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Research Article

Deep Brain Stimulation of the Subthalamic Nucleus Parameter Optimization for Vowel Acoustics and Speech Intelligibility in Parkinson's Disease

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Purpose: The settings of 3 electrical stimulation parameters were adjusted in 12 speakers with Parkinson's disease (PD) with deep brain stimulation of the subthalamic nucleus (STN-DBS) to examine their effects on vowel acoustics and speech intelligibility.
Method: Participants were tested under permutations of low, mid, and high STN-DBS frequency, voltage, and pulse width settings. At each session, participants recited a sentence. Acoustic characteristics of vowel production were extracted, and naive listeners provided estimates of speech intelligibility.
Results: Overall, lower-frequency STN-DBS stimulation (60 Hz) was found to lead to improvements in intelligibility and acoustic vowel expansion. An interaction between speaker sex and STN-DBS stimulation was found for vowel measures. The combination of low frequency, mid to high voltage, and low to mid pulse width led to optimal speech outcomes; however, these settings did not demonstrate significant speech outcome differences compared with the standard clinical STN-DBS settings, likely due to substantial individual variability.
Conclusions: Although lower-frequency STN-DBS stimulation was found to yield consistent improvements in speech outcomes, it was not found to necessarily lead to the best speech outcomes for all participants. Nevertheless, frequency may serve as a starting point to explore settings that will optimize an individual's speech outcomes following STN-DBS surgery.
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Parkinson's disease (PD) is a neurodegenerative movement disorder characterized by the cardinal features of tremor, rigidity, bradykinesia, and postural instability. PD is also associated with secondary motor symptoms, one of which is hypokinetic dysarthria, a speech disorder characterized by phonatory, prosodic, and articulatory deficits. Approximately 50%–90% of individuals with PD will develop hypokinetic dysarthria over the course of the disease (Logemann, Fisher, Boshes, & Blonsky, 1978; Müller et al., 2001; Mutch, Strudwick, Roy, & Downie, 1986). Hypokinetic dysarthria can be characterized by a cluster of deviant perceptible speech symptoms, including monoloudness, monopitch, reduced stress, short phrases, variable rate, short rushes of speech, and imprecise consonants (Darley, Aronson, & Brown, 1969). Acoustic studies of parkinsonian speech have demonstrated reductions in speech intensity (Fox & Ramig, 1997; Ho, Iansek, & Bradshaw, 2001; Holmes, Oates, Phyland, & Hughes, 2000), reduced variation of fundamental frequency, abnormal voice quality (Gamboa et al., 1997; Holmes et al., 2000; Kent, Vorperian, Kent, & Duffy, 2003; Rosen, Kent, Delaney, & Duffy, 2006), and reduced acoustic distinctiveness in both consonant (Lam & Tjaden, 2016; McRae, Tjaden, & Schoonings, 2002; Tjaden & Wilding, 2004) and vowel production (Lam & Tjaden, 2016; McRae et al., 2002; Rusz et al., 2013; Skodda, Visser, & Schlegel, 2011; Tjaden, Lam, & Wilding, 2013; Watson & Munson, 2008; Weismer, Jeng, Laures, Kent, & Kent, 2001).

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Dopaminergic replacement therapy (levodopa) is considered the primary treatment for PD, though many individuals will develop motor complications and a "wearing-off" effect of the benefits of medication over time (Aquino & Fox, 2015). Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a common adjunct surgical treatment for the motor symptoms associated with PD, typically recommended for individuals who have developed adverse motor fluctuations and side effects to the standard pharmaceutical treatment (Limousin, Krack, & Pollak, 1998; Okun, 2012). Following STN-DBS, the amount of levodopa that individuals require to manage their motor symptoms is typically reduced, and the motor symptoms become managed primarily by STN-DBS (Okun & Foote, 2004; Vingerhoets et al., 2002). In some cases, patients may eliminate their medication completely following surgery.

The purpose of STN-DBS is to deliver electrical stimulation to the subthalamic nucleus in order to modulate the neural activity that is responsible for the adverse symptoms of PD (Okun, 2012). At the same time, care must be taken to minimize the spread of the STN-DBS current to other unintended neural structures (Isaias & Tagliati, 2008). The modulation of neural activity as well as control of the electrical field size of STN-DBS stimulation is achieved in large part through the manipulation of three electrical STN-DBS parameters: frequency, voltage, and pulse width. Frequency refers to the number of electrical pulses delivered per second, voltage to the amplitude of voltage fluctuation of the electrical signal, and pulse width to the duration of the electrical pulse delivered to the target (Isaias & Tagliati, 2008). Standard therapeutic STN-DBS settings generally use 120–180 Hz, 1–5 V, and 60–200 μs pulse width stimulation (McIntyre, Savasta, Walter, & Vitek, 2004).

Although STN-DBS has been shown to be highly effective for the cardinal motor impairments associated with PD (Deuschl et al., 2006; Krack et al., 2003; Limousin et al., 1998), its effects on speech are variable and, in many cases, detrimental (Aldridge, Theodoros, Angwin, & Vogel, 2016; Iulianella, Adams, & Gow, 2008; Krack et al., 2003; Skodda, 2012). For example, Krack and colleagues (2003) reported improved motor function as measured by the Unified Parkinson's Disease Rating Scale (UPDRS; Goetz et al., 2007) up to 5 years postsurgery in all measures, except for speech. A retrospective review of 50 patients who had received STN-DBS and were dissatisfied with the outcomes found that the primary complaint (74%) was due to a worsening of axial symptoms, which refer to symptoms not affecting the extremities, including speech (Farris & Giroux, 2013).[1] Evidence suggests that the standard STN-DBS parameter settings used to minimize the primary motor symptoms may be suboptimal for other symptoms, including speech (Chenausky, MacAuslan, & Goldhor, 2011; Farris & Giroux, 2013; Törnqvist, Schalén, & Rehncrona, 2005; Tripoliti, Zrinzo, & Martinez-Torresetal, 2011).

