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Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease

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Behavioural abnormalities such as impulse control disorders may develop when patients with Parkinson's disease receive dopaminergic therapy, although they can be controlled by deep brain stimulation of the subthalamic nucleus. We have recorded local field potentials in the subthalamic nucleus of 28 patients with surgically implanted subthalamic electrodes. According to the predominant clinical features of each patient, their Parkinson's disease was associated with impulse control disorders ($n = 10$), dyskinesias ($n = 9$) or no dopaminergic mediated motor or behavioural complications ($n = 9$). Recordings were obtained during the OFF and ON dopaminergic states and the power spectrum of the subthalamic activity as well as the subthalamo-cortical coherence were analysed using Fourier transform-based techniques. The position of each electrode contact was determined in the postoperative magnetic resonance image to define the topography of the oscillatory activity recorded in each patient. In the OFF state, the three groups of patients had similar oscillatory activity. By contrast, in the ON state, the patients with impulse control disorders displayed theta-alpha (4–10 Hz) activity (mean peak: 6.71 Hz) that was generated 2–8 mm below the intercommissural line. Similarly, the patients with dyskinesia showed theta-alpha activity that peaked at a higher frequency (mean: 8.38 Hz) and was generated 0–2 mm below the intercommissural line. No such activity was detected in patients that displayed no dopaminergic side effects. Cortico-subthalamic coherence was more frequent in the impulsive patients in the 4–7.5 Hz range in scalp electrodes placed on the frontal regions anterior to the primary motor cortex, while in patients with dyskinesia it was in the 7.5–10 Hz range in the leads overlying the primary motor and supplementary motor area. Thus, dopaminergic side effects in Parkinson's disease are associated with oscillatory activity in the theta-alpha band, but at different frequencies and with different topography for the motor (dyskinesias) and behavioural (abnormal impulsivity) manifestations. These findings suggest that the activity recorded in parkinsonian patients with impulse control disorders stems from the associative-limbic area (ventral subthalamic area), which is coherent with premotor frontal cortical activity. Conversely, in patients with L-dopa-induced dyskinesias such activity is recorded in the motor area (dorsal subthalamic area) and it is coherent with cortical motor activity. Consequently, the subthalamic nucleus appears to be implicated in the motor and behavioural complications associated with dopaminergic drugs in Parkinson's disease, specifically engaging different anatomo-functional territories.

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Abbreviations: ICD = impulse control disorders; LID = L-dopa-induced dyskinesias; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

The use of dopaminergic therapy for Parkinson's disease is associated with motor and behavioural side effects, of which L-dopa-induced dyskinesias (LID) and psychiatric complications are the most frequent and troublesome (Voon *et al.*, 2009). Psychiatric complications include impulse control disorders (ICD) such as compulsive gambling, excessive shopping, increased sexual and eating desire, stereotypic behaviours (typically punding and hobbyism) and the dopamine dysregulation syndrome characterized by addictive excessive dopaminergic therapy (Lawrence *et al.*, 2003; Bonvin *et al.*, 2007). These may occur in isolation or in different combinations causing severe disruption to the patient's family, social and emotional life. To improve these psychiatric abnormalities requires a reduction in dopaminergic treatment, although in practice this is limited by the worsening of the parkinsonian motor features. Deep brain stimulation of the subthalamic nucleus provides an improvement of the OFF parkinsonian state, allowing a significant reduction in the daily consumption of dopaminergic drugs (Rodriguez-Oroz *et al.*, 2005; Deuschl *et al.*, 2006). Dyskinesias are also improved, mainly related to dose reduction, and therefore as an indirect effect of surgery (Krack *et al.*, 1999; Vingerhoets *et al.*, 2002; Russmann *et al.*, 2004). Similarly, some retrospective studies (Witjas *et al.*, 2005; Bandini *et al.*, 2007; Knobel *et al.*, 2008) and a recent prospective study (Thobois *et al.*, 2010) have revealed that ICD can be improved after subthalamic nucleus deep brain stimulation provided a reduction of dopaminergic drugs is achieved. Negative results and controversy in this regard are probably explained by instances when patients remained on high doses of dopaminergic drugs (Lim *et al.*, 2009).

Subthalamic nucleus deep brain stimulation can also trigger abnormal impulsivity in patients with Parkinson's disease, such as hypersexuality (Romito *et al.*, 2002; Doshi and Bhargava, 2008), manic behaviour or shopping (Krack *et al.*, 2001; Kulisevsky *et al.*, 2002; Romito *et al.*, 2002; Herzog *et al.*, 2003; Mandat *et al.*, 2006; Mallet *et al.*, 2007; Raucher-Chene *et al.*, 2008) and increased impulsivity (Witt *et al.*, 2004; Frank *et al.*, 2007; Ballanger *et al.*, 2009). Interestingly, in some patients with Parkinson's disease with ICD induced by subthalamic nucleus deep brain stimulation, the abnormal behaviour was provoked by stimulation with a ventral contact of the electrode and suppressed by switching off this contact (Kulisevsky *et al.*, 2002; Mandat *et al.*, 2006; Mallet *et al.*, 2007; Raucher-Chene *et al.*, 2008). This abnormal behaviour was not observed when the active contact was a more dorsal one, which is in a position compatible with the motor region of the subthalamic nucleus (Rodriguez-Oroz *et al.*, 2001), while the greatest anti-parkinsonian benefits were achieved (Lanotte *et al.*, 2002; Starr *et al.*, 2002). In two such cases, the localization of the four contacts of the quadripolar electrode was ascertained with an interactive brain atlas to show that the hypomanic state was exclusively caused by stimulation through a ventral contact in the anteromedial subthalamic nucleus territory, which corresponds to the limbic area of the nucleus (Parent and Hazrati, 1995; Mallet *et al.*, 2007). These observations suggest a role for the subthalamic nucleus in impulse control and in the origin of impulsivity in patients with Parkinson's disease, as well as indicating an anatomo-functional division within the subthalamic nucleus that may underlie different clinical manifestations. Accordingly, the dorsal area would appear to be involved in parkinsonian motor features and the medioventral in behavioural aspects.

In patients with Parkinson's disease, the oscillatory activity of the subthalamic nucleus recorded through the electrodes implanted for deep brain stimulation displays dopamine-dependent changes whereby the OFF to ON motor state is signalled by a marked reduction in beta band activity (Brown, 2003). In addition, in patients with LID there is a peak at 4–10 Hz at the subthalamic nucleus (Alonso-Frech *et al.*, 2006). Here for the first time we report an oscillatory theta-alpha activity in the ventral subthalamic nucleus associated with ICD in patients with Parkinson's disease. This activity is distinct from that associated with LID and was also coherent with EEG activity recorded in frontal areas.

Materials and methods

Patients

Patients with Parkinson's disease, in whom electrodes for chronic stimulation had been bilaterally implanted in the subthalamic nucleus over the last five years, were studied. All patients fulfilled the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (Hughes *et al.*, 1992). The patients were classified into three groups: (i) patients with Parkinson's disease with ICD (Parkinson's disease-ICD) as the main complication of dopaminergic treatment, who had a history of no or only mild dyskinesias and who did not exhibit dyskinesias during the recording session; (ii) patients with Parkinson's disease with severe dyskinesias associated with chronic L-dopa treatment and no ICD (Parkinson's disease-LID), who had dyskinesias during the recording session in the ON state, as assessed by a neurologist (M.A. or M.C.R.) and (iii) patients with Parkinson's disease free of ICD or clinically relevant dyskinesias (Parkinson's disease-controls), who were offered surgery because of severe OFF episodes and gait freezing and in whom dyskinesias did not occur during the recording session.

The diagnosis of ICD was suspected when there was a clearly recognized history of behavioural disorders such as dopamine dysregulation syndrome, punding, hobbyism, gambling, shopping or increased sexuality or eating, which was directly related to dopaminergic treatment for >6 months prior to the assessment for surgery. In the surgical protocol, each patient was routinely asked about any abnormal behaviour and a psychiatrist evaluated all patients while under treatment with their usual medication prior to surgery. ICD was confirmed when patients fulfilled the diagnostic criteria for organic or 'functional'

mood disorders (International Classification of Diseases-10). Following such assessment, the administration of dopaminergic agonists was reduced or stopped and selective serotonin reuptake inhibitors and/or atypical antipsychotics were prescribed for 1–2 months in order to improve the behavioural abnormalities prior to surgery. Thus, ICD improved in most patients but remained present at the time of surgery. The Parkinson's disease Impulse-Compulsive Questionnaire (Weintraub *et al.*, 2009), which only became available during the study, was completed retrospectively by each patient to confirm the presence of ICD.

