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Parafascicular Thalamic Nucleus Activity in a Rat Model of Parkinson's Disease

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Abstract

Parkinson's disease is associated with increased oscillatory firing patterns in basal ganglia output, which are thought to disrupt thalamocortical activity. However, it is unclear how specific thalamic nuclei are affected by these changes in basal ganglia activity. The thalamic parafascicular nucleus (PFN) receives input from basal ganglia output nuclei and directly projects to the subthalamic nucleus (STN), striatum and cortex; thus basal ganglia mediated changes on PFN activity may further impact basal ganglia and cortical functions. To investigate the impact of increased oscillatory activity in basal ganglia output on PFN activity after dopamine cell lesion, PFN single-unit and local field potential activities were recorded in neurologically intact (control) rats and in both non-lesioned and dopamine lesioned hemispheres of unilateral 6-hydroxydopamine lesioned rats anesthetized with urethane. Firing rates were unchanged 1–2 weeks after lesion; however, significantly fewer spontaneously active PFN neurons were evident. Firing pattern assessments after lesion showed a larger proportion of PFN spike trains had 0.3–2.5 Hz oscillatory activity and significantly fewer spike trains exhibited low threshold calcium spike (LTS) bursts. In paired recordings, more PFN-STN spike oscillations were significantly correlated, but as these oscillations were in-phase, results are inconsistent with feedforward control of PFN activity by inhibitory oscillatory basal ganglia output. Furthermore, the decreased incidence of LTS bursts is incompatible with inhibitory basal ganglia output inducing rebound bursting in PFN after dopamine lesion. Together, results show that robust oscillatory activity observed in basal ganglia output nuclei after dopamine cell lesion does not directly drive changes in PFN oscillatory activity.

Keywords

low threshold calcium spike (LTS) bursts; thalamosubthalamic pathway; intralaminar thalamic nucleus; basal ganglia; Parkinson's disease; slow wave oscillations

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INTRODUCTION

Over the last decade, research on the neurophysiology of Parkinson's disease has largely focused on the nature and mechanism of changes in neuronal activity in basal ganglia nuclei. These changes in basal ganglia function are believed to mediate dysfunctional effects in Parkinson's patients through impact on interconnected circuits that include thalamus and cortex. In particular, increased oscillatory activity in spike trains of basal ganglia nuclei projecting to the thalamus are reported in Parkinson's disease patients (Hurtado et al., 1999, 2005; Hutchison et al., 1994, 1997; Levy et al., 2001, 2002; Tang et al., 2007). However, although some thalamic nuclei are immediately downstream from basal ganglia output, it is unclear how changes in basal ganglia output modify thalamic activity in Parkinson's disease. Basal ganglia physiologists have hypothesized that changes in thalamic activity might include increases and decreases in firing rate, and increased bursty and oscillatory activity (Albin et al., 1989; Bergman et al., 1998; Brown and Marsden, 1998; DeLong, 1990; Magnin et al., 2000; Ni et al., 2000; Penney and Young, 1983; Pessiglione et al., 2005).

The thalamic nuclei that receive input from basal ganglia output nuclei also receive diverse inputs from cortex, brainstem, reticular thalamic nucleus and in some cases from the cerebellum (Angaut et al., 1985; Capozzo et al., 2003; Cornwall and Phillipson, 1988; Guillery and Harting, 2003; Ilinsky et al., 1999; Ilinsky and Kultas-Ilinsky, 2001; Nakano et al., 1985; Royce, 1983; Shinoda et al., 1993; Van der Werf et al., 2002). Inputs to individual thalamic nuclei are frequently characterized as either 'drivers' or 'modulators', depending on their functional role. Anatomical and electrophysiological evidence shows that drivers are typically excitatory inputs that play a critical role in carrying messages to be relayed by the thalamus to the cortex (Sherman and Guillery, 2006). For thalamic nuclei that receive input from basal ganglia output nuclei, it has been suggested that cerebellar and layer V pyramidal neurons in the cortex act as *drivers*, whereas inputs from other regions *modulate* thalamic neurons (Harding, 1973; Ilinsky and Kultas-Ilinsky, 1990; Kultas-Ilinsky and Ilinsky, 1991; Kultas-Ilinsky et al., 1997; Sherman and Guillery, 2006). Viewed from this perspective, inhibitory input from the basal ganglia might be predicted to have a modest modulatory influence on thalamic activity. However, a recent study shows that substantia nigra pars reticulata (SNpr) neurons form complex synapses (glomeruli) in ventromedial thalamus, raising the possibility that projections from basal ganglia output nuclei might act as drivers in some thalamic nuclei (Bodor et al., 2008).

The issues discussed above make it difficult to predict how changes in basal ganglia output that occur in Parkinson's disease may affect thalamic activity. One view is that the synchronized oscillatory inhibitory activity that emerges in basal ganglia output nuclei after dopaminergic lesion could disrupt ongoing information processing by inducing anti-phase oscillations in thalamic spike trains. However, it is also possible that the increased inhibitory oscillatory activity could have a driver-like effect causing in-phase spiking, as periods of sustained hyperpolarized membrane potential can induce rebound spiking of thalamic neurons via low threshold calcium spike (LTS) bursts (Jahnsen and Llinas, 1984; Llinas and Jahnsen, 1982; Steriade et al., 1990). How thalamic activity is affected by changes in basal ganglia output after dopaminergic lesion is an interesting question, not only with respect to potential disruption of thalamic function, but also in the context of whether oscillatory activity in basal ganglia output has the potential to entrain oscillatory activity throughout basal ganglia-thalamocortical networks.

In the anesthetized 6-hydroxydopamine (6-OHDA) rat model of Parkinson's disease, many inhibitory GABAergic projection neurons in basal ganglia output nuclei exhibit bursty and ~1 Hz oscillatory firing patterns (Belluscio et al., 2003, 2007; Burbaud et al., 1995; MacLeod et al., 1990; Murer et al., 1997; Rohlfes et al., 1997; Sanderson et al., 1986; Tseng et al., 2001,

2005; Walters et al., 2007). Slow wave (~1 Hz) oscillatory activity is prominent in the cortex in urethane anesthetized rats (Steriade et al., 1993a), and this cortical input is critical for expression of slow wave oscillations in the basal ganglia (Magill et al., 2001). It is hypothesized that dopamine loss increases the expression of this ~1 Hz rhythm in basal ganglia nuclei through enhanced transmission of the cortical rhythm via the indirect pathway (Murer et al., 2002; Walters et al., 2007). The present study examines the impact of increased inhibitory oscillatory activity in basal ganglia output in the anesthetized rat model of Parkinson's disease on firing rates and patterns in the parafascicular nucleus of the thalamus (PFN). The PFN is of special interest with respect to changes in basal ganglia output in Parkinson's disease because it both receives input from the basal ganglia (Gerfen and Wilson, 1996) and it projects to the striatum and subthalamic nucleus (STN) (Bevan et al., 1995; Castle et al., 2005; Lacey et al., 2007; Smith et al., 2004); therefore, dopamine lesion-induced changes in PFN activity may further impact basal ganglia function. In addition, recent studies have reported that PFN may undergo pathological changes in patients (Henderson et al., 2000a, 2000b).

The aim of this study was to investigate whether PFN activity is altered in parkinsonian rats. This was assessed using single-unit and local field potential (LFP) recordings from the PFN of neurologically intact (control) rats and in both lesioned and non-lesioned hemispheres of 6-OHDA-lesioned rats, 1–2 weeks after dopaminergic lesion. In addition, firing relationships between PFN and basal ganglia neurons were investigated by simultaneously recording PFN-STN neurons in control and lesioned rats. Results show that changes in PFN activity are subtle after dopamine lesion, and the timing of activity between PFN and STN is not consistent with inhibitory oscillatory basal ganglia output driving PFN activity.

METHODS

All experimental procedures were conducted on male Sprague-Dawley rats (Taconic Farm, Rockville, MD, U.S.A.) in accordance with the NIH Guide for Care and Use of Laboratory Animals and were approved by the NINDS Animal Care and Use Committee. Rats were housed with *ad libitum* access to chow and water in environmentally controlled conditions. Every effort was made to minimize the number of animals used.

Unilateral 6-hydroxydopamine lesion procedure and behavioral testing

Unilateral lesions were performed on rats weighing 260–360 g at the time of lesion surgery. Rats were anesthetized with ketamine (100 mg/kg, i.p., Ketaved, Vedco Inc., St Joseph, MO, U.S.A.) and xylazine (10 mg/kg, i.p., AnaSed, Lloyd Laboratories, Shenandoah, IA, U.S.A.), the incision area was shaved and a long acting local anesthetic (1% mepivacaine HCl solution s.c., Polocaine, AstraZeneca, Wilmington, DE, U.S.A.) was injected along the intended incision line. Rats were injected with desmethylinipramine (15 mg/kg i.p., Sigma-Aldrich, St. Louis, MO, U.S.A.) 30 minutes prior to the neurotoxic lesion. The rat was mounted in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, U.S.A.), ophthalmic ointment (Puralube, Fougere & Co., Melville, NY, U.S.A.) was applied to the eyes to prevent corneal dehydration and the skull exposed by a midline sagittal incision. A hole was drilled over the chosen stereotaxic coordinates above the left medial forebrain bundle and the dura was reflected. Target coordinates for the cannula were centered at anteroposterior (AP) + 4.4 mm from the lambdoid suture and lateral –1.2 mm from lambda in the flat skull position and the cannula was lowered 8.3 mm from the skull surface. Six µg of 6-hydroxydopamine HBr (6-OHDA) in 3 µL of 0.9% saline solution containing 0.008% ascorbic acid (Sigma-Aldrich) were infused via a cannula into the medial forebrain bundle. Following the infusion, the cannula remained at the target site for an additional 3 minutes to prevent diffusion of the neurotoxin. Body temperature was maintained at 36–38 °C throughout the procedure by a heating pad. The

post-operative diet of lesioned rats was supplemented with fruit and gelatin to maintain normal weight.

