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Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation

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Apathy has been reported to occur after subthalamic nucleus stimulation, a treatment of motor complications in advanced Parkinson's disease. We carried out a prospective study of the occurrence of apathy and associated symptoms, predictors and mechanisms in the year following subthalamic stimulation. Dopamine agonist drugs were discontinued immediately after surgery and levodopa was markedly reduced within 2 weeks. Apathy and depression were assessed monthly, using the Starkstein apathy scale and the Beck Depression Inventory. Dopamine agonists were re-introduced if patients developed apathy or depression. Preoperative non-motor fluctuations were evaluated using the Ardouin Scale. Depression, apathy and anxiety were evaluated both on and off levodopa. Analysis of predictors of apathy was performed using a Cox proportional hazard model. Twelve patients who developed apathy and a control group of 13 patients who did not underwent [^{11}C]-raclopride positron emission tomography scanning before and after oral intake of methylphenidate. In 63 patients with Parkinson's disease treated with subthalamic stimulation, dopaminergic treatment was decreased by 82% after surgery. Apathy occurred after a mean of 4.7 (3.3–8.2) months in 34 patients and was reversible in half of these by the 12-month follow-up. Seventeen patients developed transient depression after 5.7 (4.7–9.3) months and these fell into the apathy group with one single exception. At baseline, fluctuations in depression, apathy and anxiety scores were greater in the group with apathy. Fluctuations in apathy, depression and anxiety ratings during a baseline levodopa challenge were also significant predictors of postoperative apathy in univariate analysis, but not motor and cognitive states or the level of reduction of dopaminergic medication. The multivariate

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model identified non-motor fluctuations in everyday life and anxiety score during the baseline levodopa challenge as two independent significant predictors of postoperative apathy. Without methylphenidate, [^{11}C]-raclopride binding potential values were greater in apathetic patients bilaterally in the orbitofrontal, dorsolateral prefrontal, posterior cingulate and temporal cortices, left striatum and right amygdala, reflecting greater dopamine D2/D3 receptor density and/or reduced synaptic dopamine level in these areas. The variations of [^{11}C]-raclopride binding potential values induced by methylphenidate were greater in non-apathetic patients in the left orbitofrontal cortex, dorsolateral prefrontal cortex, thalamus and internal globus pallidus and bilaterally in the anterior and posterior cingulate cortices, consistent with a more important capacity to release dopamine. Non-motor fluctuations are related to mesolimbic dopaminergic denervation. Apathy, depression and anxiety can occur after surgery as a delayed dopamine withdrawal syndrome. A varying extent of mesolimbic dopaminergic denervation and differences in dopaminergic treatment largely determine mood, anxiety and motivation in patients with Parkinson's disease, contributing to different non-motor phenotypes.

Keywords: Parkinson's disease; apathy; subthalamic nucleus stimulation; dopamine; depression; anxiety

Abbreviations: ACC = anterior cingulate cortex; BA = Brodmann area; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BP = binding potential; DBS = deep brain stimulation; DLPFC = left dorsolateral prefrontal cortex; MP = methylphenidate; OFC = orbitofrontal cortex; PCC = posterior cingulated cortex; SAS = Starkstein Apathy Scale; SPM = statistical parametric mapping; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale; VAS = visual analogue scale

Introduction

Parkinson-related apathy was initially described in the pre-levodopa (L-dopa) era using the term of lethargy (Naville, 1922). With the advent of L-dopa, an improvement in motor symptoms and an 'awakening' effect on motivation were reported (Barbeau, 1969; Cotzias *et al*., 1969; Yahr *et al*., 1969). Apathy is currently defined as a distinct psychiatric syndrome, characterized by a lack of motivation, manifested by diminished goal-directed cognition and behaviour, with decreased emotional involvement (Marin, 1991). Although it is a frequent symptom of major neuropsychiatric disorders (Starkstein and Leentjens, 2008; Cavanna *et al*., 2009), current psychiatric classification systems do not provide a definition of apathy. A key feature of parkinsonian apathy is the autoactivation deficit, defined as a loss of self-driven behaviour that is reversible with external stimulation, initially described by Laplane *et al*. (1984) in the context of bilateral basal ganglia lesions (Schmidt *et al*., 2008). A clear definition of apathy is complex, because symptoms of apathy, such as lack of interest or pleasure, may overlap with those of depression. However, several studies have implied that apathy and depression are distinct syndromes (Starkstein *et al*., 1992; Aarsland *et al*., 1999; Isella *et al*., 2002; Kirsch-Darrow *et al*., 2006; Dujardin *et al*., 2007). Together with anxiety and depression, apathy belongs to the spectrum of neuropsychiatric symptoms of early, untreated disease, and a possible role for dopamine depletion has been discussed (Czernecki *et al*., 2008; Schmidt *et al*., 2008; Aarsland *et al*., 2009; Chaudhuri and Schapira, 2009; Rodriguez-Oroz *et al*., 2009). Apathy can be related to motor severity (Pedersen *et al*., 2009, 2010), but this is not always the case (Isella *et al*, 2002). The prevalence of apathy is estimated at around 40% in the general Parkinson's disease population (Starkstein *et al*., 1992; Brown and Pluck, 2000) but it is relatively rare when dementia and depression are excluded (Pedersen *et al*., 2009) as is the case in surgical candidates who typically present with an overall hyperdopaminergic profile (Ardouin *et al*., 2009*a*). Estimating the prevalence of apathy is difficult due to the fact that it belongs to the spectrum of non-motor fluctuations. Indeed, the commonest fluctuating non-motor symptoms are mood-related, with OFF-period anxiety, apathy and fatigue occurring in up to 75% of patients (Nissenbaum *et al*., 1987; Witjas *et al*., 2002; Fox and Lang, 2008). On the contrary, during ON-periods, patients with Parkinson's disease can experience an elation in mood that may be associated with alertness and euphoria (Nissenbaum *et al*., 1987; Fox and Lang, 2008). Apathy may also be observed in other disorders such as Alzheimer's disease (Holthoff *et al*., 2005), schizophrenia (Schlagenhauf *et al*., 2008), fronto temporal dementia (Peters *et al*., 2006) and progressive supranuclear palsy (Levy and Dubois, 2006). A common dysfunction of the limbic cortico-basal ganglia-thalamo-cortical loop is thought to explain the occurrence of apathy in these different pathologies (Bhatia and Marsden, 1994; Levy and Dubois, 2006). A link between apathy and dysfunction of the dopaminergic system is suggested by the model of drug addiction (Volkow *et al*., 2009). Indeed, in this model, the dopaminergic system is downregulated, leading to apathy in periods of abstinence (Wu *et al*., 1997; Volkow *et al*., 2009). Conversely, the administration of a stimulant drug induces a major extracellular dopamine release, notably within the ventral striatum, which is associated with self-reports of experiencing a 'high' and euphoria (Villemagne *et al*., 1999; Volkow *et al*., 2009). Thus convergent evidence suggests that in Parkinson's disease, apathy is probably related to lesions of mesolimbic dopaminergic cells in the ventral tegmental area, which play an important role in motivated behaviour (Javoy Agid and Agid, 1980).

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is recognized as a major advance in the treatment of severe Parkinson's disease (Krack *et al*., 2003). Despite its safety from a cognitive point of view, some executive functions may be affected and behavioural changes may be encountered (Ardouin *et al*., 1999; Houeto *et al*., 2002; Smeding *et al*., 2006; Witt *et al*., 2008). Psychiatric disorders reported after STN stimulation consist of such opposite conditions as apathy and depression on

the one hand, or mania and impulse control disorders on the other (Krack *et al*., 2001, 2003; Houeto *et al*., 2002; Romito *et al*., 2002; Funkiewiez *et al*., 2004; Czernecki *et al*., 2005; Drapier *et al*., 2006; Smeding *et al*., 2006; Ulla *et al*., 2006; Mallet *et al*., 2007). Apathy has been reported as a frequent complication of STN DBS, both in the early postoperative period (Krack *et al*., 1998, 2003; Saint-Cyr *et al*., 2000; Houeto *et al*., 2002; Funkiewiez *et al*., 2004; Drapier *et al*., 2006; Czernecki *et al*., 2008) and in the long-term follow-up (Krack *et al*., 2003; Troster, 2009). The precise incidence of apathy after STN stimulation is unknown and discrepancies in reported frequency reflect differences in the time of assessment, instruments used and strategy of dopaminergic treatment management (Voon *et al*., 2006). Apathy that occurs after dopaminergic medication withdrawal allowed by surgery shows an excellent response to dopamine agonists (Czernecki *et al*., 2008). For this reason, postoperative apathy has been considered as a reversible dopamine withdrawal state. However, it has also been suggested that STN stimulation may directly induce apathy via a limbic side effect mechanism (Fields and Troster, 2000; Drapier *et al*., 2006; Le Jeune *et al*., 2008, 2009; Temel *et al*., 2009). Indeed, although postoperative apathy responds well to dopaminergic treatment (Czernecki *et al*., 2008), dopamine withdrawal alone is not a sufficient explanation as no correlation has been found between the decrease in dopaminergic medication and the occurrence of apathy (Funkiewiez *et al*., 2004; Drapier *et al*., 2006; Castelli *et al*., 2007). Thus, underlying mechanisms of postoperative apathy seem to imply complex interactions between dopaminergic mesolimbic denervation and dopaminergic treatment management. The variability in occurrence of postoperative apathy thus raises the question whether there are susceptibility factors capable of rendering some patients with Parkinson's disease more vulnerable to develop apathy than others? To address this issue, we used a clinical approach based on detailed preoperative motor, cognitive and neuropsychological evaluation of a large cohort of patients with Parkinson's disease, candidates for STN DBS, followed by monthly postoperative assessments of apathy and depression. In addition, a PET study compared the dopaminergic denervation in a subgroup of patients who developed postoperative apathy, to a control group that did not develop apathy over a 1-year follow-up period. These patients were studied with PET using [^{11}C]-raclopride, a dopamine D2/D3 receptor ligand before and after a challenge with methylphenidate (MP), a drug that increases the synaptic concentration of dopamine by blocking the dopamine transporters, providing measures of both presynaptic endogenous dopamine release and postsynaptic dopamine receptor availability.

