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INTRODUCTION

Vocal production and reception systems are major components of the dynamic human sensorimotor communication loop. Normal function of peripheral and central structures may become disrupted due to primary impairment of either the sensory or motor limb of this loop.

Close coupling between the two systems is evident from studies that reveal how isolated injury of one system impacts function of the other. Humans with impaired hearing produce abnormal speech in intonation, pitch, and voice intensity despite unimpaired peripheral effector structures capable of producing normal speech. Conversely, monkeys with surgically induced permanent injury of the larynx that produce abnormal social communication calls demonstrate degraded auditory cortical neuronal responses to species-specific vocalizations and related frequency modulation sweeps despite unimpaired peripheral hearing, suggesting central auditory processing impairment. Such reciprocal interdependency of sensory and motor systems of the communication loop is therefore manifested as altered vocal production in hearing loss and degraded vocal reception in laryngeal injury.

Unilateral vocal fold paralysis (UVFP) is a clinical condition that occurs as a sequela of neck or chest surgery, idiopathic etiologies, malignant neoplasms, or cardiopulmonary conditions. UVFP is classically viewed as an isolated peripheral motor condition, without consideration for possible central motor and auditory consequences that may arise from communication loop interdependencies. A human communication research

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effort centered on UVFP would be both patient-focused and provider-receptive because some expertly treated patients will still fail to meet vocal production goals.\textsuperscript{6,8} Dysphonia arising from UVFP compromises communicative function\textsuperscript{9} and lowers quality of life.\textsuperscript{10,11} Developing innovative behavioral, psychometric, and neuroimaging evaluation tools would help to advance patient care.

For vocal motor control assessment, a powerful behavioral tool to probe vocal production responses to sensory feedback change is response to pitch perturbation. Here, the pitch of auditory feedback of the speaker’s own ongoing speech is perturbed unexpectedly. The speaker will typically compensate by changing vocal pitch output to offset perturbation to feedback input.\textsuperscript{12} Increases in feedback pitch will trigger decreases in vocal output pitch and vice versa. The pitch perturbation compensatory response measures how well an individual adjusts their pitch production in response to hearing subtle changes to their own voice. This exquisite self-monitoring action is instantaneous, subconscious, and ubiquitous, and quickly dampens as soon as feedback perturbation ends. The timing and magnitude of vocal responses to feedback perturbation are measures of vocal motor control performance that may be related to interactions of the motor system with auditory and somatosensory systems. For assessment of central auditory processing, validated audiological tests can be used, including those that measure speech intelligibility under conditions of temporal modification, signal compression, gap introduction, and noise addition in different configurations.\textsuperscript{13} Performance degradation on some or all of the aforementioned tests would be highly indicative of central auditory processing impairment.

In this pilot study, we address two objectives. We evaluate whether UVFP is accompanied by vocal motor control impairment by examining pitch perturbation response to a specific task. We also assess whether UVFP is accompanied by central auditory processing deficits by examining performance using standard audiological assays. We contrast a cohort of UVFP treated by type I thyroplasty against a cohort of healthy controls to measure differences in pitch perturbation response and susceptibility of central auditory processing performance degradation under temporal domain and noise addition challenges.

**MATERIALS AND METHODS**

The study was approved by the institutional review board. A total of 22 subjects enrolled in the study: 10 UVFP study patients and 12 healthy controls. Inclusion criteria for subjects with UVFP were age between 20 and 80 years, English-speaker, clinically confirmed paralysis > 12 months (mean in days (standard deviation (SD), range)) = 707 (364, 399–1209) or known intraoperative transection of the recurrent laryngeal nerve, and treatment with type I thyroplasty > 3 months (mean in days (SD, range)) = 887 (562, 125–1850) before study participation. All treated UVFP subjects had documented satisfactory surgical outcomes as evidenced by complete glottal closure on postoperative videolaryngostroboscopy.\textsuperscript{14–17} Exclusion criteria were high vagal nerve injury, prior laryngeal trauma, history of laryngeal cancer or radiation, and unwillingness or contraindication to undergo neuroimaging studies. All participants gave written informed consent.

