Temporal Evolution of Oscillations and Synchrony in GPi/Muscle Pairs in Parkinson’s Disease

José M. Hurtado, Leonid L. Rubchinsky, Karen A. Sigvardt, Vicki L. Wheelock, and Conrad T. E. Pappas

1Center for Neuroscience, University of California, Davis; 2Department of Neurology and 3Department of Neurosurgery, University of California Davis Medical Center, Sacramento; and 4Clinical Neuroscience, Kaiser Permanente, Sacramento, California

Submitted 13 August 2004; accepted in final form 2 October 2004

Hurtado, José M., Leonid L. Rubchinsky, Karen A. Sigvardt, Vicki L. Wheelock, and Conrad T. E. Pappas. Temporal evolution of oscillations and synchrony in GPi/muscle pairs in Parkinson’s disease. J Neurophysiol 93: 1569–1584, 2005. First published October 20, 2004; doi:10.1152/jn.00829.2004. Both standard spectral analysis and time-dependent phase correlation techniques were applied to 27 pairs of tremor-related single units in the globus pallidus internus (GPi) and EMG of patients with Parkinson’s disease (PD) undergoing stereotactic neurosurgery. Over long time-scales (~60 s), GPi tremor-related units were statistically coherent with restricted regions of the peripheral musculature displaying tremor. The distribution of pooled coherence across all pairs supports a classification of GPi cell/EMG oscillatory pairs into coherent or noncoherent. Analysis using ~2-s sliding windows shows that oscillatory activity in both GPi tremor units and muscles occurs intermittently over time. For brain/muscle pairs that are coherent, there is partial overlap in the times of oscillatory activity but, in most cases, no significant correlation between the times of oscillatory subepisodes in the two signals. Phase locking between coherent pairs occurs transiently; however, the phase delay is similar for different phase-locking subepisodes. Noncoherent pairs also show episodes of transient phase locking, but they occurred less frequently, and no preferred phase delay was seen across subepisodes. Tremor oscillations in pallidum and EMGs are punctuated by phase slips, which were classified as synchronizing or desynchronizing depending on their effect on phase locking. In coherent pairs, the incidence of synchronizing slips is higher than desynchronizing slips, whereas no significant difference was seen for noncoherent pairs. The results of this quantitative characterization of parkinsonian tremor provide a foundation for hypotheses about the structure and dynamical functioning of basal ganglia motor control networks involved in tremor generation.

INTRODUCTION

Oscillatory activity and phase synchronization are prominent features of vertebrate motor systems. Some forms of coordinated oscillatory activity play an undisputed role in motor function, but it is well known that oscillatory activity can also have disruptive consequences for neural function. Its presence is a recurrent feature in a variety of neurological diseases (Llinas et al. 1999), including several movement disorders (Farmer 2002). Oscillations in the motor cortex and related subcortical structures can propagate to the limb musculature via descending pathways (Baker et al. 2003; Gross et al. 2000; Salenius and Hari 2003) and give rise to tremors (Elble 1996; Elble and Koller 1990; Halliday et al. 2000; McAuley and Marsden 2000). One of the best known is the resting tremor of Parkinson’s disease (PD) that affects roughly 70% of PD patients. Parkinsonian tremor occurs in the 2- to 6-Hz frequency band, is predominantly present at rest, and is more prevalent in the distal than proximal segments of the upper or lower limbs (Deuschl et al. 2000).

The pathological origin of PD, the loss of midbrain dopaminergic cells, has been well known for nearly 40 yr (Hornykiewicz 1966), but despite significant advances in our understanding of the anatomy and cellular physiology of the basal ganglia (BG) structures affected by the dopamine (DA) loss, the causal link between the pathology and the symptoms remains obscure. Most recently, hypotheses regarding the pathophysiology of PD have emphasized the dynamical changes that the BG network undergoes as a result of the pathology; in this view, changes in firing patterns, not just of mean firing rates, are considered the hallmark of PD (reviewed in Bevan et al. 2002; Brown 2003; Obeso et al. 2000). This idea has been supported by physiological evidence from PD patients and animal studies, including the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of parkinsonism (Nini et al. 1995). It has been shown that following DA loss, cells in globus pallidus internus (GPi) and subthalamic nucleus (STN) enter a regime of rhythmic firing concomitant with excess synchrony (Bergman et al. 1998; Brown et al. 2001; Levy et al. 2002; Obeso et al. 2000). Given the tight interrelationship between the BG and other structures in the motor system, it is not surprising that the pathological regime of PD can affect the entire limb motor network, including corticothalamic, cerebellar, and spinal networks (reviewed in Doya 2000; Houk and Wise 1995; Middleton and Strick 2000). Several studies indicate that PD tremor-related activity is not restricted to the core BG/motor cortex network, but it involves cerebellar and spinal circuitry as well (Parker et al. 1992; Timmermann et al. 2003; Volkmann et al. 1996; Williams et al. 2002).

A prominent feature of PD dynamics is that tremor-related oscillations occurring in different locations of the network can in many cases be uncorrelated, even while their frequencies are nearly uniform. This phenomenon was first studied by Alberts et al. (1969), who compared tremor-frequency intracortical potentials to the EMGs of muscles in different limbs. Several studies of multiliglimb EMG recordings in PD patients also indicate that tremor in different limbs is largely uncorrelated
(Ben-Pazi et al. 2001; Hurtado et al. 2000; O’Suilleabhain and Matsumoto 1998; Raethjen et al. 2000). In addition, dual recordings in GPi tremor-related cells during stereotactic surgery have shown that, although cells might be correlated to restricted portions of the musculature or to each other, uncorrelated oscillations are commonplace as well (Hurtado et al. 1999; Lemstra et al. 1999). These findings are consistent with a topographic organization of the individual structures that comprise the tremor generating network.

However, the results of these studies also raise a number of questions. Clinical observations indicate that tremor in any one muscle can come and go over time; in spectral analysis terms, tremor is largely a nonstationary phenomenon. If nonstationary signals are analyzed over long periods of time, even if they contain short segments of phase locking, the correlation could be below statistical significance. A better assessment of the interactions would be obtained by analyzing these signals over time. Another common observation made during intraoperative mapping of the basal ganglia in functional neurosurgery is that the tremor-related neural activity might wax and wane while the limb tremor persists, and vice versa, persistent tremor-related activity can exist in the apparent absence of limb tremor. This raises a similar and related question regarding the temporal evolution of the correlations between tremor-related neurons within the basal ganglia and between these neurons and the peripheral musculature. Finally, the topographic organization of the different limb representations within the basal ganglia (DeLong et al. 1985) raises the question of how the neurons within and between these representations interact during tremor episodes.

The purpose of this study is to address these questions in detail. We applied time-dependent spectral techniques to tremor-related single unit and EMG recordings in PD patients. Using statistical methods that detect the onset and offset of oscillations and phase locking at high temporal resolution (Hurtado et al. 2004), we characterized the temporal properties of tremor-related oscillatory activity in the basal ganglia-muscle network. The results of this quantitative characterization of tremor dynamics provide a foundation for hypotheses about the structure and dynamical functioning of basal ganglia motor control networks involved in parkinsonian tremor.

M E T H O D S

Patients

We studied data collected from five cases of surgical treatment of patients with idiopathic Parkinson’s disease. This included all patients in our program from 1998 to 2003 who had a microelectrode-guided pallidal procedure (pallidotomy or pallidal deep brain stimulating (DBS) electrode implantation and who fulfilled our inclusion criteria of having recordings of tremor-related activity from the internal segment of the GPi and simultaneously recorded tremulous EMGs (see Table 1). Criteria for identification of neurons as being within GPi included 1) area with noted increased level of tonic activity; 2) area with tremor-related activity; 3) area with passive responses to limb movement; 4) quiet zone below GPi with optic tract below that (as indicated by light responses); 5) lesions placed in area identified in this way result immediately in improvement of one or more motor symptoms (e.g., reduction in tremor and rigidity); 6) identification of correct placement or lesion or DBS in postoperative MRI; and 7) improvement in UPDRS scores 6 mo postoperatively.

