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External cueing facilitates auditory-motor integration for speech control in individuals with Parkinson's disease

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ABSTRACT

Instructing individuals with Parkinson's disease (PD) to speak loudly and clearly with external cues leads to improvements of their speech in loudness, pitch, and articulatory movement, but the underlying neural mechanisms are largely unknown. The present event-related potential study investigated whether and how external cueing can facilitate auditory-motor control of speech production in PD. Individuals with PD and healthy controls produced sustained vowels with internal and external auditory cues while hearing their voice pitch-shifted -200 cents. Individuals with PD produced significantly larger vocal compensations than healthy controls in the internally cued condition and exhibited a significant decrease in the magnitudes of vocal compensations with external cueing. Moreover, individuals with PD produced significantly smaller N1 responses and larger P2 responses in the externally versus internally cued condition and exhibited a significant correlation between decreased vocal compensations and increased P2 amplitudes after external cueing. These findings provide the first neurobehavioral evidence that external auditory cueing can compensate for impaired auditory-motor processing of vocal feedback errors associated with PD in a top-down manner.

1. Introduction

Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder that is characterized by symptoms such as resting tremor, bradykinesia, hypokinesia, rigidity, and postural instability (Marsden, 1994). Although less well known than the motor symptoms related to impaired limb movement and postural control, individuals with PD commonly experience speech disorders termed hypokinetic dysarthria. Hypokinetic dysarthria affects approximately 70%–90% of individuals with PD during the course of their disease and is characterized by reduced voice loudness and pitch, speech dysfluency, imprecise articulation, and voice tremor (Duffy, 2005). Although researchers have made significant progress in understanding the neural basis of the movement disorders associated with PD and developing medical treatments that reduce these impairments (Haslinger et al., 2001; Morris et al., 1994; Okun, 2012; Pieruccini-Faria et al., 2015; Rodriguez-Oroz et al., 2005; Rowe et al., 2002; Terayama et al., 2012), fewer studies have investigated the mechanisms that underlie the motor speech disorders associated with PD (Clark et al., 2014; Ho et al., 1998, 1999; Jimenez-Jimenez et al., 1997; Ramig et al., 2001; Stewart et al., 1995). Moreover, most of studies have been largely behavioral, leaving the underlying neural mechanisms poorly understood.

Acoustic and perceptual studies have typically described Parkinsonian speech as being reduced in voice loudness and monotone in prosodic pitch (Ackermann and Ziegler, 1991; Darley et al., 1969; Ho et al., 1998; Illes et al., 1988). Individuals with PD are also less able to appropriately adjust their voice loudness as compared with healthy controls when competing against changes in voice auditory feedback or background noise (Ho et al., 1999, 2000). Recent work has also demonstrated that PD causes abnormal sensorimotor control of speech production. For example,

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a series of studies have shown that, as compared with healthy controls, individuals with PD produced significantly larger vocal compensations for unexpected pitch and loudness perturbations (Chen et al., 2013; Huang et al., 2016; Liu et al., 2012; Mollaei et al., 2016) and exhibited a significant correlation between the magnitudes of vocal compensations and the variability of their unaltered voice fundamental frequency (f_0) (Chen et al., 2013; Huang et al., 2016). However, when individuals with PD produced the vowel /ɛ/ in the embedded word "head" and heard F_1 perturbations, they produced smaller speech compensations than healthy controls (Mollaei et al., 2016). Because the control of formant frequency requires changes to the vocal tract through the coordinated movement of the oral articulators (e.g., lip, tongue) that is more robustly represented in the somatosensory area when compared to f_0 (Bouchard et al., 2013), decreased speech F_1 responses in PD may reflect their impaired somatosensory feedback control of speech production, which may be related to their deficits in laryngeal somatosensory function (Hammer and Barlow, 2010). As well, deficits in feedforward control of speech production have also been found for individuals with PD, as reflected by reduced vocal compensations when adapting to consistent perturbations in voice f_0 and speech F_1 feedback (Abur et al., 2018; Mollaei et al., 2013). Given that speech motor control involves a weighting of feedback (auditory and somatosensory feedback) and feedforward control systems (Civier et al., 2010), these behavioral findings suggest that individuals with PD may weight more heavily auditory feedback for speech motor control as a consequence of damage to the feedforward control and somatosensory feedback systems (Chen et al., 2013; Huang et al., 2016; Sapir, 2014). Although limited, the data that have shown increased cortical activity in auditory and motor regions during speech in PD support this hypothesis. For example, 2 positron emission tomography (PET) studies reported that individuals with PD exhibited greater blood follow in the sensory regions such as the superior temporal gyrus (STG) and inferior parietal lobule (IPL) and in the motor regions such as the premotor cortex (PMC) and supplementary motor area (SMA) during speech production compared with healthy controls (Liotti et al., 2003; Pinto et al., 2004). Similarly, Huang et al. (2016) found that individuals with PD produced significantly larger event-related potential (ERP) P2 responses to voice pitch perturbations due to increased activity in the left STG, IPL, PMC, and inferior frontal gyrus (IFG) than healthy controls. Moreover, applying low-frequency repetitive transcranial magnetic stimulation to depress activity in the right STG, a region that plays a critical role in the detection and correction of auditory feedback errors during speech production (Parkinson et al., 2012), led to significant improvement of speech articulation in individuals with PD (Brabenec et al., 2018).

Among the many approaches to the treatment of hypokinetic dysarthria caused by PD, a behavioral therapeutic approach that exploits external cueing has shown significantly improved speech production in individuals with PD. For example, when individuals with PD are instructed to speak loudly and clearly or to imitate the normal speech of others, many aspects of their speech improve significantly, including louder speech volume, higher speech intelligibility, more variable prosodic pitch, and more precise articulatory movements (Clark et al., 2014; Dromey and Ramig, 1998; Goberman and Elmer, 2005; Tjaden et al., 2013; Weir-Mayta et al., 2017). This approach has been shown to be particularly effective for improving the regulation of speech loudness such that individuals with PD can control their loudness and healthy controls when given explicit loudness instructions (Ho et al., 1999, 2000) or when they are trained to speak loudly with external cueing while receiving the Lee Silverman Voice Treatment (LSVT) LOUD (Ramig et al., 1995, 2001). These findings parallel the use of external cues to improve limb motor control (e.g., handwriting, stride length, and gait velocity) in individuals with PD (Cerasa et al., 2006; Lewis et al., 2000; Morris et al., 1996; Oliveira et al., 1997; Smith et al., 2014; Thaut et al., 1996).

