Dopaminergic therapy promotes lateralized motor activity in the subthalamic area in Parkinson’s disease

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Treatment of patients with Parkinson’s disease with levodopa has profound effects on both movement and the pattern of movement-related reactivity in the subthalamic nucleus (STN), as reflected in the local field potential (LFP). The most striking change is the promotion of reactivity in the gamma frequency band, but it remains unclear whether the latter is itself a pathological feature, possibly associated with levodopa induced dyskinesias, or is primarily physiological. Gamma band reactivity in the cerebral cortex of humans without Parkinson’s disease occurs contralateral to movement, so we posited that lateralization of subcortical gamma reactivity should occur following levodopa if the latter restores a more physiological pattern in patients with Parkinson’s disease. Accordingly, we studied movement-related changes in STN LFP activity in 11 Parkinson’s disease patients (age 59 ± 2.7 years, three females) while they performed ipsi- and contralateral self-paced joystick movements ON and OFF levodopa. A bilaterally symmetrical gamma band power increase occurred around movement onset in the OFF state. Following levodopa this feature became significantly more pronounced in the subthalamic region contralateral to movement. The physiological nature of this asymmetric pattern of gamma reactivity was confirmed in the STN of two tremor patients without Parkinson’s disease. Although levodopa treatment in the Parkinson’s disease patients did not lead to lateralization of power suppression at lower frequencies (8–30 Hz), it did increase the degree of power suppression. These findings suggest that dopaminergic therapy restores a more physiological pattern of reactivity in the STN of patients with Parkinson’s disease.

Keywords: deep brain stimulation; local field potentials; Parkinson’s disease; subthalamic nucleus; synchronous oscillatory activity

Abbreviations: DBS = deep brain stimulation; ERD = event-related desynchronization; ERS = event-related synchronization; LFP = local field potential; STN = subthalamic nucleus


Introduction

Our understanding of the pathophysiology of the basal ganglia in humans has been greatly advanced by the recent renaissance in functional neurosurgery for movement disorders, particularly Parkinson’s disease. Such surgery makes it possible to record both neuronal and local field potential (LFP) activity from basal ganglia targets. The results of LFP recordings have proven particularly instructive as these signals can be picked up directly from the electrodes used for deep brain stimulation (DBS) in the few days between implantation and subsequent connection of...
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increased reactivity of subcortical beta activity following Parkinson’s disease has been the propensity for neuronal synchronization in the subthalamic nucleus (STN) and globus pallidus at frequencies between 8 and 30 Hz in patients withdrawn from antiparkinsonian medication (Brown et al., 2001; Cassidy et al., 2002; Levy et al., 2002; Priori et al., 2002; Williams et al., 2002; Silberstein et al., 2003; Amimnov et al., 2004; Kühn et al., 2004; Priori et al., 2004; Kühn et al., 2005; Williams et al., 2005; Alonso-Frech et al., 2006; Devos et al., 2006; Fogelson et al., 2006; Wingeier et al., 2006). This activity, evident as oscillation in the LFP over these frequencies, has been related to the bradykinetic state, which it may serve to promote (Brown, 2003; Dostrovsky and Bergman, 2004; Brown and Williams, 2005). In line with this, levodopa, which ameliorates bradykinesia, reduces the level of synchronization over 8–30 Hz at rest (Brown et al., 2001; Levy et al., 2002; Priori et al., 2002, 2004; Alonso-Frech et al., 2006; Kühn et al., 2006b) and may increase the additional suppression of this activity that occurs prior to and during voluntary movement (Doyle et al., 2005; Devos et al., 2006).