The global motor state was assessed preoperatively in all patients in OFF and ON conditions using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) and the LID status was assessed with a specific dyskinesia scale (Langston *et al.*, 1992; Goetz *et al.*, 1994). The L-dopa equivalent daily dose was calculated for each patient as follows: L-dopa/day dose (mg) = L-dopa (mg) + [L-dopa retard (mg) × 0.77]. In the case of entacapone/tolcapone co-administration, the L-dopa dose was multiplied by 1.33. For dopaminergic agonists, the formula used was [rotigotine (mg) × 5] + [ropinirole (mg) × 20] + [pramiprexole (mg) × 67] + [cabergoline (mg) × 67] + [pergolide (mg) × 100] (Grosset *et al.*, 2004).

A neuropsychological evaluation was administered preoperatively during the ON state to ensure that patients were not cognitively impaired (Rodriguez-Oroz *et al.*, 2009). Depression was also rated using the Yesavage Geriatric Depression Rating Scale (Yesavage *et al.*, 1982) to exclude patients with severe depression. The Ethics Committee for Medical Research approved the study and all patients provided their informed consent before entering the study. Three patients, two in the Parkinson's disease-LID group and one in the Parkinson's disease-control group, were included in a previous report (Alonso-Frech *et al.*, 2006).

Surgery

The procedure used was the one that has been routinely carried out by our group for several years (Guridi *et al.*, 2000; Rodriguez-Oroz *et al.*, 2001; see Supplementary material for details).

A Medtronic 3389 electrode with four active contacts (0, 1, 2 and 3 from ventral to dorsal and each 1.5 mm high at 0.5 mm intervals; total length 7.5 mm) was placed at the selected coordinates in the subthalamic nucleus with the most ventral contact (contact 0) placed in the ventral part of the nucleus. The clinical assessment of the efficacy and adverse effects of deep brain stimulation was performed intraoperatively before securing the electrode in the chosen position. The electrode was then fixed with a burr hole ring and cap and connected to percutaneous connectors with extension wires that exited through a small incision in the skin. The correct placement of the electrodes was corroborated in all subjects by postoperative MRI. Chronic stimulation (3.21 ± 0.82 V, 70.2 ± 16.5 μs, 178.4 ± 13.3 Hz) induced a mean reduction of 69.8% (SD 16%) in the OFF UPDRS-III score in the first year postoperatively, in general agreement with our own and other groups results (Rodriguez-Oroz *et al.*, 2000, 2004, 2005; Ostergaard *et al.*, 2002; Welter *et al.*, 2002; Krack *et al.*, 2003; Tamma *et al.*, 2003; Kleiner-Fisman *et al.*, 2006). Regarding the evolution of ICD, it was suppressed in six patients, improved in three and unchanged in one (Table 2). Monopolar stimulation using a single contact was applied in 33 nuclei (59% of the electrodes) and using two contacts in seven nuclei (Supplementary Table 1). Thus, monopolar stimulation was applied in 40 out of 56 nuclei (71.5% of the electrodes). Bipolar stimulation was used to avoid side effects, mainly dysarthria ($n = 4$), capsular stimulation with contralateral facial contraction ($n = 2$) and dyskinesias ($n = 5$), or because a higher motor benefit was encountered ($n = 5$). In addition, in three patients belonging to the ICD group, stimulation through the ventral contact induced a euphoric state, which reverted by switching off the stimulator. Stimulation through the dorsal contacts was used to avoid such misbehaviour.

Recording procedure and data acquisition

Signals were recorded 4–5 days after implantation of the electrodes in the subthalamic nucleus and before internalizing the connector cables and the implantable pulse generator. Subthalamic nucleus field potentials were recorded by connecting the different leads of the wire corresponding to each contact on the electrode to differential amplifiers using a custom-made cable and a sequential bipolar montage, giving a total of three channels per side (0–1, 1–2 and 2–3). In 15 patients studied prior to 2007, the subthalamic nucleus bipolar signal was filtered at 0.3–100 Hz, amplified 50 000-fold (Digitimer C-150, Welwyn Garden City, Hertfordshire, UK) and sampled at a frequency of 200 Hz. In the other 13 patients, the signal was filtered at 0.3–1000 Hz, amplified 50 000-fold and sampled at 2000 Hz. Five EEG channels (C3, Cz, C4, F3 and F4, referenced to both ear lobes) were obtained simultaneously. The C3, C4 and Cz electrodes overlie the sensorimotor cortex, including the primary motor cortex (M1) and the supplementary motor area, while the F3 and F4 electrodes are placed in a more anterior position overlying the premotor cortex but in close vicinity to the dorsolateral prefrontal cortex. The EEG signal was filtered using similar settings to those used in the subthalamic nucleus signals, amplified 20 000-fold (Brain Atlas amplifiers, Bio-logic Systems, Mundelein, IL, USA), and sampled at 200 Hz in 15 patients and at 2000 Hz in 13 patients. Both subthalamic nucleus and EEG signals were stored on a PC using Spike2 software and a CED 1401 plus A/D converter (Cambridge Electronic Design, Cambridge, UK).

Patients were first studied in the OFF motor state after overnight withdrawal of all anti-parkinsonian drugs (>12 h). None of the patients had severe or moderate rest tremor during the recording, probably due to the impact effect that is frequently observed in the first days after surgery. Subsequently, they were given the usual morning dose of L-dopa (150–250 mg) and studied again after reaching the ON motor state, as evaluated by a neurologist (M.A. or M.C.R.). The patients were instructed to stay awake, relaxing with their eyes open and to avoid voluntary movements during the initial 10 min of the recording (in the OFF state), as well as during a 10 min period after reaching the ON motor state. Signals were recorded continuously with Spike2 software during the rest periods. Two 5 min segments of OFF and ON resting activity were selected offline for further analyses (see below).

Signal analysis

All analyses were performed using MATLAB 7.7 software (Mathworks, Natick, MA, USA). Data corresponding to the 13 patients with a sampling frequency of 2000 Hz were first low-pass filtered at 100 Hz and subsequently down-sampled to match a common sampling rate of 200 Hz.

Power spectrum analysis

Time-evolving power spectra of subthalamic nucleus and EEG channels were estimated for all the patients in each motor state (OFF and ON), using the fast Fourier transform with blocks of 1024 samples, a Hanning window and a 75% overlap, until the whole recording was

analysed. The transforms obtained offered a resolution of ~0.2 Hz and 1 s. This makes it possible to obtain an estimation of the frequency distribution and the temporal evolution of the oscillatory activity for each patient in the OFF and ON motor states, hemispheres and recording channels. Thus each recording was reviewed and segments of activity recorded at rest over 300 s were selected for each patient in the OFF and ON motor states. We estimated the Welch periodogram (Halliday *et al.*, 1995) using non-overlapping sections of 1024 points and with a Hanning window, giving a resolution of ~0.2 Hz per bin. In these spectra, the mean power was measured in two different frequency bands: theta-alpha (4–10 Hz) and beta (12–30 Hz) in the ON and OFF motor states. With these values we calculated the relative mean ON to OFF power ratio in each band (mean power ON/mean power OFF). Relative power values were chosen instead of absolute power values in order to reduce inter-subject variability and facilitate the normalization of the data. We also measured the peak frequency of the spectral peaks that appeared in the spectrum of the theta-alpha range. We defined a peak when its power was >2 SD over the baseline spectrum.

Coherence analysis

We estimated the coherence between the different subthalamic nucleus channels and their corresponding ipsilateral EEG channels, as outlined previously (Halliday *et al.*, 1995). The coherency between two signals is a measure of their linear relationship at a specific frequency. The definition of coherency and its statistical analysis is given in the online supplementary material.

