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Phase Relationships Support a Role for Coordinated Activity in the Indirect Pathway in Organizing Slow Oscillations in Basal Ganglia Output after Loss of Dopamine

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Abstract

The goal of the present study was to determine the phase relationships of the slow oscillatory activity that emerges in basal ganglia nuclei in anesthetized rats after dopamine cell lesion in order to gain insight into the passage of this oscillatory activity through the basal ganglia network. Spike train recordings from striatum, subthalamic nucleus (STN), globus pallidus (GP), and substantia nigra pars reticulata (SNpr) were paired with simultaneous local field potential (LFP) recordings from SNpr or motor cortex ipsilateral to a unilateral lesion of substantia nigra dopamine neurons in urethane anesthetized rats. Dopamine cell lesion induced a striking increase in incidence of slow oscillations (0.3–2.5 Hz) in firing rate in all nuclei. Phase relationships assessed through paired recordings using SNpr LFP as a temporal reference showed that slow oscillatory activity in GP spike trains is predominantly antiphase with oscillations in striatum, and slow oscillatory activity in STN spike trains is in-phase with oscillatory activity in cortex but predominantly antiphase with GP oscillatory activity. Taken together, these results imply that after dopamine cell lesion in urethane anesthetized rats, increased oscillatory activity in GP spike trains is shaped more by increased phasic inhibitory input from the striatum than by phasic excitatory input from STN. In addition, results show that oscillatory activity in SNpr spike trains is typically antiphase with GP oscillatory activity and in-phase with STN oscillatory activity. While these observations do not rule out additional mechanisms contributing to the emergence of slow oscillations in the basal ganglia after dopamine cell lesion in the anesthetized preparation, they are compatible with 1) increased oscillatory activity in the GP facilitated by an effect of dopamine loss on striatal ‘filtering’ of slow components of oscillatory cortical input, 2) increased oscillatory activity in STN spike trains supported by convergent antiphase inhibitory and excitatory oscillatory input from GP and cortex, respectively, and 3) increased oscillatory activity in SNpr spike trains organized by convergent antiphase inhibitory and excitatory oscillatory input from GP and STN, respectively.

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Keywords

Parkinson's disease; subthalamic nucleus; substantia nigra; globus pallidus; striatum; bursting; local field potentials

Dopamine cell death is associated with changes in firing rate and pattern in several basal ganglia nuclei. Understanding how loss of dopamine induces alterations in basal ganglia activity is critical to understanding motor system dysfunction associated with Parkinson's disease (PD) and the physiological role of dopamine in this network. Firing pattern changes in the subthalamic nucleus (STN) and the basal ganglia output nuclei, the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNpr), appear especially relevant to PD symptomatology. This is evidenced by the efficacy of STN and GPi lesion and deep brain stimulation treatments in advanced PD, procedures that eliminate or modify STN and GPi output (Baron et al., 1996; Gill and Heywood, 1997; Lang et al., 1997; Limousin et al., 1998; Krack et al., 2000; Lozano, 2001; Obeso et al., 2001; Benabid, 2003). The symptomatological relief associated with these therapies supports the idea that dopamine cell death triggers alterations in STN and GPi/SNpr activity that exert dysfunctional effects on downstream nuclei and contribute to the disabilities of PD.

Animal models of PD provide an opportunity to explore the effect of dopamine cell loss on firing patterns in individual basal ganglia nuclei. In addition, they provide an opportunity to examine relationships between interconnected nuclei to gain insight into the extent to which firing pattern changes in individual nuclei are linked to broader changes engaging the entire basal ganglia network. In one commonly used animal model of PD, the anesthetized rodent with a unilateral 6-hydroxydopamine (6-OHDA)-induced medial forebrain bundle lesion, a number of studies have found that firing patterns in STN and SNpr become more bursty (Sanderson et al., 1986; MacLeod et al., 1990; Hollerman and Grace, 1992; Burbaud et al., 1995; Hassani et al., 1996; Murer et al., 1997; Rohlf et al., 1997; Tseng et al., 2000, 2001a; Vila et al., 2000; Magill et al., 2001; Ni et al., 2001; Belluscio et al., 2003; Tai et al., 2003). This bursty activity has been shown to be correlated with slow oscillations in cortical EEG (Magill et al., 2001; Tseng et al., 2001b; Belluscio et al., 2003). While one must be cautious about generalizing from results obtained in anesthetized preparations, these preparations have a property that is useful for probing changes in network function. Cortical activity in anesthetized animals, as reflected by cortical EEG and local field potential (LFP) recordings, is highly synchronized and characterized by slow frequency oscillations (Steriade et al., 1993; Contreras and Steriade, 1995, 1997; Amzica and Steriade, 1998; Steriade, 2001). In anesthetized rats, this synchronized activity has a periodicity of ~1 Hz. As this oscillatory activity is relatively stable in the cortex over time, it can be viewed as a probe or input signal for assessing the effects of dopamine loss on passage of slow oscillatory activity through the basal ganglia.

Murer, Tseng and coworkers have shown that striatal neurons are more depolarized after dopamine cell lesion and fire more frequently in conjunction with the slow oscillations that are prominent in cortical EEG in anesthetized rats (Tseng et al., 2001b). This raises the possibility that the altered firing patterns observed in basal ganglia output nuclei after dopamine cell lesion are due to increased activity in the striatum, transmitted through the direct or indirect pathways to the SNpr. Other studies have stressed the importance of cortical or other input to the STN, and/or local changes in the STN in mediating changes in firing patterns in the external segment of the globus pallidus (GP) and the SNpr after loss of dopamine (Magill et al., 2001; Tseng et al., 2001b; Murer et al., 2002; Belluscio et al., 2003). Information about phase relationships of the oscillatory activity emerging in these

nuclei could provide insight into how firing pattern changes in the striatum, GP, and STN are interrelated and contribute to changes in the basal ganglia output nuclei.

The goal of the present study was to determine phase relationships between oscillatory activity in the striatum, STN, GP, and SNpr after dopamine cell lesion in urethane anaesthetized rats. Changes in firing pattern and oscillatory activity in the slow and low delta (0.3-2.5 Hz) frequency range in these four basal ganglia nuclei were assessed. LFPs in the SNpr and motor cortex were used as temporal references to determine phase relationships of the slow oscillations within this network. Phase relationships were further examined in paired recordings from GP-SNpr and STN-SNpr via spike cross-correlograms. These relationships allow insight into how firing pattern changes in individual nuclei relate to changes in oscillatory activity throughout the basal ganglia network and argue that convergent activity contributes to the emergence of slow oscillations in basal ganglia output.

EXPERIMENTAL PROCEDURES

Nigrostriatal Lesions and Behavioral Testing

Male Sprague-Dawley rats (Taconic Farms, Germantown, NY, USA) weighing 275-325 g at the time of surgery were anesthetized with ketamine (100 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) and placed in a stereotaxic apparatus with the incisor bar at -3.5 mm. A hole was drilled in the skull above the appropriate coordinates and a 27-gauge injection cannula lowered to the left medial forebrain bundle: 4.4 mm rostral to the lambdoid suture, 1.2 mm lateral to the sagittal suture and 8.3 mm ventral to the surface of the skull. Six μ g of 6-OHDA HBr in 3 μ l of 0.9% saline containing 0.1% ascorbic acid were infused via the cannula over 3 min. The cannula was left in place for 3 min after the infusion. Rats were injected with desmethylinipramine (15 mg/kg, i.p.) 30 min prior to the intracerebral infusion to protect noradrenergic neurons. The post-operative diet of lesioned rats was supplemented with fruit and enriched jello to maintain weight. Five to seven days after surgery, rats were screened for lesion efficacy by step testing (Olsson et al., 1995). Only rats that demonstrated a strong lesion effect in behavior (number of steps by contralateral limb/number of steps by ipsilateral limb < 10%) were used for electrophysiology.