Despite emerging behavioral evidence regarding the beneficial effects of external cueing on speech production in individuals with PD, the neural mechanism involved in this improvement remains poorly understood. Specifically, it is largely unknown whether externally derived sensory information improves impaired sensorimotor integration for speech control in individuals with PD. To address this question, the present study investigated whether and how external cueing facilitates auditory feedback control of speech production in PD at the behavioral and cortical levels. Both individuals with PD as well as healthy controls were instructed to produce sustained vowels with internal or external auditory cues while hearing their voice unexpectedly pitch-shifted downward 200 cents (100 cents = 1 semitone). The scale of cents allowed normalization of voice f_0 across the participants. The participants' vocal and cortical ERP responses to pitch perturbations were measured and compared across the group and condition. We hypothesized that providing external auditory cues would lead to improved behavioral and neural responses during vocal pitch regulation in individuals with PD. Considering that impaired speech motor control caused by PD is reflected by abnormally enhanced vocal compensations for feedback errors (Chen et al., 2013; Huang et al., 2016; Liu et al., 2012; Mollaei et al., 2016) and that smaller vocal responses to pitch perturbations are generally accompanied by smaller N1 responses and larger cortical P2 response (Guo et al., 2017; Liu et al., 2018; Scheerer et al., 2013), we predicted that individuals with PD would produce decreased vocal and cortical N1 responses and increased cortical P2 responses in the externally versus internally cued condition, indicating the facilitatory effects of external cueing on auditory feedback control of speech production in individuals with PD.

2. Methods

2.1. Subjects

Twenty-eight individuals (18 male and 10 female; 60.18 ± 8.87 years), who were diagnosed as idiopathic PD according to the clinical criteria of UK Parkinson's disease Society Brain Bank (Hughes et al., 1992), were recruited from The First Affiliated Hospital of Sun Yat-Sen University. All individuals with PD were right-handed and native Chinese speakers. The mean disease duration since diagnosis was 4.2 ± 2.9 years, and the mean Hoehn and Yarh score was 1.8 ± 0.6. Cognitive profile was assessed using the mini-mental state examination and in the normal range (>24). The severity of PD motor symptoms was mild to moderate stage (mean score: 19.3 ± 9.6), evaluated by the Unified Parkinson's Disease Rating Scale. Individuals with PD were receiving daily Levodopa and other medicines (e.g., selegiline, piribedil, and pramipexole), but they were tested during their off-medication state (12 hours) to maximize the measured effects. Twenty-eight neurologically normal participants (18 male and 10 female; 60.35 ± 9.75 years) were recruited as healthy controls, and they did not differ from individuals with PD in their age ($t = -0.204$, d.f. = 27, $p = 0.840$), sex, and language. They reported no history of speech, hearing, and language disorders. Both individuals with PD and healthy controls passed a binaural hearing screening with thresholds of 25 dB hearing level at 250, 500, and 1000 Hz and 40 dB hearing level or less at 2000 and 4000 Hz. Neither individuals with PD nor healthy controls had musical experience or had received formal vocal training. All participants provided informed consent, and the research protocol was approved by the Institutional Review Board of The First Affiliated Hospital at Sun Yat-sen University in

accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Procedure

The present experiment consisted of 2 experimental conditions: an internally cued condition and an externally cued condition. Two pitch target stimuli were created as auditory cues by recording a professional female singer singing the vowel /u/ at C4 (261.63 Hz) and a professional male singer singing the vowel /u/ at D3 (146.83 Hz). The voice signals were processed using the method outlined by Moulines and Charpentier (1990) and implemented in Praat software (Boersma, 2001) to ensure that the f_0 for each target was precisely 261.63 Hz and 146.83 Hz. These 2 pitch targets were chosen so that both the male and female participants could produce the targets comfortably: C4 was used for female participants, whereas D3 was used for male participants.

Before the experiment, participants were instructed to speak the vowel /u/ to match 1 of 2 pitch targets (i.e., C4 or D3) they heard with 3–5 practice trials. The voice f_0 levels were measured using a fast Fourier transform algorithm in LabChart software (v.7.0 by AD Instruments) to ensure that all participants were able to match the pitch targets as required. Following practice, participants produced sustained /u/ sounds to match the pitch targets during the internally and externally cued conditions. The order of these 2 conditions was counterbalanced across all participants. For the internally cued condition, both individuals with PD and healthy controls were first asked to listen to and remember the pitch target. Then, they produced sustained vowels to match the pitch target they remembered without any explicit auditory cues in the production of consecutive vocalizations. In contrast, each time participants produced sustained vowels in the externally cued condition, they first heard the pitch target.

Across the 2 conditions, the participants heard their pitch shifted downward 200 cents for 200 ms while they vocalized. Each vocalization lasted approximately 4–5 seconds, during which the participants' voice pitch was unexpectedly perturbed 4 times. The presentations of pitch perturbations was pseudorandomized; the first pitch perturbation occurred with a delay of 1500–2500 ms relative to the vocal onset, and the succeeding pitch perturbations were presented with an interstimulus interval of 700–1000 ms. Before initiating the next vocalization, all participants were required to pause 2–3 seconds to avoid vocal fatigue. During each of the 2 conditions, participants produced 25 consecutive vocalizations, leading to a total of 100 perturbation trials per condition.

2.3. Apparatus

The experimental sessions took place in a sound-treated booth. To minimize the masking effects of air-borne and bone-conducted feedback, the acoustic recording system was calibrated to provide voice feedback that was 10 dB sound pressure level higher than that of the participant's vocal output. During the recording of the acoustic signals, participants' voices were transduced through a dynamic microphone (DM2200, Takstar Inc.), amplified with a MOTU Ultralite Mk3 FireWire audio interface, and pitch-shifted through an Eventide Eclipse Harmonizer. A custom developed MIDI software program (Max/MSP v.5.0 by Cycling 74) was used to control the Eventide Eclipse Harmonizer to pitch-shift the voice feedback, whereby acoustic parameters including the direction, magnitude, and timing of the pitch perturbations were manipulated. In addition, this program generated transistor-transistor logic (TTL) control pulses to mark the perturbation onset. Finally, the voice signals were amplified by an ICON Neo Amp headphone amplifier and presented to participants through insert earphones (ER-1; Etymotic Research Inc.). The original and pitch-shifted voice signals and the TTL pulses were digitally sampled at 10 kHz by a PowerLab A/D converter (model ML880; ADInstruments) and recorded using LabChart software.

