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Slow oscillatory activity and levodopa-induced dyskinesias in Parkinson's disease

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The pathophysiology of levodopa-induced dyskinesias (LID) in Parkinson's disease is not well understood. We have recorded local field potentials (LFP) from macroelectrodes implanted in the subthalamic nucleus (STN) of 14 patients with Parkinson's disease following surgical treatment with deep brain stimulation. Patients were studied in the 'Off' medication state and in the 'On' motor state after administration of levodopa–carbidopa (po) or apomorphine (sc) that elicited dyskinesias in 11 patients. The logarithm of the power spectrum of the LFP in selected frequency bands (4–10, 11–30 and 60–80 Hz) was compared between the 'Off' and 'On' medication states. A peak in the 11–30 Hz band was recorded in the 'Off' medication state and reduced by 45.2% ($P < 0.001$) in the 'On' state. The 'On' was also associated with an increment of 77. 6% ($P < 0.001$) in the 4–10 Hz band in all patients who showed dyskinesias and of 17.8% ($P < 0.001$) in the 60–80 Hz band in the majority of patients. When dyskinesias were only present in one limb ($n = 2$), the 4–10 Hz peak was only recorded in the contralateral STN. These findings suggest that the 4–10 Hz oscillation is associated with the expression of LID in Parkinson's disease.

Keywords: dyskinesias; subthalamic nucleus; oscillatory activity; Parkinson's disease

Abbreviations: DA = dopamine; DBS = deep brain stimulation; DID = dyskinesia–improvement–dyskinesia; GPi = globus pallidus pars interna; FFT = fast Fourier transformation; LID = levodopa-induced dyskinesias; LFP = local field potentials; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; STN = subthalamic nucleus

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Introduction

Levodopa-induced dyskinesias (LID) are observed in the majority of patients with Parkinson's disease who have been treated for 5–10 years with levodopa (Schrag and Quinn, 2000). LID may become highly disabling in Parkinson's disease. They are one of the primary limitations to the therapeutic efficacy of levodopa and also a principal motive for recommending surgical treatment (Fahn, 2000; Lang, 2000). LID can be divided into two main types according to the pattern of presentation (Muenter and Tyce, 1971; Luquin *et al.*, 1992; Obeso *et al.*, 2004): (i) choreic and dystonic movements during the period of peak levodopa plasma levels and clinical benefit ('On' dyskinesia), (ii) repetitive movements, usually of the legs, that occur at the beginning and end of the levodopa effect [diphasic dyskinesias or dystonia–improvement–dystonia (DID)] and coincide with parkinsonism in other body parts.

Recording of single unit neuronal activity in animal models and in patients during surgery has established that LID are physiologically characterized by a decreased firing frequency and abnormal firing patterns in the subthalamic nucleus (STN) and globus pallidus pars interna (GPi) (Hutchison *et al.*, 1998; Merello *et al.*, 1999; Papa *et al.*, 1999; Lozano *et al.*, 2000; Vitek and Giroux, 2000; Levy *et al.*, 2001; Stefani *et al.*, 2002). These findings support the model of basal ganglia pathophysiology that has fostered the current resurgence of functional neurosurgery for Parkinson's disease and other movement disorders. However, a number of

paradoxes and unexplained observations have emerged over the years (Marsden and Obeso, 1994; Obeso *et al.*, 2000). The most outstanding of these is that pallidotomy in patients with Parkinson's disease who suffer from LID drastically abolishes the involuntary movements to the extent that higher doses of levodopa are tolerated while simultaneously improving parkinsonian features (Lang, 2000). This is at odds with the model, which maintains that the lesion (plus increased levodopa intake) should further reduce neuronal activity in the output nuclei of the basal ganglia and, as such, it should fall more deeply into the hypoactive, dyskinetic range (Lozano *et al.*, 2000; Obeso *et al.*, 2000; Vitek and Giroux, 2000).

In the last few years it has been recognized that in addition to the firing rate the functional state of the basal ganglia may also be characterized by changes in oscillatory neuronal activity or rhythms (Bevan *et al.*, 2002; Heimer *et al.*, 2002). Thus, recordings from macroelectrodes implanted in the STN or GPi for deep brain stimulation (DBS) have shown that in the 'Off' parkinsonian state there is a predominant peak in the 11–30 Hz (beta band). Moreover, when patients are treated with dopaminergic (DA) drugs, this beta rhythm is drastically attenuated and activity in the 60–80 Hz gamma band predominates (Brown *et al.*, 2001; Levy *et al.*, 2001; Williams *et al.*, 2002; Silberstein *et al.*, 2003). In monkeys with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) induced parkinsonism and patients with Parkinson's disease, beta oscillatory activity in the STN and GPi has also been documented by microrecording (Wichmann *et al.*, 1994; Hutchison *et al.*, 1998; Heimer *et al.*, 2002; Brown, 2003). Thus, it has been suggested that rather than modifications of firing rate alone considering the changes in the oscillatory activity could provide a more comprehensive picture of what happens in the basal ganglia under different states of DA activation (Brown, 2003). Indeed, this may perhaps help in understanding some of the paradoxes of the basal ganglia model (Marsden and Obeso, 1994; Brown, 2003). Here, we have recorded local field potentials (LFP) from the STN of patients with Parkinson's disease treated with DBS and found a significant correlation between the appearance of a peak at a slow band frequency (4–10 Hz) and the presence of LID.

