Different Functional Loops between Cerebral Cortex and the Subthalamic Area in Parkinson’s Disease

We investigate the extent to which functional circuits coupling cortical and subthalamic activity are multiple and segregated by frequency in untreated Parkinson’s disease (PD). To this end, we recorded EEG and local field potentials (LFPs) from macroelectrodes inserted into the subthalamic nucleus area (SA) in nine awake patients following functional neurosurgery for PD. Patients were studied after overnight withdrawal of medication. Coherence between EEG and SA LFPs was apparent in the theta (3–7 Hz), alpha (8–13 Hz), lower beta (14–20 Hz) and upper beta (21–32 Hz) bands, although in the alpha and upper beta bands dominated. Theta coherence predominantly involved mesial and lateral areas, alpha and lower beta coherence the mesial and ipsilateral motor areas, and upper beta coherence the midline cortex. SA LFPs led EEG in the theta band. In contrast, EEG led the depth LFP in the lower and upper beta bands. SA LFP activity in the alpha band could either lead or lag EEG. Thus there are several functional sub-loops between the subthalamic area and cerebral cortical motor regions, distinguished by their frequency, cortical topography and temporal relationships. Tuning to distinct frequencies may provide a means of marking and segregating related processing, over and above any anatomical segregation of processing streams.

Keywords: EEG, oscillations, Parkinson’s disease, subthalamic nucleus, synchronization

Introduction

Parkinson’s disease (PD) is a common and disabling disease. Its pathophysiology is still relatively poorly understood. The last few years have seen a shift in emphasis from the tonic inhibition and excitation effects encapsulated in the Albin-DeLong model (Albin et al., 1989; DeLong, 1990) to a schema in which the nature of the synchronized bursting of the basal ganglia is critical in determining pathophysiology (Marsden and Obeso, 1994; Obeso et al., 1997; Brown and Marsden, 1998). Several types of synchronization have been identified in untreated parkinsonism and their relative importance in the pathophysiology of PD remains unclear (reviewed in Brown, 2003). First, there is an excessive synchronization and bursting in the frequency range of rest and action tremor in PD and the primate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD, although the precise frequencies involved varies between species and the relationship of bursting to clinical tremor is still unclear (Bergman et al., 1994; Nini et al., 1995; Hutchison et al., 1998; Magnin et al., 2000; Magarinos-Ascone et al., 2000; Goldberg et al., 2002; Silberstein et al., 2003). Second, there is abnormal synchronization and bursting in the so-called beta band (14–30 Hz) in the basal ganglia in both MPTP treated primates (Raz et al., 1996) and in parkinsonian humans (Levy et al., 2000, 2001, 2002a,b; Marsden et al., 2001; Brown et al., 2001; Cassidy et al., 2002; Priori et al., 2002; Williams et al., 2002). Whether activity throughout the beta band is of similar significance is unclear, and there have been some suggestions that the lower and upper beta bands may be functionally distinct (Priori et al., 2002; Williams et al., 2002; Vorobyov et al., 2003). Similarly, previous studies have failed to distinguish between subthalamic nucleus (STN)-EEG coherence in the theta band, covering the frequency range of parkinsonian rest tremor, and that in the alpha band (Williams et al., 2002). Further, no one study has determined which activities predominate in STN-cortical circuits in untreated PD, nor whether the oscillatory activities in this state are independently generated or harmonically related. Finally, although there is some evidence to suggest that the beta activity is driven from the cortex (Marsden et al., 2001; Brown et al., 2001; Williams et al., 2002), it remains unclear whether this drive is identical throughout the beta band and whether synchronization in the theta and alpha bands is driven by the cortex or drives the motor cortex.

Here we posit that the more functionally significant forms of synchronization within the basal ganglia of untreated PD will involve simultaneous activity in large populations of local neurons, and thereby oscillations in local field potentials (Goldberg et al., 2004; Magill et al., 2004a,b; Kühn et al., 2005), and will be coupled to similar activity in motor areas of the cerebral cortex and hence coherent with EEG. Accordingly, we simultaneously recorded scalp EEG and local field potentials (LFPs) from macroelectrodes (MEs) inserted in the area of the subthalamic nucleus (SA) in awake PD patients in the few days following functional neurosurgery. Data were collected following overnight withdrawal of dopaminergic treatment, so as to promote oscillation at tremor and beta frequency (Brown et al., 2001; Williams et al., 2002). Our aims were first, to determine the predominant frequencies in the coupling between cortical and subthalamic activities, and second, to determine the extent to which coupling in different frequency bands may be differentiated with respect to cortical topography and direction of drive.

