2018

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Defne Abur, Rosemary A Lester-Smith, Ayoub Daliri, Ashling A Lupiani, Frank H Guenther, Cara E Stepp. 2018. "Sensorimotor adaptation of voice fundamental frequency in Parkinson's disease.." PLoS One, Volume 13, Issue 1:e0191839.

https://hdl.handle.net/2144/27108

Journal of Speech, Language, and Hearing Research

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Journal:	*Journal of Speech, Language, and Hearing Research*
Manuscript ID	JSLHR-S-16-0346
Manuscript Type:	Research Article
Date Submitted by the Author:	31-Aug-2016
Complete List of Authors:	Abur, Defne; Boston University, Speech, Language, and Hearing Sciences Lester-Smith, Rosemary; Boston University, Speech, Language, and Hearing Sciences Daliri, Ayoub; Boston University, Department of Speech, Language, and Hearing Sciences, Sargent College of Health and Rehabilitation Sciences Lupiani, Ashling; Boston University, Speech, Language, and Hearing Sciences Guenther, Frank; Boston University, Cognitive and Neural Systems Stepp, Cara; Boston University, Speech, Language, and Hearing Sciences
Keywords:	Neurologic disorders, Psychoacoustics, Speech motor control, Voice

SENSORIMOTOR ADAPTATION OF VOICE FUNDAMENTAL FREQUENCY IN PARKINSON'S DISEASE

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Running Head: Voice Sensorimotor Adaptation in Parkinson's

Key words: sensorimotor adaptation, speech motor control, Parkinson's disease, fundamental frequency

ABSTRACT

Purpose: This study examined adaptive responses to auditory perturbation of fundamental frequency (f_o) in speakers with Parkinson's disease (PD) as compared to control speakers.

Method: Sixteen speakers with PD and nineteen control speakers produced sustained vowels while they received perturbed auditory feedback (i.e., f_o gradually shifted upward or downward). Pitch acuity was quantified for all participants using a just-noticeable-difference (JND) paradigm. Twelve listeners provided estimates of the speech intelligibility for PD speakers by transcribing Sentence Intelligibility Test stimuli presented with multi-speaker babble.

Results: While control speakers generally showed consistent compensatory (opposing the perturbation) responses, speakers with PD showed no learning on average, with individual speakers showing highly variable responses. For individuals in the PD group, the degree of compensation to perturbation was not significantly correlated with age, years since diagnosis, disease progression, pitch acuity, or intelligibility.

Conclusions: These findings indicate that there is an impairment in the auditory-motor integration (motor learning) process in PD. The pitch acuity results showed no significant differences between speaker groups, suggesting that the f_o control deficit in PD is not the result of purely perceptual mechanisms. Future work is needed to better characterize auditory-motor integration associated with PD.

INTRODUCTION

Parkinson's disease (PD) is a slowly progressing neurodegenerative condition. It affects approximately 3 – 5% of the population over the age of 85 years (Fahn, 2003), with a prevalence that is predicted to increase drastically (Dorsey et al., 2007). In addition to the cardinal motor deficits such as bradykinesia, rigidity, tremor, and postural instability, over 90% of individuals with PD develop hypokinetic dysarthria, a motor speech disorder (Logemann, Fisher, Boshes, & Blonsky, 1978). This frequently encompasses dysprosody, which can involve 'monopitch', or the perception of reduced fluctuation in fundamental frequency (f_o) during speech production (Canter, 1963; Goberman & Elmer, 2005). These disruptions in typical prosodic patterns in speakers with PD have been shown to negatively influence listeners' perceptions of the speakers' tone, personality, and mood (Jaywant & Pell, 2010) and to correlate to listeners' perception of the 'naturalness' of their speech (Anand & Stepp, 2015). Given the importance of prosody for speech intelligibility and social communication in PD (McNamara & Durso, 2003; Miller, Noble, Jones, & Burn, 2006; Monrad-Krohn, 1947; Pell, Cheang, & Leonard, 2006), it is necessary to better characterize the underlying causes of prosodic impairments in order to improve the assessment and treatment of speech in PD. This study aims to investigate the patterns of sensorimotor adaptation to perturbation of voice f_o in speakers with PD to clarify deficits in f_o control in PD.

Sensorimotor function has been previously examined in healthy controls in both the visuomotor and auditory-motor domains. Studies of visuomotor control involve distortion of visual feedback during voluntary movement (Kagerer, Contreras-Vidal, & Stelmach, 1997; Nakajima, 1988). These studies have revealed that individuals generally show compensatory (opposing the direction of the perturbation) 'adaptive' responses to gradual modifications in visual feedback as well as compensatory 'reflexive' responses to brief, unanticipated perturbations in visual feedback. Studies of auditory-motor control involving gradual modification of auditory feedback have also revealed similar motor adaptation to feedback perturbation. As f_o was gradually increased, speakers showed compensatory adaptive responses, gradually lowering their f_o across the experiment (Jones & Keough, 2008; Jones & Munhall, 2000, 2002, 2005; Keough & Jones, 2009; Patel, Niziolek, Reilly, & Guenther, 2011). Studies involving brief, unanticipated perturbation of auditory feedback similarly showed that speakers had compensatory reflexive responses: as f_o was suddenly increased, speakers responded by quickly lowering their f_o (Burnett & Larson, 2002; Larson, Burnett, Bauer, Kiran, & Hain, 2001). Adaptive responses to gradual modifications involve auditory-motor integration (i.e. motor learning), which requires the use of both feedforward and feedback control, whereas reflexive responses primarily involve only the feedback system.

The interactions of the feedforward and feedback mechanisms during speech production can be accounted for by the Directions Into Velocities of Articulators (DIVA) model, a neural network model of speech motor skill acquisition and speech production. According to DIVA, adults primarily rely on *feedforward* speech motor control to quickly generate motor programs that were learned during prior productions (Guenther, 2006). The *feedback* system detects errors between expected and actual sensory feedback, which in turn produces corrective motor commands, and updates the feedforward system (Guenther, Ghosh, & Tourville, 2006). Thus, in typical speakers, gradual perturbations of auditory feedback result in motor learning in the form of compensatory adaptations (Houde & Jordan, 1998; Jones & Keough, 2008; Jones & Munhall, 2005; Lametti, Nasir, & Ostry, 2012; Villacorta, Perkell, & Guenther, 2007), whereas sudden, unexpected perturbations in auditory feedback result in fast (~150 ms) ‘reflexive’ compensatory responses (Burnett, Freedland, Larson, & Hain, 1998; Tourville, Reilly, & Guenther, 2008)

Studies of sensorimotor adaptation in PD have revealed some atypical responses to both gradual and reflexive perturbations in the visual domain. Mongeon, Blanchet, and Messier (2013) investigated both adaptive responses to gradual modifications and reflexive responses to brief, unanticipated perturbations of visual feedback related to hand trajectory during a reaching movement in individuals with PD and healthy controls. They found that individuals with PD exhibited reduced response magnitudes to sudden visual perturbations compared to healthy controls. However, during gradual visual perturbations, individuals with PD showed adaptation magnitudes similar to healthy controls. In contrast, Contreras-Vidal and Buch (2003) found reduced adaptive responses to gradual perturbation of visual feedback and continued errors once the perturbations were removed in individuals with PD.

