Voice Tremor Response to Deep Brain Stimulation in Relation to Electrode Location in the Posterior Subthalamic Area

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BACKGROUND: **Deep brain stimulation of the motor thalamus or the posterior subthalamic area (PSA) shows promising results for patients with voice tremor, although only for about 50% of patients. There are indications that voice tremor requires more focused stimulation within the target area compared with hand tremor. The objective of the present study was to determine the most efficient location for reducing voice tremor within the PSA.**

METHODS: **Thirty-seven patients with essential tremor were evaluated off stimulation and in a set of experimental conditions with unilateral stimulation at increasing amplitude levels. Two listeners performed blinded assessments of voice tremor from recordings of sustained vowel productions.**

RESULTS: **Twenty-five patients (68%) had voice tremor. Unilateral stimulation reduced voice tremor for the majority of patients, and only 6 patients had poor outcomes. Contacts yielding efficient voice tremor reduction were deeper relative to the midcommissural point (MCP) and more posterior relative to the posterior tip of the subthalamic nucleus (pSTN) ($z^{MCP} = -3.1$, $y^{pSTN} = -0.2$) compared with poor contacts ($z^{MCP} = -0.7$, $y^{pSTN} = 1.0$). High-amplitude stimulation worsened voice tremor for 7 patients and induced voice tremor in 2 patients. Hand tremor improved to a greater extent than voice tremor, and improvements could be seen throughout the target area.**

CONCLUSIONS: **Our results indicate that efficient voice tremor reduction can be achieved by stimulating contacts located in the inferior part of the PSA, close or slightly posterior to the pSTN. We observed cases in which voice tremor was induced by high-amplitude stimulation.**

INTRODUCTION

Voice tremor is challenging to treat. Deep brain stimulation (DBS) is arguably the most promising treatment alternative for patients with voice tremor,[1] yet about 50% of patients treated with DBS have voice tremor symptoms that remain virtually unaffected by stimulation, whereas others have a good effect of the treatment.[2-4] Why voice tremor outcomes after DBS differ between patients to such an extent is unclear, but a few suggestions have been put forward. One common assumption is that bilateral stimulation is needed to alleviate voice tremor[1]; however, this assumption is now being challenged by reports showing that unilateral stimulation may indeed be as effective as bilateral.[5-7] More recently, the importance of electrode location and the field of stimulation within the target area has been highlighted for voice tremor. Matsumoto et al.[3] investigated the effects of bilateral DBS in the ventral intermediate nucleus (Vim) in 18 patients with essential tremor (ET). They found that voice tremor persisted in patients if the stimulation volume spread outside the Vim. The same effect was not observed for hand tremor. The authors concluded that voice tremor may require more focused stimulation compared with hand tremor,[3] and thus that voice tremor may be more difficult to target by DBS.

Key words
- Caudal zona incerta
- Deep brain stimulation
- Electrode location
- Essential tremor
- Posterior subthalamic area
- Voice tremor

Abbreviations and Acronyms
AC-PC: Anterior and posterior commissures
cZi: Caudal zona incerta
DBS: Deep brain stimulation
ET: Essential tremor
ICC: Intraclass correlation coefficient
M: Mean
MCP: Mid-commissural point
PSA: Posterior subthalamic area
pSTN: Posterior tail of the subthalamic nucleus
SD: Standard deviation
Vim: Ventral intermediate nucleus of the thalamus

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The neuroanatomical target of interest for the current report lies below the Vim, within the posterior subthalamic area (PSA)/caudal Zona incerta (cZi). The cZi is an emerging target for ET, and we have previously shown that cZi-DBS may be effective for voice tremor symptoms with, however, large individual variations in outcome.[2] In our previous investigation, we did not analyze voice tremor outcomes in relation to electrode location, and although electrode location within the PSA has been analyzed regarding tremor before,[8] the focus has never been on voice tremor specifically.

The purpose of this study was to determine the most efficient location for reducing voice tremor within the PSA. To do this, we investigated how voice tremor responded to unilateral cZi stimulation at different stimulation amplitudes in patients with ET and related the results to the specific locations of electrodes.

MATERIAL AND METHODS

Participants

All patients previously undergoing surgery for ET with cZi-DBS at Umeå University Hospital with a minimum follow-up of 12 months were invited to participate in the current study ($n = 52$). Eight patients declined participation, 4 patients were unable to participate due to other unrelated diseases, 2 patients died before data could be collected, and 1 patient chose to no longer participate. Patient characteristics for the remaining 37 patients (17 women, 20 men) are presented in Table 1. The study was approved by the Regional Ethical Review (Dnr: 2014-67-32M). Written informed consent was obtained from all participants.

