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RAPID PUBLICATION

Neurons in the Globus Pallidus Do Not Show Correlated Activity in the Normal Monkey, but Phase-Locked Oscillations Appear in the MPTP Model of Parkinsonism

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SUMMARY AND CONCLUSIONS

1. To test the mode of functional connectivity in the basal ganglia circuitry, we studied the activity of simultaneously recorded neurons in the globus pallidus (GP) of a behaving rhesus monkey. The cross-correlograms of pairs of neurons in the GP were compared with those of neurons in the thalamus and frontal cortex and to the cross-correlograms of pallidal pairs after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment.

2. In contrast with cortical and thalamic neuronal activity, almost all pairs (n = 76/81 pairs; 93.8%, 1,629/1,651 histograms; 98.7%) of GP neurons in the normal monkey were not driven by a common input.

3. The monkey was systemically treated with MPTP until the appearance of parkinsonian signs and an intermittent 7- to 11-Hz action/postural tremor. After the MPTP treatment, many pallidal neurons (49/140; 35%) became oscillatory, and 19% (n = 31/162) of pallidal pairs had oscillatory cross-correlograms.

4. These results support the model of parallel processing in the basal ganglia of normal monkeys and suggest a breakdown of the independent activity in the parkinsonian state.

INTRODUCTION

A central question concerning the circuitry of the basal ganglia is how the multiple and diverse inputs impinging on the striatum and the subthalamic nucleus from most cortical areas are processed until the output is projected from the relatively small internal segment of the globus pallidus (GPi) via the thalamus to the frontal cortex. Two distinctly different models, "funneling" and "parallel processing," have been suggested (Alexander et al. 1986; Percheron and Filion 1991). Physiological studies of single neurons (Alexander and Crutcher 1990; DeLong et al. 1985), and recent anatomic studies (Hoover and Strick 1993) support the hypothesis of parallel independent processing. Alternatively, the strong reduction (funneling) in the number of neurons from the striatum to GPi, and the wide dendritic arborization of pallidal neurons, oriented at right angles to the incoming striatal axons with small number of contacts between a striatal axon and a single pallidal cell, suggest that pallidal neurons with overlapping dendritic disks are integrating the same inputs from many striatal neurons (Francois et al. 1995; Kemp and Powell 1971; Percheron et al. 1984). The excitatory projections from the subthalamic nucleus may also operate as a source of common excitation of a vast collection of pallidal neurons (Kitai and Kita 1987; Parent and Hazrati 1993).

A possible test of these two hypotheses may be provided by simultaneous recordings from several pallidal neurons. The funneling hypothesis predicts that pallidal neurons with shared common inputs would frequently fire in coherence, whereas the parallel processing hypothesis implies little or no correlation among pallidal neurons. We therefore cross-correlated the spike trains of simultaneously recorded pallidal neurons. For comparison, we also correlated the activity of pairs of neurons in the thalamus (of the same monkey) and in the frontal cortex of a second monkey.

Dysfunctions of the basal ganglia–thalamocortical circuits are associated with a variety of movement abnormalities, e.g., akinesia (poverty of movement), muscular rigidity and tremor in Parkinson's disease, and involuntary choreatic movements in hemiballismus and Huntington's chorea. Parkinson's disease and the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) animal model of Parkinsonism result from a loss of dopamine within the striatum (Burns et al. 1983; Langston et al. 1984), leading to dramatic changes in the firing rate and patterns of single neurons in the basal ganglia (Bergman et al. 1994; Filion and Tremblay 1991; Miller and DeLong 1987; Rothblat and Schneider 1993) and to reduced specificity of pallidal neurons (Filion et al. 1988; Miller and DeLong 1988; Tremblay et al. 1989). To test whether these modifications are associated with changes in the level of synchronization in the globus pallidus, we also studied the firing patterns and cross-correlograms of spike trains of simultaneously recorded pallidal neurons after systemic MPTP treatment.

Parts of this study have been reported in abstract form (Feingold et al. 1994; Nini et al. 1994).