In the speech domain, adaptive responses to gradual alterations in the acoustical characteristics of vowels (i.e. formants; Mollaei, Shiller, & Gracco, 2013) have been studied in speakers with PD. Speakers with PD had reduced adaptive responses compared to healthy control speakers when analyzed on a group level. However, articulatory motor control (which primarily affects formants) may differ from control of vocal parameters such as f_o (Guenther et al., 2006; Larson, Altman, Liu, & Hain, 2008; Perkell et al., 2000). In support of this possibility, vocal characteristics in PD have a distinct manifestation compared with articulatory symptoms (Ho, Iansek, Marigliani, Bradshaw, & Gates, 1999; Logemann et al., 1978; S. Skodda, Grönheit, & Schlegel, 2012). To our knowledge, adaptive responses to gradual perturbation of f_o have not yet been studied in PD. Reflexive responses to sudden, brief, perturbations in f_o in PD have revealed *larger* compensatory response magnitudes in PD (Chen et al., 2013; Liu, Wang, Metman, & Larson, 2012; Mollaei, Shiller, Baum, & Gracco, 2016) and longer response durations (Kiran & Larson, 2001) relative to control speakers. In the current work, auditory-motor control of f_o was investigated by comparing adaptive responses to gradual perturbation of f_o in speakers with PD relative to control speakers. We hypothesized that speakers with PD would show reduced adaptation to gradual perturbation of f_o as compared to control speakers due to disordered sensorimotor integration.

METHOD

A. Participants

Twenty-one speakers with PD and twenty-eight control speakers were recruited to participate in the study. Four speakers with PD were excluded from the study group due to abnormal hearing thresholds for older adults (N=2, see section C) or inability to complete the main experimental task (N=2). Eight control speakers were excluded from the study group due abnormal hearing thresholds (N = 6), perceptually atypical voice (N=1), and failure of a pre-study cognitive screening (N=1). One speaker with PD and one control speaker were excluded due to data analyses restrictions on the primary experimental task (see section G). Thus, sixteen speakers with PD aged 52 – 73 years (7 female) and nineteen healthy control speakers aged 50 – 77 years (8 female) were included in the study (see Table 1). The complete study lasted two sessions. Fourteen speakers with PD and eleven control speakers completed both sessions, and two speakers with PD and eight control speakers completed a single session. All speakers with PD were diagnosed with idiopathic PD by a neurologist prior to participation in the study and were receiving daily levodopa/carbidopa therapy. Additionally, many were regularly taking the following medications: dopamine agonists (N = 4), Monoamine oxidase B (MAO-B) inhibitors (N = 3), Catechol-O-Methyl Transferase (COMT) inhibitors (N = 2), Amantadine (N = 2), anticholinergics (N = 1), anti-epileptics (N = 1), anti-depressants (N = 3), and Citrulline (N = 1). Twelve naïve listeners aged 18 – 23 years (6 female) were included in the study to assess the speech intelligibility of speakers with PD (see section G). Control speakers and listeners denied any known neurological, speech, hearing, cognitive, or language disorders. All participants provided written consent in compliance with the Boston University Institutional Review Board.

B. Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

Part III (Motor Examination) of the Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Ratings Scale (MDS-UPDRS; Goetz et al., 2008) was administered to each participant with PD to assess the motor signs of PD. This documents the severity of abnormalities during execution of motor function tasks such as speech, upper and lower extremity movements, and walking. The first author, certified to administer MDS-UPDRS, scored each examination per protocol. The UPDRS total motor score (see Table 1) was used as a correlate of disease progression.

C. Hearing Thresholds

Each participant underwent pure-tone hearing threshold testing at 250, 500, 1000, 1500, 2000, 3000, and 4000 Hz using Etymotic 3A insert earphones and the Grason-Stadler GSI 18 Screening Audiometer. All participants had hearing thresholds within normal range for older adults (under 25 dB HL for frequencies 1000 Hz and below, and under 40 dB HL above 1000 Hz; Schow, 1991). None of the participants wore hearing aids.

D. f_o Adaptation Procedure

All experimental sessions were conducted in a sound-attenuating audiometric booth. Participants were seated in front of a computer monitor and wore a Shure omnidirectional MX153 earset microphone positioned at approximately 45 degrees from the midline and 7 cm from the corner of the mouth. The microphone signal was amplified via an RME Quadmic II microphone preamplifier and digitized via a MOTU Ultralite-mk3 Hybrid soundcard with a sampling rate of 48000 Hz. The auditory feedback was amplified at least 5 dB relative to the sound pressure level (SPL) at the microphone (based on relative dB between microphone and ear; Cornelisse, Gagnne, & Seewald, 1991). For calibration, the intensity of the auditory feedback in the headphones was measured using an IEC 60318-1 coupler (Type 4153, Bruel & Kjaer Inc., Norcross, GA) connected to a sound level meter (Type 2250A Hand Held Analyzer with Type 4947 ½" Pressure Field Microphone, Bruel & Kjaer Inc., Norcross, GA) such that a electrolarynx (TruTone Artificial Larynx, Griffin Laboratories, Temecula, CA) input with an intensity of 75 dB SPL approximately 7 cm from the microphone resulted in at least 80 dB SPL output in the headphones. Auditory feedback was administered via Sennheiser HD 280 Pro headphones, which attenuate air-conducted sound by approximately 32 dB (Sennheiser Electronic Corporation). The f_o was manipulated using Audapter[1] (Cai, Boucek, Ghosh, Guenther, & Perkell, 2008), a MATLAB software package for configurable real-time manipulation of acoustic parameters of speech, using the ASIO4ALL driver. The total processing delay was 25 ms, which is below the threshold at which delayed auditory feedback can cause speech dysfluency (Stuart, Kalinowski, Rastatter, & Lynch, 2002; Yates, 1963).

