Mechanisms of body weight gain in patients with Parkinson’s disease after subthalamic stimulation

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Chronic bilateral subthalamic stimulation leads to a spectacular clinical improvement in patients with motor complications. However, the post-operative body weight gain involved may limit the benefits of surgery and induce critical metabolic disorders. Twenty-four Parkinsonians (61.1 ± 1.4 years) were examined 1 month before (M1) and 3 months after (M1+3) surgery. Body composition and energy expenditure (EE) were measured (1) over 36 h in calorimetric chambers (CC) with rigorous control of food intakes and activities [sleep metabolic rate, resting activities, meals, 3 or 4 sessions of 20 min on a training bicycle at 13 km/h and daily EE] and (2) in resting conditions (basal metabolic rate) during an acute L-dopa challenge (M1) or according to acute ‘off’ and ‘on’ stimulation (M1+3). Before surgery, EE was compared between the Parkinsonian patients and healthy subjects matched for height and body composition (metabolic rate during sleep, daily EE) or matched to predicted values (basal metabolic rate).

Before surgery, in Parkinsonian men but not women, (1) daily EE was higher while sleep metabolic rate was lower compared to healthy matched men (+9.2 ± 3.9 and −8.2 ± 2.3%, respectively, P < 0.05) and (2) basal metabolic rate (L-dopa ‘on’) was higher than predicted basal metabolic rate (+11.5 ± 4.0%, P < 0.05) but was further increased without L-dopa (+8.4 ± 3.2% vs L-dopa ‘on’, P < 0.05). EE during daily activities was higher during ‘off’ periods compared to ‘on’ periods for both men (+19.3 ± 3.3%, P < 0.0001) and women (+16.1 ± 4.7%, P < 0.01). After surgery, there was a 3.4 ± 0.6 kg (P < 0.0001) body weight increase together with fat mass (P < 0.0001) and fat-free mass (P < 0.05) in Parkinsonian men and a 2.6 ± 0.8 kg (P < 0.05) body weight increase together with fat mass (P < 0.05) in Parkinsonian women. Sleep metabolic rate increased in men (+7.5 ± 2.0%, P < 0.01) to reach control values but remained unchanged in women. Daily EE decreased significantly in both men and women (−7.3 ± 2.2% and −13.1 ± 1.7%, respectively, P < 0.01) but there was no correlation between daily EE changes and body weight gain.

Parkinson’s disease is associated with profound alterations in the central control of energy metabolism. Normalization of energy metabolism after DBS-STN implantation may favour body weight gain, of which quality was gender specific. As men gained primarily fat-free mass, a reasonable weight gain may be tolerated, in contrast with women who gained only fat. Other factors such as changes in free-living physical activity may help to limit body weight gain in some patients.

Keywords: energy metabolism; metabolic syndrome; chronic bilateral subthalamic stimulation; Parkinson’s disease

Abbreviations: BMR = basal metabolic rate; DBS = deep brain stimulation; EE = energy expenditure; LIDs = L-dopa-induced dyskinesias; SMR = sleep metabolic rate; STN = subthalamic nucleus

Introduction

Parkinson’s disease is a neurodegenerative disorder that mainly affects the nigrostriatal dopaminergic system. Onset is generally between 50 and 65 years of age, and prevalence is 100 to 150/100,000, with the incidence increasing with age. The four cardinal clinical characteristics of Parkinson’s disease are bradykinesia, rigidity, rest tremor and postural instability. Dopaminergic therapy such as l-dopa and dopamine agonists usually leads to a dramatic improvement of symptoms, but disease progression nevertheless remains inevitable. Although weight loss is often observed in the evolution of Parkinson’s disease, the mechanisms involved remain unknown. For some authors, it results from a decrease in food intakes triggered by a depressive syndrome combining loss of appetite, hypersalivation and dysphagia (Broussolle et al., 1991; Andersson and Sidenvall, 2001; Chen et al., 2003; Lorefalt et al., 2004; Cheshire and Wszolek, 2005; Palhagen et al., 2005). Others underline that an increase in energy expenditure (EE) due to the rigidity or to motor complications such as motor fluctuations and l-dopa-induced dyskinesias (LIDs) should be also considered (Lorefalt et al., 2004). Bilateral Deep Brain Stimulation (DBS) in the subthalamic nucleus (STN) is now considered the gold standard surgical treatment for patients presenting Parkinson’s disease with intractable motor complications (Krack et al., 2003). Chronic DBS-STN greatly reduces motor fluctuations such as end-of-dose akinesia and on-off phenomena as well as dystonia while off medication. Furthermore, STN stimulation leads to a dramatic improvement in LIDs because it allows a 50% reduction in antiparkinsonian treatment. Consistently with other reports (Moro et al., 1999; Gironell et al., 2002; Barichella et al., 2003; Macia et al., 2004; Tuite et al., 2005; Perlemoine et al., 2005), we have observed body weight gain in ~30% of our population of patients after DBS-STN implantation, reaching close to 8% of pre-surgery body weight at 3 months post-surgery. Certain patients have presented a weight gain of up to 20 kg within the first 12 months post-surgery. The consequences of DBS therapy-induced weight gain have not been assessed with accuracy, but there is clearly an increased incidence of metabolic and cardiovascular disorders. The underlying mechanisms of body weight gain following DBS-STN remain unknown. Among other hypothesis put forward, Macia et al. (2004) proposed a post-operative decrease in EE. Indeed, the reduction in non-exercise activity thermogenesis due to decreased motor fluctuations and dystonia might be considered as a risk factor for body weight gain. Therefore, Parkinsonian patients presenting severe motor fluctuations may be particularly at risk for post-operative weight regain due to the high pre-operative energy expenditure involved.

The aim of this prospective study was to identify the mechanisms causing body weight gain in patients with Parkinson’s disease following DBS-STN. We therefore measured body composition and the various components of daily energy expenditure using whole body indirect calorimetry, at 1 month before and 3 months after DBS-STN implantation, in 24 Parkinsonian men and women.

