ELSEVIER

Thalamus & Related Systems 1 (2001) 203–211

Thalamus & Related Systems

www.elsevier.com/locate/tharel

Effect of deep brain stimulation on amplitude and frequency characteristics of rest tremor in Parkinson's disease

Anne Beuter [a,b,c,*], Michèle S. Titcombe [a,b], François Richer [a], Christian Gross [c], Dominique Guehl [c]

[a] *Cognitive Neuroscience Centre (DS-5749), University of Quebec at Montreal, P.O. Box 8888, Station Centre Ville, Montréal, Que., Canada H3C 3P8*

[b] *Physiology Department, Centre for Nonlinear Dynamics in Physiology and Medicine, McGill University, 3655 rue Drummond, Montréal, Que., Canada H3G 1Y6*

[c] *Service d'Explorations Fonctionnelles du Système Nerveux, CHU de Bordeaux, Hôpital du Haut Levêque, 33600 Pessac, France*

Accepted 2 October 2001

Abstract

The effect of chronic high frequency deep brain stimulation (DBS) on rest tremor was investigated in subjects with Parkinson's disease (PD). Eight PD subjects with high amplitude tremor (Group 1) and eight PD subjects with low amplitude tremor (Group 2, used as a reference group) were examined by a clinical neurologist and tested with a velocity laser to quantify time and frequency domain characteristics of tremor. Possible rebound effects in rest tremor when DBS was stopped for 60 min were also explored. Participants received DBS of the internal globus pallidus (GPi) ($n = 7$), the subthalamic nucleus (STN) ($n = 6$) or the ventrointermediate nucleus of the thalamus (Vim) ($n = 3$). Tremor was recorded with a velocity laser under two conditions of DBS (on–off) and two conditions of medication (L-Dopa on–off). Correlations between clinical and experimental results for tremor amplitude was 0.70 with no medication and no stimulation. In Group 1, DBS decreased tremor amplitude but also increased spectral concentration and median frequency significantly. Under medication, the changes in tremor with and without stimulation were not statistically significant (Group 1). When stimulation was stopped for 60 min, a rebound in tremor amplitude was observed and median frequency remained stable in Group 1. None of the comparisons examined produced significant effects in Group 2. Taken together, these results suggest that beyond its effect on tremor amplitude DBS acted also on tremor frequency and did not modify tremor characteristics in subjects with low amplitude tremor.

Keywords: High frequency chronic stimulation; Time and frequency domain analysis

1. Introduction

Parkinson's disease (PD) is characterised by the progressive loss of dopamine neurons in the substantia nigra of the midbrain, and is associated with motor symptoms including tremor, bradykinesia and rigidity. Tremor is a highly sensitive manifestation of the motor system. In PD, it becomes more regular or harmonic, its frequency is shifted to a lower range, its amplitude increases, the shape of its oscillations changes, and it fluctuates over time (Beuter and Edwards, 1999; Edwards and Beuter, 2000). These changes are subtle and intermittent at first and become more permanent and obvious as the disease progresses.

Albe-Fessard et al. (1962) observed that during the electrophysiological steps preparing a thalamotomy, stimulation of the thalamus decreased tremor (see Speelman and Bosch, 1998 for a review). Since that time it has been shown that chronic high frequency thalamic stimulation (also called electrical neuroinhibition, neuromodulation, high frequency stimulation and deep brain stimulation, DBS) can decrease tremor amplitude in a spectacular way (Benabid et al., 1991; Caparros-Lefebvre et al., 1993). These dramatic effects have also been observed with lesions or stimulation of the globus pallidus (GPi) (Siegfried and Lippitz, 1994; Gross et al., 1997) and the subthalamic nucleus (STN) (Limousin et al., 1995; Krack et al., 1997) and have been shown to relieve not only tremor but also other symptoms of PD such as rigidity and dyskinesia (see Benabid et al., 2000 for a review). According to Schuurman et al. (2000), both lesion and stimulation of the thalamus are thought to be as effective for tremor reduction but thalamic stimulation is associated with fewer adverse effects than thalamotomy. Stimulation has become a standard technique for relieving tremor not only in PD, but also in essential tremor (Vuong et al., 2000) and multiple sclerosis (Benabid et al., 1998; Gross and Lozano, 2000

* Corresponding author. Address as of January 2002: Faculté des Sciences du Sport et de l'Education Physique, Université Wontpelier I, Montpelier, France.

E-mail address: a.beuter@staps.univ-montpl.fr (A. Beuter).

1472-9288/01/$ – see front matter
PII: S1472-9288(01)00020-6

for a review). The decrease in tremor is well documented for the Vim, the STN and the GPi (Kumar et al., 1998; Benabid et al., 1996; Limousin-Dowsey et al., 1999; Speelman et al., 1998). In a review of 17 studies on the effect of DBS, Gross and Lozano (2000) noted a 45–97% decrease in tremor. Thus, it seemed interesting to us to characterise precisely this decrease in tremor amplitude and in fluctuation of amplitude (typical of PD tremor) both in a group of subjects receiving DBS to relieve tremor (Group 1) or to relieve other PD symptoms (Group 2, considered as a reference group).

The effect of DBS on tremor frequency is less documented. It has been suggested that on average DBS increased tremor frequency to values that are closer to those observed in normal physiological tremor. For example, in one study, results for tremor frequency remained unchanged for thalamic stimulation of one subject (Burleigh et al., 1993). Timmer et al. (1999) applied a test for difference between peak frequencies to power spectra for postural tremor of one subject with and without DBS of the Vim and found that Vim stimulation shifted the peak frequency of the subject's postural tremor from 4.9 to 6.27 Hz ($P < 0.01$). Thus, we examined the effect of DBS on tremor frequency and spectral concentration in the two groups of subjects.

