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Cortical Networks for Speech Motor Control in Unilateral Vocal Fold Paralysis

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Objective: To evaluate brain networks for motor control of voice production in patients with treated unilateral vocal fold paralysis (UVFP).

Study Design: Cross-sectional comparison.

Methods: Nine UVFP patients treated by type I thyroplasty, and 11 control subjects were compared using magnetoencephalographic imaging to measure beta band (12–30 Hz) neural oscillations during voice production with perturbation of pitch feedback. Differences in beta band power relative to baseline were analyzed to identify cortical areas with abnormal activity within the 400 ms perturbation period and 125 ms beyond, for a total of 525 ms.

Results: Whole-brain task-induced beta band activation patterns were qualitatively similar in both treated UVFP patients and healthy controls. Central vocal motor control plasticity in UVFP was expressed within constitutive components of central human communication networks identified in healthy controls. Treated UVFP patients exhibited statistically significant enhancement (P < 0.05) in beta band activity following pitch perturbation onset in left auditory cortex to 525 ms, left premotor cortex to 225 ms, and left and right frontal cortex to 525 ms.

Conclusion: This study further corroborates that a peripheral motor impairment of the larynx can affect central cortical networks engaged in auditory feedback processing, vocal motor control, and judgment of voice-as-self. Future research to dissect functional relationships among constitutive cortical networks could reveal neurophysiological bases of central contributions to voice production impairment in UVFP. Those novel insights would motivate innovative treatments to improve voice production and reduce misalignment of voice-quality judgment between clinicians and patients.

Key Words: Unilateral vocal fold paralysis, cortical networks, speech motor control, pitch perturbation, voice quality.

Level of Evidence: 3b

INTRODUCTION

Unilateral vocal fold paralysis (UVFP) patients expertly treated by type I thyroplasty and adjunctive speech therapy may still be troubled by perception of inadequate voice quality. This outcome can be frustrating to clinicians and patients alike. Based on clinician-centric laryngeal endoscopic and auditory perceptual outcome measures, clinicians will typically conclude intervention to be successful.1–3 However, patient-centric self-reported evaluations of voice quality may differ from clinician-centric assessments, accounting for the relatively modest correlation between the two judgments of outcome in treated UVFP.4–7 Clinicians may believe that posttreatment voice quality was satisfactorily achieved and not much more can be done, but some patients will still feel their desired voice quality has not yet been fully reached.

Incomplete acceptance of voice outcome in expertly treated UVFP may originate from peripheral and central sources. In the setting of optimized peripheral intervention, understanding changes to central auditory, vocal motor control, and judgment of voice-as-self networks integral to voice production may provide new insights that would motivate innovative brain-based therapies. The ultimate goal of this cortical networks approach is to further improve voice quality and narrow the gap in voice quality judgment between clinicians and patients.

We hypothesize that, despite expert peripheral intervention in UVFP, cortical networks important for the control of voice production are abnormal. In a recent study by Naunheim et al. (doi: 10.1002/lary.27680), UVFP patients treated by type I thyroplasty exhibited a 32.5% reduction in compensatory vocal responses to pitch
feedback perturbations compared to healthy controls. Treated UVFP patients also showed a higher rate of abnormal central auditory processing, particularly for time-compressed speech and sentences in noise. Those data suggest that impaired compensatory responses to feedback perturbations in UVFP may be arising from changes in brain networks that subserve vocal motor control and auditory feedback.

We further hypothesize that misalignment of voice quality assessment between clinicians and treated UVFP patients arises from judgment of restored voice by patients as not originating from themselves, based on self versus non–self categorization. A neuroimaging biomarker for the categorization of self versus non-self,12–14 including self-generated speech,11 is medial prefrontal cortex activity. We have recently demonstrated that a pitch perturbation task can be used to probe not only vocal motor control but also to examine medial prefrontal cortex activity in relationship to categorization of written words as originating from self versus non-self.12 In the context of voice quality as a form of body dysmorphic disorder,13 treatment differences of perceived appearance productions by treated UVFP patients may be analogous judgments on non-self. In the context of voice quality as a form of self versus non-self,12 categorization of written words as originating from self versus non-self,12 is medial prefrontal cortex activity. We have recently demonstrated that a pitch perturbation task can be used to probe not only vocal motor control but also to examine medial prefrontal cortex activity in relationship to categorization of written words as originating from self versus non-self.12

