J. Tokyo Med. Univ., **75**(3) : 315-322, 2017

Involvement of psychological factors in spasmodic dysphonia

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Abstract

Spasmodic dysphonia (SD) is considered to be due to dystonia of the intrinsic laryngeal muscles. Adductor SD (ADSD), the most common type, occurs in many young women in Japan, but not in other countries, and age distribution differs also. However, frequent episodes of dysphonia suggest the involvement of psychological factors, as symptoms may be exacerbated in stressful situations. Functional MRI studies have indicated that brain activity in the insula, limbic system, and other parts involved in emotions differs between SD patients and healthy individuals. In the present study, ADSD patients were divided into high and low anxiety groups based on 2 psychological tests, the State-Trait Inventory (STAI) and Social Anxiety Disorder Scale (SADS), to investigate potential associations with functional MRI findings. For MRI, a block model was used in which the phrase "*Yabu no naka kara usagi ga pyokon-toe dete kimashita*" ("A rabbit jumped out of a thicket") was repeated at 30-sec intervals. This phrase is widely used in Japan to induce ADSD symptoms. Parts of the limbic system associated with emotions were significantly activated in the high anxiety group on vocalization. Findings for the basal ganglia were compatible with dystonia in the low anxiety group. However, in the high anxiety group, activity in the caudate nucleus was attenuated and the medial globus pallidus activated. These findings suggest that psychological factors are involved in ADSD, and that ataxia in the high anxiety group arose by a different mechanism from that for dystonia.

Introduction

Spasmodic dysphonia (SD) is a disease of unknown cause in which spasm of the intrinsic laryngeal muscles causes vocalization disorders, and there are no abnormal organic findings in the larynx[1]. It is currently considered as localized dystonia in the intrinsic laryngeal muscles, but many points remain unclear.

Spasmodic dysphonia is broadly divided into three types : adductor, abductor, and mixed. In the adductor type, in which spasmodic movement is mainly in the thyroarytenoid muscle (inner muscle), adduction of the vocal cords causes speech to be strangled, with tremor and choppiness in the voice ; in the abduction type, spasm mainly occurs in the posterior cricoarytenoid muscle (rear muscle), which results in involuntary abduction of the vocal cords, causing symptoms such as hoarseness and loss of voice ; and in the mixed type both adductor and abductor SD are present[2]. A survey of 55 facilities in Japan reported incidences of the adductor, abductor, and mixed type as 95.7%, 4.1%, and 0.1%, respectively[3]. Therefore, the present study focused on adductor SD (ADSD), the most common type, which occurs in many young women in Japan. This is not the case in other countries and the age distribution generally differs from that in Japan. Also, we often encounter patients in whom a psychological background is suspected because they feel that their symptoms are aggravated in stressful situations or that symptoms only appear when under stress. For this reason, it was considered to be a disease

Received February 10, 2017, Accepted June 23, 2017
Key words : spasmodic, functional MRI, dysphonia, dystonia
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due to psychological factors until around 30 years ago.

Based on the sex and age distributions in Japan, as well as the occurrence of episodes suggesting psychogenic factors mentioned above, it is difficult to conclude that SD is a type of dystonia only having purely neurological factors.

Functional MRI studies have revealed greater activity in parts of the brain connected with emotions, such as the insula and the limbic system, in SD patients than in healthy subjects[4]. For this reason, although SD is a localized type of dystonia, there is considered to be strong emotional involvement in some patients.

The objective of the present study was to investigate differences in brain activity between low and high anxiety groups upon vocalization using functional MRI, with particular focus on areas connected with the emotion, as well as the basal ganglia.

Participants and Methods

The participants comprised 12 patients (3 men, 9 women ; age range, 25–49 yr ; mean age, 44 yr) attending our department in whom ADSD had been diagnosed. A diagnosis of ADSD required the presence of the characteristic features of strangled or choppy speech and tremor, but no organic abnormalities on laryngoscopy.