A secondary objective was to examine the effect of stopping stimulation for 60 min. One study used a 10-min stop (Ceballos-Baumann et al., 1999) but generally little or no specific guidance to clinicians is provided in the literature. We know that tremor reappears within seconds when stimulation is stopped (Benabid et al., 1998; Caparros-Lefebvre et al., 1993; Titcombe et al., 2001). Recent reports on tremor assessed qualitatively (UPDRS) after discontinuing thalamic stimulation in PD vary from a clear tendency of tremor rebound (Hariz et al., 1999) to an inconsistent rebound increase of tremor (Vuong et al., 2000). Thus, we decided to quantify tremor amplitude and frequency every 15 min during a 60-min period after stopping DBS.

2. Methods

2.1. Subjects

Sixteen subjects diagnosed with PD participated in the study. All subjects were receiving chronic stimulation either uni- or bilaterally for the relief of PD symptoms including tremor, dyskinesia, or rigidity. They were all under 70 years of age and included 11 males and 5 females. They included eight subjects ($n = 8$) with high amplitude tremor (Group 1: subjects 1–8) receiving stimulation of the GPi ($n = 2$), the STN ($n = 3$) and the Vim ($n = 3$) for tremor, and eight subjects ($n = 8$) with low amplitude tremor (Group 2: subjects 9–16) receiving stimulation of the STN ($n = 3$) and the GPi ($n = 5$) for rigidity or dyskinesias. The average age for Group 1 was 58.5 years (S.D. = 9.8 years) and it was 52.8 years (S.D. = 10.2 years) for Group 2. All participants were clinically stable at the moment of the tests, they did not show cognitive impairment (scores above 130/144 on the Mattis scale) and did not suffer from a major depressive disorder. All subjects, but one, were right-handed as determined by the Edinburgh Handedness Inventory (scores between 60 and 100). The only left-handed subject (Group 1: subject 5) had a score of −100. Since tremor is not affected by gender (Louis et al., 1998), we tested males and females. All subjects were under minimum dopaminergic therapy (ranging from 300 to 1200 mg per day of L-Dopa) at the time of the study and took no other PD related medications.

2.2. Experimental procedures

All subjects gave informed consent and institutional ethics procedures were followed. The subjects selected were asked to refrain from taking their medication at least 12 h before the beginning of the tests and were allowed to have no more than one coffee at breakfast on the two testing days. Rest tremor was recorded on the most affected side with a velocity-transducing laser (Beuter et al., 1994; Norman et al., 1999). This laser (Bruel and Kjaer, Naerum, Denmark) is a safe (Class II) helium–neon laser. The laser beam is split with one part directed at the finger and the other, called the reference, directed at a rotating disk inside the laser. Back scattered light from the rotating disk is used to determine the sign of the velocity signal. Finger tremor was detected and converted into a calibrated voltage output proportional to finger velocity. Velocity is more sensitive than acceleration to low frequency components that are inherent to pathological and physiological tremor (Norman et al., 1999). The system did not require a special calibration procedure. The laser was placed at about 30 cm from the index finger tip and the laser beam was directed perpendicular to a piece of reflective tape placed on the finger tip (Fig. 1). Each tremor test lasted 60 s. Positive velocity was recorded when the subject extended the finger and negative velocity when the subject flexed the finger.

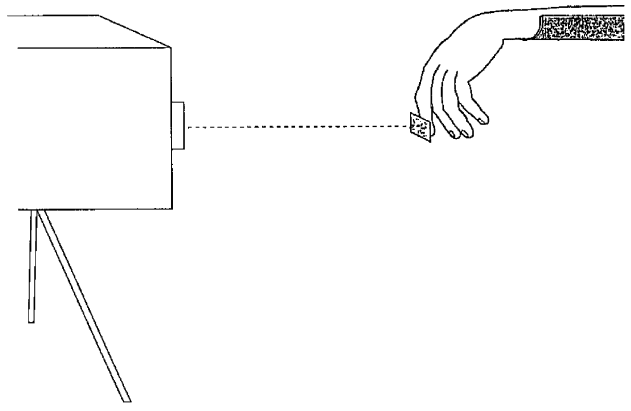

Fig. 1. Schematic representation of the position of the laser beam on the index fingertip covered with a piece of reflective paper during rest tremor recording.

Participants removed their watch and sat on a chair with their forearms resting on special foam padded supports. The tests started after a settle-down time of 5 min as suggested by Ito (1961). The subject's wrist hung freely over the edge of the padded support (Fig. 1). The experiment was done over a 2-day period. The conditions, counterbalanced across subjects, included the following.

1. *The* L-*Dopa condition* (*no stimulation*): After 12 h without medication, the subject took 150% of his or her morning dose of L-Dopa (Modopar). The testing started as soon as the clinical neurologist administering the UPDRS (Part III) estimated that the medication was fully effective. Usually, it took between 20 and 40 min.
2. *The DBS condition* (*stimulation only*): The subject was tested after being off medication for 12 h but with the stimulator on without interruption.
3. *The "off" condition* (*no medication and no stimulation*): The subject off medication for at least 12 h was tested after the stimulator was switched off for at least 1 h. During this hour, rest tremor was measured every 15 min for 60 s.
4. *The "on" condition* (*on medication and on stimulation*): This condition was tested after the subject took his or her medication and the clinical neurologist determined based on the UPDRS (Part III) that medication was fully effective. Stimulation had been on for at least 1 h.