The electroencephalogram (EEG) signals were recorded from each participant's scalp using a 64-electrode Geodesic Sensor Net that was connected to a high-input impedance Net Amps 300 amplifier ($Z_{in} \approx 200$ MΩ; Electrical Geodesics Inc.), digitally sampled at a frequency of 1 kHz and saved onto a Mac Pro computer using NetStation software (v.4.5; Electrical Geodesics Inc.). For the measurement of cortical ERPs to pitch perturbations, an experimental DIN sync cable was used to send the TTL control pulses that marked the perturbation onset to the EEG recording system. During the online recording, the EEG signals across all channels were referenced to the vertex (Cz) (Ferree et al., 2001). The impedance of individual sensors was adjusted and kept below 50 kΩ throughout the experiment because the amplifier accepts scalp-electrode impedances up to 40–60 kΩ (Ferree et al., 2001).

2.4. Data analyses

The measurement of vocal responses to pitch perturbations was performed using IGOR PRO software (v.6.0 by WaveMetrics Inc.). First, the voice f_0 contours in Hertz were extracted from the voice signals using an autocorrelation method in Praat software (Boersma, 2001), and then converted to the cent scale using the following formula: cents $= 100 \times (12 \times \log_2(f_0/\text{reference}))$ [reference = 195.997 Hz (G3 note)]. The voice f_0 contours for each condition were then segmented into epochs using a window of −200 to +700 ms relative to the perturbation onset. The segmented waveforms were subjected to a visual inspection procedure, whereby individual segmented trials that contained vocal interruptions or signal processing errors were excluded from analyses. Finally, artifact-free individual trials were baseline-corrected by subtracting the mean f_0 values in the baseline period (−200 ms to 0) from the f_0 values after the perturbation onset and averaged to generate an overall response for each condition. The magnitude and latency of vocal responses were measured as the f_0 value and time when the voice f_0 contours reached their maximum value.

NetStation software was used for the offline analysis of the EEG signals. First, they were filtered using a band-pass filter with cutoff frequencies of 1–20 Hz and segmented into epochs from −200 to +500 ms relative to the perturbation onset. Then, an artifact detection procedure was applied to the segmented epochs to exclude trials whose voltage values exceeded ±55 μv of the moving average over an 80-ms window from further analysis. Individual electrodes were rejected if they contained artifacts in more than 20% of the epochs, and files were marked bad if they contained more than 10 bad channels. Finally, artifact-free trials were rereferenced to the average of the electrodes on each mastoid, averaged, and baseline-corrected to generate an overall cortical ERP response. The amplitudes and latencies of the N1 and P2 responses were measured as the negative and positive peaks in the time windows of 80–180 and 160–280 ms after the perturbation onset, respectively.

2.5. Statistical analyses

The magnitudes and latencies of vocal and cortical ERP responses to pitch perturbations were analyzed using repeated-measures analyses of variance (RM-ANOVAs) in SPSS (v.20.0). Two-way RM-ANOVAs were conducted to examine the differences in the magnitudes and latencies of vocal compensations as a function of group (individuals with PD vs. healthy controls) and condition (internal cue vs. external cue), in which group was chosen

as a between-subject factor and condition was chosen as a within-subject factor. The amplitudes and latencies of cortical N1 and P2 responses were subjected to three-way RM-ANOVAs, including a between-subject factor of group and 2 within-subject factors of condition and electrode site. Ten electrodes, including FC1, FC2, FCz, FC3, FC4, C1, C2, Cz, C3, and C4, were included in the analysis based on previous findings that showed mostly prominent and robust cortical ERPs to pitch perturbations at frontal and central regions (Chen et al., 2012; Scheerer et al., 2013). Subsidiary RM-ANOVAs were performed if higher order interactions between any of those variables were significant, and Bonferroni adjustments for multiple comparisons were used for post hoc analyses. Probability values were corrected using Greenhouse-Geisser for multiple degrees of freedom when violations of sphericity assumption occurred, whereas original degrees of freedom were reported for interpretation. Effect size indexed by partial η^2 was calculated to describe the size of differences between the conditions.

3. Results

3.1. Behavioral findings

Fig. 1 shows the grand-averaged voice f_o contours in response to pitch perturbations for individuals with PD (A) and healthy controls (B) and the T-bar plots of the magnitudes (C) and latencies (D) of vocal responses across the conditions. The internally cued condition elicited larger vocal compensations for pitch perturbations than the externally cued condition for individuals with PD, whereas this effect was smaller for healthy controls. A two-way RM-ANOVA conducted on the magnitudes of vocal responses revealed significant main effects of condition [$F(1, 54)=7.131$, $p = 0.010$, partial $\eta^2 = 0.117$] and group [$F(1, 54)=4.743$, $p = 0.034$, partial $\eta^2 = 0.081$] as well as a significant interaction between condition and group [$F(1, 54)=4.916$, $p = 0.031$, partial $\eta^2 = 0.083$]. Subsidiary analyses showed that individuals with PD produced significantly larger vocal compensations than healthy controls for the internally cued condition [$F(1, 54)=8.402$, $p = 0.005$, partial $\eta^2 = 0.135$], whereas the 2 groups did not differ significantly for the externally cued condition [$F(1, 54)=1.543$, $p = 0.220$, partial $\eta^2 = 0.028$] (see Fig. 1C). On the other hand, the externally cued condition elicited significantly smaller vocal compensations than the internally cued condition for individuals with PD [$F(1, 27) = 7.987$, $p = 0.009$, partial $\eta^2 = 0.228$], whereas the main effect of condition was not significant for healthy controls [$F(1, 27) = 0.204$, $p = 0.655$, partial $\eta^2 = 0.007$] (see Fig. 1C). In addition, the latencies of vocal responses were not modulated as a function of condition [$F(1, 54) = 0.680$, $p = 0.413$, partial $\eta^2 = 0.012$] and group [$F(1, 54) = 1.088$, $p = 0.302$, partial $\eta^2 = 0.020$] (see Fig. 1D). The interaction between condition and group was also not significant [$F(1, 54) = 0.004$, $p = 0.951$, partial $\eta^2 < 0.001$].

