

Dopamine depletion increases the power and coherence of β -oscillations in the cerebral cortex and subthalamic nucleus of the awake rat

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Keywords: basal ganglia, beta band, Parkinson's disease, synchronization

Abstract

Local field potentials (LFPs) recorded from the subthalamic nucleus (STN) of untreated patients implanted with stimulation electrodes for the treatment of Parkinson's disease (PD) demonstrate strong coherence with the cortical electroencephalogram over the β -frequency range (15–30 Hz). However, studies in animal models of PD emphasize increased temporal coupling in cortico-basal ganglia circuits at substantially lower frequencies, undermining the potential usefulness of these models. Here we show that 6-hydroxydopamine (6-OHDA) lesions of midbrain dopamine neurons are associated with significant increases in the power and coherence of β -frequency oscillatory activity present in LFPs recorded from frontal cortex and STN of awake rats, as compared with the healthy animal. Thus, the pattern of synchronization between population activity in the STN and cortex in the 6-OHDA-lesioned rodent model of PD closely parallels that seen in the parkinsonian human. The peak frequency of coherent activity in the β -frequency range was increased in lesioned animals during periods of spontaneous and sustained movement. Furthermore, administration of the dopamine receptor agonist apomorphine to lesioned animals suppressed β -frequency oscillations, and increased coherent activity at higher frequencies in the cortex and STN, before producing the rotational behaviour indicative of successful lesion. Taken together, these results support a crucial role for dopamine in the modulation of population activity in cortico-basal ganglia circuits, whereby dopaminergic mechanisms effectively filter out synchronized, rhythmic activity at β -frequencies at the systems level, and shift temporal couplings in these circuits to higher frequencies. These changes may be important in regulating movement.

Introduction

The synchronization of rhythmic neuronal activity within specific time intervals is thought to be important for brain function and dysfunction (Engel *et al.*, 2001). Excessive synchronization of neuronal activity in the basal ganglia is increasingly recognized as a critical functional change accompanying the parkinsonian state (see reviews by Bergman *et al.*, 1998; Brown & Marsden, 1998; Bevan *et al.*, 2002; Brown, 2003). Such synchronization is evident at the levels of pairs of neurons or larger neuronal populations. Hitherto, studies in parkinsonian animal models have concentrated on investigations of synchronization between single neurons within the monkey pallidum, largely assessed through cross-correlation analysis (Bergman *et al.*, 1998; Boraud *et al.*, 2002). These studies emphasize the role of pathological activity that is synchronized at frequencies under 15 Hz, including those frequencies associated with parkinsonian tremor (Nini *et al.*, 1995; Raz *et al.*, 2000; Heimer *et al.*, 2002; Goldberg *et al.*, 2004). In contrast, studies of synchronized activity in patients with Parkinson's disease (PD) have assessed both the pallidum and subthalamic nucleus (STN), and have explored the synchronization of population activity in

these structures and the cerebral cortex, an important source of input to the basal ganglia. The synchronization of the activities of single neurons (Levy *et al.*, 2000, 2001, 2002b), as well as the synchronization within and between the rhythmic activities of local populations of neurons, as shown by oscillations in local field potentials (LFPs), have been investigated (Brown *et al.*, 2001; Marsden *et al.*, 2001; Priori *et al.*, 2002; Williams *et al.*, 2002; Silberstein *et al.*, 2003). Collectively, these investigations in parkinsonian humans suggest synchronization preferentially occurs at 15–30 Hz, in the so-called β -frequency band, and is ameliorated, together with motor symptoms, by dopaminergic medication. Although these and other studies suggest that the dopamine-dependent modulation of synchronized activity in cortico-basal ganglia circuits is a prerequisite for normal function, the exact nature of this modulation is not known.

The aims of this study were twofold. First, we wished to test whether activity within and between frontal cortex and STN is synchronized in the β -frequency band in the unilateral 6-hydroxydopamine (6-OHDA)-lesioned rodent model of PD, and whether synchronized activity is reduced or otherwise different in the non-lesioned animal. Second, we sought to determine the temporal evolution of the effects of dopamine receptor stimulation on oscillatory activity in the 6-OHDA-lesioned rat, thereby further characterizing the nature of dopaminergic modulation of synchronized population synchrony in the cortico-basal ganglia circuits.

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Received 4 October 2004, revised 16 December 2004, accepted 20 December 2004

Materials and methods

Experimental procedures were carried out on 26 adult male rats (HsdCpb:WU strain; Harlan-Winkelmann, Germany), and were conducted in accordance with the European Communities Council Directive (86/609/EEC) for care of laboratory animals and with the Society for Neuroscience policy on the use of animals in research. All experiments conformed to local department and institutional guidelines on the ethical use of animals (LAGetSi, Berlin). Every care was taken to minimise the number of animals used.

Unilateral lesion of dopaminergic neurons and electrode implantation

Unilateral 6-OHDA injections were carried out on 16 rats. Control (vehicle) injections were performed in another 10 rats (age-matched). Sixty minutes before the injection of 6-OHDA, all animals received a bolus of desipramine (25 mg/kg, i.p.; Sigma, Germany), to minimize the uptake of 6-OHDA by noradrenergic neurons, and pargyline (50 mg/kg, i.p.; Sigma), to maximize the toxic effects of 6-OHDA on dopaminergic neurons (Schwartz & Huston, 1996a). Anaesthesia was induced and maintained with chloral hydrate (400 mg/kg, i.p.; Sigma, Germany). Animals were then placed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA), a small craniotomy was made over the left substantia nigra, and the overlying dura mater removed. The neurotoxin 6-OHDA (hydrochloride salt; Sigma) was dissolved immediately before use in ice-cold 0.9% w/v NaCl solution containing 0.01% w/v ascorbate to a final concentration of 8 mg/mL. Then 1.0 μ L of 6-OHDA solution (or vehicle in controls) was injected at a rate of 0.5 μ L/min through a steel cannula (0.2 mm outside diameter) attached to a 10 μ L Hamilton microsyringe (Cole-Parmer, London, UK) into the region adjacent to the median forebrain bundle (A: -4.2 mm; L: 1.1 mm; V: -7.6 mm). Stereotaxic coordinates were calculated from Bregma and the atlas of Paxinos & Watson (1986). The cannula was left in place for 5 min before being withdrawn.