A clinical neurologist examined the subjects using Part III, item 20 (scores between 0 and 4), of the UPDRS (Fahn and Elton, 1987) before each testing condition. This item takes into account both amplitude and frequency of occurrence of tremor episodes. The clinical examination was performed immediately before each tremor test. One subject was tested before and after surgery (subject 5). Subjects who were not feeling well enough on the first testing session (i.e. subjects 2, 6, 8 of Group 1 and subject 10 from Group 2) were tested again at a later date. When DBS was stopped for 60 min, the subject generally relaxed in the testing chair, read or changed seat and remained in the testing room. This test was not completed by subjects receiving Vim stimulation because it was too stressful and tiring for these subjects to remain without stimulation for 1 h.

2.3. Data acquisition

Data were collected using the MacLab data acquisition system (version 3.5.6/S, AD Instruments Pty Ltd, Castle Hill, Australia) and sampled at 100 Hz. Raw data were exported to S-Plus (Stat. Sci. Inc., Seattle, WA) for analysis and converted from volts to mm/s. For the calculation of characteristics based on the Fourier power spectrum, only frequencies below 20 Hz were used. A 3-point median filter was applied to raw data sets to interpolate across artifacts in the data created by the rotation of the laser wheel.

Quadripolar leads were implanted stereotactically uni- or bilaterally in the Vim, GPi or STN, and DBS was applied for 24 h a day. Stimulation parameters are presented in Table 1. Note that the cyclic mode of stimulation (e.g. 1 min on and 1 s off) was used in six subjects to optimise the stimulation parameters while avoiding side effects. Furthermore,

Table 1
Stimulation parameters for Group 1 (subjects 1–8) and Group 2 (subjects 9–16)

Subject	Sex[a] and age (year)	Stimulated target[b]	Intensity (v)	Pulse duration (μs)	Frequency (Hz)	Mode (Cont/Cycl)[c]	Stimulation contacts[d]
Group 1 (high amplitude tremor)							
1	M 54	GPi	2.4	90	185	Cont	−, −, −, NS
2	M 52	GPi	3.7	120	160	Cycl	−, NS, NS, NS
3	F 71	Vim	3.3	60	130	Cont	−, NS, NS, NS
4	M 67	Vim	5.3	90	185	Cont	NS, NS, −, −
5	M 40	Vim	1.3	90	135	Cont	NS, NS, −, −
6	F 61	STN	2.0	90	185	Cycl	NS, −, −, NS
7	F 59	STN	2.4	90	185	Cycl	NS, NS, −, NS
8	M 64	STN	2.8	90	135	Cont	−, −, NS, NS
Group 2 (low amplitude tremor)							
9	M 68	GPi	3.7	90	185	Cont	−, −, −, NS
10	M 59	GPi	3.7	70	185	Cont	−, −, NS, NS
11	M 57	GPi	4.6	90	185	Cont	NS, +, −, −
12	M 54	GPi	4.0	90	185	Cycl	−, −, −, NS
13	F 50	GPi	4.0	90	130	Cont	+, −, −, NS
14	M 57	STN	2.8	90	185	Cont	NS, NS, NS, −
15	M 40	STN	2.5	90	135	Cycl	NS, −, − NS
16	F 37	STN	2.2	90	185	Cycl	−, −, −, NS

[a] M: male; F: female.

[b] Target structures: GPi, internal globus pallidus; Vim, ventrointermediate nucleus of the thalamus; STN, subthalamic nucleus.

[c] Mode of stimulation: Cont, continuous; Cycl, cyclic (e.g. 1 min on, 1 s off).

[d] Stimulation contact points listed in order of proximal distal direction: "+", positive stimulation; "−", negative stimulation; "NS", contact points that are not stimulated.

the polarity of the stimulation allowing an improved control of current within the stimulated structure (Ranck, 1975) was based on a compromise between clinical improvement and adverse effects.

2.4. Tremor characteristics

Four parameters were computed from the 60 s signal samples.

1. *Amplitude* measured using the root mean square (RMS) of the filtered velocity signal. Increasing tremor amplitude is the most obvious sign of abnormality.
2. *Amplitude fluctuations* measured as amplitude variability in an envelope around tremor oscillation (demodulation) normalised with respect to tremor amplitude. Increasing scores indicate that tremor amplitude is fluctuating over time and this is considered as a sign of abnormality (Edwards and Beuter, 2000).
3. *Spectral concentration* measured by the concentration of power in a narrow frequency range. It is the sum over all frequency bins of the product of each frequency and its associated power in the spectrum sorted in descending order of power, divided by the total power of the spectrum. In physiological tremor, power is distributed over a large part of the spectrum and in pathological tremor it is usually concentrated in one peak. Decreasing scores are a sign of abnormality and indicate that power is concentrating in fewer and narrower peaks (Beuter and Edwards, 1999).
4. *Median frequency* measured as the frequency below which lies 50% of the power in the spectrum between 0 and 15 Hz. A broad spectrum associated with normal physiological tremor produces a higher score, thus decreasing scores are a sign of abnormality (Beuter and Edwards, 1999).

3. Results

First, we examine the effect of DBS on tremor amplitude and frequency characteristics when the two groups of subjects are off and on medication, and second, we examine the effect of stopping DBS for 60 min. Before presenting these results, we report briefly the correlation between clinical scores and quantitative tremor results obtained immediately after the clinical scoring. RMS of tremor amplitude and UPDRS scores are presented in Table 2 for the "off" condition (no medication and no stimulation). The three other conditions are not reported since the clinical scores for tremor were "0" for Group 2 and some of the subjects of Group 1. Note however, that when a clinical score of tremor is "0", tremor is still measured by the laser as shown by the RMS scores (Table 2) and is similar in terms of amplitude to physiological tremor recorded in healthy subjects. The Spearman rank correlation coefficient for the "off" condition was 0.70 ($P < 0.005$).