Subjects and methods

Subjects

The study enrolled 24 non-smoker patients with Parkinson’s disease (17 men and 7 women) aged 61.1 ± 1.4 years. History of disease was 9.9 ± 0.6 years for the men and 10.1 ± 1.5 years for the women. Furthermore, 24 non-smoker healthy controls (17 men and 7 women) aged 66.7 ± 0.9 years patient-matched for height and body composition were recruited. Twenty-three patients with Parkinson’s disease (16 men and 7 women) completed the whole study. One man refused to participate in the post-operative EE measurements but accepted the assessment of body composition. All patients were suffering from idiopathic Parkinson’s disease according to the criteria of the ‘Parkinson’s Disease Society Brain Bank’ (Hughes et al., 1992). The diagnosis of Parkinson’s disease had been established for 5 years or more in all subjects. All subjects had taken a medical examination and had the go-ahead to undergo the surgery according to the French consensus conference of treatment of Parkinson’s disease (Consensus Conference Proceedings, 2000). They all suffered from severe motor fluctuations and LIDs that were not improved by changes in their antiparkinsonian treatment. Selection criteria were: an excellent response to l-dopa tested during an acute l-dopa challenge (>50%), no postural instability during the best ‘on’ period (postural instability = 0 from item 29 of UPDRS part III), absence of dementia (Mini Mental Status >24, Mattis scale >130/144) and normal magnetic resonance imaging. Were excluded all subjects presenting diabetes, thyroid disease, psychosis related to the antiparkinsonian drugs, and severe depression with suicidal tendencies. All women were post-menopausal. The study protocol was approved by the regional Medical School Ethics Committee (AU474) and was performed according to the principles set out in the Declaration of Helsinki and to French legislation (the Huriet law). The nature and potential risks of the study were fully explained and written informed consent was obtained from each participant.

General study design

The study lasted for 4 months for each patient. After medical controls at inclusion, patients were studied 1 month before (M−1) and 3 months after (M+3) STN-DBS surgery. Before each measurement period, patients were asked to complete a 7-day dietary questionnaire. The same measurements were then taken over a first 4-day period at M−1 and a second at M+3. On day 1, a clinical examination and an interview on health and medical history were performed. Biological tests were carried out on day 2, and the patients entered the calorimetry chamber on the same evening. EE and heart rate were continuously recorded during the 36 h following entry into the calorimetry chamber. Therefore, patients were in the calorimetric chambers during day 3. They came out in fasted state on the morning of the fourth day. Basal metabolic rate (BMR) was then measured in resting conditions in the morning during an acute l-dopa challenge in both the ‘off’ and ‘on’ states at M−1; at M+3, this was again measured during
similar acute l-dopa challenge but under two different stimulation conditions: stimulation switched ‘on’ and stimulation switched ‘off’. Finally, body composition was assessed using dual X-ray absorptiometry (DEXA).

For the healthy subjects, the study lasted for 1 week. After medical control at inclusion, body composition was assessed using DEXA. The subjects then entered the calorimetry chamber in the evening, and EE was recorded during 36 h, as described for Parkinsonian patients.

Measurements in the calorimetric chambers
EE and heart rate were measured continuously using two open-circuit whole-body calorimetric chambers (Morio et al., 1997a, b). Gas analysers were calibrated every 12 h during the measurement period using standard gas mixtures. Gas exchanges were computed from the minute-by-minute measurement of outlet air flow, differences in gas concentrations, atmospheric pressure, chamber air temperature and hygrometry, and taking into account drifts in the gas analysers and variations in the volumes of CO2 and O2 in the chambers (Vermorel et al., 1995). The validity of gas exchange measurements was checked gravimetrically by comparing the amounts of gases (CO2, O2) analysed with the amounts expected from the minute-by-minute measurement of outlet air flow, differences in gas concentrations, atmospheric pressure, chamber air temperature and hygrometry, and taking into account drifts in the gas analysers and variations in the volumes of CO2 and O2 in the chambers (Vermorel et al., 1995). The validity of gas exchange measurements was checked gravimetrically by comparing the amounts of gases (CO2, O2) analysed with the amounts expected from the weights of the gases (CO2, N2) injected into the chambers during a 24 h period (Vermorel et al., 1995). For chambers 1 and 2, O2 recovery rates were 95.4 ± 0.3 and 98.2 ± 0.2%, respectively, and CO2 recovery rates were 100.6 ± 0.2 and 102.5 ± 0.1%, respectively.

Twenty-four-hour urine was collected from 7 a.m. on day 3 to 7 a.m. on day 4 to determine urinary nitrogen excretion. EE was calculated using the Weir’s equation (De Weir, 1949) based on the measurement of gas exchanges corrected for urinary nitrogen excretion.

Twenty-four-hour EE (daily EE) was calculated from 7 a.m. on day 3 to 7 a.m. on day 4. EE during the time awake was measured from 7 a.m. to 11 p.m. on day 3. EE during activities was computed over 15–30 min periods. Sleeping metabolic rate (SMR) was taken as energy expenditure during the least-active period of the night in the calorimetric chamber. This period averaged 137 ± 84 min. Increases in energy expenditure above 15% associated with heart-rate peaks were considered as resulting from waking up and were excluded from the SMR studies.

Activity program in the calorimetric chambers
The activity program in the calorimeters consisted of four 20 min cycling sessions without any load and at about 50 rpm. Meals were served at given times: breakfast at 8 a.m., lunch at noon and dinner at 7 p.m. Assistance with dressing was planned on each morning when necessary. Energy expenditure during this period of time was corrected when necessary. During the remaining time, activities were left to the patient’s discretion. Patients were asked to use a patient diary to note as accurately as possible their activities and any periods of motor fluctuation. Investigators simultaneously maintained similar records.

Food intakes in the calorimetric chambers
Dietary energy supply was calculated individually using the factorial method (Morio et al., 1997a, b). For this purpose, daily EE was calculated from the duration and the energy cost of the various activities performed while in the calorimetric chambers (e.g. cycling) (Morio et al., 1997a, b) and a predicted BMR (Harris and Benedict, 1918). Dietary energy supply broke down as 50% of energy as carbohydrates, 35% as lipids and 15% as proteins.