Surgical and Recording Procedures

All experiments were conducted in accordance with the NIH Guide for Care and Use of Laboratory Animals and approved by the NINDS Animal Care and Use Committee. Seven to 10 days after lesion, recordings were made in intact rats or in rats with unilateral 6-OHDA-induced dopamine cell lesions. Extracellular unit activity and LFPs of STN neurons in lesioned rats ipsilateral to the dopamine cell lesion or in intact rats were recorded through the same electrode. STN activity was simultaneously recorded with SNpr or motor cortex LFP activity. Extracellular unit activity and LFPs of striatal, GP, or SNpr neurons ipsilateral to lesion were also recorded with SNpr LFPs in the lesioned hemisphere. Recordings were conducted under urethane anesthesia (1.25 g/kg, i.p. initially, with additional supplements as needed). LFP activity also provided an indication of depth of anesthesia and effort was made to achieve levels of anesthesia that were sufficient to limit reflexive responses but not to induce burst suppression patterning in the LFP. All surgical sites and pressure points were infiltrated with the local anesthetic mepivacaine hydrochloride and ear bar tips were coated with 2% lidocaine gel. Ocular lubricant Lacrilube was applied to prevent corneal drying. Rats were placed into a stereotaxic apparatus (Kopf, Tujunga, CA, USA), the scalp reflected, and holes drilled in the skull over the target areas. Body temperature was maintained at 36-38°C using a heating pad.

With micromanipulators (MO-8, Narishige, East Meadow, NY, USA), glass recording electrodes filled with 2% Pontamine Sky Blue dye in 2 M NaCl were lowered through craniotomies to the SNpr, STN, GP, striatum, or motor cortex. Spike trains and LFPs were recorded with single barrel microelectrodes with $\sim 4\text{ M}\Omega$ resistances (measured at 135 Hz) with tip diameter of 1-2 μm . Electrode location varied in each nucleus without consistent placement in a specific subregion or, in the case of paired recordings, in topographically related regions. Recording sites were not differentially distributed in the lesioned hemisphere as compared with the intact hemisphere.

Extracellularly recorded action potentials were amplified (World Precision Instruments Duo 773, World Precision Instruments, Sarasota, FL, USA) and monitored on digital oscilloscopes (Hewlett-Packard, Palo Alto, CA, USA) and audio monitors (Grass, West Warwick, RI, USA). Spikes and LFPs were sampled at 25 kHz and 1000 Hz and band pass filtered at 250-5000 Hz and 0.1-100 Hz, respectively. Discriminated signals were collected on a PC with a CED interface and Spike2 data acquisition and analysis software (Cambridge Electronic Design, Cambridge, UK). All waveforms were biphasic (+/-). Final recording sites were marked by iontophoresis of dye with 15 min of constant current injection ($-18\text{ }\mu\text{A}$). Brains were then frozen. Twenty μm sections were mounted on subbed slides for histological examination. Only units confirmed as being within the target nucleus by location of dye deposit and/or electrolytic lesion were analyzed. Prior sites (when multiple recording sites were investigated) were reconstructed from coordinates to ascertain placement. The extent of neuronal loss in substantia nigra pars compacta was also histologically verified.

Respiration was monitored via a force sensing resistor (406, Interlink Electronics, Camarillo, CA, USA) placed under the animals, which registered contact force variations due to breathing. Incorporation of the resistor into a working device was implemented by the Research Services Branch, NIMH. Current from the sensor was band pass filtered (0.5-10 Hz), amplified, digitized, and stored using Spike2 acquisition software. Cardiac activity was monitored with surface EKG electrodes, lead II (Grass, West Warwick, RI, USA).

Data Analysis

For data analyses, 300 s of spike train and LFP data were isolated from baseline. These epochs were selected from the 5-10 min of baseline activity, were representative of neuronal activity, and free from artifacts. To evaluate neuronal activity, firing rates and patterns were characterized. Firing rate and the mean and standard deviation of the interspike intervals (ISI) were determined. To assess firing pattern regularity, the coefficient of variation of the interspike intervals (ISI CV) was employed; ISI CV was calculated by dividing the standard deviation of the ISIs in each 300 s epoch by the mean ISI of the epoch. In addition, spike train burstiness was assessed by the density discharge histogram method of Kanoeke and Vitek (1996), as described previously (Kreiss et al., 1997; Allers et al., 2005). A discharge density histogram with a bin width equal to twice the mean ISI was used for assessing burstiness with a burstiness index of 0.5 (see Magill et al., 2000; Wilson et al., 2004b). In some cases, a discharge density histogram with bin widths equal to 3 times the mean ISI was also used to assess differences in burstiness with a less stringent burstiness index cutoff criterion of 0.3. A spike train was identified as bursty if its discharge density histogram distribution was significantly different from a Poisson distribution of the discharge density histogram (χ^2 test set at a significance level of 0.05) and positively skewed, and the number of bursts/1000 spikes was > 5 .

Spiking and LFP activity were analyzed for significant oscillatory activity maintained over time within the frequency range of 0.3-2.5 Hz. Lomb periodogram-based power spectra were generated from 300 s epochs of spike data (Kaneoke and Vitek, 1996). The application

of this method to basal ganglia spike trains for analysis of recurrent oscillations in the multisecond and delta Hz ranges has been described in detail elsewhere (Ruskin et al., 1999, 2003; Allers et al., 2005). The Lomb algorithm is essentially comparable to fast Fourier transform (FFT) analyses with the practical advantage that this algorithm oversamples the data allowing for increased precision in slow oscillatory frequencies (Shrager, 2001). The Lomb periodogram was applied to autocorrelations of spike train activity binned at 50 ms with 10 s lag intervals. Spectral peaks in the periodogram were considered significant if they surpassed a significance level of $p=0.05$ in comparison with independent Gaussian random values. The dominant frequency (the frequency with the greatest spectral power) was reported here as the peak frequency for each 300 s data segment. Similar analyses were conducted on LFP activity; LFPs were smoothed to 20 Hz, high pass filtered at 0.2 Hz, and binned at 50 ms.

Phase relationships between spikes and LFPs were assessed using spike-triggered waveform averages and plotted as polar histograms. LFP channels were smoothed to 20 Hz and band pass filtered at 0.3-4.0 Hz. Spike-triggered waveform averages were calculated for 2 s before and after the spike trigger over a 300 s epoch. Phase relationships between spikes from paired recordings in SNpr and GP, and SNpr and STN were assessed with cross-correlations with a bin size of 5 ms over the same 300 s epochs. Cross-correlograms were scramble-corrected by the subtraction of a cross-correlogram produced from the same data after random shuffling of one of the spike trains using a Spike2 script. Scramble-corrected cross-correlograms with peak-to-trough amplitudes closest to the origin greater than 2.5 times the standard deviation (SD) of the corrected cross-correlograms were considered significant. Correlated oscillations were confirmed by the presence of a significant peak in Lomb analyses of the corrected cross-correlograms. Phase lag data were calculated from cubic splined scramble-corrected cross-correlograms.

