Exploring the Neural Bases of Primary Muscle Tension Dysphonia: A Case Study Using Functional Magnetic Resonance Imaging

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Summary: Primary muscle tension dysphonia (pMTD) is a voice disorder that occurs in the absence of laryngeal pathology. Dysregulated activity of the paralaryngeal muscles is considered the proximal cause; however, the central origin of this aberrant laryngeal muscle activation is unclear. The Trait Theory (Roy and Bless, 2000a,b) proposed that specific personality traits can predispose one to laryngeal motor inhibition and pMTD, and this inhibition is mediated by a hyperactive "behavioral inhibition system (BIS)" composed of limbic system structures (and associated prefrontal connections). This case study used functional magnetic resonance imaging to detect brain activation changes associated with successful management of pMTD, thereby evaluating possible neural correlates of this poorly understood disorder.

Method. A 61-year-old woman with moderate-to-severe pMTD underwent functional magnetic resonance imaging scans before and immediately after successful treatment using manual circumlaryngeal techniques. Experimental stimuli were blocks of repeated vowel production and overt sentence reading.

Results. Significantly greater activation was observed pre- versus posttreatment in all regions of interest during sentence production, that is, periaqueductal gray, amygdala, hypothalamus, anterior cingulate cortex, hippocampus, dorsolateral prefrontal cortex, Brodmann area 10, and premotor and inferior sensorimotor cortex.

Conclusions. Our findings are compatible with overactivation of neural regions associated with the BIS (cingulate cortex, amygdala, hypothalamus, periaqueductal gray) and motor inhibition networks (eg, [pre-]supplementary motor area) along with the dorsolateral prefrontal cortex and medial prefrontal cortex. Heightened input from limbic regions combined with dysfunctional prefrontal regulation may interfere with laryngeal motor preparation, initiation, and execution thereby contributing to disordered voice in pMTD.

Key Words: Muscle tension dysphonia–Conversion disorder–Functional voice disorder–Trait Theory–Behavioral inhibition system–fMRI.

INTRODUCTION

The larynx is regarded by many as the "valve of emotion"—the control valve that regulates the release of intense human emotions such as fear, anger, sadness, and joy—so when the voice becomes disordered, it is not uncommon for clinicians to propose psychological factors including emotional states or stress as primary causal mechanisms.[1–4] This is especially true in the case of *primary muscle tension dysphonia* (pMTD), a voice disorder wherein no known structural or neurologic pathology of the larynx exists to explain the partial or complete voice loss.[5–7] Some confusion surrounds this diagnostic category because pMTD potentially includes a variety of medically unexplained voice disorders, such as vocal hyperfunction, hyperkinetic dysphonia, tension-fatigue syndrome, muscle misuse, functional, nonorganic, psychogenic, or conversion dysphonia.[6,8–13] Although each diagnostic label implies some degree of etiologic heterogeneity, whether these disorders are qualitatively different and etiologically distinct remains undetermined. Voice disorder taxonomies have yet to be adequately operationalized; consequently, such diagnostic labels often lack clear thresholds or discrete boundaries to determine patient inclusion or exclusion. When applied clinically, these various diagnostic labels often reflect clinician supposition, bias, or preference. However, at the purely phenomenological level, there may be few empirically tractable differences that reliably distinguish these voice disorders.

Recently, pMTD has become the preferred diagnostic label to describe hyperfunctional voice problems presumably related to dysregulated or imbalanced laryngeal and paralaryngeal muscle activity.[14] Because the laryngeal musculature is simply responding to commands originating in the central nervous system, the *muscle tension* portion of the pMTD diagnosis places emphasis on the presumed role of dysregulated muscle activation as the *proximal* cause of the dysphonia. However, the diagnostic label is decidedly neutral regarding the possible central source(s) of this aberrant laryngeal muscle activity. Although a variety of mechanisms have been offered, the precise etiology and pathophysiology underlying the development and maintenance of pMTD remains unknown, and considerable uncertainty exists surrounding possible predisposing, precipitating, and perpetuating causes of the disorder (see Roy[4] for a complete review).

Despite uncertainty regarding the central origins of pMTD (and whether it is a single disorder or many disorders), a wide array of psychopathological processes contributing to its formation have been proposed.[15] The activation of paralaryngeal muscles in response to stress, emotion, anxiety, or conflict

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over speaking out is often cited as the common denominator.[3,16] Historically, one psychological explanation for such medically unexplained voice disorders is "conversion disorder." In conversion voice disorders, psychological factors are judged to be associated with the voice symptoms because stressors or emotional trauma are said to precede the onset of the dysphonia. In short, patients are believed to unconsciously *convert* psychological distress into a voice symptom. The voice loss, whether partial or complete, is also often interpreted to have symbolic meaning. That is, the voice loss symbolizes the patient's inability to express particular feelings often associated with a breakdown in communication between the patient and someone important in their life,[1] and is frequently described in terms of primary or secondary gain.

Although conversion disorder has maintained a relatively prominent place as an explanatory construct for such medically unexplained voice disorders, certain authorities have offered alternative models to account for pMTD. In these models, the profound sensitivity of the larynx to emotion and the related adverse effects of paralaryngeal muscle activation are highlighted. These explanatory models emphasize both the inhibitory effects of laryngeal muscle activity on voice production and the role of life stress or interpersonal difficulties that stimulate internal conflict (particularly in situations involving conflict over self-expression or speaking out). This inner conflict or stress (especially in individuals who have difficulty expressing emotions or opinions) ostensibly becomes channeled into musculoskeletal tension in or around the larynx, which physically inhibits voice production.[2,3,17–19] Unlike in conversion disorder, these theories discount the role of primary and secondary gain, and instead emphasize the inhibitory effects of aberrant laryngeal muscle activation patterns on voice production.

The "Trait Theory" of pMTD also shares the theme of inhibitory laryngeal behavior, but attributes this muscularly inhibited voice production to specific personality dimensions or traits and related neural substrates.[16,20–22] In brief, the Trait Theory offers that the combination of personality dimensions (such as introversion and neuroticism) leads to predictable and conditioned laryngeal inhibitory responses to certain environmental signals or cues involving perceived threat, novelty, punishment, and frustration. For instance, when undesirable punishing or frustrating outcomes have been paired with previous attempts to speak out, this can lead to centrally mediated, muscularly inhibited voice production in a predisposed individual. This type of conditioned laryngeal motor inhibition in the context of threat or punishment cues is interpreted as part of a defensive cascade in pMTD, which includes a variant of the "freeze" response often observed in other animals in response to threat.[23] The authors argued that this conflict between laryngeal inhibition (motor freezing) and volitional activation of voice has its origins in nervous system functioning, and contributes to incomplete or disordered vocalization (in an otherwise structurally and neurologically intact larynx).