Psychological testing

All the patients were surveyed based on a questionnaire concerning trait anxiety (disposition to feel anxiety), state anxiety (current state of anxiety), and social anxiety (degree of stress and anxiety in interacting with others). The State–Trait Anxiety Inventory (STAI) was used for trait anxiety and state anxiety and the Social Anxiety Disorder Scale (SADS) for social anxiety. The STAI comprises 20 items concerning state anxiety and 20 for trait anxiety, with responses on a 4-point scale and scores rated according to 5 levels : I, extremely low ; II, low ; III, normal ; IV, high ; and V, very high. The SADS comprises 31 items, with responses rated from 0–4 according to intensity and overall scores evaluated according to 4 levels : 44 or below, mild anxiety ; 45–74, moderate anxiety ; 75–104, severe anxiety ; and 105 or above, very severe anxiety. Participants classified as IV or V according to STAI and moderate to very severe according to SADS were assigned to the high anxiety group, while the others were assigned to the low anxiety group. Areas of brain activation were compared between them during vocalization.

Brain function imaging analysis with fMRI

Magnetic resonance imaging was performed by using the GE Health Care system with a static magnetic field strength of 1.5 tesla. Using GRE type EPI for the MRI protocol, the settings were as follows : TE, 40 msec ; TR, 3,000 msec ; FA, 90° ; slice thickness, 5 mm ; slice gap, 1 mm ; and FOV, 256 mm. The functional images obtained were analyzed using Statistical Parametric Mapping (SPM8 : The Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London), a statistical image analysis software package developed with the numerical computing software Matlab R2015b (The Mathworks, Inc. USA).

A block design was used for the experiment (Fig. 1). The task assigned was repeatedly reading the phrase "*Yabu no naka kara usagi ga pyokon-toe dete kimashita*" ("A rabbit jumped out of a thicket"). This phrase is widely used in Japan because it readily induces SD symptoms. At ON, the task was performed for 30 sec and at OFF there was a break of 30 sec with no vocalization. ON and OFF were alternated 3 times each. The scan time was 3 sec and the number of slices per scan for both resting and vocalization for a single task was 10. Voice volume, speaking speed, and mouth movement were rehearsed beforehand, and the start and end of the task were announced by the tester using a microphone.

There are individual differences in head motion and head size in MRI images. Therefore, in SPM motion correction was conducted and the participants' brains normalized to MNI (Montreal Neurological Institute) space. In the analysis, it was necessary to standardize individual periods of minute brain activity in voxel units with that in the neighboring area by carrying out spatial smoothing[5]. Group analysis was employed, applying the random effect model (voxel levels, $p < 0.001$, uncorrected).

After conducting analysis on individuals, brain activation was compared between the high anxiety and low-anxiety groups defined in Psychological Testing. A paired t test was used for the intergroup analysis, and the significance level was set at $p < 0.05$ uncorrected at the cluster level. In the SPM statistical processing, t-values, cluster size, and activation location were obtained for areas where activation was significant. Although brain activation locations in terms of MNI coordinates could be determined, they could not be directly converted to Brodmann's areas. Therefore, they were converted to Talairach coordinates.

The present research was approved by the Ethics Committee of Tokyo Medical University and written informed consent was received from the participants.

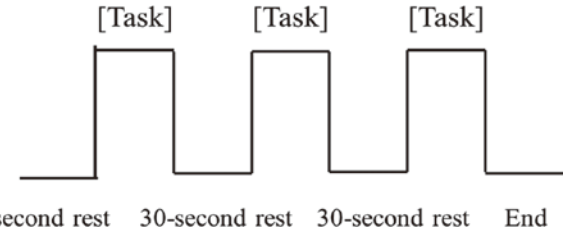

Fig. 1 Task design Task and 30-sec rest repeated

Results

Survey on anxiety

According to STAI, 8 participants with trait anxiety (67%, Fig. 2) and 9 with state anxiety (75%, Fig. 3) were classified as IV or V. According to SADS, 8 participants (67%, Fig. 4) were classified as moderate to very severe anxiety.

