



## Long-term effects of unilateral deep brain stimulation on voice tremor in patients with essential tremor

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### ABSTRACT

**Introduction:** Voice tremor (VT) is a common symptom of Essential tremor (ET). Deep brain stimulation (DBS) is an established treatment for ET overall, however, its effect on VT is less clear. The aim of this study was to evaluate long-term effects of DBS on VT and to investigate how VT symptoms develop over time in patients with ET.

**Methods:** VT scores for the cohort of 81 ET patients that had undergone DBS surgery in the caudal zona incerta (cZi) were analyzed retrospectively. Thirty-four patients had preoperative VT and long-term evaluations were available for 19 patients. Longitudinal effects of cZi-DBS were investigated 1, 3 and 5 years postoperatively. VT progression was evaluated based on preoperative-, and off stimulation postoperative assessments.

**Results:** Unilateral cZi-DBS reduced average voice tremor by 58% at the 3-year follow-up and by 67% 5 years after surgery. Four patterns of VT development were identified among patients, and the effectiveness of cZi-DBS in alleviating voice tremor symptoms showed differing patterns for these subgroups.

**Conclusions:** This retrospective analysis of a small cohort of patients suggests that cZi-DBS may reduce VT in the long-term for patients with ET overall, but the pattern of VT progression likely influences the effectiveness of the treatment. These results also suggest that unilateral cZi-DBS may be more efficacious when treating patients with mild to moderate VT. A prospective, blinded, controlled clinical trial in patients with ET is needed to determine developmental patterns of VT, and the safety and efficacy of cZi-DBS for the treatment of VT.

Essential tremor (ET) is the most common tremor disorder with an estimated prevalence of 4.6% in the population aged 65 years and above [1]. The disorder is characterized by a postural-kinetic tremor, primarily in the upper extremities, but other parts of the body may be affected as well. Voice tremor (VT) is the third most frequent symptom of ET [2,3] with reported prevalence ranging from 12.4 to 30% [3,4] up to 62% [5]. The large discrepancy between prevalence estimates could be attributed to the heterogeneity of ET but may also reflect the heterogeneous nature of VT itself [6]. The symptoms of VT may range from very mild, barely perceptible, to severe where it can have a profound negative impact on patient communication and daily life [7,8]. According to patient reports, VT symptoms are slowly progressive although this has never been scientifically documented [6].

VT is not easily treated [9]. Locally injected botulinum toxin type A may reduce VT originating from the larynx [10], but may not alleviate VT originating from structures such as jaw or tongue. Deep brain stimulation (DBS) is a surgical treatment for medically refractory ET that can be very effective in controlling tremor, especially of the upper

extremities [9,11]. The efficacy of DBS on VT is, however, less clear [9]. Factors that have been suggested to affect the outcome include severity of VT symptoms off stimulation [12,13], patients' age [14], and side of stimulation [9]. Bilateral stimulation has been proposed to be more effective than unilateral in reducing VT, with studies reporting an additional improvement of approximately 80% after implantation of the second electrode [13,15]. However more recent reports have argued that unilateral DBS can be equally effective [16,17]. Overall, there are few studies reporting specifically on VT outcomes after DBS and long-term data are scarce in the literature. Table 1 summarizes key properties and results for the five evaluations that report VT outcomes in the long-term, i.e. at least 36 months after DBS surgery.

When evaluated across an entire sample of patients, the long-term effect of DBS on VT appears to be small and insignificant. However, we argue that there are three reasons why it is difficult to appreciate the efficacy of DBS on VT based on previous studies (Table 1). First, since previous reports may have included both patients with and without VT at baseline in the evaluation, the true treatment effect may have been

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**Table 1**

An overview of previously published investigations that report long-term ( $\geq 36$  months) effects of DBS on voice tremor. The mean ETRS voice tremor score and standard deviations are presented for the preoperative (baseline) and long-term follow-up evaluation (off and on DBS). Unilateral and bilateral results are listed separately if this data were reported in the original study.