Data are presented as the mean $\pm$ standard error of the mean (SEM). Data were statistically evaluated with paired t-test, grouped t-test, Mann Whitney U Rank Sum test, or analysis of variance (ANOVA) with Student-Newman-Keuls post-hoc analyses. Criterion of significance was $p < 0.05$. Statistics were generated with the statistical software package SigmaStat (SPSS Scientific, San Rafael, CA, USA). Polar data are presented as the mean phase angle of the distribution $\pm$ the angular deviation (analogous to standard deviation) and as polar histograms. Distribution of phase angles was tested against the null hypothesis of a random distribution with the Rayleigh test (Batschelet, 1981). The p-value for the Rayleigh test indicates the degree of grouping of the polar data and depends on the strength of the phase concentration and the number of data points.

Drugs

Desmethylinipramine HCl, urethane and 6-hydroxydopamine (6-OHDA) HBr, were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Ketamine HCl was purchased from Fort Dodge Animal Health (Fort Dodge, IA, USA), mepivacaine HCl from Winthrop Pharmaceuticals (New York, NY, USA) and xylazine from Phoenix Pharmaceutical, Inc. (St. Joseph, MO, USA). The ocular lubricant Lacrilube was purchased from Allergan Pharmaceuticals (Irvine, CA, USA).

RESULTS

The emergence of slow oscillatory firing patterns in the basal ganglia of the anesthetized rat after dopamine cell lesion was confirmed by analysis of spike trains from single unit recordings of neurons in the striatum, GP, STN and SNpr in intact rats and in the lesioned hemisphere of rats with 6-OHDA-induced unilateral medial forebrain bundle lesion. Identical analytical techniques were applied to all spike trains to assess the relative extent to

which firing pattern changes were expressed in the individual nuclei. Phase relationships of oscillatory firing patterns observed in the different nuclei after dopamine cell lesion were then assessed with reference to oscillatory activity in the SNpr, a basal ganglia output nucleus. This approach had the advantage of allowing both direct comparisons of SNpr, STN, GP, and striatal firing patterns with population activity in the SNpr, as reflected in SNpr LFP, and indirect comparisons of STN, GP and striatal firing patterns with each other. Paired recordings were also obtained from STN and cortical LFPs in order to reference spiking activity in the STN to cortical slow wave activity. In addition, to confirm and extend the results from spike-LFP correlations, spike train cross-correlations were also assessed for phase and strength in cases where both neuronal spike trains showed oscillations in the paired recordings involving GP and SNpr, and STN and SNpr. Results for individual nuclei are described below.

SNpr Spike Train Firing Patterns and Spike-LFP Phase Relationships after Dopamine Cell Lesion

SNpr firing patterns—SNpr spike trains in the lesioned hemisphere of dopamine cell lesioned rats had more irregular firing patterns than those recorded in intact rats (Fig. 1A). Interspike interval variability, as reflected in ISI CV values, for SNpr spike trains recorded in lesioned rats was 48% greater than in control rats (Table 1). SNpr spike train autocorrelograms were constructed and analyzed for oscillatory activity using the Lomb periodogram algorithm. Lomb based spectral analysis showed that 44% of SNpr spike trains from the lesioned hemisphere had significant 0.3-2.5 Hz oscillations in firing rate (Fig. 1B). In the intact preparation, no SNpr spike train demonstrated significant oscillations in this range. When burstiness was assessed (Kaneoke and Vitek, 1996) in the lesioned hemisphere using a Poisson mean of 2 with a burstiness index = 0.5, 19% of SNpr spike trains were significantly bursty; with a less stringent criterion, using a burstiness index = 0.3, 31% of SNpr spike trains were significantly bursty. None of the SNpr spike train recorded in intact rats were significantly bursty with either index value. Firing rates of neurons recorded in the SNpr of the two preparations were not significantly different (Table 1), despite the marked difference in firing pattern after dopamine loss. These observations are consistent with a number of studies showing increased burstiness or oscillatory activity in the SNpr 2-8 weeks after dopamine cell lesion in anesthetized rats (Sanderson et al., 1986; MacLeod et al., 1990; Burbaud et al., 1995; Murer et al., 1997; Rohlf et al., 1997; Tseng et al., 2000, 2001a; Belluscio et al., 2003).

SNpr spike-SNpr LFP phase relationships—SNpr LFP recordings were obtained in the lesioned hemisphere in conjunction with SNpr single unit activity. Relationships between spikes and simultaneously recorded LFPs for those spike trains with significant oscillations were typically antiphase. SNpr spikes routinely occurred in or near the troughs (or peak negativity) of the LFP oscillations, consistent with the idea that the trough of the LFP reflects the period when SNpr neurons are most depolarized and have a higher probability of generating action potentials (Fig. 1C; $n=9$). The average phase angle was $167 \pm 45^\circ$ with a significant unimodal clustering between SNpr firing rate oscillations and SNpr LFP oscillations.

STN Spike Train Firing Patterns, STN-Cortex and STN-SNpr Phase Relationships after Dopamine Cell Lesion

STN firing patterns—Firing patterns of STN neurons recorded ipsilateral to dopamine cell lesion were markedly more patterned than those recorded in intact animals (Fig. 2A). In lesioned rats, a notable burst/pause firing pattern was evident in almost all STN spike trains. Lomb-based analyses showed that the firing rates of STN spike trains varied in a periodic manner in the dopamine denervated hemisphere. Significant oscillations were observed in

the 0.3-2.5 Hz frequency range in 89% of spike train autocorrelograms (n=46) from STN neurons recorded ipsilateral to the dopamine cell lesion (Fig. 2B). In intact animals, notably fewer spike trains (26%) yielded autocorrelograms that were significantly periodic in the 0.3-2.5 Hz range (n=23). Additional analysis of these spike train firing patterns determined that most STN spike trains (94%) in the lesioned hemisphere were significantly bursty with bursts occurring at an average rate of 56 bursts per 1000 spikes. In contrast, none of the STN neurons recorded in intact rats had firing patterns that were significantly bursty over the 300 s epochs examined. These increases in oscillatory and bursty firing patterns observed in the lesioned hemisphere were also reflected in interspike interval variability; the ISI CV of STN spike trains in lesioned rats was 135% greater than in the intact rats (Table 1). Interspike interval variability in the STN was more than that in the SNpr; STN ISI CV was 119% greater than that for the SNpr in the lesioned hemisphere and 38% greater than the SNpr ISI CV in control rats. Overall firing rate was also increased after dopamine cell lesion; firing rates of STN neurons ipsilateral to dopamine cell lesions were significantly greater (66%) than those in intact animals (Table 1).

These results are consistent with other studies carried out in urethane anesthetized rats, as well as in rats anesthetized with chloral hydrate, ketamine, or combined urethane-ketamine anesthesia 1-8 weeks after dopamine cell lesion (Hollerman and Grace, 1992; Hassani et al., 1996; Vila et al., 2000; Magill et al., 2001; Ni et al., 2001; Tai et al., 2003). In the present study, differences between intact and lesioned animals were optimized by analyzing activity over a relatively long time period (300 s) and by the use of urethane alone. Combined use of urethane and ketamine produced a greater degree of burstiness in the intact state (Magill et al., 2000).

