

UNIFORM QUALITATIVE ELECTROPHYSIOLOGICAL CHANGES IN POSTOPERATIVE REST TREMOR

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ABSTRACT

Ablation and deep brain stimulation (DBS) can treat pharmacologically uncontrollable tremor. Here, we compared the postoperative electrophysiological changes in resting hand tremor after 32 ablations and 12 DBS implantations in patients with severe tremor dominant idiopathic Parkinson's disease (PD) and essential tremor (ET). Short- and long-term accelerometric data were acquired after surgery and compared to the preoperative tremor.

After effective surgical treatments, significant rest tremor reduction and increase in both frequency and approximate entropy (ApEn) were detected in all PD cases irrespective of the type and target of intervention. However, long-term effect of DBS implantation on tremor reduction was significantly better compared to ablative treatments.

In case of thalamotomy, the postoperative increase in frequency and ApEn was significantly larger in essential tremor compared to PD, suggesting that the etiology of tremor may influence the size of the similar changes.

In cases, where clinical tremor re-emerged 6-12 months after the surgery, no change in frequency and ApEn was detected on the second postoperative day despite of an initial tremor reduction and clinical improvement similar to the effective operations.

Our results suggest that uniform postoperative changes in rest tremor, the increase in frequency and ApEn could be due to attenuation of pathological oscillators, and might be immediate indicators of the effectiveness of neurosurgical treatments relieving tremor.

Keywords: tremor, frequency, approximate entropy

Abbreviations: ApEn=approximate entropy; ET=essential tremor; FTMTRS=Fahn-Tolosa-Marin Tremor Rating Scale; PD=idiopathic Parkinson's disease; PS=power-spectrum; TR=tremor reduction;

INTRODUCTION

Physiological tremor is a normal phenomenon derived from oscillators of the central nervous system, peripheral loop mechanisms, cardioballistic movements and modified by mechanical properties of limbs¹. Using power-spectral analysis, physiological tremor reveals as irregular, 5-12 Hz tremor with several, but often without any remarkably dominant peaks. In contrast, pathological tremor of Parkinson's disease (PD) and essential tremor (ET) is characterized by regularity, presence of one dominant peak on the power-spectrum (PS) and usually lower tremor frequency^{2,3}.

Several studies have demonstrated that deep brain stimulator (DBS) implantation not only normalizes the intensity and regularity of pathological tremors, but postsurgical frequency increase in tremor EMG also occurs^{4,5}. Beside stimulation, ablation of certain anatomical targets can treat pathological tremors. Nevertheless, in 2-13% of the neurosurgical interventions the observed tremor reduction is only transitory⁶. The postoperative accelerometrical changes of such effective and ineffective ablative treatments are not known in details.

MATERIALS AND METHODS

Patients

The effect of 44 surgical procedures (32 ablations and 12 DBS implantations) of 33 patients (28 PD and 5 ET) was evaluated in prospective, long-term follow-up measurements. All patients underwent functional neurosurgical treatment (7 bilateral, 24 unilateral operations and 6 repeat operations because of unsuccessful intervention) to relieve tremor between December 2001 and December 2003 and gave informed consent according to the Local Ethical Committee. (See supplement file). All PD patients had dominant, Type 1 tremor. The diagnosis of ET and PD was in accordance with the current guidelines⁷. All examined patients had severe preoperative tremor (more than 45 points on FTMTRS⁸ part A and B). In addition, all ET patients had moderate, but visible resting tremor besides the serious postural-kinetic one.

Operative techniques

Unilateral ablation was performed on patients presenting symptoms mainly related to unilateral tremor unresponsive to medical therapy with or without rigidity. In case of bilateral symptoms unilateral ablation and contralateral DBS implantation were applied. A single ET patient received bilateral DBS implantation after ineffective thalamotomy. Indication, anatomical localization, target selection, micro-recording and surgical procedure were carried out following current guidelines^{9, 10}.

Measurements

The baseline examination was carried out 2 days before the surgery. “Short-term” effect was evaluated by analyzing the postoperative tremor 2 days after intervention. To examine “long-term” effects, recordings were made 3 months after the operation. During each occasion, 2 or 3 at least 7-15 minutes long measurements were recorded and FTMTRS⁸ were applied at least 6 hours after

drug withdrawal. Besides, all the patients were followed for at least 1 year by physical examination and applying FTMTRS but in some cases without accelerometry.

During recordings, subjects were positioned in a straight back chair. Their forearms were pronated and supported at the ulnar styloid process, while wrists were slightly dangling and able to move freely. The subjects were instructed to relax their forearms¹¹. Calibrated accelerometers (ADXL-105, Analog Devices Inc., USA) were attached to the dorsal surface of both hands in the area of the third metacarpus.

