doi:10.1093/brain/aws078 Brain 2012: 135; 1463–1477 | 1463

BRAIN
A JOURNAL OF NEUROLOGY

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

Eugénie Lhommée,[1,2] Hélène Klinger,[3,4] Stéphane Thobois,[3,4] Emmanuelle Schmitt,[1,2] Claire Ardouin,[1,2] Amélie Bichon,[1,2] Andrea Kistner,[1,2] Valérie Fraix,[1,2] Jing Xie,[3,4] Magaly Aya Kombo,[1,2] Stephan Chabardès,[2,5] Eric Seigneuret,[2,5] Alim-Louis Benabid,[5,*] Patrick Mertens,[6] Gustavo Polo,[6] Sebastien Carnicella,[2] Jean-Louis Quesada,[7] Jean-Luc Bosson,[7] Emmanuel Broussolle,[3,4] Pierre Pollak[1,2,†] and Paul Krack[1,2]

1 Movement Disorder Unit, Department of Psychiatry and Neurology, CHU de Grenoble, Joseph Fourier University, 38043 Grenoble, France
2 INSERM, Unité 836, Grenoble Institut des Neurosciences, 38043 Grenoble, France
3 Université Lyon I, Hospices Civils de Lyon, Hôpital Neurologique Pierre Wertheimer, Service de Neurologie C, 69003 Lyon, France
4 CNRS, UMR 5229, Centre de Neurosciences Cognitives, 69003 Lyon, France
5 Neurosurgery Department, CHU de Grenoble, Joseph Fourier University, 38043 Grenoble, France
6 Université Lyon I, Hospices Civils de Lyon, Hôpital Neurologique Pierre Wertheimer, Service de Neurochirurgie A, 69003 Lyon, France
7 Centre d'Investigation Clinique CHU de Grenoble, Laboratoire TIMC-IMAG, CNRS, UMR 5525, Joseph Fourier University, Grenoble F-38041 France

*Present address: Clinatec, DRT/LETI, CEA-Grenoble, 38000 Grenoble, France
†Present address: Hôpitaux Universitaires de Genève, Service de Neurologie, 1211 Genève 14, Switzerland

Correspondence to: Eugénie Lhommée,
CHU de Grenoble,
Pavillon de neurology,
BP 217, 38043 Grenoble Cedex 9, France
E-mail: ELhommee@chu-grenoble.fr

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 ($P \leqslant 0.001$)

Received October 18, 2011. Revised February 2, 2012. Accepted February 3, 2012. Advance Access publication April 15, 2012

and reduction in on-euphoria ($P \leqslant 0.001$). There was an inversion in the number of patients functioning in an overall appetitive mode (29 before versus 2 after surgery, $P \leqslant 0.0001$) 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 $\geqslant$14) or depression (defined by the Beck Depression Inventory scale $\geqslant$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, punding, 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 $\geqslant 2$ associated with one or several of the nine following behavioural addictions items >2: excessive eating behaviour, creativity, hobbyism, punding, 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 $\geqslant 2$, all nine above-mentioned behavioural addiction items $\leqslant 2$.

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 ($\geqslant 2$), 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 $\geqslant 2$) 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 ($P \leqslant 0.0001$ for both comparisons, McNemar test; see Table 2). A Wilcoxon test also showed a significant decrease in non-motor OFFs and ONs ($P \leqslant 0.001$ 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 hypomaniac 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, $P \leqslant 0.001$ 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 ($P \leqslant 0.01$ for Beck Depression Inventory and $P \leqslant 0.001$ 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.

