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Influence of bilateral Stn-stimulation on psychiatric symptoms and psychosocial functioning in patients with Parkinson's disease

K. Kalteis[1,2], **H. Standhardt**[1], **I. Kryspin-Exner**[2], **T. Brücke**[3], **D. Volc**[4], and **F. Alesch**[1]

[1] Department of Neurosurgery, Medical University of Vienna,
[2] Department of Clinical and Health Psychology, Institute of Psychology, University of Vienna,
[3] Department of Neurology, Wilhelminenspital, and
[4] Department of Neurology, Confraternität, Vienna, Austria

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Summary. Deep brain stimulation of the subthalamic nucleus is an effective treatment for advanced Parkinson's disease. There is some evidence that subthalamic stimulation not only affects motor function, but also mood, behaviour and cognition. In the present study we investigated the effects of subthalamic stimulation on psychiatric symptoms and psychosocial functioning in a consecutive series of patients with Parkinson's disease. 33 patients were assessed three times prior to surgery and at three, nine weeks as well as three, six and twelve months after surgery. We found significant improvements in depression, anxiety, psychological symptoms and distress after surgery. In most cases the amelioration followed surgery and was stable in the course of time. Individual analysis indicated deterioration in three patients despite motor improvement. The results suggest that stimulation of the subthalamic nucleus has a positive influence on psychiatric symptoms, psychosocial functioning and distress. We observed a decline in a minority of patients.

Keywords: Deep brain stimulation, subthalamic nucleus, Parkinson's disease, psychiatric symptoms, psychosocial functioning, distress.

Abbreviations

BDI Beck Depression Inventory, *BRMES* Bech-Rafaelsen Melancholia Scale, *BPRS* Brief Psychiatric Rating Scale, *CGI* Clincial Global Impression, *DBS* deep brain stimulation, *GAS* Global Assessment Scale, *HAMA* Hamilton Anxiety Scale, *MMSE* Mini Mental State Examination, *PD* Parkinson's disease, *POMS* Profile of Mood States, *SCL-90-R* Symptom-Checklist 90-R, *STAXI* State-Trait Anxiety Inventory, *Stn* subthalamic nucleus, *Stn-DBS* deep brain stimulation of the subthalamic nucleus, *UPDRS* Unified Parkinson's disease Rating Scale, *VAS* Visual analogue scale

Introduction

Parkinson's disease is a progressive disorder, which not only affects the motor pathways, but also limbic and associative loops (Ring

et al., 2002; Alexander et al., 1986, 1990). Deep brain stimulation (DBS) of the subthalamic nucleus (Stn) is an effective treatment to improve motor function in patients with advanced Parkinson's disease (PD). Short- and long-term outcome of Stn-DBS have already been reported and have demonstrated marked improvement in motor function and a reduced need for antiparkinsonian drug treatment (Krause et al., 2004; Krack et al., 2003; Herzog et al., 2003a; Pollak et al., 2002). The effects of Stn-stimulation on mood, cognition and behaviour are not well understood. Most of the studies concerning neuropsychological functions showed no general decline in cognitive function (Woods et al., 2002). Patients older than 69 years and patients who were cognitively impaired prior to surgery have a higher risk of global cognitive deterioration (Saint-Cyr et al., 2000; Trepanier et al., 2000). The most common finding was a decline in verbal fluency after surgery (Funkiewiez et al., 2004; Ardouin et al., 1999). Some authors reported mild to moderate deterioration in executive function, verbal memory, and visuospatial function after surgery (Dujardin et al., 2001; Alegret et al., 2001) or a mild improvement in executive function (Alegret et al., 2001). The effects of Stn-DBS on psychiatric functions are not clear. Some studies reported positive changes in mood, depressive and anxiety symptoms after surgery (Funkiewiez et al., 2004; Daniele et al., 2003; Ardouin et al., 1999). Others demonstrated marked adverse influence; most of them are single case reports. Registered mood changes are depression (Berney et al., 2002; Thobois et al., 2002; Doshi et al., 2002; Ostergaard et al., 2002; Houeto et al., 2002), mania (Herzog et al., 2003b; Kulisevsky et al., 2002; Romito et al., 2002a), visual hallucinations (Varma et al., 2003; Diederich et al., 2000) and behavioural changes, like apathy, irritability, emotional lability, hypersexuality and aggressive behaviour (Krack et al., 2003; Houeto et al., 2002; Dujardin et al., 2001; Romito et al., 2002a). Some episodes are related to a misplacement of the electrodes (Stefurak et al., 2003; Bejjani et al., 2002, 1999; Kulisevsky et al., 2002; Doshi et al., 2002) or to changes of the stimulation parameter (Okun et al., 2004; Sensi et al., 2004; Diederich et al., 2000). The changes may be related to a modification of the activity of the basal ganglia-thalamo-cortical circuits by chronic stimulation of the subthalamic nucleus. There is a lack of prospective studies.

The aim of this study was to investigate the effects of Stn-DBS on psychiatric symptoms and psychosocial functioning in a consecutive series of 35 patients with idiopathic PD, who underwent bilateral Stn-DBS.

Patients and methods

Patients

Patients were selected for deep brain stimulation according to the CAPSIT-PD protocol (Defer et al., 1999). The inclusion criteria for the study included:

- A diagnosis of idiopathic PD determined by the presence of at least two of the four cardinal motor symptoms
- No signs indicating atypical parkinsonism or other diagnosis other than idiopathic PD
- A clear responsiveness to Levodopa as demonstrated by an apomorphine test before surgery (Pinter et al., 1999)
- Intractable disabling motor fluctuations, dyskinesia, or freezing episodes
- A normal brain magnetic resonance imaging (MRI) scan
- A mini-mental state examination score (MMSE) of more than 24 points

Exclusion criteria were a previous neurosurgical history, native language other than German, history of substance abuse; a presence of a severe psychiatric disease (psychotic episodes, major depression) based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; Saß et al., 1998) and withheld informed consent.

