European Journal of Neuroscience, Vol. 23, pp. 1956–1960, 2006 doi:10.1111/j.1460-9568.2006.04717.x

SHORT COMMUNICATION
Reduction in subthalamic 8–35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease

Andrea A. Kühn,[1,2] Andreas Kupsch,[2] Gerd-Helge Schneider[3] and Peter Brown[1]
[1]Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, Queen Square, London WCIN 3BG, UK
[2]Department of Neurology and
[3]Department of Neurosurgery, Charité, University Medicine Berlin, Campus Virchow, Berlin, Germany

Keywords: beta activity, human, Parkinsonism, subthalamic nucleus

Abstract

Strong synchronization of neuronal activity occurs in the 8–35 Hz band in the subthalamic nucleus (STN) of patients with Parkinson's disease (PD) and is evident as oscillatory local field potential (LFP) activity. To test whether such synchronization may contribute to bradykinesia and rigidity, we sought correlations between the suppression of synchronization at 8–35 Hz in STN and the reduction in Parkinsonism with levodopa. LFPs were recorded on and off medication from STN deep-brain stimulation electrodes in nine PD patients. LFP power was calculated over the frequencies of the most prominent spectral peak within the 8–35 Hz frequency band on each of 17 sides (off medication), and over the frequencies of any peak in the 60–90 Hz band, if present (seven sides, on medication). Levodopa-induced reduction of LFP power over these two frequency ranges was then correlated with improvement in motor impairment as assessed by the Unified Parkinson's Disease Rating Scale (UPDRS). The reduction in peak activity in the 8–35 Hz band with levodopa positively correlated with the improvement in the contralateral hemibody motor UPDRS score with levodopa ($r = 0.811$, $P < 0.001$) as well as with hemibody subscores of akinesia-rigidity ($r = 0.835$, $P < 0.001$), but not tremor. A trend for negative correlations was found between peak 60–90 Hz LFP power and UPDRS hemibody score, suggesting that positive correlations were relatively frequency-specific. Our results support a link between levodopa-induced improvements in bradykinesia and rigidity and reductions in population synchrony at frequencies < 35 Hz in the region of the STN in patients with PD.

Introduction

How basal ganglia dysfunction leads to parkinsonism is not yet entirely clear. Depth recordings in patients with Parkinson's disease (PD) have established the existence of synchronization within neuronal populations of the basal ganglia in several different frequency bands (Cassidy *et al*., 2002; Levy *et al*., 2002; Priori *et al*., 2004; Kühn *et al*., 2005), leading to a new schema for basal ganglia disorders in which the nature of synchronized bursting within the basal ganglia is critical in determining parkinsonism (Marsden & Obeso, 1994; Brown, 2003). This synchronization tends to predominate in the beta band (14–35 Hz), and it has been suggested that excessive synchronization in the beta band may contribute to parkinsonism (Brown, 2003). In support of this theory, a decrease in beta power occurs before and during movement (Levy *et al*., 2002; Priori *et al*., 2002; Kühn *et al*., 2004; Doyle *et al*., 2005). In addition, there is a strong relationship between reaction times and suppression of beta activity within the subthalamic nucleus (STN) of PD patients (Kühn *et al*., 2004).

However, these observations do not specifically address whether high background levels of synchronized activity might contribute to more general features of motor impairment in PD, not just delayed motor onset. In addition, the posited involvement of beta synchrony in parkinsonism ignores the fact that parkinsonism is seen in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated rhesus monkeys in which synchronization predominates over the lower 8–15 Hz range, and may not simply be accounted for by the presence of tremor, as in the MPTP-treated vervet monkey (Filion & Tremblay, 1991; Bergman *et al*., 1994; Nini *et al*., 1995; Raz *et al*., 1996). The latter raises the possibility that it is population synchrony *per se* across a broad band, rather than just in the beta band, that may contribute to parkinsonism (see also Brown & Williams, 2005; Fogelson *et al*., 2005; Williams *et al*., 2005). Accordingly, here we seek a correlation between antiparkinsonian treatment-induced reduction in synchronization across the whole 8–35 Hz frequency band, as evidenced by the suppression of peaks in spectra of subthalamic local field potential (LFP) activity, and simultaneously assessed improvement in motor function, as measured clinically with the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS).

