Brain Activity During Phonation in Women With Muscle Tension Dysphonia: An fMRI Study

***Maryna Kryshtopava, †·‡Kristiane Van Lierde, †Iris Meerschman, †Evelien D'Haeseleer, §Pieter Vandemaele, ¶Guy Vingerhoets, and *Sofie Claeys,** *†§¶*Ghent, Belgium, and* ‡*Pretoria, South Africa*

Summary: Objectives. The main objectives of this functional magnetic resonance imaging (fMRI) study are (1) to investigate brain activity during phonation in women with muscle tension dysphonia (MTD) in comparison with healthy controls; and (2) to explain the neurophysiological mechanism of laryngeal hyperfunction/tension during phonation in patients with MTD.

Methods. Ten women with MTD and fifteen healthy women participated in this study. The fMRI experiment was carried out using a block design paradigm. Brain activation during phonation and exhalation was analyzed using *BrainVoyager* software.

Results. The statistical analysis of fMRI data has demonstrated that MTD patients control phonation by use of the auditory, motor, frontal, parietal, and subcortical areas similar to phonation control by healthy people. Comparison of phonation tasks in the two groups revealed *higher* brain activities in the precentral gyrus, inferior, middle and superior frontal gyrus, lingual gyrus, insula, cerebellum, midbrain, and brainstem as well as *lower* brain activities in the cingulate gyrus, superior and middle temporal gyrus, and inferior parietal lobe in the MTD group. No differences were found between the two groups regarding exhalation control.

Conclusions. The findings in this study provide insight into phonation and exhalation control in patients with MTD. The imaging results demonstrated that in patients with MTD, altered (higher/lower) brain activities may result in laryngeal tension and vocal hyperfunction.

Key Words: Phonation–Phonation control–Exhalation control–Muscle tension dysphonia–fMRI.

INTRODUCTION

The prevalence of functional dysphonia is 41% in the working-age population (25–64 years) seeking consultation in an ear, nose, and throat department. Female professional voice users are predominantly affected (43% women vs. 36% men).[1] The term muscle tension dysphonia (MTD) is often used to describe functional voice disorder with increased vocal hyperfunction. Vocal hyperfunction can be defined as the involvement of excessive muscle force and physical effort during phonation.[2] It develops from incoordination of muscles or excessive muscle usage in phonation.[3] Causes of MTD include environmental (external) or systemic (internal) factors or stimuli. Common factors or stimuli are upper respiratory infection, second-hand smoke, laryngopharyngeal reflux (LPR), significant vocal demands, or stressful life events.[4] In MTD, hyperfunctional vocal behavior is often a result of inappropriate compensatory strategies for muscle activities adopted in response to environmental or systemic stimuli.[5] However, the pathophysiological mechanism of MTD is not fully understood.[5–9] The major pathophysiological finding in patients with functional voice disorders is that the hyoid and larynx positions are higher in such patients than in controls.[10] The only muscles which may be affected in this context is the thyrohyoid muscle which raises the larynx to the hyoid, the anterior belly of the digastric muscle, and the mylohyoid muscle in the submental region that pulls the hyoid upwards.[11] Van Houtte et al[8] have found thyrohyoid muscle overactivity during phonation in patients with MTD compared with a healthy group. However, no studies have verified that the anterior belly of the digastric muscle and the mylohyoid muscle are consistently activated in MTD. Moreover, the neurophysiological background of functional voice disorder is currently unknown.

Human phonation can be defined as a laryngeal motor behavior that extends from reflexive and unlearned limbic laryngeal actions[12,13] to highly skilled laryngeal sensorimotor control to support speech or singing.[14] Phonation requires coordination of the respiratory, laryngeal, and articulatory systems, and subglottic pressure.[15–19] During development of phonation, and particularly of vocal quality, laryngeal motor control becomes increasingly skilled and rapid. Moreover, the balance of aerodynamic and muscle forces adapts to rapidly changing vocal requirements, including modulations of pitch, loudness, and rate. Based on preliminary data on voice and speech control, it is known that sensory feedback (auditory and somatosensory)[20] plays an important role in development of phonation (Figure 1A).[22,23] However, the sensory feedback control is too slow to support required rapid and skilled vocal movements. Most of these movements are preprogrammed. These programs require the generation of internal representations (neural "models") of the sensorimotor transformations required to generate the set of motor commands that will execute a desired movement. Once these neural models are learned, the internal system can then predict likely sensory consequences of a motor command prior to the arrival of actual sensory feedback. Thus, online feedback control

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From the *Department of Otorhinolaryngology, University Hospital Ghent, Ghent, Belgium; †Department of Speech, Language and Hearing Sciences, Ghent University, Ghent, Belgium; ‡Department of Speech-Language Pathology and Audiology, University of Pretoria, Pretoria, South Africa; §Department of Radiology and Nuclear Medicine, University Hospital Ghent, Ghent, Belgium; and the ¶Faculty of Psychology and Educational Sciences, Ghent University, Ghent, Belgium.

Address correspondence and reprint requests to Maryna Kryshtopava, Department of Otorhinolaryngology, Ghent University Hospital, De Pintelaan, 185 1P1, 9000 Ghent, Belgium. E-mail: maryna.kryshtopava@ugent.be

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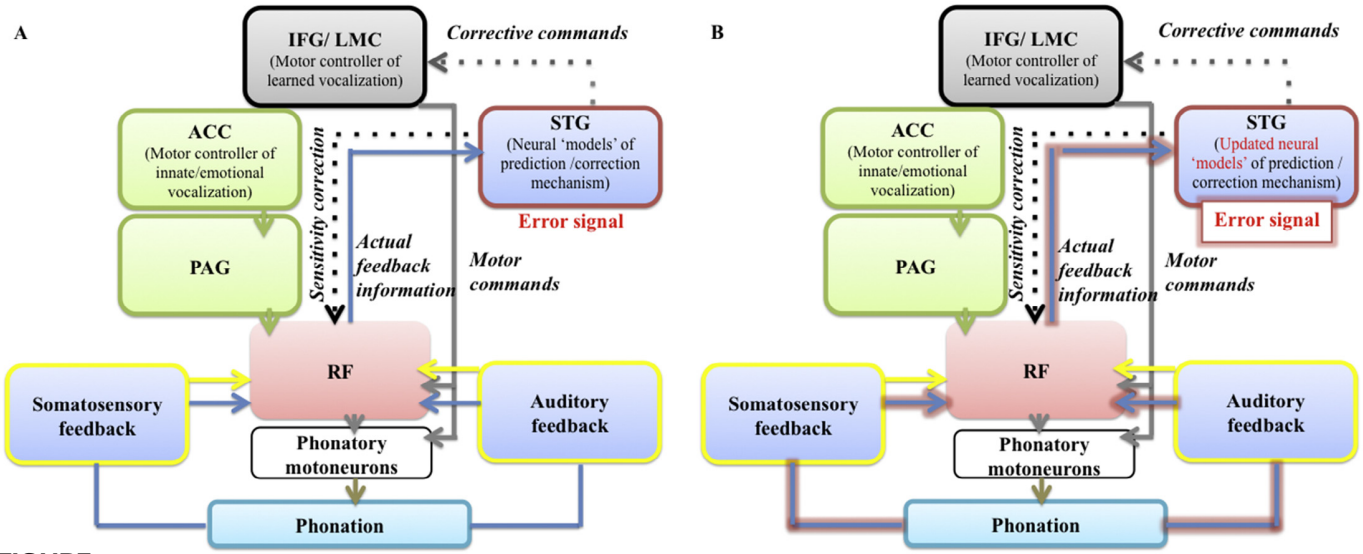