METHODS

Two rhesus monkeys were trained to alternate between two spatial delayed release paradigms. Trials were initiated when the monkey touched a central key and a central red light was turned on. After a variable delay (3–6 s), one of the two target keys was illuminated for 0.2 s. Then, after a second variable delay (1–4 s) a GO signal (dimming of the central red light) instructed the monkey to release the central key and to touch the target key. 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, he was rewarded with 0.15 ml juice, 0.4 s after touching the target key. In the second behavioral paradigm ("NO-GO"), the monkeys were rewarded

for continuing to touch the central key for at least 1.2 s (twice the maximal reaction time of the GO mode) after the GO signal. Otherwise, the stimuli and timing were identical to those of the first paradigm. A 4-s nonspatial signal instructed the monkey to change his behavioral mode every four correct trials. Trials were applied with an intertrial interval of 4 s.

After training, a recording chamber was vertically attached to the skull, under pentobarbital sodium (Nembutal) anesthesia, and in aseptic conditions. The chambers were positioned to allow recording of the activity of frontal cortex (*monkey C*) and of pallidal and thalamic neurons (*monkey E,* target stereotaxic coordinates: A12, L7) (Snider and Lee 1961; Winters et al. 1969). During the recording sessions the monkey's head was immobilized, and four glass-coated tungsten microelectrodes confined within a cylindrical guide (1.8 mm OD) were advanced to the globus pallidus, nucleus ventralis anterior of the thalamus (*monkey E*), or the frontal cortex (*monkey C*). All procedures were conducted according to the Hebrew University guidelines for animal care.

The activity of four to eight single neurons was recorded while the monkeys performed the behavioral task. 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 the stable spike waveforms, stationary firing rate, and constant responses to behavioral events) are included in this study.

Auto- and cross-correlograms were calculated for all possible periods (based on the different behavioral events and modes) for each pair. Both raw and normalized (by shift predicator) cross-correlograms were calculated. All correlograms were calculated for delays of 500 ms (bin equal 1 ms), and only histograms with at least 1,000 spikes were included in the data base. A feature extraction program detected and quantified (on a 0 to 10 scale) significant deviations from random (Poisson) discharge patterns of single neurons and independent firing of neuronal pairs (Abeles 1982). Phenomena were accepted as significant if their grade was

TABLE 1. *Frequency of double-sided peaks in raw cross-correlograms of cortical, thalamic, and pallidal neuronal pairs*

Structure	Number of Histograms	Histograms With No Sign of Peaks, %	Histograms With Nonsignificant Peaks, %	Histograms With Significant Peaks, %
Globus pallidus	1,651	84.6	9.2	6.2
Thalamus	580	64.9	18.4	16.7
Frontal cortex	203	66.6	12.8	20.6

A feature-extraction program detected and graded (from 0 to 10) any deviations from the confidence limits determined by 2 independent processes. The program gives grades of 0–5 to histograms with weak signs of a double-sided peak (nonsignificant peaks). Grades of 6–10 (significant peaks) are given to those correlograms in which clear phenomena are readily detected. Cross-correlograms were calculated for several behavioral periods for each pair. Number of neuronal pairs equal 81, 37, and 65 in the globus pallidus, thalamus, and frontal cortex, respectively.