Correspondence: Dr A. Kühn, [1]Sobell Department of Motor Neuroscience and Movement Disorders, as above.
E-mail: a.kuhn@ion.ucl.ac.uk

Received 28 September 2005, revised 13 January 2006, accepted 6 February 2006

Materials and methods

Patients and surgery

All patients [$n = 9$, age 62 ± 3 years (mean ± SEM), disease duration 12.6 ± 1.4 years] participated with informed consent and the permis-

sion of the local ethics committees. Their clinical details are summarized in Supplementary material, Table S1. Implantation of bilateral STN deep brain stimulation (DBS) electrodes was performed in all subjects for treatment of severe PD. The DBS electrode used was model 3389 (Medtronic Neurological Division, Minneapolis, MN, 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 visualization of STN in individual stereotactic magnetic resonance images (MRI) and the results of microelectrode recordings (patients 1, 2, 4, 5, 7, 8). Correct placement of the DBS electrodes in the region of the subthalamic nucleus was further supported by: (i) effective intraoperative macrostimulation; (ii) postoperative T2-weighted MRI compatible with the placement of at least one electrode contact in the STN region (Supplementary material, Fig. S1 for a representative example of postoperative MRI), as performed by an experienced neurosurgeon (Marwan Hariz) from another institution who was blinded to the clinical and electrophysiological results; (iii) significant improvement in UPDRS motor score during chronic DBS off medication compared with UPDRS off medication with stimulator switched off (mean improvement 53.9 ± 5.3%, $P = 0.008$, Wilcoxon Signed Ranks Test); and (iv) significant decrease in the levodopa-equivalent dose in all patients (mean reduction of 71.2 ± 6.9%, $P = 0.008$, Wilcoxon Signed Ranks Test).

Recordings and clinical assessment

Patients were studied 5.7 ± 0.3 days postoperatively during the period of externalization 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-med) and about 1 h after the patient had taken 200 mg of levodopa or 1.5 times their usual morning levodopa dose (ON-med). The mean duration of LFP recordings was 324.2 ± 31.6 s OFF-med and 303.3 ± 42.5 s ON-med. Deep brain activity was recorded bipolarly from adjacent contact pairs (01, 12, 23) of each DBS electrode. 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, Dallas, TX, USA) and recorded through a 1401 analog/digital converter (Cambridge Electronic Design, Cambridge, UK) onto a computer using Spike2 software (Cambridge Electronic Design). Signals were sampled at either 625 Hz ($n = 3$) or 1 kHz ($n = 6$) and monitored on-line.

At the same time, assessment of parkinsonian motor symptoms ON-med and OFF-med was performed using the UPDRS motor score. Half points were used to increase the sensitivity of the test. Changes in motor symptoms with levodopa were calculated using hemibody scores (sum of UPDRS motor score subitems 20–26) contralateral to the recording site. The percentage improvement of UPDRS was calculated as [100 × (hemibody score OFF-med − hemibody score ON-med)/hemibody score OFF-med].

Analysis

Data were down-sampled to a common sampling rate of 512 Hz. Using the discrete Fourier transform, autospectra of the LFP were estimated by dividing the records into a number of disjoint sections of equal duration (512 points), and estimating spectra by averaging across these discrete sections (Halliday *et al*., 1995). Based on the hypothesis that 8–35 Hz activity may promote bradykinesia and rigidity, we picked the contact pair that displayed the maximum 8–35 Hz activity OFF-med for further analysis. In 14 out of 17 DBS electrodes (82%), this contact pair included at least one contact that most likely lay within the STN according to the postoperative MRI. At this contact pair, the maximum peak within the 8–35 Hz frequency band was determined in individual OFF-med recordings. The existence of a peak was confirmed by control charting and change point analysis, using commercial software (Changing-Point Analyser 2.0 shareware program; Taylor Enterprises, Illinois, IA, USA, http://www.variation.com; for previous applications see Kühn *et al*., 2004; Fogelson *et al*., 2005). In contrast to the study by Doyle *et al*. (2005), peak power was measured over the individually defined peak frequency and the adjacent two bins on either side of the peak frequency (i.e. over a 5-Hz band) in the OFF-med recordings and repeated in the ON-med recordings using the same narrow frequency band. Thereafter, the percentage decrease in power ON-med was calculated [(power OFF-med − power ON-med)/power OFF-med × 100]. 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 patient 7). The reduction of maximum power in the 8–35 Hz range following levodopa treatment was then correlated with the improvement in contralateral hemibody UPDRS scores with levodopa. We also subdivided the contralateral hemibody scores into their tremor and akinesia-rigidity components (UPDRS subitems 20 and 22–26) to test for correlations between oscillatory activity and these components of the extrapyramidal syndrome.