Animals were implanted with recording electrodes 4 weeks (\pm 3 days) after the injection of 6-OHDA or saline. Rats were anaesthetized with chloral hydrate (400 mg/kg, i.p.) and placed in a stereotaxic frame (David Kopf Instruments). A concentric, bipolar 'semi-microelectrode' (customized SNE-100; Rhodes Medical Instruments, USA) was implanted in the left STN under stereotaxic conditions (A: 3.8 mm; L: 2.5 mm; V: -7.6 mm), as previously described (Brown *et al.*, 2002). Semi-microelectrodes were constructed from stainless steel cannulae and wires, which were insulated with epoxy (except at the two electrode contacts). The outer contact was 100 μ m in length and had a diameter of 150 μ m. The inner contact had a diameter of 25 μ m (only the tip of the inner wire was exposed). The two recording contacts were separated by 100 μ m. Stainless steel screws (1 mm diameter) were positioned above each frontal cortex (A: -2.7 mm; L: \pm 2.0 mm), each cerebellar hemisphere (A: -12.0 mm; L: \pm 2.0 mm) and centrally over an area of thickened nasal bone rostral to the cerebral cortex (A: -5.7 mm; L: 0.0 mm). Thereafter, the microelectrode and screws were fixed to the skull with dental cement (Technovit; Heraeus-Kulzer GmbH, Germany). Animals were allowed at least 72 h to recover from the surgery before recording began.

Electrophysiological recording and behavioural testing

The extent of the 6-OHDA lesion was assessed 4–5 weeks after toxin injection by challenge with apomorphine (Hudson *et al.*, 1993;

Schwartz & Huston, 1996b). Following a 15-min period in the recording chamber, animals received a single bolus of apomorphine (0.05 mg/kg, s.c.; Sigma) and were returned to the chamber for observation. The numbers of contraversive and ipsiversive turns were then counted.

During recordings of spontaneous and apomorphine-induced activity patterns, animals were placed in a Plexiglas bowl within a Faraday cage. Residual mains artefact (50 Hz) was minimized by the use of 'Humbugs' (Quest Scientific, Vancouver, Canada). The electrocorticogram (ECoG) was recorded from the screw above the left frontal cortex (ipsilateral to STN recording) or right frontal cortex. Screws in the nasal bone and above the cerebellum were used as the ground and the ECoG reference for differential recording, respectively. STN LFPs were recorded from the concentric semi-microelectrode in a bipolar (differential) configuration. Signals were recorded in the active animal through the use of a commutator. Raw STN and ECoG signals were AC-coupled, amplified (\times 1000–5000) and then band-pass filtered (0.1–100 Hz; Neurolog 100AK and 104A modules; Digitimer, UK). Conditioned signals were sampled at 512 Hz using a 12-bit A-D card (PCM-DAS16S, ComputerBoards, Middleboro, USA) and a portable computer running a custom-written program. Subsequent off-line signal processing was performed using commercial software (Spike2 software; Cambridge Electronic Design, Cambridge, UK). Data traces were digitally high-pass filtered off-line (cut-off at 0.5 Hz; Spike2) before analysis (see below). Recordings were made during rest and movement periods. During rest periods animals were completely still but alert. Movement recordings were defined as periods of sustained motor activity involving walking and exploring. Behavioural states were identified and noted by continuous visual inspection by one or two of the experimenters. Movement periods lasting 10–30 s were concatenated to produce epochs of 60 s for comparison with rest periods of 60 s duration. Periods of grooming and other stereotyped behaviour were excluded from analysis due to artefacts and the possibility that they contain their own distinctive neuronal activities (Aldridge & Berridge, 1998).

Histological processing

After recording, animals were transcardially perfused under deep anaesthesia with 30 mL 0.1 M phosphate-buffered saline, followed by 100 mL 4% w/v paraformaldehyde in 0.1 M phosphate buffer. Brains were removed and postfixed in 4% w/v paraformaldehyde for at least 24 h before being sectioned at 20- μ m intervals in the coronal plane. Cresyl violet staining was performed on coronal sections for histological verification of all recording sites. Only animals with correct placement of the recording electrode in the STN were included in the analysis (Fig. 1F). Furthermore, free-floating serial sections (20 μ m) of mesencephalon were cut and processed for tyrosine hydroxylase (TH) immunohistochemistry and then counterstained with Cresyl violet in order to perform stereology-based counting of TH-immunoreactive (TH-IR) neurons, as previously described (Meissner *et al.*, 2003). Cell counts were performed using a computer-based image analyser (Visioscan v4.12, Biocom, San Diego, USA). Unbiased stereological techniques (Gundersen *et al.*, 1988; West & Gundersen, 1990; West, 1999) were used to estimate cell number in the substantia nigra pars compacta (SNc). Every four sections, the boundaries of the SNc were delineated by examining the size and shape of the different TH-IR neuronal groups, their cellular relationship to axonal projections and nearby fibre bundles (Paxinos & Watson, 1986; German *et al.*, 1996). The volume of SNc, V_{SNc} , was calculated using the formula:

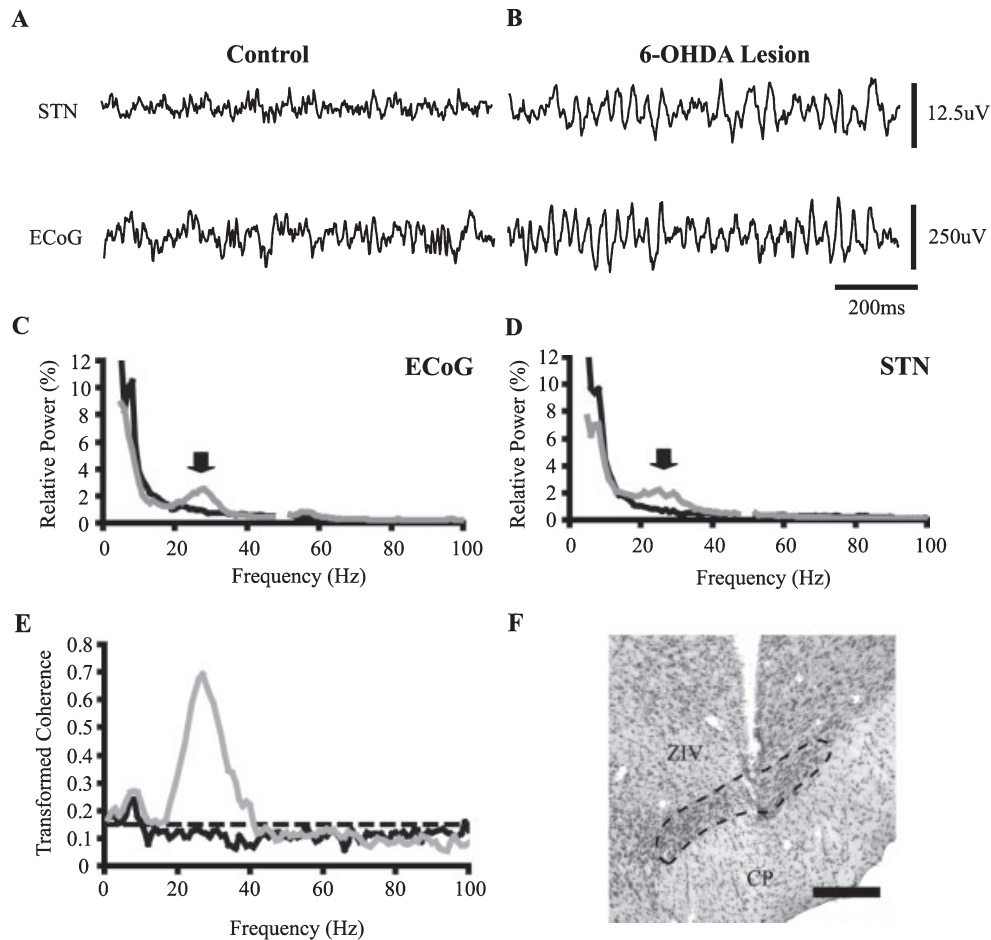


FIG. 1. 6-Hydroxydopamine (6-OHDA) lesions increase the power and coherence of β (22–32 Hz) oscillations in the cerebral cortex and subthalamic nucleus (STN) of the awake rat. (A, B) LFPs recorded in the STN and ipsilateral frontal cortex (electrocorticogram, ECoG) of 6-OHDA-lesioned animals at rest (B) were dominated by β -range oscillations that were not present in controls at rest (A). (C, D) Mean power spectra of both ECoG (C) and STN (D) activity recorded from lesioned animals ($n = 10$; grey lines) had clear peaks in the β -frequency range (arrows) that were absent in control animals ($n = 5$; black lines). Power at mains artefact frequency has been omitted. (E) Mean transformed coherence spectrum between STN and ECoG in lesioned animals ($n = 10$; grey line) displayed a large, significant peak between 20 and 35 Hz, which was not seen in the spectrum of control animals ($n = 5$; black line). (F) Electrode placement in the STN (borders indicated by dashed line) was confirmed with light microscopy. CP, cerebral peduncle; ZIV, ventral division of zona incerta. Horizontal calibration bar is 300 μm .

$$V_{\text{SNc}} = \Sigma S t d$$

where ΣS is the sum of surface areas, t is the average section thickness (12 μm after immunohistochemical processing) and d is the distance between the sections (Theoret *et al.*, 1999). Eight sections, the first being randomly chosen, were used and optical dissectors were distributed using a systematic sampling scheme. Dissectors (50 μm length, 40 μm width) were separated from each other by 30 μm (x) and 20 μm (y). In these dissectors, the nuclei of the neurons being in focus were counted (Gundersen *et al.*, 1988). To be included in the count, the cell body of a neuron had to be entirely in the dissector, or at least cross the dissector border by more than half its surface (Gundersen *et al.*, 1988). Only two consecutive borders (of four) of the dissectors were considered (Gundersen *et al.*, 1988). The following formula was used to estimate the number of TH-IR neurons:

$$N = V_{\text{SNc}} = \Sigma S \times (\Sigma NC_{\text{dis}} / \Sigma V_{\text{dis}})$$

where N is the estimated cell number, V_{SNc} is the volume of the SNc, ΣNC_{dis} is the number of cells counted in the dissectors and ΣV_{dis} is the

total volume of all the dissectors (Theoret *et al.*, 1999). The mean estimated number of neurons and SEM were then calculated.

Data analysis

Rhythmic neuronal activity was characterized by calculating power spectra (Fast Fourier Transform with Hanning window function; block size of 512 data points, giving 1.0 Hz resolution) using Spike2 software. Power was expressed as percentage total power over 5–45 Hz and 55–100 Hz to normalize the data across animals. Power at very low frequencies (< 5 Hz) was excluded so as to minimize the contribution of movement artefact and ‘DC drift’, and that at ~ 50 Hz was excluded to avoid inclusion of residual mains artefact. The frequency relationships between activity in cortex and STN were further defined by coherence analysis using the approach outlined by Halliday *et al.* (1995). Coherence is a measure of the linear association (correlation) between two signals across frequencies. It is a bounded measure taking values from 0 to 1, where 0 indicates that there is no linear association (i.e. that one process is of no use in linearly predicting another process) and 1 indicates a perfect linear association. Coherence, $|\text{Rab}(\lambda)|^2$, was calculated using the formula:

$|Rab(\lambda)|^2 = |fab(\lambda)|^2 / f_{aa}(\lambda) f_{bb}(\lambda)$. In this equation, f characterizes the spectral estimate of two signals, a and b , for a given frequency, λ . The numerator includes the cross-spectrum for a and b , $fab(\lambda)$, whereas the denominator includes the autospectra for a , $f_{aa}(\lambda)$, and b , $f_{bb}(\lambda)$. Timing information between the ECoG and STN LFP signals was calculated from the phase spectrum, defined as the argument of the cross-spectrum, $\arg\{fab(\lambda)\}$. The 95% confidence limits (CL) for all parameters were estimated as outlined by Halliday *et al.* (1995). The square root of the coherence was normalized prior to group analysis, while using a Fisher transform to stabilize variances prior to statistical analysis.

All standard power and coherence comparisons were performed on 60 s of data for each animal in each condition (rest or movement). Significant peaks in coherence were defined as three contiguous bins above the 95% CL. Two frequency bands were selected for comparison between groups based on the most prominent activities in the mean transformed coherence between STN LFPs and ECoGs in the lesioned and control animals. The first band was 5–11 Hz, representing the three bins either side of the peak at 8 Hz, while the second was 22–32 Hz, representing the five bins either side of the peak at 27 Hz. Differences in power and transformed coherence between behavioural conditions and between lesioned and control animals were evaluated with paired and unpaired two-tailed t -tests as appropriate. It should be noted that the analysis of data in the frequency domain, as performed here, is biased against the detection of stochastic, non-oscillatory synchronization, although the extent to which the latter occurs is unclear (Bergman *et al.*, 1994; Nini *et al.*, 1995; Raz *et al.*, 1996, 2000, 2001).