Data analysis

Data processing and subsequent analyses were performed by using Spike2 (version 5.04, Cambridge Electronic Design Ltd., UK). When technical artifacts had been eliminated, the recordings were down-sampled to 200 Hz and filtered by a low-pass finite-impulse filter with a cut-off frequency of 35Hz. Although rest tremor in both hands was recorded, only the side contralateral to the intervention was analyzed.

Interventions were evaluated by two independent investigators either as 'effective' or 'ineffective' based on the clinical symptoms and FTMTRS 6-12 months after the surgery.

Characterization of tremors

(1) Tremor reduction:

Fast Fourier Transformation quantitatively describes the components of waveform data in the frequency domain and creates a plotting called power-spectrum, which can be converted to energy (i.e. intensity or power). Total power (TP) was calculated as the area under the curve in the range of 3-15 Hz. Postsurgical improvement was quantified by a relative value:

Tremor reduction (TR) = (preoperative-TP) / (postoperative-TP).

Consequently, larger value indicates more reduction in tremor.

(2) Frequency of rest tremor (Fr) was determined by comparing autocorrelation and power-spectrum with the original accelerometric waveform data to ensure accurate results. The interpeak intervals of autocorrelation curve and the length of a periodic tremor oscillation measured on the accelerometric recording were identical; their inverse value gave the dominant frequency of tremor.

(3) Irregularity of tremor (approximate entropy, ApEn):

Irregularity was quantified by approximate entropy (ApEn), a method measuring the unpredictability of fluctuations¹². Recording containing many recurring patterns has a relatively small ApEn, i.e. a more regular value, contrary to a more complex and less predictable process, which has a higher, i.e. a more irregular value¹³. During ApEn calculations the suggested parameters were used ($m=2$, $r=0.2 \times SD$)⁵.

(4.) Morphology of power-spectra:

Morphology of PS was qualified by the number of peaks in the range of 3-15Hz. A peak in PS was defined as an increase of at least 3 frequency bins from the surrounding bins on either side.

Statistical analysis

All statistical analyses were carried out using SPSS software package (version 11, SPSS Inc, Chicago, USA). Statistical significance level was set to 5%. Since none of the critical variables were normally distributed, nonparametric Wilcoxon signed ranks test and Mann-Whitney test were performed.

RESULTS

Changes in Parkinsonian rest tremor after effective neurosurgical treatments

Thirty-two operations to control Parkinsonian tremor in 28 patients were considered effective and analyzed. First we examined, whether the type of intervention (ablation vs. DBS implantation) and the target of ablation (thalamotomy vs. pallidotomy) may influence various characteristics of resting tremor.

1. The intensity of tremor (total power) decreased significantly on the second postoperative day ($p < 0.001$). Both clinical and electrophysiological improvements (tremor reduction, TR) were maintained and detectable 3 months after surgery in all patients. However, a small but significant increase in intensity of rest tremor compared to the short-term values was observed in all cases 3 months after surgery, indicating that part of the postoperative effect was transitory (short-term TR: 46.7 vs. long-term: 28.9). In addition, the long-term effect of DBS implantation was significantly better compared to ablative treatments in PD patients (TR: 48.5 vs. 23.9), although short-term data were similar (**Figure 1A**). When thalamotomy and pallidotomy were compared, neither short- nor long-term tremor reductions were different.

2. An increase in frequency (range: 0.90-4.35 Hz) of rest tremor was detected on the second day and three months later in all cases (**Supplement**). In contrast to the intensity of tremor, the value of short- and long-term shifts did not differ significantly (2.20 vs. 2.22Hz). The type of surgical procedure (**Figure 1B**) and the target of intervention did not influence the size of the frequency-increase. This uniform increase in frequency was confirmed by 4 individual cases, where the effects of unilateral DBS implantation combined with contralateral ablation were similar (**Figure 1A**)

3. Both short- and long-term irregularity of tremor (ApEn) were significantly increased after effective operations (from 0.52 to 0.58, $p < 0.001$), suggesting that the tremor became more

irregular, similar to physiological tremor. Neither the type nor target of intervention influenced the size of ApEn increase (**Figure 1B**).

4. While *power-spectrum* (PS) of the original pathological tremor consisted of a single peak with its harmonics, 3-9 peaks appeared after effective treatments suggesting attenuation of the pathological oscillators. (**Figure 2A, Table 1**).

Taking together, increase in frequency, irregularity and change in the morphology of PS were observed after effective surgery irrespective of the type and target of interventions, while quantitatively the long-term tremor reductive effect of DBS implantation was significantly larger (**Figure 1A**).