Study	Prevalence of VT in the study cohort at baseline	DBS target	N (u/b)	Follow-up (months)	Mean ETRS VT score			% Improvement ON DBS compared to OFF DBS
					Baseline	Long-term		
						OFF	ON	
Fytagoridis et al. [18] (2012)	–	PSA	16/2	36–60 (M = 48.5)	0.3 ± 0.5	0.5 ± 0.9	0.2 ± 0.4	60% (NS)
Sydow et al. [19] (2003)	–	Vim	12/7	66–93 (M = 78.4)	u: 0.4 ± 0.5 (n = 14)	u: 0.6 ± 1.0	u: 0.3 ± 0.5	u: 50% (NS)
					b: 1.0 ± 0.8 (n = 4)	b: 1.3 ± 1.1	b: 0.4 ± 0.8	b: 69% (NS)
Putzke et al. [13] (2005)	90%	Vim	0/5	36	1.7 ± 1.1 (n = 21)	1.0 ± 0.8	0.0 ± 0.0	100% (NS)
Blomstedt et al. [20] (2007)	–	Vim	19/0	66–102 (M = 86)	0.7 ± 1.0	0.8 ± 1.2	0.7 ± 1.2	12.5% (NS)
Baizabal-Carvalho et al. [21] (2014)	–	Vim	6/7	114–164 (M = 132.5)		1.38	0.77	44% (SIG)

VT, voice tremor; N, number of patients; u, unilateral; b, bilateral; PSA, posterior subthalamic area; Vim, ventral intermediate nucleus of the thalamus; M, mean; NS, non-significant; SIG, significant.

underestimated due to the inclusion of patients that were not able to improve in terms of VT. Second, recent evaluations have highlighted a substantial degree of individual variability in VT outcomes with DBS [14,22]. Therefore, the small and inconsistent effects may also partly be due to a lack of detail in the reporting. Third, the progression in VT severity over time in patients with ET has not previously been investigated [6]. It cannot be assumed that VT symptoms progress in a uniform way across patients, and both the natural progression of VT severity and its interaction with the effects of DBS treatment demand more attention.

We report here on the long-term effects of DBS on VT in patients with ET. All patients had VT before surgery and were treated with DBS targeting the caudal zona incerta (cZi) in the posterior subthalamic area (PSA). The primary aim of the study was to evaluate the effect of unilateral cZi-DBS on VT, 1 year, 3 years, and 5 years after surgery. The secondary aim was to investigate how VT symptoms developed over time and whether the nature of VT progression had an influence on the treatment effect.

## 1. Material and methods

VT severity is routinely assessed by item 3 of Essential tremor rating scale (ETRS), using a 5-point scale for severity rating (a score of 0 indicating no VT symptoms and a score of 4 representing severe VT) [23]. We retrospectively analyzed ETRS assessments for the cohort of patients with ET that have undergone cZi-DBS at Umeå university hospital. Bilateral DBS was considered in younger patients with significant bilateral symptoms. The surgical procedure included frame based surgery with electrode implantation somewhat postero-medial of the posterior tail of the subthalamic nucleus, at the level of the maximal diameter of the red nucleus, as have been previously described [24]. Inclusion criteria were: 1) a score of 1 or more on VT, i.e. item 3 of ETRS, before surgery (baseline), 2) ETRS evaluations made on and off DBS at baseline and 1 year and 3 years after surgery, respectively, and 3) no previous DBS or lesional surgery on either side. See [Suppl. Figure 1](#) for an overview of the patient inclusion procedure. Nineteen patients (16 unilateral, 3 bilateral) fulfilled the criteria and were included in the study. For 13 of these patients, additional evaluations performed 5 years after surgery were also available. The 3 bilaterally implanted patients were evaluated separately for the right side (i.e. the hand

dominant side) with the right electrode turned off. The stimulation was switched off for a minimum of 30 min before the evaluations. Patient demographics and clinical characteristics of included patients are presented in [Supplementary Table 1](#). The three included bilateral patients were on average younger at onset of ET and time of surgery compared to patients with unilateral implants, however, the two patient groups were similar in terms of overall tremor severity and VT levels before surgery ([Suppl. Table 1](#)). Approval for this study was granted by the Regional Ethical Review Board in Umeå and all patients had given their consent to their evaluations being used for research purposes.