The phase relationships between cortical and STN activity were determined for lesioned animals from 60-s recordings made during rest. Phase estimates were derived from spectral analysis using blocks of 1024 data points (0.5 Hz resolution). Linear regression (Microsoft Excel) was performed on a frequency range of 10 Hz (10 bins), centred on the peak coherence above 15 Hz in individual spectra. For plots where the phase gradient was significant, the phase delay was derived as previously described (Grosse *et al.*, 2002).

Time-evolving power and coherence spectra were constructed from overlapping windows of data and plotted for rest periods and post-apomorphine periods (Matlab 6.5, Mathworks, Natick, USA). Power spectra (1 Hz resolution) were constructed using 10-s windows with 5-s overlap. Coherence spectra (2 Hz resolution) were constructed using the same window size and overlap. For histograms and statistics, spectral analysis was performed on three 20-s epochs recorded before apomorphine administration, nine 20-s epochs recorded after apomorphine but before rotation and, lastly, three 20-s epochs recorded during rotation. Raw power (as opposed to percentage total power) or transformed coherence in the β -frequency range was averaged across all animals to give a single value at each 20-s time point. In the case of coherence plots, coherence values below the level of significance (95% CL) were given values of zero. The 20-s epochs of data were used to compile histograms of power and coherence of activity in the β -frequency range throughout the period after injection with apomor-

phine as a percentage of levels present before injection (see below). For statistical analysis, groups of three consecutive 20-s epochs were averaged to give five 60-s periods covering 60 s of activity before injection, 180 s after injection but before the first rotation, and 60 s immediately following onset of rotation behaviour. General linear models were used to compare differences between these time periods (SPSS for Windows version 11, SSPS, Chicago, Illinois, USA). Changes in β -frequency activity after apomorphine injection as compared with rest were further examined using *post-hoc* paired t -tests.

Linear regression was used to examine the correlations between the frequencies at which peak power and coherence occurred, and their temporal relationship with respect to the onset of apomorphine-induced rotation behaviour. The frequencies of the peak power and coherence between 20 and 44 Hz were averaged across the spectra from all relevant animals. This broad band was chosen to allow for increases in the frequencies of activity over time, as described in the results. Regression was performed on each of the 20-s time points in the 180 s preceding the first rotation.

P -values of ≤ 0.05 were considered significant. All group data are expressed as mean \pm SEM unless stated otherwise.

Results

Verification of recording sites and 6-OHDA lesions

Histological analyses confirmed that both poles of the bipolar electrodes were outside of STN in 11 of 26 animals implanted and recorded. Data derived from these animals were not considered further because the recording electrodes varied greatly in location. Thus, only animals with correct placement of the recording electrode in the STN (see Fig. 1F) were included in the analysis. Ten animals with electrodes implanted in STN had previous intracerebral injections of 6-OHDA, and five successfully implanted animals were injected with saline.

The extent of the 6-OHDA lesion was assessed in each animal 4–5 weeks after toxin injection (after recording drug-free, spontaneous activity) by challenge with apomorphine (0.05 mg/kg, s.c.). The lesion was considered successful in those animals that made at least 90 net contraversive rotations in 20 min (Hudson *et al.*, 1993; Magill *et al.*, 2001). The mean number of contraversive rotations exhibited by those animals that were both successfully lesioned and implanted in STN ($n = 10$) was 175 ± 18.8 . In good agreement with this, the same lesioned animals showed a dramatic decrease in the number of TH-IR neurons in the SNc of the lesioned hemisphere, as compared with the contralateral SNc (62 ± 51 and 12562 ± 562 neurons, respectively). Control animals that received intracerebral injections of saline did not exhibit rotational behaviour after administration of apomorphine.

Oscillations in the β -frequency range are increased by dopamine depletion

Oscillations at about 20–30 Hz were clearly observable in the raw LFPs recorded in the frontal cortex (i.e. the ECoG) and STN of most

FIG. 2. Time-evolving coherence spectrum recorded during periods of rest and movement. Coherence plot was derived from 10-s overlapping windows of data recorded in one lesioned animal. At rest (red bars), sustained coherence between ECoG and STN LFP was seen at 25–30 Hz. A period of continuous exploratory movement (green bar) was associated with a distinct increase (~ 5 Hz) in the frequency of coherent activity.

FIG. 3. Power of β (22–32 Hz) oscillations in the cortex and subthalamic nucleus (STN) of 6-OHDA-lesioned rats is decreased by apomorphine. (A) Time-evolving power spectra of electrocorticogram (ECoG) and STN LFP activity simultaneously recorded from a lesioned animal recorded after injection of apomorphine. Power of prominent β -frequency oscillations remains high in both channels immediately after injection ($t = 0$ s; arrows) but begins to decrease after ~ 100 s, and is much reduced by the time of onset of rotation behaviour. A gradual increase in the frequencies of the oscillatory activity above 15 Hz in both cortex and STN is also clearly visible. (B) Histograms of average power (\pm SEMs; power normalized with respect to rest) of ECoG and STN activity over 22–32 Hz across all lesioned animals ($n = 5$). Reductions in power precede the rotations, although this was only found to be statistically significant for ECoG. In these histograms, times indicate timing with respect to the first rotation in each animal (time = 0), rather than with respect to time of injection.

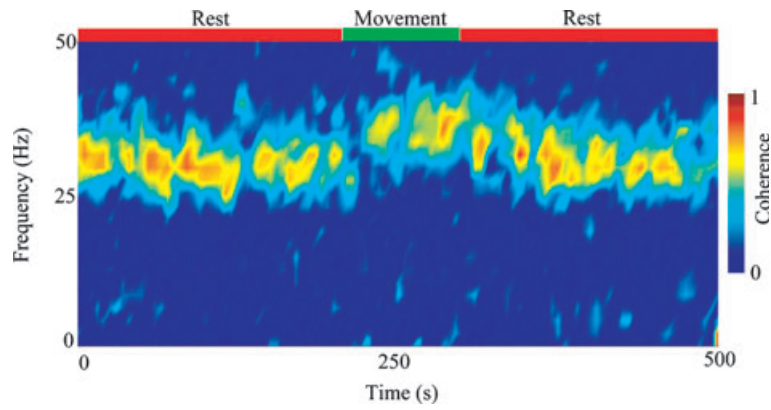


FIG. 2.

