Parkinsonism and Related Disorders 16 (2010) 115–118

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Neuropsychological changes 1-year after subthalamic DBS in PD patients: A prospective controlled study☆

Lorys Castelli*, Laura Rizzi, Maurizio Zibetti, Serena Angrisano, Michele Lanotte, Leonardo Lopiano

Department of Neuroscience, University of Turin, via Cherasco 15, 10126 Turin, Italy

ARTICLE INFO

Article history:
Received 7 April 2009
Received in revised form
11 August 2009
Accepted 13 August 2009

Keywords:
Parkinson's disease
Deep brain stimulation of the subthalamic nucleus
Cognitive functions

ABSTRACT

Objective: This study aimed at investigating the neuropsychological effect of DBS of the Subthalamic Nucleus in patients with advanced Parkinson's disease (PD).
Methods: A standardized neuropsychological test battery, assessing reasoning, memory and executive functions, was administered to 27 PD patients who underwent DBS-STN (DBS group) and to a matched control group of 31 PD patients under optimal medical treatment (MED group). Patients were evaluated at baseline and at the end of 1 year.
Results: Change score analysis (T1 minus T0 scores) demonstrated a significant decline in phonemic verbal fluency in the DBS group compared with the MED group ($p < 0.005$), while there were no significant changes between the two groups for the other cognitive tests. Single cases analysis by means of multivariate normative comparisons revealed that 4 out of 27 DBS patients (15%) showed cognitive deterioration one year post surgery. These patients were significantly more compromised from a motor standpoint (UPDRS, section III) than the 23 DBS PD patients who had no cognitive decline post surgery.
Conclusion: Results of this prospective controlled-study showed that phonemic verbal fluency declined one year after DBS-STN, while the other cognitive domains did not change significantly. Nevertheless, single case analysis highlighted the fact that a subgroup comprising 15% of DBS-STN patients (4/27) showed significant cognitive decline 1 year after surgery.

1. Introduction

Bilateral Deep Brain Stimulation of the Subthalamic Nucleus (DBS-STN) is an established treatment for motor symptoms in patients with advanced Parkinson's disease (PD) [1]. Nevertheless its effect on cognitive functions is still a matter of debate and controversial. Globally, neuropsychological evidence seems to be consistent with the general safety of the surgical procedure and post-surgical cognitive deterioration is relatively rare [2,3] however, some studies have pointed out decline in specific cognitive domains – in memory and particularly in executive functions [3–5].

Parsons and colleagues carried out a meta-analysis on 28 cohort studies published between 1990 and 2006 that included 612 patients [2]. Results highlighted significant, albeit small, declines in executive functions, verbal learning and memory, and in fluency tasks (phonemic and semantic). The authors concluded that DBS-STN for PD seems safe from a cognitive standpoint provided that appropriate patients were selected for the surgery. However, declines in verbal fluency tasks were frequently observed; this side-effect is reported in 30–50% of the patients after the surgery [2]. Decline in memory, attention and other executive functions are less common and severe cognitive impairment is relatively rare (1–2%) [2].

Studies with large patient cohorts confirmed that DBS-STN did not lead to general cognitive deterioration but that verbal fluency significantly declined after surgery [6–8] and that age seems to be a predictor of decline in executive functions, as well as in attention and memory [7].

A relevant limitation of the majority of the neuropsychological studies carried out on PD patients who underwent DBS is the lack of a control group of PD patients just on drug therapy. To date few controlled studies have been conducted, with a follow-up periods ranging from 3 to 6 months [4–6,9]. As noted by York and colleagues, outcome studies are needed that include a PD disease control group for comparison, to distinguish between the progression of the disease and the modifications related to the surgical procedure and to the chronic stimulation of STN [5].

On this basis, we carried out a prospective case-control study comparing the cognitive status of 27 PD patients who underwent bilateral DBS-STN to that of a matched control group of 31 PD

☆ The review of this paper was entirely handled by an Associate Editor, Vincenzo Bonifati.

* Corresponding author. Tel.: +39 11 6638034; fax: +39 11 6335668.
E-mail address: castelli_lorys@hotmail.com (L. Castelli).