3.2. ERP findings

Fig. 2 shows the grand-averaged ERP waveforms (left) and topographical distributions of N1 and P2 amplitudes (right) in response to pitch perturbations as a function of condition for individuals with PD (top) and healthy controls (bottom). Fig. 3 shows

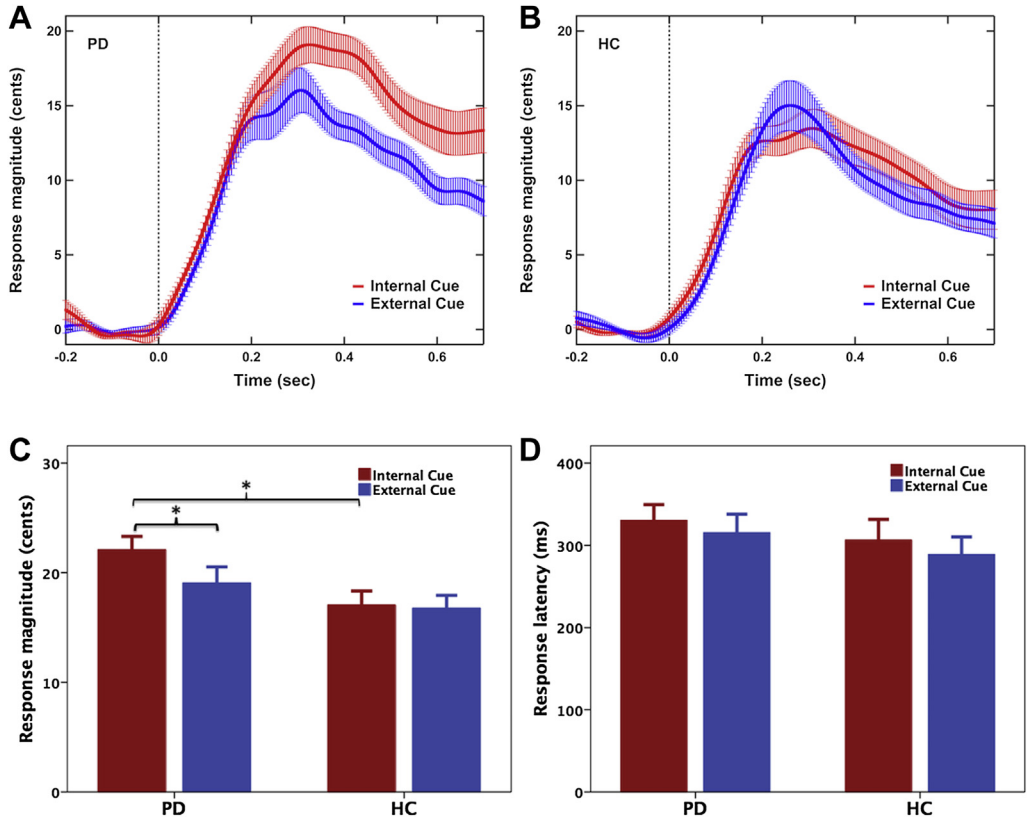

Fig. 1. Grand-averaged voice f_o contours (A, B) and T-bar plots of the magnitudes and latencies (mean and standard errors) of vocal compensations (C, D) in response to pitch perturbations under the internally (red) and externally (blue) cued conditions for individuals with PD and healthy controls. Vertical bars across the voice f_o contours represent the standard errors of the mean vocal responses. The asterisks indicate that individuals with PD produced significantly larger vocal compensations than healthy controls in the internally cued condition [$F(1, 54) = 8.402$, $p = 0.005$, partial $\eta^2 = 0.135$] and that the internally cued condition elicited significantly larger vocal compensations than the externally cued condition for individuals with PD [$F(1, 27) = 7.987$, $p = 0.009$, partial $\eta^2 = 0.228$]. Abbreviations: PD, Parkinson's disease; HC, healthy control. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

