Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

10 Years Follow-Up of Deep Brain Stimulation in the Caudal Zona Incerta/ Posterior Subthalamic Area for Essential Tremor

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ABSTRACT: Background: Long-term data on the effects of deep brain stimulation (DBS) for essential tremor (ET) is scarce, especially regarding DBS in the caudal Zona incerta (cZi) and the posterior subthalamic area (PSA).
Objectives: The aim of this prospective study was to evaluate the effect of cZi/PSA DBS in ET at 10 years after surgery.
Methods: Thirty-four patients were included. All patients received cZi/PSA DBS (5 bilateral/29 unilateral) and were evaluated at regular intervals using the essential tremor rating scale (ETRS).
Results: One year after surgery, there was a 66.4% improvement of total ETRS and 70.7% improvement of tremor (items 1–9) compared with the preoperative baseline. Ten years after surgery, 14 patients had died and 3 were lost to follow-up. In the remaining 17 patients, a significant improvement was maintained (50.8% for total ETRS and 55.8% for tremor items). On the treated side the scores of hand function (items 11–14) had improved by 82.6% at 1 year after surgery, and by 66.1% after 10 years. Since off-stimulation scores did not differ between year 1 and 10, this 20% deterioration of on-DBS scores was interpreted as a habituation. There was no significant increase in stimulation parameters beyond the first year.
Conclusions: This 10 year follow up study, found cZi/PSA DBS for ET to be a safe procedure with a mostly retained effect on tremor, compared to 1 year after surgery, and in the absence of increase in stimulation parameters. The modest deterioration of effect of DBS on tremor was interpreted as habituation.

Essential tremor (ET) is the most common adult movement disorder with a prevalence of about 5% in the population above 65 years of age. Of patients who seek medical care up to 50% do not respond adequately to drug therapy,[1] in which case stereotactic neurosurgical procedures, including deep brain stimulation (DBS) constitute established alternatives. Traditionally, the ventral intermediate nucleus of the thalamus (Vim) has been the target of choice, but the caudal zona incerta (cZi)/posterior subthalamic area (PSA) is becoming more common. (These terms are used interchangeably in the literature and we will hereforth refer to this as the cZi/PSA). DBS in both targets has proved effective in the short term, but real long term data on the effects of DBS for ET is scarce, and this is especially true regarding cZi/PSA DBS. Our aim in this prospective study was to evaluate the effects of cZi/PSA DBS for ET 10 years after surgery.

Methods

In the autumn of 2004, as part of an open-label prospective study, the brain target for DBS was changed from the Vim to

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the cZi/PSA for all patients with essential tremor referred for DBS surgery at the University hospital of Umeå. Data were collected until the March 31, 2021. All patients with cZi/PSA DBS for ET implanted at least 10 years before the study's cut-off point were included in the present analysis. The final sample consisted of 34 consecutive patients, 17 of whom were available at the 10 years follow-up.

The diagnosis of idiopathic ET was confirmed by a senior movement disorders neurologist before the introduction of the consensus tremor classification in 2018.[2] The study was approved by the Ethical Committee at the University of Umeå, and informed consent obtained in accordance with the Declaration of Helsinki.

Surgical Technique

The surgical technique has been described in detail previously.[3] The operations were frame-based (Leksell frame model G, Elekta Instruments, Linköping, Sweden) implantations of the DBS electrode 3387 or 3389 (Medtronic, Minneapolis, MN, USA) in the cZi/PSA. Bilateral implantations were only performed in patients below the age of 70 with a significant tremor in both upper extremities. The target was defined on stereotactic T2-weighted MRI as lying slightly posterior and medial to the visualized posterior tail of the subthalamic nucleus (STN) on the axial scan showing the maximal diameter of the red nucleus (RN).[4] The lead was implanted with the patient awake to allow for intraoperative evaluation using macrostimulation through the DBS electrode. Microelectrode recording was not used. Before implantation of the pulse generator (IPG) and the connection cables, the electrode location was verified on an intraoperative stereotactic CT merged with the preoperative MRI (Fig. 1).

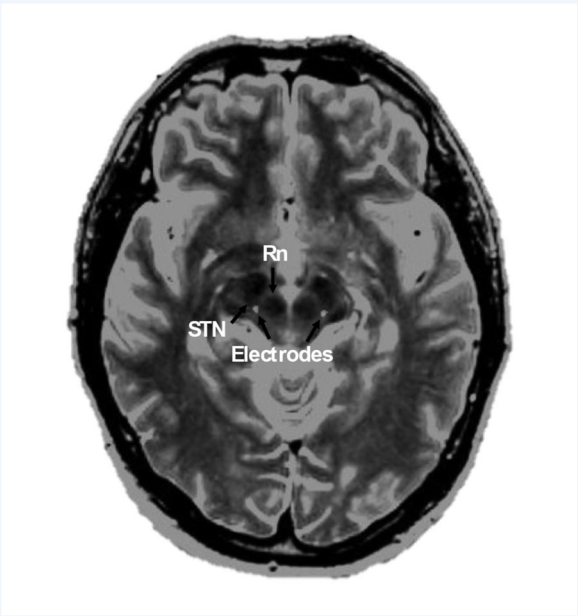

Figure 1. Preoperative T2 MRI fused with postoperative CT demonstrating the leads in the caudal zona incerta (cZi) within the posterior subthalamic area (PSA), posteromedial to the subthalamic nucleus (STN) at the level of the maximal diameter of the red nucleus (Rn)

