Deficits in monitoring self-produced speech in Parkinson's disease

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Abstract

Objective: Speech deficits are common in Parkinson's disease (PD), but the underlying neural mechanisms are not well understood. Paradoxically, patients may not subjectively be aware of their own speech deficits such as hypophonic speech. This suggests an impairment in monitoring self-produced speech.

Methods: We measured evoked electroencephalographic responses to self-produced and passively heard sounds (/a/ phonemes) in age-matched controls (N=20), and PD patients who had minor speech impairment, but reported subjectively experiencing no speech deficits (N=20).

Results: During speaking, auditory evoked activity 100 ms after phonation (N1 wave) was less suppressed in PD than controls when compared to the activity evoked by passively heard phonemes. Source reconstruction showed that activity in auditory cortex was stronger in PD patients than control participants already 200 ms before phonation as well as during a later time period (400–500 ms after phonation). The P2 wave did not differ between the patient and control groups, consistent with the assumption that the patients did not correct for their speech deficits.

Conclusions: The findings indicate that auditory cortical activity is abnormally modulated during speech in early PD patients who do not subjectively notice speech impairment. We suggest that this mechanism may play a key initial role in producing speech deficits in PD.

Significance: Our study is the first to show abnormal early auditory cortical electrophysiological correlates of monitoring speech in PD patients.

Key words: Parkinson's disease, speech deficit, corollary discharge, efference copy, hypophonia

Introduction

The majority of patients with Parkinson's disease (PD) show speech impairments typically classified as hypokinetic dysarthria (Ho et al. , 1998; Logemann et al. 1978; Sapir et al., 2001). The major speech symptoms are inaccurate articulation, variable speech rate, monotonic and hypophonic loudness of speech, and harsh voice quality. Yet, unlike primary motor symptoms of PD, speech deficits often do not respond to dopamine therapy (Louis, Winfield, Fahn, & Ford, 2001; Skodda, Visser, & Schlegel, 2010), and dysarthria is a well-known side-effect of deep-brain stimulation (Follett et al., 2010). Speech impairment was for a long time seen as a late symptom of PD, emerging as a by-product of the primary motor symptoms. More recent studies show that speech abnormalities are present early in the disease, and could even be considered a potential biomarker of PD (Hlavnika et al., 2017; Moreau & Pinto, 2019). Yet, treatment of speech deficits remain difficult because its neural basis is not understood (Pinto, Ozsancak, et al., 2004).

Speech requires the brain to continuously monitor how well produced actions match the desired outcome (Hickok, 2012). The brain tracks how well produced actions (such as the loudness of spoken words) match the attempted outcome by relying on corollary discharge (CD) signals. According to current models, the CD signals are predictions about the sensory consequences of the produced actions which the brain communicates to sensory cortical areas (Guenther, Ghosh, & Tourville, 2006; Houde & Nagarajan, 2011). During speech, frontal speech control areas communicate such prediction signals to the auditory and somatosensory cortex. The sensory areas, in turn, communicate mismatch signals (prediction errors) back to the speech production system, enabling rapid and efficient adjustment of speech. That is, if the produced speech does not match the attempted (i.e. predicted) speech, prediction errors communicate this mismatch to the speech control system, enabling the individual to rapidly modulate their speech volume.

Similar predictive mechanisms may also contribute to speech perception (Cope et al., 2017; McClelland et al., 2006; Norris et al., 2016).

Patients with PD respond abnormally to perturbations in speech output when compared to neurologically healthy control participants. Depending on whether the fundamental frequency or first formant frequency is perturbed, the patients produce either an abnormally large (Chen et al., 2013; Liu, Wang, Metman, & Larson, 2012; Mollaei, Shiller, Baum, & Gracco, 2016) or small (Mollaei et al., 2016; Mollaei, Shiller, & Gracco, 2013) correction to their speech. Some studies have not observed differences in compensation magnitude between PD patients and control participants (Abur et al., 2018; Kiran & Larson, 2001). While perceptual and speech motor control abnormalities alone could in part explain the speech deficits, they could also be a sign of altered speech self-monitoring. Specifically, it has been suggested that PD patients' brain detects a mismatch between produced and heard speech, but corrective response is not properly subsumed into subsequent speech commands due to the deficit in the dopaminergic system (Abur et al., 2018). Deficits in speech self-monitoring is also suggested by the fact that PD patients are often not fully aware of their speech deficits (Kwan & Whitehill, 2011), whereas they are typically well aware of their primary motor symptoms (Leritz et al., 2004). PD patients overestimate the volume of their own speech, and report experiencing speaking in loud voice, although their speech sound pressure level is actually reduced (Fox & Ramig, 1997; Ho ert al., 2008).

The aim of the present study was to examine the electrophysiological correlates of speech-monitoring in PD patients. Brain imaging studies have reported that activation in frontal areas during speech in PD differs from control participants (Arnold, Gehrig, Gispert, Seifried, & Kell, 2014; Baumann et al., 2018; Liotti, Ramig, Vogel, New, & Cook, 2003; Pinto, Thobois, et al., 2004; Rektorova, Barrett, Mikl, Rektor, & Paus, 2007), and the results of Arnold et al. (2014) suggest that activation related to speech monitoring is abnormal in PD patients. The drawback of brain imaging

studies is that they typically give no insight into the time-course of activity in different brain areas. Here we examined the time-course auditory evoked activity when participant either produced phonemes or listened to a recording of the same phonemes. A large body of studies shows that during speech the amplitude of auditory evoked cortical activity is suppressed when compared to a condition where the same sounds are passively listened (Chang et al., 2013; Curio et al., 2000; Ford & Mathalon, 2005; Ford et al., 2013; Houde et al., 2002). This phenomenon is called the speaking-induced suppression (SIS), and it is assumed to reflect the influence of the CD signals on auditory cortex. On scalp recorded electroencephalography (EEG), SIS is strongest over central sites (Cz electrode) around 100 ms after speech/sound onset (i.e. N1 wave). Large SIS amplitudes correspond to large prediction errors: When speech output is artificially perturbed, the SIS reduces because the N1 wave in the active speech condition is increased in size (Behroozmand, Liu, & Larson, 2011).

There is very little research on how neural correlates of speech and speech self-monitoring are affected by PD. The only electrophysiological study we know of is by Huang et al. (2016) who studied how control participants and PD patients responded to frequency-altered speech output. The authors observed that PD did not affect the amplitude of the SIS (i.e. N1 wave), but modulated the later P2 evoked response. This finding suggests that in PD the detection of a mismatch between produced and expected speech output is not altered (i.e. SIS) but later processing stages (i.e. P2 wave) through which corrective responses are initiated, do function differently in PD and healthy controls. However, because the study by Huang et al. (2016) used perturbed speech, the question whether SIS to normal (non-perturbed) speech could be altered in PD remains open. Perturbed speech produces reduced SIS and increased P2 responses when compared to non-perturbed speech in neurologically healthy participants (Behroozmand et al.,

2011; Heinks-Maldonado, Mathalon, Gray, & Ford, 2005). Hence, it could be argued that the perturbed-speech paradigm is not sensitive to detect changes in SIS.