Postoperative changes in resting essential tremor

In PD patients, neurosurgical treatments had a qualitatively similar, significant impact on electrophysiological properties of rest tremor. To determine, whether the described findings were disease specific, we analyzed the effects of 8 interventions on resting essential tremor. Although ET is regarded as postural-kinetic tremor, pathological resting essential tremor were both visually and accelerometrically detectable at rest in all cases. The presence of this symptom allowed the comparison of the effects on rest tremor in both ET and PD after thalamotomies.

Remarkably, short- and long-term tremor reductions after thalamotomy were not different between PD and ET. However, the size of frequency shift was significantly larger in ET than in PD (3.12Hz vs. 2.22Hz), indicating that the etiology of pathological tremor may influence the magnitude of frequency-shift (**Figure 3**). Although an increase in postoperative ApEn was detected similar to PD, this increase was significantly higher in ET as well. The preoperative PS of rest tremor in ET was very similar to that observed in PD, characterized by a single dominant peak with its harmonics (**Figure 2B**). The pattern of power-spectra was characterized by appearance of several peaks after thalamotomy indicating a similar attenuation of pathological oscillators as

observed in PD (**Figure 2**).

Since these data altogether indicated qualitatively similar, but quantitatively different postoperative changes in different rest tremors, next we examined tremor after unsuccessful operations.

Differences between ‘effective’ and ‘ineffective’ neurosurgical interventions

First, the power-spectra were analyzed in 7 cases (6 PD and 1 ET), where clinical tremor re-appeared 6-12 months after surgery indicating ineffectiveness of the applied intervention. A single dominant peak, similar to untreated tremors, characterized the postoperative PS morphology in all 7 cases (**Figure 4 and Table 1**).

This unchanged PS morphology suggested that unsuccessful operations might not have altered the rest tremor properties. To this end, we examined all the other characteristics of rest tremor in 4 patients after ineffective surgery (3 PD and 1 ET). Unexpectedly, two days after the surgical procedures tremor was significantly reduced similar to effective operations. However, 3 months later, the postoperative rest tremor intensity increased to near the baseline. More importantly, a lack of increase in frequency was evident as early as on the second postoperative day despite of clinical improvement (frequency-shift: -0.09 Hz, statistically not significant, **Supplement, Figure 4**). Similarly, ApEn and the morphology of PS remained unchanged.

Altogether, these data indicated that tremor frequency did not change after ineffective operations despite of transient clinical improvement and decreased intensity, thus predicting long-term outcome.

DISCUSSION

In the present study we compared the effects of different effective and ineffective neurosurgical treatments on resting Parkinsonian and essential tremor. Both DBS implantations and obsolete ablative treatments were examined to get a more complex view of tremor genesis.

Postsurgical changes in PS morphology, frequency-shift and irregularity of rest tremor after ablative treatments have not been analyzed in details so far. By examining the effects of 25 effective ablative treatments on Parkinsonian rest tremor, an increase in frequency, ApEn and number of peaks on power-spectra were detected, indicating that postoperative tremor became more similar to physiological tremor. Although effective surgical treatments changed all examined characteristics in a similar way, electrophysiologically a small, but statistically significant worsening was detected between the short- and long-term states. Meanwhile, neurological examination and FTMTRS did not show any worsening. This may be the result of subclinical reactivation of pathological oscillators or alternatively the vanishing of the temporary suppressive effect of postoperative edema. By comparing thalamotomy and pallidotomy, no significant difference could be observed in any of the analyzed parameters.

When effects of DBS implantations were examined, we noticed an increase in number of peaks on the power-spectra similar to ablations. In addition, an increase in frequency and ApEn of rest tremor was found confirming previous data, indicating higher irregularity in tremor genesis^{4,5}.

Beside the better long-term tremor reductive effect of DBS implantations against ablations, no qualitative or quantitative difference could be observed in any other examined tremor characteristics. This was confirmed in individual cases of PD and ET as well, where unilateral ablation combined with contralateral DBS implantation resulted in analogous changes. Consequently, ablation and DBS implantation may similarly influence the pathological oscillators responsible for tremor.

In order to determine, if the described postoperative changes are disease-specific or general, resting essential and Parkinsonian tremors were also compared after thalamotomy. In the observed ET cases, pathological rest tremor could be detected even visually beside the postural-kinetic one, which allowed us to compare rest tremor properties of different etiologies. Remarkably, the etiology of tremor determined the size of frequency-shift and ApEn change indicated by a significantly larger increase in ET.

To fully analyze postoperative changes, characteristics of rest tremor after ineffective interventions and their repeat operations were also examined. Interestingly, the postoperative short-term tremor reduction did not differ significantly between effective and ineffective treatments. However, about 20 times larger, statistically significant increase was observed three months later in unsuccessfully compared to the successfully treated cases, which became more prominent at 12 months control measurement. **(Table 1)** Remarkably, frequency of rest tremor, PS morphology and ApEn remained unchanged even on the second postoperative day in contrast to successful operations, while clinical tremor was equally reduced in both cases. Thus, whichever factor is responsible for considerable tremor reduction, it suppresses solely the intensity of rest tremor, but has no effect on other tremor characteristics. This differential effect on morphology of tremor may predict the outcome of surgery very early, even when short-term tremor reduction still does not indicate ineffectiveness. In other words, not the reduction of tremor intensity, but the change of tremor frequency, irregularity and power-spectrum morphology indicates the further effectiveness of surgery.