Regions of brain activation

The 8 participants with high anxiety and 4 with low anxiety for trait anxiety were compared for regions of brain activation. The regions activated in the high anxiety group comprised the ventral anterior cingulate cortex [Brodmann's area (BA) 32], the secondary visual cortex (BA18), the associative visual cortex (BA19), part of the cingulate cortex (BA30), the retrosplenial cingulate cortex (BA29), and the medial globus pallidus (Fig. 5, Table 1). The regions showing attenuated activity in the high anxiety group comprised the primary auditory cortex (BA41) and fusiform gyrus (BA 37) (Table 2).

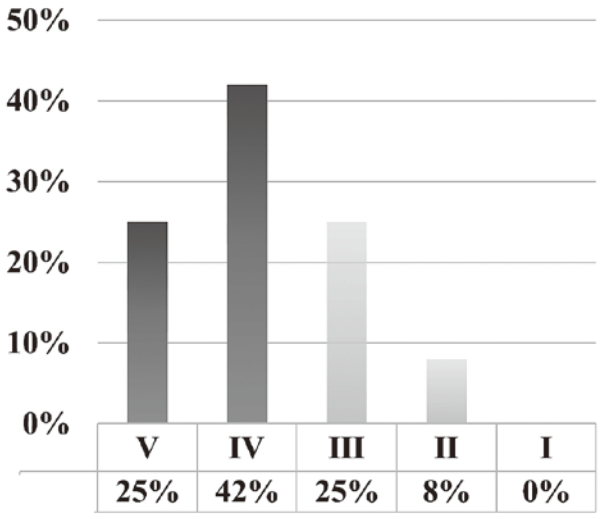

Fig. 2 Severity classification results for trait anxiety using STAI

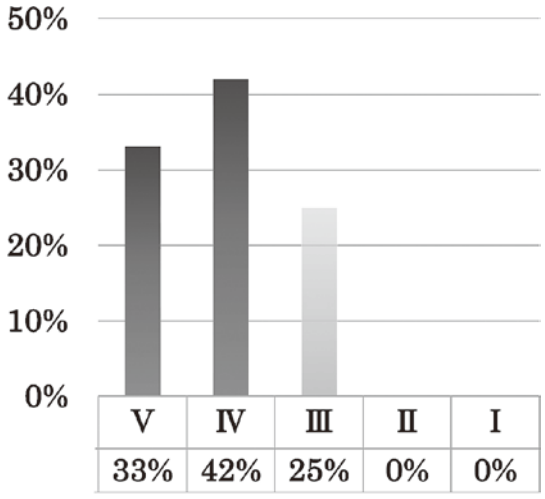

Fig. 3 Severity classification results for state anxiety using STAI

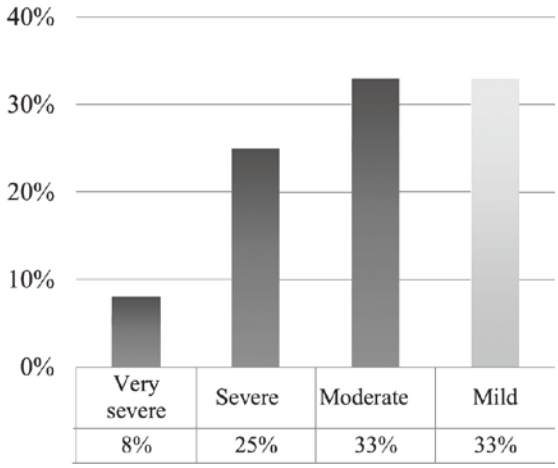

Fig. 4 Severity classification results for social anxiety using SADS

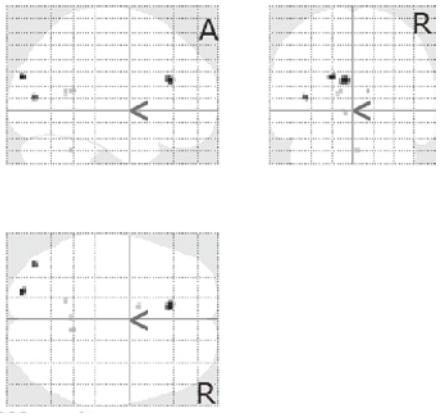

Fig. 5 Area of activation in high anxiety group for trait anxiety (black regions) on normalized SPM-glass brain. Arrow indicates origins of MNI coordinates. A : anterior ; R : right

For state anxiety, regions of brain activation were compared between a group of 9 participants with high anxiety and 3 with low anxiety. In the high anxiety group, the regions of activation comprised the ventral anterior cingulate cortex (BA 32), the secondary visual cortex (BA 18), the associative visual cortex (BA 19), and the medial globus pallidus (Fig. 6, Table 3). The regions showing attenuated activity in the high anxiety group comprised the primary auditory cortex (BA41), the superior temporal gyrus (BA22), the temporopolar area (BA38), the dorsal posterior cingulate cortex (BA31), the caudate body, and the medial globus pallidus (Fig. 7, Table 4).

