 2):463–83.
[5] Naumann M, Pirker W, Reiners K, Lange KW, Becker G, Brucke T. Imaging the pre- and postsynaptic side of striatal dopaminergic synapses in idiopathic cervical dystonia: a SPECT study using [^{123}I] epidepride and [^{123}I] beta-CIT. Mov Disord 1998;13:319–23.
[6] Perlmutter JS, Stambuk MK, Markham J, Black KJ, McGee-Minnich L, Jankovic J, et al. Decreased [^{18}F]spiperone binding in putamen in dystonia. Adv Neurol 1998;78:161–8.
[7] Preibisch C, Berg D, Hofmann E, Solymosi L, Naumann M. Cerebral activation patterns in patients with writer's cramp: a functional magnetic resonance imaging study. J Neurol 2001;248:10–7.
[8] Ceballos-Baumann AO, Passingham RE, Warner T, Playford ED, Marsden CD, Brooks DJ. Overactive prefrontal and underactive motor cortical areas in idiopathic dystonia. Ann Neurol 1995;37:363–72.
[9] Ibanez V, Sadato N, Karp B, Deiber MP, Hallett M. Deficient activation of the motor cortical network in patients with writer's cramp. Neurology 1999;53:96–105.
[10] Schaefer S, Freeman F, Finitzo T, Close L, Cannito M, Ross E, et al. Magnetic resonance imaging findings and correlations in spasmodic dysphonia patients. Ann Otol Rhinol Laryngol 1985;94(Pt 1):595–601.
[11] Hirano S, Kojima H, Naito Y, Tateya I, Shoji K, Kaneko K, et al. Cortical dysfunction of the supplementary motor area in a spasmodic dysphonia patient. Am J Otolaryngol 2001;22:219–22.
[12] Isshiki N, Haji T, Yamamoto Y, Mahieu HF. Thyroplasty for adductor spasmodic dysphonia: further experience. Laryngoscope 2001;111:615–21.
[13] Hirano M. Clinical examination of voice. New York: Springer Verlag; 1981.
[14] Isshiki N. Vocal efficiency index. In: Stevens KN, HIrano M, editors. Vocal fold physiology. Tokyo: University of Tokyo Press; 1981. p. 193–208.
[15] Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.
[16] Roy N, Ford CN, Bless DM. Muscle tension dysphonia and spasmodic dysphonia: the role of manual laryngeal tension reduction in diagnosis and management. Ann Otol Rhinol Laryngol 1996;105:851–6.
[17] Thickbroom GW, Byrnes ML, Sacco P, Ghosh S, Morris IT, Mastaglia FL. The role of the supplementary motor area in externally timed movement: the influence of predictability of movement timing. Brain Res 2000;874:233–41.
[18] Matsuzaka Y, Aizawa H, Tanji J. A motor area rostral to the supplementary motor area (presupplementary motor area) in the monkey: neuronal activity during a learned motor task. J Neurophysiol 1992;68:653–62.
[19] Tanji J, Shima K. Role for supplementary motor area cells in planning several movements ahead. Nature 1994;371:413–6.
[20] Picard N, Strick PL. Motor areas of the medial wall: a review of their location and functional activation. Cereb Cortex 1996;6:342–53.
[21] Passingham RE. Functional specialization of the supplementary motor area in monkeys and humans. Adv Neurol 1996;70:105–16.
[22] Deiber MP, Honda M, Ibanez V, Sadato N, Hallett M. Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: effect of movement type and rate. J Neurophysiol 1999;81:3065–77.
[23] Ceballos-Baumann AO, Sheean G, Passingham RE, Marsden CD, Brooks DJ. Botulinum toxin does not reverse the cortical dysfunction associated with writer's cramp. A PET study. Brain 1997;120(Pt 4):571–82.
[24] Boecker H, Dagher A, Ceballos-Baumann AO, Passingham RE, Samuel M, Friston KJ, et al. Role of the human rostral supplementary motor area and the basal ganglia in motor sequence control: investigations with H2 15O PET. J Neurophysiol 1998;79:1070–80.
[25] Hirano S, Kojima H, Naito Y, Honjo I, Kamoto Y, Okazawa H, et al. Cortical speech processing mechanisms while vocalizing visually presented languages. Neuroreport 1996;8:363–7.
[26] Sakurai Y, Momose T, Iwata M, Sudo Y, Ohtomo K, Kanazawa I. Cortical activity associated with vocalization and reading proper. Brain Res Cogn Brain Res 2001;12:161–5.
[27] Freedman M, Alexander MP, Naeser MA. Anatomic basis of transcortical motor aphasia. Neurology 1984;34:409–17.
[28] Penfield W, Jasper H. Epilepsy and functional anatomy of human brain. Boston: Brown; 1954.
[29] Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME. Positron emission tomographic studies of the cortical anatomy of single-word processing. Nature 1988;331:585–9.
[30] Ashtekar CS, Jaspan T, Thomas D, Weston V, Gayatri NA, Whitehouse WP. Acute bilateral thalamic necrosis in a child with *Mycoplasma pneumoniae*. Dev Med Child Neurol 2003;45:634–7.
[31] Yamamoto T, Yamashita M. Thalamo-olivary degeneration in a patient with laryngopharyngeal dystonia. J Neurol Neurosurg Psychiatry 1995;59:438–41.
[32] Odergren T, Stone-Elander S, Ingvar M. Cerebral and cerebellar activation in correlation to the action-induced dystonia in writer's cramp. Mov Disord 1998;13:497–508.
[33] Hirano S, Kojima H, Naito Y, Honjo I, Kamoto Y, Okazawa H, et al. Cortical processing mechanism for vocalization with auditory verbal feedback. Neuroreport 1997;8:2379–82.
[34] Chase RA. Effect of delayed auditory feedback on the repetition of speech sounds. J Speech Hear Disord 1958;23:583–90.