To determine if positive correlations were frequency-specific we also assessed power changes within the 60–90 Hz (gamma) band. Analogous to peak definition in the low-frequency range, only those recordings that showed a distinct gamma peak ON-med ($n = 7$ STN) were used in this analysis. Gamma peaks were defined ON-med because gamma activity is more likely to occur during dopaminergic stimulation (Brown *et al*., 2001; Cassidy *et al*., 2002). Peaks in this band were confirmed by control charting and change point analysis and power measured over a 5-Hz band centred on the peak frequency.

Correlations were performed using bivariate correlation for non-parametric data (Spearman's Rho) as described in the results (SPSS for Windows version 11, SSPS Inc, Chicago, IL, USA). The effect of levodopa on LFP power was tested using the two-tailed Wilcoxon signed ranks test.

Results

In individual recordings, the greatest peak between 8 and 35 Hz in the power spectrum was observed more often in the beta band (14–35 Hz, 11/17 sides) than the alpha band (8–13 Hz, 6/17 sides), but this probably related to the broader nature of the beta band. The mean power of individually defined LFP peaks in the 8–35 Hz frequency band was significantly reduced after levodopa intake by 58.9 ± 7.5% ($P < 0.001$, Wilcoxon signed rank test; examples of raw LFP data and corresponding power spectra are given in Supplementary material, Fig. S1). The reduction in peak 8–35 Hz power with levodopa positively correlated with the improvement in contralateral hemibody UPDRS score with levodopa ($r = 0.811$, $P < 0.001$, $n = 17$ STN; Fig. 1A). Separate correlations of improvement in tremor and akinesia-rigidity with levodopa-induced reduction in peak 8–35 Hz power revealed a positive correlation with akinesia-rigidity ($r = 0.835$, $P < 0.001$; Fig. 1B) but not tremor ($r = 0.254$, $P = 0.544$). Note that alpha and beta activities are similarly distributed within the scatter plots illustrated in Fig. 1A and B. Indeed, the correlations in the two bands were similar in strength in

