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Patterning of globus pallidus local field potentials differs between Parkinson's disease and dystonia

Paul Silberstein,[1] Andrea A. Kühn,[1,3] Andreas Kupsch,[3] Thomas Trottenberg,[2] Joachim K. Krauss,[4] Johannes C. Wöhrle,[5] Paolo Mazzone,[6] Angelo Insola,[7] Vincenzo Di Lazzaro,[8] Antonio Oliviero,[8] Tipu Aziz[2] and Peter Brown[1]

[1]*Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, London and* [2]*Department of Neurological Surgery, Radcliffe Infirmary, Oxford, UK,* [3]*Department of Neurology, Charité Campus Virchow, Humboldt University Berlin, Berlin,* [4]*Department of Neurosurgery and* [5]*Department of Neurology, University Hospital, Klinikum Mannheim, Mannheim, Germany,* [6]*Operative Unit of Functional and Stereotactic Neurosurgery and* [7]*Operative Unit of Neurophysiology, CTO 'A. Alesini' Hospital and* [8]*Institute of Neurology, Università Cattolica, Rome, Italy*

Correspondence to: Dr P. Brown, Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, Queen Square, London WCIN 3BG, UK. E-mail: p.brown@ion.ac.uk

Summary

Here we test the hypothesis that there are distinct temporal patterns of synchronized neuronal activity in the pallidum that characterize untreated and treated parkinsonism and dystonia. To this end we recorded local field potentials (LFPs) from the caudal and rostral contact pairs of macroelectrodes implanted into the pallidum of patients for the treatment of Parkinson's disease (12 cases recorded on and off medication, 17 macroelectrodes) and dystonia (10 cases, 19 macroelectrodes). Percentage LFP power in the 11–30 Hz band was decreased and that in the 4–10 Hz band increased across both contact pairs in treated Parkinson's disease compared with untreated Parkinson's disease. Dystonic patients had even less 11–30 Hz power and greater 4–10 Hz power compared with untreated or treated Parkinson's disease patients. The change in the 4–10 Hz band in patients with dystonia was particularly manifest in the more rostral contact pair, presumed to be within or bridging the globus pallidus externus. We conclude that untreated and treated Parkinson's disease and dystonia are characterized by different spatiotemporal patterns of activity in the human pallidum.

Keywords: local field potentials; dystonia; Parkinson's disease

Abbreviations: A–D = analogue-to-digital conversion; GPe = globus pallidus externus; GPi = globus pallidus internus; HFS = high-frequency stimulation; LFP = local field potential; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; STN = subthalamic nucleus

Introduction

High-frequency stimulation (HFS) of the pallidum has been shown to be of therapeutic benefit in the treatment of Parkinson's disease (Siegfried and Lippitz, 1994; Bejjani *et al*., 1997, 1998; Davis *et al*., 1997; Gross *et al*., 1997; Pahwa *et al*., 1997; Siegfried and Wellis, 1997; Yelnik *et al*., 2000) and dystonia (Kumar *et al*., 1999; Coubes *et al*., 2000). In Parkinson's disease, stimulation of the pallidum improves motor performance by 54% (SD 33%) on evaluation of the UPDRS (Unified Parkinson's Disease Rating Scale) Part III (Volkmann *et al*., 2001) and may completely abolish levodopa-induced dyskinesias (Krack *et al*., 1998*a*; Yelnik *et al*., 2000). Generalized dystonia can be improved by up to 90% by pallidal stimulation (Kumar *et al*., 1999; Coubes *et al*., 2000).

The therapeutic success of pallidal functional neurosurgery for movement disorders has revealed two related paradoxes. First, how does lesioning or HFS of one of the two major outflow stations of the basal ganglia, the globus pallidus internus (GPi), improve parkinsonism without any clear deleterious effects upon motor function (Marsden and Obeso,

1994; Bar-Gad and Bergman, 2001)? Secondly, how do the same interventions improve such disparate states as parkinsonism (Baron *et al*., 1996; Tronnier *et al*., 1997; Yelnik *et al*., 2000), dyskinesia (Baron *et al*., 1996; Krack *et al*., 1998*b*; Yelnik *et al*., 2000) and dystonia (Tronnier and Fogel, 2000; Coubes *et al*., 2000; Vercueil *et al*., 2001)?

It has been suggested that the first of these paradoxes might be explained if the parkinsonian state was characterized by abnormal patterning of pallidal outflow, so that no activity is better than bad or noisy activity, although the precise nature of such abnormal patterning was not specified (Marsden and Obeso, 1994). In line with this, microelectrode studies from the GPi in normal monkeys and monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as well as Parkinson's disease patients on and off levodopa therapy have shown alterations not only in neuronal firing rates but also in the temporal patterning and synchronization of neuronal activity (Raz *et al*., 2000; Levy *et al*., 2001). Local field potential (LFP) recordings in the GPi, which probably represent the product of synchronous activity in a population of neurons (Brown *et al*., 2001), also demonstrate an altered pattern of frequency-dependent coupling between the GPi, the subthalamic nucleus (STN) and the motor cortex in patients with Parkinson's disease, dependent on the dopaminergic state (Cassidy *et al*., 2002; Williams *et al*., 2002). Thus the bulk of evidence points to a difference in patterning in the off and on states. The knock-on effects of such patterning could be either obliterated by pallidotomy or suppressed by high-frequency pallidal stimulation (Anderson *et al*., 2003).

The paradoxical improvement in differing disease states with pallidal lesions and stimulation might also be explained if there was more than one type of abnormal patterning of pallidal outflow. Here, the evidence is more limited, but in dystonia patterns of neuronal discharge have been reported that differ from those in normal primates (Lenz *et al*., 1999; Vitek *et al*., 1999;), although the extent to which they may differ from those in parkinsonian primates and Parkinson's disease patients is unclear.

Here we test the hypothesis that there are distinct temporal patterns of synchronized neuronal activity in the pallidum that characterize parkinsonism and dystonia. LFPs were recorded from the different contacts of macroelectrodes inserted into the pallidum of patients for the treatment of Parkinson's disease and dystonia. Patients were studied while alert, during the interval between implantation and subsequent connection of the macroelectrode to a subcutaneous stimulating device. By recording the LFP from macroelectrode contacts rather than single-unit activity from microelectrodes we were able to concentrate on changes in the synchronous activity across many neurons, as unsynchronized neuronal activity is cancelled out and lost in the LFP. We focused our attention on LFP activity in the 4–10, 11–30 and 65–85 Hz bands, as past work suggests that these activities may differ in functional significance (Brown *et al*., 2001; Williams *et al*., 2002). The results confirm that untreated Parkinson's disease, treated Parkinson's disease and dystonia can be distinguished by the pattern of synchronization of local activity evident in the LFPs recorded from the human globus pallidus.

Methods

Patients and surgery

All patients participated with informed consent and with the agreement of the joint ethical committee of the National Hospital for Neurology and Neurosurgery and the Institute of neurology, London; the Ethics Committee of The Clarité-Universitätsmedizin, Berlin, Campus Virchow-Klinikum and the Ethics Committee of the A. Alesini Hospital, Rome. Clinical details are summarized in Table 1.

