

HIGHER MAGNITUDE ACCUMBAL PHASIC FIRING CHANGES AMONG CORE NEURONS EXHIBITING TONIC FIRING INCREASES DURING COCAINE SELF-ADMINISTRATION

U. E. GHITZA,^a V. F. PROKOPENKO,^b M. O. WEST^b
AND A. T. FABBRICATORE^{b*}

^aBehavioral Neuroscience, Clinical Pharmacology and Therapeutics Research Branches, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Department of Health and Human Services, 5500 Nathan Shock Drive, Baltimore, MD 21224, USA

^bDepartment of Psychology, Rutgers University, 152 Frelinghuysen Road, Piscataway, NJ 08854, USA

Abstract—Studies using i.v. cocaine self-administration in rats have documented *rapid-phasic* changes in the firing rate of nucleus accumbens neurons within seconds of cocaine-reinforced lever presses, as well as changes that occur over the course of the cocaine self-administration experiment, i.e. *tonic* changes in firing rate. During the self-administration period of the experiment, individual neurons exhibit either a tonic increase, a tonic decrease, or no tonic change in firing rate, relative to the neuron's firing rate during the pre-drug period. We evaluated whether rapid-phasic changes in firing were differentially associated with tonically reduced or tonically elevated firing of nucleus accumbens core and shell neurons in cocaine self-administering rats. Rapid-phasic firing patterns within seconds of the cocaine-reinforced lever press were exhibited predominantly by core neurons that also exhibited tonic increases in firing. Conversely, core neurons that did not exhibit such rapid-phasic firing patterns were more likely to show tonically reduced firing. Moreover, core neurons were more likely than shell neurons to exhibit: 1) tonic increases in firing and 2) rapid-phasic increases in firing preceding the cocaine-reinforced lever press. These differences between accumbens subterritories may be related to their distinct involvement in operant responding; the present findings are consistent with an emerging literature which implicates shell in contextual stimulus-induced responding, and core in processing the instrumental response via its discrete output to classic basal ganglia structures. The distinct tendency of the core to exhibit increased firing, coupled with its dichotomous firing outputs (i.e. tonic decreases without rapid phasic responses or tonic increases with rapid phasic responses), may reflect particular sensitivity of these neurons to excitatory limbic afferent signaling involved in instrumental responding. Enhanced phasic responsivity in the core may be an integral component of the mechanism inherent in normal reward processing which is subverted by chronic drug exposure. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: addiction, electrophysiology, reward, motivation, conditioned, ventral striatum.

*Corresponding author. Tel: +1-732-382-9548; fax: +1-732-445-2263. E-mail address: tonio@rci.rutgers.edu (A. T. Fabbriatore).
Abbreviations: DA, dopamine; FR1, fixed-ratio 1; MSN, medium spiny neuron; NAcc, nucleus accumbens; PETH, peri-event-time histogram; S:B, signal-to-background ratio; S^D, discriminative stimulus.

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The nucleus accumbens (NAcc) is a component of the mesocorticolimbic dopamine (DA) system necessary for the acquisition and maintenance of self-administration of various abused drugs (Roberts et al., 1980; Pettit et al., 1984; Zito et al., 1985; Wise and Bozarth, 1987; Koob and Bloom, 1988; Porrino et al., 1991). Extracellular single unit recording studies of NAcc neurons in animals self-administering cocaine on a fixed-ratio 1 (FR1) schedule have revealed firing rate changes over the hours of a cocaine self-administration session (*tonic* increases or decreases) (Peoples et al., 1998; Fabbriatore et al., 2001) and also within seconds of the cocaine-reinforced lever press (*phasic* increases or decreases) (Carelli et al., 1993; Chang et al., 1994; Peoples et al., 1997). Preliminary data from our laboratory have revealed that during cocaine self-administration, phasic changes in NAcc firing rate are differentially distributed among tonic categories: phasic changes are more prevalent among tonically increased neurons than tonically decreased neurons (Ghitza et al., 2001). This tendency for phasic changes to occur in neurons that also exhibit tonic increases may reflect processing related to drug-taking behavior distinct from that of tonic decrease neurons, which tend to lack phasic changes. An analysis of the distribution of accumbal neurons which differentially express tonic and phasic firing patterns may provide insight into the discrete neurophysiological factors inherent in the circuitry mediating drug-taking behavior. Such an analysis contrasts with a recent report which assessed NAcc “lever-press” (i.e. rapid phasic) firing changes only in neurons that exhibited “tonic inhibition” over the hours of a cocaine self-administration session (Peoples and Cavanaugh, 2003). The aim of the present study is to account for the tonic and phasic firing rate changes of each accumbal neuron recorded and to determine whether phasic changes are differentially distributed between both tonic categories.