STN spike-cortical LFP phase relationships—To assess the phase relationships between slow oscillatory activity in STN spike trains and in cortical LFPs, a second electrode was placed in the ipsilateral motor cortex while STN activity was recorded. Cortical LFPs showed slow oscillations in amplitude characteristic of recordings from anesthetized animals (Steriade et al., 1993). Spectral analysis revealed that the peak frequencies of the STN firing rate oscillations (mean main peak: 1.0 ± 0.1 Hz) typically matched dominant frequencies of the simultaneously recorded motor cortex LFP oscillations (mean main peak: 1.2 ± 0.1 Hz) in lesioned rats. Similar results have been observed in STN-cortical electro-encephalogram recordings reported by Magill et al. (2001). STN oscillatory activity typically had a consistent phase relationship with simultaneously recorded cortical LFP (Fig. 2C). STN spike-triggered cortical LFP waveform averages showed STN spikes occurring most commonly during the trough of the cortical LFP oscillations in the 0.3-2.5 Hz range. A mean phase angle of $171 \pm 26^\circ$ and a strong unimodal concentration (Fig. 2C; n=14) were observed.

STN spike-SNpr LFP phase relationships and STN spike-SNpr spike cross correlations—To assess the phase relationships between oscillatory activity in the STN and SNpr, a second electrode was placed in the SNpr to allow recording of SNpr LFP while the first electrode was advanced through the STN in a series of tracks while recording STN spike trains (Fig. 2D). Spectral analysis of SNpr LFPs slow oscillations showed peak frequencies (mean main peak: 0.9 ± 0.1 Hz) were similar to peak frequencies of oscillations in STN firing rate (mean main peak: 0.9 ± 0.1 Hz). STN spiking activity had an antiphase relationship with simultaneously recorded SNpr LFP (Fig. 2D; n=23). Spike-triggered waveform averages showed STN spikes occurring most frequently at or near the trough of the SNpr LFP oscillation (corresponding to 180° on the phase plot). The mean phase angle for spikes from STN spike trains with significant oscillations plotted with respect to SNpr LFP spike-triggered waveform was $169 \pm 24^\circ$ with a significant unimodal distribution. As the troughs in the extracellularly recorded LFP reflects the time when the surrounding tissue

is depolarized and SNpr neurons are most likely to fire action potentials (Fig. 2D), the spike triggered waveform averages show that STN neurons are bursting in-phase with the periods of increased SNpr activity, as shown diagrammatically in Fig. 6. These results also indicate that the STN bursting activity occurs in a relatively synchronous manner across the population of STN neurons recorded, as STN spike trains demonstrated a consistent phase relationship with the SNpr LFP recorded through a second electrode held in a constant position in the SNpr.

Phase relationship data obtained from STN spike-triggered SNpr LFP waveform averages were confirmed by examination of STN spike-triggered SNpr spike cross-correlations. Of those recorded STN-SNpr pairs where both spike trains had significant oscillations in firing rate (5 of 11), cross-correlograms of 5 of 5 pairs had significant peaks (7.7 ± 0.6 times the SD of the scramble-corrected cross-correlogram), and significant slow oscillations (as reflected by Lomb periodogram analysis) (Fig. 5A) reflecting correlated activity in the two spike trains. Phase differences varied between 3 and 106 ms with a median value of 7 ms (-13 to 27° shift).

Striatal Spike Train Firing Patterns and Striatal-SNpr LFP Phase Relationships after Dopamine Cell Lesion

Striatal firing patterns—To explore effects of dopamine loss on striatal activity in the context of firing pattern changes in the SNpr, STN and GP, striatal spike trains in urethane anesthetized rats were first analyzed for oscillatory activity in intact and dopamine-lesioned hemispheres. Lomb periodogram based spectral analysis of spike train autocorrelograms illustrated that spiking activity of striatal neurons was significantly periodic in the dopamine denervated hemisphere and in the intact hemisphere (Fig. 3A). Significant oscillations were observed in the 0.3-2.5 Hz frequency range in 100% of spike train autocorrelograms ($n=9$) from striatal neurons recorded ipsilateral to the dopamine cell lesion (Fig. 3B). In intact animals, fewer spike trains (42%) yielded autocorrelograms that were significantly periodic ($n=12$). This may have been due in part to the slower rates observed in the striata of intact rats.

Firing patterns of most (80-100%) striatal neurons in both intact and lesioned hemispheres were significantly bursty, when burstiness was assessed over 300 s intervals with the density histogram method using a Poisson mean of 2 (burstiness index = 0.5), mean number of bursts per 1000 spikes and the mean number of spikes in a burst were significantly greater in the lesioned hemisphere (88.6 ± 4.1 vs. 48.6 ± 5.1 bursts/1000 spikes and 7.4 ± 0.4 vs. 4.3 ± 0.7 spikes/burst). In addition, striatal ISI CV increased by 48% with dopamine loss (Table 1). Striatal firing rate in the lesioned hemisphere was 2.4 times greater than in intact rats (Table 1). These observations are consistent with intracellular recording studies (Tseng et al., 2001b) that demonstrated striatal neurons have more depolarized membrane potentials during both the down-states and up-states and fire more spikes per up-state after dopamine cell lesion.

Striatal spike-SNpr LFP phase relationships—When striatal activity was recorded in the lesioned hemisphere in conjunction with SNpr LFP recordings (Fig. 3C; $n=6$), spectral analysis of striatal firing rate slow oscillations showed peak frequencies (mean main peak: 1.0 ± 0.2 Hz) similar to peak frequencies of SNpr LFP oscillations (mean main peak: 1.0 ± 0.2 Hz). Striatal spike activity was bursty (as described above) and showed a similar relationship to SNpr LFP as that observed in STN-SNpr recordings (see below and Fig. 2D); striatal spikes occurred at or near the trough of the SNpr LFP with an average phase angle of $168 \pm 23^\circ$ and significant unimodal clustering (Fig. 3C). These results are not consistent with direct input from the striatum shaping the firing rate oscillations in the SNpr, as

inhibitory striatal activity would be coincident with the periods of faster firing rates in the SNpr oscillatory cycle; they are consistent with an impact of striatal activity on oscillations in GP firing rates (see below, Fig. 6).

GP Spike Train Firing Patterns and GP Spike-SNpr LFP Phase Relationships after Dopamine Cell Lesion

GP firing patterns—To examine relationships between oscillatory activity in the GP and other basal ganglia nuclei, firing patterns were assessed in GP spike trains recorded from intact rats and the lesioned hemisphere of rats with unilateral dopamine cell lesions (Fig. 4A). In lesioned rats, GP firing patterns were considerably more irregular than in intact rats, often showing intermittent pauses in firing (Fig. 4A); a 4-fold increase in ISI CV compared to GP spike trains recorded from intact rats was noted (Table 1). Interspike intervals in GP spike trains were, however, more regular than STN spike trains and less regular than SNpr spike trains in the lesioned hemispheres: the mean ISI CVs for GP spike trains was 64% of that for STN spike trains and 134% of that for SNpr spike trains. In the intact hemispheres, the interspike intervals in GP spike trains were more regular than both the STN and SNpr spike trains. Consistently, fewer spike trains were significantly bursty in the GP than in the STN or SNpr, when assessed with the density histogram method. Using a burstiness index were significantly bursty in the lesioned hemisphere; when the less stringent burstiness index of 0.3 was used, there was a significant increase in the incidence (20%) of GP spike trains that were bursty. In intact rats, no GP spike trains were significantly bursty with either measure. Results are consistent with those reported by Hassani et al. (1996), Ni et al. (2000a), and Magill et al. (2000,2001) in anesthetized rats and by Pan and Walters (1988) in locally anesthetized, immobilized rats.