Indications for surgery were medication-refractory severe dystonia and treatment-resistant Parkinson's disease with or without levodopa-induced dyskinesias. Dyskinesias were severe preoperatively in nine out of the 12 Parkinson's disease patients (13 out of a total of 17 macroelectrodes in the Parkinson's disease patients). Patients were recorded 1–6 days postoperatively, at a time when levodopa-induced dyskinesias tended to be less evident because of temporary microlesional effects. There was no difference in the delay between surgery and recording between Parkinson's disease (mean 3.4 days) and dystonic (mean 2.9 days) patients, and Parkinson's disease patients were recorded on and off medication on the same day. Off-period dystonias were not seen in any of the Parkinson's disease patients during recording. The operative procedure and beneficial clinical effects of stimulation have been described previously (Siegfried and Lippitz, 1994; Volkmann *et al*., 1998, 2001). Macroelectrodes were inserted bilaterally, with the exception of six Parkinson's disease patients in whom implantation was unilateral. The macroelectrode used was model Medtronic 3387 (Medtronic Neurological Division, Minneapolis, MN, USA) with four platinum–iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length) and centre-to-centre separation of 3 mm. Contact 0 was the most caudal and contact 3 was the most rostral. Macroelectrodes were connected to a battery-operated programmable pulse-generator (Itrel II or Kinetra 7428; Medtronic) after an interval of 2–7 days. Eight of the nine dyskinetic patients and all 10 dystonic patients improved following pallidal stimulation.

Electrode placement

The intended coordinates at the tip of contact 0 were 19–22 mm from the midline of the patient, 2–3 mm in front of the midcommissural point and 6 mm below the anterior commissure–posterior commissure line, i.e. within the GPi. Under these circumstances, with a trajectory that is angled by 70–80° in the sagittal plane and by 75–85° in the coronal plane, the most rostral contact pair is likely to lie in the globus

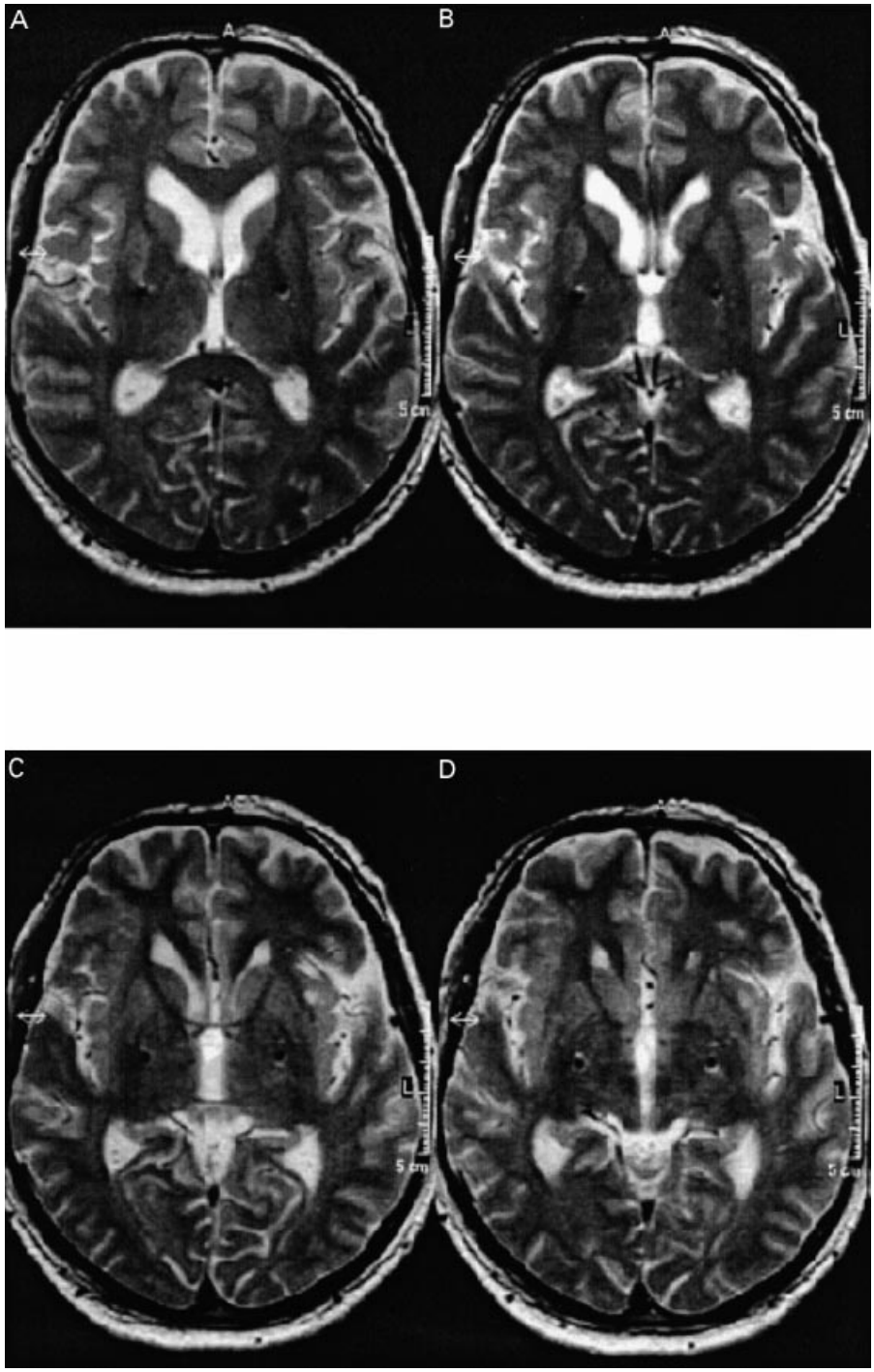

Fig. 1 Axial MRI sections of 3 mm thickness (0 mm between sections) presented rostrocaudally (**A**–**D**) in Case 14, with cervical dystonia. Contacts 01 are in the region of GPi (**C**, **D**) whereas contacts 23 are in the region of GPe (**A**, **B**) bilaterally. The macroelectrode tip was visualized in the section below D (not shown).

pallidus externus (GPe) (Yelnik *et al*., 2000; Peppe *et al*., 2001). Intraoperatively, the correct placement of the electrodes was verified by teleradiography using ventriculography, Guiot's landmarks/volumetric fusion and a long-distance biorthogonal X-ray system. In addition, macrostimulation of the pallidum and surrounding structures, including the internal capsule and the optic tract, was performed intraoperatively. All patients received preoperative high-resolution MRI. Postoperative imaging consisted of CT (n = 2, Cases 12 and 13) or MRI (n =13, Cases 2, 4, 6, 9, 10, 14, 16–22). Where postoperative CT was performed, the macroelectrode position was superimposed on preoperative

MRI using image fusion systems. No postoperative imaging was performed in seven cases (Cases 1, 3, 5, 7, 8, 11 and 15). Postoperative imaging, where available, was consistent with the placement of macroelectrode contacts 0 and/or 1 and 2 and/or 3 in the GPi and GPe/GPe–putamen border, respectively (Fig. 1). Note that postoperative images have been previously published in Cases 1 (Brown *et al*., 2001), 4 (Brown *et al*., 2002) and 13 (Brown *et al*., 2002).