FIGURE 1. A schematic diagram of laryngeal neural control of normal phonation (A) and phonation in muscle tension dysphonia (B) (modified from a neural model of vocalization proposed by Zarate[21]). **A.** The vocal motor control system (central columns), reflexogenic system (yellow-outlined boxes and yellow arrows), and feedback system (blue boxes and arrows). The lower level of the vocal motor control system, the reticular formation (RF) (red box), generates complete vocal patterns to phonatory motoneurons (white box). The middle level of the motor control system, the anterior cingulate cortex (ACC) and periaqueductal gray (PAG) (green boxes), guides emotional vocalization. The upper level of the laryngeal motor control system, the laryngeal motor cortex (LMC), is responsible for producing learned/skilled vocalizations (ie, speech and song) and requires inputs from the inferior frontal gyrus (IFG) for motor planning of voice (other modulatory brain regions of the LMC are not depicted) (gray box). Feedback from phonation is processed by the ascending somatosensory (left) and auditory (right) pathways and transmitted to the superior temporal gyrus (STG) (blue boxes and arrows; the only selected regions of these pathways are shown) via the RF (red box). Sensory feedback from phonation provides actual information (how it feels), whereas the STG (red-outlined box; other possible brain regions involved in the prediction/correction mechanism are not depicted) provides information on the expected state (how should it feel) relying on a neural "models." The mismatch between actual sensory feedback and sensory predictions of motor commands indicates an error signal that, if large enough, would trigger changes in the neural models generating alterations in motor control (sending corrective commands [gray dotted arrow]) and sensory perception (changing sensitivity [black dotted arrow]). **B.** In MTD, the sensory stimulation associated with phonation is altered (indicated with red glowing arrows) and may trigger changes in the neural models: the mismatch between actual sensory information and prediction of the sensory outcome of motor commands (how should it feel) indicates an error signal (red glowing box). The error signal updates the neural models that in turn generate corrective commands to the motor controller as well as alter sensory perception. The updated or new neural models may support the symptoms of MTD by altering motor cortical commands in the areas responsible for motor control (eg, the LMC, IFG) and changing sensory perception (changes in sensitivity) in the areas responsible for sensory control (eg, the STG). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

is achieved primarily via the neural models, whereas actual feedback is used to train and update these neural models. Hence, the neural models play an important role in executing rapid and skilled laryngeal vocal movements.[24–26] On the one hand, these neural models reinforce or correct the motor activation in the brain[26] to support rapid skilled vocal movements.[24,25] On the other hand, these neural models adjust brain processing to the current sensory information to improve vocal performance.[27] Any changes in the larynx require adaptation and updating of these neural models.[26] Feedback provides necessary information and plays a key role in learning, maintaining, and updating the neural models and can also be used to correct overt prediction/feedback mismatch errors[28] (Figure 1A).

From a more fundamental neurobiological point of view, the modulation in sensory feedback brings about significant central neuroplastic changes.[29,30] Neural plasticity or brain plasticity is the ability of the central nervous system to change and adapt in response to environmental cues, experience, behavior, injury, or disease. Neural plasticity can result from a change in function within a particular neural substrate in the central nervous system through alterations in neuronal excitability.[31] Changes in the function of a neural substrate can then alter behavior secondary to environmental influences such as experience, learning, development, aging, change in use, injury, or response to injury such as unmasking due to the loss of surround inhibition with reduced afferent input.[32–34] Neural plasticity may alter the function of the original neural substrate used to produce a regular behavior.[35] Understanding how the brain adapts to a changing environment will provide insight into how this adaptation influences the development of phonation and its disorders. A recent study has suggested an association between the internal representations/neural models of the sensorimotor transformations and MTD.[36] However, there are no studies that evaluate neural correlates of phonation in MTD.

Neuroimaging techniques are objective tools recently used to describe neural pattern associated with control of normal vocalization[18,37–47] and voice disorders.[48–57] Recent functional magnetic resonance imaging (fMRI)[37,38,40,41,49] and positron emission tomography[39] studies have identified key regions involved in non-disordered phonation which are located in the sensorimotor cortex region, premotor cortex region, superior temporal gyrus (STG), insula, cingulate gyrus/cortex, supramarginal gyrus, lingual gyrus, thalamus, cerebellum, midbrain periaqueductal gray (PAG), and basal ganglia.[37–41,49] More specifically, the sensorimotor cortex region functionally includes the primary motor cortex (M1) and primary somatosensory cortices (S1) and is anatomically located on/in the pre/postcentral gyrus in the frontal lobe and central sulcus.[58] The role of M1 is to generate neural impulses that control the execution of laryngeal movements.[41] Other regions of the cortex involved in motor function are called the secondary motor cortices. These regions include the premotor cortex and the supplementary motor area (SMA), and are anatomically located on/in the precentral gyrus and superior/middle/inferior frontal gyrus (SFG, MFG, IFG).[58] The premotor cortex is involved in the sensory guidance of movement and adjusts the larynx before reaching for the phonation task. The SMA is involved in the planning and in coordination of complex movements,[56,59,60] such as vocal pitch modulation.[18] The SMA and the premotor regions both send information to the M1 as well as to brainstem motor regions. That is the main pathway for control of voluntary laryngeal movements in humans (Figure 1A). The midbrain PAG projects to the reticular formation of the lower brainstem, thus representing a neuroanatomic and functional relay station within the anterior cingulate cortex-PAG-brainstem pathway (Figure 1A). The anterior cingulate cortex and PAG guide the phonation for innate and emotional vocalization.[61–65] Moreover, activity of the cerebral cortex depends on impulses from the other modulatory brain regions. The cerebellum is involved in motor planning and coordination of laryngeal movements.[66] The lingual gyrus is involved in simple phonemic tasks processing.[67] The middle temporal gyrus (MTG) and STG are responsible for vocal self-monitoring[68] and voice processing,[69] respectively. The insula participates in auditory vocal monitoring and detection, such as auditory attention and tuning in to novel auditory stimuli, temporal processing, and phonological processing[70] and integration of sounds with a speaker's emotions and attitudes.[71] Neural activity in the inferior parietal lobe reflects increased engagement of attentional resources.[72] Although our understanding of the neural correlates of non-disordered phonation in humans has increased significantly since the advent of neuroimaging, imaging studies of voice disorders are limited to a few specific voice pathologies such as spasmodic dysphonia,[48–52] Parkinson disease,[53–55] and idiopathic unilateral vocal fold paralysis.[56,57] This was the rationale to investigate the neural control of phonation in MTD patients.

In this study, an fMRI evaluation of the neural control during phonation and exhalation was performed with a recently proposed protocol.[73] The experimental paradigm used consisted of sustained phonation of the sound /i/ on different pitch (habitual and high) levels and prolonged exhalation tasks.[73] The phonation tasks were designed to explore the interplay between respiratory and laryngeal control, whereas the exhalation tasks explored respiratory control separately. Additionally, the phonation tasks revealed the neural control associated with changes in respiratory and laryngeal adjustments to obtain vocal pitch modulations: comfortable and high. Comfortable phonation (ie, habitual fundamental frequency [F0]) relies on a usual muscle tension (in as comfortable state as possible) in both the voicing and respiratory system. High phonation relies on a maximal/high muscular activity of the intrinsic and extrinsic laryngeal muscles and the respiratory system. In addition, this experimental paradigm allowed us to investigate laryngeal control maps that were generated by subtraction of the exhalation condition from the phonation condition. This approach is based on a study by Loucks et al,[38] which showed that the neural control of exhalation for phonation is similar to the neural control of voluntary exhalation in healthy people, except for a difference in the STG activation due to the auditory feedback. These results were obtained during fMRI data analysis by subtracting patterns of neural control for voluntary exhalation from those during for phonation, considering the fact that if activity in a particular region of the brain during one task is greater than during another task, this particular region of the brain is involved in specific task-related activity.[74,75]

The aims of this study were (1) to investigate brain activity during phonation in women with MTD in comparison with healthy controls; and (2) to explain the neurophysiological mechanism of laryngeal hyperfunction/tension during phonation in patients with MTD. The authors hypothesized that compared with healthy controls, MTD patients may have altered brain activities related to phonation control. This altered brain activities of phonation control may be secondary to a peripheral sensory perturbations such as a poor vocal quality, upper respiratory infection, LPR, vocal demands, or life stress. Moreover, the authors hypothesized that the theory of the neural models explains vocal hyperfunction during phonation in MTD patients.

MATERIALS AND METHODS

The study was performed as a prospective, interventional study. The Ethics Committee of Ghent University Hospital approved (B670201420193) the study protocol.

