

Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours

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Addictions to dopaminergic drugs or to pleasant behaviours are frequent and potentially devastating neuropsychiatric disorders observed in Parkinson's disease. They encompass impulse control disorders, punding and dopamine dysregulation syndrome. A relationship with dopaminergic treatment is strongly suggested. Subthalamic stimulation improves motor complications and allows for drastic reductions in medication. This treatment might, therefore, be considered for patients with behavioural addictions, when attempts to reduce dopaminergic medication have failed. However, conflicting data have reported suppression, alleviation, worsening or new onset of behavioural addictions after subthalamic stimulation. Non-motor fluctuations are also a disabling feature of the disease. We prospectively investigated behaviour in a cohort of 63 patients with Parkinson's disease, before and 1 year after subthalamic stimulation using the Ardouin scale, with systematic evaluation of functioning in overall appetitive or apathetic modes, non-motor fluctuations, dopaminergic dysregulation syndrome, as well as behavioural addictions (including impulse control disorders and punding) and compulsive use of dopaminergic medication. Defined drug management included immediate postoperative discontinuation of dopamine agonists and reduction in levodopa. Motor and cognitive statuses were controlled (Unified Parkinson's Disease Rating Scale, Mattis Dementia Rating Scale, frontal score). After surgery, the OFF medication motor score improved (−45.2%), allowing for a 73% reduction in dopaminergic treatment, while overall cognitive evaluation was unchanged. Preoperative dopamine dysregulation syndrome had disappeared in 4/4, behavioural addictions in 17/17 and compulsive dopaminergic medication use in 9/9 patients. New onset of levodopa abuse occurred in one patient with surgical failure. Non-motor fluctuations were significantly reduced with improvements in off-dysphoria ($P \leq 0.001$)

and reduction in on-euphoria ($P \leq 0.001$). There was an inversion in the number of patients functioning in an overall appetitive mode (29 before versus 2 after surgery, $P \leq 0.0001$) to an overall apathetic mode (3 before versus 13 after surgery, $P < 0.05$). Two patients attempted suicide. Improvement in motor fluctuations is linked to the direct effect of stimulation on the sensory-motor subthalamic territory, while improvement in dyskinesias is mainly explained by an indirect effect related to the decrease in dopaminergic drugs. Our data suggest that non-motor fluctuations could similarly be directly alleviated through stimulation of the non-motor subthalamic territories, and hyperdopaminergic side effects might improve mainly due to the decrease in dopaminergic medication. We show an overall improvement in neuropsychiatric symptomatology and propose that disabling non-motor fluctuations, dopaminergic treatment abuse and drug-induced behavioural addictions in Parkinson's disease may be considered as new indications for subthalamic stimulation.

Keywords: Parkinson's disease; dopamine; behaviour; subthalamic nucleus; deep brain stimulation

Abbreviations: DBS = deep brain stimulation; DSM = Diagnostic and Statistical Manual of Mental Disorders; STN = subthalamic nucleus

Introduction

Subthalamic nucleus (STN) deep brain stimulation (DBS) improves motor fluctuations, dyskinesia (Limousin *et al.*, 1998) and quality of life in advanced Parkinson's disease (Deuschl *et al.*, 2006). While the technique has shown no deterioration in overall cognitive function in randomized controlled studies comparing STN DBS to best medical treatment (Deuschl *et al.*, 2006; Follett *et al.*, 2010; Williams *et al.*, 2010), the topic of potential neuropsychiatric effects is still controversial (Hariz *et al.*, 2008; Volkmann *et al.*, 2010).

Due to conflicting results in the literature, neurologists are unable to predict behavioural outcome when proposing STN DBS to their patients (Houeto *et al.*, 2002; Witjas *et al.*, 2005; Ardouin *et al.*, 2006; Smeding *et al.*, 2006; Voon *et al.*, 2006; Witt *et al.*, 2008; Lim *et al.*, 2009; Follett *et al.*, 2010). Indeed, various causes of transient and chronic psychic side-effects of STN DBS, which are not mutually exclusive, have been proposed. These include:

- (i) adaptation to motor improvement can be difficult from a psycho-socio-familial point of view (Perozzo *et al.*, 2001; Houeto *et al.*, 2006; Schupbach *et al.*, 2006) especially due to unrealistic expectations (Okun and Foote, 2004; Rodriguez *et al.*, 2007; Montel and Bungener, 2009), and because DBS questions the 'identity' of patients (Witt *et al.*, 2011);
- (ii) surgery may lead to decompensation of premorbid latent psychiatric symptoms (Houeto *et al.*, 2002; Romito *et al.*, 2002);
- (iii) the direct effect of DBS on limbic-associative STN is thought to explain various behavioural or emotional modifications: acute well-being with positive psycho-stimulant effects such as euphoria and a decrease in sedation (Funkiewiez *et al.*, 2003, 2006), mirthful laughter (Krack *et al.*, 2001), mania (Herzog *et al.*, 2003; Mallet *et al.*, 2007; Ulla *et al.*, 2011), impulsive behaviour in high conflict situations (Frank *et al.*, 2007; Ballanger *et al.*, 2009), improvement in obsessive compulsive disorder (Mallet *et al.*, 2002, 2008), improvement in apathy with acute stimulation

(Czernecki *et al.*, 2005), or in contrast, increase in apathy on chronic subthalamic stimulation (Drapier *et al.*, 2006; Le Jeune *et al.*, 2009). Acute depression or aggressive behaviour may also fall into the category of disinhibited behaviours related to STN DBS (Krack *et al.*, 2010). Improvement of motor symptoms allows a decrease in dopamine replacement therapy, which could unmask hypodopaminergic symptoms (apathy, depression, anxiety) related to the disease (Krack *et al.*, 1998; Czernecki *et al.*, 2008; Thobois *et al.*, 2010), and/or improve presurgical dopamine dysregulation syndrome or impulse control disorders (Witjas *et al.*, 2005; Ardouin *et al.*, 2006).

The effects of STN DBS on processes underlying mood and behaviour are, therefore, complex and certainly multifactorial. The literature offers apparently contradictory results which are difficult to interpret. With regard to hypodopaminergic characteristics, controlled studies show alleviation or stability of anxiety and depression scores when looking at a cohort at a given time (Daniele *et al.*, 2003; Houeto *et al.*, 2006; Castelli *et al.*, 2008; Witt *et al.*, 2008), with individual cases of worsening (Funkiewiez *et al.*, 2004) and a higher suicide rate than in the general population (Voon *et al.*, 2008). Other work shows chronic worsening of apathy with chronic stimulation, attributed either to stimulation of the STN (Drapier *et al.*, 2006; Le Jeune *et al.*, 2009) or to reduction in dopamine replacement therapy (Krack *et al.*, 2003; Funkiewiez *et al.*, 2004; Czernecki *et al.*, 2008; Thobois *et al.*, 2010).

With regard to hyperdopaminergic behaviours, the question of the indication of STN DBS in impulse control disorders remains open, since studies report both worsening or new onset of impulse control disorders or dopamine dysregulation syndrome, and, improvement or full recovery from impulse control disorders or dopamine dysregulation syndrome (Broen *et al.*, 2011; Demetriades *et al.*, 2011).