Recordings

Subjects were seated or supine and recorded at rest. In the parkinsonian patients, recordings were divided into those performed in the practically defined off state, after overnight withdrawal of antiparkinsonian medication, and those performed over a period 45–135 min after ingestion of levodopa, during the clinical effect of this drug. These states will be termed 'on' and 'off' (drug). The mean test dose of levodopa given in combination with a decarboxylase inhibitor was 200 mg. LFPs were recorded bipolarly from the adjacent four contacts of each macroelectrode (0–1, 1–2, 2–3). They were filtered at 1–300 Hz and amplified (×100 000 to ×500 000). Signals were sampled at 1 kHz and monitored on-line. Amplification, filtering and recording were performed using a custom-made 9 V battery-operated portable high-impedance amplifier (its front end input stage was the INA128 instrumentation amplifier; Texas Instruments, Dallas, TX, USA) and recorded through a 12-bit analogue-to-digital conversion (A–D) card (PCM-DAS16S; ComputerBoards, Middleboro, MA, USA) with a maximum throughput rate of 330 kHz, onto a portable computer using a custom-written program in Berlin (except in Cases 21 and 22, in whom A–D conversion was performed with a CED 1401; Cambridge Electronic Design, Cambridge, UK), Mannheim and Oxford. Amplification, filtering and recording were performed using a Nicolet Viking IIe and thereafter through an A–D card onto a portable computer in Rome and, using a Schwartzer 34 amplifier system (Schwartzer Medical Diagnostic Equipment, Munich, Germany) and Brainlab software (OSG, Rumst, Belgium) in Amsterdam. With one exception, recordings were made by either P.B. and/or A.A.K.

Analysis

Only LFPs recorded from contact pairs 01 and 23 were analysed, as contacts 0 and/or 1 and 2 and/or 3 were likely to be placed in GPi and GPe, respectively (see above) and did not share a contact. LFPs were digitally filtered at 50 Hz. A fast Fourier transform was performed on non-overlapping sections of equal length using commercial software (Spike 4; Cambridge Electronic Design). Results were averaged across sections and the autospectra determined over 4–100 Hz. The mean number of segments averaged was 800 per subject (range 110–2200). Spectral estimates were derived from long records, so that changes in power could have arisen from a persistent change in activity or periods of altered activity. Inspection of the signals suggested that the latter was only important in the 4–10 Hz band, where bursts of activity were frequently seen to last 1–4 s in dystonic patients. The segment length used was 1024 points, giving a frequency bin size approximating 1 Hz. Thus segment lengths were 1 s in duration, so that significant departures from local stationarity within these blocks was unlikely, even in the case of the 4–10 Hz bursts. Power was expressed as the percentage of the total power in the 4–45 and 55–100 Hz range in each subject and summed across bins to give the percentage power in the 4–10, 11–30 and 65–85 Hz bands. These bands were chosen on the basis of past work that suggests that these activities may differ in functional significance (Brown *et al*., 2001; Williams *et al*., 2002). The 0–4 and 45–55 Hz ranges were omitted so as to avoid inclusion of movement artefact and mains noise, respectively. Relative rather than absolute power was measured to allow comparison across disease groups, as absolute power would be more likely to be dependent on proximity to the LFP source than relative power and to vary with minor changes in recording technique. At this stage it remains unclear whether absolute or proportional changes in neuronal synchronization across different frequency bands are likely to be the more relevant to abnormal motor activity. Statistical analysis was performed using a repeated measures general linear model, as described in the Results section (SPSS for Windows version 11; SSPS, Chicago, IL, USA). Where results were non-spherical, Greenhouse–Geisser correction was used and the corrected degrees of freedom are shown in the text. *Post hoc* paired and unpaired two-tailed *t* tests were applied where appropriate. As multiple *post hoc* tests were performed, significance levels are presented with Bonferroni correction. Discrete peaks in LFP power spectra were defined as more than two contiguous bins with mean power greater than twice that of the adjacent two contiguous bins on each side.

Results

Representative autospectra, expressed as a percentage of the total power up to 100 Hz, are shown for a patient with Parkinson's disease (treated and untreated) and a patient with dystonia in Fig. 2. The three candidate frequency bands (4–10, 11–30 and 65–85 Hz) are shown by the boxed areas. A discrete peak was found consistently only in the 11–30 Hz band. Only five Parkinson's disease patients showed a discrete peak in the 65–85 Hz band, and this was present only after drug treatment. A further two patients with dystonia had a discrete peak in the 65–85 Hz band.

Comparison of LFPs in treated and untreated Parkinson's disease

The percentages of total power picked up at 17 macroelectrodes in 12 parkinsonian patients were entered into the general linear model with frequency band (three levels: 4–10,

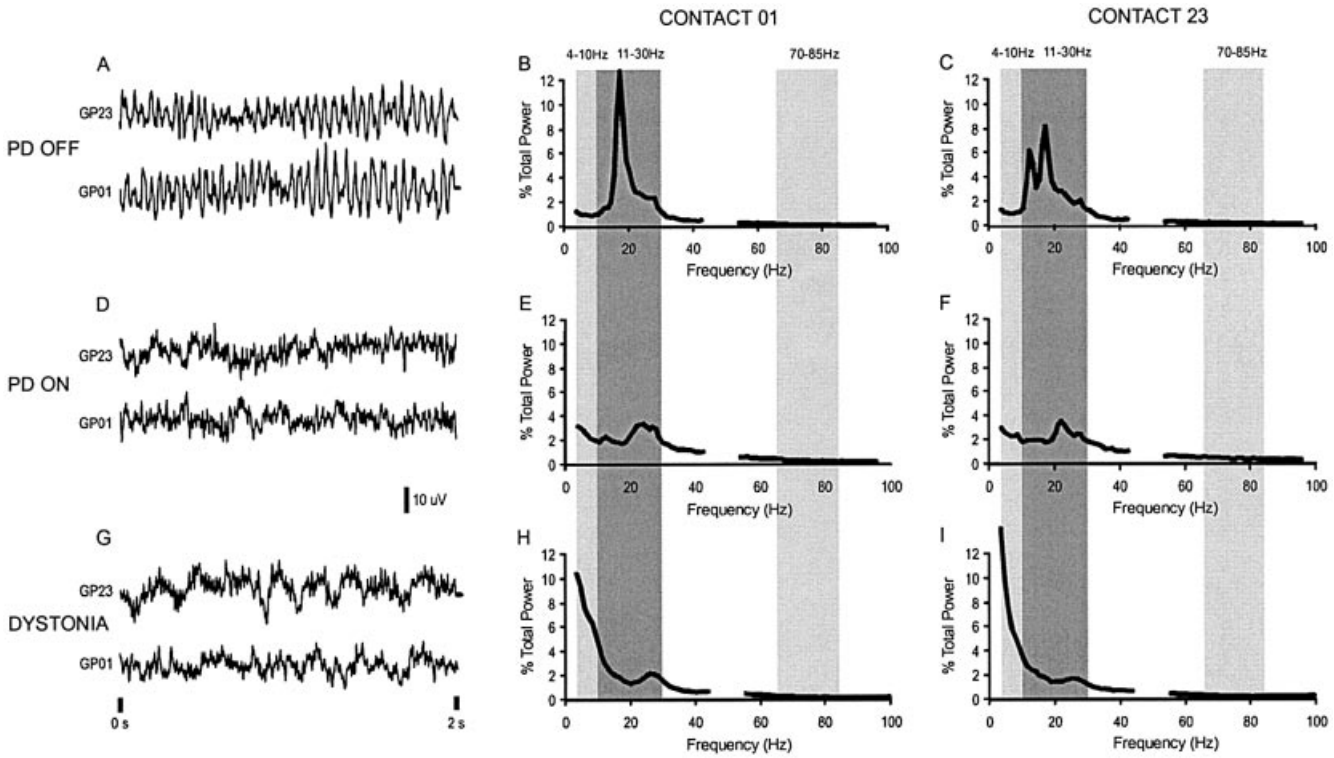

Fig. 2 Raw data and LFP autospectra in Case 11 with Parkinson's disease off (**A**, **B**, **C**) and on (**D**, **E**, **F**) levodopa and in Case 13 with dystonia (**G**, **H**, **I**). Raw data (**A**, **D**, **G**) from electrode pairs 01 and 23 are labelled. LFP autospectra from contact pair 01 are shown in **B**, **E** and **H** and from contact pair 23 in **C**, **F** and **I**. Autospectra are expressed as a percentage of total power up to 100 Hz. The three candidate frequency bands, 4–10, 11–30 and 65–85 Hz, are shown by the boxed areas.