Materials and Methods

Patients and Surgery

All patients participated with informed consent and the permission of the local ethics committees. We studied nine patients, mean age of 59.7 ± 1.7 years (three female). Their clinical details are summarized in Table 1. The operative procedure and beneficial clinical effects of stimulation of the subthalamic nucleus (STN) have been described previously (Limousin et al., 1995; Starr et al., 1998; Esselink et al., 2004). MEs were inserted after STN had been identified by ventriculography and preoperative magnetic resonance imaging (MRI). Simultaneous implantation of bilateral MEs was performed in all cases. The intended...
coordinates at contact 1 were 11-15 mm from the midline, 0-3 mm behind the midcommissural point and 4-6 mm below the anterior commissure-posterior commissure (AC-PC) line. Intraoperative electrode localization was tested by macro-stimulation in all patients. No microelectrode recordings were made. The ME was used model 3389 (Medtronic Neurological Division, Minneapolis, MN) with four platinum-iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length) and a center-to-center separation of 2 mm. Contact 0 was the most caudal and contact 3 was the most rostral. The patients derived a mean ± SEM of 51 ± 6% and 40 ± 8% reduction in OFF treatment motor UPDRS scores with i-dopamine (i-Dopa) and therapeutic deep-brain stimulation, respectively. Pre-operative assessment of the clinical efficacy of i-Dopa was determined <4 months prior to surgery. Post-operative scores were collected 6 months after the operation. There was a significant difference between pre-operative and 6 months post-operative equivalent total daily i-Dopa dose (Wilcoxon, P = 0.011). Post-operative equivalent total daily levodopa dose was reduced to 66 ± 8% of the pre-operative dose. No post-operative imaging was performed in the patients.

**Recordings**

Subjects were supine or seated and recorded while at rest after the patient had been off medication overnight (OFF), although it is acknowledged that patients were only likely to have been partially withdrawn from the effects of dopaminergic therapy after overnight abstinence. Deep-brain activity was recorded from the adjacent four contacts of each macroelectrode in the subthalamic area (SA-ME) giving a frequency resolution of 1 Hz. In the frequency domain, estimates of the autospectrum of the EEG, $f_{AA}(\lambda)$, and LFP, $f_{BB}(\lambda)$, were constructed, along with estimates of coherence, $|R_{AB}(\lambda)|^2$, given by

$$|R_{AB}(\lambda)|^2 = \frac{f_{AA}(\lambda) f_{BB}(\lambda)}{f_{AB}(\lambda) f_{BA}(\lambda)},$$

where $\lambda$ denotes the frequency and $f_{AD}(\lambda)$ is the cross spectrum between the signals.

**Analysis**

Recorded activity was analysed in Spike2 v4.0 (Cambridge Electronic Design, Cambridge, UK). For the estimation of coherence 400 s of artifact-free data were selected for each subject OFF medication (359, 380 and 398 s from three recordings). LFP and EEG signals were originally recorded referenced to linked ears but later the following bipolar electrodes were derived and analysed offline: left and right SA-ME 0-1, 1-2 and 2-3, and Cz-Pz, Pz-Cz, C3-F3, P3-C3, C4-F4 and P4-C4. The EEG, denoted by subscript A, and LFP, denoted by subscript B, were assumed to be realizations of stationary zero mean time series. The principal statistical tool used for data analysis in this study was the discrete Fourier transform and parameters derived from it, all of which were estimated by dividing the records into a number of disjoint sections of equal duration, and estimating spectra by averaging across these discrete sections (Halliday et al., 1995). A Hanning window filter was used for all spectral analyses. Segment lengths of 1024 points were used, giving a frequency resolution of 1 Hz. In the frequency domain, estimates of the autospectrum of the EEG, $f_{AA}(\lambda)$, and LFP, $f_{BB}(\lambda)$, were constructed, along with estimates of coherence, $|R_{AB}(\lambda)|^2$, given by

$$|R_{AB}(\lambda)|^2 = \frac{f_{AA}(\lambda) f_{BB}(\lambda)}{f_{AB}(\lambda) f_{BA}(\lambda)},$$

where $\lambda$ denotes the frequency and $f_{AB}(\lambda)$ is the cross spectrum between the signals.

Coherence is a measure of the degree to which one can linearly predict change in one signal given a change in another signal (Brillinger 1981; Rosenberg et al., 1989; Halliday et al., 1995). It is without units, and is bounded from 0 to 1, with a coherence of 0 indicating non-linearly related signals and a value of 1 signifying two identical signals. Because

