Activity of Pallidal and Striatal Tonically Active Neurons Is Correlated in MPTP-Treated Monkeys But Not in Normal Monkeys

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The goal of this study is to assess the function of tonically active neurons (TANs) of the striatum and their malfunction in the parkinsonian state. We recorded multiple spike trains of striatal TANs and pallidal neurons, which are the main target of striatal projections. Recordings were performed in two vervet monkeys before and after the induction of tremulous parkinsonism by systemic injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP). We then calculated cross-correlograms between TANs and pallidal neurons to evaluate the interactions between them.

In the normal monkeys, only 1.3% (2/152) of the cross-correlograms displayed significant peaks, and 8.6% (13/152) displayed significant oscillations. After MPTP treatment, 42.8% (83/194) of the cross-correlograms displayed significant peaks or troughs, or both, and 58.8% (114/194) displayed significant 3–19 Hz periodic oscillations. The frequency content of the coherent oscillations matched the frequency content of the activity of individual TANs, but was only weakly related to that of individual pallidal cells.

These results confirm the notion that in the normal state neurons in the basal ganglia tend to fire independently, whereas in the parkinsonian state they exhibit synchronized oscillatory activity. The low level of correlated activity in the normal state demonstrates that TANs have only a slight effect on pallidal activity during execution of familiar behavior. The high level of oscillatory correlated activity in the parkinsonian state further suggests that coherent oscillations of the whole basal ganglia circuitry underlie the clinical features of Parkinson's disease.

Key words: cross-correlations; neuronal oscillations; Parkinson's disease; striatum; TAN; globus pallidus

The striatal neurons are classified according to their spiking activity as phasically active neurons and tonically active neurons (TANs) (Crutcher and DeLong, 1984; Kimura et al., 1984). After behavioral conditioning, TANs respond to salient events (Graybiel et al., 1994; Ravel et al., 1999), suggesting that they play a role in learning (Graybiel et al., 1994). Several studies (Wilson et al., 1990; Aosaki et al., 1995; Kawaguchi et al., 1995) indicate that TANs are the cholinergic interneurons of the striatum. Although these cells constitute only 1–5% of the total population of striatal neurons (Kawaguchi et al., 1995), they give rise to extensive and dense local axonal arbors, permeating the striatum with cholinergic markers (Mesulam et al., 1992; Yelnik et al., 1993). Acetylcholine modulates calcium (Howe and Surmeier, 1995) and potassium currents (Gabel and Nisenbaum, 1999) in striatal projection neurons via muscarinic receptors. Finally, acetylcholine can modulate the efficacy of corticostriatal connections (Calabresi et al., 2000) affecting the information passing through the striatal projection neurons.

Parkinson's disease is mainly characterized by a decrease in striatal dopamine content (Hornykiewicz and Kish, 1987). Yet there are many indications that the cholinergic system also plays a role in the pathophysiology of the disease. The striatal dopaminergic and cholinergic systems interact with each other (Kitai and Surmeier, 1992; Di Chiara et al., 1994). The excitability of cholinergic interneurons has been shown to be modulated by dopamine receptor activation: D1-like receptor activation is excitatory (Aosaki et al., 1998), whereas D2-like receptor activation is inhibitory (Yan et al., 1997; Pisani et al., 2000). Application of D2-class dopaminergic antagonists caused a decrease in the responses of TANs to external stimuli but did not influence the tonic activity of these neurons both *in vivo* and *in vitro* (Watanabe and Kimura, 1998; Bennett and Wilson, 1999). Cholinergic antagonists are effective agents for treatment of neurological parkinsonian deficits (Jankovic and Marsden, 1988). Furthermore, loss of dopaminegric innervation leads to a decrease of the stereotypical reward-related response of the TANs (Aosaki et al., 1994; Raz et al., 1996).

