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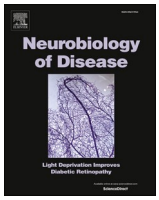

Intelligibility of speech in Parkinson's disease relies on anatomically segregated subthalamic beta oscillations

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ABSTRACT

Background: Speech impairment is commonly reported in Parkinson's disease and is not consistently improved by available therapies – including deep brain stimulation of the subthalamic nucleus (STN-DBS), which can worsen communication performance in some patients. Improving the outcome of STN-DBS on speech is difficult due to our incomplete understanding of the contribution of the STN to fluent speaking.
Objective: To assess the relationship between subthalamic neural activity and speech production and intelligibility.
Methods: We investigated bilateral STN local field potentials (LFPs) in nine parkinsonian patients chronically implanted with DBS during overt reading. LFP spectral features were correlated with clinical scores and measures of speech intelligibility.
Results: Overt reading was associated with increased beta-low ([1220) Hz) power in the left STN, whereas speech intelligibility correlated positively with beta-high ([2030) Hz) power in the right STN.
Conclusion: We identified separate contributions from frequency and brain lateralization of the STN in the execution of an overt reading motor task and its intelligibility. This subcortical organization could be exploited for new adaptive stimulation strategies capable of identifying the occurrence of speaking behavior and facilitating its functional execution.

1. Introduction

Parkinson's disease (PD) is characterized by a complex phenotype of progressive speech impairment termed hypokinetic dysarthria (Darley et al., 1969). This clinical entity encompasses multiple symptoms related to several aspects of motor speech production, including respiration, phonation, articulation, and prosody, sometimes coexisting with higher order cognitive language deficits (Magee et al., 2019). Numerous acoustic and perceptual variables can be assessed to quantify hypokinetic dysarthria, such as vocalization loudness and pitch, alterations in

Abbreviations: AE, articulation entropy; ASR, automatic speech recognition; Conf, confidence score; CV, coefficient of variation; D, number of deletions; DBS, deep brain stimulation; DNN-HMM, deep neural network-hidden Markov model; ECG, electrocardiogram; EMG, electromyography; I, number of insertions; LEDD, levodopa equivalent daily dose; LFP, local field potentials; MFCC, Mel-Frequency Cepstrum Coefficients; MER, microelectrode recordings; N, number of words in the reference; PD, Parkinson's disease; PSD, power spectral density; S, number of substitutions; STN, subthalamic nucleus; TENS, transcutaneous electrical nerve stimulation; TTL, transistor-transistor logic; UPDRS-III, Unified Parkinson Disease Rating Scale motor part III; WER, word error rate..

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prosody, and speech articulation (Rusz et al., 2021). However, not all of these variables contribute to speech intelligibility (Darley et al., 1969; Aldridge et al., 2016), and this has significantly biased our understanding of speech impairment in PD and the effects of anti-parkinsonian treatments, especially deep brain stimulation (DBS).

DBS of the subthalamic nucleus (STN-DBS) is a mainstay treatment for advanced PD and provides substantial clinical benefit to the cardinal motor signs of PD (Kleiner-Fisman et al., 2006). Its effect on speech impairment, however, is highly variable (Aldridge et al., 2016). Some studies have demonstrated improvements in loudness, maximum phonation time, and movement of articulators, paradoxically coupled with reduced intelligibility (Rousseaux et al., 2004; Klostermann et al., 2008; Tripoliti et al., 2011). Positive and negative changes of voice intensity, syllabic diadochokinetic rates, and speaking rate have also been reported, as well as increased likelihood of stuttering in implanted patients (Toft and Dietrichs, 2011; Tsuboi et al., 2015; Picillo et al., 2017). The impact of such changes on global speech function and participation in everyday communication contexts has been poorly evaluated (Rusz et al., 2021; Aldridge et al., 2016), despite progressive decline of speech intelligibility being reported in up to 70% of implanted subjects (Tripoliti et al., 2011; Tsuboi et al., 2015; Fasano et al., 2010; Wertheimer et al., 2014). The causes of speech deterioration remain largely unknown. The spread of electrical stimulation to unwanted structures such as pyramidal tracts (Tsuboi et al., 2015; Mahlknecht et al., 2017) and pallido- or cerebello-fugal pathways (Tripoliti et al., 2011; Fenoy et al., 2017) has been described, but may only account for a few cases (Tsuboi et al., 2015). A DBS-related dysfunction of the direct contribution of the STN in speech production is also possible (Tsuboi et al., 2015; Tripoliti et al., 2008).