At the same time treatment with levodopa is associated with synchronization at higher frequencies, in the so-called gamma band, particularly during voluntary movement (Cassidy et al., 2002; Williams et al., 2002; Obeso et al., 2004; Alegre et al., 2005; Foffani et al., 2005; Fogelson et al., 2005; Alonso-Frech et al., 2006; Devos et al., 2006). The implication has been that dopaminergic therapy is making the pattern of population activity in the STN more physiological (Brown, 2003; Brown and Williams, 2005) in line with its effects on oscillatory activity at the cortex (Devos et al., 2003; 2004). However, hitherto there has been little support for this contention, and aspects such as the increased reactivity of subcortical beta activity following levodopa remain contentious (Priori et al., 2002; Alegre et al., 2005). Nor is it intuitively obvious that treatment with levodopa, itself associated with involuntary movements in those patients in whom recordings are available, necessarily normalizes population activity in the basal ganglia. One approach to this issue is to look for similarities between the pattern of LFP activity in the STN following treatment with levodopa in patients with Parkinson’s disease and that found in the cerebral motor cortex of patients without obvious movement disorders, as the motor cortex is both related in function and shows coherent activity with basal ganglia sites (Cassidy et al., 2002; Williams et al., 2002; Fogelson et al., 2006). The LFP, or more precisely the electrocorticographic activity, in the motor cortex of patients with epilepsy but no extrapyramidal syndrome, shows activity in the gamma band that increases with movement (Crone et al., 1998a; Pfurtscheller et al., 2003). One striking feature of this physiological cortical gamma activity, which distinguishes it from oscillatory activities at lower frequencies, is that it occurs strictly contralateral to the side of movement. If the subcortical gamma activity following treatment with levodopa were a feature of physiological activity in basal ganglia-cortical loops then one would predict similar lateralization of movement-induced increases in gamma activity in the STN. So far studies with small patient numbers (5–6 patients on therapy) have had conflicting results in this regard (Alegre et al., 2005; Devos et al., 2006). Here, we confirm this prediction in patients with Parkinson’s disease who have been treated with levodopa and provide further support that such lateralized gamma band reactivity is a hallmark of physiological processing by confirming its presence in the STN of two patients without Parkinson’s disease. We also confirm that treatment with levodopa leads to an increased, but symmetrical, LFP reactivity in the 8–30 Hz frequency band.

Material and methods

Parkinson’s disease patients and surgery

Eleven patients (age 59 ± 2.7 years, three females) were studied who underwent bilateral implantation of DBS electrodes in the STN for the treatment of severe Parkinson’s disease (Table 1). Each gave their informed consent to take part in the study, which was approved by the joint ethics committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology, London, and the ethics committee of the Charité, Berlin, in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki 1967). Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971).

Implantation was performed under local anaesthesia using Leksell’s Frame (Eleka, Sweden) or the Riechert-Mundinger Frame (patients in Berlin). The DBS electrode used was model 3389 (Medtronic Neurological Division, MN, USA) with four platinum-iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length) and a centre-to-centre separation of 2 mm. Contact 0 was the lowermost and contact 3 the uppermost. The intended coordinates for STN were 12 mm lateral from the midline, 3 mm behind the midcommisural point and ~4 mm below the AC-PC line. Adjustments to the intended surgical coordinates were made according to the direct visualization of STN on individual preoperative stereotactic T2-weighted MRI (Hariz et al., 2003) and, in cases 4–7 and 10 from Berlin, ventriculography and intraoperative microelectrode recordings. Intraoperative electrical stimulation and immediate postoperative stereotactic MRI were performed in all patients in order to confirm targeting. Postoperative scanning confirmed that at least one contact was within the STN (Table 1). Correct placement of the DBS electrode in the STN was also supported by significant improvement in Unified Parkinson’s Disease Rating Scale (UPDRS) motor score during DBS OFF levodopa ON stimulation compared to UPDRS OFF levodopa OFF stimulation (mean improvement 48.36% ± 6, two-tailed paired t-test: t = 5.5, P = 0.0003; Table 1).

