

Cocaine or Selective Block of Dopamine Transporters Influences Multisecond Oscillations in Firing Rate in the Globus Pallidus

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Previous studies have shown that direct-acting dopamine agonists modulate the multisecond oscillations which are present in globus pallidus spike trains *in vivo* in awake rats. To investigate possible modulation by endogenous dopamine and by other monoamines, and by drugs with abuse potential, cocaine or selective monoamine uptake blockers were injected systemically during extracellular recording of single globus pallidus neurons and the results analyzed with spectral and wavelet methods. Both cocaine and the selective dopamine uptake blocker GBR-12909 significantly shortened the period of multisecond oscillations, as well as increasing overall firing rate. Cocaine effects were blocked by dopamine antagonist

pretreatment, as well as by N-methyl-D-aspartate receptor antagonist (MK-801) pretreatment. Desipramine and fluoxetine (blockers of norepinephrine and serotonin uptake, respectively) had no significant effects on multisecond oscillations. The results suggest that dopamine has a primary role among monoamines in modulating multisecond oscillations in globus pallidus activity, and that tonic dopaminergic and glutamatergic transmission is necessary for normal slow oscillatory function.

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Periodicities in brain electrical activity occur in many nuclei and in many frequency ranges, and have been described in the electroencephalogram, in field potentials, and in the spiking activity of single neurons. Much of the attention that brain periodicities have received has been directed to the range of frequencies

from 1 Hz (the slow end of the delta rhythm) up to roughly 60 Hz (the fast end of the gamma rhythm). However, recent studies have demonstrated that much slower periodic oscillations are commonly present in the spike trains of tonically firing neurons in the basal ganglia. The firing rates of a majority of neurons in the globus pallidus (GP), the subthalamic nucleus, the substantia nigra pars reticulata and the entopeduncular nucleus oscillate *in vivo* with slow periods, most often in the range of 10–60 s (0.1–0.017 Hz) (Ruskin et al. 1999a; Ruskin et al. 1999c; Wichmann et al. 1999; Allers et al. 2000). These multisecond periodicities in tonic activity are present in awake rats, but are markedly attenuated by general anesthesia (Ruskin et al. 1999a).

One of the most striking characteristics of these slow oscillations is their strong modulation by dopamine

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(DA) receptor activation (Ruskin et al. 1999a; Ruskin et al. 1999c; Allers et al. 2000). Systemically injected DA agonists shift oscillatory periods from mean periods of 25–30 s to 5–15 s, depending on drug and dose. Spectral analysis reveals that DA receptor activation also increases the spectral power (i.e. the regularity) of multi-second periodicities. Therefore, in addition to the well-characterized ability of systemically-administered DA agonists to change the mean firing rate of basal ganglia neurons, they also change basal ganglia firing patterns at multisecond time scales. The use of selective DA receptor agonists and antagonists has shown that this modulation of slow firing pattern involves both the D₁ and D₂ subfamilies of DA receptors (Ruskin et al. 1999a; Ruskin et al. 1999c).

These initial studies of DAergic influences on multi-second periodicities utilized direct-acting DAergic drugs. More recently, we have found that D-amphetamine and methylphenidate, drugs that act on monoamine transmission indirectly, also modulate slow oscillations (Ruskin et al. 2001). These drugs are noted for their effects on attention and locomotor activity, including beneficial effects on these parameters in patients with attention deficit/hyperactivity disorder. D-amphetamine and methylphenidate also have serious abuse potential. To further explore the potential for abused/addictive substances to affect multisecond oscillatory activity, the present study examined the effects of cocaine on spiking activity in the GP. Since these three drugs raise levels of more than one brain monoamine, this study also tested the effects of the selective uptake blockers GBR-12909, desipramine and fluoxetine (selective for the DA, norepinephrine (NE) and serotonin (5-HT) uptake systems, respectively) to determine the relative importance of each monoamine. In addition, because many of the effects of direct-acting dopamine agonists on mean firing rate in the basal ganglia depend on *N*-methyl-D-aspartate (NMDA) receptor activity (Kelland and Walters 1992; Allers et al. 1996; Huang et al. 1998), the NMDA receptor antagonist MK-801 was utilized to test for a similar dependence of the effects of monoamine uptake blockade on multisecond periodicities.

METHODS

Extracellular single unit activity was recorded in the GP of male Sprague-Dawley rats (250–400 g) in accordance with the National Institutes of Health (USA) Guide for the Care and Use of Laboratory Animals. In previous studies of GP unit activity, we have found that the incidence of multisecond oscillations was greatly attenuated when animals were under general anesthesia (Ruskin et al. 1999a). Therefore, in the present study GP neurons were recorded in awake, immobilized rats as

previously described (Ruskin et al. 1999a). Briefly, all surgical procedures (tracheotomy, scalp incision, skull drilling) were performed with rats under halothane anesthesia. Halothane anesthesia was induced in an induction chamber, and was maintained during surgery by administration of additional halothane as needed. To prevent discomfort, all surgical sites and pressure points were injected with the long-acting local anesthetic mepivacaine, and ear bar tips and tracheal cannulas were coated with 2% lidocaine anesthetic gel. Corneal drying was prevented with LaciLube. A tracheotomy was performed, and the trachea was cannulated. Rats were placed in a stereotaxic frame, and a hole was drilled in the skull over the GP. After surgical procedures were finished, halothane anesthesia was discontinued, the animal was paralyzed with gallamine triethiodide (16 mg/kg i.v.) injected through the tail vein, and artificial respiration immediately begun with a rodent ventilator (model 683, Harvard Apparatus). Artificial respiration rates were adjusted to maintain exhaled CO₂ between 3.6 and 4.5%. Supplements of gallamine were given every 10–15 min. Body temperature was maintained at 36–38°C with a heating pad.

Glass microelectrodes (2.5–6 MΩ at 135 Hz) filled with 2 M NaCl containing 1% Pontamine Sky Blue were lowered stereotaxically through skull holes to the following coordinates: 0.8–1.2 mm posterior to Bregma, 2.6–3.0 mm lateral to the midline, 5.0–7.0 mm ventral to dura. Fine vertical control of microelectrode placement was accomplished with micromanipulators (MO-8, Narashige). Single unit activity was amplified (model 725, WPI) and monitored with an audio monitor and digital oscilloscope. Signals were band-pass filtered between 250 and 5000 Hz, and spikes were identified with a voltage/window discriminator and recorded by Spike2 software (version 3.14, Cambridge Electronic Design). All recorded GP units had biphasic +/– waveforms (type II; Kelland et al. 1995), and had baseline firing rates between 13 and 92 Hz (mean = 36 Hz). Five to six minutes of baseline activity was recorded before the i.v. injection of experimental drugs through the tail vein. Drugs were injected as a single bolus, except for GBR-12909, which in some instances was injected in four divided doses at 1-min intervals. Units were further recorded for 10–20 min. In some cases, a second drug was then injected and units were held for another 10 min. One unit was recorded per rat. After data collection, Pontamine Sky Blue was iontophoresed to mark the recording site for later histological confirmation.