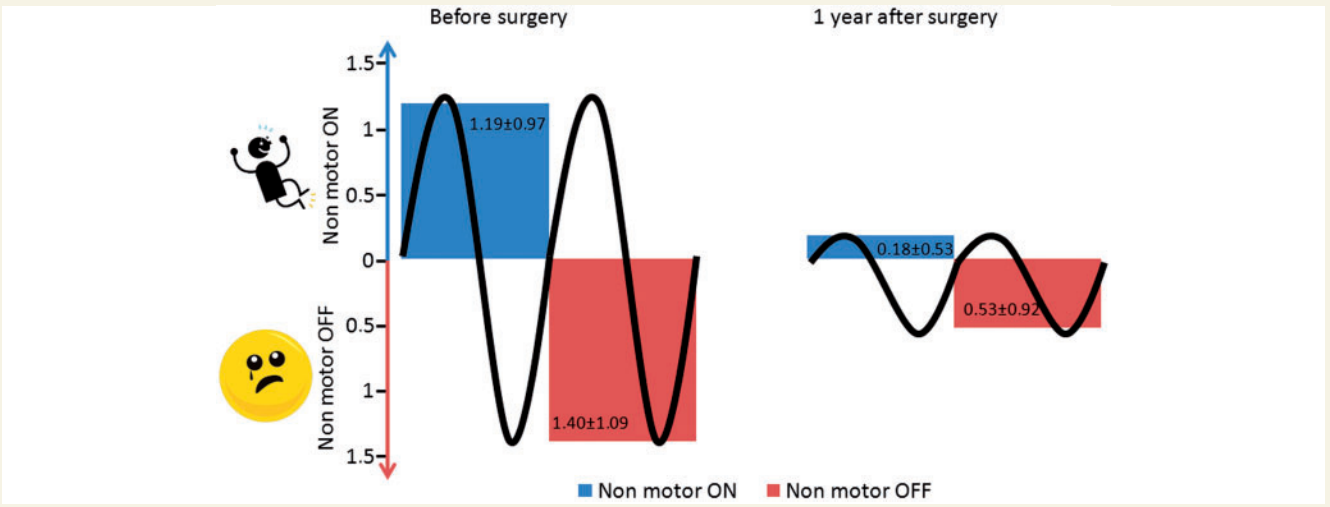

Figure 1 Non-motor fluctuations, Ardouin scale mean (±SD) severity scores (max = 4) at baseline and 1-year follow-up.

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).

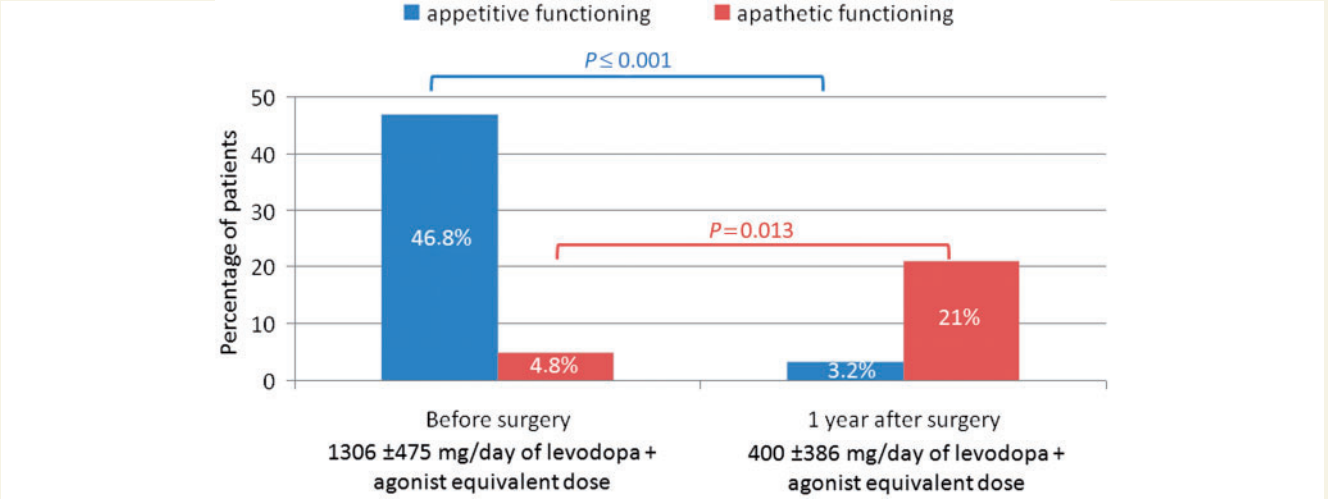

Figure 2 Ardouin scale apathetic and appetitive functioning modes. Data are expressed in percentages of patients with relevant item scores ⩾2 at baseline and 1-year follow-up.