Several studies indicate an important role for the STN in speaking. The STN has direct monosynaptic connections with the motor, premotor, and auditory parts of the opercular network (Jorge et al., 2022). Intraoperative microelectrode recordings (MER) of single-cell STN activity during vocalization have demonstrated phoneme encoding with altered resolution and latencies in speech-impaired PD patients (Tankus and Fried, 2019; Tankus et al., 2021a; Tankus et al., 2021b) and changes related to planning and production of monosyllabic utterances (Lipski et al., 2018) and possibly syntax programming (Watson and Montgomery, 2006). Furthermore, studies on STN local field potentials (LFPs) have established subthalamic neural correlates of speech with both event-related and block experimental designs. For example, there is evidence for STN activity linked to performance in verbal fluency tasks such as word generation (Wojtecki et al., 2017), switching between semantic categories (Anzak et al., 2011), and inhibition of spoken responses (Brittain et al., 2012; Wessel et al., 2016; Ghahremani et al., 2018). Event-related changes in multiple frequency bands during production of monosyllabic utterances (Chrabaszcz et al., 2019) and non-propositional speech (Hebb et al., 2012; Niketeghad et al., 2014) have been reported, along with a correlation between low-frequency power in the STN during voicing and vowel articulation accuracy (Dastolfo-Hromack et al., 2022). However, how STN activity shapes everyday, complex communication remains to be established. Indeed, only two of the cited works (Hebb et al., 2012; Niketeghad et al., 2014) studied connected speech, as opposed to monosyllabic or vocalic utterances.

Investigating the neural underpinnings of complex features of speech is crucial for a better understanding of human speech as a multifaceted phenomenon (Simonyan et al., 2013; Fuertinger et al., 2018) – especially with respect to speech intelligibility (Van Lancker et al., 2010), which is the most clinically relevant aspect for the patient. We aimed to specifically address this knowledge gap and identify the subthalamic neural correlates of speech intelligibility in parkinsonian subjects.

2. Material and methods

2.1. Patients and surgery

We studied nine right-handed patients diagnosed with idiopathic PD and chronically treated with STN-DBS via a sensing-capable device (Percept PC™, Medtronic PLC). Most patients were evaluated 3 months after surgery during routine clinical follow-ups, while two were evaluated shortly after a planned substitution of their implantable pulse generator due to battery end of life after 4 and 6 years of chronic stimulation. Recordings (audio recordings and LFP) were acquired in a quiet room in the morning at least 12 h (overnight) after their last dose of antiparkinsonian medication and 1 h after pausing the stimulation (i.e., meds-off/stim-off). Disease severity was assessed using the Unified Parkinson's disease Rating Scale motor part III (UPDRS-III). Severity of non-axial symptoms was the sum of tremor, rigidity, and bradykinesia scores; severity of axial symptoms was the sum of facial expression, arising from chair, posture, gait, and postural stability score (Defazio et al., 2016). We also used the UPDRS-III non-axial items to determine the lateralization of symptoms and consequently the STN contralateral and ipsilateral to the clinically most affected side (i.e., STN_W and STN_B). UPDRS-III item 3.1 (speech) was used to clinically assess hypokinetic dysarthria.

All patients were German speakers, and none had a history of speech or language disorders unrelated to PD. The surgical procedure has been described previously (Steigerwald et al., 2008). The precise localization of the active contacts used for chronic stimulation and LFP recording was performed using Lead-DBS, an open-source MATLAB toolbox (Horn and Kühn, 2015). Preoperative T1-weighted magnetic resonance images (MRI) of each patient were fused with their postoperative computed tomography (CT) images. The images of all patients were then normalized into the Montreal Neurological Institute (MNI) space using the Advanced Normalization Tools (ANTs) and the DISTAL minimal atlas (Avants et al., 2011; Ewert et al., 2018). Leads reconstruction was afterwards performed using the and the TRAC/CORE algorithm (Horn and Kühn, 2015). Finally, the coordinates of each contact in the MNI space and the 2D visualization were produced using the Lead Group function offered by the Lead-DBS (Treu et al., 2020) (Supplementary Fig. S1 and Supplementary Table S1).

The local Institutional Review Board approved the study, and all patients gave informed consent according to the Declaration of Helsinki.

2.2. Overt reading task, audio recordings, and analysis

All participants performed an overt reading task while sitting comfortably. A standardized German text (137 words, 247 syllables) was placed on the table at a comfortable reading distance. Patients were instructed to read the text once without interruptions, starting at a verbal cue. Each patient was recorded during several readings (three to six, according to their compliance) of the same text ("reading trials"), allowing for rest intervals between repetitions to avoid fatigue. Silent intervals between repetitions were excluded from the analysis. Speech was recorded by means of a unidirectional microphone (DST99 S, AKG, Harmon, Austria) placed on the table in front of the patient, 40 cm from their mouth. The microphone was connected to an audio hardware interface (Scarlett 2i2, FocusRite PLC, UK) with dedicated software (Pro Tools First, Avid Technology, USA) that allowed data recording and saving on a workstation placed behind the patient. Speech samples were digitized at 44.1 kHz with 16-bit resolution. For each trial, amplification gain was manually adjusted to optimize the signal-to-noise ratio.

All audio recordings were re-sampled to 16 kHz before extracting the following measures of speech quality: (i) articulation entropy (AE) as a measure of articulatory precision, and (ii) mean confidence score (Conf) and word error rate (WER) as measures of speech intelligibility.