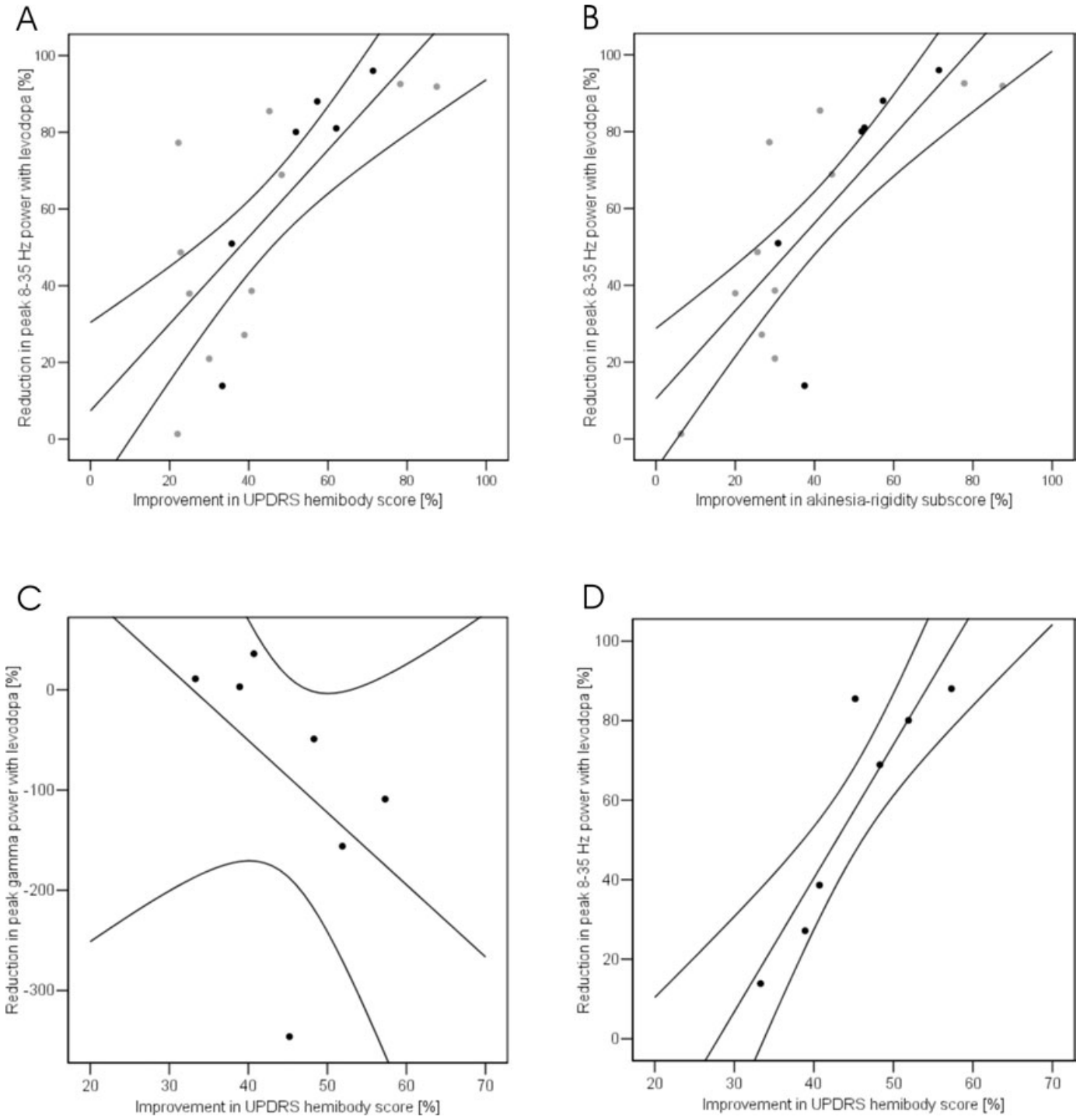

FIG. 1. Scatter plots. (A) Reduction in power of peaks in the 8–35 Hz band with levodopa correlates with improvement in UPDRS hemibody motor score after levodopa ($r = 0.811$, $P < 0.001$) and (B) with improvement in akinesia-rigidity UPDRS subscore ($r = 0.835$, $P < 0.001$). Note that alpha (black dots) and beta (grey dots) activities are similarly distributed within the scatter plot. (C) Levodopa-induced reduction in gamma (60–90 Hz) peaks showed a trend for negative correlation with improvement in contralateral hemibody motor UPDRS score after levodopa ($r = –0.643$, $P = 0.119$, $n = 7$ sides), i.e. an increase in gamma activity with levodopa tended to be associated with improvement in motor symptoms after levodopa. (D) Correlation of levodopa-induced reduction in peak 8–35 Hz power with UPDRS hemibody scores after levodopa for the same seven sides illustrated in C ($r = 0.893$, $P = 0.007$). Positive correlations are frequency-specific. Black lines represent the mean linear correlation and the 95% confidence limits.

those patients who simultaneously displayed both alpha and beta peaks ($n = 5$ sides). There was a positive correlation between improvement in contralateral hemibody UPDRS score and modulation in alpha power ($r = 1$, $P < 0.01$) as well as with reduction in beta power ($r = 0.900$, $P = 0.037$; data not shown).

Modulation of gamma power with levodopa (in $n = 7$ sides that displayed a distinct gamma peak ON-med) revealed a trend for a negative correlation with motor improvement ($r = –0.643$, $P = 0.119$; Fig. 1C). In the same subgroup of seven sides, reduction in 8–35 Hz peak frequency activity with levodopa positively

correlated with levodopa-induced motor improvement ($r = 0.893$, $P = 0.007$; Fig. 1D), corroborating the frequency specificity of positive correlations.

Discussion

We have shown that the levodopa-induced reduction in peak 8–35 Hz power is strongly positively correlated with the improvement in UPDRS motor score following this drug. Although correlation does not prove causation, the demonstration of a strong correlation supports the hypothesis that levodopa-induced suppression of synchronized oscillatory activity in the 8–35 Hz band may be related to improvement in parkinsonism, particularly akinesia and rigidity.