### 1.1. Data analysis

Comparisons of average VT severity on cZi-DBS and off cZi-DBS at each evaluation point were carried out with the Wilcoxon signed-rank test. Holm-Bonferroni's correction was applied due to multiple comparisons. Effect sizes for significant differences were calculated as  $r = Z/\sqrt{N}$  [25] for which  $|r| \geq 0.5$ ,  $|r| \geq 0.3$  and  $|r| \geq 0.1$  were considered large, medium and small effect sizes respectively [26]. VT development was identified by comparing VT scores off stimulation, from baseline up to the last follow-up.

## 2. Results

The effects of unilateral cZi-DBS on VT, contralateral arm tremor and total ETRS scores for the entire patient cohort are presented in [Table 2](#). Wilcoxon signed-rank testing indicated that average VT level was lower on cZi-stimulation compared to off stimulation at all three evaluations: one year ( $Z = -2.333$ ,  $p = 0.020$ ,  $r = 0.38$ ), three years ( $Z = -2.919$ ,  $p = 0.004$ ,  $r = 0.47$ ) and five years ( $Z = -2.220$ ,  $p = 0.026$ ,  $r = 0.44$ ) after surgery.

Individual assessments of VT levels at baseline and the three follow-ups are presented in [Table 3](#). As shown in [Table 3](#), some patients no longer exhibited VT symptoms in the postoperative off evaluations (i.e. 7 patients at the 1-year evaluation, 6 patients at the 3-year evaluation, and 4 patients at the 5-year evaluation). Among patients that had VT off stimulation, cZi-stimulation reduced VT for 50% (6 out of 12 patients) one year after surgery, for 77% (10 out of 13 patients) three years after surgery, and for 67% (6 out of 9 patients) five years postoperatively.

VT development due to disease progression was evaluated by

**Table 2**  
Group-level effects of cZi-DBS. Mean ETRS score ± standard deviations from baseline and the 1-, 3- and 5-year evaluations (off and on DBS) are presented. Improvements are expressed as percentage reduction comparing DBS ON with DBS OFF. Effect size (*r*) are indicated for significant differences.

Item	Max score	Base-line		Short-term 1-year evaluation			Long-term 3-year evaluation			Long-term 5-year evaluation		
		No DBS	DBS	OFF	ON	% Impr. ON vs. OFF	OFF	ON	% Impr. ON vs. OFF	OFF	ON	% Impr. ON vs. OFF
Follow-up (months)		19	19	12.3 ± 0.9			39.2 ± 8.0			64.9 ± 17.5		
Number of patients evaluated		19	19				19			13		
Voice tremor (item 3)	4	1.3 ± 0.6	1.0 ± 1.0	0.6 ± 0.6	0.6 ± 0.6	40% <i>p</i> = 0.020 <i>r</i> = 0.38	1.2 ± 1.1	0.5 ± 0.6	58% <i>p</i> = 0.004 <i>r</i> = 0.47	1.5 ± 1.4	0.5 ± 0.9	67% <i>p</i> = 0.026 <i>r</i> = 0.44
Arm tremor (contra) (item 5/6)	12	6.6 ± 2.0	5.8 ± 1.6	0.4 ± 0.7	0.4 ± 0.7	93%	6.0 ± 2.6	1.1 ± 1.2	82%	5.7 ± 3.1	0.9 ± 1.1	84%
Sum ETRS (item 1–21)	144	55.4 ± 11.8	59.0 ± 13.6	25.4 ± 9.9	25.4 ± 9.9	57%	61.6 ± 19.1	31.7 ± 13.4	49%	61.9 ± 25.0	29.2 ± 13.8	53%

ETRS, essential tremor rating scale; contra, contralateral to DBS.

comparing VT assessments made off stimulation (Table 3). Four patterns of development were identified in the cohort: 1) Six patients (32%, including all three bilaterally operated patient and three unilateral patients) experienced a progressive increase in symptom severity over time (Deteriorating VT), 2) five patients (26%) had stable VT symptoms over time (Stable VT), 3) four patients (21%) had no VT in any of the postoperative evaluations off stimulation (No VT), and 4) four patients (21%) had symptoms which fluctuated between being non-existent and mild levels (Fluctuating VT). A summary of patient characteristics, stimulation parameter settings and treatment outcomes for the identified subgroups is presented in Suppl. Table 2. The subgroups were similar regarding gender, age, age at onset of symptoms, duration of disease and baseline voice- and arm tremor. No statistical testing of differences between subgroups was performed due to the small number of patients within the subgroups.