No prospective studies assessing the whole spectrum of hypo- and hyperdopaminergic behavioural and mood modifications after STN DBS in Parkinson's disease have been conducted to date. One explanation of this deficiency is the lack of a single tool allowing the assessment of the wide spectrum of behavioural changes

specific to Parkinson's disease. Furthermore, the nosography of these behaviours is problematic, since the Diagnostic and Statistical Manual of Mental Disorders (DSM) psychiatric definitions do not always correspond to the psychiatric symptomatology of patients with Parkinson's disease, especially for depression (Gotham *et al.*, 1986; Brooks and Doder, 2001) and impulse control disorders. In Parkinson's disease, most studies on addictive behaviours use the term 'impulse control disorder' when referring to pathological gambling, compulsive shopping, hypersexuality and binge eating (Weintraub *et al.*, 2010). However, among these disorders, only pathological gambling comes under the DSM-IV definition of an impulse control disorder, and will be classified in the Addiction and Related Disorders section of the DSM-V in the near future (Okai *et al.*, 2011; APA, DSM-5 website development). Moreover, patients with Parkinson's disease suffer not only from these last four behavioural addictions, but can also develop other behavioural modifications such as cyberaddiction, hobbyism, gardening, painting and sewing, without the sterile stereotypy and compulsivity required to merit a diagnosis of punding (Evans *et al.*, 2004; McKeon *et al.*, 2007; Fasano and Petrovic, 2010; Lhommée *et al.*, 2011).

A common underlying neurobiology with drug addictions has been postulated for some impulsive–compulsive behaviours such as pathological gambling (Grant, 2008; Volkow *et al.*, 2009). Patients with Parkinson's disease and impulsive–compulsive behaviours have heightened ventral striatal dopamine release in the ON drug condition in response to reward-related cues (O'Sullivan *et al.*, 2011). These findings are consistent with the hypothesis that, as a result of neural sensitization in vulnerable individuals, reward-related cues are attributed pathological incentive salience (Robinson and Berridge, 1993), leading to compulsive pursuit of appetitive behaviours. Dopamine dysregulation syndrome, which combines abuse of dopaminergic medication with repetitive appetitive behaviours has also been conceptualized as a hedonistic homeostatic dysregulation, accompanied by the occurrence of an intense negative withdrawal state, typical of drug addiction, on withdrawal of the medication (Koob and Le Moal, 1997; Giovannoni *et al.*, 2000; Lawrence *et al.*, 2003). Based on these common neurobiological substrates between addictions and the full spectrum of hyperdopaminergic behaviours, we chose to use the previously proposed label of 'behavioural addictions' (Holden, 2001; Grant *et al.*, 2010) to classify the full protean range of repetitive appetitive behaviours encountered in patients with Parkinson's disease on dopaminergic treatment, including impulse control disorder and punding, as well as appetitive behaviours such as cyberaddiction or excessive hobbyism. The Ardouin scale offers the possibility of assessing changes in usual activities, ranging from subtle, subsyndromal or even beneficial behaviour, to severe psychiatric pathologies encompassing the entire spectrum of habits sensitive to dopaminergic medication in Parkinson's disease (Ardouin *et al.*, 2009).

The Ardouin scale also allows assessment of function on both apathetic or appetitive modes (Ardouin *et al.*, 2009). Functioning on an appetitive mode is the opposite of functioning on an apathetic mode. As apathy, a state characterized by simultaneous diminution in the overt behavioural, cognitive and emotional

concomitants of goal-directed behaviour (Marin, 1991), appetitive functioning includes cognitive, emotional and behavioural aspects. 'Appetitive' is generic and concerns the mode of approach to one or multiple pleasant behaviours. Sensitivity to sensory stimuli is heightened (Kulisevsky *et al.*, 2009; Villa *et al.*, 2011) and seeking of pleasure increased, going up to a failure to resist pleasurable activity. The appetitive patient is typically passionate, enthusiastic, excited and curious and has a proliferation of his centres of interest and activities. While these aspects are mostly positive, at an extreme level these thoughts or activities will become unrealistic and behaviour disorganized leading to a negative impact on social life. Appetitive behaviour is not driven by the search for a release in inner tension as is the case in behavioural addiction, drug addiction, dopamine dysregulation syndrome and punding (Koob and Le Moal, 1997; Lawrence *et al.*, 2003; Grant *et al.*, 2010).

Non-motor fluctuations, corresponding to rapid oscillations between hypo- and hyperdopaminergic states, constitute a frequent and disabling complication of dopaminergic treatment (Witjas *et al.*, 2002; Stacy *et al.*, 2005; Ardouin *et al.*, 2009; Thobois *et al.*, 2010; Weintraub and Burn, 2011). An acute dopamine withdrawal syndrome has been described in patients with impulse control disorders after discontinuation of dopamine agonist drugs (Rabinak and Nirenberg, 2010). We have recently shown that patients with Parkinson's disease undergoing successful STN DBS, enabling a marked decrease in dopamine replacement therapy, are at risk of developing a delayed dopamine withdrawal syndrome that can occur with a mean delay of several months. Patients with preoperative non-motor fluctuations and more diffuse mesolimbic dopaminergic denervation were shown to have an increased risk of developing such a postoperative dopamine withdrawal syndrome, characterized by higher scores on apathy, anxiety and depression scales (Thobois *et al.*, 2010). In the present study, using a systematic evaluation of non-motor fluctuations and hyperdopaminergic symptoms, we investigated, in the same cohort of 63 patients, whether this risk might be compensated by beneficial effects on non-motor fluctuations, impulse control disorders and dopamine dysregulation syndrome, as previously suggested by small retrospective studies (Witjas *et al.*, 2005; Ardouin *et al.*, 2006).

Materials and methods

Study population and design

The population and the design of the study were reported previously (Thobois *et al.*, 2010), and are therefore described here only briefly. A total of 63 consecutive patients underwent STN DBS in two centres. 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) age under 70 years; and (iv) the absence of surgical contraindications, dementia or of major ongoing psychiatric illness, as previously described (Krack *et al.*, 2003). Specific exclusion criteria were the presence of apathy (defined by the Starkstein Apathy Scale ≥ 14) or depression (defined by the Beck Depression Inventory scale ≥ 20) in the preoperative

Table 1 Characteristics of patients with Parkinson's disease and acute motor and non-motor fluctuations at baseline and follow-up

| n = 63 | Before surgery (baseline) | | One year after surgery (12 months) | | P-value |
|---|---------------------------|-------------|------------------------------------|-------------|----------|
| General characteristics | | | | | |
| Sex (% male) | 63.5 | | | | |
| Age at surgery (years) | 57.8 ± 7.2 | | | | |
| Disease duration (years) | 10.5 ± 3.1 | | | | |
| Medication and motor state | | | | | |
| Total L-DOPA dose (mg/day) | 1026 ± 459 | | 284 ± 312 | | ≤ 0.001 |
| Total dopamine agonist equivalent dose (mg/day) | 279 ± 143 | | 116 ± 255 | | ≤ 0.001 |
| Total L-DOPA + agonist equivalent dose (mg/day) | 1306 ± 475 | | 400 ± 386 | | ≤ 0.001 |
| | ON | OFF | ON | OFF | |
| Unified Parkinson's Disease Rating Scale motor score /108 | 10.33 ± 6.6 | 36.4 ± 12.8 | 11.2 ± 7.5 | 20.3 ± 13.7 | ≤ 0.001* |
| Duration of dyskinesias (n = 62) | 1.48 ± 0.95 | | 0.47 ± 0.74 | | ≤ 0.001 |
| Disability of dyskinesias (n = 62) | 1.24 ± 1.07 | | 0.26 ± 0.54 | | ≤ 0.001 |
| Off duration (n = 62) | 1.67 ± 0.75 | | 0.39 ± 0.75 | | ≤ 0.001 |
| Cognition | | | | | |
| | | | 3 months after surgery | | |
| Mattis Dementia Rating scale/144 (n = 58) | 139.1 ± 3.7 | | 137.7 ± 5.3 | | 0.098 |
| Frontal Score/50 (n = 59) | 41.8 ± 6.5 | | 40.8 ± 7.5 | | 0.367 |
| Verbal fluency /10 | 8.8 ± 1.5 | | 7.4 ± 1.8 | | ≤ 0.001 |
| Graphic series /10 | 8.3 ± 2.4 | | 8.1 ± 2.6 | | 0.626 |
| Gestual series /10 | 9.1 ± 1.6 | | 8.8 ± 2.3 | | 0.314 |
| Wisconsin card sorting test /20 | 15.4 ± 4.1 | | 16.5 ± 3.9 | | 0.043 |
| Acute non-motor fluctuations | | | | | |
| | ON | OFF | ON | OFF | |
| Beck Depression Inventory | 8.4 ± 5.4 | 12.2 ± 6.9 | 6.5 ± 5 | 8.2 ± 7.1 | 0.008* |
| Beck Anxiety Inventory | 9 ± 10.2 | 15.8 ± 10 | 4.3 ± 7.5 | 7 ± 9.4 | ≤ 0.001* |
| Starkstein Apathy Scale (n = 61) | 6.2 ± 3.5 | 11.2 ± 6.4 | 9.4 ± 4.5 | 10 ± 5 | ≤ 0.001* |