35 consecutive patients, who met the defined inclusion/exclusion criteria, underwent bilateral implantation of electrodes in the subthalamic nucleus in the period of February 2001 to November 2002. All patients gave their written informed consent. The data of two patients were excluded from the study: one patient withdrew informed consent after three months postoperatively. The other patient was affected by a surgical complication (cerebral haemorrhage). The study

includes valid data of 33 patients with PD (22 men, 11 women). Because of two deaths, there are data of 31 patients for the whole assessment period. The two patients died of cardiovascular diseases, which were not related to DBS surgery or stimulation, six respectively ten months after surgery. We noted following transient psychiatric side effect: one patient was confused and disoriented after electrode implantation. Another patient developed a psychotic episode during the electrode implantation, which required antipsychotic treatment. The mean age $\pm$ SD of the patients was 60.2 ± 7.9 (range 38 to 72). The mean education years were 11.1 ± 2.6 (range 8 to 17). The mean disease duration at surgery was 13.5 ± 4.8 (range 7 to 25) and the mean Hoehn and Yahr stage was 3.8 ± 0.6 (range 3 to 5). The mean score of the Mini Mental State Examination was 27.9 ± 1.37 (range 25 to 30).

Surgical procedure

34 patients were treated with bilateral implantation surgery in a single operative session (Lead 3389, Medtronic Inc.). In one case, due to a lack of co-operation, the second side had to be operated one week later. Targeting of the Stn was performed using stereotactic ventriculography, computerized tomography (CT), and magnetic resonance imaging (MRI). The physiological definition of the target was done using microelectrode recording, intraoperative clinical testing and intraoperative test stimulation. Intra- and postoperative x-rays were used to control and document the electrode position. In all the patients a testing phase of several days using an external pulse generator was performed prior to the implantation of the permanent pulse generator. All patients were provided with dual channel devices (Kinetra 7428, Medtronic Inc.).

Methods

Assessment time and condition

All patients were examined at eight assessment times. To avoid short-term mood fluctuations and to establish a baseline score, the patients were evaluated three times prior to surgery: eight to six weeks (t_1), four weeks (t_2) and two weeks (t_3). Other psychological variables (Symptom-Checklist 90-R; clinical rating scales) were estimated two times before surgery (t_1 and t_3). All patients were evaluated with medication except for the Unified Parkinson's Disease Rating Scale (with and without medication). To investigate short- and long-term effects of bilateral subthalamic deep brain stimulation we assessed psychiatric symptoms and psychosocial functioning at five times: three weeks after surgery at the time of discharge from the hospital (t_4), nine weeks (t_5), three (t_6), six (t_7), and twelve months (t_8) after surgery. All patients were evaluated with medication and with stimulation turned on after surgery. To avoid an influence on mood by discontinuation of the medication we did not evaluate the motor score in the condition off medication during this study period. The electrical parameter programming and the reduction of antiparkinsonian drugs took several weeks and were completed at nine weeks after surgery.

Psychological assessment

The psychological assessment was chosen according to the following considerations: tenable duration (about 2–3 hour), and inclusion of well-established tests commonly used in the assessment of mood, psychological symptoms and distress. A clinical interview to detect the presence of psychiatric disorders or behavioural disturbances was conducted in all patients. All interviews and clinical rating scales were performed by the same neuropsychologist during the whole assessment period. Psychiatric status and changes during the observation period were documented by established research rating scales, which include Bech-Rafaelsen Melancholia Scale (BRMES), Hamilton Anxiety Scale (HAMA), Global Assessment Scale (GAS) and Global Clinical Impression (CGI). The neurological impairment was assessed with the Unified Parkinson Disease Rating Scale (UPDRS). All patients completed as self-report measurements the Profile of Mood States (POMS), Beck Depression Inventory (BDI), Visual Analogue Scale for Mood (VAS), State-Trait Anxiety Inventory (STAI-X1/X2), and Self-Report Symptom Inventory 90 Items-Revised (SCL-90-R). All scales are recommended to evaluate treatment effects with sufficient reliability and did not require parallel test versions.

Clinical rating scales

Bech-Rafaelsen Melancholia Scale (BRMES)

The BRMES is a frequently used rating scale to estimate the severity of depressive syndromes. It consists of eleven items, each item scored on a five-point scale (Stieglitz et al., 1998).

Hamilton Anxiety Scale (HAMA)

The HAMA is a common rating scale to assess the degree of anxiety. It consists of 14 items, which evaluate the somatic and psychic symptoms of anxiety and the general degree (Hamilton et al., 1959).

Brief Psychiatric Rating Scale (BPRS)

The BPRS is a commonly used rating scale. The BPRS assesses five subscales: Depression/Anxiety, Anergia,

Thought Disturbance, Activation, Hostility/Suspiciousness, which can be computed to a total score (Overall et al., 1969).

Global Assessment Scale (GAS)

The GAS rates psychological, social, and occupational functioning on a continuum from 1 to 100. It does not include impairment in functioning due to physical disability (Saß et al., 1998).

Clinical Global Impression (CGI)

The CGI consists of three items with seven categories to evaluate the severity of the disease (1), the degree of improvement (2) and the therapeutic efficacy (3) in a follow-up assessment (National Institute of Mental Health, 1976).

Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS assess the severity of PD. The UPDRS consists of four parts: I. Mentation, behaviour, mood, II. Activities of daily living, III. Motor examination, IV. Complications of therapy (Fahn et al., 1987).

Self-rating scales

Profile of Mood Scale (POMS)

This modified version consists of 35 adjectives clustered in four subscales (Depression, Fatigue, Vigor, Irritability) by which subjects describe their mood during the week before (Bullinger et al., 1990).

Visual Analogue Scale for Well-being (VAS)

The patient has to state his present condition on a line with two extreme poles of well-being and uncomfortable feeling (McCormak et al., 1990).

Beck Depression Inventory (BDI)

The BDI is a commonly used 21-item questionnaire that measures depressive symptoms (Hautzinger et al., 1995).

State-Trait Anxiety Inventory (STAI-X1/STAI-X2)

The STAI consists of two rating scales: STAI-X1 evaluates anxiety related to certain situations whereas STAI-X2 measures anxiety as a trait (Laux et al., 1981).

Self-Report Symptom Inventory 90 Items-Revised (SCL-90-R)

The SCL-90-R is a measurement of the impairment due to somatic and psychological symptoms and distress. It consists of nine subscales and three global judgements (Franke, 1995).

Data analysis

Given the inconsistent reports on mood and psychological functions, a two-sided analysis of variance was performed on each of the mood and psychological variables, using assessment time as repeated measures. For variables that showed significant differences, error bars illustrate the pattern of differences. In case of comparing two tests (some baseline data) we used the paired t test. Nonparametric analyses (Friedman test or Wilcoxon test) were made when required by the distribution of the data or by the prerequisites of the rating scales. For variables, which showed significant differences in the Friedman test, we examined the pattern of difference by the Wilcoxon test (Bonferroni correction of the p-value for multiple single comparisons: $\alpha^* = 0.003$, except for the CGI-scale: $\alpha^* = 0.005$). The significance level was considered at $p \leq 0.01$, because of the large number of scales. Due to the fact that the sample size is rather small we also interpreted results between $p = 0.01$ and $p = 0.05$ as a trend towards significance.

To evaluate postoperative changes among individual patients, we subtracted the individual postoperative raw scores (times 8) from the baseline data. These difference values from each patient were transformed to a standard (z) score. The clinical criteria of more than $+1.0$ SD was used to note individual postoperative improvements, while a decrease of more than -1.0 SD was used to list individual postoperative declines.

Results

The comparison of the preoperative data (t_1, t_2, t_3 or t_1, t_3) showed no significant differences in all scales except for *Anxiety*. The subscale *Anxiety* (SCL-90-R) increased significantly from t_1 to t_3 ($T = -2.934$, $p = 0.007$), close to the surgery date anxiety was significantly higher. In general preoperative data illustrated no significant differences, thus we combined the preoperative scores to one baseline mean score.

All mean values and SD of the clinical rating scales are described in Table 1. The

Table 1. Comparison of mood and mental function before (baseline) and after bilateral subthalamic stimulation (pre-/postoperative comparison, mean, SD, p values). Lower score indicates fewer symptoms. *Higher score demonstrates better function

Clinical rating scales (n = 33)	Baseline	t_4 (3 weeks)	t_5 (9 weeks)	t_6 (3 months)	t_7 ($n_7 = 32$) (6 months)	t_8 ($n_8 = 31$) (12 months)	p
BRMES – Depressive Symptoms	10.5 (3.9)	8.8 (3.5)	5.8 (4.0)	6.5 (4.0)	6.0 (4.3)	6.1 (3.9)	**<0.001**
HAMA – Somatic Symptoms	5.8 (2.6)	2.7 (1.9)	3.3 (2.3)	3.0 (1.8)	3.0 (2.1)	3.3 (2.0)	**0.001**
HAMA – Psychological Symptoms	8.7 (3.0)	8.0 (3.0)	5.6 (2.6)	6.3 (2.3)	6.3 (2.9)	6.1 (2.8)	**0.002**
HAMA – Total Score	14.7 (4.9)	10.7 (4.1)	8.5 (4.2)	9.4 (3.7)	9.3 (4.3)	9.6 (3.8)	**<0.001**
BPRS – Depression/Anxiety	11.1 (2.9)	10.0 (3.6)	8.0 (2.3)	8.9 (2.6)	8.3 (2.7)	7.4 (2.0)	**<0.001**
BPRS – Anergia	6.1 (1.5)	6.1 (1.9)	5.7 (1.6)	5.2 (1.0)	5.4 (1.4)	5.4 (1.4)	0.025
BPRS – Thougt Disturbances	4.2 (0.4)	4.2 (0.7)	4.2 (0.7)	4.1 (0.4)	4.1 (0.3)	4.3 (1.0)	0.416
BPRS – Activation	6.6 (1.3)	6.4 (2.0)	5.7 (1.5)	5.7 (1.4)	5.4 (1.4)	4.8 (1.5)	**<0.001**
BPRS – Hostility-Suspiciousness	3.8 (1.5)	3.9 (1.5)	3.8 (1.7)	3.7 (1.4)	3.5 (1.9)	3.5 (1.2)	0.131
BPRS – Total Score	31.6 (5.1)	30.7 (6.5)	27.3 (4.6)	27.7 (4.8)	26.7 (4.5)	24.7 (3.2)	**<0.001**
GAF – Psychosocial Functioning*	65.1 (5.7)	66.7 (9.4)	73.1 (6.5)	74.7 (8.1)	74.9 (9.3)	74.6 (8.1)	**<0.001**
CGI – Change	–	2.3 (0.9)	1.9 (0.9)	2.0 (0.8)	1.7 (0.7)	1.8 (0.9)	**0.007**
CGI – Efficacy	–	2.0 (0.5)	1.5 (0.7)	1.5 (0.6)	1.3 (0.5)	1.4 (0.5)	**<0.001**
CGI – Adverse effects	–	1.2 (0.5)	1.0 (0.0)	1.1 (0.2)	1.0 (0.3)	1.2 (0.5)	0.126