In this study we investigated how TANs interact with other cells and structures of the basal ganglia in normal state and after MPTP-induced parkinsonism. To do that, we used simultaneous recordings of neuronal activity in the striatum and in the main target of striatal projections, the globus pallidus.

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MATERIALS AND METHODS

Two vervet monkeys (monkeys H and I: *Cercopithecus aethiops aethiops*, female, weight 3–3.5 kg) were trained to perform a visuomotor task. After training, a stainless steel recording chamber was attached to their skulls to allow recording of the simultaneous activity of TANs and pallidal neurons. Details of the task, surgery, data recording methods, MPTP treatment, and histology are given elsewhere (Raz et al., 1996). The monkeys' care and surgical procedures were in accordance with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals* (1996), and with the Hebrew University guidelines for the use and care of laboratory animals in research, supervised by the institutional animal care and use committee.

We used histological and electrophysiological criteria to define the cells as TANs (Raz et al., 1996) or as cells from the external or internal segments of the globus pallidus (GPe and GPi, respectively) (DeLong, 1972). Only correlograms with >500 spikes of the TAN and 1000 spikes of the pallidal cell, recorded simultaneously for >200 sec, were included in the study. The correlograms were calculated for ±500 msec offset, using 1 msec bins. In all the cross-correlograms TANs were used as the trigger unit. Namely, each correlogram illustrates the firing probability of the pallidal cell as a function of the time that elapsed from the firing of the TAN. We tested the null hypothesis of independent activity (i.e., flat cross-correlogram) by searching for significant peaks, troughs, or periodic oscillations in the cross-correlogram. A cross-correlogram was considered to have a significant peak/trough if there were more than three consecutive bins with a value higher/lower than the baseline firing rate of the pallidal cell by ±2.5 SDs. The power spectra of the cross-correlograms were calculated after subtracting the baseline firing rate (reducing the DC offset). We searched the power spectra for significant peaks between 3 and 19 Hz. To assess the statistical significance of each peak, we calculated two parameters: (1) the signal-to-noise ratio (SNR), which was defined as the difference between the peak power and the mean power between 3 and 30 Hz, divided by the SD of the entire power spectrum (0–500 Hz); and (2) the oscillation index (OI), defined as the area under the peak, divided by the total power in the spectrum. A peak was considered significant if the SNR was >5 SD or if it had an OI of >5%.

We estimated the phase shift of the oscillatory cross-correlograms at the peak frequency using the phase of their Fourier transform. For pairs with more than one significant peak, we measured the power, frequency, and phase of all significant peaks and considered the pair as oscillatory in all those frequencies. For all oscillatory pairs we also calculated the autocorrelograms of each cell and searched them for oscillations. Results of the single unit data and cross-correlograms within the nuclei appear elsewhere (Raz et al., 1996, 2000). Data of well isolated single neurons, as well as mixtures of two to three neurons that were recorded from a single electrode, were not significantly different and are presented together.

To estimate the effect of the single neuron oscillations on the cross-correlograms, we performed a linear regression analysis of the dominant oscillation frequencies (i.e., the frequency of the peak with highest power in the power spectrum) for pairs with significant oscillations in their cross-correlograms and in both autocorrelograms. We also calculated the correlation coefficients of the power spectra (between 1 and 30 Hz) of oscillatory cross-correlograms and the autocorrelograms of the cells composing them.

RESULTS

We recorded the activity of 152 pairs of a putaminal TAN and a pallidal neuron in 17 recording sessions in the normal state (8 and 9 d with monkeys H and I, respectively). Of these pairs, 132 were TAN-GPe and 20 were TAN-GPi. After MPTP treatment we recorded the activity of 194 pairs during 11 post-MPTP recording sessions (4 and 7 d with monkeys H and I, respectively). Of these, 172 were TAN-GPe and 22 were TAN-GPi.