For social anxiety, regions of brain activation were compared between a group of 8 participants with high anxiety and a group of 4 with low anxiety (Table 5). The regions showing attenuated activity in the high anxiety group comprised the dorsal posterior cingulate cortex (BA31), the caudate body, and the pulvinar (Fig. 8, Table

Table 1 Regions activated in high anxiety group for trait anxiety, *t*-Value : contrast weights vector, Cluster size : voxels, Lt. : left, Rt. : right

t-Value	Cluster size	Local maxima of cluster Talairach coordinates (x, y, z)	Location (Brodmann's area)
7.02	28	− 8, 26, 20	Lt. Anterior Cingulate, (32)
6.32	7	− 18, − 91, 16	Lt. Cerebrum, (18)
5.71	7	− 36, − 81, 3	Lt. Middle Occipital Gyrus, (19)
4.43	4	− 11, − 56, 9	Lt. Posterior Cingulate, (30)
4.54	3	8, − 50,9	Rt. Posterior Cingulate, (29)
4.45	3	− 8,3, − 4	Lt. Medial Globus Pallidus

Table 2 Regions with attenuated activity in high anxiety group for trait anxiety, *t*-Value : contrast weights vector, Cluster size : voxels, Lt. : left, Rt. : right

t-Value	Cluster size	Local maxima of cluster Talairach coordinates (x, y, z)	Location (Brodmann's area)
5.60	22	54, − 32, 10	Rt. Superior Temporal Gyrus, (41)
5.19	11	31, − 38, − 8	Rt. Parahippocampal Gyrus, (37)

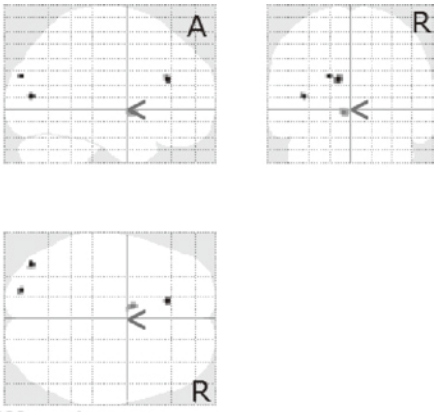

Fig. 6 Area of activation in high anxiety group for state anxiety (black regions) on normalized SPM-glass brain. Arrow indicates origins of MNI coordinates. A : anterior ; R : right

