Subthalamic nucleus, sensorimotor cortex and muscle interrelationships in Parkinson’s disease

J. F. Marsden,1 P. Limousin-Dowsey,1,2 P. Ashby,3 P. Pollak2 and P. Brown1

Summary

Ten patients with Parkinson’s disease were seen following bilateral or unilateral implantation of macroelectrodes into the subthalamic nucleus. Local field potentials (LFPs) were recorded from adjacent subthalamic nucleus macroelectrode (STNME) contacts simultaneously with EEG activity over the supplementary motor (Cz-FCz) and sensorimotor (C3/4-FC3/4) areas and EMG activity from the contralateral wrist extensors during isometric and phasic wrist movements. Significant coherence was seen between STNME LFPs and Cz-FCz, STNME LFPs and C3/4-FC3/4, and STNME LFPs and EMG over the range 7–45 Hz. EEG phase-led STNME LFPs by 24.4 ms (95% confidence interval 19.8 to 29.0 ms). EMG also led STNME LFPs, but time differences tended to cluster around one of two values: 6.3 ms (–0.7 to 13.3 ms) and 46.5 ms (26.2 to 66.8 ms). Recordings from the STNME contact that demonstrated the most consistent coherence with Cz-FCz in the 15–30 Hz band coincided with the contact which, when electrically stimulated at high frequencies, produced the most effective clinical response in eight out of nine (89%) subjects (P < 0.01). Oscillatory activity at 15–30 Hz may therefore prove of use in localizing the subthalamic nucleus target that provides the best clinical effect on stimulation. These results extend the hypothesis that coherent activity may be useful in binding together related activities in simultaneously active motor centres. The presence of coherence between EEG and STNME LFPs in both the beta and the gamma band (as opposed to only the beta band between EEG and cerebellar thalamus) suggests that there may be some relative frequency selectivity in the communication between different motor structures.

Keywords: subthalamic nucleus; deep brain stimulation; Parkinson’s disease; beta oscillations; coherence

Abbreviations: ANOVA = analysis of variance; GUH = Department of Clinical and Biologic Neurosciences, Grenoble; KCH = Kings College Hospital; LFP = local field potential; NHNN = National Hospital for Neurology and Neurosurgery; STNME = subthalamic nucleus macroelectrode; TWH = Toronto Western Hospital

Introduction

In recent years there has been increasing interest in oscillatory activity within the human sensorimotor system. Oscillations coherent between the contralateral sensorimotor cortex and muscle can be recorded in humans making voluntary muscle contractions (Conway et al., 1995; Salenius et al., 1997; Brown et al., 1998; Halliday et al., 1998), and during motor tasks functionally active areas of the cortex are themselves coherent with each other (Classen et al., 1998; Gerloff et al., 1998; Andres et al., 1999). The precise function and genesis of these cortical rhythms remain unclear. Their reflection in the pattern of spinal motor neurone discharge raises the possibility that the same rhythmicities may be conducted to other subcortical projection sites, such as the cerebellum, thalamus and subthalamic nucleus, and thus, perhaps, provide a timing mechanism or a means by which related activities in widely distributed parts of the motor system are bound together.

Recordings from the human cerebellar thalamus (nucleus ventralis intermedius) support the hypothesis that certain oscillatory activities are distributed over cortical and subcortical levels (Marsden et al., 2000a). In this recent study, patients receiving functional neurosurgery to treat tremor were investigated. They were recorded while the leads were exposed externally in the interval between the stereotactic implantation of stimulating electrodes and the subsequent subcutaneous re-routing of the leads to an internal stimulator. Activity in the cerebellar thalamus was coherent with that picked up over the ipsilateral motor cortex or contralateral
between different motor structures. However, no coherence was found between the cerebellar thalamus and either EEG or EMG in the higher gamma band, despite the fact that there is strong evidence that the motor cortex modulates muscle activity in both the beta and the gamma band (Conway et al., 1995; Brown et al., 1998; Brown, 2000; Marsden et al., 2000b).