11–30 and 65–85 Hz), treatment state (two levels: on and off levodopa) and contact pair (two levels: contacts 01 and 23) as main effects. A significant main effect for frequency [$F(1,19) = 47.841$, $P < 0.001$] and significant interactions between drug state and frequency [$F(1,19) = 9.510$, $P = 0.005$] and between contact and frequency [$F(1,22) = 6.663$, $P = 0.011$] were found. *Post hoc* analysis revealed an increase in the relative power in the 4–10 Hz band ($P < 0.05$) and a decrease in the 11–30 Hz band in the treated state ($P < 0.05$). The interaction between contact and frequency across treatment states was due to an increase in power in the 4–10 Hz band at the most caudal contact, presumed to be in the GPi ($P < 0.01$). The results are summarized in Fig. 3.

A subgroup analysis between LFPs recorded in untreated Parkinson's disease patients with and without tremor was also performed. The percentage of total power picked up at seven macroelectrodes in five tremulous patients was compared with that in 10 macroelectrodes in seven non-tremulous patients. The percentage of total power was entered into the general linear model with frequency band (three levels: 4–10, 11–30 and 65–85 Hz), presence of tremor (two levels: tremor and no tremor) and contact pair (two levels: contacts 01 and 23) as main effects. A significant main effect for frequency [$F(1,17) = 46.514$, $P < 0.001$] was found. No main effect for tremor or significant interactions were found.

Comparison of LFPs in untreated Parkinson's disease and dystonia

The percentages of total LFP power detected at 19 macroelectrodes in the dystonic patients were compared with those in the untreated parkinsonian patients. The percentage of total power was entered into the general linear model with frequency band (three levels: 4–10, 11–30 and 65–85 Hz), disease (two levels; untreated Parkinson's disease and dystonia) and contact pair (two levels: contacts 01and 23) as main effects. A significant main effect for frequency [$F(1,41) = 90.169$, $P < 0.001$] and a significant interaction between frequency and disease state [$F(1,41) = 23.847$, $P < 0.001$] were found. *Post hoc* analysis showed this to be due to marked differences in power in the 4–10 Hz ($P < 0.001$) and 11–30 Hz bands ($P < 0.0001$). The results are summarized in Fig. 3.

Comparison of LFPs in treated Parkinson's disease and dystonia

The percentage of total LFP power picked up in the dystonic patients was also compared with that in the treated parkinsonian patients. The percentage of total power was entered into the general linear model with frequency band

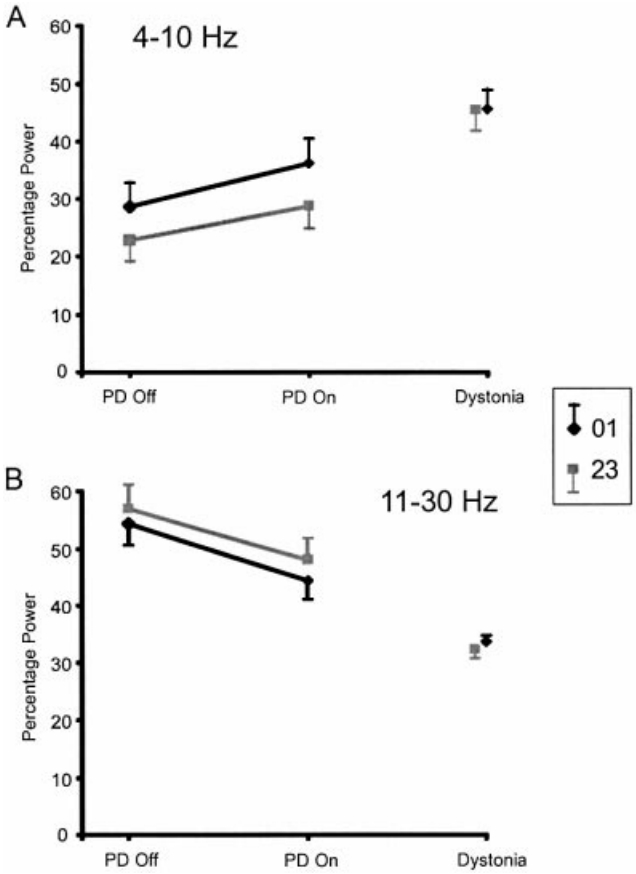

Fig. 3 Mean percentage total LFP power in (**A**) the 4–10 Hz and (**B**) 11–30 Hz bands for contact pairs 01 and 23 in untreated and treated Parkinson's disease and dystonia. Percentage power in the 4–10 Hz band is greater at contact pair 01 than 23 in treated and untreated Parkinson's disease. Percentage power in the 4–10 and 11–30 Hz bands was increased and decreased, respectively, when Parkinson's disease patients were treated. These power changes were even more marked in dystonic patients, particularly at contact 23. See Results section for statistical analysis. No significant effects were seen in the 65–85 Hz band and these data are not illustrated. Error bars denote the standard errors of the mean.

(three levels: 4–10, 11–30 and 65–85 Hz), disease (two levels: treated Parkinson's disease and dystonia) and contact pair (two levels: contacts 01 and 23) as main effects. There was a significant main effect for frequency [$F(1,43) = 82.310$, $P < 0.001$], a significant two-way interaction between frequency and disease [$F(1,43) = 9.234$, $P = 0.002$] and a significant three-way interaction between patient disease, frequency and contact [$F(2,56) = 4.063$, $P = 0.030$]. *Post hoc* tests indicated that the two-way interaction between frequency and disease state was due to an increase in the 4–10 Hz ($P < 0.05$) and a decrease in the 11–30 Hz ($P < 0.01$) percentage power in the dystonic patients. The three-way interaction between disease, frequency and contact was due to an increase in the 4–10 Hz activity at the most rostral electrode ($P < 0.05$). Finally, dystonic patients on medication and those without medication at the time of recording (Table 1) were compared using the general linear model. There was a main effect for frequency [$F(1,20) = 63.459$, $P < 0.001$], but no significant interactions involving treatment or contact, suggesting that drug treatment did not affect our results.

