Predicting Auditory Feedback Control of Speech Production From Subregional Shape of Subcortical Structures

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Abstract: Although a growing body of research has focused on the cortical sensorimotor mechanisms that support auditory feedback control of speech production, much less is known about the subcortical contributions to this control process. This study examined whether subregional anatomy of subcortical structures assessed by statistical shape analysis is associated with vocal compensations and cortical event-related potentials in response to pitch feedback errors. The results revealed significant negative correlations between the magnitudes of vocal compensations and subregional shape of the right thalamus, between the latencies of vocal compensations and subregional shape of the left caudate and pallidum, and between the latencies of cortical N1 responses and subregional shape of the left putamen. These associations indicate that smaller local volumes of the basal ganglia and thalamus are predictive

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of slower and larger neurobehavioral responses to vocal pitch errors. Furthermore, increased local volumes of the left hippocampus and right amygdala were predictive of larger vocal compensations, suggesting that there is an interplay between the memory-related subcortical structures and auditory-vocal integration. These results, for the first time, provide evidence for differential associations of subregional morphology of the basal ganglia, thalamus, hippocampus, and amygdala with neurobehavioral processing of vocal pitch errors, suggesting that subregional shape measures of subcortical structures can predict behavioral outcome of auditory-vocal integration and associated neural features. *Hum Brain Mapp* 39:459–471, 2018. © 2017 Wiley Periodicals, Inc.

Key words: auditory feedback; sensorimotor integration; speech production; subcortical morphology; shape analysis

INTRODUCTION

Speech production is a unique motor accomplishment [Kent, 2000]. Auditory feedback serves as a teaching signal during the acquisition of speech motor skills [Guenther, 1995] and a guiding signal for the online control of speech movements after speech acquisition [Houde and Nagarajan, 2011]. Alterations in auditory feedback (AAF) lead to compensatory adjustments of vocal outputs in fundamental frequency (F_0), intensity, and formant frequency [Bauer et al., 2006; Burnett et al., 1998; Houde and Jordan, 1998]. The neural mechanisms underlying this compensatory control process, however, remain poorly understood.

To address this issue, a number of neuroimaging studies have explored the cortical sensorimotor networks that support auditory-motor control of speech production. For example, evidence from event-related potentials (ERPs) studies has shown the modulation of the N1-P2 complex in response to voice pitch perturbations in healthy populations [Behroozmand et al., 2009; Chen et al., 2012; Liu et al., 2011; Scheerer et al., 2013] and patients with neurological diseases [Huang et al., 2016; Li et al., 2016]. These two components are hypothesized to reflect the online detection and correction of voice feedback errors at the cortical level [Behroozmand et al., 2014; Chen et al., 2015]. Other studies using electrocorticography (ECoG), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI) have revealed enhanced brain activity to voice pitch perturbations in multiple brain regions including the superior temporal gyrus (STG), primary motor cortex (M1), superior temporal sulcus (STS), premotor cortex (PMC), supplementary motor area (SMA), inferior frontal gyrus (IFG), and inferior parietal lobule (IPL) [Behroozmand et al., 2015; Chang et al., 2013; Greenlee et al., 2013; Kort et al., 2014; Parkinson et al., 2012; Tourville et al., 2008; Zarate and Zatorre, 2008]. A direct relationship between the magnitude of vocal compensation for pitch perturbations and activity in the STG and PMC has also been observed [Behroozmand et al., 2015; Chang et al., 2013]. Moreover, regional homogeneity of intrinsic brain activity in the STG, M1, PMC, SMA, and IFG is predictive of vocal and ERP responses (N1 and P2) to pitch perturbations [Guo et al., 2016].