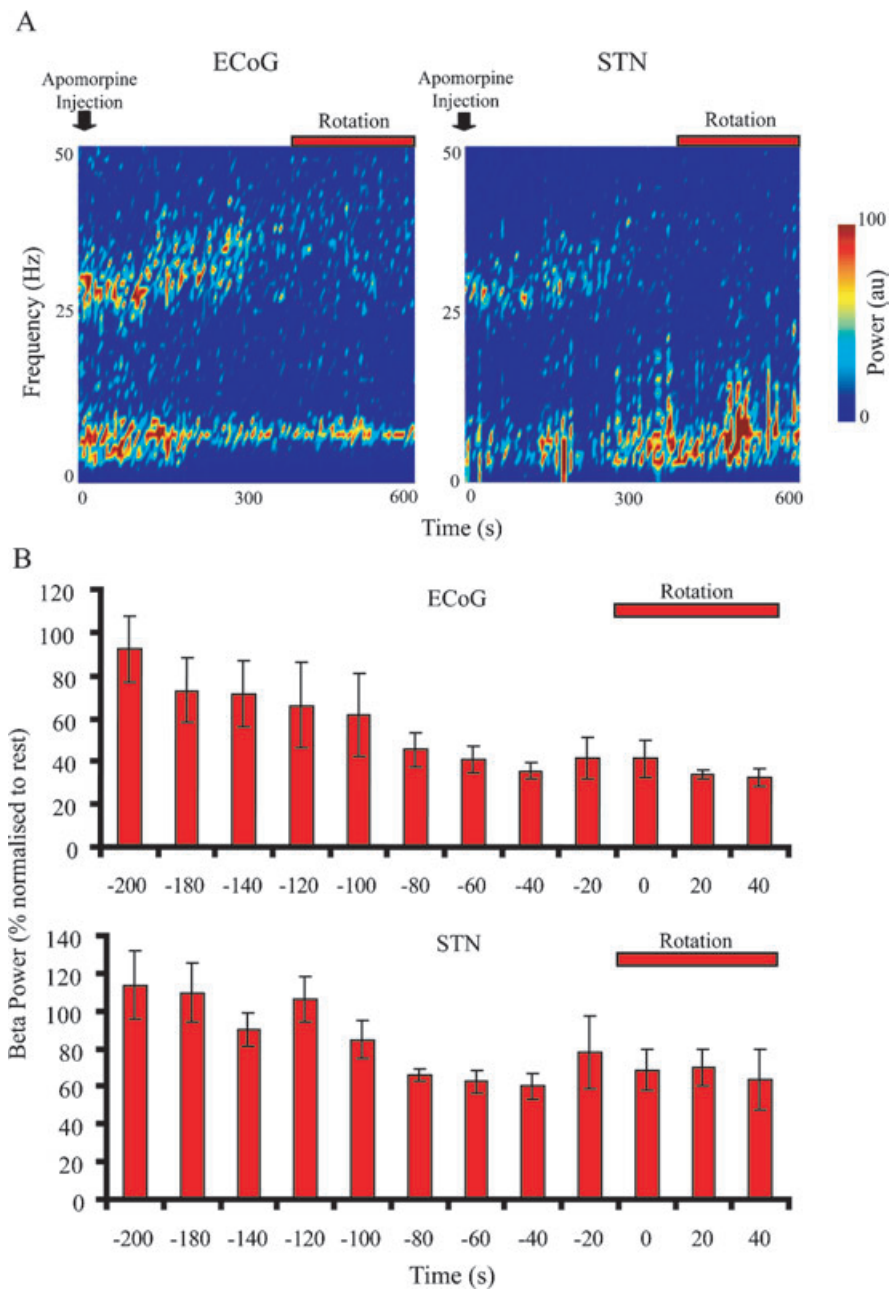


FIG. 3.

6-OHDA-lesioned animals at rest, but not control animals at rest (Fig. 1A and B). The power spectra derived from ECoG and STN recordings in both lesioned and control animals at rest displayed peaks within the range of 5–11 Hz (Fig. 1C and D). Power in the 5–11 Hz band of the ECoG was significantly higher (50%; $P < 0.005$) in control animals ($n = 5$; $7.8 \pm 0.4\%$ of total power) than lesioned animals ($n = 10$; $3.6 \pm 0.6\%$). Nearly all power spectra derived from recordings in lesioned animals displayed a prominent peak in the β -frequency band (22–32 Hz), in both ECoG (9/10) and STN (8/10), whereas such peaks were generally absent or much reduced in spectra derived from recordings in control rats (ECoG 2/5; STN 0/5). In good agreement, power in the β -frequency band was significantly higher in lesioned animals compared with controls, in both ECoG (136%; $P < 0.001$; Fig. 1C) and STN recordings (200%; $P < 0.001$; Fig. 1D).

Differences in the power of β -frequency oscillations in lesion and control animals at rest were mirrored by differences in the coherence between STN LFPs and ECoGs. A small, but significant, peak at about 8 Hz was present in the mean transformed coherence spectra of both groups (Fig. 1E). Transformed coherence in the 5–11 Hz band was not significantly different between the groups. However, all spectra derived from recordings in lesioned animals ($n = 10$) also had a large (mean peak transformed coherence of 0.8 ± 0.1), broad (mean width 17.3 ± 2.4 Hz) and highly significant peak in coherence between 23 and 31 Hz (26.4 ± 2.8 Hz; Fig. 1E). Accordingly, mean transformed coherence in the β -frequency band (22–32 Hz) was significantly higher in lesioned animals compared with controls ($P < 0.001$). Nevertheless, the majority of healthy animals (4/5) did have significant peaks of coherence between cortex and STN in the β -frequency band. However, these peaks were relatively small (mean peak transformed coherence 0.23 ± 0.02) and narrow (mean width 3.0 ± 0.0 Hz), and varied in frequency across the β -frequency band (24.5 ± 2.8 Hz), such that a clear peak was not visible in the spectrum of mean transformed coherence derived for all five control animals (Fig. 1E). Significant phase relationships were found in the β -frequency band for eight of 10 lesioned animals; three animals showed ECoG leading STN (4.6 ± 0.8 ms), while five animals showed STN leading ECoG (7.9 ± 0.8 ms).