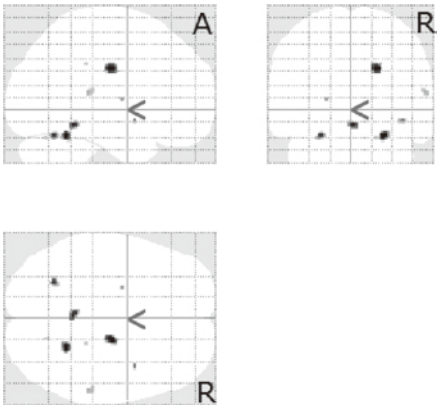

Fig. 7 Area of attenuated activity in high anxiety group for state anxiety (black regions) on normalized SPM-glass brain. Arrow indicates origins of MNI coordinates. A : anterior ; R : right

Table 3 Regions activated in high anxiety group for state anxiety, *t*-Value : contrast weights vector, Cluster size : voxels, Lt. : left, Rt. : right

t-Value	Cluster size	Local maxima of cluster Talairach coordinates (x, y, z)	Location (Brodmann's area)
5.04	21	− 8, − 1, − 4	Lt. Medial Globus Pallidus
6.14	16	− 11, 26, 20	Lt. Anterior Cingulate, (32)
6.33	9	− 36, − 81, 3	Lt. Middle Occipital Gyrus, (19)
5.72	5	− 18, − 89, 16	Lt. Middle Occipital Gyrus, (18)

6).

Among regions associated with emotions focused on in the high anxiety groups for trait and state anxiety, the ventral anterior cingulate cortex (part of limbic system associated with emotions) was activated, as was also the medial globus pallidus in the basal ganglia. On the other hand, activity in the caudate nucleus (part of the basal ganglia) was attenuated in the group with high anxiety for state anxiety and social anxiety.

Discussion

Functional MRI allows detection of slight increases in signal intensity arising from changes in the oxidative state of blood in blood vessels due to enhanced nerve

Table 4 Regions with attenuated activity in high anxiety group for state anxiety, *t*-Value : contrast weights vector, Cluster size : voxels, Lt. : left, Rt. : right

t-Value	Cluster size	Local maxima of cluster Talairach coordinates (x, y, z)	Location (Brodmann's area)
5.55	34	15, −19, 25	Rt. Caudate, Caudate Body
4.43	13	50, −36, 8 48, −32, 10	Rt. Middle Temporal Gyrus, (22) Rt. Superior Temporal Gyrus, (41)
4.73	5	34, 1, −9	Rt. Superior Temporal Gyrus, (38)
4.26	1	19, −38, 28	Rt. Cingulate Gyrus, (31)
4.46	1	−20, −9, 5	Lt. Cerebrum, Lateral Globus Pallidus

Table 5 Regions activated in high anxiety group for social anxiety, *t*-Value : contrast weights vector, Cluster size : voxels, Lt. : left, Rt. : right

t-Value	Cluster size	Local maxima of cluster Talairach coordinates (x, y, z)	Location (Brodmann's area)
6.60	34	−47, −73, 17	Lt. Middle Temporal Gyrus, (39)
6.13	22	10, 8, 32	Rt. Cingulate Gyrus, (24)
5.99	14	−34, −81, 1	Lt. Middle Occipital Gyrus, (18)
4.76	4	−22, −77, 31	Lt. Occipital Lobe, (7)
4.54	4	−18, −89, 15	Lt. Middle Occipital Gyrus, (18)
4.27	3	36, −69, −14	Rt. Fusiform Gyrus, (19)
4.27	1	−32, −21, −7	Lt. Hippocampus

