Brain Activity in Patients With Adductor Spasmodic Dysphonia Detected by Functional Magnetic Resonance Imaging

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Summary: Objectives. Spasmodic dysphonia (SD) is considered a focal dystonia. However, the detailed pathophysiology of SD remains unclear, despite the detection of abnormal activity in several brain regions. The aim of this study was to clarify the pathophysiological background of SD.

Study Design. This is a case-control study.

Methods. Both task-related brain activity measured by functional magnetic resonance imaging by reading the five-digit numbers and resting-state functional connectivity (FC) measured by 150 T2-weighted echo planar images acquired without any task were investigated in 12 patients with adductor SD and in 16 healthy controls.

Results. The patients with SD showed significantly higher task-related brain activation in the left middle temporal gyrus, left thalamus, bilateral primary motor area, bilateral premotor area, bilateral cerebellum, bilateral somatosensory area, right insula, and right putamen compared with the controls. Region of interest voxel FC analysis revealed many FC changes within the cerebellum-basal ganglia-thalamus-cortex loop in the patients with SD. Of the significant connectivity changes between the patients with SD and the controls, the FC between the left thalamus and the left caudate nucleus was significantly correlated with clinical parameters in SD.

Conclusion. The higher task-related brain activity in the insula and cerebellum was consistent with previous neuroimaging studies, suggesting that these areas are one of the unique characteristics of phonation-induced brain activity in SD. Based on FC analysis and their significant correlations with clinical parameters, the basal ganglia network plays an important role in the pathogenesis of SD.

Key Words: Spasmodic dysphonia–Resting-state functional connectivity–Disease severity–Basal ganglia network–Focal dystonia.

INTRODUCTION

Spasmodic dysphonia (SD) has unique clinical characteristics, such as irregular movement of the vocal folds during speech production and a strained or strangled, hoarse, and effortful voice with breaks in pitch and phonation.[1] The clinical manifestations of the disorder and various experimental results have indicated that SD is a focal dystonia.[2] Although this hypothesis has been widely accepted, the detailed pathophysiology of SD remains unclear, despite the detection of abnormal activity in several brain regions.

In recent years, less invasive investigation of brain activity has become possible using various functional brain imaging techniques. Numerous studies have reported the brain activity of patients with various focal dystonias,[3] revealing abnormal (increased or reduced) brain activities in the primary sensory and motor cortices, accessory motor cortices, basal ganglia, thalamus, and cerebellum. The brain regions that are affected are consistent among the various forms of focal dystonia. An abnormality in the motor loop, namely a mismatch between sensory input and motor output, in the basal ganglia might underlie the pathophysiology of dystonia.[4] Abnormal activity of the cerebellum might also be associated with dystonia.[5,6]

Several studies have reported the functional imaging findings of SD, indicating abnormal (increased or reduced) brain activities compared with healthy controls in the cerebellum, basal ganglia, thalamus, sensorimotor area, insula, auditory cortex, supplementary motor area (SMA), and anterior cingulate cortex (ACC).[1,7–10] The findings resemble those of a task-related functional magnetic resonance imaging (fMRI) study of other types of focal dystonias.[3] However, the increased and reduced brain activities were not consistent among the above reports, possibly owing to differences in the disease severity and duration in the subjects and the tasks used.[11]

Resting-state fMRI measures spontaneous low-frequency fluctuations in blood oxygen level–dependent (BOLD) contrast, and it can detect the functional architecture of the brain. Application of this technique has allowed for the identification of various resting-state networks and spatially distinct areas of the brain, demonstrating synchronous BOLD fluctuations at rest.[12] Neuroimaging research focusing on resting-brain activity, when subjects receive no external stimulation, has been increasing.[13] A statistically significant overlap between resting-state functional connectivity (FC) and task-activation maps was obtained.[14] There have been some reports of resting-state FC in patients with dystonia, but there are no such reports in patients with SD.

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TABLE 1.
Case Profiles

Case	Age at fMRI Examination (y)	Sex	G Rating	Overall Severity Scale	Disease Duration (mo)
1	43	F	1	3	82
2	66	F	3	6	74
3	34	F	2	5	158
4	37	F	2	5	120
5	36	F	2	5	145
6	26	F	3	7	82
7	23	F	2	5	26
8	29	F	1	3	12
9	33	F	2	6	162
10	30	F	1	4	121
11	23	F	1	2	63
12	32	F	3	7	24

Thus, the aim of this study was to clarify the pathophysiological background of SD by measuring task-related brain activity and resting-state FC.