Only peaks with significant coherence values ($Z > 1.96$, $P < 0.05$) in a bandwidth of five bins (~1 Hz) in the theta-alpha band were considered and their frequency and magnitude measured.

Neuroimaging: location of electrode contacts

Preoperative (CT and MRI) and postoperative (MRI) images were converted to the ANALYZE format and the SPM2 program was used to co-register CT and MRI brain images from each patient pre- and postoperatively. To determine the location of the electrode, all images were processed with custom-designed software running under MATLAB 7.7. The nine rods of the stereotactic frame visible by CT were marked in order to orientate the images to the coordinates of the stereotactic frame (Saw *et al.*, 1987; Grunert, 1999; Li *et al.*, 1999). With respect to the mid-intercommissural point (anterior commissure–posterior commissure coordinates), the coordinates for each individual patient were determined from the frame's coordinates and a point within the interhemispheric cerebral fissure in the preoperative MRI, which define the mid-sagittal plane and its two orthogonal planes. The anterior commissure–posterior commissure midpoint was established as the origin of the anterior commissure–posterior commissure coordinates. Any other data point for MRI was also situated into the frame coordinates and transformed into the anterior commissure–posterior commissure coordinates via a transformation matrix (Taub, 2000). More details are given in the supplementary material and Supplementary Fig. 1.

Topographic analysis of local field potentials

In order to study the distribution of the theta-alpha activity (4–10 Hz) recorded in the subthalamic nucleus of patients with Parkinson's disease, we looked for phase reversals in contiguous channels of the subthalamic nucleus recordings. The presence of a phase reversal between two successive bipolar channels indicates that the activity observed with opposite polarity in both channels may have its origin around a common electrode (i.e. the activity with opposite polarity in channels 0–1 and 1–2 is probably generated around contact 1). Initially, the raw oscillatory activity around the theta-alpha peak frequency was band-pass filtered, using a 2 Hz bandwidth linear finite impulse response filter (2 Hz difference between the upper and lower cut-off frequencies). The Hilbert transform was then applied to calculate the phase time series associated with the filtered signal. We then calculated the phase difference between the adjacent channels recorded at each nucleus in order to detect the contact where the phase reversal of activity was located. To assess the statistical significance of the phase difference measurements, a Rayleigh test of uniformity of angle was used (Valencia *et al.*, 2006). According to the asymptotic formula, the significance of a value $c = \left\| (1/N) \sum_{i=1}^{N} e^{i\Phi_i} \right\|$ determined from N segments (each segment containing >5 cycles of the filtered signal) and where Φ_i is the phase difference in each single segment, can be calculated as e^{-Nc^2}.

The presence of a significant phase reversal (ideally a phase difference of 180° but which might vary depending on the angle of penetration of the electrode with respect to the generator) between the signal recorded in two adjacent contact pairs was used to locate the probable origin of theta-alpha activity in each nucleus. In some nuclei there was no phase reversal (the 3 channels were 'in phase') and in such instances either the most ventral (0–1) or the most dorsal (2–3) filtered channel had the highest amplitude (suggesting an origin at or beyond the external contacts 0 or 3). The location of the phase reversals together with the contact coordinates obtained in the image analysis allowed us to more accurately represent the topography of low-frequency oscillatory activity in the subthalamic nucleus.

Statistics

Statistical analyses were carried out with Statistical Package for the Social Sciences (SPSS) 15.0 software for Windows (SPSS Inc., Chicago, Illinois, USA) using the following tests:

(i) Clinical features: an ANOVA or a Kruskal–Wallis test (depending on whether the variables were normally distributed) was used to search for statistical differences between the clinical and demographic features of the three groups of patients.

(ii) Oscillatory activity power analysis: the transformation to the normal distribution described by van Albada and Robinson (2007) was used to normalize the relative power values in the ON to OFF motor states. Briefly, this transformation is based on the fact that a uniform distribution can be obtained from any continuous variable by computing its cumulative distribution function. Thus the normalization of non-Gaussian variables can be reached by the application of a function (inverse error function) that transforms a uniform distribution to a normal distribution. After normalization of the data, in each frequency band, a three-way ANOVA was used to compare the mean relative powers within the three different groups: Parkinson's disease-ICD, Parkinson's disease-LID and Parkinson's disease-controls (Factor 1: group), in both subthalamic nuclei (Factor 2: hemisphere) and at the three different contact pairs, dorsal (2–3), intermediate (1–2) and ventral (0–1) (Factor 3: dorsoventral axis).

(iii) Oscillatory activity peak frequency analysis: in the ON state, the frequency values of the spectral peaks in the theta-alpha band

from the Parkinson's disease-ICD and Parkinson's disease-LID groups were also normalized (van Albada *et al.*, 2007). Three-way ANOVA was then used to compare the differences in the peak frequency in the two sub-groups (Parkinson's disease-ICD and Parkinson's disease-LID), identifying peak activity at 6–10 Hz.

(iv) Cortico-subthalamic nucleus coherence analysis: subthalamic nucleus-EEG links with significant coherence values were divided into 12 groups depending on three factors, namely the groups of patients (Parkinson's disease-ICD, Parkinson's disease-LID and Parkinson's disease-controls); the frequency of the coherence peak (theta 4–7.5 Hz; alpha 7.5–10 Hz); and the cortical region where the EEG electrode had been placed (motor: C3, C4 and Cz, premotor-dorsolateral prefrontal cortex: F3 and F4). A contingency table was prepared with the data grouped in this way and the exact Fisher test was used to search for differences between the conditions included in the design. Finally, we studied the dorsoventral coordinates of the subthalamic nucleus pairs in the boxes which showed significant deviations from expected values.

Results

Twenty-eight patients with Parkinson's disease were included in the study; ten patients classified as Parkinson's disease-ICD, nine classified as Parkinson's disease-LID and nine classified as Parkinson's disease-controls (having neither ICD nor dyskinesias, refer to 'Methods' section for details). The general clinical characteristics of the patients are summarized in Table 1 (for individual details see Supplementary Table 1) and a summary of the behavioural abnormalities of the Parkinson's disease-ICD group is shown in Table 2. There were no differences in age ($F = 2.5$, $P = 0.1$), disease duration ($F = 2.4$, $P = 0.12$), UPDRS-III score in the OFF ($F = 0.3$, $P = 0.7$) and ON ($F = 3.7$, $P = 0.2$) motor states, L-dopa dose ($F = 0.59$, $P = 0.56$), treatment with dopamine agonists ($F = 0.86$, $P = 0.44$) or L-dopa equivalent daily dose ($F = 0.15$, $P = 0.87$) between the groups. Antipsychotic drugs and antidepressants were not significantly different in the three groups of patients (Fisher's exact test $P > 0.7$ for all comparisons). There were more male patients in the Parkinson's disease-ICD group.

Recordings were obtained from 19 subthalamic nuclei in the 10 patients in the Parkinson's disease-ICD group, 15 nuclei in the nine patients in the Parkinson's disease-LID group and 18 nuclei in the nine patients in the Parkinson's disease-control group. EEG recordings were analysed from nine patients in the Parkinson's disease-ICD group, eight patients in the Parkinson's disease-LID group and nine patients in the Parkinson's disease-control group. Other subthalamic nucleus (four nuclei in four patients) and EEG

Table 1 General characteristics of the patients

	Gender (male)	Age (years)	Disease duration (years)	UPDRS-III OFF	UPDRS ON	L-dopa/day (mg)[a]	Dopamine Agonist (mg)[b]	Total L-dopa equivalent daily dose (mg)[c]
Parkinson's disease-ICD ($n = 10$)	9	53.4 (11.4)	9.2 (3)	40.5 (12.5)	14.1 (5.9)	753.8 (606.3)	286.9 (297.3)	1040.7 (688.6)
Parkinson's disease-LID ($n = 9$)	4	61.7 (4.2)	15.9 (11)	42.7 (10.7)	11.3 (6.4)	986.1 (503.4)	183.7 (142)	1169.8 (530.6)
Parkinson's disease-Controls ($n = 9$)	6	58.7 (5.2)	10.8 (3.4)	38.1 (12.3)	9 (6.5)	745.2 (334.6)	278.5 (205.9)	1023.7 (464.9)

Values are stated as mean (SD).
a The L-dopa/day dose (mg) was calculated as follows: L-dopa (mg) + L-dopa retard (mg) × 0.77. In case of entacapone/tolcapone co-administration the L-dopa dose was multiplied by 1.33.
b Dopamine agonist = L-dopa equivalents of dopaminergic agonists. The formula used was: [rotigotine (mg) × 5] + [ropinirole (mg) × 20] + [pramiprexole (mg) × 67] + [cabergoline (mg) × 67] + [pergolide (mg) × 100].
c Total L-dopa equivalent daily dose = dopaminergic agonists + L-dopa.