Although the Trait Theory highlights the role of specific personality traits that may predispose to laryngeal motor inhibition, it also asserts that this inhibition is mediated by a "behavioral inhibition system (BIS)" and related neural structures. The BIS is described as an attentional system that is sensitive to cues of threat, punishment, nonreward or frustration, and novelty that functions to interrupt ongoing behavior to facilitate the processing of these cues in preparation for a response.[24–26] The term inhibition in the context of pMTD is used to refer to different processes through which ongoing behavior (ie, voicing) is stopped or suppressed.

The BIS, as described by Gray,[24] originally included the septo-hippocampal system with connections to the prefrontal cortex. However, more recent descriptions of the BIS outline an expanded set of neural structures including the cingulate cortex, amygdala, hypothalamus, and periaqueductal gray (PAG) where the septo-hippocampal system and amygdala play major roles within the distributed BIS.[25] Thus, the BIS includes an interconnected neural and functional hierarchy ranging from the PAG at its lowest level to the prefrontal cortex at its highest level. According to the Trait Theory, these key limbic system structures (and associated prefrontal connections) of the BIS, which are typically activated in response to threat or emotional cues, become dysfunctional in pMTD and interfere with voluntary control over phonation. Although there is evidence to support the fundamental tenets of the Trait Theory (ie, that individuals who possess certain personality traits may be susceptible to developing pMTD[20,22] or to altered vocal function[27–30]), little is known regarding the neurobiological bases of pMTD and the putative role of neural structures related to the BIS.

A neurobiological basis for pMTD is certainly plausible because there are two parallel vocal pathways, the (1) limbic vocal control pathway (anterior cingulate cortex [ACC]-PAG to motoneurons) and the (2) laryngeal motor cortical pathway (sensorimotor cortex to motoneurons), that have points of convergence.[31,32] Both pathways make contact with the phonatory motoneurons through the reticular formation, nucleus retroambiguus, and solitary tract nucleus,[33,34] and are integrated at the level of the basal ganglia.[35] The ACC, and cingulate cortex overall, plays a central role because it integrates emotional, cognitive, and behavioral information[36] and because the laryngeal motor cortex has bidirectional connections with the cingulate cortex and integrates signals from the prefrontal cortex, insula, putamen, and thalamus for voice for speech.[32,35] Thus, the limbic vocal pathway controls involuntary and voluntary emotional vocalizations[35] and may play a role in the pathogenesis of pMTD.

Although much progress has been made in understanding the central control of vocalization (see Simonyan[37] for a summary) and the functional connectome of speech,[38] researchers acknowledge that more needs to be learned regarding changes in the ventral sensorimotor cortex for phonation under various tasks or conditions, including emotional expression, and how interactions with various cortical and subcortical brain regions shift.[39–41] Functional magnetic resonance imaging (fMRI) offers a noninvasive method to study brain activity and has been used to shed light on the biological bases of a variety of neurologic and psychiatric disorders. The purpose of this study was to use fMRI to detect brain activation changes associated with successful management of a single case of pMTD, thereby evaluating possible neural correlates of this poorly understood disorder and the putative role of the BIS.

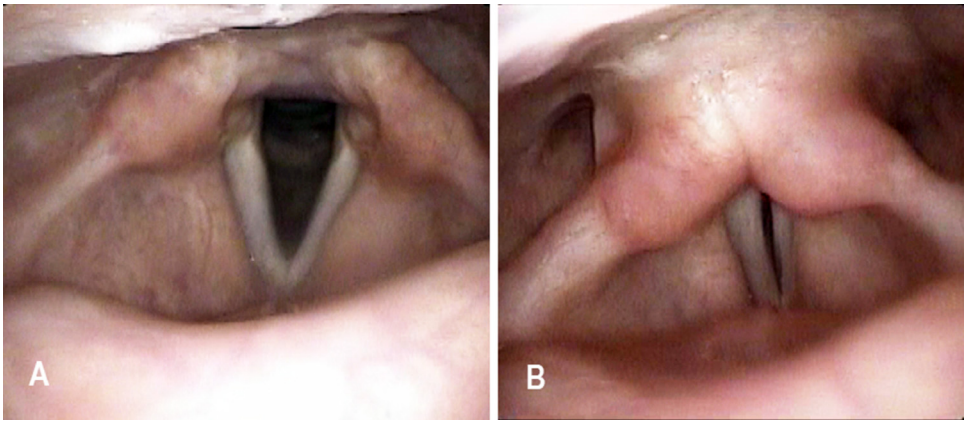

FIGURE 1. Pretreatment still images of the vocal folds and surrounding structures in the maximally abducted (**A**) and in the adducted position during phonation (**B**). These images obtained from flexible videolaryngoscopy confirm the absence of structural pathology of the vocal folds. Mild mediolateral and anteroposterior compression of the supraglottic structures is observed within the context of incompletely adducted vocal folds during phonation (ie, **B**).

MATERIALS AND METHODS

Participant

The University of Utah Institutional Review Board approved this study. The participant, a 61-year-old married woman and nonsmoker, presented with a year-long history of fluctuating dysphonia with worsening symptoms over the previous month. According to the patient, the onset of the voice disturbance was originally associated with symptoms of a "sinus infection" which resolved, leaving her with a persistent voice disorder (with no episodes of complete remission). A diagnosis of pMTD was offered after comprehensive voice evaluation by an otolaryngologist and speech-language pathologist who specialize in voice disorders, which confirmed no evidence of structural or neurologic vocal fold pathology sufficient to account for the dysphonia (Figure 1). Her dysphonia in connected speech was judged as moderate-to-severe and characterized by a strained high-pitched breathy voice quality with transient aphonic voice breaks. The Cepstral Spectral Index of Dysphonia (CSID) (calculated using the second and third sentences from the Rainbow Passage,[42] ie, $CSID_{RB}$) was 39.7, and the CSID for sustained vowel production (ie, $CSID_{SV}$) was 38.1, with both values residing within the moderate range of severity.[43,44] The patient self-assessed her current voice as only 20% of normal. Voice Handicap Index (VHI)[45] score was 78 of 120, also compatible with a moderate-to-severe level of voice-related handicap. Approximately 3 months before the evaluation at our specialty center, she had undergone Nissen fundoplication for presumed laryngopharyngeal reflux with no apparent improvement in voice. Her medical history was negative for mental illness, including no history of (or medications for) anxiety or depression or other psychopathology.

fMRI stimuli and procedure

The patient underwent the identical protocol in the fMRI scanner before and immediately after successful treatment (wherein her voice was restored to normal using manual circumlaryngeal techniques). The patient was very familiar with MRI scans as she had undergone numerous MRI procedures, including five head and neck scans over the past 8 years (all related to postresection monitoring of a facial neuroma). All of these procedures were acquired in the same facility and scanner used in this experiment, with the most recent MRI scan of the head and neck region only 2 weeks before her participation in this study.