Studies that have examined the effects of STN-DBS on specific speech outcomes have found changes in speech intelligibility and speech acoustics (see Aldridge et al., 2016, for a review). Hypokinetic dysarthria is in part characterized by a reduced range of motion of speech movements and is often associated with reduced speech intelligibility, which refers to a typical listener's ability to understand a spoken utterance (Kent, Weismer, Kent, & Rosenbek, 1989; Yorkston, Strand, & Kennedy, 1996). Reductions in speech intelligibility following STN-DBS have been reported in the literature, though outcomes tend to be highly variable across individuals (Aldridge et al., 2016; Plaha, Ben-Shlomo, Patel, & Gill, 2006; Rousseaux et al., 2004; Sidtis, Cameron, Bonura, & Sidtis, 2012; Törnqvist et al., 2005; Tripoliti et al., 2011, 2014; Tsuboi et al., 2014). Perceptual ratings of speech intelligibility may provide more general indicators of impairment following STN-DBS, though on their own are not informative of the specific speech characteristics that are impaired. Much attention has been given to identifying acoustic measures of speech that may be able to predict speech intelligibility in PD. Among these are vowel acoustic measures such as acoustic vowel space and second formant slopes (De Bodt, Huici, & Van De Heyning, 2002; Kim, Kent, & Weismer, 2011; Kim, Weismer, Kent, & Duffy, 2009; Lansford & Liss, 2014; Tjaden & Wilding, 2004). Reductions in acoustic vowel space reflect reduced range of tongue motion during vowel production, whereas reduced rate of change in formant transitions is associated with reduced tongue range and/or speed.

Although some authors have reported impaired vowel expansion following STN-DBS (Dromey & Bjarnason, 2011; Martel-Sauvageau et al., 2014; Martel-Sauvageau, Roy, Cantin, et al., 2015; Sidtis, Alken, Tagliati, Alterman, & Van Lancker Sidtis, 2016), others have found increased vowel space, for example, in prolonged vowels (Tanaka et al., 2016). Still others have found an interaction between STN-DBS and levodopa medication, finding improved vowel articulation following STN-DBS when individuals were on but not off their titrated levodopa doses (Martel-Sauvageau, Roy, Cantin, et al., 2015). Similarly, formant transitions have demonstrated variable effects of STN-DBS. Given that formant transition slopes directly reflect speech movement and have been linked to speech intelligibility, the slope of the second formant (F2) has been suggested as a promising indicator of the effects of STN-DBS on speech (Weismer, Yunusova, & Bunton, 2012), though substantial individual differences in F2 slopes following STN-DBS have been reported (Dromey & Bjarnason, 2011).

A small number of studies have tested different STN-DBS stimulation parameter combinations to determine whether different settings compared to the standard ones chosen for the primary symptoms may yield improvements in speech symptoms. Törnqvist et al. (2005) systematically manipulated STN-DBS parameters and found that speech intelligibility and listener perceptions of articulatory precision

[1]Note that that speech is not always included as an axial symptom, and some authors have distinguished upper body and lower body axial symptoms (Moreau et al., 2016). Kent (2004) has suggested that this distinction may be an oversimplification that does not accurately describe speech symptoms, because although speech musculature is axial, speech motor control is lateralized in the brain.

and voice quality improved with lower frequency and voltage stimulation relative to the standard clinical settings. Moreau et al. (2011) tested two frequency settings (60 and 130 Hz) as well as with STN-DBS turned off and found that the lower-frequency condition led to improvements in speech intelligibility, acoustic measures of voice and prosody, and maximum phonation time. Additional studies lend evidence to the finding that low-frequency stimulation may yield better results in axial symptoms, including speech-related outcomes (see di Biase & Fasano, 2016, for review). It remains unclear whether a different combination of STN-DBS parameter settings (e.g., frequency, voltage, pulse width) may result in improved speech outcomes relative to the standard clinical STN-DBS settings selected to ameliorate the primary motor symptoms in PD. In this study, we refer to combinations of settings at which speech is least impaired, that is, that yield the overall best speech outcomes, as "optimal" STN-DBS speech settings.

Purpose

The purpose of this study was to systematically examine the effects of three STN-DBS parameter settings (frequency, voltage, pulse width) on acoustic measures of vowel production and speech intelligibility in PD. Three research questions are of interest:

1. What are the effects of the three STN-DBS electrical parameter settings on vowel acoustics and speech intelligibility?
2. Are there combinations of settings that lead to improved speech outcomes relative to the standard clinical STN-DBS settings? If so, what are they?
3. What is the strength of the relationship between acoustic measures of vowel production and speech intelligibility under STN-DBS, and do these relationships change depending on the stimulation settings?

To the authors' knowledge, this is the first study to examine the effects of three STN-DBS parameters and their combinations on speech outcomes in individuals with PD.

Method

Participants

Twelve individuals with PD (seven men, five women) were recruited for this study from the Movement Disorder Clinic at University Hospital in London, Ontario, Canada. Inclusion criteria for participants included (a) diagnosis of idiopathic PD with debilitating motor symptoms, (b) severe motor fluctuations with disabling off periods and dyskinesia during on phases, (c) physiological eligibility for STN-DBS, (d) absence of dementia or psychiatric abnormalities as assessed by the Mini-Mental State Examination, and (e) English proficiency. Participants were enrolled in the study prior to their STN-DBS implantation surgery. Human Subjects Research Ethics Board Western University Ethics (103928) approved the study. All participants provided informed consent.

Participant demographics are reported in Table 1. Medication information is provided for both the first visit (preoperative, V1) and final visit (V8) because the amount of prescribed medication was decreased over time following STN-DBS surgery. Levodopa equivalent dose calculations were performed as per Tomlinson et al. (2010).

Deep Brain Stimulation Visit Protocol

The current study was part of a larger investigation of multiple motoric responses to STN-DBS. Participants attended a total of seven visits. The first visit (Visit 1) occurred prior to surgery. In the following 3 weeks, surgery took place, and STN-DBS stimulation was turned on. All subsequent visits (Visits 2–7) occurred over a period of 6 months and involved four sessions over the course of 1 day. The first session (Session 1) was conducted with the clinical settings assigned to the participants by the neurologist in order to suppress their primary symptoms. The three subsequent sessions (Sessions 2–4) were conducted with the device set to a randomized experimental setting by programming each of the three electrical parameters to a low, mid, or high setting, outlined in Table 2. Subjects rested for 30 minutes in between setting changes to allow for the new setting to fully take effect. At the end of each visit, the participants were returned to the standard clinical settings prescribed by the neurologist. If necessary, further adjustments in the participants' clinical programming were made to minimize their primary parkinsonian motor symptoms. With the exception of Visit 1 (baseline testing), participants were tested off-medication.

This study examined the effects of speech at baseline (Visit 1) and Visits 2–7 to determine the effect of STN-DBS parameter permutations. Settings for each of the three electrical parameters (frequency, voltage, pulse width) were binned into three categories: low, mid, and high. This binning procedure was selected to assess the relative contribution of each setting, as well as to optimize potential clinical recommendations. Parameter setting bins are reported in Table 2.[2]

An additional measure, total electrical energy delivered (TEED), was also calculated at each session using the following formula (Isaias & Tagliati, 2008):

$$\text{TEED} = \frac{\text{voltage}^2 * \text{frequency} * \text{pulse width}}{\text{impedance}} * 1 \text{ second.} \quad (1)$$

[2]One value was used for each experimental parameter bin (e.g., low frequency corresponded with 60 Hz), tested at Sessions 2–4. The participants' clinical settings, tested at Session 1, were also included in the analysis and are included in the range (shown in parentheses) for each parameter bin.