Hoehn and Yahr scores and Unified Parkinson’s Disease Rating Scale scores (UPDRS) were determined in preoperative and postoperative visits off and on anti-parkinsonian medication by a neurologist (V.L.W.). The total UPDRS score in Table 1 was composed of items 1–4 on medication, items 5–31 (activities of daily living and motor scores) off medication, and items 32–42 (complications of therapy) on medication. Motor scores included only a single score for each item (i.e., did not include scores for each extremity). We obtained data from a total of 17 recording sessions from the posteroventral GPi, each lasting ~1 min.

Recordings

Data were collected during microelectrode-guided mapping of the posteroventral pallidum prior to lesion or the placement of a DBS electrode. Details of the procedure have been previously described (Hurtado et al. 2004). Briefly, the coordinates of the target site for the first electrode pass, the optic tract just ventral to the ventral border of GPi, were determined from MRIs of the brain in relation to fiducial markings on the stereotactic frame (Radionics, Burlington, MA). EMGs were recorded from one to four of the following arm and leg muscles: abductor pollicis brevis (APB), wrist extensor (WE), wrist flexor (WF), biceps (BI), quadriceps (QUAD), gastrocnemius (GAST), and tibialis anterior (TA). At the time of surgery, patients had been off anti-parkinsonian medication for ~8–10 h. Informed consent was obtained from all patients. The protocol for collection of intraoperative data was approved by the Institutional Review Boards of the University of California Davis and Kaiser Permanente Research Foundation.

Microelectrode recordings were obtained with 50-μm, beveled, stainless steel electrode (Frederick Haer and Company, Bowdoinham, ME), with an impedance of ~0.5–1.0 MQ at 1 KHz. Signals were amplified (10,000 times) and band-pass filtered between 500 Hz and 10 KHz (Bak Electronics, Germantown, MD). EMGs were recorded with Grass disk electrodes (Astro-Med, West Warwick, RI), amplified (2,000 times), band-pass filtered in the range of 30 Hz to 1 KHz, and full wave rectified prior to spectral analysis. This last step was to recover the low-frequency myoelectric signal from the amplitude-modulated activity in the EMG signals. Neuronal and EMG signals were digitized at 10 kHz using an A/D board (RC Electronics Santa

### TABLE 1. Patient demographics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Duration of Disease</th>
<th>Type of Surgery</th>
<th>Side of Surgery</th>
<th>Preoperative UPDRS Scores</th>
<th>Postoperative UPDRS Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preoperative Hoehn and Yahr</td>
<td>Postoperative Hoehn and Yahr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tremor Score</td>
<td>Motor Score</td>
</tr>
<tr>
<td>A</td>
<td>M</td>
<td>63</td>
<td>14</td>
<td>Palli-X</td>
<td>Right</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>B</td>
<td>M</td>
<td>65</td>
<td>16</td>
<td>Palli-DBS</td>
<td>Left</td>
<td>2.5</td>
<td>9</td>
</tr>
<tr>
<td>C</td>
<td>F</td>
<td>74</td>
<td>13</td>
<td>Palli-X</td>
<td>Right</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>D</td>
<td>M</td>
<td>63</td>
<td>6</td>
<td>Palli-X</td>
<td>Right</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>E</td>
<td>M</td>
<td>61</td>
<td>10</td>
<td>Palli-X</td>
<td>Right</td>
<td>2.5</td>
<td>4</td>
</tr>
</tbody>
</table>
Barbara, CA) with software provided by that company. Neuronal spikes were threshold extracted (>2 SD above baseline) and down sampled at a 1-ms resolution. Single units were further assessed by confirming the presence of a clear refractory period (>1–2 ms) in the autocorrellogram and stability in spike shape and amplitude over the recording period. Multiunit data were discarded from the analysis.

**Standard spectral analysis**

Standard statistical spectral methods were used to compute overall (i.e., over ~60 s) spectral properties of the signals, as described previously (Brillinger 1981; Hurtado et al. 1999; Percival and Walden 1993; Rosenberg et al. 1989). The terms “overall spectra” and “overall coherence” are used to distinguish these computations from the time-dependent coherence measure we apply later. All analysis was performed in MATLAB (MathWorks, Natick, MA). For overall spectral estimation, we used a multiple window method (Carter 1987; Percival and Walden 1993) as follows: epochs of paired neural-EMG recordings were subdivided into Nwin 1-s segments with no overlap and multiplied with a Hanning tapering window to reduce spectral leakage. The discrete Fourier transform (DFT) of each segment d_{i,k} (channel i, segment k) was computed using the FFT algorithm from the MATLAB library. The frequency bin for the DFT and all overall spectral estimates is 1 Hz. To obtain the power spectrum, a direct spectral estimate (i.e., periodogram) from each 1-s segment was computed by taking the magnitude square of its DFT at each frequency, \hat{P}(\omega) = |d_i(\omega)|^2, where \omega is the frequency, and the spectrum is estimated as the average of all direct estimates, \hat{P}(\omega) = \sum_{i=1}^{N} \hat{P}_i(\omega). To extract significant peaks, we consider as a null hypothesis a flat spectrum with the same total power as the observed spectrum as follows. For a stationary process, the spectrum follows a \chi^2 distribution (Brillinger 1981; Percival and Walden 1993)

\[ \hat{P}_{null} = E[P_{null}] \times \frac{\chi^2}{v} \]  

where v is the degrees of freedom, \hat{P}_{null} is the empirical (i.e., sample) spectrum in the null condition, and E[\hat{P}_{null}] is the expected value. For \text{N}_{\text{win}} independent windows, the degrees of freedom are v = 2N. Under the null hypothesis of a flat spectrum, E[\hat{P}_{null}] should be constant across frequencies. For evaluation purposes, the constant value was taken as the average of the empirical spectra in E[\hat{P}_{null}] \equiv \hat{P}(\omega)\. This assures that the null distribution has equal power as the empirical spectrum. In our case, the average was taken in the frequency range between 1 and 35 Hz. Departures from the null condition (i.e., peaks) are obtained at \alpha = 0.002 significance level, and significant peaks in the range of tremor (2–6 Hz) were considered as evidence of tremor-related activity.

Overall coherence is computed from the formula

\[ C_{\text{null}} = \frac{\hat{P}(\omega)}{f(\omega)f(\omega')} \]  

where \hat{P}(\omega) is the estimated cross spectrum between channels i,j \hat{f}(\omega) = (1/N_{\text{win}}) \sum_{i=1}^{N} d_{i,\omega} d_{j,\omega}^{*}, where the bar denotes complex conjugate, and N_{\text{win}} is the number of nonoverlapping analysis windows.

To distinguish between noncoherent and coherent pairs, we test the null hypothesis of independent activity. We define as a cut-off level \gamma as the value of coherence such that the probability \( P(\gamma > \gamma) = 0 = \alpha \). This is the maximum value consistent with the zero coherence hypothesis at the significance level \alpha. A cut-off value \gamma is a function of \alpha and N is given by

\[ \gamma = 1 - (1 - \alpha)^{-1} \]  

(Rosenberg et al. 1989). The validity of this binary classification (coherent/noncoherent) was tested by building a histogram of coherence values across all recorded pairs and checking the modes. The method is described below.

An example of a digitized EMG and threshold-extracted spike train is shown in Fig. 1A. The overall power spectrum of each of these signals and their coherence spectrum is shown in Fig. 1B. Recording pairs having a significant peak in their coherence spectrum are expected to maintain a relatively constant phase lag at that frequency throughout the recording period. We display the distribution of phase differences over the sample windows as an angular histogram (Fig. 1B). Clustering around an angular bin is expected when coherence is high.