Participants

Patients included in this study had a confirmed diagnosis of MTD by voice assessment protocol. The inclusion criteria for participants were as follows: (1) age between 21 and 45 years old, (2) female gender, (3) right-handedness, (4) being a native speaker of Flemish, (5) no organic laryngeal pathology (eg, nodules, polyps, laryngeal edema), and (6) no history of neurologic or psychiatric disease. The inclusion criteria for healthy subjects also were absence of vocal pathology and videostrobolaryngoscopic symptoms of laryngeal pathology.

Ten patients (mean age: 33.2 years, age range: 21–47 years) and 15 healthy subjects (mean age: 24.3 years, age range: 21–28 years) met the inclusion criteria and were recruited in the study. The rationale to include only middle-aged healthy women was to reduce intragroup variance during fMRI data analysis. Healthy participants were recruited from the employees of Ghent

University using an open advertisement. The patients with MTD were recruited at the Department of Otorhinolaryngology and Department of Speech, Language and Hearing Sciences at Ghent University Hospital, Belgium. Written informed consent was obtained from all participants.

Questionnaires and Voice Handicap Index (VHI)

Prior to MRI scanning, all participants filled in a prescan MRI-safety questionnaire, the Edinburgh Handedness Inventory measurement scale, and a Personal History Questionnaire. These questionnaires were used to select participants who satisfy inclusion criteria, such as fMRI compatibility, medical history, lifestyle, and other participant characteristics. The psychosocial impact of vocal quality, as perceived by the subject, was measured by means of the validated Dutch translation of the VHI-10.[76] This instrument assesses a subject's perception of disability, handicap, and distress resulting from voice difficulties. It consists of 10 questions that cover emotional (two questions), physical (three questions), and functional (five questions) aspects of the respondent's voice. The questions are rated on a five-point ordinal scale: never (0), almost never (1), sometimes (2), almost always (3), and always (4). The total score ranges from 0 (no problem perceived) to 40. After scanning, participants completed a Post-Scan MRI Checklist, which asks for information on the effects of the MRI equipment and its environment (ie, magnetic field, acoustic noise).

Clinical examination and voice assessment protocol

The same otorhinolaryngologist (S.C.) and speech therapist (E.D.) examined each subject clinically following a standard evaluation protocol. This protocol included a standard ear, nose, and throat and videostrobolaryngoscopic examination.[77] Clinical examination included focal palpation of tension around the larynx. The voice assessment protocol included a perceptual rating of the voice during connected speech by using the GRBASI scale and an objective vocal quality evaluation by means of the Dysphonia Severity Index (DSI).[78] The GRBASI scale consists of five well-defined parameters: G (overall grade of hoarseness), R (roughness), B (breathiness), A (asthenic), and S (strained).[79,80] A sixth parameter, I, for instability of the voice, was added later to the original scale.[81] A four-point rating scale (0: normal, 1: slight, 2: moderate, and 3: severe) is used to indicate the grade of each parameter (Table A1). The objective parameters of the voice assessment protocol included the frequency range (F-low to F-high), the intensity range (I-low to I-high), aerodynamics (maximum phonation time and vital capacity), and the acoustic microperturbations (jitter and shimmer) of voice during phonation of the vowel sounds /a/ and /i/. The voice range was measured using the voice range profile module from the Computerized Speech Lab Model 4500 (CSL, KayPENTAX, Lincoln Park, NJ). Recordings were made using a handheld microphone (mouth-to-microphone distance = 7 cm). The acoustic analysis was performed with the Multi-Dimensional Voice Program from the CSL. All measurements took place in a sound-treated room. Based on these results, the DSI was calculated using the following formula: $(0.13 \times \text{maximum phonation time}) + (0.0053 \times \text{F-high}) - (0.26 \times \text{I-low}) - (1.18 \times \text{Jitter}) + 12.4$.[78]

The DSI[78] is a multiparameter approach designed to establish an objective and quantitative correlate of the perceived vocal quality. The index ranges from −5 to +5 for severely dysphonic voices to normal voices. The more negative the index, the worse is the vocal quality. A DSI of 1.6 is the threshold separating normal voices from dysphonic voices.[83] In addition, voice samples based on the production of sustained vowels /a/ and /i/ were used to determine the habitual fundamental frequency (F0) and the highest frequency (F-high) for each subject.

Subject selection was also based upon videostrobolaryngoscopic examination. The videostrobolaryngoscopy included phonation of the vowel sounds /a/ and /i/ at modal/comfortable, low-pitched, and high-pitched voice quality. The following videostrobolaryngoscopic indicators (at modal, low, and high pitch) were evaluated by the otorhinolaryngologist (S.C.) involved in our study: symmetry (symmetrical or asymmetrical), regularity (regular, irregular, or inconsistent), glottal closure (complete, incomplete, or inconsistent), type of gap (longitudinal, posterior, anterior, irregular, oval, or hour-glass), amplitude (increased, normal, reduced, or none), mucosal wave (normal, reduced, or none), and supraglottic activity.[77] Laryngeal supraglottic compression during videostrobolaryngoscopy was quantified by using the SERF protocol[84] by the otorhinolaryngologist (S.C.). The stroboscopy examination rating form (SERF) form features a laryngeal image with concentric circles superimposed. Mediolateral and anterior-posterior laryngeal constrictions were evaluated separately by determining which numbered circle corresponded best to the observed degree of constriction (from 0: no constriction to 4: very severe constriction).

Diagnosis of MTD was based on the following key features: (1) psychological or personality factors and stress influences[85,86] and a history of vocal technical misuse/abuse and extraordinary voice demands[87–90] that were identified in the clinical history of patients; (2) a clinical sign of elevated extrinsic laryngeal muscle tension on palpation[91,92]; (3) voice assessment protocol with the DSI[78] (Table A1); and (4) features of MTD seen on videostrobolaryngoscopy[87] (Table A2). In MTD patients, the DSI range was from −13.2 to +2.5 (mean DSI = −0.96) for phonation of the vowel sound /a/ and from −5.2 to 3.3 (mean DSI = 1.01) for phonation of the vowel sound /i/ (Table A1). In MTD patients, mean F0 of the vowel /i/ was 197.6 Hz (F0 range: 169–241.8 Hz) and mean F-high of the vowel /i/ was 528.9 Hz (F-high range: 311.1–680.3 Hz); mean F0 of the vowel /a/ was 193.4 Hz (F0 range: 164.2–232.7 Hz) and mean F-high of the vowel /a/ was 557.3 Hz (F-high range 329.6–932.3 Hz) (Table A1). Diagnosis of MTD on videostrobolaryngoscopy was established when one or more of the following features were present: (1) open posterior commissure with a reduced amplitude and asymmetry of the mucosal waves; (2) a supraglottic contraction in which the ventricular folds are adducted to the midline; (3) an anteroposterior contraction, which results in a foreshortening of the glottal aperture obscuring the posterior half to two-thirds of the vocal folds; or (4) complete anteroposterior contraction or squeeze of the supraglottis with approximation of the arytenoids to the petiole: "sphinteric larynx."[8,93,94] The diagnosis agreement between the voice therapist and the laryngologist was made and calculated using percent agreement.

Percent agreement is 71%. Based on the percent agreement between the voice therapist diagnosis of MTD and the laryngologist diagnosis of MTD, 10 patients were included in the study and 4 patients were excluded from the study because of disagreements.

Each healthy subject had unchanged measures of a voice assessment protocol and a DSI value corresponding to a normal voice quality[78] (mean DSI of the vowel /a/: +3.9, DSI range +1.7 to +6.2; mean DSI of the vowel /i/: +3.8, DSI range +1.2 to +7.4) (Table A1). In healthy participants, mean F0 of the vowel /i/ was 211 Hz (F0 range: 172.5–229.3 Hz) and mean F-high of the vowel /i/ was 799.3 Hz (F-high range: 622.3–1046.5 Hz); mean F0 of the vowel /a/ was 199.5 Hz (F0 range: 161.2–217.7 Hz) and mean F-high of the vowel /a/ was 848.6 Hz (F-high range: 622.3–1174.7 Hz) (Table A1). Videostrobolaryngoscopic evaluations of the healthy participants showed normal laryngeal structure and function during phonation of /i/ and /a/ at modal/comfortable, low-pitched, and high-pitched voice quality (Table A1).

fMRI experimental protocol

The fMRI experiment was performed with the recently proposed protocol.[73] A blocked design fMRI experiment consisted of multiple epochs of stimulation lasting 14.5 seconds followed by a period of rest ranging between 11 and 20 seconds (variable jittering). Jittered interstimulus intervals—rest periods—were used to better determine the shape of whole hemodynamic response functions and to find a good baseline to evaluate response peaks.[95] The block of maximum 34.5 seconds was repeated 12 times for each condition. Each experimental condition had a total duration of 414 seconds. All participants were tested under three different conditions, which were randomized in the different order for each participant. These conditions were: (1) *comfortable phonation*: prolonged phonation of a vowel /i/ (similar to the "ee" in "see") on a habitual pitch level; (2) *high-pitched phonation*: prolonged phonation of the same vowel /i/ using a high voice pitch; and (3) *prolonged exhalation*: voluntary sustained "unvoiced" oral exhalation.