Table 1. Participant demographics.

Participant	Age	Years of PD	MoCA	Preoperative UPDRS III	Final visit UPDRS III	Preoperative LED	Final visit LED
PDM1	61	10	24	45	12.5	1,050	710
PDM2	65	14	26	13	10	1,654	250
PDM3	67	7	23	43.5	18.5	1,725	200
PDM4	67	13	24	28.5	4.5	1,200	300
PDM5	68	10	27	6.5	10	1,550	850
PDM6	52	9	29	13	11.5	1,063	512.5
PDM7	58	5	23	27	17	700	0
PDF1	69	17	22	13.5	11	2,375	450
PDF2	69	11	27	30	11	750	375
PDF3	64	9	28	20.5	17.5	1,438	500
PDF4	57	6	25	7.5	6.5	1,375	0
PDF5	54	17	26	35	8.5	2,191	0
Mean	62.5	10.7	25.3	23.6	11.5	1,422.6	345.6

Note. PD = Parkinson's disease; MoCA = Montréal Cognitive Assessment; UPDRS III = Unified Parkinson's Disease Rating Scale (Part III: Motor Examination); LED = Levodopa equivalent dose.

Speech Tasks

Participants completed the same speech tasks at each session.[3] All participants wore a unidirectional condenser headset microphone (DPA 4060) placed 6 cm from the mouth. The microphone was attached to a portable digital audio recorder (M-Audio Microtrack 2). Participants were asked to repeat the sentence "She saw Patty buy two poppies" twice following a live voice demonstration by the examiner. The first instance of the sentence was used in all subsequent analyses unless there was interference (e.g., coughing, saying a different word).

Intelligibility

Intelligibility ratings were collected from two first-year graduate students in speech-language pathology with limited exposure to dysarthric speech.[4] These participants listened to all utterances twice using headphone presentations of two randomized lists. Ratings were given along a 100-mm visual analog scale marked from "low intelligibility" to "high intelligibility." The placement of a mark on the line was assigned as a percentage (e.g., a mark at 70 mm is henceforth referred to as a rating of 70% intelligibility). Intelligibility ratings from the second list were averaged across listeners and used in the final analysis. Ratings from the second list were used in order to control for familiarization with the stimuli, given that listeners heard the same sentence spoken each time. The average interrater Pearson product–moment correlation between the two listeners was $r = .63$, with an average intrarater Pearson product–moment correlation across the two lists of $r = .8$.

Acoustic Analysis

Acoustic analysis was performed by the first author using Praat software, version 6.0.15 (Boersma & Weenink, 2011).

Vowel Centralization

The degree of vowel centralization was measured using the four-vowel articulation index (VAI; Roy, Nissen, Dromey, & Sapir, 2009; Sapir, Ramig, Spielman, & Fox, 2011), a metric that has successfully distinguished acoustic vowel production in individuals with PD (Sapir et al., 2011). Measures such as the VAI and its inverse, the formant centralization ratio, were developed in order to capture acoustic vowel differences in speakers with dysarthria for whom conventional vowel metrics (such as vowel space area) were not sufficiently sensitive (Karlsson & van Doorn, 2012; Martel-Sauvageau et al., 2014; Martel-Sauvageau, Roy, Cantin, et al., 2015; Martel-Sauvageau, Roy, Langlois, & Macoir, 2015; Roy et al., 2009; Rusz et al., 2013; Sapir, Ramig, Spielman, & Fox, 2010; Skodda et al., 2011). The VAI measures the coefficient of vowel centralization in such a way that minimizes the effects of interspeaker variability (Roy et al., 2009). Interspeaker variability is thought to be a likely explanation for the poor sensitivity of other vowel

Table 2. Parameter setting binning.

Setting	Frequency (Hz)	Voltage (V)	Pulse width (μs)
Low	60 (60–90)	2 (1–2.9)	90 (60–90)
Mid	120 (100–130)	3 (2–3.9)	150 (130–150)
High	180 (160–180)	4.5 (4–4.5)	210 (180–210)

[3]The full protocol involved approximately 2–3 hr of testing unrelated to this study. These included additional speech tasks as well as a number of tasks related to gait and limb kinematics.

[4]Although several studies have used a similarly small group of listeners (e.g., Adams, Dykstra, Jenkins, & Jog, 2008; Dromey, 2003; Dykstra, Adams, & Jog, 2012, 2015; Moreau et al., 2011; Rousseaux et al., 2014; Tanaka et al., 2016; Tripoliti et al., 2014), there is presently no published evidence that provides clear guidelines on the number of listeners required to obtain a stable measure of intelligibility.

metrics, such as vowel space area. A larger VAI value reflects less centralization and thus more precise articulation.

VAI was measured as follows: first and second vowel formants (F1 and F2) were measured and averaged over the middle 30 ms of the four vowels /i/ ("she"), /ae/ ("Patty"), /a/ ("saw"), and /u/ ("two") for each utterance. Formant predictions in Praat were optimized on a speaker-by-speaker basis using a customized Praat script. For each utterance, the VAI was constructed according to the following formula (Roy et al., 2009; Sapir et al., 2011):

$$\mathrm{VAI} = \frac{\mathrm{F2i} + \mathrm{F2ae} + \mathrm{F1ae} + \mathrm{F1a}}{\mathrm{F1i} + \mathrm{F1u} + \mathrm{F2u} + \mathrm{F2a}}. \quad (2)$$

In this formula, formant values in the numerator are expected to decrease with centralization, whereas formant values in the denominator are expected to increase. Therefore, a larger VAI value reflects less centralization, that is, greater vowel expansion.

Second Formant Slope

In addition, measures of second formant (F2) dynamics in the diphthong /ai/ in "buy" were recorded. F2 slope reflects the average speed of lingual movements by measuring the change in formant values (i.e., formant extent in Hz) over a specific duration (milliseconds). F2 slope transition onsets and offsets were calculated based on the 20 Hz/20 ms rule (Weismer, Kent, Hodge, & Martin, 1988).

Vowel Duration

Vowel duration was measured from the amplitude versus time display of the voice-related periodic acoustic signal for each vowel. Conventional acoustic criteria were used to determine the onsets and offsets of the vowels.

Statistical Analysis

To address each of the research questions, the following analyses were performed.