**Pooled coherence histogram**

Building a histogram of combined or “pooled” coherence values across patients, neural/EMG pairs, and recording episodes is complicated by two problems. First, coherence estimators obtained with different numbers of independent windows (N) are not comparable since the bias and variance of the estimator depends crucially on N (Amjad et al. 1997; Carter 1987). Second, our number of recorded pairs was too limited to generate a meaningful histogram. We adopted a bootstrapping strategy to address these problems. In this scheme, the following sequence was repeated n = 10^5 times: first, a recording session was selected at random from the database, with replacement; the probability of choosing any particular session was made proportional to that session duration. From the chosen session a neural/EMG pair is obtained; if more than one EMG channel was available, one was selected randomly. Second, the paired neural/EMG data were subdivided into nonoverlapping 1-s segments, as described in the previous section. Third, from these (paired) segments, a group of 20 is randomly drawn, and their coherence is computed. The total of 10^5 coherence values obtained was pooled to form a histogram; pooling was legitimate since each coherence estimate was computed from the same number of segments (n = 20).

The bias and variance of the coherence estimator depends also on the “underlying” coherence (Carter 1987). To equalize variances across coherence values, we used the Fisher transform of coherence, tanh^{-1}(\sqrt{\gamma}), which returns values close to a normal distribution with variance that is not dependent on the underlying coherence (Amjad et al. 1997).

**Time-frequency analysis, SNR, and tremor-on-off index**

We implemented a method to extract the intervals of significant oscillatory activity in the EMG and neuronal data. This step is important for the phase reconstruction procedure that follows, since a phase can be meaningfully defined only for signals that are oscillatory. First, a time-frequency spectrum, \hat{P}(\omega,t) (\omega: frequency; t: time) was computed for each data series. For each point in time, we applied the same calculation scheme as for the overall spectral analysis, with the sole difference being that here we used overlapping windows (90%) to obtain a higher temporal resolution. Data were windowed into 1-s sliding windows (100-ms offset between subsequent windows), a Hanning taper was applied to each window, and the direct spectra were computed from its FFT, as described before. The spectra of 10 adjacent windows were averaged to yield a spectral estimate. One such estimate was obtained every 100 ms, spanning 1.9 s of data (i.e., 10 1-s windows 100-ms offset) and with a frequency resolution of 1 Hz.

Episodes of tremor activity are defined as intervals where the spectral peak in the tremor range (2–6 Hz) is substantially higher than the baseline (noise) level. A cut-off level was obtained by
A and B: summary of standard spectral analysis. A: tremor-related activity in simultaneously recorded threshold-extracted single unit spike train in globus pallidus internus (Gpi) and EMG from the abductor pollicis (APB; scale bar = 250 μV). Ten seconds of data are subdivided into 10 nonoverlapping 1-s segments (dashed lines) B: power spectra of Gpi (arbitrary units) and EMG (μV²/s/Hz) activity (graphs with gray background) and coherence spectrum (graph with white background); for a 10-s period (dashed lines, 1% significance level). Bottom left: histogram of the phase differences between the 2 signals for the 10 analysis windows. Both spike train and EMG have a significant peak at 4 Hz. Peak at 4 Hz in the coherence spectrum indicates that the unit and muscle are correlated within the tremor band, and the histogram shows that the phase between the 2 remains relatively constant. C: time-frequency methods. Panels show the time-frequency power spectra from Gpi (top) and APB EMGs (bottom). Time-dependent signal-to-noise ratio (SNR; green trace, scale on left) is overlaid on the time-frequency spectra; dashed green line marks SNR threshold level. Note that there is power in the tremor band when SNR > threshold. Band-pass filtered data (gray traces) and raw data corresponding to each time-frequency spectra are shown below each panel (scale = 50 μV). Note that tremor range oscillations visible in the raw and filtered signals coincide with times where SNR > threshold. D: impulse response of the filter. E: phase reconstruction and phase coherence methods. Top: complex Gabor representation of an oscillatory brain signal; only 2 cycles are displayed for clarity. Angle $\phi$ is represented as a point in the unit circle (thin circle) by projecting into it (arrow). Middle: phase evolution of 2 oscillators (Gpi and EMG) overlaid in the unit circle. $\phi_G$, $\phi_E$ are phase angles at a particular point in time. Their difference, $\Phi$, is a point in the unit circle that represents the phase lag. Bottom: thin vectors represent values $\Phi$ at different times during the interval of analysis. Their average is shown as a thick vector. Modulus (length) of this vector is always $<1$. Its value is high (near 1) if $\Phi$ varies little over time and low (near 0) if $\Phi$ is highly variable. The phase coherence index $\Phi$ is the square of the modulus.

Taking a flat power spectrum as a null hypothesis and considering departures at a significance level $\alpha = 0.002$ as significant peaks. The null distribution of the averaged spectrum, $P_{null}$, is $\chi^2$, and we approximate $E[P_{null}]$ by the average of the power in the frequency range 1–35 Hz, $E[P_{null}] \equiv \langle P(\omega) \rangle$. For the degrees of freedom, we must consider that, in this case, there is substantial overlap between adjacent windows, and the assumption of independence is thus violated. We therefore estimated the equivalent degrees of freedom for nonindependent windows from a procedure described in detail in Thomson and Chave (1991). For an overlap level of 90%, using $N_{win} = 10$ and considering Hanning tapers, the degrees of freedom parameter is $v = 4.87$. At a significance level $\alpha = 0.002$, the corresponding cut-off value is 3.78 (i.e., $p \left( \frac{X^2}{v} \geq 3.78 \right) = \alpha$). Peaks that surpass the spectral average baseline 3.78 times were thus considered significant ($P < 0.002$). Since we are extracting phases in the tremor range, we consider peaks in the 2- to 6-Hz range.

To implement this criterion over time, we defined a signal to noise ratio (SNR) as a function of time, $SNR(t)$, as the ratio of maximum power in the tremor frequency band over the average signal power in the broader band 1–35 Hz

$$SNR(t) = \frac{\max_{\omega_a \leq \omega \leq \omega_b} [P(\omega,t)]}{\text{avg}_{\omega_a \leq \omega \leq \omega_b} [P(\omega,t)]}$$

where $\omega_a$, $\omega_b$ are the limits of the tremor band (2–6 Hz), $\omega_b = 35$ Hz, and $\omega_a = 1$ Hz. From the previous considerations, we used a threshold value of $SNR(t) > 3.78$ to extract the segments where tremor oscillations are significant. We confirmed the validity of the threshold by visually inspecting tremor-related neural activity and tremor EMG series and checking that this threshold index discriminates well between oscillatory and nonoscillatory intervals (Fig. 1C). Intervals above and below this threshold are referred to as “tremor-on” and “tremor-off” intervals, respectively. It is important to note that this separation between nonoscillatory and oscillatory episodes is necessary for a valid phase reconstruction, since phase variables defined over nonoscillatory data are misleading.
Tremor-on and tremor-off intervals were represented by a binary variable as a function of time \( \tau(t) \), as

\[
\tau(t) = \begin{cases} 
0, & \text{SNR}(t) < \text{SNR}_{\text{thres}} \\
1, & \text{SNR}(t) \geq \text{SNR}_{\text{thres}} 
\end{cases}
\]  

(that is, \( \tau = 0 \) for tremor-off intervals and \( \tau = 1 \) for tremor-on intervals). This index was computed for neuronal activity and EMG recordings. Since one SNR point, spanning 1.9 s of data, was obtained every 100 ms, gaps in tremor (i.e., periods of \( \tau = 0 \)) that lasted < 1 s and were in the midst of tremor-on periods (\( \tau = 1 \)), were considered nonsignificant and set to the value \( \tau = 1 \). We did this correction because a drop in the SNR value for such short times does not reflect a lasting interruption in tremor (the total time extent for computing a SNR point was 1.9 s, i.e., 10 1-s windows with 90% overlap). These short interruptions were caused by the appearance of a series of phase slips in quick succession and are treated separately in phase slips and estimation of associated phase advance.

This transformation from continuous SNR to binary indexes provides a way to extract episodes of significant tremor, where a phase can be defined with relative certainty, and it simplifies the analysis of temporal incidence of tremor.