1353-8020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.parkreldis.2009.08.010

patients under optimal medical treatment. Neuropsychological tests were administered at baseline (T0) and at the end of 1 year (T1).

2. Methods

2.1. Patients

Fifty-eight PD patients were involved in the study which was approved by the ethics committee of Molinette University Hospital: all subjects gave written informed consent.

Twenty-seven patients who consecutively underwent bilateral DBS-STN (DBS group) were assessed for cognitive functions two weeks prior to surgery (T0) and 1 year after the surgical procedure (T1). The control group comprised 31 patients receiving optimal medical treatment (MED group). They were assessed at the same time points as the DBS group (T0 and T1).

Patients of the DBS group underwent successful bilateral DBS-STN. The surgical procedure has been described elsewhere [10]. A post-operative 3D MRI combined with the pre-operative CT scan was performed to exclude surgical complications and to check the final position of the electrodes. The inclusion criteria for surgery were the diagnosis of idiopathic PD, the presence of severe motor fluctuations and drug-related dyskinesias, the absence of marked atrophy or focal abnormalities on brain MRI, less than 70 years of age, the absence of dementia (possible or probable dementia according to DSM IV criteria) or severe cognitive decline (performance above the normative cut-off in most of the neuropsychological tests described above) and the absence of a clinically relevant depression or severe psychiatric disorders (psychiatric interview).

The MED group was composed of 31 patients with advanced PD under optimal medical treatment. MED patients were consecutively recruited from the waiting list for STN-DBS surgery, after being judged suitable for the surgical treatment itself. So, all the subjects met the same inclusion criteria (see above) of the DBS group.

Patients in the MED group were matched for age, sex, duration and severity of the disease (UPDRS, section III) [11], and levodopa equivalent daily dosage (LEDD) to the DBS group. Demographic and clinical characteristics of the two groups are listed in Table 1. None of the patients showed severe psychiatric side-effects during the one year follow-up.

2.2. Neuropsychological test battery

To determine cognitive status, both groups were administered a standardized neuropsychological test battery, assessing reasoning (Raven Colour Matrices), memory (Bi-syllabic Words Repetition test, Corsi's Block Tapping test, Paired Associate Learning) and attentional-executive functions (Trail Making B, the Nelson Modified Card Sorting test, Phonemic and Category Verbal Fluency tasks). The Bi-syllabic Words Repetition test is a short-term verbal memory test taken from the Spinnler and Tognoni handbook [12]; Paired Associate Learning is a subscale of the Wechsler Memory Scale [13]. Two parallel forms were used for all the memory tests in order to avoid the test re-test effect. The battery has been described in detail elsewhere [8].

2.3. Procedure

The neuropsychological tests were performed under optimal clinical conditions for all the subjects.

DBS patients were assessed pre-operatively in the "medication-on" state (daily optimal dosage of dopaminergic drugs) and post-operatively in the "stimulation-on"/"medication-on" condition (optimal clinical condition).

MED patients were assessed under optimal medical treatment ("medication-on") both at T0 and T1.

The motor evaluation of PD patients was performed according to the Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD) [11]. Data from section III of UPDRS were reported in Table 1.

2.4. Statistical analysis

T-tests for unpaired were run to compare clinical and demographical variables between the two groups. *T*-tests for paired sample were used to analyze motor symptoms and LEDD modifications within groups. A MANCOVA with age and level of education as covariates was run to compare neuropsychological test scores of the two subgroups at T0. This analysis allowed us to determine whether the entire set of means (all the neuropsychological variables) was different between the DBS group and the MED group at T0.

Change scores were then calculated as the score at T1 minus the score at T0, and the two groups were compared through a MANOVA. Correlations were analysed through Pearson correlation analysis.

Finally the multivariate normative comparisons described by Huizenga and colleagues were applied to identify how many patients in the DBS group differed significantly from the control group (MED group) on the neuropsychological profile (single cases analysis) [14].

Table 1
Demographic and clinical characteristics of the DBS group and the MED group at baseline assessment (T0). Mean, standard deviation and *T*-test analysis are shown.

