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Pitch variability in patients with Parkinson's disease: Effects of deep brain stimulation of caudal zona incerta and subthalamic nucleus

Fredrik Karlsson¹, Katarina Olofsson², Patric Blomstedt³, Jan Linder³, & Jan van Doorn¹

1 Department of Clinical Sciences, Division of Speech and Language Pathology, Umeå University, Umeå, Sweden.

2 Department of Clinical Sciences, Division of Otorhinolaryngology, Umeå University, Umeå, Sweden.

3 Department of Pharmacology and Clinical Neuroscience, Division of Clinical Neuroscience, Umeå University, Umeå, Sweden

* Corresponding author

Fredrik Karlsson, PhD

Department of Clinical Sciences, Division of Speech and Language Pathology

Umeå University

SE-90185 Umeå

Sweden

Tel. +46 90 785 89 70

Email. fredrik.karlsson@ling.umu.se

Abstract

Objective

The purpose of the present study was to examine the effect of deep brain stimulation (DBS) of the subthalamic nucleus (STN) and the caudal zona incerta (cZi) pitch characteristics of connected speech in patients with Parkinson's disease (PD).

Methods

Sixteen patients were evaluated preoperatively and 12 months after DBS surgery. Eight patients were implanted in the STN (aged 51-72 yrs; $\bar{x}$ =63 yrs). Six received bilateral implantation and two unilateral (left) implantation. Eight patients were bilaterally implanted in the cZi (aged 49-71 yrs; $\bar{x}$ =60.8 yrs). Preoperative assessments were made after an L-Dopa challenge (approximately 1.5 times the ordinary dose). All postoperative examinations were made off and on stimulation, with a clinically optimized dose of L-dopa. Measurements of pitch range and variability were obtained from each utterance in a recorded read speech passage.

Results

Pitch range and coefficient of variation showed an increase in patients under STN-DBS. Patients under cZi-DBS showed no significant effects of treatment on investigated pitch properties.

Conclusions

STN-DBS was shown to increase pitch variation and range. The results provided no evidence of cZi-DBS having a beneficial effect on PD patients' pitch variability.

Introduction

Patients with Parkinson's disease (PD) often have a reduced intensity variation (mono loudness), increased average pitch and a monotonous voice (monopitch) (e.g. Darley, Aronson, & Brown, 1969; Goberman & Coelho, 2002; R. D. Kent & Kim, 2003; Pinto et al., 2004; Skodda, Grönheit, & Schlegel, 2011; Stewart et al., 1995). Pitch level, variability and range provide the frame within which tonal components of prosodic contrasts may function, and reduced ability in voluntary manipulation of pitch therefore constitutes a key component in dysprosody (MacPherson, Huber, & Snow, 2011). Pitch range correlates significantly with intelligibility of speech in dysarthria (Kim, Kent, & Weismer, 2011; Laures & Weismer, 1999) and reductions in this aspect of speech has been described as the second most severe deviation in speech of dysarthric patients (Darley et al., 1969).

In acoustic terms, pitch is manifested as the frequency of the first harmonic of the source spectrum (f_0), and the variability and range of f_0 have been used to evaluate both disease effects and effects of treatment in several clinical populations where speech is affected (e.g. (Bunton, Kent, Kent, & Rosenbek, 2000; Diehl, Watson, Bennetto, Mcdonough, & Gunlogson, 2009; Kim et al., 2011; Kuschmann, Lowit, Miller, & Mennen, 2010; Ma, Whitehill, & So, 2009; Mennen, Schaefler, Watt, & Miller, 2008; Skodda, Rinsche, & Schlegel, 2009; Van Lancker Sidtis, Pachana, Cummings, & Sidtis, 2006)). In patients with PD, an overall reduced variability in f_0 for both male and female patients has been observed in association with the disease (Bunton et al., 2000; Goberman & Coelho, 2002; Holmes, Oates, Phyland, & Hughes, 2000; Jones, 2009; Metter &

Hanson, 1986; Rusz, Cmejla, Ruzickova, & Ruzicka, 2011; Trail et al., 2005), reducing intelligibility (Bunton, Kent, Kent, & Duffy, 2001). Thus, variability and range of f_0 are viewed as potent objective measures of desired treatment effects of monopitch of PD patients speech.

