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

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Abstract

**Background:** Speech deficits are common in Parkinson's disease (PD), but the underlying neural mechanisms are not well understood. The classical view has linked PD speech problems to a dysfunction of vocal muscles. Paradoxically, patients may not subjectively be aware of their own speech deficits such as hypophonic speech. We hypothesized that this reflects an impairment in monitoring self-produced speech at auditory cortex level.

**Methods:** We measured evoked electroencephalographic responses to self-produced and passively heard sounds (phonemes) in early-stage PD patients with subclinical speech impairment (N=20) and age-matched controls (N=20).

**Results:** During speaking, auditory evoked activity 100 ms after phonation was less suppressed in PD than controls when compared to the activity evoked by passively heard phonemes. Source reconstruction analysis 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).

**Conclusions:** The findings indicate that auditory cortical activity is abnormally modulated during speech in early PD patients who do not subjectively notice speech impairment. This suggests deficits in internal monitoring of self-produced sounds at subclinical stages of speech problems. We suggest that, instead of vocal muscle incoordination, this mechanism may play a key initial role in producing speech deficits in PD, particularly hypophonia.

## Introduction

The majority of patients with Parkinson's disease (PD) show speech impairments typically classified as hypokinetic dysarthria [1–3]. The major speech symptoms are inaccurate articulation, variable speech rate, monotonic and hypophonic loudness of speech, and harsh voice quality. Speech impairment in PD is typically attributed to deficits in the motor control of speech organs. Yet, unlike primary motor symptoms of PD, speech deficits often do not respond to dopamine therapy [4,5], and dysarthria is a well-known side-effect of deep-brain stimulation [6]. Treatment of speech deficits is difficult in part because its neural basis is not understood.

Just like any other actions, speech requires the brain to continuously monitor how well the produced actions match the desired outcome [7]. We hypothesized that speech deficits in PD reflect problems in monitoring self-produced speech. PD patients are often not fully aware of their speech deficits [8], whereas they are typically well aware of their primary motor symptoms [9]. 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 [10,11]. PD patients also respond abnormally to perturbation in their speech, suggesting deficits in monitoring mechanisms [12,13]. While the auditory processing capacity of PD patients may not generally differ from healthy controls, the patients could have selective deficits in processing spoken language[14].

The brain tracks how well produced actions such as spoken words match the desired 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[15]. 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. Similar mechanisms could also contribute to speech perception[16–18].

The functioning of the auditory speech self-monitoring system can be examined by comparing the auditory evoked activity produced by self-produced speech to the same sounds when they are not self-produced. 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 [19–23]. 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 around 100 ms after speech/sound onset (i.e. N100 wave of the event-related potential, ERP).

We hypothesized that hypophonic speech observed in advanced PD may be due to abnormal speech self-monitoring through which the individual keeps track of how the produced sounds match the desired outcome. This could be due to abnormal CD signals, or deficits in comparing the CD prediction to the incoming auditory activation[24]. These deficits could, in turn, reflect pathological changes in e.g. dopamine system in the PD [25]. Demonstration of an altered SIS in PD would be an important discovery because it would suggest that the neural mechanism underlying speech impairment relates in part to abnormal monitoring of speech production, instead of pure deficit in motor control.

## 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. Comparison of the demographical information, and clinical and neuropsychological measurements are presented in Table 1. 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.

**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)

Mini Mental-State (MMSE) questionnaire was used to assess cognitive impairment [26]. 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 [27]. 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. 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.

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 patients can therefore be considered being in OFF phase.

*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.

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).

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. First, the signal from the headphones was 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 [28] on Matlab 2014b. Channels were first automatically inspected, and bad channels interpolated. 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 [29]. 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.

Because the scalp-recorded N1 ERP wave (during which SIS is should be present) is modulated by various cortical sources (including e.g. frontal areas in addition to superior temporal

cortices [30–32]), we estimated auditory cortical activity using source reconstruction. Source reconstruction analysis was performed in Brainstorm software [33], following the guidelines provided by Stropahl et al. [34]. 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 [35], was applied to the data [36]. Because we did not have the individual participants' anatomical images, an MNI anatomical template [37] 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) [38,39]. 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) [40]. 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 [41]. 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 x 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], $t = -0.99$, $p = 0.32$).