Discussion

We have demonstrated that untreated Parkinson's disease, treated Parkinson's disease and dystonia can be distinguished by the pattern of the LFP recorded from the human globus pallidus. That fluctuations in the cortical LFP are linked to the timing of synchronous neuronal discharges has been known for some time (Creutzfeldt *et al*., 1966; Frost, 1968) but it has only recently become evident that the same may be true of LFP changes in the basal ganglia. Thus there is good concordance between oscillations evident in LFPs and those in single units (Goto and O'Donnell, 2001; Levy *et al*., 2002*a*) and LFP fluctuations are tightly linked to postsynaptic effects in terms of coupling between LFPs in distant sites (Brown *et al*., 2001; Williams *et al*., 2002). Our results therefore suggest that untreated Parkinson's disease, treated Parkinson's disease and dystonia may be distinguished by different patterns of synchronization of local activity within the globus pallidus.

Figure 4 summarizes the core results. However, before examining our findings in detail, we should bear in mind some of the potential limitations of our study.

Limitations of human recordings

One of the major limitations with pathophysiological investigations of patients receiving HFS is that the placement of macroelectrodes within their targets is presumptive and not backed up by histological confirmation, as in animal studies. Postoperative imaging cannot provide absolute confirmation of electrode placement and, even so, was available in only 70% of cases. We limited the effects of variance in electrode positioning by recording many patients. To achieve this we collaborated across several surgical centres, but this itself introduced the possibility of systematic bias, albeit non-intended, in the achieved target between centres.

On the other hand, the intended surgical coordinates were the same across patients, postoperative imaging (where available) was consistent with positioning of the distal contacts of the macroelectrode in GPi, and all but one of the dyskinetic parkinsonian patients and all of the dystonic patients were clinically improved following deep-brain stimulation, consistent with reasonable target accuracy. In addition, two findings point to some overall consistency of electrode placement between patients. First, a significant two-way interaction between contact and frequency was seen across treatment groups in Parkinson's disease, indicating relatively consistent localization of macroelectrode contacts between patients with Parkinson's disease. Secondly, a significant three-way interaction involving contact was

Table 1 *Summary of cases*

Case	Age (years), sex	Disease duration (years)	Diagnosis and predominant symptoms before operation	Globus pallidus macro-electrode	Pre-op on/off motor UPDRS or BFM/TWSTR* dystonia scales	Medication (daily dose)	Surgical centre
1	49, F	17	PD, bradykinesia, dyskinesias	Bilateral	12/80	Levodopa 1500 mg	Rome
2	52, F	9	PD, dyskinesia, tremor	Left	21/90	Apomorphine 72 mg	Rome
3	61, M	27	PD, bradykinesia, dyskinesias	Left	38/78	Levodopa 400 mg, ropinirole 5 mg	Rome
4	60, M	11	PD, tremor, dyskinesias	Bilateral	8/51	Levodopa 1100 mg, pergolide 3 mg	Rome
5	60, F	24	PD, bradykinesia, dyskinesias	Left	11/48	Levodopa 700 mg	Rome
6	56, F	9	PD, bradykinesia, rigidity	Bilateral	47/61	Levodopa 1150 mg, amantadine 100 mg	Rome
7	64, M	9	PD, bradykinesia, rigidity, tremor, dyskinesias	Bilateral	20/56	Levodopa 1000 mg, ropinirole 6 mg	Rome
8	65, M	14	PD, bradykinesia, rigidity	Bilateral	38/72	Levodopa 1400 mg, entacapone 1200 mg	Rome
9	59, F	15	PD, dyskinesia, tremor	Right	32/53	Levodopa 450 mg, pergolide 1.5 mg, selegiline 5 mg	Oxford
10	68, M	10	PD, tremor, dyskinesias	Right	48/97	Apomorphine 120 mg	Rome
11	39, M	7	PD, bradykinesia	Right	15/80	Levodopa 1300 mg, ropinirole 4 mg	Rome
12	37, M	10	PD, dyskinesia	Right	7/65	Levodopa 150 mg, ropinirole 4 mg	Rome
13	49, F	3	Idiopathic generalized dystonia with fixed posture left arm and mobile spasms right arm	Bilateral	120	None	Oxford
14	49, M	6	Cervical dystonia, non-mobile antecollis	Bilateral	23*	Clobazam 30 mg, amitriptyline 75 mg, trimipramine 25 mg	Berlin
15	23, F	16	Primary generalized dystonia	Bilateral	Not available	None	Amsterdam
16	43, M	19	Cervical dystonia, non-mobile torticollis with laterocollis	Bilateral	14.5*	Clonazepam 6 mg	Berlin
17	58, F	10	Idiopathic segmental dystonia, predominantly mobile, involvement of neck and trunk	Bilateral	23	Lisuride 50 μg	Berlin
18	74, F	20	Idiopathic cervical dystonia, predominantly dystonic head tremor	Bilateral	19*	None	Mannheim
19	39, M	10	Idiopathic cervical dystonia, non-mobile antecollis	Bilateral	24*	None	Mannheim
20	20, M	6	Primary generalized dystonia	Left	62	Artane 35 mg, clonazepam 2 mg	Mannheim
21	63, M	5	Multisegmental dystonia with predominant phasic torticollis	Bilateral	23	Promethazine 100 mg, diazepam 2.5 mg, diclofenac 150 mg	Berlin
22	46, F	9	Generalized idiopathic non-familial dystonia	Bilateral	16	None	Berlin

M = male; F = female; PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale; BFM = Burke–Fahn–Marsden dystonia rating scale; TWSTR = Toronto Western Spasmodic Torticollis Rating Scale (denoted by * in table).

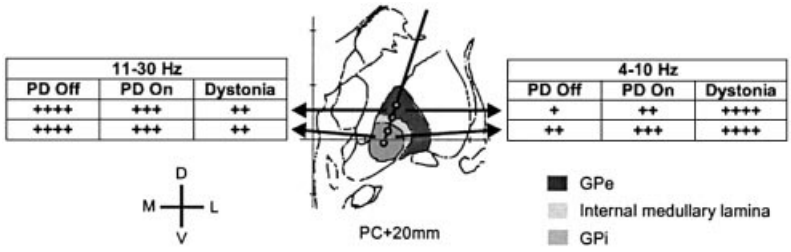

Fig. 4 Intended orientation and localization of the macroelectrode shown superimposed on the traced Schaltenbrand and Wahren atlas at the posterior commissure (PC) +20 mm (after Yelnik *et al*., 2000) with a summary of the LFP findings. Note that the 4–10 Hz activity is greater at the lower contact pair in Parkinson's disease, but that this difference is lost in dystonia due to the greater increase in 4–10 Hz activity at the rostral contact pair.

observed between treated Parkinson's disease and dystonic patients, pointing to relatively consistent localization of macroelectrode contacts within these patient groups. Excessive variance in the position of each contact between patients would have obviated any interactions involving contact as a main effect. Nevertheless, the possibility that differences between Parkinson's disease and dystonic patients, which were treated largely at different centres, arose from minor systematic bias in achieved targeting should be borne in mind.

Another limitation in clinical studies is the inability to entirely control for muscle activity. All our patients were recorded at rest, but the three clinical groups are likely to have had different degrees of involuntary activity: rigidity and rest tremor in untreated parkinsonian patients, dyskinesias in treated parkinsonian patients and spontaneous dystonic activity in subjects with dystonia. The question therefore arises whether differences in LFPs between the patient groups were directly or indirectly responsible for the clinical differences or were the product of the different patterns of afferent activity accompanying the differing types of involuntary muscle contraction. In practice, however, levodopa-induced dyskinesias were diminished or absent at the time of recording due to microlesional effects and there was no difference between tremulous and non-tremulous Parkinson's disease patients. Nevertheless, in the light of the limitations discussed above we must be cautious in our interpretation of differences in LFPs between clinical groups, seeking, wherever possible, corroboration from animal studies. In this regard it is particularly notable that our finding that LFP power is elevated in the 4–10 Hz band and decreased in the beta band in dystonic patients compared with either treated or untreated Parkinson's disease patients is closely paralleled by the LFP changes in the globus pallidus of the dt^{sz} mutant hamster. This mutant has attacks of predominantly sustained dystonic posturing lasting several hours (Gernert *et al*., 1998). In this animal model of paroxysmal dystonia, spectral changes in the theta and beta bands persist between attacks, suggesting that the changes are not a consequence of the attacks and accompanying afferent activity.