Table 2 Summary of the behavioural abnormalities in patients with Parkinson's disease and ICD evaluated with the Parkinson's disease Impulse-Compulsive Questionnaire and the effect of the surgery

Patient	Gambling	Buying	Sex	Eating	DDS	Hobbying and punding	Walkabout	Effect of surgery
ICD1	+	+	+	–	+	–	–	Suppressed
ICD2	+	–	–	–	–	+ (computers/play guitar)	–	Suppressed
ICD3	+	+	–	–	+	–	–	Suppressed[a]
ICD4	–	+	+	+ (binge eating of sweets)	+	+ (collecting watches)	+	Remaining walkabout
ICD5	+	–	+	+	–	+ (hunting)	–	Remaining hunting and sex
ICD6	–	–	+	–	+	+ (writing novels and poetry, computers, checking mail)	–	Suppressed[a]
ICD7	+	+	+	–		–	–	Reduced severity
ICD8	–	–	–	–	–	+ (Cleaning)	–	Suppressed
ICD9	–	+	–	–	–	–	–	Suppressed
ICD10	–	–	–	–	+	–	–	Not improved

DDS = Dopamine dysregulation syndrome.
a Mild abnormal impulsivity reappeared when dopaminergic treatment was transiently increased.

recordings (one patient in the Parkinson's disease-ICD group and one in the Parkinson's disease-LID group) were disregarded because of a low signal-to-noise ratio due to technical issues that arose during recording.

Supplementary Fig. 2 shows the topographical distribution of the different electrode contacts in the three groups of patients along the dorsoventral axis. There was a small difference in positioning between the LID group and the other two groups, with the electrodes in patients with dyskinesia 0.7–1 mm more dorsal ($F = 8.182$, $P < 0.001$). However, there was no difference between the three groups in the coordinates of the contacts used for stimulation ($F = 0.94$, $P = 0.4$).

Power spectrum of the oscillatory activity

The OFF motor state showed a typical homogenous pattern in the power spectrum analysis for the three groups of patients. Two frequency peaks dominated the spectrum in the beta range, one in the low-beta (12–20 Hz) and another in the high-beta range (20–30 Hz: Fig. 1A and left side of Fig. 2).

Likewise, in the ON motor state, the gamma band (55–100 Hz) was also similar for the three groups of patients. In the subthalamic nucleus of patients with Parkinson's disease, a gamma activity band has previously been associated with the ON state (Brown *et al.*, 2001; Lopez-Azcárate, 2010), although an increase in the gamma band is not always observed during the ON period (Alonso-Frech *et al.*, 2006). In this study, the gamma peak in the ON state was only evident in a few patients (2 out of 10 in the Parkinson's disease-ICD group, 3 out of 9 in the Parkinson's disease-LID group and 2 out of 9 in the Parkinson's disease-controls group). Thus, no correlation between increased gamma activity and LID or ICD could be established. By contrast, changes in the theta-alpha range were detected in the ON motor state that appeared to be specific to each clinical group of patients with Parkinson's disease.

Parkinson's disease-impulse control disorders

In the ON state, a spectral peak appeared in the theta-alpha range (Figs 1B and 2A, right) that had a mean peak frequency of 6.71 Hz (SD = 1.05 Hz; Fig. 3). The temporal evolution of the power spectrum of the oscillatory activity in the (0–40 Hz) range is illustrated in Fig. 2A for the most ventral contact pair (0–1) of a representative patient (Patient PD-ICD-3) in both the OFF and ON states. The attenuation in the low-beta band and the increase in the theta-alpha band (5.8 Hz in this case) in the ON state is clearly evident.

Parkinson's disease L-dopa-induced dyskinesias

When dyskinesia was experienced in the ON state, a peak in the spectrum was found in the theta-alpha range with a mean frequency of 8.38 Hz (SD = 0.88 Hz; Fig. 1B). The frequency of this peak was significantly higher than the frequency of the peak found in the Parkinson's disease-ICD group (Fig. 3). A recording from the central contacts (pair 1–2) of the subthalamic nucleus in a representative patient (Patient PD-LID-8) illustrates the typical beta suppression and the appearance of a band of activity at 7.5 Hz (Fig. 2B, right).

Parkinson's disease-controls

The ON state of these patients was characterized by the typical low beta attenuation alone (Fig. 1B). No theta-alpha band activity was observed when the OFF and ON states of a typical patient

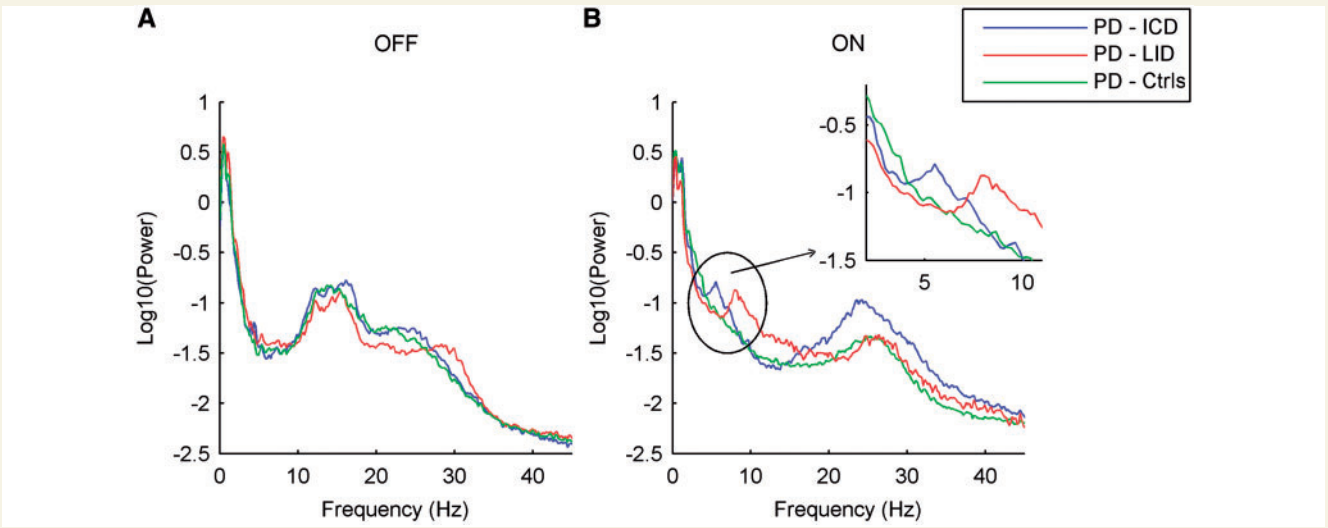

Figure 1 Mean power spectrum in the 0–45 Hz range (logarithmic scale) at all contact pairs in the three groups of patients [Parkinson's disease-ICD (PD-ICD), $n = 19$ nuclei; Parkinson's disease-LID (PD-LID), $n = 15$ nuclei; Parkinson's disease-controls (PD-Ctrls), $n = 18$ nuclei]. In the OFF state (**A**), the spectra of the three groups are similar, mainly characterized by the presence of two peaks in the beta range (12–30 Hz). In the ON state (**B**), apart from the common decrease in the low-beta range, a theta peak (~6.71 Hz) appears in the Parkinson's disease-ICD group and an alpha peak (~8.38 Hz) in the Parkinson's disease-LID group. No theta-alpha peak is present in the Parkinson's disease-control group.