Periods during which the volunteers had to perform a task were visually indicated during 10 seconds by a gray loading bar, whereas resting periods were indicated by a black cross. Two visual instructions between the actual tasks were presented in the subject's native language indicating the type of task (2 seconds) (ie, in Dutch: "Gewone Stem," "Hoge Stem," or "Verlengde Uitademing") and a visual cue to start inspiration (2.5 seconds) (ie, in Dutch: "Inademen"). All visual commands were generated using a commercially available experiment generator (Presentation, Neurobehavioral Systems Inc., Berkeley, CA) and were reflected in a mirror on the head coil.

Prior to scanning, all participants were trained by a speech therapist to produce a sustained vowel /i/ during 10 seconds using a comfortable pitch as well as a high pitch, and to sustain exhalation for the same duration. The speech therapist and participants performed subjective assessment of the vocal pitch. Objective measures of the vocal quality during task production were not used, as these measures were not implemented in the fMRI experiment.

MRI acquisition

The fMRI images were acquired on a 3-Tesla MR scanner (Siemens Magnetom Trio, Erlangen, Germany) using the standard 32-channel head coil. Initially, an anatomic T1-weighted magnetic resonance dataset covering the whole head at 1 mm^3 isotropic resolution was acquired (high-quality three-dimensional magnetization-prepared rapid acquisition with gradient echo images, repetition time = 1950 ms, inversion time =1100 ms, echo time = 3.93 ms, flip angle = 12°). An axial T2*-sensitive gradient-echo echo-planar imaging technique with an in-plane resolution of 2×2 mm^2 was used to generate the functional images (repetition time = 2000 ms, echo time = 36 ms, flip angle = 70°, acquisition matrix = 96×128). Forty consecutive sections of 3-mm thickness with 0.5-mm gap between slices in an axial-to-coronal orientation were acquired. A total of 176 volumes were recorded for experimental run, resulting in a total investigation time of 25 minutes.

Subjects were positioned head-first and supine inside the magnet bore and fitted with a OptoACTIVE noise cancelling MRI headphone and a FOMRI-III noise cancelling microphone (OptoActive, Optoacoustics Ltd, Moshav Mazor, Israel). The OptoACTIVE system provided a high level of noise reduction and self-monitoring of voice during phonation. Each participant's head was immobilized in the standard head coil using neck cushions to minimize motion artifacts. The subjects were instructed to keep their jaw, lips, and tongue motionless while performing the tasks and to keep their jaw slightly open to minimize movements during phonation (eg, movements of orofacial muscles), which might also cause artifacts during fMRI scanning. In addition, participants reduced articulatory gestures due to sustained phonation of the vowel /i/ at a constant pitch during phonation tasks. The project leader (S.C.) and MRI operator (M.K.) monitored the performance of tasks throughout the experiment through a control room speaker to insure that each participants correctly performed the phonation tasks.

Image analysis steps

All steps of fMRI data preprocessing and fMRI data analysis (intragroup and intergroup) were performed using the *BrainVoyager QX Version 2.4* software package (Brain Innovation, Maastricht, The Netherlands).[44] Preprocessing included 3D motion correction, and slice timing correction and normalization to a standard echo-planar imaging template based on neuroanatomic atlas of Talairach and Tournoux.[96] Finally, normalized images were spatially smoothed on volume time course (VTC) files with a Gaussian kernel for the full width at the half maximum of 8 mm (the voxel size of resultant VTC was $3 \times 3 \times 3$ mm^3). A statistical parametric map was calculated using the approach of the general linear model (GLM). For each experiment, a *BrainVoyager* protocol file was derived, representing the onset and duration of the events for the different conditions and rest period as a baseline. From the created protocols, the design matrices for the calculation of the GLM were defined automatically. To account for hemodynamic response, each of the predictors was derived by convolution of the block design with a model for the two gamma hemodynamic response functions.[75] Previously, the GLM design matrix was improved by defining

proper noise predictors using the independent component analysis approach.[97] After fitting the GLM,[98] group t-maps were generated by invoking the Analysis of Covariance-Random Effect Analysis tool and using a subtraction approach[38,74,75] for fMRI data analysis of the comfortable phonation, high-pitched phonation, and prolonged exhalation as well as for the comparisons between conditions of phonation and prolonged exhalation. Activation maps were generated by thresholding the statistical maps using $P < 0.001$, 10 voxels, uncorrected.[99]

Comparison of two groups (MTD vs. healthy) was performed using a "combine maps" approach ($P < 0.005$, 10 voxels, uncorrected). First, the separate maps for the different subjects (VTC for 25 subjects in total) and for the contrasts/conditions chosen in every subject were created. Second, the different maps were separated into different groups (G1 and G2), which enabled specific statistics on the basis of the maps separated into groups. Then the *t* test (G1 vs. G2) to compare the activation pattern found in the groups was used. All subjects in G1—MTD group and G2—healthy group were selected. *BrainVoyager* automatically created a new map into Overlay Maps dialog that contained the result for the specified conditions: comfortable, high-pitched phonation, and prolonged exhalation. The neuroimaging activation maps were checked to display the results in the volumetric (VMR) dataset. Comparison of two groups was performed using a subtraction approach[38,74,75] for fMRI data analysis of the comfortable phonation, high-pitched phonation, and prolonged exhalation as well as for the comparisons between conditions of phonation and prolonged exhalation.

RESULTS

There were no significant group differences at our initial false discovery rate-corrected threshold. However, exploratory analyses at a lowered threshold ($P < 0.001$ 10 voxels, uncorrected) have revealed significant activation in the brain. The data analysis has shown that areas of activation in the MTD and control groups resembled those in other fMRI studies on phonation involving simple voice production tasks in healthy people.[37,38,40,42,47,49] Brain activation during phonation was observed in the bilateral precentral gyrus, right SFG, MFG, and IFG, lingual gyrus, cingulate gyrus, STG, thalamus (ventral posterior lateral nucleus), and bilateral cerebellum in the two groups (Table 1). Statistical analysis also identified a significant effect of exhalation ($P < 0.001$, 10 voxels, uncorrected) in the bilateral precentral gyrus, cingulate gyrus, right lingual gyrus, and bilateral cerebellum in both groups (Table 2), which is corroborated by recent fMRI study by Loucks et al.[38]

Comparison of phonation (comfortable, high-pitched) tasks with prolonged exhalation tasks identified activation in the bilateral STG and insula in the two groups (Table 2). However, the fMRI data analysis for the high-pitched phonation compared with comfortable phonation did not reveal any significant activation in the brain in the two groups.

Comparison of phonation tasks ($P < 0.005$, 10 voxels, uncorrected) in the two groups (MTD vs. healthy) revealed *higher* brain activities during phonation (comfortable pitch, high-pitched) in the precentral gyrus, SFG, MFG, and IFG, lingual gyrus, insula, cerebellum, midbrain, and brainstem—laryngeal motor control-related areas—in the MTD group (Table 3, Figure 2). Areas with *lower* activation during phonation (comfortable, high-pitched) were observed in the cingulate gyrus, MTG and STG, and inferior parietal lobe in the MTD group in comparison with healthy controls (Table 4, Figure 3). No differences were found between the two groups regarding exhalation control. Comparison of prolonged exhalation tasks in the two groups (MTD vs. healthy) indicated a completely overlapping pattern of responses in the cerebral regions mentioned above (Table 2). Furthermore, comparison of phonation (comfortable and high-pitched) tasks with prolonged exhalation tasks in the two groups (MTD vs. healthy) revealed areas with *higher* activation in the middle and superior frontal gyrus, and midbrain in the MTD group (Table 3, Figure 2) and areas with *lower* activation in the left MTG for comfortable phonation and in the right inferior parietal lobe for high-pitched phonation in the MTD group (Table 4, Figure 3).