The effect of DBS treatment was evaluated separately within the four subgroups in order to investigate whether the specific VT developmental pattern influenced the outcome (Fig. 1). The Deteriorating VT group received better effect of DBS (67% VT reduction three years after surgery, and 83% reduction after five years), compared to the Stable VT group (33% and 0% respectively) (Suppl. Table 2). The Fluctuating VT subgroup showed long-term group-level improvements (Fig. 1), but a fluctuating result pattern within individual patients over time (Table 3). Average stimulation parameters and contact coordinates did not differ between the subgroups, nor did average stimulation settings change considerably over time within a group (Suppl. Table 2). Average arm tremor levels on DBS were also similar across subgroups (Fig. 1).

### 3. Discussion

VT is a prevalent symptom in ET and constitutes a severe problem for some patients seeking advanced treatment. The aim of this study was to provide a detailed investigation of the short- and long-term effects of unilateral cZi-DBS on VT. We retrospectively analyzed our patient cohort including all patients with ET that had undergone DBS surgery targeting the cZi at our clinic. Out of a total of 81 patients, 34 patients (42%) had VT before surgery. The inclusion criteria for this study were met by 19 of these patients.

Unilateral cZi-DBS was found to reduce average VT levels, both in the short-term and in the long-term. The positive treatment effects were most pronounced in the two long-term evaluations, three- and five years after surgery, when DBS reduced VT severity by 58% and 67% respectively. Our results thus corroborate the findings of previous reports suggesting that unilateral stimulation may be sufficient to treat VT [16,17], also in the long-term. However, most patients investigated here had mild to moderate VT symptoms, and it is not clear whether unilateral cZi-DBS would have been equally effective in a population with more severe VT.

Although the present study included only patients with VT before surgery, we found that some patients no longer exhibited symptoms of VT in the postoperative off evaluations. Why some patients became symptom-free after surgery is unclear. Fluctuations in VT symptom severity over time have been reported before [17], however, our observations may also be suggestive of persistent microlesional effects [11] in some of the patients. Microlesional effects are very pronounced in the cZi and considered to be characteristic for this target [27], and it is possible therefore that our averaged results not only reflect the effect of stimulation but also the effect of surgery itself. It is also possible that microlesional effects of the inactive (right) electrode influenced long-term results for the three bilaterally operated patients included in this study. Certainly, microlesional effects can create problems when evaluating the effects of unilateral stimulation in patients with bilateral implants, but considering that all three bilateral patients in the present study had a progressive deterioration of VT over time, any such contribution is likely to have been limited.

ET is a heterogeneous condition and there is a need to explore and

**Table 3**

An overview of ETRS VT scores and subgroup affiliation for individual patients. Levels of improvement are expressed as percent reduction in VT ON DBS compared to OFF DBS. Subgroup affiliation is based on the nature of VT development from assessments made OFF DBS.