The adaptive responses to f_o perturbation were recorded under three conditions: ‘‘shift-up", "shift-down", and "control", with the order counterbalanced across participants. Each condition consisted of 160 trials that were 11 s in duration. Participants were instructed to produce a sustained /ɑ/ for 3 s when "aaa" was displayed in green on the computer monitor and to then rest their voice until the next trial began. The "shift-up" and "shift-down" conditions consisted of trials over four ordered stages: baseline, ramp, hold, and after-effect. In the "shift-

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[1] Audapter downsampled the microphone signal to 16,000 Hz, shifted the voice f_o, presented auditory feedback in the headphones, and saved the audio data.

up" condition, the first 20 utterances, referred to as the *baseline*, were produced while receiving typical (unperturbed) feedback. In the following 60 trials, referred to as the *ramp*, the f_o in the auditory feedback increased by 0.0169 semitones (ST) with each successive trial, reaching a total level of 1 ST of perturbation above the participant's true f_o. For the next 40 trials, referred to as the *hold*, the f_o of the auditory feedback was maintained at the level of +1 ST of perturbation. In the last 20 trials, referred to as the *after-effect*, the auditory feedback was the same as the baseline (i.e., there was no f_o perturbation). The "shift-down" condition was identical, except that, during the ramp, the f_o of the auditory feedback decreased by 0.0169 ST in each successive utterance, reaching a total level of -1 ST of perturbation by the end of the ramp. Perturbations during the ramp and hold phases were applied throughout the entire period of voicing. In the "control" condition, participants received their typical (unperturbed) feedback during all 160 trials (similar to the baseline and after-effect periods of the "shift-up" and "shift-down" conditions). The participants did not receive any information about differences among the three conditions.

E. Pitch Acuity

All participants completed a pitch discrimination task to assess auditory acuity to f_o, or pitch acuity. Each trial consisted of two pure tones, presented via Sennheiser HD 280 Pro headphones. Each tone was 2 seconds in duration. The tones in each trial were separated by approximately 20 ms and were presented in random order. Stimulus presentation was controlled using a custom-written MATLAB (The Mathworks, Inc., 2013, Version 8.1.0.604 [R2013b]) script. Tones were played at an intensity of 65 dB, calibrated using the same method as the adaptation procedure but using the MATLAB generated stimuli as the input. Participants were asked to judge whether the tones were the 'same' or 'different'. The initial difference between the two tones was 0.4 ST (10 Hz) with a reference tone of 440 Hz. Two consecutive correct judgments resulted in a progressively smaller difference (downstep) between the two tones in subsequent trials, whereas an incorrect judgment resulted in a progressively larger difference (upstep) between subsequent sets of tones, with a set ratio of downstep = upstep/2.448. The magnitude of the upstep was initially 0.2 ST (5 Hz). As trial number increased, the upstep decreased to 0.1 ST (2.5 Hz), 0.05 (1.27 Hz), and 0.01 (0.25 Hz), at the tenth, twentieth, and thirtieth trial, respectively. The experiment continued until there were 16 'reversals' (an upstep followed by a downstep, or vice versa). Catch trials with no difference between the two tones were presented pseudo-randomly in 33% of trials to ensure data validity and attention to the task. Each participant performed between 36 and 85 trials, with an average of 70 trials. The duration of this task was 6 – 10 min.

F. Speech Intelligibility Test (SIT)

Speakers with PD completed a randomly generated short Speech Intelligibility Test (SIT; Yorkson, Beukelman, Hakel, & Dorsey, 2007) . The SIT consisted of a set of 11 sentences increasing in word count from 5 to 15 words per sentence. All speakers wore a Shure omnidirectional MX153 earset microphone positioned at approximately 45 degrees from the midline and 7 cm from the corner of the mouth. For all recordings, the microphone signal was amplified via an RME Quadmic II microphone preamplifier, digitized via a MOTU Ultralite-mk3 Hybrid soundcard, and recorded using Audacity (Audacity Team, 2012, Audacity®. Version 2.0.0. audio editor and recorder) with a sampling rate of 44,100 Hz. Speakers were instructed to read the sentences in their typical speaking voice.

G. Data Analysis

To determine adaptive responses, the mean f_o was calculated over each trial using an autocorrelation method via Praat (Boersma & Weenink, 2014, Version 5.4.08 – Version 6.0) scripts. All trials were inspected and manually corrected for tracking issues or noise by selecting a stable portion of the signal with a minimum duration of 1 second. The mean f_o of each trial was converted to ST relative to the mean f_o of the baseline of that condition. In order to account for normal variation in f_o over the course of 160 trials, the f_o during the control condition in which no perturbation was applied was subtracted from the “shift-up” and “shift-down” conditions to determine the resulting adaptive responses. Data from one speaker with PD and one control speaker were excluded due to unstable vocal control during the control condition (defined as a greater than 3 ST range within one phase (baseline, ramp, hold, and/or after-effect). Since the control condition was used to normalize the “shift-up” and “shift-down” conditions, this large degree of variability was determined to result in adaptive responses that were likely not representative. Consequently, data from these two participants was excluded from the final dataset. Two additional control speakers had unstable vocalizations during the control condition; however, they were able to return to repeat the task more than a week later and the second run was included in the study. Two control speakers experienced no auditory feedback during one of the adaptation conditions due to equipment failure and returned to repeat those conditions; one speaker returned five days later and the other speaker returned twenty eight days later. One control speaker experienced equipment failure during the “shift-up” condition, resulting in partial completion, exposing the participant to only 73 trials of perturbation. This speaker completed a full “shift-up” condition directly after the partial run. In total, eleven control speakers and fourteen speakers with PD completed all three conditions: “shift-up”, “shift-down”, and control. Eight control speakers and two speakers with PD were only able to complete the control condition and either the “shift-up” or “shift-down” condition. Given the counterbalancing of condition order and excluded participants, fifteen total adaptive responses were successfully recorded and used in analyses for each “shift-up” and “shift-down” condition for both the control and PD group. The two-way mixed-model analyses of variance (ANOVAs) were performed on the “shift-up” and “shift-down” adaptive responses to assess the effects of group (between-participant; speakers with PD vs. control speakers), phase (within-participant; baseline, ramp, hold, after-effect), and their interaction. Factor effect sizes were quantified using the squared partial curvilinear correlation, η_p^2. An alpha of 0.05 or less was determined to be statistically significant. A two tailed z-test was used to determine whether individual adaptive responses during the hold phase were significantly different than zero (no response). These were performed for both the “shift-up” and “shift-down” conditions. A Bonferroni correction was applied to the interpretation of the z-test for the 60 multiple comparisons (30 participants × 2 conditions), such that an alpha of 0.05/60 = 0.0008 or less was determined to be statistically significant. For the “shift-up” condition, individual adaptive responses were termed as compensating if they were statistically less than zero and as following if they were statistically greater than zero. For the “shift-down” condition, individual adaptive responses were termed as compensating if they were statistically greater than zero and as following if they were statistically less than zero. In both conditions, responses were termed as unresponsive if they were not statistically different from zero.