In addition to the identification of the cortical areas involved in auditory-motor control of speech production, a growing literature has shown the contributions of a number of subcortical structures. For example, the basal ganglia and thalamus have been implicated in speech production and phonological processing [Bohland and Guenther, 2006; Hebb and Ojemann, 2013]. Activation of the putamen, pallidum/caudate, and thalamus has been observed when participants are exposed to pitch perturbations during sustained vowel phonations [Parkinson et al., 2012; Zarate and Zatorre, 2008] or F1 perturbations during the production of monosyllabic words [Tourville et al., 2008]. Relatedly, dysfunctions of the basal ganglia and thalamus caused by Parkinson's disease (PD) are associated with abnormally enhanced compensations for voice pitch perturbations [Chen et al., 2013; Huang et al., 2016; Liu et al., 2012] and reduced compensations for speech F1 perturbations [Mollaei et al., 2013, 2016]. Other subcortical structures not typically considered central to speech production have also been shown to contribute to auditory feedback control of speech production. For example, the hippocampus and amygdala, two medial temporal lobe subcortical structures that are traditionally linked to specific memory processes [Phelps, 2004], have been implicated in the online processing of language production [Duff and Brown-Schmidt, 2012] and emotional vocalization [Fecteau et al., 2007]. Recent evidence has shown abnormally enhanced vocal compensations for pitch perturbations in patients with temporal lobe epilepsy (TLE) and Alzheimer's disease (AD) [Li et al., 2016; Ranasinghe et al., 2017], who have been found to be associated with atrophy in the hippocampus and/or amygdala [Bernasconi et al., 2003; Tang et al., 2015b]. In addition, AD patients exhibited significant correlations between executive dysfunction and increased compensation magnitude and between memory dysfunction and reduced compensation persistence [Ranasinghe et al., 2017]. It is thus suggested that, in addition to memory function, the hippocampus and amygdala may also play an important role in the feedback-based control of vocal production.

In recent years, there has been growing interest in uncovering the relationship between neuroanatomical

measures of subcortical structures and cognitive functions and/or motor skills. However, because global volumetric analyses of subcortical structures using a voxel-based morphometry approach are not sensitive enough to reliably detect subtle regional alterations and brain-behavior effects [Nemmi et al., 2015; Serbruyns et al., 2015], a new method termed shape analysis has been proposed that allows accurate localization of distinct subregional volumetric changes within each subcortical structure [Patenaude et al., 2011]. For example, bilinguals have been shown to exhibit expansions of their bilateral putamen and thalamus as compared to monolinguals, and a significant correlation between a bilingual production index and morphology of the right caudate [Burgaleta et al., 2016]. And patients with PD, a disease that causes local atrophy in the caudate [Apostolova et al., 2010], the putamen [Menke et al., 2014], or both [Nemmi et al., 2015; Sterling et al., 2013], exhibited reductions in cognitive function associated with atrophy of the caudate and the putamen [Apostolova et al., 2010; Sterling et al., 2013] and reductions in motor function associated with atrophy of the putamen and thalamus [Nemmi et al., 2015]. More importantly, the shape analysis approach can help us in better understanding of the functional relevance of the morphological changes of distinct subregions within subcortical structures. For example, localized shape measures of the subregions projecting to the prefrontal, posterior parietal and temporal cortices in the right thalamus, the subregions projecting to the limbic cortices in the putamen, and the subregions projecting to executive regions in the caudate in elderly were positively correlated with training-induced improvement in performing a difficult bimanual tracking task [Chalavi et al., 2016]. Additionally, the regionally specific atrophy of the hippocampus and amygdala observed in AD patients [Miller et al., 2013; Qiu et al., 2009] has been found to be predictive of the decline of various cognitive functions [Tang et al., 2014, 2015b]. In viewing the observed functional topography within subcortical structures, subregional shape analyses offer great potential for the identification of shape characteristics in the subcortical regions mediating sensorimotor processing.

The success of these recent studies of the functional topography within subcortical structures suggests that subregional shape analyses could identify the functional relevance of the morphology of subcortical structures important for auditory-vocal integration. The aim of this study was to investigate the contributions of subcortical structures, namely, the putamen, caudate, pallidum, thalamus, hippocampus, and amygdala, to the auditory-motor processing of voice feedback errors by means of shape analysis. Specifically, the relationship between the localized shape morphometrics of distinct subregions within each subcortical structure and the latencies and magnitudes of vocal and ERP responses (N1 and P2) to pitch perturbations was examined. Since individual subregions within these subcortical structures have distinct connections to the cortical areas and thus likely contribute to

distinct functions [Behrens et al., 2003; Tziortzi et al., 2014], we hypothesized regionally specific roles of subcortical structures in auditory-motor integration for voice control.

METHODS

Subjects

Forty-four native Mandarin Chinese speakers (21 male and 23 female, age: 23 ± 3 years) participated in this experiment. They were right-handed and had not been diagnosed with language, hearing, or neurological disorders. All participants had normal hearing as assessed by an audiometric screen (thresholds of ≤ 25 dB HL for octave frequencies between 250 and 4000 Hz). All procedures were approved by the Institutional Review Board of The First Affiliated Hospital at Sun Yat-sen University of China and were in accordance with the World Medical Association 2013 Declaration of Helsinki.