Values are expressed in mean (±SD) scores. Stimulator was 'on' at 12 months.

*Comparisons of mean values for delta OFF minus ON before surgery versus delta OFF minus ON after surgery.

'ON drug' evaluation condition. The sample characteristics are described in Table 1.

The assessments took place in the month preceding surgery and 12 months (±1 month) later, with the exception of the cognitive status, which was controlled 3 months after surgery. An exhaustive evaluation of mood, behaviour and cognition was carried out by a clinical neuropsychologist with specific expertise in the assessment of neuropsychiatric symptoms in Parkinson's disease during chronic treatment conditions. Acute non-motor fluctuation evaluations, however, took place during the L-DOPA test in both ON and OFF drug conditions (on stimulation condition at postoperative statement). The surgical procedure, pharmacological treatment and stimulation management of patients are described in Thobois *et al.* (2010). It is important to stress that, 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 the patients' motor state within the 2 weeks immediately following surgery, the patient being hospitalized during this period. The management of dopaminergic medication differed from normal practice; the decrease in medication, particularly of dopamine agonists, was more aggressive than is customary. We aimed to treat patients with L-DOPA only, and to study the effects of dopamine agonists in the event of apathy (ongoing study in a larger population ClinicalTrials.gov NCT01020682). The ethics committee of Grenoble University approved the study and all the patients gave written informed consent.

Outcome measures

Motor function

The Unified Parkinson's Disease Rating Scale part III or motor score were used to assess the beneficial effects of L-DOPA and subthalamic stimulation on the Parkinsonian motor signs; part IV was used to assess the duration and severity of dyskinesias and the duration of OFF-periods (Fahn *et al.*, 1987).

Cognitive status

Overall cognitive function was assessed using the Mattis Dementia Rating Scale (Mattis *et al.*, 1976). The degree of frontal-subcortical deterioration was evaluated using the frontal score, a more specific test battery measuring frontal executive function (Pillon *et al.*, 1986). It included the simplified version of the Wisconsin Card Sorting Test (Nelson, 1976), verbal fluency tests (Cardebat *et al.*, 1990), graphic and motor series (Luria, 1966).

Psychiatric history

The Mini International Neuropsychiatric Interview (Sheehan *et al.*, 1998) was used to screen current and previous psychiatric events based on DSM-IV criteria (1994). This consists of a semi-structured interview, with filter questions leading the precise evaluation of the specific domains if required. It screened the most common

psychiatric items of the DSM-IV, including mood disorders (major depressive episode, dysthymic disorder, manic or hypomanic episode), anxiety disorders (panic disorder, agoraphobia, social phobia, obsessive–compulsive disorders, post-traumatic stress disorder, generalized anxiety disorder), alcohol and drug addictions, anorexia and bulimia nervosa, psychotic disorders and antisocial personality disorders.

Mood and behavioural modifications: Ardouin scale

This previously described instrument (Ardouin *et al.*, 2009) is subject to a process of validation in Parkinson's disease (Rieu *et al.*, 2011) and in the general population. It is a semi-structured interview consisting of 21 items assessing patients' general psychological state (six items: depressive mood, hypomanic or manic mood, anxiety, irritability, hyper-emotivity and psychotic symptomatology), overall functioning in apathetic mode (one item), non-motor fluctuations [two items: non-motor stimulation ON medication (motor ON) and non-motor stimulation OFF medication (motor OFF)], and hyperdopaminergic behaviours (12 items: nocturnal hyperactivity, diurnal somnolence, excessive eating behaviour, creativity, hobbyism, punning, risk-seeking behaviour, compulsive shopping, pathological gambling, hypersexuality, compulsive dopaminergic medication use and overall functioning in an appetitive mode). Each item rates the frequency and intensity of a symptom's occurrence in the preceding month on a scale ranging from 0 (absent) to 4 (severe), firstly by means of open questions (the patient is initially allowed to express himself as freely as possible) and subsequently, by means of more detailed questions to obtain scores. Each item is rated independently in accordance with specific topic scoring guidelines (Ardouin *et al.*, 2009). A score of 0 indicates no modification of the patient's usual habits; a score of 1 reflects a slight modification; a score of 2 is indicative of a moderate modification in usual behaviour that is usually significant enough to require therapeutic adjustment; and a score >2 equates with clear-cut maladaptive pathological behaviour requiring immediate care. The following hyperdopaminergic profiles were defined at the time of the study thanks to existing definitions of dopamine dysregulation syndrome (Giovannoni *et al.*, 2000) and of behavioural addiction (Holden, 2001; Grant *et al.*, 2010). Patients:

- (i) presented a dopamine dysregulation syndrome defined as dopaminergic compulsive medication use item ≥ 2 associated with one or several of the nine following behavioural addictions items >2 : excessive eating behaviour, creativity, hobbyism, punning, risk seeking behaviour, compulsive shopping, pathological gambling, hypersexuality and nocturnal hyperactivity;
- (ii) presented a behavioural addiction defined as one or several of the above nine behavioural addiction items scoring >2 ;
- (iii) presented an isolated dopaminergic compulsive medication use defined as dopaminergic compulsive medication use item ≥ 2 , all nine above-mentioned behavioural addiction items ≤ 2 .

In the absence of any available normative data, the choice of these cut-offs was driven by adaptation of the DSM-IV definition of substance dependence (APA, 1994): the individual continues his behaviour despite significant related problems; there is a pattern of repeated self-administration that usually results not in tolerance as in drug dependence, but often in psychological withdrawal and compulsive acts (occurrence of behaviour in greater qualitative severity or over a longer period than was originally intended; expression of a persistent desire to reduce or to regulate behaviour; often there have been many unsuccessful efforts to decrease or discontinue use; a great deal of time is spent carrying out the behaviour; the person's daily activities

all revolve around the substance; important social, occupational or recreational activities may be given up or reduced because of the behaviour; the individual may withdraw from family activities and hobbies in order to perform his behaviour in private; despite recognizing the contributing role of the behaviour to a psychological problem, the person continues to indulge in the behaviour). Nocturnal hyperactivity occupies a particular place which will be revealed during the discussion.