Electrode Location

The patients recruited to this study had been previously implanted in the cZi. The surgical procedure has been described in detail previously.[9] The brain target was identified anatomically on stereotactic thin slice T2-weighted axial magnetic resonance images. The target point lay slightly posteromedial to the visualized posterior tail of the subthalamic nucleus (pSTN) on the scan showing the maximal diameter of the red nucleus (Figure 1). The Vim was not targeted and the trajectory was not intentionally adapted so as to pass through the atlas target in the Vim. An intraoperative stereotactic computed tomography scan was performed and fused with the preoperative stereotactic magnetic resonance imaging for verification of the electrode position. All procedures were performed by the same surgeon (P.B.). Microelectrode recording was not performed.

Recording Procedure

Two sustained vowels/a/were recorded at up to 11 different stimulation settings according to a recording protocol previously reported in detail.[5] In the present study, we used sustained vowels produced off stimulation and at unilateral stimulation with increasing stimulation amplitudes, from 0.5V up to 4.5V in 0.5-V increments. A single contact was active on stimulation, i.e., the contact that had the best effect on contralateral hand tremor with the largest therapeutic window in the 12-month evaluation. Frequency and pulse width remained fixed at 140 Hz and 60 μs, respectively. For bilateral patients, the electrode for the hand dominant side was active with the other electrode turned off. See Table 1 for an overview of stimulation parameters used for the individual patients. A 60-minute washout period was introduced before recording patients off stimulation. A 5-minute pause was introduced before beginning each recording on stimulation. Patients treated with tremor-reducing medication refrained from taking their medication on the day of recording. The procedure took place in a single session and lasted for approximately 2 hours.

Perceptual Assessment

The first second of each vowel production was cut from the sample to remove the perceptual effect of an overly forceful start of phonation. Assessments were based on the following 3 seconds of each vowel. Two raters (authors L.S. and F.K.) independently rated voice tremor using the Visual Sort and Rate methodology,[10] which facilitates blinded ratings on a visual analogue scale (0–1000). All vowels produced by a patient were presented to the raters on a computer screen. Three anchor stimuli (positioned at 100, 150, and 650 mm, respectively) were used to provide external references for the rating scale. The 100-mm reference stimulus marked the boundary for the presence of voice tremor: Vowels considered free from voice tremor were placed to the left of the 100-mm reference stimulus; vowels with voice tremor were placed to the right of the 100-mm reference stimulus according to perceived voice tremor severity (101–1000 mm).

Contralateral hand tremor (postural, action, and rest tremor) was scored immediately after each recording by a DBS nurse using item 5/6 of the Essential tremor rating scale.[11]

Statistical Analysis

All statistical comparisons of voice tremor severity were based on the averaged voice tremor ratings for each patient and stimulation condition. Voice tremor was considered to be absent if the average rating of the 2 vowels was less than 100 (i.e., to the left of the 100-mm reference stimulus).

Between-group differences were examined using Mann–Whitney U or Kruskal–Wallis tests with post-hoc tests (Dunn's test with Holm-Bonferroni correction). Inter-rater reliability was assessed using a 2-way mixed, absolute agreement, average measures intraclass correlation coefficient (ICC).[12]

Analysis of the Results of Assessments

Hand and voice tremor response to stimulation was classified as being either: 1) efficient, 2) moderate, or 3) poor. We employed an operational categorization of stimulation amplitude levels in which the patient's chronic amplitude setting for the active electrode provided the boundary level separating high-amplitude from low-amplitude stimulation. In cases with an efficient response to stimulation, the tremor symptom (hand or voice) completely subsided with low-amplitude stimulation (i.e., at or below the patient's clinical amplitude level). In cases with a moderate response, the tremor symptom was either never eliminated or required high-amplitude stimulation for complete suppression. In cases with a poor response, the stimulation had negligible effects on the tremor. Patients who never had voice tremor or only exhibited the symptom on a single occasion on stimulation were excluded from the analysis.

Table 1. Patient Characteristics, Voice Tremor Improvement During Chronic Stimulation, Chronic Stimulation Parameter Settings, and Information About Stimulation Settings Used During the Increasing Stimulation Amplitude Condition