**Clinical Voice Production**

Voice production quality was analyzed in three ways: subjective, perceptual, and instrumental. For subjective evaluation, study subjects completed the Voice Handicap Index (VHI), a 30-item validated self-report voice assessment instrument.\textsuperscript{18} For perceptual assessment, a senior speech language pathologist (S.L.S.) met with each subject and analyzed voice production using the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V).\textsuperscript{19} For instrumental voice analysis, we used the Analysis of Dysphonia in Speech and Voice, which is part of the Computerized Speech Lab (CSL), Model 4500 (Kay Pentax; Montvale, NJ). Laryngeal videostroboscopy examination (Olympus America; Center Valley, PA) was performed to confirm unilateral vocal fold immobility and to assess glottal competence.

**Vocal Motor Control**

Vocal motor control was assessed using a pitch perturbation task. This task has often been used to examine how auditory processing governs the control of phonation. In this task, subjects produce an immediate corrective response in their ongoing vocal production to unexpected perturbations of the pitch of their auditory feedback, often without knowledge of their corrective action.\textsuperscript{12} 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, which could alter the pitch of the incoming speech in real time (12 ms feedback delay). In each trial, the feedback alteration system briefly perturbed the auditory feedback subjects heard as they phonated. 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 pseudorandomly distributed across the trial.

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. Trials with pitch tracking errors or incomplete utterances were excluded (rejection rates: UVFP = 37%, control = 29%). 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: $\text{cents} = 100 \times \log_2(\text{pitch frequency(Hz)}) / \text{mean pitch frequency of preperturbation baseline(Hz)})$.\textsuperscript{20} Responses to both upward and downward pitch perturbations were combined into a single dataset by flipping the polarity of the responses to upward perturbations, making all compensatory responses positive.

Multidimensional pitch perturbation data in this study were comprised of a single dependent variable (magnitude of the compensatory response) and several independent variables (group, subject, time, and trial epoch). Variables were classified in the following manner: 1) categorical for group (UVFP, control), 2) fixed effect for subject, and 3) repeated measures for time and trial epoch. To ensure robust statistical analysis, we used a
Peripheral and Central Hearing

All subjects underwent pure tone audiometry to document peripheral hearing thresholds. This was performed using a clinical, high-frequency capable audiometer (Grayson Stadler GSI-61, Eden Prairie, MN) in a double-walled sound suite meeting current American National Standards Institute (ANSI) standards (ANSI S3.6-1996). Word recognition score was determined using the Northwestern NU-6 recognition test in quiet at presentation levels relative to the 2000 Hz threshold.22 A battery of central auditory tests was delivered. It consisted of the Gaps-in-Noise test23 (Auditec, St Louis, MO), Quick Speech-in-Noise24 (Etymotic Research Inc.; Elk Grove Village, IL), Quick Time Compressed Sentence Test and Quick Competing Speaker Sentence Test (Neurotone, Inc, Eden Prairie, CA),25 Revised Speech Perception in Noise Test,26 and Listening in Spatialized Noise–Sentences Task27 (Phonak, Warrenville, IL). Subjects wore Etymotic Research (ER-3A) insert earphones during testing. Normal versus abnormal determination on any particular central auditory test was based on normative values that provided cutoffs.

RESULTS

Demographics

Ten UVFP study patients and 12 healthy controls participated in the study. The mean age in years (SD) of each cohort was 55.2 (14.7) and 48.1 (18.0) years, respectively (P = 0.4). The UVFP cohort had three men and seven women, whereas the control cohort had eight men and four women. The etiologies of UVFP were surgical transection in five subjects, idiopathic in four subjects, and lung disease in one subject. All UVFP patients underwent unilateral type I thyroplasty with a silastic implant at least 3 months prior to enrollment. All subjects had stable voice and complete glottal closure, as determined by our laryngologist (k.c.y.) and speech language pathologist (s.l. s.). All study participants provided analyzable data for clinical voice production and central and peripheral hearing assessments. However, one UVFP subject failed to complete the vocal motor control task. This analysis was based on nine UVFP and 12 control subjects.

