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RAPID PUBLICATION

Neuronal Synchronization of Tonically Active Neurons in the Striatum of Normal and Parkinsonian Primates

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SUMMARY AND CONCLUSIONS

1. Previous studies indicate that tonically active neurons (TANs) are the cholinergic interneurons of the striatum and predict that their activity is synchronized. To test whether TANs do fire synchronously, and whether dopamine depletion affects their synchronization, we recorded the simultaneous activity of several TANs in the putamens of two vervet monkeys before and after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment.

2. Cross-correlation analysis revealed that most pairs of TANs (33 of 54; 61.1%) fire synchronously at ±60-ms delay. Correlated activity was more common between neurons with characteristic response to reward (17 of 19 pairs; 89.5%).

3. Cross-correlation study of 24 triplets of TANs showed synchronization of spiking activity of all 3 TANs in only 29.2% of cases (7 of 24 triplets). Correlated activity of two of three possible pairs was found in 25% of the cases.

4. After MPTP treatment and the development of parkinsonian symptoms, most TANs' auto- and cross-correlograms (22 of 28 units; 78.6%; and 23 of 28 pairs; 82.1%) became oscillatory. The number of correlated pairs was slightly increased (24 of 28; 85.7%). The strength of the synchronization was not significantly different from the normal values.

5. These findings support the notion that TANs function as distributed, partially overlapping synchronized networks. However, a normal dopaminergic system is not essential for synchronization of TANs; on the contrary, dopaminergic activity may even have a desynchronizing effect on the basal ganglia's system.

INTRODUCTION

Cholinergic interneurons represent only 1–5% of the total population of striatal neurons (Aosaki et al. 1995; Kawaguchi et al. 1995). Yet, anatomic and clinical studies strongly suggest that they play a major role in the functions of the basal ganglia in health and disease. The cholinergic interneurons give rise to very extensive and dense local axonal arbors, permeating the striatum with cholinergic markers (Mesulam et al. 1992; Yelnik et al. 1993). Their dendrites show little respect for the patch/matrix compartmental boundaries of the striatum. Therefore they are positioned to integrate the actions of the main striatal compartments (Bolam and Bennet 1995). The pathological hallmark of Parkinson's disease is a decrease in striatal dopamine content (Hornykiewicz and Kish 1987); however, the cholinergic system plays a critical role in the pathophysiology of Parkinson's disease. The striatal dopaminergic and cholinergic systems interact with each other at several levels (Di Chiara et al. 1994; Kitai and Surmeier 1992; Lehmann and Langer 1983), and cholinergic antagonists are effective agents for treatment of most neurological deficits of parkinsonism (Barbeau 1962; Jankovic and Marsden 1988).

The striatal neurons may be classified according to their spiking activity in behaving animals (Crutcher and DeLong 1984; Hikosaka et al. 1989; Kimura et al. 1984). Phasically active neurons are characterized by a short-duration action potential, very low spontaneous activity, and phasic responses to relevant behavioral events. Tonically active neurons (TANs) have a broader action potential, a spontaneous firing rate of 3–15 Hz, and after training show strong and robust responses to reward application (Aosaki et al. 1994b; Apicella et al. 1991). Recent studies (Aosaki et al. 1995; Kawaguchi et al. 1995; Wilson et al. 1990) indicate that TANs are the cholinergic interneurons of the striatum.

The strong resemblance between the temporal patterns of neuronal responses of widely distributed TANs led Graybiel et al. (1994) to suggest that the TANs form a distributed network with synchronized activity. The fact that dopamine depletion resulted in a drastic reduction in the acquired response to reward further suggests that the dopaminergic system modulates the responses of TANs (Aosaki et al. 1994a), and therefore may also be involved in their synchronization. In this study we tested directly whether TANs do fire in synchrony and whether depletion of dopamine reduces their synchronization.

Parts of this study have been reported in abstract form (Raz et al. 1995).