Evaluation

The patients were evaluated before surgery, then off/on-stimulation after 1, 3–5, and 10 years using the Essential tremor rating scale (ETRS). The evaluations were performed in accordance with our clinical routine in an un-blinded fashion by a DBS nurse with a long experience of scoring ETRS. ETRS data were missing for one patient at year 1. The evaluations off-stimulation were performed after the DBS had been turned off during the night. The stimulation parameters were optimized 6 weeks after the implantation and thereafter controlled and adjusted on an annual basis, or when needed.

Statistics

Non-parametric tests were used due to the non-normal distribution of data. The results were presented as means with standard deviations or standard errors where applicable. Mann–Whitney test and Kruskal Wallis test were used to compare the long-term effect of cZi/PSA DBS between different patients (two or more independent groups, respectively). Wilcoxon signed ranks test or Friedman's Anova were used to assess the effect over time within patients (two or more interdependent groups respectively). The differences between distributions in categorical variables were assessed by the Pearson's chi-square test. A *P*-value of ≤0.05 was considered significant. A dropout analysis was performed to address patient attrition.

Results

Dropout Analysis

The study sample included 34 patients (15 women and 19 men). Seventeen patients were lost to follow-up. Background characteristics of participants (patients followed up for 10 years) and dropouts (patients lost to follow up) are presented in Table 1.

Overall, there were more men and individuals with earlier disease onset and a longer disease duration among dropouts than among participants. However, the dropouts were not a homogeneous group. Three persons dropped out voluntarily: an older man was in too poor general health to participate, and two younger women reported good effect, but did not have time to attend the follow-up visit after 10 years. Fourteen patients died before the end of the study. The mean age at death was 78 ± 5.4, and the mean length of life after surgery was 7.3 ± 1.4 years. As shown in Table 1, the deceased dropouts had later disease onset, longer disease duration and were almost 30 years older at surgery than alive dropouts.

Dropouts, particularly deceased dropouts, had higher ETRS score than participants at all evaluation points both on and off stimulation (Fig. 2). The postoperative ETRS score changed

TABLE 1 *Background characteristics of participants (patients followed up for 10 years) and dropouts (patients lost to follow up prior to the study cut-off at 10 years)*

			Dropouts		
		Participants ($n = 17$)	Total ($n = 17$)	Deceased ($n = 14$)	Alive ($n = 3$)
Sex	Women	52.9% (9)	35.3% (6)	28.6% (4)	66.7% (2)
	Men	47.1% (8)	64.7% (11)	71.4% (10)	33.3% (1)
Age at disease onset	Mean ± SD	43.1 ± 19.6	38.6 ± 22.2	41.4 ± 22.0	25.7 ± 22.1
Age at surgery	Mean ± SD	65.0 ± 8.9	65.8 ± 15.9	70.7 ± 8.2	42.7 ± 24.8
Disease duration	Mean ± SD	21.4 ± 15.4	27.2 ± 18.6	29.4 ± 20.0	17.3 ± 2.5
Number of uni/bilaterally implanted patients		14/3	15/2	14/0	1/2

Note: No differences between the sub-samples were statistically significant.

somewhat over time in all patients, however the change was smaller among participants than among dropouts. By year 3–5, the effect of surgery on ETRS score deteriorated by 11% among participants and by 23% among all dropouts compared to year 1 (statistically significant).

Hence, the participants and dropouts were not similar. Excluding dropouts from the study would dramatically improve the results, suggesting stronger effect of surgery on the ET.

To avoid this overestimation, the analyses in the sections below include all patients evaluated at each respective year: 34 individuals at baseline, 33, 30 and 17 individuals at year 1, 3–5 and 10, respectively.

Overall Effect Change during 10 Years

The stimulation resulted in a significant improvement in total ETRS (by 66.4%), tremor (item 1–9, by 70.7%) and hand function (item 11–14, by 56.3%) at 1 year after surgery when compared with preoperative baseline scores. A significant improvement was maintained over time, but reduced to 50.8%, 55.8% and 44.3%, respectively, at 10 years after surgery (Fig. 3). The difference between mean scores on and off stimulation remained statistically significant at each respective evaluation. See Table 2 for details.

No progress of disease was seen, as the ETRS scores off stimulation remained largely unchanged over 10 years compared to baseline (Table 2). This was further analyzed in unilaterally implanted patients, where hand tremor (item 5/6) and hand function were unchanged at 10 years on both sides off stimulation, and on the ipsilateral side on stimulation, while deteriorating on the contralateral side (Fig. 4).