The extent of the dopaminergic denervation was tested behaviorally 5–7 days after the lesion using the step test (Olsson et al., 1995). Only rats that demonstrated a strong lesion effect (number of steps by contralateral limb/number of steps by ipsilateral limb <5%) were used for electrophysiological recordings. Similar studies in our lab (Parr-Brownlie et al., 2007) and others (Olsson et al., 1995; Tseng et al., 2005) have shown that severely impaired stepping behavior is associated with more than 95% of dopamine depleted in the ipsilateral striatum or loss of more than 95% of dopamine neurons in the ipsilateral substantia nigra pars compacta.

Single unit and local field potential (LFP) recording procedures

Extracellular single-unit and LFP recordings were conducted in the PFN 7–13 days after unilateral 6-OHDA infusion. In this study, the non-lesioned hemisphere refers to the hemisphere contralateral to unilateral dopamine cell lesion, and the lesioned hemisphere pertains to the hemisphere ipsilateral to 6-OHDA infusion. In some experiments PFN neurons were simultaneously recorded in both the dopamine lesioned and non-lesioned hemispheres. Single-units and LFPs were also recorded in the PFN of control (neurologically intact) rats weighing 270–360 g at the time of surgery. To examine the firing relationship between PFN and basal ganglia nuclei, neurons were simultaneously recorded from PFN and STN in control rats or in the 6-OHDA-lesioned hemisphere in some experiments. PFN-STN paired recordings permit indirect assessment of phase relationships between basal ganglia output nuclei and PFN because correlated STN-SNpr spike train activity is in-phase (Walters et al., 2007). In addition, it was of interest to assess STN-PFN relationships directly as there are some reciprocal connections (Castle et al., 2005). SNpr neurons were not used to assess firing relationships between PFN and basal ganglia nuclei because few SNpr neurons (~5%) exhibit ~1 Hz oscillatory activity in neurologically intact urethane-anesthetized rats compared to STN (~20%) (Belluscio et al., 2003; Tseng et al., 2005; Walters et al., 2005, 2007).

All recordings were conducted under urethane anesthesia (1.4 g/kg i.p. with additional doses as needed, Sigma-Aldrich). Rats were shaved, mepivacaine HCl solution was injected s.c. along the intended incision line, surface electrocardiogram (ECG) electrodes were placed in the axilla and pelvic regions (Lead II, Grass, West Warwick, RI, U.S.A.) and ophthalmic ointment was applied to the eyes. Rats were placed in a stereotaxic frame with a heating pad to maintain body temperature and a force sensing resistor (Interlink Electronics, Camarillo, CA, U.S.A.) was placed under the diaphragm region. ECG and respiration were monitored to ensure the animals' well being. Craniotomies were made over the target coordinates, relative to bregma (flat skull position) for PFN (AP -4.2 mm, lateral $\pm$ 1.3 mm) or STN (AP -3.8 mm, lateral $\pm$ 2.4 mm).

Glass microelectrodes with impedances of 4–7 M Ω (measured at 135 Hz, tip diameter 1–2 μ m) were used to record extracellular action potentials and LFPs. Glass electrodes were filled with 1% Pontamine Sky Blue dye in 2 M NaCl solution. Electrodes were lowered into the brain until they were just above the target structures (dorsoventral from the dura: PFN 4.8–6.5 mm; STN 7.0–8.0 mm) and advanced slowly using hydraulic microdrives (Narishige International USA Inc, East Meadow, NY, U.S.A.) to isolate single cells. Sampling rates were 27 kHz and 1 kHz for unit and LFP activities, respectively (Micro 1401, Cambridge Electronic Design, Cambridge, U.K.). Action potentials were amplified (3000 $\times$), bandpass filtered (250–5000 Hz) and monitored on oscilloscopes (Hewlett-Packard, Palo Alto, CA, U.S.A.) and audiomonitors (Grass, West Warwick, RI, U.S.A.). LFPs were amplified (2000 $\times$) and bandpass filtered (0.1–100 Hz). Discriminated signals were digitized, stored and analyzed using Spike2 data acquisition and analysis software (Cambridge Electronic Design). The majority of neurons in

the PFN (207/250, 83%) and STN (53/57, 93%) had biphasic action potentials with the first deflection positive. Neuronal spike trains were recorded for at least 6 minutes.

Data Analysis

For analyses of spontaneous activity, one 300 s epoch of simultaneously recorded spiking and LFP activities that was free of artifacts was used from every recorded neuron. Data are represented as means $\pm$ standard error of the means (SEM).

Two types of “burst analyses” were conducted on recorded data. First, spike train burstiness was assessed in all recorded spike trains by the density discharge histogram method as described previously (Kaneoke and Vitek, 1996; Parr-Brownlie et al., 2007; Walters et al., 2007). This analysis defines a burst as a period of time where there are significantly more spikes compared to other periods in the spike train, and was used to categorize the general firing pattern of the spike train. A burstiness index ≥ 0.5 was used for this analysis, so that the bin width of the discharge density histogram was twice the mean interspike interval (ISI). A spike train was classified as bursty if it met the following criteria: the distribution of its discharge density histogram was significantly different from a Poisson distribution of the discharge density histogram (chi square test set at a significance level of 0.05), the histogram was positively skewed, there were at least 3 spikes in the burst, firing rate was greater than 1.0 Hz and the number of bursts/1000 spikes was >5 . Second, the characteristics of low threshold calcium spike (LTS) bursts were examined in only PFN spike trains. These spike bursts are a feature of thalamic relay neurons in anesthetized and sleeping animals, and are caused by deinactivation of transient calcium channels following sustained hyperpolarization of thalamic membrane potential (Jahnsen and Llinas, 1984; Llinas and Jahnsen, 1982; Steriade et al., 1990). The following criteria were used to define LTS bursts: the first ISI in the burst was ≤ 5 ms, subsequent ISIs in the bursts were ≤ 7 ms, and the burst was preceded with a silent period of at least 100 ms (Jahnsen and Llinas, 1984; Lacey et al., 2007; Lu et al., 1992; Steriade et al., 1985, 1990). LTS bursts contained 2–5 spikes.

Spike train regularity was determined using interspike interval coefficient of variation (ISI CV). The number of spontaneously active neurons per recording track in the PFN was assessed in a subset of recordings. For this analysis, recording tracks were used if they were obtained when the PFN recording was between AP -4.1 mm to -4.3 mm (relative to bregma) and at least 1 neuron was encountered per track. Spontaneously active neurons were assessed over a track distance of 1.5 mm in the dorsoventral orientation.

Oscillatory characteristics of spike train activity were analyzed by the method of Kaneoke and Vitek (1996). Briefly, a Lomb periodogram based analysis was performed on spike train autocorrelograms (50 ms bins, 10 s lag). For evenly sampled data, the Lomb algorithm is similar to a fast Fourier transform (FFT) (Shrager, 2003). In figures showing periodogram spectra, points above the dashed line ($p=0.05$) reflect frequencies with power significantly greater than expected in comparison with independent Gaussian random values.

LFP data were smoothed to 20 Hz. For power analyses, smoothed LFPs were high pass filtered at 0.2 Hz (Spike2). Variability in the mean amplitude of LFP recordings was determined by calculating the root mean square (RMS) over the first 50 s of 300 s epochs, and reflects the relative change in LFP power (Moran et al., 2006; Zaidel et al., 2008). LFP power was calculated using FFT with 256 blocks and a measure of total power was obtained by summing the area of individual 0.078 Hz bins over the 0.3–2.5 Hz range from 300 s epochs of data. Only one LFP recording was used from each recording track for LFP power analyses.

Synchronization of oscillatory spiking activity was assessed using the LFP ~ 1 Hz oscillation as a temporal marker (Fries et al., 2001). The temporal relation between spiking and LFP activities was assessed using spike triggered waveform averages (STWAs) generated from LFP

recordings smoothed to 20 Hz and bandpass filtered at 0.3–2.5 Hz (Spike2). The phase relationships of neuronal spiking were calculated from STWAs with the convention that spikes occurring at the peak or at the trough were considered to be at 0° or 180° phase, respectively.

The relationships between simultaneously recorded spike trains from PFN and STN were evaluated with cross correlograms constructed from 300 s epochs using Spike2 analysis software (5 ms bins, 8 s lag). The STN spike train was used as the reference spike (time zero). To assess the significance of the correlation in firing pattern between each pair of neurons, a baseline firing rate was determined over the first or last 0.5 s of the cross-correlogram, whichever had the largest standard deviation (SD). Thresholds were defined as the baseline $\pm$ 3 SD. If at least three consecutive bins of the cross-correlogram exceeded the threshold, the neuron pair was classified as correlated. For correlated pairs, the time between peak activity in the PFN neuron with respect to the STN neuron was measured on correlograms with smoothed (cubic spline) bins.

The effects of lesion on firing rate, spontaneously active neurons per track, LTS bursts per spike train, variability in LFP recordings and LFP power were compared using either t-test (STN data set) or one factor analysis of variance (ANOVA, PFN data set) with Holm-Sidak post-hoc comparisons if the data were normally distributed. In cases where data were not normally distributed, non-parametric tests (Mann-Whitney U test or Kruskal-Wallis ANOVA with Dunn's method post-hoc comparisons) were used. ISIs in LTS bursts were analyzed by a 3 way ANOVA, with hemisphere (control, non-lesioned and lesioned), size of LTS bursts (doublets to quintuplets), and position of the ISI in LTS bursts (first ISI vs second ISI etc.) as factors. Post-hoc comparisons were made using Bonferroni's test. Incidences of spike trains with bursty activity, oscillatory activity or LTS bursts were compared between hemispheres using chi square or Fisher's exact probability tests. The distribution of phase angles in STWAs was analyzed by polar statistics using the Rayleigh test (Batschelet, 1981) and data are presented in the text as mean $\pm$ angular deviation. Comparisons of distributions between hemispheres were analyzed by a Mann Whitney U test (Batschelet, 1981). Criterion for statistical significance was $p \leq 0.050$.