Two theories have been suggested to explain the phenomenon of tremor frequency and ApEn increase observed after DBS implantation in PD and ET patients^{4, 5}. According to the first theory, DBS itself is able to reset the frequency of certain central oscillator loops. Alternatively, DBS may suppress certain oscillators. Since we observed accelerometrically very similar effects of ablation and DBS, suppression rather than resetting oscillators seems more probable.

Several theories suggest that the highly synchronized pathological tremor generators are superimposed on the physiological oscillators^{2, 3}. Presumably if the neurosurgical interventions (either ablations or DBS implantations) destruct the actions of these pathological oscillators, the physiological tremor generators come to the front resulting in higher tremor frequency, irregularity (ApEn) and multi-peaked power-spectrum. However, in the case of ineffective treatments, the pathological oscillators are not destructed permanently, so they can continuously override physiological tremor generators. The unchanged tremor frequency, the low ApEn value and a single dominant peak on power-spectrum indicate that post-surgical tremor is still highly synchronized. The clinically well detectable short-term tremor reduction might be due to microthalamic-effect or microedema, which can temporarily decrease the intensity of tremor but not sufficient to alter its accelereometric properties.

Taking together, our results suggest that effective neurosurgical treatments result in a qualitatively uniform pattern in tremor characteristics. The multi-peaked rest tremor power-spectrum, the increase in irregularity and frequency could be due to attenuation of pathological oscillators and the release of previously suppressed physiological tremor generators. Moreover, the presence of these changes might be immediate indicator of the effectiveness of neurosurgical treatments relieving tremor, even when temporal clinical improvement and decreased intensity do not allow this early distinction.

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LEGENDS

Figure 1.

(A) Short-term (ST) and long-term (LT) tremor reduction after effective interventions (25 ablations, 7 DBS implantations) in PD patients were compared. Since tremor reduction values did not follow the normal distribution, the lower and upper border of boxplot represent the 25th and 75th percentiles, while the middle line indicates the median. Error-bars show the minimum and maximal values. (B) Pre- and postoperative rest tremor ApEn is plotted against frequency in cases of ablations and DBS implantations. Preoperative values are marked by gray squares, while the 2nd day postoperative values are indicated by black squares.

Figure 2.

(A) Pre- and postsurgical power-spectrum of a PD patient after effective pallidotomy (left panel) and contralateral DBS implantation to STN (right panel) is presented. Presurgical tremor is indicated by dotted line, while tremor on the 2nd postoperative day is represented by solid line. Shift in frequency after surgery is indicated by horizontal arrow. Pre- and postoperative tremor power have different scales. (B) Pre- and postsurgical power-spectrum of an ET patient after thalamotomy and contralateral DBS implantation is presented.

Figure 3.

Rest tremor frequency before and after successful thalamotomies in PD and ET. The postoperative frequency values are significantly increased in all individual cases ($p < 0.001$), the size of increase were significantly larger in the ET group ($p < 0.05$).

Figure 4.

The figure illustrates both the short (A) and long-term (B) postoperative power-spectra compared to the preoperative ones in a single case after an ineffective thalamotomy and an effective re-operation. The left panel indicates ineffective thalamotomy, while the right panel shows effective re-operation of the very same patient. Presurgical tremor is indicated by dotted line, while the tremor observed on the second postoperative day (A) and the third postoperative month (B) is represented by solid lines. Of note, pre- and postoperative scales are different (preoperative: left axis, postoperative: right axis). Horizontal arrow indicates the postoperative frequency shift. Similar changes have been recorded in another 3 PD patients after effective re-operations.

Table 1.

Characteristics of postsurgical rest tremor after ineffective operations compared to effective interventions. The intensity of tremor (total power, TP), the tremor frequency and the number of peaks on power-spectrum (PS) is compared between effective and ineffective neurosurgical interventions. For definitions of tremor characteristics and the efficiency of surgery refer to text.

TABLE AND FIGURES

Table 1. Characteristics of postsurgical rest tremor after ineffective operations compared to effective interventions.

