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Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity

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ABSTRACT

Parkinson's disease (PD) is associated with exaggerated oscillatory synchrony in the basal ganglia at frequencies over 8–35 Hz. Studies have demonstrated a suppression of local field potential (LFP) activity in the subthalamic nucleus (STN) upon treatment with the dopamine prodrug, levodopa, with the degree of suppression of power in the 8–35 Hz band correlating with the improvement in combined measures of bradykinesia and rigidity. However, these studies do not explicitly address the question of what is more important in predicting clinical change — synchronisation of neuronal activity or the specific frequency within the 8–35 Hz band over which the latter occurs. In addition, they have not demonstrated a relationship between treatment-induced changes in synchronisation and changes in bradykinesia or rigidity on their own. To this end, we collected and analysed LFP and clinical data in 30 patients with PD. We found significant correlations between levodopa-induced power suppression and rigidity and bradykinesia, when these clinical features were considered separately, but only when power suppression profiles were re-aligned to the frequency of peak synchronisation. Under these circumstances correlations with rigidity persisted despite partialising out the effect of bradykinesia and vice versa. These data suggest that levodopa-induced improvements in both rigidity and bradykinesia scale with the degree of suppression of oscillatory power in the STN LFP, and that this is true irrespective of the frequency at which synchronisation occurs across a broad band from 8–35 Hz.

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Introduction

There seems little doubt that patients with advanced Parkinson's disease (PD) have prominent and synchronised neuronal oscillation at frequencies over 8–35 Hz in their cortico-basal ganglia loops (Engel et al., 2005; Schnitzler and Gross, 2005; Uhlhaas and Singer, 2006; Hammond et al., 2007). This activity is suppressed by treatments that improve parkinsonism and seems intimately related to voluntary movement, which is preceded by its suppression (Hammond et al., 2007). Indeed, the timing of the suppression correlates with the timing of subsequent movement (Kühn et al., 2004; Loukas and Brown, 2004; Williams et al., 2005; Doyle et al., 2005). These core observations led to the suggestion that such oscillatory activity may, when exaggerated, relate to bradykinesia (Brown, 2003). Whether this is true of activities across the whole 8–35 Hz band is unclear, with some reports suggesting that synchrony over the 13–20 Hz range may be of greater pathological significance (Priori et al., 2004; Marceglia et al., 2006). Any relationship between synchrony and rigidity is also unclear, although it is in line with the hypothesised role of physiological oscillatory activity in cortico-basal ganglia loops in promoting the postural state (Brown, 2007).

The relationship between oscillatory synchrony and clinical impairment can be investigated in patients with Parkinson's disease through recordings of neuronal activity made intra-operatively or recordings of local field potentials (LFPs) made just after functional neurosurgery, while leads from deep brain stimulation electrodes are still externalised. The usual target in such surgery is the subthalamic nucleus (STN). Two small studies have reported a positive correlation between % change in combined bradykinesia and rigidity scores and % change in the power in the STN LFP peak following treatment with levodopa (Kühn et al., 2006; Ray et al., 2008). A further intra-operative study has demonstrated a positive correlation between the incidence of oscillatory neurons in STN and the patient's benefit from dopaminergic medications, although not with baseline motor deficits off medication (Weinberger et al., 2006). However, these studies do not explicitly address the question of what is more important in predicting clinical change — synchronisation of neuronal activity or

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the specific frequency within the 8–35 Hz band over which the latter occurs. In addition, they have not demonstrated a relationship between treatment-induced changes in synchronisation and changes in bradykinesia or rigidity on their own. To this end, we collected and analysed LFP and clinical data in a large sample of patients, including those previously reported by Kühn et al., 2006 and Ray et al., 2008, and a further 14 cases.

Methods

Patients and surgery

All patients had PD and participated with informed consent and the permission of the ethics committees of the Charite University Hospital, Berlin, Germany and the John Radcliffe Hospital, Oxford, UK. Their clinical details are summarised in Table 1. Implantation of STN DBS electrodes was performed bilaterally in all but two cases (18 and 30). The DBS electrode used was model 3389 in Berlin and 3387 in Oxford (Medtronic Neurological Division, Minneapolis, USA). Contact 0 was the most caudal and contact 3 was the most rostral. The intended coordinates at the tip of contact 0 were 12 mm from the midline, 0–2 mm behind the midcommissural point and 4–5 mm below the anterior commissural–posterior commissural line. Adjustments to the intended coordinates were made in accordance with the direct visualisation of STN in individual stereotactic MRI and the results of microelectrode recordings (cases 1–23). Correct placement of the DBS electrodes in the region of the STN was further supported by: [1] effective intra-operative macrostimulation; [2] post-operative T2 weighted MRI compatible with the placement of at least one electrode contact in the STN region; [3] significant improvement in Unified Parkinson's Disease Rating Scale (UPDRS) motor score during chronic DBS (Table 1).