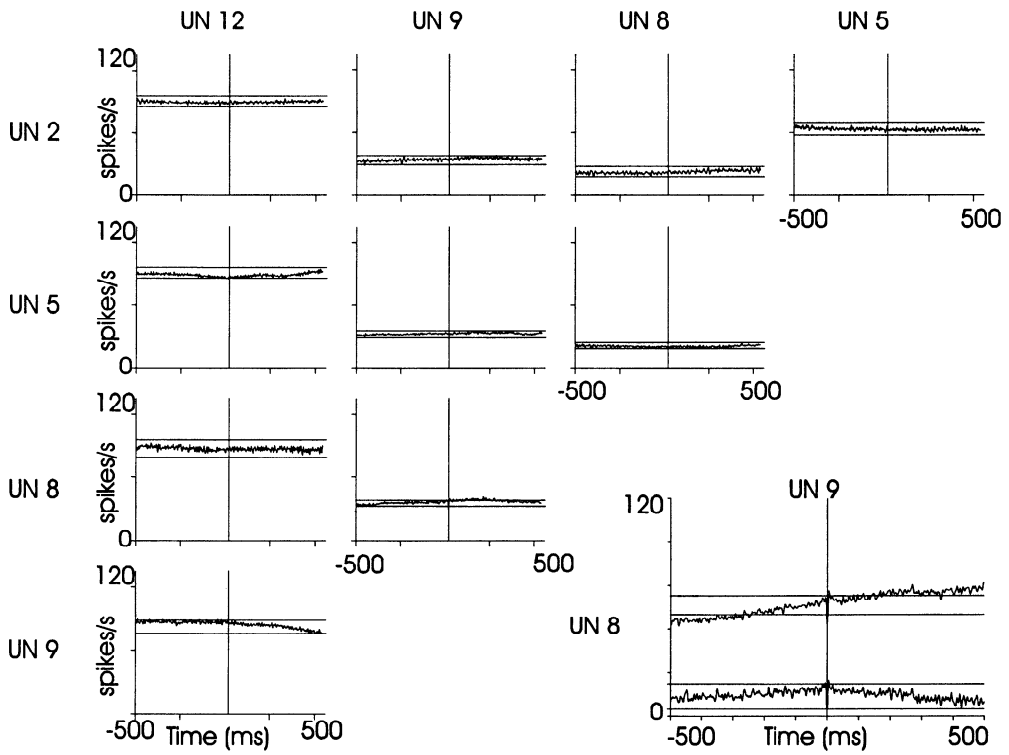

FIG. 1. Cross-correlation matrix of 5 simultaneously recorded pallidal cells before 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment. Identification of the trigger units appears in the *top row,* and of the reference units in the *left column.* Units were recorded by 4 electrodes (*units 8* and *9* were recorded by the same microelectrode and sorted by their different shapes of action potential). The matrix displays all possible correlation pairs, calculated for the precue period in the GO behavioral mode. The right *inset* (enlarged) shows the raw (*top trace*) and the normalized (*bottom trace*) cross-correlograms of *units 8* and *9* in the delay period between the right spatial cue and the GO signal. All correlograms were calculated with 1 ms bin and smoothed by convolution with a Gaussian curve (σ = 1 ms). Top and bottom straight lines: 99% confidence limits for 2 independent spike trains.