Pharmalogical treatment with levodopa is the most frequently used treatment for PD (De Letter, Santens, & Van Borsel, 2004). Previous reports concerning the effect of this treatment on pitch variability have found either no effect (Goberman & Coelho, 2005; Ho, Bradshaw, & Iansek, 2008; Skodda et al., 2011), a small but inconsistent improvement (Goberman, Coelho, & Robb, 2002) or a positive outcome (De Letter et al., 2007). Thus, it is possible that dopaminergic treatment may have a positive effect on pitch variability, but this effect may be dependent on external factors such as the overall stage of the disease as well as the specific disease profile of the patient (De Letter et al., 2007; Ho et al., 2008)

Deep brain stimulation (DBS) in the subthalamic nucleus (STN) is an established surgical treatment for a selected group of PD patients (Klostermann, Krugel, & Wahl, 2012; Tripoliti et al., 2011; Volkmann, Daniels, & Witt, 2010). STN-DBS has been shown to have reduce the cardinal symptoms of PD related to motor function (e.g. Krack et al., 2003). The outcomes of STN-DBS are more varied regarding speech and the effects are to a certain degree dependent on variations in methodology and the specific subsystem of speech analyzed. Evaluation of speech using the unified Parkinson's disease rating scale (UPDRS) (Fahn, RL, & Committee, 1987; Martínez-Martín et al., 1994) have demonstrated positive effects (Fasano et al., 2010; Østergaard, Sunde, & Dupont, 2002); positive but transient effects (Bejjani et al., 2000; Krack et al., 2003); negative

effects (Krause, Fogel, Mayer, Kloss, & Tronnier, 2004; Santens, De Letter, Borsel, Reuck, & Caemaert, 2003; Tripoliti et al., 2011; 2008; Wang et al., 2006), while other studies have found the effects to vary with the stimulation parameters (Pinto et al., 2005). The variation in UPDRS outcome concerning speech may to some extent be due to the perceptual nature of the score. Speech proficiency is rated in terms of progression or worsening, UPDRS scores do not specify which aspect of the speech is affected.

An issue of particular importance for the assessment of DBS and its influence on the specific subsystem of the speech is the effect of lateralization of speech motor subsystems. In this and other studies, STN-DBS has been administered uni-, and bilaterally in PD patients, opening up potential influence of differences in lateralization in the brain for speech-related motor control. While temporal and segmental aspects of prosody have been associated with the left hemisphere (Belin et al., 1998; Zatorre & Belin, 2001; Zatorre, Evans, & Meyer, 1992), pitch processing has been more strongly linked to the right hemisphere (Belin et al., 1998; Sidtis, 1980; 1981; Van Lancker Sidtis et al., 2006; Zatorre et al., 1992; Zatorre & Belin, 2001). Thus, voice quality and prosodic aspects are likely to be more influenced by STN-DBS involving the right side of the brain.

Acoustic studies have confirmed that prosodic properties in PD patients' speech may be improved by STN-DBS. Improvements have been observed in overall voice quality in terms of acoustic harmonic-to noise ratios (Van Lancker Sidtis, Rogers, Godier, Tagliati, & Sidtis, 2010), pitch range and voice stability (Alatri et al., 2008; Dromey, Kumar, Lang, & Lozano, 2000; Gen-

til, Chauvin, Pinto, Pollak, & Benabid, 2001; Hoffman-Ruddy, Schulz, Vitek, & Evatt, 2001). Thus, STN-DBS has been shown to strengthen acoustic parameters that are important to the perception of voice and prosodic distinctions in treated patients.

Recently, the caudal zona incerta (cZi) has been suggested as an alternative target to STN in PD, showing greater improvements in motor effects compared to STN-DBS in a non randomized longitudinal study (Plaha, Ben-Shlomo, Patel, & Gill, 2006). Detailed speech-related effects of cZi-DBS compared to STN-DBS have been the focus of only two previous studies (Karlsson et al., 2011; Lundgren et al., 2011) that compared off- and on-stimulation states for the two targets. Karlsson et al. (Karlsson et al., 2011) showed that while STN-DBS caused improvements in articulation rate in simple speech tasks (rapid syllable repetition), cZi-DBS had adverse effects. Further, cZi-DBS was shown to cause a decreased proficiency in reaching the articulatory targets in plosive consonants on stimulation, especially at relatively high articulation rates. Results concerning voice intensity indicated that STN-DBS may increase voice intensity while cZi-DBS reduced it (Lundgren et al., 2011). Thus, while STN-DBS may strengthen articulatory proficiency, articulation rate and speech intensity, these properties may be adversely affected by cZi-DBS.