Recordings and clinical assessment

Patients were studied 3–6 days postoperatively during the period of externalisation of DBS electrodes prior to their connection to the stimulator device. In all patients LFP recordings were performed at rest after the patient had been off medication overnight (OFF-drug) and about 1 h after the patient had taken 200 mg of levodopa or 1.5 times their usual morning levodopa dose (ON-drug). The minimum duration of LFP recordings was 100 s OFF-drug and 100 s ON-drug. Deep brain activity was recorded bipolarly from adjacent contact pairs (01, 12, 23) of each DBS electrode, with the exception of the left side in case 16, in which recordings failed for technical reasons. In Berlin, with one exception, signals were amplified and filtered at 1–250 Hz using a custom-made, high impedance amplifier (which had as its front end input stage the INA128 instrumentation amplifier, Texas Instruments Incorporated 12500 TI Boulevard Dallas Texas, USA) and recorded through a 1401 A-D converter (Cambridge Electronic Design [CED], Cambridge, UK) onto a computer using Spike2 software (Cambridge Electronic Design). In case 21 a digitimer amplifier (D 360, Digitimer, Welwyn Garden City, Herfordshire, U.K) was used. Signals were sampled at 1 kHz (with 3 exceptions that were sampled at 625 Hz) and monitored on-line. In Oxford signals were amplified and filtered at 0.2–1 kHz using CED 1902 amplifiers, sampled at 4 kHz and recorded through a CED 1401 A-D converter onto a computer using Spike2 software.

Patients differed in the timing of their ON-drug and OFF-drug clinical assessments using the UPDRS motor score. In Berlin, these were performed on the same day as the electrophysiological recordings. In Oxford, these were performed peri-operatively, a mean of 3 months from surgery (Ray et al., 2008). Changes in motor symptoms with levodopa were calculated using hemibody scores for bradykinesia (sum of UPDRS motor score sub-items 23–26 including finger taps, open and close hand movements, rapid alternating pronation and supination hand movements, and leg movements), rigidity (sum of UPDRS motor score sub-item 22 for arm and leg) and rest tremor (sum of UPDRS motor score sub-item 20 for arm and leg) contralateral to the recording site. The percentage improvement of UPDRS for each item was calculated as ([hemibody score OFF−med-hemibody score ON-med]/hemibody score OFF-med)×100.

Analysis

Where necessary, data were interpolated (3 cases from Berlin) or down-sampled (cases from Oxford) to a common sampling rate of 1 kHz. Using the discrete Fourier transform, autospectra of the LFP were estimated by dividing the records into a number of disjoint sections of equal duration (1024 points) affording to a frequency resolution of ~1 Hz (0.98 Hz), and estimating spectra by averaging across these discrete sections. Based on the hypothesis that 8–35 Hz activity may promote bradykinesia and rigidity (see Introduction), we picked the contact pair that displayed the maximum 8–35 Hz activity OFF-med for further analysis. The maximum peak within the 8–35 Hz frequency band was determined for this contact pair in individual OFF-drug recordings.

Fifty-one (89%) of the available 57 spectra (one for each electrode) in the OFF-drug state had one major peak in the 8–35 Hz band. This had the same peak frequency (±2 Hz; mean absolute difference in frequencies 0.25+[SD] 0.78) as ON-drug or the peak was altogether absent ON-drug (21 sides) (Fig. 1A). One side in one patient failed to show a distinct peak within the 8–35 Hz band OFF-med and was excluded from further analysis (left STN in case 7). Five other sides were not included in subsequent analysis because the pattern of their LFPs would have lead to an artificial over-estimate of the effect of levodopa on LFP reactivity around the frequency of the peak in the OFF-drug state (Fig. 2). Specifically, three sides had a single peak OFF- and ON-drug, but the peak ON-drug was 8, 11 and 5 Hz higher than off (left and right in case 13, right in case 14; 39%, 64% smaller than off, 57% bigger than off, respectively). One side had 2 peaks OFF-drug, but the biggest peak OFF-drug was 3 Hz higher ON-drug and even bigger (77%) than when OFF-drug, although the smaller peak OFF-drug was modestly (12%) smaller still ON-drug (left in case 14). Finally one side had two peaks OFF-drug (right in case 19). The bigger of the two, at lower frequency was bigger OFF-drug and 58% smaller ON-drug, but the second peak became 450% bigger ON-drug (Fig. 1B).

The 51 simple OFF- and ON-drug pairs of spectra were selected for further analysis as the suppression of synchronisation by levodopa could be captured through the analysis of the change in a single peak. Spectra were taken from 5–45 Hz: frequencies <5 Hz were omitted to avoid confounds due to movement artifact secondary to tremor or dyskinesias, and frequencies around 50 Hz were rejected to avoid contamination by line noise. Only one contact pair (that with the highest 8–35 Hz activity OFF-drug) was selected for analysis per side and this was fixed for OFF- and ON-drug data. Spectra for each side across subjects were re-aligned to the peak power value in the OFF-drug state within the 8–35 Hz band of interest and the percentage change in power ON-drug per 1 Hz bin was calculated as ([power OFF-drug−power ON-drug]/power OFF-drug)×100. The % change in power in each 1 Hz bin with levodopa treatment was then correlated with the % change in contralateral hemibody bradykinesia, rigidity and tremor UPDRS sub-scores with levodopa. This meant that correlations between power and motor impairment were possible according to frequencies defined with respect to their closeness or distance from the spectral peak in the OFF-drug state. We elected to use % change in spectra to reduce the variance introduced by slight differences in surgical targeting between sides and patients. Similarly, we used the % change in clinical scores to limit domination of the results by those with the severest scores.

Percentage changes in bradykinesia and rigidity sub-scores and power in all but three frequency bins (5–7 Hz) were normally

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