To address Question 1, speech intelligibility and acoustic measures were modeled as a function of parameter settings as well as speaker sex. Baseline speech measures (collected at Visit 1, prior to STN-DBS surgery) were removed for these models, as the primary goal was to compare the STN-DBS parameters. Full linear mixed effects regression models were fit for each dependent variable (speech intelligibility, VAI, F2 slope, F2 transition extent, vowel duration) using the lmer() function from the "lme4" package in R (Bates, Mächler, Bolker, & Walker, 2015). Fixed effect predictor variables for the full models included each of the STN-DBS electrical parameters (frequency, voltage, and pulse width), speaker sex, as well as the interaction terms between each parameter and speaker sex. Sex was included as a fixed effect to account for speech differences that may arise due to anatomical differences as well as to account for any differences in response to STN-DBS stimulation.

All models included by-speaker random intercepts in order to account for the variability beyond that captured by the fixed effects. Backward stepwise elimination was performed on the full models to determine the predictors resulting in the best model fit. The fixed effects that were found to be significant contributors in the final models for each outcome speech variable are reported in the results. Estimated differences of least squares means for all pairwise comparisons were calculated for the predictors contained in the final models. p values were calculated from the F test using Satterthwaite approximations, and effect sizes were calculated by dividing the estimated differences by the residual standard deviation (the estimated standard deviation of the errors) for each final fitted model. Inspection of the models using Q–Q plots and plots of residuals against fitted values confirmed that models met the assumptions for normality and homoskedasticity.[5] Note that, athough only one sentence was elicited per session, each STN-DBS parameter (frequency, voltage, pulse width) necessarily was assigned a setting (low, mid, high) at each session. Thus, when individual parameters are reported, the values are averaged over all sessions for each parameter setting.

To address Question 2, two comparisons were made. First, the standard clinical settings were compared with the optimal speech settings. The standard clinical settings were defined as the final STN-DBS settings (at Visit 7) chosen by the neurologist in order to suppress the patients' primary parkinsonian symptoms. These were the final settings that the participants left the study using. Optimal settings, as defined above, were identified as combinations of settings associated with the least amount of speech impairment. With regard to the speech measures of interest, less impairment is associated with higher intelligibility, larger VAI values (indicating less centralized vowel space), greater F2 slope and transition (indicating increased range of lingual movement over time during the production of the vowel), and greater vowel duration (indicating a slower rate of speech). The optimal speech settings were identified in the following way. All permutations of frequency, voltage, and pulse width across all speech outcome variables were compared, leading to 20 total combinations. For each speech outcome variable, the top 25%, or the five combinations with the best outcomes, of the combinations were assessed. The most commonly occurring settings leading to these optimal results were identified. Eleven out of the 12 participants underwent testing using at least one overall optimal setting. Mean values for each speech outcome variable were aggregated across the 11 speakers, and comparisons with speech outcomes corresponding to the standard clinical settings were tested using paired, two-tailed t tests (in the case of normally distributed variables) or Wilcoxon rank tests (in the case of non-normally distributed variables).

[5]A small proportion of the vowel durations (1.2%) were found to be greater than 3 *SD*s longer than the mean, thus resulting in a slightly skewed residual distribution. The modeling procedure described above was then implemented with these outliers removed.

Second, due to the anticipated individual variability, an additional comparison was made for speech intelligibility between the standard clinical settings and the settings that led to each individual's best intelligibility rating following surgery. The associated STN-DBS settings were thus not the same across all speakers for this comparison. This comparison was included in order to determine whether improvements in speech outcomes could be demonstrated at all relative to the standard clinical settings.

Finally, to address Question 3, the relationships between each acoustic measure of speech and speech intelligibility were correlated. Correlations were performed under three separate conditions, presurgery, under the standard STN-DBS settings, and under the optimal STN-DBS settings, in order to determine if and how the relationship between acoustic speech variables and intelligibility changed. Correlations between TEED and intelligibility were also performed in the standard and optimal STN-DBS settings. A Shapiro–Wilk test of normality demonstrated a normal distribution for speech intelligibility and non-normal distributions for VAI, F2 slope, F2 extent, vowel duration, and TEED; therefore, Spearman's coefficient correlations were performed.

Results

Effects of Individual STN-DBS Parameters

Results are displayed in Figures 1 through 5. Sex is shown in cases where it was retained as a significant predictor in the final models (VAI, F2 transition extent). Full tables of the pairwise comparisons of least squares mean differences for final models are reported in Supplemental Material S1–S3.

Figure 1. Intelligibility (%) by parameter settings. The first panel reports intelligibility levels for each of the following scenarios: Pre–deep brain stimulation, the standard clinical setting, and the optimal setting. The last three panels correspond to each electrical parameter (frequency, voltage, pulse width) and are ordered low, mid, high within each panel. Error bars represent standard errors.

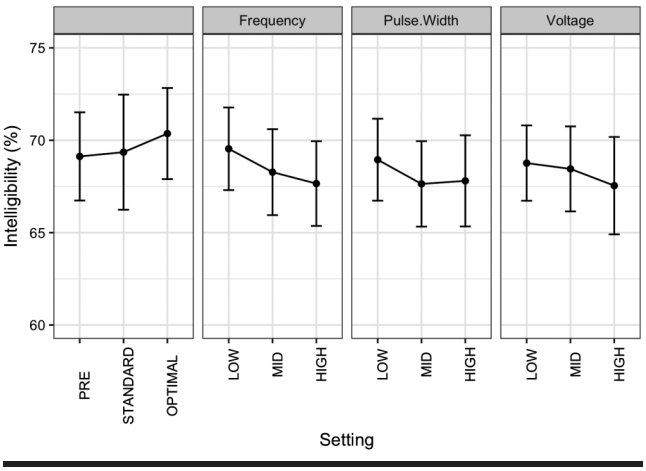
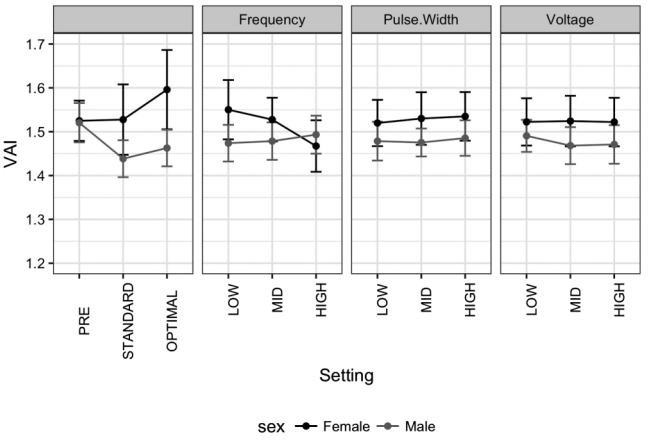


Figure 2. Vowel articulation index (VAI) by parameter settings. Error bars represent standard errors.