Clinical Voice Production

Subjective, perceptual, and instrumental outcomes were contrasted for the two cohorts (Table I). For subjective self-report vocal quality assessment, the VHI mean (SD, range) of the UVFP cohort was 31.6 (21.1, 8–64) and the control cohort was 3.3 (4.4, 0–13). Voice Handicap Index scores of 34, 44, and 61 have previously been associated with mild, moderate and severe dysphonia, respectively;18 by these measures, two subjects had moderate dysphonia and one had severe dysphonia. The UVFP cohort exhibited statistically significant (P < 0.05, t test) poorer voice quality on VHI. The VHI = 31.6 (21.1) voice outcome of the UVFP cohort in this pilot study was consistent with a recent literature review of 16 studies of voice outcome following unilateral vocal fold paralysis surgery, where VHI = 30.9 (11.2).28 For perceptual vocal quality rating by an experienced clinician, the CAPE-V mean (SD, range) was 29.6 (22.6, 0–83) for the UVFP cohort and 4.8 (11.3, 0–10) for the control cohort. The UVFP cohort was found to have statistically significant (P < 0.05, t test) poorer voice quality on CAPE-V. The CAPE-V = 29.6 (21.6) voice outcome of the UVFP cohort in this pilot study was consistent with a report on voice outcome in 35 consecutive study patients treated by office-based injection laryngoplasty for glottal insufficiency, 20 with either vocal fold paralysis or paresis, for which CAPE-V = 31.0 (21.9).29

Instrumental measures of voice production, however, did not reveal significant differences between cohorts, perhaps due to large variability within the UVFP cohort.

<table>
<thead>
<tr>
<th>Voice Production Measurements.</th>
<th>U1</th>
<th>U2</th>
<th>U3</th>
<th>U4</th>
<th>U5</th>
<th>U6</th>
<th>U7</th>
<th>U8</th>
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<th>C1</th>
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<th>C10</th>
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<tr>
<td>VHI</td>
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<td>64</td>
<td>9</td>
<td>51</td>
<td>8</td>
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<td>55</td>
<td>32</td>
<td>29</td>
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<td>0</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>13</td>
<td>3</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>9</td>
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<td>CAPE-V</td>
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<td>10</td>
<td>73</td>
<td>0</td>
<td>83</td>
<td>28</td>
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<td>0</td>
<td>10</td>
<td>0</td>
<td>6</td>
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<tr>
<td>CSID</td>
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<td>−11.1</td>
<td>9.0</td>
<td>−32.4</td>
<td>30.9</td>
<td>32.2</td>
<td>5.5</td>
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<td>−18.5</td>
<td>−26.3</td>
</tr>
</tbody>
</table>

Unilateral vocal fold paralysis and healthy control cohorts differed on VHI and CAPE-V (all P < 0.05). C = control; CAPE-V = Consensus Auditory-Perceptual Evaluation of Voice; CSID = Cepstral-Spectral Index of Dysphonia; U = unilateral vocal fold paralysis; VHI = Voice Handicap Index.
For the Cepstral-Spectral Index of Dysphonia, an assessment of dysphonia severity (higher score indicates poorer voice), the UVFP cohort mean (SD, range) was 1.6 (22.6, −32.4 to 32.1) on all voiced sentences. Because the demarcation for dysphonia-positive demarcation is 23.4 and the UVFP cohort mean was below this cutoff value, no comparison was performed against the control cohort.

**Vocal Motor Control**

When presented with 100-cent pitch perturbations, UVFP study patients responded with reduced compensatory change compared to healthy controls. This reduction was observed from 150 ms following pitch feedback perturbation onset to the peak of the compensatory response at 550 ms (Fig. 1). The mean pitch compensatory response across all trials in this time interval was 32.5% lower in the UVFP cohort compared to the control cohort (UVFP = 5.2 [0.4], control = 7.7 [0.6]; \(P < 0.0001\), LMM).

Vocal motor output capacity of the UVFP cohort to respond fully to pitch perturbation was evaluated by measuring within-trial and across-trial pitch variability during the 200 ms pre-perturbation baseline time window. As shown in Figure 2, within-trial and across-trial pitch variability for both cohorts was much larger than the comparator compensatory response for healthy controls (mean (SD) = 7.7 (0.6) cents, see above). The baseline pitch variability mean (SD) in cents for the two cohorts were UVFP within-trial = 27.7 (4.3), UVFP across-trial = 20.7 (2.8), control within-trial = 22.6 (2.1), and control across-trial = 17.1 (1.3). Although the pitch variability was greater for the UVFP cohort, this difference did not reach statistical significance (within-trial, \(P = 0.31\); across-trial, \(P = 0.26\); \(t\) tests). Therefore, the observed difference in compensatory response to pitch perturbation between the two cohorts cannot simply be ascribed to vocal motor capacity insufficiency in the UVFP cohort.