Table 2
Rest tremor amplitude measured by Part III of the UPDRS (Item 20) and by the RMS of velocity data (mm/s)

Subject	Side tested	UPDRS	RMS (mm/s)
Group 1			
1	Left	2	211.78
2	Right	4	310.13
3	Left	1	19.66
4	Right	4	174.65
5	Left	4	87.01
6	Left	3	270.12
7	Right	4	52.39
8	Left	4	123.07
Group 2			
9	Right	2	4.91
10	Left	0	3.21
11	Left	0	5.98
12	Right	0	1.31
13	Right	0	1.28
14	Right	1	1.65
15	Right	2	1.22
16	Left	0	4.84

3.1. Effect of DBS on rest tremor

Fig. 2 illustrates the effect of DBS of the GPi and the STN on tremor amplitude when subjects are without medication. As can be seen in Fig. 2, when tremor amplitude is large, it is also more regular (Group 1, top) and when tremor amplitude is small, it tends to be more irregular (Group 2, bottom). As expected, under DBS tremor oscillations disappear almost completely in all subjects of Group 1 (shown only for subjects 2 and 8 in Fig. 2, solid line). For subjects of Group 1 receiving stimulation of the Vim, the results in tremor amplitude are similar (not shown). For subjects from Group 2, the irregularity of tremor which is typical of normal physiological tremor remains relatively unaffected by DBS (Fig. 2). Results for the two groups are compared (Table 3) using the Wilcoxon signed rank test of differences between means. As can be seen, for Group 1 tremor amplitude decreases significantly while median frequency and spectral concentration increase significantly. These results remain significant after a Holm adjustment (Howell, 1998). Amplitude fluctuations do not change significantly but increase in six out of eight subjects (Group 1) under DBS. No significant differences are noted for Group 2 (Table 3).

When subjects were on medication, DBS did not affect tremor significantly (Table 3). A trend was observed for tremor amplitude but the variability of tremor across subjects prevented the effect from reaching statistical significance ($P = 0.07$).

Irrespective of target stimulated (GPi, STN, or Vim), we observed a decrease in rest tremor amplitude due to DBS for subjects in Group 1 who were off medication: a 92–99% decrease for GPi ($n = 2$), a 83–99% decrease for Vim ($n = 3$) and a 95–98% decrease for STN ($n = 3$). With medication, the change in tremor amplitude showed a trend but was

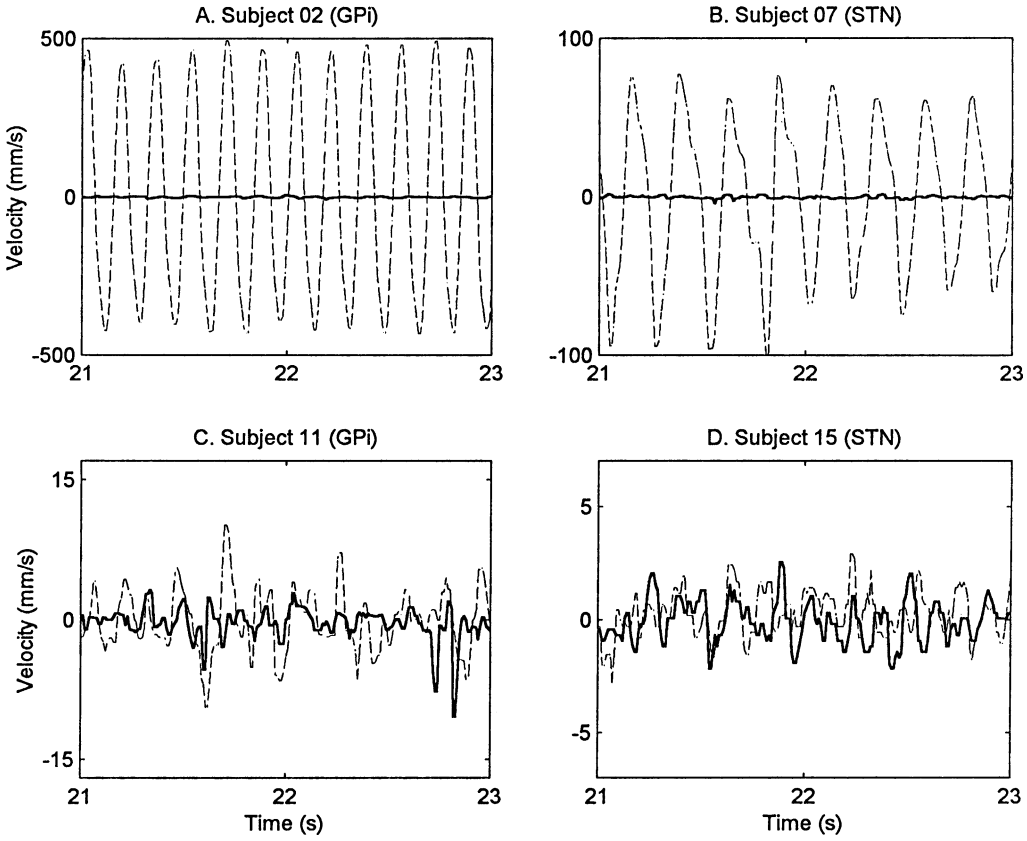

Fig. 2. Effect of DBS on rest tremor amplitude of subjects of Group 1 (top) and Group 2 (bottom) without medication: DBS on (solid line) and DBS off (dashed line). Stimulated targets are indicated in brackets (i.e. GPi on left and STN on right). Note the difference in scale for the vertical axis.

variable across the targets stimulated. We report these observations only for the interest of the reader, since the small size of subgroups based on stimulation target (GPi, STN or Vim) prevents valid differential analysis.