Patients and methods

Patients

Fourteen patients with a mean age of 55 years (41–69) and disease duration of 10.5 years (7–15) were studied. Their clinical features were typical of those currently considered candidates for treatment with DBS of the STN and they were similar to patients previously studied by our group (Obeso *et al.*, 2001; Rodriguez-Oroz *et al.*, 2005). The patients were not adequately controlled with available pharmacological treatments and fulfilled the CAPSIT (Core Assessment Program for Surgical Intervention Therapies) criteria for surgical treatment with DBS. The mean daily levodopa dose equivalent (100 mg of standard levodopa = 130 mg of controlled-released levodopa = 10 mg bromocriptine = 1 mg pergolide = 1 mg lisuride = 1.5 mg pramipexole = 5 mg ropinirole) was 1125 mg (range 725–1760). The mean Unified Parkinson's Disease Rating Scale (UPDRS) part III (0–118) in the 'Off' and 'On' motor state was 58 (36–64) and 17 (9–22), respectively. Eleven out of the 14 patients displayed dyskinesias in response to chronic levodopa. These 11 patients were recorded while showing dyskinesias and the other 3 were studied in the absence of LID. The CAPIT (Core Assessment Program for Intracerebral Transplantation) dyskinesia scale was used for evaluation (Langston *et al.*, 1992). This scale evaluates the intensity and duration of dyskinesias from 0 (absent) to 5 (very severe, continuous and generalized) and separately scores 'Off' period dystonia, diphasic (DID) and 'On' dyskinesias. Accordingly, moderate and severe dyskinesias are associated with scores between 3 and 5. At the time of the study, a marked benefit in the motor response to oral levodopa plus carbidopa (250–325 mg; $n = 12$) or subcutaneous administration of apomorphine (4.5 and 5 mg, $n = 2$) was observed with a mean reduction of 73% in the UPDRS motor score. The study was included in the Parkinson's disease surgical protocol at our centre; it was approved by the institutional ethics committee and each patient gave written informed consent.

Surgical technique

The surgical procedure involved a standard stereotactic approach as described previously (Guridi *et al.*, 1999; Obeso *et al.*, 2001). Macroelectrodes (Model 3389, Medtronic Neurological Division, Minneapolis, MN, USA) were bilaterally implanted into the STN in a single operation. The STN was localized using a CT–MRI fusion-based technique (Stereoplan Radionics, Burlington, MA, USA) and through intraoperative microrecording (platinum–iridium electrodes) and microstimulation, as performed routinely by our group (Rodriguez-Oroz *et al.*, 2001). Emphasis was placed on defining the dorsolateral region of the STN, which corresponds to the motor segment of the nucleus (Rodríguez-Oroz *et al.*, 2001). To achieve this, a mean of 3.1 recording tracks were required per nucleus and patient. Intraoperative fluoroscopy was used to monitor the position of the macroelectrode during the implantation phase. The most ventral contact of the DBS electrode was positioned to match the end of the STN as estimated by microrecording. Definitive placement of the macroelectrode was assessed by MRI 1–3 days after surgery. In most instances the electrode was positioned within the motor region of the STN on the basis of the findings obtained by microrecording (Rodriguez-Oroz *et al.*, 2001).

LFP recordings and pharmacological response

Recording sessions were conducted 2–4 days after surgery, having ensured that the patients' general state was satisfactory, their attention was normal and they could collaborate appropriately. The LFP from the STN were recorded from the implanted macroelectrodes through the external connection. The electrode (Medtronic 3389) has a total length of 7.5 mm and contains four platinum–iridium cylindrical contacts of 1.27 mm diameter, 1.5 mm length and with a centre-to-centre separation of 2 mm. The four adjacent contacts were labelled as 0, 1, 2 and 3 starting at the most caudal site. The contacts were arranged in a bipolar montage for recording: 0–1, 1–2, 2–3. EEG activity was also recorded via Ag–AgCl electrodes placed at FC3-FC4-C3-C4-Cz in reference to linked earlobes (A1–A2). Electromyography (EMG) signals were recorded with bipolar disposable surface electrodes (Neuroline) placed on the limb muscles where tremor or dyskinesias had been clinically detected. The motor state was carefully and continuously monitored during the study in order to detect possible changes in any body segment. Particular attention was paid to the presence of dyskinesias, even when of minor amplitude. STN activity was amplified 100 000-fold and filtered at 0.3–100 Hz

(Digitimer D-150, Cambridge, UK) before being digitized at 200 Hz by an analogical/digital converter connected to a PC (CED—Cambridge Electronic Design 1401 plus, Cambridge, UK). The EEG activity was amplified 20 000-fold, filtered at 0.3–100 Hz (Biologic, USA) and digitized at 200 Hz using the same A/D converter. The acquisition and offline analysis of all signals was performed using the Spike 2 software (Cambridge Electronic Design).

All sessions took place in the morning with patients in the 'Off' motor state after overnight withdrawal of antiparkinsonian medication. The 'On' motor state was subsequently achieved by oral administration of levodopa (50% over and above the usual morning dose). In two patients who had a delayed onset response to levodopa, a bolus of apomorphine (4, 5 and 5 mg, s.c.) was given to induce the 'On' response. The efficient dose of apomorphine for either patient had been estimated before surgery and was shown to reliably induce a motor response similar to that achieved by levodopa.

Subjects were seated in an armchair and recordings were continuously registered at rest while in the 'Off' motor state (five patients exhibited tremor at rest), 'intermediate' state (i.e. diphasic dyskinesias and beginning of the motor improvement) and in the best motor response ('On' motor state). The mean length of the recordings was 88.5 min (60–120). Segments with artefacts were discarded for offline analysis. Thus, a mean of 4.6 (range = 3–11) artefact-free segments of STN activity, lasting between 240 and 1216 s, were analysed for each patient. At least one segment corresponding to each of the 'Off', 'intermediate' and 'On' states was obtained from every patient. During the study, four patients had diphasic dyskinesias that were moderate to severe (mean score = 3.5) and 11 patients showed choreic dyskinesias in the 'On' motor state. These were present over most of the 'On' period and were fairly severe (mean dyskinesia score = 3.8).

Data analysis

The bipolar channels used for the analysis were always those with either the highest power value or the greatest power change. First, a fast Fourier transformation (FFT) was performed on non-overlapping sections of the same length (256 points, 1.28 Hz/bin resolution) from each segment of STN activity using the Spike 2 software package. The results were averaged across sections and the resulting average (0–100 Hz) was presented as a power histogram (squared volt/frequency). The number of averaged sections per segment was 761–3765 (mean = 1672) and distinctive frequency peaks from each segment-average were identified. These peaks were defined as more than two contiguous bins (2.5 Hz wide) with an absolute power two times greater than the two adjacent bins immediately preceding and following (two either side) the selected frequency (Silberstein *et al.*, 2003). As a second approach, the absolute power of the LFP within selected frequency bands (4–10, 11–30 and 60–80 Hz) was compared between the 'Off' and 'On' motor state in all subjects. These bands were chosen according to our initial experiences in recording LFP in Parkinson's disease patients (Obeso *et al.*, 2004), as well as from published data, indicating that these activities best differentiate between different motor states and may be functionally significant (Brown *et al.*, 2001; Williams *et al.*, 2002; Silberstein *et al.*, 2003; Priori *et al.*, 2004). For the purpose of this study we assessed the entire range of the beta band as a whole, although its subdivision into two components (Priori *et al.*, 2004) might be useful in some instances. In individual subjects, the absolute power was applied to correlate specific changes (i.e. the 4–10 Hz band) in STN activity and dyskinesias during a given period (i.e. DID) or when restricted to a given body part.