Methods

Clinical study of predictors of postoperative apathy

Patients

We performed a prospective study on the occurrence of apathy in the year following STN DBS in patients undergoing surgery for Parkinson's disease in two centres. Sixty-three patients were treated with STN DBS and included in the present study. A further two patients also signed the study protocol, but in both cases a frontal haematoma related to ventriculography with reversible symptoms prevented scheduled electrode implantation, resulting in their exclusion from the study. The selection criteria were (i) clinically diagnosed Parkinson's disease; (ii) severe L-DOPA-related motor complications despite optimal adjustment of anti-parkinsonian medication; (iii) an age under 70 years; and (iv) the absence of surgical contraindications, of dementia or of major ongoing psychiatric illness, as previously described (Krack *et al*., 2003). Specific exclusion criteria for the present study were (i) the presence of apathy before surgery as defined by a Starkstein Apathy Scale (SAS) (Starkstein *et al*., 1992) score $\geqslant$14; or (ii) the presence of moderate to severe depression (score $\geqslant$20) on Beck Depression Inventory (BDI) (Beck *et al*., 1996) in the ON-drug evaluation condition. The ethics committee of Grenoble University approved the study and all the patients gave written informed consent. The study protocol also included participation in a double-blind pharmacological study evaluating the effects of piribedil on parkinsonian apathy. In this ongoing study (ClinicalTrials.gov NCT01020682), patients developing apathy during the first 9 months after surgery were treated with either piribedil (a D2/D3 agonist) or placebo for 3 months; thus at the 12-month assessment, all patients had open treatment. If the BDI score was >20, patients had open treatment.

Procedures

Surgical procedure was as previously described (Krack *et al*., 2003). Targeting was based on ventriculography, MRI and peroperative microrecording. Leads were implanted bilaterally in one session under local anaesthesia (DBS-3389; Medtronic, Minneapolis, MN, USA). All patients had a postoperative MRI. Leads were connected a few days later under general anaesthesia to a neurostimulator (Kinetra, Medtronic, Minneapolis, MN, USA). For the purpose of the present study, dopamine agonists were discontinued on the day of surgery in all patients, and L-DOPA treatment was reduced to the maximum extent permitted by patients' motor state within the first 2 weeks after surgery, the patient being hospitalized during this period. A minimum of 3×25 mg of L-DOPA was maintained in all patients in order to avoid the confounding effect of the complete suppression of dopaminergic drugs on dopamine receptors availability and density (Thobois *et al*., 2004). Adjustments of optimal stimulation parameters were performed during the 2 weeks following surgery. A monthly assessment of apathy and depression—experienced by the patients during the previous 4 weeks—was carried out by phone, using the SAS and the BDI. Dopamine agonists were re-introduced only if patients developed apathy (score $\geqslant$14 on the SAS) or depression (score $\geqslant$20 on the BDI). All patients had a full Unified Parkinson's Disease Rating Scale (UPDRS) at baseline and at 12-month follow-up, both on and off L-dopa (Krack *et al*., 2003). Postoperatively, patients were assessed under the ON-stimulation condition. The UPDRS includes assessment of depression (item 3), apathy (item 4), activities of daily living (UPDRS II), motor signs (UPDRS III), duration of dyskinaesias (item 32), disability related to dyskinaesias (item 33) and duration of off-periods (item 39). Baseline and postoperative neuropsychological evaluation included the Mattis Dementia Rating Scale for global cognitive assessment, and an assessment of frontal-lobe dysfunction (Krack *et al*., 2003). Severity and intensity of hyperdopaminergic behaviours were systematically evaluated and quantified at baseline and 12-month follow-up, using the Ardouin Scale based on a semi-structured interview, each item being rated in five points from absent (0) to severe (4). Hyperdopaminergic behavioural modifications were qualified as pathological and corresponding to behavioural

addictions if rated >2 on this scale (Ardouin *et al*., 2009*a*). If patients had an addiction to dopaminergic treatment (item addiction to dopamine ⩾2) (Ardouin *et al*., 2009*a*) in addition to a behavioural addiction, a diagnosis of dopamine dysregulation syndrome was made (Evans and Lees, 2004). The presence of ON-drug euphoria corresponded to a rating >2 on the 'non-motor ON' item and the presence of OFF-period dysphoria corresponded to a rating >2 on the 'non-motor OFF' items (Ardouin *et al*., 2009*a*). The non-motor fluctuations that each patient experienced in daily life on their usual treatment were assessed by adding the two items 'non-motor ON' and 'non-motor OFF' from the Ardouin scale (Ardouin *et al*., 2009*a*). The maximum possible score for non-motor fluctuations in this scale is 8 and a score of >2 was taken as indicative of the presence of clinically relevant non-motor fluctuations. In addition, at baseline, a non-motor assessment comprising an evaluation of depression (BDI) (Beck *et al*., 1996), apathy (SAS) (Starkstein *et al*., 1992), anxiety (Beck Anxiety Inventory, BAI) (Beck *et al*., 1988) and the Norris visual analogue scale (VAS) asthenia subscore (Norris, 1971; Guelfi, 1989) was added during the L-dopa test in both ON and OFF drug conditions. Using these scales in OFF and ON conditions, the patients were asked to answer in function of how they really felt at the moment of the examination (Czernecki *et al*., 2002). Changes in L-dopa and dopamine agonists were expressed as the total L-dopa-equivalent daily dosage (Thobois, 2006).

Statistical analysis of clinical data

Analysis was by intention to treat including all implanted patients even when dopamine agonists could not be discontinued or if L-dopa could not be decreased. All data analyses were performed using Stata (version 10.1). Data were summarized in terms of size and frequency for categorical data and by mean scores ± standard deviation for quantitative data. Student's *t*-test was used to compare continuous data. Mann–Whitney or Wilcoxon tests were applied for non-Gaussian assumption. Independence between qualitative parameters was assessed using either the chi-square test or with Fisher's exact test. Univariate and multivariate analyses were performed using stepwise Cox proportional hazard models with forward selection and presented as hazard ratios with 95% confidence intervals. For all Cox models, proportional hazards assumption was validated on the basis of Schoenfeld residuals. The Kaplan–Meier method was used to generate survival curves. Survival time was summarized by median (25th and 75th percentile) and compared using the log-rank test. *P*-values <0.05 were considered statistically significant.

PET study

Patients

Evaluation of motor (UPDRS III) and non-motor symptoms (SAS, BDI, BAI) reflect the chronic state ON stimulation and minimal drug treatment at the time of the PET study. The control group consisted of patients who had not developed apathy at the 12-month postoperative control. [^{11}C]-raclopride PET scan was performed as soon as the diagnosis of apathy was confirmed for the apathetic group ($n = 12$; 6.8 ± 3.4 months after surgery) and before a dopamine agonist treatment targeting the lack of motivation was initiated. For the non-apathetic group, PET scan was made at the end of the follow-up ($n = 13$; 12 months) if no apathy was disclosed.

PET protocol

All patients were OFF-drug on the day of PET study for at least 12 h before the scan acquisition, with stimulation 'ON'. PET scans were performed as previously described (Thobois *et al*., 2004). All patients underwent two [^{11}C]-raclopride PET scans on the same day. The first one was performed without any treatment. The second one was performed 2 h after patients received an oral dose of 0.5 mg/kg MP, a drug that increases the synaptic concentration of dopamine by blocking dopamine transporters (Volkow *et al*., 1998). Before the second PET, the clinical effects of MP were assessed using a timed tapping test for the motor consequences (Nutt *et al*., 2007) and the Norris VAS asthenia subscore (Norris, 1971; Guelfi, 1989) for the psychotropic changes. The mean (±SD) [^{11}C]-raclopride injected activity for the non-apathetic patients was 210.5 ± 38 milli Becquerel (MBq) (baseline) and 219.8 ± 38 MBq (after MP), and that for the apathetic patients was 208.3 ± 36 MBq (baseline) and 203.1 ± 29 MBq (after MP). The mean dose of MP was 35.5 ± 6 mg (range: 25–45) for the apathetic patients and 36.2 ± 8 mg (range: 30–55) for the non-apathetic patients. This dose is known to be sufficient to block >50% of the dopamine transporter after 120 min (Volkow *et al*., 2009). Images were reconstructed as previously reported (Thobois *et al*., 2004).

Image analysis

Regions of interest analysis

Briefly, regions of interest (10 × 30 mm) were placed along the axis of each putamen and on each caudate nucleus head (10 × 10 mm) on five consecutive planes. The non-specific background activity was averaged from a cerebellar elliptical region of interest of 5 ± 0.5 cm^3 (Thobois *et al*., 2004). The [^{11}C]-raclopride binding potential (BP) (B_{max}/K_d) was determined from the distribution volume, evaluated using a graphical approach and a tissue input function (Logan *et al*., 1996).

Statistical parametric mapping analysis

Image and statistical analysis were performed in MATLAB 6 (Math Works, Natick, MA, USA) using software for statistical parametric mapping (SPM 2 Wellcome Department of Cognitive Neurology, MRC Cyclotron Unit, London, UK). Voxel-based parametric images of BP were generated with the same reference region as that for the region of interest approach. BP images were spatially normalized and smoothed as previously described (Thobois *et al*., 2004).