**Tremor-on-off correlation for paired recordings**

To determine whether there are temporal correlations between the tremor-on-off intervals for different neural and EMG channel pairs, we computed a (0 lag) correlation coefficient \( R_{i,j}^{(0)} \) between the \( \tau \) of channel pairs \((i,j)\), over each recording episode

\[
R_{i,j}^{(0)} = \frac{\text{cov}(\tau_i, \tau_j)}{\sqrt{\text{var}(\tau_i) \text{var}(\tau_j)}}
\]  

A value of \( R_{i,j}^{(0)} \) close to 1 means that channels \( i,j \) tend to be in the tremor-on or -off states concurrently, whereas a value close to 0 indicates that the tremor-on- and -off states in both channels are independent; a value near –1 means that one channel is likely to be tremor-off when the other is tremor-on. The statistical significance of \( R_{i,j}^{(0)} \) was assessed by estimating the distribution of correlation coefficients under the null hypothesis of \( R_{i,j}^{(0)} = 0 \) and obtaining cut-off values from this distribution. To estimate the distribution, independent pairs of \( \tau_i(t) \) and \( \tau_j(t) \) series were generated using surrogate data. A set of surrogate series \( \tau_i(t) \) can be constructed by time-shifting either of the original series by a random step, while keeping circular boundary conditions. The \( R_{i,j}^{(0)} \) (superscript \( s \) for surrogate) was computed for 500 surrogate data pairs, and the 95th and 5th percentiles of the distribution were used as the cut-off to determine significant correlation (or anticorrelation). In cases where either of the \( \tau_{ij}(t) \) was 1 or 0 for all \( t \), the variance is zero and \( R_{i,j}^{(0)} \) has no meaning.

A caveat of this analysis is that there may be a loss of information when transforming the SNR measure to a binary index, and therefore significant correlations in SNR could be masked. We therefore computed the correlation coefficients of the original SNR, and the answers were identical to those obtained by using the tremor index.

**Phase reconstruction procedure**

The goal of the phase reconstruction procedure is to obtain an angular phase variable as a function of time from the oscillatory time series. The phase variable indicates the amount of completion of an oscillation cycle at any given point in time and is used to quantify phase locking between oscillatory signals. Importantly, a phase reconstruction method yields meaningful results only if the signal is oscillatory (Hurtado et al. 2004; Pikovsky et al. 2001; Rosenblum et al. 2001). We therefore restrict the analysis of phase to tremor-on intervals.

The steps in the phase reconstruction methods have been described in detail elsewhere (Hurtado et al. 2004). In summary, after spike extraction in the neuronal signal and rectification in EMGs, signals were band-pass filtered in the range of tremor activity. We used a digital FIR filter, 2- to 6-Hz passband, stop 0–1 (–60 dB) and 7 Hz Nyquist, (–80 dB), sampled at 1 kHz. The parameters yielded an almost flat response in the passband, and rejection of out of band activity with a sharp rolloff. A filter of relatively high order (2,530) was necessary to obtain good out of band rejection together with a flat response in the tremor range and little distortion in the time location of peaks. We compared the original series to the filtered ones to check that filtering did not alter peak locations and that it was sensitive enough to follow the shifts in phase in the original data. The process of filtering entails a loss of temporal resolution, since it is equivalent to convolving the data with a moving window. High filter orders such those used here imply longer windows. We measured the time as localization of our filter by taking the square of its impulse response as a distribution (Percival and Walden 1993) and computing its SD. In our case, this was 188 ms, meaning that the lost of temporal precision due to filtering happened within a very narrow window of time, even though the total filter length was about 5 s (Fig. 1D).

Phase is obtained from the filtered series by using the Gabor representation, \( \zeta(t) \), that projects the oscillatory series on to the complex plane and results in a rotational trajectory around the complex origin (Gabor 1946; Rosenblum et al. 2001). Its real part is the Hilbert transform of the signal \( \text{Im}[\zeta(t)] = \tilde{x}(t) = H[x(t)] \). The complex trajectory \( \zeta(t) \) is projected onto the unit circle (Fig. 1E):

\[
z(t) = \frac{\zeta(t)}{|\zeta(t)|}
\]

and the phase of the signal is obtained as the angular variable \( \phi(t) = \arg[\zeta(t)] = \arg[z(t)](t) \approx \omega t \). As a result, we obtained a discrete series of \( \phi(t_k), k = 1, 2, \ldots, N \), where \( \Delta t = t_{k+1} - t_k \) is the sampling period (1 ms), and \( N \) is the number of samples. The “raw” instantaneous frequency \( \omega(t) \) is defined here as the first-order differential of \( \phi(t) \), \( \omega(t_k) = \omega_k = \frac{\phi_{k+1} - \phi_k}{\Delta t} \). Ideally, \( \omega \) varies slowly over time (Boashash 1992); the problem of discontinuities is treated in Phase slips and estimation of associated phase advance.

**Phase slips and estimation of associated phase advance**

Phase slips are discontinuities in the phase evolution of an oscillator, leading to abrupt phase advances. To detect slips, we took advantage of the fact that they would appear as “spikes” in the derivative of phase, which is the instantaneous frequency, \( \omega(t) \) (Fig. 2A, arrows). We therefore referred to these events as \( \omega \)-spikes. \( \omega \)-spikes were extracted from \( \omega(t) \) by setting as threshold the frequency limits of the band-pass filter that was used in the phase construction procedure (Fig. 2A, dashed lines). The rationale for this choice is that the instantaneous frequency is expected to remain within the frequency band of the signal (Boashash 1992); large departures can be considered singularities. A flat band-pass response and good out of band rejection of the filter were important in the procedure of phase slip extraction because they guaranteed that the only out of band activity visible corresponded to singularities (i.e., phase slips) and minimized false positives in slip detection due to poor filtering. Importantly, only slips occurring in the midst of an oscillation episode, (i.e., with high SNR) were considered as such.

In addition to obtaining the time location of slips, we estimated the amount of phase advance associated with each event. For this purpose, we compared the phase value shortly after the slip to the “forecasted” phase value had the slip not taken place. The forecasted phase was obtained by time integrating a smoothed estimate of the instantaneous frequency, \( \tilde{\omega} \) (Fig. 2B). The smoothed slips were first “erased” from the raw instantaneous frequency approximation, and the gaps (threshold crossing ± 100 ms) were filled by cubic interpolation from the
neighboring endpoints. \( \hat{\omega} \) was obtained by filtering the resulting series (moving average filter, 750 ms width). The forecasted phase series, \( \hat{\phi}(t) \) was computed as the time integral of \( \hat{\omega} \). The additional phase advance due to the slip is the difference between the forecasted phase (with no slip) and the observed phases, \( \delta \hat{\phi} = \hat{\phi}(t_M) - \hat{\phi}(t_M) \).

Importantly, this estimate has a margin of error due to the smoothing procedure used to obtain the forecasted phase advance, \( \hat{\phi} \). The error arises because \( \hat{\phi} \) is the integral of the smoothed instantaneous frequency \( \hat{\omega} \), whereas \( \phi \) equals the integral of the raw instantaneous frequency \( \omega \) (see Fig. 2B). Even if no phase slip takes place, the smoothed and raw series would differ, and \( \delta \hat{\phi} \) would drift away from the zero expected value. The error should be accounted for in the estimate of \( \delta \phi \) for phase slips. We studied the distribution of that error by computing \( \delta \hat{\phi} \) for randomly selected data segments where no slips occurred. From this distribution (data not shown), we found that the angular departure was \( |\delta \hat{\phi}| < 45^\circ \) in 95% of the cases. Consequently, slips less than \( \pm 45^\circ \) in magnitude were considered nonsignificant, and a conservative error bound of \( \pm 45^\circ \) was added to all slip angle estimates.

To determine whether there is a preferred angle of phase slipping for a given channel, we studied the distribution of slip advance angles for each recording session and tested the null hypothesis of a uniform circular distribution. An eight-bin circular histogram (45° bin size) of phase advance values was built, and an entropy index was calculated from this histogram. To obtain the null distribution of the entropy index, we numerically computed the index for uniformly distributed angles in the circle. An identical number of events was generated, and the index was computed a 100 different times. From this null distribution, a cut-off value was obtained at the 5th lowest percentile. Entropy values less than the cut-off were indicative of significant clustering.