The tonal properties of speech in cZi-DBS implanted PD patients have, however, not been the subject of any previous investigation. The present study, therefore, aimed to evaluate the effects of cZi-DBS on f_0 in connected speech, and to compare these effects with those found for STN-DBS patients.

Method

Patients

Sixteen patients (12 male and 4 female) with idiopathic PD were included in this prospective non-randomised study. Eight patients (aged 51-72 yrs, $\bar{x}$ =63 yrs at the time of Pre-op baseline measurement) were implanted in the STN (six bilateral and two left side unilateral). The remaining eight patients, (aged 49-71 yrs, $\bar{x}$ =60.8 yrs at the time of Pre-op baseline measurement), were implanted bilaterally in the cZi. The surgical procedure has been described in previous reports (Blomstedt & Hariz, 2006; Karlsson et al., 2011; Lundgren et al., 2011). An overview of the patients in both groups is presented in Table 1. The two patient groups were the same (Lundgren et al., 2011) or an expanded set (Karlsson et al., 2011) of the group of patients investigated in previous comparisons of STN and cZi effects on speech (Karlsson et al., 2011; Lundgren et al., 2011). The selection for surgery was based on overall motor function and no consideration was taken with regard to speech status.

Table 1: Characteristics of patients in the two surgical treatment groups. Mean age (with standard deviation and range) as well as median Unified Parkinson's disease rating scale – motor scores, UPDRS-III, (and range) in the preoperative recordings (Pre-op) are provided. There were no statistical differences between the groups for age, duration since diagnosis, or any of the UPDRS-III scores.

Preoperative characteristic	STN group (n=8)	cZi group (n=8)
Age (Pre-op), years	63.0±7.9 (51-72)	60.8 ± 9.0 (49-71)
M/F	6/2	6/2
Duration since diagnosis (years)	6.8 ± 1.7 (4-9)	6.1 ± 2.8 (2-10)
UPDRS III Off medication	39.5 (32-57)	35.5 (29-58)
UPDRS-III On medication	19.5 (6-36)	20.0 (10-42)
Speech (UPDRS III Item 18), Off medication	1.0 (0-2)	1.0 (0-2)
Speech (UPDRS III Item 18), On medication	0.5 (0-2)	1.0 (0-1)
DBS surgery		
Bilateral	4M,2F	6M,2F
Unilateral (left)	2M	

Table 2: Length of utterance (in number of words and syllables) and a classification of the linguistic function for each of the analyzed utterances.

Utterance number	Number of words	Number of syllables	Linguistic function
1	18	28	Statement
2	8	13	Statement
3	17	25	Statement
4	8	12	Retold "Wh" question followed by statement
5	5	8	Retold statement followed by first person statement
6	17	24	Retold statement
7	16	25	First person statement followed by retold statement
Total	89	135	

Study design

All patients were evaluated before and 12 months after surgery. The Pre-op baseline assessments were performed with PD medication 1.5 times the normal daily dose, in order to assure that the patient was in the "on" state when evaluated. The postoperative evaluations were all performed within the optimal time in the patients' medication cycle under two conditions: off stimulation (Stim OFF) and on stimulation (Stim ON). Recordings were made 60 minutes after DBS had been switched on or off, respectively. The study has been approved by the Regional Ethical Review Board in Umeå (Dnr: 08-093M: 2008-08-18) and all examinations have been conducted in accordance with local and national guidelines for good clinical practice.

Speech material

The speech material used in this study was complete utterances extracted from readings of a standard 89 word Swedish passage (Lundgren et al., 2011). The passage consists of seven utterances, described in Table 2 in terms of number of words and syllables within the utterance as well as the linguistic nature of the utterance. The diverse nature of the read speech utterances decreases the likelihood of floor- or ceiling effects in that the full range of pitch variability is covered, from statements that are the least variable to dual voiced questions that are the most variable. The passages were recorded under all three testing conditions: at Pre-op baseline, Post-op off and on stimulation.

Recordings were made using a calibrated head-mounted microphone (Sennheiser MKE 2 P-C), with a 15 cm mouth to microphone distance. The samples were recorded on a digital audio flash

recorder (Marantz PMD 660) or in the case of some early recordings a digital audio tape recorder (Panasonic SV 3800) at sampling rate of 44.1 or 48 kHz. A calibration tone (80 dB, 1 kHz) was used at the start of each recording in order to afford normalized comparisons of amplitude of the acoustic signal. All recordings were made in a sound-treated recording booth.