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*., 2011*b*), 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 Ardouin 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 Ardouin 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 (Ardouin *et al*., 2009; Voon *et al*., 2011*a*). 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; Umemura *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 Ardouin 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 Ardouin 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 Ardouin 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 Ardouin scale, because Parkinson's disease depression does not have the same features as psychiatric depression (Gotham *et al*., 1986). The Ardouin 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 Ardouin 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 $\geqslant 2$).

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 Ardouin 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*., 2011*a*), 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.

References

Aarsland D, Marsh L, Schrag A. Neuropsychiatric symptoms in Parkinson's disease. Mov Disord 2009; 24: 2175–86.

Agid Y, Schupbach M, Gargiulo M, Mallet L, Houeto JL, Behar C, et al. Neurosurgery in Parkinson's disease: the doctor is happy, the patient less so? J Neural Transm Suppl 2006; 70: 409–14.

Ambermoon P, Carter A, Hall W, Dissanayaka N, O'Sullivan J. Compulsive use of dopamine replacement therapy: a model for stimulant drug addiction? Addiction 2011; 107: 241–7.

APA. Diagnostic and statistical manual of mental disorders. 4th edn. American Psychiatric Association; 1994.

APA. http://www.dsm5.org/proposedrevision/pages/proposedrevision.aspx?rid=210 (29 March 2012, date last accessed). Washington DC: DSM-5 Website development.

Ardouin C, Chereau I, Llorca PM, Lhommee E, Durif F, Pollak P, et al. [Assessment of hyper- and hypodopaminergic behaviours in Parkinson's disease]. Rev Neurol 2009; 165: 845–56.

Ardouin C, Voon V, Worbe Y, Abouazar N, Czernecki V, Hosseini H, et al. Pathological gambling in Parkinson's disease improves on chronic subthalamic nucleus stimulation. Mov Disord 2006; 21: 1941–6.

Ballanger B, van Eimeren T, Moro E, Lozano AM, Hamani C, Boulinguez P, et al. Stimulation of the subthalamic nucleus and impulsivity: Release your horses. Ann Neurol 2009; 66: 817–24.

Bandini F, Primavera A, Pizzorno M, Cocito L. Using STN DBS and medication reduction as a strategy to treat pathological gambling in Parkinson's disease. Parkinsonism Relat Disord 2007; 13: 369–71.

Baunez C, Nieoullon A, Amalric M. In a rat model of parkinsonism, lesions of the subthalamic nucleus reverse increases of reaction time but induce a dramatic premature responding deficit. J Neuroscience 1995; 15: 6531–41.

Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988; 56: 893–7.

Beck AT, Steer RA, Brown GK. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess 1996; 67: 588–97.

Bejjani BP, Arnulf I, Demeret S, Damier P, Bonnet AM, Houeto JL, et al. Levodopa-induced dyskinesias in Parkinsonïs disease: is sensitization reversible? Ann Neurol 2000; 47: 655–8.

Broen M, Duits A, Visser-Vandewalle V, Temel Y, Winogrodzka A. Impulse control and related disorders in Parkinson's disease patients treated with bilateral subthalamic nucleus stimulation: a review. Parkinsonism & Related Disorders 2011; 17: 413–7.

Brooks DJ, Doder M. Depression in Parkinson's disease. Curr Opin Neurol 2001; 14: 465–70.

Cardebat D, Doyon B, Puel M, Goulet P, Joanette Y. [Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level]. Acta Neurol Belg 1990; 90: 207–17.