The mean logarithmic power was calculated for the whole patient population and compared for each band during the 'Off' and 'On' motor states. The values of the percentage reduction or increase were calculated by comparing the mean power during 3 min periods in the 'On' and 'Off' states. The artefact-free periods were selected from the last recorded segment before L-dopa intake ('Off' state) and the segment coinciding with the best clinical effect ('On').

All artefact-free segments of STN activity representing an 'Off–On' cycle from each patient (mean = 4.7 segments per patient) were merged into a single file, resulting in traces of 975–4820 s in duration (mean = 2141). A custom program allowed us to select the frequency band to analyse (4–10, 11–30, 60–80 Hz) and to calculate the power of the selected frequency band (by means of an FFT along the 'Off–On' cycle in 20 s epochs. Statistical analysis was performed using the SPSS software package for Windows (version 9; Chicago, IL, USA). A matched-pairs *t*-test was applied to compare the difference in logarithmic power between the 'Off' and 'On' motor states in the presence or absence of dyskinesias.

Results

Modification of oscillatory activity according to the DA state

Fourteen recording sessions were obtained from 28 STN. In the 'Off' motor state, a peak was found in the 11–30 Hz band in all patients (Fig. 1A) while in the patients who had severe tremor at rest the predominant peak coincided with the tremor frequency (4–6 Hz). The 'On' motor state was characterized by two distinctive peaks that were registered in the 60–80 Hz and 4–10 Hz bands (Fig. 1A). In most instances, the transition from the 'Off' to the 'On' motor state occurred gradually over several minutes (Fig. 1B). This transition was characterized by a reduction of 45.2% ($P < 0.001$) in the logarithmic power of the 11–30 Hz band and an increment of 17.8% ($P < 0.001$) and 77.6% ($P < 0.001$) in the 60–80 and 4–10 Hz bands, respectively (Fig. 1C). In three patients, no clear peak in the 60–80 Hz band was recorded during the 'On' state. Furthermore, in another three patients, who did not develop dyskinesias, there was no increment in the 4–10 Hz band (*see* below).

Oscillatory activity and LID

A significant increment (77.6%) in the 4–10 Hz band was observed in all patients who developed dyskinesias in response to medication. The increment in the logarithmic power of the 4–10 Hz band observed was similar when the periods of diphasic versus 'On' dyskinesias were compared. Patients who did not exhibit dyskinesias in response to levodopa or apomorphine did not show any such increment, and this difference between groups was statistically significant ($P < 0.05$) (Fig. 2A). Moreover, in one patient with DID and an excellent 'On' response without dyskinesias, the increment in the 4–10 Hz band was only recorded before the 'On' motor state and the associated increment in the 60–80 Hz band (Fig. 2B). In three patients who displayed both DID and 'On' dyskinesias, the slow band activity increased with the