Functional MRI tasks consisted of two overt voice or speech conditions across two unique scanner sessions (pre- and posttreatment) completed on the *same* day. Each task was presented in a blocked design in which the participant alternated between six 30-second rest blocks and six 30-second active blocks for a total of 6 minutes per task. During both pre- and posttreatment scanner sessions (ie, scanner session 1 and scanner session 2, respectively), the patient was instructed during the active blocks to either (1) repeat a sustained vowel "ah" for approximately 1 second at 1-second intervals (resulting in 15 productions during the 30-second active block), or (2) read aloud simple declarative, emotionally neutral sentences such as "They put the dirty dishes in the sink" and "She put toothpaste on her toothbrush" (resulting in six sentence productions during the 30-second active block). The vowel task represented a simple voice task compared with sentence reading, which, given its complexity, is arguably a more ecologically valid task to evaluate voice for speech. Previous research has shown that in contrast with simple syllable productions, speech production also engages prefrontal and cingulate areas, with the latter also promoting emotional vocalizations and prosody in speech.[32,38,41,46] Thus, this particular context was used to better evaluate the role of the limbic system and inhibition networks in speech production. Visual stimuli for the tasks were presented on a translucent slide screen at the back of the scanner, which was viewed through a mirror mounted on top of the head coil. Stimulus presentation was controlled by *E-Prime* software (Psychology Software Tools, Inc., Pittsburgh, PA; https://pstnet.com/products/e-prime/).

After the initial scanner session (ie, completed in her pretreatment, disordered voice), the patient underwent a single 1-hour voice therapy session with an experienced speech-language pathologist (SLP DH) who specializes in the treatment of pMTD and the use of manual circumlaryngeal techniques. Because dysregulated laryngeal muscle tension is frequently offered as

the proximal cause of pMTD, many voice therapies aim to reduce, re-coordinate, or rebalance such muscle tension. In this regard, manual circumlaryngeal techniques, including laryngeal reposturing and circumlaryngeal massage, have been reported to be extremely effective and efficient in the management of functional voice disorders such as pMTD.[47,48] The interested reader is referred to Roy[48] for a complete description of these manual techniques. In short, during the production of sustained vowels, the clinician assessed the immediate voice effects of several reposturing maneuvers applied serially in a trial-and-error fashion. These laryngeal reposturing or repositioning maneuvers involved brief displacement including compression of the anterior larynx by exerting inward and downward digital pressure directed over the body of the hyoid, over the inferior aspect of the hyoid bone, as well as within the thyrohyoid space (as the patient vocalized). In addition, elevation of the larynx was physically impeded by applying downward traction laterally over the superior border of the thyroid lamina. These manual reposturing maneuvers aimed to momentarily interfere with habituated patterns of muscle misuse, and by perturbing the laryngeal mechanism elicit brief moments of improved voice. While reposturing the larynx, any transient moments of improved voice quality or pitch were immediately identified and reinforced for the patient. These brief moments were then shaped and extended while using digital cueing. Eventually, trials were undertaken wherein digital cues were faded and the patient was asked to rely on sensory feedback (ie, auditory, kinesthetic and vibrotactile) to maintain improved voicing. Based on the patient's response, additional attempts were made to sustain improvement beyond vowel prolongation into short phrases often loaded with nasal consonants, and then automatic serial speech (rapid counting, reciting the days of the week, months of the year). Once improvement was established, oral reading was then introduced and the patient was asked to vary loudness and pitch to establish control and flexibility within these contexts. Using these techniques, a perceptually normal voice was reestablished and confirmed by the patient's report, the treating SLP, and the researchers. In addition, posttreatment CSID values for the Rainbow Passage ($CSID_{RB}$ = 12.01) and sustained vowel production ($CSID_{SV}$ = 9.45) were both within normal range (ie, <19).[43] Once normal voice was reestablished and maintained, the patient immediately returned to the scanner and all previously described tasks were repeated (ie, scanner session 2). It is also worth noting that contact initiated with the patient at 6 months posttreatment confirmed maintenance of normal voice.

fMRI data acquisition

The patient was scanned on a Siemens 3T Trio magnetic resonance scanner with a 12-channel head coil (Siemens, Erlangen, Germany). Functional MRI data were acquired with a susceptibility-weighted gradient echo gradient echo echo-planar imaging (EPI) sequence (field-of-view 22 cm, matrix 64×64, repetition time [TR] = 2.08 seconds, echo time [TE] = 30 milliseconds, slice thickness 3 mm with no gap, axial slices aligned with the inferior edge of the corpus callosum, flip angle 75°). Thirty-five slices were acquired during each repetition time. The first five image volumes of each task were discarded to ensure signal equilibrium. Distortions caused by variations in magnetic susceptibility were removed during postprocessing using field map data acquired with a separate sequence. Anatomic T1-weighted images were acquired using an MPRAGE sequence (field-of-view 25.6 cm, matrix 256×256, TR = 2 seconds, inversion time = 1.1 seconds, TE = 2.15 milliseconds, slice thickness 1 mm, flip angle 8°, signal averages = 1, GRAPPA = 2 with 77 reference lines). Padding was placed around the patient's head to minimize patient movement during the scan.

fMRI data analysis

Preprocessing and statistical analyses were carried out with *SPM12* (http://www.fil.ion.ucl.ac.uk/spm). Images were realigned to correct for head motion, unwarped to remove susceptibility distortion, and slice-time corrected to the first slice using *SPM12*'s Fourier phase-shift interpolation. The mean-realigned EPI image was co-registered with the anatomic image. All images were spatially normalized to the Montreal Neurological Institute (MNI) template, and voxel sizes resampled to $2 \times 2 \times 2$ mm. EPI images were smoothed using isotropic 6-mm Gaussian kernels and statistically analyzed using an epoch design convolved with the hemodynamic response function. Low-frequency noise was removed with a high-pass filter with a cutoff period of 128 seconds, and an autoregressive AR(1) model was fitted to the residuals to account for temporal autocorrelation.