**Table 1**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Disease duration (years)</th>
<th>Pre-operation medication (daily dose in mg)</th>
<th>Post-operation medication (daily dose in mg)</th>
<th>Predominant symptoms</th>
<th>Side studied</th>
<th>Clinically effective contact - monopolar</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>57</td>
<td>8</td>
<td>1200 l-Dopa 1.25 Pergolide</td>
<td>750 l-Dopa 2 Pramipexole</td>
<td>bradykinesia, rigidity</td>
<td>RT</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>65</td>
<td>25</td>
<td>200 l-Dopa 300 Amantadine 1.8 Lisuride 5 Selegeline</td>
<td>125 l-Dopa 300 Amantadine 0.8 Lisuride</td>
<td>bradykinesia</td>
<td>RT</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>54</td>
<td>15</td>
<td>600 L-Dopa 8 Périgolde</td>
<td>500 l-Dopa 5 Périgolde</td>
<td>bradykinesia, tremor</td>
<td>RT</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>56</td>
<td>13</td>
<td>600 l-Dopa 10 Selegeline 300 Amantadine 300 Entacapone</td>
<td>300 l-Dopa 5 Selegeline 100 Amantadine 0.8 Pramipexol</td>
<td>dyskinesias</td>
<td>RT</td>
<td>12(bipolar)</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>54</td>
<td>11</td>
<td>500 l-Dopa 4 Benhexol 600 L-Dopa 4 Périgolde</td>
<td>200 l-Dopa 2 Benhexol</td>
<td>tremor, dyskinesias</td>
<td>RT</td>
<td>02</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>63</td>
<td>16</td>
<td>750 l-Dopa 1200 Entacapone 3 Pergolide 200 Amantadine 800 Entacapone</td>
<td>600 l-Dopa 1200 Entacapone 200 Amantadine 30 Domperidone</td>
<td>tremor, dyskinesias</td>
<td>RT</td>
<td>01</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>56</td>
<td>11</td>
<td>1900 l-Dopa 3 Pergolide 200 Amantadine 800 Entacapone</td>
<td>700 l-Dopa 3 Pergolide 200 Amantadine 30 Domperidone</td>
<td>bradykinesia tremor, rigidity</td>
<td>RT</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>66</td>
<td>36</td>
<td>450 l-Dopa 5 Selegeline 5 Ropinirole</td>
<td>400 l-Dopa 11 Ropinirol 4 trihexyphenidyl LT 1</td>
<td>tremor, rigidity, bradykinesia</td>
<td>RT</td>
<td>13 (bipolar)</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>66</td>
<td>10</td>
<td>800 l-Dopa 5 Selegeline 4 trihexyphenidyl</td>
<td>300 l-Dopa 4 trihexyphenidyl 4 trihexyphenidyl</td>
<td>tremor, bradykinesia, rigidity</td>
<td>RT</td>
<td>1</td>
</tr>
</tbody>
</table>
coherence is a measure of the linear association between two signals, the EEG/LFP waveforms must be phase-locked (temporally coupled) and their amplitudes must have a constant ratio to be coherent at any given frequency. The coherence estimates can be interpreted as providing an estimate of the contribution of EEG to LFP activity and vice versa.

First-order partial coherence functions were estimated to assess whether ‘partialization’ with a third process (hereafter referred to as the ‘predictor’) accounted for the relationship between two other processes (Rosenberg et al., 1989, 1998; Halliday et al., 1995). The partial coherence can be viewed as representing the fraction of coherence between, for example, Cz-Fz and SA-ME that is not shared with a third signal, say P3-Pz. Thus, if sharing of the signal between Cz-Fz, SA-ME and P3-Pz were complete, then partialization of the coherent activity between Cz-Fz and SA-ME with P3-Pz as the predictor would lead to zero coherence. It follows that if the coherent activity between Cz-Fz and SA-ME were kept completely separate from P3-Pz, partialization with P3-Pz as the predictor would have no effect on the coherence between Cz-Fz and SA-ME signals. Note that the partial coherence function is based on the assumption of linearity, so that failure of the partial coherence to drop compared to the ordinary coherence does not exclude non-linear interactions between the different signals. The function performs best when tested signals have similar signal-to-noise ratios — a reasonable approximation when dealing with EEG and LFP. Example applications of first-order partial coherence functions to problems in neuroscience are given in Halliday et al. (1999), Kocsis et al. (1999), Spauschus et al. (1999) and Mima et al. (2000).

Timing information between the EEG and LP signals was calculated from the phase spectrum, defined as the argument of the cross-spectrum \( \phi_k(t) \). Confidence limits (CL) for all parameters were estimated according to methods outlined in Halliday et al. (1995).

A peak in coherence was defined as three or more contiguous 1 Hz bins exceeding the 95% confidence limit or background coherence, whichever was higher. Phase was only analysed over those frequencies showing significant coherence between LFPs and cortex. The constant time lag between two signals was calculated from the slope of the phase estimate (divided by \( 2\pi \)) after a line had been fitted by linear regression (Gotman, 1983). The time lag was only calculated from the gradient from a minimum of 4 contiguous points of significant coherence and where the linear relationship accounted for \( r^2 > 0.85 \) of the variance (\( P < 0.05 \)).

To demonstrate the focality of recorded LFP activity a waveform cross-correlation was performed (Spike2 v4.0) between the pass-band filtered (7–32 Hz) signals of adjacent bipolar SA-ME contact pairs (e.g. 01 with 12 and 12 with 23). Polarity reversal, indicating signal generation at the site of the shared ME contact, was considered to occur when there was a peak at time 0 ± 10 ms that was negative and maximal amongst other negative peaks in the waveform cross-correlogram. For example, if polarity reversal around contact 1 of the right SA-ME (R-SA-ME) would be confirmed by a negative peak around time zero in the cross-correlation of the LFP recorded at R-SA-ME contacts 01 and 12 (for examples, see Kühn et al., 2004). The number of polarity reversals detected (\( n = 9 \)) precluded any statistical comparison of the number of contacts showing both polarity reversal and being used for clinical stimulation versus the number of such associations arising by chance.

The frequency bands of interest were defined as follows: theta (5–7 Hz), alpha (8–13 Hz), lower beta (14–20 Hz) and upper beta (21–32 Hz). Coherences were normalized for statistical analysis using the Fisher transformation of the modulus of the coherency (square root of the coherency). Group analyses were determined for the bipolar contact on each side in each subject that had the greatest coherence with Cz-Fz in each of the four frequency bands, unless otherwise stated. Analyses of variance (ANOVA)s followed by relevant post-hoc two-tailed paired \( t \)-tests were performed unless otherwise stated. Mean values with SEM are used throughout the text.