Effect Change in Different Patient Groups

There were no statistically significant or clinically relevant differences in evolution of ETRS over time between men and women, or between younger and older persons or in relation to early or late onset of disease, neither on nor off stimulation (data not shown). Deeper stratification was not possible due to the small sample. However, there were significant differences in treatment effects between uni- and bilaterally implanted patients, as shown in the next section.

Treatment Effect in Uni- and Bilaterally Operated Patients

There were 29 unilaterally and 5 bilaterally implanted patients. Bilaterally operated patients had on average earlier disease onset (13.6 ± 5.1 years vs 45.6 ± 18.6 years old), longer disease duration (31.4 ± 17.0 vs 23.3 ± 17.4 years) and younger age at surgery (44.8 + 16.2 vs 68.9 + 8.0). No differences were statistically significant.

As illustrated in Fig. 5, the treatment effect was stronger in bilateral compared to unilateral patients on stimulation, while the ETRS scores were higher off stimulation. The effect on stimulation diminished over the years in both groups, although more in bilateral patients.

Total ETRS scores improved by 61.6% 1 year after surgery, and were 47.8% better than preoperational baseline after 10 years in unilateral patients (all values statistically significant). In bilateral patients, total ETRS scores improved by 91.8% 1 year after (statistically significant), and were still 64.6% better than preoperational baseline after 10 years (not statistically significant). The deterioration of tremor and hand function scores was similar in magnitude. Nevertheless, treatment effect remained considerable even after 10 years compared to baseline evaluations in both groups.

Stimulation Parameters and Energy Consumption

The mean coordinates of the implanted electrodes were for the deepest contacts 10.4 mm lateral of the midline, 7.8 mm behind the midcommissural point and 5.1 mm below the AC-PC plane.

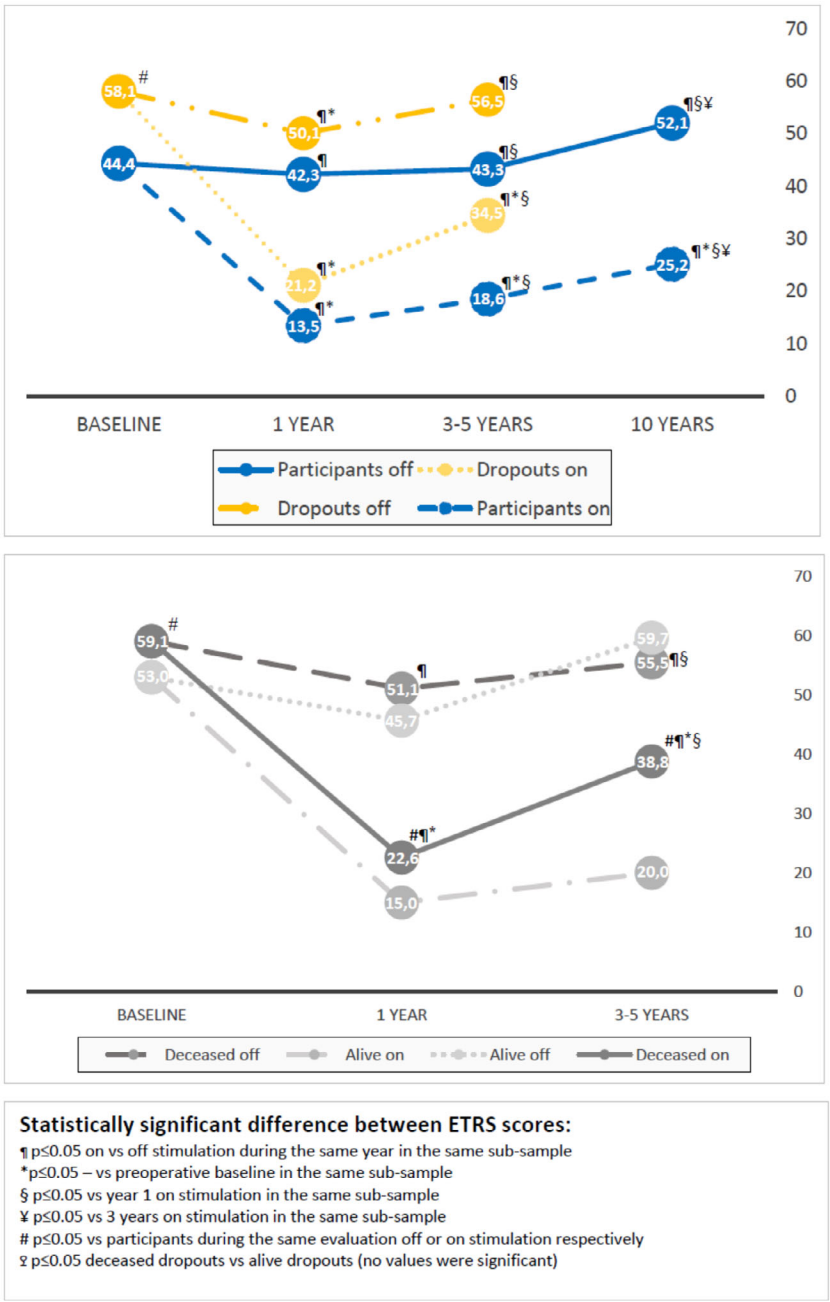

Figure 2. Mean total ETRS scores among participants and dropouts on and off stimulation at different evaluation time points