Castelli L, Zibetti M, Rizzi L, Caglio M, Lanotte M, Lopiano L. Neuropsychiatric symptoms three years after subthalamic DBS in PD patients: a case-control study. J Neurol 2008; 255: 1515–20.

Czernecki V, Pillon B, Houeto JL, Pochon JB, Levy R, Dubois B. Motivation, reward, and Parkinson's disease: influence of dopatherapy. Neuropsychologia 2002; 40: 2257–67.

Czernecki V, Pillon B, Houeto JL, Welter ML, Mesnage V, Agid Y, et al. Does bilateral stimulation of the subthalamic nucleus aggravate apathy in Parkinson's disease? J Neurol Neurosurg Psychiatry 2005; 76: 775–9.

Czernecki V, Schupbach M, Yaici S, Levy R, Bardinet E, Yelnik J, et al. Apathy following subthalamic stimulation in Parkinson disease: a dopamine responsive symptom. Mov Disord 2008; 23: 964–9.

Daniele A, Albanese A, Contarino MF, Zinzi P, Barbier A, Gasparini F, et al. Cognitive and behavioural effects of chronic stimulation of the subthalamic nucleus in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2003; 74: 175–82.

De la Casa-Fages B, Grandas F. Dopamine dysregulation syndrome after deep brain stimulation of the subthalamic nucleus in Parkinson's disease. J Neurol Sci 2011. Advance Access published on November 2, 2011, doi:10.1016/j.jns.2011.08.014.

Demetriades P, Rickards H, Cavanna AE. Impulse control disorders following deep brain stimulation of the subthalamic nucleus in Parkinson's disease: clinical aspects. Parkinsons Dis 2011 2011; 658415.

Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 2006; 355: 896–908.

Djamshidian A, Averbeck BB, Lees AJ, O'Sullivan SS. Clinical aspects of impulsive compulsive behaviours in Parkinson's disease. J Neurol Sci 2011; 310: 183–8.

Drapier D, Drapier S, Sauleau P, Haegelen C, Raoul S, Biseul I, et al. Does subthalamic nucleus stimulation induce apathy in Parkinson's disease? J Neurol 2006; 253: 1083–91.

Evans AH, Katzenschlager R, Paviour D, O'Sullivan JD, Appel S, Lawrence AD, et al. Punding in Parkinson's disease: its relation to the dopamine dysregulation syndrome. Mov Disord 2004; 19: 397–405.

Fahn S, Elton RL, Fahn S, Marsden CD, Calne D, Goldstein M. Unified Parkinson's disease rating scale. Recent Developments in Parkinson's disease. Florham Park, NJ: MacMillan Health Care Information; 1987. p. 153–63.

Fasano A, Petrovic I. Insights into pathophysiology of punding reveal possible treatment strategies. Mol Psychiatry 2010; 15: 560–73.

Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med 2010; 362: 2077–91.

Frank MJ, Samanta J, Moustafa AA, Sherman SJ. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. Science 2007; 318: 1309–12.

Freeston MH, Ladouceur R, Thibodeau N, Gagnon F, Rheaume J. The Beck Anxiety Inventory. Psychometric properties of a French translation]. Encephale 1994; 20: 47–55.

Funkiewiez A, Ardouin C, Caputo E, Krack P, Fraix V, Klinger H, et al. Long-term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood and behaviour in Parkinson's disease. J Neurol Neurosurg Psychiatry 2004; 75: 834–9.

Funkiewiez A, Ardouin C, Cools R, Krack P, Fraix V, Batir A, et al. Effects of levodopa and subthalamic nucleus stimulation on cognitive and affective functioning in Parkinson's disease. Mov Disord 2006; 21: 1656–62.

Funkiewiez A, Ardouin C, Krack P, Fraix V, Van Blercom N, Xie J, et al. Acute psychotropic effects of bilateral subthalamic nucleus stimulation and levodopa in Parkinson's disease. Mov Disord 2003; 18: 524–30.