Histology

Following the completion of recordings, the last recording sites were marked by iontophoresis ($-18 \mu\text{A}$ for 25 min) of the Pontamine blue dye. After rats were sacrificed, brains were removed, frozen and 20 μm sections were cut on a cryostat. Slices containing either the PFN or STN were stained with neutral red (FD NeuroTechnologies Inc., Baltimore, MD, U.S.A.) to verify the site of the last recording. Sites of neurons recorded earlier in the experiment were reconstructed based on recording coordinates. Only neurons that were confirmed to be in the target structures were used for analyses. Recording sites in PFN and STN are shown in Figure 1.

RESULTS

Effect of dopamine loss on spike train activity in STN

To confirm that PFN data in the present study were obtained from rats with robust changes in basal ganglia activity after dopamine cell lesion, STN neurons were recorded simultaneously with PFN neurons in a subset of rats. Dopamine cell lesion was associated with profound changes in STN spike train activity (Table 1). Most notably, significantly more STN spike trains (28/29, 97%, from 7 rats) from the dopamine lesioned hemisphere exhibited oscillatory activity in the 0.3–2.5 Hz range 7–13 days after 6-OHDA infusion as compared to the control hemisphere (6/28, 21%, from 6 rats, $p=0.001$). Incidence of a bursty firing pattern, mean bursts per 1000 spikes, ISI CV and mean firing rate were significantly larger in the dopamine lesioned

than control hemisphere ($p < 0.05$). Results are consistent with previous reports of firing pattern changes in the rodent STN and basal ganglia output nuclei after loss of dopamine from this laboratory (Parr-Brownlie et al., 2007; Walters et al., 2005, 2007) and others (Belluscio et al., 2003, 2007; Breit et al., 2006; Burbaud et al., 1995; Hassani et al., 1996; Hollerman and Grace, 1990; MacLeod et al., 1990; Magill et al., 2001; Murer et al., 1997; Ni et al., 2001; Perier et al., 2000; Rohlf et al., 1997; Sanderson et al., 1986; Tai et al., 2003; Tseng et al., 2001, 2005; Vila et al., 2000).

Effect of dopamine loss on spike train and LFP activity in PFN

To investigate whether the PFN is affected by dopamine cell lesion-induced increases in oscillatory activity in basal ganglia output, PFN spike trains and LFP activity were examined. Figure 2A shows representative spike trains and LFPs recorded from control, non-lesioned (contralateral to 6-OHDA infusion) and dopamine lesioned hemispheres.

Firing rate and ISI CV did not differ between spike trains recorded in control ($n=102$, from 18 rats), non-lesioned ($n=32$, from 14 rats) and lesioned ($n=116$, from 27 rats) hemispheres (Fig. 2B,C), nor did incidence of bursting activity as calculated by the density histogram method (Kaneoke and Vitek, 1996). There were no significant differences in mean bursts per 1000 spikes (19 ± 4 ; 25 ± 7 ; 17 ± 4) in control, non-lesioned and lesioned hemispheres, respectively.

Previous studies have reported neuronal loss in the PFN in Parkinson's patients and in dopamine lesioned rats 5 weeks after 6-OHDA infusion (Aymerich et al., 2006; Henderson et al., 2000a, 2000b). However, Kusnoor et al. (2007) have recently reported no degeneration of PFN neurons in 6-OHDA lesioned rats. Since neuronal activity after injection may affect anatomical staining, the present study also compared the number of spontaneously active neurons encountered per track in control and dopamine lesioned hemispheres. Strikingly, dopamine cell lesion ($n=16$ rats) was associated with a significant 34% reduction in spontaneously active PFN neurons per recording track when compared to the control hemisphere ($n=15$ rats, Fig. 2B, $p=0.050$).

Consistent with observations in the STN, dopamine cell lesion significantly increased the number of PFN spike trains that exhibited oscillatory activity in the 0.3–2.5 Hz frequency range. However, overall, the effect of dopamine cell lesion on PFN activity was more subtle than that observed in the STN. Some PFN spike trains (30/102, 29%) exhibited significant periodicity in control rats (Fig. 2C,D), a proportion similar to that observed in the STN (21%) in control rats. After 6-OHDA infusion, the proportion of spike trains with oscillatory activity increased significantly in the PFN in the dopamine lesioned hemisphere (58/116, 50%, $p=0.008$), although not as robustly as in the STN (97%). The incidence of spike trains with oscillatory activity in the non-lesioned hemisphere (12/32, 38%) did not differ from the control hemisphere. This increase in the proportion of spike trains with oscillations in the lesioned hemisphere reflected an actual increase in the number of spike trains with oscillations and was not simply the result of the decrease in the number of spontaneously active neurons. In the subset of rats from which the number of spontaneously active neurons was assessed, the incidence of spike trains with significant oscillations was significantly larger ($p=0.038$) in the dopamine lesioned hemisphere (43/87, 49%) than in the control hemisphere (30/91, 33%).

PFN LFPs recorded in control, non-lesioned and lesioned hemispheres were also dominated by ~1 Hz activity, consistent with LFP recordings in STN (Fig. 2A, also see Fig. 3A and 4C). Total PFN LFP power in the 0.3–2.5 Hz range did not differ significantly between recordings in control (37 LFPs from 18 rats), non-lesioned (22 LFPs from 14 rats) and dopamine lesioned (51 LFPs from 27 rats) hemispheres (Fig. 2E). This lack of significant change in measures of PFN LFP slow wave power is in contrast with observations in the STN, where total STN LFP power in the 0.3–2.5 Hz range was significantly larger in the dopamine lesioned hemisphere

($1.7 \pm 0.2 \text{ mV}^2 \text{ Hz } 10^{-3}$, 12 LFPs from 7 rats) than in the control hemisphere ($1.1 \pm 0.2 \text{ mV}^2 \text{ Hz } 10^{-3}$, 9 LFPs from 6 rats, $p=0.050$). In fact, it is interesting to note that there was a trend ($p=0.078$) for PFN LFP power to be reduced in the dopamine lesioned hemisphere. This was associated with a significant decrease in PFN LFP amplitude as assessed by RMS about the mean LFP. PFN LFP amplitude was significantly reduced ($p=0.002$) in the lesioned hemisphere ($0.15 \pm 0.01 \text{ mV}$, $n=51$) relative to the control hemisphere ($0.19 \pm 0.01 \text{ mV}$, $n=37$), but the non-lesioned hemisphere ($0.17 \pm 0.01 \text{ mV}$, $n=22$) did not differ significantly from control or lesioned hemispheres.

Simultaneously recorded neuronal activity in PFN and STN after dopamine loss

To examine the possibility that oscillations in PFN spike trains might be entrained by inhibitory oscillatory activity in basal ganglia output nuclei, phase relationships between firing patterns in the PFN and STN were examined. Spike trains and LFPs in the PFN were simultaneously recorded with spike trains and LFPs from the STN in control and dopamine lesioned hemispheres (Fig. 3A). Consistent with the glutamatergic projection from STN to basal ganglia output nuclei, a previous study has shown that STN neuronal activity is in-phase with neuronal activity in basal ganglia output nuclei (Walters et al., 2007). Therefore, STN-PFN paired recordings provide indirect evidence of the firing relationship between basal ganglia output nuclei and PFN. Cross-correlograms in Figure 3B show examples of correlated oscillatory neuronal activity in the PFN and STN in control and dopamine lesioned hemispheres. Few (4/28, 14%) PFN-STN spike trains in the control hemisphere exhibited significantly correlated activity in cross-correlograms (Fig. 3B,C). In contrast, significantly ($p=0.001$) more cross-correlograms showed significant correlations between PFN and STN spike trains after dopamine lesion (19/29, 66%, Fig. 3B,C). However, the anti-phase relationship between STN and PFN spike train oscillations that was predicted if inhibitory basal ganglia output was driving PFN oscillatory activity was not observed; all correlated PFN-STN spike trains had oscillatory activity that was in-phase.

Inspection of the timing of PFN spiking relative to STN spiking in pairs with significantly correlated cross-correlograms provided a hint that dopamine cell lesion might produce a subtle change in relative timing of oscillatory activity between these two nuclei (Fig. 3C). In 3 of 4 (75%) correlated PFN-STN pairs in the control hemisphere, PFN neurons fired before STN neurons (average difference of 13 ms, Fig. 3C). In contrast, in the lesioned hemisphere, PFN neurons fired before STN in only 37% (7/19) of PFN-STN pairs with correlated cross-correlograms; PFN neurons fired on average 10 ms after STN neurons (Fig. 3C). While a change in firing relationship between the two nuclei would provide some evidence of a change in the balance of inputs to PFN, this analysis did not reach statistical significance.

Effect of dopamine loss on LTS bursts in PFN

A distinguishing characteristic of thalamic relay neurons is their potential to fire LTS bursts following a period of sustained hyperpolarization (Deschenes et al., 1984; Jahnsen and Llinas, 1984; Llinas and Jahnsen, 1982; Sherman and Guillery, 2006). Although PFN-STN phase relationships did not support the idea that dopamine lesion-induced oscillations in inhibitory basal ganglia output might simply modulate ongoing activity in PFN spike trains, it remained possible that basal ganglia output might induce 1 Hz in-phase periodicity in PFN firing patterns through intermittent induction of LTS bursts. Therefore, effects of dopamine cell lesion on the incidence and timing of LTS bursts in PFN were also examined.

Incidence of LTS bursts—In the present study, bursts containing 2–5 spikes with short ISIs ($\leq 5 \text{ ms}$ for the first ISI in the burst, $\leq 7 \text{ ms}$ for subsequent ISIs in the burst) preceded by a silent period of at least 100 ms were defined as LTS bursts. Analysis of 300 s epochs from PFN spike trains showed that while few (8%) of all ISIs ($n=78089$) from the control hemisphere

were classified as occurring within LTS bursts (Fig. 4A), most (116/134, 87%) spike trains examined in control and non-lesioned hemispheres contained at least one LTS burst. Dopamine cell lesion was associated with significantly fewer PFN spike trains exhibiting LTS bursts (75/116, 65%, $p=0.001$, Fig. 4B).