Basal metabolic rate measurements
BMR was measured after an overnight fast using Deltatrac II (Datex-Engstrom Division, Instrumentarium Corp., Helsinki, Finland). At M − 1, BMR was first measured for 45 min without l-dopa. Then, l-dopa treatment (200 mg, Modopar Dispersible, Roche) was administered and BMR was measured again for a further 45 min after a 60 min delay corresponding to the period when patients were in the ‘on’ phase. At M + 3, the patients were administered their l-dopa treatment at the same dose as pre-operatively, and BMR was measured for 45 min with stimulation switched ‘on’. This situation is characterized by minimal involuntary movements. Then, STN-DBS was stopped and BMR was measured for a further 45 min after a 1 h delay, in order to suppress the main effect of the stimulation (Tuïte et al., 2005; Perlemoine et al., 2005). BMR measured with l-dopa ‘on’ (M − 1) and stimulation ‘on’ (M + 3) were compared to predicted values given by the Harris and Benedict equation (1918).

Body composition measurements
Body mass was measured to the nearest 0.1 kg on SECA 709 scales (SECA, Les Mureaux, France). Height was measured to the nearest 0.2 cm. A total body scan was performed using DEXA (Hologic QDR 4501, Hologic Inc., Waltham, US) to determine total and regional (arms, legs and trunk) body composition. Fat-free mass (FFM) was calculated as the sum of lean mass, soft tissue and bone mineral content (Treuth et al., 1994). FFM at M + 3 was corrected for the presence of the stimulator box (i.e. FFM was cut by about 40 g).

Blood sampling
After an overnight fast, blood samples were collected and the plasma was kept at −80°C until further analysis. Plasma testosterone concentrations were determined using the Human Testosterone Assay (Immunossay Kit, BioSource International Inc., Camarillo, California, USA).

Dietary questionnaire
For 7 days before each measurement period, the patients were asked to fill in a dietary record: for each meal or snack consumed; they had to record the names of foods and drinks, the method of cooking and the seasoning used. The quantities of each food were recorded either by weight or estimated using domestic measures. On final day of each measurement period, this food record was double-checked with a dietician using a validated food picture book to estimate the quantities consumed (Le Moullec et al., 1995). Then, quantitative food data were converted into energy and nutrient intakes using ‘Geni’ dietetics software (Gestion des Enquêtes Nutritionnelles Informatisée, Micro6, Villers-lès-Nancy, France), which takes its composition tables from ‘Regal’ (Favier et al., 1995).

Surgery
A stereotactic frame (Leksell G frame, Elekta, Sweden) was fitted with its repositioning kit (Elekta, Sweden) under local anaesthesia,
without withdrawal of the antiparkinsonian drug therapy. Stereotactic 1.5 Tesla MRI (Sonata, Siemens, Germany) was then performed with a voxel size of $0.52 \times 0.62 \times 2\,\text{mm}^3$ (field of view $= 270\,\text{mm}$; matrix $= 512 \times 435$; slice thickness $= 2\,\text{mm}$). The stereotactic markers of the repositioning kit and the subthalamic anatomy of nuclei and bundles were visualized together by performing a T2-weighted sequence: Turbo Spin Echo (TSE) sequence, TR = 8000 ms, TE = 10 ms; 24 images in the coronal plane, acquisition time $\cong 10$ min. A 10 mm exploration from the ventral thalamus to the anterior half of the STN and the Substantia Nigra was planned. On the following day, the frame was repositioned under conditions of local anaesthesia without antiparkinsonian therapy. Pre-operative X-ray controls were carried out during the procedure to check that the coordinates and the tracts followed the planning. The two quadripolar electrodes (DBS Medtronic 3389, Medtronic, Minneapolis, USA) were placed during the same procedure. For each side, the electrode was implanted after electro-physiological mapping using two exploration electrodes (Alpha Omega, Israel) introduced with guide tubes: one on the planned tract and a second one on the parallel tract located 2 mm anteriorly. Electro-physiological analysis consisted of micro-recordings of neuronal activity with 500 $\mu$m step checkpoints followed by monopolar acute stimulation tests with 1 mm step checkpoints. A neurologist (PD, MU) assessed the effect of acute stimulation for contralateral rest tremor, rigidity (wrist, elbow and ankle) and bradykinesia (thumb–index tapping). One contact of the DBS electrode was placed where the best efficacy of the acute stimulation was found. A few days later, the electrodes were connected to a pulse generator (Kineta, Medtronic, Minneapolis, USA). Stimulation settings and the antiparkinsonian therapy were adapted postoperatively according to the efficacy of chronic stimulation.

**Assessment of DBS-STN**

One month before surgery, response to L-dopa was evaluated using part III of the Unified Parkinson’s Disease Rating Scale (UPDRS, a standardized evaluation of all the motor signs of the disease, with a score range of 0 to 108) in the off-state after a 12 h withdrawal of antiparkinsonian medication and after taking 1.5 times the usual morning L-dopa dose, using a dispersible L-dopa formulation (Modopar Dispersible, Roche). The other tests included UPDRS part I (mental state, with a score range of 0 to 16), part II (activities of daily living, with a score range of 0 to 52), part IV (L-dopa complications), classification by Hoehn and Yahr stage and the Schwab and England scale which also measures activities of daily living (with a score range from 0 to 100%). At the 3-month follow-up visit, we systematically explored the acute motor effects of all four contacts of the electrode on each side to select the most effective one. We then assessed the efficacy of acute DBS-STN during an acute levodopa challenge using part III of UPDRS, under four conditions: (1) ‘Off’ stimulation and ‘off’ drug therapy after a 12 h withdrawal of antiparkinsonian medication and after stimulation had been switched ‘off’ for at least 1 h; (2) ‘On’ stimulation and ‘off’ drug therapy after stimulation had been switched ‘on’ for at least half an hour; (3) ‘On’ stimulation and ‘on’ drug therapy 1 h after intake of the same dose of levodopa as pre-operatively and (4) ‘Off’ stimulation and ‘on’ drug therapy after stimulation had been switched ‘off’ for at least 1 h. Each session was video-recorded. The same tests as performed pre-operatively were repeated. Dosages of antiparkinsonian medication were expressed as a total equivalent dose, and the stimulation were recorded bilaterally.