Experimental drugs used include (–)-cocaine HCl, desipramine HCl (Norpramin), S(–)-eticlopride HCl, fluoxetine HCl (Prozac), GBR-12909 2·HCl (Vanoxerine), haloperidol, (+)-MK-801 hydrogen maleate (Dizocilpine), and R(+)-SCH-23390 HCl. All experimental drugs were from Research Biochemicals Inc., except for haloperidol (McNeil Pharmaceuticals). Drugs were dissolved in

0.9% NaCl, except for fluoxetine and GBR-12909 which were dissolved in distilled water, and SCH-23390 which was dissolved as a 10X stock solution in 0.001 N HCl before dilution to final volume with saline.

Spectral analysis of GP spike trains was performed by two methods. For assessing the significance of periodic activity, 180 s data segments from pre- and post-drug epochs were analyzed with the Lomb periodogram (Kaneoke and Vitek 1996), performed on binned spike trains. This method provides a measure of statistical significance for spectral features: spectra were tested against the null hypothesis that binned spiking activity had a random Gaussian distribution, resulting in an exponential distribution of spectral power. This null hypothesis was rejected at the $p = .01$ level. For spectral analysis, spiking activity was binned with 200 ms bins (example spike trains in figures are shown binned at 500 ms), and periodicities were analyzed in the range of 1.5–60 s (0.67–0.017 Hz). Periodicities slightly faster than 1.5 s in this preparation often relate to ventilation (Ruskin et al. 1999a). For example, of the presently recorded GP neurons, 11.4% had significant oscillations in this range, all having periods between 0.77 and 0.84 s. This coincides with the range of ventilator speeds, and when ventilator action was recorded simultaneously during the recording of a neuron with this type of activity ($n = 5$), the neuronal oscillatory period and the ventilator period were equal to within 1%. These ventilator-related oscillations were not further analyzed. 180 s data segments were chosen from baseline, and from the 5–10 min and (when available) 15–20 min time ranges after drug injection. To assess drug effects on oscillatory period, the period of the “main” spectral peak, i.e. the tallest (most powerful) spectral peak within the studied range, was taken from the power spectrum of each analyzed segment, and these numbers were analyzed with ANOVA followed by *post hoc* Dunnett’s comparisons to baseline. Data segments that had no significant periodicity in the 1.5–60 s range were not entered into this analysis. To assess drug effects on oscillatory regularity (i.e. spectral power) apart from effects on oscillatory period, the total area under the spectral curve within the 1.5–60 s range was measured, including those cases where there were no significant spectral peaks, and these data were analyzed with repeated-measures ANOVA followed by *post hoc* Dunnett’s comparisons to baseline. The α level for ANOVA and *post hoc* tests was $p = .05$.

In a second method of spectral analysis, focusing on the evolution of periodic activity over time, entire recordings or recording segments were represented as time-frequency plots of spectral power. These scalograms were based on the continuous wavelet transform and are analogous to Fourier transform-based spectrograms. A wavelet-based approach was used to optimize time resolution across all examined frequencies, com-

pared to the single time resolution of windowed Fourier transform analysis. Scalograms were produced with the Time-Frequency Toolbox (<http://www-syntim.inria.fr/fractales/Software/TFTB>) with Matlab 5.3.1 (The MathWorks), and were computed with the Morlet wavelet (15 s half-width at coarsest scale), with 256 frequencies being sampled within the analyzed range. Spiking activity was binned at 0.75 s, to reach a Nyquist limit of 1.5 s (0.67 Hz). Spectral power was plotted on a \log_{10} scale, with greater power represented by redder color. The color axis was scaled so that the power levels within the scalogram data for a single neuron spanned the full color range (blue to red).

RESULTS

Multisecond Periodicities in Baseline Activity

As reported previously (Ruskin et al. 1999a; Ruskin et al. 1999c), the baseline firing rate of most GP neurons recorded in awake rats oscillated at time scales of seconds to minutes (Figures 1 and 2). These periodic variations could be large in amplitude: in the baseline segment shown in Figure 2, Panel A, the firing rate varies up to 180% and down to 60% of the overall mean. Using the Lomb algorithm to assess the periodicity of these oscillations (examples in Figure 2), 80% of neurons displayed oscillations in baseline firing rate (with periods between 1.5 and 60 s) that were sufficiently powerful (i.e., regular) to be considered statistically significant. Oscillatory periods of the most powerful spectral peak from each baseline power spectrum are plotted in Figure 3. These baseline oscillatory periods varied widely from neuron to neuron (within the 1.5–60 s range), but mean values for all treatment groups were approximately 30 s (28.2 ± 2.1 s for all neurons combined).

Effects of Selective Monoamine Uptake Blockers

Most recorded units had significant slow oscillations both before and after the injection of selective monoamine uptake blockers (Table 1). However, among GBR-12909, desipramine and fluoxetine, only the selective DA uptake blocker GBR-12909 robustly effected these oscillations. Particularly striking oscillations appeared after the i.v. injection of this drug (3.2 mg/kg), and, once they had appeared, could be remarkably stable (Figure 1). Spectral analyses indicated that these oscillations occurred at a faster rate compared to baseline (Figures 1 and 3, Panel A). The mean oscillatory period within the 5–10 min post-drug epoch was ~ 10 s, and this reduction in period was still significant out to 20 min after drug injection, at which time a DA antagonist was typically administered (Figures 1 and 3, Panel A). In addition, GBR-12909 increased the power (regularity) of the multisecond oscillations. This was visible in

