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Laryngeal control in Parkinson patients following deep brain stimulation of the
subthalamic nucleus and caudal zona incerta

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Short title: Laryngeal control in Parkinson's patients under DBS treatment

Abstract

Laryngeal hypokinesia is a common symptom in Parkinson's disease (PD) affecting quality of life. Deep brain stimulation (DBS) is well recognized as a complementary method for treatment of motor symptoms in PD but the outcomes on laryngeal control have yet not been clearly elucidated. The present study examined the effect of caudal Zona incerta (cZi)-DBS (n=8, aged 51-72 yrs; median=63 yrs) and subthalamic nucleus (STN)-DBS (n=8, aged 49-71 yrs; median=61 yrs) on control on onset and offset of phonation in fluent speech. The patients were evaluated in a preoperatively (Med ON, 1.5 times the ordinary Levodopa dose) and 12 months postoperatively (Med ON, ordinary Levodopa dose). The results provided evidence of a progressive reduction in the ability to manifest alternations between voicing and voiceless states in fluent speech. Mean portion produced with inappropriate voicing increased from 47.6% to 55.3% and from 62.9% to 68.6% of the total duration for the two groups of patients between Pre-op and Post-op, Stim OFF registrations. The medial and final parts of the fricative was more affected than the initial part, indicating an increased voicing lead into the following vowel. We propose this reduction in laryngeal control is be due to either progression of the disease or an effect of reduction of administered Levodopa dosage. Patients' proficiency in alternating between voiced and voiceless states in fluent speech remained unaffected by both STN-DBS and cZi-DBS.

Introduction

Laryngeal hypokinesia, rigidity and resistance are well attested features of Parkinson's disease (PD) (e.g. [1-3]). An increased mean thyroarytenoid (TA) muscle activation and laryngeal somatosensory deficits has been observed for PD patients compared to age matched controls [4-6]. As a consequence, PD patients often make segmental voicing errors when speaking [6], which has been indicated as an important source of reduced intelligibility of speech in dysarthric patients [7-9].

Treatment of patients' onset and offset control of phonation is afforded by both pharmacological and surgical treatment options. Laryngeal functioning is improved with clinically optimized Levodopa medication by a reduction the TA hypertonicity in patients where hypertonicity is seen as an effect of PD[2]. Surgical treatment using *low* frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been shown to increase patients' proficiency in achieving vocal fold closure in simple speech tasks [10]. No previous report have however investigated the combined effect of STN-DBS and Levodopa on laryngeal on- and offset in PD patients' connected speech.

Regarding DBS in the cZi and adjacent areas, promising results have been presented for motor effects [11-16] and it has been suggested as a possibly more effective target than the STN on axial symptoms of PD [17]. The effects of cZi-DBS on speech are, however, largely unknown, with the exception of two previous reports from our group, indicating it to be less beneficial to intensity and articulation rate and precision in articulatory coordination than STN-DBS [18,19]. A comparative account of treatment effects of cZi-DBS and STN-DBS on the laryngeal onset and offset control in speech has, however, not been previously provided.

The present investigation aimed at investigating the laryngeal motor proficiency needed for regulating phonation in fluent speech in patients treated with either STN-DBS or cZi-DBS.

Method

Patients

Sixteen patients (12 males and 4 females, aged between 49 and 72 years) with idiopathic PD were included in this prospective non-randomised study. Eight patients were implanted in the STN (six bilateral and two left side unilateral), followed by eight implanted bilaterally in the cZi. The patients had been selected on clinical grounds for DBS surgery. An overview of the patients is presented in Table 1. These patients have participated in studies on other aspects of speech after cZi-DBS and STN-DBS [18,19].). The study has been approved by the Regional Ethical Review Board in Umeå (Dnr: 08-093M: 2008-08-18).

Surgical procedure

The surgical procedures for the respective targets have been previously described in detail [20]. Targets and trajectories were identified on MRI using the Frame Link planning station (Medtronic, Minneapolis, MN, USA). In the STN the target was chosen at a line connecting the anterior borders of the red nuclei, at the level of their maximal diameter, 1.5 mm lateral of the medial border of the STN. The target in the posterior subthalamic area was chosen at the same level and slightly posterior-medial to the STN. The electrode implantation was performed in local anesthesia and the effect was evaluated using macro stimulation. A stereotactic CT was performed during surgery and the images were fused with the preoperative MRI for identification of the electrode position.