**Statistical analysis**

Results are reported as means ± SEM. The paired Student’s two-tailed $t$ test was used for BMR and resting EE comparisons between ‘on’ and ‘off’ conditions. An unpaired Student’s two-tailed $t$ test was used for BMR comparisons between measured and predicted values. Repeated measure analysis of variance was used for comparisons between $M−1$ and $M+3$ values for body composition and energy expenditure. Analysis of variance with FFM as covariate, was used for comparison between male and female Parkinson patients and between patients and control subjects. Correlation coefficients are Pearson product–moment correlations. Results were considered statistically significant at the 5% level. Statistics were analysed using Statview 5.0 software (SAS Institute Inc., Cary, NC).

**Results**

**Surgery outcomes**

**Acute motor effect of DBS-STN**

In the off-medication state, acute stimulation led to a $60.5 \pm 2.9\%$ improvement in UPDRS part III ($P < 0.0001$). All the sub-scores of UPDRS part III improved: tremor score ($+88.3 \pm 19.4\%$, $P < 0.0001$), rigidity score ($+64.7 \pm 6.6\%$, $P < 0.0001$) and akinesia score ($+51.8 \pm 7.1\%$, $P < 0.0001$). Part II of UPDRS improved by $37.4 \pm 7.4\%$ ($P < 0.0001$). Schwab and England scale improved by $26.6 \pm 4.7\%$ ($P < 0.0001$). Finally, Hoehn and Yahr scale improved by $16.5 \pm 6.4\%$ ($P < 0.01$) (Table 1).

Even in the on-medication state, UPDRS part III improved by $27.3 \pm 6.4\%$ with stimulation turned on ($P < 0.01$). UPDRS part III sub-scores also improved: tremor score ($+90.9 \pm 37.2\%$, $P < 0.05$), rigidity score ($+36.5 \pm 11.8\%$, $P < 0.01$) and akinesia score ($+37.2 \pm 10.9\%$, $P = 0.01$). There were no changes in activities of daily living scores using either the Schwab and England scale or the Hoehn and Yahr scale. In contrast, UPDRS part II worsened by $83.4 \pm 2.3\%$ (before surgery: $3.3 \pm 0.7\%$ vs after surgery: $6.0 \pm 0.8\%$; $P < 0.01$) (Table 1).

**Chronic effect of DBS-STN**

Motor complications related to L-dopa treatment as assessed by UPDRS part IV dramatically improved. LID duration decreased by $83.3 \pm 17.1\%$ ($P < 0.0001$), LID disability fell by $90.8 \pm 17.5\%$ ($P < 0.0001$), and off-period duration fell by $59.2 \pm 10.1\%$ ($P < 0.0001$). L-dopa equivalent daily dose significantly decreased from $1173.8 \pm 88.8\,\text{mg}$ at baseline to $685.0 \pm 66.8\,\text{mg}$ at 3 months after surgery (i.e. $−40.1 \pm 7.8\%$, $P < 0.0001$) (Table 1). The stimulation settings were: $2.7 \pm 0.1$ and $2.8 \pm 0.1\,\text{V}$ (right and left sides, respectively), $148.0 \pm 4.5\,\text{Hz}$ and $69.0 \pm 5.3\,\mu\text{s}$. Seven patients showed worsened dysarthria following surgery. One patient suffered from transient hypomania, one presented an episode of depression, and
UPDRS III (off drug/on stimul.) 1.3
UPDRS III (off drug/off stimul.) 1.1
Duration of dyskinesia (UPDRS IV) 1.6
Hoehn and Yahr ‘Off’ 1.7
Schwab and England ‘Off’ 67.0
Schwab and England ‘On’ 92.6
UPDRS III (off drug/off stimul.) 31.4
UPDRS III (off drug/on stimul.) 13.8
UPDRS III (on drug/off stimul.) 6.4
UPDRS III (on drug/on stimul.) 6.8
L-dopa equivalent dose (mg/day) 1174.8

Table 1 Parkinsonian symptoms before and after surgery

<table>
<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>After surgery</th>
<th>P</th>
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<tbody>
<tr>
<td>UPDRS I</td>
<td>1.3 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>UPDRS II ‘Off’</td>
<td>17.2 ± 0.8</td>
<td>10.8 ± 1.1</td>
<td>&lt;0.0001</td>
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<tr>
<td>UPDRS II ‘On’</td>
<td>3.3 ± 0.7</td>
<td>6.0 ± 0.8</td>
<td>&lt;0.01</td>
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<tr>
<td>Duration of dyskinesia (UPDRS IV)</td>
<td>1.5 ± 0.2</td>
<td>0.2 ± 0.1</td>
<td>&lt;0.0001</td>
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<tr>
<td>Dyskinesia severity (UPDRS IV)</td>
<td>1.4 ± 0.2</td>
<td>0.1 ± 0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of ‘Off’ phases (UPDRS IV)</td>
<td>1.6 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>&lt;0.0001</td>
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<tr>
<td>Hoehn and Yahr ‘Off’</td>
<td>2.4 ± 0.1</td>
<td>2.0 ± 0.1</td>
<td>&lt;0.01</td>
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<tr>
<td>Hoehn and Yahr ‘On’</td>
<td>1.7 ± 0.2</td>
<td>1.4 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Schwab and England ‘Off’</td>
<td>670.2 ± 2.8</td>
<td>850.0 ± 1.7</td>
<td>&lt;0.0001</td>
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<tr>
<td>Schwab and England ‘On’</td>
<td>92.6 ± 1.3</td>
<td>93.3 ± 1.6</td>
<td>NS</td>
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<td>UPDRS III (off drug/off stimul.)</td>
<td>31.4 ± 1.9</td>
<td>35.3 ± 2.9</td>
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<td>UPDRS III (off drug/on stimul.)</td>
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<td>10.6 ± 1.3</td>
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<td>UPDRS III (on drug/off stimul.)</td>
<td>6.4 ± 0.7</td>
<td>6.8 ± 0.9</td>
<td>&lt;0.01</td>
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<tr>
<td>UPDRS III (on drug/on stimul.)</td>
<td>6.8 ± 0.9</td>
<td>685 ± 67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>L-dopa equivalent dose (mg/day)</td>
<td>1174 ± 89</td>
<td>685 ± 67</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Note: Results are expressed as means ± SEM. The dose of levodopa equivalent medication was calculated as the dose of dopamine agonist plus levodopa. Off-medication evaluations were performed when the patient had taken no antiparkinsonian treatment for the previous 12 h; Off-stimulation evaluations were performed after stimulation has been switched off for at least 1 h. vs on drug/off stimul.; # vs on drug/off stimul.

one other was confronted with neuropsychological disorders such as apathy.