While spike trains recorded in the GP were more regular than those in the SNpr and STN in lesioned rats, most GP neurons in the lesioned hemisphere exhibited rhythmic variations in firing rate (Fig. 4A). Lomb based periodogram analysis of 300 s epochs showed 80% of GP spike trains recorded in the lesioned hemisphere had significant slow oscillations in firing rate with main peak frequencies in the 0.3-2.5 Hz range (Fig. 4B; n=15). Only 6% of the GP spike trains from intact rats had significant oscillations in this range (n=16). Interestingly, the marked difference in firing pattern between GP spike trains from intact and lesioned rats was not reflected in mean firing rate: a 15% reduction in firing rate of GP neurons from the lesioned hemisphere was not significantly different (Table 1).

GP spike-SNpr LFP phase relationships and GP spike-SNpr spike cross-correlations—When GP activity was recorded in conjunction with SNpr LFP, spectral analysis of SNpr LFP slow oscillations showed peak frequencies (mean main peak: 1.2 ± 0.1 Hz) similar to peak frequencies of oscillations in GP firing rate (mean main peak: 1.3 ± 0.1 Hz). In contrast to the STN-SNpr LFP recordings, GP spike-triggered SNpr LFP waveform averages demonstrated that GP neurons had a clear tendency to spike most frequently during the peaks of SNpr LFP oscillations, corresponding to times when firing rate in the SNpr was reduced (Fig. 4C). These results are consistent with an antiphase relationship between GP and SNpr firing rate oscillations, and also consistent with an antiphase relationship between GP and STN firing rate oscillations (Fig. 6). There was an $\sim 0^\circ$ phase angle for GP spikes plotted with respect to spike-triggered SNpr LFP waveforms in 11 of 12 recordings showing significant spike train oscillations (Fig. 4C). One spike train showed the opposite relationship with the SNpr LFP ($\sim 180^\circ$). The mean phase angle for these recordings was $4 \pm 34^\circ$ (n=12) with a significant unimodal distribution.

Phase relationship data obtained from GP spike-triggered SNpr LFP waveform averages were confirmed by GP spike-triggered SNpr spike cross-correlations. Of those recorded GP-

SNpr pairs where both spike trains had significant oscillations in firing rate (7 of 11), 5 of 7 pairs had cross-correlograms with significant peaks (7.0 ± 0.4 times the SD of the scramble-corrected cross-correlogram) and significant slow oscillations (as reflected by Lomb periodogram analysis) reflecting correlated activity in the two spike trains (Fig. 5B). The phase relationship between the firing of these GP and SNpr neurons varied between 2 and 25 ms with a median value of 9 ms (168 to 183° phase shift).

DISCUSSION

The goal of this study was to determine relationships between firing patterns in a series of interconnected basal ganglia nuclei to gain insight into how loss of dopamine enhances expression of oscillatory and synchronized activity in basal ganglia output in an animal preparation where cortical input has a stable slow rhythm. The preparation used in the present study, the urethane anesthetized rat, has the advantage that cortical activity is dominated by relatively regular, slow oscillations in the 1 Hz range. Single unit recordings found that loss of dopamine was associated with a widespread increase in expression of 1 Hz range oscillatory activity throughout the basal ganglia. Slow oscillations (0.3-2.5 Hz) in firing rate emerged in 80-100% of the spike trains in the striatum, GP, and STN, and 44% of spike trains in the SNpr 7-10 days after dopamine cell lesion. Consideration of the phase relationships of these oscillatory firing patterns in the context of the functional neuroanatomy of the network supports the hypothesis that loss of dopamine alters striatal activity and facilitates transmission of slow oscillations from cortex through striatum to the GP (Murer et al., 2002). Phase relationships of oscillatory activity in the GP, STN and SNpr argue that emergence of slow oscillatory activity in the SNpr is supported by the convergence of antiphase inhibitory oscillatory input from the GP and excitatory oscillatory input from the STN.

Firing Patterns in the Basal Ganglia Network after Dopamine Cell Lesion

To compare firing patterns and phase relationships in spike trains from striatum, STN, GP and SNpr in urethane anesthetized rats, the same analyses were applied to all nuclei. Variability in interspike intervals, as assessed by ISI CV, was significantly increased in all basal ganglia nuclei examined. Increases in burstiness, as assessed by the density histogram method, were most evident in the STN and SNpr, and increases in spikes per burst were observed in the striatum. Mean firing rates were significantly increased in the STN and the striatum but not significantly altered in the GP and SNpr at this post lesion time point. In general, the firing pattern changes observed are consistent with previous reports of alterations in individual basal ganglia nuclei in anesthetized, dopamine-depleted preparations at time periods 1-10 weeks after lesion (Sanderson et al., 1986; MacLeod et al., 1990; Hollerman and Grace, 1992; Burbaud et al., 1995; Hassani et al., 1996; Murer et al., 1997; Rohlf et al., 1997; Magill et al., 2000, 2001; Ni et al., 2000a, 2001; Tseng et al., 2000, 2001a; Vila et al., 2000; Belluscio et al., 2003; Tai et al., 2003). It is interesting to note that dopamine receptor antagonist-induced reductions in dopamine receptor stimulation also induce changes in firing pattern in basal ganglia output nuclei in anesthetized rats (Degos et al., 2005).

Phase Relationships of Oscillatory Activity within the Basal Ganglia Network with Respect to Basal Ganglia Output after Dopamine Cell Lesion

SNpr LFP as a common temporal reference—SNpr firing rate oscillations, when observed, were consistently antiphase with oscillations in simultaneously recorded SNpr LFP. This allowed use of LFP recordings from the SNpr as a common temporal reference to obtain insight into how alterations in activity at ‘upstream’ sites in the basal ganglia, such as

the striatum, GP and STN, might be contributing to the emergence of oscillatory activity in basal ganglia output after loss of dopamine (Fig. 6).

Cortex, Striatum, and GP relationships—Analysis of phase relationships of oscillatory activity in the striatum and GP in the present study supports the view that after dopamine loss, an increase in striatal output contributes to the emergence of oscillations in GP spike train firing patterns. When SNpr LFP oscillations were used as a temporal reference, the bursts in striatal activity were found to coincide with periods when pallidal neurons were, on average, less active.

The firing patterns observed in the striatum in these recordings are consistent with a considerable body of literature which has shown that striatal activity in anesthetized preparations is organized into ‘up-states’ and ‘down-states’ by slow, ~1 Hz oscillations in cortical activity (Wilson and Kawaguchi, 1996; Stern et al., 1997; Mahon et al., 2001; Tseng et al., 2001b; Murer et al., 2002; Goldberg et al., 2003). The increase in spikes per burst in striatal spike trains in the present study in lesioned rats is consistent with an intracellular recording study by Tseng, Murer and colleagues (Tseng et al., 2001b; Murer et al., 2002), which found that a population of striatal neurons is more depolarized after dopamine cell lesion and has an increased probability of firing in the ‘up-state’, leading to an increased number of spikes per oscillatory cycle.