Our hypotheses were as follows. If PD patients monitoring of their own speech output is altered, this should be reflected in the SIS amplitude. The amplitude of the SIS reflects how well the produced speech matches the predicted speech. Amplified SIS in PD compared to healthy controls would suggest that PD patients' speech control system suppresses auditory evoked activity more than controls. Reduced SIS would indicate that the PD patients' auditory cortex detects higher-than-normal mismatch between produced and predicted speech (compared to controls). This would be expected if we assume that due to speech impairment the produced speech does not match the intention. As the P2 wave has been observed to increase in response perturbed speech-output (Behroozmand et al., 2011; Heinks-Maldonado et al., 2005), it can be interpreted as a correlate of corrections to the speech output. Hence, if PD patients do correct for mismatches in their speech, this should be observed as changes in the P2 wave. Importantly, we tested patients and control participants who did not subjectively report experiencing any speech impairments. Hence, the hypothesis is that, in contrast to the results of Huang et al. (2016), we should not observe changes in P2 amplitude (assuming that neither patients or controls make corrections). We tested patients with small or non-existent speech deficits also because this makes comparison to control participants more straightforward. However, because hypophonia is a common speech deficit in PD, we expected to observe mild signs of hypophonic speech with psychophysical testing.

Methods

The experiment was approved by the Ethics committee of the hospital district of South-West Finland. A written informed consent was obtained prior the study. The study was conducted

according to the principles of the Declaration of Helsinki. Participants received a small fee for participating.

Participants

We tested 20 PD patients and 20 age-matched control participants without neurological disease. PD patients had been diagnosed using the UK Brain Bank criteria or MDS clinical criteria. One control participant was left-handed, others were right-handed. The two groups were similar with respect to other measures than motor and speech deficits, which were assessed using the MDS-UPDRS scale (Movement Disease Society, Unified Parkinson's Disease Rating Scale, part III, motor symptoms). None of the patients or control participants reported experiencing any problems with speech.

Mini Mental-State (MMSE) questionnaire was used to assess cognitive impairment (Folstein, Folstein, & McHugh, 1975). One PD patient was excluded from the data analysis because his MMSE-score suggested possible mild cognitive impairment (MMSE score was 23). Beck's Depression Inventory was used to asses depression (Beck, 1976). One PD patient was excluded due to relatively high score (27 total score) in BDI. Finally, one patient had to be excluded because of a technical failure during EEG recording, and two control participants were excluded because of massive artifacts in EEG. Therefore, the final sample was 17 patients and 18 control participants. Comparison of the demographical information, and clinical and neuropsychological measurements are presented in Table 1. We also performed the analyses by including the two PD patients who were excluded due to low MMSE and high BDI scores, and the results did not change.

Table 1. Comparison of demographic, clinical and neuropsychological data between PD and control groups				
	Control	**PD**	**test statistic***	**p**
N	18	17	n/a	n/a
sex (male/female)	(6/12)	(7/10)	5.1	0.08
Age (mean +/- SD)	67.0 (6.1)	69.5 (7.7)	0.9	0.4
levodopa equivalent daily dose (mean +/- SD)	n/a	568 (492)	n/a	n/a
Self-reported speech deficits	0	0	n/a	n/a
Disease duration, years (mean +/- SD)	n/a	6 (5)	n/a	n/a
Mini-mental state score (mean +/- SD)	28.1 (1.3)	28.1 (1.6)	0.6	0.5
Beck's depression inventory	4.7 (3.0)	6.3 (2.5)	1.4	0.2
MDS-UPDRS, motor (mean +/- SD)	4.9 (3.5)	23.0 (10.2)	6.7	< 0.001
MDS-UPDRS, speech (mean +/- SD)	0.05 (0.2)	0.5 (0.7)	2.4	0.02
* t statistic (continuous variables) or Chi-squared statistic (categorical data)				

Eleven patients were on levodopa medication, and sixteen were treated with MAO-inhibitors and/or dopamine agonists. One patient was on anti-cholinergic medication. The mean levodopa equivalent dose across the patients was 568 mg (SD = 492 mg). The patients were asked to go through a voluntary medication break before the test session to counteract possible intervening effects of medication. Twelve patients underwent the medication break, and did not take their morning medication during the day of the study (at least 12 h break in medication). These twelve patients can therefore be considered being in OFF phase (the remaining patients are in ON phase, and did not go through the medication brake).

Task and procedure

In the psychophysical task the participants listened to /a/ phonemes from a loudspeaker (Creative T40 Series II), and they were asked to repeat the phoneme with a matching volume. There were five different volume levels, ranging from weak to loud speaking volumes (on average 67 dB), but otherwise the phonemes were identical. This procedure was repeated 65 times in total (13 times for each volume level). The participant's response was measured using a microphone (Vivitar

TVM-1) positioned halfway between the loudspeaker and the participant. Response amplitude was determined by calculating the mean absolute amplitude of samples that were higher than 50% of the maximum absolute amplitude. Before each test session the position of the microphone was calibrated to ensure that volume was measured accurately. This calibration consisted of playing an identical phoneme as a response from a loudspeaker positioned where the participants head should be. This procedure yielded near perfect correspondence between stimulus and response, verifying that the volume measurement was accurate. No EEG was measured during this task. Our hypothesis was that if the patients show hypophonic speech they should systematically produce lower volume responses than control participants, as shown by Clark et al. (Clark, Adams, Dykstra, Moodie, & Jog, 2014).

In the EEG condition, the participant was first asked to utter the phoneme /a/ approximately every 5 seconds for 10 minutes with their normal speaking volume while minimizing facial movements ("Speak condition"). The participants wore headphones with a microphone. White noise and the participant's own speech was played back through the headphones. In the second condition ("Listen condition") the same phonemes they had just spoken were played back to them through the headphones (again with white noise in the background). With the white noise added to suppress direct perceptions of one's own speech, the volume of the spoken/listened phonemes could be matched. In both Speak and Listen conditions the white noise was identical, and played throughout the recording (i.e. not just during vocalization).

To accurately measure the onset time of the phonemes, the signal from the loudspeakers of the headphones was recorded by the EEG amplifier. The auditory signal is thus measured by the same system as brain activity, which means that the two signals are perfectly synchronized. Markers were inserted to the EEG data to the time-points that corresponded to the onsets of

phonemes following a semi-automated procedure during off-line analysis. First, only the signal from the headphones was selected and high-pass filtered at 100 Hz; because only high-frequency information is present, the transient onset of sound could be easily detected. Second, if the signal remained above a predefined threshold for minimum of 10 samples, a marker was added to the timepoint where the threshold was first crossed. All markers and trials were inspected by the researcher, and any trials where the onset of the sound was unclear, were excluded from the analysis. As seen in Figure 2A, which shows the EEG-recorded audio signal averaged over the two groups, the marker was accurately added to the onset of the sound.