In the above assessments, the ECoG was referenced to a screw over the cerebellum, raising the possibility that the ECoG signal was biased towards cerebellar activity rather than cerebral cortical activity. To test for this possibility, we reconfigured the ECoG electrodes to register the differential between the frontal cerebral cortices of both hemispheres. Differences in ECoG power and ECoG STN coherence between control and lesioned animals were robust and persisted after changing the ECoG recording configuration. There was a prominent peak in the β -frequency band (mean peak frequency of 25.5 ± 1.0 Hz) in power spectra derived from bipolar ECoG recorded between the ipsilateral and contralateral cortices of lesioned rats ($n = 5$). Power in the β -frequency band was significantly higher ($P < 0.001$) in the reconfigured bipolar ECoG from lesioned animals ($n = 5$; $2.8 \pm 0.20\%$) as compared with control animals ($n = 6$; $1.6 \pm 0.11\%$). Coherence spectra derived from the bipolar ECoG and STN recordings in lesioned animals also displayed a peak in the β -frequency band (23.8 ± 0.9 Hz; $n = 5$). Transformed coherence in this frequency band was significantly higher ($P < 0.05$) in lesioned animals (0.38 ± 0.1 ; $n = 5$) than in control animals (0.07 ± 0.004 ; $n = 4$). Taken together, these experiments confirm that the ECoG was generated by the underlying cortex and, thus, was not related to the use of a cerebellar reference electrode.

There were no significant differences in either the 5–11 Hz band or the β -frequency band between rest and movement conditions in control or lesion animals when analyses were carried out using data

averaged over 60-s periods. However, time-evolving coherence analysis over 10-s time windows revealed a small increase in the frequency of coherent activity in lesioned animals over periods where movement was recorded (Fig. 2). The peak frequency of coherent activity above 15 Hz was significantly higher (paired t -test < 0.02) during these movement periods (32.2 ± 1.0 Hz) than during randomly selected periods of rest (29.3 ± 0.9 Hz). The magnitude of peak coherence during these periods, however, was not significantly different between movement and rest.

Coherent activity in cortex and STN of lesioned animals was also dependent on the laterality of the ECoG recording site. Mean transformed coherence between the right (contralateral) ECoG and STN was significantly lower than that between the left (ipsilateral) ECoG and STN ($n = 5$, $P < 0.05$).

Effects of apomorphine on oscillations in the β -frequency range

Recordings were made free of movement artefact in five 6-OHDA-lesioned animals before and after apomorphine administration and the subsequent rotation behaviour. In these animals we investigated the temporal evolution of power spectra following apomorphine injection. Time-evolving power spectra of both ECoG and STN LFPs indicated that the power of β -frequency oscillations (22–32 Hz) decreased preceding rotation (Fig. 3A). To investigate this phenomenon in more detail, spectral analysis was performed on each 20-s epoch in the 180 s before the first rotation and compared with each 20-s epoch in the 60-s period preceding apomorphine injection and in the 60-s period immediately following first rotation. Histograms of power in the 22–32 Hz range in both ECoG and STN recordings suggested a drop in β -frequency activity before rotation, as compared with the activity present before the injection (Fig. 3B). A general linear model of raw power in this frequency band determined from the five 60-s periods described above (60 s of rest, 180 s to 0 s before rotation, and the first 60 s of rotation) confirmed a main effect of time for ECoG activity ($F_{4,16} = 14.173$; $P < 0.0001$) but not STN. *Post-hoc* Bonferroni-corrected t -tests showed that both 60-s periods immediately before and after the first rotation had significantly less power in the ECoG in the β -frequency range compared with that at rest ($P < 0.01$).

Apomorphine administration also induced changes in the coherence of activity present at 22–32 Hz in ECoGs and STN LFPs; these changes were similar in their evolution to the changes in power described above (Fig. 4A and B). A general linear model of transformed coherence in this frequency band also confirmed a main effect of time ($F_{4,14} = 9.878$; $P < 0.0005$). *Post-hoc* Bonferroni-corrected t -tests showed that the 120-s period immediately before and the 60 s immediately after the first rotation had significantly less coherence in the β -frequency range compared with that at rest ($P < 0.01$). Overall, the reductions in the power and coherence of β -frequency activity preceded and, thus, were not caused by, apomorphine-induced rotation. In addition to the drop in coherence in the β -frequency range, a shift in the dominant frequency of coherent activity was also observed (Fig. 4A and C) after injection of apomorphine in all five of the lesioned animals recorded. The frequencies at which the peak power and coherence of oscillations occurred between apomorphine injection and the first rotation were determined in serial 20-s epochs (see Fig. 4C for an example from a single animal) and were then averaged across these five animals for each epoch. Linear regression was carried out to determine the effect of apomorphine on the mean frequencies of the peak power and coherence as a function of time before rotation. A positive correlation between time before onset of rotation and mean frequency of peak power was found for ECoG