In speakers with PD only, the average degree of compensation during the hold phase of the “shift-up” and “shift-down” adaptive tasks was calculated as the mean of the response during the hold phase for “shift-down” responses and the additive inverse of the mean of the response during the hold phase for “shift-down” responses (with larger positive values indicating larger degrees of compensation, regardless of condition). The average degree of compensation was compared to participant age, years since diagnosis, UPDRS total motor score, intelligibility, and pitch acuity using Pearson-product moment correlation coefficients. The potential effects of sex on "shift-up" and "shift-down" average degree of compensation were assessed using two two-sample, two-sided Student's *t*-tests. A Bonferroni correction was applied to the interpretation of the *t*-test and Pearson's correlation *p*-values to account for the 13 multiple comparisons (10 correlations, 2 tests for an effect of sex, and pitch acuity test), such that an alpha of 0.05/13 = 0.0038 or less was determined to be statistically significant.

Pitch acuity of each speaker was quantified as a just-noticeable-difference (JND) in ST and was calculated by averaging data from the last six reversals in the adaptive forced-choice procedure. This estimated the degree of f_o difference that could be detected by the participant with 70.9% accuracy (Macmillan & Creelman, 2004). A two-sample, two-sided, Student's *t*-test was used to compare pitch JND values between all 19 control speakers and all 16 speakers with PD.

Of the 16 speakers with PD, one speaker did not complete the SIT due to having missed the second session. The remaining 15 SIT speech recordings from the PD group were normalized to have equal amplitudes and were then combined with multi-speaker babble from five male and five female voices using a custom script in MATLAB (Mathworks, 2013 Version 8.1.0.604 [R2013a]). The resulting signal-to-noise ratio (SNR) was 3.5 dB. Stimuli were presented via Sennheiser HD 280 Pro headphones at a level of 70 dB SPL. The calibration procedure was the same as described for the adaptation procedure but the normalized speech samples playing from the MATLAB script were used as the input. Twelve listeners were instructed to listen to recordings and transcribe what they heard to the best of their ability after listening to each speech sample a maximum of two times. The order of presentation of the speech samples was randomized per listener to prevent order bias. Initial intelligibility scores for the listener transcriptions of the SIT sentences were calculated with a custom script in MATLAB (Mathworks, 2013 Version 8.1.0.604 [R2013a]). Scores were calculated as the total words matching phonemically between the listener transcription and the SIT sentences divided by the total number of words (Garcia & Dagenais, 1998; Hustad, Jones, & Dailey, 2003). A document was generated with calculated scores and was then hand-checked for each listener to include misspellings and homonyms as correct (Hustad et al., 2003). The intelligibility score used in further analyses was the SIT sentence scores of each speaker with PD averaged over all listeners and sentences.

RESULTS

Consistent with previous studies in typical speakers (Jones & Munhall, 2000, 2005), control speakers generally compensated to the sensorimotor adaptation task. Control speakers generally decreased their f_o during the ramp and hold phases of their “shift-up” responses and increased their f_o during the ramp and hold phases of their “shift-down” responses (see Figure 2). At a group level, our results in speakers with PD are consistent with previous work showing reduced compensations in speakers with PD relative to control speakers during gradual vowel formant perturbation (Mollaei et al., 2013; see Figure 1). Overall, the adaptive responses showed significant interactions between group and phase for both “shift-up” and “shift-down” paradigms (Figure 2; both $p < 0.001$). Results of the mixed-model ANOVAs are shown in Tables 2 and 3. During the hold phase, although the control speakers showed average compensatory responses of -0.91 ST (SD = 0.59 ST) for “shift-up” and 0.80 ST (SD = 0.84 ST) for “shift-down”, the average responses of speakers with PD were only 0.07 ST (SD = 1.07 ST) for “shift-up” and 0.08

ST (SD = 1.10 ST) for “shift-down”. However, at an individual level, the responses are qualitatively different between control speakers and speakers with PD: while most control speakers showed a clear compensation to perturbations in f_o, speakers with PD displayed highly variable responses spanning both the compensatory and following (i.e., the same direction as the perturbation) directions (see Figure 2). For the “shift-up” condition, the PD group had six compensatory, four non-responsive, and five following responses. In the control group, fourteen of the fifteen “shift-up” responses were compensatory; one was non-responsive and no responses were following. For the “shift-down” condition, the PD group had five compensatory, seven non-responsive, and three following responses. In the control group, twelve responses were compensatory, three were non-responsive, and no responses were following.

The average pitch JND of control speakers was 0.48 ST (SD = 0.52 ST) and the average for speakers with PD was 0.52 ST (SD = 0.51 ST); there was not a statistically significant difference between the two groups ($df = 32$, $T = -0.19$, $p = 0.85$).