Patient	Sex/ Handedness	Age at Recording, Years	Age at Onset of ET, Years	Duration of Disease at Recording, Years	Time Since Surgery, Months	Side of Electrode Implant(s)	On Tremor-Reducing Medication	Voice Tremor Improvement with Chronic Stimulation Compared with Off Stimulation*	Chronic Stimulation Settings (Contact, Amplitude, Pulse Width, Frequency) (Contact Labeling According to the Medtronic Nomenclature)	Electrode/Contact Used During Unilateral Stimulation at Increasing Amplitudes
B1	F/R	39	16	23	86	B	Propranolol	N/A†	L: 1—, 1.1 V, 90 μs, 125 Hz; 2—, 1.9 V, 90 μs, 125 Hz R: 10—, 1.3 V, 90 μs, 125 Hz; 11—, 1.5 V, 90 μs, 125 Hz	L/1—
B2	F/R	70	7	63	62	B	—	100%	L: 3—, 2.1 V, 60 μs, 150 Hz R: 10—11—, 1.7 V, 60 μs, 150 Hz	L/2—
B3	F/R	54	15	39	75	B	—	100%	L: 3—, 2.2 V, 60 μs, 160 Hz R: 10—, 2.1 V, 60 μs, 160 Hz	L/3—
B4	F/R	59	13	46	47	B	—	(Voice tremor induced at chronic stimulation)	L: 2— 3—, 1.0 V, 60 μs, 130 Hz R: 10—, 1.7 V, 60 μs, 130 Hz	L/2—
B5	F/R	65	55	10	20	B	Propranolol	58%	L: 1—, 1.6 V, 60 μs, 140 Hz R: 9—, 1.9 V, 60 μs, 140 Hz	L/1—
B6	M/R	61	40	21	13	B	—	100%	L: 1—, 1.2 V, 60 μs, 140 Hz R: 9—, 1.7 V, 60 μs, 140 Hz	L/1—
B7	M/R	52	40	12	50	B	—	78%	L: 1—2+, 2.5 V, 60 μs, 140 Hz R: 8+ 9—, 3.6 V, 60 μs, 140 Hz	L/1—
B8	M/R	62	50	12	12	B	—	41%	L: 2—, 3.2V, 60 μs, 160 Hz R: 10—, 2.0V, 60 μs, 160 Hz	L/2—
B9	M/R	68	20	48	119	B	—	100%	L: 0— 1—2+, 2.5 V, 60 μs, 160 Hz R: 8—, 2.8 V, 60 μs, 160 Hz	L/0—
B10	M/R	68	35	33	44	B	—	N/A†	L: 2—, 1.6 V, 60 μs, 140 Hz R: 10—, 0.8V, 60 μs, 140 Hz	L/2—
B11	M/R	57	7	50	24	B	—	N/A†	L: 1—, 2.3V, 60 μs, 160 Hz R: 9—, 2.0 V, 60 μs, 160 Hz	L/1—
L1	F/R	74	60	14	12	L	—	24%	L: 3—, 2.3 V, 60 μs, 140 Hz	L/3—
L2	F/R	81	50	31	60	L	—	N/A†	L: 2—, 2.4 V, 60 μs, 140 Hz	L/2—
L3	F/R	79	67	12	78	L	—	100%	L: 1—, 2.2 V, 60 μs, 150 Hz	L/1—
L4	F/R	70	58	12	16	L	—	N/A†	L: 1—, 1.7 V, 60 μs, 140 Hz	L/1—
L5	F/R	83	7	76	55	L	Propranolol	33%	L: 1— 2—3+, 1.9 V, 60 μs, 140 Hz	L/2—
L6	F/R	89	59	30	117	L	—	N/A†	L: 2—, 1.3 V, 60 μs, 135 Hz	L/1—
L7	F/R	77	51	26	120	L	—	100%	L: 1—, 1.5 V, 60 μs, 145 Hz	L/1—

ET, essential tremor; F, female; R, right; B, bilateral; N/A, not available; M, male; L, left; N, number of patients.

*Recordings and assessments of voice tremor during chronic stimulation were collected at the same time as recordings and assessments of voice tremor during unilateral stimulation.

†No voice tremor symptoms off and on chronic stimulation.