In addition, given the mounting evidence for core/shell functional compartmentation (Pulvirenti et al., 1992; Robledo and Koob, 1993; Maldonado-Irizarry and Kelly, 1994; Pontieri et al., 1995; Carlezon and Wise, 1996; Ikemoto et al., 1997, 2005; Corbit et al., 2001; Rodd-Henricks et al., 2002; Ito et al., 2004), we evaluated whether these changes in firing are differentially distributed between these NAcc subterritories.

EXPERIMENTAL PROCEDURES

Fifty-two male (280–350 g) Long-Evans rats (Charles River, Raleigh, NC, USA) were implanted with a catheter in the jugular vein.

An array of 16 microwires (diameter of each uninsulated wire tip, 50 μm) (California Fine Wire, Grove City, CA, USA) was implanted in the NAcc according to the atlas of Paxinos and Watson (1997). The surgery, coordinates, and procedures used for postoperative maintenance were described in a previous report (Peoples and West, 1996). Training sessions were conducted seven days per week, each session limited to 6 h or 80 infusions, whichever was first attained. Each day of training, drug accumulation curves (Peoples et al., 1997, 1999; Fabricatore et al., 2001) were used to determine whether stable lever press behavior and drug levels were maintained throughout the self-administration session. A stable drug level throughout the session was ascertained by uninterrupted, regularly-spaced lever pressing. Rats self-infused cocaine at intervals similar to those described in previous studies (Peoples and West, 1996; Peoples et al., 1998, 1999), such that neurons could be studied on all necessary time bases. Neural recordings began at least 20 min before the start of the self-administration session and were conducted during late training sessions (at least 12 days after the beginning of self-administration training) when lever pressing behavior was consistent throughout the session.

Over the course of several years, cocaine self-administration experiments were conducted by two different researchers in this laboratory, each evaluating changes in the firing rates of accumbens neurons using one of two schedules of reinforcement (described below). Each study characterized tonic and rapid-phasic firing of accumbens core and shell neurons. The observation of similar changes in firing within the same populations of accumbens neurons in the two separate data pools prompted post hoc quantitative comparisons between them (described below).

Cocaine self-administration on FR1 schedule. A group of animals ($N=33$) self-administered cocaine on an FR1 schedule. Prior to the onset of each self-administration session, a nonretractable response lever was mounted on a side wall of the chamber. Each reinforced lever press was followed immediately by a 0.77 mg/kg/0.2 ml i.v. infusion of cocaine, a 7.5 s tone that corresponded to the duration of the syringe pump (Razel Scientific Instruments, Stamford, CT, USA) operation, and a 40 s time out, during which a stimulus light was turned off, and lever presses had no programmed consequence.

Discriminative stimulus (S^D)-controlled cocaine self-administration sessions. A separate group of rats ($N=19$) was used in the S^D -controlled cocaine self-administration schedule. Prior to the onset of each self-administration session, a nonretractable response lever was mounted on a side wall of the chamber. Each lever press in the presence of an audible tone (3.5 kHz, 70 dB or 750 Hz, 70 dB counterbalanced across animals) produced an i.v. infusion of cocaine (0.35 mg/kg infusion), terminated the tone and started an inter-tone interval which varied unpredictably between 3 and 6 min. If a lever press did not occur during the 2 min tone presentation period, the tone was terminated and an inter-tone interval began. Timing of tones was programmed to approximate the timing of spontaneous self-infusions of the same dose that rats exhibit in a FR1 schedule of reinforcement. Further details concerning this experimental design were described in a previous report (Ghitza et al., 2003).

Evaluation of generalizability of data by comparing FR1 cocaine self-administration data to S^D -controlled cocaine self-administration data. Qualitative analyses of the neural data suggested that there were similarities in firing patterns on both the tonic and rapid-phasic time bases irrespective of cocaine self-administration schedule. These similarities prompted quantitative comparisons (i.e. two tailed Mann-Whitney U tests, $\alpha=0.05$) to statistically test whether this was indeed the case.