2.3. Articulation entropy

AE was proposed by Jiao et al. (Jiao et al., 2017) as a language-independent and unsupervised metric for measuring articulatory precision (i.e., the accuracy with which the speech articulators achieve their targets) in continuous speech samples. The processing details for estimating the AE can be found in (Jiao et al., 2017). In brief: (1) a voice activity detection algorithm (Sohn et al., 1999) automatically segmented the voiced parts from the non-voiced ones (e.g., silence and noise) and the intensity of the signal was normalized; (2) the Mel-Spectrum with cubic root compression features (MelRoot3) (Tu et al., 2014) was extracted from short-term (length = 20 ms) and long-term (length = 160 ms) sliding windows, to capture short-term speech acoustics and longer articulatory features, respectively; (3) assuming that the MelRoot3 features were sampled from an unknown continuous distribution, the distribution entropy was estimated using the Rényi entropy (Wehrl, 1978). The resulting value was used as a proxy for the working phonetic inventory: the larger the entropy, the more precise the articulation. Previous research (Jiao et al., 2017; Stegmann et al., 2020) linked AE reductions to the presence and progression of dysarthria in neurodegenerative diseases, such as PD and amyotrophic lateral sclerosis.

2.4. Mean confidence score and WER

To measure speech intelligibility, we implemented an automatic speech recognition (ASR) system. Specifically, we used the Kaldi speech recognition toolkit (Povey et al., 2011) via the offline VOSK API (https://alphacephei.com/vosk/). The implemented ASR model is based on a hybrid deep neural network-hidden Markov model (DNN-HMM) that takes as input Mel-Frequency Cepstrum Coefficients (MFCC) features and i-vectors (Povey et al., 2018; Weerts et al., 2021). The ASR system converts the spoken language into text and outputs a sequence of recognized words with timestamps of beginning and end, and a confidence score between 0 and 1 (i.e., 1 = the algorithm is 100% confident in recognizing that word). Considering that we used an ASR model pre-trained on non-dysarthric, typical speech, there exists a bias in the speech recognition confidence, in that higher confidence is observed in more intelligible speech (De Russis and Corno, 2019; Gutz et al., 2022). Thus, for each trial we computed the mean confidence score as the average of the confidence scores obtained for all recognized words. Moreover, we calculated the WER, which is the most widely used metric for assessing speech recognition performance (Nassif et al., 2019). WER was obtained using the following equation:

$$WER = \frac{S + D + I}{N} \quad (1)$$

where S is the number of substitutions (i.e., when a spoken word is replaced by another one), D is the number of deletions (i.e., when a spoken word is missed by the algorithm), I is the number of insertions (i.e., when a non-spoken word is inserted by the algorithm), and N is the number of words in the reference (S + D + correct words). WER is measured as a percentage of words. The higher the WER, the lower the speech recognition accuracy and hence the intelligibility (De Russis and Corno, 2019).

2.5. LFP recordings and analysis

The STN LFPs were recorded bilaterally at 250 Hz from all non-adjacent contact pairs of the chronically-implanted DBS electrodes. In addition to LFP recordings during the speech task, we collected LFPs for 5 min when the patients were at rest, with eyes open and staring at a marker placed two meters away at eye level.

The LFPs were synchronized with an auxiliary electromyography (EMG) probe (FREEMG, BTS Bioengineering, Italy) placed on the neck at the cable connecting the implantable pulse generator to the leads, using external artefacts by transcutaneous electrical nerve stimulation (TENS) as previously described (Thenaisie et al., 2021; Canessa et al., 2016a; Arnulfo et al., 2018). EMG and audio recordings were aligned to the rising edge of an external 0 to 5 V analogue input (transistor-transistor logic [TTL]) recorded by both devices. This approach allowed all signals to be brought onto the same timeline.

We removed the mean from all LFP recordings and applied a notch filter at 50 Hz using *iirnotch* function in Matlab with quality factor of 50. The LFPs were bandpass filtered between 1 and 80 Hz using a 5th order Butterworth filter for all channels. Heartbeat contamination (electrocardiogram [ECG] signal) was removed from LFPs using a manual algorithm based on temporal template removal (Canessa et al., 2016b).

The power spectral density (PSD) of all LFP bipolar recordings was estimated using the *pwelch* method, with 1 s time windows and 50% overlap, normalized to the total power. The LFP spectrograms of each reading trial and resting state interval were also obtained.

We then estimated the power within different frequency bands (delta [1 4) Hz, theta [4 7) Hz, alpha [7 12) Hz, beta [1230) Hz, and gamma [30 80) Hz) for each trial. We also studied beta-low ([12 20) Hz) and beta-high ([20 30) Hz) oscillations following recent studies suggesting a distinctive contribution of these sub-bands in motor control (Canessa et al., 2020; Vissani et al., 2021).

Parametric or non-parametric tests comparing LFP power and speech features across different conditions were performed according to the Kolmogorov Smirnov test for normality. We computed the correlation between the beta power of bipolar LFP recordings and the speech features (i.e., AE, WER, and Conf). Correlation between variables was estimated through Pearson's linear correlation coefficient ρ (*corrcoef* function in Matlab) and tested under the null hypothesis of no correlation with alpha = 0.05.

3. Results

3.1. Clinical and demographic characteristics

Clinical severity and stage, UPDRS-III scores, levodopa equivalent daily dose (LEDD), and demographic characteristics are listed in Table 1.