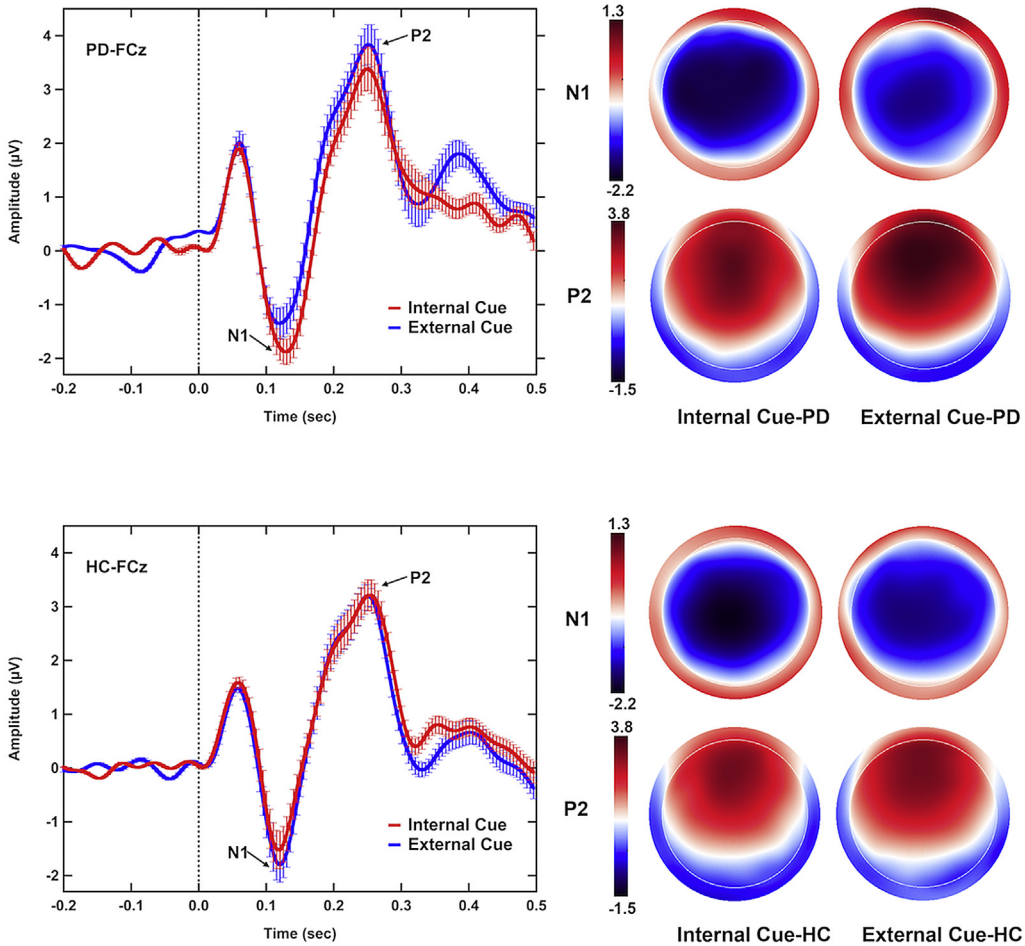

Fig. 2. Grand-averaged ERP waveforms at electrode FCz (left) and topographical distributions of N1 and P2 amplitudes (right) in response to pitch perturbations under the internally (red) and externally (blue) cued conditions for individuals with PD (top) and healthy controls (bottom). Vertical bars across the ERP waveforms represent the standard errors of the mean cortical responses. Abbreviations: ERP, event-related potential; HC, healthy control; PD, Parkinson's disease. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the T-bar plots of the amplitudes and latencies of the N1 and P2 responses as a function of condition and group. As can be seen in Figs. 2 and 3, there were differential effects of internal versus external cueing on the N1 and P2 responses for individuals with PD, as reflected by a decrease in the size of the N1 amplitudes but an increase in the size of the P2 amplitudes elicited by the externally cued condition relative to the internally cued condition. In contrast, the differences in the cortical responses between the internally and externally cued conditions were less prominent for healthy controls.

A three-way RM-ANOVA conducted on the N1 amplitudes revealed a significant main effect of electrode site [$F(9, 486) = 4.297$, $p = 0.004$, partial $\eta^2 = 0.074$], but the main effects of condition [$F(1, 54) = 3.541$, $p = 0.065$, partial $\eta^2 = 0.062$] and group [$F(1, 54) = 0.377$, $p = 0.542$, partial $\eta^2 = 0.007$] did not reach significance. However, there was a significant interaction between condition and group [$F(1, 54) = 10.308$, $p = 0.002$, partial $\eta^2 = 0.160$]. Subsidiary two-way RM-ANOVAs for individuals with PD showed that the internally cued condition elicited significantly larger N1 amplitudes than the externally cued condition [$F(1, 54) = 10.730$, $p = 0.003$, partial $\eta^2 = 0.284$] (see Fig. 3A). The main effect of electrode site [$F(9, 243) = 2.304$, $p = 0.072$, partial $\eta^2 = 0.079$] and the interaction between condition and electrode site [$F(1, 54) = 0.777$, $p = 0.546$, partial $\eta^2 = 0.028$] did not reach significance. In contrast, healthy controls did not exhibit significant main effects of condition [$F(1, 54) = 1.116$, $p = 0.300$, partial $\eta^2 = 0.040$] and electrode site [$F(1, 54) = 2.437$, $p = 0.073$, partial $\eta^2 = 0.083$], as well as interactions between condition and electrode site [$F(9, 243) = 1.242$, $p = 0.298$, partial $\eta^2 = 0.044$]. In addition, N1 amplitudes did not differ significantly between individuals with PD and healthy controls in the internally cued condition [$F(1, 54) = 2.780$, $p = 0.101$, partial $\eta^2 = 0.049$] or the externally cued condition [$F(1, 54) = 0.225$, $p = 0.637$, partial $\eta^2 = 0.004$]. Regarding the N1 latencies, there were no significant main effects of condition [$F(1, 54) = 1.446$, $p = 0.234$, partial $\eta^2 = 0.026$], electrode site [$F(9, 486) = 0.715$, $p = 0.540$, partial $\eta^2 = 0.013$], and group [$F(1, 54) = 0.702$, $p = 0.406$, partial $\eta^2 = 0.013$] (see Fig. 3B). No significant interactions among these variables were found ($p > 0.3$).

A three-way RM-ANOVA conducted on the P2 amplitudes revealed a significant main effect of electrode site [$F(9, 486) = 48.716$, $p < 0.001$, partial $\eta^2 = 0.474$], which was primarily caused by larger P2 amplitudes for the midline and medial electrodes relative to the lateral electrodes. The main effects of condition [$F(1, 54) = 3.129$, $p = 0.083$, partial $\eta^2 = 0.055$] and group [$F(1, 54) = 1.198$, $p = 0.279$, partial $\eta^2 = 0.022$] did not reach significance, but there was a significant interaction between condition and group [$F(1, 54) = 4.152$, $p = 0.046$, partial $\eta^2 = 0.071$]. Subsidiary two-way RM-ANOVAs revealed significantly larger P2 amplitudes in the externally cued condition relative to the internally cued condition for individuals with PD [$F(1, 27) = 6.324$, $p = 0.018$, partial