Pre- versus posttreatment comparisons of blood-oxygenation-level dependent (BOLD) brain activation associated with each task were computed for small-volume regions of interest (ROIs) related to our a priori hypotheses of differential activation in neural regions associated with the BIS, as well as additional areas involved in emotion and action regulation, self-evaluation, and sensorimotor control for voice. Ten ROIs were selected based on the extant fMRI literature describing central laryngeal motor pathways and the putative neural substrates of fear, anxiety, and stress (see seminal work of Dietrich et al[49] for a review). Thus, in addition to specific neural substrates of the BIS, we also examined other neural systems through which abnormal emotional processing could lead to consequences in the vocal motor system. The ROIs consisted of the PAG, and bilaterally for the hypothalamus, amygdala, hippocampus, ACC, dorsolateral prefrontal cortex (dlPFC), Brodmann area 10 (BA 10), Brodmann area 6 (BA 6), and the inferior precentral and postcentral gyri.

Five ROIs were supplied by the Neuromorphometrics atlas distributed with *SPM12* (ACC, hippocampus, amygdala, and precentral and postcentral gyri). The inferior portion of the precentral and postcentral gyri was used, from z = 0 mm to 40 mm, to concentrate on areas responsible for vocalization.[37,46,50,51] Three ROIs (BA 6, BA 10, and dlPFC) came from the Brodmann area atlas distributed with *MRIcron* (http://people.cas.sc.edu/rorden/mricron, version 1, June 2015). The dlPFC consists of BA 46 and the portions of BA 9 more lateral than x = +28 mm or −28 mm. The PAG was defined as a sphere of radius 8 mm located at MNI coordinates 1 −29 −12 using *MarsBaR* software (http://marsbar.sourceforge.net, version 0.44).[52] The hypothalamus model came from *PickAtlas* software and was dilated by a factor of 4 within that software (http://fmri.wfubmc.edu/software/PickAtlas, version 2.4).

The smaller volume ROIs reduced the multiple comparisons problem and allowed one to detect small effects that occurred within that volume. Multiple comparisons were controlled for voxels within each ROI with cluster-extent thresholding combined with an uncorrected voxel threshold of $P < 0.001$ to produce clusters with family-wise error correction of $P < 0.05$ (FWE-corr output from *SPM12*). *P*-values are therefore corrected for multiple voxels within each ROI but not corrected for multiple ROIs tested.

RESULTS

Table 1 shows family-wise error-corrected ROI results for the "vowel ah" task pre- versus posttreatment, and Table 2 shows the "overt sentence reading" task pre- versus posttreatment (ie, session 1 vs. session 2). Tables 1 and 2 provide details including MNI coordinates for the peak value within each significant cluster. All contrasts are relative to the rest condition. Overall, fewer significant differences at $P < 0.05$ were observed between pre- and posttreatment for the repeated "ah" productions compared with the sentence reading task. For the vowel task, only activity in the left PAG and midline ACC (peak in the anterior middle cingulate cortex [aMCC]) was significantly greater pre- compared with posttreatment. Considering a significance level of $P < 0.10$, inspection of Tables 1 and 2 revealed that increased activity was observed in both tasks for the PAG, hypothalamus, ACC, and hippocampus pre- compared with posttreatment.

In contrast, the overt sentence reading task was associated with greater variety and number of activation patterns across all of the ROIs. Specifically, the pretreatment condition was associated with increased activity for the midline PAG, right amygdala, left hypothalamus, left ACC (peak activity in the subgenual ACC), left hippocampus, left dlPFC, bilateral BA 10, bilateral BA6 (primarily left including [pre-]supplementary motor area [SMA]), and bilateral inferior precentral and postcentral gyri (including left laryngeal motor cortex). Decreased activation (in the pretreatment condition) was also observed in the amygdala and hypothalamus (bilaterally), and right hippocampus. Figure 2 displays areas of significantly increased brain activity during the pretreatment condition (ie, scanner session 1 during dysphonic voice) compared with the posttreatment condition (ie, session 2 during normal voice) from the ROI analysis of the "overt sentence reading" task.

DISCUSSION

The purpose of this study was to use fMRI to detect brain activation changes associated with successful management of a single case of pMTD, thereby to evaluate possible neural correlates of this poorly understood disorder. Our findings confirmed that one session of successful voice therapy was associated with a shift in brain activations underlying voice and speech production. As predicted based on the Trait Theory, brain activity pretreatment was characterized by hyperactivity of regions involved in limbic-motor pathways compared with posttreatment. The hyperactivity was especially expansive during overt sentence reading in contrast with a simple voice task and encompassed a network of limbic, prefrontal, and sensorimotor ROIs suggesting a role for emotion, arousal, or inhibitory mechanisms to interfere with voluntary control over phonation contributing to disordered voice in pMTD.

Our results bear striking parallels with dysfunctional limbic-motor interactions observed in conversion disorders, more recently known as functional neurologic symptom disorders. Based on *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[53] criteria, the definition for conversion disorder includes (1) having at least one symptom of altered voluntary motor or sensory function, (2) the presence of clinical findings supporting incompatibility between symptom and neurologic or medical conditions, (3) that the symptom is not better explained by another medical or mental disorder, and (4) that the disorder causes clinically significant distress or impairment. Although our patient did not undergo a neurologic or psychiatric examination and did not receive a differential diagnosis of conversion disorder, the history and voice medical examination (as

TABLE 1.
Family-wise Error-corrected Region of Interest Results for the "Vowel Ah" Task Pre- Versus Posttreatment (ie, Session 1 vs. Session 2, All Contrasts vs. Rest Condition).

ROI	Side	Activation: Increased/ Decreased (Pre vs. Post)	MNI Coordinates			Cluster Size (in Voxels)	*P*-FWE-corr
			x	*y*	*z*		
Periaqueductal gray	L	Increased	–2	–32	–18	15	0.010
Amygdala							None
Hypothalamus	R	Increased	10	0	–4	2	0.051
Anterior cingulate cortex	Midline	Increased	0	24	22*	33	0.030
Hippocampus	R	Increased	28	–30	–12	9	0.075
Dorsolateral prefrontal cortex							None
BA 10							None
BA 6							None
Inferior precentral gyrus							None
Inferior postcentral gyrus	R	Decreased	66	–12	22	14	0.058

Notes: MNI coordinates in millimeter of the peak value in the cluster; $P < 0.001$ uncorrected.
* Peak in anterior middle cingulate gyrus.
Abbreviations: BA, Brodmann area; L, left; *P*-FWE-corr, family-wise error-corrected; R, right; ROI, region of interest.