Electroencephalography

EEG was measured with 64 active electrodes with NeurOne Tesla amplifier. Sampling rate was 500 Hz. In addition, EOG was measured from electrodes placed beside and below the right eye. EEG was processed using EEGLAB v14.1.1 software (Delorme & Makeig, 2004) on Matlab 2014b. Channels were first automatically inspected, and bad channels interpolated. The channel used to measure the auditory signal was removed before EEG analysis. EEG was fist high-pass (0.1 Hz) and then low-pass (40 Hz) filtered. Speech related and other EEG artefacts were removed using artifact subspace reconstruction (ASR). ASR resembles principle component analysis (PCA) in that data is reconstructed after first excluding artifactual components. ASR rejects components automatically by determining thresholds based on clean segments of EEG data. Here, ASR was utilized instead of PCA or independent component analysis (ICA) because large speech-related artefacts remained in the data after PCA or ICA-based artifact rejection. For technical details of ASR, the reader is referred to (Mullen et al., 2015). After ASR, data was epoched, removed electrodes were interpolated, and the data referenced to linked mastoids. Epochs containing abnormal data were

rejected using pop_jointprob function. This left on average 105 (SD = 53) trials per condition per participant for the EEG analyses.

Source reconstruction analysis was performed in Brainstorm software (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011), following the guidelines provided by Stropahl et al. (Stropahl, Bauer, Debener, & Bleichner, 2018). The source reconstruction procedure estimates the current in large number of sources distributed over the cortex. Dynamic statistical parametric mapping, which estimates the location of deep sources more accurately than minimum-norm solutions (Lin et al., 2006), was applied to the data (Dale et al., 2000). Because we did not have the individual participants' anatomical images, an MNI anatomical template (Holmes et al., 1998) was used. This means that the localization accuracy of the current approach cannot be compared to brain imaging. However, here our motivation to use source reconstruction was not spatially precise localization, but extract rough time course of activity from auditory cortices. During source reconstruction, prestimulus interval between -600 and -400 ms was used to calculate the noise covariance matrices. This time-window was chosen because we assumed that preparatory activation could be present right before speech onset. The boundary element method (BEM), as implemented in OpenMEEG, was used as a head model (default parameters) (Gramfort et al., 2013; Stenroos, Hunold, & Haueisen, 2014). The orientation of the current dipole was constrained to be perpendicular with respect to cortical surface. The source localization was performed on each participant's averaged evoked response.

The time course of auditory cortical activity was extracted from the source reconstructed data. We extracted the maximum amplitude of dipoles in the posterior ramus of the lateral sulcus, based on the Destrieux atlas (region 41) (Destrieux, Fischl, Dale, & Halgren, 2010). This region was selected because it showed the strongest auditory evoked activation in the listen

condition (across all participants; see Fig. 3). The absolute mean value of dipoles in this region was used as a measure of activation strength.

Statistical analysis

The results of the psychophysical task were analyzed using linear mixed-effects model. The model included the intensity of the test stimulus, group, and their interaction as predictors. Control group was coded as 0 (i.e. baseline), and the PD group as 1.

Evoked EEG analysis was performed in two steps. First, we characterize scalp recorded ERPs and SIS. Second, source reconstruction was run to estimate the time-course of activations in auditory cortices. Statistical analysis of scalp recorded SIS was performed on electrode Cz as this site typically (and also in our study) shows strongest effect. We used the non-parametric permutation approach to test for statistical significance (Maris & Oostenveld, 2007). First, we calculated the SIS by subtracting Listen condition ERPs from the Speak condition ERPs. We then compared if the SIS was different in PD when compared to control group using a t test performed on each time point between -200 and 600 ms relative to stimulus/speech onset. Statistical significance of the difference was determined by comparing the observed test statistics to a null distribution obtained by random permutation of the data. To obtain the null distribution we randomly shuffled the group labels and calculated the t tests 1000 times. A cluster of consecutive statistically significant ($p < .05$) effects whose summed absolute t-value was highest was saved after each permutation; these values make up the null distribution. A difference between PD and control group was counted as statistically significant if the probability of observing such cluster mass of t values was smaller than 2.5% when compared to the null distribution. This type of clustering method takes into account the fact that true differences cluster together in time. The source reconstructed activity (auditory cortical ROI) was analyzed in the same manner.

The datasets are available for download at https://osf.io/eys97/.

Results

Speech deficits, and the psychophysical task

While most participants and PD patients were assessed to not have speech deficits according to the item representing speech deficit in MDS-UPDRS, PD patients were observed to have speech deficits more frequently than control participants (Table 1). Six of the 17 patients were rated with some speech deficits in the UPDRS (i.e. score 1 or 2).

Our hypothesis was that even though patients reported no speech deficits, weak hypophonia would be detectable using psychophysical assessment. Both, patients and control participants produced higher volume speech to louder test stimuli, as shown in Figure 1. In general, for low volume phonemes participants/patients tended to produce a higher volume sound than the test stimulus, whereas for higher sound volumes they tended to underestimate the loudness. When analyzed using Test Stimulus Amplitude × Group linear mixed-effects regression (df = 1696) where individual participants' intercepts are allowed to vary randomly, the main effect of Test Stimulus Amplitude strongly predicted their response ($\beta = 0.49$, CI = [0.45–0.52], $t = 28.05$, $p < .0001$), and the interaction between Test Stimulus Amplitude and Group also reached statistical significance ($\beta = -0.08$, CI = [-0.13–-0.035], $t = -3.36$, $p = 0.0008$). This interaction indicates that, on average, the influence of Test Stimulus Amplitude (i.e. slope) was smaller in PD patients. However, as seen in Figure 1, this effect is influenced by few individual patients, and when the between-subject variation in the slope is taken into account as a random-effect factor (in addition to intercept), the interaction is not statistically significant ($\beta = -0.068$, CI = [-0.20–0.06], $t = -0.99$, $p = 0.32$).

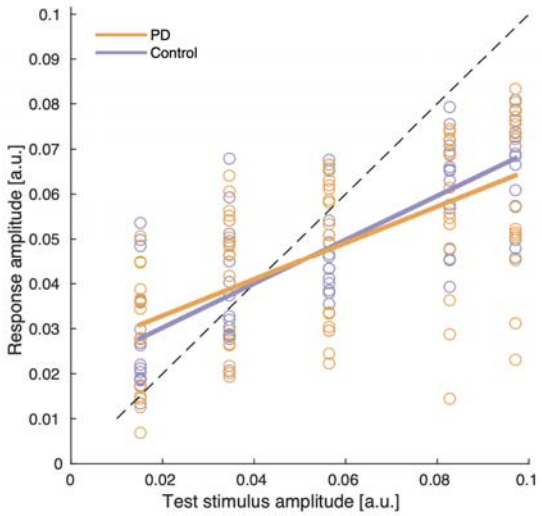

Figure 1. Results of the psychophysical task. PD patients and control participants are depicted as different colors (PD = orange). Dots represent individual participants/patients. The solid lines show the fixed-effects results of the linear model (Test Stimulus Amplitude × Group linear mixed-effects model, with by-subject intercepts). The dashed line is a reference line that denotes perfect correspondence between test stimulus and response amplitude.

EEG

As shown in Figure 2, ERPs time-locked to the onset of the spoken (Speak condition; Fig. 2B) or heard (Listen condition, Fig. 2C) phoneme were calculated. In both conditions, N1 (negative peak at 80 ms), and P2 (positive peak at 190 ms) peaks are observed. ERPs of the patient and control groups did not differ statistically significantly in the Speak condition. In the Listen condition the patients showed reduced amplitudes between 35–80 ms: This is shown in the scalp map, which displays the result of the t test (i.e. plotted values are t values). The topography of the ERPs in the Speak and Listen condition is shown in Figure 2D (averaged across patients and control participants).