Tremor patients and surgery

Two patients with non-parkinsonian tremor participated with consent according to the Declaration of Helsinki and with
<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Disease duration (years)</th>
<th>Predominant symptoms</th>
<th>Motor UPDRS pre-op (ON/OFF levodopa)</th>
<th>Motor UPDRS post-op (OFF levodopa ON/OFF DBS)</th>
<th>Contacts most likely within STN based on MRI</th>
<th>Medication (daily dose)</th>
<th>Contacts used (R/L hand)</th>
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<td>1*</td>
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<td>4</td>
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<td>Dyskinesias, on-off</td>
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<td>16/35</td>
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<td>Levodopa 650 mg</td>
<td>Off: R12/R23</td>
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<td>16</td>
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<td>13/61</td>
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<td>14/61</td>
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<td>67/90</td>
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<td>Levodopa 800 mg</td>
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<td>64/M</td>
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<td>R STN: 1, 2</td>
<td>Levodopa 1200 mg</td>
<td>Off: R12/R01</td>
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* Left-handed patients.
agreement of the local ethical committees. Case 1 was drawn from a cohort of patients undergoing simultaneous unilateral dual implantation of DBS macroelectrodes as part of a comparative clinical study of the efficacy of stimulation at different sites for essential tremor at the University Hospital of Umeå, Sweden. The first DBS electrode was aimed to target the nucleus ventralis intermedius thalami (Vim) with the caudal contact within zona incerta (Zi). The second electrode was aimed to target STN. Case 2 was implanted in London with an electrode bridging posterior STN (rostral contact 3) and the preliminiscal radiation on the left for treatment of dystonic tremor in the right upper limb. Neither patient was receiving pharmacological treatment for their tremor at the time of surgery or postoperative recording.

Case 1 was a 57-year-old male with a 5-year history of action and postural tremor of the left > right upper limb and head. Tremor was alcohol responsive. There was a family history of tremor affecting the patient’s three siblings and his father. The patient did not take any medication. On examination there were no abnormal neurological signs, other than severe tremor. The Essential Tremor Rating Scale score was 20. No evidence of a dopaminergic lesion was found on a pre-operative DAT scan.

Case 2 was a 64-year-old male with a 17-year history of dystonic left upper limb and head tremor. His father also suffered from tremor. On examination there were no abnormal neurological signs, other than severe postural and action tremor. MRI of brain showed a few scattered hyperintensities consistent with small vessel disease and copper studies were normal. The patient did not respond to a sustained trial of levodopa. They did not have signs, other than severe postural and action tremor. MRI of brain showed a few scattered hyperintensities consistent with small vessel disease and copper studies were normal. The patient did not respond to a sustained trial of levodopa. They did not have DAT scan.

**Paradigm and recordings**

Patients were studied 1–6 days postoperatively, in the interval between DBS electrode implantation and subsequent connection to a subcutaneous stimulator. The subjects were seated comfortably in a chair and recorded while making self-paced movements of a joystick forward and then immediately backward, repeated approximately every 10–20 s. This task was performed separately with left and right hands, and, in the case of the Parkinson’s disease patients, ON and OFF medication (Fig. 1). In the latter instance, recordings were made from the STN after patients had been off antiparkinsonian medication overnight and again about 1 h after they had taken a minimum of 200 mg levodopa. Deep brain activity was recorded bipolarly from the adjacent four contacts of each DBS electrode (0–1, 1–2, 2–3), amplified (×100 000) and, in the Parkinson’s disease patients, pass band filtered at 1–250 Hz. EMG was simultaneously recorded from the first dorsal interosseous (1DI) of the active hand using bipolar Ag-AgCl surface electrodes, amplified (×10 000) and pass band filtered at 10 Hz–1 kHz. Joystick movements were also recorded. In the Parkinson’s disease patients, amplification was performed using a D150 amplifier (Digitimer Ltd, Welwyn Garden City, UK) or a custom-made battery-operated portable high impedance amplifier (previously described in Kuhn et al., 2004). All signals were recorded using a 1401 analogue-to-digital converter (1401, Cambridge Electronic Design, Cambridge, UK) using Spike 2 software (Cambridge Electronic Design) and sampled at rates of 625–2 kHz. For the two tremor patients, signals were amplified and band pass filtered between 1 and 90 Hz (sampling rate 184 Hz) and 1.5–200 Hz (sampling rate 1200 Hz) in cases 1 and 2, respectively (Biopotential Analyzer Diana, St Petersburg, Russia).