DBS, deep brain stimulation; LEDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson's Disease Rating Scale.

3.2. Speech intelligibility

We complemented the clinical evaluation of patients' speech with quantitative measures of speech articulation and intelligibility obtained by analyzing the audio recordings acquired during the overt reading task (see Methods). We measured speech articulation with the AE, and speech intelligibility with Conf and WER (see Methods). The latter showed the largest variability across reading trials, as indicated by the coefficients of variation (CV; average over all patients: $CV_{AE} = 0.165$; $CV_{Conf} = 0.0497$; $CV_{WER} = 0.461$). All three measures showed significant differences across patients (Kruskal-Wallis test; AE: $H(8) = 38.14$, $p < 0.001$; Conf: $H(8) = 32.93$, $p < 0.001$; WER: $H(8) = 36.64$, $p < 0.001$).

We then checked whether speech articulation and speech intelligibility were correlated. We found that AE correlated with Conf ($\rho = 0.827$, $p = 0.006$, Fig. 1A) and anti-correlated with WER ($\rho = -0.896$, $p = 0.001$, Fig. 1B) indicating that more precise articulatory movements resulted in higher speech intelligibility.

Speech quality measures were then compared with clinical scores. Speech intelligibility measures (i.e., Conf and WER) significantly correlated with UPDRS-III speech score (item 3.1) (Table 2), indicating that the task-related speech quality measures were coherent with the clinical evaluation. Moreover, we found no significant correlation between speech quality measures and the UPDRS-III total score and axial or non-axial sub-scores (Table 2), indicating the specificity of the task for the speech condition.

Table 1
Demographic and clinical data. All patients were clinically examined after overnight withdrawal of all antiparkinsonian medications (meds-off) with active DBS (stim-on) with chronically-used DBS parameters, and after pausing the stimulation for about 1 h (stim-off).

	P01	P02	P03	P04	P05	P06	P07	P08	P09
Sex	F	F	M	M	M	F	M	M	M
Age at onset, years	44	56	52	53	28	42	49	53	48
Disease duration at surgery, years	13	6	17	11	16	11	6	7	5
LEDD pre-DBS, mg	1067	1200	450	1095	860	1811	2050	1635	760
LEDD post-DBS[1], mg	420	325	100	890	80	805	453	405	170
Time from surgery at evaluation, months	53[2]	3	3	3	3	67[2]	3	3	3
UPDRS-III stim-off, total score	54	20	50	57	50	49	52	54	40
UPDRS-III stim-off, axial score	18	4	11	8	4	6	3	8	8
UPDRS-III stim-off, non-axial score	26	14	28	42	42	37	46	43	28
UPDRS-III stim-off, left/right side score	15/9	8/4	16/11	14/24	22/14	17/17[3]	16/25	21/16	16/10
UPDRS-III stim-off speech score	3	1	4	2	1	2	1	0	1
UPDRS-III stim-on, total score	49	12	30	33	11	31	17	40	9
UPDRS-III stim-on, axial score	18	3	8	6	1	6	2	6	2
UPDRS-III stim-on, non-axial score	17	7	13	20	7	18	12	31	4
UPDRS-III stim-on, left/right side score	12/4	3/3	10/3	5/13	5/1	11/6	5/6	17/10	3/1
UPDRS-III stim-on, speech score	3	1	3	1	0	2	0	0	0

[1] 12 months after surgery.
[2] P01: 1 month and P06: 2 days after internal pulse generator replacement due to battery end of life, time from initial DBS surgery is reported.
[3] Left-body prevalence of symptoms confirmed by history and prior clinical assessments.