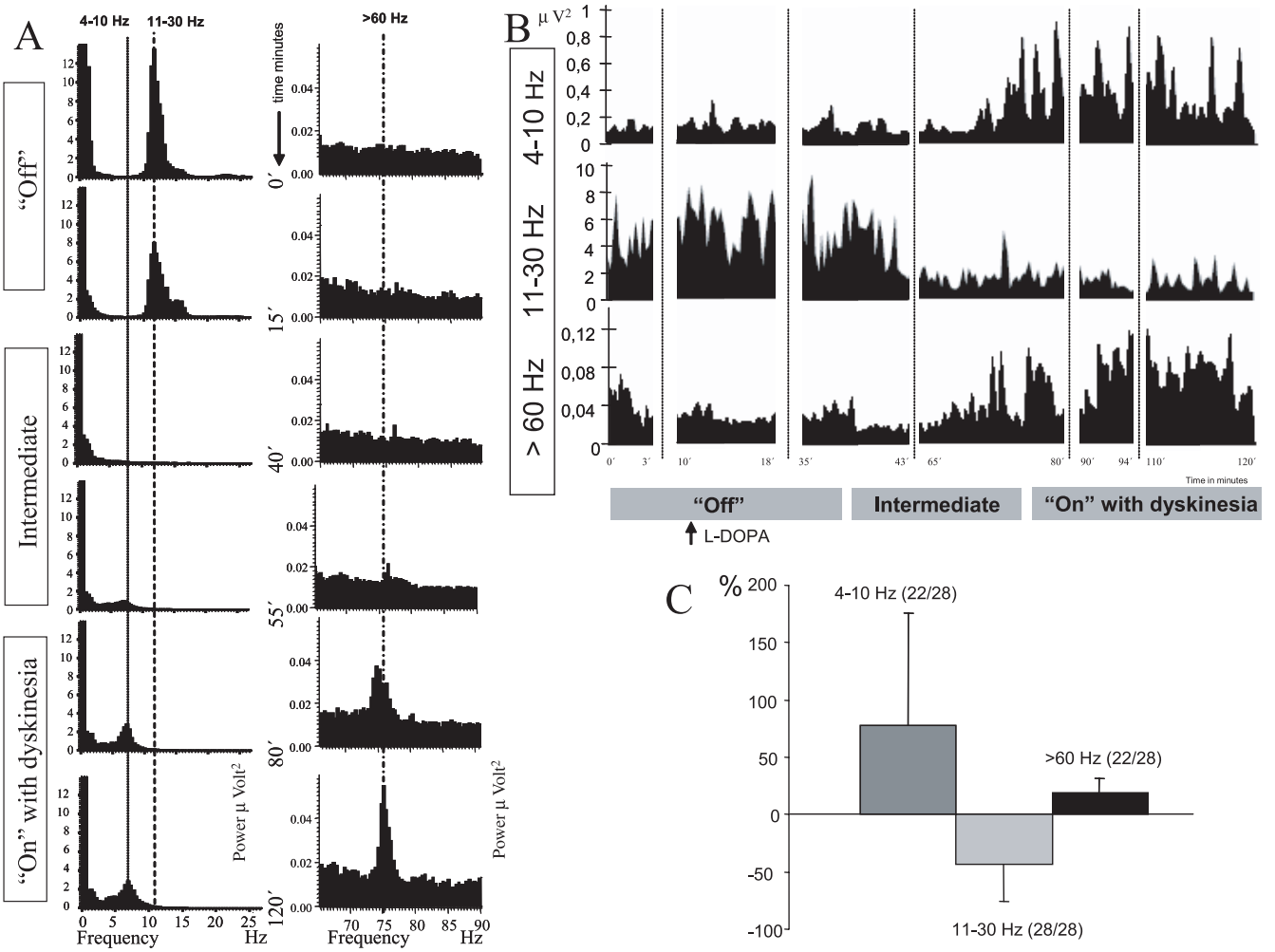

Fig. 1 Evolution of the LFPs recorded from the STN in one patient. Autospectra of the predominant peaks for the 11–30, 4–10 and 60–80 Hz bands (**A**, left STN) and its evolution from the 'Off' motor state to the beginning of the motor improvement (intermediate) and the 'On' state with dyskinesias (**B**, right STN). The discontinuous traces and numbers at the bottom indicate the period of valid recording in minutes. (**C**) Relative magnitude of the change in the logarithmic power in the three bands from the 'Off' to the 'On' motor states and the number of recorded subthalamic nuclei (in brackets) where this occurred.

onset of DID and this increase lasted for the whole period of 'On' dyskinesias.

Specificity of the findings

Topographically, the changes in LFP were specifically distributed within the STN (Fig. 3). In the majority of studies the maximal reduction in the 11–30 Hz band and the increment in the 60–80 Hz band predominantly took place at the level of the second more dorsal contact (Fig. 3), which is usually the one within the motor region of the STN. However, the increment in activity of the 4–10 Hz band was not so clearly confined to the dorsal region, and 45% of recordings showed that the major change in the 4–10 Hz band occurred in the most ventral recording sites.

In most patients ($n = 9$) LID were bilateral. In two patients with asymmetrical LID the association between the presence of dyskinesias in specific limbs and the appearance of a peak in the 4–10 Hz band could be studied. An absolute increment in the 4–10 Hz band in the right STN (+85%) coupled with a slight reduction (−8%) in the left STN was observed in one patient who developed dyskinesias only in the left lower limb during the 'On' state. In this subject, the typical increment in the 60–80 Hz band occurred bilaterally, in accordance with the general motor improvement in the 'On' motor state (Fig. 4). A bout of choreic dyskinesias exclusively in the right hemi-body that lasted for some 10 min was experienced by another subject before the dyskinesias became generalized and affected the left limbs as well. Accordingly, the increment in the 4–10 Hz band occurred first in the left STN and only appeared in the right STN when the dyskinesias appeared in the left hemi-body (Fig. 5). No attempt was made to establish whether or not the changes in the 4–10 Hz band appeared before or after the dyskinesias were observed.

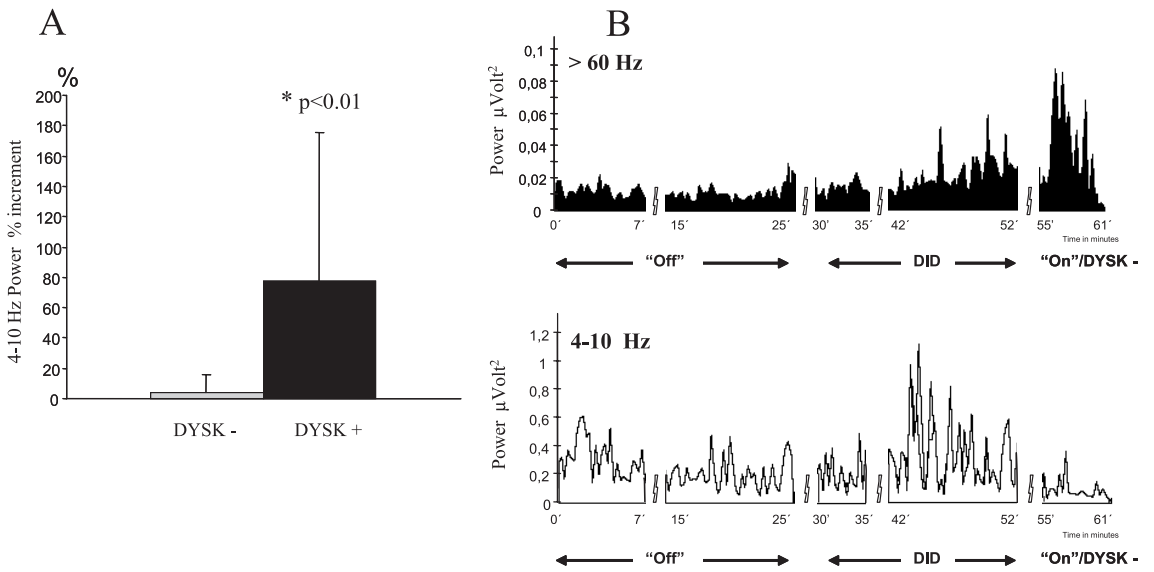

Fig. 2 (**A**) Magnitude of the increment in the 4–10 Hz band in patients with (n = 11) and without dyskinesias (n = 3) at the time of the study. (**B**) Comparative evolution of the autospectra for the >60 Hz and the 4–10 Hz bands in a patient who had tremor at rest, developed diphasic dyskinesias (DID) but had no dyskinesias during the 'On' motor state. The discontinuous traces and numbers at the bottom indicate the period of valid recording in minutes.