It should also be noted that changes in the power at 4–10 Hz could have potentially included movement-related artefact. This will have been limited by the fact that the spectral content of dystonia and dyskinesias is generally <4 Hz (Manson *et al*., 2000) and by our use of a differential amplifier. In practice, it also seems unlikely that changes in the 4–10 Hz band were substantially affected by movement, as differences tended to be asymmetrically distributed across contacts.

The effect of levodopa upon LFPs in Parkinson's disease was marked, raising the question whether drug treatments in the dystonic patients may have accounted for the differences between these and Parkinson's disease subjects. However, no differences were found between treated and untreated dystonic patients.

Finally, it should be remembered that recordings were performed several days after implantation, when regional oedema may still have been significant, as suggested by the microlesional effect noted in some patients. Nevertheless, the delay between operation and recording did not differ systematically between patient groups or across treatment conditions in the same Parkinson's disease patients, so that it cannot account for the spectral differences between or within groups.

Pallidal LFP changes and bradykinesia

The finding of an increase in synchronization at 11–30 Hz when Parkinson's disease patients were withdrawn from levodopa is consistent with previous studies. Nini *et al*. (1995) demonstrated a pronounced tendency towards synchronization at frequencies <30 Hz in the primate GPi following treatment with MPTP, which was not seen in healthy monkeys (Nini *et al*., 1995). Microelectrode studies in patients with Parkinson's disease have also demonstrated synchronization of single units in the STN (Levy *et al*., 2000, 2002*b*) and GPi (Levy *et al*., 2001) at 11–30 Hz, particularly in tremulous patients. Some of this synchronization of pallidal activity may be related to the greater influence of striatal tonically active neurons in the parkinsonian state (Raz *et al*., 2001). In addition, coherence (coupling) has been

reported between LFPs in the STN and GPi at 11–30 Hz and between these structures and the cerebral cortex in parkinsonian patients (Brown *et al*., 2001; Williams *et al*., 2002). The LFP power and coupling in this frequency band are attenuated by the ingestion of levodopa (in keeping with the present results) and during movement (Cassidy *et al*., 2002; Williams *et al*., 2002), leading to the hypothesis that activity at 11–30 Hz may be essentially antikinetic in nature (Brown, 2003). If this is correct, pallidal functional neurosurgery could improve parkinsonism without any clear deleterious effects upon motor function by reducing an abnormal and antikinetic patterning of pallidal outflow in the 11–30 Hz band (Brown, 2003).

It is noteworthy that no difference emerged in pallidal LFPs in the high gamma band (65–85 Hz) between treated and untreated Parkinson's disease. This is in contrast to LFP spectra from the human subthalamic nucleus, which commonly demonstrate a discrete peak in the high gamma band following treatment with levodopa (Cassidy *et al*., 2002). The result also contrasts with studies of the coherence between LFPs in STN and GPi that show coupled activity in the high gamma band following treatment (Brown *et al*., 2001). However, as coherence is effectively normalized by auto-spectral power, strong coupling may be evident despite very little pallidal power at these frequencies. Neither is it necessarily the case that an increase in the coupling between spatially segregated neuronal populations in a particular band should entail an increase in local synchronization at the same frequency. Within the motor areas of the human cerebral cortex, for example, local power and inter-regional coherence/coupling may relate to different aspects of cortical function that might, to some extent, operate independently of each other (Gerloff *et al*., 1998).

It is also of interest that no difference was found between tremulous and non-tremulous patients with respect to proportional LFP power. A significant postoperative reduction in tremor due to microlesional effects in our tremulous patients may potentially account for this, but, in addition, it seems likely that tremor-synchronized pallidal oscillatory activity makes only a small contribution to the LFP. Hutchison *et al*. (1997) specifically searched for hand-related internal pallidal cells with tremor-synchronized oscillatory activity in three patients undergoing microelectrode exploration prior to pallidotomy, but found such activity in only 12% of 228 neurons sampled. Raz and colleagues (Raz *et al*., 2000) reported a 40% increase in oscillatory pallidal single-cell activity after two vervet monkeys were treated with MPTP, with frequencies distributed bimodally around 7 and 13 Hz. They found that oscillatory activity and tremor were phasic and dynamic phenomena and that in only 11% of records was there significant dependence between the timing of tremor and neuronal oscillations. Hurtado *et al*. (1999), in their case report of recordings from a single parkinsonian pallidum, similarly found that single cells may, over time, oscillate in both a phase-locked and an independent manner from limb tremor at a single joint. Thus, whilst cells with tremor-synchronized activity are clearly present in the parkinsonian pallidum, they may make a relatively small contribution to LFP rhythmicity. Our averaging over long segments, including non-tremor periods, is further likely to have diminished the impact of tremor-related oscillation on the LFP.

Pallidal LFP changes and hyperkinesia

Excessive movement (hyperkinesia) clearly dominated the clinical picture in our dystonic patients, but was also present in our Parkinson's disease patients when treated with levodopa (although dyskinesias were often temporally suppressed shortly after surgery). Thus, it is interesting that there was a gradient of LFP change, whereby treated Parkinson's disease patients had more 4–10 Hz and less 11–30 Hz activity than untreated Parkinson's disease patients and dystonic patients had more 4–10 Hz activity and less 11–30 Hz activity than treated parkinsonian patients. These changes were even more marked when compared with untreated Parkinson's disease patients, consistent with the conclusion that the difference in oscillatory activity between dystonia and Parkinson's disease cannot be ascribed to treatment with levodopa. As noted above, it has been suggested previously that synchronization of neuronal activity at 11–30 Hz may have an essentially antikinetic effect in the basal ganglia (Brown, 2003). Consequently, the reduction in beta activity amongst our treated Parkinson's disease and dystonic patients may have contributed to hyperkinesia.

What is the possible basis for the 4–10 Hz LFP activity at the neuronal level? Microelectrode studies demonstrate a tendency for neuronal discharge in the GPi, and its input STN, to occur in three modes: irregular, bursting (i.e. an inconstant period of time between grouped discharges) and oscillatory (Levy *et al*., 2001). The bursting and oscillatory modes, in particular, are likely to have a major spectral content in the 4–10 Hz band. The oscillatory mode is accompanied by a strong tendency to synchronization between neurons at the frequency of parkinsonian rest and action tremor, and is more prominent in the untreated parkinsonian state (reviewed in Brown, 2003). Presumably, therefore, the overall increase in power at 4–10 Hz with levodopa treatment in Parkinson's disease represents an exacerbation of the bursting mode. The degree of synchronization between neurons during non-oscillatory bursting is unclear, but the available evidence is in favour of this mode actually increasing when parkinsonian patients are treated with the dopamine agonist apomorphine (Merello *et al*., 1999; Levy *et al*., 2001) or when MPTP-treated green monkeys undergo STN lesioning (and become dyskinetic but less tremulous) with ibotenic acid (Wichmann *et al*., 1994). Indeed, bursting may be particularly prominent during dyskinesias in primates and Parkinson's disease patients (Yoshida, 1991; Levy *et al*., 2001) and during hemiballismus (Suarez *et al*., 1997).