Statistical analysis of PET data

Categorical comparisons of mean [^{11}C]-raclopride voxel-based BP values between both groups of patients with Parkinson's disease before MP were made using appropriately weighted categorical contrasts ($BP\text{-}Raclo_{apathetic} - BP\text{-}Raclo_{nonapathetic}$; $BP\text{-}Raclo_{nonapathetic} - BP\text{-}Raclo_{apathetic}$) to generate SPMs for both increases and decreases in [^{11}C]-raclopride BP values on a voxel-by-voxel basis. In addition, variations of the mean [^{11}C]-raclopride voxel-based BP values before and after MP (=Delta MP) were compared in apathetic and non-apathetic patients [$(BP\text{-}Raclo\text{-}_{apathetic} - BP\text{-}Raclo\text{-}MP_{apathetic}) - (BP\text{-}Raclo\text{-}_{nonapathetic} - BP\text{-}Raclo\text{-}MP_{nonapathetic})$; $(BP\text{-}Raclo\text{-}_{nonapathetic} - BP\text{-}Raclo\text{-}MP_{nonapathetic}) - (BP\text{-}Raclo\text{-}_{apathetic} - BP\text{-}Raclo\text{-}MP_{apathetic})$]. Finally, using a covariate-only model, covariations of the tracer uptake with the severity of the apathy using the Starkstein apathy score were performed. These analyses were limited to the limbic regions (prefrontal, temporal, cingulate cortices) and basal ganglia using appropriate masks created in MATLAB using VoiTool. The contrasts were used to derive between conditions *Z*-scores on a voxel-by-voxel basis using the general linear model (Friston *et al*., 1995). Only voxels surviving an uncorrected threshold of $P \leqslant 0.001$ and a cluster of ⩾10 voxels

were considered significant. These voxels were rendered on a single subject stereotactically normalized brain MRI and localized using their coordinates in Montreal Neurological Institute space.

Results

Clinical study

Baseline evaluation

There was no difference in the baseline characteristics, the usual motor and neuropsychological evaluations and treatment of the patient group that developed apathy during the 12-month follow-up (Apathy group) and those of the patient group that did not (Non-apathy Group) (Table 1). Four patients fulfilled criteria for dopamine dysregulation syndrome at baseline. Seventeen other patients had one or several behavioural addictions, but without compulsive dopamine replacement consumption. Non-motor fluctuations in everyday life (Table 1) as well as acute fluctuations of asthenia VAS, depression, anxiety and apathy during the L-DOPA challenge (Table 2) were found to be more severe in the Apathy Group.

Changes in medication

At baseline the total daily dose of L-dopa equivalent was 1617 ± 818 mg and 59 patients were treated with a dopamine agonist. One month after surgery (M1), the total L-dopa equivalent daily dosage was decreased to 288 ± 325 mg (–82%). In four patients, discontinuation of dopamine agonists proved impossible due to ensuing restless legs syndrome. At 12 months, 23 patients were again on agonist medication and the total L-dopa equivalent daily dosage was 440 ± 395 mg (–73%). There was no difference in the postoperative decrease of dopaminergic treatment between the Apathy and Non-apathy groups (data not shown).

Outcome

Evaluation at 12 months in the 63 patients showed an improvement in the UPDRS motor score from 36.3 ± 12.5 at baseline OFF drug to 19.9 ± 13.6 (–45.2%) in the OFF-drug ON-stimulation condition at 12 months, and no change in the ON drug condition (10 ± 6.5 versus 11 ± 7.5). Duration of dyskinesias improved from 1.51 ± 0.97 to 0.47 ± 0.74 (–69%), disability from 1.27 ± 1.08 to 0.26 ± 0.54 (–80%) and duration of OFF periods from 1.65 ± 0.74 to 0.39 ± 0.75 (–76%). There was no difference in the improvement of motor fluctuations and dyskinesias between the apathy and no-apathy groups (data not shown). Dopamine dysregulation syndrome disappeared in all four patients and behavioural addictions disappeared in all 17 patients who displayed pathological behaviours at baseline.

Complications

Four patients had transient symptomatic contusion (psychosis $n = 1$, somnolence $n = 1$, stereotypies $n = 1$, confusion $n = 1$) and one had asymptomatic contusion along the trajectory of electrodes on postoperative MRI. Four patients had transient postoperative confusion ($n = 1$) or behavioural changes without MRI-confirmed contusion (psychosis $n = 2$, emotional liability $n = 1$). Transient general health complications occurred in four patients (urinary

Table 1 Baseline characteristics, motor and non-motor evaluation of the total cohort split up for the apathy and non-apathy groups

Parameters	Total population ($n = 63$)	Patients with no subsequent apathy: Non-apathy group $n = 29$	Patients with subsequent apathy: Apathy group $n = 34$	*P*
Age	57.8 ± 7.2 [30.4; 69.5]	58.1 ± 4.9 [47.3; 69.5]	57.5 ± 8.7 [30.4; 69.5]	0.9450[a]
Duration of disease	10.5 ± 3.1 [5; 19]	10.3 ± 2.6 [5; 15]	10.6 ± 3.4 [5; 19]	0.6361[b]
Age at diagnosis	47.3 ± 7.3 [18; 62]	47.8 ± 5.2 [36; 58]	46.9 ± 8.8 [18; 62]	0.8037[a]
Sex (% male)	63.5% (40)	69% (20)	58.8% (20)	0.442[c]
Depression (UPDRS Part I, item 3)	0.46 ± 0.71 [0; 4]	0.34 ± 0.55 [0; 2]	0.56 ± 0.82 [0; 4]	0.2818[a]
Apathy (UPDRS Part I, item 4)	0.21 ± 0.48 [0; 2]	0.21 ± 0.49 [0; 2]	0.21 ± 0.48 [0; 2]	0.9750[a]
Activities of daily living OFF drug, $n = 62$	20.5 ± 6.1 [4; 36]	20 ± 6.5 [4; 28]	21 ± 5.9 [9; 36]	0.5244[b]
Activities of daily living ON drug	4.6 ± 3.4 [0; 17]	4 ± 3.2 [0; 14]	5.1 ± 3.5 [0; 17]	0.2170[a]
Duration of dyskinaesia	1.51 ± 0.97 [0; 4]	1.38 ± 0.98 [0; 4]	1.62 ± 0.95 [0; 4]	0.3326[b]
Disability of dyskinaesias	1.27 ± 1.08 [0; 4]	1.24 ± 1.02 [0; 3]	1.29 ± 1.14 [0; 4]	0.9370[a]
Duration of OFF periods	1.65 ± 0.74 [0; 3]	1.55 ± 0.69 [0; 3]	1.73 ± 0.79 [1; 3]	0.3330[b]
Mattis Dementia Rating Scale	139.1 ± 3.7 [128; 144]	138.8 ± 4.3 [128; 144]	139.4 ± 3.2 [133; 144]	0.8406[a]
Frontal lobe function	41.8 ± 6.5 [24.5; 50]	43.1 ± 6.2 [26.9; 50]	40.7 ± 6.7 [24.5; 50]	0.0990[a]
Non-motor fluctuations	46.0% (29)	31% (9)	58.8% (20)	0.027[c]
Total L-dopa dose	1343 ± 805 (300; 3150)	1272 ± 606 (400; 2750)	1402 ± 947 (300; 3150)	0.9505[a]
Total dopamine agonist equivalent	274 ± 141 (0; 600)	265 ± 161 (0; 600)	282 ± 123 (0; 600)	0.6435[b]
Hoehn and Yahr ON stage	1.70 ± 0.70 (0; 3)	1.74 ± 0.71 (0; 3)	1.66 ± 0.69 (0; 3)	0.6558[b]
Hoehn and Yahr OFF stage	2.78 ± 0.80 (0; 5)	2.76 ± 0.73 (0; 5)	2.79 ± 0.87 (0; 5)	0.8627[b]

Results are given as mean ± SD [minimum maximum] for quantitative data, as percentage and size for qualitative data.
a Mann–Whitney.
b *t*-test.
c Chi-square.

Table 2 Comparison of the motor and non-motor evaluations during the L-dopa test at baseline between the apathy and non-apathy groups

	Patients with no subsequent apathy: Non-apathy group $n=29$				Patients with subsequent apathy: Apathy group $n=34$				Delta OFF–ON Apathy versus Non-apathy
	OFF L-dopa	ON L-dopa	Delta OFF–ON	*P*	OFF L-dopa	ON L-dopa	Delta OFF–ON	*P*	*P*
SAS apathy	8.9 ± 5.1	5.5 ± 3.2	3.3 ± 4.7	⩽0.001[a]	12.8 ± 7	6.5 ± 3.6	6.3 ± 6.5	⩽0.001[a]	0.0450[b]
VAS asthenia	35.6 ± 14.6	17.6 ± 12.9	18.0 ± 20.9	⩽0.001[a]	46 ± 15.6	18.6 ± 13.1	27.3 ± 19	⩽0.001[c]	0.0685[d]
BDI depression	9.9 ± 6	7.7 ± 5.4	2.1 ± 4.4	0.0056[a]	14.6 ± 7	9.4 ± 6	5.1 ± 6.7	⩽0.001[a]	0.0180[b]
BAI anxiety	12.9 ± 8.2	9.4 ± 10.7	3.5 ± 5.8	0.0056[a]	18.2 ± 10.6	9.1 ± 9.9	9.1 ± 10.1	⩽0.001[a]	0.0192[b]
UPDRS motor score	36.3 ± 10.7	9.9 ± 6.5	26.4 ± 8.6	⩽0.001[a]	36.2 ± 14.1	10.2 ± 6.6	26.0 ± 10.4 $n=32$	⩽0.001[a]	0.8770[d]

Results are expressed as mean ± SD.
a Wilcoxon test.
b Mann–Whitney test.
c Paired Student *t*-test.
d Unpaired Student *t*-test.