METHODS

Two vervet monkeys (*monkeys H* and *I; Cercopithecus aethiops aethiops*) were trained to perform a visual-motor task. *Monkey H* was trained to alternate between GO and NO-GO delayed release behavioral paradigms (see details in Nini et al. 1995). Briefly, trials were initiated when the monkey touched a central key after an intertrial interval of 4 s. After a variable delay (3–6 s), one of the two target keys was illuminated for 0.25 s. A trigger signal was given after a second variable delay (1–8 s). In one paradigm ("GO"), the monkeys were trained to release the central key and to touch the target key as fast as possible. If the monkey released the central key and touched the correct target key during the allowed reaction and movement periods, it was rewarded with 0.15 ml of juice 0.2–0.6 s after touching the target key. The juice reward was paired with a buzzer sound (reward signal). In the second behavioral paradigm ("NO-GO"), the monkeys were rewarded for continuing to touch the central key after the GO signal for the maximal allowed GO reaction time. Otherwise, the stimuli and

timing were identical to those of the first paradigm. A 4-s nonspatial signal instructed the monkey to change its behavioral mode every four correct trials. *Monkey I* was trained exclusively with the GO mode, with a fixed 0.25-s delay between the offset of the visual cue and the GO signal.

After training, recording chambers were attached to the skull to allow access to the dorsolateral striatum. The recording chamber was tilted 50° laterally in the coronal plane, targeting stereotaxic coordinates A12, H1, L9 (Contreras et al. 1981). Surgery was performed under general anesthesia (induction by ketamine hydrochloride 13 mg/kg im and maintenance with Isoflurane 0.5–1% inhalation anaesthesia) with the use of aseptic techniques. All procedures were conducted according to Hebrew University guidelines for animal care.

The activity of two to five single TANs was simultaneously recorded while the monkeys performed the behavioral task, and after systemic treatment with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP, Aldrich, Milwaukee, WI; 0.4–0.5 $mg \cdot kg^{-1} \cdot day^{-1}$ im in *monkeys I* and *H,* respectively, for a total of 4 days). During the recording sessions the monkey's head was immobilized and four to eight glass-coated tungsten microelectrodes confined within a cylindrical guide (1.6 mm ID) were advanced into the putamen. Neuronal activity from each electrode was sorted and classified as belonging to a single neuron by a template-matching algorithm (Worgotter et al. 1986), implemented by a PC-based spike sorter (MSDL5, Alpha-Omega Engineering, Nazareth, Israel). Only spike trains emitted by well-isolated single neurons (as judged by stable spike waveforms, stationary firing rates, and consistent responses to behavioral events) were included in this study. TANs were defined according to the following criteria. *1*) Tonic firing rate between 4 and 15 spikes/s (Fig. 1*A*). *2*) Spike waveform: the amplified output of the electrode was band-passed filtered (300–5,000 Hz, 8-pole Butterworth filter), yielding a bi- or multiphasic wave shape to the spikes. Only spikes for which the cumulative duration of first negative and positive waves exceeded 0.9 ms were included in the study (Fig. 1*B*). *3*) Recording location in the striatum: neurons were included in the TAN data base if the electrophysiological characteristics of their neighboring cells confirmed striatal definitions (Crutcher and DeLong 1984) and/or if the histological reconstruction of the electrode tracks proved to be in the striatum.

The spike trains of pairs of TANs were analyzed to check for their synchronization level. Auto- and cross-correlograms were calculated for the entire recording session, and for all possible periods (on the basis of the different behavioral events and modes) within the session. All correlograms were calculated for delays of 0–500 ms (bin = 1 ms) and only histograms with ≥1,000 spikes were included in the data base. All raw correlograms with significant signs of deviations from independent firing patterns were normalized by subtraction of a peristimulus predictor (Aertsen et al. 1989; Gerstein and Perkel 1972). This subtraction removes the contributions of stimulus- or movement-induced covariation of single neuron firing rates to the pairwise correlations. Assuming that the behavioral events only add spikes, but do not affect the neuronal interactions, the normalized (stimulus-corrected) correlograms reflect the net effect of the interactions between the studied neuronal pairs (Eggermont 1990). Synchronization strength and synchronization duration of two correlated neurons (with significant double-sided peak in the crosscorrelogram) were calculated after the correlograms were smoothed by convolution with a Gaussian curve (σ = 5 ms). Synchronization strength was defined as $Ac/\sqrt{(N_1 * N_2)}$. The expected number of coincidences of spikes was estimated from the flanks (±400–500 ms) of the cross-correlogram. *Ac* is the number of coincidences minus the number of expected coincidences, and N_1 and N_2 are the total number of spikes of the two units, respectively; see Ahissar et al. (1992) and Das and Gilbert (1995) for details of a similar normalization method.