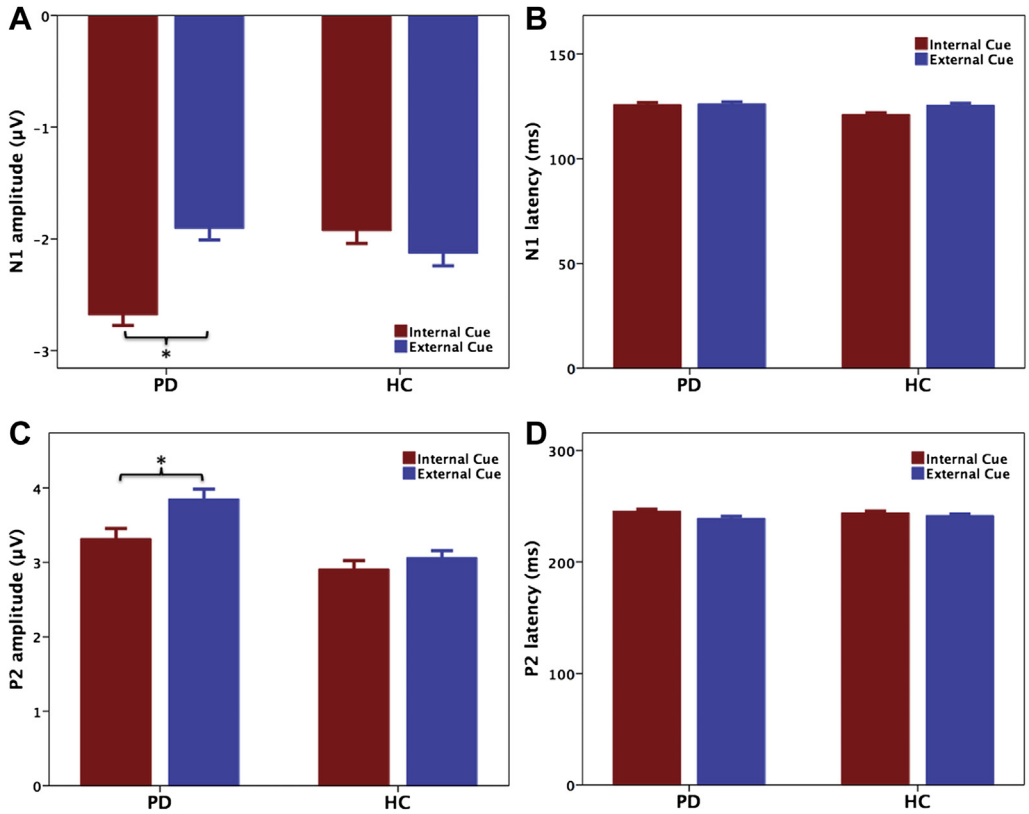

Fig. 3. T-bar plots of the amplitudes and latencies (means and standard errors) of N1 (A, B) and P2 (C, D) responses to pitch perturbations under the internally (red) and externally (blue) cued conditions for individuals with PD and healthy controls. The asterisks indicate that individuals with PD produced significantly smaller N1 amplitudes [$F(1, 54) = 10.730$, $p = 0.003$, partial $\eta^2 = 0.284$] and larger P2 amplitudes [$F(1, 27) = 6.324$, $p = 0.018$, partial $\eta^2 = 0.190$] in the externally versus internally cued condition. Abbreviations: PD, Parkinson's disease; HC, healthy control. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

$\eta^2 = 0.190$], but P2 amplitudes did not differ significantly as a function of condition for healthy controls [$F(1, 27) = 0.358$, $p = 0.554$, partial $\eta^2 = 0.013$] (see Fig. 3C). Although there was a tendency for individuals with PD to exhibit larger P2 amplitudes than healthy controls (see Fig. 3C), the difference in P2 amplitudes between the 2 groups was not significant for either the internally [$F(1, 54) = 0.572$, $p = 0.453$, partial $\eta^2 = 0.010$] or externally cued condition [$F(1, 54) = 2.544$, $p = 0.117$, partial $\eta^2 = 0.045$]. Regarding the P2 latencies, main effects of condition [$F(1, 54) = 2.330$, $p = 0.133$, partial $\eta^2 = 0.041$], group [$F(1, 54) = 0.005$, $p = 0.945$, partial $\eta^2 < 0.001$], and electrodes [$F(9, 486) = 1.187$, $p = 0.318$, partial $\eta^2 = 0.022$] did not reach significance (see Fig. 3D). There were also no significant interactions among these variables ($p > 0.4$).

3.3. Brain-behavior correlations

To examine the specific contributions of changes in cortical activity to changes in vocal motor behavior as a consequence of external cueing, we used Pearson correlation analyses to correlate any changes in the magnitudes of vocal responses with any changes in the amplitudes of cortical N1/P2 responses for the externally versus internally cued condition. As shown in Fig. 4, the external-internal vocal response magnitudes were not significantly correlated with the external-internal N1 amplitudes ($r = 0.323$, $p = 0.093$). However, there was a significant negative correlation between the external-internal vocal response magnitudes and the external-internal P2 amplitudes ($r = -0.453$, $p = 0.015$), indicating that enhanced cortical P2 responses made significant contributions to suppressed vocal responses to pitch perturbations that followed external auditory cueing.

4. Discussion

To the best of our knowledge, this study is the first demonstration that internal and external auditory cueing differentially modulate the neurobehavioral processing of vocal pitch regulation in individuals with PD. Behaviorally, individuals with PD produced significantly larger vocal compensations for pitch perturbations than healthy controls in the internally cued condition and exhibited a significant decrease in the magnitude of vocal compensations when given external auditory cues. At the level of cortex, individuals with PD produced significantly smaller N1 responses and larger P2 responses in the externally versus internally cued condition. Moreover, they exhibited a significant correlation between suppressed vocal compensations and enhanced P2 responses. In contrast, these behavioral and neural effects did not exist for healthy controls. Our findings provide evidence that external auditory cueing can facilitate auditory-motor processing of vocal pitch errors in individuals with PD at the levels of both behavior and cortex, suggesting that the improvement of speech motor deficits in PD with external cueing strategy can occur in a top-down manner.

4.1. Neurobehavioral effects of external cueing

Consistent with other studies (Chen et al., 2013; Huang et al., 2016; Liu et al., 2012; Mollaei et al., 2016), the present study revealed larger vocal compensations for pitch perturbations for individuals with PD than for healthy controls in the internally cued condition. These results lend further support to the hypothesis that PD leads to the progressive impairment of cognitive and motor processes that rely on internal cues (Hsieh et al., 1995; Lewis et al.,