Intelligibility

Backward elimination for speech intelligibility led to a final model containing frequency as a fixed effect. Fixed effects of pulse width, voltage, and sex, as well as all interaction terms, were not found to improve the model fit and were thus eliminated. The residual standard deviation of the final model was 5.078. Pairwise comparisons of least squares means differences demonstrated that low versus high frequency led to an increase in intelligibility (estimated difference = 2.896, $p = .005$, effect size = .57). Mid versus high frequency trended toward an increase in intelligibility but did not reach significance at $p < .05$ (estimated difference = 1.706, $p = .055$, effect size = .336). Low versus mid frequency was not significant.

VAI

The final model fit by backward elimination for VAI included fixed effects of frequency and sex as well as their

Figure 3. F2 slope (Hz/ms) by parameter settings. Error bars represent standard errors.

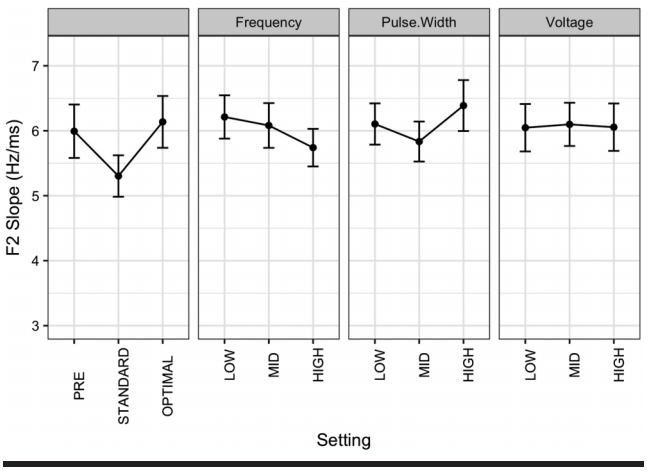
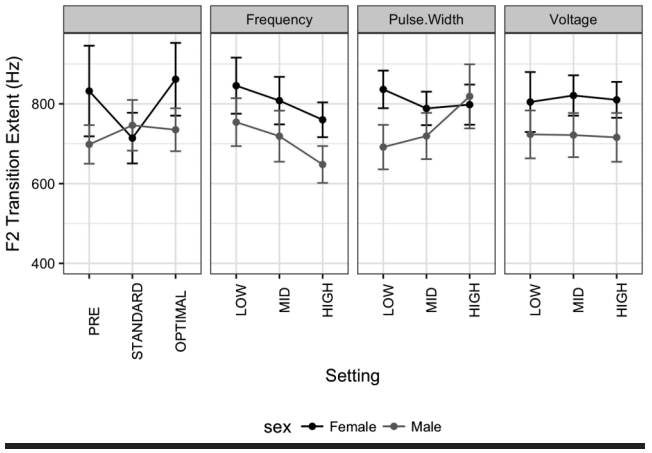
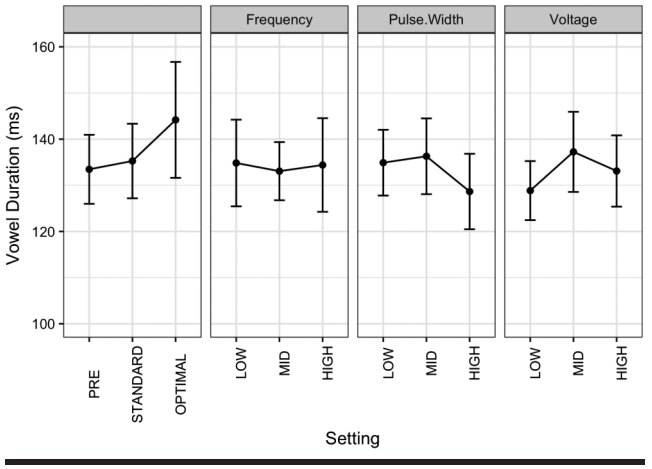


Figure 4. F2 transition extent (Hz) by parameter settings. Error bars represent standard errors.



interaction. Voltage and pulse width, as well as their interactions with sex, were eliminated in the final model. The residual standard deviation for the final model was 0.098. A main effect of frequency was found, and follow-up pairwise comparisons demonstrated that low frequency was associated with an increase in VAI compared to high frequency (estimated difference = 0.048, $p = .017$, effect size = .488). A nonsignificant trend demonstrated increased VAI in mid versus high frequency (estimated difference = 0.032, $p = .061$, effect size = .325). No significant differences were found between low and mid frequency. No main effect of sex was found, though there were significant interactions between sex and frequency. Specifically, for female participants, low frequency (estimated difference = 0.097, $p = .001$, effect size = .986) and mid frequency (estimated difference = 0.065, $p = .011$, effect size = .661) were associated with increased VAI and thus less vowel centralization compared to high-frequency stimulation.

Figure 5. Vowel duration (ms) by parameter settings. Error bars represent standard errors.



F2 Slope and Transition Extent

None of the predictors included in the full model were found to yield an improvement in model fit for F2 slope. The final model for F2 transition extent included fixed effects of frequency, pulse width, and sex, as well as both interaction terms with sex. Voltage and its interaction with sex were eliminated. The residual standard deviation was 144.155. Higher-frequency stimulation was found to be associated with a smaller F2 transition extent compared to low (estimated difference = 107.784, $p < .001$, effect size = .748) and mid frequency (estimated difference = 62.581, $p = .015$, effect size = .434). No main effects were found for either sex or pulse width; however, an interaction between these two predictors was found such that, for male participants, lower pulse width was associated with a smaller transition extent (estimated difference = −94.91, $p = .012$, effect size = −.658). No other comparisons were significant.

Vowel Duration

All of the predictors in the original full model for vowel duration were removed during the backward elimination procedure, and thus, no significant effects or interactions were found.

Standard Clinical STN-DBS Setting Versus Optimal STN-DBS Speech Setting

The first panels of Figures 1 through 5 display the average values for each of the dependent speech variables for the presurgery baseline session as well as the final clinical and overall optimal settings.

The final clinical settings chosen by the neurologist for each patient were as follows. Frequency was set to an average of 121 Hz ("mid"; range: 90–130 Hz). Voltage was set to an average of 3.6 V ("mid"; range: 2.5–4.5 V). Pulse width was set to an average of 96 μs ("mid"; range: 90–130 μs). Speech for 10 of the 12 speakers was collected at all six postsurgery visits and at five of the visits for the remaining two, resulting in 70 instances of the standard clinical settings.