The greater the number of spikes in LTS bursts, the stronger the impact of LTS bursts on temporal integration at downstream sites. Over all hemispheres, the majority (8019/10616, 76%) of LTS bursts contained 2 spikes (doublets), and example doublets in LTS bursts are shown in representative spike trains in Figure 2A. LTS bursts that contained 3–5 spikes ($n=2597$) were rarer than doublets, and representative spike trains with example triplets are shown in Figure 4C. There was a trend for dopamine cell lesion to reduce the proportion of spike trains (35%, 40/116) that contained only LTS bursts consisting of doublets compared with control ($n=48$) and non-lesioned ($n=17$) hemispheres, $p=0.067$, Fig. 4B). However, dopamine cell lesion did not significantly affect the proportion of spike trains that contained mixed types of LTS bursts (doublets and triplets etc.). In addition, dopamine lesion did not affect the mean number of LTS bursts per spike train in those spike trains that contained only doublets or contained mixed types of LTS bursts (Fig. 4B). Therefore, dopamine cell lesion selectively reduced the proportion of recorded neurons that exhibited LTS bursts, but did not affect the number of spikes per LTS bursts.

Timing of LTS bursts—Although the number of spikes in LTS bursts did not change with lesion, it was possible that the lesion could have altered the timing of LTS bursts with respect to the slow ~1 Hz oscillations prominent in spike trains and LFPs in the PFN. To examine this possibility, the phase of only those spikes contained in LTS bursts was determined with respect to simultaneously recorded PFN LFPs, and compared between control, non-lesioned and dopamine lesioned hemispheres. Only spike trains with at least 50 LTS bursts were used for this analysis and example spike trains are shown in Figure 4C.

Dopamine loss did not affect the timing of LTS bursts. STWAs constructed with spikes in LTS bursts showed that spikes were significantly clustered ($p<0.05$) approximately midway between the peak and trough of simultaneously recorded LFPs in control, non-lesioned and lesioned hemispheres. Mean phases were $117 \pm 30^\circ$ ($n=31$), $81 \pm 53^\circ$ ($n=9$) and $130 \pm 45^\circ$ ($n=30$) in control, non-lesioned and lesioned hemispheres, respectively, and did not differ significantly between the hemispheres. In the same 70 spike trains, an equivalent analysis of PFN spike phase for only those spikes that were not incorporated in LTS bursts (single spikes) was performed and revealed that single spikes were also significantly ($p<0.05$) clustered with respect to PFN LFP. Consistent with the LTS burst spike-LFP relationship, there was also no significant difference in mean phase in single spike-LFP relationships between control ($148 \pm 36^\circ$, $n=31$), non-lesioned ($124 \pm 53^\circ$, $n=9$) and lesioned ($155 \pm 45^\circ$, $n=30$) hemispheres in PFN.

Timing of spikes in LTS bursts compared to single spikes—While results did not show an effect of dopamine cell lesion on the timing of spikes in LTS bursts with respect to PFN LFP, they highlighted a difference in the timing of spikes in LTS bursts relative to single spikes (see Fig. 4C). Interestingly, further analysis revealed that the spike-LFP relationship for spikes in LTS bursts was significantly different from that for single spikes in both control ($p=0.001$) and lesioned ($p=0.042$) hemispheres. This analysis showed that, on average, spikes in LTS bursts (control and lesioned hemispheres combined) occurred 28 degrees (approximately 100 ms with a dominant average LFP frequency of 0.78 Hz) earlier than single spikes relative to troughs in LFP activity (peak depolarization of neurons in the surrounding tissue, Fig. 4D).

ISI of LTS Bursts—PFN LTS burst ISIs in all hemispheres were generally typical of those shown in other thalamic nuclei (Domich et al., 1986; Steriade et al., 1990). As visual inspection

of Figure 5A shows, ISIs were found to be progressively longer within a burst, and the duration of the first ISI is predictive of the total number of spikes in the LTS bursts. ISIs were significantly different ($p=0.001$) in all comparisons between the first, second, third and fourth ISI in LTS bursts (Fig. 5B). Mean ISIs for doublets were significantly longer ($p=0.001$) than triplets and quadruplets, but not quintuplets (Fig. 5C).

The effect of dopamine cell lesion on the duration of ISIs within LTS bursts was examined in PFN spike trains. This analysis showed that dopamine cell lesion was associated with a subtle lengthening of ISIs in LTS bursts; ISIs differed significantly ($p=0.001$) between all 3 hemispheres, being shortest for the control hemisphere and longest for the dopamine lesioned hemisphere (Fig. 5D). These results suggest that dopamine cell lesion may modulate the impact of LTS bursts at downstream sites by reducing temporal summation. However, an increase in mean ISIs in LTS bursts in the lesioned hemisphere of only 0.2 ms is likely to have little functional significance when the membrane time constant of cortical or striatal neurons following stimulation of thalamic inputs is 10 fold larger (Sugimori et al., 1978; Usrey et al., 2000).

DISCUSSION

The present study utilized a rat model of Parkinson's disease to investigate how dopamine loss affects activity in the PFN of the thalamus. The aim was to examine how PFN activity is affected by the robust bursty and 0.3–2.5 Hz oscillatory activity in spike trains from basal ganglia output nuclei that emerges 1–2 weeks after dopamine cell lesion in urethane-anesthetized rats (Belluscio et al., 2003, 2007; Burbaud et al., 1995; Murer et al., 1997; Tseng et al., 2001, 2005; Walters et al., 2007). Results showed that while there was a significant increase in the proportion of PFN spike trains exhibiting slow oscillatory activity in rats with dopamine cell lesion, as compared to control (neurologically intact) rats, the increase in oscillatory activity in PFN was markedly smaller than that observed in the STN (or in basal ganglia output nuclei) under equivalent conditions. Moreover, phase relationships between oscillations in simultaneously recorded PFN and STN spike trains, combined with data from a previous study showing an in-phase firing relationship between STN and SNpr (Walters et al., 2007), did not support the possibility that oscillatory activity in PFN spike trains was entrained by inhibitory output from the basal ganglia. There was also no evidence that inhibitory activity from basal ganglia output nuclei increased oscillatory activity in PFN spike trains by increasing the incidence of LTS bursts. Furthermore, dopamine cell lesion did not affect firing rate, ISI CV, spike train burstiness, LFP power in the 0.3–2.5 Hz range or the temporal relationship between PFN spikes with respect to PFN LFPs. However, LFP amplitude and the number of spontaneously active neurons recorded in the PFN after dopamine lesion were reduced. These results argue that robust oscillatory activity in basal ganglia output associated with dopaminergic lesion does not drive increases in oscillatory activity in PFN in the anesthetized 6-OHDA-lesioned rat, and raise questions about the impact of synchronized oscillatory activity from basal ganglia output nuclei on other downstream thalamic nuclei.

Loss of Spontaneously Active PFN Neurons

Degeneration of 30–70% of PFN neurons has been reported in post-mortem studies of Parkinson's patients (Henderson et al., 2000a, 2000b). However, conflicting data are reported from studies investigating neuronal integrity in the PFN in rodent models of Parkinson's disease. While one study showed a relatively rapid effect of dopamine loss on viability of PFN neurons that project to the striatum (Aymerich et al., 2006), another study has recently reported no evidence of degeneration of PFN soma over similar post-lesion time periods (Kusnoor et al., 2007). Relevant to these reports, dopamine cell lesion was associated with 34% fewer spontaneously active PFN neurons per track in the present study. The apparent silencing of a

subpopulation of neurons could contribute to the significant decrease in LFP amplitude and the trend for reduced LFP power observed in the dopamine lesioned hemisphere in the present study. These results highlight that some PFN neurons may be functionally compromised following loss of dopamine and the need to clarify factors contributing to variable outcomes in assessment of PFN neuronal integrity.

The lack of dopamine lesion-induced change in firing rate and bursty firing pattern observed in the present study 1–2 weeks after 6-OHDA lesion is consistent with a previous electrophysiological study (Ni et al., 2000), but inconsistent with studies reporting indirect measures of PFN activity using metabolic markers (Aymerich et al., 2006; Orioux et al., 2000). Neuronal firing rate in thalamic nuclei has been predicted to decrease in Parkinson's disease (Albin et al., 1989; DeLong, 1990). While the present data do not support this hypothesis, it seems unlikely that the lack of change in PFN firing rate is due to recordings being conducted in anesthetized animals as no change in thalamic firing rate has also been reported in awake primates after loss of dopamine (Pessiglione et al., 2005).

In-Phase Relationship Between PFN and STN

Data collected from Parkinson's patients during implantation of deep brain stimulation electrodes have provided evidence that synchronized oscillatory activity in basal ganglia output contributes to motor deficits experienced by patients. This has led to interest in whether synchronized oscillatory basal ganglia output might entrain oscillatory activity in the thalamus and throughout thalamocortical-basal ganglia networks (Brown, 2000; Leblois et al., 2006). Oscillatory signals and/or LTS burst firing have been postulated to underlie the pathophysiology of parkinsonian resting tremor (Llinas and Jahnsen, 1982; Schnitzler et al., 2006; Schnitzler and Gross, 2005). The urethane-anesthetized rodent model of Parkinson's disease permits examination of the phase relationships between oscillatory activity in spike trains recorded from neurons in basal ganglia nuclei and PFN. Many SNpr neurons exhibit synchronized ~1 Hz oscillatory activity after dopamine cell lesion in-phase with ~1 Hz oscillatory activity in STN (Walters et al., 2007). The present study used this model to examine whether increases in oscillatory inhibitory output from the basal ganglia induce anti-phase oscillations in thalamic activity through inhibitory modulation of activity in the thalamus. Also investigated was the possibility that the increased inhibitory oscillatory basal ganglia output could have a driver-like effect on thalamic activity, inducing in-phase oscillatory activity in thalamic spike trains by triggering rebound spiking of thalamic neurons via LTS bursts. Recent data from avian brains suggest that spikes from basal ganglia output nuclei can have an important role on the timing of LTS bursts in the thalamus (Luo and Perkel, 1999; Person and Perkel, 2005, 2007). This has led to speculation that rebound bursting in the thalamus in association with inhibitory basal ganglia output, especially when pathologically synchronized, might contribute to in-phase spiking between basal ganglia output and thalamic nuclei in Parkinson's disease models (Farries and Wilson, 2007).