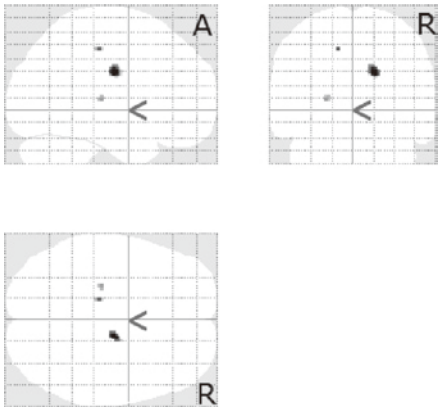

Fig. 8 Area of attenuated activity in high anxiety group for social anxiety (black regions) on normalized SPM-glass brain. Arrow indicates origins of MNI coordinates. A : anterior ; R : right

activity. An increase in local blood flow in the brain due to greater nerve activity results in an increase in oxyhemoglobin and a relative decrease in deoxyhemoglobin. Compared to oxyhemoglobin, deoxyhemoglobin has a stronger paramagnetic nature, and a decrease in local deoxyhemoglobin causes an increase in signal intensity via shortening of T2. With functional MRI, changes in the balance between local blood flow in the brain and oxygen metabolism are detected and reproduced as functional images[6)7)]. As it is non-invasive and excellent in terms of temporal and spatial resolution, functional MRI is now widely used in clinical research.

Research on SD using functional MRI has suggested the involvement of emotions[4)] In the present study, the SD patients were divided into groups based on differences in emotional state and differences in brain activity investigated using functional MRI.

Association with emotions

In previous research on brain function in SD patients using fMRI, an association with the insula, a part of the brain connected with emotions, has been noted. Kiyuna and Simoyan compared sustained vocalization of vowels between SD patients and normal subjects and reported an increase in activation in the insula for both during vocalization[4)7)]. The insula is considered to be widely involved in functions linked to the emotions and other cognitive functions and, as a paralimbic cortex, to have a dense network of connections with the limbic system. In the present study, no abnormal activity was observed in the insula. Further study is planned to investigate this finding in a larger sample of subjects.

Activation was observed in the ventral anterior cingulate cortex and dorsal anterior cingulate cortex in SD patients. It has been noted that these areas are involved in emotions, with the involvement of the ventral anterior cingulate cortex being particularly great[8)]. In the field of neurology, disparity between primary dystonia and psychogenic disease had previously been an issue. Psychogenic dystonia is now distinguished from dystonia with purely neurological factors, and most SD patients are considered to fall into the latter category. However,

Table 6 Regions with attenuated activity in high anxiety group for social anxiety, *t*-Value : contrast weights vector, Cluster size : voxels, Lt. : left, Rt. : right

t-Value	Cluster size	Local maxima of cluster Talairach coordinates (x, y, z)	Location (Brodmann's area)
5.43	34	12, −17, 24	Rt. Caudate, Caudate Body
4.48	5	−22, −27, 4	Lt. Pulvinar
4.77	3	−13, −29, 39	Lt. Cingulate Gyrus, (31)

in recent years it has been demonstrated that an area of the basal ganglia striatum receives input concerning emotions from the limbic system and that this is associated with regulation of dopamine within the basal ganglia[9]. Furthermore, it has been reported that one mechanism for the onset of dystonia is abnormality in the neurological mechanism that connects emotions and movement[10]. In the field of neurology, this is viewed as a very important discovery, and the present results provide further backing for it. In neurology, while psychogenic dystonia is basically distinguished from dystonia due to purely neurological factors, there are few patients with SD (considered to be laryngeal dystonia) in whom psychological factors are suspected. This may be the reason for the variety in treatment methods for the symptoms of SD.

The present results suggest that looking for the involvement of psychological factors through psychological testing and carefully conducting patient interviews could be helpful in selecting effective approaches to treatment in a clinical setting.

Basal ganglia

Basal ganglia abnormalities have been observed in dystonia[10]. With excitement of the caudate nucleus and putamen, areas of input to the basal ganglia, the area for output, the medial globus pallidus, will be excessively suppressed. A function of the medial globus pallidus is suppression of the thalamus, and if this can no longer be performed, stimulation of the cerebral cortex by the thalamus will be abnormal. Thus, in dystonia, the caudate nucleus is activated while activity in the medial globus pallidus is attenuated.