Treatment with MPTP induced severe parkinsonian symptoms in both monkeys. A detailed description of the clinical phenomena induced by MPTP treatment is given elsewhere (Raz et al., 2000). Briefly, both monkeys displayed akinesia, flexed posture, rigidity, and tremor after MPTP treatment. They could not feed themselves and required feeding with a liquid diet (Ensure Plus, Abbott Laboratories). Qualitative examination of the tyrosine hydroxylase immunohistochemistry slides clearly revealed severe loss of dopaminergic cells in the midbrain of both monkeys, matching the severity of the induced parkinsonism (Elsworth et al., 2000).

In the normal state only a small fraction of the cross-correlograms (2/152; 1.3%) displayed significant peaks. Typical cross-correlograms in this state are depicted in Figure 1, *A* and *B*. After MPTP treatment the correlated activity was much more pronounced, and 42.8% (83/194) of the pairs displayed significant peaks or troughs. Figure 1, *C* and *D*, illustrates the cross-correlograms for pairs of cells that were recorded after MPTP treatment. Although detection of significant peaks and troughs was performed independently of oscillation detection, almost all (83/85; 97.6%) cross-correlograms with significant peaks or troughs displayed significant periodic oscillations, indicating that the peaks and troughs in the cross-correlograms result from the oscillations.

The number and percentage of cross-correlograms with significant 3–19 Hz periodic oscillations are given in Table 1. A small fraction (8.6%) of the cross-correlograms in the normal state was oscillatory. This fraction increased dramatically (to 58.8%) after MPTP treatment. In 20.6% (22/107) of the oscillatory TAN-GPe pairs we found a significant second oscillation frequency. No second oscillation frequency was detected in TAN-GPi pairs.

After MPTP treatment the oscillation frequencies were clustered ~10 and 15 Hz (Fig. 2*A*,*B*). Phase shifts of oscillatory correlations between TAN-GPe pairs were widely distributed, with a tendency toward positive phase shifts (Fig. 2*C*). Phase shifts of oscillatory correlations between TAN-GPi pairs were centered at zero (Fig. 2*D*).

Forty-eight pairs, all TAN and GPe, that were recorded after MPTP treatment exhibited significant oscillations in their cross-correlograms and in both their autocorrelograms. Linear regression for the oscillations frequencies of the cross-correlograms and the autocorrelograms indicated a significant correlation between the two ($R^2 = 0.37$; $p < 0.001$). Figure 3, *A* and *B*, demonstrates this result for these pairs, showing that the cross-correlogram frequency is closely related to that of the TAN, and less so to that of the GPe cell.

Figure 3, C and D, shows the distribution of correlation coefficients between the power spectra of the oscillatory cross-correlograms and autocorrelograms of the TANs and pallidal cells composing them. Note also Figure 1, *C* and *D*, which shows the similarity of the spectra of individual cells. Most oscillatory cross-correlograms had a power spectrum that was closely related to the power spectrum of the TAN (82/114; 71.9% had correlation coefficient >0.36; $p < 0.05$), but only a few were related to the power spectrum of the pallidal cell (31/114; 27.2% had a correlation coefficient >0.36; $p < 0.05$). This was even more pronounced for pairs with oscillations in both cross-correlograms and autocorrelograms, where most (46/48; 95.8%) were related to the TAN oscillations and only 33.3% (16/48) were related to the pallidal cell. This analysis could not be performed for the normal state because of the very small number of oscillatory cross-correlograms in this state.

DISCUSSION

We report here the results of a cross-correlation study of pairs of TANs and pallidal neurons. In normal monkeys very little correlated activity was observed between the TANs and pallidal cells. However, after MPTP treatment and the development of tremulous parkinsonism, significant coherent oscillations emerged between the TANs and pallidal cells, indicating a major change in the striatal–pallidal network activity.