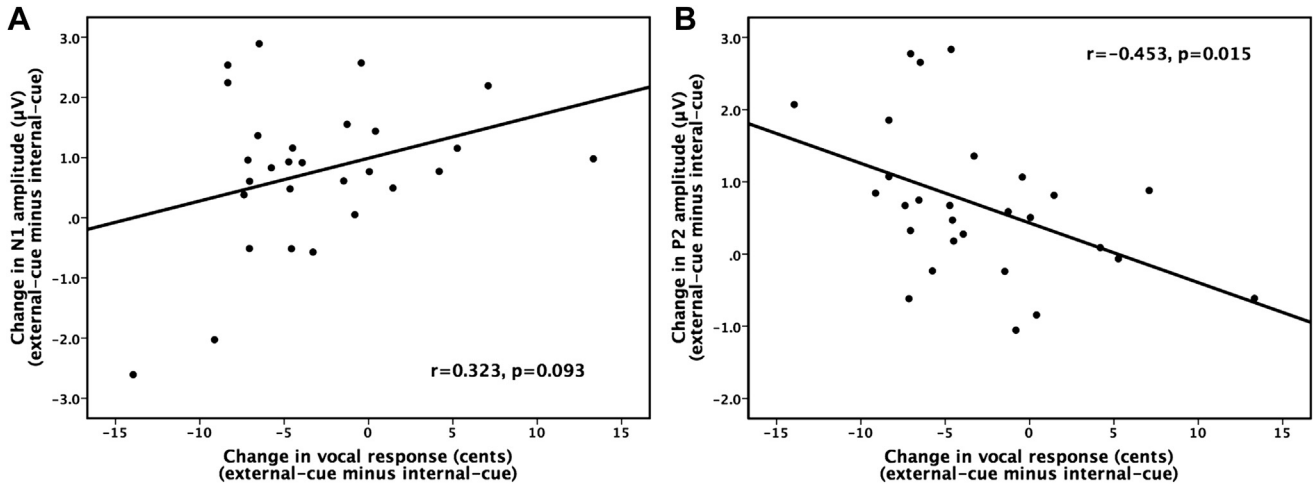

Fig. 4. The changes of vocal response magnitudes are plotted against the changes of N1 and P2 amplitudes in response to pitch perturbations in individual with PD during the externally versus internally cued condition. The external-internal vocal response magnitudes were not significantly correlated with the external-internal N1 amplitudes ($r = 0.323$, $p = 0.093$) (A), whereas there was a significant negative correlation between the external-internal vocal response magnitudes and the external-internal P2 amplitudes ($r = -0.453$, $p = 0.015$) (B). Abbreviation: PD, Parkinson's disease.

2000; Sapir, 2014). Of particular interest in the present study were the modulatory effects of external cueing on vocal pitch regulation in individuals with PD, as reflected by significantly smaller vocal compensations in the externally versus internally cued condition. Because patients with PD, Alzheimer's disease, and temporal lobe epilepsy are associated with significantly larger vocal compensations for pitch perturbations relative to healthy controls (Chen et al., 2013; Li et al., 2016; Liu et al., 2012; Mollaei et al., 2016; Ranasinghe et al., 2017), the abnormally enhanced vocal compensations could serve as a behavioral index of impaired speech motor control caused by these neurological disorders (Ranasinghe et al., 2017). In light of this point, the observation of suppressed vocal compensations in individuals with PD following external cueing may reflect an improvement in their ability to monitor incoming sensory feedback and control speech production. These findings are in line with previous research that showed considerable improvements in speech production when individuals with PD are given explicit instructions (Clark et al., 2014; Dromey and Ramig, 1998; Goberman and Elmer, 2005; Ho et al., 1999, 2000; Tjaden et al., 2013; Weir-Mayta et al., 2017). As well, they parallel the use of external auditory or visual cues to improve movement disorders in individuals with PD, such as lines on the paper to improve handwriting and a visual cue to regulate stride length (Ford et al., 2010; Lewis et al., 2000; Morris et al., 1996; Oliveira et al., 1997; Thaut et al., 1996).

A remarkable finding in the present study is that providing external auditory cues led to suppressed N1 responses and enhanced P2 responses that were significantly correlated with suppressed vocal compensations in individuals with PD. To date, the neural impact of external cueing on speech motor deficits in individuals with PD has been rarely investigated. There are 2 PET studies that focused on the changes in the speech motor networks after individuals with PD received explicit loudness instructions in the course of LSVT LOUD. Liotti et al. (2003) found that significant improvement in speech loudness was accompanied by increases in right-lateralized activity in the anterior insular, basal ganglia (BG), and dorsolateral prefrontal cortex (DLPFC) and decreased activity in the primary motor cortex (M1), SMA, and PMC. Narayana et al. (2010) reported significant correlations between improved speech volume and increased activation in the right M1, STG, and DLPFC. In line with these studies, the observed modulations of N1 and P2 responses for individuals with PD reflect alterations of the cortical sensorimotor networks that underlie improved speech motor control associated with external cueing. Note that, the P2 responses for individuals with PD were relatively but not statistically larger than those for healthy controls, which is in contrast to the findings reported by Huang et al. (2016) that individuals with PD produced significantly larger P2 responses to pitch perturbations than healthy controls. This inconsistency may be related to the difference in the experimental methods.

4.2. Neural mechanisms of external cueing

Despite the well-documented beneficial effects of external cueing on speech production in individuals with PD (Clark et al., 2014; Dromey and Ramig, 1998; Goberman and Elmer, 2005; Ho et al., 1999; Tjaden et al., 2013), the underlying neural mechanisms remain poorly understood. However, previous studies of the benefit of external cueing on other voluntary movements suggest that these sensory cues activate a compensatory neural mechanism that reduces motor symptoms in PD (Lewis et al., 2000; Morris et al., 1996; Thaut et al., 1996). Specifically, while internally cued movements preferentially involve the cortico-BG (CBG) network (Jueptner and Weiller, 1998; Vaillancourt et al., 2007), externally cued movements prominently activate the cortico-cerebellar (CC) network (Gowen and Miall, 2007; Purzner et al., 2007). Moreover, Yu et al. (2007) reported a significant correlation between decreased activity in the contralateral putamen and increased activity in the ipsilateral cerebellum in individuals with PD during a motor-timing task, further supporting the compensatory role of the CC network in response to damage in the CBG network. Therefore, it has been proposed that impaired limb control that relies on internal cueing in individuals with PD is caused by their dysfunctional CBG network and that these impairments can be improved with external cues because the CC network that remains intact compensates for the CBG network (Jahanshahi et al., 1995; Lewis et al., 2000, 2007).

Speech production involves both feedforward and feedback (auditory and somatosensory) control (Civier et al., 2010), which engages both cortical areas such as the STG, IFG, and IPL (Behroozmand et al., 2017; Chang et al., 2013; Parkinson et al., 2012; Zarate and Zatorre, 2008) and subcortical regions that include the BG and cerebellum (Golfinopoulos et al., 2011; Mollaei et al., 2013; Parrell et al., 2017; Tourville et al., 2008). It is suggested that there is a dynamic balance between feedback and feedforward control

during speech production and that impairment of feedforward control system may shift the balance toward feedback control system (Civier et al., 2010; Parrell et al., 2017). For individuals with PD, dysfunctions in their CBG network may comprise critical elements of the feedforward system and lead to greater reliance on the feedback system. Moreover, individuals with PD often have deficits in laryngeal somatosensory function (Hammer and Barlow, 2010), and the loss of somatosensory feedback caused by anesthesia of the vocal tract has been shown to lead to an increased weighting of auditory feedback as reflected by increased vocal compensations for pitch perturbations (Larson et al., 2008). These findings suggest that feedforward control and somatosensory feedback may be impaired in individuals with PD, resulting in their increased sensitivity to or reliance on auditory feedback, which may in turn be responsible for their excessive vocal compensations for vocal pitch errors during the internally cued condition. When provided external auditory cues, individuals with PD may recruit brain regions within their intact CC network to compensate for the affected CBG network and restore the function of the feedforward system, allowing them to rely less on auditory feedback and produce suppressed vocal compensations.