The primary objectives of this pilot study are to identify the neural substrates of auditory feedback processing, vocal motor control, and judgment of voice-as-self by measuring activation patterns of brain networks during a pitch perturbation task in UVFP treated by type I thyroplasty. We examine the beta (12–30 Hz) cortical rhythm noninvasively using magnetoencephalographic imaging (MEGI), a robust neurophysiological measure of cortical activity. We report on MEGI findings by contrasting treated UVFP patients and healthy controls.

MATERIALS AND METHODS

Twenty subjects were enrolled in the study. Nine were UVFP patients, and 11 were healthy controls. The study was approved by the institutional review board, and all participants gave informed consent. Subjects were included if they were English speakers between 20 and 80 years of age, had a clinically confirmed paralysis (> 12 months of paralysis) or known intraoperative transection of the recurrent laryngeal nerve, and had treatment by type I thyroplasty with or without arytenoid adduction for a minimum of 3 months prior to study participation. To ensure stable voice outcomes, all treated UVFP patients had satisfactory surgical outcomes as evidenced by complete glottal closure on videolaryngostroboscopy.14 Prior laryngeal trauma, history of laryngeal cancer or radiation, high vagal injury evidenced by palatal or pharyngeal weakness, and contraindication to undergo neuroimaging studies were the key exclusion criteria.

Pitch Perturbation Task

The pitch perturbation task has often been used to examine how auditory processing governs the control of phonation. Subjects produce an immediate corrective response in their ongoing vocal production following unexpected perturbations of the pitch of their auditory feedback.15–17 The experiment consisted of 120 phonation trials. In each trial, subjects produced a sustained utterance of the vowel sound /a/, starting when a green dot appeared on a projection screen directly in their line of sight and terminating when this dot disappeared (approximately 2.4 seconds). Their vocal output was picked up by a microphone, passed through a feedback alteration system, and fed back to them via earphones, allowing them to have immediate auditory feedback of their phonation. The feedback alteration system was a vocoder program running on a computer that could alter the pitch of the incoming speech in real time (12 ms feedback delay). The perturbation raised or lowered pitch by 100 cents (1/12 of an octave or equivalent to the difference between adjacent keys on a piano) and lasted 400 ms. To minimize predictability, the perturbation started between 200 ms and 500 ms after voice onset, and direction of the perturbation was distributed across the trials in an unpredictable pattern.

Vocal production was recorded throughout the experiment. From the recordings for each subject, the raw audio data for each trial was first analyzed for pitch time course using an autocorrelation-based tracking method.14 Trials with pitch tracking errors or incomplete utterances were excluded. An analysis interval of 1,200 ms (from 200 ms before to 1,000 ms after perturbation onset) was extracted and converted from Hertz to cents using the formula: cents = 100 × \(\log_2(\text{pitch frequency(Hz)}/\text{mean pitch frequency of preperturbation baseline(Hz)})\).18 Behavioral responses to both upward and downward pitch perturbations were combined by flipping the polarity of the responses to upward perturbations, making all compensatory responses positive. Perturbation response time courses were analyzed using a linear mixed effects model (LMM) (SAS 9.4 Proc MIXED, SAS Institute Inc., Cary, NC) with group (UVFP, control) as the main categorical factor, subject as the fixed effect, and time and trial epoch as repeated measures.