Subgroup	Patient	Side of electrode	Score for ETRS item 3 (voice tremor)												
			Base-line				Short-term 1-year evaluation			Long-term 3-year evaluation			Long-term 5-year evaluation		
			No DBS	OFF	ON	% Impr.	OFF	ON	% Impr.	OFF	ON	% Impr.	OFF	ON	% Impr.
Deteriorating VT	1	L	1	1	1	0	1	1	0	3	1	67			
	2	L	1	1	0	100	2	1	50	–	–	–			
	3 (b)	L	2	1	1	0	2	0	100	3	0	100			
	4 (b)	L	1	1	0	100	3	1	67	4	1	75			
	5 (b)	L	1	1	1	0	1	0	100	2	0	100			
Stable VT	17	L	2	2	1	50	3	1	67	–	–	–			
	6	L	3	3	2	33	3	2	33	3	3	0			
	7	L	2	3	1	67	2	1	50	–	–	–			
	8	L	1	1	1	0	1	1	0	1	1	0			
	18	L	1	1	1	0	1	1	0	–	–	–			
Fluctuating VT	19	L	2	2	1	50	2	1	50	–	–	–			
	9	L	1	1	1	0	0	0	N/A	1	0	100			
	10	R	1	0	0	N/A	0	0	N/A	1	0	100			
	11	L	1	0	0	N/A	1	0	100	1	1	0			
No VT	12	L	1	0	0	N/A	1	0	100	0	0	N/A			
	13	L	1	0	0	N/A	0	0	N/A	0	0	N/A			
	14	L	1	0	0	N/A	0	0	N/A	0	0	N/A			
	15	L	1	0	0	N/A	0	0	N/A	–	–	–			
	16	L	1	0	0	N/A	0	0	N/A	0	0	N/A			

ETRS, essential tremor rating scale; VT, voice tremor (item 3); b, bilaterally operated; L, left electrode; R, right electrode; N/A, not applicable; –, follow-up not due at the time of writing.

Deteriorating VT, a deterioration in voice tremor over time.

Stable VT, consistent and stable voice tremor severity over time.

Fluctuating VT, inconsistent voice tremor where VT symptoms fluctuate between being non-existent and being mild.

No VT, no voice tremor in any of the follow-up evaluations.

characterize possible clinical subtypes of ET to gain a better understanding of the disorder [28]. Although the present study investigated a relatively homogenous group of patients, all of whom had symptoms of VT at baseline, our data demonstrated a clinically relevant heterogeneity in the way that VT developed over time. Four subgroups based on VT developmental patterns were identified and the specific pattern of VT progression was found to influence the treatment result.

The largest and most persistent long-term improvements were seen among patients with a progressive increase in symptom severity. Despite a worsening in VT symptom severity over time, this subgroup of patients improved consistently throughout the investigated time period with a 67% and an 83% reduction in VT, three and five years after surgery. In contrast, for patients with stable VT symptoms, the treatment effect VT waned over time, from a 33% improvement 3 years after surgery, to 0% improvement at the last follow-up.

We could not observe any systematic differences in DBS treatments between subgroups, neither regarding stimulation location and parameter settings nor in its effectiveness in alleviating arm tremor. Subgroups were also similar in terms of age and baseline voice tremor; two factors that have otherwise been suggested to influence VT outcome with DBS [13,14]. We, therefore, suggest that the differences in long-term VT results with DBS treatment observed in this study were due in part to differences in pattern of VT development. However, independent investigations are warranted, first and foremost to corroborate the existence of different VT developmental patterns, and then in order to investigate an eventual interaction between developmental pattern and VT outcomes in the long-term.

Unlike previous studies, the present investigation included only patients with VT symptoms preoperatively and was thus able to show more prominent long-term effects of DBS on VT than previously reported. The natural progression of VT severity was also taken into

account. We argue that the lack of control over these two factors may lead to a substantial underestimation of the efficacy of DBS in reducing VT in patients with ET.

#### 4. Conclusions

Beneficial effects of unilateral cZi-DBS on ET VT symptoms may still be observed five years after surgery. The way that VT itself progresses may, however, show strong variability, and four developmental patterns were identified in the current study. The pattern of VT development may constitute an important factor influencing the effectiveness of DBS in alleviating VT in the long term. The cohort of patients investigated here however included only few patients with specific developmental patterns, and our results should therefore be interpreted with caution. Interpretations of these results are further limited by the lack of a control group, small sample size, and the retrospective nature of this analysis. A prospective, blinded, controlled clinical trial in patients with essential tremor is needed to determine developmental patterns of voice tremor and the safety and efficacy of cZi-DBS for the treatment of voice tremor.