Giovannoni G, O'Sullivan JD, Turner K, Manson AJ, Lees AJ. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. J Neurol Neurosurg Psychiatry 2000; 68: 423–8.

Gotham AM, Brown RG, Marsden CD. Depression in Parkinson's disease: a quantitative and qualitative analysis. J Neurol Neurosurg Psychiatry 1986; 49: 381–9.

Grant JE. Impulse control disorders. New-York: Norton; 2008.

Grant JE, Potenza MN, Weinstein A, Gorelick DA. Introduction to behavioural addictions. Am J Drug Alcohol Abuse 2010; 36: 233–41.

Halbig TD, Tse W, Frisina PG, Baker BR, Hollander E, Shapiro H, et al. Subthalamic deep brain stimulation and impulse control in Parkinson's disease. Eur J Neurol 2009; 16: 493–7.

Hariz MI, Rehncrona S, Quinn NP, Speelman JD, Wensing C. Multicenter study on deep brain stimulation in Parkinson's disease: an independent assessment of reported adverse events at 4 years. Mov Disord 2008; 23: 416–21.

Herzog J, Reiff J, Krack P, Witt K, Schrader B, Muller D, et al. Manic episode with psychotic symptoms induced by subthalamic nucleus stimulation in a patient with Parkinson's disease. Mov Disord 2003; 18: 1382–4.

Holden C. 'Behavioural' addictions: do they exist? Science 2001; 294: 980–2.

Houeto JL, Mallet L, Mesnage V, Tezenas du Montcel S, Behar C, Gargiulo M, et al. Subthalamic stimulation in Parkinson disease: Behaviour and social adaptation. Arch Neurol 2006; 63: 1–6.

Houeto JL, Mesnage V, Mallet L, Pillon B, Gargiulo M, Tezenas du Moncel S, et al. Behavioural disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry 2002; 72: 701–7.

Kimber TE, Thompson PD, Kiley MA. Resolution of dopamine dysregulation syndrome following cessation of dopamine agonist therapy in Parkinson's disease. J Clin Neurosci 2008; 15: 205–8.

Knobel D, Aybek S, Pollo C, Vingerhoets FJ, Berney A. Rapid resolution of dopamine dysregulation syndrome (DDS) after subthalamic DBS for Parkinson disease (PD): a case report. Cogn Behav Neurol 2008; 21: 187–9.

Koob GF, Le Moal M. Drug abuse: Hedonic homeostatic dysregulation. Science 1997; 278: 52–8.

Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Dowsey Limousin P, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003; 349: 1925–34.

Krack P, Hariz MI, Baunez C, Guridi J, Obeso JA. Deep brain stimulation: from neurology to psychiatry? Trends Neurosci 2010; 33: 474–84.

Krack P, Kumar R, Ardouin C, Dowsey PL, McVicker JM, Benabid AL, et al. Mirthful laughter induced by subthalamic nucleus stimulation. Mov Disord 2001; 16: 867–75.

Krack P, Limousin P, Benabid AL, Pollak P. Chronic stimulation of subthalamic nucleus improves levodopa-induced dyskinesias in Parkinson's disease. Lancet 1997; 350: 1676.

Krack P, Pollak P, Limousin P, Benazzouz A, Deuschl G, Benabid AL. From off-period dystonia to peak-dose chorea: the clinical spectrum of varying subthalamic nucleus activity. Brain 1999; 122: 1133–46.

Krack P, Pollak P, Limousin P, Hoffmann D, Xie J, Benazzouz A, et al. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. Brain 1998; 121: 451–7.

Kramer JC, Fischman VS, Littlefield DC. Amphetamine abuse. Pattern and effects of high doses taken intravenously. JAMA 1967; 201: 305–9.

Kulisevsky J, Pagonabarraga J, Martinez-Corral M. Changes in artistic style and behaviour in Parkinson's disease: dopamine and creativity. J Neurol 2009; 256: 816–9.