Magnetoeencephalographic Imaging

Neural activation data were collected during this pitch feedback perturbation task. Magnetic fields were recorded in a shielded room using a whole-head 275 axial gradiometer MEGI system (MEG International Services Ltd., Coquitlam, BC, Canada) at a bandwidth of 1 to 70 Hz and a sampling rate of 1,200 Hz. Three fiducial coils (nasion, left preauricular, and right preauricular) were placed to localize head position relative to the sensor array and coregistered with the structural magnetic resonance imaging (MRI) scan to generate head shape. Head localization was performed at the beginning and ending of each task block to register head position and measure head movement during the task. Third-order gradient noise filters were applied to the data, and correction for direct-current-offset was based on the whole trial. Noisy sensors and trials with artifacts (head movement, eye blinks, or saccades) were eliminated prior to analysis. A 3-Tesla MRI scanner (Discovery MR750, GE Medical system, Waukesha, WI) was used to acquire high-resolution structural T1-weighted fast spoiled gradient echo bra volume images (120 axial slices, field of view = 512 × 512 mm2, repetition time = 7,232 ms, echo time = 2.78 ms, in-plane voxel dimensions 0.5 × 0.5 mm2, slice thickness = 1.5 mm) to reconstruct MEGI data in source space. Subject-specific anatomical MRIs were spatially normalized to a standard Montreal Neurological Institute (MNI) template using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), with the resulting parameters applied to each subject’s source space reconstruction. MEGI sensor data were marked at perturbation onset and compared to a baseline period prior to the cue for vocal production. Channels and trials with activity consistently >1.5 pT were discarded. A forward model lead field describing the magnetic field strength at each sensor arising from a dipole source at each voxel was computed using a multiple local spheres spherical volume conductor model.17 Spatiotemporal estimates of neural sources were
then generated using a time–frequency optimized adaptive spatial filtering technique implemented in the Neurodynamic Utility Toolbox for MEG (http://nutmeg.berkeley.edu) to localize induced changes in oscillatory power. A tomographic volume of source locations (voxels) was computed through an adaptive spatial filter (5-mm lead field) that weighs each location relative to signals of the MEG sensors.17 Source power at each location was derived through a noise-corrected pseudo-F statistic, expressed in logarithmic units (decibels), comparing signal magnitude during an active experimental time window to a baseline control window.17

Difference in neuronal activity at each pitch perturbation time window in each voxel relative to the baseline period was evaluated statistically using nonparametric randomization tests in accordance to published methods.17–19 Statistical maps that were reported here were thresholded at \( P < 0.05 \) and corrected for multiple comparisons using a cluster-correction threshold of 18 voxels. We examined a robust neurophysiological measure of cortical activity, the beta (12–30 Hz) cortical rhythm,\textsuperscript{20} for which the power decreases over sensory and motor brain regions during motor behaviors.\textsuperscript{21–23} We report task-induced power fluctuations in beta band neural oscillations that were time-locked to perturbation onset, relative to a pre-cue baseline in 100 ms epochs, from 0 ms to 525 ms.

**RESULTS**

**Demographics and Clinical Outcome Measures**

The two cohorts consisted of nine UVFP patients and 11 healthy controls (Table I). The etiologies of UVFP were inhomogeneous: four surgical transection, four idiopathic, and one lung cancer. Of the nine UVFP patients, there were three men and six women. Of the 11 controls, there were eight men and three women. Handedness was strongly right in both cohorts, with one missing datum in each. Side of nerve injury and concurrent arytenoid adduction were also inhomogeneous in the UVFP cohort (Table I). The mean age in years (standard deviation) of each cohort was 54.2 (14.4) for UVFP patients and 46.0 (16.8) for healthy controls (\( P = 0.3 \)). At least 3 months prior to enrollment, all UVFP patients were treated by type I thyroplasty with a silastic implant; two of nine had concurrent arytenoid adduction (Table I). The hearing profiles of both cohorts showed normal thresholds from 0.5 kHz to 8 kHz in both ears, with the exception of one subject in each cohort who had mild high-frequency hearing loss (> 25 dB). To ensure stable voice and complete glottal closure, all subjects were examined by our laryngologist (K.C.Y.) and speech language pathologist (S.L.S.). With documented postoperative glottal competence in all treated UVFP patients, regression analysis of the clinician-centric Consensus Auditory-Perceptual Evaluation of Voice\textsuperscript{24–26} and patient-centric Voice Handicap Index\textsuperscript{27} showed a correlation coefficient = 0.65 (\( P < 0.01 \)).