Previous studies employing this approach have shown that at central electrode sites the amplitude of the N1 ERP produced by the spoken phoneme is decreased when compared to the same stimuli when passively heard—this is called the SIS. As can be seen in Fig. 2D at time point 80 ms (N1), this same pattern is observed in the present study. This is assumed to reflect the CD

signal: the speech production systems of the brain communicate top-down predictions (CD) about the upcoming speech, and hence the auditory cortex "knows to expect" the phoneme. The P2 time window reveals a similar, but weaker effect.

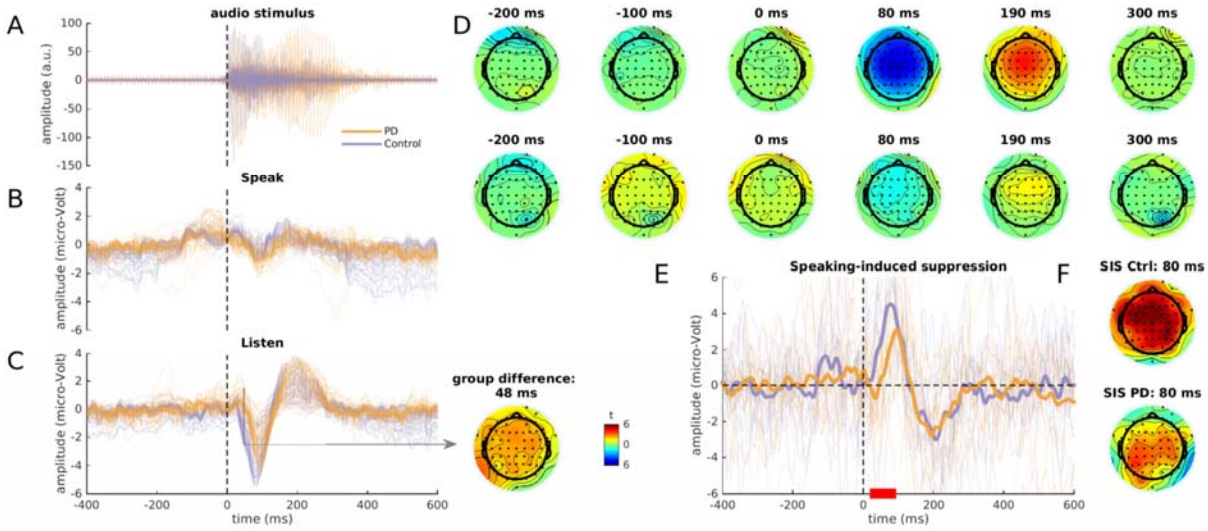

Figure 2. Auditory ERPs. In each panel the orange line is PD patients, and blue line is the control group. A) The auditory signal recorded by EEG (average over all participants/patients). B) A butterfly plot of ERPs in the Speak condition. C) Plot of ERPs in the Listen condition. Each line depicts one channel. Scalp map on the right shows the topography of group differences at 48 ms (color represents t values of independent samples t tests). D) Scalp topographies at different timepoints in Listen (above) and Speak (below) conditions, averaged across PD patients and control participants. Colormap limits are -5 (blue) to 5 µV (red). E) SIS in central electrode (Cz). Faint lines in the background are individual participants' data, and the bold lines are group averages. The red box on the x-axis shows the time window where the two groups differ according to the cluster-mass permutation test. F) Topography of SIS in control participants and patients at 80 ms after stimulus onset. The color here is the t statistic of a one sample t test against zero (scale same as in panel C).

The SIS is shown in Figure 2E (electrode Cz). The red markers on the x-axis show the statistically significant differences between the groups (independent samples t tests): PD patients show a reduced SIS around 100 ms (i.e. N1 time window). Figure 2F shows the result of mass univariate t tests for control participants and patients: the scalp distribution *t values* reflecting SIS

at 80 ms after speech/sound onset localizes to central frontal electrodes as expected. No statistically significant differences between groups was observed for the P2 wave.

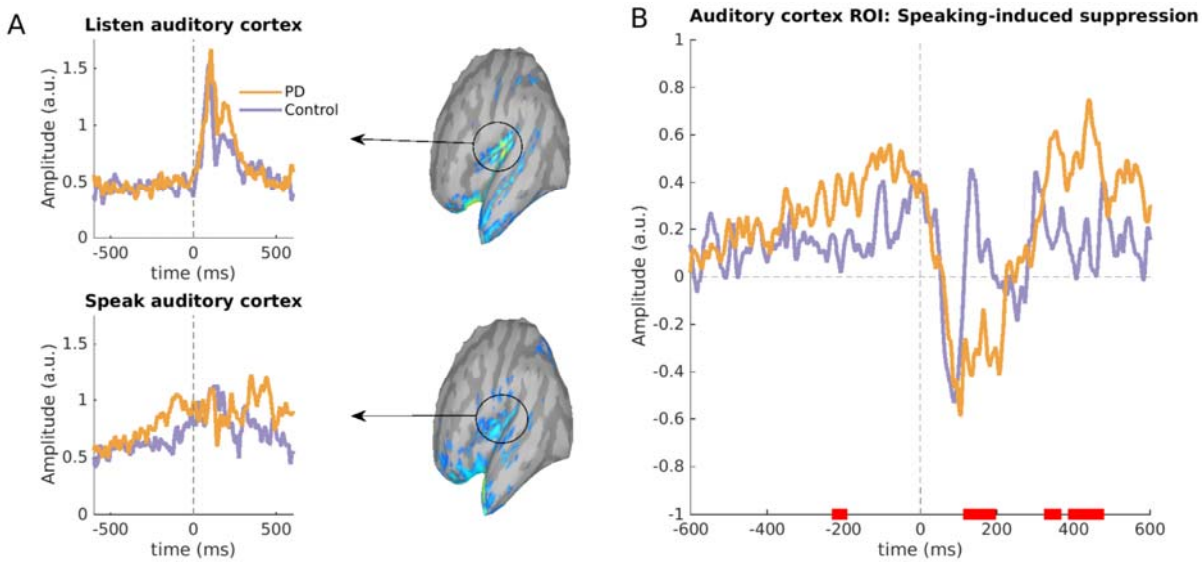

Figure 3. Source reconstruction results visualized. A) Right: Cerebral activations in the Listen (top) and Speak (below) conditions at 100 ms after phonation, presented on an inflated cerebral hemisphere. The left panels show the time course of the averaged signal from the left and right auditory cortical ROIs. The orange line is PD, and the blue line the control group. B) SIS in PD patients and control participants in the ROI. The red markers on the x axis show statistically significant effects corrected for multiple comparisons.

During speech, the CD signal is assumed to modulate activity in auditory cortex. ERP waves reflect the summed activity of multiple overlapping components during the N1 time window (Godey, Schwartz, De Graaf, Chauvel, & Liégeois-Chauvel, 2001; Näätänen & Picton, 1987; Zouridakis, Simos, & Papanicolaou, 1998). Source-reconstruction was run to estimate the time-course of activation of the auditory cortex (BA41). As shown in Figure 3A, when sounds were passively listened, the auditory cortex activation revealed two activation peaks whose latencies closely resembled the latencies of the N1 and P2 ERP waves. During speech the activation is smaller, and begins before the onset of the spoken sound, especially in PD patients. The estimated auditory cortical SIS is shown in Figure 3B: negative values here indicate suppression of activity,

and positive values stronger activity in the Speak condition relative to Listen condition. First of all, the source reconstructed data verifies the SIS observed in ERPs: suppression of auditory cortical activity begins around 50 ms after phonation. Second, the patient and control groups show differences in auditory cortical activity. Compared to control participants, activation is PD patients is stronger during speaking already before phonation (around 200 ms before phonation). In patients the suppression of auditory cortical activity during speech lasts longer when compared to control participants (100–200 ms; although notably this effect is related to stronger activity in patients during the Listen condition). At later time-window, PD patients' auditory cortex shows stronger activation during speech than listening (400–500 ms).