Lardeux S, Pernaud R, Paleressompoulle D, Baunez C. Beyond the reward pathway: coding reward magnitude and error in the rat subthalamic nucleus. J Neurophysiol 2009; 102: 2526–37.

Lawrence AD, Evans AH, Lees AJ. Compulsive use of dopamine replacement therapy in Parkinson's disease: reward systems gone awry? Lancet Neurol 2003; 2: 595–604.

Le Jeune F, Drapier D, Bourguignon A, Peron J, Mesbah H, Drapier S, et al. Subthalamic nucleus stimulation in Parkinson disease induces apathy: a PET study. Neurology 2009; 73: 1746–51.

Lhommée E, Schmitt E, Bichon A, Krack P. Apathy and behavioural addictions in Parkinson's disease: two opposite sides of the same coin? Pratique Neurologique 2011; 2: 123–30.

Lim SY, O'Sullivan SS, Kotschet K, Gallagher DA, Lacey C, Lawrence AD, et al. Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson's disease. J Clin Neurosci 2009; 16: 1148–52.

Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 1998; 339: 1105–11.

Limousin P, Pollak P, Hoffmann D, Benazzouz A, Benabid AL. Abnormal involuntary movements induced by subthalamic nucleus stimulation in parkinsonian patients. Mov Disord 1996; 11: 231–5.

Luria AR. Higher cortical functions in man. New-York: Basic Books; 1966.

Mallet L, Mesnage V, Houeto JL, Pelissolo A, Yelnik J, Behar C, et al. Compulsions, Parkinson's disease, and stimulation. Lancet 2002; 360: 1302–4.

Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D, et al. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med 2008; 359: 2121–34.

Mallet L, Schupbach M, N'Diaye K, Remy P, Bardinet E, Czernecki V, et al. Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behaviour. Proc Natl Acad Sci USA 2007; 104: 10661–6.

Mamikonyan E, Siderowf AD, Duda JE, Potenza MN, Horn S, Stern MB, et al. Long-term follow-up of impulse control disorders in Parkinson's disease. Mov Disord 2008; 23: 75–80.

Marin RS. Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci 1991; 3: 243–54.

Mattis S, Bellak L, Karatsu TE. Mental status examination for organic mental syndrome in the elderly patient. Geriatr psychiatry 1976; 77–121.

McKeon A, Josephs KA, Klos KJ, Hecksel K, Bower JH, Michael Bostwick J, et al. Unusual compulsive behaviours primarily related to dopamine agonist therapy in Parkinson's disease and multiple system atrophy. Parkinsonism Relat Disord 2007; 13: 516–9.

Montel SR, Bungener C. Coping and quality of life of patients with Parkinson disease who have undergone deep brain stimulation of the subthalamic nucleus. Surg Neurol 2009; 72: 105–10; discussion 10–1.

Nelson HE. A modified card-sorting test sensitive to frontal lobe disease. Cortex 1976; 12: 53–60.

Okai D, Samuel M, Askey-Jones S, David AS, Brown RG. Impulse control disorders and dopamine dysregulation in Parkinson's disease: a broader conceptual framework. Eur J Neurol 2011; 18: 1379–83.

Okun MS, Foote KD. A mnemonic for Parkinson disease patients considering DBS: a tool to improve perceived outcome of surgery. Neurologist 2004; 10: 290.

O'Sullivan SS, Evans AH, Lees AJ. Dopamine dysregulation syndrome: an overview of its epidemiology, mechanisms and management. CNS Drugs 2009; 23: 157–70.

O'Sullivan SS, Wu K, Politis M, Lawrence AD, Evans AH, Bose SK, et al. Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. Brain 2011; 134: 969–78.

Perozzo P, Rizzone M, Bergamasco B, Castelli L, Lanotte M, Tavella A, et al. Deep brain stimulation of subthalamic nucleus: behavioural modifications and familiar relations. Neurol Sci 2001; 22: 81–2.