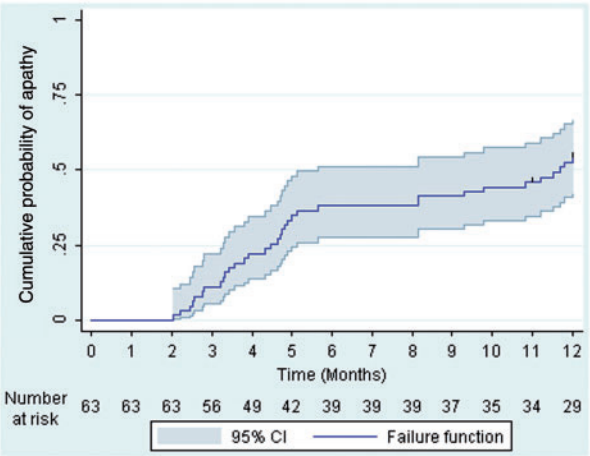

Figure 1 Kaplan–Meier curve of appearance of apathy.

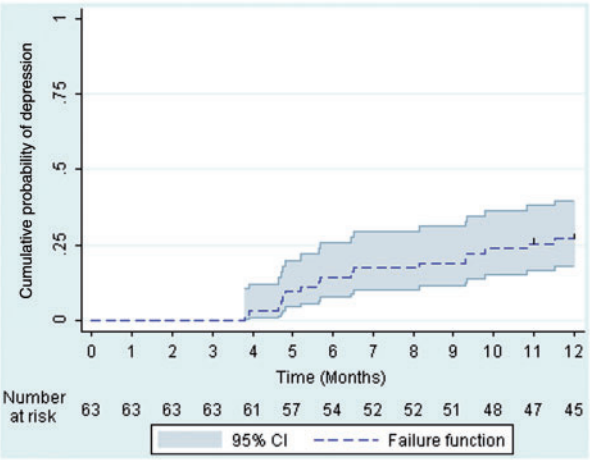

Figure 2 Kaplan–Meier curve of appearance of depression.

retention $n=1$, dysuria $n=1$, akinetic crisis complicated by aspiration pneumonia and cardiorespiratory arrest requiring reanimation $n=1$, gastroenteritis $n=1$). Electrodes were misplaced in one patient. Electrode migration ($n=1$) and cable fracture necessitated re-operation ($n=1$). Infections required temporary removal of the subcutaneous material ($n=1$) or removal of the subcutaneous and intracerebral material still effective at 12 months ($n=1$). Other side effects were worsening of dysarthria ($n=16$), freezing of gait ($n=6$), worsening of falls ($n=5$), worsening of restless legs syndrome ($n=6$) and eyelid apraxia ($n=3$). Apathy and depression are reported above. One patient displayed psychotic symptoms 6 months after surgery on reintroduction of a dopamine agonist for his apathy. One patient, whose dopamine agonists could not be stopped because of the unmasking of a severe restless legs syndrome, developed transient hypomania.

Monthly follow-up of apathy and depression

The median duration of apathy-free survival in 63 patients was 11.5 (4.5–12) months [median (25;75 percentile)] (Fig. 1). Thirty-four patients developed apathy after 4.7 (3.3–8.2) months, from 2 to 12 months. At 12 months, 17 of the 34 patients were no longer apathetic. Depression (BDI sore ⩾20) occurred in 17 patients after 5.7 (4.7–9.3) months, from 3.8 to 11.5 months. The median duration of depression-free survival in the 63 patients was 12 (10.8–12) months (Fig. 2). Depression was transient in all patients with a maximum duration of 4 months. Out of 17 depressive patients, 16 were also in the Apathy Group and only 1 patient with depression was in the Non-Apathy Group ($P<0.0003$). Two patients attempted suicide (one of them following an infection requiring explantation of the neurostimulator and electrodes).

Analysis of predictors of apathy

In the univariate analysis, non-motor fluctuations in everyday life >2/8 (Ardouin scale) and acute fluctuations measured by the VAS and by specific scales for apathy (SAS), depression (BDI) and anxiety (BAI) during the L-DOPA test proved to be significant

Table 3 Predictors of apathy: univariate analysis

Parameters $n=63$	Hazard ratio	Confidence interval 95%	P
Delta apathy (SAS) per unit	1.095	[1.036; 1.157]	0.001
Delta depression (BDI) per unit	1.073	[1.023; 1.126]	0.004
Delta anxiety (BAI) per unit	1.051	[1.016; 1.088]	0.004
Delta VAS–Asthenia per unit	1.024	[1.005; 1.043]	0.013
Delta UPDRS III $n=61$ per unit	0.989	[0.949; 1.031]	0.617
Non-motor ON yes versus no	2.417	[0.993; 5.883]	0.052
Non-motor OFF yes versus no	1.409	[0.610; 3.250]	0.422
Non-motor fluctuations yes versus no	2.515	[1.244; 5.085]	0.010
Decrease in total L-dopa equivalent per 100 mg of L-dopa equivalent	1.03	[0.98; 1.08]	0.205
Total preoperative L-dopa equivalent per 100 mg of L-dopa equivalent	1.0278	[0.9828; 1.0749]	0.229
Mattis Dementia Rating Scale at baseline per unit	1.057	[0.959; 1.164]	0.266
UPDRS III Off at baseline $n=61$ per unit	0.992	[0.960; 1.025]	0.634

Univariate Cox proportional hazard model. Delta refers to fluctuations at baseline between OFF-drug and ON-drug conditions assessed during a L-dopa challenge. The hazard ratio of 1.1 for delta apathy indicates that for any increase of one point on the Starkstein apathy score at baseline OFF-drug compared with baseline ON-drug condition, the risk of developing apathy will increase by 10%. A delta of 5 points on the apathy score will lead to a 1.6-fold, a delta of 10 points to a 2.5-fold increase in postoperative apathy. The presence of non-motor fluctuations at baseline corresponds to 2.5-fold increases of the risk of developing apathy.

Table 4 Predictors of apathy: multivariate analysis

Parameters	Hazard ratio	Confidence Interval 95%	P
Delta anxiety (BAI) per unit	1.054	[1.019; 1.090]	0.002
Non-motor fluctuations yes versus no	2.754	[1.348; 5.626]	0.005

Multivariate stepwise Cox proportional hazard model with forward selection. Note that all significant variables in the univariate analysis have been integrated in the multivariate analysis.

predictors of apathy, whereas L-DOPA response of motor signs, total dopaminergic treatment at baseline and decrease in dopaminergic treatment after surgery did not (Table 3). A multivariate analysis integrated non-motor fluctuations in everyday life >2/8 (Ardouin scale); acute fluctuations of VAS, SAS, BDI and BAI during the L-DOPA test; L-DOPA response of motor signs; total dopaminergic treatment at baseline and decrease in agonist dosage; decrease in L-dopa dosage and decrease in total L-dopa equivalent dosage after surgery; and non-motor ON (Ardouin scale) and non-motor OFF (Ardouin scale). Non-motor fluctuations of the Ardouin scale and fluctuations in BAI emerged from among these as predictors of apathy (Table 4).

PET study

Clinical characteristics of the patients

No difference was noted in baseline characteristics between apathetic and non-apathetic patients before surgery (Table 5). Non-motor fluctuations were present in both groups with a trend for higher fluctuations and higher OFF-drug scores in the apathetic group, but this did not reach significance.

At the time of the PET, dopamine agonists were stopped in both groups (100% reduction) and L-dopa was reduced by 88% in non-apathetic patients versus 89.7% in apathetic patients. In addition to the higher scores on the SAS, apathetic patients had higher scores on the BAI and on the BDI than the non-apathetic ones (Table 5).

Clinical evaluation after MP intake

After MP intake, both apathetic and non-apathetic patients presented a significant improvement in tapping test scores of 16% for the apathetic and 6% for the non-apathetic patients, respectively ($P<0.01$). Only the apathetic patients experienced a beneficial effect on asthenia and affective subscores of the VAS (Table 5).

PET data

Before MP, the region of interest analysis showed the mean (±SD) [^{11}C]-raclopride BP values of 2.2 (0.5) and 2 (0.8) in the caudate nucleus and 3.5 (1.1) and 3.1 (0.8) in the putamen of apathetic and non-apathetic patients, respectively. After MP the reduction of BP was greater for non-apathetic patients in the same regions with a percentage of decrease of 3% ($P=0.4$) in apathetic patients versus 8.8% ($P<0.05$) in non-apathetic patients for both the caudate nucleus and putamen.

Using SPM, at baseline (i.e. without MP intake), differences of [^{11}C]-raclopride BP values were noted when both groups of patients were compared. The [^{11}C]-raclopride BP values were greater in apathetic patients bilaterally in the orbitofrontal cortex (OFC) [Brodmann area (BA) 10/11/47], posterior cingulate cortex (PCC) (BA 31) and temporal cortex (BA 36/20) and the left dorsolateral prefrontal cortex (DLPFC) (BA 9/46), dorsal and ventral striatum bilaterally, the left thalamus and the right amygdala. These results are presented in Fig. 3 and in Table 6.