**Analysis**

Data were interpolated to a common sampling rate of 1 kHz. This was justified as, with one exception, the lowest original sampling rate was 625 Hz, and therefore much higher than either our low pass filter (250 Hz) or our frequency band of interest (<100 Hz). The one exception was one of the tremor patients who was recorded with a sampling rate of 184 Hz, which still remained higher than the low pass filter (90 Hz). Only frequencies up to 90 Hz were analysed in this patient. Using Spike 2 software, the onset of movements was visually detected from both joystick position and EMG traces and marked. Movements were only marked when they were not preceded or followed by another movement within a period of 9 s. The mean number of movements marked was 16 (range, 7–28) and the mean duration of analysed recordings was 424 s ± 57 s.

The first analysis step was to calculate the event-related spectral power for all contact pairs for a period of 4.5 s before to 4 s after movement onset. Spectra were estimated using the discrete Fourier transform as outlined in Halliday et al. (1995) and Brown (2000). STN LFP were assumed to be realizations of stationary, zero mean time series and to satisfy a mixing condition, whereby sample values were independent (Brillinger, 1981). Records were divided into a number of sections of equal duration with a block size of 1024 data points, affording a frequency resolution of ~1 Hz. Spectra were estimated by averaging across sections and a Hanning window filter was used. Blocks were shifted by 10 ms and averaged again until the whole record length had been analysed (using a modified Spike 2 script). Event-related desynchronization (ERD) and synchronization (ERS) were defined as the percentage power decrease (ERD) or power increase (ERS) in relation to a premovement baseline (~4.5 to ~4 s) period. Thereafter, we identified the DBS contact pair that afforded the highest mean percentage power change over 40–85 Hz and over 8–30 Hz for a period of 500 ms before and after movement onset on each side (Table 1).

Time-evolving mean percentage event-related power change for each selected contact pair was estimated separately for left and right hand joystick movements in both the ON and OFF states for each implanted side. For visualization purposes, matrices of event-related percentage power changes were thresholded so that power

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Fig. 1 Examples of raw data in Case 8. Self-paced joystick movement made with the right hand OFF and ON levodopa and simultaneously recorded right FDI EMG and raw LFP from contralateral (left) and ipsilateral (right) STN.
values within the 99% confidence limits of the averaged baseline power were set to 100% (i.e. defined as no change). For quantitative analysis at low frequencies, where movement-modulated peaks in spectra of LFP power are pronounced (Brown et al., 2001; Cassidy et al., 2002; Levy et al., 2002; Priori et al., 2002; Williams et al., 2002; Silberstein et al., 2003; Alegre et al., 2004; Amirnovin et al., 2004; Kühn et al., 2004; Priori et al., 2004; Kühn et al., 2005; Williams et al., 2005; Alonso-Frech et al., 2006; Fogelson et al., 2006), we determined the frequency with the most pronounced mean ERD between 500 ms before and 500 ms after movement onset over 8–30 Hz, in accordance with the frequency distribution of the ERD in grand averages of event-related power change (Fig. 2) and previous observations (Alegre et al., 2003; Williams et al., 2005; Kühn et al., 2006a). Note that separate analyses limited to the beta band (13–35 Hz) gave similar results (data not shown). The percentage change in power was measured at this individually defined frequency and over the two (1 Hz) bins on either side of this frequency (i.e. over a 5 Hz band). Additionally, we estimated the post-movement ERS at the same frequencies over the period of 2–4 s after movement onset.