Discussion

Models of speech production (Guenther et al., 2006; Houde & Nagarajan, 2011) assume that self-produced sounds are compared to estimated speech output during early cortical processing stages, enabling reflexive adjustment of speech (Niziolek, Nagarajan, & Houde, 2013). Our study is the first to show abnormal early cortical electrophysiological correlates of monitoring non-perturbed self-produced speech in PD patients. The reduced SIS suggests that in PD, brain detected a higher than normal mismatch between predicted and produced speech. The patients themselves reported experiencing no speech impairments, although neurological examination (UPDRS speech item) revealed weak speech impairment.

What caused the modified the SIS in patients?

A likely answer to why was SIS reduced in PD patients is that their speech output did not match the predictions. However, increased prediction error during speech production should be reflected as increased N1 amplitude in the Speak condition (Behroozmand et al., 2011), but in the present

results, patients and control participants showed comparable N1 amplitudes during speaking. In contrast, the reduced SIS in PD patients was due to reduced early N1 wave amplitudes in the Listen condition. In other words, a more accurate description of the result is that the PD patients showed increased prediction errors to self-produced phonemes when their auditory evoked response to the listen condition is taken into account. Similar result of reduced SIS which is driven by changes in the responses in the passive listening condition has been reported in schizophrenia patients when compared to healthy controls (Ford et al., 2013; Perez et al., 2012).

The above suggests that the speech defects in PD could be influenced by aberrant early auditory responses to heard phonemes. While most previous auditory ERP studies report that later evoked potentials are modulated by PD (Cavanagh, Kumar, Mueller, Richardson, & Mueen, 2018; Huang et al., 2016; Solís-Vivanco et al., 2015; Tanaka et al., 2000), PD patients have been reported to be less sensitive to detect first formant differences during passive listening of vowels (Mollaei, Shiller, Baum, & Gracco, 2019). We performed source reconstruction to better characterize auditory cortical activity, as ERPs reflect multiple generators already during the N1 time-window (Godey et al., 2001; Näätänen et al., 1997). Because a similar early difference in the Listen condition was not observed in the source reconstructed auditory cortex activity, the difference in the ERPs (in the Listen condition) could be driven by frontal influences on (not self-produced) speech perception. Frontal areas have been shown to causally modulate auditory cortical activity (Cope et al., 2017), and over-active frontal regions have been systematically linked with speech deficits in PD (Arnold et al., 2014; Liotti et al., 2003; Pinto, Thobois, et al., 2004). Alternatively, the reduced N1 could reflect deficits in subcortical regions, as auditory evoked brain stem potentials are modulated by PD (Fradisa et al., 1988; Liu et al., 2017). We propose that aberrant subcortical auditory evoked activity, or higher-level frontal activity could bias speech

perception in PD, but acknowledge that this conclusion is speculative, and at present without direct experimental evidence.

Whereas scalp recorded ERPs did not reveal group differences in ERPs during speaking, the source reconstruction results suggested that auditory cortex is differently modulated by speech production in PD than control participants. Interestingly, the source reconstruction results showed that during speaking auditory cortex is modulated already before speech onset, especially in PD patients. This activation could reflect speech-production related preparatory activation, but the possibility that it correlates merely with e.g. muscular artifact in PD patients cannot be excluded. The source reconstructed activity could also reflect the activation of frontal motor regions whose activity was incorrectly localized to auditory cortex. Chang et al. (2013), who performed direct recording in human subjects, showed that activity in vocal motor cortex increased up to 400 ms before speech onset. Consistent with the present results, Sörös et al. (2017) observed that activity in EEG beta band activity is increased in PD patients when compared to healthy controls during speech preparation. Note that while the SIS is considered to mark the suppressive *consequence* of CD signal on auditory cortex, the CD signal itself should be triggered right before the motor command (as the CD signal is assumed to be the copy of the motor command).

In sum, while the present results suggest that SIS is reduced in PD patients, the source of this effect remains open. The reduced SIS could be attributed to a mismatch between predicted and produced speech, but it could also be related to deficits in the self-monitoring process per se (due to deficits in processing speech-like stimuli, or abnormalities in top-down modulation of auditory cortical activity during speech).

Why PD patients do not notice and correct for their speech impairment?

The amplitude of the P2 wave has been observed to increase in situations where participants correct for perturbations in their speech output (Behroozmand et al., 2011; Heinks-Maldonado et al., 2005; Huang et al., 2016). We did not observe any differences between the PD and control groups in the amplitude of the P2 wave, suggesting that the patients did not produce corrections to their speech (or both groups produced similar corrections). Why did the patients not initiate corrections? Firstly, as discussed above, one could argue that the reduced SIS does not reflect an increased prediction error, but reflects deficits in comparing incoming speech stimuli to top-down predictions. Secondly, if we assume that the reduced SIS does signal a mismatch between produced and predicted speech, the patients could have trouble correcting their speech production based on the prediction errors (Abur et al., 2018). In the terminology of the state feedback control model (Houde & Nagarajan, 2011), the difficulty could be in combining the prediction error with the next vocal tract state estimate, or result from a failure to generate updated controls based on the corrected state estimate.

The lack of subjective experience of speech deficit is a well-known feature of PD, and is one of the major factors that hinder voice-therapeutic treatments of speech impairment in PD. Conscious auditory perception correlates with ERP amplitudes in the P2 time-window (Eklund & Wiens, 2019). This suggests that P2 amplitude evoked by self-produced speech may be a marker of subjective perception of one's own speech, and the N1/SIS processing stage (where mismatch between predicted and produced speech is calculated) is not consciously experienced by the subject. If the conclusion that speech impairment in PD is mediated by deficits in taking into account auditory cortical prediction errors to update speech control is correct, then interventions that target these processes may help the patients to subjectively notice and correct for their speech deficit. Incorporation of sensory prediction errors into subsequent speech-production processes are assumed rely on motor cortex, ventral premotor cortex, and inferior frontal cortex

in the right hemisphere (Houde & Nagarajan, 2011; Tourville, Reilly, & Guenther, 2008). Neuromodulation of these areas could thus improve speech in PD. Previous neuromodulation studies have predominantly targeted the primary motor areas, superior temporal sulcus, or the left dorsolateral prefrontal cortex (Brabenec et al., 2019; Dias et al., 2006; Eliasova et al., 2013).

Our results differ from those reported by Huang et al. (2016), who observed that PD and control groups did not differ with respect to SIS/N1 amplitudes, but differed with respect to P2 amplitudes. That Huang et al. (2016) observed an enhanced P2 modulation in PD patients when compared to controls is in line with the fact that the PD patients also produced stronger corrections to speech in response to perturbation than control participants. We suggest that our paradigm, which did not employ speech perturbation, was more sensitive to detect differences in SIS.