**Body composition**

**Before surgery**

Before surgery, eight men and one woman were overweight (25 < BMI < 30 kg/m²) and one man and one woman were obese (BMI > 30 kg/m²). FFM, appendicular muscle mass and trunk FFM were significantly higher in men than in women (P < 0.0001, Table 2). Fat mass and trunk fat mass (kg) were not significantly different between men and women. In contrast, fat mass expressed as percentage of body weight was significantly higher in women than in men (P < 0.05, Table 2).

**Changes observed 3 months after DBS-STN**

Three months after surgery, body weight was significantly increased by 3.4 ± 0.6 kg in men (ranging from −1.5 to 7.9 kg, P < 0.0001) and 2.6 ± 0.8 kg in women (ranging from 0.3 to 5.2 kg, P < 0.05). Hence, BMI increased significantly by 1.1 ± 0.2 and 1.0 ± 0.3 kg/m² in men and women, respectively (P < 0.0001 and P < 0.05). However, BMI remained at roughly the same level in both men and women (Table 2). FFM (+3.5 ± 0.6%, P < 0.0001), appendicular muscle mass (+4.5 ± 1.3%, P < 0.01) and trunk FFM (+2.7 ± 0.8%, P < 0.01) were significantly increased in men but remained unchanged in women (P = NS, Table 2). Fat mass and trunk fat mass significantly increased after surgery in both men and women (men: +8.6 ± 3.1 and +12.6 ± 4.6%, respectively, P < 0.05; women: +20.0 ± 8.3 and +26.0 ± 11.1%, respectively, P < 0.05) (Table 2). Finally, in men, plasma testosterone concentrations in the on-medication state significantly decreased after surgery (2.44 ± 0.26 ng/ml) compared to baseline values (2.90 ± 0.32 ng/ml, i.e. −11.5 ± 8.3%, P < 0.05).

**Energy expenditure**

EE of patients with Parkinson’s disease before and after surgery are presented in Table 3. EE was significantly higher in men than in women at all the periods studied (24 h, SMR, awake period, lunch, cycling, at rest, P < 0.05 to P < 0.0001, Table 3). Differences in FFM mostly explained these gender differences in EE, except for SMR before surgery and for lunch after surgery (P < 0.05).

**EE before surgery**

EE during resting activities measured in the calorimetric chambers (i.e. while reading, writing or watching television in standing, sitting or lying position) were significantly higher in ‘off’ periods compared to ‘on’ periods in both men (+19.3 ± 3.3%, P < 0.0001) and women (+16.1 ± 4.7%, P < 0.01, Fig. 1).

**Effect of l-dopa treatment on BMR before surgery**

BMR with l-dopa ‘on’ (i.e. 200 mg) was significantly higher than the predicted values in men (+11.5 ± 4.0%, P < 0.05, Fig. 2A) but not in women. Furthermore, in men, BMR was significantly higher without l-dopa treatment (l-dopa ‘off’) than with medication (l-dopa ‘on’) (+8.4 ± 3.2%, P < 0.05, Fig. 2A).

**Comparison between pre-surgery patients and matched healthy control volunteers**

Healthy control volunteers were matched to Parkinsonian patients according to height, BMI, FFM and fat mass (Table 4). Control-group men had a higher average age.
than Parkinsonian men (+6.8 years, \( P < 0.01 \)), whereas there was no age difference in the women’s groups. All body composition features were similar between pre-surgery Parkinsonian patients and healthy subjects (Table 4).

SMR was significantly correlated to FFM for both female and male patients \((r > 0.65, P < 0.05)\) (Fig. 3A). Relation between SMR and FFM was similar between female patients and controls (Fig. 3A). Furthermore, SMR adjusted for differences in FFM was similar between female patients and healthy controls \((-3.4 \pm 3.8\% , P = \text{NS})\). In contrast, slope and \( y \) intercept of the linear regression between SMR and FFM were significantly different between male patients and control men. Although SMR was lower in male patients compared to control \((-8.2 \pm 2.3\% , P < 0.05)\), the difference was not significant after adjustment for differences in FFM (Fig. 3A).

Furthermore, daily EE was not correlated to FFM in male and female patients \((r < 0.50, P = \text{NS})\) contrary to controls of both genders \((r > 0.80, P < 0.001)\) (Fig. 3C). Despite similar FFM and activity programs, daily EE before surgery was significantly higher in male Parkinsonians compared to control men \((+9.2 \pm 3.9\% , P < 0.05)\) but not significantly different between Parkinsonian women and healthy controls \((+10.5 \pm 7.0\% , P = \text{NS})\).

### Table 2 Patient characteristics and body composition before and after surgery

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 17)</th>
<th>Women (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before surgery</td>
<td>After surgery</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.4 ± 1.7</td>
<td>61.7 ± 2.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.8 ± 1.4</td>
<td>160.0 ± 1.9*</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>76.9 ± 2.3</td>
<td>80.2 ± 2.2†</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2 ± 0.7†</td>
<td>26.3 ± 0.7†*</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>597 ± 14</td>
<td>617.1 ± 1.3‡</td>
</tr>
<tr>
<td>Appendicular muscle mass (kg)</td>
<td>25.0 ± 0.8</td>
<td>26.1 ± 0.8¹*</td>
</tr>
<tr>
<td>Trunk fat-free and bone-free mass (kg)</td>
<td>28.6 ± 0.6</td>
<td>29.5 ± 0.6¹*</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>17.2 ± 1.4</td>
<td>18.4 ± 1.4#*</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>22.1 ± 1.3</td>
<td>22.6 ± 1.2</td>
</tr>
<tr>
<td>Trunk fat mass (kg)</td>
<td>8.6 ± 0.8</td>
<td>9.4 ± 0.9ª*</td>
</tr>
</tbody>
</table>

**Note:** Results are expressed as means ± SEM. BMI, body mass index (kg/m²). Significantly different from men: #P < 0.05; †P < 0.01; *P < 0.0001. Significantly altered after surgery: *P < 0.05; †P < 0.01; *P < 0.0001.