We therefore investigated the hypothesis that there may be some relative frequency selectivity in the communication between different motor structures. In particular, there is growing evidence that the basal ganglia may be important in sustaining the cortical driving of muscle in the beta and gamma ranges (Brown, 1997, 2000; Brown and Marsden, 1998). We hypothesized that we would be able to observe coherence between activity in a key basal ganglia structure, such as the subthalamic nucleus and the motor cortex, in both the beta and the gamma band. We also made two subsidiary predictions. First, as rhythmic cortical activity drives EMG, subthalamic activity and EMG should also be coherent in the beta and gamma bands. Secondly, subthalamic activity is likely to lag behind cortical activity, reflecting direct and indirect (corticostriatopallidal) projections from the cortex to the subthalamic nucleus.

We recorded local field potentials (LFPs) from a subthalamic nucleus macroelectrode (STNME) after functional neurosurgery in cooperative, awake parkinsonian patients while recording simultaneously from active muscle and cortex. The recording of STNME LFPs, as opposed to the action potentials of individual neurones, as performed previously (Lenz et al., 1988, 1994; Hua et al., 1998; Hutchison et al., 1998; Magnin et al., 2000), has the advantage that the detection of both subthreshold and supra-threshold oscillatory activity affecting populations of neurones is facilitated and consequently, also, the detection of possible coherence with other sites. Importantly, we recorded patients after treatment with the dopamine precursor levodopa, so that normal corticomuscular rhythmicities would be present (Brown, 1997, 2000; Brown and Marsden, 1998). We also recorded, as far as was possible, over both the supplementary motor and the sensorimotor cortex, as there is evidence that both send strong direct projections to the subthalamic nucleus (Parent and Hazrati, 1995). The results show that coherence within a band from 7 to 43 Hz may occur between STNME LFPs, the sensorimotor cortex and muscle, extending the hypothesis that coherent activity represents a common element in coding activity in simultaneously active motor centres, and suggesting that there might be some relative frequency selectivity in the communication between different motor structures.

Methods
Ten patients with Parkinson’s disease participated with informed consent and the approval of the combined ethics committees of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery. A clinical effect of STNME stimulation was seen in all subjects. The STNME contacts that gave the best clinical response on chronic stimulation and other clinical details are given in Table 1. The contacts, voltage and frequency that produced the most marked clinical effect were assessed by one of the investigators (P.L.-D. or P.A.), blind to any of the results and independent of the experiments.

Patients were seen at the National Hospital for Neurology and Neurosurgery (NHNN; Subjects 1–6), Kings College Hospital (KCH; Subject 7), the Department of Clinical and Biologic Neurosciences, Grenoble (GUH; Subjects 8 and 9) or the Toronto Western Hospital (TWH; Subject 10). The operative procedure and beneficial clinical effects of stimulation have been described previously (Hutchison et al., 1998; Limousin et al., 1998). Macroelectrodes were inserted after the subthalamic nucleus had been identified on MRI/CT and localized using microelectrode recording and microstimulation whilst the subject was awake but off antiparkinsonian medication (Hutchison et al., 1998). The macroelectrode position was confirmed postoperatively by CT or MRI scanning. The macroelectrode (model 3387m or 3389m DBS; Medtronic, Minneapolis, Minn., USA) had four platinum–iridium cylindrical surfaces (diameter 1.27 mm, length 1.52 mm) with a centre-to-centre separation of 3 or 1.5 mm. Contact 0 was the most caudal and contact 3 was the most rostral. In five of the 10 subjects, a macroelectrode was inserted bilaterally either in a two-stage operation with 3–4 months separation (Subjects 1, 2 and 4) or simultaneously (Subjects 8 and 9). This resulted in LFPs being sampled from a total of 15 STNMEs.

All subjects were assessed after treatment with 100–200 mg levodopa (in combination with a dopa decarboxylase inhibitor). Subjects performed either an isometric contraction of the wrist extensors (tonic task) or self-paced phasic wrist extension and flexion movements (phasic task), as we were interested in whether the pattern of STNME LFP–EEG and STNME LFP–EMG coherence would alter with task, as does the coherence between the motor cortex and EMG (Brown et al., 1998; Kilner et al., 1999; Marsden et al., 2000b). The forearm was supported in pronation and all movements were unconstrained. In the subjects from NHNN, wrist position was monitored using an electrogoniometer.