In the Ardouin scale:

- (i) a score >2 indicates the presence of a marked to severe modification in the past month, the evaluation being based on repeated and/or prolonged periods of time devoted to the behaviour, the disturbance or total disruption of usual previously normal social and occupational activities, requiring therapeutic adaptation of dopaminergic treatment;
- (ii) for dopaminergic compulsive medication use, the cut-off is lower (≥ 2), taking into account dopaminergic compulsive medication use with a score of 2 characterized as followed: 'often, the patient increases the dosage or the frequency of his medication, and feels tense and anxious if he can't. However he tries to limit his behaviour because of the known risks and of the recommendations of those close to him/her'. As dopaminergic treatment is typically fractionated in advanced Parkinson's disease in order to avoid OFF periods as much as possible, patients with Parkinson's disease (unlike other drug addicts) are unlikely to devote long periods of time to their addictive behaviour. Moreover, as their treatment is prescribed and available, unlike in other drug addictions, craving for medication itself is unlikely to totally disrupt social and occupational activities. We therefore diagnosed dopaminergic compulsive medication use in the presence of a dysphoric state in the OFF medication condition sufficiently severe to cause the patient to bring forward and increase his dopaminergic medication.

Acute non-motor fluctuations

The Beck Depression Inventory for depressive mood (Beck *et al.*, 1996), the Starkstein Apathy Scale for levels of motivation (Starkstein *et al.*, 1992) and Beck Anxiety Inventory for levels of anxiety (Beck *et al.*, 1988; Freeston *et al.*, 1994) were self-assessment tools added during the L-DOPA tests in both ON and OFF drug conditions. A higher score expresses a more dysphoric state (on depression, motivation and anxiety variables). Using these scales in OFF and ON conditions, the patients were asked to answer according to how they really felt at the moment of examination (Czernecki *et al.*, 2002).

Statistical analyses

All data analyses were performed using Stata release 11.1 (StataCorp) software. Data were summarized in terms of size and frequency for categorical data and by mean scores \pm SD for quantitative data. An exact McNemar's test was used to compare paired qualitative parameters. For continuous data a Student's *t*-test was applied or a Mann–Whitney test in the event of non-Gaussian assumption or a Wilcoxon test for paired comparisons. Independence between qualitative parameters was assessed using either the Chi-square test or Fisher's exact test. *P*-values <0.05 were considered statistically significant.

Results

Whole sample analyses

Medication, motor and cognitive outcome

The overall outcome including surgical complications has already been reported in detail (Thobois *et al.*, 2010) and therefore will only be summarized here. STN DBS has been associated with an improvement in parkinsonian symptomatology as measured by the Unified Parkinson's Disease Rating Scale motor score and by motor complications (part IV items), and allows, as scheduled, a significant reduction in dopamine replacement therapy (Table 1). Specifically, 1 year after surgery, the OFF medication motor score of the Unified Parkinson's Disease Rating Scale improved (−45.2%), allowing for a 73% reduction in dopaminergic treatment. The comparison between preoperative and 3-month postoperative cognitive variables did not show any difference (Table 1) for global scores (Mattis Dementia Rating scale and Frontal score). However, significant reduction in verbal fluency and better performance in Wisconsin card sorting test were observed.

Psychiatric history

Comparative analyses of current or previously diagnosed preoperative versus postoperative defined psychiatric episodes using the Mini International Neuropsychiatric Interview revealed no differences.

Lifetime: the most frequent disorders experienced in the course of a lifetime were major depressive episodes (22.2% of patients before surgery and 25.4% after), hypomanic episodes (12.7% of patients before surgery and 19.1% after), panic disorders (9.5% of patients before surgery and 4.8% after) and agoraphobia (9.5% before and 7.9% after surgery).

Current life: current life percentage of prevalence of major depressive disorder was 0% before surgery and 3.2% after surgery. Current mania or hypomania concerned 6.4% of patients before surgery and 0% after. Ongoing anxiety disorders, including panic disorder, agoraphobia, social phobia, obsessive–compulsive disorders, post-traumatic stress disorder and generalized anxiety disorder were diagnosed in 7.9% of patients before surgery and 4.8% after. No diagnosis of psychotic disorder, bulimia nervosa and drug addiction was made either before surgery or after.

Mood and behavioural modifications: Ardouin scale

The most frequent disturbing preoperative symptomatology noted using Ardouin scale (score ≥ 2) were non-motor fluctuations. During motor OFF periods, 41.9% of patients experienced dysphoric mood, anxiety, sadness accompanied occasionally by the conviction that they would remain in this state for the rest of their lives. During motor ON periods, 35.5% of patients experienced artificial euphoria, an urge to talk, psychological strength and dynamism. After surgery we noticed a highly significant diminution of this symptomatology, both in prevalence and severity. Non-motor OFFs continued to affect only a residual 14.5% of patients and non-motor ONs continued to affect as few as 6.5% of patients ($P \leq 0.0001$ for both comparisons, McNemar test; see Table 2). A Wilcoxon test also showed a significant

decrease in non-motor OFFs and ONs ($P \leq 0.001$ for both comparisons; Fig. 1). The evolution of patients' general psychological evaluation 1 year on from STN DBS is represented in Table 2, and shows a significantly lower number of patients affected by hypomanic or maniac mood following surgery, and stability in depressive mood, anxiety, irritability, hyperemotivity and psychotic symptoms. Figure 2 illustrates a drastic inversion in the functioning of patients: prevalence of apathetic functioning mode increased significantly after surgery (three patients before versus 13 patients after), whereas postoperative prevalence of appetitive functioning mode, was, on the contrary, significantly reduced (29 patients before versus two patients after). Finally, hyperdopaminergic behaviours, often encountered in the preoperative assessment (Table 2) were globally diminished at the 12-month follow-up. Nocturnal hyperactivity, diurnal somnolence, excessive eating behaviour, creativity, hobbyism and dopaminergic compulsive medication use was in particular significantly less frequent after surgery (but eight patients were still affected by excessive eating behaviour after surgery). There were clear improvements in punding, compulsive shopping, pathological gambling and hypersexuality, but preoperative population sizes were too small to reach significance level. Risk seeking behaviour frequency (~5%) remained unchanged.

Acute non-motor fluctuations

Dysphoric state was significantly lower in the ON medication condition than in OFF medication condition, as measured with the Beck Depression Inventory, Beck Anxiety Inventory and Starkstein Apathy Scale ratings, at preoperative and postoperative assessments (Wilcoxon paired test, $P \leq 0.001$ for each ON versus OFF comparison, at baseline and 12 months), except for apathy at 12 months. Moreover, the amplitude of these non-motor fluctuations was significantly diminished at 12 months ($P \leq 0.01$ for Beck Depression Inventory and $P \leq 0.001$ for Beck Anxiety Inventory and Starkstein Apathy Scale).

Suicide attempts

Two patients attempted suicide, one of them following an infection requiring explantation of the neurostimulator and electrodes, the other 2 months after surgery in a context of high irritability and hyperemotivity, without nevertheless meeting the criteria for a major depressive disorder.