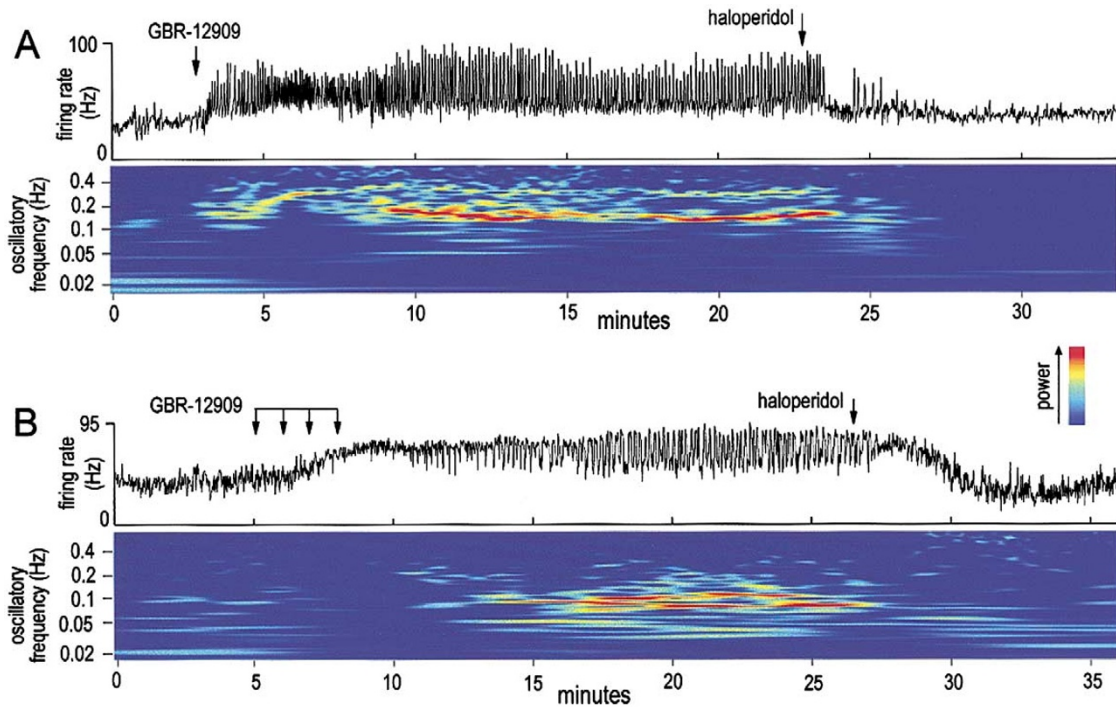


Figure 1. Effects of DA uptake blockade on multisecond oscillations in firing rate in GP neurons. Two complete firing rate records are shown, with accompanying wavelet-based time vs. frequency plots (scalograms) for illustration of oscillatory frequency between 0.67 and 0.017 Hz (1.5–60 s). The frequency (y) axis of the scalograms is \log_{10} (Hz). Redder colors represent higher power (scale bar). Both neurons had somewhat irregular slow activity in baseline, which appears in the scalograms as low-power bands between 0.025 and 0.017 Hz (40–60 s). In both units, 3.2 mg/kg GBR-12909 (given as bolus dose in Panel A, divided doses in Panel B), caused the emergence of faster, and more regular, oscillations in firing rate which are readily apparent in the firing rate records. The scalograms illustrate the emergence of these oscillations as the appearance of powerful bands centered around 0.15 Hz (7.5 s) in Panel A, and 0.1 Hz (10 s) in Panel B. These faster oscillations appeared promptly after GBR-12909 injection in A, but were somewhat delayed in Panel B. GBR-12909 also increased average firing rate in both neurons. In both units, oscillatory activity remains fairly stable until the injection of 0.2 mg/kg haloperidol, a D_2 antagonist, which reversed the effects of GBR-12909 on multisecond pattern and average firing rate.

scalograms as the emergence of higher power bands (Figure 1), and was quantified by the measurement of spectral area in Lomb algorithm-generated power spectra. GBR-12909 increased mean spectral power by almost 70% (Figure 4).

In contrast to GBR-12909, neither the NE uptake blocker desipramine nor the 5-HT uptake blocker fluoxetine had significant effects on oscillatory period (Figure 3, Panels B and C). Also, neither drug significantly affected spectral power (data not shown). After desipramine injection, there did appear to be a modest preponderance of oscillation periods below ~ 20 s. To address the possibility that this pattern might indicate the existence of a “desipramine-responsive” subpopulation, more detailed analyses were performed. Neurons were characterized as having high or low baseline firing rate (defined by a median split), or as responding to desipramine with increases or decreases in firing rate (compared to baseline). Separate ANOVAs on desipramine effects on oscillatory period for each of these groups were all non-significant. In addition, post-desipramine

oscillatory period did not significantly correlate with baseline firing rate or with post-desipramine firing rate (as absolute rate or as percent of baseline). However, these data do not rule out the possibility of a “desipramine-responsive” subpopulation of neurons or rats.

In addition to effects on multisecond oscillations, GBR-12909 was the only selective monoamine uptake blocker to have robust effects on overall firing rate. This drug increased overall firing rates in all tested neurons, whereas desipramine and fluoxetine had only minor effects (Figure 5).

GBR-12909 (3.2 mg/kg) given i.v. to freely-moving rats induced a pattern of strong downward sniffing and/or chewing, sometimes combined with slow or intermittent locomotion. This pattern was present in both the 5–10 and 15–20 min post-drug time ranges.

Effects of Cocaine

Striking multisecond oscillations appeared after injection of the non-specific monoamine uptake blocker co-