Utterances produced in 91 readings of the standard text were selected as the basis of the present investigation. From this set of recordings, utterances with a strong presence of dysfluency or where the patient started over in the reading were excluded from the data set. The remaining 642 utterances were submitted for further acoustic analysis. The distribution of those utterances across the various experimental conditions is shown in Table 3.

Acoustic analysis

The utterances included in the study were submitted for acoustic analysis of pitch characteristics using the Praat software package (Boersma & Weenink, 2001), version 5.2.23. A pitch contour was computed using the autocorrelation method with a pitch floor set at 75 Hz and ceiling at 600 Hz (15 candidates, automatic time stepping, very accurate estimates and program default settings in all other parameters) for all included utterances. The resulting pitch contour was subsequently analyzed in terms of coefficient of variation of pitch across each utterance. This statistic (standard deviation/mean) has been used previously to provide a gender-normalized estimate of pitch variability in PD patients (Harel, Cannizzaro, Cohen, Reilly, & Snyder, 2004). An 80% inter-quantile range was computed for each utterance, discarding pitch values above the 90th quantile and below the 10th quantile of pitch values. This estimate of pitch range has been used previ-

ously in intonation research in order to reduce the effect of individual extreme values and any errors returned by the pitch extraction algorithm used (Kim et al., 2011; e.g. Mennen, Scobbie, de Leeuw, Schaeffler, & Schaeffler, 2010).

Statistical analysis

A hierarchical repeated measures analysis of variance (ANOVA) was employed on the dependent variables (mean pitch, pitch coefficient of variation and pitch range) in order to investigate effects of cZi-DBS and STN-DBS. The analyzed utterance was treated as a within-subject factor. A similar analysis was also performed for effects of recording session, comparing Pre-op with Post-op, off stimulation recordings. Post-hoc testing of main effects was done using Tukey's Honest Significant Differences.

Table 3: Number of analyzed utterances in the preoperative and the 12 months postoperative recordings. Post-op recordings were made off and on stimulation (Stim OFF and Stim ON).

	Condition			
	Pre-op	Post-op (12months)		
Implantation site		Stim OFF	Stim ON	Total
STN	77	112	117	306
cZi	112	112	112	336
Total	189	224	229	642

Results

The variability of pitch across the utterances (as quantified by the coefficient of variation in pitch values) is displayed in Figure 1. Statistical testing, using utterance as a within-subject factor, showed a significant interaction effect between stimulation condition and implantation site in f_0 coefficient of variation ($F(2,528)=4.7, p<0.01$). Post-hoc testing confirmed a significantly higher coefficient of variation on stimulation compared to off stimulation for STN-DBS ($p<0.01$) and a higher variability in f_0 for the STN group compared to the cZi group on stimulation. No other contrasts displayed in Figure 1 were significant.

The higher pitch variability in f_0 due to STN-DBS was confirmed in pitch range estimates. For the 80% inter-quantile range (Figure 2), a significant interaction effect was found for stimulation condition and implantation site ($F(2,526)=12.51, p<0.001$). Post-hoc testing confirmed a higher pitch range for STN-DBS in on stimulation recordings compared to off stimulation ($p=0.01$) and a higher range in STN-DBS patients compared to cZi-DBS patients on stimulation ($p=0.01$).

Pitch properties were confirmed to depend on the linguistic function of the utterance. Both pitch coefficient of variation ($F(6,526)=6.2, p<0.01$) and range ($F(6,526)=5.9, p<0.05$) increased in utterance types where a more varied pitch is expected due to the prosodic properties of the utterance (i.e. utterances 4-6 where the two voices or question intonation may be expected to increase the range of pitch used). No treatment effects or differences between patient groups were, how-

ever, observed. Thus, the increase in pitch range and variability was due to STN-DBS in all utterance types, and did not depend on the prosodic nature of the utterance.

The rise in pitch coefficient of variation observed for the whole group of STN patients on stimulation (Figure 1) occurred in bilaterally implanted patients only. As seen in Figure 3, the pitch coefficient of variation for the two unilateral STN-DBS speakers does not appear to be affected by stimulation. Reliable statistical testing of this difference is not afforded by the current data set, but almost complete overlap between confidence intervals in unilateral patients on stimulation compared to off stimulation was observed. The results, therefore, strongly suggest that unilateral (left hemisphere) patients do not show the effect of STN-DBS observed in bilaterally implanted patients.

