Voice Tremor Outcomes of Subthalamic Nucleus and Zona Incerta Deep Brain Stimulation in Patients With Parkinson Disease

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Summary: Objectives: We aimed to study the effect of deep brain stimulation (DBS) in the subthalamic nucleus (STN) and caudal zona incerta (cZi) on level of perceived voice tremor in patients with Parkinson disease (PD).
Study Design: This is a prospective nonrandomized design with consecutive patients.
Methods: Perceived voice tremor was assessed in patients with PD having received either STN-DBS (8 patients, 5 bilateral and 3 unilateral, aged 43.1−73.6 years; median = 61.2 years) or cZi-DBS (14 bilateral patients, aged 39.0−71.9 years; median = 56.6 years) 12 months before the assessment. Sustained vowels that were produced OFF and ON stimulation (with simultaneous L-DOPA medication) were assessed perceptually in terms of voice tremor by two raters on a four-point rating scale. The assessments were repeated five times per sample and rated in a blinded and randomized procedure.
Results: Three out of the 22 patients (13%) were concluded to have voice tremor OFF stimulation. Patients with PD with STN-DBS showed mild levels of perceived voice tremor OFF stimulation and a group level improvement. Patients with moderate/severe perceived voice tremor and cZi-DBS showed marked improvements, but there was no overall group effect. Six patients with cZi-DBS showed small increases in perceived voice tremor severity.
Conclusions: STN-DBS decreased perceived voice tremor on a group level. cZi-DBS decreased perceived voice tremor in patients with PD with moderate to severe preoperative levels of the symptom.
Key Words: Voice tremor−Parkinson disease−DBS−STN−cZi.

INTRODUCTION

Parkinson disease (PD) is a neurodegenerative condition where the balance between basal ganglia signaling pathways is disrupted[1] because of the loss of dopaminergic projections from the substantia nigra to the striatum.[2,3] As a result, various forms of tremor, such as resting tremor,[4] action tremor,[5] and postural tremor,[4] may be observed in patients. The tremor patterns observed in patients with PD are predominately asymmetrical and have cycle frequencies of between 4−6 Hz (resting tremor) and 5−12 Hz for postural tremor. Head and neck regions are generally not affected by PD tremor[6−8] but the jaw is often affected.[9] Of patients with PD, 65%−89% report voice impairment and as many as 55%−64% have been assigned with audible voice tremor of true phonatory/laryngeal origin.[10]

Voice tremor may be caused by tremor in one of the respiratory, phonatory, and articulatory voice production subsystems, and this imposes specific challenges for classification as well as selection of putative treatment of the symptom. Selective tremors in the larynx have been reported to respond well to locally deposited botulinum toxin,[5] but such symptomatic treatment may not be as easily targeted at other locations. Surgical treatment with deep brain stimulation (DBS)[11] is a viable symptomatic treatment for patients with tremor-dominant PD with declining response to pharmacological treatment and functionally disabling motor disturbances.[12] The ventral intermediate thalamic nucleus of thalamus and the subthalamic nucleus (STN) remains the most frequently used targets for treatment of PD symptoms, but regions in the posterior subthalamic area, including the prelemniscal radiations[13] and caudal zona incerta (cZi), have recently been highlighted as alternative targets.

Although speech outcomes of both STN and cZi-DBS have received considerable attention in reports from the last 10 years,[14−17] evaluations of possible voice production effects are less frequent. The few available reports indicate that STN-DBS reduce perceived voice tremor severity,[18] glottic tremor frequency,[19] and the acoustic perturbation measure jitter.[20] The effect of cZi-DBS on voice tremor has not been studied in patients with PD, but a recent evaluation of patients with essential tremor who received cZi-DBS indicated that 6 out of 13 patients (46%) with perceived voice tremor OFF stimulation showed a marked improvement due to cZi-DBS.[21] Hawkshaw and Sataloff[22] recently proposed that STN-DBS may be a successful treatment option for carefully selected patients. Whether neurogenic voice disorders should be considered an indication for DBS surgery remains an open question that will require further research. However, the positive outcomes of DBS treatment on perceived voice tremor in patients with essential tremor raises the question whether surgical treatment by DBS may affect the audible voice tremor also in patients with PD, and, if so, which target is best suited

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TABLE 1.
An Overview of the Age and Gender Distribution of Patients With PD in STN- and cZi-DBS, as Well as the Number of Patients That Received Unilateral and Bilateral Stimulation

Characteristics	STN Patients (n = 8)	cZi Patients (n = 14)
Median age, age ranges in years	61.2 (43.1–73.6)	56.6 (39.0–71.9)
Gender	5 Males, 3 females	11 Males, 3 females
Bilateral/unilateral	5 Bilateral/3 unilateral (left)	14 Bilateral

for optimal treatment with minimized side effects. The purpose of the present report was therefore to describe and compare the effects of STN-DBS and cZi-DBS treatments on perceived voice tremor in patients with PD.