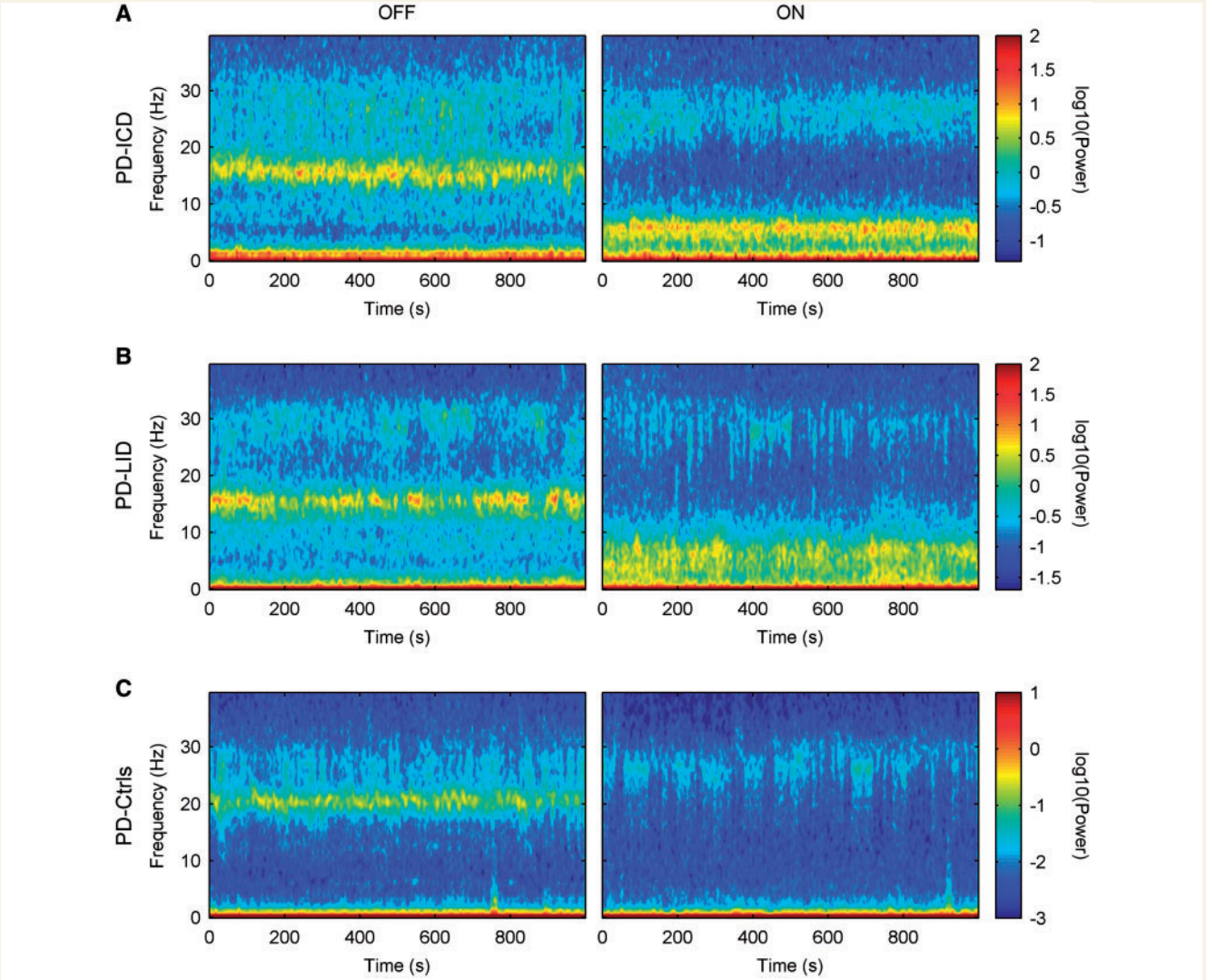

Figure 2 Temporal evolution of the power spectrum in the 0–40 Hz range in both motor states during rest periods (OFF and ON). (**A**) Patient PD-ICD-3 (left subthalamic nucleus, contacts 0–1). (**B**) Patient PD-LID-8 (left subthalamic nucleus, contacts 1–2). (**C**) PD-Ctrl-5 (right subthalamic nucleus, contacts 1–2).

without ICD or LID were compared. It is shown for the central contact pair (1–2) of a representative patient (Patient PD-Ctrl-5) in Fig. 2C.

Statistical analysis of the power and frequency of the alpha-theta peak

The changes in power from the OFF to ON motor state for the different activity bands were assessed by three way ANOVA. Since there was no relative power difference between the groups for the beta band, the theta-alpha band was the only activity band that behaved differently depending on the patient group. The overall ANOVA revealed a significant effect of group factor (Parkinson's disease-ICD, Parkinson's disease-LID or Parkinson's disease-controls: $F = 61.69$, $P < 0.0001$), while there was no difference for the subthalamic nucleus in the right/left hemispheres ($F = 3.28$, $P = 0.072$) nor for the dorsoventral axis ($F = 0.32$, $P = 0.73$). *Post hoc* analysis revealed that both the Parkinson's disease-ICD and Parkinson's disease-LID groups presented a significantly higher relative power in the theta-alpha range compared to the Parkinson's disease-control group, although there was no difference in power between patients with Parkinson's disease with LID and ICD.

When the differences in the theta-alpha peak frequency between the Parkinson's disease-ICD and Parkinson's disease-LID groups were assessed by three way ANOVA (the two groups that showed a spectral peak in this frequency range), the theta-alpha peak frequency was significantly higher in the Parkinson's disease-LID group than in the Parkinson's disease-ICD group (factor: group, $F = 63.12$; $P < 0.0001$; Fig. 3).

Topography of the theta-alpha activity

The intranuclear location of each contact pair in the dorsoventral axis of the nucleus might differ among patients. Therefore we

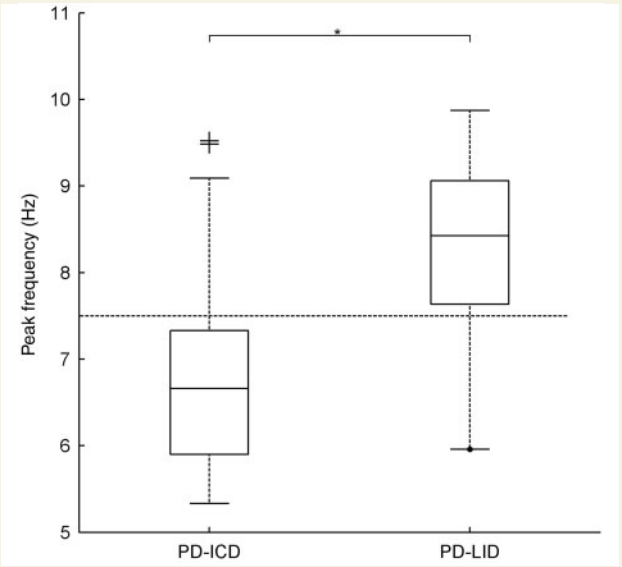

Figure 3 Boxplot of the theta-alpha peak frequency in both Parkinson's disease-ICD (PD-ICD) and Parkinson's disease-LID (PD-LID) groups. A peak at ~6.71 Hz is observed in the Parkinson's disease-ICD group whereas a different peak at ~8.38 Hz is present in the Parkinson's disease-LID group. *$P < 0.001$.

used the location of the phase reversal based on the postoperative MRI analysis as a better topographical indicator of the origin of the activity. The topographical distribution of theta-alpha band was analysed in patients with Parkinson's disease with ICD and LID based on the localization of the electrode contacts where this activity was generated according to the phase reversal (Fig. 4). Accordingly, this activity was mainly generated in the ventral contacts in the Parkinson's disease-ICD group, while it was found in the dorsal contacts in the Parkinson's disease-LID group (Fig. 5A). Indeed, the topography of this band differed in each group (Fig. 5B) and while in the Parkinson's disease-ICD group the theta-alpha activity was generated in the ventral-intermediate portion of the subthalamic area (from −2 to −8 mm from the intercommissural line), this activity had a clear dorsal distribution in the Parkinson's disease-LID group (from 0 to −2 mm from the intercommissural line) (*t*-test for independent samples, $P < 0.0001$).