At the conclusion of the experiment the monkeys were killed with an overdose of pentobarbital sodium and perfused transcardially with normal saline followed by 4% formaldehyde. Alternate 50-μm sections were stained with cresyl violet and tyrosine hydroxylase immunohistochemistry. Recording location was verified by histological reconstruction of the guide and the electrodes' tracks. The tyrosine hydroxylase immunohistochemistry data were used to assess the degree of dopaminergic cell loss in the midbrain.

RESULTS

Many (28 of 58; 48.3%) of the TANs exhibited characteristic responses (~200-ms pause in the tonic firing, frequently flanked by brief excitatory bursts) to the reward signal (Fig. 1, *C* and *D*) and/or to other behavioral events (Figs. 1*D* and 2*A*). Most (33 of 54; 61.1%) of the simultaneously recorded TAN pairs presented significant double-sided peaks in their cross-correlograms (Fig. 2*C*). The synchronized activity was not restricted to zero delay; positive correlations occurred at a delay of up to 40–80 ms. Mean duration of the double-sided peak was 119.7 ± 23.9 (SD) ms (n = 33). Synchronized activity was more common between neurons with similar responses to the reward (17 of 19; 89.5%) than between pairs in which at least one neuron had no significant response to the reward (16 of 35; 45.7%, $P < 0.005$, χ^2 test). A significant peak in the cross-correlogram can be the result of direct or indirect (e.g., shared inputs) neural interaction between units but also the result of a coupling of the firing of both neurons to a behavioral event (stimulus or movement). The firing correlations of TANs remained significant in all normalized (stimulus-corrected) correlograms (Fig. 2*C, inset*).

The nature of correlations among TANs was further examined by the study of 24 triplets of simultaneously recorded TANs. Often we found positive correlations only between one (9 of 24; 41.2%) or two (6 of 24; 25%) of three possible TAN pairs. Significant double-sided peaks across all three correlograms were only found in 29.2% of cases.

The monkeys were rendered parkinsonian with systemic MPTP treatment. The main behavioral effects were a marked loss of spontaneous movements (akinesia), muscular rigidity, flexed posture, and frequent episodes of low-frequency (5–7 Hz) resting and/or action/postural tremor. The monkeys were no longer able to perform the behavioral task, and therefore during the recording sessions the monkeys were seated in the primate chair and were faced with the same stimuli (including the juice reward and the reward signal) as in the normal behavioral paradigm even if they did not touch the center or target keys. Postmortem analysis revealed >80% loss of dopaminergic cells (tyrosine hydroxylase immunohistochemistry) and abundant microgliosis (Nissl) in the substantia nigra.

The neural activity of the TANs was resampled after the development of the parkinsonian signs. At this stage we recorded the activity of 28 TANs. The number of TANs that showed the characteristic response to the reward signal decreased dramatically. Only three units (10.7%) showed a typical response, whereas seven additional units exhibited atypical responses (>300-ms pause in the tonic firing with no excitatory bursts). Nevertheless, the proportion of correlated TAN pairs did not decrease. Synchronized activity was found between most TAN pairs (24 of 28; 85.7%, Fig. 3*B*),