What is the evidence that non-oscillatory bursting is also a feature of dystonia? In addition to changes in firing rate, microelectrode recordings from the globus pallidus in

dystonic patients reveal marked abnormalities in the temporal patterning of neuronal discharge, neurons firing in irregularly grouped discharges with intermittent pauses (Lenz *et al*., 1999; Vitek *et al*., 1999; Vitek, 2002). Furthermore, analysis of interspike intervals in the endopeduncular nucleus (the homologue of GPi) of dystonic dt^{sz} hamsters shows an increased proportion of neurons with a burst-like firing pattern compared with normal animals (Gernert *et al*., 2002). Evidence also exists from animal models of dystonia of burst discharge in other nodes of corticobasal ganglionic loops involved in motor control. Increased bursting has been noted in the monkey motor thalamus after induction of dystonia by intrathalamic injection of the GABA antagonist bicuculline (Macia *et al*., 2002), and dystonic movements corresponding to putaminal burst discharge have been seen after intraputaminal injection of bicuculline in the cat (Yamada *et al*., 1995).

Together, these observations suggest that abnormal neuronal bursting may be an important pathophysiological substrate for the development of hyperkinesias, including levodopa-induced dyskinesia and dystonia, and that this may be related to the increase in 4–10 Hz activity in our parkinsonian patients after treatment with levodopa and the even greater relative 4–10 Hz activity in dystonic compared with parkinsonian patients.

If this is correct, pallidal functional neurosurgery could improve dyskinesias and dystonia (as opposed to parkinsonism) by reducing an abnormal pattern of pallidal outflow in the 4–10 Hz band. Consonant with this is the report that myoclonic dystonia is associated with a preponderance of LFP power at 4–8 Hz in the pallidum (Liu *et al*., 2002). Note that the presence of increased 4–10 Hz activity in patients in whom surgery has led to a temporary amelioration of dyskinesias through microlesional effects does not obviate any association between these oscillations and the propensity to dyskinesias. On the other hand, it does suggest that these changes are not simply the consequence of hyperkinesia, perhaps through afferent activity. Similar observations have been made of the dystonic dt^{sz} mutant hamster, in which increases in LFP activity in the theta band occur during and between paroxysmal hyperkinesias (Gernert *et al*., 1998).

Spatiotemporal differences between Parkinson's disease and dystonia

Topographic differences in spectral activity were also noted between macroelectrode contacts. In Parkinson's disease patients there was a gradient of 4–10 Hz activity such that this was maximal at the most caudal contact, whether or not patients were treated. Interestingly, other studies have also suggested that there may be functional topographic differences within the globus pallidus in Parkinson's disease (Bejjani *et al*., 1997; Krack *et al*., 1998*b*; Yelnik *et al*., 2000). In contrast, when dystonic patients were compared with Parkinson's disease patients there was a general increase in 4–10 Hz activity that was most marked in the rostral contact pair. As discussed in the Methods section, the likely localization of one or both rostral contacts was the GPe, and the localization of abnormalities to the GPe in dystonia is not unprecedented. In humans, microelectrode studies have shown changes in the frequency and pattern of neuronal firing between the GPe and GPi. Mean firing rate is reduced in the GPe but not the GPi in dystonia compared with Parkinson's disease on medication (Lenz *et al*., 1998). Consistent with this finding, the mean firing rate in the GPe was significantly lower than in the GPi in two out of the three cases of generalized dystonia reported by Vitek *et al*. (1999).

Conclusion

In conjunction with other lines of evidence, our studies of pallidal LFPs suggest that untreated Parkinson's disease is associated with an increased tendency to synchronization over the 11–30 Hz range and a decreased tendency to synchronization at 4–10 Hz. The major change in dystonia is a decrease in relative power in the 11–30 Hz band and an increase in relative power in the 4–10 Hz range compared with treated or untreated Parkinson's disease. The latter is focused at macroelectrode contacts that are more likely to be in the GPe than the GPi. The observations potentially offer an explanation for two of the enduring paradoxes of pallidal functional neurosurgery, namely, how this intervention improves such disparate states as parkinsonism, levodopa induced dyskinesias and dystonia, and how such improvement is achieved without any clearly deleterious effects upon motor function. It seems likely that each pathological state is associated with its own abnormal spatiotemporal pattern of pallidal activity, so that the success of functional neurosurgery may lie in the suppression of disruptive noisy activity across a number of frequency bands.

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References

Anderson ME, Postupna N, Ruffo M. Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. J Neurophysiol 2003; 89: 1150–60.

Bar-Gad I, Bergman H. Stepping out of the box: information processing in the neural networks of the basal ganglia. Curr Opin Neurobiol 2001; 11: 689–95.

Baron MS, Vitek JL, Bakay RA, Green J, Kaneoke Y, Hashimoto T, et al. Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. Ann Neurol 1996; 40: 355–66.

Bejjani B, Damier P, Arnulf I, Bonnet AM, Vidailhet M, Dormont D, et al. Pallidal stimulation for Parkinson's disease. Two targets? Neurology 1997; 49: 1564–9.

Bejjani BP, Damier P, Arnulf I, Papadopoulos S, Bonnet AM, Vidailhet M, et al. Deep brain stimulation in Parkinson's disease: opposite effects of stimulation in the pallidum. Mov Disord 1998; 13: 969–70.

Brown P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. Mov Disord 2003; 18: 357–63.

Brown P, Oliviero A, Mazzone P, Insola A, Tonali P, Di Lazzaro, V. Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. J Neurosci 2001; 21: 1033–8.

Brown P, Williams D, Aziz T, Mazzone P, Oliviero A, Insola A, et al. Pallidal activity recorded in patients with implanted electrodes predictively correlates with eventual performance in a timing task. Neurosci Lett 2002; 330: 188–92.

Cassidy M, Mazzone P, Oliviero A, Insola A, Tonali P, Di Lazzaro V, et al. Movement-related changes in synchronization in the human basal ganglia. Brain 2002; 125: 1235–46.

Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B. Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. Lancet 2000; 355: 2220–1.

Creutzfeldt OD, Watanabe S, Lux HD. Relations between EEG phenomena and potentials of single cortical cells. I. Evoked responses after thalamic and epicortical stimulation. Electroencephalogr Clin Neurophysiol 1966; 20: 1–18.

Davis KD, Taub E, Houle S, Lang AE, Dostrovsky JO, Tasker RR, et al. Globus pallidus stimulation activates the cortical motor system during alleviation of parkinsonian symptoms. Nat Med 1997; 3: 671–4.

Frost JD Jr. EEG–intracellular potential relationships in isolated cerebral cortex. Electroencephalogr Clin Neurophysiol 1968; 24: 434–43.

Gerloff C, Uenishi N, Hallett M. Cortical activation during fast repetitive finger movements in humans: dipole sources of steady-state movement-related cortical potentials. J Clin Neurophysiol 1998; 15: 502–13.

Gernert M, Richter A, Rundfeldt C, Loscher W. Quantitative EEG analysis of depth electrode recordings from several brain regions of mutant hamsters with paroxysmal dystonia discloses frequency changes in the basal ganglia. Mov Disord 1998; 13: 509–21.