A different approach was necessary for the quantitative analysis of power change in the gamma band, as here discretely reactive activities were not always evident in individual matrices of event-related percentage power changes. Accordingly, we elected to analyse the whole of the gamma band modulated by movement (40–85 Hz) as it appeared in grand averages (Fig. 2) of event-related power change for those DBS contact pairs affording the highest mean percentage change in this band for a period of 200 ms before to 500 ms after movement onset on each side (Table 1).

All statistical analyses were conducted using SPSS v12 (SPSS Inc. Chicago, IL, USA). Percentage values of ERD/ERS were normally distributed as confirmed by the one-sample Kolmogorov–Smirnov test. Our principal ANOVA, repeated in both low frequency and gamma bands, was that performed on % power changes with main effects STATE (2 levels: OFF and ON) and LATERALITY (2 levels: ipsilateral and contralateral to hand movement). Further subsidiary ANOVAs, as detailed in the Results, were performed to explore the data and particularly to examine factors previously highlighted in the literature. Mauchly’s test confirmed the sphericity of the data entered in the ANOVAs. Post hoc two-tailed, paired Student’s t-tests were used to confirm relevant differences in event-related power. Means ± standard error of the means are given in the text.

Results

Alpha-beta ERD and ERS in patients with Parkinson’s disease

Grand averages of event-related power changes in those contact pairs showing the greatest gamma frequency band change on each side in the ON state demonstrated a significant gamma ERS which just preceded movement in onset and persisted for about 0.5 s thereafter (Fig. 2). Although still present, these appearances were less marked in grand averages drawn from the same patients withdrawn from their usual antiparkinsonian medication overnight (compare Fig. 2A and B with Fig. 2C and D). In addition, the gamma ERS was bigger contralateral to the movement, but only in the ON state. This asymmetry was not observed in an earlier smaller study (Alegre et al., 2005). In individual subjects, a significant gamma ERS was present in at least one contact pair following treatment in all conditions, but this was only the case in six patients withdrawn from medication.

We used the mean percentage power change in the whole 40–85 Hz band for quantitative analysis, estimating this from 200 ms before to 500 ms after movement onset in the OFF and ON states. An ANOVA was performed with main effects STATE (2 levels: OFF and ON) and LATERALITY (2 levels: ipsilateral and contralateral to hand movement). This confirmed a main effect of STATE \( F(1,21) = 7.48, P = 0.012 \) for the 8–30 Hz band but no main effect of LATERALITY. A post hoc two-tailed paired t-test indicated that the ERD was increased after levodopa treatment \( (t = 2.7, P = 0.012) \) (Fig. 3A–C).

Another ANOVA was performed with main effects STATE and WORSE AFFECTED SIDE (two levels: lesser and worse affected sides). Here, there was no effect of WORSE AFFECTED SIDE or interaction between main effects. A main effect of LATERALITY was, however, found when an ANOVA with main effects STATE and LATERALITY was repeated for the % power change in the post-movement ERS from 2 to 4 s after movement onset \( F(1,21) = 5.1, P = 0.035 \). There was no main effect of STATE or interaction between main effects. A post hoc two-tailed paired t-test verified that the beta ERS was increased contralaterally to the movement side.

Gamma ERS in patients with Parkinson’s disease

Grand averages of event-related power changes in those contact pairs showing the greatest gamma frequency band change on each side in the ON state demonstrated a significant gamma ERS which just preceded movement in onset and persisted for about 0.5 s thereafter (Fig. 2).
that the premovement onset gamma ERS was significantly larger after levodopa medication ($t = 2.1, P = 0.048$). Thus the effect of levodopa on the gamma ERS could not have been due to altered reafference following changes in motor performance.

Next we confirmed that an interaction between STATE and LATERALITY for data from 200 ms before to 500 ms after movement remained when only the subjects that exhibited a percentage improvement of >30% (all cases except 7, 9, 11; see table) were included in the analysis [$F(1,15) = 4.54$,
Post hoc two-tailed paired $t$-tests indicated that the gamma ERS was significantly larger during contralateral hand movements ($t = -3.6, P = 0.02$ for 11 subjects; $t = 2.9, P = 0.011$ for 8 subjects) but only after levodopa medication and not during the OFF state (Fig. 4A and B).