Recent studies suggest that abnormal firing patterns and oscillatory neuronal activity within the basal ganglia-motor cortex loop may make a major contribution to the pathophysiology of parkinsonism and other movement disorders. Analysis of neuronal firing patterns from microelectrode recordings have revealed a significant increase in correlated activity within the STN and between different nuclei of the basal ganglia in MPTP-treated monkeys (Bergman *et al*., 1994; Nini *et al*., 1995; Raz *et al*., 1996). Similarly, in PD patients, synchronization within local neuronal populations in the basal ganglia is evidenced by LFP oscillations (reviewed in Brown, 2003; Brown & Williams, 2005), and coupling has been demonstrated between single-unit and LFP recordings in STN (Levy *et al*., 2002; Kühn *et al*., 2005). Abnormal synchronization and ineffective coding of information could therefore contribute to the symptoms of PD (Brown, 2003). The present demonstration of a strong positive correlation between the reduction in peak 8–35 Hz LFP power in the STN after levodopa therapy and improvement in UPDRS following levodopa further supports the hypothesis that a pathological synchronization of neuronal activity in this frequency range contributes to the pathophysiology of parkinsonism, and helps reconcile findings in parkinsonian non-human primates where abnormal synchronization generally predominates at frequencies below those of the beta (14–35 Hz) band, previously associated with motor impairment in PD patients (Brown, 2003).

Although a broad 8–35 Hz band was involved, there was still evidence that positive correlations were relatively frequency-selective and related to bradykinesia and rigidity, but not to tremor. Thus, in the high gamma (60–90 Hz) band there was a trend for a negative correlation between levodopa-induced motor improvement and modulation of power, consistent with the proposal that high-frequency activity may be prokinetic in nature (Brown, 2003). We did not assess power changes at frequencies below 8 Hz because a distinct peak in the power spectrum at rest tremor frequencies (4–8 Hz) was only found on two sides. Moreover, LFPs at these frequencies may be contaminated by movement artefacts. Synchronization at 4–8 Hz is, however, commonly found in microelectrode recordings of pairs of neurons in parkinsonian humans and monkeys, and may positively correlate with tremor (Bergman *et al*., 1994; Raz *et al*., 1996; Levy *et al*., 2000).

The positive correlation between levodopa-induced reduction in synchronization in the STN area and levodopa's therapeutic efficacy shown here is paralleled by a similar correlation between levodopa-induced suppression of inter-regional synchronization in the cerebral cortex and the therapeutic efficacy of levodopa (Silberstein *et al*., 2005). This suggests that excessive synchronization throughout the basal ganglia-cortical loop may contribute to parkinsonism. The same may, in principle, also occur in the corticospinal system in PD, where abnormal coupling at low frequency is suppressed by levodopa in tandem with motor improvement (Salenius *et al*., 2002). However, in this system pathological coupling occurs at frequencies under 12 Hz, with corticomuscular coupling in the beta band being paradoxically increased by levodopa (Salenius *et al*., 2002). This raises the possibility that different components of the motor system have distinct patterns of susceptibility to oscillatory processes in the parkinsonian state, as also suggested by the fact that parkinsonism is improved by stimulation of the subthalamic nucleus at high frequency but by stimulation of the pedunculopontine nucleus at low frequency (Jenkinson *et al*., 2004). Nevertheless, correlations between reductions in synchronization and treatment effects support a link between synchronized oscillatory activity in the 8–35 Hz band at subthalamic and cortical levels and bradykinesia and rigidity in PD.

Supplementary material

The following supplementary material may be found on
http://www.blackwell-synergy.com

Table. S1. Summary of patient details (all patients had idiopathic Parkinson's disease).

Fig. S1. Example of levodopa-induced modulation of oscillatory LFP activity in a representative patient.

Acknowledgements

Peter Brown is supported by the Medical Research Council of Great Britain, and Andrea Kühn by a fellowship from the Charité (Rahel Hirsch Stipendium). We thank Marwan Hariz for evaluation of DBS electrode localization in all patients and Thomas Trottenberg and Anatol Kivi for help with clinical evaluation of patients.

Abbreviations

DBS, deep brain stimulation; LFP, local field potentials; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MRI, magnetic resonance imaging; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; STN, subthalamic nucleus.

References

Bergman, H., Wichmann, T., Karmon, B. & DeLong, M.R. (1994) The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. *J. Neurophysiol.*, **72**, 507–520.

Brown, P. (2003) Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. *Mov. Disord.*, **18**, 357–363.

Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P. & Di Lazzaro, V. (2001) Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J. Neurosci.*, **21**, 1033–1038.

Brown, P. & Williams, D. (2005) Basal ganglia local field potential activity: character and functional significance in the human. *Clin. Neurophysiol.*, **116**, 2510–2519.

Cassidy, M., Mazzone, P., Oliviero, A., Insola, A., Tonali, P., Di Lazzaro, V. & Brown, P. (2002) Movement-related changes in synchronization in the human basal ganglia. *Brain*, **125**, 1235–1246.