**Phase correlation statistics**

To quantify time-locking between pairs over time, we used a time-dependent phase coherence index \( \gamma \) (details in Hurtado et al. 2004). The phase coherence is always \( \leq 1 \), taking a value of 1 only when the relative phase \( \Phi \) remained constant throughout the observation period. A similar measure has been used by others (Lachaux et al. 1999; Rosenblum et al. 2001). For each data pair, the relative phase series is obtained by taking the difference of angles between the individual phase series \( \Phi_j = \phi_j(t) - \phi_k(t), j = k - N, \ldots k \), where the \( \tau_j \) is the sampling point (see Fig. 1E).

The time-dependent phase coherence is defined as

\[
\gamma_{\Phi}(t) = \frac{1}{N} \sum_{i=-N}^{N} e^{i\phi_{ij}},
\]

where \( N \) indicates the number of consecutive data samples to be considered in the coherence computation. A small value of \( N \) provides an index with a higher temporal resolution, but lower statistical power. In this study we used \( N = 1,500 \), which at the sampling rate of 1 kHz corresponds roughly to six cycles of tremor oscillation. Values of phase coherence were only considered when both channels had significant oscillations (i.e., SNR above threshold).

We used a statistical method to test for phase locking against the null hypothesis of independent processes by studying the distribution of \( \gamma \) for independent processes with similar temporal characteristics \( \gamma_{\text{null}} \) (see Hurtado et al. 2004). Briefly, surrogate versions of the instantaneous frequency, \( \hat{\omega} \), are created from \( \omega \). To do this, we created surrogates having the same power spectrum as the \( \omega \) series, randomizing the phase spectrum while preserving the amplitude spectrum. We erased the \( \omega \)-spikes caused by phase slips prior to the computation.

**FIG. 2.** Phase slip methods. A: detection of phase slips. Time evolution of raw instantaneous frequency \( \omega \) of a GPi unit. Smooth instantaneous frequency estimate \( \hat{\omega} \) is overlaid (thick dashed line). Thin dashed lines mark upper and lower frequency thresholds for \( \omega \)-spike extraction. Arrow points to extracted events. B: phase advance estimation, details of \( \omega \) (thick line), and \( \hat{\omega} \) (thick dashed line) at the time around the \( \omega \)-spike occurrence. Bottom traces: phase evolution of the oscillation at the time around \( \omega \)-spike occurrence; sinusoidal traces are the real part of the complex Gabor representation. Arrow points to the phase slip location. The “predicted” phase evolution if no slip occurred (overlaid dashed line) is the time integral of \( \hat{\omega} \). This particular slip was quantified as a 140° advance (~30% of a cycle). C: top traces: GPi oscillator from B (black trace) with the EMG oscillator overlaid (phase evolution of EMG, white trace); note that throughout the time, the phase lag between GPi and muscle is preserved. Bottom traces: predicted phase evolution (dashed) overlaid on the same EMG oscillation as above; note the large variation in phase lag between both cases over time. Circular histograms on the right show the distribution of phase lag values during the time observed for the actual oscillator (top) and predicted (bottom). D: histogram of phase coherence values for a given channel, we studied the distribution of phase slip advance angles for each recording session and tested the null hypothesis of a uniform circular distribution. An eight-bin circular histogram (45° bin size) of phase advance values was built, and an entropy index was calculated from this histogram. To obtain the null distribution of the entropy index, we numerically computed the index for uniformly distributed angles in the circle. An identical number of events was generated, and the index was computed a 100 different times. From this null distribution, a cut-off value was obtained at the 5th lowest percentile. Entropy values less than the cut-off were indicative of significant clustering.
of surrogates because ω-spikes contribute to power at all frequencies. From the surrogate ȧt, we obtained a series of surrogate ȯ that are entered into the computation of the null distribution γ̂_{ind}. From γ̂_{ind} we obtained a 95% cut-off level γ̂_{ind}^{.95}, to detect times of significant synchronization. In addition, we used the 50% cut-off level, γ̂_{ind}^{.5}, as a reference to obtain the duration of intervals as described below. From the previous analysis step, we could obtain periods of phase locking at a 0.05 significance level. However, even for independent processes, some periods with γ > γ̂_{ind}^{.95} above the 95% cut-off (γ > γ̂_{ind}^{.95}) will randomly occur (on average, 5% of the time). To determine whether events above cut-off actually reflect a significant transient synchronization, we examined their duration. For a set of 200 surrogate independent pairs (generated as specified above), we determined the distribution of duration for intervals above the 50% cut-off level 2. A recorded pair was considered to show transient coherence if it contained at least one interval γ > γ̂_{ind}^{.5} with duration in the upper 95% and 2) if the γ within the interval γ > γ̂_{ind}^{.5} in question crossed the γ̂_{ind}^{.5} line at least once.

Synchronizing and desynchronizing phase slips

We describe here a statistical method to determine whether a phase slip in a channel promotes or destroys the synchrony between it and a second (reference) oscillatory signal (Fig. 2C). For this analysis, only phase slips that occur during an interval of synchronization between the two channels are selected. A time segment around the ω-spike associated with the slip is selected (t_{sl} ± 850 ms, where t_{sl} is the time of threshold crossing) and the phase coherence around the slip occurrence, γ̂_{sl}, is computed over that interval. For the computation of γ̂_{sl}, the interval t_{sl} ± 100 ms is eliminated from the calculation because the particular shape of an ω-spike is not a robust feature of the dynamics but depends on the details of numerical methods (filter settings, etc.). A random phase advance chosen from an uniform distribution in the circle is introduced into the channel with the phase slip at t = t_{sl} and the value of γ with the random slip, γ̂_{random}, is computed. This procedure is repeated 100 times, and the histogram of γ̂_{random} is computed. A slip is considered “synchronizing” if its γ̂_{sl} is in the highest 25th percentile of the γ̂_{random} distribution, “desynchronizing” if it is below the lowest 25th percentile, and “neutral” if it falls within the median 50th percentile (Fig. 2D). This procedure was carried out for single unit recordings, taking each muscle as a reference (neuronal slips), and also for each muscle, taking the neuronal signal as a reference (EMG slips).

A bootstrapping test was performed to determine whether synchronizing slips are significantly more probable in pairs that are coherent overall versus pairs that are noncoherent. Slips from all recordings in our database with overall coherence were listed, and groups of 30 were successively drawn randomly and with replacement. For each group, the number of synchronizing, desynchronizing, and neutral slips was counted. This procedure was repeated 5,000 times, drawing a new set of 30 slips each time. The frequencies of each event type (synchronizing, desynchronizing, and neutral) were averaged over all repetitions to yield an estimated probability distribution for each case. The same procedure was done for slips occurring in noncoherent pairs, and also for slips in EMGs.

RESULTS

Our data base included 9 single GPi units and 27 single unit/EMG pairs (see Table 2). Each of these nine units was identified as a GPi single unit by the following criteria: 1) the unit was a well-isolated neuron with a stable spike shape and stable amplitude significantly above the noise level over the recording period; 2) the spike autocorrelogram had a clear refractory period (>1–2 ms); 3) the area from which the unit was recorded had a noted increased level of tonic activity; 4) the area from which the unit was recorded had tremor related activity; 5) the area had passive responses to limb movement; 6) there was a quiet zone below GPi with optic tract below the quiet zone (as indicated by light responses); 7) lesions placed in the area identified as GPi during mapping resulted immediately in improvement of one or more motor symptoms (e.g., reduction in tremor and rigidity); 8) the lesion or DBS was correctly placed in GPi as confirmed by postoperative MRI; and 9) the patient showed improvement in UPDRS scores 6 mo postoperatively (see Table 1).

The analysis of the GPi/EMG tremor data was done in two steps. First, we computed statistical power and coherence spectra for pairs of GPi single units and EMGs from several muscles using a multiple window method. These computations provide statistical estimators over a time scale of tens of seconds (usually 1 min), corresponding to a few hundred tremor cycles. Although these estimators lack temporal resolution, they provide insights into the spatial (i.e., anatomical) characteristics of the networks that give rise to tremor activity. We refer to them as “overall” spectral properties.