Examination of the top 25% of parameter settings combinations leading to the best outcomes across all speech variables led to the identification of three combinations that occurred most frequently. These three combinations, considered optimal STN-DBS settings for speech, are reported in Table 3. All participants with the exception of one (PDF4) received at least one optimal combination during the experimental STN-DBS programming sessions,

[6]Not all participants were able to tolerate all experimental settings, and some became fatigued toward the end of a visit. If a participant found an experimental setting to be uncomfortable, it was immediately terminated. As such, not all participants underwent the same number of experimental sessions. In total, 43 sessions of a possible 288 were omitted (15%). Of these, 39 were omitted due to patient fatigue or adverse effects of stimulation, and four sessions were missed because one patient (PDM7) missed one of the visits.

Table 3. Optimal deep brain stimulation of the subthalamic nucleus speech settings: Top three occurring parameter setting combinations leading to optimal speech outcomes across all variables.

Frequency	Voltage	Pulse width
Low	Mid	Low
Low	Mid	Mid
Low	High	Mid

and some participants underwent more than one,[6] resulting in a total of 27 instances of the optimal setting. Averages for all speech outcome measure were averaged across participants, resulting in one value for each dependent speech variable associated with the optimal settings.

F2 slope was found to be significantly steeper with the overall optimal setting (6.1 Hz/ms vs. 5.3 Hz/ms, p = .042). No other significant differences were found for any of the measures between the standard clinical and the overall optimal settings. That is, despite the finding that certain parameter adjustments were associated with improvements in speech outcomes overall, as demonstrated from the regression models, the combinations of these parameters did not yield significantly different speech outcomes when compared to the standard clinical settings. Means and p values are reported in Table 4. Individual participants' speech intelligibility under presurgery, standard clinical settings, and optimal settings are reported in Figure 6.

Five of the 11 participants demonstrated an improvement in intelligibility with the overall optimal settings compared to the standard clinical settings (PDM1, PDM2, PDM4, PDM7, PDF3). All of these participants also demonstrated deterioration in intelligibility with the standard clinical settings compared to their presurgery speech. That is, most of the individuals whose speech intelligibility worsened following STN-DBS surgery were able to demonstrate improvements under a different combination of STN-DBS settings. This improvement ranged from 4.0% (PDF3) to 12.25% (PDM7).

Similarly, all participants whose speech intelligibility improved following STN-DBS under the standard clinical settings compared to their presurgery speech (PDM3, PDM6, PDF1, PDF2, PDF5) demonstrated worsening intelligibility with the optimal speech settings. That is, those individuals who saw an improvement in their speech with the standard clinical STN-DBS settings did not benefit additionally from more optimal speech settings (in fact, the optimal settings led to reductions in intelligibility). One participant (PDM5) saw reductions in intelligibility both in presurgery and standard clinical settings and further reductions in the overall optimal settings.

Examination of each participant's best intelligibility revealed substantial variability. The numbers of participants whose best intelligibility rating occurred with each STN-DBS parameter setting are reported in Table 5.

[6]Not all participants were able to tolerate all experimental settings, and some became fatigued toward the end of a visit. If a participant found an experimental setting to be uncomfortable, it was immediately terminated. As such, not all participants underwent the same number of experimental sessions. In total, 43 sessions of a possible 288 were omitted (15%). Of these, 39 were omitted due to patient fatigue or adverse effects of stimulation, and four sessions were missed because one patient (PDM7) missed one of the visits.

Table 4. Means for each speech outcome measure at presurgery, under the standard clinical and optimal deep brain stimulation of the subthalamic nucleus settings.

Speech variable	Presurgery	Standard	Optimal	p
Intelligibility (%)	69.13	69.40	70.36	0.861
VAI	1.52	1.48	1.51	0.240
F2 slope (Hz/ms)	5.99	5.30	6.14	0.042
F2 extent (Hz)	754.10	732.90	781.10	0.147
Vowel duration (ms)	133	135	144	0.520

Note. p values were obtained from the pairwise tests for each speech outcome comparing the standard clinical and optimal settings. VAI = vowel articulation index.

Relationship Between Speech Variables and Intelligibility

Spearman's coefficient correlations and associated p values corresponding to speech intelligibility presurgery, as well as under the standard and optimal STN-DBS settings, are reported in Table 6. In the presurgery speech, only F2 slope was found to significantly correlate with speech intelligibility, such that better intelligibility was associated with a steeper slope. Under the standard STN-DBS settings, none of the speech measures demonstrated a significant relationship with intelligibility, though a negative

Figure 6. Speech intelligibility for all speakers at baseline, under the standard clinical STN-DBS settings, and under the optimal STN-DBS settings. Speakers are ordered by their baseline intelligibility. STN-DBS = deep brain stimulation of the subthalamic nucleus.

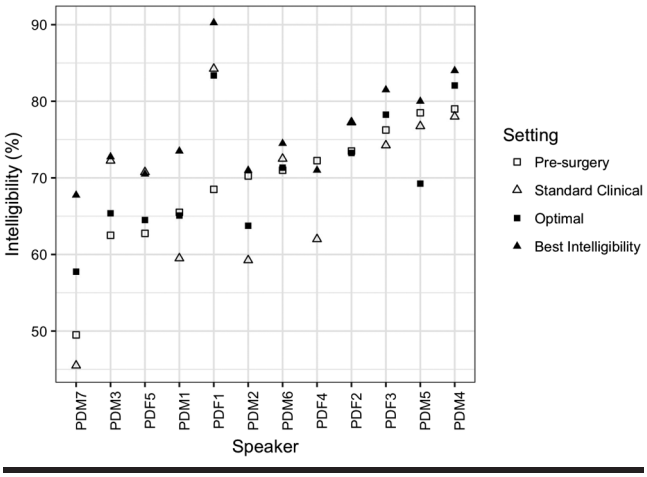


Table 5. Number of participants whose best intelligibility was elicited under each deep brain stimulation of the subthalamic nucleus parameter setting.

Parameter	Low	Mid	High
Frequency	4	6	2
Voltage	2	6	4
Pulse width	7	5	0

trend with TEED was found. Under the optimal settings, however, all speech variables with the exception of F2 slope were associated with a significant positive relationship with speech intelligibility. VAI demonstrated a moderate positive relationship, whereas F2 extent and vowel duration demonstrated weak positive relationships with intelligibility. TEED was no longer found to demonstrate any relationship with intelligibility.

In other words, although no clear relationship was evident under the standard STN-DBS settings, under the optimal settings, an increase in intelligibility was associated with a decrease in vowel centralization, an increase in the extent of F2 transition, and a slower articulatory rate of speech as indicated by increased vowel durations.