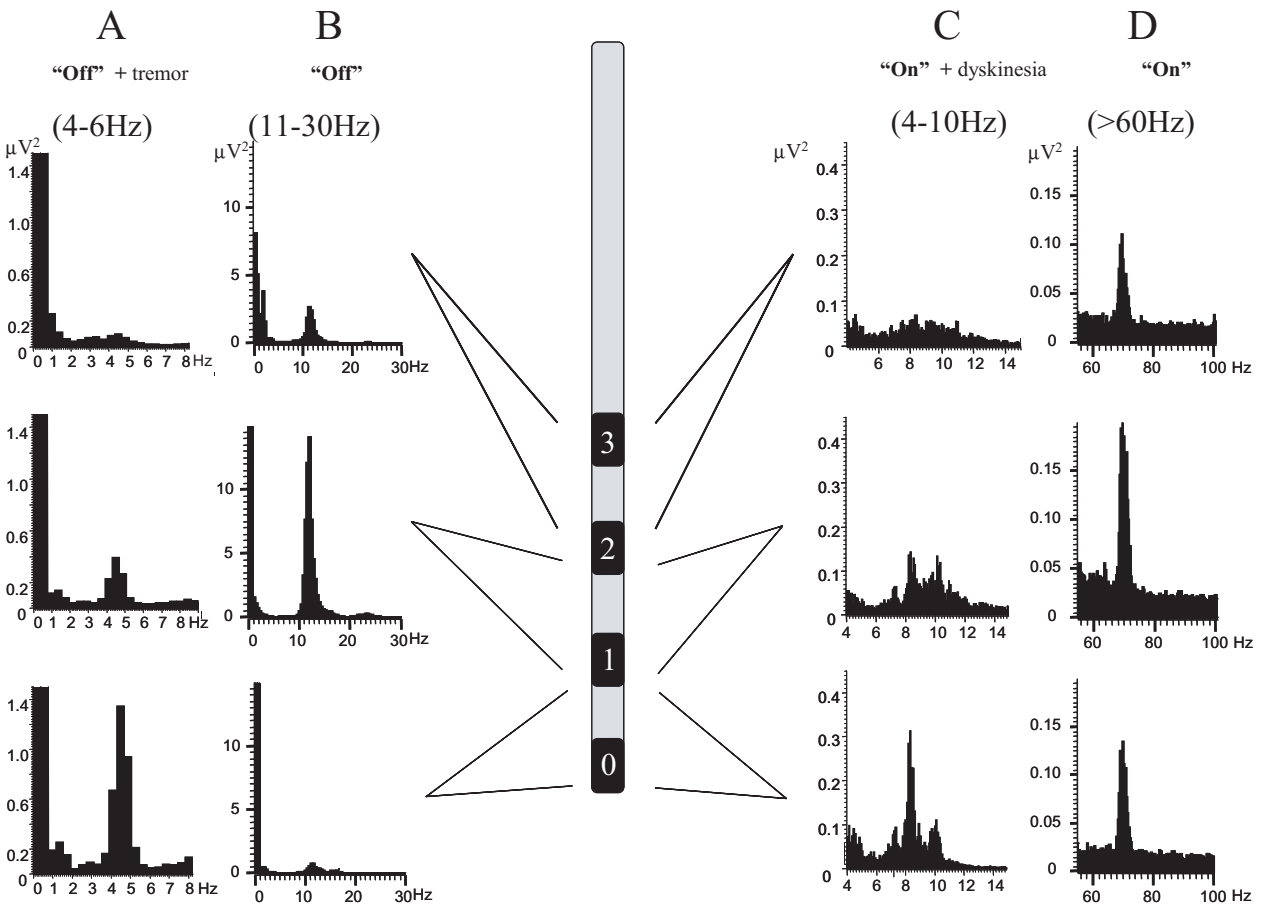

Fig. 3 Evolution of the LFP autospectra throughout the 'Off–On' cycle and the predominant site of recording with respect to the three bipolar contacts in the STN. In the 'Off' motor state (left) in a patient with tremor (**A**), there is a predominant peak at around 5 Hz while in a patient without tremor (**B**) there is only a peak at around 11–12 Hz that is maximal at the second-most dorsal STN contact. In the 'On' + dyskinesias motor state (right), the same patient shown in **B** exhibited a 4–10 Hz peak predominantly at the ventral recording site (**C**) and a 60–80 Hz peak at all three sites although the middle contact predominated (**D**).