In the present study, phase relationships between oscillatory activity in the STN and PFN spike trains are not consistent with the hypothesis that increased oscillatory inhibitory input from basal ganglia output nuclei induced anti-phase oscillations in thalamic activity through feedforward modulation of ongoing thalamic activity. Despite the fact that a greater proportion of PFN spike trains showed significant oscillatory activity following loss of dopamine, and more PFN-STN neuronal pairs showed significantly correlated oscillatory activity, the firing relation between STN (and basal ganglia output nuclei) and PFN neurons was consistently in-phase in both control and dopamine lesioned hemispheres. This led to investigation of whether the in-phase relationship might result from increased incidence of LTS bursts after dopaminergic lesion.

LTS Bursts in PFN After Dopamine Cell Lesion

The present study found no evidence that the in-phase relationship between oscillatory activity in STN and PFN in 6-OHDA lesioned rats was associated with periodic LTS bursts triggered by the increase in synchronized inhibitory oscillatory activity from basal ganglia output nuclei. Comparison of properties, incidence and timing of LTS bursts in control rats with those observed in dopamine lesioned rats revealed that significantly fewer spike trains exhibited LTS bursts after dopaminergic lesion. These results show that increases in LTS bursts did not contribute to the increased incidence of in-phase oscillatory activity in the PFN after dopamine cell lesion.

Although fewer LTS bursts occurred in PFN spike trains after dopaminergic lesion when significantly more spike trains of basal ganglia output neurons exhibit oscillatory activity (Belluscio et al., 2003, 2007; Tseng et al., 2001, 2005; Walters et al., 2007), LTS bursts did exhibit properties in both control and dopamine lesioned hemispheres similar to those reported in other thalamic nuclei; the first ISI in a burst was predictive of the total number of spikes in the burst, and ISIs increased from the first ISI to the second and so on. Results are consistent with Lacey and colleagues' (2007) finding in control rats that the incidence of LTS bursts in PFN neurons is low. In the present study only 8% of PFN spikes were incorporated into LTS bursts in control rats and the majority of LTS bursts were doublets.

The present study also did not find any evidence of a functional change in the timing of spikes in LTS bursts after dopamine loss. While mean ISIs in LTS bursts increased significantly by 0.2 ms after dopamine cell lesion, this may be of little functional significance at downstream structures. Spikes in LTS bursts were consistently earlier, with respect to the trough in PFN LFP activity, than single spikes (spikes outside LTS bursts) in both control and lesioned rats, suggesting that PFN action potential initiation during membrane depolarization (single spikes) or following sustained membrane hyperpolarization (LTS bursts) is not altered by dopamine cell lesion. The timing of LTS bursts versus single spikes may have important effects on downstream structures; it is possible that the earlier phase of spikes in LTS bursts do not coincide with "up-state" membrane potentials at downstream neurons. If this is the case, an advantage of the high frequency spiking associated with LTS bursts is increased reliability of synaptic transmission. Nevertheless, while temporal summation at downstream structures was not affected by loss of dopamine, the reduced number of neurons exhibiting LTS bursts indicates that spatial summation may be impaired.

PFN Relationships Within the Basal Ganglia-Thalamocortical Network

Results discussed above indicate that mechanisms other than LTS bursts need to be considered to account for the in-phase relationships between STN and PFN oscillations in both control and dopamine lesioned preparations observed in the present study. A robust source of excitatory (driver) oscillatory input to the PFN in the anesthetized rat, that would establish in-phase relationships between PFN and STN, is layer V pyramidal neurons in cortex (Cornwall and Phillipson, 1988; Reep et al., 1987; Royce, 1983). In-phase firing relationships between cortex and STN are reported in dopamine lesioned anesthetized rats (Parr-Brownlie et al., 2007; Walters et al., 2007), and in-phase relationships between STN and PFN oscillations are consistent with cortical input having substantial, direct influence on PFN oscillatory activity. While cortical input is critical for oscillatory activity in thalamic spike trains in anesthetized rats (Steriade et al., 1993b), pyramidal neuron activity in the cortex does not increase after loss of dopamine (Mallet et al., 2006; Parr-Brownlie et al., 2007), thus cortical input is unlikely to drive the increased incidence of oscillatory activity in PFN spike trains after dopamine lesion in the present study. Nevertheless, oscillatory cortical input may play a role in the significant decrease in PFN LFP amplitude after loss of dopamine; LFP amplitude may be dampened by

coincident increased inhibitory oscillatory activity from basal ganglia output nuclei with excitatory oscillatory input from the cortex.

Other routes of transmission that could account for in-phase activity in STN and PFN include direct STN innervation of PFN, STN-SNpr-reticular thalamic nucleus-PFN (Hazrati et al., 1995; Kolmac and Mitrofanis, 1997; Tsumori et al., 2000), or STN-pedunculo pontine nucleus-PFN (Capozzo et al., 2003; Cebrian et al., 2005; Erro et al., 1999; Wiklund and Cuenod, 1984; Woolf and Butcher, 1986). Anatomical connections via these routes are consistent with in-phase spiking between STN and PFN in control rats. A small (2%) proportion of STN neurons project directly to PFN (Castle et al., 2005), and oscillatory activity in the ~1 Hz range is dramatically increased in the STN after dopamine lesion. The effect of dopamine cell lesion on phase relationship between reticular thalamic (RTn) and basal ganglia nuclei remains unknown. However, RTn receives dopaminergic input from A8-A10 mesencephalic groups (Freeman et al., 2001), indicating that dopamine loss might directly affect activity in this nucleus. While dopamine cell lesion alters the phase relationship between pedunculo pontine (PPN) nucleus and cortex (Aravamuthan et al., 2008), the phase relationship associated with dopaminergic lesion is not consistent with PPN driving activity in the PFN.

Currently, the possibility that basal ganglia-thalamocortical circuits engage in synchronous oscillatory activity is of considerable interest with respect to mechanisms underlying motor system dysfunction in Parkinson's disease (Leblois et al., 2006; Zaidel et al., 2008). If oscillatory activity in basal ganglia output could elicit in-phase oscillations in target nuclei like the PFN, such an effect could contribute to reciprocal thalamocortical resonance, enhancing oscillatory activity in both areas. However, while incidence of spike trains with oscillatory activity was modestly increased in the PFN after dopamine cell lesion, the present data do not support basal ganglia-mediated induction of LTS bursts as a mechanism contributing to this change, nor do the data indicate that increased oscillatory activity in basal ganglia output exerts significant oscillatory inhibition of ongoing PFN activity in the anesthetized rats. While it is possible that the response of PFN neurons to synchronized and oscillatory activity in basal ganglia output could be different in the unanesthetized state, especially since the oscillatory activity observed in basal ganglia output is in a higher (10–30 Hz) frequency range in awake models of Parkinson's disease, it is interesting to note that Pessiglione et al. (2005) does not report a change in firing pattern in thalamic regions receiving input from globus pallidus internus or SNpr in the awake MPTP lesioned primate. In summary, the present data indicate that robust changes in firing patterns in basal ganglia output nuclei do not induce comparable changes in neuronal activity in the PFN and argue that input from basal ganglia output nuclei plays a modulatory, as opposed to 'driver-like', role in regulating PFN activity in the parkinsonian state.

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Reference List

- Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci* 1989;12:366–375. [PubMed: 2479133]
- Angaut P, Cicirata F, Serapide P. Topographic organization of the cerebellothalamic projections in the rat. An autoradiographic study. *Neuroscience* 1985;15:389–401. [PubMed: 4022330]
- Aravamuthan BR, Bergstrom DA, French RA, Taylor JJ, Parr-Brownlie LC, Walters JR. Altered neuronal activity relationships between the pedunculo pontine nucleus and motor cortex in a rodent model of Parkinson's disease. *Exp Neurol* 2008;213:268–280. [PubMed: 18601924]