Continues

Table 1. Continued

Patient	Sex/ Handedness	Age at Recording, Years	Age at Onset of ET, Years	Duration of Disease at Recording, Years	Time Since Surgery, Months	Side of Electrode Implant(s)	On Tremor-Reducing Medication	Voice Tremor Improvement with Chronic Stimulation Compared with Off Stimulation*	Chronic Stimulation Settings (Contact, Amplitude, Pulse Width, Frequency) (Contact Labeling According to the Medtronic Nomenclature)	Electrode/Contact Used During Unilateral Stimulation at Increasing Amplitudes
L8	F/R	79	61	18	40	L	–	N/A†	L: 1– 2–, 1.2 V, 60 μs, 160 Hz	L/1–
L9	F/R	72	47	25	47	L	Propranolol	78%	L: 1–, 2.1 V, 60 μs, 160 Hz	L/1–
L10	F/R	76	55	21	40	L	–	100%	L: 1– 2–, 2.6 V, 60 μs, 140 Hz	L/2–
L11	M/R	80	69	11	72	L	–	35%	L: 0– 1–2+, 2.4V, 90 μs, 140 Hz	L/1–
L12	M/R	75	10	65	36	L	–	N/A†	L: 1–, 2.8 V, 90 μs, 120 Hz	L/1–
L13	M/R	75	55	20	59	L	–	N/A†	L: 2–, 2.2 V, 60 μs, 160 Hz	L/2–
L14	M/R	62	8	54	79	L	Propranolol	68%	L: 0– 1–, 1.8 V, 60 μs, 170 Hz	L/1-
L15	M/R	68	15	53	120	L	Propranolol	N/A†	L: 1–, 1.5 V, 60 μs, 160 Hz	L/1–
L16	M/R	85	55	30	112	L	–	18%	L: 2–, 2.6V, 60 μs, 160Hz	L/2–
L17	M/R	81	67	14	113	L	–	100%	L: 1–2+, 3.7V, 60 μs, 140 Hz	L/1–
L18	M/R	78	55	23	35	L	–	47%	L: 1–, 1.6V, 60 μs, 140 Hz	L/1–
L19	M/R	76	30	46	13	L	Propranolol	(6% deterioration)	L: 2– 3–, 1.7 V, 60 μs, 140 Hz	L/2–
L20	M/R	68	15	53	20	L	Primidone	100%	L: 3–, 1.8 V, 60 μs, 160 Hz	L/3–
L21	M/R	65	15	50	26	L	–	25%	L: 0– 1–, 2.0 V, 60 μs, 160 Hz	L/1–
L22	M/R	68	10	58	39	L	–	N/A†	1– 2–, 1.7 V, 60 μs, 160 Hz	L/2–
L23	F/R	82	50	32	130	L	–	N/A†	L: 1– 2–, 1.7 V, 60 μs, 140 Hz	L/1–
R1	F/R	75	58	17	129	R	–	48%	R: 1–, 2.8 V, 60 μs, 160 Hz	R/1–
R2	M/L	75	18	57	36	R	–	N/A†	R: 2–, 2.3 V, 60 μs, 130 Hz	R/2–
R3	M/L	68	50	18	131	R	–	23%	R: 1–, 1.4 V, 60 μs, 130 Hz	R/1–
N = 37	F: 46% M: 54%	71 ± 10 (39–89)	38 ± 21 (7–69)	33 ± 19 (10–76)	62 ± 39 (12–131)	B: 30% L: 62% R: 8%	Tremor reducing medication: 22% No medication: 78%	57% ± 48 (–100% to 100%)	2.0 V ± 0.6 62 μs ± 8 147 Hz ± 13	L: 92% R: 8%

ET, essential tremor; F, female; R, right; B, bilateral; N/A, not available; M, male; L, left; N, number of patients.

*Recordings and assessments of voice tremor during chronic stimulation were collected at the same time as recordings and assessments of voice tremor during unilateral stimulation.

†No voice tremor symptoms off and on chronic stimulation.

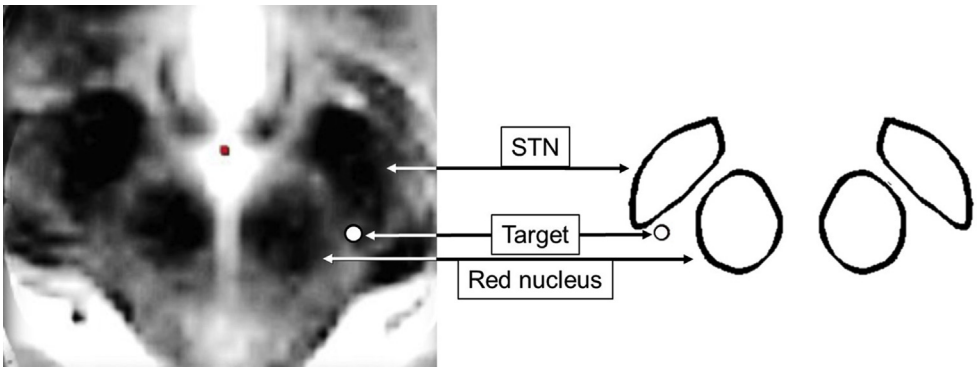

Figure 1. T2 magnetic resonance imaging and schematic view of the target area in the axial plane, at the level of the maximal diameter of the red nucleus. The target point is visually identified in relation to the posterior tip of the subthalamic nucleus (STN) and the red nucleus. In relation to the anterior and posterior commissures, it will typically be located at a laterality of 12 mm, 7.5 mm behind, and 4 mm below the midcommissural point.