**Results**

**Spectral Analysis**

All patients were studied after an overnight withdrawal of antiparkinsonian medication. Three of the patients (cases 2, 4 and 9) showed clinical evidence of temporary microlesional/edema effects from surgery in so far as tremor and off-period severity were reduced during the first few days after surgery. (Depth LFP recordings were made during this period in these three subjects.) Figure 1A shows an example of raw SA-ME LFPs and EEG recorded in case 8. Note that EEG is generally of higher amplitude than the bipolar SA-ME LFP. Oscillatory activity at ~20 Hz is evident in the latter. Average coherence spectra between the three SA-ME bipolar contacts on each side and the six EEG electrode pairs (Cz-Fz, Pz-Cz, C3-F3, P3-C3, C4-F4, P4-C4) showed a broad band of elevated coherence from 3–32 Hz with peaks in the alpha and upper beta frequency range (Fig. 1B). There was no clear evidence of discrete peaks in the theta and lower beta bands in the averaged data, although in cases 4, 5 and 8 coherence in the theta band exceeded that in the alpha band and in cases 2 and 3 coherence in the lower beta band was greater than that in the upper beta band. In addition, there were subjects in whom theta and alpha (cases 3 and 9) and lower and upper beta (cases 3, 5 and 9) had peaks of similar size. No peaks in coherence were seen from 35 to 250 Hz.

**Differential Topography of Coherence in the STN Area**

Friedman’s test showed that the distribution of the maximum coherence within the four frequency bands (theta, alpha, lower beta and upper beta) was not statistically different across the SA-ME contacts (Fig. 2). However, there was a highly significant correlation between the more caudal contact position and the occurrence of maximal coherence with EEG in the four frequency bands (Spearman’s \( r = 0.850, P < 0.0001 \)). Note that,
Differential Topography of Coherence at the Cortex

We utilized a two-way ANOVA for the comparison of the cortical topography of the four frequencies across the subjects. Frequency band (3–7, 8–13, 14–20 and 21–32 Hz) and area (midline, ipsilateral and contralateral to the SA-ME) were used as factors. The areas were defined as follows: midline — average of Cz–Fz to L-SA-ME, Pz–Cz to L-SA-ME, Cz–Fz to R-SA-ME, Pz–Cz to R-SA-ME; ipsilateral to the ME — average of C3–F3 to L-SA-ME, P3–C3 to L-SA-ME and C4–F4 to R-SA-ME, P4–C4 to R-SA-ME; contralateral to the ME — average of C3–F3 to R-SA-ME, P3–C3 to R-SA-ME and C4–F4 to L-SA-ME, P4–C4 to L-SA-ME coherence.

There was no main effect for frequency band, but there was a significant main effect for area ($F = 21.441, P < 0.0001$) and an interaction between area and frequency band ($F = 4.509, P = 0.007$). Mean transformed subcortico-cortical coherence averaged across all four frequency bands was greater in the midline (0.119 ± 0.02) than over lateral areas ipsilateral (0.089 ± 0.02, $P = 0.002$) and contralateral (0.082 ± 0.01, $P < 0.0001$) to the sampled SA. Within frequency bands the differences in topography in the 3–7 Hz band were not statistically significant (Fig. 3A). The transformed coherence in the 8–13 Hz band was greater in the midline than contralaterally ($P = 0.007$). In the 14–20 Hz band the transformed coherence was greater in the midline than ipsilaterally ($P = 0.013$) or contralaterally ($P = 0.003$). In the 21–32 Hz band the transformed coherence was also greater in the midline than ipsilaterally ($P = 0.007$) or contralaterally ($P = 0.005$). The increased coherence with mesial areas could not have arisen from the presence of burr holes as this would have had the converse effect, leading to elevated coherence in lateral cortical areas close to the burr holes.

To determine the differences in relative topography between frequency bands, for each subject we normalized the coherence to that which was greatest out of the three cortical areas. This was performed for each of the four frequency bands, giving us the relative coherence over ipsilateral, midline and contralateral cortex. We then performed three separate Friedman’s tests for each of the three areas across the four frequency bands. There were differences between the four frequency bands ipsilaterally ($P = 0.004$) and contralaterally ($P = 0.013$), but not in the midline (Fig. 3B). Post-hoc Wilcoxon tests showed that ipsilaterally the relative coherence in the theta ($P = 0.028$) and alpha ($P = 0.008$)
Partial Coherence

Partial coherence analysis was used to confirm that our results were related to independent loops of coherent activity between the SA ME and lateral and mesial cortical areas. In particular, partial coherence was used to address two possible confounds. First, the prominent alpha peak in SA ME to EEG coherence might not specifically relate to coupling in the alpha band between SA and frontal cortex, but rather to volume conduction from more posterior cortical areas where alpha activity can be more prominent. To this end we used partialization of C3-F3 to L-SA-ME and C4-F4 to R-SA-ME coherence with P3-PZ and P4-PZ signals as respective predictors. A paired t-test comparing the nine pairs (n = 18) of partialized coherences with the corresponding unpartialized coherences (C3-F3 to L-SA-ME and C4-F4 to R-SA-ME) showed no difference (P = 0.291). Figure 4A illustrates this and is evidence that the coupling of activity from parietal cortical areas, including the posterior cortical alpha rhythm.