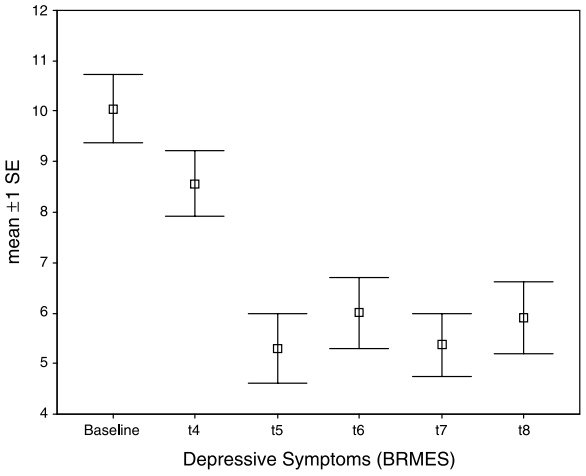

Fig 1. Depression (BRMES): mean ± 1 SE from baseline to t_8

depression score (BRMES, $F = 16.280$, $p = <0.001$) decreased significantly from baseline to all other time points. Postoperatively we noted a slight initial improvement at three weeks followed by a more profound improvement at nine weeks. At this level the improvement remained stable over the observed period (Fig. 1).

Somatic symptoms ($F = 12.512$, $p = 0.001$), psychic symptoms (HAMA, $F = 11.025$, $p = 0.002$) and the total score of anxiety ($F = 16.483$, $p = 0.002$) improved significantly after surgery. The somatic symptoms improved immediately after surgery and then stabilized over the course of time. The extent of somatic anxiety increased at twelve months after surgery, the degree of anxiety was higher compared to three weeks but significant lower compared to baseline. Regarding to the psychic anxiety a significant decrease appeared at nine weeks postoperatively, and then the improvement stabilized. The total value of anxiety decreased at three weeks after surgery and then again at nine weeks where it became stable. At twelve months the degree of anxiety increased to the level at three weeks after surgery.

The subscale *Thought Disturbance* ($Chi^2 = 4.076$, $p = 0.538$), *Anergia* ($Chi^2 = 13.308$, $p = 0.021$) and *Hostility* ($Chi^2 = 12.171$, $p = 0.033$) remained unchanged. *Anxiety/Depression* ($Chi^2 = 53.689$, $p = 0.000$), *Activation* ($Chi^2 = 26.790$, $p = <0.001$), and the *total BPRS score* ($Chi^2 = 50.356$, $p = <0.001$) improved significantly. The amelioration in *Anxiety/Depression* developed nine weeks after surgery and stayed stable up to one year. The mean ranks of *Activation* showed a significant improvement between baseline and three weeks as well as three and six months after surgery compared to one year postoperatively. The *total score of psychiatric symptoms* decreased from baseline to all other time scores except for the first postoperative assessment.

The global assessment of psychosocial functioning (GAS) improved significantly ($Chi^2 = 56.174$, $p = <0.001$) after surgery. The paired Wilcoxon test showed a significant difference between baseline data and all other points of time, except for the first postoperative assessment. Another significant difference was found between three weeks postoperatively and the other postoperative time points. The psychological state (CGI) changed significantly between the postoperative time points ($Chi^2 = 14.177$, $p = 0.007$); a better psychological state was demonstrated at six months after surgery compared with three weeks. The efficacy of treatment as regards to psychological function indicated a significant difference between postoperative time points ($Chi^2 = 32.027$, $p = <0.001$). The improvement appeared at three months postoperatively and then stabilized. Adverse effects on psychological functions remained unchanged (CGI; $Chi^2 = 7.193$, $p = 0.126$).

The ADL score enhanced significantly after surgery (compared with baseline on medication: $Chi^2 = 48.362$, $p = <0.001$; compared with baseline off medication: $Chi^2 = 79.299$, $p = <0.001$). The deterioration in the ADL was reduced by 37% to 45% over the course of time compared to baseline on medication and 66% to 71% compared to baseline off medication. The motor function improved after surgery (compared with base-

Table 2. Comparison of ADL and motor function before (baseline) and after bilateral Stn-stimulation (pre-/postoperative comparison, mean, SD, p values). Lower score indicates better function. Baseline: off and on medication; after surgery (t_4–t_8): on medication and on stimulation

UPDRS	Baseline m (SD)	t_4 (3 weeks) m (SD) on med/on stim	t_5 (9 weeks) m (SD) on med/on stim	t_6 (3 months) m (SD) on med/on stim	t_7 (6 months) m (SD) on med/on stim	t_8 (12 months) m (SD) on med/on stim	p
ADL (part II)	12.0 (5.9) on med	7.3 (3.8)	6.7 (3.2)	6.0 (4.3)	6.0 (4.4)	6.3 (4.6)	**<0.001**
	21.3 (7.1) off med	–	–	–	–	–	
ADL improvement in % (compared with baseline on med)		37%	41%	47%	49%	45%	
(compared with baseline off med)		66%	68%	72%	79%	71%	
Motor examination (part III)	18.0 (9.3) on med	10.6 (6.8)	10.4 (7.3)	8.7 (7.3)	8.6 (7.3)	7.9 (7.6)	**<0.001**
	45.2 (14.0) off med	–	–	–	–	–	
Motor improvement in % (compared with baseline on med)		41%	43%	50%	50%	54%	
(compared with baseline off med)		77%	77%	80%	81%	83%	