TABLE 2.
Family-wise Error-corrected Region of Interest Results for the "Overt Sentence Reading" Task Pre- Versus Posttreatment (ie, Session 1 vs. Session 2, All Contrasts vs. Rest Condition)

ROI	Side	Activation: Increased/ Decreased (Pre vs. Post)	MNI Coordinates			Cluster Size (in Voxels)	*P*-FWE-corr
			x	*y*	*z*		
Periaqueductal gray	Midline	Increased	0	–26	–10	47	0.002
Amygdala	R	Increased	26	–6	–16	2	0.048
	R	Increased	16	–2	–22	2	0.048
	R	Decreased	16	–4	–16	9	0.021
	L	Decreased	–18	–8	–14	6	0.029
Hypothalamus	L	Increased	–12	–10	–6	4	0.039
	R	Decreased	8	–6	–12	12	0.015
	L	Decreased	–8	2	–8	5	0.034
Anterior cingulate cortex	L	Increased	–6	32	–12	188	0.0001
Hippocampus	L	Increased	–22	–28	–8	55	0.004
	L	Increased	–20	–14	–22	32	0.015
	R	Decreased	24	–16	–14	20	0.032
Dorsolateral prefrontal cortex	L	Increased	–28	52	32	54	0.019
BA 10	L	Increased	–12	42	–8	118	0.001
	R	Increased	12	48	–10	104	0.002
BA 6	L	Increased	–48	–10	46	244	0.0001
	L	Increased	–16	–2	76	145	0.001
	R	Increased	32	–6	44	69	0.021
	L	Increased	–10	10	50*	51	0.047
Inferior precentral gyrus	L	Increased	–48	–12	36†	91	0.002
	L	Increased	–50	6	34	46	0.011
	R	Increased	54	–6	36	42	0.014
Inferior postcentral gyrus	L	Increased	–48	–14	36	181	0.0001
	R	Increased	58	–10	34	199	0.0001

Notes: MNI coordinates in millimeter of the peak value in the cluster; $P < 0.001$ uncorrected.
* (Pre-)supplementary motor area.
† Laryngeal motor cortex.
Abbreviations: BA, Brodmann area; L, left; *P*-FWE-corr = family-wise error-corrected; R, right; ROI, region of interest.

in many cases of pMTD) would satisfy the DSM-5 diagnostic criteria of conversion disorder. Therefore, for comparison purposes, in the following section, we explore an expanding literature on the neurobiological foundations of motor conversion disorders (MCDs) to guide our discussion.

Parallels with studies on patients with MCD

Patients with MCD differ functionally from healthy controls in brain areas related to negative emotion regulation, motor initiation and execution, and motor inhibitory processes.[54–56] A meta-analysis of studies proposed a core network that includes the dlPFC, medial PFC (mPFC), superior frontal gyrus, insula, amygdala, and aMCC.[54] In our case study, we found greater activation pre- versus posttreatment in all ROIs during overt sentence production, that is, limbic (PAG, amygdala, hypothalamus, hippocampus), mPFC (ACC/MCC, BA 10), dlPFC, cognitive-motor ([pre-]SMA), as well as premotor and inferior sensorimotor cortex (including the laryngeal motor cortex).

Heightened BOLD activations in the amygdala in patients with MCD, particularly heightened amygdala-SMA functional connectivity, is a recurring theme based on a variety of experimental paradigms including visual emotional stimuli, stressful memories, and action selection tasks.[54,57–59] Recently, Hassa et al[55] proposed that their study in patients with MCD and hemiparesis provided the first evidence of a direct mechanism linking altered negative emotion processing and motor control networks, specifically motor inhibitory networks. The study showed that left amygdala hyperactivity only occurred during combined emotional stimulation and passive wrist movement on the affected side (visual negative stimuli), and that functional connectivity was heightened between the left amygdala and right (pre-)SMA as well as subthalamic nucleus.

In our data, activation in the right amygdala and left (pre-)SMA was increased pre- compared with posttreatment for the complex speech production condition but not for simple repeated vowel productions. The hemisphere of peak activations in the amygdala and SMA varied in other studies of MCD with a mix of left and right.[55,58,60,61] The amygdala is well known for processing fear but is more generally involved in the evaluation of affective stimuli[62] with potential consequences for autonomic responses and action tendencies.[63] The amygdala-PAG circuit can freeze behavior, but the amygdala's "braking" action can also be shifted to adaptive fight-or-flight responses, for example when the ventromedial PFC and ACC intervene.[64] Thus, top-down control of amygdala-PAG activity is important to keep motor defense mechanisms in check.[58,64] The hyperactivity of the PAG