- Aymerich MS, Barroso-Chinea P, Perez-Manso M, Munoz-Patino AM, Moreno-Igoa M, Gonzalez-Hernandez T, Lanciego JL. Consequences of unilateral nigrostriatal denervation on the thalamostriatal pathway in rats. *Eur J Neurosci* 2006;23:2099–2108. [PubMed: 16630057]
- Batschelet, E. *Circular Statistics in Biology*. New York: Academic Press; 1981.
- Belluscio MA, Kasanetz F, Riquelme LA, Murer MG. Spreading of slow cortical rhythms to the basal ganglia output nuclei in rats with nigrostriatal lesions. *Eur J Neurosci* 2003;17:1046–1052. [PubMed: 12653980]
- Belluscio MA, Riquelme LA, Murer MG. Striatal dysfunction increases basal ganglia output during motor cortex activation in parkinsonian rats. *Eur J Neurosci* 2007;25:2791–2804. [PubMed: 17561844]
- Bergman H, Feingold A, Nini A, Raz A, Slovin H, Abeles M, Vaadia E. Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates. *Trends Neurosci* 1998;21:32–38. [PubMed: 9464684]
- Bevan MD, Francis CM, Bolam JP. The glutamate-enriched cortical and thalamic input to neurons in the subthalamic nucleus of the rat: convergence with GABA-positive terminals. *J Comp Neurol* 1995;361:491–511. [PubMed: 8550895]
- Bodor AL, Giber K, Rovo Z, Ulbert I, Acsady L. Structural correlates of efficient GABAergic transmission in the basal ganglia-thalamus pathway. *J Neurosci* 2008;28:3090–3102. [PubMed: 18354012]
- Breit S, Lessmann L, Unterbrink D, Popa RC, Gasser T, Schulz JB. Lesion of the pedunculopontine nucleus reverses hyperactivity of the subthalamic nucleus and substantia nigra pars reticulata in a 6-hydroxydopamine rat model. *Eur J Neurosci* 2006;24:2275–2282. [PubMed: 17042796]
- Brown P. Cortical drives to human muscle: the Piper and related rhythms. *Prog Neurobiol* 2000;60:97–108. [PubMed: 10622378]
- Brown P, Marsden CD. What do the basal ganglia do? *Lancet* 1998;351:1801–1804. [PubMed: 9635969]
- Burbaud P, Gross C, Benazzouz A, Coussenmacq M, Bioulac B. Reduction of apomorphine-induced rotational behaviour by subthalamic lesion in 6-OHDA lesioned rats is associated with a normalization of firing rate and discharge pattern of pars reticulata neurons. *Exp Brain Res* 1995;105:48–58. [PubMed: 7589317]
- Capozzo A, Florio T, Cellini R, Moriconi U, Scarnati E. The pedunculopontine nucleus projection to the parafascicular nucleus of the thalamus: an electrophysiological investigation in the rat. *J Neural Transm* 2003;110:733–747. [PubMed: 12811634]
- Castle M, Aymerich MS, Sanchez-Escobar C, Gonzalo N, Obeso JA, Lanciego JL. Thalamic innervation of the direct and indirect basal ganglia pathways in the rat: Ipsi- and contralateral projections. *J Comp Neurol* 2005;483:143–153. [PubMed: 15678473]
- Cebrian C, Parent A, Prensa L. Patterns of axonal branching of neurons of the substantia nigra pars reticulata and pars lateralis in the rat. *J Comp Neurol* 2005;492:349–369. [PubMed: 16217789]
- Cornwall J, Phillipson OT. Afferent projections to the parafascicular thalamic nucleus of the rat, as shown by the retrograde transport of wheat germ agglutinin. *Brain Res Bull* 1988;20:139–150. [PubMed: 2836036]
- DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* 1990;13:281–285. [PubMed: 1695404]
- Deschenes M, Paradis M, Roy JP, Steriade M. Electrophysiology of neurons of lateral thalamic nuclei in cat: resting properties and burst discharges. *J Neurophysiol* 1984;51:1196–1219. [PubMed: 6737028]
- Domich L, Oakson G, Steriade M. Thalamic burst patterns in the naturally sleeping cat: a comparison between cortically projecting and reticularis neurones. *J Physiol* 1986;379:429–449. [PubMed: 3560000]
- Erro E, Lanciego JL, Gimenez-Amaya JM. Relationships between thalamostriatal neurons and pedunculopontine projections to the thalamus: a neuroanatomical tract-tracing study in the rat. *Exp Brain Res* 1999;127:162–170. [PubMed: 10442408]
- Farries, MA.; Wilson, CJ. Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience; 2007. Nigrothalamic transmission studied in rats in vitro. Program No. 515.3. Online

- Freeman A, Ciliax B, Bakay R, Daley J, Miller RD, Keating G, Levey A, Rye D. Nigrostriatal collaterals to thalamus degenerate in parkinsonian animal models. *Ann Neurol* 2001;50:321–329. [PubMed: 11558788]
- Fries P, Reynolds JH, Rorie AE, Desimone R. Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* 2001;291:1560–1563. [PubMed: 11222864]
- Gerfen, CR.; Wilson, CJ. The Basal Ganglia. In: Swanson, LW.; Bjorklund, A.; Hokfelt, T., editors. *Handbook of Chemical Neuroanatomy*. Vol. 12. Amsterdam: Elsevier Science BV; 1996. p. 371–468.
- Guillery RW, Harting JK. Structure and connections of the thalamic reticular nucleus: Advancing views over half a century. *J Comp Neurol* 2003;463:360–371. [PubMed: 12836172]
- Harding BN. An ultrastructural study of the termination of afferent fibres within the ventrolateral and centre median nuclei of the monkey thalamus. *Brain Res* 1973;54:341–346. [PubMed: 4196752]
- Hassani OK, Mouroux M, Feger J. Increased subthalamic neuronal activity after nigral dopaminergic lesion independent of disinhibition via the globus pallidus. *Neuroscience* 1996;72:105–115. [PubMed: 8730710]
- Hazrati LN, Pinault D, Parent A. The thalamic reticular nucleus does not send commissural projection to the contralateral parafascicular nucleus in the rat. *Brain Res* 1995;679:123–134. [PubMed: 7648254]
- Henderson JM, Carpenter K, Cartwright H, Halliday GM. Degeneration of the centre median-parafascicular complex in Parkinson's disease. *Ann Neurol* 2000a;47:345–352. [PubMed: 10716254]
- Henderson JM, Carpenter K, Cartwright H, Halliday GM. Loss of thalamic intralaminar nuclei in progressive supranuclear palsy and Parkinson's disease: clinical and therapeutic implications. *Brain* 2000b;123:1410–1421. [PubMed: 10869053]
- Hollerman JR, Grace AA. The effects of dopamine-depleting brain lesions on the electrophysiological activity of rat substantia nigra dopamine neurons. *Brain Res* 1990;533:203–12. [PubMed: 2126975]
- Hurtado JM, Gray CM, Tamas LB, Sigvardt KA. Dynamics of tremor-related oscillations in the human globus pallidus: a single case study. *PNAS* 1999;96:1674–1679. [PubMed: 9990083]
- Hurtado JM, Rubchinsky LL, Sigvardt KA, Wheelock VL, Pappas CT. Temporal evolution of oscillations and synchrony in GPI/muscle pairs in Parkinson's disease. *J Neurophysiol* 2005;93:1569–1584. [PubMed: 15496492]
- Hutchison WD, Lozano AM, Davis KD, Saint-Cyr JA, Lang AE, Dostrovsky JO. Differential neuronal activity in segments of globus pallidus in Parkinson's disease patients. *NeuroReport* 1994;5:1533–1537. [PubMed: 7948856]
- Hutchison WD, Lozano AM, Tasker RR, Lang AE, Dostrovsky JO. Identification and characterization of neurons with tremor-frequency activity in human globus pallidus. *Exp Brain Res* 1997;113:557–563. [PubMed: 9108220]
- Ilinsky I, Ambardekar AV, Kultas-Ilinsky K. Organization of projections from the anterior pole of the nucleus reticularis thalami (NRT) to subdivisions of the motor thalamus: light and electron microscopic studies in the Rhesus monkey. *J Comp Neurol* 1999;409:369–384. [PubMed: 10379824]
- Ilinsky IA, Kultas-Ilinsky K. Fine structure of the magnocellular subdivision of the ventral anterior thalamic nucleus (VAmc) of *Macaca mulatta*: I. Cell types and synaptology. *J Comp Neurol* 1990;294:455–478. [PubMed: 2341621]
- Ilinsky, IA.; Kultas-Ilinsky, K. Neuroanatomical organization and connections of the motor thalamus in primates. In: Kultas-Ilinsky, K.; Ilinsky, I., editors. *Basal Ganglia and Thalamus in Health and Movement Disorders*. New York: Kluwer Academic/Plenum Publishers; 2001. p. 77–91.
- Jahnsen H, Llinas R. Electrophysiological properties of guinea-pig thalamic neurones: An in vitro study. *J Physiol* 1984;349:205–226. [PubMed: 6737292]
- Kaneoke Y, Vitek JL. Burst and oscillation as disparate neuronal properties. *J Neurosci Methods* 1996;68:211–223. [PubMed: 8912194]
- Kolmac CI, Mitrofanis J. Organisation of the reticular thalamic projection to the intralaminar and midline nuclei in rats. *J Comp Neurol* 1997;377:165–178. [PubMed: 8986879]
- Kultas-Ilinsky K, Ilinsky IA. Fine structure of the ventral lateral nucleus (VL) of the *Macaca mulatta* thalamus: cell types and synaptology. *J Comp Neurol* 1991;314:319–349. [PubMed: 1723998]

- Kultas-Ilinsky K, Reising L, Yi H, Ilinsky IA. Pallidal afferent territory of the *Macaca mulatta* thalamus: neuronal and synaptic organization of the VAdc. *J Comp Neurol* 1997;386:573–600. [PubMed: 9378853]
- Kusnoor, SV.; Bubser, M.; Deutch, AY. Neuroscience Meeting Planner Program No.590.13. San Diego, CA: Society for Neuroscience; 2007. Dopaminergic regulation of the parafascicular and centrolateral thalamic nuclei. Online
- Lacey CJ, Bolam JP, Magill PJ. Novel and distinct operational principles of intralaminar thalamic neurons and their striatal projections. *J Neurosci* 2007;27:4374–4384. [PubMed: 17442822]
- Leblois A, Boraud T, Meissner W, Bergman H, Hansel D. Competition between feedback loops underlies normal and pathological dynamics in the basal ganglia. *J Neurosci* 2006;26:3567–3583. [PubMed: 16571765]
- Levy R, Dostrovsky JO, Lang AE, Sime E, Hutchison WD, Lozano AM. Effects of apomorphine on subthalamic nucleus and globus pallidus internus neurons in patients with Parkinson's disease. *J Neurophysiol* 2001;86:249–260. [PubMed: 11431506]
- Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. Synchronized neuronal discharge in the basal ganglia of Parkinson's patients is limited to oscillatory activity. *J Neurosci* 2002;22:2855–2861. [PubMed: 11923450]
- Llinas R, Jahnsen H. Electrophysiology of mammalian thalamic neurones in vitro. *Nature* 1982;297:406–408. [PubMed: 7078650]
- Lu SM, Guido W, Sherman SM. Effects of membrane voltage on receptive field properties of lateral geniculate neurons in the cat: contributions of the low-threshold Ca^{2+} conductance. *J Neurophysiol* 1992;68:2185–2198. [PubMed: 1337104]
- Luo M, Perkel DJ. A GABAergic, strongly inhibitory projection to a thalamic nucleus in the zebra finch song system. *J Neurosci* 1999;19:6700–6711. [PubMed: 10414999]
- MacLeod NK, Ryman A, Arbuthnott GW. Electrophysiological properties of nigrothalamic neurons after 6-hydroxydopamine lesions in the rat. *Neuroscience* 1990;38:447–456. [PubMed: 2124665]
- Magill PJ, Bolam JP, Bevan MD. Dopamine regulates the impact of the cerebral cortex on the subthalamic nucleus-globus pallidus network. *Neuroscience* 2001;106:313–330. [PubMed: 11566503]
- Magnin M, Morel A, Jeanmonod D. Single-unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients. *Neuroscience* 2000;96:549–564. [PubMed: 10717435]
- Mallet N, Ballion B, Le MC, Gonon F. Cortical inputs and GABA interneurons imbalance projection neurons in the striatum of parkinsonian rats. *J Neurosci* 2006;26:3875–3884. [PubMed: 16597742]
- Moran A, Bar-Gad I, Bergman H, Israel Z. Real-time refinement of subthalamic nucleus targeting using Bayesian decision-making on the root mean square measure. *Mov Disord* 2006;21:1425–1431. [PubMed: 16763982]
- Murer MG, Riquelme LA, Tseng KY, Pazo JH. Substantia nigra pars reticulata single unit activity in normal and 6-OHDA-lesioned rats: effects of intrastriatal apomorphine and subthalamic lesions. *Synapse* 1997;27:278–293. [PubMed: 9372551]
- Murer MG, Tseng KY, Kasanetz F, Belluscio M, Riquelme LA. Brain oscillations, medium spiny neurons, and dopamine. *Cell Mol Neurobiol* 2002;22:611–632. [PubMed: 12585682]
- Nakano K, Kohno M, Hasegawa Y, Tokushige A. Cortical and brain stem afferents to the ventral thalamic nuclei of the cat demonstrated by retrograde axonal transport of horseradish peroxidase. *J Comp Neurol* 1985;231:120.
- Ni ZG, Bouali-Benazzouz R, Gao DM, Benabid AL, Benazzouz A. Time-course of changes in firing rates and firing patterns of subthalamic nucleus neuronal activity after 6-OHDA-induced dopamine depletion in rats. *Brain Res* 2001;899:142–147. [PubMed: 11311875]
- Ni ZG, Gao DM, Benabid AL, Benazzouz A. Unilateral lesion of the nigrostriatal pathway induces a transient decrease of firing rate with no change in the firing pattern of neurons of the parafascicular nucleus in the rat. *Neuroscience* 2000;101:993–999. [PubMed: 11113348]
- Olsson M, Nikkha G, Bentlage C, Bjorklund A. Forelimb akinesia in the rat Parkinson model: differential effects of dopamine agonists and nigral transplants as assessed by a new stepping test. *J Neurosci* 1995;15:3863–3875. [PubMed: 7751951]