Table 3. Comparison of mood and mental function before (baseline) and after bilateral subthalamic stimulation (pre-/postoperative comparison, mean, SD, p). Lower score indicates fewer symptoms. *Higher score demonstrates better function

Self rating scales (n = 33)	Baseline	t_4 (3 weeks)	t_5 (9 weeks)	t_6 (3 months)	t_7 ($n_7 = 32$) (6 months)	t_8 ($n_8 = 31$) (12 months)	p
POMS – Depression	11.1 (7.6)	11.3 (9.9)	6.5 (7.8)	7.3 (7.7)	8.0 (8.1)	8.1 (9.2)	0.081
POMS – Fatigue	9.8 (3.9)	8.2 (5.0)	5.9 (4.5)	7.6 (5.0)	7.8 (5.2)	7.3 (5.2)	0.048
POMS – Vigor*	7.5 (3.9)	8.3 (5.5)	10.0 (4.8)	8.5 (5.3)	9.7 (4.9)	9.3 (5.3)	0.182
POMS – Irritability	5.6 (4.2)	5.0 (5.0)	4.7 (5.4)	4.3 (4.9)	4.8 (5.6)	4.5 (4.8)	0.381
VAS – Well being	53.9 (15.8)	42.1 (29.3)	37.5 (24.4)	38.6 (24.0)	35.4 (16.9)	40.8 (20.8)	0.062
BDI – Depressive Symptoms	13.8 (6.2)	8.3 (6.6)	7.8 (5.9)	7.5 (6.4)	8.5 (6.6)	7.9 (5.6)	**0.003**
STAI – State Anxiety	47.0 (7.8)	42.3 (12.4)	40.0 (10.3)	39.2 (9.5)	40.4 (10.3)	40.1 (9.6)	0.012
STAI – Trait Anxiety	44.6 (7.9)	41.2 (11.5)	38.4 (10.0)	39.2 (10.7)	38.4 (9.7)	39.4 (9.4)	0.019
SCL-90-R – Somatization	1.6 (0.5)	0.5 (0.3)	0.7 (0.3)	0.6 (0.4)	0.6 (0.4)	0.6 (0.4)	**<0.001**
SCL-90-R – Obsessive-Compulsive	0.8 (0.4)	0.6 (0.5)	0.5 (0.4)	0.5 (0.4)	0.6 (0.5)	0.5 (0.4)	0.055
SCL-90-R – Interpersonal Sensitivity	0.8 (0.5)	0.4 (0.5)	0.5 (0.4)	0.5 (0.4)	0.5 (0.5)	0.4 (0.4)	0.017
SCL-90-R – Depression	0.8 (0.4)	0.6 (0.5)	0.5 (0.5)	0.6 (0.5)	0.5 (0.5)	0.5 (0.5)	0.078
SCL-90-R – Anxiety	0.9 (0.4)	0.5 (0.4)	0.4 (0.5)	0.3 (0.4)	0.4 (0.4)	0.4 (0.5)	**0.001**
SCL-90-R – Hostility	0.4 (0.4)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.8 (0.4)	0.3 (0.3)	0.103
SCL-90-R – Phobic Anxiety	0.5 (0.4)	0.4 (0.6)	0.4 (0.4)	0.4 (0.4)	0.3 (0.4)	0.4 (0.6)	0.166
SCL-90-R – Paranoid Ideation	0.6 (0.4)	0.4 (0.5)	0.4 (0.5)	0.5 (0.4)	0.4 (0.4)	0.4 (0.4)	0.053
SCL-90-R – Psychoticism	0.4 (0.3)	0.3 (0.4)	0.2 (0.3)	0.2 (0.3)	0.2 (0.3)	0.3 (0.4)	0.079
SCL-90-R – General Severity Index	0.7 (0.3)	0.5 (0.4)	0.4 (0.3)	0.5 (0.3)	0.5 (0.3)	0.4 (0.4)	**0.008**
SCL-90-R – Positive Symptom Distress Index	1.5 (0.3)	1.3 (0.5)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	1.3 (0.4)	0.125
SCL-90-R – Positive Symptom Total	42.3 (13.6)	29.7 (18.0)	28.3 (17.8)	28.7 (16.8)	28.3 (17.6)	27.9 (20.5)	**0.002**

line on medication: $Chi^2 = 58.543$, $p = <0.001$; compared with baseline off medication: $Chi^2 = 73.829$, $p = <0.001$). The impairment was reduced by 41% to 54% compared to baseline on medication and 77% to 82% compared to baseline off medication. All mean values (SD) and the percentage improvement of the UPDRS are listed in Table 2.

The mean values (SD) of levodopa equivalent dose were at baseline: 1617.47 mg (852.31), nine weeks after surgery: 454.03 mg (180.11), three months: 459.42 mg (183.62), six months: 461.29 mg (149.87) and twelve months after surgery: 491.61 mg (241.81). The average reduction of dopaminergic medication (dopa equivalent mg/24 hours) was 70% at twelve months after surgery compared to baseline. The levodopa equivalent dosage was calculated from Diener et al. (2004).