It remains to be demonstrated that the medium spiny neurons showing increased burstiness after loss of dopamine are, in fact, the striatopallidal neurons. However, as striatopallidal neurons preferentially express D2 dopamine receptors and D2 receptor stimulation reduces the response of medium spiny neurons to cortical input (Gerfen et al., 1990; Robertson et al., 1992; Cepeda et al., 1993), it is consistent that dopaminergic denervation of the striatopallidal neurons would lead to increased response to cortical input. Selective loss of spines on D2 bearing striatal neurons provides an additional mechanism that could contribute to altered processing of cortical activity by striatopallidal neurons (Day et al., 2006). While the hypothesis that increased striatal output contributes to emergence of significant oscillations in GP spike trains is based only on correlative data in the present study, the phase relationships of the oscillations in the GP with respect to striatal activity are consistent with the inhibitory nature of striatopallidal projections.

Striatum, STN, and GP relationships—After dopamine cell lesion, relationships between striatum, GP and STN firing patterns inferred by referencing to SNpr LFPs and by cross-correlations of GP-SNpr and STN-SNpr spike trains support the view that oscillations in both striatal and STN spike trains are typically antiphase with those in GP spike trains. These data argue that after loss of dopamine, GP spike train firing pattern oscillations are influenced more by inhibitory input from the striatum than by excitatory input from the STN. If the STN exerted a dominant influence on the oscillatory firing pattern in the GP, phase relationships would be reversed.

Goldberg and coworkers have pointed out that because striatal synapses in the GP considerably outnumber STN synapses, the more robust striatal projection to the GP would be expected to have a greater influence than the STN in organizing activity in the GP (Shink and Smith, 1995; Goldberg et al., 2003), consistent with observations in the present study. Interestingly, however, in intact rats anesthetized with either ketamine/xylazine alone or in combination with urethane, in-phase relationships between GP activity and cortical EEG or striatal up-states have been observed, either consistently (Goldberg et al., 2003) or in a subset of recordings (Magill et al., 2000). These observations show that, in rats with an intact dopamine system, the GP firing patterns are more affected by STN input than by striatal input (Goldberg et al., 2003) and support the view that the level of dopamine

receptor stimulation is an important factor in modulating the relative roles of the striatum versus the STN on GP output. That said, it should also be noted that while the present study indicates a dominant influence of the striatum on the phase of slow oscillations in GP firing patterns, STN undoubtedly also influences aspects of firing pattern in the GP in lesioned animals. Ni et al. (2000a) have shown that STN lesion reduces the number of GP spike trains (~20%) identified as bursty after dopamine depletion.

Oscillatory activity in the SNpr in the context of striatal, GP, and STN input—

As the SNpr receives inhibitory input from the striatum and GP and excitatory input from the STN, phase relationships between striatum, GP and STN firing rate oscillations are highly relevant to the emergence of oscillatory activity in the SNpr after dopamine cell lesion in anesthetized rats (Terman et al., 2002). The present observation that GP and STN slow oscillations are typically antiphase is consistent with oscillations in inhibitory input from the GP and excitatory input from the STN collaborating in entraining oscillatory activity in the basal ganglia output nuclei. Oscillations in firing rate were observed in 44% of the SNpr spike trains in the lesioned hemisphere (Figs. 5, 6) and in most cases, GP spiking coincided with the phase of the slow oscillation in SNpr firing rate when SNpr neurons were less active, and STN spiking coincided with the phase when SNpr neurons were more active.

In contrast, phase relationships between oscillatory activity in the striatum and SNpr are not consistent with direct input from the striatum to the SNpr (i.e., via the direct pathway) exerting a dominant influence on the SNpr neurons expressing oscillatory activity in the anesthetized rat. Input to the SNpr from direct inhibitory striatonigral projections would dampen oscillatory activity driven by input from the GP and STN. In the context of the familiar dual circuit model of the basal ganglia (Albin et al., 1989; Alexander and Crutcher, 1990; DeLong, 1990), the present results argue that activity in the indirect pathway from the striatum to the SNpr via the GP and STN plays a more prominent role than the direct pathway in establishing slow oscillatory activity in the basal ganglia output nuclei after loss of dopamine. On the other hand, only 30-50% of the SNpr neurons are showing significant oscillations in the present study, a proportion consistent with other studies examining SNpr activity in the anesthetized dopamine cell lesioned preparation (Sanderson et al., 1986; Burbaud et al., 1995; Murer et al., 1997; Rohlfis et al., 1997; Tseng et al., 2000, 2001a; Belluscio et al., 2003). The observation that this proportion is considerably smaller than the proportion showing oscillatory activity in other areas of the basal ganglia suggests that the direct pathway is exerting a relatively greater influence, and counteracting the effect of the indirect pathway, on those SNpr neurons that fail to show oscillatory activity in the lesioned rats.

Increased Burstiness and Oscillations in the STN: Relevance to Phase Relationships in Anesthetized Rats and *In Vitro* Studies

Identifying the factors that induce alterations in firing pattern and rate in the STN after dopamine cell loss has been an important goal in PD research. The therapeutic efficacy of deep brain stimulation of the STN and GPi supports the significance of firing pattern changes in these nuclei with respect to PD motor symptoms. In particular, attention has focused on the STN as dysfunctional changes in SNpr and GPi activity are thought to be driven by dysfunctional changes in the STN. The present results support the hypothesis that one process contributing to increased burstiness and oscillations in the STN in a preparation where cortical activity is dominated by slow oscillatory activity is the modified interplay between cortical and pallidal input that results from dopamine lesion-induced alterations in striatopallidal and pallidal activity.

Phase relationships derived from STN spike-triggered cortical LFP waveform averages indicate that STN spiking is greatest during the trough of the LFPs recorded from within the cortex which coincides with the intervals of increased cortical spiking activity (Goldberg et al, 2004; Parr-Brownlie et al., 2006). Thus, phase relationships support a scenario in which increased oscillatory inhibitory input from the GP converges with antiphase excitatory input from cortex to contribute to changes in STN firing patterns after loss of dopamine.

Other inputs in addition to the GP, such as those from cortex, pedunculopontine and parafascicular nuclei (Orieux et al., 2000,2002;Breit et al., 2001; but see Ni et al., 2000b) could also be affected by loss of dopamine and play a role in modulating STN firing patterns after dopamine cell lesion. Cortical input to the basal ganglia appears critical as cortical ablation dramatically reduces the incidence of slow oscillations in the GP and STN after dopamine lesion in the anesthetized rat (Magill et al., 2001). However, a recent study in anesthetized rats with unilateral dopamine cell lesions did not find increased firing rates or increased oscillatory activity in either the anterior cingulate or motor cortex pyramidal neurons in the lesioned hemisphere (Parr-Brownlie et al., 2006). These results argue that while cortical input to the STN from these areas may be a critical partner in establishing the patterned activity that emerges in the STN after dopamine cell lesion in the anesthetized preparation, increases in cortical input, per se, are not contributing to the emergence of patterned activity in the STN.

On the other hand, recordings from organotypic co-cultures of STN and GP neurons have shown that the STN-GP network can, in the absence of cortical and striatal input, generate synchronous burst firing and oscillatory activity in slow frequencies (Plenz and Kitai, 1999), similar to those observed in the anesthetized preparation. In these co-cultures, STN bursts are both in-phase and antiphase to the bursts in the GP. However, these mechanisms do not appear sufficient to generate slow oscillatory activity in the STN-GP network in brain slices that preserve connectivity between GP and STN (Loucif et al., 2005). Nevertheless, these observations provide evidence that GP and STN networks have intrinsic mechanisms for supporting oscillatory activity in slow frequency ranges and led Plenz and Kitai (1999) to propose that activity in the indirect pathway supports changes in firing patterns observed after dopamine loss *in vivo*.