Table 2. Group-Level Characteristics of Patients Grouped by Voice Tremor Response to Unilateral Stimulation at Increasing Amplitude Levels

	Voice Tremor Response to Unilateral Stimulation			
	Efficient*	Moderate†,‡	Poor	Voice Tremor Induced by Stimulation
Proportion of patients	37.0%	33.3%	22.2%	7.4%
Sex, female/male	5/5	5/4	1/5	1/1
Bilateral/unilateral DBS	7/3	2/7	0/6	0/2
Side of stimulation at unilateral evaluation, left/right	10/0	7/2	6/0	2/0
Age at evaluation, years	65 ± 10 (52–79)	72 ± 8 (62–83)	75 ± 8 (65–85)	74 ± 9 (68–81)
Disease duration, years	31 ± 17 (10–50)	33 ± 24 (12–76)	30 ± 18 (11–53)	42 ± 15 (31–53)
Time since surgery, months	56 ± 41 (13–120)	74 ± 42 (12–131)	46 ± 38 (12–112)	90 ± 42 (60–120)
Voice tremor off stimulation	287 ± 225 (70–796)	577 ± 160 (348–746)	283 ± 195 (169–675)	N/A
Max amplitude at unilateral evaluation, volts	3.0 ± 0.7 (2.0–4.5)	2.8 ± 1.1 (1.0–4.5)	3.7 ± 1.1 (2.0–4.5)	3.3 ± 0.4 (3.0–3.5)
x coordinate, MCP	11.4 ± 1.3	12.3 ± 1.4	12.3 ± 1.3	12.7 ± 0.5
y coordinate, MCP	−7.1 ± 1.2	−6.6 ± 1.2	−6.5 ± 0.9	−7.7 ± 0.3
z coordinate, MCP	−3.1 ± 1.8	−2.1 ± 1.6	−0.7 ± 1.9	−1.5 ± 2.5
x coordinate, pSTN	2.2 ± 1.0	2.3 ± 1.3	2.4 ± 0.7	2.5 ± 0.6
y coordinate, pSTN	−0.2 ± 0.9	0.1 ± 0.6	1.0 ± 0.7	−1.7 ± 0.6
z coordinate, pSTN	1.4 ± 1.6	2.0 ± 1.3	2.9 ± 1.9	1.9 ± 2.0

Values are mean values ± standard deviations (range). Positive values of coordinates relative to pSTN are more medial, anterior, and superior.
DBS, deep brain stimulation; N/A, not applicable; MCP, midcommissural point; pSTN, posterior tip of the subthalamic nucleus.
*Including 5 patients with worsened voice tremor severity at high-amplitude stimulation.
†Including 2 patients with worsened voice tremor severity at high-amplitude stimulation.
‡Five patients with incomplete resolution of voice tremor and 4 patients with complete resolution during high-amplitude stimulation.

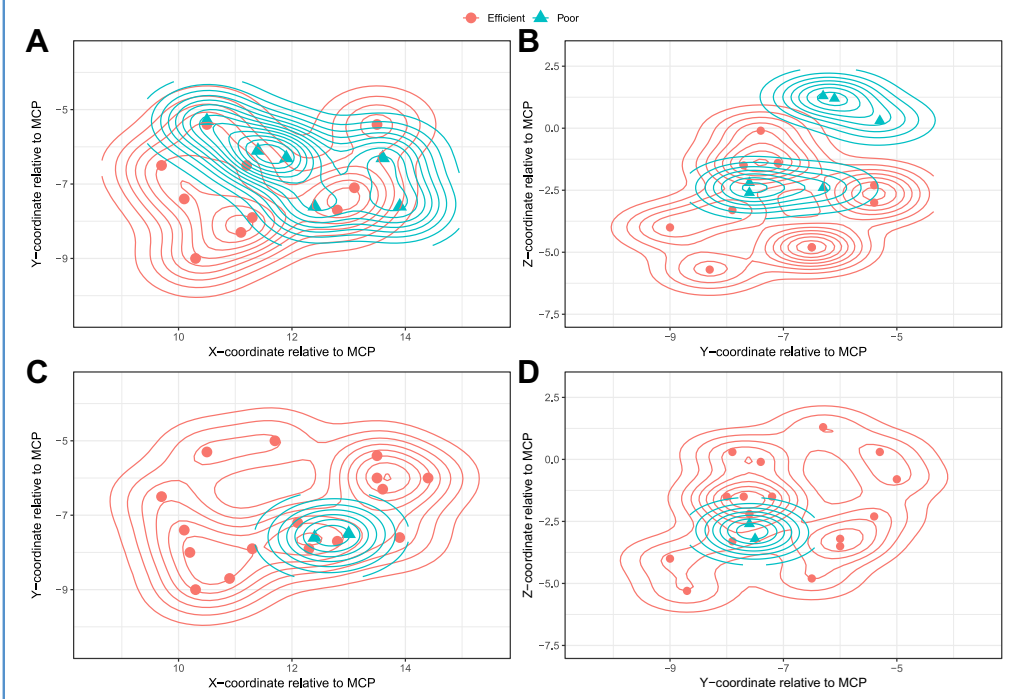

Figure 2. Distribution of efficient and poor contacts relative to the midcommissural point (MCP). *Upper row*: for voice tremor on the axial plane (**A**) and the sagittal plane (**B**). *Lower row*: for hand tremor on the axial plane (**C**) and the sagittal plane (**D**).