Discussion

Impact of STN-DBS Stimulation Parameter Settings on Speech

In summary, the results presented above suggest that, overall, lower STN-DBS frequency settings are consistently associated with higher intelligibility and greater acoustic vowel expansion (as demonstrated by reduced vowel centralization and increased diphthong F2 transition extents). This was demonstrated both in the regression models, in which low frequency was consistently found to predict better speech outcomes, as well as in the identification of the optimal settings, all of which involved low frequency. Main effects of the other parameters, namely, voltage and pulse width, were not found, though interactions between sex and frequency (for VAI) and sex and pulse width (for F2 extent) indicate a more complex relationship. The optimal clinical settings presented in Table 3 suggest that, when in combination with low frequency, non–low voltage and non–high pulse width are associated with better speech outcomes. The individual results, however, are not as straightforward, as the single best intelligibility rating only occurred under a low-frequency setting for four participants. The exploration of individual differences should be interpreted with caution, given that the "best intelligibility" refers to a single utterance in a single condition.

Table 6. Spearman's coefficient correlations between intelligibility and acoustic speech measures as well as TEED, presurgery, as well as under the standard and optimal deep brain stimulation of the subthalamic nucleus settings.

	Presurgery		Standard settings		Optimal settings	
Measure	*r*	*p*	*r*	*p*	*r*	*p*
VAI	.126	.697	.462	.131	.689	**< .001**
F2 slope	.706	**.010**	.322	.308	–.032	.874
F2 extent	.322	.308	–.049	.880	.405	**.036**
Vowel duration	–.308	.331	.266	.404	.395	**.041**
TEED	NA	NA	–.573	.051	.166	.417

Note. *p* values that are less than .05 are bolded. TEED = total electrical energy delivered; VAI = vowel articulation index; NA = not applicable.

Regarding the effects of frequency modulations, lower versus higher STN-DBS frequency has been shown to lead to better speech outcomes (Moreau et al., 2011; Törnqvist et al., 2005) as well as other axial symptoms (Brozova, Barnaure, Alterman, & Tagliati, 2009; Moreau et al., 2008; Ricchi et al., 2012; Vallabhajosula et al., 2015; Xie et al., 2015), both immediately and over time (see Baizabal-Carvallo & Alonso-Juarez, 2016; di Biase & Fasano, 2016, for reviews). In a recent review of speech outcomes in individuals with PD following STN-DBS, Skodda, Grönheit, and Schlegel (2012) found that the majority of studies in which the presence of dysarthria was noted also reported using relatively high voltage and frequency stimulation. Although the precise mechanism of STN-DBS on speech remains unclear (Montgomery & Gale, 2008), it has been suggested that the presence of dysarthria during stimulation could be related to a spread of current to neural pathways important for speech production (Skodda et al., 2012). Speech, which is typically more resistant to levodopa and DBS treatments, may be less likely to be subject to further detriment when treated with lower frequency (di Biase & Fasano, 2016); in some cases, it may even improve compared to when DBS is turned off (Moreau et al., 2011). For example, Törnqvist et al. (2005) found that lower STN-DBS frequency (70 Hz) was associated with greater speech intelligibility compared to higher-frequency stimulation (130 Hz or 185 Hz). Similarly, Moreau et al. (2011) demonstrated that lower-frequency STN-DBS (60 Hz) was associated with improvements in speech intelligibility compared to higher-frequency stimulation (100 Hz) and when stimulation was turned off. Although the authors did not systematically manipulate voltage and pulse width, TEED was kept constant. The findings of this study are in keeping with previous research with respect to low frequency, though, in contrast, better speech outcomes (as identified by the optimal settings in Table 3) tended to be associated with mid or high voltage when combined with low frequency. No study to the authors' knowledge has systematically examined the effects of pulse width on speech following STN-DBS, though our results similarly point to a potential relationship between pulse width and frequency, such that low or mid pulse width, when combined with low frequency, were associated with improvements in speech.

Although these findings indicate that speech detriments following STN-DBS have the potential to be lessened, it is not known whether these effects would last. Speech

was tested approximately 30 minutes to 1 hour after the stimulation settings were changed, but longer-term speech effects were not investigated. For this reason, we cannot speculate as to whether the effects observed would persist. There is currently very little research examining the long-term effect of alternate STN-DBS settings on speech, and findings are variable (Xie et al., 2017). There is some evidence to suggest that the beneficial effects of low-frequency STN-DBS stimulation on gait and other axial symptoms including speech may be transient (Ricchi et al., 2012), though others have found longer-term sustained benefits (Moreau et al., 2008, 2011; Xie, Kang, & Warnke, 2012; Xie et al., 2015; Zibetti et al., 2016). This is an important consideration and should be addressed in future studies.

Relationship Between Intelligibility and Speech Variables

Distinct relationships between speech intelligibility and the acoustic speech variables were revealed across conditions. Specifically, in the presurgery condition, F2 slope was found to be the only acoustic variable to significantly demonstrate a relationship with intelligibility, a trend consistent with previous literature on speech intelligibility in PD (Kim et al., 2011; Tjaden, Richards, Kuo, Wilding, & Sussman, 2013). Postsurgery speech, however, revealed a different trend. Under the standard STN-DBS settings, none of the acoustic variables were found to correlate with intelligibility. Under the optimal settings, findings revealed a pattern opposite that found in the presurgery speech: All acoustic measures, with the exception of F2 slope, were found to significantly correlate with intelligibility in the expected directions (higher intelligibility was associated with increased acoustic space and longer vowel durations). Interestingly, despite the suggestion that F2 slope may provide an ideal metric of speech changes following STN-DBS given its sensitivity to dysarthria and speech movement (Weismer et al., 2012), F2 slope was not found to differ as a function of STN-DBS parameter modulations in this study, nor was it found to correlate with intelligibility, despite demonstrating a significant relationship with intelligibility prior to STN-DBS. F2 slope was found, however, to significantly improve in the optimal settings compared to the standard clinical settings, though its relationship with intelligibility was not maintained. F2 slope has shown variable response to STN-DBS in one previous study (Dromey & Bjarnason, 2011). F2 slope, despite being a good indicator of dysarthria in general (Kim et al., 2009), may be subject to greater variability in individuals with PD. Variable speaking rate associated with PD may be one confounding factor. The variability in patient response to STN-DBS may further exacerbate these differences. Although vowel duration, an indirect measure of speech rate, was found to correlate with speech intelligibility, it was not found to be significantly affected by any changes to the STN-DBS parameter settings. Speech intelligibility, VAI, and F2 transition extent, on the other hand, were found to demonstrate change in response to the STN-DBS settings. Therefore, it appears that, although vowel rate was correlated with intelligibility, it cannot necessarily explain the changes in intelligibility and vowel articulation.

Sex was found to improve the model fits for VAI and F2 transition extent, but not for intelligibility. Given this difference, it may be the case that the observed sex difference arises from one of two plausible cases. Although VAI is meant to be more robust to speaker differences, including those between male and female, sex differences in formant frequency may have still exerted greater influence on the acoustic measures than on the perceptual measure of intelligibility. Another possibility is that vowel-specific measures may reveal sex differences, whereas more global measures of speech production, such as intelligibility ratings, may not.