Stimulation parameters over time are displayed in Table 3. Pulse effective voltage (PEV) was used as a measurement of stimulation strength ($\sqrt{[U^2 \times pps \times pw}$, where U = voltage (V), pps = pulses per second (Hz) and pw = pulse-width (μs)]).[5] A minor increase in the energy delivered was seen from the start around week six to year 1, but no further increase was seen 10 years after surgery. There were no significant differences between uni- and bilateral patients in any of the variables (data not shown). Sixteen of the 34 patients underwent a single IPG replacement due to battery depletion during the follow-up period. Of the 20 patients surviving after 10 years 13 had Kinetra, of which 5 were replaced, and 5 had Activa PC, of which all needed to be replaced.

Complications

No hemorrhages, infections or erosions occurred in this cohort. Only one major complication was seen in a 72 year old woman

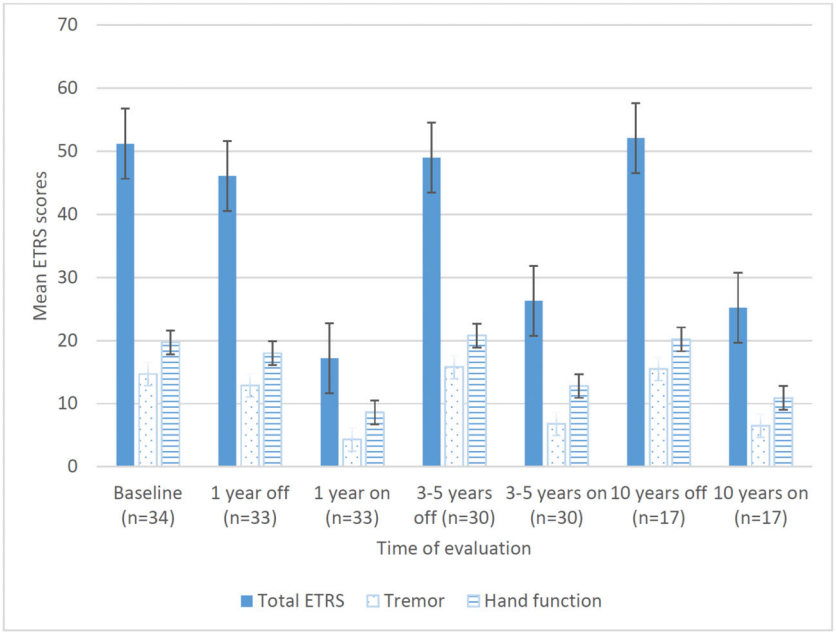

Figure 3. Mean scores for Total Essential Tremor Rating Scale (ETRS), tremor (items 1–9) and hand function (items 11–14) at different evaluations on and off stimulation (with error bars). Numbers between brackets indicate the number of patients at each evaluation time point

TABLE 2 *Mean (±SD) scores for Total Essential Tremor Rating Scale (ETRS), tremor (items 1–9) and hand function (items 11–14) at different evaluations on and off stimulation*

	Baseline ($n = 34$)	1 year evaluation ($n = 33$)		3–5 years evaluation ($n = 30$)		10 years evaluation ($n = 17$)	
		Off	On	Off	On	Off	On
Total ETRS (items 1–21)	51.2 ± 16.6	46.1 ± 19.1★,★★★	17.2 ± 11.4★,★★★	49.0 ± 21.4★★	26.3 ± 17.1★,★★,★★★★	52.1 ± 16.7★★	25.2 ± 10.2★,★★,★★★,★★★★
Tremor (items 1–9)	14.7 ± 7.7	12.9 ± 8.4★★	4.3 ± 3.6★,★★	15.8 ± 9.4★★	6.8 ± 4.6★,★★,★★★	15.5 ± 6.5★★	6.5 ± 3.3★,★★,★★★
Hand function (items 11–14)	19.7 ± 7.3	18.0 ± 7.0★★	8.6 ± 5.6★,★★	20.8 ± 7.7★★	12.8 ± 7.5★,★★,★★★	20.2 ± 6.0★★	10.9 ± 4.8★,★★,★★★

Note: Maximum scores: Total ETRS = 144, Tremor items = 80, Hand function = 32.
★$P \leq 0.05$ – vs baseline.
★★$P \leq 0.05$ on vs off-stimulation during the same year.
★★★$P \leq 0.05$ vs year 1 on stimulation.
★★★★$P \leq 0.05$ vs 3 years on stimulation.

who suffered a suspected stroke shortly after surgery with the development of hemiparesis. This was deemed to be a consequence of surgery. The symptoms were mostly in regression after 5 months, with a remaining weakness of the leg.

Further, 26 complications deemed as minor were recorded.