The active contacts were then classified according to the symptom response pattern as efficient, moderate, or poor on hand tremor and voice tremor, respectively. Results from the contact efficacy evaluations along with information about contact location relative to the mid-commissural point (MCP) and the pSTN were used to examine whether some stimulation locations were more effective than others on voice tremor.

RESULTS

Voice Tremor Response to Stimulation

The mean interrater reliability was good, ICC = 0.78,[13] with a moderate to good 95% confidence interval for the ICC (0.63–0.85).[13] Twenty-seven of the 37 patients evaluated had voice tremor off stimulation or in at least 2 of the evaluations on stimulation. Ten patients (37%) had an efficient response to stimulation, 9 patients (33%) had a moderate response, and 6 patients (22%) had a poor response (Table 2). Two patients (7%) developed voice tremor as an adverse effect of high-amplitude stimulation. Adverse effects of high-amplitude stimulation also were observed in 7 patients with otherwise efficient (N = 5) or moderate (N = 2) response to stimulation at lower amplitude levels.

Patients grouped by voice tremor response were similar in age, disease duration, and time elapsed since DBS surgery (Table 2). A Kruskal–Wallis test indicated that voice tremor off stimulation differed between the efficient, moderate, and poor response groups (P = 0.011). Pairwise comparisons of groups (Dunn's test) indicated more severe voice tremor off stimulation in the moderate response group (mean [M] = 577, standard deviation [SD] = 160) compared with both the efficient (M = 287, SD = 225; Z = 9.39, P = 0.005) and the poor response groups (M = 283, SD = 195; Z = 8.89, P = 0.022).

Distribution of Efficient and Poor Contacts in Terms of Voice Tremor Alleviation

The distribution of efficient and poor contacts relative the MCP (Figure 2) and the pSTN (Figure 3) was visualized using kernel density estimation with a bandwidth of 0.6. Relative to the MCP, efficient contacts were located in a more medial, posterior, and ventral part of the PSA compared with poor contacts (Figure 2A, B). A Mann–Whitney U test confirmed that efficient contacts (M = −3.1, SD = 1.8) were on average deeper than the poor contacts (M = −0.7, SD = 1.9; U = 49.0, P = 0.042); however, the difference in laterality (P = 0.118) and anteroposterior location (P = 0.220) between efficient and poor contacts was not statistically significant.

Relative to the pSTN, a similar trend was seen with efficient contacts located in a more posterior and ventral part of the PSA (Figure 3A, B). The average efficient contact had a more posterior location (M = −0.2, SD = 0.9) than the average poor contact (M = 1.0, SD = 0.7; U = 52.5, P = 0.011). The difference in depth (P = 0.147) was not statistically significant.