Histology. Electrophysiological data were compiled from only: 1) a single recording of each microwire and 2) histologically

confirmed NAcc microwire tip placements. The histological procedures used to verify the location of each recorded neuron were described in a previous report (Ghitza et al., 2003). Using coronal sections, the location of each wire was demarcated by a small electrolytic lesion and was plotted (by an investigator blind to the recorded neuronal activity) on the coronal plate (Paxinos and Watson, 1997) that most closely corresponded to its antero-posterior position. Recorded neurons were confirmed to be located in either the core or shell subterritory by eliminating all lesion centers within 150 μm of any intra- or extra-accumbal border.

Analysis of firing rate data according to histological demarcation of accumbens. Subterritorial distribution of firing was analyzed in two ways: 1) wire placements were defined as by Zahm and Brog's (1992) three subterritory classification in which neurons were localized to shell, core or rostral pole and 2) wire placements were defined according to the two subterritory classification used by Jongen-Relo et al. (1994) and Reidel et al. (2002) in which the shell and core subsume the medial and lateral regions of the rostral extent of the accumbens, respectively. In addition, the shell was subdivided into medial and ventral subregions. Wires placed in the medial shell subregion were confined to the area (coordinates relative to bregma): 1) at or posterior to 2.3 mm and anterior to 0.7 mm anteroposterior, and 2) medial to 1.4 mm mediolateral. Wire tips within the shell region located laterally to this region were categorized as ventral shell wires.

Construction of peri-event time histograms (PETHs). Rapid-phasic changes in firing that occurred within seconds of the instrumental drug-seeking response (lever press) were determined by constructing rasters and PETHs that display neuronal discharges within the 12 s before and after each lever press. Cocaine-reinforced lever presses were used as the drug-taking responses (nodes) around which all histograms were constructed. For each neuron, one histogram was constructed from a cocaine self-administration session during late training (at least 12 days after the beginning of self-administration training).

Using these histograms, the magnitude of changes in firing was standardized and calculated for all NAcc neurons. During cocaine self-administration, accumbens neurons that exhibited rapid-phasic changes in firing related to the instrumental response did not exhibit these changes in firing prior to -3 s relative to the lever press. Therefore, for the FR1 schedule of cocaine self-administration, the baseline period was -9 to -3 s relative to each lever press (40 nodes, yielding a total baseline period of 240 s). For S^D -controlled cocaine self-administration, the period between -6 to -3 s relative to each lever press served as the baseline period (between 70 and 80 nodes, yielding a total baseline time of 210–240 s), thus equating the baseline periods of the two schedules.

For changes in firing that commenced prior to the lever press, a ratio, $(B)/(A+B)$, was calculated for every neuron as a measure of magnitude of change in firing (relative to baseline). 'A' was equal to the mean firing rate of the neuron during the *baseline period* before each lever press. Analysis of the *firing window* began at -3 s. The firing window was determined as follows: 1) The onset of the firing window was defined as the first of four consecutive 100 ms bins in which the neuron exhibited at least a 20% change from baseline firing rate. These criteria were utilized in order to rule out any spurious fluctuations in spontaneous activity and yet be sensitive enough to detect relatively small changes. 2) The offset of the firing window was defined as either the first of four consecutive 100 ms bins after the onset of the firing window when the neuron no longer exhibited at least a 20% change from baseline or as the time of the lever press (defined as time 0), whichever occurred first. 'B' was equal to the firing rate of the neuron during the firing window. The use of percentage change in firing to determine the onset and offset of firing patterns is consistent with methodology described in the literature (Carelli

et al., 2000; Carelli and Ijames, 2001). Moreover, the raster of every neuron was visually inspected to ensure that every PETH was representative of the pattern of discharges on individual trials as depicted in the raster.

For changes in firing that commenced following the lever press, a ratio, $B/(A+B)$, was calculated for every neuron in the following manner. 'A' was equal to the *baseline* firing rate. The firing window was determined as follows: 1) The onset of the firing window was defined as the first of four consecutive 100 ms bins in the 6 s following the lever press in which the neuron exhibited at least a 20% change from baseline. 2) The offset of the firing window was defined as the first of four consecutive 100 ms bins after the onset of the firing window when the neuron no longer exhibited at least a 20% change in firing relative to baseline. 'B' was equal to the mean firing rate of the neuron during the firing window.