All mean values and standard deviations of the self-rating scales are described in Table 3. Compared with the preoperative baseline data, there were no significant changes in mood and well-being. Only fatigue showed a trend toward improvement. (*POMS*: *Depression/Anxiety*: $F = 3.271$, $p = 0.081$, *Fatigue*: $F = 4.282$, $p = 0.048$, *Vigor*: $F = 1.876$, $p = 0.182$, *Irritability*: $F = 0.791$, $p = 0.381$; *VAS*: $F = 3.792$, $p = 0.062$).

The extent of depressive symptoms (*BDI*, $F = 10.858$, $p = 0.003$) improved significantly from baseline to all other time scores. The enhancement appeared immediately after surgery and stabilized. The *State Anxiety* (*STAI-X1*, $F = 7.171$, $p = 0.012$) and the *Trait Anxiety* (*STAI-X2*, $F = 6.196$, $p = 0.019$) showed a trend toward improvement from baseline to all other time scores.

The symptoms scales of the *SCL-90-R* indicated the following significant results: *Somatization* ($F = 18.003$, $p = <0.001$) and *Anxiety* ($F = 12.404$, $p = 0.001$). At three weeks after surgery we noted a profound improvement in *Somatization*, which declined slightly at nine weeks. At three months the improvement stabilized between the level at baseline and three weeks postoperatively (Fig. 2). Regarding *Anxiety*, there was a progressive improvement over the first two time periods and then stabilized. At six and twelve months after surgery we noted a decline of this marked improvement to the level measured at three weeks. The global scales *Global Severity Index* ($F = 8.221$, $p = 0.008$) and the *Positive Symptom Total* ($F = 12.189$, $p = 0.002$) showed a marked and stable improvement after surgery (Fig. 3, PST similar).

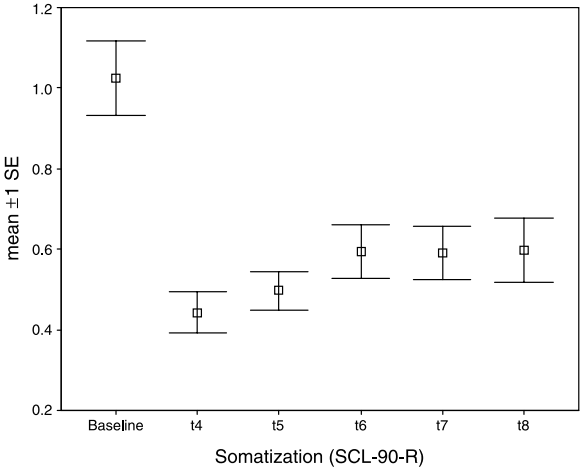

Fig 2. Somatization (SCL-90-R): mean ± 1 SE from baseline to t_8

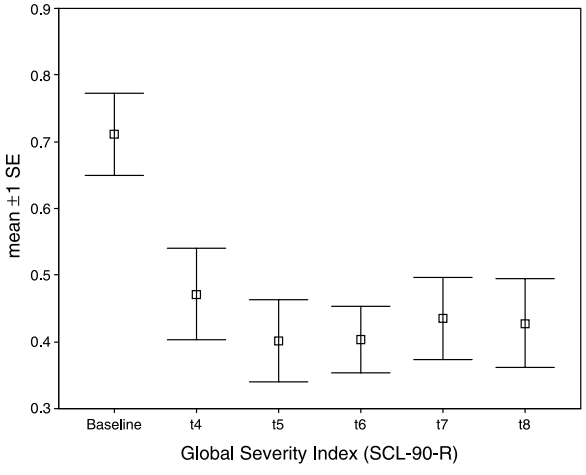

Fig 3. Global Severity Index (SCL-90-R): mean ± 1 SE from baseline to t_8

Table 4. Percentage of patients, their z-scores improved or declined more than 1 SD (compared baseline and one year postoperatively)

Self-Rating Scales (n = 31)	Improvement (1 SD > +1)	No change (SD +1 to −1)	Decline (1 SD > −1)
POMS – Depression	17%	63%	20%
POMS – Fatigue	17%	60%	23%
POMS – Vigor	10%	73%	17%
POMS – Irritability	20%	63%	17%
VAS – Well being	10%	77%	13%
BDI – Depressive Symptoms	13%	71%	16%
STAI – State Anxiety	23%	65%	13%
STAI – Trait Anxiety	16%	71%	13%
SCL-90-R – Somatization	13%	74%	13%
SCL-90-R – Obsessive Compulsive	19%	61%	19%
SCL-90-R – Interpersonal Sensitivity	19%	61%	19%
SCL-90-R – Depression	13%	74%	13%
SCL-90-R – Anxiety	13%	77%	10%
SCL-90-R – Hostility	13%	74%	13%
SCL-90-R – Phobic Anxiety	6%	84%	10%
SCL-90-R – Paranoid Ideation	6%	84%	10%
SCL-90-R – Psychoticism	13%	74%	13%
SCL-90-R – General Severity Index	19%	65%	16%
SCL-90-R – Positive Symptom Distress Index	19%	71%	10%
SCL-90-R – Positive Symptom Total	13%	74%	13%

Interpersonal Sensitivity ($F = 6.434$, $p = 0.017$) indicated no significant change, but a trend toward improvement after surgery. The subscales *Obsessive-Compulsive* ($F = 4.014$, $p = 0.055$), *Depression* ($F = 3.343$, $p = 0.078$), *Paranoid Ideation* ($F = 4.089$, $p = 0.053$), *Psychoticism* ($F = 3.328$, $p = 0.079$), *Phobic Anxiety* ($F = 2.023$, $p = 0.166$), *Hostility* ($F = 2.844$, $p = 0.103$) and the global scale *Positive Symptom Distress Index* ($F = 2.496$, $p = 0.125$) showed no significant change.