Nevertheless, the compensatory role of the CC network during motor and cognitive tasks in PD is still a matter of debate (Martinu and Monchi, 2013). The primary concern is that the CC network is not intact but affected by PD pathophysiology, as evidenced by a decrease in cerebellar gray matter in individuals with PD that present tremor (Benninger et al., 2009) or a significant contraction in the left cerebellum in individuals with early-stage PD (Borghammer et al., 2010). Moreover, the CBG and CC networks are not completely distinct but overlapping through direct interactions and cortical associations (Hackney et al., 2015). Therefore, similar to the CBG network, the CC network may also be compromised by PD. On the other hand, activity in the BG and/or cerebellum was not significantly correlated with treatment outcomes of LSVT LOUD (Narayana et al., 2010). In addition, it is suggested that the cerebellum plays a crucial role in feedforward control of speech but is not essential for feedback control of speech (Parrell et al., 2017). Thus, it is less likely that the facilitatory effects of external cueing on vocal pitch regulation in individuals with PD are the result of the compensatory mechanisms that depend on cerebellar activity.

As an alternative explanation, we propose that external cueing may facilitate auditory feedback control of vocal pitch production in individuals with PD via the top-down modulation of the speech motor systems. This hypothesis is motivated by our findings that suppressed vocal compensations were accompanied by changes in cortical activity as reflected by decreased cortical N1 and increased cortical P2 responses for individuals with PD when given external auditory cues. The N1 component receives contributions from the temporal regions and is thought to reflect the early detection of deviant auditory feedback (Martin et al., 2008). Individuals with PD are impaired in perceiving self-produced speech as characterized by an overestimation of their speech volume (Fox and Ramig, 1997; Ho et al., 2000), which is thought to be related to their increased sensitivity to auditory feedback during the online monitoring of speech production (Huang et al., 2016; Sapir, 2014). Thus, decreased N1 responses in the externally versus internally cued condition suggest that individuals with PD may become less sensitive to vocal feedback perturbations when provided external auditory cues. In contrast to N1, the P2 component is thought to reflect the later auditory-motor interactions that require high-order cognitive processing, as evidenced by the modulation of P2 responses to voice pitch perturbations as a function of focused and divided attention (Hu et al., 2015; Liu et al., 2015, 2018). Moreover, working memory training led to a combination of suppressed vocal compensations and enhanced P2 responses due to increased activity in the left middle frontal gyrus, IPL, right IFG, and insula (Guo et al., 2017). Thus, the observation of larger P2 responses in the externally versus internally cued condition in individuals with PD may reflect an increased recruitment of cognitive areas (e.g., frontal regions) that generate an inhibitory influence on speech motor behaviors. This argument is supported by a significant correlation we observed between suppressed vocal compensations and enhanced P2 responses in individuals with PD following external cueing. Similarly, significant correlations were found between improved speech volume and increased activity in the cortical frontal and temporal regions for individuals with PD after LSVT LOUD (Narayana et al., 2010). Taken together, the modulation of vocal compensations for pitch perturbations and associated cortical N1 and P2 responses may be the result of a top-down mechanism elicited by external cueing, which causes individuals with PD to rely less on auditory feedback and inhibit excessive vocal compensations when producing an externally cued target f_0.

4.3. Clinical implications

Until now, few studies have offered evidence of neural changes related to speech production as a result of external cueing in individuals with PD. Together with 2 PET studies that reported improved voice intensity after LSVT LOUD in individuals with PD that was correlated with increased activity in auditory and motor regions as well as prefrontal regions (Liotti et al., 2003; Narayana et al., 2010), the present findings suggest a top-down mechanism triggered by external cueing that facilitates auditory-vocal integration in PD and highlight the importance of cognitive functions mediated by prefrontal regions in speech motor control. Historically, much emphasis has been placed on the extensive vocal training required for the treatment of motor speech disorders. A growing body of literature, however, has shown that precise control of speech production is influenced by cognitive functions such as attention and working memory (Guo et al., 2017; Liu et al., 2015; Scheerer et al., 2016; Tumber et al., 2014). Moreover, deficits in executive function and working memory in individuals with Alzheimer's disease have been shown to be significantly correlated with abnormal vocal compensations for pitch perturbations (Ranasinghe et al., 2017). Therefore, training targeted at improving cognitive functions may enhance the treatment effect of external cueing on speech motor deficits in PD. Future clinical evidence is needed to support this hypothesis.

4.4. Limitations

Several limitations to our work should be acknowledged. Although differential patterns of the cortical processing of vocal pitch regulations were observed for individuals with PD when provided internal and external auditory cues, it is not likely to localize the precise neural sources involved in these facilitatory effects due to low spatial resolution of the EEG technique. Future research should be conducted to reveal the neural networks that underlie this improvement using other neuroimaging techniques such as functional magnetic resonance imaging and PET. On the other hand, cognitive profile of individuals with PD evaluated by the mini-mental state examination was in the normal range, but this method lacks adequate sampling of cognitive functions (e.g., attentional control, working memory) and is not sensitive to cognitive deficits common to PD in the early stage of the disease. Given the influence of auditory attention and working memory on the auditory-motor processing of speech production (Guo et al., 2017; Liu et al., 2015; Tumber et al., 2014), a comprehensive assessment of cognitive functions should be included in the future studies to examine the possible effects of cognitive deficits

associated with PD on the improvement of speech motor control with external cues. Finally, a series of studies have shown that auditory feedback control of speech production is sensitive to language experience (Chen et al., 2012; Liu et al., 2010; Mitsuya et al., 2013, 2015). Specifically, Mandarin speakers compensate for vocal pitch perturbations to a lesser degree than English speakers (Ning et al., 2014, 2015). It is thus possible that the beneficial effects of external cueing on speech motor deficits in PD observed in the present study may be influenced by language experience. This possibility needs to be explored in future studies.

5. Conclusion

The present study investigated the behavioral and neural effects of external versus internal cueing on auditory feedback control of speech production in individuals with PD. The results showed decreased vocal compensations for pitch perturbations that were significantly correlated with increased P2 responses and decreased N1 responses for individuals with PD when provided external auditory cues. These findings provide neurobehavioral evidence, for the first time, that external cueing can compensate for deficits in the auditory-motor control of speech production via the top-down modulation of the speech motor systems.

Disclosure

The authors declare no conflict of interest.

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