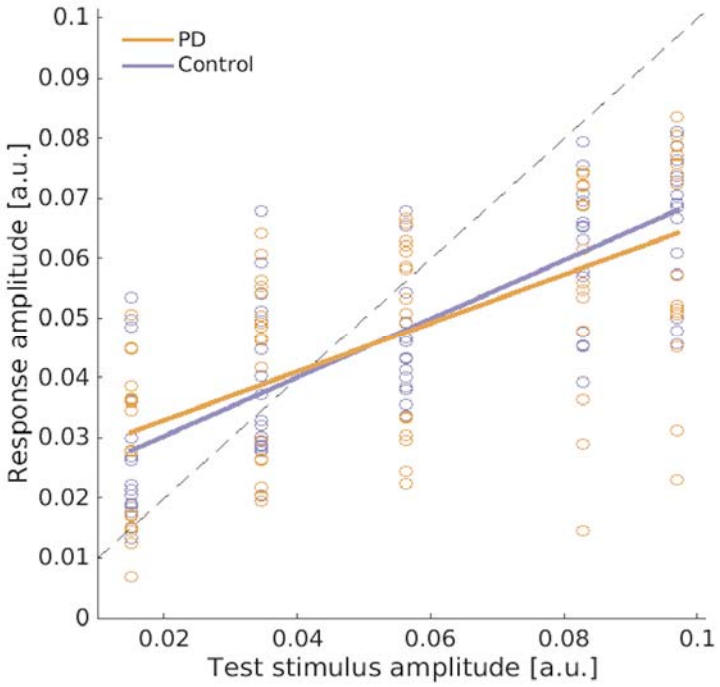


*Figure 1. Results of the psychophysical task. PD patients and control participants are depicted as different colors (PD = orange). Dots represent individual participants/patients. The solid lines show the linear model.*

*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 (as shown in the scalp map). 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. As can be seen in Fig. 2D at time point 80 ms (N1), this same pattern is observed in the present study. This difference between the Speak and Listen conditions 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.

The SIS – the difference between the Speak and Listen conditions – is shown in Figure 2E (electrode Cz). The red markers on the x-axis show the statistically significant differences between the groups: PD patients show a reduced SIS around 100 ms (i.e. N1 time window). Figure 2F shows the scalp distribution of the SIS at 80 ms after speech/sound onset in control participants and patients.