Outcome of patients with a hyperdopaminergic profile

In our cohort of 63 patients, at preoperative assessment, the use of the Ardouin scale permitted the diagnosis of the following hyperdopaminergic profiles in 30 patients, including:

(i) four patients with dopamine dysregulation syndrome, among whom various addictive behaviours were present: hypersexuality ($n = 1$) pathological gambling ($n = 1$) risk-taking behaviour ($n = 1$) cyber-addiction ($n = 3$) excessive puzzle playing ($n = 1$); (ii) 17 patients with one or several behavioural addictions (without compulsive medication use): punding ($n = 1$) creativity ($n = 5$) compulsive shopping ($n = 1$) excessive eating behaviour ($n = 7$) and varying

Table 2 Ardouin scale percentage of prevalence of each disorder (patients with a score ≥ 2) before (baseline) and 1 year after surgery

| Ardouin Scale (n = 62) | Baseline (%) | One year (%) | P-value |
|--|--------------|--------------|--------------|
| Mood evaluation | | | |
| Depressive mood | 8.1 | 11.3 | 0.774 |
| Hypomaniac mood, mania | 12.9 | 0 | 0.008 |
| Anxiety | 22.6 | 11.3 | 0.092 |
| Irritability, aggressiveness | 14.5 | 6.5 | 0.227 |
| Hyperemotivity | 35.5 | 24.2 | 0.189 |
| Psychotic symptoms | 0 | 0 | 1.000 |
| Functioning on an apathetic mode | 4.8 | 21 | 0.013 |
| Non-motor fluctuations | | | |
| ON | 35.5 | 6.5 | ≤ 0.001 |
| OFF | 41.9 | 14.5 | ≤ 0.001 |
| Hyperdopaminergic behaviours | | | |
| Nocturnal hyperactivity | 30.6 | 3.2 | ≤ 0.001 |
| Diurnal somnolence | 17.5 | 4.8 | 0.022 |
| Excessive eating behaviour | 37.1 | 12.9 | 0.002 |
| Creativity | 19.4 | 6.5 | 0.008 |
| Hobbyism | 33.9 | 1.6 | ≤ 0.001 |
| Punding | 3.2 | 0 | 0.500 |
| Risk-taking behaviour | 4.8 | 4.8 | 1.000 |
| Compulsive shopping | 8.1 | 1.6 | 0.219 |
| Pathological gambling | 4.8 | 0 | 0.250 |
| Hypersexuality | 3.2 | 0 | 0.500 |
| Dopaminergic compulsive medication use | 19.4 | 1.6 | 0.003 |
| Functioning on an appetitive mode | 46.8 | 3.2 | ≤ 0.001 |

Statistical values were obtained using exact McNemar test.

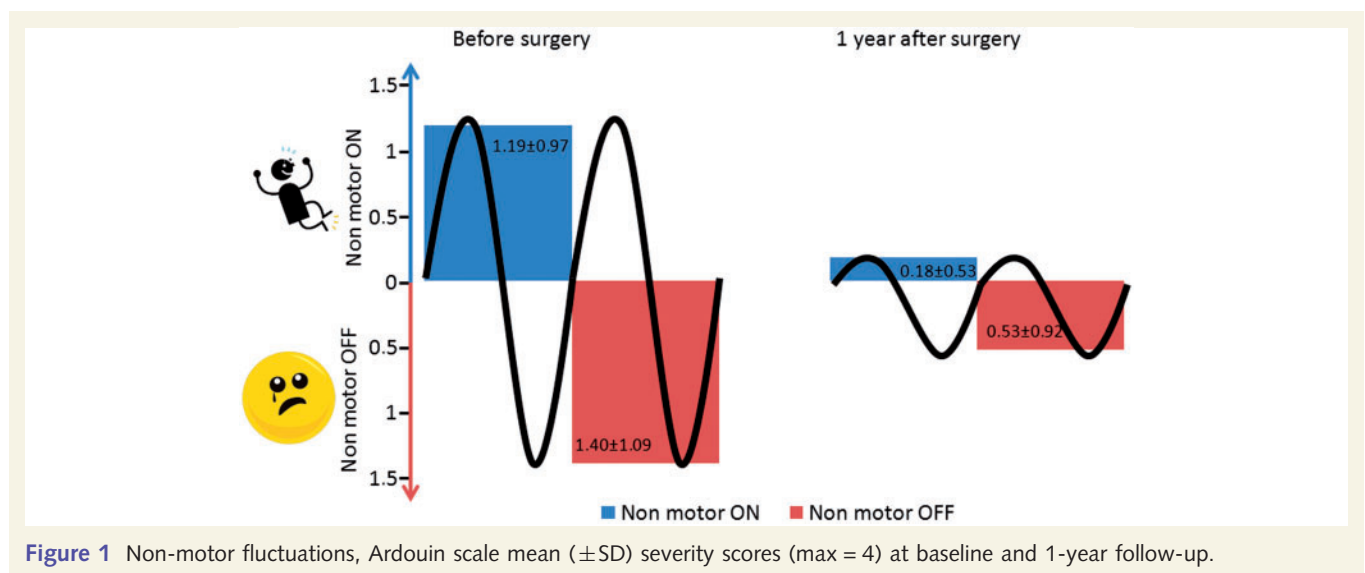


Figure 1 Non-motor fluctuations, Ardouin scale mean (\pm SD) severity scores (max = 4) at baseline and 1-year follow-up.

diurnal/nocturnal hyperactivity: philately, computer use, Internet surfing, gambling without money on the net or offline, bringing work home, housework, cooking, embroidery, decorating, do-it-yourself, gardening ($n = 12$). Of the 8 patients, 17 of them exhibited multiple behavioural addictions. Cases 1 and 2 illustrate this co-occurrence of different behavioural addictions (see case studies in Supplementary material); and (iii) nine patients with isolated dopaminergic compulsive medication use.

At the time of postoperative assessment, only one diagnosis of isolated dopaminergic compulsive medication use was made. At the preoperative assessment, this patient was not diagnosed as having a hyperdopaminergic profile. Misplacement of electrodes had occurred for the patient in question, consequently dopamine replacement therapy could not be diminished (total L-DOPA + agonist equivalent dose = 1400 and 1600 mg/day at preoperative and postoperative assessments, respectively).

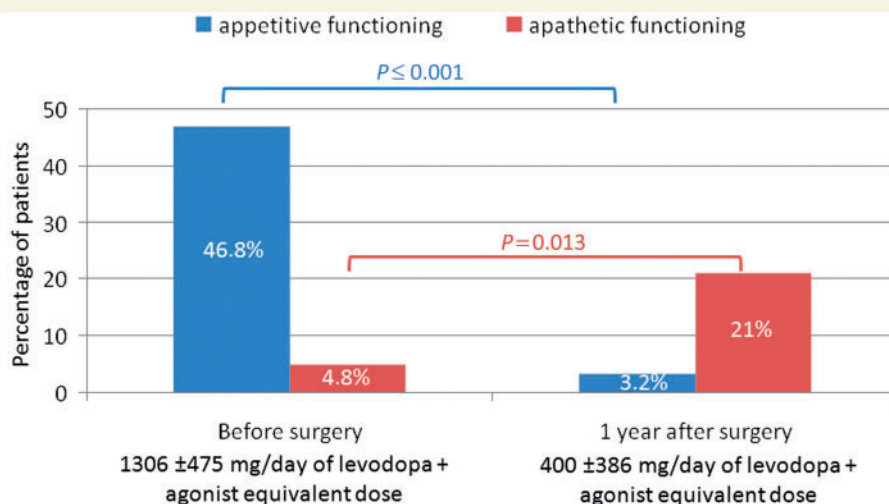


Figure 2 Ardouin scale apathetic and appetitive functioning modes. Data are expressed in percentages of patients with relevant item scores ≥ 2 at baseline and 1-year follow-up.

This patient did not fulfil dopamine dysregulation syndrome criteria at postoperative assessment as his shopping behaviour did not reach sufficient severity on the Ardouin scale due to absence of financial consequences. However, following surgery, without his wife's consent, he bought a car, a TV, an oven and do-it-yourself equipment and had unusual thirst for sex (also with no consequences on the couple's relationship). To sum up, 30/30 patients with Parkinson's disease with some form of addictive habit at their preoperative assessment were free from their addiction at the 1-year follow-up. One patient with surgical failure experienced new onset of dopaminergic compulsive medication use.