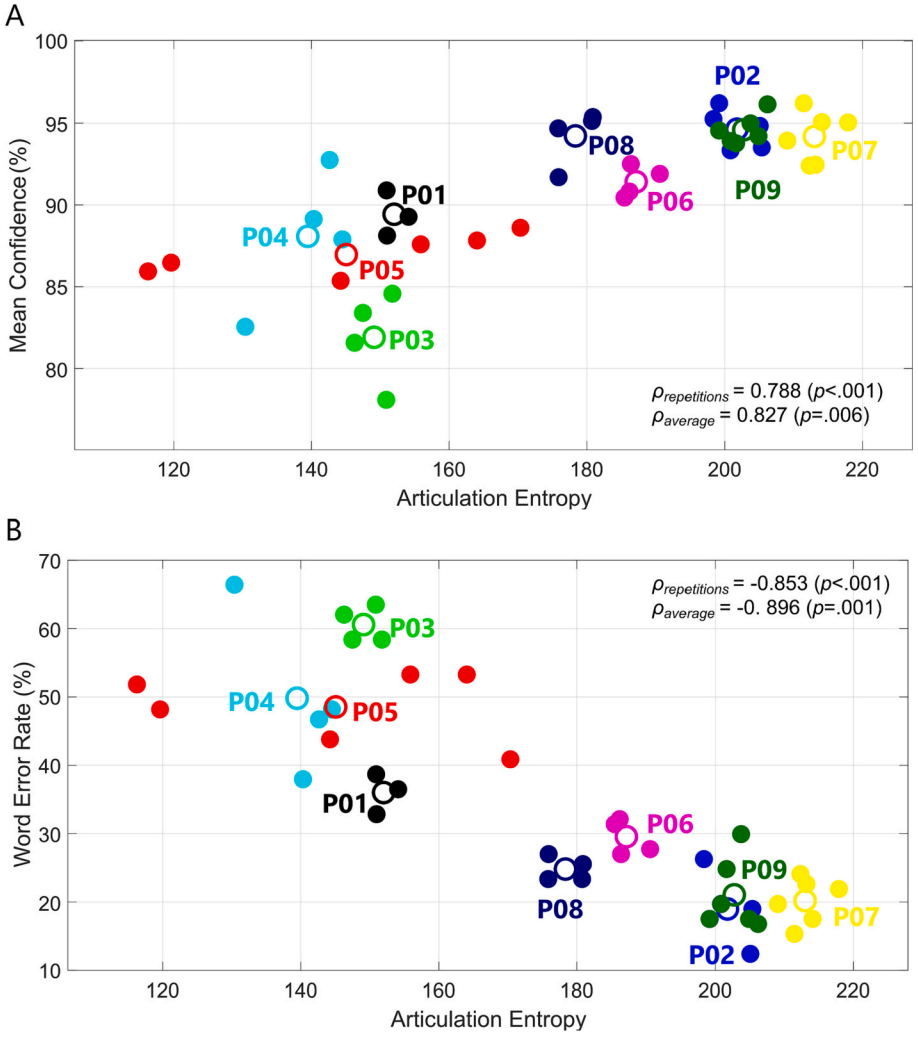

Fig. 1. Speech degradation in parkinsonian subjects. Correlations of articulation entropy (AE) with confidence in word recognition (Conf) (A) and with word error rate (WER) (B). Filled dots indicate trials and open dots averages of each patient. Patients are identified by different colors. $\rho_{repetitions}$ indicates the Pearson's correlation coefficient over all 42 repetitions; $\rho_{average}$ is the Pearson's correlation coefficient calculated on the nine averaged points (i.e., participants).

Table 2
Clinical correlations with speech features. Correlations between quantitative measures of speech quality (columns) and clinical scores (rows), including the UPDRS-III speech score, the axial and non-axial scores, and the total UPDRS III score (see Material and methods – Patients and surgery). ρ = Pearson's correlation coefficient; AE, articulation entropy; Conf, mean confidence score; p, *p*-value; UPDRS, Unified Parkinson's Disease Rating Scale; WER = word error rate.

Speech feature / *UPDRS-III*	AE		WER		Conf	
	ρ	p	*ρ*	p	*ρ*	p
Speech	−0.52	0.15	0.68*	0.04	−0.78**	0.01
Axial	−0.49	0.18	0.32	0.4	−0.36	0.33
Non-axial	−0.15	0.3	0.14	0.72	−0.03	0.92
Total	−0.53	0.14	0.47	0.2	−0. 4	0.27

3.3. Subthalamic activity and speech production

During the task, we recorded the LFPs from three non-adjacent contact pairs in the left (STN_L) and right (STN_R) STN (see Methods) during the resting state and overt reading. At rest, a prominent and stable beta activity was present in all recordings (Supplementary Fig. S2). For each patient and for each hemisphere, we selected the contact pair with the highest beta power to investigate correlations with the reading task.

Compared to the resting state, the beta ([12 30) Hz) power of the STN_L during speech production increased (paired *t*-test, p = 0.02, effect size = 0.145, Fig. 2A,C), while no change was detected in the STN_R ($p = 0.91$, Fig. 2B,C). This was specifically due to the increased power in the beta-low ([12 20) Hz) band (paired *t*-test, STN_L: $p = 0.01$, effect size = 0.108; STN_R: $p = 0.2$; Fig. 2A,D). Beta-high ([20 30) Hz) power was not modulated by speech production in either hemisphere (paired *t*-test, STN_L: $p = 0.5$; STN_R: $p = 0.55$; Fig. 2A,E). No other band displayed significant modulation associated with speech production (Supplementary Table S2).

We tested whether changes in beta-low power were due to a downward shift in the peak frequency of beta oscillatory activity (as reported in [56]), but no speech production-related beta peak frequency shift was observed (paired t-test, STN_L: $p = 0.19$ and STN_R: $p = 0.47$; Supplementary Fig. S3).

The lateralization of the effect was not due to disease lateralization: when partitioning the hemispheres based on associated clinical load (see Methods), we found no difference in beta power between conditions (paired t-test, STN_W: $p = 0.34$; STN_B: $p = 0.15$; Supplementary Fig. S4 and Supplementary Table S4).

Our results indicate that in PD, overt reading is associated with a specific increase in beta-low power in the LFPs of the left STN.