Pre-press firing was separated from post-press firing for purposes of interpreting their possible correlations with behavior, although, as described in previous studies, some neurons exhibit changes in firing both before and after the lever press (Peoples et al., 1997; Ghitza et al., 2004; Fabbriatore et al., 2004).

Some neurons failed to exhibit a 20% change either pre- or post-press, and therefore, in order to include them with all other neurons in the analysis, a standard firing window was assigned to them. This was defined as the average firing window exhibited by neurons that showed at least a 20% change (one pre-press, and one post-press firing window). The pre-press window averaged 1.4 s and the post-press window averaged 2.3 s for the cocaine self-administration under S^D control. For the FR1 cocaine self-administration, the pre-press window averaged 1.6 s and the post-press window averaged 4.3 s.

To evaluate group differences, planned comparisons using a two-tailed Mann-Whitney U test with an alpha level of 0.05 (Castellan and Siegel, 1988) were conducted between groups of neurons to assess differences in the magnitude of phasic changes in firing between core and shell neurons. Analyses comparing ventral shell with other subregions are subjects of a different study (Fabbriatore et al., 2004). Mann-Whitney U tests were conducted (because these data did not exhibit a normal distribution) to evaluate core and shell differences using both the Zahm and Brog (1992) and Jongen-Relo et al. (1994) subterritorial designations.

Analysis of tonic firing patterns

Each neuron's pre-drug firing rate ('A') was defined as the firing rate during the 20 min neural recording period before the beginning of the cocaine self-administration period. This firing rate was compared with the mean firing rate during the entire self-administration period for the S^D -controlled schedule, or, for FR1 schedule, to the mean of the firing rates during the 20 min period 2 h into self-administration and during the last 20 min of self-administration ('B'). The cocaine self-administration period lasted between 6 and 7 h. A ratio, $B/(A+B)$, was calculated for every neuron to determine the magnitude of tonic changes in firing relative to the 20 min pre-drug period. A value of $B/(A+B)$ greater than 0.5 indicates a tonic increase in firing whereas a value less than 0.5 indicates a tonic decrease in firing, while 0.5 indicates no change. $B/(A+B)$ values approaching 0.0 or 1.0 indicate strong (e.g. 10-fold) tonic decreases or increases in firing, respectively.

To evaluate whether a correlation exists between rapid-phasic firing and tonic firing patterns across all core and shell neurons, a Spearman's rho coefficient ($\alpha=0.05$) was calculated between magnitude of tonic firing and magnitude of rapid-phasic firing of each neuron. Spearman's rho was utilized since the data were not normally distributed. Magnitude of rapid-phasic firing was measured as the absolute value of the difference between 0.5 (no change from baseline) and the $B/(A+B)$ value.

A planned comparison using a two-tailed Mann-Whitney U test with an alpha level of 0.05 was conducted to assess differ-

ences in the magnitude of tonic firing between groups of core versus shell neurons.

Assessments of tonic and phasic firing of every neuron were independent because tonic changes in firing rate were measured against the average firing rate during the pre-cocaine-self-administration period, whereas phasic changes in firing rate were measured against the baseline firing rate during the -6 to -3 or the -9 to -3 s period relative to the lever press (within the cocaine self-administration period).

RESULTS

Behavior

After 12–18 sessions of cocaine self-administration, animals maintained stable drug levels of approximately 2–4 mg/kg, as reported previously (Peoples et al., 1997; Fabbriatore et al., 2001; Ghitza et al., 2004). Animals typically made between 50 and 70 cocaine-reinforced lever presses in a 6–7 h session. Greater detail describing behavior during cocaine self-administration has been previously reported (Peoples and West, 1996; Ghitza et al., 2004).

Neurophysiological results: similarities between operant schedules

All results were consistent for both the FR1 and the S^D -controlled cocaine self-administration schedules. Both core neurons ($z=-1.17$; $P>0.05$; two-tailed Mann-Whitney U test) and shell neurons ($z=-0.92$; $P>0.05$; two-tailed Mann-Whitney U test) exhibited similar within-subterritory tonic changes in firing irrespective of schedule. Secondly, both core neurons ($z=-1.84$; $P>0.05$; two-tailed Mann-Whitney U test) and shell neurons ($z=-1.33$; $P>0.05$; two-tailed Mann-Whitney U test) exhibited similar rapid phasic changes between schedules. Moreover, the same subterritorial differences in firing pattern prevalence (described below) were observed for both schedules, consistent with previous reports indicating similar core versus shell differences for FR1 (Fabbriatore et al., 2004) and S^D -controlled (Ghitza et al., 2004) cocaine self-administration. Because of these marked consistencies between schedules, henceforth, data from both were combined for all analyses (Fig. 1).