Out of 30 patients with a hyperdopaminergic profile at their preoperative assessment, 18 (4/4 with dopamine dysregulation syndrome, 5/9 with dopaminergic compulsive medication use and 9/17 with behavioural addiction) developed apathy at some point during the postoperative year, based on assessment using the Starkstein Apathy Scale (see 'Materials and methods' section in Thobois *et al.*, 2010), and 10 were apathetic according to the Ardouin scale (functioning in an apathetic mode score ≥ 2) at the 12-month follow-up.

Discussion

We have described the outcome of neuropsychiatric symptomatology in a cohort of 63 patients with advanced Parkinson's disease after 1 year of subthalamic stimulation with a 73% mean decrease of dopaminergic medication. Using specific tools, we showed: (i) an overall decrease in hyperdopaminergic symptomatology with disappearance of preoperative dopamine dysregulation syndrome, behavioural addictions (including impulse control disorders) and dopaminergic medication abuse; (ii) a marked decrease in non-motor fluctuations; and (iii) an inversion of the proportion of patients with Parkinson's disease functioning in an overall appetitive mode to an overall apathetic mode.

Improvement of dopamine dysregulation syndrome, behavioural addiction and dopaminergic compulsive medication use

Preoperative dopamine dysregulation syndrome (four patients), behavioural addictions (17 patients) or dopaminergic compulsive medication use (nine patients) had disappeared in all 30 patients at the 1-year follow-up.

Why are the results in the present study better than in the existing literature?

This clear-cut result based on a prospective behavioural evaluation and the defined management of dopaminergic medication, will help to restore law and order in an ongoing controversial debate about the outcome of preoperative impulse control disorders following STN DBS, which is based on retrospective studies with contradictory outcomes (Voon *et al.*, 2006; Broen *et al.*, 2011; Demetriades *et al.*, 2011). Indeed, on one hand, the use of STN DBS has been proposed to allow improvement in dopamine dysregulation syndrome, impulse control disorders or other behavioural addictions made possible by postoperative reductions in dopamine replacement therapy, based on clinical outcomes in retrospective studies (Witjas *et al.*, 2005; Ardouin *et al.*, 2006; Bandini *et al.*, 2007; Knobel *et al.*, 2008). Impulse control disorders and other behavioural addictions in Parkinson's disease are clearly linked to dopamine replacement therapy (Weintraub *et al.*, 2010; Ambermoon *et al.*, 2011; Voon *et al.*, 2011b), and reduction of dopamine replacement therapy, and in particular of dopamine agonists, can improve impulse control disorder in the context of surgery (Kimber *et al.*, 2008; Mamikonyan *et al.*, 2008; Sohtaoglu *et al.*, 2010). On the other hand, several studies have reported no improvement, worsening of pre-existing behavioural addictions (Lim *et al.*, 2009) or new onset addictions following STN DBS (Smeding *et al.*, 2007; Halbig *et al.*, 2009;

Lim *et al.*, 2009; De la Casa-Fages and Grandas, 2011). Authors usually argue that the worsening is mainly related to electrode position and spread of stimulation effects into the limbic portion of the STN (Djamshidian *et al.*, 2011). However, as we had no single new occurrence of impulse control disorder, with the single exception of a patient with severe restless legs syndrome not allowing arrest of dopamine agonist (see Case 2, Supplementary material), we believe that management of medication and stimulation parameters are the main explanatory factors. In the largest retrospective series of reported preoperative impulse control disorders in patients treated with STN DBS, postoperative worsening of impulse control disorders was associated with a very high dose of dopamine replacement therapy (mean of 2745 mg/day of L-DOPA equivalent units at postoperative assessment), while improvement in impulse control disorder was associated with a major decrease in dopamine replacement therapy (mean of 329 mg/day of L-DOPA equivalent units at postoperative assessment) (Lim *et al.*, 2009). This last result is in line with our results, indicating that improvement in hyperdopaminergic behaviours is mainly related to reductions in dopaminergic treatment (see Case 1, Supplementary material). However, failed surgery, with misplaced electrodes outside the STN, not allowing for reduction in medication, might also explain the persistence of pre-existing hyperdopaminergic behaviours or new onset of isolated dopamine compulsive medication use as was the case in the single failed surgery in this series. Ultimately, the quality of longitudinal behavioural assessment and the optimal management of hypo- and hyperdopaminergic behaviours will substantially contribute to overall surgical outcome and quality of life.

Subthalamic nucleus versus internal pallidum deep brain stimulation debate

While STN DBS allows for a decrease in dopamine replacement therapy, this is not the case for internal pallidal DBS (Krack *et al.*, 1998; Follett *et al.*, 2010). Postoperative behavioural addictions have also been reported after internal pallidal DBS (Lim *et al.*, 2009). Therefore, in patients presenting with a disabling hyperdopaminergic syndrome, the STN may be a better target, providing optimal drug management. This is in opposition to the prevailing view that the internal pallidum is a safer target, especially concerning psychiatric side-effects (Hariz *et al.*, 2008; Follett *et al.*, 2010), and needs to be explored in future studies comparing the outcome of DBS in these two targets.

Psychotropic effects of subthalamic nucleus deep brain stimulation and dopamine replacement therapy

Acute STN DBS by itself induces impulsive behaviours (Baunez *et al.*, 1995; Krack *et al.*, 2001; Frank *et al.*, 2007). The role of the STN is to withhold unwanted motor, cognitive and emotional actions. Therefore, the occurrence of new onset of impulse control disorder as a consequence of functional inactivation of the limbic STN by DBS in the same way as the occurrence of dyskinesia as a consequence of functional inactivation of the sensorimotor STN by DBS does not come as a surprise and is perfectly in line with the known function of the STN (Krack *et al.*, 2010). STN DBS has psychotropic effects that are very similar if not identical to L-DOPA, explaining that the occurrence of disinhibited behaviour

will depend on management of both dopaminergic drugs and STN DBS, which do have synergic additive behavioural effects (Funkiewiez *et al.*, 2003).

Subthalamic nucleus deep brain stimulation: a new indication for cocaine addiction?

Compulsive medication use was alleviated in all our patients on chronic STN DBS. This is compatible with results in rodent model showing that STN stimulation can reduce motivation to seek and take cocaine, a drug that enhances dopaminergic tone (Rouaud *et al.*, 2010). Interestingly, STN neurons are able to encode specific information regarding the value of rewards (Lardeux *et al.*, 2009) and it has been suggested that cocaine addiction might be a new indication for STN DBS (Lardeux *et al.*, 2009; Krack *et al.*, 2010). Improvement in dopaminergic medication abuse in patients with Parkinson's disease on chronic subthalamic stimulation strengthens this suggestion coming from fundamental research in the field of addiction. Cocaine withdrawal states are clinically similar to dopamine withdrawal states and both are characterized by striatal dopamine depletion (Wu *et al.*, 1997). The psychotropic effect of STN DBS can explain the improvement in non-motor OFF states as well as the disappearance of craving for L-DOPA shown in this study and this mechanism of subthalamic stimulation may also contribute to its beneficial effects on cocaine addiction in the rat.