### Table 3 Energy expenditure before and after surgery

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 16)</th>
<th>Women (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before surgery</td>
<td>After surgery</td>
</tr>
<tr>
<td>Daily EE (kJ/day)</td>
<td>11 607 ± 325</td>
<td>10 735 ± 340†</td>
</tr>
<tr>
<td>Sleeping MR (kJ/h)</td>
<td>261.4 ± 6.5</td>
<td>281.2 ± 94†</td>
</tr>
<tr>
<td>EE (kJ/h) during:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>awake period (men = 15, women = 6)</td>
<td>6796 ± 22.1</td>
<td>606.5 ± 22.5²*</td>
</tr>
<tr>
<td>lunch (men = 15, women = 7)</td>
<td>510.2 ± 178</td>
<td>459.5 ± 13.5*</td>
</tr>
<tr>
<td>rest (men = 14, women = 6)</td>
<td>504.2 ± 18.3</td>
<td>461.9 ± 20.6*</td>
</tr>
<tr>
<td>cycling (men = 14, women = 6)</td>
<td>1355.1 ± 395</td>
<td>12176 ± 45.7*</td>
</tr>
<tr>
<td>BMR (kJ/h) (men = 17, women = 7)</td>
<td>303.5 ± 79</td>
<td>295.9 ± 4.6</td>
</tr>
</tbody>
</table>

**Note:** Results are expressed as means ± SEM. EE, energy expenditure measured in calorimetric chambers. Awake EE = daily EE minus sleeping EE extrapolated to 8 h. Rest = EE while reading, writing or watching television. Cycling = on an Ergocycle bike set at 13 km/h. BMR, basal metabolic rate measured in resting conditions, before surgery with L-dopa medication, and after surgery with L-dopa medication and stimulation on. BMR was measured outside the calorimetric chambers using a portable device. Significantly different from men: #P < 0.05; †P < 0.01; #P < 0.0001. Significantly altered after surgery: *P < 0.05; †P < 0.01; *P < 0.0001.

**Effect of DBS-STN on BMR after surgery**

Effect of DBS-STN on BMR was evaluated after patients had received a 200 mg L-dopa challenge. There were no significant changes in BMR in either men or women regardless of whether stimulation was ‘on’ or ‘off’ \((P = \text{NS}, \text{Fig. 2B})\).

**Changes in EE 3 months after surgery**

SMR remained unchanged in Parkinsonian women \((-2.4 ± 2.4\% , P = \text{NS})\). It is interesting to note that SMR increased in men \((+7.5 ± 2.0\% , P = \text{NS})\). However, it was not significantly different from pre-surgery values and from control men after adjustment for differences in FFM.
Women Periods "on" during 'on' periods before surgery. EE while eating was consistent with the EE measured during the same activities. Basal metabolic rate under conditions of L-dopa on (open square) and 'off' (filled square) periods before surgery in 16 men and 7 women after surgery (Fig. 3B). Daily EE was significantly reduced after surgery in men (−8.8 ± 3.2%, P < 0.05), but not in women (+0.3 ± 11.0%, P = NS). Finally, after surgery, EE during the cycling sessions (i.e. controlled physical activity) was significantly decreased in both men (−9.6 ± 3.5%, P < 0.05) and women (−15.8 ± 5.1%, P < 0.05) (Table 3).

Energy intake before and after surgery
Energy intake in free living conditions was significantly higher in Parkinsonian men than in Parkinsonian women, before (10 138 ± 406 vs 7062 ± 167 kJ/day, respectively, P < 0.0001) and after surgery (9898 ± 507 vs 6596 ± 532 kJ/day, respectively, P < 0.01). There was no significant change in energy intake after surgery in either men or women (P = NS).

Search for predictive factors of body weight gain after surgery
Extent of BW gain was not correlated to the duration of the disease, patient age or the pre-operative L-dopa equivalent dose. No significant correlation was found between changes in daily EE and BW or fat mass gain after surgery. However, regarding the symptoms of Parkinson’s disease, changes in daily EE were positively correlated with changes in BW or fat mass gain after surgery. (Fig. 3B). Daily EE was significantly reduced after surgery in both men (−7.3 ± 2.2%, P < 0.01) and women (−13.1 ± 1.7%, P < 0.01, Table 3) and was not significantly different from that of controls (Fig. 3D). EE during the awake period (i.e. spontaneous EE not related to controlled physical activity) was similarly and significantly decreased in both men (−10.5 ± 2.7%, P < 0.01) and women (−15.0 ± 2.2%, P < 0.01). EE during resting activities was significantly lower in both men (−8.2 ± 3.4%, P < 0.05) and women (−13.4 ± 2.9%, P < 0.01) in comparison with the EE measured during the same activities during ‘on’ periods before surgery. EE while eating was significantly reduced after surgery in men (−8.8 ± 3.2%, P < 0.05), but not in women (+0.3 ± 11.0%, P = NS). Finally, after surgery, EE during the cycling sessions (i.e. controlled physical activity) was significantly decreased in both men (−9.6 ± 3.5%, P < 0.05) and women (−15.8 ± 5.1%, P < 0.05) (Table 3).

Table 4 Characteristics and body composition of healthy-matched controlled subjects

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 17)</th>
<th>Women (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.1 ± 1.0</td>
<td>65.8 ± 1.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.6 ± 1.1</td>
<td>159.1 ± 2.9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>76.8 ± 2.1</td>
<td>63.7 ± 2.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2 ± 0.5</td>
<td>25.2 ± 0.9</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>60.2 ± 1.4</td>
<td>41.1 ± 1.2</td>
</tr>
<tr>
<td>Appendicular muscle mass (kg)</td>
<td>25.0 ± 1.1</td>
<td>15.1 ± 0.4</td>
</tr>
<tr>
<td>Trunk fat-free and bone-free mass (kg) (men = 16, women = 4)</td>
<td>28.3 ± 0.7</td>
<td>20.7 ± 0.7</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>16.5 ± 0.9</td>
<td>22.8 ± 1.9</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>21.2 ± 0.9</td>
<td>35.4 ± 1.6</td>
</tr>
<tr>
<td>Trunk fat mass (kg) (men = 16, women = 4)</td>
<td>8.4 ± 0.6</td>
<td>99 ± 1.3</td>
</tr>
</tbody>
</table>

Note: Results are expressed as means ± SEM. BMI, body mass index (kg/m²). Significantly different from patients with Parkinson’s disease (Table 1): *P < 0.05.