The patients were explicitly asked for any negative microlesional effects before the start of stimulation,[6] and minor affection of speech was the most common complication, reported by eight patients. This was, as we have previously reported,[6] interpreted as dysphasia, but in three of the patients a minor dysarthric component was also present. Six patients noticed affection of motor function/gait balance. These side effects stopped within days to weeks.

In one patient a malfunction of the IPG affected some contacts, but had no relevance for the clinical outcome. In another patient a suspected poor connection between the IPG and connection cable with intermittent sensations of electrical leakage was resolved by external manipulation of the device. Two patients underwent revisions due to straining extension cables. In one patient the electrode was misplaced too medially close to the red nucleus, and a suboptimal effect with 75% tremor reduction had to be accepted to avoid stimulation induced side effects. A

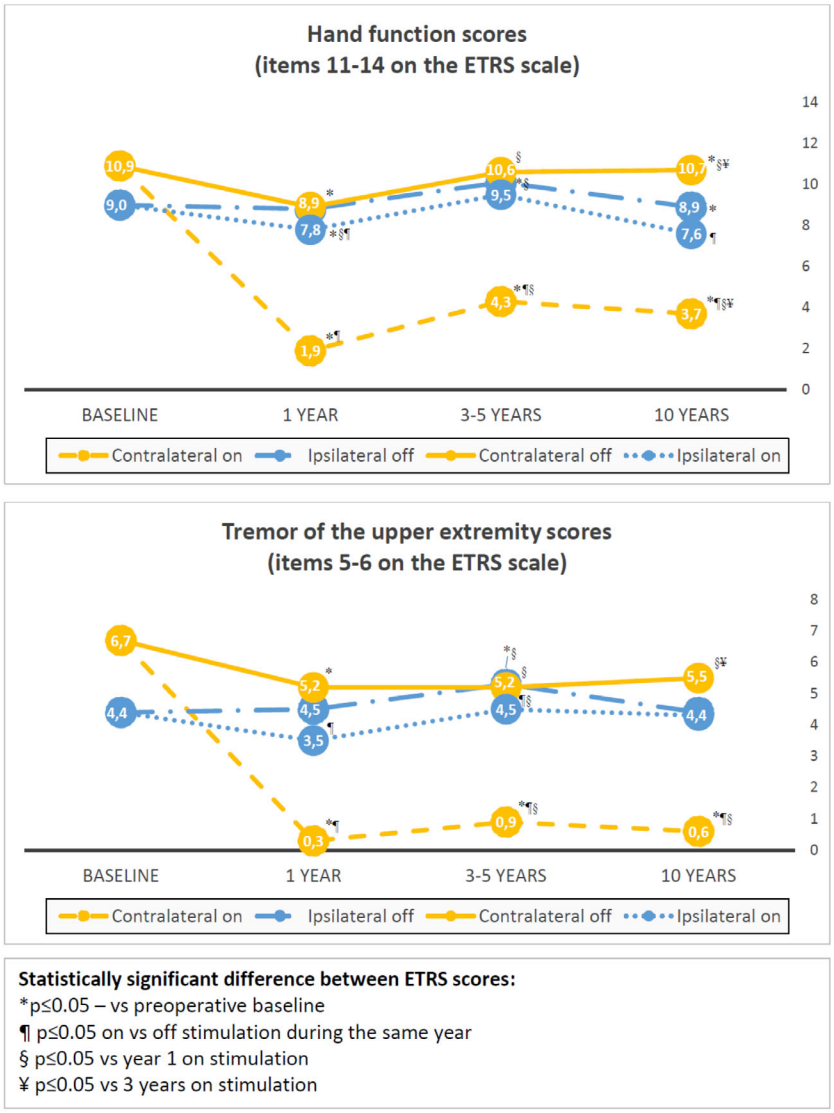

Figure 4. Change in ETRS scores during 10 years of follow-up in unilaterally implanted patients

good effect was achieved after several years when the depleted IPG was replaced with a new model, providing more advanced programming options. One patient complained over painful paresthesia in the tongue for some seconds, each morning when she started the stimulation. This was resolved when the IPG was changed to a new model upon depletion, providing more advanced programming options.

Development of clinically relevant tolerance/ataxia necessitating multiple changes of the stimulation parameters was noted in six patients, after a mean time of 4 years (range 0.5–10 years) after surgery. Temporary stimulation-induced side effects seen during the optimization of stimulation parameters are not reported here.

Discussion

Even though many patients undergoing DBS for ET have a long life expectancy, the long-term effects of DBS in the cZi/PSA, beyond 4 years after surgery, have not hitherto been studied. In the present prospective study a cohort of 34 patients was followed for 10 years demonstrating the safety and efficacy of cZi/PSA DBS over time.