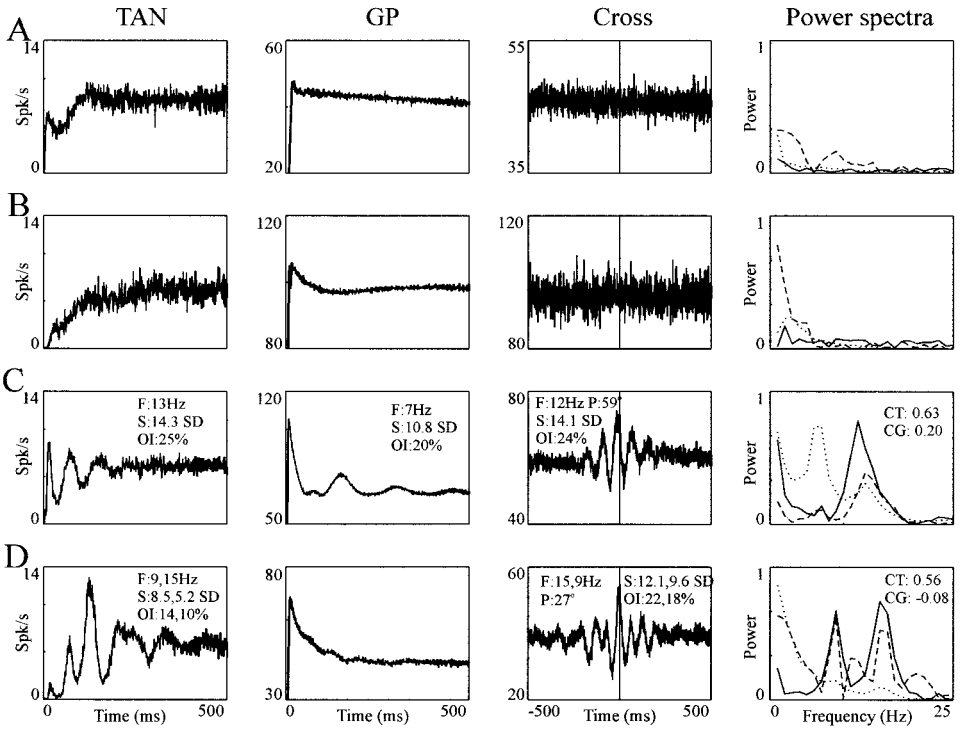

Figure 1. Examples of cross-correlograms with the autocorrelograms of the respective cells and their power spectra. The *first column* is the autocorrelogram of the TAN, the *second column* is the autocorrelogram of the pallidal cell, the *third column* is the cross-correlogram, and the *fourth column* is the power spectra of all three. All correlograms were calculated with a bin size of 1 msec, and no smoothing was performed. The *y*-axis displays the conditional firing rate. Power spectra of cross-correlograms are represented by *solid lines*, with *y*-scale of 1–1500. Power spectra of TAN are shown by *dashed lines*, with *y*-scale of 1–1000. Power spectra of GP cells are shown by *dotted lines*, with *y*-scale of 1–3000. *A*, *B*, Normal monkey. *C*, *D*, MPTP-treated monkey. *A*, *C*, and *D* are of TAN-GPe pairs; *B* is of a TAN-GPi pair. Details for correlograms with significant oscillations are given on the graph: *F*, frequency in Hz; *P*, phase shift in degrees; *S*, signal-to-noise ratio; *OI*, oscillation index; *CT*, correlation coefficient of the power spectrum of the cross-correlogram and TAN autocorrelogram; *CG*, correlation coefficient of the power spectrum of the cross-correlogram and pallidal cell autocorrelogram.

Table 1. Percentage and number of cross-correlograms with significant oscillations

	State	TAN-GPe	TAN-GPi	TAN-GPe/i
H	Normal	8.5% (5/59)		8.5% (5/59)
	MPTP	63.5%** (33/52)	41.7% (5/12)	59.4%** (38/64)
I	Normal	9.6% (7/73)	5% (1/20)	8.6% (8/93)
	MPTP	61.7%** (74/120)	20% (2/10)	58.5%** (76/130)
Total	Normal	9.1% (12/132)	5% (1/20)	8.6% (13/152)
	MPTP	62.2%** (107/172)	31.8%* (7/22)	58.8%** (114/194)

Significant oscillations are defined as SNR >5 SD or OI >5%.