Gernert M, Bennay M, Fedrowitz M, Rehders JH, Richter A. Altered discharge pattern of basal ganglia output neurons in an animal model of idiopathic dystonia. J Neurosci 2002; 22: 7244–53.

Goto Y, O'Donnell P. Network synchrony in the nucleus accumbens in vivo. J Neurosci 2001; 21: 4498–504.

Gross C, Rougier A, Guehl D, Boraud T, Julien J, Bioulac B. High-frequency stimulation of the globus pallidus internalis in Parkinson's disease: a study of seven cases. J Neurosurg 1997; 87: 491–8.

Hurtado JM, Gray CM, Tamas LB, Sigvardt KA. Dynamics of tremor-related oscillations in the human globus pallidus: a single case study. Proc Natl Acad Sci USA 1999; 96: 1674–9.

Hutchison WD, Lozano AM, Tasker RR, Lang AE, Dostrovsky JO. Identification and characterization of neurons with tremor-frequency activity in human globus pallidus. Exp Brain Res 1997; 113: 557–63.

Krack P, Pollak P, Limousin P, Hoffmann D, Xie J, Benazzouz A, et al. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. Brain 1998a; 121: 451–7.

Krack P, Pollak P, Limousin P, Hoffmann D, Benazzouz A, Le Bas JF, et al. Opposite motor effects of pallidal stimulation in Parkinson's disease. Ann Neurol 1998b; 43: 180–92.

Kumar R, Dagher A, Hutchison WD, Lang AE, Lozano AM. Globus pallidus deep brain stimulation for generalized dystonia: clinical and PET investigation. Neurology 1999; 53: 871–4.

Lenz FA, Suarez JI, Metman LV, Reich SG, Karp BI, Hallett M, et al. Pallidal activity during dystonia: somatosensory reorganisation and changes with severity. J Neurol Neurosurg Psychiatry 1998; 65: 767–70.

Lenz FA, Jaeger CJ, Seike MS, Lin YC, Reich SG, DeLong MR, et al. Thalamic single neuron activity in patients with dystonia: dystonia-related activity and somatic sensory reorganization. J Neurophysiol 1999; 82: 2372–92.

Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. J Neurosci 2000; 20: 7766–75.

Levy R, Dostrovsky JO, Lang AE, Sime E, Hutchison WD, Lozano AM. Effects of apomorphine on subthalamic nucleus and globus pallidus internus neurons in patients with Parkinson's disease. J Neurophysiol 2001; 86: 249–60.

Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO. Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. Brain 2002a; 125: 1196–209.

Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. Synchronized neuronal discharge in the basal ganglia of parkinsonian patients is limited to oscillatory activity. J Neurosci 2002b; 22: 2855–61.

Liu X, Griffin IC, Parkin SG, Miall RC, Rowe JG, Gregory RP, et al. Involvement of the medial pallidum in focal myoclonic dystonia: a clinical and neurophysiological case study. Mov Disord 2002; 17: 346–53.

Macia F, Escola L, Guehl D, Michelet T, Bioulac B, Burbaud P. Neuronal activity in the monkey motor thalamus during bicuculline-induced dystonia. Eur J Neurosci 2002; 15: 1353–62.

Manson AJ, Brown P, O'Sullivan JD, Asselman P, Buckwell D, Lees AJ. An ambulatory dyskinesia monitor. J Neurol Neurosurg Psychiatry 2000; 68: 196–201.

Marsden CD, Obeso JA. The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. Brain 1994; 117: 877–97.

Merello M, Balej J, Delfino M, Cammarota A, Betti O, Leiguarda

R. Apomorphine induces changes in GPi spontaneous outflow in patients with Parkinson's disease. Mov Disord 1999; 14: 45–9.

Nini A, Feingold A, Slovin H, Bergman H. 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 1995; 74: 1800–5.

Pahwa R, Wilkinson S, Smith D, Lyons K, Miyawaki E, Koller WC. High-frequency stimulation of the globus pallidus for the treatment of Parkinson's disease. Neurology 1997; 49: 249–53.

Peppe A, Pierantozzi M, Altibrandi MG, Giacomini P, Stefani A, Bassi A, et al. Bilateral GPi DBS is useful to reduce abnormal involuntary movements in advanced Parkinson's disease patients, but its action is related to modality and site of stimulation. Eur J Neurol 2001; 8: 579–86.

Raz A, Vaadia E, Bergman H. Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine vervet model of parkinsonism. J Neurosci 2000; 20: 8559–71.

Raz A, Frechter-Mazar V, Feingold A, Abeles M, Vaadia E, Bergman H. Activity of pallidal and striatal tonically active neurons is correlated in mptp-treated monkeys but not in normal monkeys. J Neurosci 2001; 21: RC128.

Siegfried J, Lippitz B. Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms. Neurosurgery 1994; 35: 1126–9.

Siegfried J, Wellis G. Chronic electrostimulation of ventroposterolateral pallidum: follow-up. Acta Neurochir Suppl (Wien) 1997; 68: 11–3.

Suarez JI, Metman LV, Reich SG, Dougherty PM, Hallett M, Lenz FA. Pallidotomy for hemiballismus: efficacy and characteristics of neuronal activity. Ann Neurol 1997; 42: 807–11.

Tronnier VM, Fogel W. Pallidal stimulation for generalized dystonia. Report of three cases. J Neurosurg 2000; 92: 453–6.

Tronnier VM, Fogel W, Kronenbuerger M, Steinvorth S. Pallidal stimulation: an alternative to pallidotomy? J Neurosurg 1997; 87: 700–5.

Vercueil L, Pollak P, Fraix V, Caputo E, Moro E, Benazzouz A, et al. Deep brain stimulation in the treatment of severe dystonia. J Neurol 2001; 248: 695–700.

Vitek JL. Pathophysiology of dystonia: a neuronal model. Mov Disord 2002; 17 Suppl 3: S49–S62.

Vitek JL, Chockkan V, Zhang JY, Kaneoke Y, Evatt M, DeLong MR, et al. Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. Ann Neurol 1999; 46: 22–35.

Volkmann J, Sturm V, Weiss P, Kappler J, Voges J, Koulousakis A, et al. Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. Ann Neurol 1998; 44: 953–61.

Volkmann J, Allert N, Voges J, Weiss PH, Freund HJ, Sturm V. Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. Neurology 2001; 56: 548–51.

Wichmann T, Bergman H, DeLong MR. The primate subthalamic nucleus. III. Changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. J Neurophysiol 1994; 72: 521–30.

Williams D, Tijssen M, Van Bruggen G, Bosch A, Insola A, Di Lazzaro V, et al. Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans. Brain 2002; 125: 1558–69.

Yamada H, Fujimoto K, Yoshida M. Neuronal mechanism underlying dystonia induced by bicuculline injection into the putamen of the cat. Brain Res 1995; 677: 333–6.

Yelnik J, Damier P, Bejjani BP, Francois C, Gervais D, Dormont D, et al. Functional mapping of the human globus pallidus: contrasting effect of stimulation in the internal and external pallidum in Parkinson's disease. Neuroscience 2000; 101: 77–87.

Yoshida M. The neuronal mechanism underlying parkinsonism and dyskinesia: differential roles of the putamen and caudate nucleus. Neurosci Res 1991; 12: 31–40.

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