During each task, LFPs from the contralateral STNME were recorded simultaneously with EMG from the forearm extensor muscles. EMG (and EEG) was recorded with bipolar 9 mm diameter Ag–AgCl electrodes. EMG was bandpass-filtered at 56–300 Hz (NHNN and GUH) or 2–1000 Hz (TWH) and amplified (×1000–5000). EMG was digitally rectified off-line. LFPs were recorded from the adjacent four contacts of the macroelectrode (0–1, 1–2, 2–3). One subject (Subject 9) with a bilateral implant had previously had a globus pallidus internus macroelectrode implant, which was not stimulated during the course of the experiment. As the macroelectrode contacts had a maximum centre-to-centre separation of 3 mm, it is estimated that, at best, only one or
Table 1  Summary of clinical ratings (off medication/off stimulation Hoehn and Yahr score), best contacts for clinical effect and the effects of medication on distal upper limb function

<table>
<thead>
<tr>
<th>Subject, sex, age (years), (H&amp;Y rating)</th>
<th>Best contact: frequency/voltage/pulse width</th>
<th>UPDRS on medication: tremor/rigidity/bradykinesia</th>
<th>UPDRS off medication: tremor/rigidity/bradykinesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, M, 47 (3)</td>
<td>L* STN 2– (monopolar) 145 Hz/2.5 V/60 µs 130 Hz/2.3 V/60 µs</td>
<td>R† 0/1/1</td>
<td>R 1/2/2</td>
</tr>
<tr>
<td>2, M, 58 (3)</td>
<td>LSTN 2– 3+ 130 Hz/3.0 V/60 µs R STN 2– (monopolar) 130 Hz/3.6 V/60 µs</td>
<td>R 1/1/1</td>
<td>R 1/2/1</td>
</tr>
<tr>
<td>3, F, 45 (4)</td>
<td>RSTN 2– 1+ 160 Hz/2.8 V/60 µs</td>
<td>L 0/0/1</td>
<td>L 0/1/2</td>
</tr>
<tr>
<td>4, F, 51 (3)</td>
<td>L STN 3– (monopolar) 130 Hz/3 V/60 µs R STN 2– (monopolar) 130 Hz/2.5 V/60 µs</td>
<td>R 0/0/1</td>
<td>R 1/2/3</td>
</tr>
<tr>
<td>5, F, 58 (5)</td>
<td>L STN 3– 1+ 130 Hz/2.3 V/60 µs</td>
<td>R 0/1/1</td>
<td>R 1/4/3</td>
</tr>
<tr>
<td>6, M, 56 (4)</td>
<td>R STN 0– 2+ 130Hz/5.6V/60 µs</td>
<td>L 0/1/2</td>
<td>L 0/2/3</td>
</tr>
<tr>
<td>7, M, 66, (4)</td>
<td>R STN 1– 2+ 300 Hz/3 V/80 µs</td>
<td>R 1/3/3</td>
<td>R 0/3/2</td>
</tr>
<tr>
<td>8, M, 45 (4)</td>
<td>L STN 3– (monopolar) 145Hz/3.6 V/60 µs R STN 3– (monopolar) 130 Hz/2.2 V/60 µs</td>
<td>R 0/1/0</td>
<td>R 0/3/2</td>
</tr>
<tr>
<td>9, M, 60 (4)</td>
<td>L STN 2– (monopolar) 145 Hz/2.6 V/60 µs R STN 2– (monopolar) 130 Hz/2 V/60 µs</td>
<td>R 0/2/0</td>
<td>R 2/3/3</td>
</tr>
<tr>
<td>10, M, 63 (unavailable)</td>
<td>R STN 3– (monopolar) 170 Hz/1.7 V/60 µs</td>
<td>L 0/0/2</td>
<td>L 0/3/1</td>
</tr>
</tbody>
</table>

Distal upper limb function was assessed, in the absence of any chronic electrical stimulation, with the Unified Parkinson’s Disease Rating Scale (UPDRS; scores 20, 22, 24). With monopolar stimulation, the case of the stimulator was always the anode. H&Y = Hoehn and Yahr; STN = subthalamic nucleus macroelectrode.