*Significant difference from the homologous group in the normal state at $p < 0.05$, χ^2 test.

**Significant difference from the homologous group in the normal state at $p < 0.01$, χ^2 test.

Several previous studies support the prediction that TANs and pallidal cells are correlated: GPe and GPi are the major targets of striatal output (Gerfen and Wilson, 1996). The cholinergic interneurons have dense local axonal arbors, which connect them to many striatal projection neurons (Mesulam et al., 1992; Yelnik et al., 1993). The activity of the TANs themselves is highly correlated (Raz et al., 1996), and there is strong convergence of striatal projections to the globus pallidus (Percheron et al., 1994; Kimura et al., 1996). However, this prediction was not met in the normal monkeys, where very little correlated activity between TANs and pallidal cells could be observed. This result therefore fails to support the hypothesis that TANs are a part of a corticostriatal–pallidal axis with very strong functional connections between the different nuclei. The lack of TAN–pallidal correlation may be a result of the weak effective connectivity between single cells in the normal brain that cannot be detected by the cross-correlation method (Nambu et al., 2000). An alternative explanation assigns TANs with mainly a modulatory effect on the corticostriatal synapses. In such a case, we would predict dynamic modification of corticostriatal correlations that do not necessarily affect the level of correlations of TANs with pallidal cells.

Acetylcholine is an important neuromodulator in the striatal network. Muscarinic receptors (both M1 and M2) are abundant on striatal projection neurons (Hersch and Levey, 1995). Acetylcholine may affect information processing in this structure in numerous ways. Acetylcholine affects the excitability of striatal projection neurons (Gabel and Nisenbaum, 1999). It modulates calcium (Howe and Surmeier, 1995) and potassium (Gabel and Nisenbaum, 1999) currents in these neurons, and it changes the synaptic efficacy of corticostriatal projections (Calabresi et al., 2000). Previous studies reported a typical response of TANs to cues predicting salient events and suggested that they play a major role in learning (Graybiel et al., 1994; Ravel et al., 1999). Thus, it is also possible that the level of correlated activity of TANs and pallidal cells is dynamically modulated during the learning process and remains low after its completion. This notion is supported by previous studies that demonstrate changes in the activity of TANs (Graybiel et al., 1994; Apicella et al., 1996) and striatal projection neurons (Kawagoe et al., 1998; Jog et al., 1999) throughout learning. However, a further study is required to examine this hypothesis.