In vitro studies have made considerable progress in characterizing the neurophysiological properties of the STN neurons and exploring how different patterns of inhibitory and excitatory input might affect STN activity (Mintz et al., 1986; Nakanishi et al., 1987; Beurrier et al., 1999; Bevan and Wilson, 1999; Bevan et al., 2000, 2002a,b; Wigmore and Lacey, 2000; Zhu et al., 2002; Do and Bean, 2003; Hallworth et al., 2003; Wilson et al., 2004a,b; Baufreton et al., 2005; Surmeier et al., 2005; Kass and Mintz, 2006). With respect to the interplay of excitatory and inhibitory input, GABAergic inhibition can increase the efficiency of STN response to excitatory input by promoting recovery of inactivated voltage-dependent Na⁺ (Na_v) channels (Baufreton et al., 2005). This process could contribute to the increase in oscillations in the beta frequency (15-30 Hz) range observed in STN after dopamine cell lesion in awake preparations (Baufreton et al., 2005). This appears less suited for shaping slow oscillations, however, as, in the present results, phase relationships show that peak activity in the GP precedes the period of STN bursting by several hundred ms. A recent report by Kass and Mintz (2006), potentially relevant to the firing pattern triggered in the STN by slow antiphase oscillations in cortical and pallidal input, describes three coexisting patterns in STN neurons including pacemaker firing, burst mode, and a bistable state involving a relatively long-lasting silent plateau depolarization that tends to be preceded by a burst discharge. Relatively small changes in baseline membrane potentials, perhaps like those induced by alternating levels of excitatory input from cortex and inhibitory input from the GP, can trigger changes in STN firing between

these patterns. Studies examining the properties of STN neurons in brain slices from rats sacrificed after dopamine cell lesion have suggested that loss of dopamine within the STN (Gajendiran et al., 2005) and compensatory responses to alterations in glutamatergic and GABAergic input (Shen and Johnson, 2005) may also contribute to alterations in STN response after dopamine cell lesion.

Relevance to Awake Preparations and Faster Frequencies

The present observations shed light on previously conflicting results obtained in the STN in an awake, immobilized, locally anesthetized rat preparation (Kreiss et al., 1997; Allers et al., 2005). These studies in awake animals reported a significant increase in STN firing rate but no increased burstiness in STN spike trains after dopamine lesion. An obvious explanation for this difference between the awake and anesthetized preparations is the relative lack of slow oscillatory activity in the cortex in the awake preparation. It is interesting to note in this context that increases in burstiness are observed in STN recordings from sleeping unanesthetized rats (Urbain et al., 2000) when slow oscillatory activity would likely be increased in the cortex. Burstiness in neuronal activity in the GP and GPi is also more evident in the primate model of PD when the monkeys are asleep (Gatev and Wichmann, 2004).

These considerations call attention to the fact that one must be cautious about the relevance of data from anesthetized preparations with respect to the awake state. Conduction time differences with regard to direct and indirect routes from cortex to basal ganglia output nuclei will become more of an issue with patterned activity at the faster frequencies dominant in the awake state, and phase relationships at points where excitatory and inhibitory inputs converge will presumably play out differently than those observed here where conduction times are relatively insignificant with respect to the periods of the slow oscillations. However, frequencies relevant to the emergence of tremor and bradykinesia in PD may be slow enough to engage basal ganglia circuits in a manner comparable to the slow oscillations examined here, producing patterned output that disrupts thalamocortical activity. The present data suggest that in-phase input in slow frequency ranges from cortical areas projecting to functionally related regions of the STN and striatum could contribute to entraining slow oscillations in basal ganglia output after dopamine cell death.

In summary, the synchronized oscillations widely expressed in cortical activity in anesthetized rats were used in the present study to examine phase relationships of slow oscillations in the basal ganglia network in the context of the excitatory and inhibitory components of the direct and indirect pathways. Results are consistent with a role for changes in striatal processing of cortical input, increased transmission of slow oscillations through the indirect pathway, and convergence of oscillatory output from the STN and GP in shaping the temporal characteristics of oscillatory firing patterns that emerge in basal ganglia output in the anesthetized rats after dopamine cell lesion.

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Glossary

Abbreviations:

EEG electroencephalogram

GP	globus pallidus external segment
GPI	globus pallidus internal segment
ISI CV	interspike interval coefficient of variation
LFP	local field potential
PD	Parkinson's disease
SNpr	substantia nigra pars reticulata
STN	subthalamic nucleus
6-OHDA	6-hydroxydopamine

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Figure 1.

Characteristics of SNpr spike trains and relationship between SNpr spikes and SNpr LFPs. A. Typical spike trains from SNpr neurons in a neurologically intact rat (left) and ipsilateral to a unilateral dopamine cell lesion (right). After a unilateral dopamine cell lesion, SNpr spike trains recorded ipsilateral to the lesion showed more bursty and oscillatory activity (right) than SNpr spike trains from intact rats (left). B. Spectral analyses of SNpr spike train autocorrelograms and incidence of spike trains with 0.3-2.5 Hz oscillatory firing pattern from SNpr spike trains illustrated in A. Spectral analysis of spike train autocorrelograms by Lomb periodograms revealed significant oscillations in the 0.3-2.5 Hz range in SNpr firing rate in the lesioned animal but not in the intact. Note the absence of significant oscillations in the SNpr spike train from an intact rat (left) and the presence of significant oscillations with a main peak oscillation at 0.7 Hz in the SNpr spike train from a lesioned rat (middle). Dashed horizontal lines in the spectra indicate the $p=0.05$ level of significance. C. SNpr spike and SNpr LFP relationships in the lesioned hemisphere. As illustrated by the representative example on the left, SNpr spikes occurred most frequently at or near the trough ($\sim 180^\circ$) of the SNpr LFP oscillation. SNpr spike-triggered SNpr LFP waveform average (middle) confirmed this observation. Polar histogram plot (right) summarizes the

distribution of phases of SNpr spikes with respect to SNpr LFP for all significantly oscillating SNpr spike trains recorded with SNpr LFPs. Data are based on 300 s epochs; examples in A and C are representative 10 and 6 s epochs of 300 s epochs. * $p < 0.05$ compared with intact

Figure 2.