Dropout

By necessity, very long-term evaluations entail attrition of patients. In the current study, 50% of the patients were not

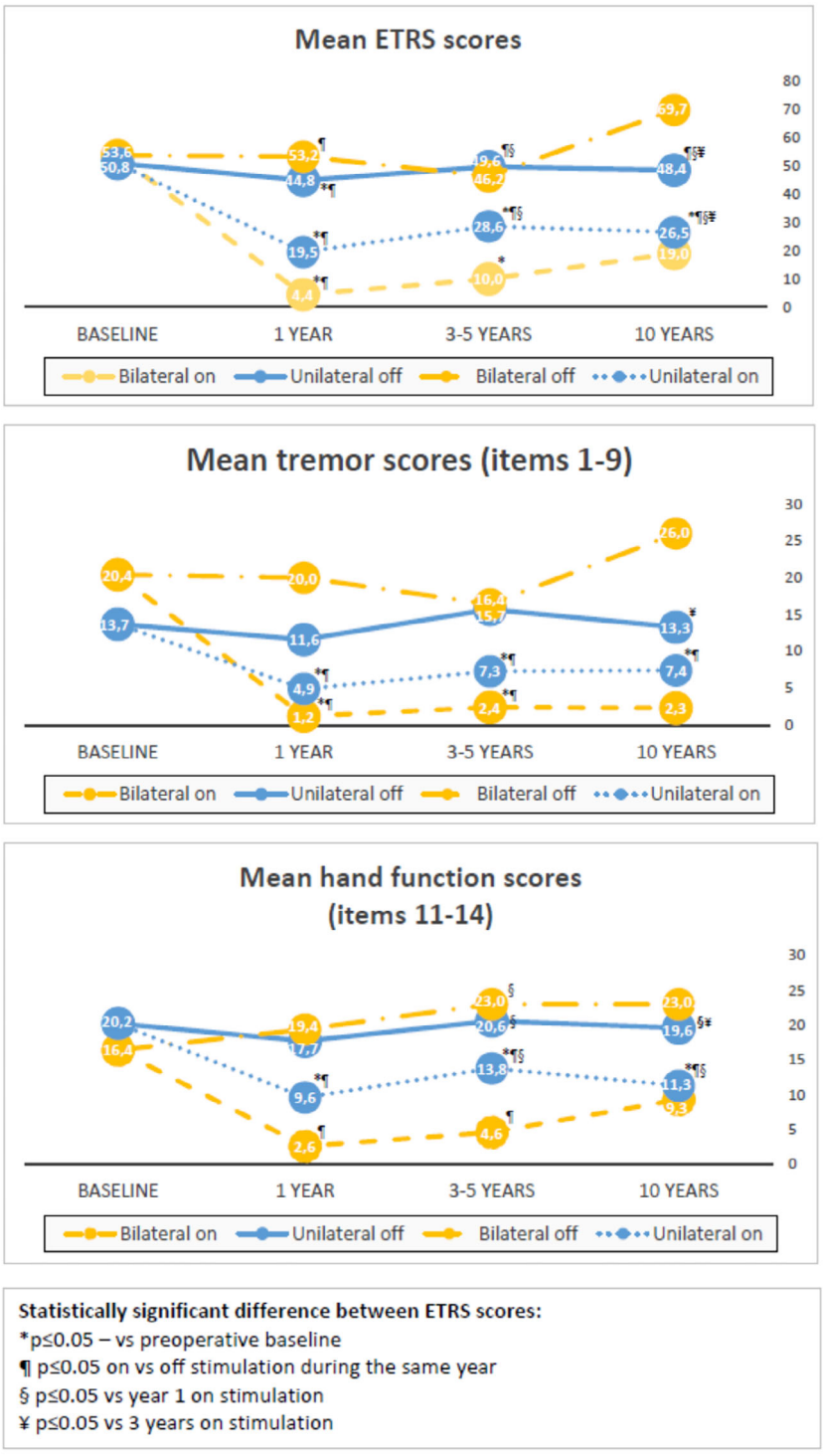

Figure 5. Mean scores for Total Essential Tremor Rating Scale (ETRS), tremor (items 1–9) and hand function (items 11–14) at different evaluations on and off stimulation in uni- and bilaterally implanted patients

available for follow-up after 10 years. This is in accordance with the studies described further below: Baizabal-Carvallo et al[7] lost 66% of their patients to follow-up; Sydow et al[8] lost 49% and Cury et al[9] lost around 40%.

In our study, the deceased patients who did not complete the 10 year evaluation were older, with a longer disease duration, a more severe disease and a more pronounced decrease of the stimulation effect over time than the survivors. The higher

TABLE 3 *Stimulation settings (means with ± standard deviation)*

	All patients				
	6 weeks ♀	**1 year**	**3 years**	**5 years**	**10 years**
Mono−/bipolar	31/7	29/9	26/8	29/4	17/4
Pulse width (uS)	61.6 ± 6.8	63.2 ± 9.3	62.6 ± 8.6	63.6 ± 9.9	61.4 ± 6.5
Frequency (Hz)	163.6 ± 19.9*	163.9 ± 20.6*	162.8 ± 20.0*	151.7 ± 18.9*	147.6 ± 11.4*
Amplitude (V)	1.8 ± 0.7*	2.2 ± 0.8*	2.3 ± 0.6*	2.1 ± 0.6*	2.2 ± 0.8*
Energy (PEV)	0.18 ± 0.08*	0.23 ± 0.08*	0.23 ± 0.06*	0.21 ± 0.06*	0.21 ± 0.09*

Note: ♀ One unilateral patient's information is missing for week 6, hence 38 instead of 39 electrodes.
*p ≤0.05 – vs 6 weeks.

tremor score before and after surgery was likely a consequence of the higher age, as we have previously demonstrated.[10] However, the larger deterioration of the effect of stimulation seems rather to be explained by a more pronounced tendency to habituation in this group. The reason for this cannot be identified based on the current material.