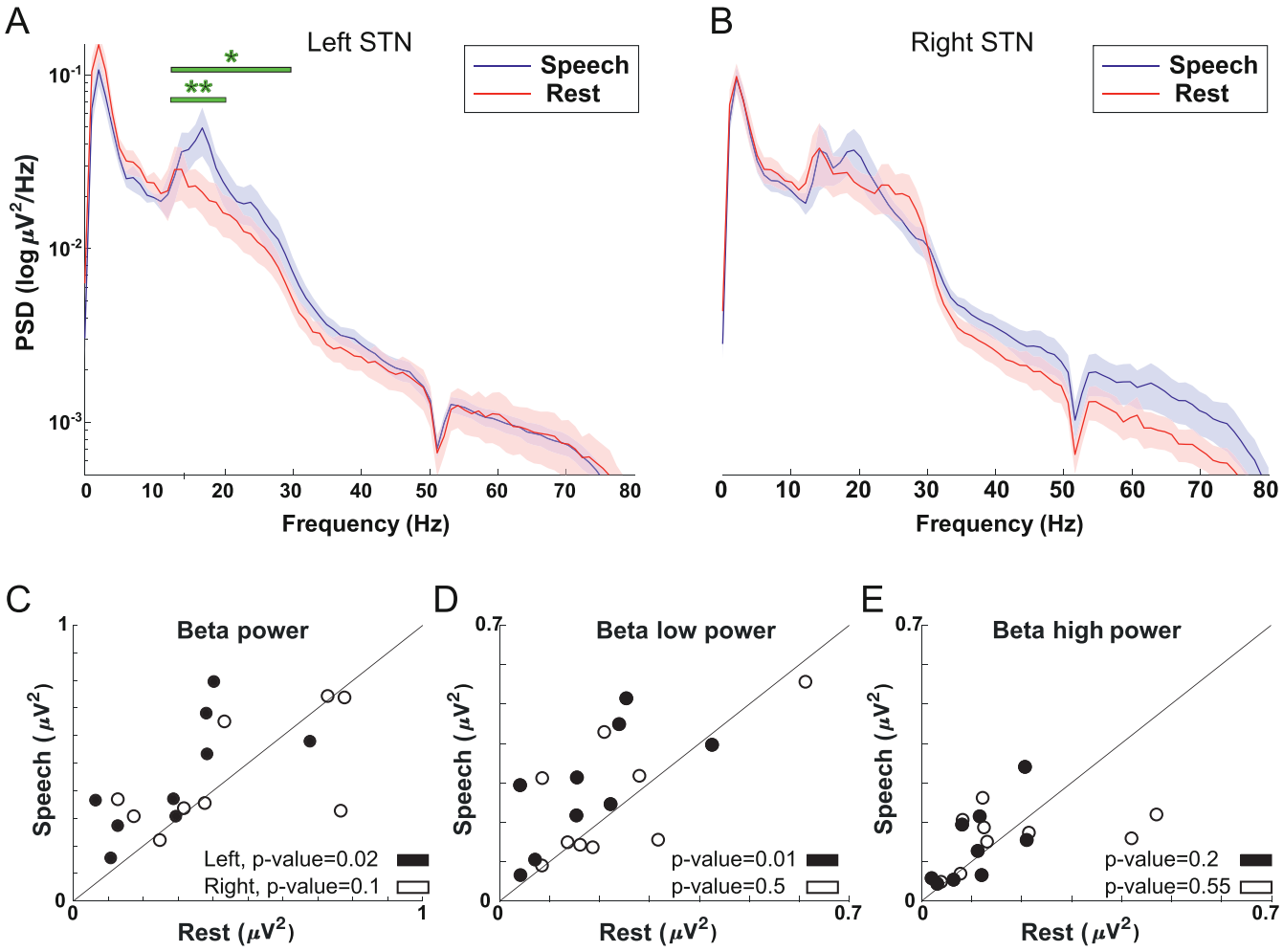

Fig. 2. Task-related variations in local field potentials (LFP). Power spectral densities (PSD) of subthalamic (STN) LFP during rest (red line) and overt reading (blue line) for the (A) left and (B) right STN. Shaded areas indicate the standard deviation around the mean value. Green lines indicate significant differences between the two conditions for the beta band ([12 30) Hz; $p = 0.02$, one asterisk), and beta-low band ([12 20) Hz; p = 0.01, two asterisks). (C) Comparison between beta power during the resting state and speech task for the left (filled dots) and right (open dots) hemisphere. Diagonal line indicates identity. Inset reports paired *t*-test significance. Same as (C) for the beta-low (D) and beta-high ([20 30) Hz) band (E). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4. Subthalamic activity and speech intelligibility

We then studied the relationship between STN LFP power in the beta band and speech quality. We found no significant correlation between AE, WER, and Conf with LFP power over the whole beta band (Table 3) or over the beta-low range (Table 3) in the STN_L or STN_R. Beta-high power in the STN_R LFP instead showed a significant correlation with speech articulation and intelligibility (STN_R: $p = 0.01$ with AE, $p < 0.001$ with WER, $p = 0.01$ with Conf; Table 3 and Fig. 3). No other STN LFP band power correlated with speech quality measures (Supplementary Table S3).

Note that in this case, the beta peak frequency significantly correlated with AE ($\rho = 0.72, p = 0.03$) and displayed correlations on the cusp of significance with WER ($\rho = -0.61, p = 0.08$) and Conf ($\rho = 0.59, p = 0.09$) (Supplementary Fig. S5).