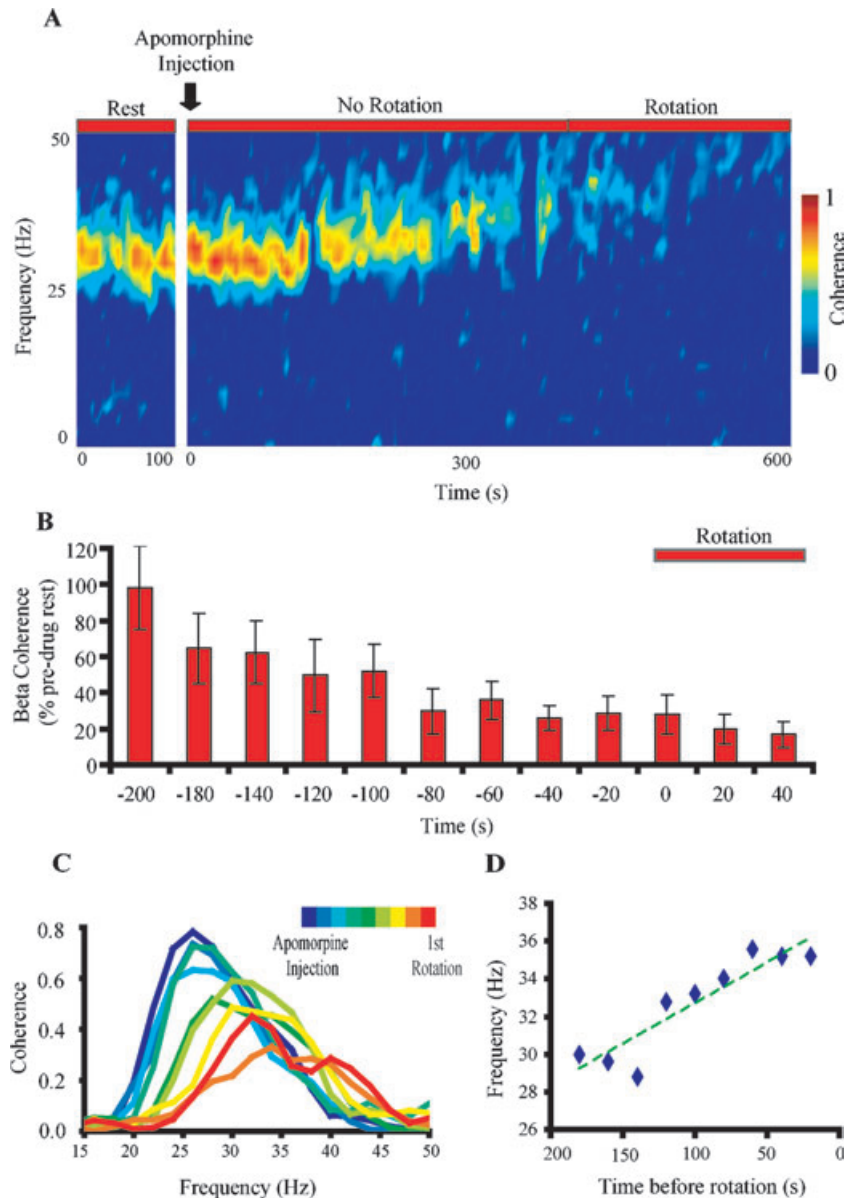


FIG. 4. Magnitude and dominant frequency of coherent activity in the cortex and STN of 6-OHDA-lesioned rats is altered by apomorphine. (A) Time-evolving coherence spectrum recorded before and after injection of apomorphine in the same lesioned animal as seen in Fig. 3. Coherence between ECoG and STN LFP is dominated by β -frequency activity at rest. As with power spectra, coherence at β -frequencies decreases and also shifts to higher frequencies during the time between injection and the onset of rotations. (B) Histogram showing mean transformed coherence (\pm SEMs; normalized with respect to rest) over 22–32 Hz across all lesioned animals ($n = 5$). (C) Coherence in 20-s epochs in a single lesioned animal recorded after injection of apomorphine. Colour changes from dark blue to red indicate chronological order of 20-s epochs from injection (dark blue) to first rotation (red). A gradual shift in peak coherence to higher frequencies and lower magnitude is evident after injection. (D) Regression analysis of the mean frequency of peak coherence (five lesioned animals) in each 20-s epoch before the first rotation (time = 0 s) induced by apomorphine administration.

($r^2 = 0.6$, $P < 0.01$), but not STN LFP. A positive correlation was also seen between time before onset of rotation and the peak frequency of coherence between cortex and STN ($r^2 = 0.80$, $P < 0.001$; Fig. 4D).

Discussion

The central findings of this study are threefold. First, the preferential synchronization of oscillatory population activity within and between the STN and frontal cortex in the β -frequency band in the 6-OHDA-lesioned rodent closely agrees with the patterns of activity prevalent in

the parkinsonian human (Marsden *et al.*, 2001; Williams *et al.*, 2003; Kühn *et al.*, 2004). Second, periods of spontaneous movement are associated with a small but significant increase in the peak frequency of coherent activity in the β -frequency range in cortex and STN. Third, administration of the dopamine receptor agonist apomorphine to 6-OHDA-lesioned rats leads to a suppression of β -frequency oscillations. At the same time, there is also a shift of coherence between STN LFP and ECoG to higher frequencies, similar to, but more marked than, the shift seen with spontaneous movement. Both of these apomorphine-induced changes precede rotational behaviour. The latter findings suggest that, at the systems level, dopaminergic mechanisms effectively filter out activity that is synchronized at

β -frequencies, whilst promoting the expression of oscillations at other frequencies. These changes in network properties appear to be important in the regulation of movement.

Interpretation of LFP recordings

Before considering our findings in greater detail, we should explore some of the limitations and assumptions of our experimental approach. First, it is possible that increased coherence between ECoGs and STN LFPs in the 6-OHDA-lesioned animal is a mere by-product of local increases in the power of synchronized activity in the β -frequency band in STN and cortex. However, this is unlikely because increases in the power of non-correlated activities would have been expected to decrease, rather than increase, coherence. Thus, for coherence to increase, there must have been a correlated increase in the amplitude of phase-locked activity at both recording sites (Florian *et al.*, 1998). Second, the question arises as to what extent the coherence between STN LFPs and ECoG was due to the temporal coupling of local oscillatory activity in STN and cortex, or the volume conduction of synchronous cortical activity to STN. We used a bipolar recording configuration, thereby avoiding a common reference that may sometimes lead to contamination of STN LFPs with cortical activity (see Wennberg & Lozano, 2003). In addition, there was a temporal (i.e. phase) difference between the cortical and STN signals in 80% of animals. Although the phase relationship between cortical and subthalamic activities varies, presumably as a result of small relative differences in the cortical areas and STN domains recorded in different animals, temporal differences were nevertheless significantly different to zero and therefore incompatible with volume-conducted activity. Third, we assume that the oscillations present in STN LFPs and ECoGs reflect the synchronized activity of local neuronal populations. There is much evidence from studies of laminated structures, such as the cortex, that LFPs are representative of the aggregate activity of local neuronal populations (Creutzfeldt *et al.*, 1966; Frost, 1968; Murthy & Fetz, 1992, 1996; Baker *et al.*, 1997; Donoghue *et al.*, 1998). The basal ganglia do not share the laminar structure seen in the cortex but, nevertheless, there is evidence to support the notion that LFPs recorded in these nuclei also reflect synchronized aggregate activity (Levy *et al.*, 2002a; Berke *et al.*, 2004; Goldberg *et al.*, 2004; Magill *et al.*, 2004a). Cortical stimulation produces highly synchronized responses in STN neurons that are, in turn, reflected in the field potential (Magill *et al.*, 2004a). The fact that cortical stimulation elicits a stereotypical LFP within STN, but not neighbouring areas, also argues that the population activity reflected in the STN LFP is dominated by current flow in STN neurons (Magill *et al.*, 2004a). Furthermore, *in vivo* recordings from rat nucleus accumbens show that low-frequency oscillations in LFPs are a consequence of synchronous fluctuations in the membrane potentials of principal cells (Goto & O'Donnell, 2001). Specifically, temporal coupling in the β -frequency band has been demonstrated between single units and LFPs in the striatum of healthy monkeys (Courtemanche *et al.*, 2003) and the STN of parkinsonian patients (Levy *et al.*, 2002a). Moreover, β -frequency oscillations in STN LFPs are coupled to LFPs recorded in distant, but connected, sites, such as the globus pallidus and cerebral cortex, suggesting that they are at least partly associated with synchronized presynaptic and/or postsynaptic effects (Brown *et al.*, 2001; Marsden *et al.*, 2001; Williams *et al.*, 2002). Thus, β -frequency oscillations in STN LFPs may be informative about the aggregate or population activity of local neuronal elements. Finally, it should be stressed that the coherence in the β -frequency band between STN and cortex, as seen predominantly in the 6-OHDA-lesioned animal, was well above the frequency of any periodic motor phenomena, such as walking or

whiskering, and was clearly observed when the animals were alert but resting.