Changes in speech intelligibility are likely to result from other factors related to STN-DBS beyond the parameter settings examined here. Tripoliti et al. (2014) found evidence to suggest postoperative speech intelligibility was best predicted by three factors: preoperative speech intelligibility, disease duration, and electrode contact position. Additional findings suggest that electrode contact position as well as disease subtype may be implicated in speech outcomes (Fenoy, McHenry, & Schiess, 2016). More work is needed to investigate patient and surgery-specific parameters on speech detriments and their relationship to STN-DBS parameters.

Standard Clinical Versus Optimal STN-DBS Settings for Speech

With the exception of F2 slope, no group differences were found between the STN-DBS standard clinical settings and the optimal settings. Despite trends for the optimal settings to be associated with higher values, as evidenced by Figures 1 through Figure 5, closer inspection of the data revealed a large amount of individual variability. Closer inspection of the data revealed that the individuals who did see improvement with the optimal settings were the same individuals who experienced an overall worsening of intelligibility following their STN-DBS surgery. Similarly, those who did not benefit from the optimal settings compared to the standard clinical settings also saw an increase in their intelligibility compared to their presurgery baseline speech.

Although the results of the regression analysis revealed that lower frequency was associated with improved intelligibility, this difference was more pronounced when comparing low versus high frequency. Low frequency trended toward improvements in intelligibility and F2 extent when compared to mid frequency, but this result did not reach significance for any of the speech outcomes except for VAI. Therefore, although it is clear that lower frequency overall was associated with improvements in speech, the distinction between low and mid frequency may be subject to greater variability and a less clear pattern.

Closer inspection of the best intelligibility ratings for each participant revealed that this was associated with low frequency for only four participants. Two of these four (PDM1, PDM4) also improved with the overall optimal

settings, and the other two (PDF1, MDM6) did not. Further work examining individual responses to low frequency is necessary to better understand this variability. An ideal clinical implementation of such a finding would be to provide individuals with STN-DBS who are experiencing speech changes with an alternative "speech setting" that could be programmed into the DBS patient controller (Allert, Mehnert, Lehrke, Maarouf, & Sturm, 2011).

The present findings do not point toward a universal setting but do indicate that lower frequency suggests a promising starting point to tailor such a setting to an individual's specific presentation. Such an outcome would require a deeper investigation into individual speech profiles both prior to and following STN-DBS surgery, as well as a broader range of STN-DBS parameters, including electrode contact position and medication effects, all of which have been suggested as additional contributors to speech outcomes following STN-DBS surgery (Martel-Sauvageau, Roy, Cantin, et al., 2015; Tripoliti et al., 2008).

Limitations

There were several limitations to this study that warrant discussion. These can broadly be grouped into the following categories: sample size and characteristics, speech protocol limitations, and patient-specific factors. A clear limitation is the sample size of the study, which included only 12 individuals. Furthermore, although sex-based asymmetries were found for VAI and F2 extent, this finding should be interpreted with caution due to the small and unequal sex sampling. Relatively little is known about how STN-DBS differentially affects men and women (Accolla et al., 2007; Hariz, Lindberg, Hariz, & Bergenheim, 2003). Although the observed asymmetries in this study could be related to anatomical or sociolinguistic sex differences giving rise to differences in speech production (Simpson, 2009) or sex-based differences in the impact of PD (Baba, Putzke, Whaley, Wszolek, & Uitti, 2005; Lyons, Hubble, Tröster, Pahwa, & Koller, 1998; Scott, Borgman, Engler, Johnels, & Aquilonius, 2000; Wirdefeldt, Adami, Cole, Trichopoulos, & Mandel, 2011; Zappia et al., 2005), future studies involving equal numbers of men and women are required to speculate on these findings.

In addition to the speech tasks, the protocol also included a number of other motor tasks and questionnaires as part of a larger study. This led to two specific limitations in this study. First, not all patients were able to complete all sessions due to fatigue or discomfort; in some cases, patients elected to terminate one or more of the testing sessions. Second, due to the long nature of the protocol, only one utterance was elicited per session.[7] In the regression analyses presented above, the speech measures were collapsed across the predictor variables found to contribute to the model. As such, the effects were averaged across conditions (e.g., for intelligibility, the final model only included frequency as a predictor variable; therefore, the intelligibility outcomes are collapsed across low, mid, and high frequency). The exploratory analyses examining individual points in time, however, including presurgery, under the standard clinical settings, and the "best intelligibility" settings, reflected only a single utterance per participant. These results should be interpreted cautiously for this reason, and future studies should examine a greater number of spoken utterances across a smaller set of STN-DBS parameter combinations.

Patient-specific factors that were not controlled for in this study include TEED, medication levels, and electrode placement. By systematically adjusting all three electrical parameters at once, TEED was inherently modified, and this was different across participants (as TEED is a function of an individual's cortical tissue impedance levels). Although this is an important consideration, the finding of lower frequency overall (i.e., across all voltage settings) suggests that improvements in speech were not simply a result of a decrease in TEED. Furthermore, evidence suggests that frequency may be a more influential variable in STN-DBS compared to overall TEED with regard to clinical improvements (Fasano & Lozano, 2014; Moreau et al., 2008).

The effect that STN-DBS has on speech may be modulated in part by precise electrode placement (Tripoliti et al., 2008) and levodopa (Martel-Sauvageau, Roy, Cantin, et al., 2015) but were not variables of interest in this study. Follow-up work investigating specific setting combinations should consider these additional potential effects. This study sought to control for the intervening effects of levodopa medication in part by testing patients in an off-medication state.

Potential limitations to the analyses conducted in this study warrant cautionary interpretation of pre- and postsurgery outcomes as well as a consideration of the small number of listeners included in the intelligibility ratings. The purpose of this study was not to test pre- and postsurgery outcomes of STN-DBS on speech. As such, there was a lack of statistical power regarding the baseline measures. In addition, it is not uncommon for individuals to see transient benefits from stimulation changes, warranting further investigations of longer-term speech outcomes.

Summary

In summary, the findings from this study suggest that adjustments in the frequency of STN-DBS stimulation lead to consistent improvements in speech intelligibility and vowel acoustics. In particular, lower frequency was associated with improved speech outcomes. These findings demonstrate a high degree of variability present across individual speakers and should inform future considerations of STN-DBS parameter optimization.

[7]Participants were asked to say the same utterance two times, but only the first instance of each elicitation was used for the analysis unless there was a clear disruption (coughing, etc.), in which case, the second instance was used.

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