---

### Table 2. Oscillatory activity and coherence of tremor-related GPi units and EMGs

<table>
<thead>
<tr>
<th>Patient Key</th>
<th>Channel</th>
<th>Tremor Range Activity</th>
<th>Both Tremors</th>
<th>Coherent</th>
<th>Transient Coherence</th>
<th>SNR</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>GPi</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>B1</td>
<td>GPi</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>APB</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>WE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>WF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>BI</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>B2</td>
<td>GPi</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>APB</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>WE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>WF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>BI</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>C</td>
<td>GPi</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>APB</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>QUAD</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>GAST</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>D1</td>
<td>GPi</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>WE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>WF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>TA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>D2</td>
<td>GPi</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>WE</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>WF</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>TA</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>D3</td>
<td>GPi</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>WE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>TA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>D4</td>
<td>GPi</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>WE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>WF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>TA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>E</td>
<td>GPi</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>GAST</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>TA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>APB</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>WE</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>22</td>
<td>17</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GPi, globus pallidus internus; WE, wrist extensor; APB, abductor pollicis brevis; WF, wrist flexor; BI, biceps; QUAD, quadriceps; GAST, gastrocnemius; TA, tibialis anterior; NA, not applicable.
The second set of measures characterizes the temporal evolution of oscillatory activity and the synchrony between oscillations over time, with a resolution of about six tremor cycles (i.e., 1.5 s). From them, we obtain 1) a time profile of the intervals during which tremor-range oscillatory activity is present (tremor-on) and absent (tremor-off) in each of the channels, 2) the time location of phase slips in each of the oscillatory channels during the tremor-on states, and 3) a picture of the time evolution of phase locking between pairs of oscillatory channels. These high resolution measures resolve the problems of nonstationarity faced in the standard spectral measures used to compute overall coherence, that span longer analysis periods.

Distribution of overall tremor coherence reveals two classes of GPi/EMG interactions

Power spectra were computed for GPi single units (n = 9) and EMG recordings (n = 27). The duration of data epochs varied from 30 to 90 s. All single units studied exhibited a statistically significant peak in the tremor range (2–6 Hz), and 22 of the EMG episodes recorded had significant tremor. The resulting 22 neural/EMG pairs with prominent tremor-range activity in both channels amount to a total of nearly 20 min of paired tremor data from all patients, pairs, and recording epochs.

Figure 3 shows the pooled coherence histogram from these 22 pairs, constructed with the bootstrapping method described previously. A total of 10^5 coherence values was computed from data segments drawn randomly from the database, as described in METHODS. The histogram exhibits a prominent mode at low coherence (arrow) and a wider peak at higher coherence values that contains two closely spaced secondary peaks. The Fisher transform (inset), normalizes the coherence measure and reveals the modes more clearly.

The low coherence peak is consistent with the presence of independent GPi/EMG oscillations. The modal coherence in this population is shifted from zero because coherence is an upward biased estimator. For comparison, we overlaid the sample distribution of coherence values from a numerical model of independent white noise processes (white line). The distributions dropped to near zero because we selected the highest coherence value in a range of frequencies (2–6 Hz); this procedure reduced the incidence of lower values.

The presence of a distinct population of independent oscillators (i.e., 0 coherence) led us to sort our data into coherent and noncoherent pairs; the main motivation for this was to compare the temporal dynamics of one class versus the other. To this end, we used the following classification scheme: a recording was classified as noncoherent if the null hypothesis of independent oscillators could not be rejected at the 0.01 significance level. Pairs that did not conform to the null hypothesis were classified as coherent. We used the full length of the each data epoch to compute coherence for this classification. In addition, the same bootstrapping method was applied, separately, to both coherent and noncoherent subclasses to obtain their individual distributions of coherence values. The black full and dashed lines in the histogram plot show the coherence distributions obtained for these two subsets. The coincidence between the peaks on the latter and those of the full distribution indicates that our classification scheme sensibly splits the population into natural modal components. The full distribution is, of course, the sum of both groups. Note that the distribution of coherence for cell/muscle pairs classified as noncoherent (full line) is largely coincident with the theoretical distribution for independent (i.e., 0 coherence) white noise processes (white line), as expected.

The incidence of coherent and noncoherent pairs is shown at the bottom of Table 2. Of the 22 GPi/EMG pairs that had concurrent oscillations in the tremor range, 17 pairs (77%) showed significant coherence; the remaining 5 (23%) pairs were noncoherent. That many of the pairs were coherent overall is expected, given that both the unit and the muscle in each pair had tremor-related activity. The finding of concurrent, yet noncoherent, oscillatory activity at the same frequency is, however, not intuitive. One possibility is that a given tremor GPi cell is functionally linked in a preferential way to a subset of muscles, but is independent from the rest. This interpretation was supported by recordings where GPi/ tremor correlations were clearly specific to some tremulous muscles but not others. In four of the nine single units studied, we observed overall coherence between an oscillatory GPi unit and some of the recorded muscles but not others, even as these others had significant tremor. In one of our patients (patient B), we recorded two GPi units and four arm muscles. One of the units was coherent with all four muscles, but the other unit was coherent only with the three more distal muscles (APB, WE, WF), but not with the proximal muscle (BI).

The idea that tremor/GPi correlations follow a topographic order was further supported by the results of the analysis of recordings from patients with both upper and lower limb tremor. One of the patients studied here (Table 2, C) exhibited prominent tremor in both upper and lower extremities contralateral to GPi. Overall coherence between a GPi single unit
and EMGs was significant only for the two leg muscles, but not for the arm muscles (Fig. 4). This limb selectivity occurs despite the fact that the GPi single unit and all four muscles (2 arm and 2 leg) recorded had prominent oscillatory activity at 4 Hz, as visible in the power spectra. This observation complements our previous finding (Hurtado et al. 1999) that GPi oscillators during tremor are clustered according to limb preference and is in agreement with previous observations that GPi neurons have kinesthetic responses that are limb specific (De-Long et al. 1985).

Tremor-on intervals in GPi units and muscles occur intermittently and are often nonoverlapping

Recorded sessions with significant tremor activity (i.e., a significant peak in the power spectrum) were studied to determine how tremor activity in GPi and EMG evolves over time. The tremor-on-off index, which provides information on the onset and offset of significant tremor oscillations, was used for this purpose. A basic observation is that an episode of tremor-related activity (as well as muscle tremor) characterized by a significant peak in the power spectrum, consists of several tremor-on subepisodes interleaved with tremor-off lapses (Fig. 5, A and B).

For GPi/EMG pairs that are coherent, overall, one would expect that tremor-on and tremor-off episodes in the two channels are coincident in time. To test this idea, we computed a correlation coefficient between the tremor-on-off indices for GPi and EMG pairs (see METHODS). The results of this analysis are presented in the right column of Table 2. Surprisingly, some pairs that have significant coherence show no significant correlation in the timing of on- and off-tremor intervals. Even in cases where the correlation is significant, there are intervals where one but not the other channel is in a state of tremor oscillation. An example of this is shown in Fig. 5. In this session, both single unit and EMG have significant tremor over the period recorded and are coherent overall (Fig. 5A). The intervals of tremor are shown in the plot in Fig. 5B. In this case, the presence of tremor is significantly correlated ($P < 0.05$) between channels, yet periods of nonoverlapping tremor activity are present (Fig. 5B, episode 1) and alternate with periods of concurrent tremor activity (Fig. 5B, episode 2). Further details of each episode are shown in Fig. 5D. Note that in both episodes 1 and 2, there is prominent oscillatory activity in the GPi single unit, yet limb tremor is only present in episode 2. A high-frequency resolution power spectrum, estimated using the multitaper method (Mitra and Pesaran 1999; Percival and Walden 1993), shows a large drop in EMG tremor power in 1 compared with 2, with relatively unchanged power between the two episodes in GPi (Fig. 5E). This example shows the situation in a coherent GPi/muscle pair where tremor-related activity persists in GPi as tremor disappears and reappears in the EMG, although the converse situation, where tremor activity persists in the EMG but is intermittent in GPi, was also common.