Image Acquisition

All participants were scanned on a Siemens Magnetom 3T Trio Tim MRI scanner (Erlangen, Germany). During the data acquisition, they were instructed to close their eyes and relax their minds. The high-resolution structural images were obtained through a T1-weighted MPRAGE sequence with the following imaging parameters: repetition time (TR) = 2300 ms; echo time (TE) = 3.24 ms; slice thickness = 1 mm; voxel size = $1 \times 1 \times 1$ mm; flip angle = 9° ; field of view (FOV) = 256×256 mm².

Vocal Production Experiment

An AAF-based vocal production experiment was conducted after the MRI scanning. All participants were instructed to produce and maintain a steady vocalization of the vowel sound /u/s at their comfortable vocal pitch and loudness for about 5–6, during which their voice pitch feedback was randomly shifted downward 50 or 200 cents (100 cents = one semitone). Each pitch shift lasted 200 ms, and there were 5 pitch shifts during each vocalization. The first pitch shift was presented with a random delay of 500–1000 ms relative to the vocal onset, and there was an inter-stimulus interval of 700–900 ms for the succeeding pitch shifts. Prior to initiating the next vocalization, participants were required to take a break of 2–3 s to avoid the vocal fatigue. For each participant, a production of 40 consecutive vocalizations led to a total of 200 trials, including 100 trials for the –50 cents condition and 100 trials for the –200 cents condition.

All participants were tested in a sound-attenuated booth, where their voice and electroencephalographic (EEG) signals were recorded. In order to partially mask the air-borne and bone-conducted feedback, we calibrated

the acoustic recording system by amplifying the intensity of voice feedback the participant heard 10 dB SPL higher than that of his/her voice output. First, participants' voice signals that were transduced by a dynamic microphone (DM2200, Takstar Inc.) were sent to an Eventide Eclipse Harmonizer via a MOTU Ultralite Mk3 Firewire audio interface, in which they were pitch-shifted by a custom-developed Max/MSP software program (v.5.0 by Cycling 74). Transistor-transistor logic (TTL) control pulses were also generated by this program and marked the onset of the pitch shifts. Finally, participants heard their pitch-shifted voices that were amplified by an ICON NeoAmp headphone amplifier through insert earphones (ER1-14A, Etymotic Research Inc.). The signals, including the original and pitch-shifted voices and TTL control pulses, were sampled at 10 kHz by a PowerLab A/D converter (ML880, AD Instruments) and recorded using LabChart software (v.7.0 by AD Instruments).

The EEG signals were obtained using a 64-electrode Geodesic Sensor Net (Electrical Geodesics Inc.), amplified by a Net Amps 300 amplifier that accepts scalp-electrode impedances up to 40–60 k Ω ($Z_{in} \approx 200$ M Ω ; Electrical Geodesics Inc.), and recorded using NetStation software (v. 4.5, Electrical Geodesics Inc.) at 1 kHz. A DIN synch cable was used to send the TTL control pulses that signaled the onset of the pitch shifts to the EEG recording system. Throughout the online recording, the EEG signals across all channels were referenced to the vertex (Cz), and the impedance levels of individual sensors were carefully adjusted and maintained at ≤ 50 k Ω [Ferree et al., 2001].

Data Analysis

Volumetric segmentation: For each T1-weighted image, volumetric segmentations of the 12 subcortical structures (left and right caudate, putamen, pallidum, thalamus, hippocampus, and amygdala) were automatically obtained from a hierarchical segmentation pipeline [Tang et al., 2015a]. This segmentation method was based on a diffeomorphic multi-atlas likelihood-fusion algorithm in the framework of the random deformable template model [Tang et al., 2013]. We visually examined all the segmentation results used in this study to ensure a high segmentation quality.

Shape processing: To extract the localized shape morphometrics, we created a 2-D triangulated surface contouring the boundary of each 3-D volumetric segmentation with preserved smoothness and correct anatomical topology using a fully automated existing pipeline [Tang et al., 2014, 2015b]. After creating the triangulated surfaces, the localized surface-based morphometrics (the vertex-wise surface areas) of each target shape were quantified by a diffeomorphism that connected a common template shape to that target shape. The common template shape of each structure of interest was itself generated from all target surfaces using a Bayesian template estimation algorithm [Ma et al., 2010] to ensure “population averaging” by

iteratively minimizing the overall metric distance from the common template surface to each target surface until convergence. After this procedure, we used the large deformation diffeomorphic metric mapping (LDDMM) surface mapping algorithm [Vaillant et al., 2007] to map the common template surface to each individual target surface, from which a scalar field was subsequently calculated as the log-determinant of the Jacobian of the diffeomorphism. This scalar field, indexed at each vertex of the common template surface, quantifies the factor by which the diffeomorphism expands or shrinks the localized surface area in the target relative to the template in a logarithmic scale. A positive value corresponds to a localized surface area expansion of the subject relative to the template while a negative value suggests a localized surface area contraction. This structure-specific and subject-specific scalar field, referred to as the deformation marker, is what we ultimately correlated to our neurobehavioral measurements.