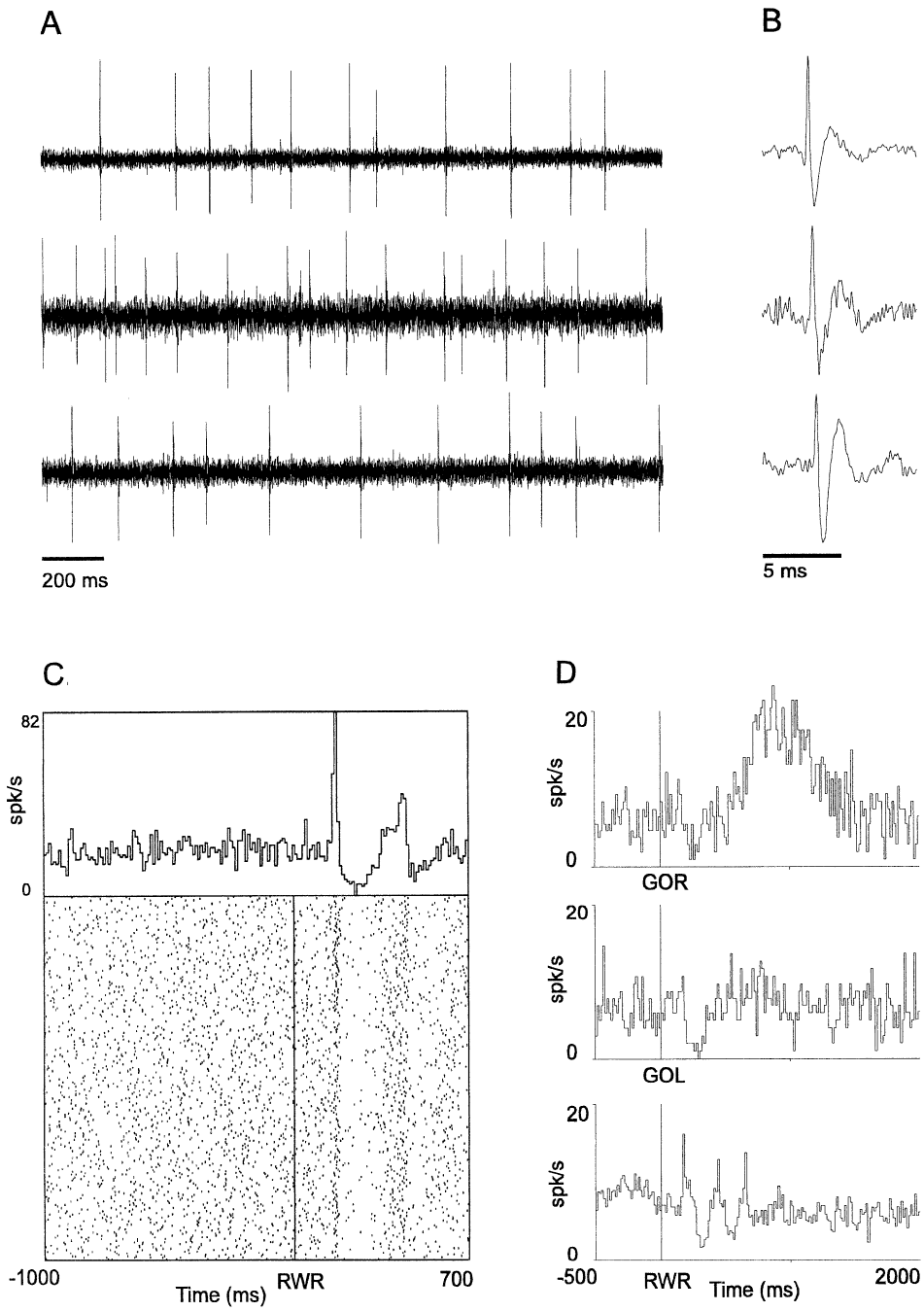

FIG. 1. Firing properties of single tonically active neurons (TANs). *A*: chart recording of the discharge pattern of the irregular-tonic activity of 3 simultaneously recorded TANs. The signal recorded by the electrodes was amplified, sampled (12 kHz/channel), and digitally filtered (300–5,000 Hz, 8-pole Butterworth filter). *B*: waveforms of spikes shown on an expanded time scale (filter setting as in *A*). *C*: raster display of the response of a single TAN to the reward signal. Each dot indicates a single action potential, and each line represents a single trial (227 trials are shown). The display is aligned along the time of the onset of the reward signal (RWR). The average response to the reward signal is shown above in the peristimulus histogram (PSTH), with a binwidth of 15 ms. *D*: PSTHs of the responses of a single TAN to reward and GO signals. GOR, GO to right signal; GOL, GO to left signal. Bin size = 15 ms.

and the strength of the synchronization was not significantly different from the normal values [normal: 0.14 ± 0.07 (n = 33); MPTP: 0.11 ± 0.06 (n = 24), $P > 0.1$, 2-tailed t-test]. However, the pattern of the autocorrelograms and cross-correlograms of most TANs (22 of 28 units, and 23 of 28 pairs) did change, becoming oscillatory mainly around 16 Hz (Fig. 3, *A, B,* and *inset*).