These findings were not influenced by the lateralization of symptom severity (Table S4).

Overall, our results suggest that LFP beta-high power in the right STN encodes intelligibility of speech in subjects with PD.

4. Discussion

We have investigated for the first time the neural correlates of intelligibility and articulatory precision of connected speech in parkinsonian patients with bilateral chronic STN-DBS. Standardized intelligibility assessments have been limited in the past to transcription of speech excerpts performed by multiple raters (Yorkston and Beukelman, 1981; Sidtis et al., 2012; Sandström et al., 2015; Grover et al., 2019). The use of computerized speech analysis and recognition (Rusz et al., 2021; Dimauro et al., 2017; Rusz et al., 2018; Moya-Galé et al., 2022) represents an important element of novelty in our research.

Our findings suggest that overt reading and the quality of the associated speech are defined by complementary subcortical neural markers. Specifically, an increase in beta-low power in the left STN determines the motor task of overt reading with respect to the resting state, whereas beta-high power in the right STN parallels speech intelligibility and global articulatory precision.

We did not find any significant correlation between power in other frequency bands and the overt reading task or its performance. This seems to be in contrast with prior research reporting a positive correlation between low-frequency (alpha and theta) power in the STN and higher articulatory precision of vowels in monosyllabic utterances (Dastolfo-Hromack et al., 2022). This difference might be attributed to several factors. First, the cited study was performed in the intraoperative setting, as opposed to the enrolment of chronically-implanted patients in our research. Indeed, a decrease in low-frequency components of the STN LFP power spectral profile has been described over time after surgery (Rosa et al., 2010), and this might contribute to the lack of related findings in our case. Furthermore, lower frequencies seem to be involved in encoding linguistic units and articulatory precision at the syllable level (Dastolfo-Hromack et al., 2022; Giraud and Poeppel, 2012), and their impact could have been masked by the longer temporal scale of our analysis and the high complexity of AE as an index of articulatory precision (Jiao et al., 2017). Importantly, we also decided to focus on the STN region with the highest beta signal for correlation studies. This choice was rendered necessary to limit the number of possible comparisons. Still, the STN region with the highest beta signal is considered the best target for DBS in clinical practice (Michmizos et al., 2015; Chen et al., 2022) – we argue that focusing on clinically useful channels would be more informative about the pathogenic mechanisms of DBS-induced speech disorders, and relevant to the ultimate goal of identifying biomarkers exploitable for speech-related, closed-loop stimulation algorithms.

Another finding in apparent contrast to current literature is the evidence of an increased beta-low power during the overt reading task compared to resting. Indeed, event-related beta-desynchronization has been reported in the STN with multiple spoken responses (Wojtecki et al., 2017; Anzak et al., 2011; Brittain et al., 2012; Chrabaszcz et al., 2019; Hebb et al., 2012). The different study paradigms used in these studies (e.g., naming letters or words with preparatory cues) may account for the diversity with our results. With a research paradigm more similar to our own (i.e., naming the months of the year or counting), Hebb et al. (Hebb et al., 2012) showed a bilateral subthalamic increase in beta power. Interestingly, the higher cognitive content of the reading task in our study might have contributed to selective left hemisphere involvement (Graves and Landis, 1985), as previously anticipated by molecular neuroimaging studies (Simonyan et al., 2013; Fuertinger et al., 2018). Indeed, the left STN might be well engaged in the lateralized parieto-frontal cognitive networks involved in linguistic processing (Scaltritti et al., 2020; Weiss and Mueller, 2012).

The correlation between speech intelligibility and right STN beta-high activity is the key finding of our study. The right STN, specifically right-lateralized beta synchronization (Wessel et al., 2016; Ghahremani et al., 2018), is involved in inhibition of spoken responses. The concept of decreased subthalamic beta oscillations prior to and during voluntary movements, and increased beta oscillations following movement termination or in case of motor response inhibition, is well established (Cassidy et al., 2002; Williams et al., 2003; Kühn et al., 2004; Weinberger et al., 2006). Accordingly, one possible interpretation of our results is that beta-high oscillatory activity plays a role in the timely closure of spoken responses, and its modulation determines articulatory precision throughout the reading task. Inaccurate termination of consonant articulation, with a tendency for voicing to continue in the closure phase, has been reported as a side effect of continuous STN-DBS (Pützer et al., 2008), which is known to suppress beta oscillations (Kühn et al., 2008; Quinn et al., 2015; Feldmann et al., 2021). A negative effect has been also reported on coordinated limb movement termination for closed-loop DBS targeting beta power, possibly by interference with post-movement beta synchronization (Iturrate et al., 2019).

The different behavior of high- and low-beta frequency ranges deserves further discussion. We previously observed in parkinsonian patients during a reach-to-grasp task that beta-low and beta-high subthalamic power modulations were respectively informative of the motor behavior (task execution vs. resting state) and of the task performance (Vissani et al., 2021). This strongly resembles the results of our present work, showing separate associations between beta-low power with overt reading behavior and beta-high power with fine-motor control leading to intelligible speech. There are several reports of different functional roles for the two beta bands (see (Yin et al., 2021) for a recent review), although a coherent view is still lacking. Our studies suggest that beta oscillations represent contiguous and distinct channels of communication, encoding with modulation in power (Canessa et al., 2016a) and frequency (Canessa et al., 2020) different aspects of a motor and non-motor behavior.