	DBS group	MED Group	*T* (df)	*p*
Number of PD patients	27	31	–	–
Sex (male/female)	17/10	16/15	0.76[a]	0.38
Age (yrs)	60.6 (6.7)	60.2 (6.6)	−0.19 (56)	0.85
Education (yrs)	8.0 (4.1)	9.0 (4.1)	0.93 (56)	0.36
Duration of disease (yrs)	15.3 (5.1)	15.6 (5.2)	0.23 (56)	0.82
LEDD (mg)	1046.1 (436.4)	1071.3 (370.3)	0.24 (56)	0.81
Severity of the disease (UPDRS section III, medication-off condition)	55.0 (11.3)	49.6 (11.9)	−1.76 (56)	0.08

[a] Chi square.

3. Results

3.1. Motor outcome

Patients in the DBS group demonstrated a significant post-operative improvement in motor symptoms (UPDRS section III: pre-operative medication-off: 55.0 (11.3) vs. post-operative stimulation-on/medication-off condition: 25.4 (9.6); $T\,(26) = 7.6$; $p < 0.0001$). Moreover, post-operatively DBS PD patients were able to reduce significantly the daily dose of their antiparkinsonian drugs (pre-operative LEDD: 1046.1 mg (436.4) vs. post-operative LEDD: 321.3 mg (260.0); $T\,(26) = 7.2$, $p < 0.0001$).

In the MED group a significant worsening, albeit small, was observed in motor symptoms (UPDRS section III: medication-off-T0: 49.6 (11.9) vs. medication-off-T1 condition: 53.6 (14.2); $T\,(30) = -4.2$; $p < 0.001$), while pharmacological treatment remained stable during the one year follow-up (LEDD T0: 1071.3 (370.3) vs. LEDD T1: 1018.1 (381.3); $T\,(30) = 0.83$; ns).

3.2. Cognitive outcome

3.2.1. Group analysis: DBS vs. MED

Neuropsychological test scores at T0 and change scores (T1 minus T0) are reported in Table 2.

The MANCOVA showed that the cognitive profiles of the DBS and the MED group were not significantly different at T0

Table 2
Neuropsychological test score at baseline (T0) and test score changes (T1 minus T0) of the DBS group and the MED group. Mean, (SD), MANCOVA (T0) and MANOVA (Change score) analysis were shown.

		DBS group	MED group	*F* (df)	*P*
Raven colour matrices	T0	26.00 (4.10)	26.85 (4.68)	1.68	0.18
	Change score	−0.22 (5.35)	0.34 (4.21)	0.2	0.65
Bi-syllabic words repetition	T0	4.44 (0.75)	4.26 (0.77)	2.16	0.10
	Change score	−0.15 (0.77)	0.10 (0.65)	1.72	0.20
Corsi's block tapping test	T0	4.41 (0.69)	4.44 (0.68)	0.19	0.90
	Change score	−0.15 (0.60)	−0.09 (0.89)	0.08	0.77
Paired associate learning	T0	10.57 (3.11)	10.74 (3.54)	1.76	0.16
	Change score	−0.39 (2.66)	0.47 (3.49)	1.07	0.30
Trail making B	T0	297.59 (197.08)	262.58 (137.73)	0.63	0.60
	Change score	12.70 (193.55)	−5.00 (114.14)	0.18	0.67
Nelson MCST					
Categories	T0	4.89 (1.34)	5.29 (1.16)	0.58	0.63
	Change score	0.55 (1.65)	0.32 (1.00)	0.44	0.51
Errors	T0	8.19 (6.21)	6.71 (5.02)	1.13	0.34
	Change score	−0.78 (8.12)	−1.90 (5.43)	0.39	0.53
Perseverations	T0	2.48 (2.19)	1.47 (2.00)	1.78	0.16
	Change score	−0.11 (5.06)	−0.42 (2.22)	0.09	0.76
Phonemic fluency	T0	36.63 (13.48)	40.31 (15.27)	1.31	0.28
	Change score	−5.22 (12.56)	5.31 (12.13)	10.52	0.002[a]
Semantic fluency	T0	16.08 (4.38)	18.81 (6.94)	3.21	0.10
	Change score	−1.43 (3.34)	0.07 (7.94)	0.84	0.36

[a] Statistically significant.