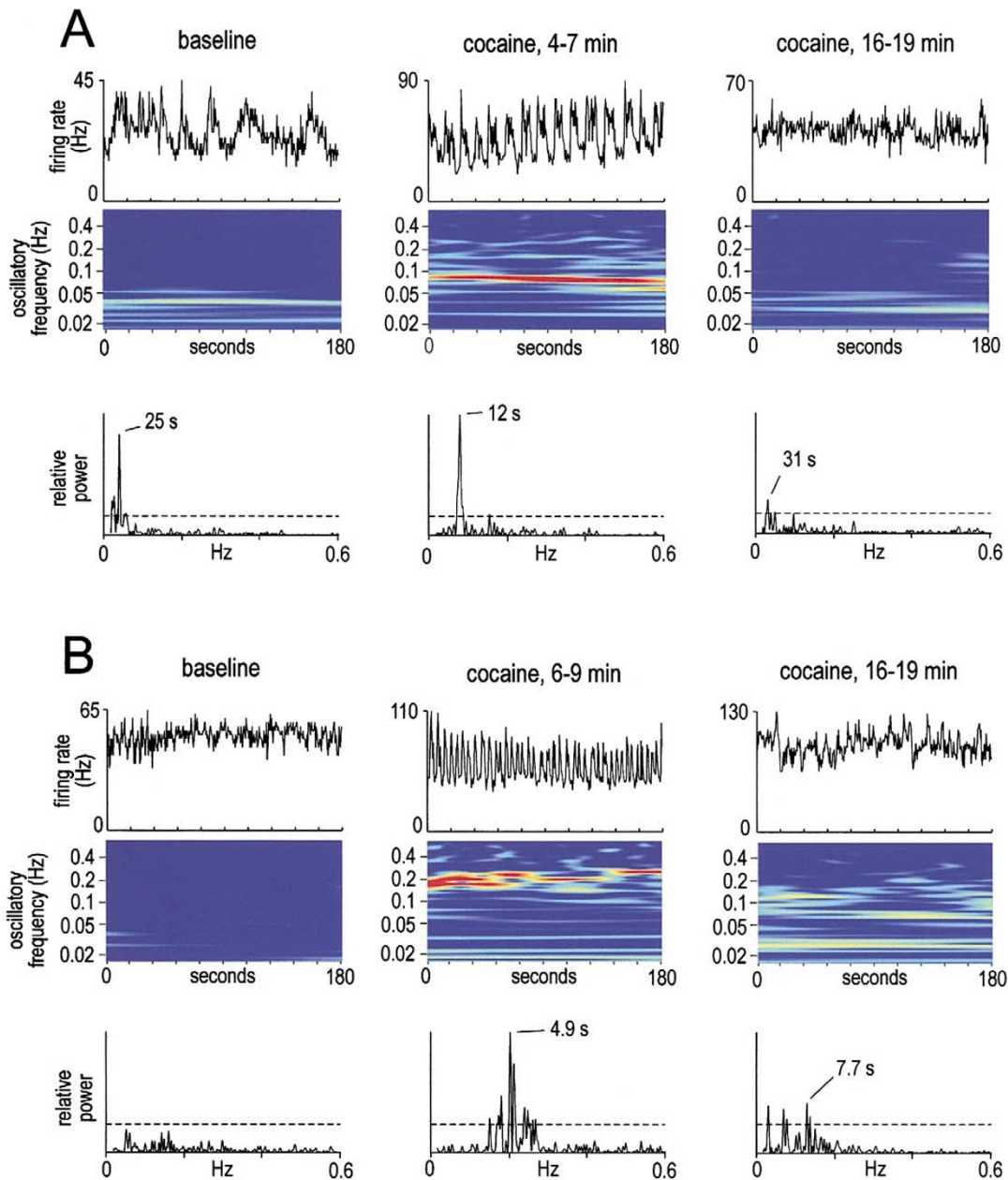


Figure 2. Effect of cocaine on oscillatory frequency in GP neurons. 180 s segments of binned spiking activity (scaled to their highest point) are shown from baseline and post-cocaine (3.2 mg/kg) epochs, with accompanying spectral analyses. Directly below the data segments (and plotted on the same time scale) are corresponding sections of the wavelet-based scalograms for each unit, showing oscillatory frequency and power over time. Conventions for scalograms are as in Figure 1; the color scale is identical for scalograms taken from a given unit. Below scalograms are power spectra derived from Lomb algorithm analyses on the same 180 s segments. These power spectra are shown with lines signifying the $p = .01$ significance level; spectral peaks above this line are considered statistically significant (see Methods). The period of the main (most powerful) significant spectral peak in each spectrum is indicated. Panel **A**: This unit had slow, somewhat irregular (but high amplitude) firing rate variations in baseline, visible in the scalogram and identified as having a main period of 25 s in the power spectrum. At 4–7 min after the injection of cocaine, oscillation period decreased to 12 s, and power (regularity) increased. A very stable and powerful band is apparent in the scalogram. Later (16–19 min after injection), the effects of cocaine spontaneously reversed: slow oscillatory activity decreased in power, and increased in period. Panel **B**: This unit did not have significant oscillatory activity in baseline. At 6–9 min after cocaine injection, very regular oscillations were noted, identified in the power spectrum as having a main period of 4.9 s. The accompanying scalogram indicates that the oscillation period varied somewhat over time. The effects of cocaine eventually wore off: 16–19 min post-drug, oscillatory power decreased (visible in both the scalogram and the power spectrum), and oscillatory activity became disorganized. Several peaks (and bands) are visible across a wide range of periods in the power spectrum (and the scalogram). Cocaine also increased average firing rates in both neurons.