How is it possible for an intermittent oscillatory pair, where there is only partial overlap in subepisodes of tremor activity, to have statistically significant overall coherence? Inspection of the phase lag histogram for the entire time period (Fig. 5C; see METHODS) indicates that there is significant clustering of the phase delay at $\sim 90^\circ$; whenever there is concurrent tremor activity, the phase difference returns to a near constant angle.
When analyzed over the entire period, this behavior gives rise to high coherence. We also performed the SNR correlation analysis for muscle/muscle pairs. Of 17 muscle pairs that were coherent at the tremor frequency, the occurrence of tremor was significantly correlated in 7 (41%) and was not in 10 (59%). This analysis of muscle/muscle pairs reveals similar independent tremor-on behavior that was found for the GPi/muscle pairs, even for muscle pairs within the same limb or limb segment.

**Phase-locking can be transient in both coherent and noncoherent GPi-muscle pairs**

The phase reconstruction outlined in **Methods** allows us to track the evolution of phase locking between oscillatory neuronal and muscle activity over time. Since phase reconstruction is meaningful only when oscillatory activity is present, this analysis was restricted to intervals where both channels were in the tremor-on state. In Fig. 6, we show the time dependence of phase coherence for two channels of the same recording session as presented in Fig. 4. Several features are revealed in these plots. First, although GPi and EMG signals are clearly oscillatory for most of the recording time, statistically significant phase locking is episodic and occupies only a fraction of the time that the two signals are concurrently oscillatory. Figure 6A shows the time evolution of phase coherence for a GPi/gastrocnemius pair with overall coherence. There are two periods of concurrent oscillatory activity (a, b); in both of them, significant phase locking is achieved for only a fraction of the time. In period a, significant phase locking begins about 4 s after the onset of concurrent oscillatory activity and ends when tremor stops in the leg muscle. In period b, phase locking also begins after the onset of concurrent tremor. Figure 6B shows the time evolution of phase coherence for a noncoherent pair of the same recording of GPi as Fig. 6A but with respect to an arm muscle (wrist extensor). This pair is statistically noncoherent overall even though tremor activity in the unit and the muscle is concurrent throughout the epoch. Despite being noncoherent, we do, in fact, find episodes of significant transient phase locking, but these episodes are of shorter duration than in the coherent pair. In summary, transient coherence is common in both pairs that are coherent overall and noncoherent pairs. In the analysis of all pairs (see Table 2, transient coherence column), we found that 20 of 22 pairs that had tremor in both channels showed at least one transient coherent episode of significant duration (see **Methods** for significance criterion) and 3 of the 5 noncoherent pairs showed significant transient episodes.

**Tremor oscillations in GPi and EMG are punctuated by shifts in phase**

Close examination of the time course of oscillatory activity reveals the presence of phase slips; these events are characterized by a sudden shift in phase, usually coincident with a decrease in oscillation amplitude lasting less than one tremor...
temporal resolution in Fig. 8). Examination of the temporal evolution of coherence in Fig. 6A shows that there is a high incidence of synchronizing phase slips in this coherent pair. In contrast, most of the phase slips in GPi in the noncoherent pair in Fig. 6B occur at points in time where there is no phase locking and therefore have no effect in the already random phase delay. During the periods of transient phase locking, we see one synchronizing and one desynchronizing phase slip.

Figure 9A summarizes the effects of phase slips in GPi for coherent and noncoherent GPi/muscle pairs. The fraction of synchronizing phase slips occurring during intervals of phase locking is significantly higher in coherent pairs than in noncoherent pairs. Phase slips in the muscle EMG can also be classified as synchronizing and desynchronizing with respect to the GPi oscillation. As is the case with GPi phase slips, EMG slips are more frequently synchronizing in coherent pairs (Fig. 9B). Note that synchronizing GPi slips are more frequent than nonsynchronizing slips only in the case of coherent pairs, whereas for noncoherent pairs, there is a nonsignificant difference between the three types. Since the slips in the upper 25th percentile of the distribution of the coherence values for random phase advances are classified as synchronizing, it is expected that, on average, one of four slips would be classified as such. Thus the overlap in the distribution in the noncoherent case would be expected if slips occur at random. However, in the case of coherent pairs, the higher incidence of synchronizing slips indicates that these slips are part of a mechanism for synchronization.

**Discussion**

**GPi/EMG tremor coherence is consistent with parallel circuits that are limb specific**

In this study, we combined classical spectral analysis with a statistical time-dependent method to scrutinize the dynamics of parkinsonian tremor, one of the landmark symptoms of basal ganglia pathophysiology in PD. Our data base included only 9 single units and 27 single unit/EMG pairs. This data base, however, enabled us to examine >20 min of paired GPi/EMG data with oscillatory activity in both channels, the equivalent of about 5,000 tremor cycles. Nonetheless, this data base is limited in size, due to the constraints inherent in human neurosurgery, and our conclusions are therefore preliminary. Multiunit data were not included in this study because it would preclude an unambiguous interpretation of phase correlations; for example, the mix of two or more same-frequency oscillatory single units that are out of phase could appear as a higher frequency phenomenon.

Standard coherence analysis here confirms the idea that tremor-related activity in a GPi site is correlated to a restricted portion of the limb musculature undergoing tremor (Hurtado et al. 1999). In that study, the hypothesis of independent oscillators was supported by recordings with dual electrodes in the GPi and simultaneous EMGs in PD patients with tremor. It was reported that spatially separated cells (≥3 mm) undergoing tremor-related oscillations at identical modal frequencies could be independent (i.e., show no significant coherence). An additional piece of evidence comes from studies of muscle tremor showing that during parkinsonian tremor the limb musculature is assembled in distinct groups of phase-locked muscles, each
spanning an individual limb or limb segment, and that different limbs oscillate independently of each other (Hurtado et al. 2000; O’Suilleabhain and Matsumoto 1998; Raethjen et al. 2000). This supports the idea first advanced by Alberts et al. (1969) that parkinsonian tremor is generated by segregated parallel networks, each involving a different limb. Here we have complemented this picture by establishing that GPi cells synchronize in a preferential manner (i.e., are coherent overall) to tremor in a restricted portion of the peripheral musculature. The idea of independent circuits has been strengthened in this study by a simultaneous recording of upper and lower limb tremor EMG and GPi tremor-related activity, with the latter showing coherence to one limb but no significant coherence to the other. The standard analysis used here is based on a classification of pairs into coherent and noncoherent groups by taking a statistical cut-off level. It could be argued that the interpretation given here is a result of artificially splitting the data based on this arbitrary cut-off value. However, the pooled coherence histogram across all patients (see Fig. 3) confirms that the subdivision between coherent and noncoherent pairs is not a statistical artifact, since the noncoherent group appears as a distinct mode in the histogram.

![Phase slips in GPi and EMG during ongoing oscillatory activity.](image)

**TABLE 3. Rates of phase slips in oscillations in pallidal units and EMGs**

<table>
<thead>
<tr>
<th>Patient Key</th>
<th>Muscle</th>
<th>Slips per Minute</th>
<th>Significant Modal Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See Table 2 for abbreviations.
Although close inspection of the histogram obtained suggests that the coherent population contains secondary peaks (Fig. 3), we did not attempt to segment them further, because the relatively small amount of data in our study precluded further subdivision.

These findings are consistent with anatomical and functional studies showing a rough topographic representation in the motor portion of different structures of the BG thalamocortical pathways (Crutcher and DeLong 1984; DeLong et al. 1985; Kaneda et al. 2002; Lenz et al. 1988). A consequence of this topographic organization is that a GPi cell is phase-correlated to a restricted region of the limb musculature, whereas tremor in other regions is generated independently by pathways that include other GPi sensorimotor fields.

When examined in temporal detail, we found that tremor activity in single units and in individual EMGs occurs intermittently. Furthermore, when analyzing the coincidence of tremor between GPi/EMG pairs, we found only partial overlap in tremor-on periods, even in cases where the GPi/EMG pair is coherent overall. Phase locking can obviously only occur during periods of overlapping tremor activity, yet we found phase locking may not be continuous for the full duration of overlap; episodes of tremor synchronization are themselves intermittent. This transient phase locking occurs in both coherent and noncoherent pairs. There are, however, important differences between phase locking in each case. Statistically noncoherent pairs phase lock only occasionally, even when there is substantial tremor-on overlap and the phase difference is highly variable from one phase locking episode to the next. In contrast, coherent pairs show longer, more frequent phase locking episodes, and the phase difference returns to a preferred value across episodes.