We compared baseline with one year postoperatively to analyse individual patterns of change in the self-rating scales. The majority of patients showed no above-average improvement or decline (see Table 4). More patients demonstrated an above-average decline than an improvement in the *Profile of Mood Scale* (*Depression*, *Fatigue*, *and Vigor*) and in the *Visual Analogue Scale of Well-being* as well as in the *Beck Depression Inventory*. Further declines were noted in *Phobic Anxiety* and *Paranoid Ideation* (*SCL-90-R*). More patients showed an above-average improvement than a decline in the *POMS-Subscale Irritability*, *State and Trait Anxiety*, *Anxiety* (*SCL-90-R*), *Positive Symptom Distress Index* and *Positive Symptom Total*.

Furthermore we analysed the individual changes of each patient (Table 5). For this purpose we combined the different self-rating scales to psychological constructs (well being, depression, state anxiety, trait anxiety, symptom distress). If the standardised score (z) of each patient improved or declined in at least 50% of the subscales in each psychological construct, we listed an above-average change (gain/loss). We identified five patients with a loss and seven patients with a gain in one psychological construct. Three patients had losses in two constructs and two patients had gains. We noted three patients with losses in at least three constructs, and three patients with gains. This individual analysis indicated that psychiatric symptoms and psychosocial

Table 5. Patients, their z-scores decreased or improved more than 1 SD in at least 50% of the subscales in psychological constructs (n = 31, compared baseline and one year postoperatively). Patients, who showed no above-average improvement or decline, are not listed

Case no.	Well-being (POMS, VAS)	Depressive symptoms (BDI)	State anxiety (STAI)	Trait anxiety (STAI)	Symptom distress (SCL-90-R)
1			loss (1/1)		
2			gain (1/1)	gain (1/1)	
3		gain (1/1)			
4	gain (4/5)	gain (1/1)	gain (1/1)	gain (1/1)	gain (6/9)
5			gain (1/1)	gain (1/1)	
7	gain (3/5)				
8		loss (1/1)		loss (1/1)	
9			gain (1/1)		
11		gain (1/1)			
13			gain (1/1)		
14	loss (5/5)				
15		loss (1/1)			
16		loss (1/1)			loss (6/9)
17	**loss (3/5)**		**loss (1/1)**	**loss (1/1)**	
19					
20	loss (4/5)		loss (1/1)		
21	loss (3/5)				
23				loss (1/1)	
25			gain (1/1)		
26	**loss (4/5)**	**loss (1/1)**	**loss (1/1)**	**loss (1/1)**	
28	**loss (3/5)**	**loss (1/1)**			**loss (10/9)**
31	gain (3/5)		gain (1/1)	gain (1/1)	
32		gain (1/1)		gain (1/1)	gain (5/10)
33					gain (6/10)

functioning declined in three patients of 31 (9.7%) despite clear motor improvement. Their psychosocial functioning worsened after surgery. All three patients reported psychosocial difficulties before surgery. Case 17 is a 66 year old woman with a 15 year history of severe PD with disabling motor fluctuations and drug induced dyskinesia. Since 20 years she is caring for her husband who had an industrial injury. She had a moderate depression treated with Amitriptylin (10 mg) before surgery. This treatment remained unchanged up to one year after surgery. Six months after surgery she reported more anxiety and less well-being. Case 26 is a 60 year old man with a twelve year history of severe PD with marked drug induced dyskinesia. Before surgery he had no history of mental disorder. He reported conflicts with his wife, three months after surgery they stopped living together and finally got divorced. He was able to pursue his work postoperatively. The deterioration in mood seems to be related to the family conflicts. Case 28 is a 63 year old man with 18 year history of severe PD with disabling motor fluctuations and drug induced dyskinesia. He had a history of moderate depression and of drug induced psychotic episodes before surgery (Trazodon 150 mg, Clozapin 25 mg, continued postoperatively). The patient and his wife also reported family conflicts. After surgery he complained loss of initiative and fatigue. None of the three patients had a cognitive decline. The changes appeared six to twelve months after surgery.

Discussion

Before surgery, psychiatric symptoms and psychosocial functioning were stable and demonstrated no significant change except for anxiety. The extent of anxiety increased closed to the surgery date; this could reflect a psychological stress reaction prior to surgery.

Motor function as well as the activities of daily living improved significantly after surgery. The antiparkinsonian medication was markedly reduced after surgery. Three of our patients were employed fulltime before surgery and remained in employment postoperatively. The global psychosocial functioning increased significantly at nine weeks postoperatively and stabilized. The efficacy of treatment as regards to a better psychological functioning appeared at three months postoperatively and remained stable. Adverse effects on psychological functioning showed no difference between the postoperative time points.