Pillon B, Dubois B, Lhermitte F, Agid Y. Heterogeneity of cognitive impairment in progressive supranuclear palsy, Parkinson's disease, and Alzheimer's disease. Neurology 1986; 36: 1179–85.

Rabinak CA, Nirenberg MJ. Dopamine agonist withdrawal syndrome in Parkinson disease. Arch Neurol 2010; 67: 58–63.

Rieu I, Chéreau I, Ardouin C, Pereira B, De Chazeron I, Tison F, et al. Mood and Behavioural evaluation in Parkinson's disease – Validation of a new scale. Supplement 1 to Parkinsonism and Related Disorders, Vol 18, 2012, Abstract CD 1.062.

Robinson TE, Berridge KC. The neural basis for drug craving: An incentive-sensitization theory of addiction. Brain Res Rev 1993; 18: 247–91.

Rodriguez RL, Fernandez HH, Haq I, Okun MS. Pearls in patient selection for deep brain stimulation. Neurologist 2007; 13: 253–60.

Rodriguez-Oroz MC, Lopez-Azcarate J, Garcia-Garcia D, Alegre M, Toledo J, Valencia M, et al. Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease. Brain 2011; 134: 36–49.

Romito LM, Raja M, Daniele A, Contarino MF, Bentivoglio AR, Barbier A, et al. Transient mania with hypersexuality after surgery for high frequency stimulation of the subthalamic nucleus in Parkinson's disease. Mov Disord 2002; 17: 1371–4.

Rouaud T, Lardeux S, Panayotis N, Paleressompoulle D, Cador M, Baunez C. Reducing the desire for cocaine with subthalamic nucleus deep brain stimulation. Proc Natl Acad Sci USA 2010; 107: 1196–200.

Sacks O. Awakenings. London: Pan Books Ltd; 1982.

Schmidt L, d'Arc BF, Lafargue G, Galanaud D, Czernecki V, Grabli D, et al. Disconnecting force from money: effects of basal ganglia damage on incentive motivation. Brain 2008; 131: 1303–10.

Schneider F, Habel U, Volkmann J, Regel S, Kornischka J, Sturm V, et al. Deep brain stimulation of the subthalamic nucleus enhances emotional processing in Parkinson's disease. Arch Gen Psychiatry 2003; 60: 296–302.

Schupbach M, Gargiulo M, Welter ML, Mallet L, Behar C, Houeto JL, et al. Neurosurgery in Parkinson disease: a distressed mind in a repaired body? Neurology 2006; 66: 1811–6.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The mini-international neuropsychiatric interview (MINI): the development and validation of a structured diagnostic interview for DSMIV and ICD-10. J Clin Psychiatry 1998; 59 (Suppl 20): 22–33; quiz 4–57.

Shore DM, Rafal R, Parkinson JA. Appetitive motivational deficits in individuals with Parkinson's Disease. Mov Disord 2011; 26: 1887–92.

Smeding HM, Goudriaan AE, Foncke EM, Schuurman PR, Speelman JD, Schmand B. Pathological gambling after bilateral subthalamic nucleus stimulation in Parkinson disease. J Neurol Neurosurg Psychiatry 2007; 78: 517–9.

Smeding HM, Speelman JD, Koning-Haanstra M, Schuurman PR, Nijssen P, van Laar T, et al. Neuropsychological effects of bilateral STN stimulation in Parkinson disease: a controlled study. Neurology 2006; 66: 1830–6.

Sohtaoglu M, Demiray DY, Kenangil G, Ozekmekci S, Erginoz E. Long term follow-up of Parkinson's disease patients with impulse control disorders. Parkinsonism Relat Disord 2010; 16: 334–7.

Spencer AH, Rickards H, Fasano A, Cavanna AE. The prevalence and clinical characteristics of punding in Parkinson's disease. Mov Disord 2011; 26: 578–86.