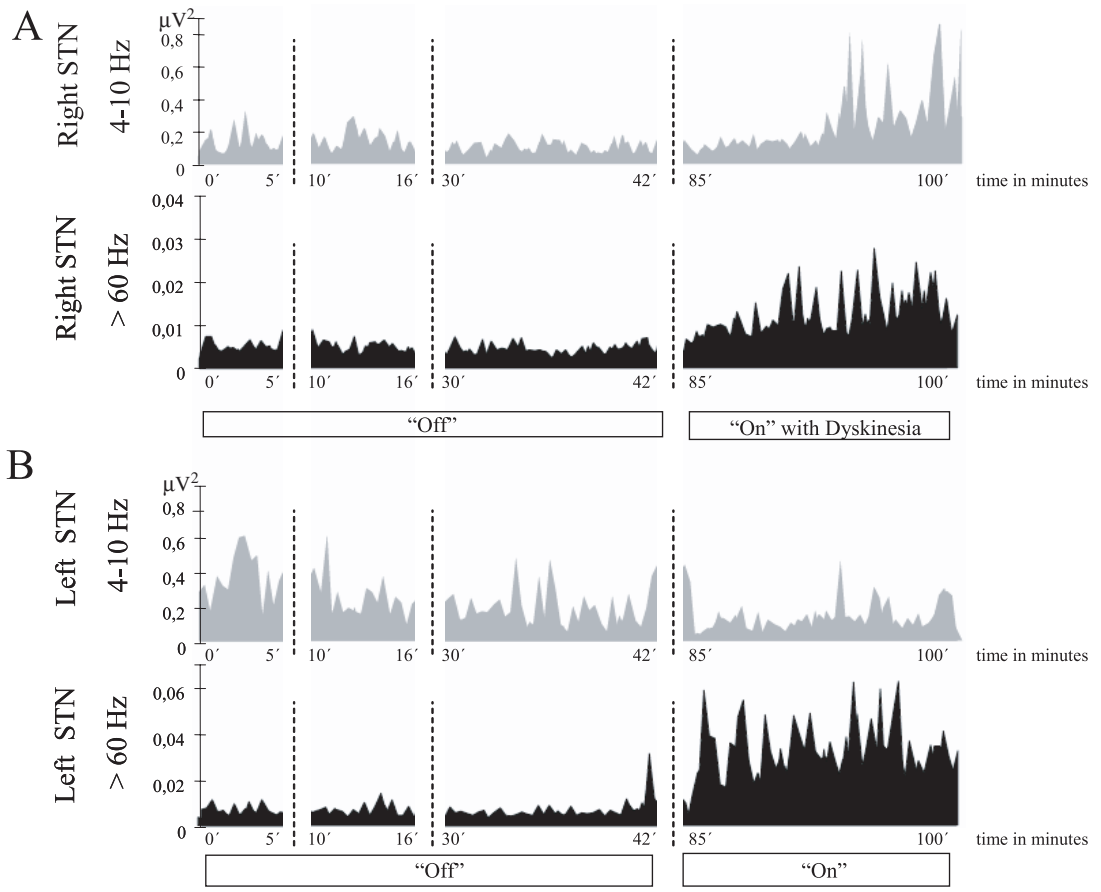

Fig. 4 Example of the LFP recorded from a patient with 'On' period dyskinesias in the left leg only. The 4–10 Hz band is only detected in the right STN (**A**) while the 60–80 Hz increased during the 'On' phase in both STN nuclei (**A** and **B**). This patient had a tremor at rest in the upper right limb explaining the presence of theta band activity in the left STN (**B**) and its attenuation after levodopa. Numbers at the bottom indicate the period of valid recording in minutes for each motor state.

Slow (4–10 Hz) oscillatory activity and the effect of involuntary movements

The relationship between the 4–10 Hz band and dyskinesias could be secondary to the somatosensory afferent activity associated with the movement and, therefore, it could be understood simply as the consequence of the dyskinesias. We have examined this issue in three subjects whose 4–10 and >60 Hz spectra could be analysed and separated into brief periods with or without dyskinesias (Fig. 6A). The mean duration of each interval analysed was 194 s for segments with dyskinesia and 208 s for segments without these movements. The periods that were free of dyskinesias were separated and analysed independently from the ones with dyskinesias. The power spectrum was analysed every 2 s and the EEG (Cz electrode), EMG and each pair contact of STN electrodes were averaged. The differences between 'Off' and 'On' periods with and without dyskinesias were calculated using factorial ANOVA (analysis of variance) without interactions with the *post hoc* test for multiple comparisons. There was a significant increment in the 4–10 Hz band ($P < 0.001$) and the 60–80 Hz band ($P < 0.001$) in the 'On' motor state when compared with the 'Off' motor state (Fig. 6B and C). However, no significant difference ($P = 0.5$) in the power of the 4–10 Hz ($P = 0.5$) (Fig. 6B) and the 60–80 Hz band ($P = 0.4$) (Fig. 6C) was detected when the recording fragments with and without dyskinesias were analysed separately (Fig. 6). The possibility that the changes induced in the frequency spectrum were artefacts of movement (i.e. due to dyskinesia) appeared less likely by examining the scalp EEG. There was no significant change in the 4–10 Hz ($P = 0.3$) bands during the recording intervals in the 'On' state whether or not dyskinesias were observed (Fig. 6E). Identical results to the findings shown in Fig. 6 for one of the patients were corroborated in another two patients. These results indicate that the modifications in the 4–10 Hz range are not due to the movements *per se* but are primarily associated with the physiological mechanisms causing dyskinesias.

Discussion

We have found that dyskinesias (both diphasic and 'On' dyskinesias) induced by DA drugs in patients with Parkinson's disease are associated with an increment in the 4–10 Hz band. Our patient population exhibited severe