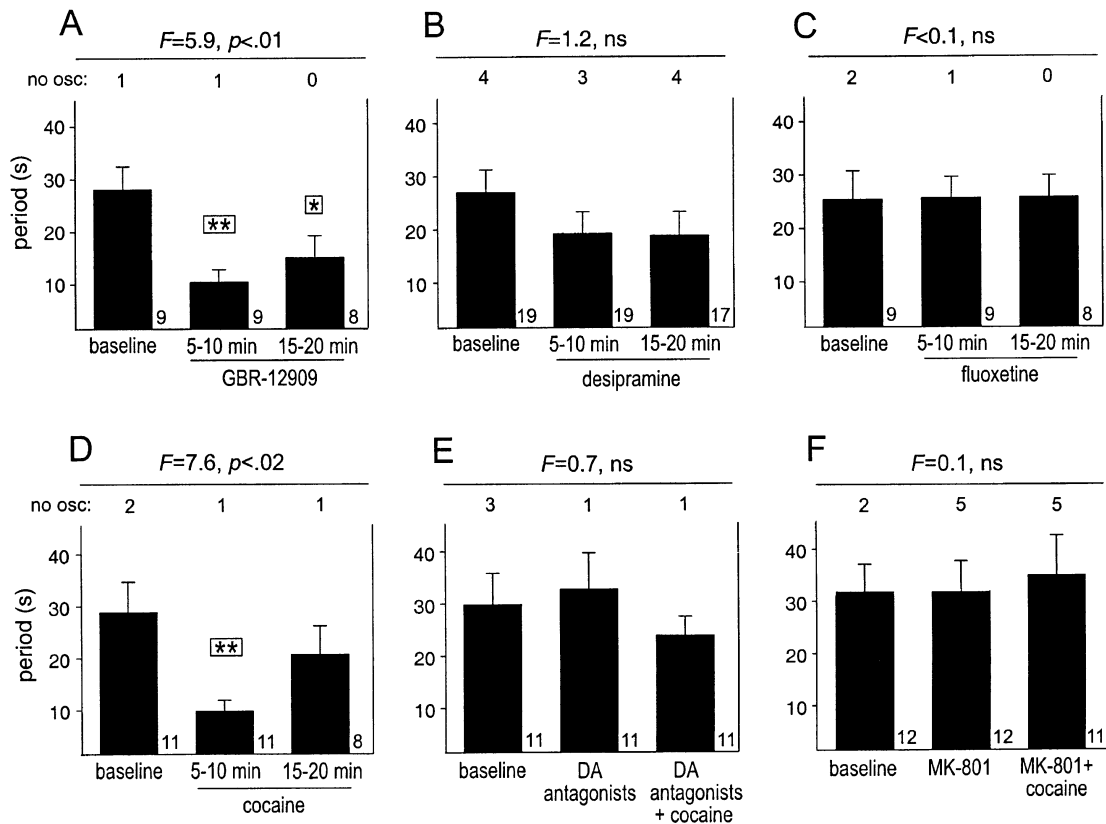


Figure 3. The effect of monoamine uptake blockers on oscillatory period, and the effect of pretreatment with DA receptor or NMDA receptor antagonists. Bars represent the mean \pm SEM of the periods of the most powerful Lomb spectral peaks (examples in Figure 2) of neurons within a particular condition. The total number of cells for each group is given at the base of each bar; the number of cells in the group that are without significant periodicity (i.e. no spectral peaks above the $p = .01$ significance level) is indicated above each bar ("no osc"). ANOVA results (F and p values) for each treatment group are given above each graph. Panels **A**, **B**, **C**: Period was significantly reduced by GBR-12909 (3.2 mg/kg), but not by desipramine (2.0 and 5.0 mg/kg) or by fluoxetine (3.2 mg/kg). Separate ANOVAs on desipramine at these two doses indicated no significant effect of either; therefore, the groups are combined here. Panel **D**: Period was also significantly reduced by cocaine (3.2 mg/kg), although this effect was no longer apparent in the 15–20 min time range. Panels **E**, **F**: The effect of cocaine was blocked by pretreatment with either combined D_1 and D_2 antagonists (SCH-23390, 0.5 mg/kg, and eticlopride, 0.2 mg/kg; "DA antagonists") or by MK-801 (0.15 mg/kg). Cocaine data in Panels **E** and **F** are from the 5–10 min range. Neither the DA antagonist treatment or MK-801 had significant effects on period alone. ns: non-significant. * $p < .05$, ** $p < .02$.

caine (Figure 2), and like GBR-12909, cocaine reduced the periods of these oscillations to a mean of ~ 10 s within the 5–10 min epoch (Figure 2 and 3, Panel D). However, cocaine effects on oscillatory period were short-lived, not lasting through the 15–20 min post-drug epoch, as illustrated by visual inspection of firing activity and scalograms (Figure 2), and confirmed by Lomb analysis (Figure 3, Panel D). Cocaine-induced increases in overall firing rate were also typically short-lived, reaching a plateau at 4–9 min and dropping thereafter. These results are consistent with the relatively short biological half-life of this drug in rats after i.v. administration (Barbieri et al. 1992). Unlike GBR-12909, cocaine did not have significant effects on spectral power. Although some units responded to cocaine with an increase in power (e.g. Figure 2, Panel B: there is an 83% increase in spectral area (middle column)

compared to baseline), there was no consistent power response (Figure 4).

Although the large majority of type II (+/- waveform) GP neurons respond to indirect-acting or direct-acting DA agonists with net increases in firing rate, rare type II neurons are found that respond with decreased net firing rate (e.g. Figure 4 in Ruskin et al. 1998). Of the eleven GP neurons recorded during cocaine treatment, one fell into this latter category. Notably, although cocaine caused a 66% decrease in overall firing rate in this one case, the unit still displayed the cocaine-induced reduction in oscillatory period similar to the typical "firing rate-increasing" population (Figure 6). Similar period reductions have been noted in rare type II units demonstrating firing rate decreases after D -amphetamine or direct-acting D_1/D_2 agonists (unpublished results).

Table 1. Expression of Multisecond Periodicities in GP Neurons

| Treatment | Before/After | Before/After | Before/After | Before/After | n |
|-----------------------|--------------|--------------|--------------|--------------|----|
| | +/+ | -/+ | +/- | -/- | |
| GBR-12909 (3.2) | 78 | 11 | 11 | 0 | 9 |
| Desipramine (2.0,5.0) | 68 | 16 | 10 | 5 | 19 |
| Fluoxetine (3.2) | 67 | 22 | 11 | 0 | 9 |
| Cocaine (3.2) | 82 | 9 | 0 | 9 | 11 |

Most GP units have significant multisecond periodicities both before and after monoamine uptake blockade. Each GP unit is classified into one of four categories based on the expression of slow oscillations in firing rate 'before' and 'after' drug injection. The 'after' category refers to the 5-10 min post-injection time range. '+' and '-' indicate the presence and absence, respectively, of statistically significant periodic activity in the 1.5-60 s range of periods. Numbers are percentages. For example, in the rats receiving fluoxetine, 67% of neurons had oscillations both in baseline and after drug injection, 22% did not have baseline oscillations but did have oscillations after drug, 11% had baseline oscillations but no oscillations after drug, and no neurons were without oscillations in baseline and drug epochs. Numbers in parentheses are i.v. doses in mg/kg.

Because cocaine caused reductions in oscillatory period similar to those caused by the selective DA uptake blocker GBR-12909, we attempted to confirm the DAergic mediation of cocaine effects with DA receptor antagonists. A pretreatment with combined D₁ and D₂ antagonists (for complete antagonism of both DA receptor subfamilies) completely prevented the effects of cocaine on oscillatory period (Figure 3, Panel E). The combined DA antagonist treatment did not change oscillatory period by itself (Figure 3, Panel E), but did significantly reduce oscillatory power compared to baseline. After subsequent cocaine injection, oscillatory power was no longer significantly different from baseline (Figure 4),

although it was also not significantly different from that after DA antagonist alone ($p = .11$, Tukey test).

Pretreatment with the non-competitive NMDA receptor antagonist MK-801 also prevented the effects of cocaine on oscillatory period, without having any effect by itself on period (Figure 3, Panel F). In addition, MK-801 by itself significantly decreased oscillatory power, and power remained reduced after subsequent injection of cocaine (Figure 4).