Template surface subdivision: Our template surfaces for the caudate, putamen, thalamus, hippocampus, and amygdala in both hemispheres were subdivided into multiple functionally distinct subregions using the approach detailed in Tang et al. [2014]. This subdivision was accomplished by transferring the boundary definitions of subregions defined in precreated atlases to our population template surfaces based on diffeomorphic surface mappings. Based on the atlases of the caudate and putamen at both hemispheres, each structure was divided using the probabilistic tractography algorithm into seven subregions respectively that projected into the limbic, executive, rostral-motor, caudal-motor, parietal, occipital, and temporal regions [Tziortzi et al., 2014]. Similarly, the thalamus in each hemisphere was divided into seven subregions that respectively projected into the primary motor, sensory, occipital, prefrontal, premotor, posterior parietal, and temporal cortices [Behrens et al., 2003]. As described in Tang et al. [2014], the subregion boundaries were manually delineated based on high-field MRI scans (7 T) in the precreated atlases of the hippocampus and the amygdala. The bilateral amygdalas were subdivided into four subregions including the basolateral, the basomedial, the centromedial, and the lateral nucleus. For the bilateral hippocampi, they were also subdivided into four subregions; CA1, CA2, CA3 combined with the dentate gyrus, and the subiculum.

Vocal data analyses: The measurement of the vocal responses to pitch feedback perturbations was performed in a custom-developed averaging program (IGOR PRO, v.6.0 by Wavemetrics Inc.) using event-related averaging techniques. First, the voice signals were transferred to a Praat software program [Boersma, 2001] to extract the voice F_0 contours in Hertz. Next, the following formula was used to convert the voice F_0 contours in Hertz to the cents scale: cents = $100 \times (12 \times \log_2(F_0/\text{reference}))$ [reference = 195.997 Hz (G4)]. The voice contours in cents were then segmented into epochs ranging from -200 to 700 ms relative to the onset of the pitch shift. To investigate the

relationship between subcortical morphology and compensatory control of vocal motor behavior, we used a presorting procedure to extract individual compensatory trials that opposed the direction of the pitch perturbations [Behroozmand et al., 2012; Li et al., 2013]. During this procedure, a positive or negative value was obtained by subtracting the mean amplitude of a prestimulus window (−200 to 0 ms) from the peak amplitude of a poststimulus window (0–200 ms). For the downward pitch perturbations, positive or negative values meant that the direction of responses was opposed to or the same as the direction of pitch perturbation. Trials associated with positive values were thus defined as compensatory responses. An additional visual inspection was performed to ensure that all compensatory trials that opposed the direction of the pitch perturbation were appropriately chosen and trials that were contaminated by signal processing errors and unexpected vocal stops were rejected. Finally, following a normalization procedure that subtracted the mean F_0 values in the baseline period (−200 to 0 ms) from the F_0 values after the perturbation onset, the artifact-free compensatory trials were averaged to generate an overall compensatory response. The magnitude of a vocal response in cents was measured as the greatest F_0 value following the response onset. The latency was defined as the peak time when the voice F_0 contours reached a maximum value.

EEG data analyses: NetStation software was used to measure the cortical responses to pitch perturbations in voice auditory feedback. The recorded EEG data were first filtered using a band-pass filter with cutoff frequencies set to 1 and 20 Hz and then segmented into epochs ranging from −200 to +500 ms relative to the onset of the pitch shift. An artifact detection algorithm was carried out to reject segmented trials with voltage values that exceeded $\pm 55 \mu\text{V}$ of the moving average over an 80 ms window. Additional visual inspection of all individual trials was performed to avoid the errors of automatic rejection. Individual electrodes that contained artifacts in more than 20% of the segments would be marked as bad electrodes, and any file that contained more than 10 bad electrodes would be excluded from future analysis. As a result, 88% of trials were retained and submitted to the following averaging procedure. Finally, after rereferencing all channels to the average of electrodes on each mastoid, we averaged and baseline-corrected all artifact-free trials to obtain an overall ERP response. ERP responses from 15 fronto-central electrodes (F1, F2, Fz, F3, F4, FC1, FC2, FCz, FC3, FC4, C1, C2, Cz, C3, and C4) [Chen et al., 2012; Hawco et al., 2009] were used to generate a grand-averaged ERP response for each condition, from which the amplitudes and latencies of N1 and P2 components were extracted as the negative and positive peaks in the time windows of 80–180 and 160–280 ms.