DISCUSSION

The neurophysiological mechanisms of how brain controls phonation are practically unknown. The purposes of this study were (1) to detect brain activity during phonation in women with MTD in comparison with healthy controls and (2) to explain the neurophysiological mechanism of laryngeal hyperfunction/tension during phonation in patients with MTD. We hypothesized that MTD patients have altered brain activities of phonation control secondary to peripheral sensory perturbations such as poor vocal quality, upper respiratory infection, LPR, vocal demands, or life stress. Moreover, the authors hypothesized that the theory of the neural models explains vocal hyperfunction during phonation in MTD patients.

Ten women with MTD and fifteen healthy women participated in the study. We implemented an experimental paradigm consisting of sustained phonation of /i/ and prolonged exhalation tasks. The phonation tasks explored both respiratory and laryngeal control as well as the neural control associated with pitch (comfortable and high) modulations. The exhalation tasks explored respiratory control and allowed to generate laryngeal control maps by subtraction of the exhalation condition from the phonation condition.[38,74,75]

In our study, brain activity in response to phonation of sound /i/ in related vocal pitch (comfortable and high) changes was observed in the bilateral precentral gyrus, right SFG, MFG, and IFG, lingual gyrus, cingulate gyrus, STG, thalamus (ventral posterior lateral nucleus), and bilateral cerebellum in the two (MTD and healthy) groups (Table 1). These results are corroborated by recent fMRI studies on phonation involving simple voice production tasks.[37,38,41,42,47,49] The previously reviewed studies have observed activity in the same auditory, motor, frontal, parietal, and subcortical brain areas during phonation that are specialized for different functions. More specifically, bilateral activations in the precentral gyrus, the MFG, and the IFG are related to laryngeal motor control areas.[41] The MTG and the STG are responsible for vocal self-monitoring[68] and sensory voice processing or sensorimotor integration for vocal production,[69,100] respectively. Cingulate cortex activity is associated with volitional motor control necessary for phonation, especially during

TABLE 1.
Brain Activation During Phonation in the Healthy and MTD Groups

	Healthy Group (n = 15)				MTD Group (n = 10)			
Area	Brodmann No.	Cluster Size (mm^3)	t(42) (Peak)	Talairach Coordinates *x, y, z*	Brodmann No.	Cluster Size (mm^3)	t(27) (Peak)	Talairach Coordinates *x, y, z*
Comfortable phonation								
Right precentral gyrus	3, 4, 6	1671	5.7	46; –5; 47	3, 4, 6	228	4.6	49; –6; 42
Left precentral gyrus	3, 4	1509	6.3	–43; –18; 35	3, 4	1324	5.0	–43; –16; 34
Right middle frontal gyrus	10	53	3.5	37; 40; 6	46	494	3.9	44; 40; –6
Right inferior frontal gyrus	9	414	4.5	52; 7; 30	9	303	6.4	52; 7; 30
Cingulate gyrus	31	912	5.1	–3; –59; 27	31	85	4.0	–7; –51; 25
Right lingual gyrus	18	540	4.5	28; –84; –2	18	369	4.7	32; –75; –7
Right superior temporal gyrus	22, 41, 42	1192	5.0	61; –30; 9	41	240	4.7	60; –24; 13
Thalamus (ventral posterior lateral nucleus)		120	4.2	10; –14; 19		59	3.7	–6; –30; 15
Right cerebellum		107	2.9	21; –53; –26		77	4.6	23; –53; –20
Left cerebellum		270	3.8	–29; –55; –26		336	5.0	–19; –56; –24
High-pitched phonation								
Right precentral gyrus	4, 6	3028	6.1	40; –10; 36	4	164	4.8	48; –6; 42
Left precentral gyrus	3, 4, 6	916	5.3	–40; –15; 38	2–4, 6	1318	6.0	–36; –14; 32
Right superior frontal gyrus	6, 8	321	5.2	23; 22; 50	8	381	5.0	22; 17; 45
Right inferior frontal gyrus	9	1095	5.4	51; 7; 31	9	134	5.6	51; 7; 31
Right middle frontal gyrus	6, 9	627	4.8	35; 25; 31	9	64	3.0	46; 31; 31
Cingulate gyrus	31	400	4.4	–9; –52; 25	31	150	4.0	–9; –52; 25
Left lingual gyrus					18	535	5.0	–10; –77; –7
Right superior temporal gyrus and insula	22, 41, 42	2234	5.5	61; –29; 9/52; –7; 4	13, 41, 42	198	4.7	58; –32; 14/41; 5; 21
Left superior temporal gyrus, insula	22	446	5.8	–47; –13; –2	22	75	4.7	–43; –22; 0
Right thalamus (ventral posterior lateral nucleus)		566	4.0	13; –10; 21/–13; –10; 21		215	3.6	17; –10; 13/–26; –18; 1
Right cerebellum		528	5.5	3; –75; –28		49	4.4	23; –54; –21
Left cerebellum		333	5.1	–34; –54; –28		268	4.6	–48; –56; –39

Notes: Regions of significant activation are listed for each condition and for relevant contrasts between the conditions. Results are presented in Talairach space ($P < 0.001$, uncorrected).

TABLE 2.
Brain Activation During Phonation and Exhalation in the Healthy and MTD Groups

	Healthy Group (n = 15)				MTD Group (n = 10)			
Area	Brodmann No.	Cluster Size (mm^3)	t(42) (Peak)	Talairach Coordinates *x, y, z*	Brodmann No.	Cluster Size (mm^3)	t(27) (Peak)	Talairach Coordinates *x, y, z*
Prolonged exhalation								
Right precentral gyrus	3, 4, 6	1332	4.7	46; −10; 35/48; 3; 19	3, 4, 6	195	4.0	46; −10; −35/36; −17; 36
Left precentral gyrus	3, 4, 6	933	4.4	−46; −16; 34	3, 4, 6	755	4.5	−41; −18; 36
Cingulate gyrus	31, 32	1042	3.4	22; 28; 19	31, 32	311	4.4	22; −9; 32
Right lingual gyrus	18, 19	2621	5.1	31; −79; −3	18, 19	605	4.3	28; −84; −2
Right cerebellum		567	3.2	19; −57; −23		88	3.2	32; −42; −28
Left cerebellum		166	2.8	−17; −60; −21		240	3.4	−28; −68; −23
Comfortable phonation > prolonged exhalation								
Right superior temporal gyrus and insula	13, 21, 22, 41	2598	5.1	52; −24; 9	13, 22, 41, 42	1214	6.7	59; −29; 8/41; −25; 8
Left superior temporal gyrus and insula	13, 21, 22, 41	975	5.9	−47; −24; 6	22, 41	2447	5.1	−45; −26; 7
High-pitched phonation > prolonged exhalation								
Right superior temporal gyrus and insula	13, 21, 22, 41	5006	5.5	50; −20; 7	13, 21, 22, 41, 42	245	5.5	40; −27; 8
Left superior temporal gyrus and insula	13, 21, 22, 41	2876	6.9	−46; −21; 4	13, 21, 22	2328	5.5	−46; −23; 3

Notes: Regions of significant activation are listed for each condition and for relevant contrasts between the conditions. Results are presented in Talairach space ($P < 0.001$, uncorrected).

pitch[101] and emotional vocal modulations.[102] Activation in the cerebellum is involved in motor planning and coordination of laryngeal movements.[66] The lingual gyrus activity involved in simple phonemic tasks processing obviates the need for more efforts for the task.[67] Additionally, in our experiment, activity in the bilateral SFG was present during the high-pitch phonation task only in the two groups. Goldberg et al[103] found that when a personal emotional response was required, participants showed activity in the SFG—the brain region associated with self-awareness-related function. In our experiment, activity in the bilateral SFG was present during the high-pitch phonation task, hypothetically reflecting greater emotional activity co-occurring with higher vocal effort required to control high-pitched phonation.