Cortico-subthalamic coherence (4–10 Hz band)

Coherence between the different subthalamic nucleus recording channels and their corresponding ipsilateral EEG channels was studied in the three groups of patients with Parkinson's disease. Significant coherence values in the theta-alpha range of the EEG-subthalamic nucleus pairs were observed in the three groups, although more commonly in the Parkinson's disease-ICD and Parkinson's disease-LID groups. The subthalamic nucleus-EEG pairs with significant coherence values in the theta-alpha band (4–10 Hz) were grouped in a contingency matrix depending on the clinical group (Parkinson's disease-ICD, Parkinson's disease-LID and Parkinson's disease-controls) and according to the theta-alpha peak frequency that differed between the Parkinson's disease-ICD and Parkinson's disease-LID groups. Indeed, pairs with significant coherence values could be classified depending on the peak frequency of coherence: theta 4–7.5 Hz and alpha 7.5–10 Hz (Fig. 3, Table 3). Finally, the subthalamic nucleus-EEG pairs could be grouped according to the position of the EEG electrode in the pair (motor: C3, C4 and Cz, or premotor/dorsolateral prefrontal cortex: F3 and F4).

From the contingency matrix with the observed and expected number of significant pairs, a Fisher's exact test revealed overall significant differences between the groups ($F = 15.664$, $P = 0.01$; Table 3). The data revealed more EEG-subthalamic nucleus pairs with significant coherence in the 4–7.5 Hz range for the Parkinson's disease-ICD group than was expected, an increase mainly found in the subthalamic nucleus-premotor/dorsolateral prefrontal cortex-EEG pairs. By contrast, there were more significantly coherent pairs than expected in the Parkinson's disease-LID group between the subthalamic nucleus and the motor cortex in the 7.5–10 Hz band. The dorsoventral coordinates of the subthalamic nucleus contacts in the Parkinson's disease-ICD group that were coherent at 4–7.5 Hz with frontal EEG channels (mean: −3.35 mm) were significantly more ventral than the coordinates of the contacts in the Parkinson's disease-LID group coherent with central EEG leads at 7.5–10 Hz (mean: −1.88 mm; $t = -2.43$, $P = 0.02$).

Discussion

In this study, a specific oscillatory activity in the theta-alpha band (4–7.5 Hz) with a peak at 6.71 Hz has been identified in patients with ICD, indicating that the subthalamic nucleus is involved in ICD induced by dopaminergic treatment in patients with Parkinson's disease. This activity was recorded 2–8 mm below the intercommissural line, which includes the ventral, subthalamic associative-limbic sub-region of the subthalamic nucleus. Moreover, there is coherent activity between the subthalamic nucleus and cortex, with the strongest subthalamic nucleus-EEG coherence present in the 4–7.5 Hz range and over skull electrodes roughly corresponding to the premotor/dorsolateral prefrontal cortex areas. These findings differ from the activity recorded in the Parkinson's disease-LID group that had a higher frequency (mean 8.38 Hz, range 7.5–10 Hz). In addition, the peak activity in the Parkinson's disease-LID group was recorded from electrodes located 0–2 mm below the intercommissural line compatible with the dorsal motor region of the subthalamic nucleus, and subthalamic nucleus-EEG coherence was found for electrodes close to the primary motor and supplementary motor area cortices in the 7.5–10 Hz range. Accordingly, we believe that this theta-alpha activity may serve as a physiological marker for ICD in Parkinson's disease, differing from that previously reported for LID.

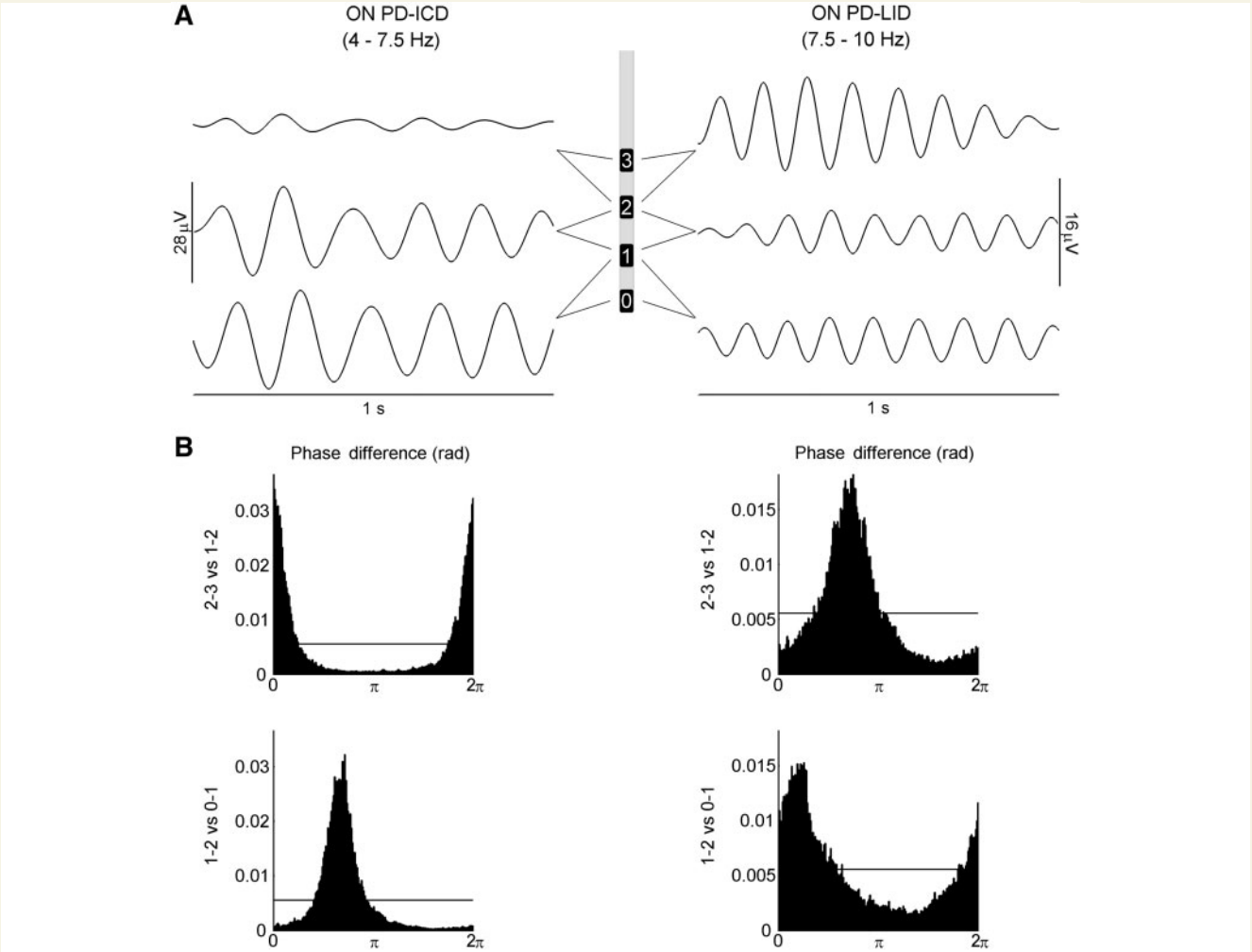

Figure 4 (**A**) Filtered local field potentials from two patients in the ON motor state [Parkinson's disease-ICD (PD-ICD) on the left and Parkinson's disease–LID (PD-LID) on the right] highlighting the phase reversal of the theta-alpha activity around contact 1 in the patient from the Parkinson's disease-ICD group and around contact 2 in the patient from the Parkinson's disease-LID group. (**B**) Statistical analysis of the phase difference (360 bins histogram, 300 s segment) from the same patients showing the phase reversal (peak in the histogram near π radians) between contact pairs 1–2 and 0–1 in the patient from the Parkinson's disease-ICD group (left). A phase reversal is also shown for the patient in the Parkinson's disease-LID group but between contact pairs 2–3 and 1–2 (right). The horizontal lines indicate the mean phase difference in an ideally random distribution.