After MP intake, variations of [^{11}C]-raclopride BP values before and after MP (i.e. the increase of synaptic dopamine release) were greater in the non-apathetic group of patients. This was observed bilaterally in the OFC (BA/11/47/10), DLPFC (BA 9/46) and anterior cingulate cortex (ACC) (BA 24/32), in the left PCC (BA 31), left thalamus, left internal globus pallidus and in the right temporal cortex (BA 20/36/35/7). These results are presented in Table 7 and Fig. 4. Finally we did not observe any significant covariations between the Starkstein apathy score and the tracer uptake.

Table 5 Characteristics of the patients enrolled in the PET study

	Non-apathetic ($n=13$)		Apathetic ($n=12$)	
Sex	3 F, 10 M		6 F, 6 M	
Age (years)	58.0 ± 4.8		55.8 ± 4.9^{NS}	
Disease duration (years)	10.5 ± 3.0		10.3 ± 2.2^{NS}	
Baseline				
Antiparkinsonian treatment (mg/day)	L-dopa: 1226.9 ± 707.9 Dopamine agonist: 32.2 ± 18		L-dopa: 1352.8 ± 969.7^{NS} Dopamine agonist: 25.7 ± 10.5^{NS}	
Mattis dementia score	138.2 ± 3.9		139.8 ± 3.4^{NS}	
	OFF L-dopa	ON L-dopa	OFF L-dopa	ON L-dopa
UPDRS III	38.6 ± 11.8	$11.2 \pm 8.4^{*}$	36.0 ± 16.3^{NS}	$12.2 \pm 8.0^{*}$
Starkstein apathy score (SAS)	8.7 ± 5.0	$6.8 \pm 4.0^{*}$	11.3 ± 7.9^{NS}	$9.0 \pm 10.5^{*}$
Beck depression inventory (BDI)	8.8 ± 5.7	$7.3 \pm 6.2^{*}$	17.9 ± 10.2^{NS}	$10.3 \pm 6.2^{*}$
Beck anxiety inventory (BAI)	11.5 ± 4.4	$6.5 \pm 6.9^{*}$	19.6 ± 14.0^{NS}	$11.3 \pm 11.1^{*}$
Norris VAS asthenia subscore	37.6 ± 13.5	$15.8 \pm 11.3^{*}$	42.8 ± 15.2^{NS}	$18.5 \pm 13.0^{*}$
At the time of the PET				
Antiparkinsonian treatment (mg/day)	L-dopa: 142.3 ± 152.6		L-dopa: 139.6 ± 159.4^{NS}	
Stimulation parameters	3.03 ± 0.5 V/ 62.3 ± 8.2 µs/ 134.2 ± 11.3 Hz		2.9 ± 0.5 V/66.5 ± 12.8 µs/ 137.9 ± 14.4 Hz	
	ON L-dopa		ON L-dopa	
UPDRS III	10.3 ± 5.9		14.5 ± 9.9	
SAS	6.1 ± 4.1		$22.4 \pm 6.8^{\S}$	
BDI	3.3 ± 2.6		$13.3 \pm 3.2^{\S}$	
BAI	0 ± 0		$12.9 \pm 10.5^{\S}$	
	MP–	MP+	MP–	MP+
Norris VAS asthenia subscore	19.0 ± 12.8	17.5 ± 10.9	37.0 ± 17.8	$26.8 \pm 16.4^{\Delta}$
Tapping test (number/2 min)	250.4 ± 14.5	$266.5 \pm 15.3^{\Delta}$	242.1 ± 13.2	$281.0 \pm 16.9^{\Delta}$

At baseline: in the OFF L-DOPA condition no statistically significant difference (NS) was observed whatever the variables between group (Mann and Whitney). After acute L-DOPA challenge, statistically significant changes of the UPDRS part III, SAS, BDI, BAI and VAS asthenia and affect scores were noted in both groups. Higher SAS, VAS, BDI, BAI scores indicate higher feelings of apathy, asthenia, sadness, anxiety. Average values are indicated as mean ± SD.
At the time of PET-scanning: treatment did not differ between groups (NS). SAS, BDI and BAI scores significantly differ between both groups ($^{\S}P<0.0001$). After methylphenidate, only apathetic patients presented a statistically significant improvement of the VAS asthenia and affect scores ($^{\Delta}P<0.05$).
Average values are indicated as mean ± SD.
MP– = before methylphenidate; MP+ = after methylphenidate.
$^{*}P<0.05$.

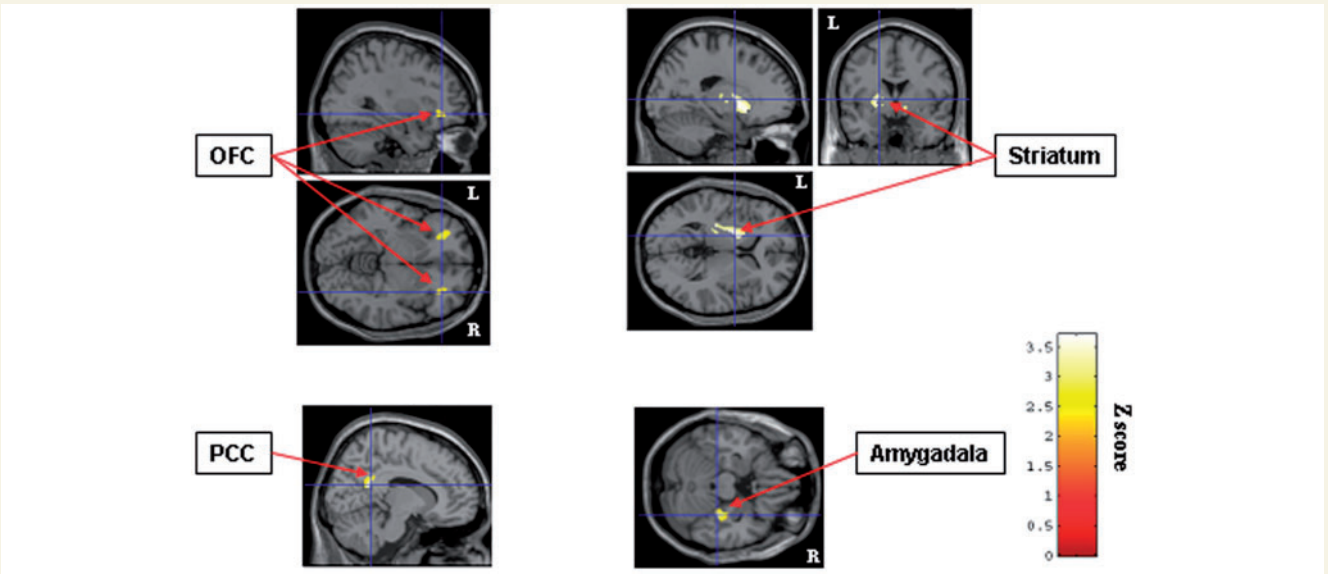

Figure 3 Areas of increased [^{11}C]-raclopride binding potential values in Apathetic versus Non-apathetic patients with Parkinson's disease (i.e. reduction of endogenous dopamine). The [^{11}C]-raclopride binding potential values were greater in apathetic patients bilaterally in the OFC (BA 10, 11, 47), PCC (BA 31) and temporal (BA 36, 20) cortices, the left DLPFC (BA 9, 46), the dorsal and ventral striatum bilaterally, the left thalamus and the right amygdala. The figure shows the OFC bilaterally, the PCC, the left striatum and the right amygdala. These regions are superimposed on a single subject brain MRI from SPM2.

Table 6 [^{11}C]-Raclopride binding in apathetic and non-apathetic Parkinson's disease patients at baseline (before MP)

Areas	Left/right	Stereotactic coordinates (regional maxima) x	y	z	Z-score	P uncorr voxel	Cluster size
Increase of binding in Apathetic versus Non-apathetic patients							
OFC (BA 11, 47, 10)	L	−28	38	−10	3.78	0.0001	245
	R	32	36	−6	3.24	0.001	24
DLPFC (BA 9, 46)	L	−32	30	12	3.28	0.001	245
PCC (BA 31)	R	12	−50	20	4.53	0.0001	113
	L	−8	−50	40	3.11	0.001	67
Temporal cortex (BA 36, 20)	L	−32	−6	−36	3.78	0.0001	108
	R	34	−32	22	4.01	0.0001	167
Amygdala	R	34	2	−24	3.22	0.001	77
Striatum (dorsal and ventral)	L	−16	6	−2	3.10	0.001	441
	L	−18	0	4	3.10	0.001	
Thalamus	L	−22	−22	6	3.05	0.001	28
Increase of binding in Non-apathetic versus Apathetic patients		None					

Table 7 Differences of variations of [^{11}C]-raclopride binding after MP

Areas	Left/right	Stereotactic coordinates (regional maxima) x	y	z	Z-score	P uncorr voxel	Cluster size
Increase of binding variations in Non-apathetic versus Apathetic patients							
OFC (BA 11, 47, 10)	L	−42	56	12	4.31	0.0001	167
		−2	62	10	3.51	0.0001	37
		−40	58	2	3.43	0.0001	71
	R	30	26	−2	3.55	0.0001	77
		2	60	12	3.67	0.0001	57
DLPFC (BA 9, 46)	R	54	0	26	4.17	0.0001	519
		8	46	32	3.25	0.001	35
	L	−42	56	12	4.31	0.0001	167
		−48	−2	26	3.17	0.001	14
ACC (BA 24, 32)	L	−2	−20	42	3.43	0.0001	65
		−2	58	2	3.38	0.0001	15
	R	2	54	2	3.45	0.0001	17
		2	−22	42	3.43	0.0001	65
PCC (BA 31)	L	−6	−50	40	3.29	0.0001	36
Temporal cortex (BA 20, 35, 36, 7)	R	32	−32	−22	4.08	0.0001	277
Internal globus pallidus	L	−12	2	2	3.10	0.001	17
Thalamus	L	−4	−6	14	3.19	0.001	246
Increase of binding variations in Apathetic versus Non-apathetic patients					None		