Statistical analyses: The magnitudes and latencies of vocal and grand-averaged N1 and P2 responses to pitch

feedback perturbations were submitted to SPSS (v. 16.0) for statistical analysis. They were subjected to one-way repeated-measures analyses of variance (RM-ANOVA), in which stimulus magnitude (−50 vs −200 cents) was chosen as a within-subject factor. The Greenhouse–Geisser was used to correct probability values for multiple degrees of freedom when the assumption of sphericity was violated. The difference was considered to be significant at an alpha level of 0.05.

The Pearson product-moment correlation coefficient (PCC) was employed to quantify the correlation between the magnitudes and latencies of vocal and cortical (N1 and P2) responses and subregional shape measures of the 12 subcortical structures. Age, intracranial volume (ICV), and gender were taken as covariates in the correlation analyses. The statistical significance of a correlation was measured by a P value obtained from nonparametric permutation tests with a total of 40,000 permutations employed. To correct for multiple correlation tests being performed simultaneously at all vertices of the template surface, we adjusted the P values to control for family-wise error rate (FWER) at a level of 0.05 based on the “maximum statistic” method [Groppe et al., 2011].

RESULTS

Vocal and ERP Responses

Figure 1 shows the individual (light color) and grand-averaged (dark color) voice F_0 contours (A) and ERP (B) waveforms in response to pitch perturbations of −50 (blue color) and −200 cents (red color). As can be seen, the extent of vocal compensation and associated cortical activity was highly variable across participants, and the −200 cents pitch perturbations elicited larger magnitudes of vocal, N1, and P2 responses than the −50 cents pitch perturbations. One-way RM-ANOVAs revealed that −50 cents pitch perturbations elicited significantly smaller magnitudes of vocal compensations than −200 cents pitch perturbations (13.9 ± 5.7 cents vs 16.2 ± 6.9 cents) ($F(1, 43) = 12.618$, $P = 0.001$), whereas there was no significant main effect of stimulus magnitude for the latencies (peak time) of vocal compensations (−50 cents: 241 ± 85 ms; −200 cents: 260 ± 82 ms) ($F(1, 43) = 1.526$, $P = 0.223$). Similarly, one-way RM-ANOVAs revealed significant main effects of stimulus magnitude on the cortical N1 and P2 responses. The amplitudes of N1 ($-2.37 \pm 1.47 \mu\text{V}$ vs $-3.29 \pm 1.83 \mu\text{V}$; $F(1, 43) = 19.521$, $P < 0.001$) and P2 responses ($2.25 \pm 1.12 \mu\text{V}$ vs $3.13 \pm 1.52 \mu\text{V}$; $F(1, 43) = 30.761$, $P < 0.001$) were significantly smaller for −50 cents pitch perturbation compared to −200 cents pitch perturbations, while the latencies of N1 (143 ± 16 ms vs 131 ± 19 ms; $F(1, 43) = 19.521$, $P < 0.001$) and P2 responses (247 ± 26 ms vs 225 ± 24 ms; $F(1, 43) = 19.582$, $P < 0.001$) were significantly longer for −50 cents pitch perturbations than for −200 cents pitch perturbations.

Figure 1.

Individual (light color) and grand-averaged (dark color) voice F_0 contours (A) and ERP (B) waveforms in response to pitch perturbations of -50 (blue color) and -200 cents (red color). [Color figure can be viewed at wileyonlinelibrary.com]

Association Between Localized Shape Measures and Vocal/ERP Responses

Vertex-wise correlation analysis revealed that, regardless of the size of the pitch perturbation, the magnitudes of vocal compensations were negatively correlated the shape measures of the subregion projecting to the temporal cortex in the right thalamus (-50 cents: mean $P = 0.04$ after

FWER correction, mean $PCC = -0.51$; -200 cents: mean $P = 0.035$ after FWER correction, mean $PCC = -0.52$; see Fig. 2), and positively correlated with the shape measures of the left hippocampal CA1 region (-50 cents: mean $P = 0.039$ after FWER correction, $PCC = 0.52$; -200 cents: mean $P = 0.028$ after FWER correction, mean $PCC = 0.53$; see Fig. 3). In the case of -50 cents pitch perturbations, the magnitudes of vocal compensations were positively

Figure 2.