**Pitch Perturbation and MEGI**

Whole-brain task-induced beta band activation patterns were qualitatively similar in both treated UVFP patients and healthy controls. Cortical plasticity of vocal motor control in UVFP was primarily expressed in

<table>
<thead>
<tr>
<th>Study Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Handedness</th>
<th>Side of Paralysis</th>
<th>Arytenoid Adduction</th>
<th>Etiology</th>
</tr>
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<tbody>
<tr>
<td>U1</td>
<td>Male</td>
<td>48</td>
<td>NR</td>
<td>Right</td>
<td>No</td>
<td>Idiopathic</td>
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<tr>
<td>U2</td>
<td>Female</td>
<td>61</td>
<td>Right</td>
<td>Left</td>
<td>No</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>U3</td>
<td>Female</td>
<td>23</td>
<td>Right</td>
<td>Left</td>
<td>No</td>
<td>Thyroidectomy</td>
</tr>
<tr>
<td>U4</td>
<td>Female</td>
<td>78</td>
<td>Right</td>
<td>Right</td>
<td>Yes</td>
<td>Thyroidectomy</td>
</tr>
<tr>
<td>U5</td>
<td>Female</td>
<td>49</td>
<td>Left</td>
<td>Left</td>
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<td>Thyroidectomy</td>
</tr>
<tr>
<td>U6</td>
<td>Female</td>
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<td>Right</td>
<td>Left</td>
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<td>Idiopathic</td>
</tr>
<tr>
<td>U7</td>
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</tr>
<tr>
<td>U8</td>
<td>Female</td>
<td>55</td>
<td>Left</td>
<td>Left</td>
<td>No</td>
<td>Parathyroidectomy</td>
</tr>
<tr>
<td>U9</td>
<td>Male</td>
<td>60</td>
<td>Right</td>
<td>Right</td>
<td>No</td>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

NR = not recorded.
controls (Fig. 1). In a contrast between the two cohorts, 2128 Laryngoscope 129: September 2019 Naunheim et al.: Cortical Networks in UVFP − Left Hemisphere MNI Coordinates Anatomical Labels (Brodmann area) Time Window of Activation

Table II lists all the brain regions that show significant activation enhancement in induced beta band activity. The activation scale and statistics are derived from nonparametric permutation tests between the two cohorts, thresholded at $P < 0.05$, and corrected for multiple comparisons using a cluster-correction threshold of 18 voxels. Warmer colors indicate smaller $P$ values. L = left; R = right.

![Fig. 2. Treated unilateral vocal fold paralysis patients exhibit enhanced beta band activity of left auditory, left premotor, and both frontal cortical regions compared to healthy controls while performing compensatory vocal responses to pitch feedback perturbations.](image)

**DISCUSSION**

This study examined changes to brain networks mediating central auditory processing, vocal motor control, and judgment of voice-as-self using a pitch perturbation task in a cohort of expertly treated UVFP patients. The qualitative similarity of whole brain task-induced beta band activation patterns in treated UVFP patients and healthy controls demonstrates that cortical plasticity of vocal motor control in UVFP is primarily expressed in functional changes within constitutive components of central human communication networks identified in healthy controls. Following the onset of pitch feedback perturbations, UVFP patients have significantly enhanced activation or over-recruitment of auditory, premotor, and frontal regions. Those findings highlight interrelationships among sensory and motor, and judgment of voice-as-self network components engaged in voice production.

Enhanced beta oscillatory activity in the central auditory network occurs within the expected time window (< 300 ms) of cortical activation following pitch perturbation onset in healthy adults. Increased auditory cortical activity may reflect a state of exaggerated error detection for which UVFP patients are chronically detecting mismatches between the quality of their voice productions and internal predictions, thus effectively responding to their treated UVFP voice as ongoing frequency-shifted feedback perturbations. This state of constant response to perceived voice production errors by auditory cortex may tax cognitive resources and have negative consequences, namely, reduced capacity to process temporally compressed complex sounds and dissociate noise from signal for complex sound identification (doi: 10.1002/lary.27680). Furthermore, abnormal central auditory cortical function may be providing ineffective feedback signals to the vocal motor control network for corrective motoric action to extinguish prediction conflicts. In this scenario, improvement of auditory cortical function by central auditory processing disorder treatments may strengthen feedback signals to improve vocal motor control. Alternatively, auditory cortex may cease to provide error correction signals to the vocal motor control network altogether after an extended period of unresolved mismatches between voice productions and internal predictions. In this time-dependent alternative scenario, improvement of central auditory function is not expected to improve vocal motor control.