Surgery	<u>Total power</u> ^a		<u>Frequency</u>		<u>Number of peaks on PS</u>	
	Effective	Ineffective	Effective	Ineffective	Effective	Ineffective
Preoperative	N/A	N/A	5.12 (40/40)	5.01 (4/4)	2.1 (40/40)	2.2 (4/4)
Postoperative 2 days	2.12% ^b (40/40)	1.41% ^b (4/4)	7.14 ^b (40/40)	4.93 ^c (4/4)	5.4 ^b (40/40)	2.2 ^c (4/4)
Postoperative 3 months	3.34% ^b (40/40)	47.62% ^{b,c} (4/4)	7.19 ^b (40/40)	5.06 ^c (4/4)	5.8 ^b (40/40)	2.0 ^c (4/4)
Postoperative 6-12 months	3.93% ^b (21/21)	89.76% ^c (4/4)	7.21 ^b (21/21)	4.87 ^c (7/7)	4.9 ^b (21/21)	2.1 ^c (7/7)

^aPostoperative total power is given in relative value as the percentage of preoperative-TP

^bStatistically significant change compared to presurgical value (p<0.01)

^cStatistically significant change compared to effective group (p<0.01)

N/A = not applicable

FIGURE 1

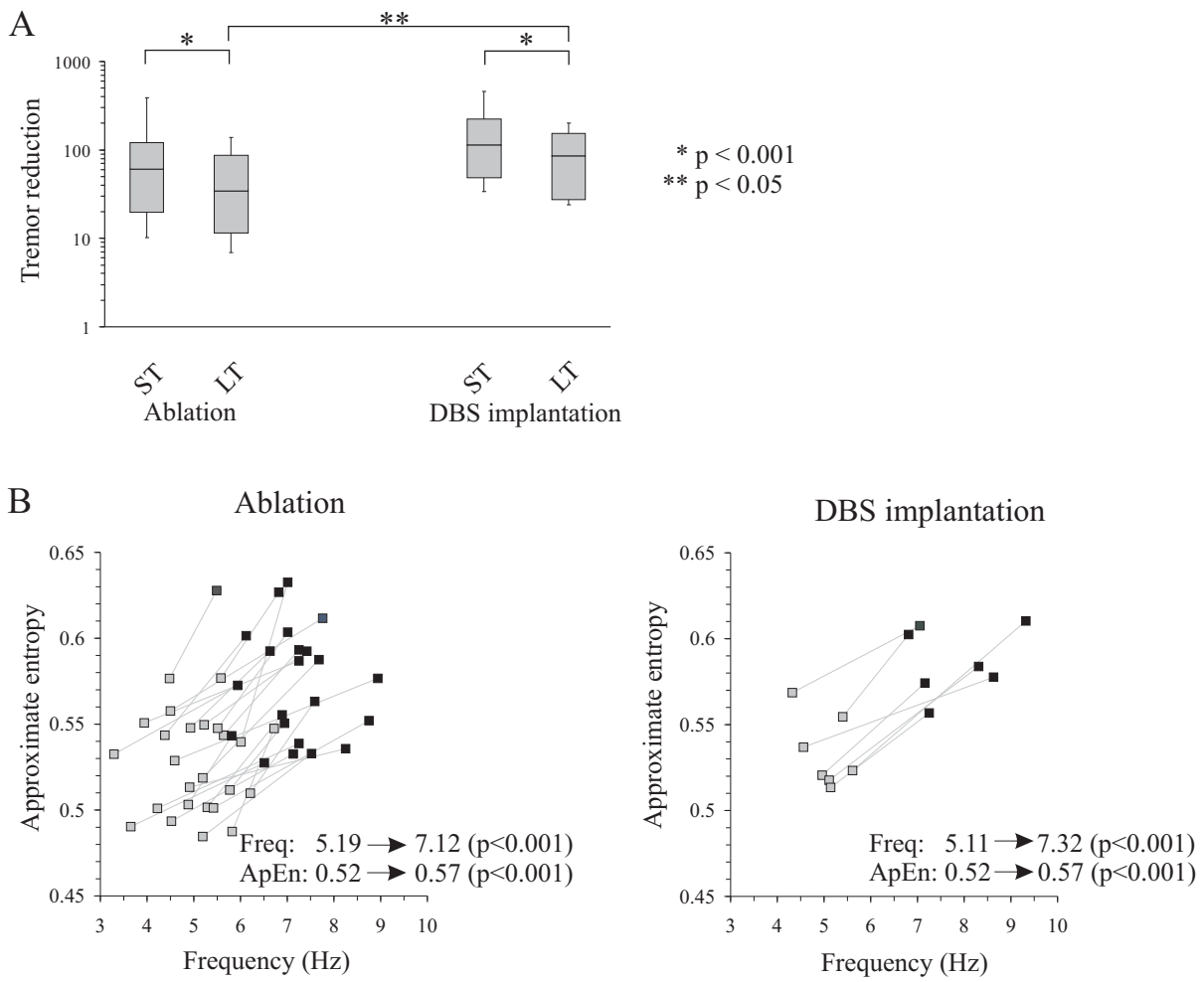


FIGURE 2

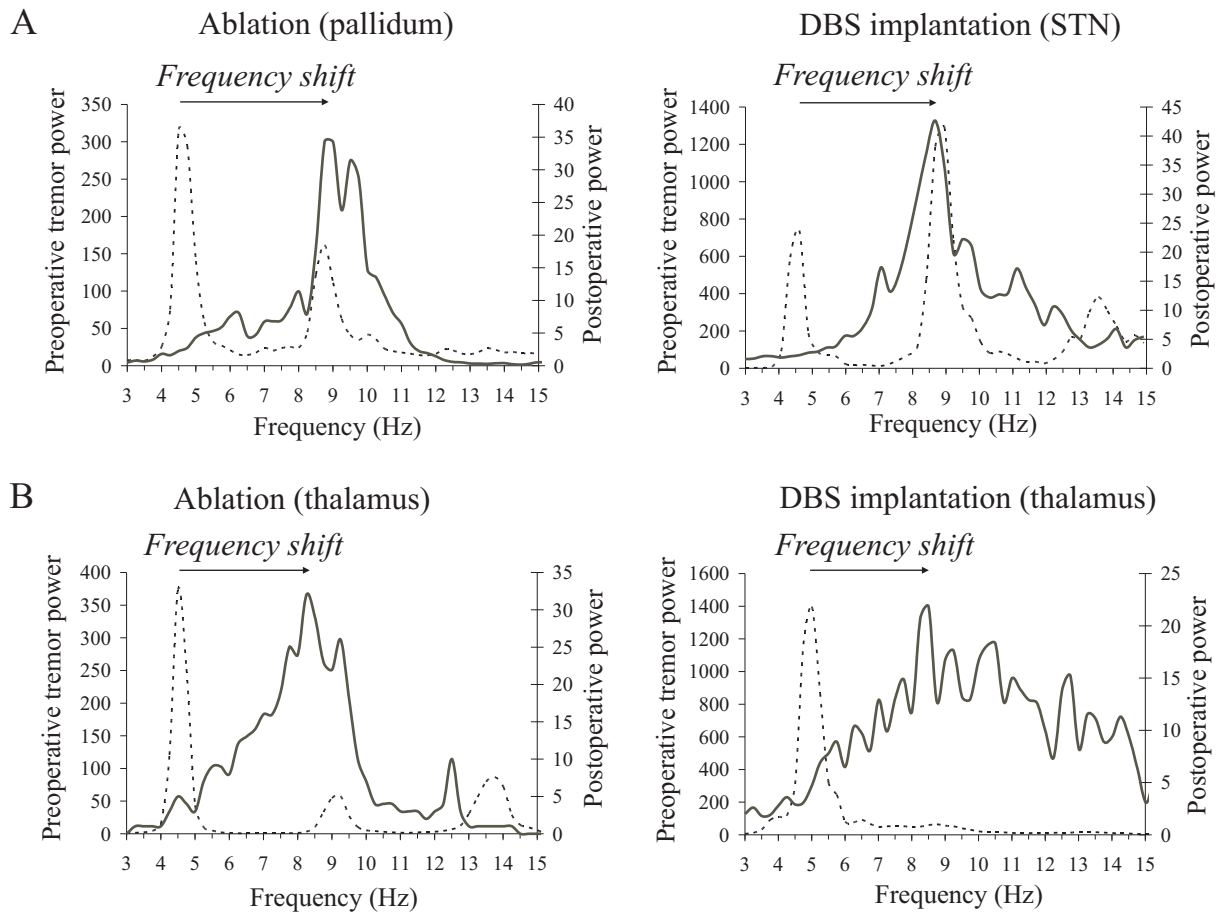


FIGURE 3

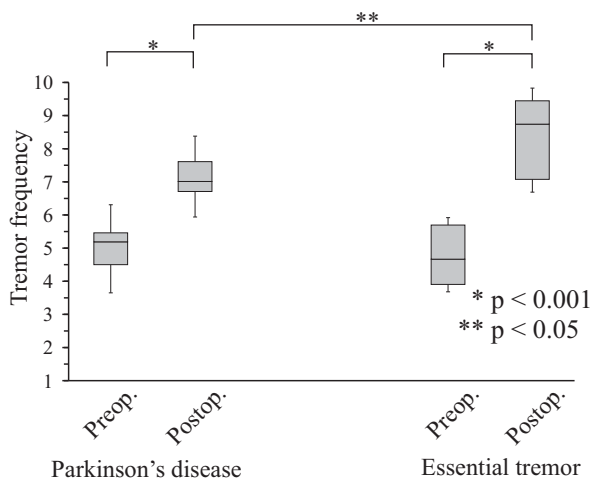
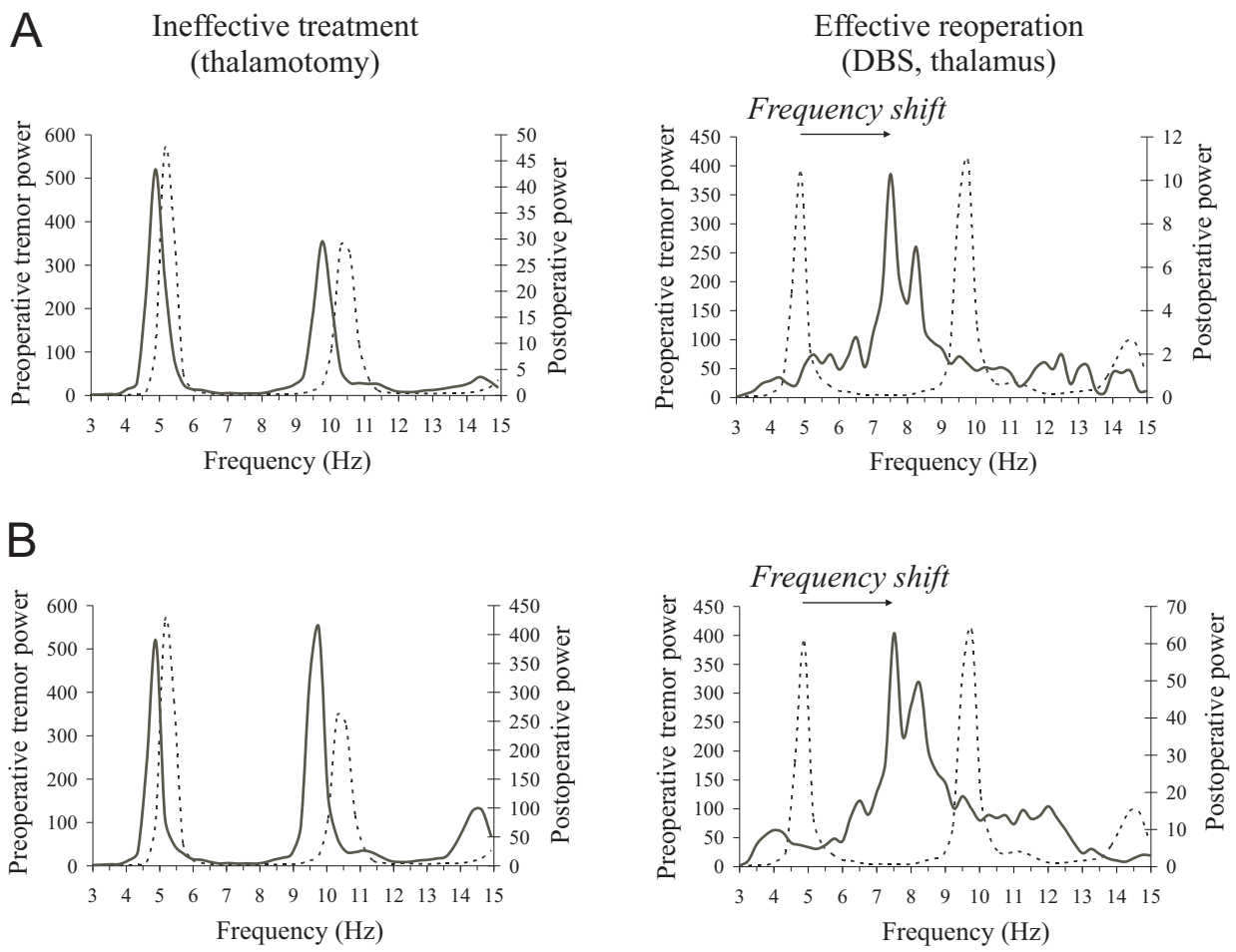


FIGURE 4



SUPPLEMENT FILE

Table. Detailed information on patients and observed tremor characteristics.