Table 3
Local field potential correlations with speech features. Correlations between beta-high and beta-low power in the left and right STN and speech quality measures. ρ = Pearson's correlation coefficient; AE, articulation entropy; Conf, mean confidence score; p, *p*-value; STN, subthalamic nucleus; WER = word error rate.

	Speech features / *Band power*	AE		WER		Conf	
		ρ	p	*ρ*	p	*ρ*	p
Left STN	Beta	−0.07	0.57	−0.16	0.34	0.11	0.38
	Beta-low	0	0.5	−0.08	0.42	0.04	0.46
	Beta-high	−0.14	0.36	−0.17	0.33	0.15	0.35
Right STN	Beta	0.16	0.34	−0.09	0.41	0.01	0.49
	Beta-low	−0.22	0.3	0.32	0.8	−0.39	0.15
	Beta-high	0.74**	0.01	−0.83**	<0.001	0.77**	0.01

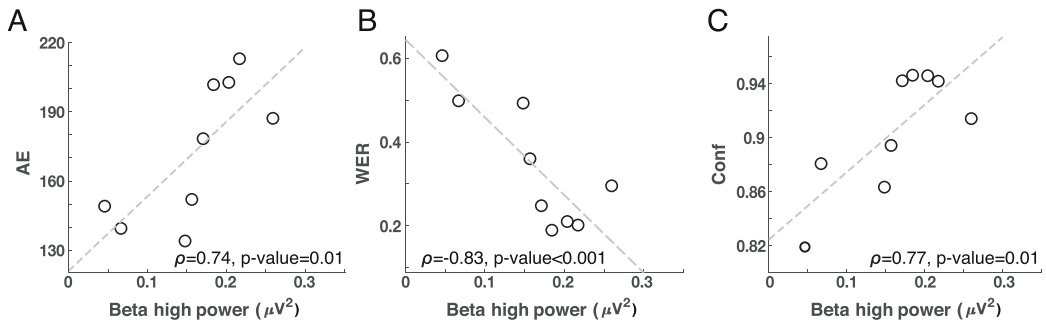

Fig. 3. Right subthalamic beta-high ([20 30) Hz) power correlations with speech features. Correlations between average beta-high power of the right subthalamic nucleus of each patient and AE, WER and Conf mean values. AE = articulation entropy, WER = word error rate, Conf = mean confidence score, ρ = Pearson's correlation coefficient.

In this context, conventional DBS could be responsible for a twofold detrimental influence on spoken production. For instance, DBS-induced limiting of beta oscillatory activity in the left STN could interfere with lateralization (Fuertinger et al., 2018) and cognitive control of speech production, including verbal fluency performance (Wojtecki et al., 2017; Anzak et al., 2011; Greif et al., 2021), while the same phenomenon in the right STN could contribute to altered articulatory precision and intelligibility. This could explain some of the high variability and lateralized effects reported in the literature regarding speech outcomes after DBS.

Some limitations of our work need to be addressed with further dedicated study. First, a full account of the precise anatomical location of the stimulated area would allow for the study of structurally and functionally connected hubs in the language network, facilitating the interpretation of results. Also, we could have achieved a higher resolution in the parsing of connected speech by including event-related analysis pertaining to syllable articulation and pauses in voicing. More importantly, one of the future steps of our research will be to use our current framework to study the effects of DBS on spontaneous speech production in the context of everyday communication. Another possible limitation of our work is that two patients were studied after IPG replacement due to battery depletion, while the others at three months after surgery. However, three months is considered a sufficient period for a fading of the lesion effect and preliminary studies have shown stability of LFP signals up to five years after surgery (Anderson et al., 2021; Mestre et al., 2016). The start of the speech recordings after discontinuing medication for 12 h and pausing the stimulator for 1 h should also have ensured that a comparable baseline condition was achieved between patients. Finally, the small number of patients recruited makes the results of our study preliminary, and future research will be needed to confirm our findings in a larger sample of patients.

In conclusion, we have provided preliminary evidence that the overt reading motor task involves a direct contribution of the STN, which is determined by brain lateralization and power modulation at different frequencies of beta oscillatory activity. These observations provide a compelling argument to be considered in the design of speech-related personalized adaptive DBS algorithms (Pozzi and Isaias, 2022).

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Availability of data and material

The data are available for researchers upon reasonable request.

Authors' contributions

FA, AB, AF, CP, AM, IUI: Conceptualization; FA, CP, IH, IUI: Data collection; IH, CP: Data curation; FA, AB, AF, AM: Formal analysis; CP, GP, AM, IUI: Funding acquisition; FA, AB, AF, CP, AM, IUI: Methodology; CP, GP, AM, IUI: Resources; AM, IUI: Supervision; FA, AB, AF, CP: Writing - original draft; IH, GP, AM, IUI: Writing - review & editing.

Declaration of Competing Interest

The authors have no conflicts of interests.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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