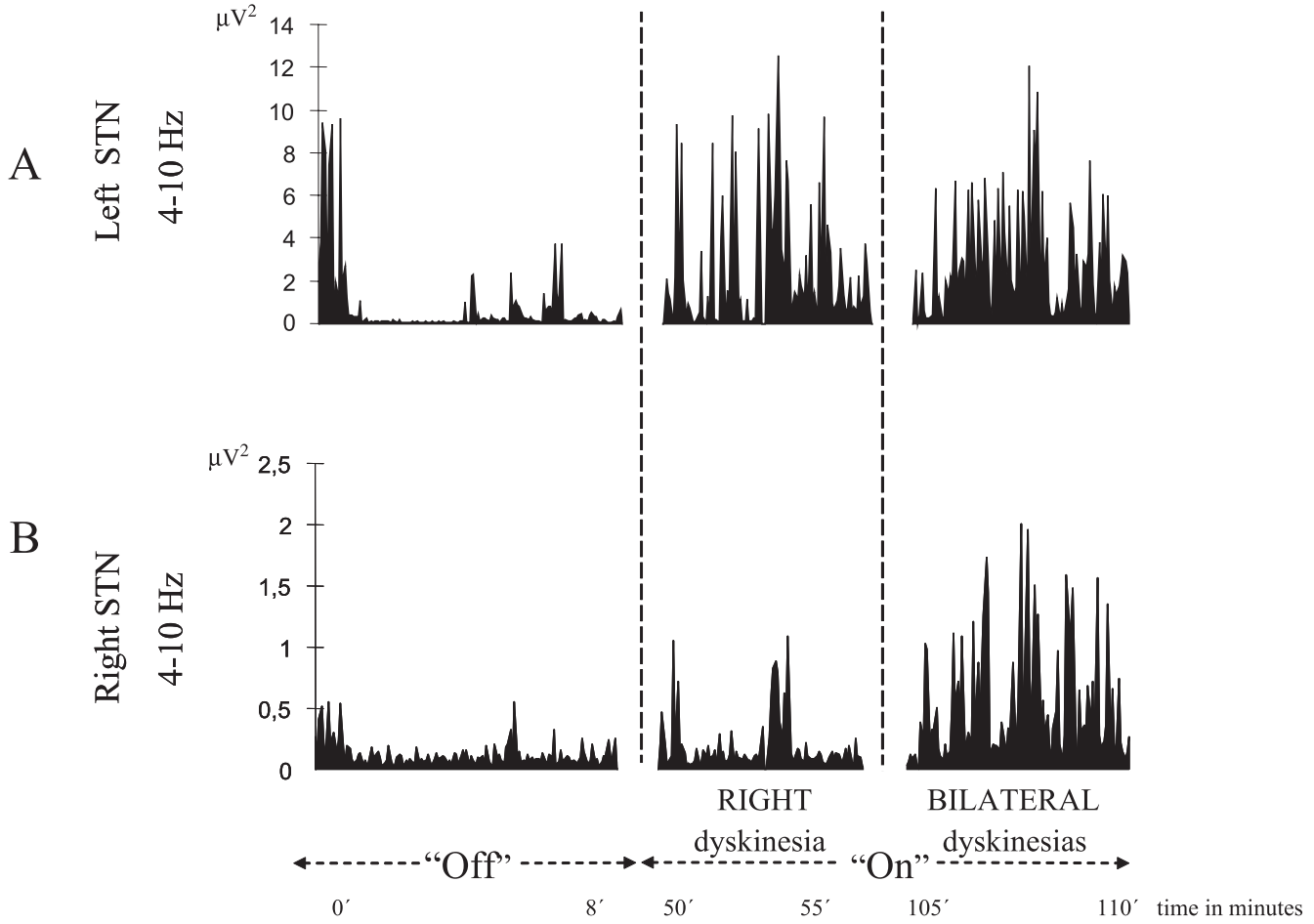

Fig. 5 Example of a patient with asymmetrical dyskinesias that first began in the right limbs, becoming bilateral several minutes later. The increment in the 4–10 Hz band in the left STN (**A**) precedes that in the right STN (**B**). The discontinuous traces and numbers at the bottom indicate the period of valid recording in minutes for each motor state.

LID both pre- and postoperatively. Thus, we were able to study LID in a relatively large number of patients after surgery when, in general, dyskinesias are attenuated in the postoperative period (Silberstein *et al.*, 2005). These findings further extend previous studies defining a clear correlation between the different motor states and the predominant oscillatory activity in the STN in Parkinson's disease (Brown *et al.*, 2001; Priori *et al.*, 2004; Fogelson *et al.*, 2005).

Methodological aspects

While the presence of slow oscillatory activity raises concerns about recording movement-induced artefacts, we believe that our data argue against such a possibility. First, electromyographic and kinematic studies have shown that the frequency of LID is typically lower than the 4–10 Hz peak recorded from the STN and scalp in our patients (Luquin *et al.*, 1992; Marconi *et al.*, 1994; Manson *et al.*, 2000). Secondly, movement-free segments of recordings showed exactly the same 4–10 Hz peak. Thirdly, we found that the topographical distribution of the changes in the spectrum recorded in the STN maintained a fairly clear relationship with the affected part of the body. Thus, the 11–30 Hz activity during the 'Off' state and the 60–80 Hz band during the 'On' state predominated bilaterally in the most dorsal region of the nucleus. In contrast, the slow 4–10 Hz band was found only in the contralateral STN when the dyskinesias were asymmetrically distributed. All these observations make it unlikely that the slow activity recorded during LID was due to a movement-induced artefact or a bias in the analysis.

Another potential concern when interpreting the data is the actual location of the recording electrodes. Admittedly, current imaging techniques (i.e. magnetic resonance) do not allow the exact location of the DBS electrode to be precisely defined. However, we placed the DBS electrode at coordinates that coincide with motor-related activity as assessed by microrecording. Moreover, a recent study has shown a close correlation between neuronal discharges and LFPs recorded from the STN (Kuhn *et al.*, 2005). In addition, experience with the recording of LFPs in the STN has shown that the contact sites outside the nucleus show a different baseline activity and do

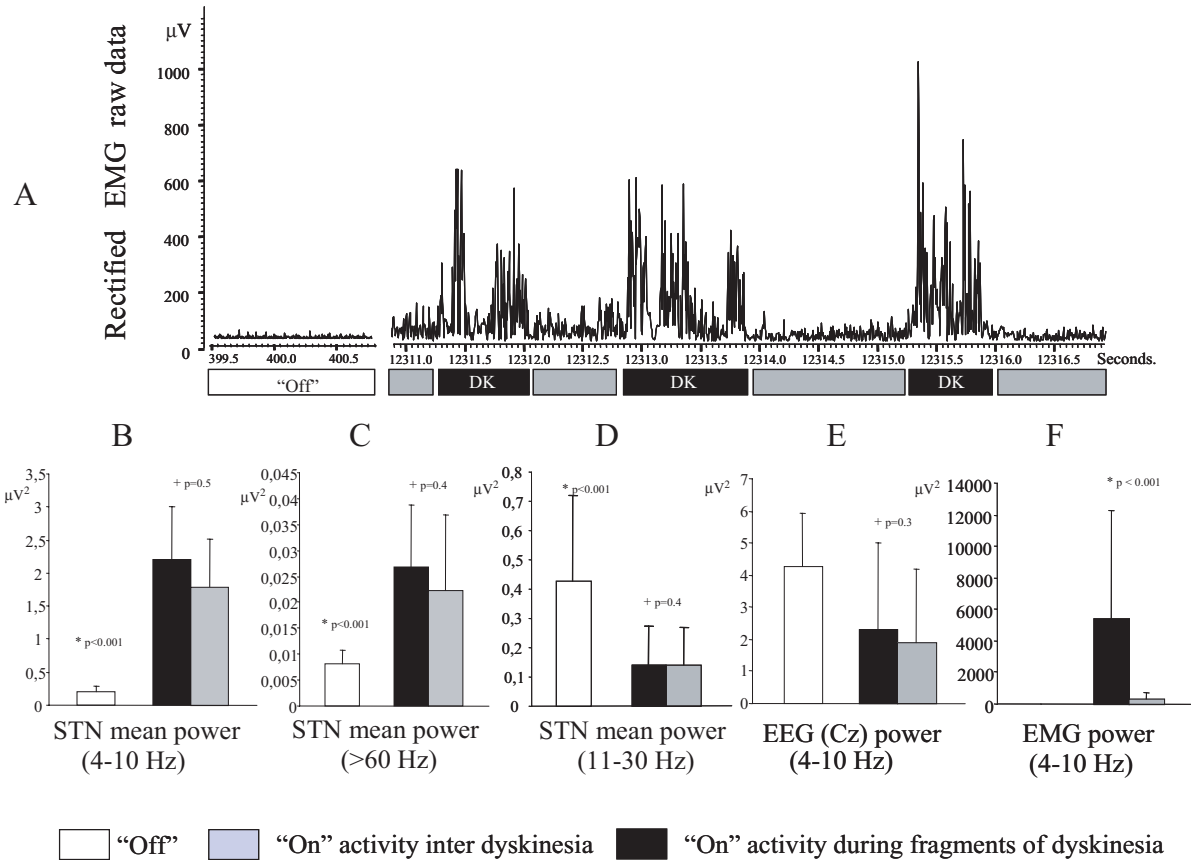

Fig. 6 Analysis of data from a patient with diphasic dyskinesias in the right leg. (**A**) The top trace is an example of electromyographic (EMG) trace recorded from the right tibialis anterior muscle. Periods that were free of dyskinesias were separated and analysed independently. The bottom graphs represent the LFP 4–10 Hz autospectra from the left STN (**B**), >60 Hz autospectra from the left STN (**C**), the 11–30 Hz autospectra from the left STN (**D**), 4–10 Hz autospectra from the scalp EEG (**E**) and the EMG (**F**) recorded in the 'Off' state (white) and in the 'On' state during periods with (black) and without dyskinesias (grey).