Dopamine and other neurotransmitter systems

Because PD is associated with changes to multiple neurotransmitter systems (Jellinger, 1991), multiple different mechanisms could underlie the observed differences between PD patients and control participants. That said, dopamine is has been associated with speech (Simonyan, Herscovitch, & Horwitz, 2013; Simonyan, Horwitz, & Jarvis, 2012), and dopamine deficiency has been proposed to lead to deficits in sensory attenuation (Friston, Bastos, Pinotsis, & Litvak, 2015; Friston et al., 2012). Previously, we observed that in PD patients performance in the double-saccade task—which is used to probe self-monitoring in the oculomotor system—correlated with changes in dopamine transporter binding in the striatum (Railo et al., 2018). Dopamine deficiency in PD leads to aberrant activity in basal ganglia-cortex loops (Rivlin-Etzion et al., 2006; Rodriguez-Oroz et al., 2009) which could lead to deficits in using prediction errors to correct for produced speech, as well as explain for deficits in perceptual processing. Because PD medication was not

systematically manipulated in the present study, potential confounds produced by the medication cannot be ruled out.

The interpretation that the changes in neural correlates of speech self-monitoring are due to dopaminergic deficiency is at odds with the fact that schizophrenia patients display similar reduced SIS (Ford et al., 2013; Perez et al., 2012) as PD patients in our study. Yet unlike PD, which is associated with reduced nigrostriatal dopamine (Kordower et al., 2013), schizophrenia patients have hyperactive striatal dopamine neurotransmission (Howes & Kapur, 2009). Thus, if changes in SIS would be due to the dopamine system, we would expect to see opposite effects in PD and schizophrenia.

Conclusion

We have provided evidence that the electrophysiological correlate of speech self-monitoring (SIS) in auditory cortex level is altered in PD. While the causes of this remain open, our results help to shed light on the time-course of aberrant auditory cortical modulation in PD. Consistent with previous reports, the present finding suggests that abnormalities in speech-related neural activity occur early in PD (e.g. Arnold et al., 2014; Moreau & Pinto, 2019). As these deficits worsen, more pronounced speech deficits are likely to emerge. Understanding why the patients fail to consciously notice their speech deficit (especially hypophonia) is crucial for developing more effective treatments for speech impairment.

Authors' roles

H.R. designed the experiment, supervised data collection, analyzed the data, and wrote the first manuscript draft. N.N and S.S. collected the data. V.K. helped to organize the research, supervised data collection, and reviewed and revised the manuscript.

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References

Abur, D., Lester-Smith, R. A., Daliri, A., Lupiani, A. A., Guenther, F. H., & Stepp, C. E. (2018). Sensorimotor adaptation of voice fundamental frequency in Parkinson's disease. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0191839

Arnold, C., Gehrig, J., Gispert, S., Seifried, C., & Kell, C. A. (2014). Pathomechanisms and compensatory efforts related to Parkinsonian speech. *NeuroImage: Clinical*. https://doi.org/10.1016/j.nicl.2013.10.016

Baumann, A., Nebel, A., Granert, O., Giehl, K., Wolff, S., Schmidt, W., … van Eimeren, T. (2018). Neural Correlates of Hypokinetic Dysarthria and Mechanisms of Effective Voice Treatment in Parkinson Disease. *Neurorehabilitation and Neural Repair*. https://doi.org/10.1177/1545968318812726

Beck, A. T. (1976). Cognitive therapy and the emotional disorders. *INT.UNIV.PRESS,NEW YORK*. https://doi.org/10.1176/appi.psychotherapy.1977.31.4.633

Behroozmand, R., Liu, H., & Larson, C. R. (2011). Time-dependent neural processing of auditory feedback during voice pitch error detection. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2010.21447

Brabenec, L., Klobusiakova, P., Barton, M., Mekyska, J., Galaz, Z., Zvoncak, V., … Rektorova, I. (2019). Non-invasive stimulation of the auditory feedback area for improved articulation in Parkinson's disease. *Parkinsonism and Related Disorders*. https://doi.org/10.1016/j.parkreldis.2018.10.011

Cavanagh, J. F., Kumar, P., Mueller, A. A., Richardson, S. P., & Mueen, A. (2018). Diminished EEG

habituation to novel events effectively classifies Parkinson's patients. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2017.11.023

Chang, E. F., Niziolek, C. A., Knight, R. T., Nagarajan, S. S., & Houde, J. F. (2013). Human cortical sensorimotor network underlying feedback control of vocal pitch. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1216827110

Chen, X., Zhu, X., Wang, E. Q., Chen, L., Li, W., Chen, Z., & Liu, H. (2013). Sensorimotor control of vocal pitch production in Parkinson's disease. *Brain Research*. https://doi.org/10.1016/j.brainres.2013.06.030

Clark, J. P., Adams, S. G., Dykstra, A. D., Moodie, S., & Jog, M. (2014). Loudness perception and speech intensity control in Parkinson's disease. *Journal of Communication Disorders*. https://doi.org/10.1016/j.jcomdis.2014.08.001

Cope, T. E., Sohoglu, E., Sedley, W., Patterson, K., Jones, P. S., Wiggins, J., … Rowe, J. B. (2017). Evidence for causal top-down frontal contributions to predictive processes in speech perception. *Nature Communications*. https://doi.org/10.1038/s41467-017-01958-7

Curio, G., Neuloh, G., Numminen, J., Jousmäki, V., & Hari, R. (2000). Speaking modifies voice-evoked activity in the human auditory cortex. *Human Brain Mapping*. https://doi.org/10.1002/(SICI)1097-0193(200004)9:4<183::AID-HBM1>3.0.CO;2-Z

Dale, A. M., Liu, A. K., Fischl, B. R., Buckner, R. L., Belliveau, J. W., Lewine, J. D., & Halgren, E. (2000). Dynamic statistical parametric mapping: Combining fMRI and MEG for high-resolution imaging of cortical activity. *Neuron*. https://doi.org/10.1016/S0896-6273(00)81138-1

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*. https://doi.org/10.1016/j.jneumeth.2003.10.009

Destrieux, C., Fischl, B., Dale, A., & Halgren, E. (2010). Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2010.06.010

Dias, A. E., Barbosa, E. R., Coracini, K., Maia, F., Marcolin, M. A., & Fregni, F. (2006). Effects of repetitive transcranial magnetic stimulation on voice and speech in Parkinson's disease. *Acta Neurologica Scandinavica*. https://doi.org/10.1111/j.1600-0404.2005.00558.x

Eklund, R., & Wiens, S. (2019). Auditory awareness negativity is an electrophysiological correlate of awareness in an auditory threshold task. *Consciousness and Cognition*. https://doi.org/10.1016/j.concog.2019.03.008

Eliasova, I., Mekyska, J., Kostalova, M., Marecek, R., Smekal, Z., & Rektorova, I. (2013). Acoustic evaluation of short-term effects of repetitive transcranial magnetic stimulation on motor aspects of speech in Parkinson's disease. In *Journal of Neural Transmission*. https://doi.org/10.1007/s00702-012-0953-1