An additional ANOVA was performed with main effects STATE and WORSE AFFECTED SIDE (two levels: lesser and worse affected sides). There was no effect of WORSE AFFECTED SIDE or interaction between main effects on the gamma ERS.

The most important difference between LFP activities in the alpha-beta and gamma bands was therefore the lateralization of the latter after treatment with levodopa.

To check that this feature did not arise through differences in analysis we repeated the ANOVA using mean percentage power changes in the 40–85 Hz band derived from the contact pairs showing the greatest beta power change in the OFF state rather than the biggest gamma power change in the ON state. The interaction between STATE and LATERALITY remained [$F(1,21) = 7.9, P = 0.01$] and post hoc tests still confirmed that the gamma ERS was significantly larger during contralateral hand movements ($t = -3.6, P = 0.02$) after levodopa medication and not during the OFF state ($t = -0.1, P > 0.05$; Fig. 4C and D).

**Changes in LFP power in patients without Parkinson’s disease**

The above data from patients with Parkinson’s disease suggested that levodopa promoted the perimovement increase in LFP power in the gamma band, particularly contralateral to the side of voluntary movement. We interpreted the lateralized gamma ERS as a physiological feature that returned with improvement in dopaminergic function. To support this hypothesis we also recorded from two tremor patients without Parkinson’s disease who were implanted in STN. These too showed a relatively lateralized gamma ERS during movement. In contact pairs that were considered to include STN on post-operative MRI, the mean percentage gamma (40–85 Hz) ERS from 200 ms before to 500 ms after movement was 369 and 300% in case 1 and 207% and 133% in case 2, contralateral and ipsilateral to the movement. The time-evolving percentage power changes are illustrated for Case 1 in Fig. 5, which also shows a movement-related ERD within the 8–30 Hz band in this patient (48 and 40%, ipsilateral and contralateral to movement).

**Discussion**

We have provided evidence that levodopa augments movement-related reactivity in the subthalamic area, and shifts it towards a more physiological pattern in patients with Parkinson’s disease. There was a bilaterally symmetrical increase in gamma activity around the time of movement OFF medication, despite the regular absence of a discrete peak in the power spectrum at rest in this frequency range in the OFF state. Upon treatment, however, gamma reactivity became more marked and, during movement, became more lateralized in line with the lateralized gamma band changes.
reported at the level of the sensorimotor cortex (Crone et al., 1998a). The gamma ERS was similarly, relatively lateralized in the STN of our two patients without parkinsonism. However, the lateralization at the level of the STN was relative rather than absolute. This is in contrast to findings at the cortical level by Crone et al. (1998a) in patients with epilepsy, although disease type and paradigm differed from the current study, and no quantitative data were reported to corroborate the purely contralateral nature of the cortical gamma ERS.

The magnitude of the 8–30 Hz band suppression around movement onset was also found to be increased after treatment with levodopa, in accordance with previous studies (Doyle et al., 2005; Devos et al., 2006) and paralleling the deepening of suppression of similar frequencies noted at the cortical level following treatment (Devos et al., 2004). Movement-related suppression of basal ganglia LFP activity in the 8–30 Hz band appears likely to be a physiological feature, as suggested by striatal recordings in healthy monkeys (Courtemanche et al., 2003) and in a non-parkinsonian patient (Sochurkova and Rektor, 2003). This suggestion was further supported by our finding of an ERD in this frequency band in the STN of case 1. However, whether the increased level of 8–30 Hz ERD in STN after levodopa approximates to that under physiological situations remains a presumption. It is also noteworthy that the movement-related suppression of 8–30 Hz activity remained symmetrical after levodopa treatment, as previously reported in Parkinson’s disease (Alegre et al., 2005) although a recent study (Devos et al., 2006) found that the power suppression within this band began earlier contralateral to voluntary movement both ON (5 patients recorded) and OFF medication (10 patients recorded).