The heterogeneity in the adaptive responses of speakers in the PD group was not explained by any of the catalogued descriptors. The Pearson’s correlations between the degree of compensation during the hold phase of the “shift-up” and “shift-down” tasks and age, years since diagnosis, UPDRS total motor score, pitch JND, and intelligibility were all nonsignificant ($p < 0.0038$; see Table 4). Likewise, *post hoc t*-tests comparing the degree of compensation during the hold phase of the “shift-up” and “shift-down” tasks as a function of sex were similarly nonsignificant. The average degree of compensation during “shift-up” for female participants was -0.68 ST (SD = 1.07 ST), whereas the average for male participants was 0.47 ST (SD = 0.66 ST); there was not a statistically significant difference between the two groups ($df = 9$, $T = -2.46$, $p = 0.04$). The average degree of compensation during “shift-down” for female participants was

0.07 ST (SD = 1.04 ST), whereas the average for male participants was 0.09 ST (SD = 1.15 ST); again, there was no statistically significant difference between the two groups (*df* = 12, T = -0.03, *p* = 0.98). Given our conservative correction for multiple comparisons, it is worth noting that, although non-significant, there were a few substantial trends. In the "shift-up" condition, there was a trend for a difference in compensation between females and males (*p* = 0.04); while females generally followed the perturbation (average compensation of -0.68 ST), on average, males tended to compensate (average compensation of 0.47 ST). The average degree of compensation during "shift-up" was associated with intelligibility (*r* = -0.45, *p* = 0.10), with less intelligible individuals compensating to a greater degree. The average degree of compensation during "shift-down" was associated with age (*r* = -0.53, *p* = 0.04); younger participants tended to have a greater degree of compensation than older participants.

DISCUSSION

A. Adaptive responses to f_o in PD

Sensorimotor adaptation has been studied extensively in PD, but only one prior study investigated sensorimotor adaptation in PD in the speech domain (Mollaei et al., 2013). Adaptive responses to perturbation of the first formant of vowels (F1) during word productions were analyzed and reported at a group level. The study found reduced responses in the PD group compared to the healthy control group (Mollaei et al., 2013). The data presented here, at a group level, are consistent with this finding. However, on an individual level, these data demonstrate qualitatively different responses between control speakers and speakers with PD. While control speakers showed relatively consistent compensatory responses to perturbation, speakers with PD had highly variable responses, with either compensatory responses, no response, or even "following" responses (changing f_o in the same direction as the perturbation). Similarly, Kiran and Larson (2001) also found more “following” reflexive responses to unanticipated perturbations of f_o in speakers with PD than in control speakers. However, these results do not clearly match previous speech adaptation work in speakers with PD.

While the group-level responses in the current findings align with those reported by Mollaei et al. (2013) the individual responses differ. The heterogeneous results seen in the current work could be due to several methodological differences between the two studies: perturbing vocal vs. articulatory characteristics of speech (f_o vs. F1), use of sustained vowels rather than words, differences in how the perturbation was introduced and the experimental set up. The perturbations of f_o and F1 involve different control systems, f_o is considered a postural parameter while F1 is considered a segmental parameter, and segmental parameters are more affected by changes in hearing status (Lane, Wozniak, Matthies, Svirsky, & Perkell, 1995; Perkell et al., 2007). This suggests that a potential feedforward system impairment in auditory-motor integration would have a greater effect on articulatory motor control relative to vocal motor control (Guenther et al., 2006). Furthermore, reduced loudness is a hallmark feature in PD (Duffy, 2013), which has a biomechanical relationship with f_o (Hixon, Klatt, & Mead, 1971; Titze, 1989). Thus, some interaction between hypophonia and f_o in the speakers with PD could have contributed to the variability in f_o adaptive responses. Other than the parameter to which the perturbation was applied, there are additional methodological differences between the current study and Mollaei et al. (2013). The duration of the word used by Mollaei et al. (2013) was most likely shorter than the sustained 3-s vowel used in the current study, and the latter would result in participants having longer exposure to the perturbation during each trial, which may affect adaptive responses. Also, the paradigm used by Mollaei et al. (2013) differed from most current speech adaptation paradigms (Houde & Jordan, 2002; Jones & Munhall, 2005; Villacorta et al., 2007): a ramp phase was not included to gradually introduce the perturbation. This paradigm difference is important to note when comparing the adaptive responses. Visuomotor studies have shown differences in responses to sudden (no ramp) and gradual introduction (with ramp) of perturbation in healthy controls (Buch, Young, & Contreras-Vidal, 2003; Kagerer et al., 1997) and speakers with PD (Venkatakrishnan, Banquet, Burnod, & Contreras-Vidal, 2011). A final consideration for the interpretation of heterogeneous responses is the potential variability in software and equipment in the experimental set up. This includes variability in auditory feedback due to the headphone frequency response, left and right headphone levels, and inter-subject differences in the amplitude and speech quality changes applied to feedback due to perturbations applied using Audapter.

The individual responses seen in the current study during the after-effect stage align well with a study of visuomotor control in PD. Contreras-Vidal and Buch (2003) found heterogeneous responses in speakers with PD during the after-effect stage of a visuomotor adaptation task that were not seen in healthy controls. Similar heterogeneous responses were found in the current work during the after-effect stage in the PD group; however, these may have been a continuation of the heterogeneous responses that were also seen in the ramp and hold.

B. Interpretation of potential neurophysiological mechanisms

The atypical responses to gradual f_o perturbation seen in the current study support the hypothesis that there may be an impairment in the auditory-motor learning process in PD. Using the DIVA model to interpret these findings, in neurotypical participants, the feedback system compares the output f_o to the target f_o, and generates an error signal due to a mismatch between the two. This error signal is then detected by the auditory feedback controller, which in turn generates a corrective motor command to oppose the unexpected shift in f_o. This is communicated to the feedforward subsystem which reduces the mismatch between target and output in future productions. The heterogeneous responses seen in the adaptive responses of the individuals with PD suggest that either: 1) the f_o perturbation was not correctly detected by the auditory system, 2) detected auditory errors were not properly translated into corrective motor commands by the auditory feedback controller, or 3) the feedforward system did not correctly modify motor commands for subsequent productions by incorporating corrective motor commands from the auditory feedback controller. These possibilities are addressed in the following paragraphs.

If atypical adaptive responses were due to a problem with f_o detection in the feedback system in speakers with PD, this would suggest less sensitive pitch discrimination compared to healthy speakers. In the current results, there was no significant difference in pitch acuity between speakers with PD and control speakers. Additionally, pitch acuity was not correlated with the degree of compensation in adaptive responses in speakers with PD. This indicates that there was not likely a deficit in auditory feedback specific to detecting pitch changes in the speakers with PD. The pitch acuity findings in the current study are in contrast with previous work that found reduced ability to discriminate pitch in 12 individuals with PD compared to 15 healthy controls (Troche, Troche, Berkowitz, Grossman, & Reilly, 2012). The conflicting results could potentially be explained by natural variation in musical experience of participants, paradigm differences, or the limited sample sizes employed by both studies. Previous work has shown that musicians may be better than non-musicians at discriminating pitch (Kishon-Rabin, Amir, Vexler, & Zaltz, 2001; Tervaniemi, Just, Koelsch, Widmann, & Schröger, 2005). Since neither Troche et al. (2012) or this current study reported musical training, it is possible that it contributed to differences between study results. The paradigm used by Troche et al. (2012)