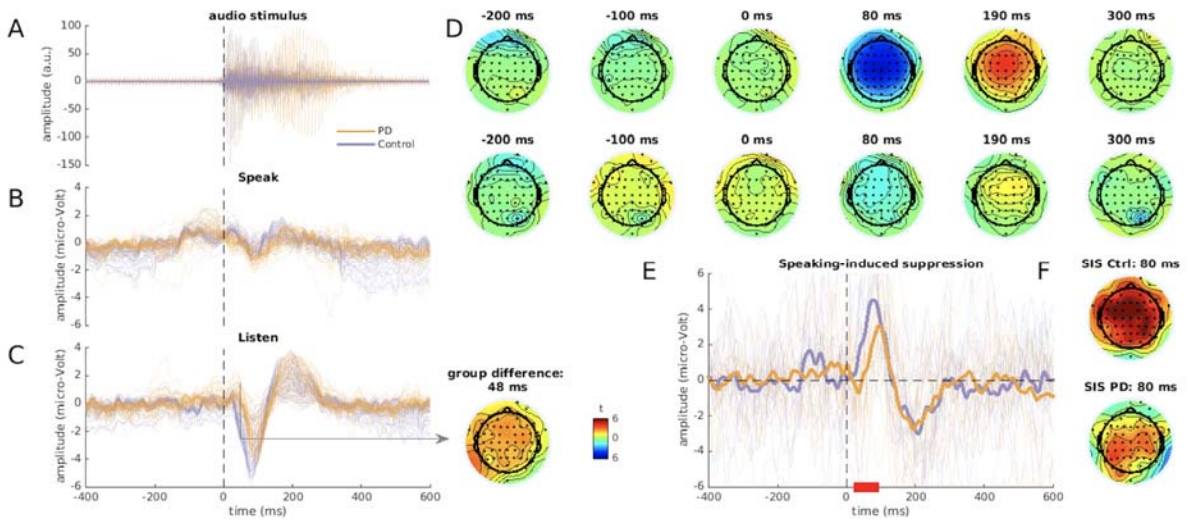


*Figure 2. Auditory ERPs. In each panel the orange line is PD patients, and blue line is the control group. A) The auditory signal recorded by EEG (average over all participants/patients). B) A butterfly plot of ERPs in the Speak condition. C) Plot of ERPs in the Listen condition. Each line depicts one 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).*

During speech, the CD signal is assumed to modulate activity in auditory cortex. Source-reconstruction was run to estimate the time-course of activation of the auditory cortex. 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. As can be seen the two groups differ in three time-windows: about 200 ms before phonation, and after speech onset at an early (100-200 ms) and late (400-500 ms) time window.

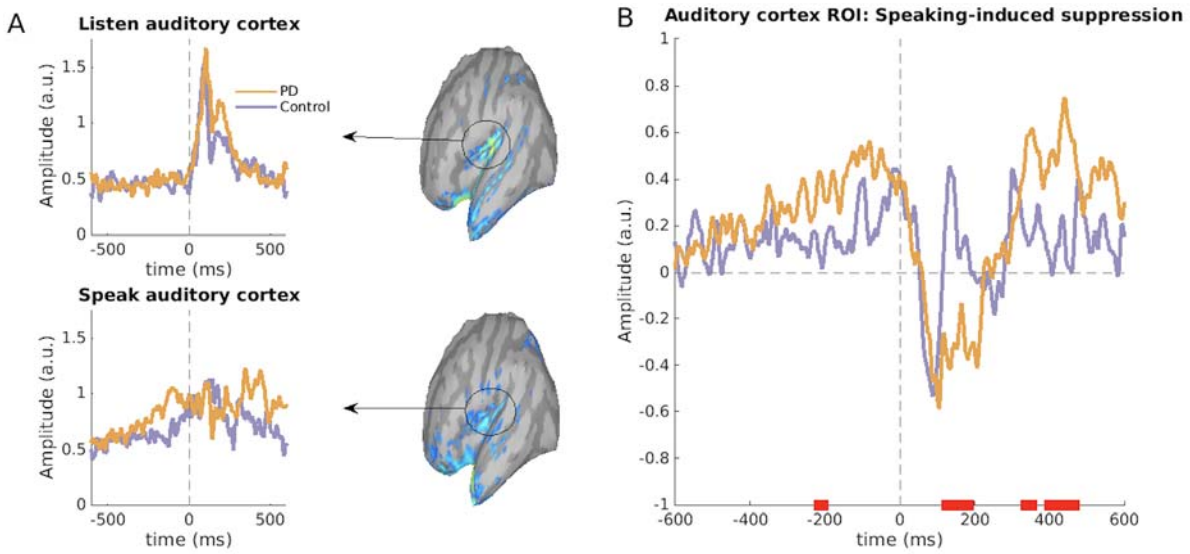


*Figure 3. Source reconstruction results visualized. A) Right: Cerebral activations in the Listen (top) and Speak (below) conditions at 100 ms after phonation, presented on an inflated cerebral hemisphere. The left panels show the time course of the averaged signal from the left and right auditory cortical 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.*

**Discussion**

The present results indicate abnormal self-monitoring of speech in early PD patients who do not yet experience speech deficits. Our results suggest that this may be the initial mechanism underlying hypophonia in PD, later aggravated by motor deficits. The finding is important because traditionally speech impairment has been assumed to merely reflect weakened motor control and rigidity of speech organs. We chose to examine early-stage PD patients with no subjective speech deficits. Had we examined patients with clear speech deficit, the differences would have been confounded by differences in speech motor control. To what extent the observed effect explains speech deficits observed in more advanced PD remains to be determined.