Discussion

In a prospective study with monthly follow-up over a 12-month period, more than half of the patients with Parkinson's disease, surgically implanted for chronic STN DBS with an 82% decrease in dopaminergic medication within 2 weeks after surgery, developed apathy in an average 6-month time period. Approximately half of the patients with postoperative apathy also developed depression. Depression was always reversible and apathy had disappeared in half of the patients at the 12-month follow-up. Pathological hyperdopaminergic behaviours were present in one-third of the patients at baseline and disappeared in all patients during follow-up. Non-motor fluctuations in daily life emerged as the

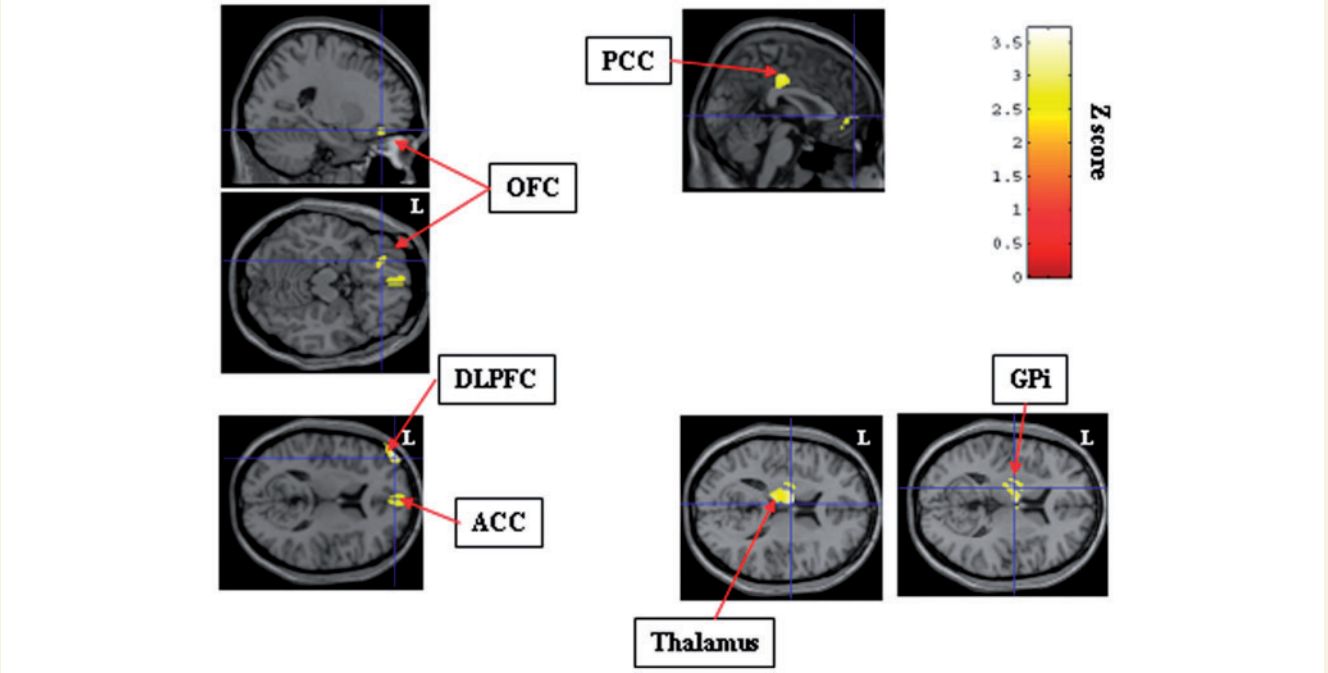

Figure 4 Areas of greater changes of [^{11}C]-raclopride-binding potential values induced by MP intake in non-apathetic versus apathetic patients with Parkinson's disease (i.e. greater methylphenidate-induced release of dopamine). After MP intake, the variations of [^{11}C]-raclopride-binding potential values before and after methylphenidate (i.e. the increase of synaptic dopamine release) were greater in the non-apathetic group of patients. This was observed bilaterally in the OFC (BA 11, 47, 10), DLPFC (BA 9, 46) and ACC (BA 24, 32) cortices, in the left PCC (BA 31), left thalamus, left internal globus pallidus (GPi) and in the right temporal cortex (BA 20, 36, 35, 7). Some of these regions are presented, superimposed on a single subject brain MRI from SPM2.

main predictors of postoperative apathy. Baseline motor fluctuations reflecting nigrostriatal dopaminergic lesions, baseline cognitive function, total dopaminergic treatment at baseline and postoperative reduction in dopaminergic treatment did not predict the occurrence of apathy. The PET study demonstrates that patients with Parkinson's disease, who develop postoperative apathy, anxiety and depression, have a greater mesocorticolimbic dopaminergic denervation than patients who do not. This preferential dopaminergic degeneration affects notably the projections to the OFC, DLPFC and cingulate cortices, the left ventral striatum and the right amygdala.

Mechanisms of apathy

Although apathy is a known complication of STN DBS in Parkinson's disease (Krack *et al*., 2003; Drapier *et al*., 2006), its mechanisms are not well understood. While depression and anxiety in the premotor phase of Parkinson's disease have been related to lesions of the mesolimbic dopaminergic system, the locus coeruleus and the raphe nuclei, the neuropathological substrate of apathy in the premotor phase is unknown (Tolosa *et al*., 2009). Severe loss of nigrostriatal dopaminergic fibres is the most consistent and specific lesion in Parkinson's disease. The other 'long length dopamine system', the ventral tegmental area, which projects to the ventral striatum (nucleus accumbens), the limbic cortex (medial prefrontal, cingulate and entorhinal areas) and other limbic structures (septum, olfactory tubercle, amygdala and pyriform cortex), is less severely damaged (Lees, 2009). Two major hypotheses have been proposed to explain the occurrence of apathy after STN DBS. First, postoperative apathy has been considered as a dopamine withdrawal syndrome because it responds to dopamine agonist treatment (Czernecki *et al.,* 2008). Second, it has been postulated that postoperative apathy corresponds to a specific side effect of stimulation of the limbic part of the STN (Drapier *et al*., 2006; Le Jeune *et al*., 2008; Temel *et al*., 2009). The main argument for this last assumption is the absence of correlation between postoperative apathy and the reduction in dopaminergic treatment. However, as acute STN DBS has psychostimulant effects (Funkiewiez *et al*., 2003) similar to those of L-dopa (Maricle *et al*., 1995; Funkiewiez *et al*., 2003), this last assumption seems unlikely. An alternative explanation, which would explain why some but not all of the patients develop postoperative apathy, would be individual variations in the neurodegenerative process. In the present study, baseline non-motor fluctuations emerged as a major risk factor for the development of postoperative apathy. In some studies apathy was associated with more severe motor symptoms (Pedersen *et al*., 2009, 2010), suggesting that apathy and more severe parkinsonism may be caused by a common underlying mechanism. Our clinical and imaging findings are very much in favour of a mesolimbic rather than a nigrostriatal lesion at the origin of parkinsonian apathy. This is also in agreement with the important role of the ventral tegmental area in motivated behaviour (Javoy Agid and Agid, 1980; Rodriguez-Oroz *et al*., 2009; Voon *et al*., 2009). Decreased

novelty seeking and reward processing, which contribute to parkinsonian apathy and are present in *de novo* Parkinson's disease, respond to dopaminergic treatment and have been related to mesolimbic dopaminergic lesions (Menza *et al*., 1993; Bodi *et al*., 2009; Rodriguez-Oroz *et al*., 2009). The present study gives strong arguments in favour of the dopaminergic hypothesis. Indeed, motor outcome does not differ between patients that become apathetic and those who do not, which indicates that electrode placement is in the dorsolateral sensorimotor rather than the more anteromedial limbic part of the STN in both groups. In our study, medication withdrawal took place immediately after surgery and stimulation parameters were increased almost exclusively during the first 2 weeks. The monthly evaluations showed that apathy occurred very progressively and not in response to changes in stimulation, which is compatible with a delayed dopamine withdrawal syndrome or with a process of desensitization rather than with an effect directly related to stimulation of the non-motor territories of the STN. Finally, the present PET study clearly shows a mesolimbic denervation as a substrate of postoperative dopamine withdrawal syndrome and strongly suggests that individual differences in denervation explain the occurrence of apathy, anxiety and depression. Our findings suggest that, in selected patients with Parkinson's disease displaying no cognitive deterioration, postoperative apathy can be seen as a model of a pure mesolimbic hypodopaminergic syndrome, which is unmasked by postoperative drug withdrawal.

Interestingly, although dopaminergic treatment was reduced immediately after surgery, the mean delay in the appearance of apathy was approximately 6 months. The long-term effects of L-DOPA on the motor signs have been neglected in the past (Fahn *et al*., 2004). The reduction in dopamine replacement therapy and the replacement of a pulsatile pharmacological treatment by a non-pulsatile, electrical one seems to contribute to progressive desensitization and disappearance not only of L-dopa -induced dyskinaesias (Krack *et al*., 1999; Bejjani *et al*., 2000; Moro *et al*., 2002) but also of ON-period related euphoria and hyperdopaminergic behaviour (Witjas *et al*., 2005; Ardouin *et al*., 2006) unmasking the hypodopaminergic face of the disease.