Had all patients survived the 10 year evaluation, then it seems likely, that based on the scores at the last follow up, the mean effect of stimulation would have been lower. This is, however, probably not an adequate way to interpret the data. In a group of patients of this age, a certain number of patients are expected to die within 10 years. It seems more reasonable to conclude that older patients, likely in poorer general health, who died within 10 years of surgery, had a more severe disease and a stronger tendency to habituation than younger patients surviving up to or beyond 10 years after surgery.

Tremor Reduction and Habituation

Although the literature on long-term effects of DBS for ET is heterogenous, a deterioration of the effect over time is commonly suggested and assumed. The long term evaluations of cZi/PSA DBS are limited to an evaluation of our own cohort after a mean follow up of 4 years[11] and a report by Plaha et al of four bilaterally implanted patients, in whom total ETRS was improved by 72.6% after ≥4 years.[12] Concerning Vim DBS for ET, there are five reports on the effects beyond 5 years. Tsuboi et al[13] reported in about 20 patients (according to personal communication with Dr. Aparna Wagle Shukla, University of Florida) followed for ≥6 years an improvement of 68% after 1 year, and 50% after ≥6 years, when compared to the baseline (*n* 97 patients).

Cury et al[9] reported ≥10-year outcome in an unknown number of patients out of 38 patients available for analysis with a mean follow-up of 8 years. In this group consisting of both unilateral and bilateral VIM DBS, the total tremor score on vs. off stimulation, improved with 66 and 48%, after 1 and ≥ 10 years, respectively.

Baizabal-Carvallo et al[7] reported 13 patients evaluated after ≥10 years where the total tremor score was improved with 39% on versus off stimulation.

Sydow et al[8] reported 19 patients followed for a mean of 6.5 years (range 5.5 to 7.7). Hand tremor for the treated side was reduced with 76.6% after 1 year and 59.4% after 6 years, compared with baseline. Hand function (both treated and non-treated side) improved with 45.4% after 1 year and 36.9% after 6 years.

In our previous experience of 19 cases with Vim DBS evaluated at a mean of 1 year (range 0.5–2 years) and 7 years (range 6–9 years) after surgery, tremor in the contralateral upper extremity was reduced by 82.4% at 1 year and 60.3% at last follow-up, compared with baseline. The corresponding percentages for hand function were 67.7% and 35.4%, respectively.[14]

In the current study, the effect of stimulation remained significant at all times, both compared to baseline and to the off stimulation condition. However, some deterioration over time was seen, most importantly regarding contralateral hand function where there was a 20% deterioration at 10 years compared with 1 year after DBS.

The deteriorating effect did not seem to be a consequence of a progression of disease, since the ETRS scores of interest off-stimulation did not increase significantly over time. Likewise, no increase was seen in hand tremor or function on stimulation at the ipsilateral side in unilaterally implanted patients, while this score deteriorated for the treated hand. This would suggest habituation/tolerance as a more likely mechanism.

An increased tremor score on stimulation between two time points can be caused by progression of the disease and/or habituation, while an increase of the scores while off stimulation should be interpreted as progression of disease. Hence, the difference (delta) between the on and off state at different points in time has been assumed to represent habituation.[15]

However, from a clinical perspective the nature and definition of habituation/tolerance is not always clear. This is also true of the relation between this phenomenon and stimulation-induced ataxia, often appearing together.[15] While the deterioration of the effect was modest on the group level, we identified six patients who over time developed what from a clinical perspective was considered as a habituation and/or stimulation-induced ataxia affecting the treated arm and leading to a diminishing effect of the treatment. This necessitated multiple changes of the stimulation parameters, and sometimes other measures such as "stimulation vacation" or a more restrictive usages of the stimulation. It is

of interest to note that we have never encountered stimulation-induced ataxia of the lower extremities, which is more commonly described in the literature.[16] Whether this is a consequence of our use of mainly unilateral DBS, turning off stimulation during the night, different brain target, or other causes is uncertain.

Unilateral Vs Bilateral Surgery

The cZi/PSA has been reported to have ipsilateral connections[17] and ipsilateral improvements of DBS for ET have been seen.[18] However, as we have previously reported, such ipsilateral effects tend to wane over time,[19] and were not present at the long term evaluation.