3.2. Effect of stopping DBS on tremor

The effect of stopping DBS for 60 min on rest tremor amplitude and frequency is presented in Table 4 and Fig. 3, respectively. This test was not performed on subjects receiving stimulation of the Vim ($n = 3$) since, as indicated above, it was too stressful for them to remain without stimulation for 60 min. Thus, only four subjects were tested in Group 1 (since subject 1, GPi, did not complete this test). This test took place after stimulation was stopped and tremor had returned. This occurred between 5 and 30 s on average. These preliminary results indicate that rest tremor amplitude increases after 15 min and then decreases after 30 min for all

Table 3
Means (with S.D.), and Wilcoxon signed rank test of the four tremor characteristics when DBS is on or off (with and without L-Dopa) for the two groups (without adjustment)

Tremor measure	Off L-Dopa			On L-Dopa		
	DBS on	DBS off	*P*-value	DBS on	DBS off	*P*-value
Group 1 (high amplitude tremor)						
Amplitude	8.2 (7.1)	156.1 (103.8)	0.003[a]	2.6 (1.3)	33.4 (75.3)	0.07
Amplitude fluctuations	0.8 (0.4)	0.4 (0.2)	0.961	0.7 (0.3)	0.7 (0.3)	0.50
Spectral concentration	2.7 (1.3)	1.0 (0.5)	0.003[a]	3.8 (0.7)	2.8 (1.3)	0.28
Median frequency	6.1 (1.8)	4.8 (0.7)	0.019[a]	5.1 (2.0)	4.4 (2.1)	0.28
Group 2 (low amplitude tremor)						
Amplitude	4.2 (3.8)	3.6 (2.0)	0.80	3.7 (3.8)	3.0 (3.1)	0.62
Amplitude fluctuations	0.5 (0.2)	0.6 (0.4)	0.27	0.7 (0.3)	0.6 (0.3)	0.87
Spectral concentration	3.2 (1.1)	3.4 (1.2)	0.76	4.0 (0.9)	4.1 (1.2)	0.47
Median frequency	6.0 (0.9)	5.4 (1.1)	0.47	5.0 (2.3)	5.3 (2.1)	0.67

[a] The comparison is still significant after a Holm adjustment for multiple comparisons (Howell, 1998).

Table 4
Effect of stopping stimulation on rest tremor amplitude for subjects receiving DBS of the GPi or STN[a]

Tremor	Subject	Stimulated target	Amplitude (RMS, mm/s)				
			0 min	15 min	30 min	45 min	60 min
Group 1	2	GPi	310.10	413.90	198.40	360.80	189.90
	6	STN	270.10	280.40	100.60	188.20	208.20
	7	STN	52.39	71.05	61.67	M[b]	M
	8	STN	123.00	472.60	390.70	388.80	386.10
Group 2	9–16	5 GPi and 3 STN	3.05 (1.95)	3.11 (2.62)	2.20 (1.07)	2.38 (1.62)	2.26 (1.15)

[a] Results for Group 2 are averaged and standard deviations are presented in parentheses.
[b] M: missing data.

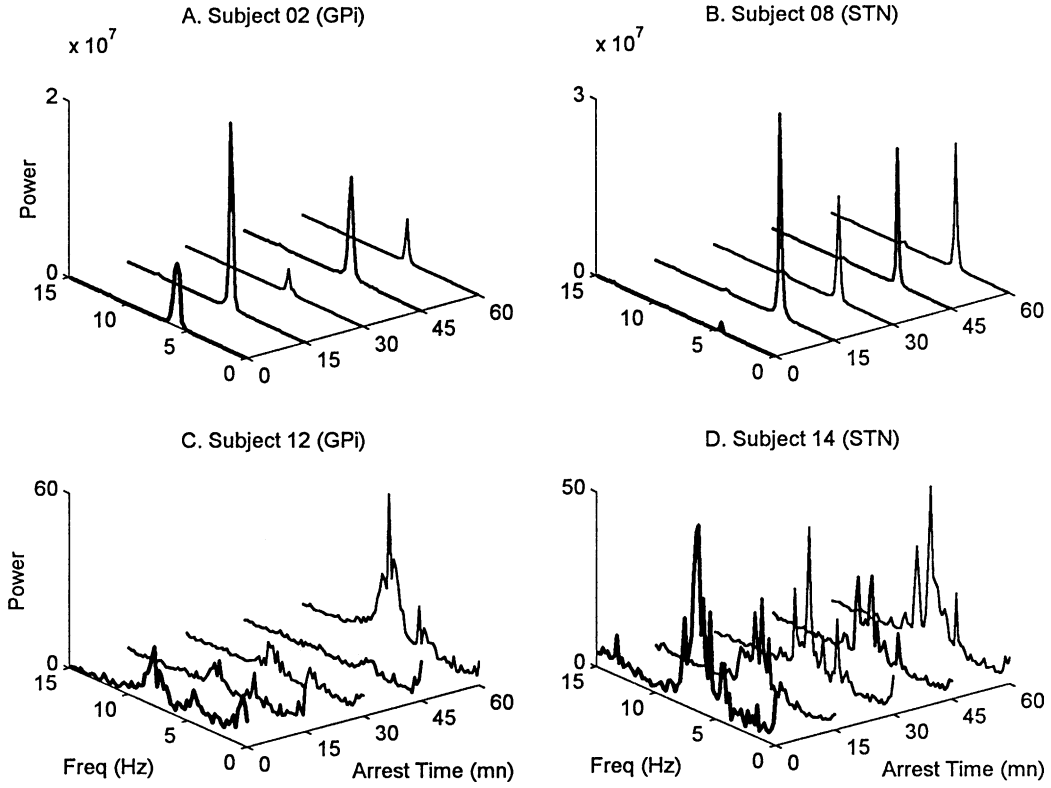

Fig. 3. Effect of stopping DBS for 60 min on rest tremor frequency of subjects of Group 1 (top) and Group 2 (bottom). Stimulated targets are indicated in brackets. Note the difference in scale for the vertical axis.

four subjects tested in Group 1. No statistical analysis was performed because of the small sample size. For subject 2, amplitude increases again after 45 min. A closer look at the raw data reveals that tremor amplitude fluctuates at that time and these fluctuations artificially increase the RMS. Fig. 3 illustrates the effect of stopping DBS on rest tremor frequency. As can be seen in this figure, subjects from Group 1 (top) have a strong spectral peak that remains stable over time while subjects from Group 2 (bottom) have a wider spectrum that presents some fluctuations over time. Note the wide difference in scale for the vertical axis. No systematic changes were observed for Group 2 (Table 4).