METHODS

Patients

Voice recordings from 22 patients with PD under clinical evaluation for treatment with DBS were included in the study. Patients were selected for DBS surgery based on clinical assessment of overall motor function. Voice function was not considered in the selection process. An overview of the patients' characteristics is shown in Table 1. Eight patients had undergone STN-DBS and 14 cZi-DBS. Three subjects in the STN-DBS group received unilateral implants (left side), whereas the remaining patients with PD had bilateral implants. The patients were evaluated within the optimal time in the patient's usual medication cycle, with stimulation both ON and OFF. All patients received DBS surgery by the same neurosurgeon (PB) at the DBS unit of the University Hospital, Umeå. All evaluations were performed within the optimal time in the patient's usual medication cycle. Participants had given their consent for participation in the research project. The study has been approved by the Regional Ethical Review Board in Umeå (Dnr: 08-093M: 2008-08-18).

Material and recording procedure

The assessed material consisted of sustained vowel productions recorded 12 months postoperatively using the Kay Elemetrics *Computer Speech Lab* system. Two productions of each vowel (/a/, /i/, and /u/) were recorded OFF stimulation and ON stimulation approximately 1.5 hours later. An overview of the material submitted to the perceptual assessment procedure is presented in Table 2. The number of vowel productions assessed was balanced across patients.

TABLE 2.
An Overview of the Number of Sustained Vowel Productions Analyzed for STN- and cZi-DBS ON and OFF Stimulation

	Number of Analyzed Productions		
Patient Group	Stim OFF	Stim ON	Total
STN	48	48	96
cZi	84	84	168
Total	132	132	264

Assessment procedure

Blinded and repeated assessments of voice tremor in the sustained vowel productions were performed separately by two raters in a randomized and blinded procedure. The perceived level of voice tremor in the sample was rated on a four-point scale (0 = No tremor, 1 = Mild tremor, 2 = Moderate tremor, 3 = Severe tremor) with an additional "Don't know" option. The two raters assessed each vowel production five times, resulting in 2640 performed assessments. The rating option "Don't know" was used 24 times; these ratings were excluded in subsequent analyses. The randomization, blinding, and presentation of stimuli were performed using the *Alvin2* stimulus presentation software package.[17] Dysarthria or voice problems other than voice tremor were not addressed.

Data analysis

Voice tremor assessments were averaged within patient and produced vowel type (/a/,/i/,/u/) and compared across stimulation conditions (stimulation OFF or ON) using the Wilcoxon signed-rank test. The STN and cZi patient groups were tested separately. Statistical testing was performed using *SPSS* version 22, using an α level of 0.01. Effect sizes for significant effects of DBS stimulation were calculated as $r = Z/\sqrt{N}$ for which $|r| \geq 0.5$, $|r| \geq 0.3$, and $|r| \geq 0.1$ were considered large, medium, and small effect sizes, respectively.[23]

Reliability

Inter-rater reliability was evaluated using Goodman and Kruskal gamma based on all ratings, and showed a significant agreement between raters ($\Gamma = 0.717$, $P < 0.001$). Intra-rater reliability was assessed using intraclass correlation coefficients (ICCs) and showed a significant agreement between the five different rating sessions for the two raters (ICC = 0.786, $P < 0.001$; ICC = 0.705, $P < 0.001$).

RESULTS

Figure 1 presents an overview of each patient's average perceived voice tremor ratings OFF and ON stimulation. Group-level comparison of perceived voice tremor in patients with STN showed a significant reduction in voice tremor at ON stimulation compared to at OFF