Differences in magnitude of pre-press phasic firing and of tonic firing across NAcc subterritories

Core neurons ($N=43$) exhibited greater increases in firing (median $B/(A+B)$ value=0.572) than did shell neurons in the seconds preceding the cocaine-reinforced lever press using both the two subterritory classification ($N=94$ for shell neurons, median $B/(A+B)$ value=0.493) ($z=-3.29$; $P=0.001$; two-tailed Mann-Whitney U test) and the three subterritory classification ($N=84$ for shell neurons, median $B/(A+B)$ value=0.493) ($z=-3.12$; $P=0.002$; two-tailed Mann-Whitney test).

Tonic pre-drug firing rates did not differ between core (median=0.330 impulses/s) and shell (median=0.248 impulses/s) neurons ($z=-1.21$; $P=0.23$; two-tailed Mann-Whitney U test).

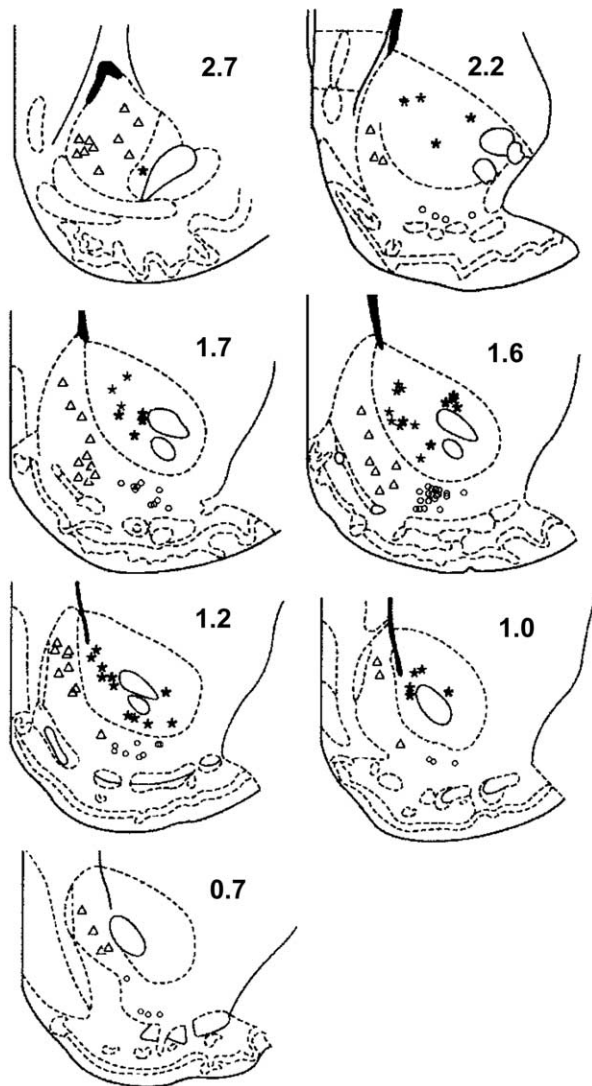


Fig. 1. Histologically verified microwire tip placements. Plates depicting the rat NAcc in serial coronal sections (Paxinos and Watson, 1997). Number at the top right of each plate represents anteroposterior distance from bregma. Core/shell differences in firing were identical using the Zahm and Brog (1992) or the Jongen-Relo et al. (1994) approaches. Histologically confirmed microwire tip placements are designated by triangles (medial shell), circles (ventral shell), or asterisks (core).

In general, tonic changes of core neurons were increases, whereas those of shell neurons were decreases. Core neurons ($N=43$) exhibited a significantly greater median $B/(A+B)$ value (0.616) than did shell neurons using the two subterritory classification ($N=94$ for shell neurons, median=0.416) ($z=-2.32$; $P=0.020$; two-tailed Mann-Whitney test) and the three subterritory classification ($N=84$ for shell neurons, median $B/(A+B)$ value=0.416) ($z=-2.26$; $P=0.024$; two-tailed Mann-Whitney test).