*L = left stimulator; R = right stimulator. †L = left hemibody; R = right hemibody.

two contacts were in the subthalamic nucleus (Hutchison et al., 1998; Ashby et al., 1999).

The 3D position of the subthalamic nucleus relative to the anterior commissure or posterior commissure was determined preoperatively by MRI. The positions of the most caudal and rostral macroelectrode contacts relative to the same reference point as used preoperatively were then determined from postoperative MRI scans. In the nine out of 10 subjects in whom the postoperative position of the distal and rostral STNME contacts could be determined accurately, at least one of the STNME contacts was within or <1 mm from the position of STN as determined from preoperative scans. The measurement error of measuring the position of anatomical landmarks relative to the anterior commissure or posterior commissure on pre- and postoperative scans was ±1 mm.

Due to the presence of dressings or EMG artefact in lateral channels, EEG records were available only from Cz-FCz in nine instances and from either C3-FC3 or C4-FC4 ipsilateral to the STNME implant in three cases. STNME LFPs and EEG were filtered at 0.5–300 Hz (NHNN, KCH and GUH) or 2–1000 Hz (TWH) and amplified (×50 000–500 000). EEG and EMG were amplified with a D150 (Digitimer,
Welwyn Garden City, UK), except in Subject 7, for whom a custom-built portable amplifier was used (E. R. Samuel, MRC Human Movement and Balance Unit). Signals were AD-converted [CED 1401 (Cambridge Electronic Design, Cambridge, UK) or an Amplicon card (Amplicon, Brighton, UK)], monitored on-line and stored either directly with SPIKE2 software (Cambridge Electronic Design) or with Dacquire software (D. Buckwell, MRC Human Movement and Balance Unit). Signals were sampled at the rates of 1 kHz (NHNW), 625 Hz (GUH) and 1142 Hz (TWH). In the last case, any effects of aliasing were felt to be minimal as the mean background noise level was only 1.2–2.6 µV/Hz in the 500 Hz to 5 kHz band. For the subjects from GUH and TWH, the data were either interpolated or decimated and resampled at 1 kHz to produce frequency spectra with an identical bin width in all subjects.

**Analysis**

During both tonic and phasic contractions, only those data segments were used for which there was wrist extensor EMG activity and an absence of artefacts such as EMG and eye movements in the accompanying EEG. Data gathered over activity and an absence of artefacts such as EMG and eye movements in the accompanying EEG. Data gathered over multiple trials of a given task were pooled.

Spectral analysis of the data was performed with programmes written by D. H. Halliday based on methods outlined by Halliday and colleagues (Halliday et al., 1995). The autospectra of simultaneously recorded signals and the coherence between them were calculated. In order to compare tonic and phasic conditions, spectra for each of these conditions were estimated from an equal number of segments for each subject. The number of segments used varied from 116 to 423 between subjects. We chose to use the maximum segment number in each subject in order to reduce the variance of the spectral estimates. The segment length was 512 points, which resulted in a frequency resolution of 1.95 Hz in all subjects (after any resampling). As multiple comparisons were performed, the confidence limits for autospectra and coherence spectra (Halliday et al., 1995) were calculated after Bonferroni correction.

Differences in the degree of coherence between tasks were evaluated. The variance of the coherence was first normalized using the Fisher transform of the coherency, where the modulus of the complex valued coherency is given by the square root of the coherency. The variance of these transformed values is given by $1/2L$, where $L$ is the number of segments used to calculate the spectra. The hypothesis that there was a difference between the modulus of the transformed coherencies was investigated by calculating the difference between the estimates and comparing this at each frequency with the value of the standardized normal variate ($Rosenberg et al., 1989$). Differences in power between tasks were also evaluated. The variance of the autospectra was stabilized using a logarithmic ($\log_{10}$) transform. The average autospectral power in the EEG, STNME or rectified EMG signals was then calculated for each subject over the frequency bands 7–14, 15–30 and 31–45 Hz. The low- and high-frequency cut-offs were chosen to avoid movement and mains artefacts. Otherwise, the bands were comparable to those used in other motor studies (Brown et al., 1998; Marsden et al., 2000b). Coherence between motor cortex and EMG changes in different directions between the 15–30 and 31–45 Hz bands according to task, suggesting that they may cover activities with different physiological significances (Brown et al., 1998; Kilner et al., 1999). The same bands were also chosen for the analysis of STNME–EEG and STNME–EMG coherence. For each subject, the autospectral power from each bipolar STNME contact was determined before averaging across all contacts. The average autospectral power was then weighted inversely by its variance and compared by one-way analysis of variance (ANOVA) (SPSS Inc. Chicago, Ill., USA, version 8) over each frequency band.