In sum, the data are broadly in keeping with the hypothesis that dopaminergic input helps normalize patterns of population activity in the STN. Consistent with this, Alegre et al. (2005) have reported that both the beta ERD and the gamma ERS tend to occur earlier ipsilateral to the more affected limbs, although we found no difference in the degree of power change with respect to the more or less affected side. Another relevant finding may be the tendency for mirror movements in Parkinson’s disease to be reduced following treatment with levodopa, consistent with a more lateralized and physiologically functioning motor circuit (Cincotta et al., 2006a, b).

Possible confounds
Given the general similarity between subcortical and cortical patterns of reactivity it is important to consider whether the power changes picked up at the bipolar contacts of the DBS electrode were really focally generated in the region of the STN. Many arguments have been put forward in support of this contention (reviewed in Brown and Williams, 2005), but the most convincing is the recent demonstration that the discharge of neurons in the STN tends to be locked to the beta activity in the LFP (Levy et al., 2002; Kuhn et al., 2005) and that the firing of neurons in both the upper STN and bordering zona incerta tends to be locked to gamma activity in the LFP (Trottenberg et al., 2006).

Another issue that should be considered is the extent to which the treatment-induced increase in reactivity could be due to changes in sensory reafference related to altered
movement patterns following therapy. However, although this may contribute to differences in reactivity after movement onset, it cannot explain the improved reactivity seen in both frequency bands that starts before movement. Thus, at least some of the change in reactivity must have been a primarily central effect of levodopa. However, whether dopaminergic effects on subthalamic oscillations were directly executed at the level of this nucleus, given the evidence for some dopaminergic innervation of the STN, or, as is more likely, were exerted indirectly through the striatum, remains to be established (Parent and Hazrati, 1995).

As mentioned above there were several inconsistencies between our results and those in earlier studies, as well as between some of these earlier studies. It is therefore important to consider how these may have arisen, particularly as the degree of change in the low frequency band is relatively modest. A strength of our study was that it benefited from a relatively large sample, as opposed to earlier reports which involved about half as many patients recorded both ON and OFF medication (Priori et al., 2002; Alegre et al., 2005; Devos et al., 2006). On the other hand, it must be acknowledged that we analysed about half as many trials as in these earlier reports, although this may not have necessarily been a major source of variance as the signal to noise ratio in the subthalamic region is generally good and noise levels fall off in proportion to the reciprocal of the square root of the number of trials. In addition, there are methodological differences between our and earlier studies. The latter involved either the filtering and squaring of activities in predefined bands (Devos et al., 2006) or spectra estimated from autoregressive models (Alegre et al., 2005). They also concentrated on the latency to onset of power suppression and increase, whereas our measure of mean power over a window derived from time-evolving averaged spectra tended to emphasize depth of change. Finally, we should add that we studied patients with fairly advanced Parkinson’s disease. It is possible that lateralization in terms of latency and depth of low frequency power suppression is seen in patients with less advanced disease, and lost in more advanced disease. However, if this were true then one might have expected lateralization of the low frequency ERD in our patients following treatment with levodopa, but we found no evidence to support this.

Relationship with cortical activities in the 8–30 Hz and gamma bands

A suppression of beta band activity occurs in the contralateral sensorimotor cortex prior to movement but becomes bilateral during movement, while a contralateral rebound in beta activity occurs after movement (Crone et al., 1998b;
Pfurtscheller et al., 2003). In patients with Parkinson’s disease, treatment with levodopa promotes this lateralization of cortical oscillatory activity in the beta band (Devos et al., 2003, 2004). This was not the case with respect to the subthalamic 8–30 Hz (and beta band) ERD here or in the study of Alegre et al. (2005), although it was reported by Devos et al. (2006). As suggested previously (Doyle et al., 2005), the cortical and subcortical beta activities could therefore have partly independent characters, and this is further supported by the absence of an effect of levodopa on the size of the 8–30 Hz power increase in the subthalamic LFP following movement (Alegre et al., 2005; Doyle et al., 2005; but see Devos et al., 2006), despite the clear potentiation of this feature present in the cerebral cortex of patients with Parkinson’s disease (Pfurtscheller et al., 1998; Devos et al., 2003).