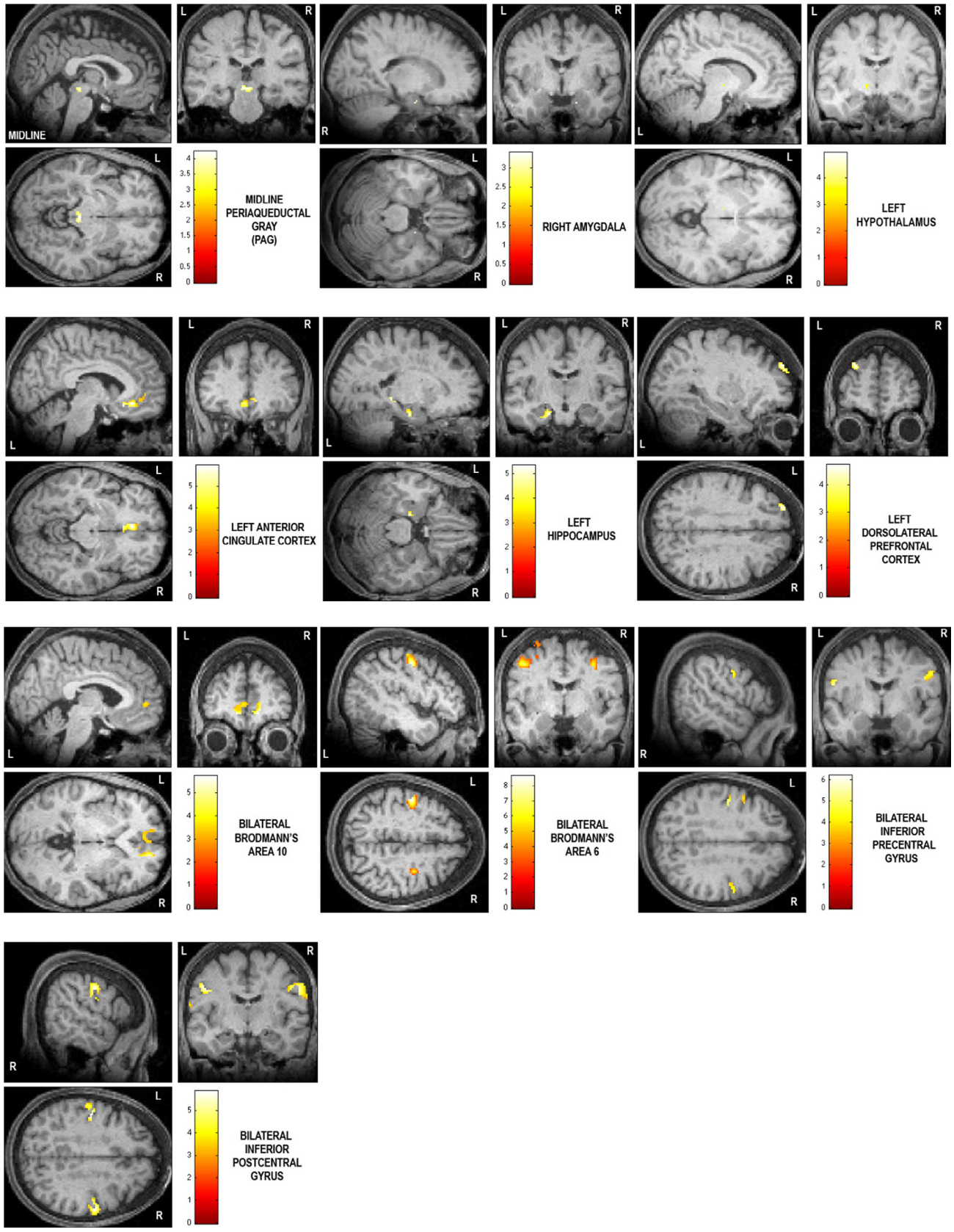

FIGURE 2. Blood-oxygenation-level dependent (BOLD) activations for all regions of interest for the "overt sentence reading" task pre- versus posttreatment (ie, session 1 vs. session 2, all contrasts vs. rest condition). Statistical maps have been thresholded at $P < 0.001$, uncorrected, with cluster sizes chosen to produce $P < 0.05$ for the cluster, corrected. The three-plane images, one set for each ROI, indicate the location and extent of clusters of activations with greater BOLD signals pre- compared with posttreatment. In the color bar, each color represents the uncorrected voxelwise t-statistic that describes the strength of the activation at each voxel. Regions colored white-yellow-orange show areas more active during pre- compared with posttreatment, with white indicating the area of strongest activation.

observed by Aybek et al[58] and in our case study underscores the crucial role of the limbic system in disrupting behavior, including vocal behavior given the existence of a limbic vocal pathway for emotional vocalizations. Meta-analyses of emotion networks have shown that the PAG co-activates with the dorsomedial PFC, which, in turn, co-activates with the amygdala.[62]

Connections with the SMA are instrumental in modulating action. The SMA plays an important role in motor initiation[65,66] and the pre-SMA in behavioral energization and inhibition.[67] The SMA, but not pre-SMA, has direct connections to the primary motor cortex[68] but more interestingly both have "hyperdirect" connections to the subthalamic nucleus enabling rapid response inhibition.[55,65,68] The subthalamic nucleus and (pre-)SMA are components of a braking system, which centers on the right lateralized inferior frontal cortex.[69] Thus, this direct access of the amygdala to components of the motor inhibition network is intriguing in MCD and likely pMTD. Voon et al[59] suggested that previously learned and mapped MCD representations may be facilitated by heightened amygdala-SMA connectivity that is inadequately counteracted by prefrontal top-down regulation of motor control. Further, Aybek et al[58] found a failure of habituation and sensitization in the amygdala in individuals with MCD, which may increase a person's vulnerability to somatic symptoms. Next, the role of prefrontal and cingulate activity will be discussed in greater detail.

Prefrontal (BAs 9/46, BA 10) and cingulate activity (ACC, MCC) are also commonly linked to conversion symptoms. The dlPFC is involved in top-down cognitive control, affective working memory, and emotion and action regulation, and BA 10 in self- and conflict evaluation.[68,70] The dlPFC connects with the SMA, ACC, and MCC. Dysfunctional prefrontal and cingulate regulation may facilitate inhibitory processes leading to MCD[54,58,59,71] and also mutism as shown in a case study by Bryant and Das.[60] The ACC fulfills a regulatory role with respect to limbic regions and may inhibit negative processing,[68] whereas the aMCC is involved in conflict monitoring, willed action, and action selection.[68,72] Importantly, the aMCC is connected with the primary motor cortex, premotor areas, dlPFC, amygdala, hypothalamus, and PAG.[68] Consistent with widespread limbic-motor connections, some studies suggested that ACC overactivity played a role in MCD,[58,60,71] but other studies could not confirm reliable overactivation of the cingulate cortex.[55,59]

Thus, although differences exist between our case study findings and the MCD literature, we did identify similar patterns of limbic-motor activations that could potentially mediate laryngeal motor inhibition or dysfunction in pMTD considering that the limbic system may interface with the laryngeal motor cortex. Our patient showed overactivity in all brain areas of the proposed core network underlying MCD (dlPFC, mPFC, superior frontal gyrus, insula, amygdala, aMCC; except insula, which was not an ROI) when she was symptomatic, that is, moderate-to-severely dysphonic. However, activity in the mPFC and amygdala is not essential for speech production, and heightened amygdala activation may instead indicate sensitization and elevated risk of dysfunctional limbic-motor interactions and pMTD. In fact, research by Davidson[63] on affective style showed that high basal amygdala activity coupled with inadequate response tendencies and top-down regulation is considered a sign of a nonresilient dispositional affective style and decreased well-being. Of note, the brain circuit for affective style (dlPFC, ventromedial PFC, orbitofrontal cortex, amygdala, hippocampus, ACC, insula) largely overlaps with the network underlying MCD. To guide the reader, Figure 3 outlines relevant limbic-motor pathways with an emphasis on currently known connections with the laryngeal motor cortex in the ventral sensorimotor cortex.