In the low anxiety group in the present study, the results were consistent with dystonia. However, differing from the case with dystonia, in the high anxiety group, activity in the caudate nucleus was attenuated and the medial globus pallidus activated (Fig. 9). These findings suggest that ataxia occurred in the high anxiety group by a mechanism differing from that involved in dystonia.

Another possible mechanism involves projections from the anterior cingulate cortex, a part associated with emotions, to the striatum[8]. In the high anxiety group, it is assumed that activity in the caudate nucleus was either directly or indirectly inhibited by hyperactivity in the anterior cingulate cortex. As the caudate nucleus has an inhibitory influence on the medial globus pallidus[11], inhibition of the former would relieve the inhibition of the medial globus pallidus.

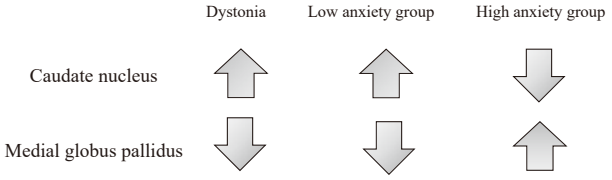

Fig. 9 Brain Activation in caudate nucleus and medial globus pallidus in dystonia patients for comparison with present subjects

The psychological survey of the present SD patients revealed that emotions were deeply involved during vocalization. Furthermore, in patients assigned to the high anxiety group according to the survey results, movement in the basal ganglia differed from that in neurological dystonia. Future research with a greater number of SD patients should enable us to differentiate patients according to whether they have psychogenic dystonia or neurological dystonia even more effectively and determine treatments more accurately matched to individual patients.

Conclusions

・Pyschological factors may be involved in ADSD.

・The present findings suggest that the mechanism of dystonia in the high anxiety group was not purely neurological. As a causative factor, it is possible that the limbic system, a system linked to the emotions, was influencing basal ganglia circuits, in particular through the anterior cingulate cortex.

Authors' disclosure of conflict of interest (COI) : The authors declare no conflict of interest regarding the content of this manuscript.

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痙攣性発声障害における心的因子の関与について

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【要旨】 痙攣性発声障害（Spasmodic Dysphonia : 以下 SD）は以前には心的要因によるものといわれていた。しかし、現在では内喉頭筋のジストニアとする考えが一般的である。一方で、本邦では若い女性に多くみられる。これは他国ではみられない特徴であるとともに、一般的ジストニアの年齢分布とも異なる。また、緊張場面で症状が増悪するなど心理的な要因の関与を示唆するエピソードも多くみられる。これまで我々は機能性 MRI を用いた研究から、痙攣性発声障害患者では島や大脳辺縁系など情動に関与する部位の脳活動が健常者と異なることを報告してきた。そこで今回は、痙攣性発声障害のなかでも大半を占める内転型痙攣性発声障害（Adductor SD : 以下 ADSD）患者に、不安検査（State-Trait Anxiety Inventory : STAI）、社交不安障害検査（Social Anxiety Disorder Scale : SADS）の 2 つの心理検査を行い高不安群と低不安群に分け、機能性 MRI の結果に関連があるかどうかを検討した。発声時機能性 MRI は「やぶのなかからうさぎがぴょこんとでてきました」の 30 秒間反復発声によるブロックモデルで行った。結果、高不安群では発声に伴って、有意に大脳辺縁系の情動関連部位が賦活していた。基底核においては低不安群ではジストニアと矛盾のない結果が得られたが、高不安群ではジストニアと異なり尾状核が減弱し、淡蒼球内節は賦活していた。以上より ADSD では心理的要素が関与している症例が存在し、高不安群ではジストニアとは異なる機序で運動失調が生じている可能性が示唆された。

〈キーワード〉痙攣性発声障害、機能性 MRI、ジストニア