Top panel: spatial surface maps showing significant correlations between vertex-wise shape measures of the right thalamus and the magnitudes of vocal compensations for pitch perturbations of -50 and -200 cents. The color bar denotes the PCC values. Bottom panel: subregions of the right thalamus that project to distinct cortical regions (primary motor, sensory, occipital, prefrontal, posterior parietal, and temporal cortices). [Color figure can be viewed at wileyonlinelibrary.com]

Figure 3.

Top panel: spatial surface maps showing significant correlations between vertex-wise shape measures of the left hippocampus and the magnitudes of vocal compensations for pitch perturbations of -50 and -200 cents. The color bar denotes the PCC values. Bottom panel: subregions of the left hippocampus, including CA1, CA2, CA3/dentate gyrus, and subiculum. [Color figure can be viewed at wileyonlinelibrary.com]

correlated with the shape measures of the right basomedial amygdala (mean $P = 0.046$ after FWER correction, mean $PCC = 0.45$; see Fig. 4). These findings indicate that individuals with smaller local volumes of the right thalamus, but larger local volumes of the left hippocampus and right amygdala produced larger vocal compensations for pitch perturbations.

We also observed significant negative correlations between the latencies of vocal compensations for -50 cents pitch perturbations and the shape measures of the subregion projecting to the executive regions in the left caudate (mean $P = 0.047$ after FWER correction, mean $PCC = -0.49$; see Fig. 5) and left pallidum (mean $P = 0.018$ after FWER correction, mean $PCC = -0.51$; see Fig. 6). These findings indicate that smaller local volumes of the left caudate and left pallidum were associated with slower compensatory vocal adjustment (longer peak times). Correlations between the latencies of vocal compensations for -200 cents pitch perturbations and sugregional shape measures of subcortical structures, however, did not reach significance after FWER correction.

Furthermore, significant negative correlations were found between the latencies of N1 responses and subregional shape of the left putamen (-50 cents: mean

$P = 0.028$ after FWER correction, mean $PCC = -0.51$; -200 cents: mean $P = 0.04$ after FWER correction, mean $PCC = 0.49$; see Fig. 7). Specifically, vertices with significant correlations belonged to the subregion of the left putamen projecting to the parietal cortex in the case of -50 cents pitch perturbations, whereas vertices with significant correlations belonged to the subregion projecting to the executive regions in the case of -200 cents pitch perturbations. Considering that the N1 response is thought to reflect preattentive detection of voice feedback errors [Korzyukov et al., 2012], this finding indicates that smaller local volumes of the left putamen were predictive of slower neural processing of voice pitch errors.

DISCUSSION

This study examined the subcortical neuroanatomical correlates of auditory-vocal integration by correlating localized shape measures of the putamen, caudate, pallidum, thalamus, hippocampus, and amygdala with vocal and cortical responses to pitch perturbations. Our results revealed that the magnitudes of vocal compensations were negatively correlated with subregional shape of the right

Figure 4.

Top panel: spatial surface maps showing significant correlations between vertex-wise shape measures of the right amygdala and the magnitudes of vocal compensations for pitch perturbations of -50 cents. The color bar denotes the PCC values. Bottom panel: subregions of the right amygdala, including basolateral, basomedial, centromedial, and lateral nucleus. [Color figure can be viewed at wileyonlinelibrary.com]

thalamus and positively correlated with subregional shape of the left hippocampus and right amygdala. Also, the latencies of vocal compensations were negatively correlated with subregional shape of the left caudate and left

pallidum, while the cortical N1 latencies were negatively correlated with subregional shape of the left putamen. These findings provide the first evidence of a relationship between subcortical morphology with auditory-motor

Figure 5.

Top panel: spatial surface maps showing significant correlations between vertex-wise shape measures of the left caudate and the latencies of vocal compensations for pitch perturbations of -50 cents. The color bar denotes the PCC values. Bottom panel: subregions of the left caudate that project to distinct cortical regions (limbic, executive, rostral motor, caudal motor, parietal, occipital, and temporal regions). [Color figure can be viewed at wileyonlinelibrary.com]

Figure 6.

Spatial surface maps showing significant correlations between vertex-wise shape measures of the left pallidum and the latencies of vocal compensations for pitch perturbations of -50 cents. The color bar denotes the PCC values. [Color figure can be viewed at wileyonlinelibrary.com]

integration during vocal pitch regulation, indicating that regionally specific shape measures within subcortical structures can predict behavioral outcome of speech motor control and associated neural activity.