Follett, K. A., Weaver, F. M., Stern, M., Hur, K., Harris, C. L., Luo, P., … Reda, D. J. (2010). Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *New England Journal of Medicine*. https://doi.org/10.1056/NEJMoa0907083

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*. https://doi.org/10.1016/0022-3956(75)90026-6

Ford, J. M., & Mathalon, D. H. (2005). Corollary discharge dysfunction in schizophrenia: Can it explain auditory hallucinations? In *International Journal of Psychophysiology*. https://doi.org/10.1016/j.ijpsycho.2005.01.014

Ford, J. M., Mathalon, D. H., Roach, B. J., Keedy, S. K., Reilly, J. L., Gershon, E. S., & Sweeney, J. A. (2013). Neurophysiological evidence of corollary discharge function during vocalization in

psychotic patients and their nonpsychotic first-degree relatives. *Schizophrenia Bulletin*. https://doi.org/10.1093/schbul/sbs129

Fox, C. M., & Ramig, L. O. (1997). Vocal Sound Pressure Level and Self-Perception of Speech and Voice in Men and Women with Idiopathic Parkinson Disease. *American Journal of Speech-Language Pathology*. https://doi.org/10.1044/1058-0360.0602.85

Fradisa, M., Samet, A., Ben-David, J., Podoshin, L., Sharf, B., Wajsbort, J., … Pratt, H. (1988). Brainstem auditory evoked potentials to different stimulus rates in parkinsonian patients. *European Neurology*. https://doi.org/10.1159/000116262

Friston, K. J., Bastos, A. M., Pinotsis, D., & Litvak, V. (2015). LFP and oscillations-what do they tell us? *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2014.05.004

Friston, K. J., Shiner, T., FitzGerald, T., Galea, J. M., Adams, R., Brown, H., … Bestmann, S. (2012). Dopamine, affordance and active inference. *PLoS Computational Biology*. https://doi.org/10.1371/journal.pcbi.1002327

Godey, B., Schwartz, D., De Graaf, J. B., Chauvel, P., & Liégeois-Chauvel, C. (2001). Neuromagnetic source localization of auditory evoked fields and intracerebral evoked potentials: A comparison of data in the same patients. *Clinical Neurophysiology*. https://doi.org/10.1016/S1388-2457(01)00636-8

Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., … Hämäläinen, M. (2013). MEG and EEG data analysis with MNE-Python. *Frontiers in Neuroscience*. https://doi.org/10.3389/fnins.2013.00267

Guenther, F. H., Ghosh, S. S., & Tourville, J. A. (2006). Neural modeling and imaging of the cortical interactions underlying syllable production. *Brain and Language*. https://doi.org/10.1016/j.bandl.2005.06.001

Heinks-Maldonado, T. H., Mathalon, D. H., Gray, M., & Ford, J. M. (2005). Fine-tuning of auditory

cortex during speech production. *Psychophysiology*. https://doi.org/10.1111/j.1469-8986.2005.00272.x

Hickok, G. (2012). Computational neuroanatomy of speech production. *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn3158

Hlavnika, J., Cmejla, R., Tykalová, T., Šonka, K., Ruzicka, E., & Rusz, J. (2017). Automated analysis of connected speech reveals early biomarkers of Parkinson's disease in patients with rapid eye movement sleep behaviour disorder. *Scientific Reports*. https://doi.org/10.1038/s41598-017-00047-5

Ho, A. K., Bradshaw, J. L., & Iansek, R. (2008). For better or worse: The effect of Levodopa on speech in Parkinson's disease. *Movement Disorders*. https://doi.org/10.1002/mds.21899

Ho, A. K., Iansek, R., Marigliani, C., Bradshaw, J. L., & Gates, S. (1998). Speech impairment in a large sample of patients with Parkinson's disease. *Behavioural Neurology*.

Holmes, C. J., Hoge, R., Collins, L., Woods, R., Toga, A. W., & Evans, A. C. (1998). Enhancement of MR images using registration for signal averaging. *Journal of Computer Assisted Tomography*. https://doi.org/10.1097/00004728-199803000-00032

Houde, J. F., & Nagarajan, S. S. (2011). Speech production as state feedback control. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2011.00082

Houde, J. F., Nagarajan, S. S., Sekihara, K., & Merzenich, M. M. (2002). Modulation of the auditory cortex during speech: An MEG study. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/089892902760807140

Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: Version III - The final common pathway. *Schizophrenia Bulletin*. https://doi.org/10.1093/schbul/sbp006

Huang, X., Chen, X., Yan, N., Jones, J. A., Wang, E. Q., Chen, L., … Liu, H. (2016). The impact of parkinson's disease on the cortical mechanisms that support auditory–motor integration for

voice control. *Human Brain Mapping*. https://doi.org/10.1002/hbm.23306

Jellinger, K. A. (1991). Pathology of Parkinson's disease - Changes other than the nigrostriatal pathway. *Molecular and Chemical Neuropathology*. https://doi.org/10.1007/BF03159935

Kiran, S., & Larson, C. R. (2001). Effect of duration of pitch-shifted feedback on vocal responses in patients with Parkinson's disease. *Journal of Speech, Language, and Hearing Research*. https://doi.org/10.1044/1092-4388(2001/076)

Kordower, J. H., Olanow, C. W., Dodiya, H. B., Chu, Y., Beach, T. G., Adler, C. H., … Bartus, R. T. (2013). Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. *Brain*. https://doi.org/10.1093/brain/awt192

Kwan, L. C., & Whitehill, T. L. (2011). Perception of speech by individuals with Parkinson's disease: A review. *Parkinson's Disease*. https://doi.org/10.4061/2011/389767

Leritz, E., Loftis, C., Crucian, G., Friedman, W., & Bowers, D. (2004). Self-awareness of deficits in Parkinson disease. *Clinical Neuropsychologist*. https://doi.org/10.1080/1385404049052412

Lin, F. H., Witzel, T., Ahlfors, S. P., Stufflebeam, S. M., Belliveau, J. W., & Hämäläinen, M. S. (2006). Assessing and improving the spatial accuracy in MEG source localization by depth-weighted minimum-norm estimates. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2005.11.054

Liotti, M., Ramig, L. O., Vogel, D., New, P., & Cook, C. I. (2003). Hypophonia in Parkinson's disease Neural correlates of voice treatment revealed by PET. *Neurology*.