The second possible confound was that much of the cortical activity recorded over lateral and mesial cortical areas was the same given the use of bipolar EEG electrodes rather than any Laplacian derivation. Accordingly, we used partialization of C3-F3 to L-SA-ME and C4-F4 to R-SA-ME coherence with the Cz-Fz signal as predictor (ipsilateral partial coherence) and partialization of Cz-Fz to L-SA-ME and Cz-Fz to R-L-SA-ME coherence with C3-F3 and C4F4 signals as predictors (midline partial coherence), respectively. Figure 4B,C contrast these partial coherences with the respective standard coherences. Note the prominence of coherence in the upper beta band over mesial cortex relative to lateral frontal cortex. The figure also makes it clear that the coupling of activity between the SA and the lateral frontal cortex is independent of mesial EEG activity (partialization has negligible effect) and that, conversely, the coupling of activity between the SA-ME and the mesial frontal cortex is independent of lateral frontal EEG (partialization has negligible effect).

We used a two-way ANOVA for the comparison of the topography of the partialized coherences in the four frequencies across the 18 SA-MEs. Frequency band (3–7, 8–13, 14–20 and 21–32 Hz), and area (midline and ipsilateral to the SA-ME) were used as factors. There was no main effect for frequency band, but there was a significant main effect for area (P = 6.886, P = 0.018) and an interaction between area and frequency band (P = 6.526, P = 0.004). Mean transformed partial coherence averaged across all four frequency bands was greater in the midline (0.106 ± 0.01) than over lateral frontal areas (0.079 ± 0.01, P = 0.018). The differences in topography in theta, alpha and lower beta bands between the ipsilateral and midline partial coherence with the SA-ME were not significant (Fig. 5A). However, the partial coherence of Cz–Fz to SA-ME was greater than that of C3–F3/C4–F4 to SA-ME in the upper beta band (P < 0.0001). The fact that the topographic difference in the upper beta band persisted when lateral and midline partial coherences were studied further indicates that the upper beta’s midline prominence was not due to the superimposition of the effects of EEG recorded near either burr hole (use of C3–F3 or C4–F4 as predictors) still left mesial coherence that exceeded lateral frontal coherence in this frequency band.

To determine the differences in relative topography between frequency bands, for each subject we normalized each partial coherence to that which was greatest out of the two cortical areas (ipsilateral and midline). This was performed for each of the four frequency bands, giving us the relative coherence over
ipsilateral and midline cortex. We then performed two separate Friedman’s tests for each of the two areas across the four frequency bands. There were differences between the four frequency bands ipsilaterally ($P = 0.018$) and but not in the midline (Fig. 5B, C). Post-hoc Wilcoxon tests showed that ipsilaterally the relative partial coherence in the theta ($P = 0.013$), alpha ($P = 0.025$) and lower beta ($P = 0.011$) bands was greater than that in the upper beta range (Fig. 5B), in keeping with the results of standard coherence analysis.

Phase

Phase was calculated for the SA-ME contacts with the highest coherences with EEG electrodes Cz-Fz, C3-F3 and C4-F4. Activity recorded from the SA-ME led EEG by an average of $35.1 \pm 13.8$ ms at 3–7 Hz (theta). At 8–13 Hz (alpha) EEG either led or lagged activity recorded from the SA-ME by $45.9 \pm 7.5$ or $43.7 \pm 9.0$ ms, respectively, although overall EEG activity in the alpha band led activity recorded from the SA-ME by an average of $5.6 \pm 11.7$ ms. EEG led activity recorded from the SA-ME by $42.0 \pm 5.0$ and $28.8 \pm 1.5$ ms at 14–20 Hz (lower beta) and
between alpha and lower beta (alpha rhythm. Coherent subcortico-cortical loops of different frequency were not only topographically organized at the cortex, but also characterized by differences phase relationships between EEG and SA. These results extend the findings of Williams et al. (2002), who suggested differences in the cortical topography of STN-cortical coupling when coherence was divided into activities below and above 10 Hz in four subjects.

Polarity Reversal

Polarity reversal was observed in 9/18 SA-MEs. Polarity reversal was seen around contact 1 in four cases (case 1 L-SA-ME/R-SA-ME, case 4 L-SA-ME, case 9 R-SA-ME) and around contact 2 in five cases (case 2 L-SA-ME, case 3 R-SA-ME, case 6 L-SA-ME, case 7 L-SA-ME, case 8 L-SA-ME). Such polarity reversal indicates signal generation at the site of the specified ME contact. Note that this technique cannot show polarity reversal at contact 0 or 3.

Discussion

The major findings of the current investigation were twofold. First, we found that there is a strong coupling between LFP activities recorded with MEs in the STN area (SA) and cortical EEG over a wide range of frequencies in the untreated parkinsonian patient. This coupling was greatest in the alpha and upper beta bands, and not at rest tremor frequencies. Second, we demonstrated that oscillatory activities within different frequency bands in the SA-cortical loop are partially functionally segregated into circuits that may have their own pathophysiological relevance. The study of partial coherences demonstrated that the coupling of activity between the SA and the lateral frontal cortex was independent of mesial EEG activity and that, conversely, the coupling of activity between the SA and the mesial frontal cortex was independent of lateral frontal EEG. In addition, the use of partial coherence showed that coupling between lateral frontal cortex and the SA was independent of posterior cortical activity, especially the posterior alpha rhythm. Coherent subcortico-cortical loops of different frequency were not only topographically organized at the cortex, but also characterized by differences phase relationships between EEG and SA. These results extend the findings of Williams et al. (2002), who suggested differences in the cortical topography of STN-cortical coupling when coherence was divided into activities below and above 10 Hz in four subjects.