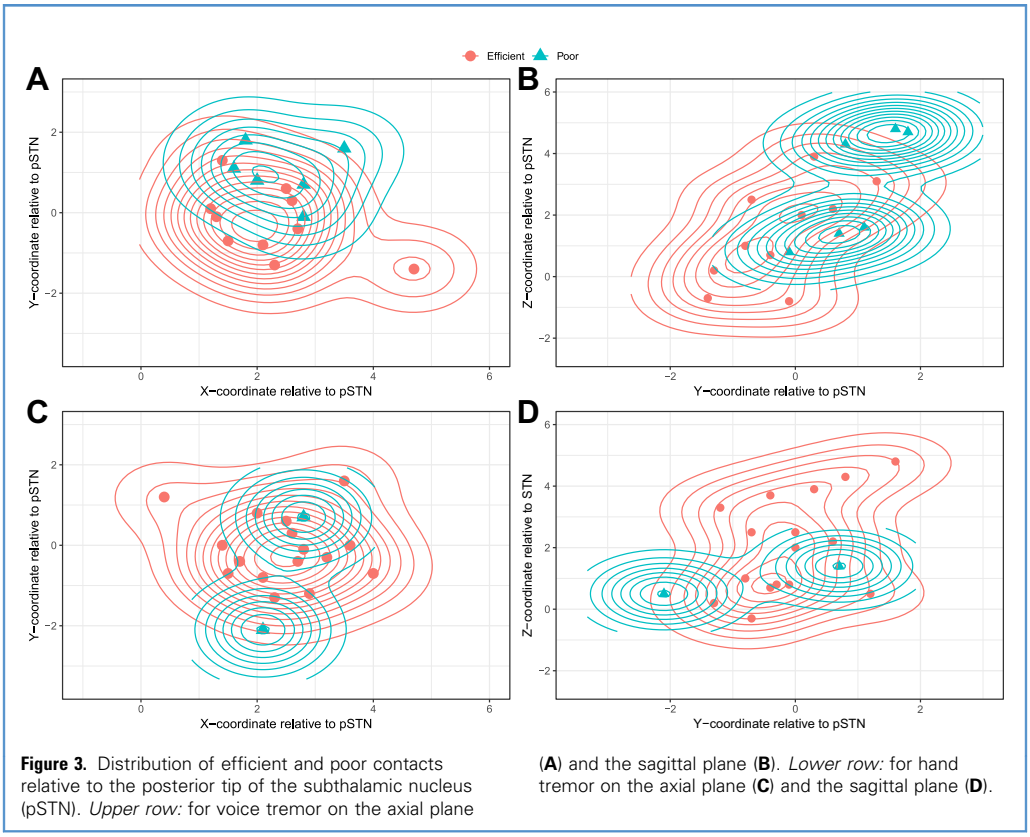

Figure 3. Distribution of efficient and poor contacts relative to the posterior tip of the subthalamic nucleus (pSTN). *Upper row:* for voice tremor on the axial plane (**A**) and the sagittal plane (**B**). *Lower row:* for hand tremor on the axial plane (**C**) and the sagittal plane (**D**).

Comparing Voice Tremor and Hand Tremor Outcomes with Unilateral cZi Stimulation

All individual contacts and their effect on voice tremor and hand tremor are visualized relative to the MCP (Figure 4). Efficient contacts for voice tremor were located in the ventromedial part of the PSA (Figure 4A, B); contacts that were effective on hand tremor were spread more evenly throughout the target area (Figure 4C, D). Contralateral hand tremor also improved to a larger extent with stimulation than voice tremor (efficient response: 59% vs. 37%, moderate response: 33% vs. 33%, poor response: 7% vs. 22%). Contacts that induced or worsened voice tremor at high-amplitudes showed no clear anatomical distribution (Figure 4A, B).

DISCUSSION

In this study, we found that unilateral cZi stimulation can improve voice tremor, but that the success of treatment may depend on the specific location of the contact. Matsumoto et al.[3] recently highlighted the importance of precise stimulation for effective voice tremor control. Our findings corroborate these results, but for another DBS target.

The location of the contacts was evaluated in the conventional manner in relation to the anterior and posterior commissures (AC-PC). The targeting is, however, not done according to the AC-PC, but in relation to the more closely related red nucleus and pSTN. We have therefore analyzed the results also in relation to the latter. We have previously demonstrated that this seems to result in more homogenous findings.[8,14]

Taken together, our results indicate that stimulation in the inferior and posterior part of the PSA might be more efficient regarding voice tremor reduction. Statistical testing demonstrated that efficient contacts were significantly deeper relative to the MCP compared with poor contacts, with a nonsignificant trend towards being more posterior. The trend that more posterior contacts were more efficient became significant when contacts were analyzed in relation to the pSTN. That stimulation below the AC-PC can be effective on overall tremor has been demonstrated before,[8,15-19] and our results indicate that stimulation below the AC-PC is effective also for voice tremor. However, this is the first study exploring the PSA in relation to voice tremor, and our finding regarding possible differences in efficacy in relation to the contact location requires replication.

More than 70% of patients in this study improved in voice tremor by unilateral monopolar cZi stimulation. These results compare well with previous studies reporting voice tremor outcomes using patients' chronic stimulation settings[2-4] and further add to the literature showing that unilateral DBS may be useful in the treatment voice tremor.[5-7] Still, about one half of the patients that improved in this study had only a moderate effect and did not receive complete symptom relief during stimulation at their clinical amplitude levels. These patients also had more severe voice tremor off stimulation compared with patients with an efficient response, indicating that unilateral stimulation may be less