Decrease in non-motor fluctuations and underlying mechanisms

Non-motor fluctuations are frequent and disabling (Witjas *et al.*, 2002). In our cohort of patients who were candidates for surgery, at baseline disabling non-motor OFF and ON were present in 41.9 and 35.5% of patients, respectively. In a previous study of the same patient population, we showed that the presence of non-motor fluctuations at baseline was the main predictor of the occurrence of postoperative non-motor withdrawal syndrome (Thobois *et al.*, 2010). As patients with a postoperative withdrawal syndrome have more diffuse mesocorticolimbic dopaminergic denervation, preoperative non-motor fluctuations can be indirectly linked to mesolimbic denervation and the ensuing postoperative withdrawal syndrome can be interpreted as an unmasking of the preoperative OFF-period symptoms, whenever the dopamine replacement therapy is reduced excessively (Thobois *et al.*, 2010). Although presurgical non-motor fluctuations predicted the occurrence of postoperative withdrawal syndromes, the present study has shown a marked postoperative improvement in non-motor fluctuations. Moreover, even when withdrawal symptoms were present they were usually less severe than in the preoperative non-motor OFF condition (see Case 3, Supplementary material), and non-motor OFF symptoms improved after surgery (Table 1 and Fig. 1). While improvement in ON-period euphoria is probably mainly related to drug decrease, the improvement in OFF-period dysphoria is probably mainly related to the positive psychotropic effects of STN DBS, which are thought to be related to current diffusion to the non-motor territories of the STN (Funkiewiez *et al.*, 2003, 2006; Schneider *et al.*, 2003). The mechanisms of improvement in non-motor symptoms parallel those relating to

stimulation of the sensorimotor STN. Indeed, acute STN DBS induces dyskinesia (Limousin *et al.*, 1996), while chronic STN DBS improves dyskinesias (Krack *et al.*, 1997, 1999). Improvement in peak-dose dyskinesia can be related mainly to the decrease in medication with accompanying progressive desensitization (Bejjani *et al.*, 2000). The improvement in OFF-period dystonia and diphasic dyskinesia is also related to the direct effect of STN DBS on the pathologic neuronal activity underlying these dyskinesias (Krack *et al.*, 1999; Rodriguez-Oroz *et al.*, 2011).

Inversion of the proportion of patients with Parkinson's disease functioning in a predominantly appetitive mode to functioning in a predominantly apathetic mode

Before surgery, none of our patients suffered from apathy during on-periods according to the Starkstein apathy scale (exclusion criterion for the study) although, based on the Arduin scale, 5% of the patients had overall functioning in apathetic mode in everyday life (Fig. 2). Half of the patients (30/63) fulfilled diagnostic criteria for hyperdopaminergic behavioural disorders encompassing dopamine dysregulation syndrome, and one or several addictive behaviours including the four most common impulse control disorders in Parkinson's disease. Half of the patients also had an overall functioning in appetitive mode according to the Arduin scale (Fig. 2).

After surgery, none of our patients suffered from disabling hyperdopaminergia, but 21% of the patients had an overall functioning in apathetic mode, and only 3% an overall functioning in appetitive mode. Although we were unable to correlate this change with a decrease in dopaminergic treatment, a causal relationship to the decrease in dopaminergic medication is likely because increase in dopamine replacement therapy can lead to reversal of apathy (Czernecki *et al.*, 2008; Thobois *et al.*, 2010). Our results yield strong arguments in favour of the hypo- and hyperdopaminergic interpretation of the main neuropsychiatric symptoms observed in Parkinson's disease (Arduin *et al.*, 2009; Voon *et al.*, 2011a). Increase in appetitive behaviour on dopaminergic treatment can be explained by the heightened response of striatal reward circuitry to reward-related cues in patients with hyperdopaminergia (O'Sullivan *et al.*, 2011). Loss of appetitive behaviour is related to the severity of Parkinson's disease (Shore *et al.*, 2011). Hypodopaminergic apathetic behaviour in Parkinson's disease can be explained by a lack of incentive motivation, a process that translates an expected reward into behavioural activation (Schmidt *et al.*, 2008). Apathy and behavioural addictions can thus be seen as two opposites on a continuum of behaviours that depend on the state of activation of dopaminergic motivational systems. Evaluation of motivated behaviours in Parkinson's disease along the lines of functioning in apathetic versus appetitive behavioural modes appears to be meaningful both on clinical and neurobiological grounds. The change from preoperative overall functioning in appetitive mode, to postoperative overall functioning in an apathetic one after STN DBS in patients with Parkinson's disease may largely explain the reported

situation of a discrepancy between the opinion of the neurologist who is happy with objective motor improvement of his patient and the patient himself who may be less happy and regret his preoperative hyperdopaminergic state (Agid *et al.*, 2006). Postoperative hypodopaminergia is not an inevitable fate (see Case 1, Supplementary material). The association of dopaminergic treatment and subthalamic stimulation can also induce non-pathologic hyperdopaminergia to the satisfaction of the patient (Witt *et al.*, 2006). Synergic effects can occur as illustrated in Case 2 with transient postoperative mania (Supplementary material). Hyperdopaminergic behavioural side-effects of STN DBS indeed occur mainly in the immediate postoperative period, rather than during long-term follow-up where hypodopaminergia is more prominent (Krack *et al.*, 2003; Uemura *et al.*, 2011).

In the management of Parkinson's disease, taking into account the motivational state in addition to motor symptoms is necessary to improve patient satisfaction. The direct psychotropic effect of STN DBS (Funkiewiez *et al.*, 2003) can contribute to postoperative hyperdopaminergic behaviour and impulsivity, while dopamine withdrawal can progressively lead to hypodopaminergia (Thobois *et al.*, 2010). Both impulsivity and hypodopaminergia may contribute to an increased risk of postoperative suicidal acts (Voon *et al.*, 2008). The transition period from overall appetitive to overall apathetic mode of functioning seems to be a period of risk for suicide attempts when the patient is still impulsive, but is starting to develop a dopamine withdrawal syndrome with apathy as its key feature, but which can also encompass an increase in anxiety and depression (Rabinak and Nirenberg, 2010; Thobois *et al.*, 2010). Two of our patients attempted suicide. This prevalence of 3% is higher than the 0.9% expected according to a large retrospective study (Voon *et al.*, 2008). So, we must assume that the experimental medical management used in this study, consisting in an abrupt discontinuation of dopamine agonists and major reduction in L-DOPA therapy, even if very effective on hyperdopaminergic pathological behavioural modifications, can be considered as dangerous. Thus, if such a medical strategy is required (in case of either disabling dyskinesia or pathologic hyperdopaminergia), we recommend very close and repetitive psychological follow-up all along the first postoperative year in order to detect delayed onset hypodopaminergia requiring cautious re-introduction of dopaminergic medications.

Is hyperdopaminergia a risk factor for dopamine withdrawal syndrome and apathy?

Stopping dopamine agonists in patients with a preoperative diagnosis of behavioural addiction does not necessarily lead to a postoperative apathy (see Case 1, Supplementary material). Patients with non-motor fluctuations reflecting the extent of underlying mesolimbic denervation are at higher risk to develop a dopamine withdrawal syndrome (Thobois *et al.*, 2010). Outside the context of surgery, it has been suggested that the presence of impulse control disorder is the main risk factor to develop dopamine withdrawal syndrome (Rabinak and Nirenberg, 2010). In our surgical cohort, 34/63 patients developed apathy at one point during the

1-year follow-up. Among them, 18 were diagnosed with hyperdopaminergic profile at baseline. This indicates that dopamine withdrawal syndrome is not specific to patients with impulse control disorders. However, apathy occurred systematically during the follow-up of patients with dopamine dysregulation syndrome at preoperative evaluation (four patients). Further studies with more patients fulfilling dopamine dysregulation syndrome diagnoses should address whether this condition can be considered as a risk factor for dopamine withdrawal states and apathy.