DISCUSSION

Synchronization of a neural network can be the result of an external common drive and/or functional connections inside the network. The considerable distances between the cholinergic neurons, and the lack of functional interactions between the spiny projection neurons of the striatum (Jaeger et al. 1994), suggest that there are few interconnections between TANs. Therefore it is more likely that the synchronization of TANs is induced by external shared source(s) rather than intrastriatal connectivity. A simple "common input" mechanism usually resulted in brief (±10 ms) synchronization due to jitter of conduction velocities and synaptic transmission (Kirkwood 1979; Knox 1981; Perkel et al. 1967). The duration of correlated activity can be broadened by loose synchronization of the input sources, as has been found between cortical and thalamic neurons (see review in Eggermont 1990; Fetz et al. 1991). The synchronization of

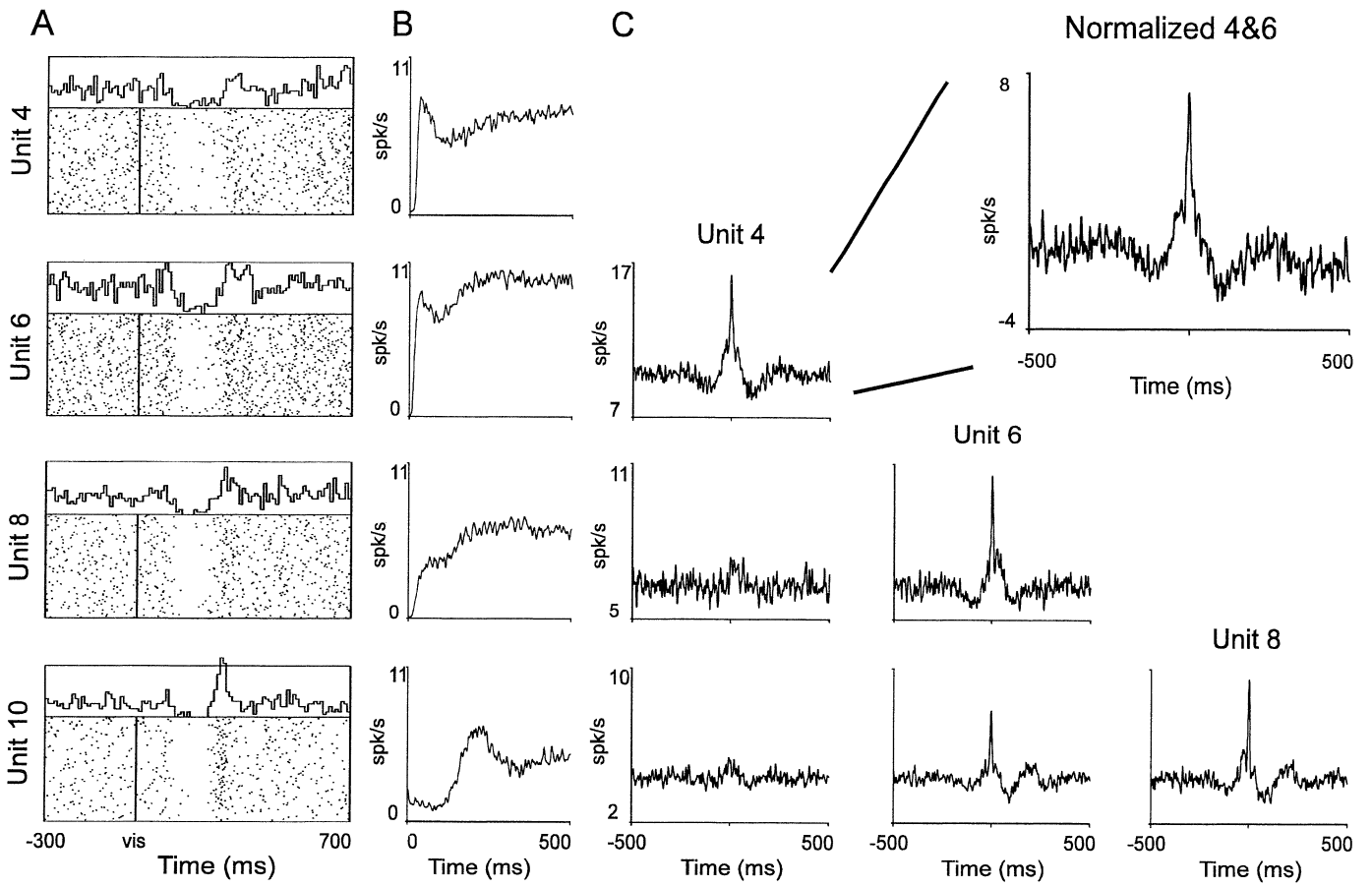

FIG. 2. Activity of 4 simultaneously recorded TANs. *A*: raster and PSTH of the responses to onset of the visual cue of 4 simultaneously recorded TANs. *Monkey I* was trained exclusively on the GO mode, and performed the task with very high rate (>95%) of correct trials; therefore the visual cue is the first indication of the future reward. Duration of the visual cue is 250 ms. All PSTHs have a common scale of 0–20 spikes/s; bin size = 10 ms; 111 trials are shown. *B*: autocorrelograms of the same TANs as shown in *A*. The correlograms were calculated with a bin size of 1 ms and smoothed by convolution with a Gaussian curve (σ = 2 ms). *C*: correlation matrix of the TANs. Identification of the trigger units appears at *top*, and identification of the reference units at *left*. The matrix displays all possible correlation pairs, calculated for the entire recording period. *Inset*: normalized (by peristimulus predictor triggered by visual cue) cross-correlogram of *units 4* and *6*. Bin size = 1 ms; smoothing: σ = 2 ms.