(Fig. 3B). Daily EE was significantly reduced after surgery in both men (−7.3 ± 2.2%, P < 0.01) and women (−13.1 ± 1.7%, P < 0.01, Table 3) and was not significantly different from that of controls (Fig. 3D). EE during the awake period (i.e. spontaneous EE not related to controlled physical activity) was similarly and significantly decreased in both men (−10.5 ± 2.7%, P < 0.01) and women (−15.0 ± 2.2%, P < 0.01). EE during resting activities was significantly lower in both men (−8.2 ± 3.4%, P < 0.05) and women (−13.4 ± 2.9%, P < 0.01) in comparison with the EE measured during the same activities during ‘on’ periods before surgery. EE while eating was significantly reduced after surgery in men (−8.8 ± 3.2%, P < 0.05), but not in women (+0.3 ± 11.0%, P = NS). Finally, after surgery, EE during the cycling sessions (i.e. controlled physical activity) was significantly decreased in both men (−9.6 ± 3.5%, P < 0.05) and women (−15.8 ± 5.1%, P < 0.05) (Table 3).

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when ‘off’ L-dopa was significantly lower in the first group (UPDRS IV score higher than one: 27.7 ± 3.3) compared to the others (UPDRS IV score equal to zero: 37.9 ± 2.1) (P < 0.01).

In other respect, patients with high pre-operative UPDRS III scores (especially the tremor sub-score) when ‘off’ L-dopa presented a strong improvement in UPDRS III scores (especially tremor sub-score, r = 0.97, P < 0.0001) and a limited body weight or fat mass gain (r = −0.68, P < 0.0001; Fig. 4B). In other words, patients with the most severe UPDRS III scores before surgery showed the greatest improvement after surgery and were at the lowest risk for gaining BW. In contrast, there was only a tendency for a higher body weight or fat mass gain in patients with the highest pre- and post-operative UPDRS IV scores compared to the other (P > 0.10). As for changes in daily EE, this can be explained by the fact that pre-operative UPDRS III score when ‘off’ L-dopa was significantly lower in the first group (UPDRS IV score higher than one) compared to the others (UPDRS IV score equal to zero) (P < 0.01).

**Discussion**

In the present study, we demonstrate that Parkinson’s disease is associated with profound alterations in energy metabolism that are normalized after DBS-STN implantation while energy intake is maintained. Parkinsonian patients had gained an average 3 kg at 3 months post-surgery. However, there were significant inter-individual variations and gender-related differences in the quality of body weight gain. In men, around two-thirds of body weight gain was due to an increase in FFM while women gained only fat. The marked changes in EE observed in this study have important implications in terms of practical and clinical recommendations for reducing energy intake as well as for scheduling progressive physical training in the early days following brain surgery.

Body weight loss is often observed with Parkinson’s disease. The 2-year prospective study conducted by Palhagen et al. (2005) showed a modest body weight loss before patients begin L-dopa treatment (−1.1 kg vs control) that becomes significant after 2 years of L-dopa therapy (−5.6 kg vs control). Conflicting results have been obtained regarding Parkinson’s disease-induced changes in body composition. In the present study, most patients presented a low percentage fat mass and had to be matched to healthy active subjects. This is consistent with Palhagen et al. (2005), Beyer et al. (1995) and Revilla et al. (1988), although not with Petroni et al. (2003). Since body weight results from the balance between energy intake and EE,
Changes in daily EE (%)

Changes in fat mass (kg)

Fig. 4 (A) Correlation between pre-operative UPDRS III score with L-dopa ‘off’ and STN-DBS-induced changes in daily EE as measured in calorimetric chambers in Parkinsonian men (filled square, n = 15) and women (filled circle, n = 6). (B) Correlation between pre-operative tremor sub-score with L-dopa ‘off’ and STN-DBS-induced changes in fat mass in Parkinsonian men (filled square, n = 17) and women (filled circle, n = 7).

each component of the balance has to be monitored. Measurements in calorimetric chambers have demonstrated increased daily EE in treated Parkinsonian patients compared to healthy subjects matched for body composition and performing the same physical activity program. These alterations in energy metabolism would explain the body weight loss of L-dopa-treated patients if food intake is not sufficiently increased to match daily energy needs. Several hypotheses have been put forward to explain body weight loss in patients with Parkinson’s disease, including a decrease in food intake caused by motor difficulties in eating (Andersson et al., 2001), reduced appetite secondary to depressive symptoms (Lorefalt et al., 2004) or to disease-related olfactory disorders (Chen et al., 2003; Cheshire and Wsolek, 2005), decreased nutrient absorption due to alterations in the autonomic nervous system as well as changes in the hypothalamic regulation of appetite (Broussolle et al., 1991; Chen et al., 2003; Pahlagen et al., 2005). However, no study to date has clearly validated these hypotheses, and one study even reported an increase in food intake (Broussolle et al., 1991). Furthermore, our data show for the first time that EE during any daily activity is substantially increased during motor fluctuations in Parkinson’s disease. This observation corroborates the significant increase in BMR without L-dopa treatment described in the literature (Macia et al., 2004; Perlemoine et al., 2005) and reproduced in the study. Although little is known about the mechanisms of action (Gurrera, 1999), we may hypothesize that changes in EE are due to muscle tone and metabolic activity. This may be caused by dopamine deficiency-mediated alterations in autonomous muscle sympathetic nerve activity (Gurrera, 1999). We propose that the increased daily EE of Parkinsonian patients is mainly related to motor fluctuations.