The phase relationship between signals was calculated over those frequency bands for which the coherence was significant. The time difference between the 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). Latency was calculated only if there were at least four contiguous data points and the standard error of the estimate of the best fit line was <0.3. These empirically derived criteria were used to improve the reliability of the latency estimate. The time domain equivalent of the phase, the cumulant density estimate, was also calculated from the inverse Fourier transform of the cross-spectrum.

**Results**

An example of simultaneous recordings of EMG, EEG and LFPs from all three STNME contacts during a tonic contraction is given in Fig. 1A. The respective power spectra are given in Fig. 1B–D. The mean power in the LFP recorded from the STNME in all 10 subjects was significantly higher during phasic as opposed to tonic contractions over the 7–14 and 31–45 Hz bands but not over the 15–30 Hz band (one-way ANOVA, $P < 0.05$) (Fig. 2A). EEG power was not significantly different between tasks over any band (Fig. 2B).

Panels E–G in Fig. 1 show spectra of the coherence between the STNME LFPs, EEG and EMG illustrated in panel A. Note that significant coherence was predominantly seen up to 45 Hz, and this is the range plotted in subsequent figures. We found significant EEG–EMG coherence in only four out of 10 subjects, presumably because we were limited to sampling only one or two EEG sites by surgical dressings. We will therefore focus on STNME LFP–EEG coherence, STNME LFP–EMG coherence, phase relationships and correlations between coherence and the effectiveness of high-frequency stimulation at the same contacts.

**STNME LFP–EEG coherence**

It was possible to record from Cz-FCz in seven of the 10 subjects (nine STNME LFP–Cz-FCz comparisons), but from
Fig. 1 Inter-relationships among cortex, STNME LFP and muscle in Subject 3 during tonic wrist extension. (A) Raw data. (B–D) Autospectra of left rectified wrist EMG (B), right STNME LFPs (C) and Cz-FCz (D). (E–G) Coherence spectra between rectified wrist extensor EMG and STNME LFPs (E), STNME LFPs and Cz-FCz (F), and rectified EMG and Cz-FCz (G). In C, E and F, spectra calculated from signals recorded between contacts 0 and 1, 1 and 2 and 2 and 3 are shown. Note that the coherence and power is lowest when signals are recorded between contacts 0 and 1.

C3-FC3 and C4-FC4 ipsilateral to the STNME in only three patients.

**STNME LFPCz–FCz coherence**

Figure 3A shows the incidence of significant differences in coherence in each condition, whilst examples from an individual subject are given in Fig. 4. The coherence during tonic contraction was more often significantly greater than that during the phasic task in both the 15–30 and the 31–45 Hz band, although the difference in the latter gamma band may have been due to power changes in the STNME LFP signal at these frequencies (Fig. 3A).

**STNME LFP–C3/4-FC3/4 coherence**

In two out of the three subjects (Subjects 6 and 9) in whom C3/4-FC3/4 was also available, the STNME LFP–C3/4-
FC3/4 coherence between 15 and 30 Hz was significantly higher during the tonic than the phasic task. In the same subjects the coherence in the 15–30 Hz band between STNME LFPs and Cz-FCz was significantly greater than the coherence between STNME LFPs and C3/4-FC3/4 (Fig. 5A and B).

**STNME LFP–EMG coherence**
The degree of coherence between muscle and STNME LFPs varied depending on the contacts between which the STNME LFPs were recorded. In 14 out of 15 subjects, the most distal contact (0–1) demonstrated the least coherence, whilst the contacts showing the highest coherence varied between 1–2 and 2–3. An example of this difference between contacts is illustrated in Fig. 1E.