Methodological issues

Neuropsychiatric assessment tools

Sensibility to change of the Arduin scale (Table 2) and the Mini International Neuropsychiatric Interview (current life of psychiatric history outcome) can be compared. Indeed, many modifications at 1-year follow-up in terms of neuropsychiatric behavioural features in the Arduin scale are observed, whereas the Mini International Neuropsychiatric Interview showed no evolution of psychiatric symptomatology. Both instruments are neuropsychiatric and at first glance would appear to evaluate the same symptomatology. However, the construction of the Mini International Neuropsychiatric Interview was based on the DSM, in a psychiatric paradigm, whereas the Arduin scale was specifically developed based on clinical experience of behavioural disorders in the context of Parkinson's disease and its medical treatment in order to detect not only pathology, but also minor behavioural changes in Parkinson's disease, or moderate changes that are meaningful but do not correspond to a given psychiatric diagnosis. For example the features required to establish a diagnosis of major depressive disorder are not systematically observed in patients who are significantly depressed according to the Arduin scale, because Parkinson's disease depression does not have the same features as psychiatric depression (Gotham *et al.*, 1986). The Arduin scale also assesses modifications in behaviour, which are not present in the DSM. The prevalence of punding in Parkinson's disease, which varies from 0.3% to 14%, is a good example of the lack of precise definition, and of the lack of a gold standard assessment tool (Spencer *et al.*, 2011). The Arduin scale has been constructed to function at clinical level and also make up for the lack of a unique tool which provides defined criteria of severity for hyper and hypodopaminergic aspects of each symptom, and which is sensitive to change in dopamine replacement therapy conditions as shown by our data (Table 2; Figs 1 and 2) and illustrated by the case reports (Figs 3, 4 and 6; Supplementary material). We included high scores in nocturnal hyperactivity led among 'behavioural addiction' in our study. Nocturnal hyperactivity cannot be strictly equated with behavioural addiction. Nocturnal hyperactivity is not one specific activity, and typically is not different from daytime hyperactivity but rather reflects the increasing time spent on various behaviours present in an individual patient (often hobbyism). Nocturnal hyperactivity also reflects the psycho-stimulant, awakening amphetamine-like effects of dopaminergic treatment (Kramer *et al.*, 1967; Sacks, 1982; Funkiewiez *et al.*, 2003). Future studies and definition of terms should include nocturnal hyperactivity in either core criteria or as a severity index of

behavioural addictions or impulse control disorders. Nocturnal hyperactivity is indeed one of the most prominent signs of hyperdopaminergia, present in one-third of our patients before surgery (score ≥ 2).

Impact of cognitive factors

Overall executive function and global efficiency did not change after surgery. As expected by previous work, we observed a statistically significant reduction in verbal fluency with low size effect (Witt *et al.*, 2008). Thus, we think that the change in the balance of behaviours presented is largely independent from intellectual status, reasoning and decision-making without emotional involvement as assessed by neuropsychological evaluation, but more specifically reflects modifications in decision-making involving cognitive and emotional motivational aspects.

How representative is our patient sample?

The prevalence of behavioural disorders in our surgical candidates is different from epidemiological data in the general Parkinsonian population (Aarsland *et al.*, 2009). Our patients were apathy-free, because of the selection criteria for inclusion in the study. Moderately severe depression was also an exclusion criterion, whereas severe ongoing depression is a contraindication for routine surgery. The neuropsychiatric features of our study population as evaluated by the Mini International Neuropsychiatric Interview fit with the typical Parkinsonian population of surgical candidates with systematical psychiatric evaluation (Houeto *et al.*, 2002). Parkinson's disease candidates for surgery are younger and non-demented and therefore more likely to be treated with dopamine agonists. Moreover, since motor complications are the target symptoms, patients are at an advanced stage of the disease and are therefore taking higher doses of total L-DOPA equivalent dosage. Surgical candidates therefore represent a population particularly at risk of developing pathological hyperdopaminergic behaviours (Lawrence *et al.*, 2003; Voon *et al.*, 2009; Weintraub *et al.*, 2010).

Based on the Arduin scale, almost half of our patients were diagnosed preoperatively with either dopamine dysregulation syndrome (6%), behavioural addiction, including impulse control disorders, (27%) or compulsive use of dopamine replacement therapy (14%). Prevalence in the general population of patients attending specialist Parkinson's disease centres is 3–4% for dopamine dysregulation syndrome (O'Sullivan *et al.*, 2009) and 13.6% for impulse control disorders (Weintraub *et al.*, 2010). Initially, hyperdopaminergic behaviours may seem to be overrepresented. However, our assessment tool takes into account not only pathological gambling, compulsive shopping, compulsive sexual behaviour and binge eating, the four behavioural addictions usually classified as impulse control disorder in the context of Parkinson's disease (Weintraub *et al.*, 2010; Voon *et al.*, 2011a), but also the whole spectrum of other behavioural addictions. When considering only hypersexuality, pathological gambling, compulsive shopping and excessive eating behaviour items, 9/63 patients had at least one of these items rated >2 , i.e. a prevalence of 14%. This is very close to the parkinsonian population attending specialist Parkinson's disease centres treated with an association of L-DOPA and dopamine agonists (Weintraub

et al., 2010), as is typically the case in a selected population of surgical candidates.

Impact of medical and psychological managements

Due to our particular management of patients in this study (systematic discontinuation of dopamine agonists and very drastic and rapid reduction of L-DOPA), we observed a clear reduction of the neuropsychiatric behavioural side-effects of dopamine replacement therapy. Patients in this study had a more aggressive drug reduction than in routine procedure. Therefore neither the complete eradication of hyperdopaminergic behaviours, nor the high percentage of apathy fully reflects the outcome of routine procedure. However, this experimental approach afforded a better understanding of underlying mechanisms, and will contribute to better management of postoperative behavioural problems in the future especially by a specific type of neuropsychological management, with repeated contacts by phone, evaluations all through the year and constant dialogue with neurologists who adapted treatments as quickly as possible (see Cases 2 and 3, Supplementary material).

Conclusion

This study provides proof of the principle that hyperdopaminergic behaviours and non-motor fluctuations can be improved with STN stimulation, albeit with the risk of unmasking hypodopaminergic symptoms. Mechanisms are complex. On the one hand, improvements in hyperdopaminergic behaviours are mainly related to the decrease in medication. In the absence of such decreases, the combined effects of STN DBS and medication can lead to a worsening of such behaviour. On the other hand, improvement in non-motor OFF-periods reflects a direct psychotropic effect of STN DBS due to (inevitable) current diffusion to the limbic STN. Both compulsive medication use and behavioural addictions seem to share common mechanisms related to dopaminergic mesocorticolimbic dysfunction. While abnormal behaviour was traditionally considered a contraindication to STN DBS, these findings lead to a change of paradigm. Hyperdopaminergic behaviours as well as non-motor fluctuations are becoming new indications for STN DBS on top of L-DOPA-induced dyskinesias and motor fluctuations although these pre-surgical behavioural disorders need to be carefully monitored with systematic screening for hypo- and hyperdopaminergic behaviours that might require fine-tuning of stimulation parameters and dopaminergic medication.

Acknowledgements

We thank Cate Dalmolin for English corrections and Marc Savasta for helpful discussions. The study sponsors had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

Funding

Programme Hospitalier de Recherche Clinique Interrégional and Euthérapie Pharmaceutical Company. Medtronic funded for

research purpose in the field of DBS (to A.L.B., S.C., P.P. and P.K.). Several authors received reimbursement of travel costs to scientific meetings by Medtronic (to A.L.B., S.C., P.P., P.K., S.T. and E.B.) and Euthérapie (to P.P., P.K., S.T. and E.B.).

Supplementary material

Supplementary material is available at *Brain* online.

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