Differences in magnitude of pre-press phasic firing and of tonic firing between medial shell and core

Since recent studies from our laboratory found differences in the firing of neurons in the medial shell subregion and

the core (Ghitza et al., 2003, 2004; Fabricatore et al., 2004), data were additionally evaluated using neurons from these same regions. Core neurons ($N=43$) exhibited greater pre-press increases in firing than medial shell neurons in the seconds preceding the cocaine-reinforced lever press using both the two subterritory classification ($N=46$ for medial shell neurons) ($z=-3.09$; $P=0.002$; two-tailed Mann-Whitney U test) and the three subterritory classification ($N=36$ for medial shell neurons) ($z=-2.76$; $P=0.006$; two-tailed Mann-Whitney test) (Table 1).

With respect to tonic changes in firing rate, core neurons ($N=43$) exhibited a significantly higher median $B/(A+B)$ value than did medial shell neurons using the two subterritory classification ($N=46$ for medial shell neurons) ($z=-2.64$; $P=0.008$; two-tailed Mann-Whitney test) (Fig. 2) and the three subterritory classification ($N=36$ for medial shell) ($z=-2.59$; $P=0.010$; two-tailed Mann-Whitney test).

Relationship between tonic and phasic changes in firing of single NAcc neurons

Phasic changes in firing in the seconds proximal to the lever press comprised either decreases or increases in firing rate, comparable to those described in previous reports (Peoples et al., 1997; Ghitza et al., 2004). Phasic decreases or increases in firing were observed among neurons exhibiting either reduced or elevated tonic firing, and, for individual neurons, any one tonic firing pattern was not exclusively associated with any one phasic firing pattern (Figs. 3, 4). Specifically, phasic increases were found in neurons exhibiting tonic increases (Fig. 3A) and tonic decreases (Fig. 3C), while phasic decreases were found in neurons exhibiting tonic increases (Fig. 3B) and tonic decreases (Fig. 3D).

While all combinations of tonic and phasic firing patterns were observed (Fig. 4), core neurons exhibiting tonic increases in firing ($N=24$) were more likely than those exhibiting tonic decreases ($N=14$) to show higher magnitude pre-press phasic changes (Fig. 4C). Specifically, individual core neurons exhibiting greater tonic increases also exhibited greater pre-press phasic changes. Conversely, core neurons exhibiting tonic decreases showed weaker pre-

Table 1. Tonic and rapid-phasic changes in firing as a function of accumbens subregion

	Tonic firing	Rapid-phasic firing
A. Two subterritory		
Core	0.616*	0.572*
Med. Shell	0.418	0.493
B. Three subterritory		
Core	0.616*	0.572*
Med. Shell	0.418	0.496

Median $B/(A+B)$ values (standardized measure of firing rate change) depicted for core and medial shell. Asterisks indicate significantly greater values in core than medial shell. (A) Comparisons using two subterritory classification (Jongen-Relo et al., 1994). Number of neurons in core=43; medial shell=46. (B) Comparisons using three subterritory classification (Zahm and Brog, 1992). Number of neurons in core=43; medial shell=36.