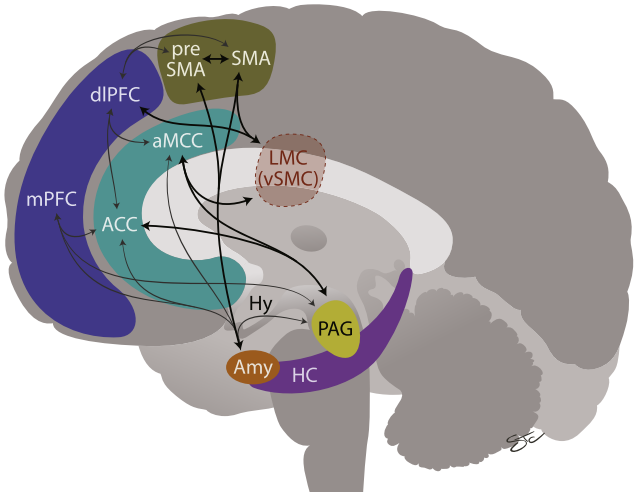

FIGURE 3. Schematic representation of connections between limbic and motor regions that may underlie dysregulated voice production in primary muscle tension dysphonia. The connections are not meant to be exhaustive but focus on the most relevant pathways based on the current literature. The weighted arrows highlight the connections of the laryngeal motor cortex, the PAG-ACC circuit for emotional vocalization, and amygdala-SMA connectivity. ACC, anterior cingulate cortex, aMCC, anterior middle cingulate cortex; Amy, amygdala; HC, hippocampus; Hy, hypothalamus; dlPFC, dorsolateral prefrontal cortex; LMC, laryngeal motor cortex; mPFC, medial prefrontal cortex; PAG, periaqueductal gray; (pre-)SMA, supplementary motor area; vSMC, ventral sensorimotor cortex.

Parallels with studies of patients with mutism, functional aphonia, and pMTD

Neuroimaging studies of patients who have received the diagnostic label of "pMTD" are extremely sparse. However, an fMRI study by Bryant and Das[60] did investigate a patient with "hysterical mutism" diagnosed with conversion disorder before and after successful psychotherapy by using speaking of the alphabet as stimuli. The interval between scans was approximately 7 months. The patient's history revealed that her disorder evolved from dysphonia to aphonia, and eventually even whispering was not possible, leaving the patient with a diagnosis of mutism. According to the patient, singing remained intact; however, singing was not readily elicited in therapy, but karaoke tasks eventually led to therapy success. Before therapy, BOLD activations were greater in the bilateral inferior frontal gyrus (IFG), bilateral MCC, and right amygdala than after therapy. After therapy, BOLD activations were greater in the right dorsal IFG than pretreatment. Functional connectivity analysis showed that no IFG connec-

tivity was observed with the target regions ACC and amygdala pretreatment. However, in the posttreatment condition, bilateral IFG showed negative connectivity with bilateral amygdala and positive connectivity with the ACC. Thus, the authors concluded that pretreatment activity in potential inhibitory networks was elevated and that connectivity results posttreatment indicated successful regulation of anxiety networks.

Perhaps closest in similarity to our case study, Spengler et al[73] recently published a brief report of two female patients with "functional" (aka psychogenic) aphonia who were scanned before and after successful circumlaryngeal therapy on the same day and compared with two healthy controls. The experimental paradigm involved emotional scenes and facial emotions, but *did not* require the participants to phonate. The focus was on assessing the amygdala-prefrontal circuit. Patients showed increased BOLD activations in the mPFC and decreased activations in the amygdala pre- compared with posttreatment. Functional connectivity analyses used the seed regions lingual gyrus, amygdala, and mPFC. Increased connectivity was observed between the amygdala and mPFC (area involving pre-SMA and aMCC) when patients were symptomatic, which paralleled other research in patients with MCD as discussed previously. The authors concluded that prefrontal top-down control of emotions became excessive and dysfunctional, leading to aphonia. Interestingly, amygdala activity was decreased in patients before therapy in this study. The discrepancy may be related to the different experimental tasks, which did not require the participants to vocalize or speak, and their specific cases of functional aphonia with a history of severe emotional and psychosocial stress, whereas our patient was diagnosed with moderate-to-severe pMTD without evidence of severe psychological distress.

Finally, a recent fMRI study of a group of middle-aged women with pMTD of mixed severity and no neurologic or psychiatric history used the simple task of comfortable vowel production to investigate neural differences between patients and vocally healthy controls.[74] Compared with healthy controls, patients with MTD had greater BOLD activations in the bilateral IFG, right middle frontal gyrus, right superior frontal gyrus, left lingual gyrus, bilateral insula, bilateral cerebellum, and PAG and lower activations in the right posterior cingulate gyrus, bilateral middle temporal gyrus, and right superior temporal gyrus. Notable is the greater activity in the inferior, middle, and superior frontal gyri and PAG, which was also seen in our case study, but the absence of significant amygdala activity. Our patient had moderate-to-severe pMTD. This raises the frequently debated question if pMTD and functional aphonia exist on a continuum or are distinct in their pathophysiology.[75,76] Some authors warn that distinctions must be made between aphonia and dysphonia to prevent overestimation of the role of psychological factors in "dysphonia."[77] Whether these vocal conditions simply represent quantitative differences along a single continuous dimension, for example, laryngeal and extralaryngeal muscle tension, or are categorically and etiologically unique, is open for debate.

Taken together, our investigation adds to the emerging literature on the neural correlates of pMTD and functional aphonia. Our research distinguishes itself from other studies by invoking speech during brain imaging pre- and posttreatment, thus allowing the detection of perturbations in well-described vocalization and speech networks. We observed increased activations especially during speech production in areas involved in the freeze response to fear (PAG), emotion processing (amygdala, hypothalamus, hippocampus), self-awareness (BA 10), top-down emotion regulation (dlPFC, mPFC), conflict monitoring and initiation of behavior (ACC, MCC), and premotor and motor control (SMA and sensorimotor cortex). In contrast with syllable productions, speech production also engages prefrontal and cingulate areas such as the ventro- and dorsolateral PFC, MCC, and posterior cingulate cortex,[38,46] a pattern that was confirmed in our data. Comparing syllable and speech production revealed differences not only in prefrontal engagement but also in cingulate activity where peak activation was in the aMCC for syllables but subgenual ACC for speech production. ACC/MCC activation has been variable in previous studies of phonation and was expected to be less likely in syllable than speech production because emotionality shapes prosody and vocalizations in speech.[32,41,78–80] In particular, the overactivation of the subgenual ACC, an undisputed affective subdivision of the cingulate cortex, coupled with PAG overactivity during speech production underscores the role of emotion processing in our case of pMTD. PAG activation and connectivity was previously documented in studies of vocalization and speech production in vocally healthy individuals,[41,78] yet the multifaceted region's significance must be further explored. The impact of PAG on voice production may be significant given its prominent role in the limbic system (ie, mediating the freeze response through the amygdala) and the option to interface with vocalization (ie, triggering and intensifying vocal responses).