Experimental limitations

Before considering our findings in greater detail, we should stress some of the limitations of our experimental approach. First, without histologival verification of electrode site or support from post-operative imaging, placement in STN should be considered presumptive, even though the surgical coordinates were those of STN. For this reason we have used the conservative terms subthalamic area (SA) and subthalamic area macroelectrodes (SA-MEs) throughout to refer to the positioning of the macroelectrode contacts in the STN and adjacent areas, such as the field of Florel and the zona incerta. The conclusion that the macroelectrodes were in the SA is supported by the effectiveness of intra-operative and chronic post-operative stimulation and by the ability to significantly reduce antiparkinsonian medication post-operatively. Authors are divided as to whether these therapeutic effects involve stimulation of the sensorimotor STN or the area slightly dorsal to the STN, which includes the field of Florel and the zona incerta, but the presence of the effective stimulation target within the SA is not in dispute (Saint-Cyr et al., 2002; Voges et al., 2002). Equally, the argument as to whether stimulation effects in the SA involve nuclear effects or white matter bundles is not germane to the present findings, as LFPs are likely to be the product of synchronized EPSPs and IPSPs, and not due to spontaneous activity in white matter (Magill et al., 2004a, b). The significant increase in coherence between EEG and LFPs from rostral to caudal contacts of the SA-MEs and the predominant use of caudal contacts for clinical stimulation also suggests that the surgery was consistent in achieving similar placement across patients, with contact 1 intended to be in STN. In addition, the SA-ME LFP activities reported here as coherent with EEG have been reported in other studies of neuronal synchronization within the STN of the parkinsonian human, where targeting has been supported by microelectrode recordings and/or post-operative imaging, or within the STN of the parkinsonian rat or monkey, where placement has been confirmed histologically (Bergman et al., 1994; Levy et al., 2000, 2001, 2002a,b; Marsden et al., 2001; Brown et al., 2001; Cassidy et al., 2002; Priori et al., 2002; Williams et al., 2002; Kühn et al., 2004; Sharott et al., 2004). In particular, a recent study using microelectrode recordings has shown that beta frequency band LFP activity is focal to the STN (Kühn et al., 2005).

Second, the question arises to what extent was the coherence between SA LFPs and EEG due to coupled oscillatory activity or the volume conduction of synchronous activity from sources such as the cerebral cortex. Unlike Wennberg and Lozano (2003), we used bipolar recordings from the contacts of our macroelectrodes, thereby avoiding a common scalp reference that may have contaminated depth signals with cortical EEG. In addition, as mentioned above, recordings from adjacent macroelectrode contact pairs showed a clearly increasing rostral to caudal gradient inconsistent with volume conduction of cortical activity. Furthermore, there were significant temporal differences between the cortical and depth signals that

Figure 6. The distribution of phase across the four frequencies. SA-ME LFPs led EEG by a mean of 35.1 ± (SEM) 13.8 ms in the theta band, while EEG led the depth LFP by 42.0 ± 5.0 and 28.8 ± 1.5 ms in the lower and upper beta bands, respectively. EEG could lead or lag LFPs by 40 ms in the alpha band.

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were incompatible with volume conduction. Finally, the polarity reversal evident in 50% of the recorded sides is a good indication that the signals recorded were generated at the site of one of the ME contacts, rather than picked up from nearby sites, such as the internal capsule. Similar patterns of polarity reversal have been previously reported for LFPs recorded from SA-MEs and equated with generators within the STN through corroboration with therapeutic efficacy and imaging (Kühn et al., 2004; Doyle et al., 2005). All in all, the collective evidence suggests that the LFPs recorded from the SA-MEs in this study were locally generated and the product of locally synchronized neuronal population activity within or neighbouring the STN. Further studies are warranted to categorically establish whether the subcortico-cortical loops of coherent activity identified in the present study involve STN per se.

Third, it should be stressed that our analytical techniques would have biased against the detection of stochastic, non-oscillatory synchronization between the cortex and the SA. However, studies in monkeys examining the simultaneous activity of pairs of globus pallidus interna (GPI), globus pallidus extrema (GPe), STN and striatal neurons have failed to find an increase in non-oscillatory synchronization after MPTP-induced parkinsonism (Bergman et al., 1994; Nini et al., 1995; Raz et al., 1996, 2000, 2001).

Fourth, the possibility should be considered that some or all of our coherent activities are harmonically related, in which case they might represent non-sinusoidal components in the same basic pattern of oscillation, rather than independently generated biological rhythms. Very much against this possibility, however, is the fact that activities in the various pass-bands differed both in their cortical topography and in their phase relationships (but see later).

Fifth, transient local edema following surgery could have changed the nature of LFPs. This seems unlikely, as oscillatory LFPs of similar character have been recorded in STN using microelectrodes, before implantation with a macroelectrode (Levy et al., 2002a). If anything, the most likely change would have been a reduction in LFP amplitude with any edema associated with macroelectrode implantation. Due to the normalized nature of coherence this would not have affected our estimates of coupling, unless the LFP were attenuated to levels approaching those of background noise over the same frequency band. In this case the effect would have been to attenuate coherence, and yet significant coherence between EEG and LFPs was recorded.