Apart from their differences in temporal resolution, the two methods of analysis differ in that the standard coherence measure takes into account interactions both in phase and in amplitude, whereas for the time-dependent analysis, we considered the correlations in phase only. The analysis of phase correlations is more appropriate for detecting synchronization in oscillatory pairs because it is sensitive to co-variations in the relative timing of the oscillations while neglecting amplitude fluctuations (Schafer et al. 1999); uncorrelated amplitude fluctuations can mask the presence of phase correlations. The pre-eminence of phase correlations in oscillatory systems is supported by a number of recent modeling studies in the field of nonlinear dynamics showing that, as the strength of coupling between different oscillators is increased, phase entrainment precedes the appearance of amplitude covariations (reviewed in Boccaletti et al. 2002; Pikovsky et al. 2001). These observations suggest that, in weakly coupled neural oscillators,
phase entrainment might be present even as the amplitudes are uncorrelated. A correlation index sensitive to both phase and amplitude such as the coherence spectrum can therefore miss the type of events where correlations exist in the timing alone, with amplitudes varying independently.

The time-dependent analysis showing that noncoherent pairs can undergo phase locking for short periods does not contradict the idea of segregated circuits, but it suggests that interaction between circuits is possible. The reason these short periods of phase locking do not contribute significantly to increase the coherence value over longer times is that the phase-lag angle varies widely from one period to the next; this results in mutual cancellation of phase angles over long periods, giving rise to low overall coherence. Importantly, pairs that appear as coherent overall in the standard measure also show episodic phase locking interleaved with periods of independent oscillatory activity.

We conjecture that interactions giving rise to transient phase locking in noncoherent pairs are of a different nature than in coherent ones. The fact that, in the latter case, the pallido-muscular phase delay returns to a similar value across locking subepisodes suggests that their locking arise from more robust interactions than in the former case. One possibility is that the fixed phase delay results from conduction delays within a limb-specific BG-thalamocortical network. In contrast, the variable delays seen in noncoherent pairs may result from weaker collateral interactions between parallel circuits.

Interactions within a parallel network

The analysis of coherence discussed above suggests the presence of parallel pathways in the BG-thalamocortical network. On the other hand, the analysis of tremor-on and -off states over time (Fig. 5) provides insights into the network within one of these parallel pathways. We observed that during an episode of tremor, a GPi tremor cell and an EMG coherent with it could be recruited into and out of tremor activity independently of each other; it was often the case that one and not the other was in a tremor on state, even though the standard coherence measure indicated that they were functionally linked overall. The same type of nonoverlap was seen when analyzing different muscles of a limb, where coherent behavior was also commonplace.

A possible interpretation of these observations is that a particular region in GPi (belonging to one of the parallel and interconnected limb BG subcircuits) is always associated with a particular territory of the limb musculature, but neither all the muscles of the affected limb nor all GPi units in the corresponding functional region are concurrently in a tremor state. Specific units or muscles in this functional subcircuit may be recruited into and out of the tremor-on state, and this recruitment process occurs more or less independently between one element of the network and its neighbors. In this picture, the tremor-on state would always be present somewhere in a set of functionally related muscles and somewhere in the pallidal limb representation. Tremor, in this case, would be a property of the population of cells at each stage of the parallel pathway, but not of the individual cells, which can be either in the tremor-on or -off state at any one time. However, since we recorded from a limited number of sites in the network, it could be argued that other cells in the vicinity of the recorded GPi cell could be closely correlated (in their tremor-on timing) to a particular EMG. The apparent lack of correlation would then be a consequence of our sampling. The problem with this interpretation is that it invokes a rather precise topography within GPi, with particular cells functionally linked to particular muscles. This is at odds with mapping studies of GPi, where individual cells respond to active or passive movements of one or more joints, suggesting a rough topography (DeLong et al. 1985). In PD, the topography is even less precise, because it has been shown in MPTP studies that a larger number of cells respond to multijoint movements (Filion et al. 1988). It is unlikely that firing in individual GPi cells map to activity of individual muscles in a precise manner.

This picture poses an apparent contradiction: a pair (GPi/muscle, GPi/GPi, muscle/muscle) can be coherent overall, yet there is little relationship between the times where each individual muscle or GPi cell enters and leaves the oscillatory state. This incongruity between the two results is resolved when one considers the properties of the phase locking process over time. Overall coherence is possible because the phases lock to a particular value during the periods of overlap and the phase value varies little across locking episodes. This finding provides a new view of the properties of the tremor network, one where tremor appears as a dynamical regime at a network level and individual components of the network participate intermittently even though the network as a whole may be oscillatory over long periods of time.

Synchronization through phase slips

When inspecting the dynamics of tremor-on periods, we found that tremor oscillations, both in pallidum and EMGs, are punctuated by phase slips (or “jumps” in phase). Similar phenomena have been described in several neural systems, in particular, in the hippocampus, where place cells advance their phase relative to the ongoing theta rhythm as animals move through the cell’s place field (O’Keefe and Recce 1993; but see Harris et al. 2002). These events can be important for the formation and the breakdown of neuronal ensembles. Consider, for example, a population of phase-locked oscillatory cells, sharing a preferred frequency. Every cell in the ensemble has a particular phase delay relative to any other and synchrony is preserved as long as the relative phase delays between the component cells is preserved. A random slip in phase in a cell would create a different pattern of phase locking, and a series of random jumps would destroy the synchrony between that cell and the rest of the population. On the other hand, phase slips could contribute to synchronization if they preserve the phase lag between two cells with slightly different oscillatory frequencies.

We computed changes in phase coherence caused by the occurrence of phase slips and classified them as synchronizing slips, desynchronizing slips, or those without significant effect. We found that synchronizing slips are substantially more common than nonsynchronizing slips in pairs that are coherent overall; phase slips are part of a mechanism of synchronization. In contrast, desynchronizing phase slips are as likely to occur as incoherent pairs. We can speculate from this that desynchronizing slips arise from either intrinsic noise of the cells or from an input pathway that is external to...
the tremor generating network. The precise cellular and network mechanisms that give rise to slips is an area for further research in in vitro preparations as well as for multiple recording studies in intact preparations.

Conclusions

The results of this study provide a richer description of the parkinsonian tremor-generating network, beyond that of previous anatomical and physiological studies. While previous evidence provide support for a shift to an oscillatory state in PD, at least in cases with tremor, and a concomitant increase in synchrony across the basal ganglia thalamocortical network, the view has been that tremor-related activity within limb-specific areas are tightly correlated and that between limb-specific areas there is no correlation. The time-dependent measure used in this study provides a different picture, one in which, during tremor episodes, limb specific regions of GPi are oscillatory overall, but the oscillation in the individual tremor-related units within that region is more sporadic. The same is true for muscular tremor. Furthermore, the synchrony between an oscillatory unit in a particular field and a particular tremulous muscle within that field is transitory. What then gives rise to the high level of synchrony, as measured by overall coherence, is that whenever there is an oscillation in both the unit and the muscle of the same limb, the phase difference between the two locks to some constant value. Furthermore, the correlation between individual units (as described by Hurtado et al. 1999) or between individual units and specific muscles are constantly being formed and broken. When one looks across limb-specific regions, the oscillatory behavior has the same intermittent nature; phase locking does form sporadically. The lack of correlation between fields (i.e., limbs) occurs because the phase difference between the unit and the muscle is not constant from one subepisode of locking to the next and therefore is only revealed by time-dependent measures of coherence. One interesting question that arises from this new picture is whether this type of behavior arises in other structures within the tremor-generating network (e.g., STN, primary motor cortex).

Acknowledgments

Present address of L. Rubchinsky: Dept. of Mathematical Sciences, IUPUI and Stark Neurosciences Research Inst., Indiana University School of Medicine, 402 N. Blackford St., Indianapolis, IN 46202–3216.

Grants

This work was supported by National Institute of Neurological Disorders and Stroke Grant NS-39121.

References