Parallels with the Trait Theory

A hyperactive BIS is central to the "Trait Theory" of pMTD and is hypothesized to contribute to laryngeal motor inhibition. Our findings are compatible with overactivation of neural regions typically associated with the BIS (cingulate cortex, amygdala, hypothalamus, PAG) and motor inhibition networks (eg, [pre-]SMA) along with the dlPFC and mPFC. Our patient activated limbic and frontal structures that could reflect a possibly conditioned aberrant vocal motor response to previous attempts to speak out as postulated by the Trait Theory. Another pathway however proposed by the Trait Theory occurs when an individual may exhibit selective internal and external hypervigilance for potential threats.[16] Minor laryngeal sensory changes may be perceived as novel and threatening leading to laryngeal inhibition, which could be relevant in this case as the patient reported that her voice problems started after a sinus infection. The PAG, hypothalamus, amygdala, and ACC are limbic system structures involved in emotion regulation and in particular identification of threat signals but also novelty. In fact, these areas form a hierarchy in the BIS and determine avoidance or approach behaviors.[25] The activation of these brain areas and their links to motor loops is essential to interrupt ongoing motor activities. The hyperarousal and activity of these structures may represent an adaptive response to threat, which becomes

dysfunctional in pMTD. This may trigger an analog of the freeze response in pMTD even during nonemotional, propositional speech behaviors resulting in partial or incomplete suppression of vocalization.

It is important to recognize however that the term "inhibition" has been used to refer to a variety of psychological and behavior processes through which ongoing behavior is stopped. In the BIS framework, motor inhibition is a behavioral outcome following attention to a cue for potential threat or punishment. However, in the cognitive neurosciences literature, inhibition typically refers to a controlled process through which a person actively inhibits a response. An initial bottom up alerting to response-relevant cues may be associated with a slowing or stopping of ongoing action (vocalization) mediated by the BIS, which is then followed by an intentional top-down withholding of a response. From our single case study, it is impossible to distinguish between these two processes which could both interfere with voice. Thus, heightened input from limbic regions combined with dysfunctional top-down control from higher order prefrontal regions may interfere with laryngeal motor preparation, initiation, and execution thereby contributing to disordered voice in pMTD.

Our finding of PAG activation appears to be a common denominator across multiple literatures that examine not only the neural correlates of voice and speech production[41,78] but also personality and voice,[49] motor conversion disorders,[58] and recently pMTD.[74] The specific role of the PAG in the pathophysiology of pMTD deserves further attention considering that the PAG-ACC link also regulates emotional vocalizations and the PAG has a gating function for vocalization.[31] The potential power play between limbic and neocortical regions during the act of speech production needs to be better understood. Although in MCD a failure of top-down regulation of limbic overactivity may be a leading factor for suppressed motor output, in pMTD, brain regions involved in motor planning or execution may be overactive in attempts to rescue voice production from conflicting limbic input, even if dysregulated or hyperfunctional voice production is the final outcome. The interpretation of increased BOLD signals is complicated because they may signify either excitatory or inhibitory neuronal activity, that is, response facilitation or inhibition. Thus, the interpretation is linked to the pre- versus posttreatment experimental design and behavioral measures, suggesting that widespread overactivity pretreatment signified dampened or inhibited energization and planning for vocal output despite motivation and attempted motor output for overt speech.

Finally, the clinical literature is replete with evidence to support that direct symptomatic therapy for pMTD can often produce rapid and dramatic improvement in voice production. It seems that some patients with pMTD may be locked in an aberrant default sensorimotor neural program involving structures within the distributed BIS. In our case study, successful behavioral intervention using manual laryngeal reposturing (and the associated external perturbation of the larynx during voicing) appeared to disrupt and eventually deactivate several components of this dysfunctional neural pattern, thereby producing a shift in activation patterns and with it normal vocalization.[23] Recovery of normal voice then likely rendered unnecessary any cognitive and emotional preoccupation with the sensorimotor functioning of the larynx or monitoring thereof. Thus, although the precise mechanism of action underlying this apparent resetting of the neural signature for normal voice is unclear, the treatment seemingly disrupted limbic-motor interactions or linkages that may have maintained, or perpetuated the pMTD.

Limitations and future directions

Limitations of our single case study include (1) limited generalizability of the results and lack of control participants. pMTD is a broad diagnostic category likely including some degree of etiologic heterogeneity and related intersubject variability. A larger cohort of patients with pMTD needs to be investigated before and after successful therapy (compared with vocally normal controls) to place our results in context. Likewise, pre- and posttreatment formal testing of psychological functioning of the pMTD cohort and controls could be instructive. (2) Our fMRI results are based on a comparison of activation patterns before and immediately after successful voice rehabilitation. In the future, it would be worth exploring whether such changes in brain activation are maintained in the long term. Thus, additional studies should explore not only the immediate effects of voice normalization, but also examine the stability of such changes posttreatment. (3) Although the choice of ROIs allowed hypothesis-driven research, the evolving research on MCD and brain networks underlying voice and speech production will lead future research to include an updated set of ROIs. Our results based on BOLD fMRI signals speak for themselves, yet functional connectivity analyses may provide another explanatory level for the seemingly dysfunctional limbic-motor interaction underlying pMTD. The choice of seed regions will have to be hypothesis-driven as well and the PAG may be a good candidate among other limbic regions and the laryngeal motor cortex. (4) It is important to acknowledge that the aberrant neural activations (that we identified in our patient with a year-long history of dysphonia) may be different from those patterns that were present at the onset (ie, precipitating vs. perpetuating neural patterns). (5) Finally, we acknowledge the possibility that the changes observed in neural patterns from scanner session 1 to scanner session 2 may have been a function of time, changing emotional state, or familiarity with the vocalization task.

CONCLUSIONS

We presented fMRI data for a patient with pMTD before and after successful voice therapy that strongly suggest that a dysfunctional limbic-motor interaction perpetuated the voice disorder. Brain activity pretreatment was characterized by hyperactivity of regions involved in limbic-motor pathways compared with posttreatment. The hyperactivity was especially expansive during overt sentence reading in contrast with a simple voice task and encompassed a network of limbic, prefrontal, and sensorimotor ROIs, suggesting a role for emotion, arousal, or inhibitory mechanisms to interfere with voluntary control over phonation contributing to disordered voice in pMTD. Clear parallels with the literature on neural networks underlying motor conversion

disorders leads to the hypothesis that heightened PAG-amygdala-SMA activity and functional connectivity coupled with dysfunctional prefrontal top-down control leads to disordered vocal control for speech production in patients with pMTD. Further, the data are compatible with the Trait Theory of voice disorders wherein the BIS plays a central role in mediating the laryngeal dysfunction and placing an additional focus on the role of heightened PAG activity. Finally, our findings confirmed that one session of successful voice therapy using manual circumlaryngeal techniques was associated with a shift in brain activations underlying voice and speech production.

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