Figure 1: Mean coefficient of variation in pitch produced by the two groups of patients under the Pre-op (Med ON), Stim OFF and Stim ON conditions (12 months Post-op, Med ON). For each estimated mean value, the confidence interval is indicated using error bars and the number of observations on which the estimate is based is provided below each mean estimate.

Figure 2: Mean 80% inter-quantile pitch range for the two groups of patients in the Pre-op base-line, Post-op off stimulation (Stim OFF) and Post-op on stimulation (Stim ON) recordings. For each estimated mean value, the confidence interval is indicated using error bars and the number of observations on which the estimate is based is provided below each mean estimate.

Figure 3: Mean coefficient of variation in pitch for bilateral and unilateral patients off and on stimulation. For each estimated mean value, the confidence interval is indicated using error bars. The number of observations on which the estimate is based is provided below each mean estimate

Discussion

There are no former reports on the explicit effect of STN-DBS and cZi-DBS on voice frequency characteristics in connected speech for treated PD patients. The data presented here show a differentiated effect of DBS depending on implantation site. For STN-DBS treated patients, the results provided evidence of patients being more variable in their pitch and using a larger pitch range during connected speech for on stimulation compared to off stimulation recordings. Thus, support is provided for viewing STN-DBS as highly beneficial in supporting potential increases in prosodic expressiveness in patients, reducing the perceived monopitch quality in patients' speech. However, the two speakers who were treated with unilateral (left) STN-DBS do not appear to show the same positive treatment effect as the bilaterally treated patients. This is in agreement with what would be expected from earlier suggestions that lateralization of pitch processing occurs primarily in the right hemisphere (Belin et al., 1998; Sidtis, 1980; 1981; Van Lancker Sidtis et al., 2006; Zatorre et al., 1992; Zatorre & Belin, 2001), and consequently that pitch variability is enhanced primarily by right hemisphere STN-DBS.

No dependence on the prosodic nature of the utterance was found in the data. There were no significant differences in the observed DBS-induced effects between utterances with relatively small expected variation (statements) compared to utterances where larger pitch variation would be expected (dual-voiced utterances). Rather, the effect on pitch variability and range is that voice characteristics of STN-DBS patients are enhanced on a global level, reducing the monopitch property described in the literature for patients with PD. It should be noted that the speech

material used here was a group of utterances extracted from readings of a standard reading passage. While this affords a comparison of similar samples across conditions, it may not be directly transferable to a spontaneous speech context (e.g. Kempler & Van Lancker, 2002). However, as a large range of intonational contours and pitch range and variability levels are featured in the speech material, it is argued that the material does afford an interpretation of patients' proficiency to vary pitch in continuous speech.

A positive effect of treatment in terms of reduced monopitch quality was, however, not observed in cZi-DBS treated patients. There were no beneficial effects on either pitch range or pitch variability under cZi-DBS. Indeed, the observation of a decreased tendency in pitch variability and range in cZi-DBS Post-op off stimulation recordings compared to Pre-op recordings is the only treatment effect observation afforded by the present data. Possible underlying causes for this decline include disease progression over the 12 months post surgery, persistent microlesional effects due to DBS surgery (Fytagoridis & Blomstedt, 2010; Rezai et al., 2006) or the effect of a reduction of levodopa level administered in the post-surgical condition. The separation of these possible underlying causes is, however, not afforded by the literature or the current research design, and should be targeted by further research.

The combined results support the conclusion that STN-DBS has a positive impact on patients' ability to produce a varied pitch. This study, therefore, corroborates the findings of previous studies reporting treatment outcomes of STN-DBS in terms of reducing the monopitch quality of PD patients' speech (Alatri et al., 2008; Dromey et al., 2000; Gentil et al., 2001; Hoffman-Ruddy et

al., 2001). For cZi-DBS, no such positive effect on pitch variability was observed in our data. Thus, while it may still be the case that limb motor function might be more effectively treated by cZi-DBS than STN-DBS (Plaha et al., 2006), this treatment advantage is not extended to the production of a varied pitch. The present investigation suggests that STN-DBS is superior to cZi-DBS in terms of reducing the presence of a monopitch quality in speech of PD patients.

Conclusion

This paper has provided evidence of a DBS-induced increase in f_0 range and variability in connected speech for bilateral STN-DBS patients on stimulation that is not observed for bilateral cZi-DBS patients. Thus, the data suggests that STN-DBS is superior to cZi in reducing the monopitch quality in speech of PD patients. Our results must, however, be interpreted with caution, as they are based on a limited number of patients in each treatment group and a controlled speech task.

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