The long episodes of low-frequency tremor detected after

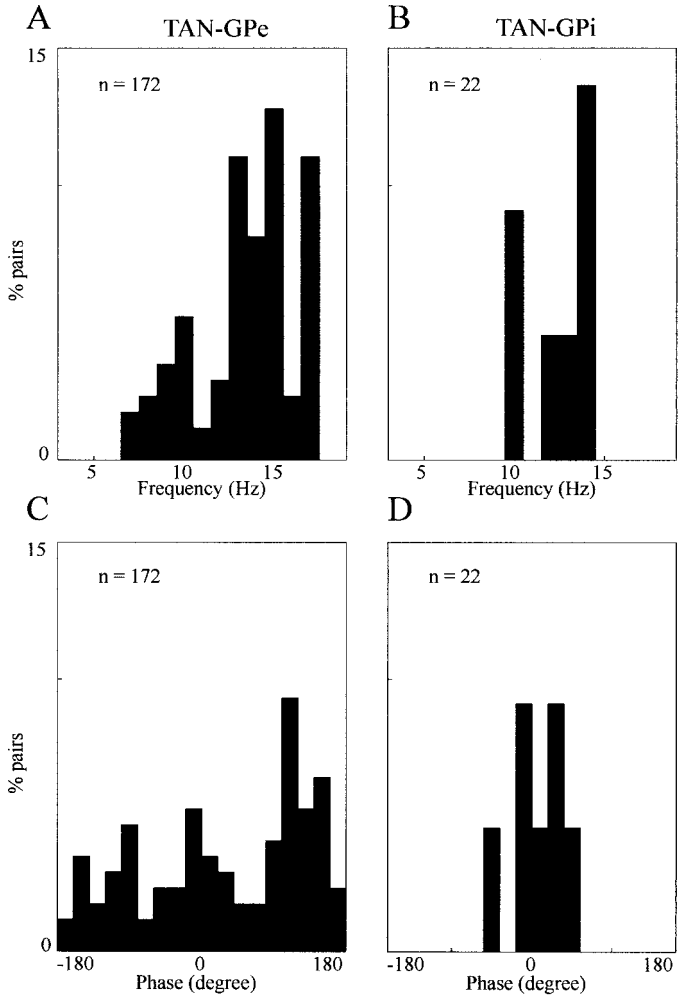

Figure 2. Distribution of the frequencies and phase shifts for oscillatory cross-correlograms in the MPTP-treated state. The *y*-axis shows the percentage of oscillatory correlograms of all correlograms recorded. *A*, *B*, Frequencies in hertz. *C*, *D*, Phase shifts in degrees. *A*, *C*, Pairs of TAN and GPe cells; *B*, *D*, pairs of TAN and GPi cells.

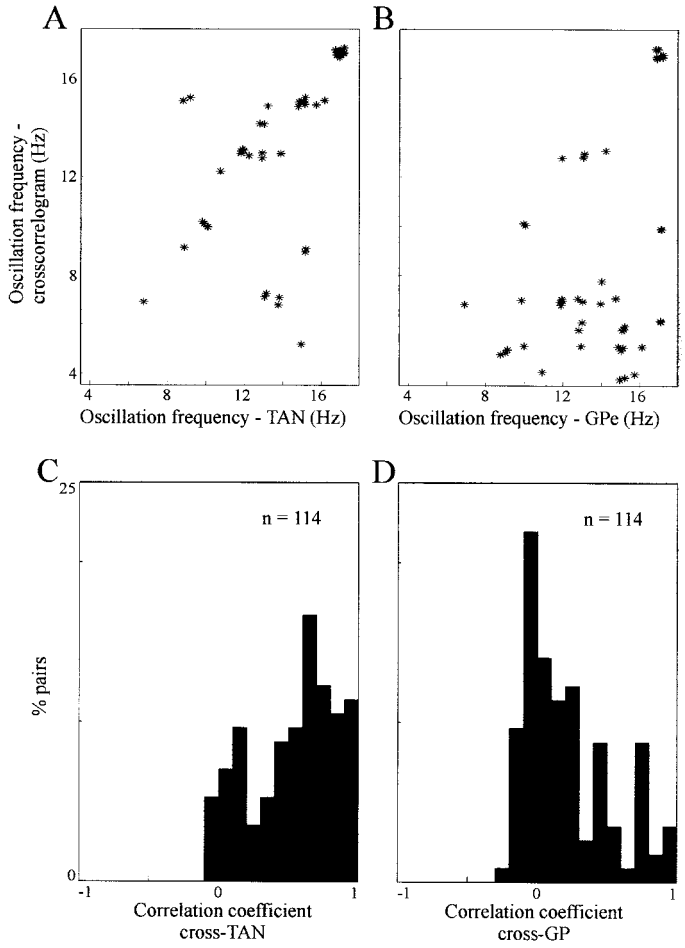

Figure 3. Dependence of oscillatory cross-correlograms on the autocorrelograms of the respective oscillatory cells. *A*, *B*, Dependence of the cross-correlogram frequency on the oscillation frequency of the TAN and GPe cell, respectively. The *x*-axis displays the frequency of the oscillatory cell, and the *y*-axis displays the frequency of the cross-correlogram. We jittered the data points horizontally and vertically by a random value of ±0–0.25 Hz to enable the reader to visualize the number of pairs in each point. *C*, *D*, Distribution of the correlation coefficients of the power spectra of oscillatory cross-correlograms and the power spectra of the respective autocorrelograms of TAN and pallidal cell pairs.