TANs does not show the multimodal distribution of synchronization durations found between cortical cells, and falls within the medium range group of cortical synchronization (Nelson et al. 1992; Vaadia et al. 1991), suggesting a more uniform mechanism underlying TAN correlated activity. Still, our results, which demonstrate that different pairs of TANs are driven by different sources, indicate that the synchronizing input source is not distributed over the entire striatum. Rather, in agreement with the previous demonstration of subgroups of TANs (Aosaki et al. 1995), the findings of TAN triplets with positive correlations only between two of three possible pairs suggest that TANs are organized in several overlapping assemblies in which each neuron can be affiliated with more than one assembly.

The nigrostriatal dopaminergic system and the glutamatergic projections from the central complex nuclei of the thalamus are the main extrinsic afferents to the cholinergic interneurons of the striatum (Lapper and Bolam 1992). In this study, systemic dopamine depletion resulted in a sharp reduction in the TANs' responsiveness to the reward signal, 16-Hz oscillatory activity, and moderate increase of TAN coupling. The appearance of ~15-Hz oscillatory activity of TANs after MPTP treatment should be further studied, especially because similar periodic oscillations were found at the subthalamic nuclei of MPTP-treated vervet monkeys (Bergman et al. 1994a,b). The reduction in the number of TANs with the characteristic response to the reward may be partially explained by the inability of the monkey to perform the task and by the "free reward" paradigm used in the parkinsonian state. These findings are in agreement with the reduction of the acquired sensory responsiveness of TANs following unilateral and selective striatal dopamine depletions (Aosaki et al. 1994a). Moreover, they cannot be simply related to the increase of coupling between TANs, because correlated activity was more common between neurons responsive to the reward in the normal state. Finally, neither MPTP nor dopaminergic antagonist treatments diminished TAN spontaneous activity, and systemic application of apomorphine reinstated the TAN responses after MPTP treatment (Aosaki et al. 1994a). Our findings that the coupling level of the TANs was not reduced after MPTP treatment further indicate that dopaminergic projections to the striatum do not convey a specific "common input" to the network of the TANs, but act as an enabling system (Aosaki et al.