Procedure

All patients were evaluated pre- as well as post-operatively 12 months after DBS. In all

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4 preoperative assessments, patients were examined with PD medication 1.5 times the normal
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6 dose. The postoperative evaluations were performed within the optimal time in the patients'
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8 medication cycle under two conditions: stimulator off (Stim OFF) and stimulator on (Stim ON)
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10 for 60 minutes before recording. In all recordings reported on here, patients were in a Med ON
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15 16 **Speech material**

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18 The speech material used in this study was extracted from readings of an 89 word
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20 standard Swedish passage. Recordings were made in a sound-treated booth, using a calibrated
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22 head-mounted microphone (Sennheiser MKE 2 P-C), with a 15 cm mouth to microphone
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24 distance. The samples were recorded on a digital audio flash recorder (Marantz PMD 660) or in
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26 the case of some early recordings a digital audio tape recorder (Panasonic SV 3800) in a 44.1 or
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28 48 kHz sampling rate. A calibration tone (80 dB, 1 kHz) was used at the beginning of each
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30 recording in order to afford normalized comparisons of the acoustic signals.
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34 35 **Phonetic analysis**

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37 In total, 91 readings of the standard text were submitted to a phonetic markup procedure.
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39 All intended productions of voiceless fricatives with an oral constriction produced between two
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41 segments with continuous voicing were included into the study. For each included consonant,
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43 start and stop times as well as the intended target were transcribed manually. In total, 1983
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45 attempted fricative consonant productions were transcribed and extracted for further analysis. An
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47 overview of the number of fricatives extracted for each condition and fricative is presented in
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49 Table 2. Glottal voiceless fricative targets ([h]) were excluded from measurements, as they are
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51 often fully voiced in inter-vocalic position in normal speakers and therefore would not provide
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53 evidence of changes in laryngeal control in the patients.
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59 60 **Acoustic analysis**

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The fricatives extracted were submitted to an acoustic analysis for the presence of voicing during the fricative using custom program in the Praat software package [21] (version 5.2.38). Estimates of voicing were extracted at 20 equally spaced intervals (“frames”) for each produced fricative using the autocorrelation algorithm (75-600Hz range). Those frames where a pitch value could be obtained were marked as voiced in the analysis and frames where pitch was not defined were marked as voiceless.

Based on the estimated number of voiced frames, two types of summary metrics were computed. First, the “percent voiced” (PV) metric was calculated as the number of voiced frames divided by the number of frames analyzed. Thus, the PV metric provided an estimate of how much of the fricative was produced with vocal fold vibration.

Second, the duration of the fricative was divided into three parts: initial (the first seven frames), medial (the next six frames) and final (the remaining seven frames). For each part, the number of voiced frames was divided by the total number of frames in the part, constituting three new quantities (“Initial third”, “Medial third” and “Final third”). The resulting quantities were designed to afford separate analysis of effects on proficiency in pausing vocal folds vibration in preparation for initializing the fricative, or starting vocal fold vibration following the fricative.

Statistical analysis

The PV metric for attempted voiceless fricative productions were submitted to between-within analyses of variance (ANOVA) testing in terms of main effects of time of recording (Pre-op or 12 months Post-op), stimulation (Stim OFF or Stim ON) and stimulation target (STN or cZi). Post-hoc testing of found main effects and interactions were conducted using the Tukey’s Honest Significant Differences (Tukey HSD) procedure. Group effects were confirmed using

non-parametric Kruskal-Wallis rank sum tests. Pre-op condition was compared with the Post-op condition with stimulation turned off (Stim OFF) within each patient group. Comparisons between the two stimulation conditions (Stim OFF and Stim ON) were made only based on the Post-op recordings. All statistical testing was conducted using the R software environment for statistical computing [22].

Results

The statistical testing provided evidence of a significantly higher mean PV in cZi and STN patient groups in Preop recordings ($F(1,1120)=67.1, p<0.001$). Mean PV was 66.4% (SD=26.3) for the cZi group, and 48.8% (SD=28.9) for the STN group, indicating that the cZi group was more affected by voicing spread than the STN group Pre-op, but with an increased medication dosage (see Figure 1).

The results further indicate an increased PV between the Pre-op condition and the 12 month follow up in the Stim OFF condition ($F(1,1120)=10.36, p<0.01$). This was significant (Tukey HSD testing at the 0.05 level) increase in mean PV was observed (Figure 1) for both groups. Further investigation into where the fricative voicing was applied showed increased occurrence predominately in the medial ($F(1,1120)=2.70, p<0.05$) and final parts ($F(1,1120)=2.8, p<0.05$) of the fricative for STN-, and in the final part for cZi patients ($F(1,862)=3.76, p<0.05$). The increase in of erroneously applied voicing leading into the following voiced segment in Post-op off stimulation recordings was greater in the STN group.

No effect of DBS treatment was found voicing of voiceless fricatives in any of the two

groups of patients. The Post-on Stim OFF and Stim ON data showed no main effect of stimulation on the use of voicing in either parametric ANOVA testing ($F_{(1,591)}=1.30, p=0.26, n.s.$; $F_{(1,591)}=0.04, p=0.87, n.s.$) or non-parametric testing using Kruskal-Wallis rank sum tests ($\chi^2=0.91, p=0.34, n.s.$; $\chi^2=0.04, p=0.87, n.s.$). Further, confidence intervals presented in Figure 1 show a substantial overlap in all sub-parts of the duration of the fricative, confirming that treatment effects due to DBS is not observed in the data.