The STNME contact that, when recorded from, showed the highest coherence with EMG did not always correspond to the STNME contact that demonstrated the highest coherence with Cz-FCz (Fig. 1E and F). This was the case in four of nine subjects, in two of whom the contacts that most frequently demonstrated the highest coherence with Cz-FCz were more rostral, but adjacent to those giving the highest coherence with EMG.

Figure 3B shows the incidence of significant differences in coherence in each task, and examples from an individual subject are given in Fig. 6. The main feature is that coherence tended to be higher within the 15–30 Hz band during tonic tasks as opposed to phasic tasks, whereas within the 31–45 Hz band coherence was higher during the phasic as opposed to the tonic task (Fig. 5B). EMG power and mean rectified EMG levels were not significantly different between tasks (Fig. 2C).

**Phase**
Examples of individual STNME LFP–Cz-FCz phase spectra are given in Figs 4C and D and 5C and of STNME LFP–EMG phase spectra in Fig. 6B and D. On average, Cz-FCz led STNME LFPs by 24.4 ms (95% confidence interval 19.8–29.0 ms). However, the lead of EMG over STNME LFPs was less uniform, with time delays clustering around 6 and 47 ms (Fig. 7). Task did not have any consistent effect on phase.

**Correlations with best electrode contact**
The cathode with the best clinical effect was contact 3 (5/15 subjects), 2 (8/15 subjects), 1 (1/15 subjects) or 0 (1/15 subjects). Often the stimulation was monopolar, the anode being the stimulator box (Table 1). The bipolar STNME site for which recorded LFPs demonstrated the highest coherence across task conditions within the beta band (15–30 Hz) was determined. In 11 out of 15 (73%) instances, the best contact pair for STNME LFP–EMG coherence included the contact that, when stimulated as the cathode, gave the best clinical response (Spearman rank correlation, \( P < 0.01 \)) (Fig. 8A). This association was even more striking
Fig. 4 Differences in STNME LFP–EEG coherence and phase with different tasks in Subject 3. Left STNME LFP (is recorded between contacts 2 and 3)–Cz-FCz coherence and phase during the tonic task (A and B) and during the phasic task (C and D). Phase is only shown over the frequencies at which coherence was significant and phase met our criteria for measurement (see Methods). The STNME LFP lag (±95% confidence limits) is given alongside the phase spectra. The sign # indicates a significant difference between the tonic and phasic tasks over the frequency band indicated.

Fig. 5 Variation of STNME LFP–EEG coherence with EEG position. Examples of individual coherence spectra for Subject 9 while performing the tonic task. Coherence between the right STNME LFP (recorded between contacts 1 and 2) and Cz-FCz (A) and C4-FC4 (B). The asterisk indicates a significant difference (χ² test) between coherence spectra, and their respective frequencies are indicated. Note that coherence between STNME LFPs–EEG was highest when signals were recorded at Cz-FCz (A). All signals were recorded simultaneously. The phase relationship between STNME LFP and Cz-FCz and the time difference (±95% confidence limit) are shown in C. EEG leads the STNME LFP.

Discussion
Intraoperative recording (Hutchison et al., 1998), perioperative imaging and the clinical efficacy of high-frequency stimulation all suggested that the macroelectrodes in the present study were within or very close to the subthalamic nucleus, and the polarity reversal of cumulant density estimates between contacts provided strong evidence that potentials were generated locally and not picked up from distant sources. The main finding was the presence of oscillatory activity in the subthalamic nucleus, which was coherent with activity in both contralateral muscle and the ipsilateral cortex.

Coherence
Coherence was found in the 7–45 Hz range. This band includes the beta and gamma ranges; there is increasing evidence that the motor cortex drives muscle in healthy subjects over these ranges (Datta et al., 1991; Farmer et al., 1993a, b). Similar activities may be detected in parkinsonian patients when recorded following treatment, as in this study (Brown, 1997). It is therefore suggested that the coherence between STNME LFPs and EMG and EEG detected in the 7–45 Hz band here may be physiological and similar to that seen in healthy subjects.