Finally, the contribution of the burr holes to the cortical topography of the coherence should be considered. C3 and C4 were only just anterior to the burr holes required for surgical implantation, and the local skull breech would have reduced the local filtering effects of the skull and other interposing tissues, leading to higher EEG voltages over local scalp areas. Nevertheless, this would have been expected to affect all EEG frequencies equally, if not disproportionately favour higher frequency activities, such as those in the upper beta band (Spelmann, 1981). Skull breech effects cannot therefore account for the fact that relative SA LFP to EEG coherence was less in the high beta band than in the remaining bands over lateral frontal areas. Neither can skull breech effects explain why overall, and in the low and high beta frequency bands in particular, SA LFP to EEG coherence was greater over mesial than lateral frontal cortex, given that electrodes in the former region were further from the burr holes.

**Is Coherence between the Subthalamic LFP and EEG in PD Pathological or Physiological?**

We found strong coherence between the SA LFP and EEG. There is no way of presently establishing whether this coupling is physiological or related to the pathophysiology of Parkinson’s disease. However, the results of non-human primate studies and of pharmacological studies in patients suggests that the coherence between the SA LFP and EEG represented, at the very least, a pathological exaggeration of physiological activity. Thus treatment with levodopa or apomorphine suppresses oscillatory beta activity in STN and STN-EEG coherence in PD (Levy et al., 2000; Cassidy et al., 2002; Williams et al., 2002), while recordings in healthy primates demonstrate relatively little synchronization of neuronal activity within STN (Wichmann et al., 1994a,b). On the other hand, cortical synchronization does occur within the bands considered (Steriade et al., 1990), and there is evidence for physiologically reactive beta synchronization in the basal ganglia (albeit not STN) in monkeys and humans (Courtemanche et al., 2003; Sochurkova and Rektor, 2003). We conclude that the coherence between the SA LFP and EEG in our untreated PD patients was, at least in part, likely to be due to a pathological exaggeration of physiological activity.

One of the major findings in the current study was the demonstration of a partial functional segregation of oscillatory activities within different frequency bands in loops linking the SA with cerebral cortex. The question arises as to whether this pattern of organization was primarily physiological or related to the pathophysiology of PD. Again, it is difficult to be categorical on this point, but various strands of evidence point to a loss of functional segregation in PD, suggesting that even more segregation might be evident in the healthy human (Filion et al., 1993; Nini et al., 1995; Bergman et al., 1998; Vitek and Giroux, 2000; Levy et al., 2000).

**Quantitative Differences between Subcortico-cortical Coupling over Different Frequency Ranges**

The coupling between LFP activities recorded with SA MEs and cortical EEG did not decay monotonically with frequency, but demonstrated clear peaks in the alpha and upper beta bands. Activities in the theta band, similar in frequency to parkinsonian rest tremor, and in the lower beta range were far less prominent in our cohort of patients. The modest coupling between the SA LFP and EEG in the theta band contrasts with the prominence of tremor related neuronal activity upon microelectrode recordings in STN (Bergman et al., 1994; Levy et al., 2002b). However, although tremor related STN activity may occur in the theta band, this may not be coupled to activity in the cortex. This would be of importance, as it would undermine theories that seek to explain bradykinesia through the effect of propagated synchronization at rest tremor frequencies on the cortex (Brown and Marsden, 1998). Indeed, the extent of synchronization of STN activity at rest tremor frequencies is uncertain. Thus, unlike activity in the beta band, the phase between pairs of STN units varies in the rest tremor range, indicating imperfect synchronization (Levy et al., 2000). Furthermore, at least in GPi, neuronal activity at rest tremor frequencies is only transiently locked to rest tremor, suggesting that there may be multiple, independent tremor generators, rather than global synchronization at rest tremor frequencies (Hurtado et al., 1999). Consistent with this, PD tremor is largely asynchronous between the limbs and sides of the body (Hurtado et al., 2000).
On the other hand, it could be posited that the major effect of tremor related neuronal activity on the cortex is exercised through oscillatory activity at harmonically related frequencies in the alpha band. This would be consistent with reports of rest tremor locking with cortical activity at harmonically related frequencies (Tass et al., 1998; Hellwig et al., 2000; Salemius et al., 2002; Timmermann et al., 2003). It is noteworthy that the phase relationships between oscillations in the alpha band suggests that this oscillation in the SA compromised two activities, one that is driven by the cortex and was likely to be independent of the activity in the beta band, and another which, like theta, tended to drive the cortex. The latter cortical driving alpha activity may plausibly reflect a harmonic of rest tremor activity.

Another feature of interest was the dominance of subcortico-cortical coupling in the upper beta band over that in the lower beta band. This is in accord with the results of Priori et al. (2002), who demonstrated a preponderance of LFP activity in the upper beta range in STN recordings, but of low beta activity in the GPi. This led these authors to suggest that oscillatory activity in the upper beta range is particularly characteristic of the indirect pathway. Nevertheless, it should be stressed that two patients in the present study had greater coherence with cortex in the lower beta band, so any preferential tuning of rhythmic activity in the SA to the upper beta range is not universal.