Stacy M, Bowron A, Guttman M, Hauser R, Hughes K, Larsen JP, et al. Identification of motor and nonmotor wearing-off in Parkinson's disease: comparison of a patient questionnaire versus a clinician assessment. Mov Disord 2005; 20: 726–33.

Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1992; 4: 134–9.

Thobois S, Ardouin C, Lhommée E, Klinger H, Lagrange C, Xie-Brustolin J, et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors, and underlying mesolimbic denervation. Brain 2010; 133: 1111–27.

Ulla M, Thobois S, Llorca PM, Derost P, Lemaire JJ, Chereau-Boudet I, et al. Contact dependent reproducible hypomania induced by deep brain stimulation in Parkinson's disease: clinical, anatomical and functional imaging study. J Neurol Neurosurg Psychiatry 2011; 82: 607–14.

Umemura A, Oka Y, Yamamoto K, Okita K, Matsukawa N, Yamada K. Complications of subthalamic nucleus stimulation in Parkinson's disease. Neurol Med Chir 2011; 51: 749–55.

Villa C, Pascual-Sedano B, Pagonabarraga J, Kulisevsky J. Impulse control disorders and dopaminergic treatments in Parkinson's disease. Rev Neurol 2011; 167: 827–32.

Volkmann J, Daniels C, Witt K. Neuropsychiatric effects of subthalamic neurostimulation in Parkinson disease. Nat Rev Neurol 2010; 6: 487–98.

Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F. Imaging dopamine's role in drug abuse and addiction. Neuropharmacology 2009; 56 (Suppl 1): 3–8.

Voon V, Fernagut PO, Wickens J, Baunez C, Rodriguez M, Pavon N, et al. Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. Lancet Neurol 2009; 8: 1140–9.

Voon V, Mehta AR, Hallett M. Impulse control disorders in Parkinson's disease: recent advances. Curr Opin Neurol 2011a; 24: 324–30.

Voon V, Gao J, Brezing C, Symmonds M, Ekanayake V, Fernandez H, et al. Dopamine agonists and risk: impulse control disorders in Parkinson's disease. Brain 2011b; 134: 1438–46.

Voon V, Krack P, Lang AE, Lozano AM, Dujardin K, Schupbach M, et al. A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease. Brain 2008; 131: 2720–8.

Voon V, Kubu C, Krack P, Houeto JL, Troster AI. Deep brain stimulation: neuropsychological and neuropsychiatric issues. Mov Disord 2006; 21 (Suppl 14): S305–27.

Weintraub D, Burn DJ. Parkinson's disease: the quintessential neuropsychiatric disorder. Mov Disord 2011; 26: 1022–31.

Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol 2010; 67: 589–95.

Williams A, Gill S, Varma T, Jenkinson C, Quinn N, Mitchell R, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. Lancet Neurol 2010; 9: 581–91.

Witjas T, Baunez C, Henry JM, Delfini M, Regis J, Cherif AA, et al. Addiction in Parkinson's disease: impact of subthalamic nucleus deep brain stimulation. Mov Disord 2005; 20: 1052–5.

Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, et al. Nonmotor fluctuations in Parkinson's disease: frequent and disabling. Neurology 2002; 59: 408–13.

Witt K, Daniels C, Reiff J, Krack P, Volkmann J, Pinsker MO, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. Lancet Neurol 2008; 7: 605–14.

Witt K, Khun J, Timmermann L, Zurowski M, Woopen C. Deep brain stimulation and the search for identity. Neuroethics 2011; 4, doi:10.1007/s12152-011-9100-1.

Witt K, Krack P, Deuschl G. Change in artistic expression related to subthalamic stimulation. J Neurol 2006; 253: 955–6.

Wu JC, Bell K, Najafi A, Widmark C, Keator D, Tang C, et al. Decreasing striatal 6-FDOPA uptake with increasing duration of cocaine withdrawal. Neuropsychopharmacol 1997; 17: 402–9.