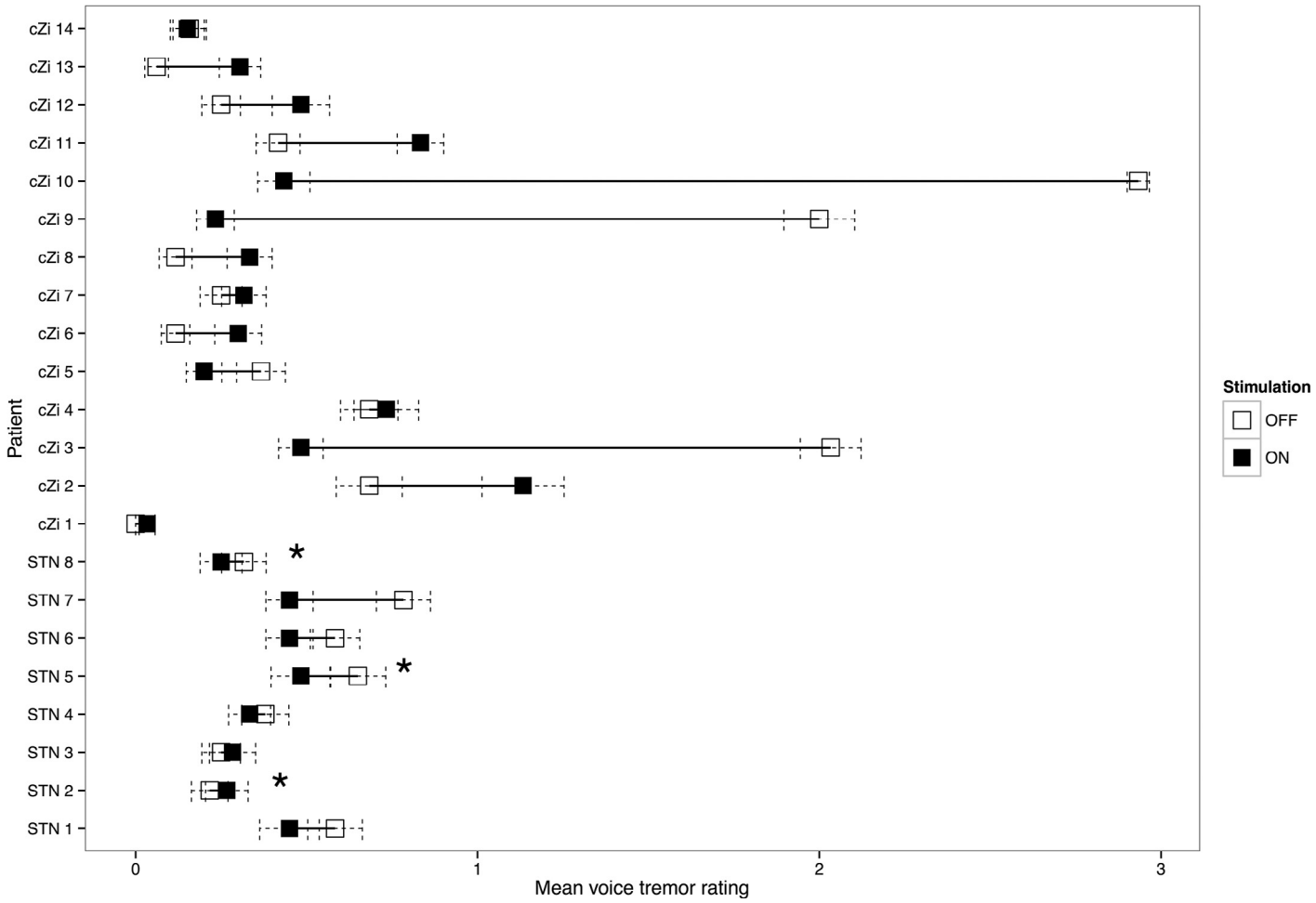

FIGURE 1. Perceived voice tremor ratings for all patients with PD OFF and ON stimulation. The average across 60 ratings of voice tremor is indicated for each patient, along with the standard error of the mean (error bars). Results for patients with PD with unilateral stimulation is indicated by filled circles and bilateral stimulation is indicated using filled squares.

($Z = -3.994$, $P < 0.001$, $r = -0.58$). A significant reduction in perceived voice tremor was also observed within each assessed vowel type when analyzed separately (/a/: $Z = -2.249$, $P = 0.025$, $r = -0.33$; /i/: $Z = -2.446$, $P = 0.014$, $r = -0.35$; /u/: $Z = -2.315$, $P = 0.021$, $r = -0.33$). Reduced voice tremor ratings were observed in six out of eight patients with STN and both in unilaterally and bilaterally operated patients. Voice tremor was more prominent in patients who had received a bilateral implantation and therefore also showed a stronger effect of STN-DBS (Table 3).

In contrast, the analyses of the cZi group failed to indicate a significant group level effect on perceived voice tremor ($Z = -1.220$, $P = 0.223$). Likewise, no effects of

TABLE 3.
Effect of STN-DBS and cZi-DBS Treatment in Patients With PD Without Perceived Voice Tremor (Average Voice Tremor Rating <1, NVT) and in Patients With PD With Perceived Voice Tremor (Average Voice Tremor Rating ≥1, VT) in the OFF-Stimulation Session