Characteristics of STN spike trains and relationships between STN spikes and cortical and SNpr LFPs. A. Typical spike trains from STN neurons in a neurologically intact rat (left) and ipsilateral to a unilateral dopamine cell lesion (right). Most STN spike trains recorded ipsilateral to lesion showed bursty and oscillatory firing patterns that were not typically observed in the intact hemisphere. B. Spectral analyses of oscillatory activity and incidence of spike trains with 0.3-2.5 Hz oscillatory firing pattern. Spectral analyses of STN spike train autocorrelograms from spike train data illustrated in A revealed no significant oscillations in STN firing rate in the intact animal and a significant periodic oscillation with a main peak frequency at 0.8 Hz in the lesioned rat. C. STN spike and cortical LFP

relationships in the lesioned hemisphere. Simultaneous recordings of STN spike trains with cortical LFPs (left) demonstrated that STN spikes occurred most frequently at or near the trough ($\sim 180^\circ$) of the cortical LFP oscillation, as illustrated also by the STN spike-triggered cortical LFP waveform average (middle). Polar histogram plot (right) summarizes the distribution of phases of STN spikes with respect to cortical LFP for all significantly oscillating STN spike trains recorded with cortical LFPs. D. STN spike and SNpr LFP relationships in the lesioned hemisphere. As shown by the representative example on the left, STN spikes occurred most frequently at or near the trough ($\sim 180^\circ$) of the SNpr LFP oscillation. STN spike-triggered SNpr waveform average (middle) confirmed this observation. Polar histogram plot (right) summarizes the distribution of phases of STN spikes with respect to SNpr LFP for all significantly oscillating STN spike trains recorded with SNpr LFPs. Data are based on 300 s epochs; examples in A, C and D are representative 10 and 6 s epochs of 300 s epochs. * $p < 0.05$ compared with intact

Figure 3.

Characteristics of striatal spike trains and relationship between striatal spikes and SNpr LFPs. A. Typical spike trains from striatal neurons in a neurologically intact rat (left) and ipsilateral to a unilateral dopamine cell lesioned (right). Most striatal spike trains displayed patterned activity in both intact (left) and dopamine cell lesioned (right) animals. B. Spectral analyses of oscillatory activity and incidence of spike trains with 0.3-2.5 Hz oscillatory firing pattern. Spectral analysis of spike train autocorrelograms by Lomb periodograms derived from 300 s epochs of the spike trains illustrated in A revealed significant oscillations in striatal spike trains from intact (left) and lesioned (right) animals in the 0.3-2.5 Hz range. Illustrated in the Lomb periodograms are a significant main peak 0.6 Hz oscillation in the intact preparation and a significant main peak oscillation of 0.9 Hz with a significant but lesser peak (not labeled) at 0.7 Hz in the lesioned preparation. C. Striatal spike and SNpr LFP relationships in the lesioned hemisphere. Simultaneous recordings of striatal spiking with SNpr LFPs (left) demonstrated that striatal spikes occurred most frequently at or near the trough ($\sim 180^\circ$) of the SNpr LFP oscillation. Striatal spike-triggered SNpr LFP waveform average (middle) confirmed this observation. Polar histogram plot (right) summarizes the distribution of phases between striatal spike firing with respect to SNpr LFP for all

significantly oscillating striatal spike trains recorded with SNpr LFPs. Data are based on 300 s epochs; examples in A and C are representative 10 and 6 s epochs of 300 s epochs. * $p < 0.05$ compared with intact

Figure 4.

Characteristics of GP spike trains and relationship between GP spikes and SNpr LFPs. A. Typical spike trains from GP neurons in a neurologically intact rat (left) and ipsilateral to a unilateral dopamine cell lesion (right). After a unilateral dopamine cell lesion, GP spike trains recorded ipsilateral to the lesion showed more patterned activity (right) than GP spike trains from intact rats (left). Pauses in GP firing were more notable than bursts in the lesioned rat. Oscillatory activity was prominent in the lesioned rat. B. Spectral analyses of GP spike train autocorrelograms and incidence of spike trains with 0.3-2.5 Hz oscillatory firing pattern from 300 s of spike train data from GP neurons illustrated in A. Note the absence of significant oscillations in the GP spike train from an intact rat (left) and the presence of a 0.7 Hz significant oscillation in the GP spike train from a lesioned rat (middle) in the 0.3-2.5 Hz range. C. GP spike and SNpr LFP relationships in the lesioned hemisphere. Simultaneous recordings of GP spiking with SNpr LFPs (left) showed that GP spiking coincided with the peak ($\sim 0^\circ$) of the SNpr LFP oscillations as illustrated by the GP spike-triggered SNpr LFP waveform average of this recording (middle). Polar histogram plot (right) summarizes the distribution of phases of GP spikes with respect to the oscillatory SNpr LFP for all significantly oscillating GP spike trains recorded with SNpr LFPs. Data are

based on 300 s epochs; examples in A and C are representative 10 and 6 s epochs of 300 s epochs. * $p < 0.05$ compared with intact

Figure 5.

Spike trains and cross-correlations showing correlated activity in slow frequency ranges between STN and SNpr, and between GP and SNpr ipsilateral to a unilateral dopamine cell lesion. Spike trains examples shown above are representative of the 300 s epochs used for cross-correlation analysis. A. Simultaneously recorded STN and SNpr spike trains illustrate in-phase activity. STN-triggered SNpr cross-correlogram shows that activity is significantly correlated (peak to trough amplitudes > 2.5 times the SD) and in-phase (2° phase difference). Lomb periodogram power spectrum shows the dominant frequency in the scramble-corrected cross-correlogram at 0.5 Hz. B. Simultaneously recorded GP and SNpr spike trains illustrate antiphase activity. GP-triggered SNpr cross-correlogram shows that spiking activity is significantly correlated with an antiphase relationship (181° phase difference). Lomb periodogram power spectrum shows the dominant frequency in the scramble-corrected cross-correlogram is 0.8 Hz. Maximal peak-to-trough amplitudes closest to the origin are 9.9 and 7.7 times the SD of the bin values for these STN-SNpr and GP-SNpr scramble-corrected cross-correlograms, respectively.

Figure 6.

Model illustrates a hypothesized scheme for passage of oscillatory signals in the slow 0.3-2.5 Hz range through the cortico-basal ganglia pathway after dopamine loss in anesthetized rats. Green lines indicate excitatory connections between nuclei and red lines indicate inhibitory connections. Examples of striatal, GP, STN, and SNpr spiking activity recorded simultaneously with SNpr LFP are shown with SNpr LFP as a common temporal reference (indicated in green). Results are consistent with loss of dopamine enhancing transmission of oscillatory activity primarily through the indirect pathway, resulting in robust oscillatory activity in the SNpr. Implied in this model are:

1. D2 receptor-bearing striatopallidal neurons transmitting patterned activity from the cortex to the GP.
2. Striatal-mediated pauses in inhibitory GP activity contributing to the timing of bursts in STN neuronal activity.
3. Pauses in inhibitory GP output coinciding with bursts in excitatory STN output supporting enhanced oscillatory activity in SNpr/GPi spike trains.

Table 1

Interspike interval coefficient of variation (ISI CV) and mean firing rates of basal ganglia spike trains in intact and dopamine cell lesioned animals recorded in urethane anesthetized rats.

	ISI CV		FIRING RATE (HZ)	
	Intact	Lesioned	Intact	Lesioned
Subthalamic Nucleus (n=23, 31)	0.69 ± 0.06	1.62 ± 0.07 *	5.5 ± 0.7	9.2 ± 0.9 *
Striatum (n=9, 12)	1.29 ± 0.09	1.91 ± 0.09 *	0.7 ± 0.2	2.3 ± 0.4 *
Globus Pallidus (n=16, 15)	0.21 ± 0.03	0.99 ± 0.09 *	26.4 ± 1.4	22.4 ± 2.5
Substantia Nigra Pars Reticulata (n=18, 16)	0.50 ± 0.07	0.74 ± 0.06 *	24.2 ± 2.8	18.4 ± 1.9

Data are expressed as mean ± sem. N's represent the number of spike trains from intact rats and lesioned rats, respectively.

* Significantly different from intact, p<0.05