Depressive symptoms showed a significant reduction in both types of scales (clinical and self-rating scales). The symptoms rated by the patients improved immediately after surgery and stabilized over the observed period. In the clinical rating scale, the extent of depressive symptoms decreased initial slightly, followed by a more profound reduction and then stabilized. Differences concerning the beginning of the improvement (first or second postoperative time point) could be explained by the influence of the setting. Three weeks after surgery the programming as well as the reduction of the dopaminergic drugs was not completed, the patients were still hospitalized. Concerning anxiety there was a trend toward improvement rated by the patients. The clinical rating showed a significant amelioration in anxiety symptoms. Somatic symptoms of anxiety improved immediately after surgery followed by a slight worsening at twelve months compared to three weeks postoperatively. Psychic symptoms of anxiety declined markedly at nine weeks postoperatively. The general degree of anxiety showed a progressive improvement over the first two time points followed by a slight worsening to the level of three weeks postoperatively. Our results are compliant with the findings of other groups. Daniele et al. (2003) reported a significant postoperative decrease in depressive and anxiety symptoms at three, six, twelve ($n = 20$) and at eighteen months ($n = 9$) postoperatively compared to baseline data. Other centers found similar improvements in depression (Tröster et al., 2003; Lagrange et al., 2002; Martinez-Martin et al., 2002; Pillon et al., 2000; Ardouin et al., 1999; Burchiel et al., 1999). Saint-Cyr et al. (2000) reported an improvement only in a subgroup, which consisted of elderly patients. Funkiewiez et al. (2004) documented an improved depression, but an increase in apathy after Stn-stimulation. Ardouin et al. (2004) found an improvement in depressive symptoms in 34 patients after three months, but not after twelve months compared to baseline. In contrast to our results, some groups observed no significant changes in depressive symptoms (Morrison et al., 2004; Krack et al., 2003; Lopiano et al., 2001; Perozzo et al., 2001). Berney et al. (2002) found no significant changes in depression in a series of 24 patients, but they identified a subgroup of six patients, which had moderate to severe depressive symptoms after surgery despite clear motor improvement. Three of them were transiently suicidal; recent studies indicated an elevated suicide risk in patients treated by Stn-DBS (Voon et al., 2004).

Daniele et al. (2003) and Martinez-Martin (2002) reported significant improvement in anxiety symptoms, but others found no significant differences in anxiety after surgery (Lopiano et al., 2001; Volkmann et al., 2001; Perozzo et al., 2001).

We found no significant changes in present mood states. In contrast Okun et al. (2003) examined mood changes in nine DBS-patients under five randomized conditions

(off stimulation and during monopolar stimulation with each of four electrode contacts). They found that optimal placement of electrodes results in overall improvement in mood and is associated with a lower incidence of adverse mood effects than stimulation outside the optimal site. Funkiewiez et al. (2003) investigated psychotropic effects of bilateral Stn-DBS and levodopa. Both treatments had beneficial psychotropic effects, although the levodopa treatment was more effective. Contrary to our design, they examined mood changes under various conditions (on, off stimulation and medication, or different electrode contacts); we investigated the influence of chronic stimulation.

The extent of psychiatric symptoms declined after the second postoperative time point. Thought disorder, anergia and hostility remained unchanged. Activation decreased three and twelve months after surgery compared to the preoperative score. Others reported an increase in apathy and thought disorder after Stn-Stimulation (Funkiewiez et al., 2004; Ardouin et al., 2004).

The distress and burden of somatic and psychological symptoms decreased significantly after baseline, also their degree of incriminating symptoms. Concerning Somatization, patients improved significantly after surgery; this may be attributed to the clear motor improvement. Anxious symptoms increased prior to surgery and declined slowly in the postoperative period. The postoperative degree of was significantly lower than the degree at the first preoperative assessment. Their Interpersonal Sensitivity showed a trend toward significant improvement, maybe related to the improvement in motor function and the absence of stigmatizing symptoms like tremor (Ellring et al., 1993). The subscales Obsessive-Compulsive, Depression, Paranoid Ideation, Psychoticism, Phobic Anxiety, Hostility and the Positive Symptom Distress Index indicated no significant changes after Stn-Stimulation. The Global Severity Index and the Positive Symptom Total decreased after surgery and stabilized over the observed year. These results demonstrate that the burden of distress and psychological as well as non-specific somatic symptoms decrease after surgery. In contrast to our results concerning obsessive-compulsive traits, Alegret et al. (2001) found an improvement after surgery. Mallet et al. (2002) reported two cases of patients, who had Parkinson's disease and a severe obsessive-compulsive disorder, which improved after treatment with Stn-DBS.

Individual analysis of our patient's data showed that 9.7% of the patients had a decline in psychiatric symptoms and psychosocial functioning. Their mood state and psychosocial functioning decreased after surgery with Stn-stimulation despite clear motor improvement. Others also documented an occurrence of depression in patients after Stn-stimulation (Thobois et al., 2002; Doshi et al., 2002; Ostergaard et al., 2002; Houeto et al., 2002) or a worsening of present depression (Romito et al., 2002b; Vesper et al., 2002). One single case of acute depression was related to stimulation of the substantia nigra (Bejjani et al., 1999). Other infrequent mood changes were acute hilarity, euphoria, hypomania, hypersexuality, mania, manic psychosis, pseudobulbar crying, aggressive behaviour and further behavioural changes (Krack et al., 2001; Kulisevsky et al., 2002; Romito et al., 2002a; Herzog et al., 2003b; Okun et al., 2004; Sensi et al., 2004). These reports suggest that the stimulation of the subthalamic nucleus may influence the limbic pathways. Recent PET-studies indicated that Stn-DBS interacts with basal ganglia loops, which are involved in the regulation of mood, behaviour and cognition (Hilker et al., 2004; Schröder et al., 2002).

Our results suggest that subthalamic stimulation has a positive impact on depressive and anxiety symptoms, activation and psychosocial functioning in most of the patients. The burden of distress and of somatic symptoms caused by PD decrease in patients treated with

Stn-Stimulation. We observed declines in psychiatric symptoms and psychosocial functioning only in a minority of patients. Further investigations are needed to explore the worsening of psychiatric symptoms after bilateral stimulation of the subthalamic nucleus in some patients.

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Authors' address: Dr. K. Kalteis, Department of Neurosurgery, Medical University of Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria, e-mail: karin.kalteis@meduniwien.ac.at