	Voice Tremor Group	Average Difference in Ratings ON Compared to OFF	Average % Change in ON Compared to OFF
STN-DBS			
Unilateral DBS	NVT	−0.1	−2.0%
Bilateral DBS	NVT	−0.1	−4.1%
cZi-DBS			
Bilateral DBS	NVT	0.2	5.2%
Bilateral DBS	VT	−1.9	−64.6%

stimulation was observed within any of the individual vowels (/a/: $Z = -0.634$, $P = 0.526$; /i/: $Z = -1.157$, $P = 0.247$; /u/: $Z = -0.358$, $P = 0.720$). However, upon inspection of Figure 1, two subgroups of patients were identified in the cZi-DBS treatment group: patients with moderate to severe levels of perceived voice tremor OFF stimulation (VT) and patients who were not perceived to have voice tremor OFF stimulation (NVT). Patients in the VT subgroup had an average voice tremor rating ≥1. Separate evaluation of the effect of cZi-DBS in the VT and NVT treatment groups indicated substantial reduction in perceptual voice tremor at ON stimulation [x = 0.38 (0.23−0.48)] compared to OFF stimulation [x = 2.3 (2.0−2.9)] for the three patients in the VT group (cZi 3, 9, and 10). An overview of the effects of cZi-DBS treatment for the VT and NVT subgroups of patients is shown in Table 3. The reduction in perceived voice tremor for these three patients (64.6%) was shown to be significant when analyzed separately ($Z = -8.5174$, $P < 0.001$, $r = -2.01$).

DISCUSSION

This report constitutes the first evaluation cZi-DBS effects on perceived voice tremor in patients with PD, as well as the first simultaneous evaluation of such effects of cZi-DBS and STN-DBS. Patients were assessed for perceived voice tremor severity 12 months after surgery in 2 conditions (OFF and ON stimulation).

The main finding of the present study was that DBS-STN alleviates the perceived voice tremor in patients with PD with moderate to severe levels of the symptoms. This corroborates earlier reports,[18−20] which likewise have shown beneficial effects of DBS-STN.

The overall prevalence and degree of severity of voice tremor OFF stimulation differed between the two treatment groups. Patients in the STN-DBS treatment group had mild levels of perceived voice tremor on average OFF stimulation, and the possibility to show substantial improvement due to treatment was therefore limited. However, the patients in this group were more often rated as having no perceived voice tremor ON stimulation compared to OFF stimulation. The effect was observed to be large on a group level and moderate when assessed within the produced vowel, indicating a consistent finding of a reduced perceived voice tremor in patients with STN-DBS. There were no discernible differences between bilateral and unilateral STN-DBS in perceived voice tremor outcomes. We did not perform an acoustic evaluation in the present report, but the results are consistent with the previous report indicating decrease in perceived voice tremor during STN-stimulation.[20] Therefore, our results lend further support to the conclusion that STN-DBS is effective in reducing perceptual perceived voice tremor in patients with PD.

Compared to the STN-DBS results, the evaluation of patients with cZi-DBS indicated more mixed effects in terms of perceived voice tremor outcomes. In contrast to the STN-DBS group, the cZi-DBS group included patients with severe levels of perceived voice tremor when OFF stimulation. These patients showed marked improvements in perceived voice tremor severity due to cZi-DBS. Patients with only mild voice tremor levels OFF stimulation, however, showed highly variable effects of cZi-DBS and no consistent finding.

Voice tremor outcomes of cZi-DBS have not been assessed in patients with PD. One previous study did, however, evaluate patients with cZi-DBS with essential tremor using a comparable assessment methodology.[22] Hägglund et al[21] reported that 92% of the patients with essential tremor with severe initial perceptual voice tremor (50% of the patients) improved after cZi-DBS, which is in clear agreement with the outcome of the results reported here. Across both studies, 1 out of 16 patients (6%) with moderate to severe levels of perceived voice tremor was not improved by cZi-DBS. Because cZi-DBS has a well-documented effect on PD on postural tremor, we expect a reduced voice tremor if the perceived voice tremor might be driven by a postural tremor. A limitation of the current study, however, is that the protocol by which voice samples were recorded did not include simultaneous registrations of the respiratory, laryngeal, and articulatory tremor. It is thus not possible to determine the source of the voice tremor, a notion which could have important clinical relevance for the clinical handling of a patient. However, taken together with previously reported data, our findings suggest that cZi-DBS may be an effective treatment for patients with moderate to severe levels of perceived voice tremor. Patients with less severe levels of voice tremor preoperatively may not show as favorable results from cZi-DBS treatment.

The methodology used in the current study was designed to control for confounding factors and bias using repeated and blinded assessments of more than one rater. The effect of STN-DBS was found to be medium to large in the studied patients, but the statistical power of the study should be regarded as low. Therefore, the results demand replication before they are transferred into clinical considerations.

CONCLUSION

The results showed a consistent reduction of perceived voice tremor in PD with STN-DBS 12 months postoperatively. Patients with moderate to severe levels of voice tremor were improved by cZi-DBS treatment, but showed more variable effects of treatment across the entire group of patients.

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