Dopamine depletion and synchronization of activity in the β -frequency band

Is synchronization of activity in the β -frequency band in parkinsonism an exaggeration of physiological activity in STN or a *de novo* pathological activity? Although we found no evidence of a discrete β -frequency peak in the power spectrum of the STN LFP of healthy non-lesioned animals, we did find low coherence between ECoGs and STN LFPs in this frequency band. In contrast, animals with successful and widespread 6-OHDA lesions of neurons in SNc displayed greatly exaggerated power within, and coherence between, the cortex and STN in the β -frequency band. Reductions in the power and coherence of β -frequency oscillations were clearly observed in these animals after administration of the dopamine receptor agonist apomorphine. Note that decreases in β -frequency power and coherence occurred well before the onset of apomorphine-induced rotation and could not therefore be ascribed to movement-related decreases in β -frequency activity, as reported when STN LFPs from parkinsonian patients are averaged around phasic movements (Cassidy *et al.*, 2002; Levy *et al.*, 2002a; Priori *et al.*, 2002; Williams *et al.*, 2003; Kühn *et al.*, 2004). The decrease in β -frequency power and coherence was found in every animal tested, supporting the idea that these and other changes in network activity may be important in the regulation of movement. It is possible that the observed reductions in β -frequency network activity were associated with changes in alertness, muscle tone, or other non-motor activities involving STN, before rotation (Chudasama *et al.*, 2003). Although non-motor activities were not specifically addressed in the present study, they are presumably of significance for movement initiation anyway and, as such, the suggestion that changes in β -frequency network activity are important in the regulation of movement is still valid. Although administration of apomorphine decreased the power and coherence of activity in the β -frequency band, it did not affect the weaker coherent activity between cortex and STN at about 6–12 Hz, which may be associated with whisker movements and exploratory behaviour (Moore *et al.*, 1999). Collectively, the above suggest that the dopaminergic mechanisms activated by apomorphine effectively serve to band-pass filter input to, and activity in, the STN in the β -frequency band. Such input is, at least in part, likely to be cortical in origin (Magill *et al.*, 2001, 2004b), whether direct (via cortico-subthalamic pathway) or indirect (via *trans*-striatal and *trans*-thalamic pathways), and appears to have greater functional impact in the 6-OHDA-lesioned animal (also see Magill *et al.*, 2001). Because apomorphine was systemically administered, and because we recorded activity at only two areas, cortex and STN, the exact site(s) of action of apomorphine are unknown. Dopamine itself has multiple presynaptic and postsynaptic actions throughout the basal ganglia (see reviews by Greengard *et al.*, 1999; Nicola *et al.*, 2000; Smith & Kievit, 2000), including the STN (Cragg *et al.*, 2004). Nevertheless, our data provide important new insights in the context of the influences of 'dopaminergic tone'.

The effects of dopaminergic stimulation were, however, not limited to a systems-level band-pass filtering of β -frequency activities. Indeed, apomorphine administration also promoted synchronized oscillatory population activity at higher frequencies. This observation is in line with studies in parkinsonian humans showing an increase in oscillations of higher frequency after dopaminergic medication (Brown *et al.*, 2001; Williams *et al.*, 2002), particularly when movements are performed following treatment (Cassidy *et al.*, 2002). The steady shift in the dominant frequency of activity over time

following apomorphine is also consistent with a dose-dependent band-pass filtering effect on activity synchronized at β -frequencies. A similar, albeit much less pronounced, increase in the frequency of coherence between STN and cortex was seen in lesioned animals during spontaneous movements, as compared with rest. This intrinsic modulation may relate to dopamine release (for review, see Hauber, 1998) from the remaining few ipsilateral dopamine neurons, and/or may involve an indirect effect of dopaminergic influences originating in the contralateral non-lesioned hemisphere. The role of coherent oscillations at the higher frequencies recorded during movement or after apomorphine is unclear, but it is of interest that these activities were most marked post-apomorphine in the period between injection and florid hyperkinesia (rotation); an intermediate state that may be the closest to 'normal' function in the lesioned animals.

The increase in the frequency of rhythmic population activity with dopamine receptor stimulation observed in the present study contrasts with the ability of dopamine receptor agonists to reduce the firing rates of single STN neurons in the 6-OHDA-lesioned animal (Kreiss *et al.*, 1997). The opposite direction of these effects underscores the complex relationship between synchronized population activity and single unit activity (Bullock, 1997; Engel *et al.*, 2001).

Concluding remarks

Our results indicate that rhythmic and synchronized population activity in the STN is likely to be strongly coupled to that in the cortex, which provides an important excitatory input to the STN (Magill *et al.*, 2000, 2001, 2004a). The findings presented here, together with those showing that the excessive synchronization of β -frequency activity in STN in patients with PD is reversed with dopaminergic medication (Brown *et al.*, 2001; Levy *et al.*, 2001, 2002a), suggest that the function of dopamine is to modulate not only the degree of synchronization of activity within the basal ganglia, and the synchronization between the cortex and basal ganglia, but also its frequency. Modulations of oscillatory activity are increasingly being recognized as potentially valuable measures of drug action (Whittington *et al.*, 2000). Given the growing evidence for the importance of synchronized activity in PD pathology (Bergman *et al.*, 1998; Boraud *et al.*, 2002; Brown, 2003), the reduction of activity synchronized in the β -frequency band in basal ganglia and/or cortex in the 6-OHDA-lesioned rat could prove to be a highly predictive model for the efficacy of novel antiparkinsonian therapies.

Acknowledgements

This work was supported by the Brain Research Trust and the Medical Research Council UK. P.J.M. holds a Fellowship by Examination at Magdalen College, Oxford, UK, and W.M. is a Marie Curie Fellow of the European Community (HPMF-CT-2001-01300).

Abbreviations

6-OHDA, 6-hydroxydopamine; CL, confidence limits; ECoG, electrocorticogram; LFP, local field potential; PD, Parkinson's disease; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; TH, tyrosine hydroxylase; TH-IR, tyrosine hydroxylase-immunoreactive.

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