Depression and anxiety

Approximately half of the patients who developed apathy also suffered from depression. In a few patients this depression was reactive to major life events, but in the vast majority it occurred simultaneously with apathy or shortly after the occurrence of isolated apathy. Depression was always reversible—mainly in response to the re-introduction of dopaminergic treatment (data not shown). Therefore, although apathy is considered as a distinct syndrome, different from depression (Starkstein *et al*., 1992; Levy *et al*., 1998), there is a high comorbidity of both entities (Starkstein *et al*., 2009) and our data are in favour of a continuum between isolated parkinsonian apathy and parkinsonian depression with an important apathetic component, both being part of a hypodopaminergic syndrome. Depression was diagnosed using the BDI. We applied a cut-off score of 20 that was originally suggested by Beck and colleagues to diagnose severe depression in non-Parkinson's disease populations. We chose this high score in order to avoid too much overlap with apathy. We could not use Diagnostic and Statistical Manual of Mental Disorders-IV criteria for the systematic monthly follow-up in such a large cohort to diagnose depression and this is a limitation of our study. The mechanisms of postoperative suicide as a delayed complication of chronic STN DBS for Parkinson's disease are multifactorial (Voon *et al*., 2008), but our data are in favour of a major contribution of dopamine withdrawal in depressive mood. Our data also corroborate the hypothesis of an important role of mesolimbic dopaminergic dysfunction in depression (Nestler and Carlezon, 2006).

In the multivariate analysis, preoperative anxiety emerged as the most important predictor of apathy next to non-motor fluctuations (which include symptoms of apathy, depression and anxiety). The study primarily intended to study the frequency and mechanisms of apathy. Depression was monitored because of the risk of suicide attempts (Voon *et al*., 2008). While in the literature there is ample discussion of the relationship and differences between depression and apathy (Starkstein *et al*., 1992; Levy *et al*., 1998), very little is known about the potential relationship between apathy and anxiety. In early untreated Parkinson's disease, depression, apathy and anxiety are the most common psychiatric symptoms indicating that anxiety is also part of a hypodopaminergic syndrome in the same way as apathy and depression (Shiba *et al*., 2000; Aarsland *et al*., 2009). A limitation of our study is the absence of monthly evaluations of anxiety; but anxiety was increased in the apathetic patients with Parkinson's disease participating in the PET study. Baseline OFF-period anxiety scores were higher in the Apathy Group and baseline anxiety fluctuations were a main predictor of postoperative apathy. Therefore, anxiety also seems to be part of the hypodopaminergic syndrome (Ardouin *et al*., 2009*a*).

Non-motor fluctuations

The concept of non-motor fluctuations is nebulous, referring to a conglomerate of fluctuations in neuropsychiatric, dysautonomic and sensory symptoms that are difficult to disentangle. Non-motor fluctuations are not only clinically relevant, frequent and disabling but they are also a key determinant of the quality of life. As these symptoms fluctuate in parallel with motor symptoms, a dopaminergic pathophysiology has been discussed (Witjas *et al*., 2002; Stacy *et al*., 2005, 2010; Rahman *et al*., 2008; Barone *et al*., 2009; Chaudhuri and Schapira, 2009). While specific validated tools have been developed to assess the full spectrum of non-motor symptoms (Chaudhuri *et al*., 2006; Goetz *et al*., 2008; Chaudhuri and Schapira, 2009), fluctuations of these symptoms have only rarely been assessed (Witjas *et al*., 2002; Stacy *et al*., 2005). In the present paper we referred to non-motor fluctuations in a more restricted neuropsychiatric sense and we took into account not only OFF-period dysphoria but also ON-period euphoria. We found non-motor fluctuations in everyday life (Ardouin *et al*., 2009*a*) to be a main predictor of postoperative apathy. The presence of non-motor fluctuations at baseline corresponds to a 2.5-fold increase in the risk of developing apathy. Such neuropsychological/behavioural fluctuations are difficult to evaluate and the lack of validated instruments is a limitation of this study. Assessment of acute psychotropic effects of L-dopa

during a L-dopa challenge contributed to a better characterization of the non-motor fluctuations in everyday life, showing that they consist of a variety of symptoms including aspects of motivation, mood and anxiety. Assessment of fluctuations in apathy (SAS), depression (BDI) and anxiety (BAI) during the acute L-dopa challenge using scales designed to evaluate a chronic state rather than an acute evaluation also proved to be useful in predicting the occurrence of apathy. These scales (which are not validated for this particular use) were used in parallel to a VAS that, although designed to assess acute effects of drugs, is less specific in regard to apathy, anxiety or depression. As an example, the hazard ratio of 1.1 for delta apathy scores indicates that an increase of one point on the Starkstein apathy score at baseline OFF-drug compared to the baseline ON-drug condition corresponds to a 10% increase in the risk of developing postoperative apathy. A baseline fluctuation of 5 points on the apathy score will lead to a 1.6-fold increase and a fluctuation of 10 points to a 2.5-fold increase in postoperative apathy. Evaluation of the psychotropic effects of L-dopa appears to be of paramount importance in the management of Parkinson's disease and such tools need to be further developed and validated. Moreover, the non-motor fluctuations—when assessed using the described methodology—are likely to reflect mesolimbic dopaminergic denervation as evidenced by neuroimaging.

Implications for the management of Parkinson's disease

The relatively high frequency of apathy observed in the present study cannot only be explained by the monthly screening using a specific apathy scale, it is also likely to be related to a more drastic reduction in dopaminergic treatment (–82% at 1 month, 73% at 1 year) compared to the 50–60% reduction in most other studies (Kleiner-Fisman *et al*., 2006). More importantly, dopamine agonist drugs were stopped in all the patients, a strategy that has not been tested so far. In the present study dopamine agonists were systematically stopped (i) because of the high frequency of pathological hyperdopaminergic behaviours in patients on therapeutic doses of dopamine agonists (Bostwick *et al*., 2009), (ii) because of the high risk of postoperative decompensation or of a new incidence of pathological behaviours when subthalamic stimulation is added to medical treatment (Houeto *et al*., 2002; Smeding *et al*., 2007; Lim *et al*., 2009) and (iii) in the light of recent experience showing that postoperative reduction in dopaminergic treatment leads to the improvement of impulse control disorders existing before surgery (Witjas *et al*., 2005; Ardouin *et al*., 2006). A further reason for discontinuing dopamine agonists was specifically to investigate the role of dopamine agonists on parkinsonian apathy (Ardouin *et al*., 2009*b*, in press). With this approach, we observed a higher than usual incidence of postoperative apathy but we did not observe a single case of new onset impulse control disorder. One year after surgery, dopamine dysregulation syndrome and behavioural addictions had disappeared in all patients. These results differ markedly from those of another study, which reports a high rate of impulse control disorders in selected patients who displayed preoperative hyperdopaminergic behaviours and remained on high doses of dopaminergic treatment (Lim *et al*., 2009). Thus, differences in medical management might largely explain the variations in reported hyperdopaminergic behavioural complications (Houeto *et al*., 2002; Witjas *et al*., 2005; Ardouin *et al*., 2006; Smeding *et al*., 2007; Lim *et al*., 2009). Differences in both the extent of mesolimbic denervation and in postoperative patient management can also resolve the seemingly paradoxical postoperative occurrence of either impulse control disorders on the one hand, or apathy, anxiety and depression on the other (Houeto *et al*., 2002; Krack *et al*., 2003; Drapier *et al*., 2006; Smeding *et al*., 2006; Voon *et al*., 2008; Lim *et al*., 2009).

It is important to note the much-delayed appearance of apathy and depression in our cohort, despite the immediate postoperative withdrawal of dopamine agonists and the reduction of L-dopa. The monthly evaluations allowed early detection of apathy and depression. While treatment for apathy with a dopamine agonist could be delayed by 3 months if patients participated in the ongoing double blind pharmacological study testing the impact of piribedil versus placebo on parkinsonian apathy, the presence of a depression score >20 was an exclusion criterion and depressed patients had early treatment intervention, consisting mainly of the re-introduction of a dopamine agonist drug. With this approach, depression was always reversible and apathy had disappeared in half of the patients by the 12-month follow-up. Depression was present almost exclusively in the Apathy group, indicating that baseline non-motor fluctuations should also be considered as a risk factor for the delayed appearance of depression and suicide risk. In a previous study postoperative depression, being single, being younger, having earlier disease onset, previous suicide attempts or a previous history of impulse control disorders or compulsive medication use were all identified as risk factors for postoperative suicide risk (Voon *et al*., 2008). Our data underline the importance of long-term neuropsychological follow-up of patients with Parkinson's disease treated with STN DBS, especially in patients at risk. Postoperative apathy is frequently associated with anxiety or depression and seems to be the tip of the iceberg of a larger spectrum of hypodopaminergic symptoms. After surgery apathy should be detected and treated early on with dopaminergic drugs in order to prevent postoperative depression with suicidal risk.

General interpretation of the PET results

Apathy being associated with depression and anxiety, our PET findings should be interpreted in light of the three components of this hypodopaminergic syndrome. At baseline, apathetic patients have greater [^{11}C]-raclopride binding mainly in limbic circuits, which may be interpreted either as an increase of the density of dopaminergic D2/D3 receptors or as a reduction of endogenous synaptic dopamine levels (Gjedde *et al*., 2005). After MP, which blocks the presynaptic dopamine transporters with a higher affinity to the mesolimbic compared to the nigrostriatal projections (Di Chiara and Imperato, 1988) and induces an increase of dopamine release (Schweri *et al*., 1985), the changes of [^{11}C]-raclopride binding were greater in Non-apathetic patients with Parkinson's disease, which suggests a greater capacity to release

dopamine. Therefore, the occurrence of apathy, anxiety and depression could be explained by a lower density of presynaptic dopaminergic terminals, especially in the mesocorticolimbic system. This could explain the unmasking of hypodopaminergic symptoms if dopaminergic treatment is decreased, as is the case after surgery. The absence of correlation between the severity of apathy and the importance of the dopaminergic degeneration may be related to the fact that apathy was not isolated, but part of a larger hypodopaminergic syndrome including apathy, anxiety and depression.