Additionally, to test whether sensory input affects brain activity during vocal pitch modulation, a comparison between comfortable pitch and high-pitch phonation in MTD and control groups was performed. Because pitch modulation is based on modifying laryngeal and respiratory control[104]—where both auditory and somatosensory inputs are different—we expected different brain activities. However, these tasks were unable to show brain activation difference between high-pitched and comfortable phonation in MTD patients and control subjects. In our study, an experimental paradigm involving phonation of the /i/ sound was used to avoid major resonance articulatory changes as used in the fMRI studies by Loucks et al,[38] Haslinger et al,[49] and Simonyan and Ludlow.[48] However, to reduce articulatory modifications during phonation, subjects performed phonation of sound /i/ with reduced labial and jaw movements rather than natural phonation tasks. For future research, to explore vocal pitch modulation control, an experimental paradigm with phonation of the vowel /a/ instead of /i/ sound may be recommended to avoid F0 coinciding with the first resonance.[105]

The exhalation tasks in the present study explored respiratory control in MTD and control groups. Statistical analysis identified a significant effect of exhalation in the bilateral precentral gyrus, cingulate gyrus, right lingual gyrus, and bilateral cerebellum in both groups (Table 2). In the fMRI study by Loucks et al,[38] a comparable pattern of responses was identified for exhalation control in healthy subjects involving the left ventrolateral cortex, precentral and postcentral gyri, right supramarginal gyrus, right lingual gyrus, right cerebellum, and thalamus. In addition, the exhalation task allowed to generate laryngeal sensorimotor control maps by subtraction of the exhalation condition from the phonation condition.[38,74,75] Because the single cluster of differential activation in SFG was the only difference for the comfortable phonation and high-pitched phonation, these conditions were combined when comparing phonation (comfortable and high) and prolonged exhalation. This comparison revealed brain activity in the bilateral STG and insula—the brain regions associated with sound perception—in the two groups (Table 2).

The group comparison of prolonged exhalation tasks in patients with MTD versus healthy controls has determined overlapping pattern of responses in the cerebral regions typically active during normal exhalation. It showed that the neural control of exhalation, specifically of exhalation for phonation

TABLE 3.
Areas With Higher Activation in the MTD Group Compared With the Control Group

Area	Brodmann No.	Cluster Size (mm^3)	t(23) (Peak)	Talairach Coordinates *x, y, z*
Comfortable phonation				
Right inferior frontal gyrus	9	628	4.5	53; 9; 28
Left inferior frontal gyrus	9, 46	179	4.4	–45; 2; 21/–43; 42; 8
Right middle frontal gyrus	47	205	3.1	42; 40; –5
Right superior frontal gyrus	6	191	3.5	7; 6; 65
Left lingual gyrus	17	579	4.0	–13; –87; –3
Right insula	13	194	3.7	31; 25; 12
Left insula	13	534	4.5	–31; 9; 18
Right cerebellum		436	3.6	36; –36; –30
Left cerebellum		224	4.2	–28; –30; –38
Midbrain PAG		94	3.1	4; –24; –3
High-pitched phonation				
Right precentral gyrus	6	83	4.0	40; 14; 40
Left precentral gyrus	9	76	2.7	–40; 21; 37
Right inferior frontal gyrus	9	73	3.2	53; 9; 28
Left inferior frontal gyrus	9	47	3.0	–49; 7; 26
Left lingual gyrus	17	522	2.9	–14; –87; –3
Right cerebellum		364	3.4	37; –37; –29
Left cerebellum		1248	4.0	–48; –56; –38
Midbrain PAG/brainstem		17/65	2.6/3.1	0; –21; –5/0; –32; –41
Comfortable phonation > prolonged exhalation				
Right middle frontal gyrus	8, 10	128	4.0	34; 38; 21
Left middle frontal gyrus	9	20	4.3	–7; 46; 31
Right superior frontal gyrus	8	30	4.1	2; 28; 49
Midbrain PAG		25	4.2	–2; –14; –11
High-pitched phonation > prolonged exhalation				
Right superior frontal gyrus	10	25	3.6	26; 59; 23
Left middle frontal gyrus	9	46	3.9	–37; 44; 28
Midbrain PAG		17	4.3	–1; –19; –8
Left cerebellum		53	4.7	–48; –56; –42

Note: Results are presented in Talairach space ($P < 0.005$, uncorrected).

in patients with MTD, is not altered.[38] This assumption is based on the conclusion of fMRI study by Loucks et al,[38] which showed that the neural control of exhalation for phonation is similar to the neural control of voluntary exhalation. Only a difference in STG activation was seen because of the auditory feedback. These results were obtained by subtracting neural control of voluntary exhalation from neural control of phonation during fMRI data analysis in order to focus on sensory feedback control of phonation. Furthermore, no difference between the two groups in the exhalation tasks allowed a comparison of these tasks with the phonation tasks to identify the regions that are involved in sensory feedback control of phonation.

The imaging results supported our hypothesis that patients with MTD, when compared with healthy subjects, may have altered brain activity related to phonation control. Compared with controls, during phonation, MTD patients showed *higher* activation in the laryngeal motor control-related areas such as the precentral gyrus, SFG, MFG, insula, midbrain, brainstem, and cerebellum. Furthermore, comparison of phonation (comfortable and high-pitched) tasks with prolonged exhalation tasks identified areas with *higher* activation in the MFG and SFG in the MTD group versus control. Thus, the brain response observed in the present study may reflect that MTD patients control their voice by use of the laryngeal motor control-related areas, midbrain, brainstem, and cerebellum. Lower neural activation was seen in the cingulate gyrus, STG and MTG, and inferior parietal lobe in the MTD group in comparison with healthy controls. Moreover, comparison of phonation (comfortable, high-pitched) with prolonged exhalation tasks identified areas with *lower* activation in the left MTG for comfortable phonation and in the right inferior parietal lobe for high-pitched phonation in the MTD group in comparison with healthy controls. Because scanner noise was minimized during scanning, the subject's own voice served as the auditory stimulus and was taken to reflect auditory cortex activation.

In patients with MTD, these altered (higher/lower) brain activities may result in laryngeal tension and voice symptoms. However, this experiment did not provide evidence of internal