While no treatment effects were observed, the results indicate overall differences in voicing distribution across the three parts of the fricative. The initial part of the fricative was found to be significantly less voiced than the medial and final part of the fricative ($F_{(2,5100)}=490, p<0.001$) for both groups (Figure 2). No significant differences were found between the medial and final part of the fricative in terms of percent of duration where voicing was applied.

Discussion

There are no former reports on laryngeal control in continuous speech produced by PD patients under DBS. The present investigation aimed at determining whether the laryngeal control in speech is affected in PD patients when under STN- or cZi-DBS.

The results showed a significant difference between the Pre-op and the Post-op recordings under identical stimulation condition (no stimulation/Stim OFF). There was a clear-cut increase in spreading of voicing into the voiceless fricative from surrounding segments in the 12 month Post-op condition (Stim OFF). The data suggests that the later parts of the fricative is

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4 more affected than the initial parts.
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9 Due to clinical considerations and to the nature of PD, the finding of a decrease in
10 laryngeal control in the Post-op conditions affords two different interpretations. First, the
11 spreading of voicing could be due to the reduction in Levodopa, since the Pre-op Med ON
12 condition was higher in the Post-op condition. This interpretation of the results is in line with a
13 previous study showing increased proficiency in regulating voicing on-, and offset in Med ON
14 compared to Med OFF [2]. Any changes in the patients medication or stimulation settings were
15 initiated and motivated by the clinical situation, as judged by a neurologist and not based on
16 systematic studies.
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31 Second, the reduction in laryngeal control in the Post-op (Stim OFF) condition could be
32 an effect of 12 months of disease progression. This interpretation is in line with previous
33 research showing decreases in laryngeal control with disease severity [6]. The degradation in
34 laryngeal control seen predominately in the longer voicing leads into the following voiced
35 segment at 12 month Post-op (Stim OFF) registrations in both STN and cZi patients may be an
36 effect of the disease progression, possibly combined with the effect of reduction in Levodopa
37 dose.
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51 The decrease in laryngeal control was not affected by DBS in STN or cZi. No difference
52 was found between the Stim ON and the Stim OFF condition in terms of percent voicing
53 produced in voiceless fricatives surrounded by voiced continuant segments. In addition, no
54 differences were observed in the separate comparisons of the initial, medial and final parts of the
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4 produced fricatives. Thus, the data shows no evidence of STN-DBS or cZi influence on laryngeal
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6 control.
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10 11 **Conclusion**

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14 This paper has demonstrated a progressive reduction in the ability to manifest alternations
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16 between voicing and voiceless states in fluent speech in a group of PD patients. We propose that
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18 this reduction in laryngeal control may be due to either progression of the disease or an effect of
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20 reduced Levodopa dosage level administered. No significant influence of STN-DBS or cZi-DBS
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22 was observed.
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30
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32 ndation and
33
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37
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Figure Captions

Table 1: Characteristics of patients in the two surgical groups. Mean age and median Unified Parkinson's disease rating scale motor scores (UPDRS-III) in the Pre-op registrations are provided. There were no statistical differences between the groups for age, duration since diagnosis, or any of the reported UPDRS-III scores.

Table 2: Overview of the manually transcribed voiceless fricatives included in the study. The total number of each fricative consonant type is provided for each condition: preoperative

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4 recording (Pre-op) and 12 months postoperative recording made with and without stimulation for
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6 each treatment group.
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14 Figure 1: Mean percentage of the duration of attempted productions of voiceless fricatives that
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16 were produced with voicing for the two groups of patients. For each estimated mean value, the
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18 confidence interval is indicated using error bars and the number of observations on which the
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20 estimate is based is provided below each mean estimate.
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26 Figure 2: Mean percentage of the duration of attempted productions of voiceless fricatives
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28 produced with voicing in the initial, medial and final part of the consonant for each patient
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30 group. For each estimated mean value, the confidence interval is indicated using error bars and
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32 the number of observations on which the estimate is based is provided below each mean
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Table 1

Characteristic	STN patients (n=8)	cZi patients (n=8)
Age (Pre-op), years	63.0 ± 7.9 (51-72)	60.8 ± 9.0 (49-71)
M/F	6/2	6/2
Unilateral/bilateral	6 bilateral/2 unilateral (left side)	8 bilateral
Duration since diagnosis, y	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)

Table 2

		Fricative			
Target	Condition	[f]	[s]	[ʃ]	Total
STN	Pre op	78	154	10	242
	Stim OFF	108	225	15	348
	Stim ON	117	235	16	368
cZi	Pre op	110	223	16	349
	Stim OFF	112	226	14	352
	Stim ON	104	208	12	324
	Total	629	1271	83	1983

Figure 1

Figure 2

Percent voiced of total duration