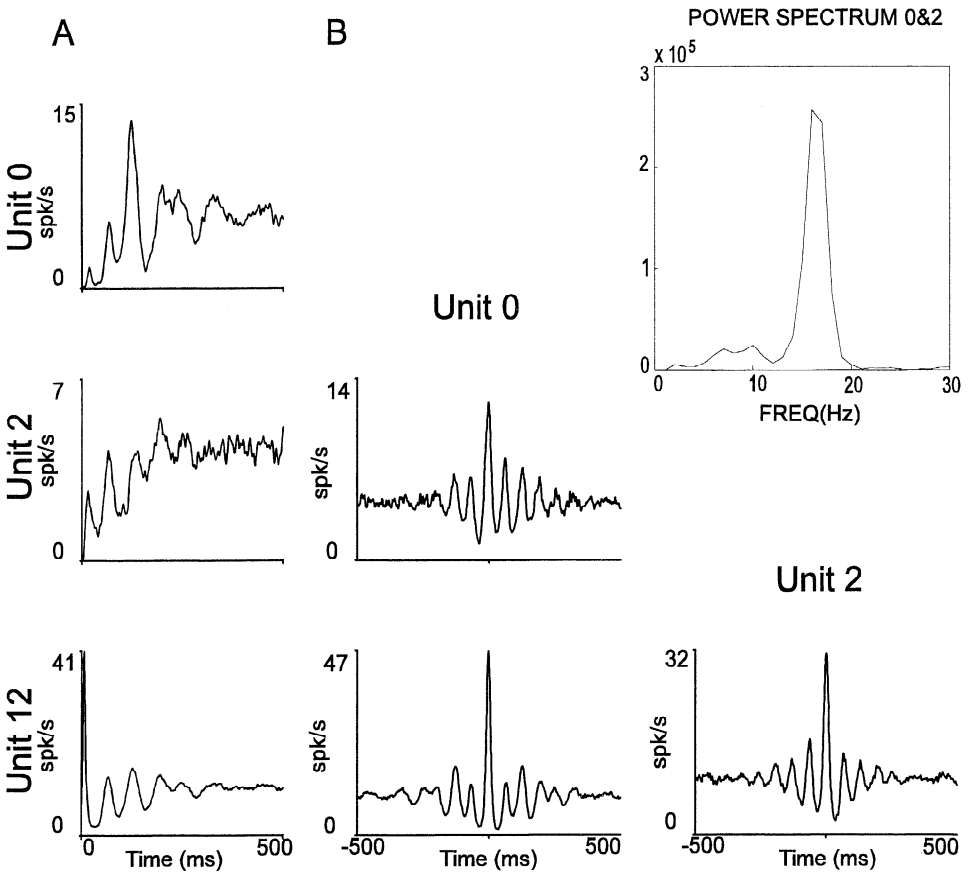

FIG. 3. Firing properties of TANs after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP) treatment. *A*: autocorrelation histograms of 3 simultaneously recorded TANs. *B*: cross-correlation matrix of the same 3 TANs. All correlograms were calculated over the entire recording period. Bin size = 1 ms; smoothing: σ = 2 ms. Identification of trigger units appears at *top*, and identification of the reference units at *left*. *Inset*: power spectrum of the correlated activity of *units 0* and *2*.

1994a; Graybiel et al. 1994). At other levels of the basal ganglia, dopaminergic depletion results in increased coupling of pallidal (Nini et al. 1995; Tremblay et al. 1989) and striatal projection neurons (Wickens 1993). These results are also in accordance with the excessive and unselective responses of pallidal neurons in parkinsonian monkeys (Filion et al. 1988; Miller and DeLong 1988). Thus we propose that dopamine acts as a source of desynchronization of spiking activity of the basal ganglia, and that a pathophysiological consequence of dopamine depletion in Parkinson's disease is increased synchronization of basal ganglia activity.

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