In summary, stopping DBS is associated with a rebound in amplitude after 15 min for subjects from Group 1 and a stable frequency. No systematic change was noted for subjects from Group 2 either in amplitude or frequency.

4. Discussion

The effect of DBS on amplitude and frequency characteristics of tremor in PD was examined in a group of subjects with high amplitude tremor (Group 1) and another group with low amplitude tremor (Group 2).

First, as expected, DBS decreases tremor amplitude in Group 1. The decrease in tremor amplitude was observed for all subjects for the three targets examined. Mean tremor amplitude remained unchanged for Group 2. The decrease in

amplitude due to DBS was clear but not significant when the subjects of Group 1 were under medication (L-Dopa). Again no effect was detected for Group 2 when under medication (L-Dopa) for the three targets examined. What was not expected, however, was the increase in amplitude fluctuations in Group 1 (six out of eight subjects) in the direction opposite to what we had predicted ($1 - P = 0.039$). Although these results in the predicted direction are not statistically significant, we think that they are interesting. We expected that DBS would reduce the fluctuations in amplitude that are associated with abnormality. It is worth noting, however, that the increase in fluctuations appeared in the form of isolated bursts of activity as if tremor were temporarily escaping its control by DBS.

Second, DBS increased median frequency in Group 1. We found a significant mean increase of 1.22 Hz in median frequency for Group 1. On the average, this increase is noted for all three targets stimulated. The mean increase is similar to the value found by Timmer et al. (1999) on one subject with Vim stimulation (i.e. 1.37 Hz). The present study differs from that of Timmer et al. (1999) in three ways. Our measure is slightly different from peak frequency (in that broadness of spectrum comes into median frequency), we examined rest tremor in several subjects, and finally these subjects received DBS of three different structures (i.e. Vim, STN and GPi). A careful examination of the power spectra suggests that the increase in median frequency may be due in part to a redistribution of power after the strong dominant peak was attenuated by DBS. Thus, this explains why median frequency is shifted to higher values. Fig. 4 illustrates this observation. For subjects from Group 1 (top), there is an obvious decrease in power associated with an attenuation of the dominant frequency peak. For Group 2 (bottom), the two power spectra overlap almost completely. Note the log scale on the vertical axis. In addition to its effect on tremor frequency, DBS also increased spectral concentration (see Table 3). The increase in spectral concentration was observed for all subjects for the three targets examined. This is consistent with the "normalisation" of median frequency noted above. Thus, under DBS tremor becomes less regular (Fig. 2, solid line). As expected, no significant differences were noted for these two characteristics in Group 2. These results suggest that under DBS pathological tremor becomes similar to normal physiological tremor in terms of amplitude and frequency. They also suggest the presence of a continuum between pathological and physiological tremor, which is in agreement with the idea that PD is a dynamical disease (Beuter and Vasilakos, 1995). In a dynamical disease, the same system can function in a normal or pathological mode depending on the values taken by its control parameter(s).