Liu, C., Zhang, Y., Tang, W., Wang, B., Wang, B., & He, S. (2017). Evoked potential changes in patients with Parkinson's disease. *Brain and Behavior*. https://doi.org/10.1002/brb3.703

Liu, H., Wang, E. Q., Metman, L. V., & Larson, C. R. (2012). Vocal responses to perturbations in voice auditory feedback in individuals with parkinson's disease. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0033629

Logemann, J. A., Fisher, H. B., Boshes, B., & Blonsky, E. R. (1978). Frequency and cooccurrence of

vocal tract dysfunctions in the speech of a large sample of Parkinson patients. *Journal of Speech and Hearing Disorders*. https://doi.org/10.1044/jshd.4301.47

Louis, E. D., Winfield, L., Fahn, S., & Ford, B. (2001). Speech dysfluency exacerbated by levodopa in Parkinson's disease. *Movement Disorders*. https://doi.org/10.1002/mds.1081

Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG- and MEG-data. *Journal of Neuroscience Methods*. https://doi.org/10.1016/j.jneumeth.2007.03.024

McClelland, J. L., Mirman, D., & Holt, L. L. (2006). Are there interactive processes in speech perception? *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2006.06.007

Mollaei, F., Shiller, D. M., Baum, S. R., & Gracco, V. L. (2016). Sensorimotor control of vocal pitch and formant frequencies in Parkinson's disease. *Brain Research*. https://doi.org/10.1016/j.brainres.2016.06.013

Mollaei, F., Shiller, D. M., Baum, S. R., & Gracco, V. L. (2019). The relationship between speech perceptual discrimination and speech production in parkinson's disease. *Journal of Speech, Language, and Hearing Research*. https://doi.org/10.1044/2019_JSLHR-S-18-0425

Mollaei, F., Shiller, D. M., & Gracco, V. L. (2013). Sensorimotor adaptation of speech in Parkinson's disease. *Movement Disorders*. https://doi.org/10.1002/mds.25588

Moreau, C., & Pinto, S. (2019). Misconceptions about speech impairment in Parkinson's disease. *Movement Disorders*, *34*(10), 1471–1475.

Mullen, T. R., Kothe, C. A. E., Chi, Y. M., Ojeda, A., Kerth, T., Makeig, S., … Cauwenberghs, G. (2015). Real-time neuroimaging and cognitive monitoring using wearable dry EEG. *IEEE Transactions on Biomedical Engineering*. https://doi.org/10.1109/TBME.2015.2481482

Näätänen, R., Lehtokoski, A., Lennes, M., Cheour, M., Huotilainen, M., Iivonen, A., … Alho, K. (1997). Language-specific phoneme representations revealed by electric and magnetic brain responses. *Nature*. https://doi.org/10.1038/385432a0

Näätänen, R., & Picton, T. (1987). The N1 Wave of the Human Electric and Magnetic Response to Sound: A Review and an Analysis of the Component Structure. *Psychophysiology*. https://doi.org/10.1111/j.1469-8986.1987.tb00311.x

Niziolek, C. A., Nagarajan, S. S., & Houde, J. F. (2013). What does motor efference copy represent? evidence from speech production. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.2137-13.2013

Norris, D., McQueen, J. M., & Cutler, A. (2016). Prediction, Bayesian inference and feedback in speech recognition. *Language, Cognition and Neuroscience*. https://doi.org/10.1080/23273798.2015.1081703

Perez, V. B., Ford, J. M., Roach, B. J., Loewy, R. L., Stuart, B. K., Vinogradov, S., & Mathalon, D. H. (2012). Auditory cortex responsiveness during talking and listening: Early illness schizophrenia and patients at clinical high-risk for psychosis. *Schizophrenia Bulletin*. https://doi.org/10.1093/schbul/sbr124

Pinto, S., Ozsancak, C., Tripoliti, E., Thobois, S., Limousin-Dowsey, P., & Auzou, P. (2004). Treatments for dysarthria in Parkinson's disease. *Lancet Neurology*. https://doi.org/10.1016/S1474-4422(04)00854-3

Pinto, S., Thobois, S., Costes, N., Le Bars, D., Benabid, A. L., Broussolle, E., … Gentil, M. (2004). Subthalamic nucleus stimulation and dysarthria in Parkinson's disease: A PET study. *Brain*. https://doi.org/10.1093/brain/awh074

Railo, H., Olkoniemi, H., Eeronheimo, E., Pääkkönen, O., Joutsa, J., & Kaasinen, V. (2018). Dopamine and eye movement control in Parkinson's disease: Deficits in corollary discharge signals? *PeerJ*. https://doi.org/10.7717/peerj.6038

Rektorova, I., Barrett, J., Mikl, M., Rektor, I., & Paus, T. (2007). Functional abnormalities in the primary orofacial sensorimotor cortex during speech in Parkinson's disease. *Movement*

Disorders. https://doi.org/10.1002/mds.21548

Rivlin-Etzion, M., Marmor, O., Heimer, G., Raz, A., Nini, A., & Bergman, H. (2006). Basal ganglia oscillations and pathophysiology of movement disorders. *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2006.10.002

Rodriguez-Oroz, M. C., Jahanshahi, M., Krack, P., Litvan, I., Macias, R., Bezard, E., & Obeso, J. A. (2009). Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms. *The Lancet Neurology*. https://doi.org/10.1016/S1474-4422(09)70293-5

Sapir, S., Pawlas, A. A., Ramig, L. O., Countryman, S., O'Brien, C., Hoehn, M. M., & Thompson, L. A. (2001). Voice and Speech Abnormalities in Parkinson Disease: Relation to Severity of Motor Impairment, Duration of Disease, Medication, Depression, Gender, and Age. *Journal of Medical Speech-Language Pathology*.

Simonyan, K., Herscovitch, P., & Horwitz, B. (2013). Speech-induced striatal dopamine release is left lateralized and coupled to functional striatal circuits in healthy humans: A combined PET, fMRI and DTI study. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2012.12.042

Simonyan, K., Horwitz, B., & Jarvis, E. D. (2012). Dopamine regulation of human speech and bird song: A critical review. *Brain and Language*. https://doi.org/10.1016/j.bandl.2011.12.009

Skodda, S., Visser, W., & Schlegel, U. (2010). Short- and long-term dopaminergic effects on dysarthria in early Parkinson's disease. *Journal of Neural Transmission*. https://doi.org/10.1007/s00702-009-0351-5

Solís-Vivanco, R., Rodríguez-Violante, M., Rodríguez-Agudelo, Y., Schilmann, A., Rodríguez-Ortiz, U., & Ricardo-Garcell, J. (2015). The P3a wave: A reliable neurophysiological measure of Parkinson's disease duration and severity. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2014.12.024

Sörös, P., Doñamayor, N., Wittke, C., Al-Khaled, M., Brüggemann, N., & Münte, T. F. (2017).

Increase in beta-band activity during preparation for overt speech in patients with parkinson's disease. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2017.00371

Stenroos, M., Hunold, A., & Haueisen, J. (2014). Comparison of three-shell and simplified volume conductor models in magnetoencephalography. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2014.01.006

Stropahl, M., Bauer, A. K. R., Debener, S., & Bleichner, M. G. (2018). Source-Modeling auditory processes of EEG data using EEGLAB and brainstorm. *Frontiers in Neuroscience*. https://doi.org/10.3389/fnins.2018.00309

Tadel, F., Baillet, S., Mosher, J. C., Pantazis, D., & Leahy, R. M. (2011). Brainstorm: A user-friendly application for MEG/EEG analysis. *Computational Intelligence and Neuroscience*. https://doi.org/10.1155/2011/879716

Tanaka, H., Koenig, T., Pascual-Marqui, R. D., Hirata, K., Kochi, K., & Lehmann, D. (2000). Event-related potential and EEG Parkinson's disease without and with dementia. *Dementia and Geriatric Cognitive Disorders*. https://doi.org/10.1159/000017212

Tourville, J. A., Reilly, K. J., & Guenther, F. H. (2008). Neural mechanisms underlying auditory feedback control of speech. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2007.09.054

Zouridakis, G., Simos, P. G., & Papanicolaou, A. C. (1998). Multiple bilaterally asymmetric cortical sources account for the auditory N1m component. *Brain Topography*. https://doi.org/10.1023/A:1022246825461