Models of speech production[15] assume that self-produced sounds are compared to estimated speech output during initial cortical processing stages, enabling reflexive adjustment of speech[42]. SIS was reduced in PD patients during this initial cortical processing stage (i.e. N1 around 100 ms after phonation). The amplitude of SIS reflects how well the predictions match the produced speech. Thus, our results suggest that PD patients' brain detected a higher than normal mismatch between desired and produced speech (i.e. increased prediction error). This could be due to the fact that phonation did not match the intended phonation. Because the patients in the

present study did not reveal clear speech deficits, it is possible that they were actually able to counteract the deficits in their speech by relying on these mismatch signals. Interestingly, PD patients often fail to subjectively notice their speech deficits, even when the deficits can be reliably measured[8,10,11]. A significant open question is why this happens. Behavioral experiments in PD patients show that PD patients adjust their speech differently than control participants when their speech is artificially perturbed[12], and Huang et al. also showed that perturbed speech differently modulated auditory evoked activity in the later P2 time-window in PD patients when compared to healthy controls [13]. Our study is the first to show abnormal early cortical electrophysiological correlates of monitoring non-perturbed self-produced speech in PD patients who do not yet experience speech impairment.

We observed that the patients showed reduced (and somewhat delayed) N1 waves when compared to control participants, when they passively listened to the phonemes. This implies that the neural processing of heard phonemes was abnormal in the patients. Because a similar 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 [16–18]. Source reconstruction results suggested that auditory cortex is modulated by speech production already before the onset of phonation (Fig. 3B). In addition to the N1 time-window (during which SIS was reduced in PD patients) the auditory cortex was activated more strongly during speech than passive listening in PD patients than controls before phonation and during a later time-window (400–500 ms after phonation). We interpret these changes as top-down modulation from other cortical areas during speech. The differences between the groups in the Listen and Speak conditions could both account for differences in SIS between patients and controls.

Brain imaging studies have reported increased activation in frontal areas during speech in PD [43,44]. These activations have been proposed to be the consequence of the speech deficits: the patients' attempts to compensate for their speech difficulties (e.g. attempts to speak louder) cause increased activations in frontal areas. In contrast to this prevailing view, we suggest that the increased activations may be part of the mechanism that causes the speech deficits. Because the increased auditory cortical activation in PD was partly observed before phonation, the activity is unlikely to reflect compensation of speech deficits. Specifically, we propose that the increased activation reflects aberrant communication of top-down predictions to auditory cortex. This abnormality could also lead to abnormal SIS after phonation, and cause speech deficits as the disease progresses.

Because PD is associated with changes to multiple neurotransmitter systems [45], multiple different mechanisms could underlie the observed differences between PD patients and control participants. That said, dopamine deficiency has been proposed to lead to deficits in sensory attenuation[24,25]. Previously, we observed that in PD patients performance in the double-saccade task – which is used to probe CD signals in the oculomotor system – correlated with changes in dopamine transporter binding in the striatum[46]. In PD, dopamine deficiency leads to aberrant activity in basal ganglia-cortex loops [47,48] which could lead to abnormal activation in frontal speech production mechanisms that communicate CD signals to sensory cortical areas.

Levodopa typically lacks efficacy for speech deficits in PD. [4,5,11,49] This could be due to a major role of non-dopaminergic frontal–posterior superior temporal circuits that underlie speech self-monitoring. If speech deficits in PD are in part caused by abnormal monitoring mechanisms, this entails that, instead of dopaminomimetic drugs, treatments that target speech self-monitoring malfunctioning may improve speech symptoms. Indeed, current voice therapeutic interventions already focus on adjusting the patient's speech monitoring[50,51]. We suggest that in

addition to voice therapy, neuromodulation of circuits involved in speech monitoring could in future prove useful in treating speech deficits. Similarly, once the circuits involved in speech self-monitoring are known, this information could be used to guide electrode placement in deep-brain stimulation to minimize negative effects on speech.

**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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