Although it is very likely that the oscillatory activity in the STN LFP was locally generated, this by no means implies that it is autonomous. Previous studies have underscored the loop character of these oscillations, demonstrating coherence between activities at various nodes in the basal ganglia cortical loop (Brown et al., 2001; Cassidy et al., 2002; Williams et al., 2002; Fogelson et al., 2006). As a general rule, these studies point to a net drive to the STN from the cortex in the beta band, but a reversal of net information flow in the gamma band, where activity tends to have a temporal lead over that in the cortex. However, it should be stressed that these conclusions are derived from analyses of spectral phase, which do not allow for bidirectional flow (Cassidy and Brown, 2003), and have only considered resting patterns of functional connectivity. The predominant direction of information flow may of course change during movement (see for example, Magill et al., 2006), and the above differential effects of levodopa treatment on oscillatory activities at the cortical and subcortical levels argues that at some level specific aspects of processing may be grafted onto the general looping architecture.

**Movement-related changes in neuronal synchronization in the basal ganglia**

Given that oscillatory activity in the subthalamic LFP likely reflects the synchronization of local neurons (Levy et al., 2002; Kühn et al., 2005; Trottenberg et al., 2006) the improved reactivity of these oscillations following therapy with levodopa suggests that dopaminergic mechanisms accentuate task-related changes in neuronal synchronization in the subthalamic region. Elsewhere it has been speculated that dopaminergic inputs may effectively work to high pass filter synchronized activity in the basal ganglia (Magill et al., 2001; Sharott et al., 2005). This may account for the reduction in baseline levels of 8–30 Hz activity and the increase in baseline gamma activity previously reported (Brown et al., 2001), but would only explain the improved task-related reactivity in these bands if movement was preceded and accompanied by release in dopamine and that this release was increased and/or the system became more sensitive to this release following levodopa. There is evidence to support the former (Magarinos-Ascone et al., 1992; Badgaiyan et al., 2003; Goerendt et al., 2003), but the latter remains speculative.

The improvements in reactivity following levodopa treatment are in the direction that should favour motor-related processing. There is increasing evidence that synchronization of local populations of neurons at frequencies of 8–30 Hz antagonizes motor-related processing and that suppression of this pattern of activity is necessary to allow voluntary movement (reviewed in Brown and Williams, 2005). Motor processing must involve rate coding, temporal coding or a combination of these processes. Recent recordings in primates confirm an inverse relationship between oscillatory LFP activity in the beta band and local task-related rate coding, so that oscillations are preferentially suppressed in the local area of the striatum showing task-related increases in discharge rate (Courtemanche et al., 2003). Parallel observations have been made in the motor cortex, as exemplified by the ’clamping’ of motor cortical single unit firing rates during periods of 20–40 Hz oscillatory synchrony (Murthy and Fetz, 1996) and the tendency of firing rate modulation to occur as oscillations decrease in motor cortical LFP (Donoghue et al., 1998). Conversely, increases in LFP activity in the gamma band are associated with net increases in local neuronal discharge rates (Trottenberg et al., 2006), so the net effect of the increased reactivity in neuronal synchrony following levodopa will be an increase in the potential for rate coding around the time of voluntary movement. The increase in gamma activity may, in addition, confer the opportunity for greater temporal coding at this time, similar to the role posited for gamma band synchronization in the visual cortex (Freiwald et al., 2001). The relative lateralization of the movement-related increase in gamma activity following levodopa would support a more specific role in motor processing than the bilateral change in the beta band. Thus, levodopa may help switch the pattern of neuronal synchronization from one that limits neuronal firing rates to one that increases discharge rates and may form the basis for the dynamic formation of neuronal assemblies suitable for motor processing.

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