In the 5-10 min post-drug time range, freely-moving rats injected with 3.2 mg/kg cocaine i.v. demonstrated strong sniffing (directed downward, upward, or at the walls of the chamber), concomitant with almost contin-

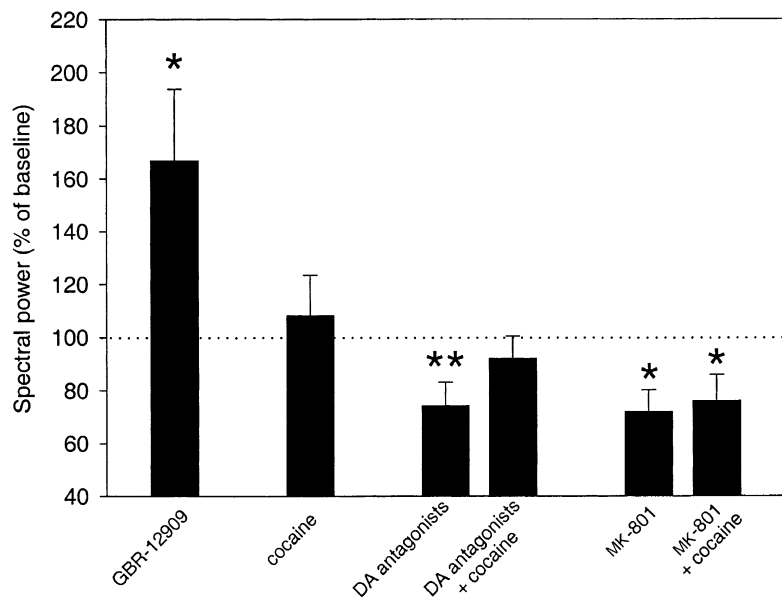


Figure 4. The effect of GBR-12909 or cocaine on oscillatory power, and the effect of pretreatment with DA receptor or NMDA receptor antagonists. Drug effects on spectral power (taken from the Lomb algorithm) are expressed as percent of baseline power. Significant main effects were found for GBR-12909 ($F = 3.8$, $p < .05$), combined injection of SCH-23390 and eticlopride (D₁ and D₂ antagonists) followed by cocaine ($F = 6.0$, $p < .01$) and MK-801 followed by cocaine ($F = 6.1$, $p < .01$). Only data for the 5-10 min time range are shown. * $p < .05$, ** $p < .02$. GBR-12909 also demonstrated a trend ($p = .10$) to increased power in the 15-20 min time range (not shown). 'n' for groups same as Figure 3.

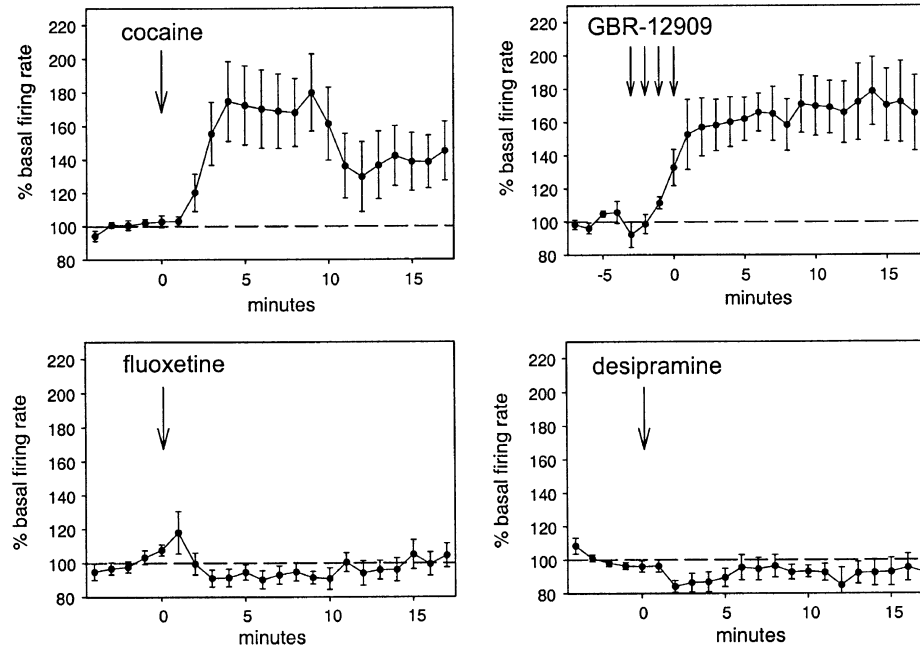


Figure 5. The effect of monoamine uptake blockers on mean firing rates in the GP. Firing rates are shown as minute-by-minute mean \pm SEM, and are expressed as percent of baseline firing rate. Cocaine (3.2 mg/kg, $n = 11$) and GBR-12909 (3.2 mg/kg, $n = 9$) increase GP firing rates up to approximately 180% of baseline. Note the shorter-acting effect of cocaine, consistent with its shorter-acting effect on multisecond periodicities. Fluoxetine (3.2 mg/kg, $n = 9$) and desipramine (5.0 mg/kg, $n = 10$) caused minor decreases in firing rate. Desipramine had similar effects at 2.0 mg/kg (not shown). In cases where GBR-12909 was injected as a single bolus dose ($n = 3$), the time of this injection is aligned with the first of the four arrows.

uous locomotion or rearing. Drug effects noticeably waned by the 15–20 min post-injection time range: rats occasionally sniffed, locomoted, or groomed, but were still most of the time.

DISCUSSION

Previous studies from our laboratory demonstrated that DA strongly modulates multisecond periodicities that are present in the spike trains of many GP neurons in awake rats. To extend these findings, the effects of other monoamines on GP firing rate oscillations were investigated. The present data show that augmenting NEergic or 5-HTergic transmission alone has minor effects on multisecond periodicities, and confirm the dominance of the DA system. These data also confirm that DA has a primary role among the monoamines for inducing increases in average firing rate in the GP (Bergstrom and Walters 1981). Because the DA agonists used in this study are indirect-acting, i.e. they augment levels of endogenous transmitter rather than directly activate receptors, these data demonstrate that an increase in endogenous DA is as effective in modulating the period and regularity (power) of slow oscillations in the GP as is direct activation of DA receptors by exogenous agonists. Work with D-amphetamine and meth-

ylphenidate supports this conclusion (Baek et al. 1999; Ruskin et al. 2001). These results are therefore relevant to drug abuse and addictive processes in humans, since abused catecholaminergic stimulants (including cocaine) act *via* endogenous transmitter.