EE during sleep and rest is often characterized by large fluctuations in Parkinson patients. Kinetics of EE were therefore analysed with caution. In particular, BMR was integrated over 45 min and SMR was determined during the night from the most stable periods of EE associated with low heart rate. The present study highlights that Parkinson’s disease is associated with gender-specific alterations in energy metabolism which might involve alterations in the central control of energy metabolism. The mechanisms underlying the gender effect on energy metabolism are still unknown and deserve further investigations. Contrasting differences have been observed between disease-associated changes in BMR and SMR in male patients. In agreement with previous studies (Levi et al., 1990; Markus et al., 1992; Palhagen et al., 2005), we found that BMR, which is the EE of resting awakened fasting subjects, was higher in male patients on long-term L-dopa treatment than expected from predicted BMR. The increased in BMR may be explained by increased muscle rigidity—despite L-dopa treatment—and/or by LIDs (Lorefalt et al., 2004) due to alterations in the central regulation of energy metabolism (Gurrera, 1999). In contrast with BMR, we found that SMR, the EE of sleeping fasting subjects, was similar to that of healthy controls after adjustment for differences in lean body mass. SMR is the minimal EE of subjects. It is mainly determined by the metabolic activity of tissues and organs such as the liver and the heart. SMR differs from BMR as it is characterized by decreased muscle tone and brain activity, and decreased body core temperature. Therefore, the difference between SMR and BMR might be related to changes in muscle tone or to a higher fall in body core temperature during sleep.

DBS-STN induced a strong improvement (+60%) in the motor component of the UPDRS scales. Furthermore, motor complications such as motor fluctuations and LIDs as well as the antiparkinsonian medications were dramatically reduced after surgery. As expected from the literature (Gironell et al., 2002; Barichella et al., 2003; Macia et al., 2004; Tuite et al., 2005; Perlemoine et al., 2005), substantial body weight gain was observed 3 months after surgery. However, the body weight gain showed high inter-individual variability (ranging from −1.5 to 7.9 kg in males, and from 0.3 to 5.2 kg in females) and its quality was gender-specific. Two-thirds of the body weight gain in men was attributable to an increase in FFM as a consequence of gains in muscle mass and trunk FFM, which translated as...
an enlarged liver and gut, because the subjects were gaining weight. Muscle mass accretion could be explained by an increased IGF-1 production due to a better nutritional state (Raynaud-Simon et al., 2002) or, more probably, by increased physical activity levels, but not by changes in testosterone production. In contrast, women only gained fat, thus demonstrating that the anabolic response associated with an improved nutritional state is gender-specific. This observation therefore questioned whether body weight gain should be considered as deleterious for both gender or whether it might even be considered as beneficial for male patients suffering from weight loss.

Interestingly, the SMR of Parkinsonian men increased after STN-DBS. Furthermore, the BMR of Parkinsonian males with stimulation ‘on’ was not significantly different from predicted values, which contrasted with the pre-operative observations. Changes in SMR was mainly explained by FFM accretion, but the patterns of change in SMR and BMR both demonstrated that STN-DBS restored the energy metabolism of male Parkinsonian patients to the same levels as healthy controls. In contrast, daily EE in the calorimetric chambers (as well as the energy expended during daily activities) decreased significantly, i.e. by 7–13%, in both men and women. This suggests that, generally speaking, the DBS-STN-induced normalization of energy metabolism had similar consequences in both genders. The reduction of EE may be due to the reduction of muscle tone related to a decrease in motor fluctuations or to a resolution of LIDs. However, changes in the central regulation of energy metabolism might also be involved. Indeed, it cannot be excluded that there may be regional effects of DBS-STN on hypothalamic centres depending on the exact location of the contacts in the STN area, which would explain the variability of the weight gain. In fact, several hypothalamic fibres cross close to the STN (Lipp et al., 2005). Furthermore, studies in rats have provided suggestive evidence that dorsomedial hypothalamic sites are involved in thermogenesis (DiMicco et al., 2002). Therefore, the underlying mechanisms may involve an effect of STN-DBS on the activity of the sympathetic nervous system which partly influences tissue or organ metabolic activity (Guerra, 1999).

In agreement with previous studies (Onod et al., 2000; Baricella et al., 2003; Macia et al., 2004; Tuite et al., 2005; Perlemoine et al., 2005), daily energy intake was not altered after surgery. Inaccuracy inherent to self-reported food intake measurement should prompt caution in the interpretation of the results. However, our team and others (Baricella et al., 2003; Tuite et al., 2005; Perlemoine et al., 2005) have highlighted that normalization of energy metabolism is an important factor contributing to body weight gain after DBS-STN. Based on our results, we can further propose that the decrease in daily EE may promote body weight gain. Indeed, it is evident that the physical activity programme in the calorimetric chambers was standardized and did not reproduce free living conditions. However, patients followed the same activity programme before and after surgery. In particular, duration and recommendation for exercise intensity were similar before and after surgery. In this context, we were able to determine with precision the DBS-STN-induced changes on EE of daily activities. This allowed us to speculate on the consequences on free living daily EE: if EE of all light and moderate daily activities is reduced after surgery, this suggests that this component of free living daily EE is likely decreased. Our limit is that we did not take into account other factors, such as hormones (e.g. adipocytokines) involved in energy metabolism (Auwerx, 2006) or changes in spontaneous physical activity which probably play a crucial role in determining the risk of body weight gain. In that respect, we did not observe significant association between body weight gain and changes in UPDRS IV score and sub-scores which contrasts with results from Barichella et al. (2003). However, we found that high post-surgery improvements in patients with high pre-operative UPDRS III scores were correlated with lower body weight gains. Therefore, we may hypothesize that subjects who greatly improved their motor fluctuations may have increased their spontaneous physical activities because their quality of life was improved. The extra cost of these activities may compensate for the decreased EE due to the normalization of the energy metabolism and may prevent body weight gain.

In conclusion, DBS-STN implantation leads to body weight gain in both male and female patients with Parkinson’s disease. The risk of body weight gain is highly variable among patients and differs between genders. As men gained primarily FFM, a reasonable weight gain may be tolerated, in contrast with women who gained only fat. Parkinson’s disease is associated with profound alterations in energy metabolism that are normalized after DBS-STN implantation. These modifications are more pronounced in men but are not related to changes in testosterone production. Restoration of energy metabolism and decreased EE due to improved motor control and/or disappearance of LIDs are propitious for body weight gain. Therefore, the pragmatic and clinical application of these results is that patients should be advised on how to reduce energy intake, especially lipid intakes which are known to favour rapid body weight gain. Furthermore, the patients should be placed on progressive physical training programs in the early days following brain surgery in order to compensate for the major decrease daily EE caused by DBS-STN.

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References