- Orieux G, Francois C, Feger J, Yelnik J, Vila M, Ruberg M, Agid Y, Hirsch EC. Metabolic activity of excitatory parafascicular and pedunculopontine inputs to the subthalamic nucleus in a rat model of Parkinson's disease. *Neuroscience* 2000;97:79–88. [PubMed: 10771341]
- Parr-Brownlie LC, Poloskey SL, Flanagan KK, Eisenhofer G, Bergstrom DA, Walters JR. Dopamine lesion-induced changes in subthalamic nucleus activity are not associated with alterations in firing rate or pattern in layer V neurons of the anterior cingulate cortex in anesthetized rats. *Eur J Neurosci* 2007;26:1925–1939. [PubMed: 17897398]
- Paxinos, G.; Watson, C. *The Rat Brain in Stereotaxic Coordinates*. San Diego: Academic Press Inc; 1997.
- Penney JB, Young AB. Speculations on the functional anatomy of basal ganglia disorders. *Ann Rev Neurosci* 1983;6:73–94. [PubMed: 6838141]
- Perier C, Agid Y, Hirsch EC, Feger J. Ipsilateral and contralateral subthalamic activity after unilateral dopaminergic lesion. *NeuroReport* 2000;11:3275–3278. [PubMed: 11043563]
- Person AL, Perkel DJ. Unitary IPSPs drive precise thalamic spiking in a circuit required for learning. *Neuron* 2005;46:129–140. [PubMed: 15820699]
- Person AL, Perkel DJ. Pallidal neuron activity increases during sensory relay through thalamus in a songbird circuit essential for learning. *J Neurosci* 2007;27:8687–8698. [PubMed: 17687046]
- Pessiglione M, Guehl D, Rolland AS, Francois C, Hirsch EC, Feger J, Tremblay L. Thalamic neuronal activity in dopamine-depleted primates: evidence for a loss of functional segregation within basal ganglia circuits. *J Neurosci* 2005;25:1523–1531. [PubMed: 15703406]
- Reep RL, Corwin JV, Hashimoto A, Watson RT. Efferent connections of the rostral portion of medial agranular cortex in rats. *Brain Res Bull* 1987;19:203–221. [PubMed: 2822206]
- Rohlf A, Nikkha G, Rosenthal C, Rundfeldt C, Brandis A, Samii M, Loscher W. Hemispheric asymmetries in spontaneous firing characteristics of substantia nigra pars reticulata neurons following a unilateral 6-hydroxydopamine lesion of the rat nigrostriatal pathway. *Brain Res* 1997;761:352–356. [PubMed: 9252038]
- Royce GJ. Cortical neurons with collateral projections to both the caudate nucleus and the centromedian-parafascicular thalamic complex: a fluorescent retrograde double labeling study in the cat. *Exp Brain Res* 1983;50:157–165. [PubMed: 6196226]
- Sanderson P, Mavoungou R, be-Fessard D. Changes in substantia nigra pars reticulata activity following lesions of the substantia nigra pars compacta. *Neurosci Lett* 1986;67:25–30. [PubMed: 3014391]
- Schnitzler A, Gross J. Normal and pathological oscillatory communication in the brain. *Nature Neuroscience* 2005;6:285–296.
- Schnitzler A, Timmermann L, Gross J. Physiological and pathological oscillatory networks in the human motor system. *J Physiol Paris* 2006;99:3–7. [PubMed: 16054347]
- Sherman, SM.; Guillery, RW. *Exploring the Thalamus and its Role in Cortical Function*. Cambridge, MA: The MIT Press; 2006.
- Shinoda, Y.; Kakei, S.; Wannier, T.; Futami, T.; Sugiuchi, Y. Input-output organisation of the ventrolateral nucleus of the thalamus in the cerebello-thalamo-cortical system. In: Minciocchi, D.; Molinari, M.; Macchi, G.; Jones, EG., editors. *Thalamic Networks for Relay and Modulation*. Oxford: Pergamon Press; 1993. p. 135-143.
- Shrager RI. On a three-term variant of the Lomb periodogram. *Astrophys Space Sci* 2003;277:519–530.
- Smith Y, Raju DV, Pare JF, Sidibe M. The thalamostriatal system: a highly specific network of the basal ganglia circuitry. *Trends Neurosci* 2004;27:520–527. [PubMed: 15331233]
- Steriade M, Deschenes M, Domich L, Mulle C. Abolition of spindle oscillations in thalamic neurons disconnected from nucleus reticularis thalami. *J Neurophysiol* 1985;54:1473–1497. [PubMed: 4087044]
- Steriade, M.; Jones, EG.; Llinas, RR. *Thalamic Oscillations and Signaling*. New York: Neurosciences Research Foundation Inc; 1990. The oscillatory mode during EEG-synchronized sleep; p. 167-237.
- Steriade M, Nunez A, Amzica F. A novel slow (< 1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. *J Neurosci* 1993a;13:3252–3265. [PubMed: 8340806]
- Steriade M, Nunez A, Amzica F. Intracellular analysis of relations between the slow (<1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. *J Neurosci* 1993b;13:3266–3283. [PubMed: 8340807]

- Sugimori M, Preston RJ, Kitai ST. Response properties and electrical constants of caudate nucleus neurons in the cat. *J Neurophysiol* 1978;41:1662–1675. [PubMed: 731295]
- Tai CH, Boraud T, Bezard E, Bioulac B, Gross C, Benazzouz A. Electrophysiological and metabolic evidence that high-frequency stimulation of the subthalamic nucleus bridges neuronal activity in the subthalamic nucleus and the substantia nigra reticulata. *FASEB J* 2003;17:1820–1830. [PubMed: 14519661]
- Tang JKH, Moro E, Mahant N, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO. Neuronal firing rates and patterns in the globus pallidus internus of patients with cervical dystonia differ from those with Parkinson's disease. *J Neurophysiol* 2007;98:720–729. [PubMed: 17537900]
- Tseng KY, Kargieman L, Gacio S, Riquelme LA, Murer MG. Consequences of partial and severe dopaminergic lesion on basal ganglia oscillatory activity and akinesia. *Eur J Neurosci* 2005;22:2579–2586. [PubMed: 16307600]
- Tseng KY, Kasanetz F, Kargieman L, Pazo JH, Murer MG, Riquelme LA. Subthalamic nucleus lesions reduce low frequency oscillatory firing of substantia nigra pars reticulata neurons in a rat model of Parkinson's disease. *Brain Res* 2001;904:93–103. [PubMed: 11516415]
- Tsumori T, Yokota S, Lai H, Yasui Y. Monosynaptic and disynaptic projections from the substantia nigra pars reticulata to the parafascicular thalamic nucleus in the rat. *Brain Res* 2000;858:429–435. [PubMed: 10708697]
- Usrey WM, Alonso JM, Reid RC. Synaptic interactions between thalamic inputs to simple cells in cat visual cortex. *J Neurosci* 2000;20:5461–5467. [PubMed: 10884329]
- Van der Werf YD, Witter MP, Groenewegen HJ. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. *Brain Res Brain Res Rev* 2002;39:107–140. [PubMed: 12423763]
- Vila M, Perier C, Feger J, Yelnik J, Faucheux B, Ruberg M, Raisman-Vozari R, Agid Y, Hirsch EC. Evolution of changes in neuronal activity in the subthalamic nucleus of rats with unilateral lesion of the substantia nigra assessed by metabolic and electrophysiological measurements. *Eur J Neurosci* 2000;12:337–344. [PubMed: 10651888]
- Walters, JR.; Hu, D.; Itoga, CA.; Parr-Brownlie, LC.; Bergstrom, DA. Do local field potentials reflect synchronized spiking activity of neuronal populations in the basal ganglia? Studies in a rodent model of Parkinson's disease. In: Bolam, JP.; Magill, PJ.; Ingham, CA., editors. *The Basal Ganglia*. Vol. VIII. New York: Springer Science+Business Media, Inc; 2005. p. 37-47.
- Walters JR, Hu D, Itoga CA, Parr-Brownlie LC, Bergstrom DA. Phase relationships support a role for coordinated activity in the indirect pathway in organizing slow oscillations in basal ganglia output after loss of dopamine. *Neuroscience* 2007;144:762–776. [PubMed: 17112675]
- Wiklund L, Cuenod M. Differential labelling of afferents to thalamic centromedian-parafascicular nuclei with [3H]choline and D-[3H]aspartate: further evidence for transmitter specific retrograde labelling. *Neurosci Lett* 1984;46:275–281. [PubMed: 6204255]
- Woolf NJ, Butcher LL. Cholinergic systems in the rat brain: III. Projections from the pontomesencephalic tegmentum to the thalamus, tectum, basal ganglia, and basal forebrain. *Brain Res Bull* 1986;16:603–637. [PubMed: 3742247]
- Zaidel A, Moran A, Marjan G, Bergman H, Israel Z. Prior pallidotomy reduces and modifies neuronal activity in the subthalamic nucleus of Parkinson's disease patients. *Eur J Neurosci* 2008;27:483–491. [PubMed: 18215242]

Figure 1.