### Topography of Subcortico-cortical Coupling

Critically, the coherence between SA LFPs and cortical EEG over different bands tended to involve different cortical regions. Coherence in the theta band was widespread, involving mesial and both lateral areas, and similar to the cortical distribution of modulatory STN activity reported by Steiner and Kitai (2001). In contrast, coherence in the alpha band preferentially occurred between SA LFPs and both the mesial and ipsilateral cortex, while that in the upper beta band principally involved mesial motor areas, including the supplementary motor area. There is also a suggestion that coherence in the lower beta range involved ipsilateral areas more than that in the upper beta band. These findings are mirrored in the distribution of cortical beta activity. In particular, there is recent evidence that the beta activity recorded in the EEG of healthy individuals consists of a lower beta activity (around 15 Hz) that is most evident over the sensorimotor cortices and upper beta activity (centred around 25 Hz) that predominates over the mesial cortical regions, including the supplementary motor area (Plurtscheller et al., 1997, 2003). It is noteworthy that mesial motor cortical areas are believed to be more involved in internally than externally generated movements (Jenkins et al., 2000) and it is internally generated movement that is most impaired in PD. In line with this, positron emission tomography studies in PD patients show that underactivity of SMA and anterior cingulate cortex in internally cued movement tasks (Samuel et al., 1997). It may therefore be relevant that the major SA LFP activity in the beta band occupied the upper range and was coupled with mesial rather than lateral cortical areas.

### Phase Relationships between SA LFPs and Cortical EEG

The coherence between SA LFPs and cortical EEG over different bands was accompanied by frequency selective phase relationships between cortex and the SA — further evidence that coupling at different frequencies reflected functionally segregated activities. SA LFP activity led EEG in the theta band, consistent with the driving of GPi by STN at tremor frequency (Brown et al., 2001) and with the observation that activity in GPi's thalamic projection site, the ventralis anterior thalami, precedes cortical activity (Volkmann et al., 1996). Together, these studies suggest the net driving of motor cortical areas at tremor frequencies through the STN-GPi-thalamo-cortical pathway. As discussed above, the situation is less clear in the alpha band as the phase seems to be determined by two activities, one with cortex and the other with the SA leading.

In contrast, EEG led SA LFPs in the lower beta and upper beta bands, in keeping with previous reports (Marsden et al., 2001; Williams et al., 2002). In the upper beta band, EEG led by ~20 ms. This is likely to be longer than the conduction time in 'hyperdirect' cortico-subthalamic projections. Stimuli applied within the motor cortex of the monkey facilitate STN neurons with a mean latency of 5.8 ms (Nambu et al., 2000) and frontal cortical potentials may be elicited with a latency of 5–8 ms after probable antidromic activation of the direct cortico-subthalamic pathways in humans (Asby et al., 2001). Thus the cortical lead of 20 ms or so suggests involvement of the indirect corticostriatal-GPe-STN pathway (Alexander and Crutcher, 1990; Parent and Hazrati, 1995). Consistent with the above, synchronization has been noted within the beta band in the striatum of healthy primates (Courtemanche et al., 2003) and animals treated with MPTP or dopaminergic antagonists, as determined by microelectrode and LFP recordings (Yurek and Randall, 1991; Dimpfel et al., 1992; Raz et al., 2001). Note that the cortical lead was longer in the lower beta than the upper beta band, further evidence of the functional heterogeneity of coupling in the two beta bands and suggestive that the lower beta cortical drive has longer nuclear delays or more indirect transmission that the upper beta drive.

### Multiple Functionally Distinct Oscillatory Subcortico-cortical Loops

The major significance of the present findings is that they suggest the presence of multiple oscillatory circuits between the SA and cerebral cortical motor areas, distinguished by their frequency, cortical topography and temporal relationships even in the same pharmacological state of PD patients withdrawn from antiparkinsonian medication. Previously, Williams et al. (2002) also drew attention to the functional differences between oscillatory activities in the STN-cortical circuit in PD patients off and on medication. Thus the ‘motor circuit’ promoted in the Albin-DeLong model (Albin et al., 1989; DeLong, 1990) may, in functional terms, consist of several, largely segregated sub-loops coupling basal ganglia and cortical activities. Coherent activity in these sub-loops preferentially occurs in distinct frequency bands, perhaps reflecting the different resonance properties of the networks concerned. It is possible that the frequency of synchronization may be exploited as a means of marking and segregating processing in the different functional sub-loops, over and above any anatomical segregation of processing streams. A prediction of the latter that remains to be tested is that synchronization within different frequency bands may be associated with different functional deficits in PD. In addition, the strong coherence within the different bands in patients off medication suggests that large neuronal populations are synchronized within
these functional sub-loops. Dopaminergic stimulation reduces STN-cortical coupling at frequencies under 60 Hz (Cassidy et al., 2002; Williams et al., 2002), presumably by reducing the synchronization between neurons within the functional sub-loops dominating in the off-state. Viewed in this light, the dramatic coupling of SA LFPs with cortical activities in untreated PD patients may be considered as further evidence of an impairment of functional segregation in PD (Filion et al., 1994; Nini et al., 1995; Bergman et al., 1998; Vitek and Giroux, 2000; Levy et al., 2000), while also demonstrating that the subcortico-cortical loops involving the SA have the capacity to preserve information about the timing of activity in groups of neurons despite relay through multiple intervening levels (Kimpo et al., 2003).

Notes

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