METHODS

Subjects

The task-related fMRI study and resting-state FC study enrolled 12 patients with adductor SD (ADSD) (12 women; mean age, 34.3 years old; age range, 23–66 years) and 16 healthy controls (16 women; mean age, 33.1 years old; age range, 22–51 years). None of the subjects in the control group had any previous history of neurologic, psychiatric, or voice disorders. All the participants in this study were strictly right-handed.

ADSD was diagnosed by otolaryngologic examinations and speech-language assessments as follows: a choked, strained or strangled voice with intermittent breaks in phonation, no anatomic abnormality of the larynx observed on fiberoptic laryngoscopy with stroboscopy, disease duration of at least 1 year (Table 1), poor improvement despite voice therapy, and symptom alleviation using a whisper or high-pitched voice.

The disease severity of patients with ADSD was evaluated by the G rating of the GRBAS classification (G, grade; R, rough; B, breathy; A, asthenic; S, strained)[15] and the overall severity scale of the Unified Spasmodic Dysphonia Rating Scale,[16] as shown in Table 1.

The study protocol was approved by our institutional review board. All the participants provided written informed consent according to the guidelines of the Ethics Committee. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Task-related fMRI study

Task design

The experimental task consisted of alternating "phonation" and "no vocalization" conditions, as shown in Figure 1. In the phonation task, the subjects read and pronounced five-digit numbers in Japanese, for example, 1-2-3-4-5. This process is shown in Figure 1 as /xxxxx/ (five-digit number) under the speaker symbol (gray representation against a white background). All the

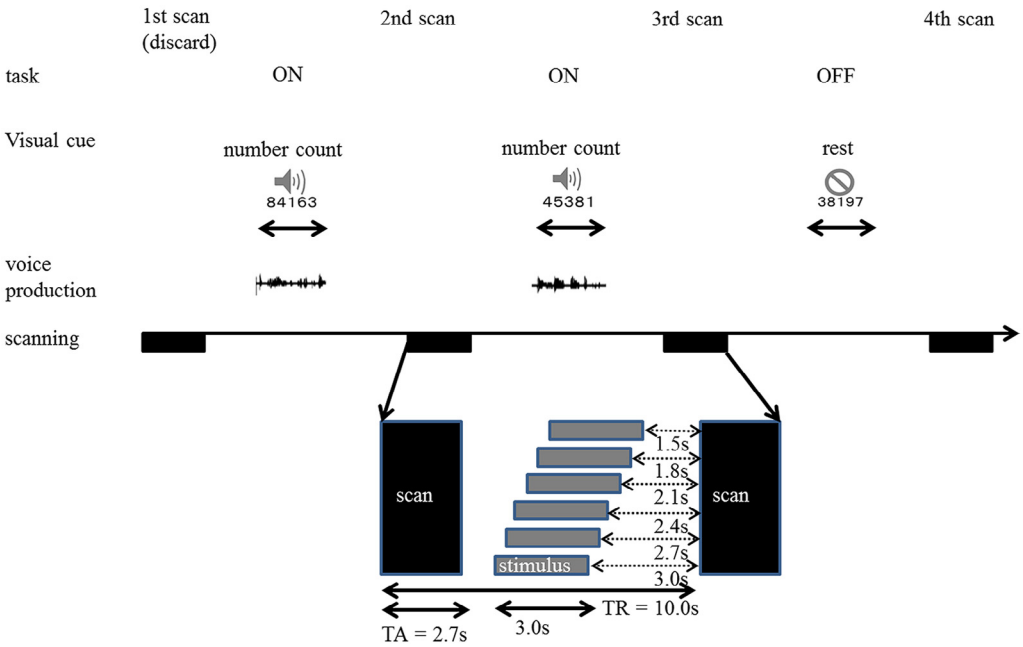

FIGURE 1. Schematic illustration of task design in the task-related functional magnetic resonance imaging study. The experimental task consisted of alternating vocalization (the reading of five-digit numbers; /xxxxx/) and no vocalization (rest) for 3 seconds to minimize scanner noise. Functional magnetic resonance imaging (fMRI) scans were acquired within the first 2.7 seconds (TA = acquisition time) of each interscan interval of 10 seconds. The 3-second experimental task (stimulus) occurred at six time points with a 300-ms interval within the 10-second interscan period. A prescanning delay between the end of the experimental stimulus and the start of single-volume MR scanning was varied stepwise between 1.5 and 3 seconds.