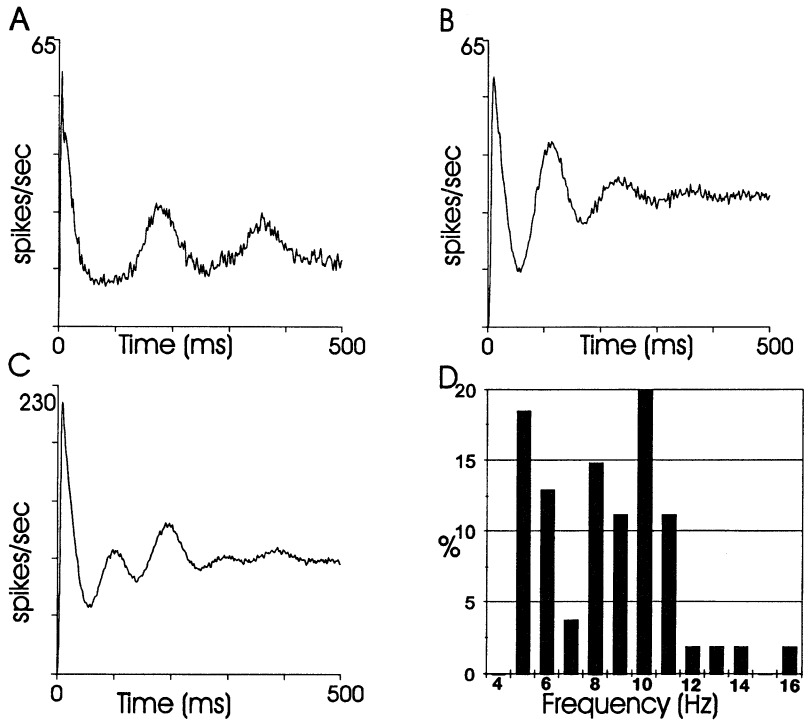

FIG. 2. Periodic oscillations of neuronal activity in the globus pallidus after MPTP treatment. *A* and *B*: examples of autocorrelograms with 5.5- and 8.5-Hz periodic oscillations (grade = 9 in both cases). *C*: example of an autocorrelogram that reveals both 5.2-Hz (grade = 8) and 10.4-Hz (grade = 7) oscillations. This correlogram can be fitted with the algebraic sum of 2 dampened cosine functions with periods of 100 and 200 ms. Smoothing is 1 ms for all correlograms. *D*: distribution of oscillation frequencies in the autocorrelograms. All oscillations with a grade ≥5 were included (n = 54).

greater than five in the raw correlograms and greater than three in the normalized correlograms. The same algorithm detects and scales oscillatory activity and estimates the oscillation frequency (Karmon and Bergman 1993).

At the conclusion of the experiment, the monkeys were killed with an overdose of pentobarbital 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. In many cases we were unable to identify the exact histological location of a single electrode (out of the 4) in the globus pallidus, and an absolute discrimination between neurons of the internal and external segments was not possible. We therefore included all pallidal units in the sample of this report. The tyrosine hydroxylase immunohistochemistry data were used to assess the degree of dopaminergic cell loss in the midbrain.

RESULTS

The cross-correlograms of 81 pallidal pairs [6 pairs recorded by the same electrode, 75 pairs by different electrodes (estimated distances: 0.73 ± 0.77 mm, mean ± SD)] were studied before the MPTP treatment. Almost all raw correlograms (1,549/1,651; 93.8%) have no significant signs (maximal grade <6) of double-sided peaks, indicating that the spike trains of the two neurons were not driven by a common input (Table 1 and Fig. 1). Even when two neurons showed covariation of their discharge in response to behavioral events, the normalized (calculated with shift predicator) spike-to-spike correlations (Perkel et al. 1967) were also flat (Fig. 1, *inset*). We found but a few histograms (22/1,651; 1.3%) with weak, but statistically significant (maximal grade equals 7), signs of double-sided peaks in both regular and normalized correlograms. The significant spike-to-spike correlations were not found in a specific behavioral epoch, and only five (5/81; 6.2%) neuronal pairs demonstrated correlated activity in more than one behavioral epoch. Otherwise, no significant differences were found between spike-to-spike correlograms of the same neuronal pair calculated over the different behavioral epochs (e.g., intertrial interval, pre- and postcue delays in the NO-GO and GO modes, arm movements and reward licking periods), which probably represent diverse levels of attentive and motor behavior. Very different results were obtained in the thalamus and frontal cortex where significant signs of double-sided peaks were found in many raw cross-correlograms (Table 1). Furthermore, many pairs (16.2 and 26.2% in the thalamus and cortex, respectively) displayed significant and strong (grades of double-sided peaks up to 9–10) spike-to-spike correlated activity.

We also tested the cross-correlograms of spike trains of units not as well isolated (multiunit activity, in our study usually estimated to delineate the summed activity of 2–3 different neurons). In this population, the proportion of pallidal pairs recorded by the same electrode was much higher than in the population of well-isolated neurons; still we did not find any correlated activity between the spike trains.

Monkey E was rendered parkinsonian with systemic MPTP treatment (MPTP hydrochloride, Aldrich, Milwaukee, WI; 0.4 $mg \cdot kg^{-1} \cdot day^{-1}$, given by intramuscular injection for a total of 6 days). The main behavioral effects were a marked loss of spontaneous movements (akinesia), muscular rigidity, severe postural instability, and infrequent short episodes of 7-to 11-Hz postural and action tremor. The monkey was no longer able to perform the behavioral task, and therefore during the recording sessions the monkeys were seated in the primate chair, and faced the same stimuli (ready light on, spatial cues, GO signal, etc.) but were rewarded even for noncorrect trials. Postmortem analysis re-