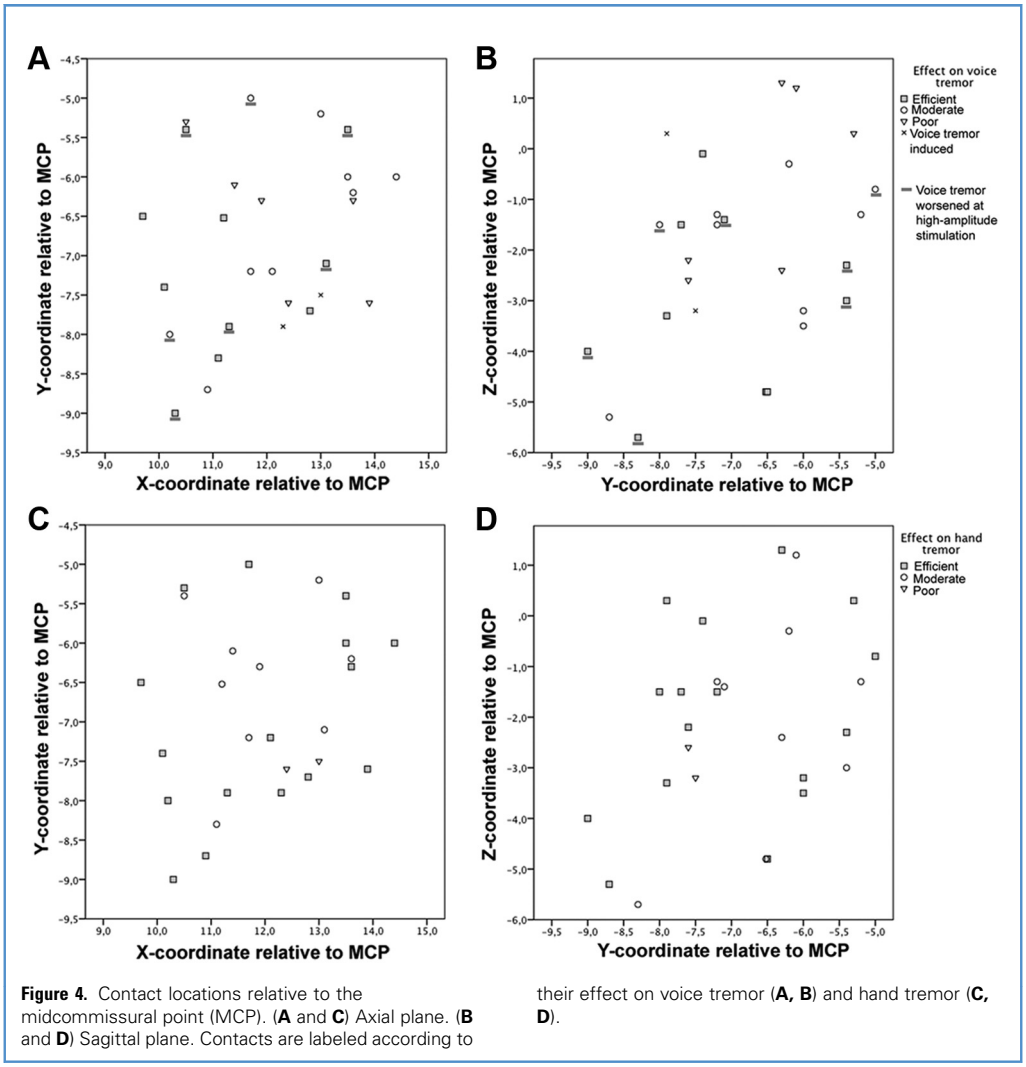

Figure 4. Contact locations relative to the midcommissural point (MCP). (**A** and **C**) Axial plane. (**B** and **D**) Sagittal plane. Contacts are labeled according to their effect on voice tremor (**A, B**) and hand tremor (**C, D**).

effective on severe voice tremor. However, it is also conceivable that some of the patients with a moderate effect would have improved by activating other contacts.

Contralateral hand tremor improved to a greater extent than voice tremor in this study, both regarding the magnitude of improvement and number of patients improving. This finding is not surprising, given that we chose to stimulate contacts that were most effective on hand tremor at the 12-month evaluation. However, and contrary to our finding on voice tremor, there was no clear association between different hand tremor outcomes and contact location within the PSA. Instead, contacts yielding effective hand tremor reduction were more evenly distributed throughout the target area, indicating that hand tremor may be more easily targeted by DBS.[3]

A novel finding from this study was that high-amplitude stimulation can aggravate or even induce voice tremor. Stimulation at so-called supratherapeutic levels has been reported to induce ataxia in patients with ET, presumably due to stimulation close to the red nucleus.[20,21] Voice tremor is also a symptom of ataxic dysarthria,[22] and it is possible that the reemergence of voice tremor at greater amplitude levels is mediated by the same mechanisms.

When evaluating the results from this study, it is important to remember that each stimulation setting was applied only for a short period. Consequently, we do not know to what extent our results would apply also to chronic stimulation over time. Another consideration is that our group analyzes were limited in statistical power due to the fact that only six patients in our cohort had a poor effect on voice tremor. Investigations of larger cohorts may elucidate whether there are additional factors related to contact location contributing to voice tremor outcomes other than the ones presented here. A further limitation is that we do not know to what extent the observed voice tremor reduction extends to spontaneous speech, nor how remaining voice tremor may affect speech intelligibility and patients' self-perceived quality of life.

CONCLUSIONS

DBS targeting the cZi may be a valid treatment for patients with voice tremor, but voice tremor can be difficult to target anatomically. This study indicates that stimulation of the inferior part of the PSA, close or slightly posterior to the pSTN, might be beneficial regarding voice tremor. Another finding of interest was that high-amplitude settings may induce voice tremor. Thus, to achieve the most favorable results for voice tremor, focused stimulation may be required, and this includes careful screening and programming of stimulation settings and an optimally placed electrode. The optimal electrode location may, however, differ depending on DBS target and results from this study need to be replicated by others.

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