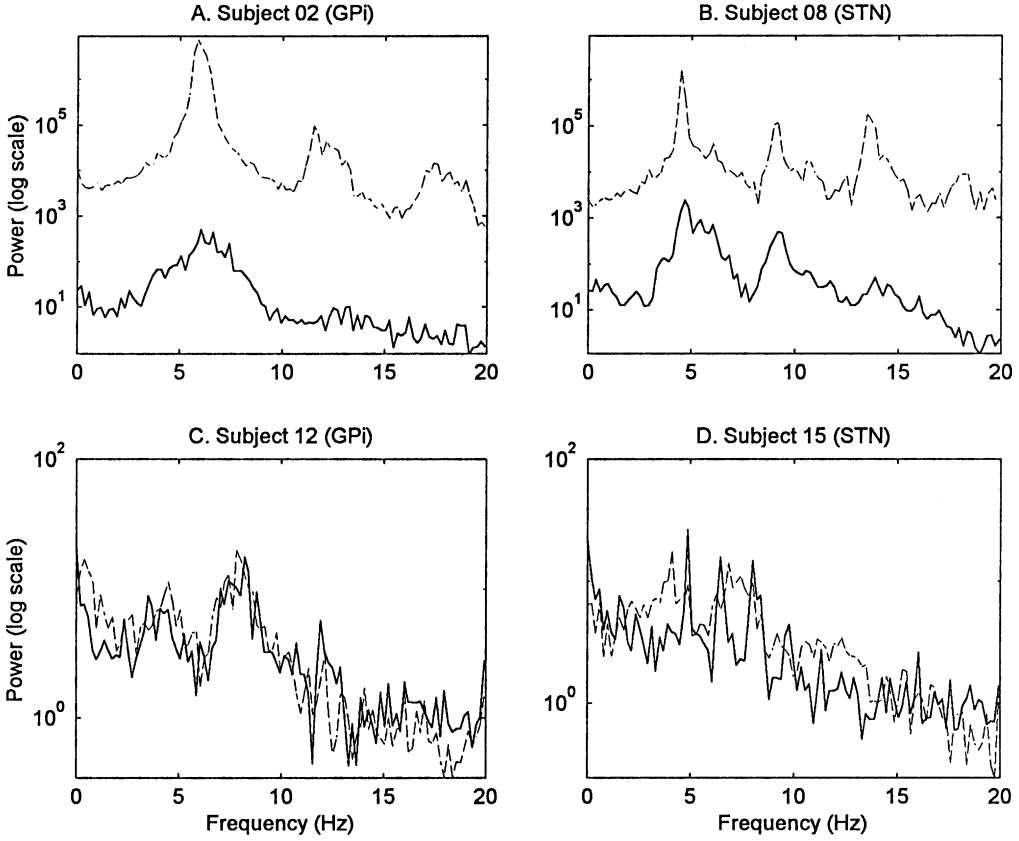

Fig. 4. Effect of DBS on tremor frequency between 0 and 20 Hz for subjects of Group 1 (top) and Group 2 (bottom) without medication: DBS on (solid line) and DBS off (dashed line). Stimulated targets are indicated in brackets (i.e. GPi on left and STN on right). Note the log scale for the vertical axis.

In a companion paper (Titcombe et al., 2001), we have proposed a simple theoretical model of tremor control by DBS related to changes of a control parameter in an oscillating system.

Third, the results indicate a correlation of 0.70 between qualitative and quantitative measures of rest tremor in the "off" condition. Previous studies reported low correlations between quantitative and qualitative measures for voluntary movements performed by subjects with PD. Beuter et al. (1999a,b) found correlation coefficients of 0.3 or below in studies in which clinical scoring and quantitative recording of tremor were done with a lag of 30–90 min. Pernat et al. (1996) also found low correlations between quantitative tests and rating scales in PD. They suggest that fluctuations in symptoms, time since last medication, and different strategies used by subjects to overcome difficulties might explain the results. In the present study, the correlation is higher than those found in previous studies. This may come from the fact that an attempt was made to control the time since medication and to record tremor immediately after its clinical scoring.

Fourth, examining tremor every 15 min for 60 min after stopping DBS is associated with a relatively stable median frequency and a rebound effect in tremor amplitude after 15 min in all subjects of Group 1 that were tested. This increase in amplitude was observed later than what was reported in previous studies (Benabid et al., 1998; Caparros-Lefebvre et al., 1993). At the practical level, our results suggest that DBS should be stopped at least 30 min before performing clinical tests to control for this rebound effect. Beyond these practical aspect, Montgomery anticipated that this rebound effect in amplitude would occur (Montgomery, personal communication, 2000) if tremor in PD were a network property due to re-entrant activity in coupled positive and negative feedback loops (Montgomery, 1994). In a personal communication, he suggested that the alternative to this network property is a bursting activity in a specific set of neurons in a pacemaker like fashion. However, he favours the network property and explains that "one would not expect a rebound increase in tremor amplitude if the mechanism is bursting pacemaker-like activity in thalamic neurons (which have slow Ca^{2+} potentials that generate bursting)". Benazzouz and Hallett (2000) also suggest that DBS involves a change in network properties. It remains to clarify how observations on rebound in tremor amplitude, increase in median frequency and spectral concentration, effect of medication and dependency on target fit into this network hypothesis. A better understanding of these mechanisms may help us understand why tremor sometimes recurs in about 20% of the patients a few months after surgery.

Acknowledgements

We would like to thank all the subjects who so willingly gave their time to participate and accepted some discomfort during the experiments. We also thank Roderick Edwards for his help with the analysis of the data. AB received financial support from NSERC (Canada), FCAR (Que.) and Coopération Québec (France).

References

Albe-Fessard, D., Arfel, G., Guiot, G., et al., 1962. Dérivations d'activités spontanées et évoquées dans les structures cérébrales profondes de l'homme. Rev. Neurol. Paris 106, 89–105.

Benabid, A.L., Pollak, P., Gervason, C., Hoffmann, D., Gao, D.M., Hommel, M., Perret, J.E., de Rougemont, J., 1991. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. The Lancet 337, 403–406.

Benabid, A.L., Pollak, P., Gao, D., Hoffmann, D., Limousin, P., Gay, E., Payen, I., Benazzouz, A., 1996. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J. Neurosurg. 84, 203–214.

Benabid, A.L., Benazzouz, A., Hoffmann, D., Limousin, P., Krack, P., Pollak, P., 1998. Long-term electric inhibition of deep brain targets in movement disorders. Mov. Disord. 13 (Suppl. 3), 119–125.

Benabid, A.L., Koudsié, A., Pollak, P., Kahane, P., Chabardes, S., Hirsch, E., Marescaux, C., Benazzouz, A., 2000. Future prospects of brain stimulation. Neurol. Res. 22, 237–246.

Benazzouz, A., Hallett, M., 2000. Mechanism of action of deep brain stimulation. Neurology 55 (6), s13–s16.

Beuter, A., Edwards, R., 1999. Using frequency domain characteristics to discriminate physiologic and Parkinsonian tremors. J. Clin. Neurophys. 16 (5), 484–494.

Beuter, A., Vasilakos, K., 1995. Tremor: is Parkinson's disease a dynamical disease? Chaos 5 (1), 35–42.

Beuter, A., de Geoffroy, A., Cordo, P., 1994. The measurement of tremor using simple laser systems. J. Neurosci. Meth. 53, 47–54.

Beuter, A., de Geoffroy, A., Edwards, R., 1999a. Analysis of rapid alternating movements in Cree subjects exposed to methylmercury and in subjects with neurological deficits. Environ. Res. 80, 64–79.