As could be expected, bilateral surgery had a more pronounced effect on total ETRS (91.8%), tremor score (94.1%) and hand function (84.1%) than unilateral surgery (61.6%, 64.2% and 52.5%, respectively) on stimulation at 1 year compared to baseline. However, the deterioration of the effect over time both on and off stimulation was larger in bilateral than unilateral patients.

A larger deterioration among bilaterally implanted patients of the effect on stimulation has previously been reported by Favilla et al.[20] Peters and Tisch[15] have suggested that"*Conceptually, bilateral stimulation could exert greater plastic force on cerebellar networks to adopt abnormal configurations, with less potential for compensation from an untreated side*." However, in order to reduce the risk for affection of speech and balance, bilateral surgery was reserved for younger patients. Hence, the two groups were not identical at baseline. This, together with the limited number of patients, means that these findings should be interpreted with caution.

Stimulation Parameters

The energy consumption increased slightly during the first year, but no further increase was seen during the following years, and after 10 years the PEV was 0.21 V, 17% higher than at 6 weeks after surgery. This compares favorably with the long term reports of Vim DBS after 5 years and beyond (Cury et al 0.24 V,[9] Blomstedt et al 0.29 V.[14] Sydow et al 0.32 V[8] and Baizabal-Carvallo et al 0.39 V[7]). The PEV according to Tsuboi et al[13] cannot be calculated since the authors have evidently duplicated the numbers for the pulse-width (92 uS) also for the frequency (92 Hz), but based on the available figures it seems likely that they would have been close to Sydow et al.[8]

The low energy consumption and the use of mainly dual channel IPGs even in unilaterally operated patients resulted in a long battery life with few IPG replacements. After 10 years of stimulation, 62% of the Kinetra IPG:s were still functioning. During the study, this IPG model was replaced by the company with a new model, the Activa PC. In all patients in whom this model was used, the battery was depleted within 10 years, supporting previous studies reporting a 35% reduction of the battery longevity in the new model.[21] However, the new programming options available in the new model, such as interleaving stimulation did actually solve one case of suboptimal treatment effect and one case of stimulation induced side effects in the present cohort.

Brain Targets

Vim is the established DBS target in ET, but there has been a growing interest in alternative targets, driven by the hope of potential advantages concerning effects and side effects. The cZi/PSA was a commonly used target for tremor during the lesional era, and many different terms have over the years been used to denominate this area just beneath the Vim, superior to the substantia nigra, lateral of the red nucleus, posteriomedial to the STN and medial to the internal capsule.[22-25] However, regardless of which name has been used, it is evident based on published images and coordinates that the target area itself has differed little between different studies,[22] which is understandable considering how small the target area is,[26] and the limitations imposed by several of the surrounding structures in the form of undesired side effects from stimulation.[27] In the current study the target was defined according to the red nucleus and STN, in the area typically targeted in the literature, and with limited variations between individual patients.

Regarding DBS, the cZi/PSA has been suggested to be superior to Vim in terms of tremor relief and current efficiency, as presented in open studies,[3,12,22,28] and recently in two randomized blinded trials.[29,30] Notably, regardless of the DBS target at hand (cZi/PSA or Vim), it is generally believed that tremor relief results from modulating the cerebello-thalamic fibers within these structures.[22,28,31-33] Further, MRI-tractography studies have demonstrated a correlation between favorable tremor control and proximity to the cerebello-thalamic tract.[34-36]

However, little is known regarding the long-term effects of cZi/PSA DBS in ET, and nothing has been published beyond 4 years after surgery. This is the first very long-term follow-up of cZi/PSA DBS for ET and the outcome seems to compare well with previous reports on the long-term effects of Vim DBS, both regarding energy consumption and tremor reduction. A direct comparison between the cZi/PSA and Vim is of course not possible based on the current study, and it is in general surprisingly difficult to compare studies on DBS for ET. This is due to a number of factors, including the use of different scales, selection of reported items, the various manners of separating/mixing unilateral and bilateral procedures, and the use of different brain targets. To compare the Vim and cZi/PSA is further complicated by the fact that these two areas are directly adjacent, and that most patients operated in one of them, is likely to have electrode contacts also in the other. A number of studies of Vim DBS have actually demonstrated that electrode contacts that reach the cZi/PSA have a better effect on tremor than those located more dorsally-rostrally in the Vim itself.[28,31,37-39]

Conclusions

In the current study, cZi/PSA DBS was demonstrated to be a safe procedure with a mostly retained effect on tremor between

1 and 10 years after surgery, in the absence of increasing stimulation parameters. No progress of disease was seen off-stimulation in this cohort over 10 years. The modest deterioration seen on-stimulation was interpreted as caused by a habituation. There was a tendency for a more pronounced deterioration among bilaterally implanted patients, but it is unclear if this was caused by the procedure itself or other differences between the groups.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

Y.B.: 1A, 2A, 2B, 2C, 3A, 3B
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Disclosures

Ethical Compliance Statement: The study was approved by the Ethical Committee at the University of Umeå (Dnr 08-009 M), and informed consent obtained in accordance with the Declaration of Helsinki. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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