The caudate and putamen receive major afferent connections from the cerebral cortex, midbrain and thalamus, while the internal segments of the pallidum send back processed information via thalamic nuclei [Doyon et al., 2009]. Distinct pathways from cortex through the basal ganglia and back to cortex lend support to the role of the basal ganglia in a wide range of sensorimotor and cognitive processes [Groenewegen, 2003]. In the context of auditory-vocal integration, songbirds studies have shown that a basal ganglia-forebrain circuit plays a role in evaluating auditory feedback and generating a motor correction for vocal errors [Andalman and Fee, 2009], and lesions of this circuit disrupt the feedback-based control of vocal

production [Brainard and Doupe, 2000]. In humans, professional singers exhibited activation of the bilateral putamen and right pallidum when compensating for pitch perturbations during singing a sustained vowel [Zarate and Zatorre, 2008], and nonsingers exhibited activation of the left putamen and bilateral caudate and pallidum when compensating for F1 perturbations during the production of monosyllabic words [Tourville et al., 2008]. Less is known, however, about the specific functions of distinct areas of the basal ganglia.

Our results showed that the subregional shape of the left caudate and left pallidum was negatively correlated with the latencies of vocal compensations, and the subregional shape of the left putamen was negatively correlated with the cortical N1 latencies. That is, smaller local volumes of the basal ganglia were predictive of slower detection and correction of voice pitch errors, further

Figure 7.

Top panel: spatial surface maps showing significant correlations between vertex-wise shape measures of the left putamen and the latencies of cortical N1 responses to pitch perturbations of -50 and -200 cents. The color bar denotes the PCC values. Bottom panel: subregions of the left putamen that project to distinct cortical regions (limbic, executive, rostral motor, caudal motor, parietal, occipital, and temporal regions). [Color figure can be viewed at wileyonlinelibrary.com]

demonstrating the involvement of the basal ganglia in the processing of feedback errors during vocal pitch regulation. These findings are line with previous research that showed a relationship between local atrophy of the nucleus accumbens and caudate and longer motor action times in humans [Boisgontier et al., 2016]. More importantly, we found differential contributions of distinct areas of the basal ganglia to speech motor control. For example, the latencies of vocal compensations were negatively correlated with the localized shape measures of the subregion projecting to the executive regions in the left caudate. The executive regions located in the frontal lobe are linked to executive processes such as inhibitory control and working memory [Tziortzi et al., 2014]. The IFG is a key structure involved in executive functions [Hampshire et al., 2010] and has been considered important for the processing of sensorimotor information during speech production [Flagmeier et al., 2014]. Caudate atrophy was previously found to be associated with executive dysfunction in PD patients [Apostolova et al., 2010]. In addition, the latencies of N1 responses were negatively correlated with the subregions projecting to the parietal cortex and the executive regions in the left putamen. One important role of the parietal cortex is to receive and transform sensory information into motor signals for sensory guidance of movements through the connections of the IPL to the motor temporal areas [Fogassi and Luppino, 2005]. The IPL has been found to be active during the generation of compensatory vocal responses to pitch perturbations [Behroozmand et al., 2015; Huang et al., 2016]. Taken together, our results suggest that the functional role of the basal ganglia in auditory-motor control of vocal production is regionally specific: the left caudate and left pallidum may be involved in initiating a rapid corrective vocal response to auditory feedback errors, while the left putamen may have a role in auditory-motor transformation to facilitate the cortical processing of auditory feedback errors. In addition, together with the finding that executive dysfunction in AD patients was predictive of enhanced vocal compensations for pitch perturbations [Ranasinghe et al., 2017], our findings that the latencies of neurobehavioral responses were significantly correlated with the subregions in the left caudate and left putamen, which connect to executive regions in the frontal lobe, suggest that executive function influences on auditory-vocal integration through the cortico-basal ganglia loop.

The thalamus receives input from the cortex via corticostriatal connections, and projects back to the prefrontal, sensorimotor, posterior parietal, and temporal cortices through thalamocortical pathways [Behrens et al., 2003]. Neuroimaging studies have shown activation of the right thalamus when participants compensate for voice pitch [Zarate and Zatorre, 2008] or speech F1 perturbations [Tourville et al., 2008]. Our results extend these studies by showing that smaller local volumes of the subregions projecting to the temporal cortex in the right thalamus are

predictive of larger vocal compensations, providing neuro-anatomical evidence for a functional role of the thalamus in auditory-vocal integration. The relationship between vocal compensation and the local volume of the right thalamus may be related to its anatomical connection to the temporal cortex, an important cortical area that has been found to be involved in auditory-vocal integration. For example, multiple auditory-related areas including the STG, STS, and Heschl's gyrus (HG) were found to be active when participants compensated for voice pitch perturbations and activity in the STG and HG was predictive of the magnitude of vocal compensation [Behroozmand et al., 2015, 2016; Chang et al., 2013; Kort et al., 2014; Parkinson et al., 2012]. The STG is also hypothesized to be involved in monitoring mismatches between predicted and actual voice feedback [Parkinson et al., 2012]. Thus, the right thalamus may play an important role in the online detection and correction of auditory feedback errors during speech production.