<u>Patient information</u>				<u>Operation information</u>			<u>Rest tremor frequency</u>			<u>Frequency shift</u>	
<u>Patient No</u>	<u>Age</u>	<u>Sex</u>	<u>Disease</u>	<u>Operation type</u>	<u>Side</u>	<u>Success</u>	<u>Fr1</u>	<u>Fr2</u>	<u>Fr3</u>	<u>Shift1</u>	<u>Shift2</u>
1	58	F	PD	Thalamotomy	R	+	5.42	8.75	8.43	3.33	3.01
2	62	F	PD	Thalamotomy	R	+	5.51	7.01	6.93	1.5	1.42
3	63	F	PD	Thalamotomy	L	+	4.88	5.81	5.94	0.93	1.06
4	70	M	PD	Thalamotomy	L	+	4.91	8.25	8.45	3.34	3.54
5	68	F	PD	Thalamotomy	R	+	5.19	7.52	7.61	2.33	2.42
6	67	F	PD	Thalamotomy	L	+	5.46	6.69	6.76	1.23	1.3
7	50	F	PD	Thalamotomy	L	+	5.77	6.94	7.01	1.17	1.24
8	71	F	PD	Thalamotomy	R	+	3.65	6.51	6.28	2.86	2.63
9	48	F	PD	Thalamotomy	R	+	4.93	6.63	6.76	1.7	1.83
10	68	M	PD	Thalamotomy	L	+	5.19	7.68	7.5	2.49	2.31
11	66	M	PD	Thalamotomy	R	+	4.5	7.76	7.77	3.26	3.27
12	71	M	PD	Pallidotomy	R	+	4.52	7.13	7.25	2.61	2.73
13	73	F	PD	Pallidotomy	R	+	5.58	6.82	6.79	1.24	1.21
14	54	F	PD	Pallidotomy	L	+	3.29	5.94	5.9	2.65	2.61
15	59	F	PD	Pallidotomy	R	+	4.48	5.49	5.39	1.01	0.91
16	74	M	PD	Pallidotomy	R	+	5.29	6.89	6.99	1.6	1.7
17	75	F	PD	Pallidotomy	R	+	6.01	7.01	7.12	1	1.11
18	63	M	PD	Pallidotomy	L	+	6.21	7.59	7.38	1.38	1.17
19	51	M	PD	DBS (STN)	R	+	4.32	7.05	7.12	2.73	2.8
20	66	F	PD	DBS (STN)	L	+	5.61	9.32	9.36	3.71	3.75
21	56	F	PD	Thalamotomy	R	+	5.82	6.72	6.71	0.9	0.89
				DBS (Vim)	L	+	5.4	6.81	6.76	1.41	1.36
22	58	M	PD	Thalamotomy	L	+	5.22	7.42	7.49	2.2	2.27
				DBS (Vim)	R	+	5.14	7.25	7.32	2.11	2.18
23	49	F	PD	Thalamotomy	R	-	5.94	5.5	5.64	-0.44	-0.3
				Pallidotomy	R	+(reop)	5.64	7.25	7.76	1.61	2.12
				DBS (STN)	L	+	4.96	7.16	7.14	2.2	2.18
24	60	M	PD	Thalamotomy	L	-	4.18	4.26	4.2	0.08	0.02
				Thalamotomy	L	+(reop)	4.22	7.25	7.38	3.03	3.16
				Thalamotomy	R	+	4.38	6.12	5.98	1.74	1.6
25	40	M	PD	DBS (Vim)	L	-	4.87	4.99	5.03	0.12	0.16
26	55	M	PD	Pallidotomy	R	+(reop)	4.59	8.94	8.95	4.35	4.36
				DBS (STN)	L	+	4.56	8.63	8.65	4.07	4.09
27	41	M	PD	DBS (STN)	L	+(reop)	5.11	8.31	8.29	3.2	3.18
28	51	F	PD	Pallidotomy	L	+(reop)	3.94	7.25	7.45	3.31	3.51
29	67	F	ET	Thalamotomy	R	+	4.75	9.09	9.51	4.34	4.76
30	58	F	ET	Thalamotomy	R	+	6.01	9.12	9.25	3.11	3.24
31	51	F	ET	Thalamotomy	R	+	4.58	8.46	8.23	3.88	3.65
				DBS (Vim)	L	+	4.96	8.43	8.54	3.47	3.58
32	69	F	ET	Thalamotomy	R	+	3.68	6.59	6.69	2.91	3.01
				DBS (Vim)	L	+	3.74	6.71	6.72	2.97	2.98
33	63	M	ET	Thalamotomy	L	-	5.15	4.88	5.1	-0.27	-0.05
				DBS (Vim)	R	+	5.09	7.02	7.5	1.93	2.41
				DBS (Vim)	L	+(reop)	4.98	6.98	6.86	2	1.88

STN= subthalamic nucleus, Vim= ventral intermedius nucleus of thalamus

LEGEND.

Table. Each subject has a unique ID. Fr1 is the frequency of rest tremor in Hz before surgery, Fr2 two days after surgery, Fr3 3 months after the intervention. Shift1 is the frequency-shift in rest tremor detected after operation (short-term change, difference of Fr2 and Fr1), Shift2 observed at control measurements (long-term change, difference of Fr3 and Fr2) compared to preoperatively recorded tremor. All effective operations are marked “+”, all ineffective ones “-”. Operations marked “+ reop” are successful repeat operations after an ineffective neurosurgical treatment. Three out of the re-operated subjects (Patient ID 26, 27, 28) had originally ineffective procedure before the start of this investigation.