**Peripheral and Central Hearing**

The battery of six central auditory tests revealed performance impairment almost exclusively in the UVFP cohort. UVFP study patients were mostly deficient on challenge tests (Fig. 3) in the temporal domain (Quick Time-Compressed Speech Test and Quick Competing

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DISCUSSION

We investigated both behavioral compensation to perturbed auditory feedback and central auditory processing in UVFP study patients who had been treated satisfactorily by type I thyroplasty. Findings of this pilot study suggest that peripheral motor impairment of the larynx can degrade central auditory processing, which in turn may contribute to vocal motor control impairment. Previous neurophysiologic studies of the pitch perturbation response found that response magnitude correlated with activity in auditory cortex.32,34

Behavioral responses to pitch perturbation demonstrated that treated UVFP study patients compensated 32.5% less compared to controls, despite adequate vocal output capacity. This difference occurred during auditory cortical activation (< 300 ms following pitch perturbation onset), suggesting that abnormal central auditory processing of feedback information may contribute to impaired compensation in treated UVFP. These results support reciprocal interdependency of sensory and motor systems of the communication loop, where primary injury of the peripheral motor limb triggers change in central auditory processing. Nonetheless, relationships between the magnitude of decreased compensatory response in UVFP patients, pathophysiological biomarkers and mechanisms, and clinical outcome implications are not yet defined and will require a dedicated study in the future to address this important issue.

We posit two theories to explain observed differences between treated UVFP and healthy control cohorts. The first theory is that communication networks for sensorimotor vocal motor control that allow for auditory feedback error processing undergo maladaptive plastic change and no longer act on feedback expectation mismatch after a period of self-identified abnormal voice production. The second theory is that impaired central auditory processing of complex communication sounds associated with chronic voice impairment in UVFP inactivates feedback error computation altogether or creates a fixed feedback error signal that no longer drives motoric programs of compensatory vocal output. Both theories may partially explain why the correlation between clinician-rated and patient-reported voice quality is modest.35–38

Surgical intervention for UVFP often restores voice quality to a satisfactory rating based on clinician-centric instruments and objective acoustical measures,39–41 yet certain treated patients are somewhat dissatisfied despite “successful” surgical intervention.6,8,42–46

Discovery of central auditory processing impairment in UVFP has immediate diagnostic and treatment implications. Because standard screening audiograms will not detect this hearing deficit, comprehensive evaluation of UVFP may require adoption of central auditory processing test batteries. For those patients identified with central auditory processing impairment, treatment can be instituted by improving quality of the sound signal, learning explicit strategies focused on comprehension, and customizing auditory training.32,47,48 The consequence of treated central auditory processing impairment on vocal motor control, specifically response behavior to pitch perturbation, is unknown.

This pilot study has limitations. First, conclusions drawn from the contrast of two relatively small cohorts will require replication studies with much greater number of subjects to address covariate effects of gender, age, and voice quality. Second, the central auditory processing test battery will require refinement to create an efficient set that can be practically implemented in busy clinics. Third, type I thyroplasty is a static restorative intervention that does not restore dynamic vocal cord length or tone. However, it should be noted that our pitch perturbation task does not require additional functionality conferred by those two factors for the UVFP cohort to match control cohort performance. Finally, the relationship between impaired vocal motor control diagnosed by reduced compensatory response to auditory feedback perturbation and clinically accepted voice production metrics will require comprehensive studies using a broad array of test conditions.

CONCLUSION

Clinical evaluation of voice production has traditionally been treated as an isolated peripheral entity without adequate consideration of reciprocal interdependency of sensory and motor systems. In this pilot study, we demonstrate that apparent isolated peripheral injury to the larynx may have important consequences that impact central motor control and auditory processing. These findings imply that a more complete restoration or optimization of communicative function in UVFP will require deeper understanding of sensory, motor, and sensorimotor aspects of the human communication loop.

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