One unexpected finding of this study was that a positive correlation existed between compensatory vocal behavior and the localized shape measures of the left hippocampal CA1 region and the right basomedial amygdala. In other words, smaller local volumes of these two structures were predictive of smaller vocal compensations for pitch perturbations. Considering that the hippocampus and amygdala are believed to play a critical role in specific memory processes [Phelps, 2004], our data provide the first evidence for an interplay between the memory-related subcortical structures and auditory-vocal integration. Two recent pitch-shift studies reported significant correlations between memory dysfunction in AD patients and longer persistence of vocal compensations [Ranasinghe et al., 2017], and between improved working memory capacity and enhanced cortical P2 responses [Li et al., 2015]. We therefore speculate that top-down signals from the working memory systems, particularly the prefrontal cortex (PFC) [Chmielewski et al., 2015], might generate an inhibitory effect on vocal motor control to prevent vocal production from being excessively influenced by auditory signals. Vocal compensation is usually far from complete; limited to 10%–20% of the size of the feedback perturbations [Burnett et al., 1998; Chen et al., 2007]. Compensatory vocal adjustments are likely inhibited because rapid full compensation for feedback perturbations would result in an unstable control of vocal motor behavior [Houde and Nagarajan, 2011]. Interestingly, evidence from animal studies has shown that inhibition of hippocampal CA1 interferes with acquisition and retrieval of contextual fear memory [Goshen et al., 2011], and that the projection between ventral medial PFC and basomedial amygdala implements top-down inhibitory control of anxiety and fear [Adhikari et al., 2015]. Inhibitory control is closely interrelated with working memory and fewer working memory resources result in impaired inhibitory control processes [Barber et al., 2013; Chmielewski et al., 2015].

The PFC is viewed as a source of inhibitory control and can inhibit memory-related areas such as hippocampus and amygdala to suppress behaviors related to motor, emotion, and memory processing by driving activation of the thalamus [Munakata et al., 2011]. This inverse coupling between the thalamus and the hippocampus and amygdala during inhibitory control can account for their differential associations with vocal compensation behavior observed in this study. Accordingly, working memory may exert top-down influences on compensatory vocal motor behavior, and the left hippocampus CA1 and right basomedial amygdala may be involved in this PFC-mediated inhibition process. In light of this point, abnormally enhanced vocal compensations for pitch perturbations observed in TLE, PD, and AD patients [Li et al., 2016; Liu et al., 2012; Ranasinghe et al., 2017] may be caused by dysfunctions of inhibitory control mechanisms that were related to lesions of memory-related subcortical structures.

Note that the observed relationship between subcortical morphology and speech motor control was found in native Mandarin Chinese speakers. A number of studies, however, have shown the language-specific processing of auditory feedback during the online control of speech production. For example, Mandarin speakers produced larger vocal compensations and smaller P2 responses to large pitch perturbations than Cantonese speakers [Chen et al., 2012; Liu et al., 2010], and English speakers compensated for vowel formants shifts in a different way from Japanese and French speakers [Mitsuya et al., 2011, 2013]. There is also behavioral evidence for the difference between tonal and nontonal language speakers in the feedback-based control of speech production, as reflected by suppressed vocal compensations for pitch perturbations produced by Mandarin speakers relative to English speakers [Ning et al., 2015]. Together with the structural and functional differences in the brains of tonal (e.g., Chinese) and nontonal language (e.g., English) speakers during speech processing [Crinion et al., 2009; Ge et al., 2015], those findings suggest that the subcortical mechanisms of speech motor control may be influenced by language experience. Future studies are required to confirm this hypothesis.

In summary, our results revealed differential associations between subregional shape of the basal ganglia, thalamus, hippocampus, and amygdala and neurobehavioral processing of feedback errors during vocal pitch regulation. These findings highlight the importance of subcortical structures in the neural mechanisms that support speech motor control, indicating that the subregional shape measures of subcortical structures differentially predict individual performance in sensorimotor integration for speech production.

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