asked participants to determine whether 32 tones with a set difference between them (either 25 Hz or 100 Hz) were the ‘same’ or ‘different’. The reference tone was 525 Hz. Each tone was 1-s in duration and tones were presented with an inter-stimulus interval (ISI) of 750 ms. Comparing response accuracy, a significant difference between the PD and healthy control group was found only for the 25 Hz difference. In the current study, a 440 Hz reference tone was used, with a tone duration of 2 s and an ISI of only 20 ms. Tones decreased or increased adaptively with correct or incorrect judgements, respectively. Acuity was quantified as a JND and no significant differences were seen between speakers with PD and control speakers. Both groups were found to have average pitch JND values of approximately 0.5 ST, equivalent to 13 Hz, which is substantially smaller than the 25 Hz difference used in Troche et al. (2012). It is possible that the longer ISI employed by Troche et al. (2012) is responsible for the poorer pitch acuity seen in speakers with PD in that study.

Assessment procedures for frequency discrimination are impacted by relative attentional and cognitive ability (Banai, 2008). In fact, reduced cognitive function has specifically been shown to interact with ISI, resulting in differentially poorer frequency discrimination in individuals with Alzheimer’s disease when long ISIs are used (Pekkonen, Jousmäki, Könönen, Reinikainen, & Partanen, 1994). Future study comparing pitch acuity measures as a function of ISI in speakers with and without PD are necessary to confirm this. Finally, especially given the heterogeneity in PD presentation, differences between the two studies may simply be a function of sample size. That said, since pitch acuity was not correlated with the adaptive responses in the PD speakers in the current study, it does not appear to be a driving factor of the adaptive responses in this sample. However, given that individuals with PD demonstrate difficulty in correcting for sensorimotor errors using the efference copy system (Demirci, Grill, McShane, &

Hallett, 1997; Klockgether & Dichgans, 1994; Rickards & Cody, 1997; Stern, Mayeux, Rosen, & Ilson, 1983), we cannot rule out the possibility that the perception during self-productions (autophonic judgments) may have contributed to the atypical adaptive responses in PD.

The atypical responses seen in the current study could also be due to a deficit in the feedback system in correcting the detected errors. However, because studies of reflexive responses to sudden, brief, perturbation of f_o have demonstrated that speakers with PD have *larger* compensatory response magnitudes (Chen et al., 2013; Liu et al., 2012; Mollaei et al., 2016) relative to control speakers, it is unlikely that the current results are due to an inability of the feedback system to compensate for detected errors in f_o. Larger compensation magnitudes suggest that the feedback system is working correctly and that, in fact, there may be a higher reliance on the feedback system in PD than in healthy speakers during reflexive responses to f_o. It is possible that speakers with PD rely more on their auditory feedback for f_o control because of a feedforward system impairment. Additionally, these larger compensations may be due to a deficiency in the weighting of somatosensory and auditory feedback in PD. This weighting in known to vary in typical speakers, but more extreme variation could explain the results shown here (Lametti et al., 2012).

The current results, together with previous work, most directly support the possibility that f_o control in speakers with PD is impaired due to a deficit in the updating of the feedforward system. This would mean the f_o changes are accurately detected and corrected by the feedback system in speakers with PD, but these corrective responses are not properly subsumed into the feedforward system. This interpretation aligns with previous work suggesting the basal ganglia have a role in generating feedforward commands (Mink, 1996; Nambu, Tokuno, & Takada, 2002) and that the striatum (the primary target of cortical projections to the basal ganglia) contributes to the motor learning process (Balleine, Delgado, & Hikosaka, 2007). Therefore, the reduced dopaminergic signals in the striatum seen in PD (Morrish, Sawle, & Brooks, 1996; Niethammer, Feigin, & Eidelberg, 2012) would impact the integration of feedback and production of consequent motor actions. This is further supported by studies which found atypical sensorimotor integration (Contreras-Vidal & Buch, 2003; Fernandez-Ruiz et al., 2003; Fucetola & Smith, 1997; Paquet et al., 2008; Schneider, Diamond, & Markham, 1987; Stern, Mayeux, & Rosen, 1984), including auditory motor integration (Mollaei et al., 2013), in PD. To clarify the contributions of the feedback and feedforward system to vocal motor control in speakers with PD, a comprehensive experiment with both reflexive and adaptive perturbations of f_0 is necessary.

C. Limitations and Future Work

A limitation of the current study, as in most studies in PD, is the heterogeneity in the presentation of the speakers with PD in terms of the timing of the onset of their symptoms and the severity of their symptoms. Individuals with PD reported with a wide range in the time between the onset of PD symptoms and their participation in this study (1.5 – 30 years), as well as in their UPDRS total motor score (ranging from 22 – 72) which documents the severity of abnormalities during execution of motor function tasks. UPDRS scores below 36 are considered mild, between 36 – 57 are moderate, and scores higher than 58 are severe (Martínez-Martín et al., 2015). Subjects in this study varied from mild to severe. The variability in disease severity is difficult to circumvent in studies of PD, as there are a wide range of motor and non-motor symptoms seen in the clinical population of individuals with PD (Chaudhuri, Healy, & Schapira, 2006; Foltynie, Brayne, & Barker, 2002; Hughes, Daniel, Blankson, & Lees, 1993; van Rooden et al., 2010). However, progression of dysprosody in PD does not appear to correlate with disease duration or severity as assessed by the UPDRS motor score (Bowen, Hands, Pradhan, & Stepp, 2013; Skodda, Rinsche, & Schlegel, 2009).