The effects of GBR-12909 or cocaine treatment on GP firing rate and pattern, prevented and reversed by DA receptor antagonists, are consistent with the marked increases in DA overflow caused by these drugs at or around the presently tested doses (Church et al. 1987; Baumann et al. 1994; Fink-Jensen et al. 1994; Engberg et al. 1997). However, our observations indicate that other transmitter systems are involved in these electrophysiological effects. For instance, pretreatment with the NMDA receptor antagonist MK-801 blocked cocaine's reduction of oscillatory period, suggesting that ongoing activity at NMDA receptors is necessary for this DA-induced effect. This type of NMDA receptor dependence has been noted for other electrophysiological effects of DA agonists in the basal ganglia (Kelland and Walters 1992; Allers et al. 1996; Huang et al. 1998), as well as for other measures of basal ganglia activity (reviewed in Huang et al. 1998). In addition, a comparison of the effects of GBR-12909 and cocaine reveals that although both drugs reduced oscillatory period (from ~ 30 s to ~ 10 s), only GBR-12909 increased oscillation power. Direct-acting DA receptor agonists such as apo-

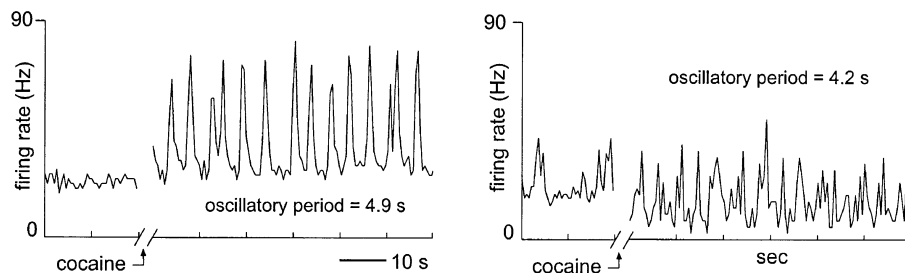


Figure 6. The lack of relationship between stimulant effects on oscillatory period effects on net firing rate. Tick marks on the time axes indicate 10-s increments. One minute of binned spiking activity (from several minutes after i.v. cocaine injection) is shown, along with a short epoch of baseline activity for comparison of overall firing rate. Both units have typical, short-period oscillations after cocaine, even though the effects of cocaine on overall firing rate in the two neurons are opposite. The net firing rate of the unit on the left increased by 57% compared to baseline, while the unit on the right responded to cocaine with a 66% decrease in net firing rate.

morphine also increase power (Ruskin et al. 1999a). Because cocaine blocks uptake of NE and 5-HT, in addition to DA uptake, these results suggest that increased NE or 5-HT levels might diminish DA-mediated increases in oscillatory power (while not affecting DA modulation of oscillatory period). A number of studies have demonstrated a reduction in DA-stimulated behaviors by 5-HTergic or NEergic systems (Ungerstedt 1971; Mabry and Campbell 1973; Grabowska 1976; Fox and Brotchie 1996, 2000; Henry et al. 1998; Rocha et al. 1998; Gainetdinov et al. 1999). More generally, the present results demonstrate that the period and power of multisecond oscillations in the basal ganglia can be independently affected, in agreement with a previous study of DA agonist effects in another basal ganglia region, the entopeduncular nucleus (Ruskin et al. 1999b).

In addition to being modulated by increased DAergic transmission, ongoing multisecond oscillations appear to partially depend on tonic DAergic and glutamatergic activity. This dependence is reflected in the significant $\sim 15\%$ decrease in oscillatory power after treatment with combined D_1/D_2 receptor antagonists or a NMDA receptor antagonist. Interestingly, although these treatments blocked the effects of cocaine on oscillatory period, they did not affect oscillatory period when given alone (similarly, oscillatory period in the subthalamic nucleus is not affected by decreased DAergic transmission due to lesion of midbrain DA neurons (Allers et al. 2000)). Since spectral power reflects oscillatory regularity, the results suggest that tonic DAergic and glutamatergic (NMDA) tone partially supports the regularity of ongoing slow oscillations. The level of DAergic tone in these immobilized rats is not likely to be higher than normal, since firing rates of substantia nigra pars compacta DA neurons are not significantly increased in immobilized rats compared to anesthetized rats (Melis et al. 1998), and since, regarding multisecond oscillations, the effects of DA antagonists alone (no change in period, small-magnitude power decrease)

are minor compared with the effects of DA agonists. On the other hand, DA antagonists have striking effects when administered during pharmacologically-stimulated DA release (Figure 1). Other transmitter systems are also involved in supporting slow oscillatory power: general anesthetics (specifically, urethane and ketamine/xylazine), which affect a number of transmitter systems, reduce spectral power in GP spike trains in the 1.5–60 s range by 50 to 60% (unpublished results), leading to a severe decrease in the incidence of statistically significant multisecond oscillations (Ruskin et al. 1999a; Ruskin et al. 2001).

The decrease in spectral power after DA antagonist administration was partially reversed by subsequent cocaine injection. Such data suggest that the non-dopaminergic effects of cocaine can increase multisecond spectral power in the absence of DAergic tone. Together with the comparison of the effects of GBR-12909 and cocaine (which indicate a decrease of DA-stimulated multisecond spectral power), the results suggest a 'normalizing' effect of 5-HT or NE release on the DAergic modulation of slow oscillatory power. This effect of 5-HT or NE appears to depend on tonic NMDA receptor activity, since there is no increase in spectral power after cocaine injection after prior injection of MK-801.

Multisecond periodicities have been noted in blood pressure (termed Mayer waves) and heart rate (Barnes and Burnham 1969; Mautner-Huppert et al. 1989). It is possible that these peripheral oscillations might somehow drive central multisecond oscillations. However, it has recently been reported that desipramine, administered i.v. to awake rats at one of the presently tested doses (2.0 mg/kg), induces particularly strong arterial pressure oscillations in the 10-s range (Bertram et al. 1999). Since, in the present study, desipramine produced (at best) inconsistent effects on oscillatory period and power, it seems probable that the multisecond oscillations in activity in the basal ganglia are not simply secondary to peripheral cardiovascular oscillations. In

addition, the DA receptors that modulate basal ganglia multisecond oscillations are located centrally, not peripherally (Ruskin et al. 1999a; Ruskin et al. 1999c).