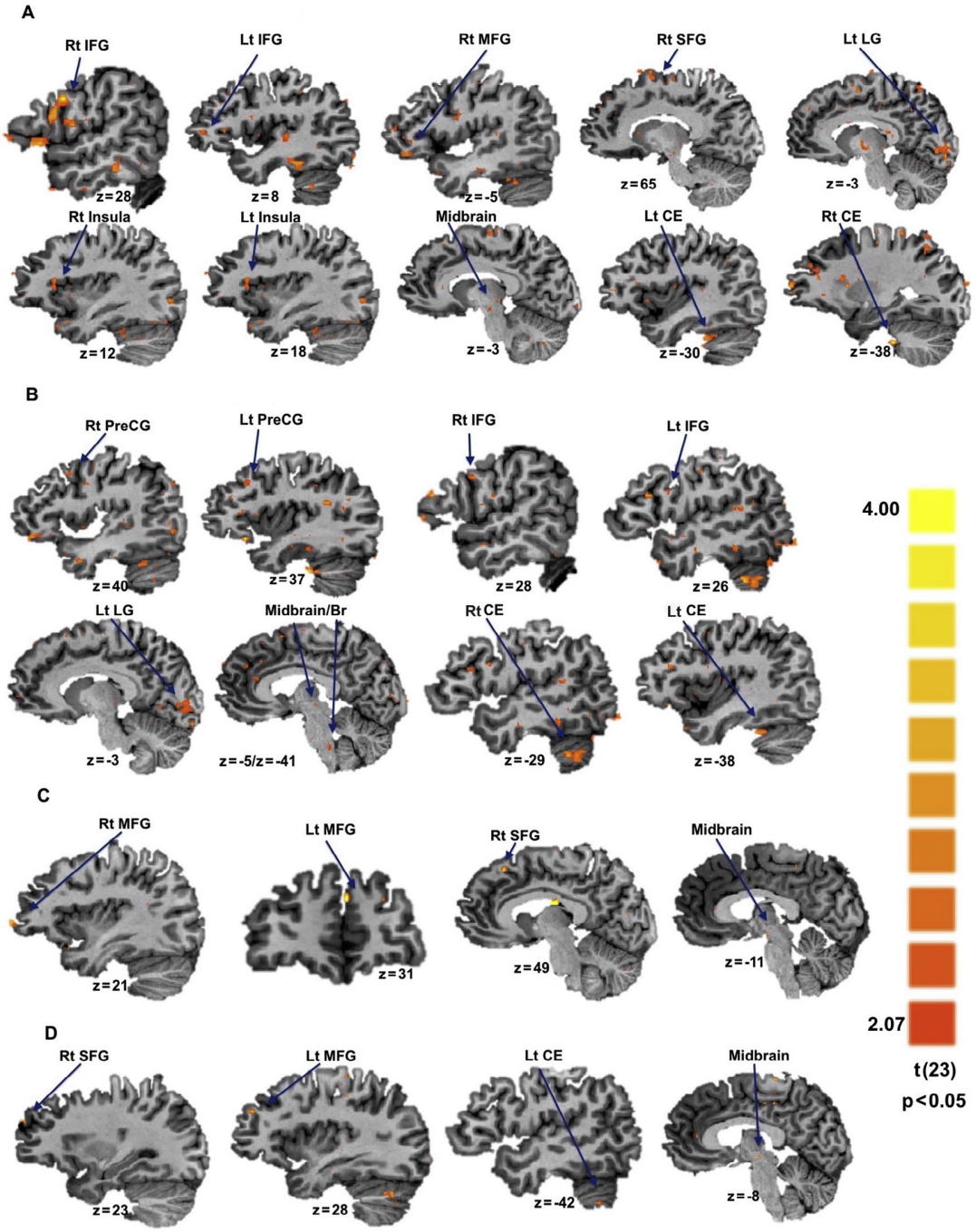

FIGURE 2. Areas of higher brain activation ($P < 0.005$, 10 voxels, uncorrected) during phonation in patients with MTD compared with controls for the conditions of comfortable phonation (**A**), high-pitched phonation (**B**), comfortable phonation > prolonged exhalation (**C**), and high-pitched phonation > prolonged exhalation (**D**). For fuller visualization of cluster extent, results are illustrated at a threshold of $P < 0.05$ (uncorrected), and an extent threshold of 10 contiguous voxels. The arrows indicate clusters of significant activation ($P < 0.005$, uncorrected), z coordinates are given below each slice. *Abbreviations:* Rt, right; Lt, left; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; LG, lingual gyrus; CE, cerebellum; PreCG, precentral gyrus; Br, brainstem.

representations/neural models of the sensorimotor transformation changes. This experiment did, however, provide evidence of altered neural correlates of phonation in MTD. In our study, altered neural activities were presented during phonation in MTD patients in comparison with healthy controls, hypothetically reflecting that the theory of the neural models may give possible explanation for MTD and particularly for imbalanced laryngeal muscle activation in MTD. In MTD, abnormal sensory feedback

TABLE 4.
Areas With Lower Activation in the MTD Group Compared With the Control Group

Area	Brodmann No.	Cluster Size (mm^3)	t(42) (Peak)	Talairach Coordinates *x, y, z*
Comfortable phonation				
Right cingulate gyrus	31	1066	–5.0	2; –34; 37
Right middle temporal gyrus	39	67	–3.0	41; –64; 15
Left middle temporal gyrus	39	570	–3.5	–41; –74; 14
Right superior temporal gyrus	22	491	–4.7	52; –49; 12
High-pitched phonation				
Cingulate gyrus	31	468	–3.0	19; –53; 11
Left middle temporal gyrus	21	75	–3.0	–55; –53; 2
Right superior temporal gyrus	21, 22	302	–3.8	51; –47; 12
Comfortable phonation > prolonged exhalation				
Left middle temporal gyrus	39	54	–4.3	–52; –62; 8
High-pitched phonation > prolonged exhalation				
Right inferior parietal lobe	40	61	–4.5	31; –48; 38

Note: Results are presented in Talairach space ($P < 0.005$, uncorrected).

(such as poor voice quality) may trigger the neural models to stimulate new patterns of muscle activation and alter sensory perception (Figure 1B). In particular, abnormal sensory feedback generates an error signal between prediction of the sensory outcome of phonation and incoming sensory feedback. The error signal updates the neural models that in turn generate corrective commands to the motor controller and change sensory perception. Altered descending motor cortical signals stimulate laryngeal motorneurons in the brainstem which might result in excessive tension of (para)laryngeal muscles or recruit muscles that are not ordinarily active. A relationship between the laryngeal motor control impairments and pathophysiology of MTD may be seen. Neural impulses from the areas that control the execution of laryngeal movements, such as the precentral gyrus, SFG, MFG, midbrain PAG, brainstem, and cerebellum, hypothetically may cause muscle tension that can disrupt phonation and produce symptoms of MTD. Simultaneously altered sensory perception might make the brain insensitive to the normal feedback even when irritants are no longer present. Thus, the pathophysiology of MTD may be viewed as a processing of abnormal sensory information throughout intact internal prediction/correction mechanism that results in updating or creating new neural models, altering muscle activation patterns and opening sensory channels for abnormal sensory inputs. In our study, lower neural activity in the sensory control-related areas such as STG, MTG, and inferior parietal lobe may reflect suppression in these areas. Neural response suppression in these areas, on the one hand, may occur because of decreased F-high in patients with MTD according to the acoustic analysis. On the other hand, neural response suppression in these areas might make the brain insensitive to the normal feedback. We also suggest that the neuroplastic changes[106,107] in the brain areas responsible for phonation control[27] (Figure 1B) may support the symptoms of MTD. Furthermore, the updated neural models generate corrective commands to the motor controller (Figure 1B), resulting in altered descending motor cortical signals. In our study, higher neural activity in the laryngeal motor control-related areas such as precentral gyrus, SFG, MFG, IFG, midbrain, brainstem, and cerebellum alters descending motor cortical signals and stimulates laryngeal motorneurons in the brainstem that may result in laryngeal tension and voice symptoms in patients with MTD.

The present fMRI study also identified problems with the experimental stimuli or procedures. The aim of this study was to investigate brain activity during phonation in women with MTD in comparison with healthy controls in three conditions: comfortable pitch, high pitch, and prolonged exhalation. However, measurements of the vocal quality were not implemented in this fMRI study. During the fMRI procedure it was not possible to make audio recordings of phonations. Therefore, the actual difference in fundamental frequency between high pitch and comfortable pitch could not be determined. Before the fMRI scanning, however, each subject was carefully trained by experienced speech therapists to perform these tasks. For future research, we recommend using voice recordings within the fMRI setup. Furthermore, voice recording during stroboscopy is necessary to compare data.

Another limitation of the present study was that a test of reproducibility was not performed prior to the fMRI study. In the previous fMRI studies, a test of reproducibility has been performed under a number of different experimental paradigms and has reported good reproducibility of data. These fMRI paradigms included visual stimulation, motor task, and cognitive tasks[108,109]; sensorimotor tasks[110,111]; or learning tasks.[112] In our study, we did not perform a test of reproducibility because of using a simple fMRI paradigm and did not perform multisite or multiscanning session scans. Although a test of reproducibility has been performed in the previous fMRI studies, Friedman et al[111]