Medication state may also have influenced the current study. All speakers with PD were tested while they were receiving L-dopa therapy which allows for variability in duration of administration as well as the individual's symptoms at the time L-dopa therapy was initiated, influencing the effects of the medication (Contin et al., 1994; Goetz, Stebbins, & Blasucci, 2000; Kishore et al., 2012; Klawans, 1986; Lesser et al., 1979). Previous research on speech production in PD has not demonstrated substantial differences in mean f_o (Goberman, Coelho, & Robb, 2005; Goberman, Coelho, & Robb, 2002; Jiang, Lin, Wang, & Hanson, 1999; Sanabria et al., 2001) or f_o variability (Bowen et al., 2013; Goberman et al., 2005; S. Skodda, Grönheit, & Schlegel, 2011) between participants on and off medication. However, during brief perturbations of f_o, larger responses were reported in speakers with PD off medication as compared to a healthy control group (Chen et al., 2013; Liu et al., 2012; Mollaei et al., 2016), whereas one study (Kiran & Larson, 2001) found that ten speakers with PD on medication did not differ from ten control speakers in terms of reflexive response magnitude. Speakers with PD were not directly compared on and off medication in these studies, but the combined results imply there could be an effect of medication on auditory-motor control. Visuomotor studies have investigated medication state as well, and present conflicting evidence (Mongeon, Blanchet, & Messier, 2013; Paquet et al., 2008; Semrau, Perlmutter, & Thoroughman, 2014). However, speech and limb motor symptoms in PD are disparate, with different progression and medical response profiles (Holmes, Oates, Phyland, & Hughes, 2000; Skodda, Grönheit, Mancinelli, & Schlegel, 2013; Skodda et al., 2009), which makes it difficult to compare results from the auditory and visuomotor domains. In summary, the effects of medication state on sensory perturbations are not well defined, especially given the heterogeneity of responses to medication in the PD population, and should be further investigated by examining adaptive responses of participants who are both on and off medication.

Another factor that could have contributed to variation in the current study is the cognitive function of individuals with PD. Previous studies have shown that as attentional demands increase, control speakers have reduced responses to sudden f_o perturbation (Tumber, Scheerer, & Jones, 2014) and gradual f_o perturbation (Scheerer, Tumber, & Jones, 2015). Many individuals with PD have cognitive deficits, particularly in attention (Ballard et al., 2002; Dujardin et al., 2013; Muslimović, Post, Speelman, & Schmand, 2005). Given the attentional demands of the 30-minute paradigm, deficits in sustained attention could have affected the responses of participants. However, attention deficits in PD appear to mainly affect dual-attention or divided attention tasks (Brown & Marsden, 1991; Woodward, Bub, & Hunter, 2002), and therefore were most likely not a concern for the current study because it was a single task experiment.

Finally, the difference seen in the average degree of compensation in the “shift-up” condition between female and male speakers with PD, although not statistically significant, suggests there may be differences in vocal motor control between female and male speakers with PD. This aligns with previous work which showed statistically significant higher average f_o variability as well as lower f_o variability decline in female speakers with PD compared to male speakers with PD (Bowen et al., 2013). However, these results are not directly interpretable and should be followed by further study.

CONCLUSION

In summary, the current study demonstrated that speakers with PD have reduced mean responses to gradual perturbation of f_o, with heterogeneous individual responses. These findings indicate that there may be an impairment in the adaptive control of voice in PD. Furthermore, the current study failed to find a significant difference in pitch acuity between speakers with PD and control speakers. Taken together with previous work, the results suggest that f_o changes can be accurately detected and corrected by the feedback system in speakers with PD, but that there is a deficit in the updating of the feedforward system. A comprehensive study of reflexive and adaptive responses to f_o and F1 perturbations, both on and off medication, is needed to better characterize the potential deficits in auditory-motor integration associated with PD. These responses, paired with auditory acuity to f_o and F1, should be investigated with relation to PD symptom severity and functional communication outcomes. These studies would clarify the underlying deficits in feedforward and feedback speech motor control associated with PD and inform the development of targeted treatments for this disorder.

ACKNOWLEDGMENTS

This work was supported by grants DC015570, DC002852, and DC04663 from the National Institute on Deafness and Other Communication Disorders (NIDCD) and a pilot grant from the Boston Rehabilitation Outcomes Center, supported by grant HD065688 from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The authors would like to thank Timothy Streeter for assistance with equipment calibration and Nicole Enos for assistance with data collection.

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Table 1. Participant characteristics (M: mean, SD: standard deviation)

	Speakers with PD	**Control Speakers**	**Listeners**
Age (years)	M = 64.8, SD = 6.3 Range: 52 - 73	M = 65.3, SD = 4.6 Range: 50 – 77	M = 21.9, SD = 2.9 Range: 18 – 23
Sex	8 F, 8 M	10 F, 9 M	6 F, 6 M
Time since diagnosis (years)	M = 6.97, SD = 7.05 Range: 1.5 – 30	N/A	N/A
Hoehn and Yahr	M = 2.1, SD = 0.6 Range: 1 – 3	N/A	N/A
UPDRS Part III score (total motor score)	M = 41.0, SD = 13.6 Range: 22 – 72	N/A	N/A

Table 2. Results of mixed model ANOVA on “shift-up” adaptive responses

Effect	**DF**	η^2_p	**F**	***p***
Group	1	0.10	5.4	0.028
Phase	3	0.10	32.8	<0.001
Group × Phase	3	0.06	19.9	<0.001

Table 3. Results of mixed model ANOVA on “shift-down” adaptive responses

Effect	**DF**	η^2_p	**F**	***p***
Group	1	0.13	4.7	0.038
Phase	3	0.12	41.3	<0.001
Group × Phase	3	0.04	12.4	<0.001

Table 4. Pearson’s Product-Moment Correlations

	“shift-up” compensation	“shift-down” compensation
age	0.31 ($p = 0.27$)	-0.53 ($p = 0.04$)
years post-diagnosis	0.27 ($p = 0.33$)	-0.02 ($p = 0.93$)
UPDRS total motor score	0.24 ($p = 0.38$)	0.03 ($p = 0.33$)
pitch JND	0.25 ($p = 0.36$)	-0.34 ($p = 0.21$)
intelligibility	-0.45 ($p = 0.10$)	0.08 ($p = 0.78$)