In terms of mechanisms of the DAergic modulation of slow oscillations, it is important to note that drug effects on oscillatory period were not related to drug effects on overall firing rate. In other neuronal systems and frequency ranges, the rate of oscillatory spiking activity or the rate of periodic bursting is positively correlated with the level of depolarization (Leresche et al. 1991; Beurrier et al. 1999; Koshiya and Smith 1999), implying a voltage-dependent mechanism. Such a relationship is not apparent for multisecond periodicities in the GP. Although treatments that increased oscillatory frequency also increased mean firing rate in a majority of neurons, some neurons demonstrated an increased oscillatory frequency simultaneously with a decreased mean firing rate. Additionally, in an earlier study of multisecond oscillations in the GP (Ruskin et al. 1999c), D_1 agonists were found to increase oscillatory frequency without having consistent effects on mean firing rate, while D_2 agonists modestly increased firing rate without having consistent effects on oscillations. Therefore, oscillatory period does not appear to be voltage-related for GP neurons when considered as a single population. Similar conclusions have been made about neurons in the entopeduncular nucleus and substantia nigra pars reticulata (Ruskin et al. 1999a). Oscillatory frequency might be positively linked to depolarization in the predominant subpopulation of GP neurons that increase average firing rate after combined D_1/D_2 receptor activation, and these neurons might drive (via local axon collaterals) other GP neurons to oscillate at a similar speed. However, this scenario seems unlikely, since there is no correlation between oscillation frequency and net firing rate (either absolute or percent of baseline) after cocaine or GBR-12909 treatment in the subpopulation with increases in average firing rate (data not shown). If oscillatory period in the GP is not related to membrane voltage, then the mechanisms by which DA modulates net firing rate and oscillatory period in the GP must differ.

Regarding the mechanism of *generation* of slow oscillations, if these oscillations (regardless of period) can occur in the GP within a wide range of membrane voltages, then they are likely not generated by voltage-dependent mechanisms within the GP. Instead, they might be generated in afferent structures and transmitted synaptically to the GP, or they might arise from network mechanisms within the GP or between the GP and other structures. There is some evidence for this last hypothesis, as reverberating oscillations have been found in organotypic co-cultures of GP and subthalamic nucleus, albeit at shorter periods (Plenz and Kitai 1999). Also, network mechanisms are clearly involved in correlating (if not also generating) multisecond oscil-

latory activity, as spatially distant basal ganglia neurons can have similar periods with constant phase relationships (Allers et al. 1999; Ruskin et al. 2000).

Although wavelet analysis has been increasingly utilized for analysis of electroencephalographic signals, fewer studies have used this technique for analysis of single unit data. Many of these latter studies have utilized wavelets for spike sorting (Zouridakis and Tam 1997) or denoising (Koshiya and Smith 1999) applications, rather than for analyzing neuronal spiking in the time-frequency domain (Przybylski 1991; Lewalle et al. 1995). Here, wavelet analysis successfully revealed multisecond periodicities in GP spiking activity, and complemented our standard spectral analysis technique, the Lomb periodogram. Apart from the obvious differences in the methodologies (producing time information in the wavelet scalogram, and statistical information in the Lomb periodogram), these two techniques routinely indicated similar oscillatory activity for a given data segment. For instance, in Figure 2, Panel A, center, both techniques indicate a strong oscillation of ~ 12 s after cocaine injection, while in the baseline epoch depicted in Figure 2, Panel B, left, both methods indicate a lack of substantial multisecond oscillatory activity. Yet there are subtle differences between the two methods, such as the more sensitive detection of the 25-s periodicity by the Lomb periodogram in Figure 2, Panel A, left. Possibly the most enlightening use of the wavelet scalogram for the present data is to reveal the nature of the multiple, statistically significant spectral peaks which are present in the Lomb periodogram in some cases. In Figure 2, Panel B, middle, the Lomb spectrum of a post-cocaine epoch shows a number of spectral peaks with periods ranging from 3.7 to 6.6 s centered on a powerful main peak of 4.9 s. Inspection of the corresponding scalogram reveals that the period of the neuron's strong oscillatory activity was continuously shifting within the analyzed time, with an overall decrease in period. Hence, in this case the multiple peaks in the Lomb spectrum arise from the period variation of the predominant oscillation over time. Alternatively, concerning the weaker oscillatory activity present in Figure 2, Panel B, right, the Lomb periodogram indicates three spectral peaks of nearly equal strength, at 7.7, 14, and 33 s. The scalogram demonstrates that the 33 s oscillation was present throughout the analyzed segment, simultaneously with the 7.7 and 14 s oscillations, which themselves were segregated to early and later parts of the segment. Therefore, the presence of multiple spectral peaks can indicate simultaneous oscillations and/or shifts in oscillation period over time.

Periodic oscillations in activity in the seconds-to-minutes range have been noted in many biological systems, and have been attributed with various functions. In particular, oscillatory fluctuations in intracellular levels of the second-messenger calcium are more effi-

cient than simple changes in mean calcium level for inducing gene expression, enzymatic activity and hormone secretion in some *in vitro* systems (Holl et al. 1988; Matozaki et al. 1990; Dolmetsch et al. 1998; De Koninck and Schulman 1998; Li et al. 1998; Charles et al. 1999; Narenjkar et al. 1999; Tomić et al. 1999). Furthermore, it was hypothesized in some of these studies that the calcium-mediated influence on effector systems is related to oscillatory frequency. The oscillations in neuronal firing rate in the present study presumably drive slow variations in intracellular calcium concentration which might be functionally significant; however, they are likely to have effects beyond signal transduction, namely at systems and behavioral levels. Such prominent temporal patterning in basal ganglia spiking activity is likely to be associated with corresponding patterning in activity of other forebrain regions (*via* the basal ganglia output pathways), and so to modulation of cognition and behavior. Cocaine and GBR-12909 (as well as D-amphetamine and methylphenidate) induce stereotyped sniffing and oral movements, stereotyped locomotion, and perseveration during the execution of learned motor behaviors (Kokkinidis and Anisman 1976; Ridley et al. 1981; Mueller et al. 1989; Paulus et al. 1993; Rosenzweig-Lipson et al. 1994; present results) in rodents and non-human primates. Cocaine or amphetamine intoxication in humans can lead to similar behaviors (reviewed in Lyon and Robbins 1975). GP neurons are well-characterized as having alterations in firing rate in relation to movement, so that multisecond oscillations in pallidal firing rate might relate to some specific periodicity of limb or body movement, or motor state. Such relationships will need to be characterized in studies of freely-moving animals. In addition to motor effects, cocaine, amphetamine and methylphenidate all produce a 'high' or 'rush' at sufficient doses in humans, and continued usage typically leads to addiction. In studies of rodents and non-human primates, all these stimulants as well as GBR-12909 (Bergman et al. 1989; Roberts 1993) support self-administration. The similarity of the effects of these drugs on basal ganglia multisecond oscillations, and their common effects on these behaviors, suggests that abnormal multisecond patterning in the forebrain (with shifted frequency range and/or increased power) might relate to the acute motor and affective/cognitive effects of stimulant treatment, and might represent a state of brain activity which induces or augments addictive processes.

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