(F (10,45) = 0.69; p = 0.72). In addition neither age nor education (covariates) were significant (Age: $F(45) = 0.70$; $p = 0.72$; Education: F (45) = 1.39; p = 0.22). Univariate comparisons on each neuropsychological test score are listed in Table 2. None of the cognitive test results appeared to be significantly different between the two groups; so, the cognitive status of the DBS and MED group of PD patients can be considered comparable at baseline assessment.

The neuropsychological change scores, for the DBS and the MED group were not significantly different (MANOVA: F(10,45) = 1.82; $p = 0.083$). Univariate comparisons showed a significant decline in the phonemic fluency test in the DBS group compared with the control group. No significant differences were noted in the results of the other neuropsychological tests (see Table 2).

A correlation analysis was run between significant variable (phonemic fluency change score) and demographic-neurological variables in the DBS group. Results did not show significant correlations between phonemic verbal fluency change score and age, duration of the disease, LEDD and UPDRS section III at T0 and change score.

3.2.2. *Single cases analysis of DBS group patients: multivariate normative comparisons*

The Multivariate Normative Comparisons showed that 4 patients out of 27 (15%) deviated in a negative sense from the norm (see Table 3).

Independent sample non-parametric tests (Mann–Whitney) were run in order to compare these 4 patients to the other 23 patients. Motor symptoms scores at T0 were found to be significantly higher in the subgroup of 4 patients with respect to the patients without cognitive deterioration (UPDRS section III, med off condition: 65.6 (7.3) vs. 53.2 (10.9); U = 15; p = 0.034). No significant differences between these two subgroups were found for age, years of education, duration of disease, neuropsychological profile at T0, LEDD, LEDD change score and UPDRS section III change score.

Table 3
Single cases analysis of the 27 DBS patients compared to the control group of 31 MED patients. Multivariate Normative Comparisons results are shown. Four patients (n2, n11, n19 and n26) significantly deviate in a negative sense from the norm.

DBS patients	Difference[a]	p Values[b]
Patient 1	0.530	0.085
Patient 2	*−33.463*	*0.0001*
Patient 3	−2.511	0.638
Patient 4	−4.249	0.203
Patient 5	4.209	0.661
Patient 6	−4.233	0.393
Patient 7	−1.555	0.932
Patient 8	−0.577	0.625
Patient 9	2.694	0.693
Patient 10	2.843	0.080
Patient 11	*−10.783*	*0.020*
Patient 12	4.961	0.060
Patient 13	−2.865	0.944
Patient 14	8.732	0.070
Patient 15	1.388	0.293
Patient 16	0.840	0.112
Patient 17	−4.002	0.666
Patient 18	−1.162	0.619
Patient 19	*−3.625*	*0.068*
Patient 20	1.466	0.183
Patient 21	−0.044	0.893
Patient 22	−4.572	0.123
Patient 23	1.573	0.235
Patient 24	0.809	0.345
Patient 25	−0.380	0.999
Patient 26	*−11.107*	*0.008*
Patient 27	−2.859	0.831

[a] Difference refers to the sum of standardized differences to the norm (considering all neuropsychological tests): negative indicates a lower score (decline) while positive indicates a higher score (improvement) with respect to the normative sample.
[b] p value is two-sided and should be lower than 0.05; p value lower than 0.10 are considered significant if difference is in expected direction (negative).

4. Discussion

To date results on the neuropsychological modification occurring after DBS-STN are controversial. Studies on this topic come to diverse conclusions, ranging from "DBS of STN seems relatively safe from a cognitive point of view," to "Bilateral subthalamic nucleus stimulation has an adverse effect on executive functions with implications for daily life of the patients and their relatives" [2,4]. Contrasting results could depend on different methodologies and instruments used to assess the cognitive status, differences in the follow-up period, in the selection of PD patients suitable for the surgical treatment and in demographic and clinical characteristics of the patients (age, disease duration and severity). Nevertheless the main limitation of the majority of these studies is the absence of a control group of PD patients under pharmacological treatment.