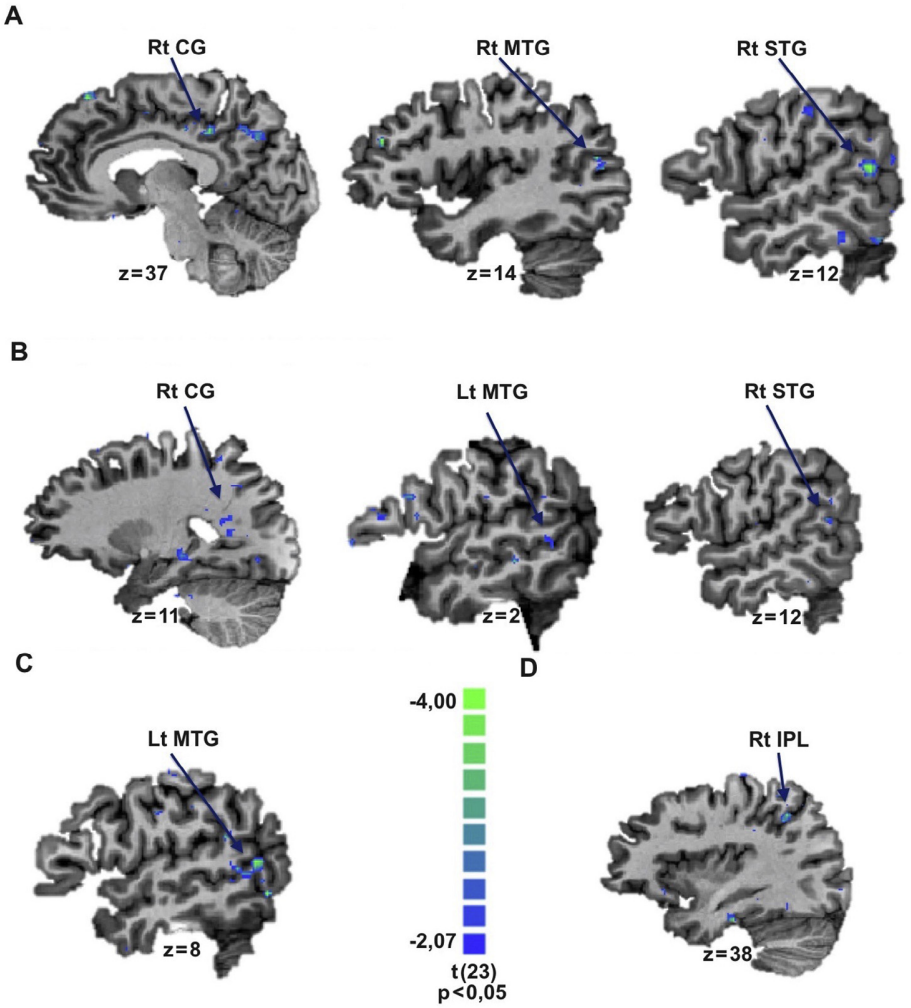

FIGURE 3. Areas of lower brain activation ($P < 0.005$, 10 voxels, uncorrected) during phonation in patients with MTD compared with controls for the conditions of comfortable phonation (**A**), high-pitched phonation (**B**), comfortable phonation > prolonged exhalation (**C**), and high-pitched phonation > prolonged exhalation (**D**). For fuller visualization of cluster extent, results are illustrated at a threshold of $P < 0.05$ (uncorrected), and an extent threshold of 10 contiguous voxels. The arrows indicate clusters of significant activation, *z* coordinates are given below each slice. *Abbreviations:* Rt, right; Lt, left; CG, cingulate gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; IPL, inferior parietal lobe.

suggested carrying out reproducibility studies prior to the fMRI study involving the main and original scientific hypothesis, especially when performing multisite or multiscanning session scans. Doing so may reveal sources of instability that would introduce a significant variance into the data, and also define if certain statistical benchmarks are met relevant to reproducibility and reliability of data. However, this was a limitation in this study, and future work in this area should include a test of reproducibility performed prior to the fMRI study in order to improve the results.

CONCLUSIONS

The neuroimaging data in this study revealed that MTD patients control phonation by use of the auditory, motor, frontal, parietal, and subcortical areas that are similar to those used during phonation control by healthy subjects. However, *higher* neural activity in the laryngeal *motor* control-related areas such as precentral gyrus, SFG, MFG, IFG, midbrain, and cerebellum as well as the *lower* neural activity in the sensory control-related areas such as STG, MTG, and inferior parietal lobe may affect the laryngeal sensorimotor control and result in laryngeal tension and voice symptoms in patients with MTD. Even with a small number of participants in the MTD group, we were able to locate brain regions important to phonation control,[42–44,47,113–115] and to compare our findings with those of earlier studies.[42–44,47,73,113–115] We also suggested that the setup conditions of future fMRI experiments should be modified in order to make vocal pitch recording possible or to rely on fixed vocal pitches. Moreover, future work in this area should include a test of reproducibility performed prior to the fMRI study in order to improve the study results.

An updated study protocol should provide further insight in the neural mechanisms of phonation related to laryngeal control in patients with MTD. In addition, future studies should relate routine voice diagnostic behavioral measures (ie, perceptual, acoustic, and aerodynamic) to brain imaging data to better understand the relationship between current clinical voice measures and the underlying neural events subserving disordered voice. A better understanding of voice production, from central sensorimotor control to the contribution of the peripheral subsystems, will help to establish biomarkers and lead to customized treatment plans, which might lead to improved clinical outcomes in treatment-seeking populations.

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APPENDICES

TABLE A1.
Voice Assessment Protocol, Voice Handicap Index, and GRBASI in Healthy Women and Women With MTD

Feature	Healthy Group (n = 15)		MTD Group (n = 10)	
Vocal Assessment Protocol	Mean (Standard Deviation [SD]) Sustained Vowel /a/	Mean (SD) Sustained Vowel /i/	Mean (SD) Sustained Vowel /a/	Mean (SD) Sustained Vowel /i/
Vocal range				
Lowest intensity (dB)	53.5 (2.5)	54.1 (3)	59 (3.3)	56.7 (2.3)
Highest intensity (dB)	101.4 (4.4)	94.3 (3.7)	94.2 (7.7)	92 (6.8)
Lowest frequency (Hz)	132.9 (20)	124.9 (45.6)	142.6 (29.1)	137.5 (25)
Highest frequency (Hz)	848.6 (166.7)	799.3 (137)	557.3 (202)	528.9 (111.5)
Fundamental frequency (F0) (Hz)	199.5 (17.4)	211.6 (16)	193.4 (34.9)	197.6 (24.3)
Aerodynamics				
Maximum phonation time[82]	19.7 (4.9)	22.6 (5.1)	12.29 (7)	21 (6.8)
Vital capacity (cm^3)	2630 (478.8)	2610 (520)	2475 (560)	2425 (462.6)
Acoustic analysis				
Jitter (%)	1.5 (0.7)	1.6 (1.0)	3.2 (2.5)	2.2 (1)
Shimmer (%)	5.3 (1.7)	2.7 (0.9)	7.9 (5.8)	4.3 (3.5)
DSI	3.9 (1.3)	3.8 (2.0)	–0.96 (4.7)	1.01 (2.4)
VHI-10	Mean	SD	Mean	SD
VHI functional	2.6	2.1	7.2	6.9
VHI physical	1.9	2.3	11.7	8.1
VHI emotional	0.6	1.0	5.2	8.4
VHI total (0–40)	5.1	4.2	24.1	22.9
GRBASI	Mean	SD	Mean	SD
G	0	0	0.9	1.1
R	0	0	0.7	0.8
B	0	0	1.1	0.9
A	0	0	0.9	1.1
S	0	0	0.4	1.1
I	0	0	0.3	0.8

TABLE A2.
Videostroboscopic Features in Healthy Women and Women With MTD

Videostroboscopic Feature	Healthy Group		MTD Group	
	n	%	n	%
Symmetry				
Symmetrical	15	100	4	40
Asymmetrical	—	—	6	60
Regularity				
Regular	15	100	4	40
Irregular	—	—	6	60
Inconsistent	—	—		
Glottic closure				
Complete	14	93.3	2	20
Incomplete	1	6.7	8	80
Type of glottal gap	—	—		
Longitudinal	—	—	5	50
Posterior	1	6.7	3	30
Anterior	—	—	1	10
Oval	—	—	—	—
Hour-glass	—	—	1	10
Amplitude				
Normal	13	86.7	3	30
Reduced	2	13.3	7	70
Increased	—	—	—	—
Mucosal wave				
Normal	16	100	3	30
Reduced	—	—	7	70
None	—	—	—	—
A-P constriction				
0	13	86.7	1	10
1	2	13.3	2	20
2	—	—	4	40
3	—	—	3	30
4	—	—	—	—
M-L constriction				
0	14	93.3	2	20
1	1	6.7	3	30
2	—	—	2	20
3	—	—	3	30
4	—	—	—	—

Abbreviations: A-P, anterior-posterior (0: no constriction, 4: severe constriction); M-L, mediolateral (0: no constriction, 4: severe constriction).

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