not exhibit the characteristic modulation of beta activity when performing a task (Kuhn *et al.*, 2004; Alegre *et al.*, 2005; Williams *et al.*, 2005). We did not perform a coherence analysis between STN oscillatory activity and EMG signals during LID mainly because of the inherent difficulty associated with the variable and irregular pattern of muscle activation that characterizes choreic movements. Future studies should include such an analysis to ascertain whether similar activity can be recorded during voluntary movement that resembles limb dyskinesias, and to examine possible task-related modifications of 4–10 Hz activity.

Finally, it may be worth mentioning that in this study we only included patients who showed a recognizable and well-defined pattern in their motor response to levodopa (or apomorphine). As such, the 'Off' state, as well as the beginning of the effect with diphasic dyskinesias, the 'On' state and the 'On' with 'peak dose' dyskinesias were clearly defined and evaluated. This approach has been routinely employed by our group to assess levodopa-related motor complications in Parkinson's disease (Vaamonde *et al.*, 1991; Luquin *et al.*, 1992).

Origin and significance of the changes in oscillatory activity

While a possible association between LID and a 4–10 Hz peak in the basal ganglia has been noted in earlier studies, the details of such an association have not yet been described. Slow oscillatory activity (3–6 Hz) in the basal ganglia (STN, GPi and globus pallidum pars externa) is closely associated with limb tremor in both MPTP monkeys and Parkinson's disease patients in the 'Off' state (Rodriguez *et al.*, 1998; Raz *et al.*, 2000; Levy *et al.*, 2000, 2002; Priori *et al.*, 2004). The increment in the 4–10 Hz band when passing from the 'Off' to the 'On' motor state may represent a specific association with the presence of involuntary movements (Silberstein *et al.*, 2003). Two recent reports are in keeping with our results. Foffani *et al.* (2005) recorded LFPs simultaneously from the STN and GPi in one patient with Parkinson's disease and found increased coherence between both nuclei at low frequencies (<10 Hz) contralateral to the side of the body where LID were observed. Silberstein *et al.* (2005) recorded the LFPs from the GPi in two patients with mild LID (clinical details were not given) and found a significant inverse correlation

between activity in the 13–30 Hz band and the presence of dyskinesias. We observed that by and large the 4–10 Hz activity in the STN was associated with dyskinesias. In two patients with asymmetrical LID, the 4–10 Hz activity was recorded only on the contralateral STN. Thus, it appears that the 4–10 Hz peak may represent a specific neuronal pattern associated with the dyskinesias elicited by DA drugs. This hypothesis is further supported by similar findings reported in the rat 6-OHDA model where the number of bursting cells increased and a significant correlation between single cell discharges and oscillatory activity in the theta band was found only in dyskinetic animals (Meissner *et al.*, 2006). Indeed, Silberstein *et al.* (2003) have suggested that the 4–10 Hz peak associated with LID in Parkinson's disease and in patients with torsion dystonia may be due to increased bursting discharges, a physiological feature that has also been encountered in animal models and patients exhibiting LID (Lozano *et al.*, 2000; Boraud *et al.*, 2001; Levy *et al.*, 2001), hemichoreaballism (Suarez *et al.* 1997) and dystonia (Gernert *et al.*, 1998; Lenz *et al.*, 1998). Whether or not bursting discharges and slow oscillations may be equated and represent a common functional alteration of the basal ganglia for most dyskinetic disorders (Silberstein *et al.*, 2003) cannot be resolved with the currently available information.

Relevance of the slow 4–10 Hz oscillation in the pathophysiology of LID in Parkinson's disease

In the 'On' dyskinetic state, neuronal activity in the STN and GPi is characterized by a reduction in the mean firing frequency, increased bursting and increased variability in the pauses between discharges (Boraud *et al.*, 2001). Together, this gives rise to a different pattern of neuronal activity in the output of the basal ganglia (Hutchinson *et al.*, 1998; Merello *et al.*, 1999; Papa *et al.*, 1999; Lozano *et al.*, 2000; Vitek and Giroux, 2000; Levy *et al.*, 2001).

The 4–10 Hz oscillatory activity could represent a specific signal that conveys a code to the thalamocortical motor projection to release involuntarily fragments of movement (i.e. dyskinesias). This possibility is supported by the observation that 5-Hz stimulation of the STN induces choreiform movements of the contralateral upper limb (Liu *et al.*, 2002). Alternatively, it could represent a functional state, setting a level of excitability that allows the occurrence of involuntary movement. The presence of a similar 4–10 Hz rhythm in the GPi of patients with torsion dystonia (Silberstein *et al.*, 2003) would favour a non-specific dysregulation of movement control. This interpretation would more easily fit with the idea that the same type of surgery (i.e. pallidotomy or DBS of the GPi) improves both LID and dystonia by eliminating or interfering with the slow oscillatory activity discussed here. A comprehensive view would be that the 4–10 Hz and the gamma rhythms, albeit recorded simultaneously, are in fact the result of synchronization of distinct neuronal populations within the STN. In keeping with this, studies measuring glucose consumption in MPTP monkeys found a significant increment in the ventral region of the STN in animals that developed LID (Mitchell *et al.*, 1992; Guigoni *et al.*, 2005). It is likely that corticobasal ganglia activity related to LID differs from the one sustaining normal movement control. Accordingly, the predominant physiological rhythms recorded in the basal ganglia may also be different.

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