Beuter, A., de Geoffroy, A., Edwards, R., 1999b. Quantitative analysis of rapid pointing movements in Cree subjects exposed to methylmercury and in subjects with neurological deficits. Environ. Res. 80, 50–63.

Burleigh, A.L., Horak, F.B., Burchiel, K.J., Nutt, J.G., 1993. Effects of thalamic stimulation on tremor, balance, and step initiation: a single subject study. Mov. Disord. 8 (4), 519–524.

Caparros-Lefebvre, D., Blond, S., Vermersch, P., Pécheux, N., Guieu, J.D., Petit, H., 1993. Chronic thalamic stimulation improves tremor and levodopa-induced dyskinesias in Parkinson's disease. J. Neurol. Neurosurg. Psychiatr. 56, 268–273.

Ceballos-Baumann, A.O., Boecker, H., Bartenstein, P., et al., 1999. A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson's disease. Arch. Neurol. 56, 997–1003.

Edwards, R., Beuter, A., 2000. Using time domain characteristics to discriminate physiologic and Parkinsonian tremors. J. Clin. Neurophys. 17 (1), 87–100.

Fahn, S., Elton, R.L. 1987. Unified Parkinson's disease rating scale. In: Fahn, S., Marsden, C.D., Calne, D.B., Goldstein (Eds.), Recent Developments in Parkinson's Disease. Macmillan Health Care, Florham Park, NJ, pp. 153–164.

Gross, R.E., Lozano, A.M., 2000. Advances in neurostimulation for movement disorders. Neurol. Res. 22, 247–258.

Gross, C., Rougier, A., Guehl, D., Boraud, T., Julien, J., Bioulac, B., 1997. High-frequency stimulation of the globus pallidus internalis in Parkinson's disease: a study of seven cases. J. Neurosurg. 87, 491–498.

Hariz, M.I., Shamsgovara, P., Johannson, F., Hariz, G.M., Fodstad, H., 1999. Tolerance and tremor rebound following long-term chronic thalamic stimulation for Parkinsonian and essential tremor. Stereotact. Funct. Neurosurg. 72, 208–218.

Howell, D.C., 1998. Méthodes Statistiques en Sciences Humaines. DeBroek University, Bruxelles.

Ito, K., 1961. Studies on minor tremor: settle down time of human minor tremor. Yonago Acta Med. 5 (2), 90–95.

Krack, P., Pollak, P., Limousin, P., Benazzouz, A., Benabid, A.L., 1997. Stimulation of subthalamic nucleus alleviates tremor in Parkinson's disease. The Lancet 350, 1675.

Kumar, R., Lozano, A.M., Kim, Y.J., Hutchison, W.D., Sime, E., Halket, E., Lang, A.E., 1998. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology 51, 850–855.

Limousin, P., Pollak, P., Benazzouz, A., Hoffmann, D., Le Bas, J.F., Broussolle, E., Perret, J.E., Benabid, A.L., 1995. Effect on Parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. The Lancet 345, 91–95.

Limousin-Dowsey, P., Pollak, P., Van Blercom, N., Krack, P., Benazzouz, A., Benabid, A.L., 1999. Thalamic subthalamic nucleus and internal pallidum stimulation in Parkinson's disease. J. Neurol. 246 (14), 542–545.

Louis, E.D., Ford, B., Pullman, S., Baron, K., 1998. How normal is "normal"? Mild tremor in a multiethnic cohort of normal subjects. Arch. Neurol. 55, 222–227.

Montgomery Jr., E.B., 1994. A model of Parkinson's disease pathophysiology based on coupled oscillators. Soc. Neurosci. Abstr. 20 (Part 1), 782.

Norman, K.E., Edwards, R., Beuter, A., 1999. The measurement of tremor using a velocity transducer: comparison to simultaneous recordings using transducers of displacement, acceleration and muscle activity. J. Neurosci. Meth. 92, 41–54.

Pernat, K., Kritikos, A., Phillips, J.G., Bradshaw, J.L., Iansek, R., Kempster, P., Bradshaw, J.A., 1996. The association between clinical and quantitative indexes of Parkinsonian symptomatology. Neuropsych. Neuropsych. Behav. Neurol. 9, 234–241.

Ranck, J.B., 1975. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res. 98, 417–440.

Schuurman, P.R., Bosch, D.A., Bossuyt, P.M., Bomsel, G.J., van Sommeren, E.J., de Bie, R.M., Merkus, M.P., Speelman, J.D., 2000. A comparison of continuous thalamic stimulation and thalamic suppression for severe tremor. N. Engl. J. Med. 342 (7), 461–468.

Siegfried, J., Lippitz, B., 1994. Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach alleviating all Parkinsonian symptoms. Neurosurgery 35, 1126–1129.

Speelman, J.D., Bosch, D.A., 1998. Resurgence of functional neurosurgery for Parkinson's disease: a historical perspective. Mov. Disord. 13, 582–588.

Speelman, J.D., Schuurman, P.R., de Bie, R.M.A., Bosch, D.A., 1998. Thalamic surgery and tremor. Mov. Disord. 13 (Suppl. 3), 103–106.

Timmer, J., Lauk, M., Vach, W., Lücking, C.H., 1999. Comput. Stat.. Comput. Stat. Data Anal. 30, 45–55.

Titcombe, M.S., Glass, L., Guehl, D., Beuter, A. 2001. Dynamics of Parkinsonian tremor during deep brain stimulation. Chaos, in press.

Vuong, K.D., Ondo, W.G., Almaguer, M., Simpson, R.K., Jankovic, J., 2000. Unilateral thalamic deep brain stimulation for essential tremor and Parkinson's disease: effects of stimulation on the non-target limb and rebound augmentation. [Abstract] Neurol. 54 (Suppl. 3), A117.