Schematic diagram of PFN and STN recording sites. A. Left panel shows recording sites (n=102) in the control hemisphere from brains reconstructed in the coronal plane on standard atlas sections (Paxinos and Watson, 1997). Right panel shows recording sites (n=116 and 32, respectively) of PFN neurons in dopamine lesioned (left) and non-lesioned (right) hemispheres. The stained tissue shows deposit of Pontamine blue dye (arrows) in both hemispheres and their locations in the schematic diagram are indicated by X. B. STN recording sites in control (left panel) and lesioned (right panel) hemispheres. Abbreviations: CM central median thalamic nucleus, fr fasciculus retroflexus, ic internal capsule, LH lateral hypothalamic area, ml medial

lemniscus, PFN parafascicular nucleus, Po posterior thalamic nucleus group, STN subthalamic nucleus, ZID zona incerta dorsal, ZIV zona incerta ventral.

Figure 2.

Characteristics of PFN spike trains and LFPs. A. Simultaneously recorded PFN spike trains and LFPs from control (top) rats, and non-lesioned (middle) and dopamine lesioned (bottom) hemispheres of unilateral 6-OHDA lesioned rats. Firing rates of these 3 neurons were 2.3 Hz, 2.3 Hz and 1.5 Hz, respectively. The dots and asterisks above spikes in spike trains indicate LTS bursts (all doublets, see methods). LTS bursts with the asterisk above are shown in greater detail to the right of each spike train. B. Bar graphs of mean firing rate (top) and the number of spontaneously active neurons per recording track (bottom) in dopamine lesioned (black bars), non-lesioned (NL, grey bars) and control (white bars) hemispheres. Dopamine lesion did not affect firing rate. Significantly fewer spontaneously active neurons per track occurred

in the lesioned hemisphere compared to the control. The non-lesioned hemisphere did not differ significantly from control or lesioned hemispheres. C. Bar graphs of incidence of bursty firing pattern (with burstiness index ≥ 0.5 , left) and ISI CV (middle) showed no significant differences between control, non-lesioned and dopamine lesioned hemispheres. Right bar graph shows significantly more PFN spike trains exhibited significant 0.3–2.5 Hz oscillatory activity in the dopamine lesioned than control hemisphere. The non-lesioned hemisphere did not differ significantly from control or lesioned hemispheres. D. Spectral analyses of PFN spike train autocorrelograms from spike trains illustrated in A above show significant periodic oscillatory activity with main peaks of 0.7–0.8 Hz from recordings in control (left), non-lesioned (middle) and lesioned hemispheres (right). Dashed horizontal lines in the spectra indicate the $p=0.05$ level of significance. E. Bar graph shows total power in LFPs in the 0.3–2.5 Hz range did not differ significantly between control, non-lesioned and lesioned hemispheres. *Significant difference of $p<0.05$ compared to the control hemisphere.

Figure 3.

Correlated activity between PFN and STN. A. Representative examples of simultaneously recorded spike trains and LFPs from PFN and STN show coincident oscillations in spiking activity in the control and dopamine lesioned hemisphere. The dots above spikes in spike trains indicate LTS bursts. B. STN-triggered PFN cross-correlograms from representative spike trains from control and dopamine lesioned hemispheres shown in A above. Cross-correlogram in the control hemisphere (left) shows that neuronal spiking was significantly correlated between PFN and STN. The peak in PFN spiking occurred 30 ms prior to STN spikes. For the lesioned hemisphere (right), the peak in PFN spiking occurred 10 ms after STN spikes. C. Population data of paired PFN-STN recordings. Bar graph (left) shows that significantly ($p=0.001$) more PFN-STN spike train pairs had significantly correlated activity in the lesioned hemisphere ($n=29$) than in the control hemisphere ($n=28$). Right bar graph shows that there was a trend for PFN neurons to fire before STN neurons in the control hemisphere, whereas in the lesioned hemisphere PFN neurons tended to fire after STN neurons. *Significant difference of $p<0.05$ compared to the control hemisphere.

Figure 4.

Characteristics and timing of PFN spikes in LTS bursts. A. Bar graph (left) shows the proportion of ISIs that met the criteria indicative of LTS bursts (see Methods). Few of all ISIs in control ($n=78,089$), non-lesioned ($n=25,988$) and lesioned ($n=109,118$) hemispheres were incorporated in LTS bursts. B. The left bar graph shows the proportion of spike trains that had no LTS bursts (black bars), contained only doublets (light grey bars) or contained a combination of 2–5 spikes in LTS bursts (mixed LTS bursts, dark grey bars). The dopamine lesioned hemisphere had significantly fewer spike trains with at least one LTS burst than control or non-lesioned hemispheres. Dopamine cell lesion did not reduce the proportion of spike trains that contained only doublets or mixed types of LTS bursts. Right bar graph shows that dopamine cell lesion did not affect the mean number of LTS bursts in spike trains that contained only doublets or mixed types of LTS bursts. C. Representative spike trains and simultaneously recorded LFPs from control (top) and dopamine lesioned (bottom) hemispheres to illustrate the timing of spikes in LTS bursts and single spikes i.e. spikes not incorporated in LTS bursts. Spike trains from control and lesioned hemispheres contained 258 and 198 LTS bursts and had firing rates of 4.1 Hz and 3.5 Hz, respectively. These spike trains both exhibit LTS bursts containing 2 and 3 spikes. Black dots and asterisks above spikes in spike trains indicate LTS bursts containing triplets and grey dots indicate LTS bursts containing doublets. LTS bursts with the asterisk above are shown in greater detail to the right of each spike train. Note that spikes from LTS bursts are between the peak and trough in LFP activity, whereas single spikes are near the trough of LFP activity. D. Phase of PFN spikes in LTS bursts (black wedges) and PFN single spikes (grey wedges) referenced to PFN LFP. Only spike trains containing at least 50 LTS bursts were included in this analysis. Data were combined for spike trains from control ($n=31$) and dopamine lesioned ($n=30$) hemispheres. STWAs show that PFN spikes in LTS bursts and single spikes are significantly clustered ($p<0.05$) with respect to PFN LFPs. The

mean phase of spikes in LTS bursts ($124 \pm 56^\circ$) was significantly lower than the phase of single spikes ($152 \pm 28^\circ$). *Significant difference of $p < 0.05$.

Figure 5.

Properties of interspike intervals (ISIs) in LTS bursts. A. Line graphs of mean ISIs in LTS bursts in control (left), non-lesioned (middle) and lesioned (right) hemispheres. The numbers of LTS bursts containing doublets, triplets, quadruplets and quintuplets are shown within each graph. The dashed line for quintuplets in control rats highlights that there were only 4 LTS bursts in this category. B–D. Effects of the position of the ISI in LTS bursts (B), number of ISIs in LTS bursts (C) and lesion (D) on mean ISI. A 3 factor ANOVA revealed that all single factors (lesion, number of ISIs and position of ISIs) were statistically significant ($p=0.001$). B. Post-hoc analysis revealed that ISI durations differed significantly ($p<0.05$) based on the position of ISIs in the LTS bursts (values were combined across the other factors (lesion and number of ISIs)). Within LTS bursts, first ISIs ($n=10616$) were significantly shorter than the second ISIs ($n=2597$), which were significantly shorter than third ISIs ($n=504$), which were significantly shorter than fourth ISIs ($n=84$). C. Post-hoc analysis showed that ISIs (combined across position of ISI and lesion factors) were significantly ($p<0.05$) longer for doublets ($n=8019$) than triplets ($n=4186$) or quadruplets ($n=1260$), but there were no significant differences between triplets, quadruplets and quintuplets ($n=336$). D. Post-hoc analysis revealed that ISIs were significantly shorter ($p<0.05$) in the control hemisphere ($n=6357$) than non-lesioned ($n=2049$) or lesioned ($n=5396$) hemispheres (data combined across the other 2 factors). Significant interactions between factors were; ISIs were significantly shorter in quintuplets at each ordinal position than doublets, triplets and quadruplets ($p=0.001$), and ISIs were significantly larger for quintuplets in the control hemisphere compared to non-lesioned and lesioned hemispheres ($p=0.001$). There were no significant interactions between all 3 factors on ISIs in LTS bursts. *Significant difference of $p<0.05$.

Table 1

Characteristics of STN spike trains (n=28 and 29, respectively) from control and dopamine lesioned hemispheres.

	Control	Lesioned
Firing Rate (Hz)	8.0 ± 0.9	$12.7 \pm 1.4^*$
ISI CV	0.72 ± 0.05	$1.74 \pm 0.11^*$
Proportion with Bursts [†]	0%	79.3% [*]
Bursts per 1000 Spikes [†]	0.6 ± 0.2	$49.8 \pm 7.7^*$
Proportion with Oscillations	21.4%	96.6% [*]

Data are means $\pm$ SEM.

* Significantly different from the control hemisphere, $p < 0.05$.

[†] As assessed by the discharge density histogram method with a burst index ≥ 0.5 (Kaneoke & Vitek, 1996).