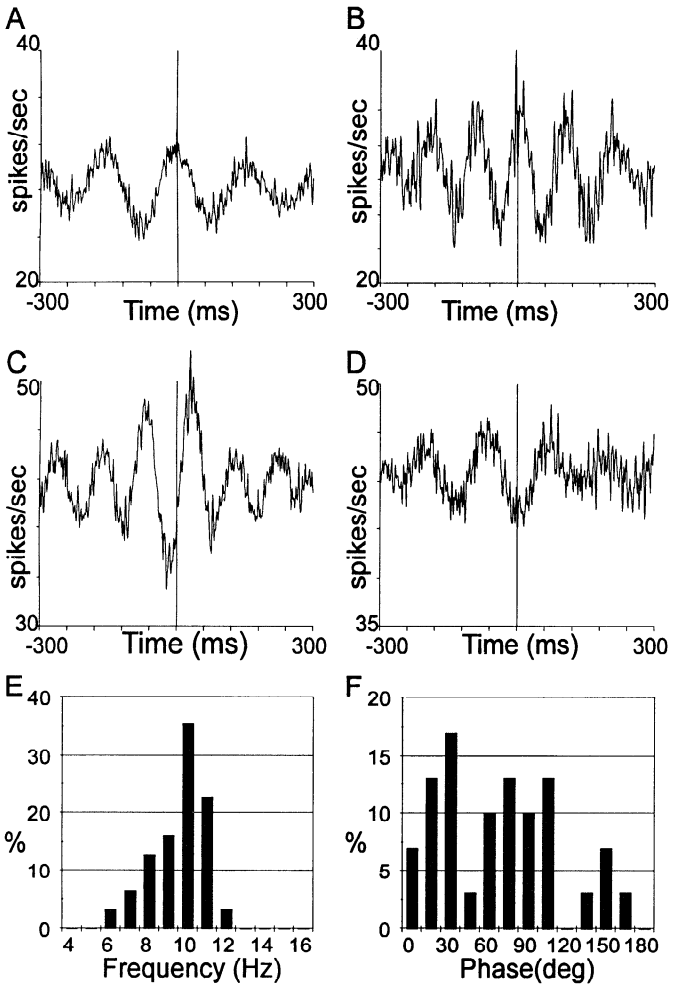

FIG. 3. Phase-locked oscillations in cross-correlograms of pairs of pallidal neurons after MPTP treatment. *A–D*: examples of cross-correlograms with 6.1-, 10.6-, 9.7-, and 7.7-Hz oscillations (grades = 7, 7, 8, and 6) and 16, 11, 147, and 180° phase shifts, respectively. Smoothing is 1 ms. *E*: distribution of oscillation frequencies in the cross-correlograms. *F*: distribution of phase shifts in oscillating cross-correlograms. All correlograms with an oscillation grade ≥5 were included (n = 31).

vealed >90% loss of dopaminergic cells (tyrosine hydroxylase immunohistochemistry) and significant cell loss with microgliosis (Nissl) in the substantia-nigra. Neuronal depletion was greater on the ventrolateral parts of the nigra. The dopaminergic innervation of the internal segment of the pallidum was preserved.

Analysis of the firing patterns of pallidal neurons after the MPTP treatment revealed a significant fraction of neurons (49/140; 35.0%) with periodic oscillatory activity (Fig. 2, *A–C*). Such oscillatory activity was never found before the MPTP treatment. The distribution of the oscillation frequencies was bimodal (Fig. 2*D*), with more neurons oscillating around 10 Hz than around 5 Hz. Only four autocorrelograms had signs of more than one oscillation frequency (Fig. 2*C*).

In addition, many pallidal pairs (31/162; 19.1%) exhibited oscillatory correlated activity (Fig. 3, *A–E*). Phase shifts were calculated as the time of the highest peak in the cross-correlogram divided by the oscillation period. All possible phase shifts were found in the oscillating cross-correlograms (Fig. 3, *B–D* and *F*), with no relation to the distances between the correlated neurons. We ruled out the possibility that the phase shifts are averages of continuously changing correlated activity by comparing the phase shifts of correlograms calculated over different behavioral epochs and over different time segments (1st and 2nd halves of the recording). Comparable phase shifts were found in all cases.