We compared a DBS group of PD patients over a period of 1 year post-operatively with a matched group of patients under pharmacological treatment, Results highlighted a selective decline in the phonemic fluency task in the DBS group compared to the MED group, while change scores on reasoning, short-term memory and verbal learning, attention, categorizing ability-perseverative errors and semantic fluency test showed no significant difference between the two groups.

The first controlled study on the neuropsychological effect of DBS also showed isolated areas of cognitive deficit in DBS patients compared to matched medically treated PD patients at 3 months follow-up [9]. Specifically, a selective decline was found in memory (delayed verbal recall) and in verbal fluency tasks. A significant decline in verbal memory in the DBS group compared with a medically treated group resulted from another controlled study with a follow-up of 6 months [5].

In a recent randomised multicentre study, neuropsychological and psychiatric outcome of 60 patients submitted to DBS of STN were compared with the ones of 63 patients under optimal pharmacological treatment [6]. The two groups of patients were assessed at baseline and after six months. The DBS group evidenced a significant decline in three tests assessing executive functions (phonemic and semantic verbal fluency and Stroop tests) in comparison with the medication group. DBS patients evidenced also declines in attention, set shifting and semantic fluency but these changes were similar to the rate of decline in the PD group. Using a similar methodology, Smeding and colleagues compared the cognitive modifications of 99 patients submitted to DBS-STN with the ones of a control group of 36 patients with a follow-up period of 6 months. The DBS group showed a greater decline than the control group in verbal fluency, colour naming, selective attention, and verbal memory [4].

Taken together results of these controlled-studies demonstrate the substantial safety of DBS-STN with regard to global cognitive status but a specific decline in some executive functions, particularly in verbal fluency tasks, and in some cases in memory, particularly in delayed recall of information.

Our findings confirm these conclusions but with a longer follow-up period than any of the other studies: patients in the DBS group demonstrated a selective decline in the phonemic fluency task compared with matched medically treated PD patients. Unlike the other controlled studies we did not observe a significant worsening in semantic fluency or memory tests [4,5,9]. This last result could depend on the different instruments used for the assessment of memory, since the test used in this study (paired associative learning) does not include delayed recall of information.

We did not find any relationship between change in verbal fluency and demographic-neurological variables. So, phonemic verbal fluency decline seems to be independent from motor and LEDD post-operative modifications. Most importantly, the comparison with a matched control group of PD patients demonstrates that the decline in verbal fluency is not due to the progression of the illness, but could be a stimulation-induced side-effect. A PET study showed that the lower number of words produced when the stimulator was switched on was related to a decreased activation of the inferior frontal cortex during execution of a verbal fluency task [15]. Nevertheless, since the same decline was found after pallidotomy and thalamotomy surgery, further studies are needed to clarify the possible causes of this common side-effect [16,17].

Single cases analysis by means of multivariate normative comparisons showed that 15% of the DBS patients deviated in a negative sense from the norm [14]. This percentage was lower than the 24% found on the 87 STN-stimulated PD patients assessed by Smeding and Colleagues (see Huizenga and colleagues' single cases analysis) [4,14].

Single case analysis allowed us to provide the evidence for a subgroup of DBS-STN PD patients who declined cognitively after surgery. In fact, even if group analysis had not revealed significant differences in cognitive profile between the DBS and MED groups except for a decline in phonemic fluency task, single cases analysis highlighted a subgroup of DBS patients who significantly declined after surgery. This subgroup of patients who experienced decline is characterized by a higher severity of disease at baseline with respect to the other 85% of DBS patients (UPDRS, section III, medication-off condition).

The strength of the present study is represented by the fact the DBS and the MED group did not differ significantly on demographic, neurological and neuropsychological variables at baseline. In spite of this our study has two main limitations.

First, patients were not randomly assigned to the DBS or MED group. Patients were consecutively recruited for the study and no selection criteria other than the position on the waiting list for surgery were applied in order to assign a patient to the DBS or the MED group. This said, it has to be noted that the DBS group presented a higher severity of the illness (UPDRS section III) than the med group at baseline, even if this difference is not statistically significant.

Second, the neuropsychological test battery was relatively brief and it did not include extensive assessment of all memory and executive domains. Specifically, it lacked of a delayed recall condition in the memory tests.