Doyle, L.M., Kühn, A.A., Hariz, M., Kupsch, A., Schneider, G.H. & Brown, P. (2005) Levodopa-induced modulation of subthalamic beta oscillations during self-paced movements in patients with Parkinson's disease. *Eur. J. Neurosci.*, **21**, 1403–1412.

Filion, M. & Tremblay, L. (1991) Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. *Brain Res.*, **547**, 142–151.

Fogelson, N., Pogosyan, A., Kühn, A.A., van Kupsch, A.B.G., Speelman, H., Tijssen, M., Quartarone, A., Insola, A., Mazzone, P., Di Lazzaro, V., Limousin, P. & Brown, P. (2005) Reciprocal interactions between oscillatory activities of different frequencies in the subthalamic region of patients with Parkinson's disease. *Eur. J. Neurosci.*, **22**, 257–266.

Halliday, D.M., Rosenberg, J.R., Amjad, A.M., Breeze, P., Conway, B.A. & Farmer, S.F. (1995) A framework for the analysis of mixed time series/point process data – theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. *Prog. Biophys. Mol. Biol.*, **64**, 237–278.

Jenkinson, N., Nandi, D., Miall, R.C. & Stein, J.F. (2004) Pedunculopontine nucleus stimulation improves akinesia in a Parkinsonian monkey. *Neuroreport*, **15**, 2621–2624.

Kühn, A.A., Trottenberg, T., Kivi, A., Kupsch, A., Schneider, G.H. & Brown, P. (2005) The relationship between local field potential and neuronal discharge in the subthalamic nucleus of patients with Parkinson's disease. *Exp. Neurol.*, **194**, 212–220.

Kühn, A., Williams, D., Kupsch, A., Limousin, P., Hariz, M., Schneider, G.H., Yarrow, K. & Brown, P. (2004) Event-related beta desynchronization in human subthalamic nucleus correlates with motor performance. *Brain*, **127**, 735–746.

Levy, R., Ashby, P., Hutchison, W.D., Lang, A.E., Lozano, A.M. & Dostrovsky, J.O. (2002) Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. *Brain*, **125**, 1196–1209.

Levy, R., Hutchison, W.D., Lozano, A.M. & Dostrovsky, J.O. (2000) High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. *J. Neurosci.*, **20**, 7766–7775.

Marsden, C.D. & Obeso, J.A. (1994) The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain*, **117**, 877–897.

Nini, A., Feingold, A., Slovin, H. & Bergman, H. (1995) Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism. *J. Neurophysiol.*, **74**, 1800–1805.

Priori, A., Foffani, G., Pesenti, A., Bianchi, A., Chiesa, V., Baselli, G., Caputo, E., Tamma, F., Rampini, P., Egidi, M., Locatelli, M., Barbieri, S. & Scarlato, G. (2002) Movement-related modulation of neural activity in human basal ganglia and its L-DOPA dependency: recordings from deep brain stimulation electrodes in patients with Parkinson's disease. *Neurol. Sci.*, **23** (Suppl. 2), S101–S102.

Priori, A., Foffani, G., Pesenti, A., Tamma, F., Bianchi, A.M., Pellegrini, M., Locatelli, M., Moxon, K.A. & Villani, R.M. (2004) Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp. Neurol.*, **189**, 369–379.

Raz, A., Feingold, A., Zelanskaya, V., Vaadia, E. & Bergman, H. (1996) Neuronal synchronization of tonically active neurons in the striatum of normal and parkinsonian primates. *J. Neurophysiol.*, **76**, 2083–2088.

Salenius, S., Avikainen, S., Kaakkola, S., Hari, R. & Brown, P. (2002) Defective cortical drive to muscle in Parkinson's disease and its improvement with levodopa. *Brain*, **125**, 491–500.

Silberstein, P., Pogosyan, A., Kuhn, A., Hotton, G., Tisch, S., Kupsch, A., Dowsey-Limousin, P., Hariz, M. & Brown, P. (2005) Cortico-cortical coupling in Parkinson's disease and its modulation by therapy. *Brain*, **128**, 1277–1291.

Williams, D., Kühn, A., Kupsch, A., van Tijssen, M.B.G., Speelman, H., Hotton, G., Loukas, C. & Brown, P. (2005) The relationship between oscillatory activity and motor reaction time in the parkinsonian subthalamic nucleus. *Eur. J. Neurosci.*, **21**, 249–258.