Most (94%) neuronal pairs with oscillatory cross-correlograms were composed of at least one oscillatory neuron. The frequency of the oscillations in the cross-correlograms tended to be correlated with the higher frequency of oscillations in the autocorrelograms (Fig. 3*E*).

DISCUSSION

The main results of this study are the demonstration of nonsynchronized activity of pallidal neurons in a normal, behaving monkey, and the development of phase-locked oscillations in the parkinsonian state. Double-sided peaks in both raw and normalized cross-correlograms were found only in 1.3% of all correlograms of pallidal pairs. Even those few statistically significant peaks were barely detectable (as judged by their low grading by the feature extracting program), suggesting that the spiking activity of most pallidal neurons is not driven by a common input. The lack of synchronization is consistent with previous studies of adjacent neurons (recorded by 1 electrode) in the globus pallidus of nonbehaving monkeys (Bergman and DeLong 1989; Bergman et al. 1994). In contrast to the pallidal pairs, many neuronal pairs in the richly connected neural networks of the brain do show correlated activity. Indeed, we found many thalamic and cortical pairs that exhibited correlated activity, as previously reported (in the cortex: Eggermont 1992; Gochin et al. 1991; Kruger and Aiple 1988; Vaadia et al. 1995; in the thalamus: Heierli et al. 1987). Pallidal afferents, particularly from the striatum (Flaherty and Graybiel 1993; Hazrati and Parent 1992; Parent and Hazrati 1993) and the subthalamic nucleus (Carpenter and Jayaraman 1990; Kitai and Kita 1987; Parent and Hazrati 1993; Smith et al. 1990), or even intrapallidal connections (Kita and Kitai 1994; Park et al. 1982; Smith et al. 1994), may serve as the substrate for synchronizing input. Nevertheless, anatomic connections can give only the "maximal aperture of the system" (Percheron et al. 1994), whereas the present results suggest that, in the normal state, the pallidal neurons act independently.

Oscillating activity has already been described in single-unit studies of the thalamus of human parkinsonian patients (Lenz et al. 1988, 1994; Ohye et al. 1974) and of the basal ganglia of MPTP-treated monkeys (Bergman et al. 1994; Filion and Tremblay 1991; Miller and DeLong 1987). Of particular interest is the finding of the same bimodal distribution of oscillation frequencies in the autocorrelograms of spike trains recorded from the pallidum of rhesus and African green monkeys. Still, 4- to 7-Hz oscillations are predominant in the African green monkey [70.4% of oscillating units (Bergman et al. 1994)], whereas 8- to 15-Hz oscillations are predominant in the rhesus monkey (64.8 and 90.3% of auto- and cross-correlograms, respectively), in parallel with the major frequency of tremor in the two species.

Finally, the oscillating neurons in the globus pallidus of the MPTP-treated monkey are phase locked. Although the MPTP-treated monkey was not engaged in a behavioral

task, the differences in the synchronization level of simultaneously recorded pallidal pairs are probably more associated with the development of the parkinsonian state. Independent activity of pallidal neurons in the normal monkey was detected in all behavioral situations, including those that demand minimal attention (like intertrial intervals or precue periods in the NO-GO mode), and also during periods when the monkey did not perform the behavioral task (data not shown). Moreover, oscillatory activity of single units is very seldom encountered in previous studies of the rhesus globus pallidus even during periods of sleep (DeLong 1969; Detari et al. 1987). Because the appearance of the synchronized oscillatory activity is highly (but not fully) correlated with the appearance of single cell oscillations, both are probably due to the development of the parkinsonian state.

The findings of phase-locked oscillations suggest that, after the development of parkinsonian symptoms, the neuronal networks of the basal ganglia-cortical circuits lose their unique ability to keep pallidal neurons completely independent, and that the common inputs (from subthalamic nucleus and/or striatum) became more dominant. Previous studies of intrinsic neuronal oscillators failed to detect correlated oscillatory activity, even when the neurons had very similar (±1%) oscillation frequencies (Ahissar and Vaadia 1990). The emergence of neuronal oscillations and tremor is therefore not only due to changes in the intrinsic properties of the neurons but reflects major changes at the network level of the basal ganglia's circuitry.

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