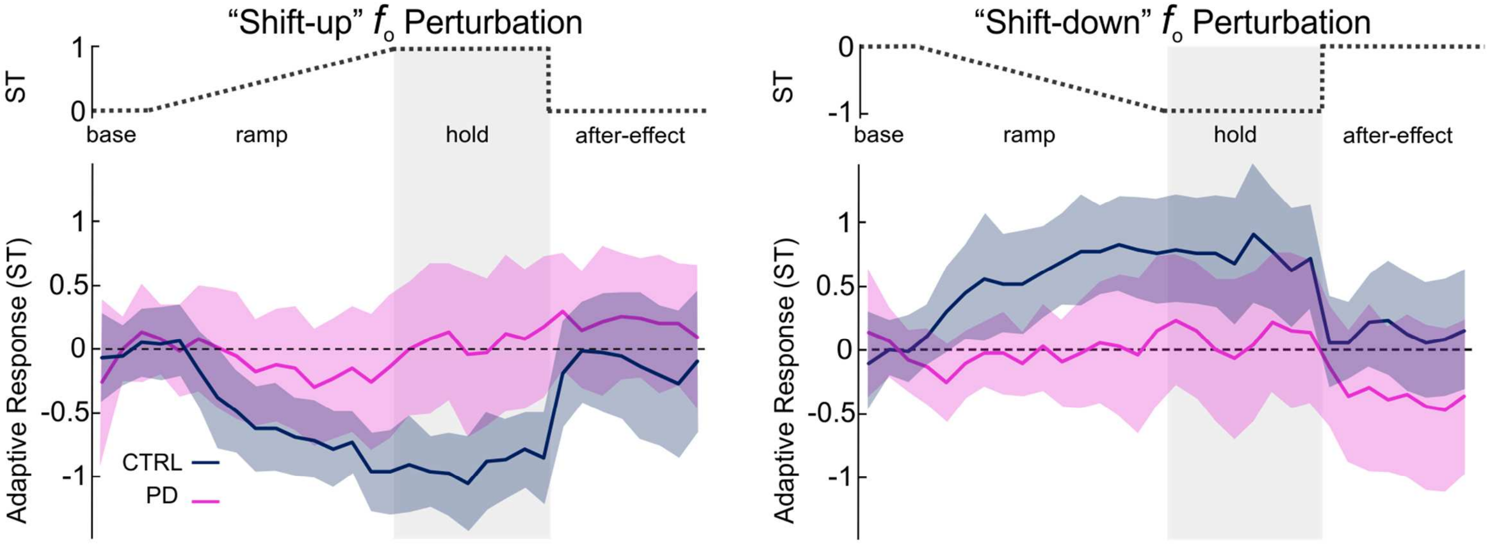

Figure 1: An adaptive "shift-up" (left) and "shift-down" (right) perturbation was applied to the f_o of auditory feedback with a maximum perturbation of 1 semitone (ST) or -1 ST respectively (schematized in upper panel). Mean adaptive responses in STs are plotted as the mean across five-trial blocks for control speakers (dark blue line) and speakers with Parkinson's disease (light pink line) with shading indicating 95% confidence intervals.

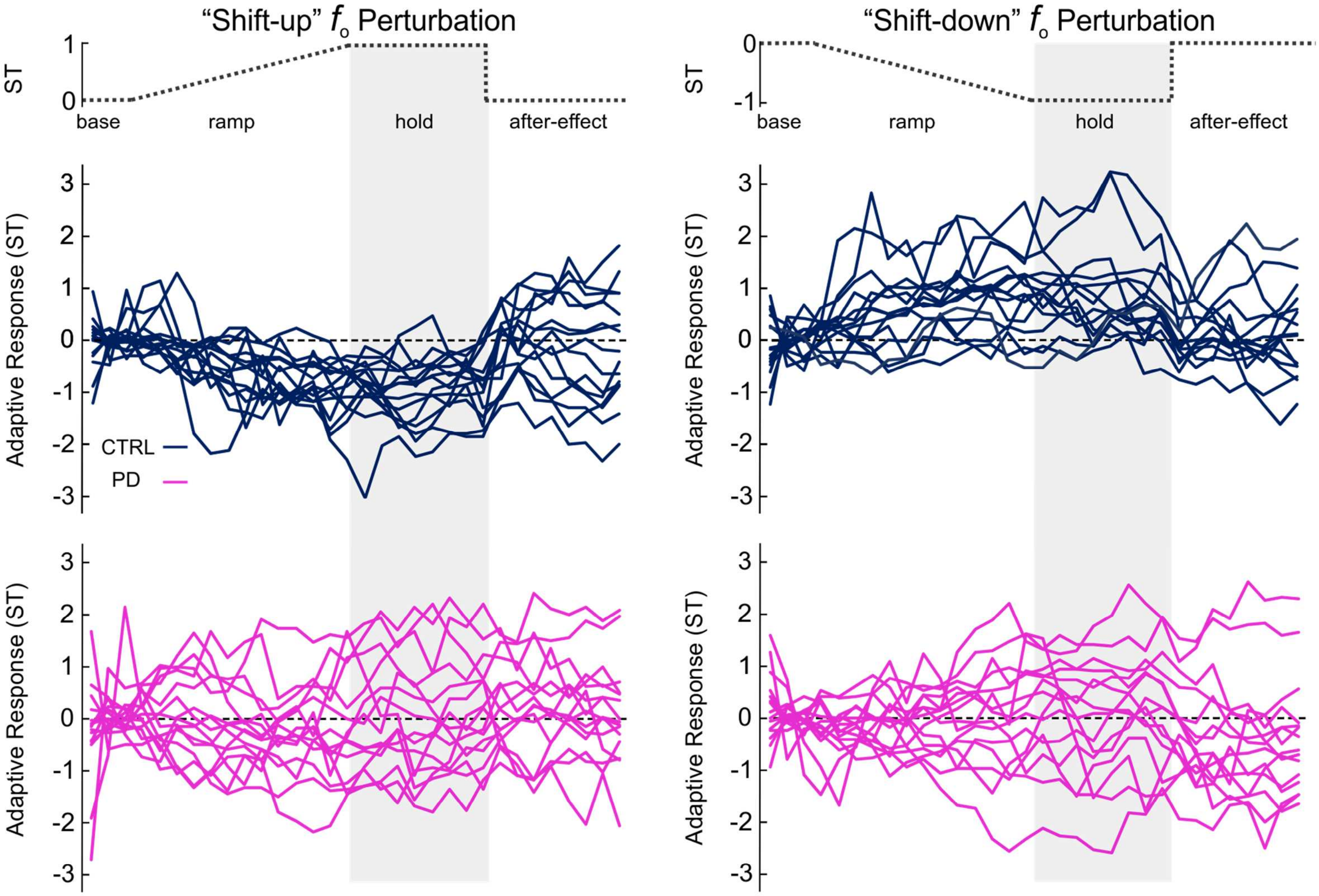

Figure 2: Individual adaptive responses in semitones (STs) for "shift-up" (left) and "shift-down" (right) perturbations (schematized in upper panel). Responses are plotted as the mean across five-trial blocks for fifteen adaptive responses from control speakers (above) and fifteen adaptive responses from speakers with Parkinson's disease (below).