Impulse control disorders and theta-alpha oscillatory activity in the subthalamic nucleus

Chronic dopaminergic treatment can induce motor and non-motor side effects, mainly LID and ICD. Indeed, in recent years there has been growing recognition of the incidence of ICD, probably related to the increased use of dopamine agonists (Grosset *et al.*, 2006; Lu *et al.*, 2006; Voon *et al.*, 2006; Weintraub *et al.*, 2006; Evans and Butzkueven, 2007; McKeon *et al.*, 2007; Quickfall and Suchowersky, 2007; Tippmann-Peikert *et al.*, 2007). It has been well established that neuronal activity in the subthalamic nucleus varies in Parkinson's disease according to medication state. Hence in the OFF state, the power of the beta band (12–30 Hz) is largest, whereas in the ON motor state, the gamma (60–100 Hz) band (Brown *et al.*, 2001; Brown, 2003; Gatev *et al.*, 2006) predominates. However, in patients exhibiting LID there is also 4–10 Hz oscillatory activity in the subthalamic nucleus (Alonso-Frech *et al.*, 2006). Despite the well-characterized OFF/ON changes associated with motor fluctuations and dyskinesias, there is hitherto no physiological hallmark for ICD in patients with Parkinson's disease. We now demonstrate that L-dopa induces specific, low frequency oscillatory activity in the theta-alpha band (4–7.5 Hz), with a peak at 6.71 Hz in patients with Parkinson's disease and ICD.

The involvement of the subthalamic nucleus in non-motor, behavioural aspects related to impulsivity and disinhibition has been documented in humans and animals. Lesion of the subthalamic nucleus by infarction or tumour is associated with behavioural alterations characterized by agitation, manic states and logorrhoea,

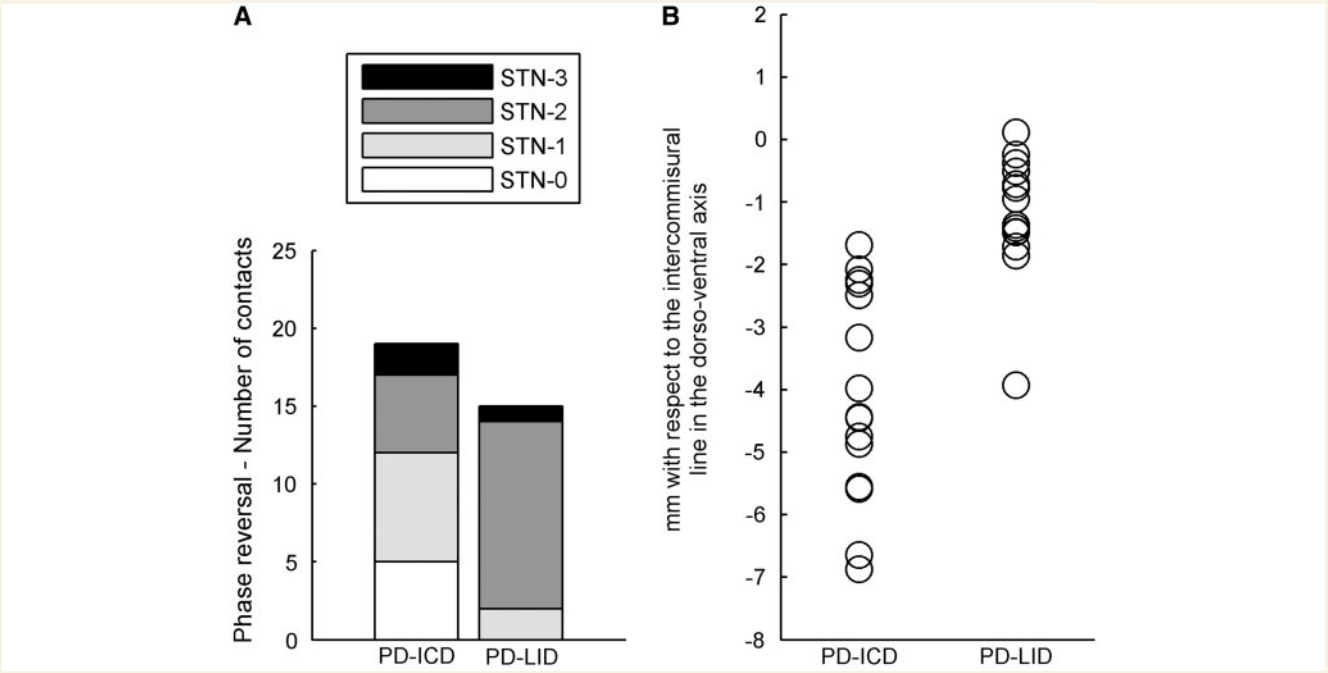

Figure 5 (**A**) Localization of the phase reversals for the different electrode contacts. In 12 out of 19 nuclei in the Parkinson's disease-ICD (PD-ICD) group, the theta-alpha activity was generated at the two most ventral contacts (0 and 1), while in 13 out of 15 nuclei in the Parkinson's disease-LID (PD-LID) group it was generated at the dorsal contacts (3 and 2). (**B**) Phase reversal contact coordinates in the dorsoventral axis with respect to the intercommisural line, highlighting the different topography according to the patient classification. STN = subthalamic nucleus.

Table 3 Contingency matrix with the observed and expected number of significant coherent pairs in the theta and alpha frequency ranges (4–7.5 Hz and 7.5–10 Hz) between the subthalamic and the cortical EEG activity when the leads are positioned overlying the primary motor/supplementary motor areas (C3, C4, Cz) or the more anterior premotor/dorsolateral prefrontal cortex areas (F3, F4)

		PD-ICD	PD-LID	PD-CTRL	Row totals
4–7.5 Hz – C3, C4, Cz	Observed	4	1	4	9
	Expected	3.2	3	2.8	
4–7.5 Hz – F3, F4	Observed	**8**	0	1	9
	Expected	**3.2**	3.0	2.8	
7.5–10 Hz – C3, C4, Cz	Observed	12	**22**	15	49
	Expected	17.4	**16.3**	15.3	
7.5–10 Hz – F3, F4	Observed	10	9	10	29
	Expected	10.3	9.7	9.1	
	Column Totals	34	32	30	96

PD-CTRL = Parkinson's disease-controls; PD-ICD = Parkinson's disease-ICD; PD-LID = Parkinson's disease-LID. Fisher's exact test: $F = 15.664$, $P = 0.01$. Bold boxes: cases in which the difference between the observed and the expected values are significant.

with or without accompanying hemiballismus (Martin, 1927; Trillet, 1995). More recently, deep brain stimulation of the subthalamic nucleus in patients with Parkinson's disease has been associated with ICD and behavioural disinhibition (Krack *et al.*, 2001; Kulisevsky *et al.*, 2002; Romito *et al.*, 2002; Herzog *et al.*, 2003; Witt *et al.*, 2004; Mandat *et al.*, 2006; Frank *et al.*, 2007; Mallet *et al.*, 2007; Doshi and Bhargava, 2008; Raucher-Chene *et al.*, 2008) and hyperactive behaviours have been reported after lesion of the subthalamic nucleus in some patients with Parkinson's disease (i.e. disinhibition, hypomania, excessive cheerfulness, talkativeness) (Alvarez *et al.*, 2005). In rats, subthalamic nucleus lesion increases the premature responses during anticipation of a visual target in a five-choice serial reaction time task and in other attention paradigms (Baunez and Robbins, 1997; Phillips and Brown, 2000), as well as increasing locomotor activity conditioned to feeding (Baunez *et al.*, 2002). Moreover, subthalamic neurons in rats and monkeys modify their firing frequency in response to reward related tasks, and in humans the subthalamic nucleus region is activated during the performance of an inhibition task (Aron and Poldrack, 2006; Li *et al.*, 2008). Together, these data indicate that the subthalamic nucleus also participates in the control of non-motor events, such as impulsivity. The specific oscillatory activity identified here in the subthalamic nucleus of patients with Parkinson's disease and ICD is consistent with the abundant clinical and experimental data demonstrating that the subthalamic nucleus is not only a structure involved in motor features of Parkinson's disease, but also engaged in behavioural control and ICD.