The range of coherence between STNME LFPs and either EEG or EMG exceeds that recorded in a recent, comparable study of the human cerebellar thalamus (Marsden et al., 2000a), in which coherence extended only into the beta band. The latter study largely involved patients with essential
tremor or cerebellar syndromes, but one patient had benign tremulous Parkinson’s disease. Together with the present study, this raises the possibility that there might be some relative frequency selectivity in the communication between different motor structures.

**Lags to the subthalamic nucleus**

On average, EEG phase-led the STNME signal by ~24 ms, with relatively narrow 95% confidence intervals. This time difference is similar to the latency of the midline frontal cortical potentials evoked by STNME stimulation (Limousin et al., 1998a) and suggests that the cortex was partly driving the STNME LFPs. There are two routes by which cortical activity could influence STNME LFPs: either indirectly via the striatum/globus pallidus externus or by a direct projection to the subthalamic nucleus (Parent and Hazrati, 1995).

The distribution of time differences between EMG and STNME LFPs was more complex. Although EMG, with one exception, led STNME LFPs, values tended to cluster around 6 and 47 ms. The latency of evoked potentials recorded from an STNME after electrical stimulation of the median nerve is ~15 ms (Ashby et al., 1999; Pinter et al., 2000). Allowing for electromechanical coupling, the longer EMG leads in the present study could be consistent with peripheral feedback from muscle. However, the shorter EMG leads would seem too short for this and suggest, instead, a corollary discharge to the subthalamic nucleus from cortical neurones projecting to the pyramidal tract (Kitai and Deniau, 1981; Giuffrida et al., 1985). For example, if we presume that the motor cortex activates the forearm extensor muscles with a latency of ~15 ms, as suggested by transcutaneous stimulation of the motor cortex, and simultaneously sends a corollary discharge to the subthalamic nucleus using pathways similar to those responsible for STNME LFP–EEG coherence, then the subthalamic nucleus would be activated ~24 ms after the cortex and ~9 ms after EMG, well within the confidence limits of our estimated STNME LFP–EMG time difference of 6 ms. The lead of EMG over STNME LFPs may therefore involve an oscillatory drive to muscle from the motor cortex that is relayed to the subthalamic nucleus either via internal reafference or by peripheral feedback. In this way, both central and peripheral reafference would be expected to display the same task specificity of oscillatory activity as corticomuscular drives (Brown et al., 1998; Kilner et al., 1999). This was reflected in the increased coherence in the beta (15–30 Hz) band between STNME LFPs and EEG or EMG during tonic tasks.
provide a means of linking together different neuronal populations. The timing of neuronal discharge is closely related to fluctuations in LFPs, which can therefore be used, as here, as a surrogate marker of the synchronization of neuronal discharge (Creutzfeldt et al., 1966; Frost, 1968). The binding potential of neuronal synchronization has received particular attention in the sensory system (Singer, 1993; Gray, 1994). However, evidence is also accumulating from both animal and human studies that disparate cortical areas involved in the same motor task may be coherent with each other (Classen et al., 1998; Gerloff et al., 1998; Andres et al., 1999; Marsden et al., 2000b). Similarly, coherent oscillations between cortical and subcortical motor structures, as shown here, may serve to bind functionally related activities between these structures (Schwarz and Thier, 1999).

Our coherence and phase results also suggest that central reafference may be an important feature in the organization of motor activities. We found evidence for central reafference to the subthalamic nucleus, as well as to the cerebellar thalamus in an earlier study (Marsden et al., 2000a). Such central reafference might help subserve timing mechanisms or allow the comparison of intended and achieved motor actions.

**Clinical implications**

Those STNME contact sites that, when recorded from, demonstrated the highest coherence with midline EEG in the beta band closely corresponded to those sites that produced the best clinical effect when they were subsequently electrically stimulated at high frequencies. Anatomical studies suggest that, although the primary motor cortex projects to the part of the subthalamic nucleus that outputs to the globus pallidus externa, the supplementary motor area projects to the part of the subthalamic nucleus that outputs to the globus pallidus interna (Joel and Weiner, 1997). Thus, the presence of beta oscillatory activity coherent with midline EEG may be a useful indication that the relevant contacts of the macro-electrode span the part of the subthalamic nucleus projecting to the globus pallidus interna and are likely to give a good clinical result upon stimulation at high frequency.

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**References**

Corticobasal ganglia interactions


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