MPTP treatment are unique to the MPTP vervet model of parkinsonism, as compared with other animal models of this disease [e.g. MPTP treatment of other primate species (Tetrud and Langston, 1995) and 6-OHDA treatment of rodents (Gerlach and Riederer, 1996) and primates (Jenner et al., 1987; Apicella et al., 1990)]. The activity of TANs is affected by dopamine (Watanabe and Kimura, 1998). In the parkinsonian state, the typical response of TANs to reward predicting events disappears (Aosaki et al., 1994), but they remain synchronized (Raz et al., 1996). Furthermore, after MPTP treatment, both TANs (Raz et al., 1996) and pallidal cells (Filion and Tremblay, 1991; Bergman et al., 1994; Raz et al., 2000) show oscillations in a frequency range that overlaps the range of the tremor frequencies. In this study we found that cross-correlograms of TANs and pallidal cells also become oscillatory. The severity of the parkinsonism induced in monkey H was greater than that of monkey I, but unlike the coherent oscillations of pallidal cells (Raz et al., 2000), there was no significant difference in the internuclei correlated activity between the two monkeys (Table 1).

In most cases, pairs with oscillatory cross-correlograms were composed of cells with oscillatory autocorrelograms. The dominant frequency and the power spectrum of cross-correlograms were closely related to the dominant frequency and the power spectrum of the TAN in the pair but not to the pallidal cell. Synchronized oscillations could stem from recording two independent oscillatory processes over a finite time. However, it is unlikely that this is the case for many of the synchronized oscillations that we encountered in this study. First, in some cases the autocorrelograms of the two cells composing a synchronized pair were not oscillatory, and the correlation between the power spectra of the cross-correlogram and autocorrelograms was low. Second, the phase distribution was also different from the flat distribution expected for two independent processes. The phase-shift distribution of pairs with GPe cells was different from that of pairs with GPi cells, suggesting that GPe is more than a relay station between the striatum and GPi (Chesselet and Delfs, 1996).

The fact that the synchronized activity is closer to the oscillatory activity of the TANs than to that of pallidal cells may be a result of the different oscillation patterns of the two groups. TANs oscillations are usually the result of rhythmic single spiking (Raz et al., 1996), whereas pallidal oscillations are the result of rhythmic bursting (Raz et al., 2000). Because the frequencies of oscil-

lations attributable to rhythmic bursts were reported to have stronger expression in the correlogram patterns than single spike oscillations (Mehta and Bergman, 1995), we expected to find the opposite result: namely that the GP oscillations should dominate the cross-correlograms. The unexpected result implies that the modulatory effect of TANs dictates the nature of coherent activity of TANs and pallidal cells. Further studies of the correlated activity of TANs and pallidal neurons under pharmacological intervention will help prove this hypothesis. Anti-muscarinic agents would be an interesting starting point, because they are known to be an effective treatment for parkinsonian tremor, and it was shown that TANs exhibit muscarinic autoreceptors (Hersch and Levey, 1995).

In cholinergic interneurons recorded *in vitro*, summation of two or three EPSPs is sufficient to trigger an action potential (Bennett and Wilson, 1998). It would therefore be easy to synchronize the TANs in the parkinsonian state with synchronized oscillatory input. The projections from the pallidum to the striatum (Spooren et al., 1996; Bevan et al., 1998; Sato et al., 2000) may be a potential source for such oscillatory input. TANs may therefore function as a system that amplifies the pallidal oscillations and serve as a key element in the generation of parkinsonian symptoms.

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