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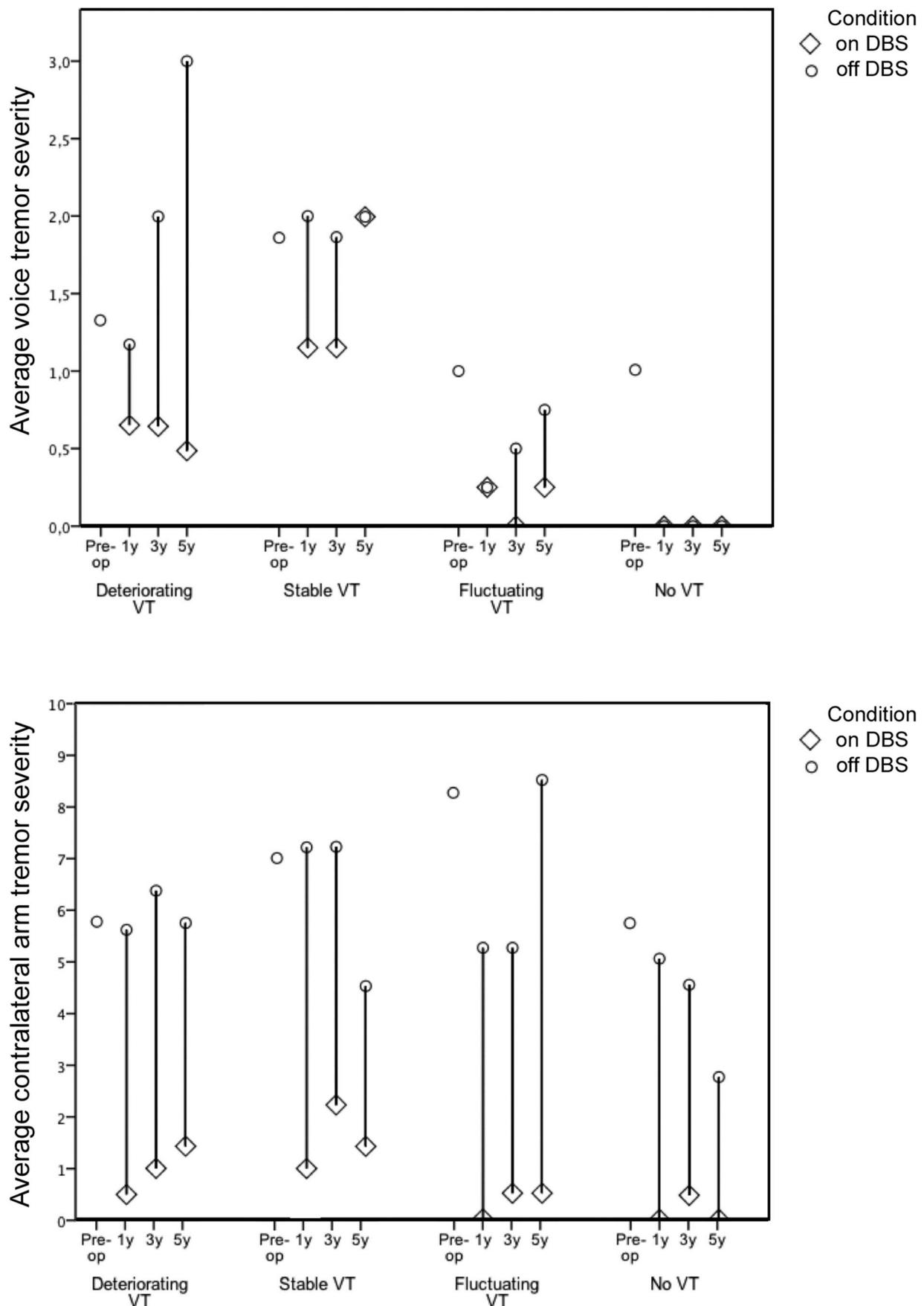


Fig. 1. Average voice tremor and arm tremor scores for each of the four subgroups from evaluations made at baseline and 1 year, 3 years, and 5 years after surgery.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2018.09.029>.

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