In conclusion, results of our prospective controlled-study showed that, as a whole, phonemic verbal fluency declined one year after DBS-STN [4–6,9]. Nevertheless, single case analysis highlighted a subgroup of 15% of DBS-STN patients that showed a relevant cognitive decline 1 year after surgery. These patients were characterized by a significantly higher severity of the disease than cognitive unchanged DBS patients. This last result points out the need for further randomized controlled study, with longer follow-up period and extensive assessment of memory and executive functions in order to identify patients at risk for cognitive deterioration after DBS-STN.

References

[1] Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, et al. Five years follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349:1925–34.
[2] Parsons TD, Rogers SA, Braaten AJ, Woods SP, Tröster AI. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. Lancet Neurol 2006;5(7):578–88.
[3] Heo JH, Lee KM, Paek SH, Kim MJ, Lee JY, Kim JY, et al. The effects of bilateral subthalamic nucleus deep brain stimulation (STN DBS) on cognition in Parkinson disease. J Neurol Sci 2008;273(1–2):19–24.
[4] Smeding HM, Speelman JD, Koning-Haanstra M, Schuurman PR, Nijssen P, van Laar T, et al. Neuropsychological effects of bilateral STN stimulation in Parkinson disease: a controlled study. Neurology 2006;66(12):1830–6.
[5] York MK, Dulay M, Macias A, Levin HS, Grossman R, Simpson R, et al. Cognitive declines following bilateral subthalamic nucleus deep brain stimulation for the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry 2008; 79(7):789–95.
[6] Witt K, Daniels C, Reiff J, Krack P, Volkmann J, Pinsker MO, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. Lancet Neurol 2008; 7(7):605–14.
[7] Funkiewiez A, Ardouin C, Caputo E, Krack P, Fraix V, Klinger H, et al. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:834–9.
[8] Castelli L, Perozzo P, Zibetti M, Crivelli B, Morabito U, Lanotte M, et al. Chronic deep brain stimulation of the subthalamic nucleus for Parkinson's disease: effects on cognition, mood, anxiety and personality traits. Eur Neurol 2006;55: 136–44. 2006.
[9] Morrison CE, Borod JC, Perrine K, Beric A, Brin MF, Rezai A, et al. Neuropsychological functioning following bilateral subthalamic nucleus stimulation in Parkinson's disease. Arch Clin Neuropsychol 2004;19:165–81.
[10] Lanotte MM, Rizzone M, Bergamasco B, Faccani G, Melcarne A, Lopiano L. Deep brain stimulation of the subthalamic nucleus: anatomical, neurophysiological, and outcome correlations with the effects of stimulation. J Neurol Neurosurg Psychiatry 2002;72:53–8.
[11] Defer GL, Widner H, Marié RM, Rémy P, Levivier M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). Mov Disord 1999;14(4):572–84.
[12] Spinnler H, Tognoni G. Standardizzazione e taratura italiana di test neuropsicologici. Ital J Neurol Sci 1987;6(Suppl. 8):1–120.
[13] Wechsler D. A standardized memory scale for clinical use. J Psychol 1945;19: 87–95.
[14] Huizenga HM, Smeding H, Grasman RP, Schmand B. Multivariate normative comparisons. Neuropsychologia 2007;45(11):2534–42.
[15] Schroeder U, Kuehler A, Lange KW, Haslinger B, Tronnier VM, Krause M, et al. Subthalamic nucleus stimulation affects a frontotemporal network: a PET study. Ann Neurol 2003;54:445–50.
[16] de Bie RM, Schuurman PR, Bosch DA, de Haan RJ, Schmand B, Speelman JD. Outcome of unilateral pallidotomy in advanced Parkinson's disease: cohort study of 32 patients. J Neurol Neurosurg Psychiatry 2001;71:375–82.
[17] Nijhawan SR, Banks SJ, Aziz TZ, Panourias I, Gregory R, Yianni J, et al. Changes in cognition and health-related quality of life with unilateral thalamotomy for Parkinsonian tremor. J Clin Neurosci 2009;16(1):44–50.