Implication of the prefrontal cortex

The present study suggests that dopaminergic denervation of the OFC, which has a role in 'drive', reward and compulsive behaviours (Volkow *et al*., 2009), is involved in the physiopathology of apathy, anxiety and depression. In drug-addicts, hypometabolism in the OFC is responsible for apathy during periods of abstinence (Volkow *et al*., 2009). Apathy has also been related to left OFC hypometabolism in Alzheimer's disease and frontotemporal dementia (Migneco *et al*., 2001; Benoit *et al*., 2002; Holthoff *et al*., 2005; Peters *et al*., 2006). Conversely, patients with Parkinson's disease and pathological gambling have an increased perfusion of the right OFC (Cilia *et al*., 2008). In addition, we also found greater dopaminergic denervation of the DLPFC in apathetic patients with Parkinson's disease, in keeping with findings of hypometabolism in drug-addicts during abstinence periods and in Alzheimer's disease (Migneco *et al*., 2001; Benoit *et al*., 2002; Volkow *et al*., 2009). In the same vein, a recent PET fluorodesoxyglucose study revealed that (mild) apathy after STN surgery was associated with a reduction of DLPFC metabolism (Le Jeune *et al*., 2009). Taken together, the dysfunction of these two prefrontal regions could explain, on the one hand, the emotional component of apathy (mediated by the OFC) and, on the other hand, the cognitive component of apathy (mediated by the DLPFC) (Levy and Dubois, 2006).

Involvement of the basal ganglia and of the thalamus

The present work underlines the crucial role of the left striatum, in particular its ventral part (including the accumbens nucleus), thalamus and internal globus pallidus (especially its ventral/limbic part) in the physiopathology of hypodopaminergic symptoms in Parkinson's disease, and it suggests a lateralization effect. A previous imaging study using a marker of both dopamine and noradrenaline transporter binding has shown that parkinsonian apathy and depression correlated with ventral striatal and thalamic dopaminergic and/or noradrenergic denervation (Remy *et al*., 2005). Conversely, in drug addiction, euphoria induced by drug intake is associated with dopamine release in the ventral striatum and is proportional to the amount of dopamine release (Drevets *et al*., 2001; Leyton *et al*., 2002; Volkow *et al*., 2009). Furthermore, during abstinence periods, drug-addicts become apathetic and have reduced dopaminergic cell activity (Wu *et al*., 1997; Volkow *et al*., 2009). Patients with Parkinson's disease and hyperdopaminergic behaviours exhibit increased ventral striatal dopamine release after L-dopa intake (Evans *et al*., 2006) or when involved in compulsive behaviour (Steeves *et al*., 2009). These findings fit well with the motivational role of ventral tegmental dopaminergic neurons and their mesocorticolimbic projections (Schultz, 1998; Wise, 2009).

The present study suggests a specific role of a left-sided basal ganglia dopaminergic denervation in the occurrence of apathy in Parkinson's disease. This is in line with functional MRI studies showing that negative manifestations in schizophrenia are linked to left striatal hypometabolism (Schlagenhauf *et al*., 2008). Inversely, in healthy subjects, the increase of incentive motivation is related to an increased density of dopamine D2 receptors in the left versus right striatum (Tomer and Aharon-Peretz, 2004). Furthermore, the less important the dopaminergic innervation in the left caudate nucleus, the less important the novelty seeking personality (Menza *et al*., 1995). All these data support a specific role of the left-sided striatum not only in motivational aspects of the personality of normal subjects but also in the occurrence of apathy, anxiety and depression in Parkinson's disease. On the other hand, dysfunction of the right-sided basal ganglia, notably the ventral pallidum, could lead to pathological gambling in Parkinson's disease (Cilia *et al*., 2008).

Implication of the temporal cortex and amygdala

The present study also points to a role of dopaminergic denervation of the limbic part of the temporal cortex and of the right amygdala in the physiopathology of apathy, anxiety and depression in Parkinson's disease. The dopaminergic innervation of the amygdala plays an important role in the processing of salient aversive stimuli in conjunction with the ACC (LeDoux, 2003; Kienast *et al*., 2008). Interestingly, basolateral amygdala neurons send excitatory projections to the nucleus accumbens (Brog *et al*., 1993) and a recent study has demonstrated that reward-seeking behaviour, which is driven by the nucleus accumbens, is under the control of both the amygdala and dopaminergic projections from the ventral tegmental area (Ambroggi *et al*., 2008). Thus, our findings could well explain the loss of the reward-seeking behaviour seen in apathy. In addition, other authors have shown a relationship between the importance of the dopaminergic and noradrenergic degeneration in the right amygdala and the occurrence of depression and anxiety in Parkinson's disease (Remy *et al*., 2005). Our results extend these findings suggesting that dysfunction of the amygdala may also be implicated in apathy.

Implication of ACC and PCC

This study highlights the role of anterior and posterior cingulate dysfunction in the pathogenesis of apathy, anxiety and depression in Parkinson's disease. Convergent arguments have shown that the PCC plays a critical role in the regulation of negative emotions by encoding the emotional significance of stimuli (Liotti *et al*., 2000; Maddock *et al*., 2003). Perfusion of the PCC is diminished in depression and anxiety (Mayberg *et al*., 2000; Simpson *et al*., 2001). Both ACC and PCC metabolism is also reduced in apathetic patients with Parkinson's disease after STN stimulation (Le Jeune

et al., 2009). In the same vein, in Alzheimer's disease, apathy is associated with reduced perfusion of the right ACC (Migneco et al., 2001; Benoit et al., 2002). Finally it has been shown that patients with Parkinson's disease with L-dopa-induced mood fluctuations, in comparison to Parkinson's disease patients without, present an increased perfusion of the PCC and medial frontal gyrus in response to L-dopa (Black et al., 2005). The present study demonstrates that the PCC is involved in the physiopathology of apathy as well as the ACC, OFC and DLPFC, all regions from which the PCC receives projections (Vogt et al., 2003).

Behavioural desensitization

Despite reduced dopamine release after an oral dose of MP, the reinforcing psychotropic effect of this drug, with improvement in subjective feelings of fatigue and unhappiness, was only significant in apathetic patients, which may, at first glance, appear as paradoxical. We cannot exclude a 'floor effect' in non-apathetic patients, but a greater postsynaptic dopaminergic sensitization in the apathetic patients with a larger presynaptic mesolimbic denervation seems more likely. Indeed, repeated and pulsatile administration of psychostimulant drugs—including dopaminergic medication—can induce prolonged sensitization of behavioural effects, which is processed by the dopaminergic mesolimbic system, especially the nucleus accumbens (Evans et al., 2006; Vezina and Leyton, 2009). This is mediated by a selective increase of dopaminergic D3 receptor density in the nucleus accumbens (Guillin et al., 2001). While the reduction of dopamine input to this receptor has been associated with depression or anhedonia in Parkinson's disease (Lemke et al., 2005), excessive stimulation of these receptors may cause dopamine dysregulation syndrome (Dodd et al., 2005). In the present study, apathetic patients have a superior density or a greater affinity of dopaminergic D2/D3 receptors, which is consistent with a sensitization phenomenon. Thus, we hypothesize that apathetic patients have a greater sensitization to dopaminergic treatment at baseline and a cross-sensitization to MP that has a preferential action on mesolimbic dopaminergic projections (Di Chiara and Imperato, 1988). This is consistent with the greater baseline non-motor fluctuations—a key feature of dopamine dysregulation syndrome (Lawrence et al., 2003)—in our patients who have developed postoperative apathy. After postoperative decrease of dopaminergic treatment, the process of sensitization would tend to reverse as is the case for L-dopa-induced dyskinaesias (Bejjani et al., 2000), thus unmasking the apathy related to mesolimbic dopaminergic denervation. Obviously, at the time of PET evaluation, desensitization was not complete, and patients still display a greater behavioural response to MP, despite having greater ventral tegmental (mesolimbic) dopaminergic denervation.

Conclusion

Patients with Parkinson's disease with non-motor fluctuations are at greater risk of developing postoperative apathy and depression as part of a delayed dopamine withdrawal syndrome. The present study provides a clear demonstration that this hypodopaminergic syndrome is related to a predominant degeneration of dopaminergic mesocorticolimbic projections.

We could speculate that, because of a lower dopaminergic tone at baseline within these mesocorticolimbic pathways, these patients with Parkinson's disease tend to increase dopaminergic medication intake in order to get the 'drive' effect of their drug. This would enhance the sensitization of the mesolimbic dopaminergic system via an upregulation of the D3 receptors, contributing to greater non-motor fluctuations and an increased risk of developing a dopamine dysregulation syndrome (Lawrence et al., 2003; Weintraub, 2008). Thus, we hypothesize that the same patients who are at risk of developing a dopamine dysregulation syndrome on dopaminergic treatment would run a greater risk of developing apathy or a broader hypodopaminergic syndrome after successful surgery allowing for marked reduction in dopaminergic medication. Monitoring of apathy and depression after surgery and their treatment with dopaminergic drugs are essential in order to prevent postoperative depression and suicide, the most important complication of STN DBS (Voon et al., 2008).

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