Topography of the low-theta activity

The 4–7.5 Hz activity in the Parkinson's disease-ICD group was mainly recorded from ventral contacts and it was coherent with

cortical activity recorded in premotor/dorsolateral prefrontal cortex electrodes. By contrast, the activity in the Parkinson's disease-LID group (7.5–10 Hz) was recorded from the most dorsal subthalamic nucleus contacts and it was coherent with central EEG scalp electrodes (primary motor cortex/supplementary motor area). The different topography of the oscillatory activity according to the main dopaminergic complication (LID or ICD) depends on the accuracy of the method used postoperatively to locate the contacts of the electrode. We tried to minimize this shortcoming by using image analysis to accurately determine the coordinates of each contact. While some degree of error may still exist in calculating the coordinates of each contact implanted in the subthalamic nucleus, we believe that the relative position of the contacts was sufficiently reliable to establish a definite correlation between oscillatory activity and the recording sites in the dorsoventral axis. Similarly, there may be concerns about the cortical area recorded through the EEG contacts. The exact anatomical region corresponding to each EEG electrode cannot be defined, although it is generally accepted that the activity recorded through contacts C3, C4 and Cz mainly originates in the primary motor cortex and supplementary motor area, whereas the F3 and F4 electrodes correspond to the premotor cortex and dorsolateral prefrontal cortex. The different topography of the EEG-subthalamic nucleus coherence at 4–7.5 Hz and 7.5–10 Hz in the cortex does fit with the data available regarding impulse inhibition and LID. Functional studies measuring regional cerebral blood flow with positron emission tomography have shown that the premotor cortex (among other areas) is activated less in patients with Parkinson's disease with subthalamic nucleus stimulation who display reduced response inhibition (Ballanger *et al.*, 2009) and, during a task requiring response inhibition, dorsolateral prefrontal cortex activation is also reduced (Thobois *et al.*, 2007). By contrast, the motor circuit (including the primary motor cortex and supplementary motor area) is more strongly activated in patients with Parkinson's disease and LID than in patients not exhibiting this complication (Rascol *et al.*, 1998; Brooks *et al.*, 2000). Thus, the coherent activity at 4.5–7 Hz recorded in the more anterior frontal areas appears to be specific and it contrasts with the dyskinetic activity at 7.5–10 Hz found in primary motor and supplementary motor area cortical regions.

These findings are perfectly compatible with the anatomo-functional division of the subthalamic nucleus (Wichmann *et al.*, 1994; Parent and Hazrati, 1995; Lardeux *et al.*, 2009) and with observations suggesting that the ventral subthalamic nucleus is involved in abnormal behaviour in Parkinson's disease while the dorsal subthalamic nucleus is related to motor aspects. Thus, ICD or manic episodes can be induced by subthalamic nucleus stimulation with a ventral contact of the electrode, an effect that is reversed after switching off this contact. In contrast, stimulation through more dorsal contacts (Kulisevsky *et al.*, 2002; Mandat *et al.*, 2006; Mallet *et al.*, 2007; Raucher-Chene *et al.*, 2008) usually provides maximum anti-parkinsonian benefit (Lanotte *et al.*, 2002; Starr *et al.*, 2002) without behavioural side effects. Moreover, dyskinesias can also be triggered by stimulation mainly in the dorsal area of the subthalamic nucleus (Zheng *et al.*, 2010) There are also electrophysiological data supporting the involvement of the ventral area in affective and cognitive matters (Brucke *et al.*, 2007). Neurons that modify their firing frequency in response to reward tasks in the rat and monkey are located in the medioventral half of the subthalamic nucleus (Matsumura *et al.*, 1992; Darbaky *et al.*, 2005; Lardeux *et al.*, 2009), in contrast to those responding to motor stimulus in the dorsal region (Wichmann *et al.*, 1994; Rodriguez-Oroz *et al.*, 2001). Moreover, local field potential recordings in patients with Parkinson's disease show that emotional stimulus led to a decrease in the alpha power recorded mainly in the ventral subthalamic nucleus (Brucke *et al.*, 2007), whereas active movement led to a decrease in the beta power recorded in the dorsal subthalamic nucleus (Alegre *et al.*, 2005). Indeed, subthalamic nucleus lesions in monkeys provoking dyskinesias are located in the dorsal subthalamic nucleus while those in the ventromedial region induce abnormal behaviour (Crossman *et al.*, 1984; Baron *et al.*, 2002).

Relationship between dyskinesias and impulse control disorders

In patients with Parkinson's disease, both LID and ICD are associated with specific changes in subthalamic nucleus oscillatory activity in the alpha-theta band that differ in terms of peak frequency and the territory where this activity is generated. We previously described a 4–10 Hz oscillatory activity in the subthalamic nucleus (Alonso-Frech *et al.*, 2006) associated with LID during recording. This activity was not so clearly confined to the dorsal region and in 45% of recordings the major change in the 4–10 Hz band occurred at ventral sites. By contrast, we find here that LID-related oscillations are by and large confined to the dorsal portion of the subthalamic nucleus. This discrepancy may be explained by a more detailed examination of the predominant clinical features of the patients and their assessment in the present work than in the earlier study (Alonso-Frech *et al.*, 2006). At that time, impulsivity was not well recognized as a clinical problem and it was not a major reason for surgery. Hence, while this may have been a clinical feature in some of these patients, it might not have been sufficiently severe to be noted. In addition, an accurate definition of the relative position of the contacts within the electrode was not available at that time. Thus, the topography of the recorded activity was not as precisely defined as in the present report. It is also noteworthy that impulsive behaviour disorders in patients with Parkinson's disease often coincide with LID (Silveira-Moriyama *et al.*, 2006) and in patients with Parkinson's disease treated with bilateral subthalamic nucleus lesions; choreic movements, as well as hyperactive and impulsive behaviours, evolve together temporally, appearing and vanishing in the same time-frame (Alvarez *et al.*, 2005). In our patients, the frequency of the oscillatory activity recorded overlaps in both subgroups. Thus, the 4–10 Hz activity may be a relatively general phenomenon associated with abnormal subthalamic nucleus activity induced by dopaminergic treatment but mediated by different circuits. Indeed, abnormal impulsivity may be seen as part of a spectrum of basal ganglia disorders, embracing motor, behavioural and emotional domains secondary to the dysfunction of different anatomical territories (Mittal *et al.*; Voon *et al.*, 2009).

Along with previous studies, our findings suggest that the subthalamic nucleus has a general function in suppressing unwanted or inadequate movements, actions and behaviours (DeLong, 1983; Frank *et al.*, 2007). We suggest that in Parkinson's disease, dopaminergic overstimulation dampens this activity, liberating dyskinesias and misbehaviour through the oscillatory activity in the same frequency band, but with different peaks expressed in different functional areas of the subthalamic nucleus that correspond to the different cortico-subcortical circuits. This idea is reinforced by the fact that in patients with Parkinson's disease and LID, L-dopa treatment produces a higher dopamine concentration in the dorsal striatum (de la Fuente-Fernandez *et al.*, 2004), whereas this effect is evident in the ventral striatum of patients with Parkinson's disease and ICD (Evans *et al.*, 2006; Steeves *et al.*, 2009) where the dopamine transporter density is also lower (Cilia *et al.*, 2010). All these data indicate that the predominant motor or behavioural side effects seen in patients with Parkinson's disease depend on the circuits in which dopaminergic activity is greater (motor-dorsal or ventral-limbic), which in turns depends on the extent of the underlying nigrostriatal or mesolimbic denervation (Thobois *et al.*, 2010).

Conclusion

In Parkinson's disease, impulsivity disorders and dyskinesias induced by dopaminergic treatment are differentially associated with oscillatory activity in the theta-alpha band and are mediated by the dysfunction of distinct anatomo-functional territories. This is in keeping with current concepts about the basal ganglia, whereby a common mechanism of action operates throughout different domains (Jankowski *et al.*, 2009). The differential engagement and neuronal activity in subregions of the subthalamic nucleus may have important implications for the selective targeting of the subthalamic nucleus or other basal ganglia nuclei as deep brain stimulation expands to the treatment of neuropsychiatric disorders (Mallet *et al.*, 2008). In addition, achieving better modulation of the abnormal oscillatory activity should help obtain the maximum benefit with the minimum undesirable side effects in patients with Parkinson's disease.

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Supplementary material

Supplementary material is available at *Brain* online.

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