**TABLE II.**

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>MNI Coordinates</th>
<th>Anatomical Labels (Brodmann area)</th>
<th>Time Window of Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>$[-56.7, 3.3, 13.3]$</td>
<td>Precentral gyrus (6)</td>
<td>25–225 ms</td>
</tr>
<tr>
<td></td>
<td>$[-62.9, -24.6, -1.8]$</td>
<td>Superior temporal gyrus (22)</td>
<td>425–525 ms</td>
</tr>
<tr>
<td></td>
<td>$[-63.7, -10.6, -9.7]$</td>
<td>Middle temporal gyrus (21)</td>
<td>25–525 ms</td>
</tr>
<tr>
<td></td>
<td>$[-63.7, -12.2, -19.9]$</td>
<td>Inferior temporal gyrus (21)</td>
<td>25–525 ms</td>
</tr>
<tr>
<td></td>
<td>$[-31.1, 58.5, 22.0]$</td>
<td>Superior frontal gyrus (10)</td>
<td>25–225 ms</td>
</tr>
<tr>
<td></td>
<td>$[-42.7, 21.9, 52.8]$</td>
<td>Middle frontal gyrus (8)</td>
<td>25–425 ms</td>
</tr>
<tr>
<td>Right</td>
<td>$[32.4, 59.2, -17.6]$</td>
<td>Superior frontal gyrus (10)</td>
<td>25–525 ms</td>
</tr>
<tr>
<td></td>
<td>$[64, -21.6, -17.6]$</td>
<td>Middle temporal gyrus (21)</td>
<td>425 ms</td>
</tr>
</tbody>
</table>

Contrast between treated unilateral vocal fold paralysis and healthy control cohorts. Brodmann area in parentheses. MNI = Montreal Neurological Institute; ms = millisecond.
Enhanced beta oscillatory activity in premotor cortex, an integral component of the vocal motor control network, is associated with decreased compensatory responses to pitch perturbations in UVFP patients, despite demonstrated vocal production capacity to perform the task as well as healthy controls. Increased activity in this region critical to voice production planning may represent a state of constant search for vocal motor control actions to effect matching with unachievable internal voice production targets. Alternatively, increased activity in premotor cortex may represent an open loop state of the vocal motor control network, one lacking the modulating feedback signals that would reduce activity due to ineffective or loss of corrective signals from auditory cortex or subcortical structures.

Enhanced beta band oscillatory activity in frontal regions is consistent with judgment of voice-as-self network activity to categorize voice quality as self versus non-self. Misalignment of voice quality assessment between clinicians and treated UVFP patients may therefore arise from judgment of restored voice by patients as not originating from themselves. Our findings suggest a potential neuroimaging biomarker for identification of voice quality as originating from self. If validated, this objective tool may be used to monitor and customize treatments.

This exploratory study has several notable limitations. First and foremost, the two contrasted cohorts are relatively small. Future replication studies with greater numbers of subjects will be needed to extend and validate findings and to address covariate effects of handedness, side of vocal fold paralysis, impact of artrytenoid adduction, and etiology of injury, among others. Second, although unilateral vocal fold paralysis is viewed predominantly as a motor deficit, combined motor and somato-sensory deficits are possible because the recurrent laryngeal nerve also innervates the subglottis and pyriform sinus. The contribution of focal peripheral neuropathy on auditory pitch perturbation feedback responses is unknown and will require future investigations. Third, MEG does not detect deep brain activity as accurately as surface cortical activity; activity differences within the basal ganglia and other deeper structures may have been overlooked. Finally, time between onset of UVFP and thyroplasty is not controlled due to the relatively small cohort size.

CONCLUSION

This study in UVFP patients expertly treated by type I thyroplasty demonstrated increased activity in cortical networks engaged in auditory feedback processing, vocal motor control, and judgment of voice-as-self during voice production with perturbation of pitch feedback. This study further corroborates that a peripheral motor impairment of the larynx can affect central human communication networks. Future research to dissect functional relationships among the constitutive cortical networks could reveal neurophysiological bases of central contributions to voice production impairment in UVFP. Those novel insights would motivate innovative treatments to improve voice production and reduce misalignment of voice quality judgment between clinicians and patients.

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