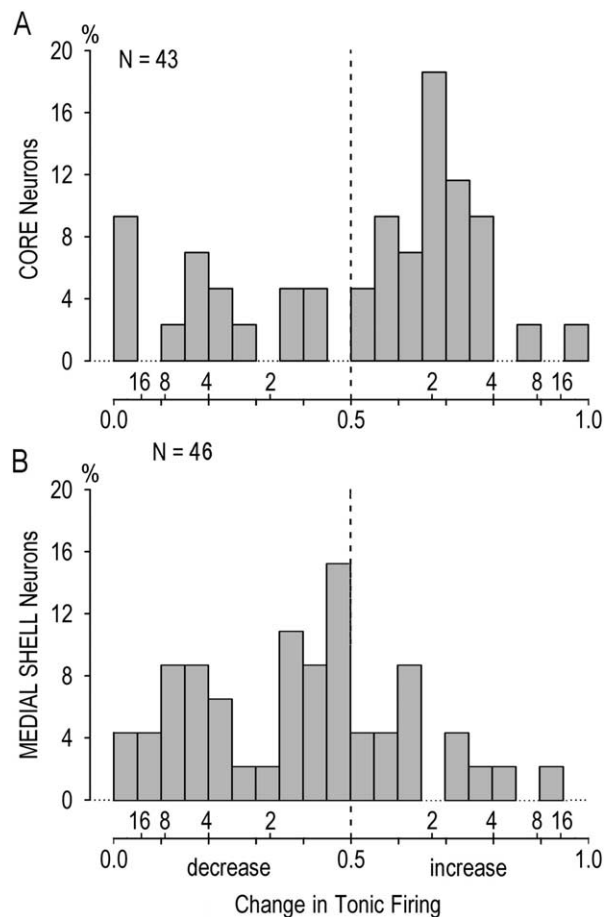


Fig. 2. Tonic firing during cocaine self-administration between NAcc subterritories. Magnitude of change in tonic firing is expressed as $B/(A+B)$ value (bottom side of x-scale), where a value of 0.5 indicates no change in firing rate (dashed vertical line). Values from 0.499–0 reflect increasingly greater magnitude decreases and 0.501–1.00 reflect increasingly greater magnitude increases. Top side of x-scale indicates two-fold, four-fold, etc. increases above, or decreases below, pre-drug value. Magnitude of $B/A+B$ values was significantly greater for core neurons than for medial shell neurons.

press phasic changes. This relationship (Fig. 5, left panel) was significant using both the two and three subterritory classification (Spearman's $\rho=0.463$; $P=0.002$; two-tailed test and Spearman's $\rho=0.426$; $P=0.005$; two-tailed test, respectively). Moreover, core neurons exhibiting tonic increases also exhibited greater post-press phasic changes (Fig. 4D). Conversely, core neurons exhibiting tonic decreases exhibited weaker post-press phasic changes. The relationship between post-press phasic and tonic firing changes in core neurons (Fig. 5, right panel) was significant using the two and three subterritory classification (Spearman's $\rho=0.306$, $P=0.046$, two-tailed test and Spearman's $\rho=0.329$, $P=0.033$, two-tailed test, respectively), albeit to a lesser degree than in the prepress phasic change comparison. Thus, core neurons exhibiting the greatest tonic decreases showed the weakest phasic changes, both pre- and post-press.

In contrast, for shell neurons ($N=94$) there was no relationship between tonic patterns and pre-press phasic

patterns using either the two or the three subterritory classification (Spearman's $\rho=0.119$, $P=0.257$, two-tailed test and Spearman's $\rho=-0.095$, $P=0.393$, two-tailed test, respectively). Additionally, for shell neurons, there was no relationship between tonic patterns and post-press phasic patterns using either the two or the three subterritory classifications (Spearman's $\rho=0.122$, $P=0.245$, two-tailed test and Spearman's $\rho=0.146$, $P=0.187$, two-tailed test, respectively).

DISCUSSION

Principal findings

Analysis of individual accumbens neurons' rapid phasic and tonic firing patterns revealed that all combinations of increases and decreases in firing rate were well-represented during cocaine self-administration. Although this was true for NAcc neurons in general, a significant relationship between tonic and phasic firing of core neurons was revealed: core neurons with tonic firing increases exhibited greater magnitude rapid-phasic firing rate changes than core neurons with tonic firing decreases.

Similar tonic and rapid-phasic firing patterns between cocaine self-administration schedules

Similar accumbal tonic and rapid-phasic firing patterns were exhibited in FR1 and S^D -controlled schedules of cocaine self-administration. Furthermore, the various combinations of tonic and rapid-phasic firing changes previously reported during FR1 cocaine self-administration (Peoples et al., 1998) were also observed for both schedules in the present study. Recent reports from this laboratory revealed similar differences between core and shell firing patterns during FR1 cocaine self-administration (Fabbriatore et al., 2004) and in S^D -controlled self-administration (Ghitza et al., 2004). In the present study, which undertook a statistical comparison of tonic and rapid phasic firing patterns in the two schedules, neither core nor shell neurons exhibited significant between-schedule differences. The consistency of these subterritorial differences between schedules both validates the combining of data pools and supports the concept of fundamental neurophysiological processing within the NAcc involved in cocaine self-administration (see below).

Advantages of using a standardized measure of firing rate change

The present method of measuring the magnitude of firing rate changes has several distinct advantages: 1) it normalizes firing rate changes across neurons with different firing rates, 2) it provides a scale which equally weights increases and decreases in firing relative to baseline, and 3) it provides a scale displaying activity of all neurons, including weak, intermediate or strong changes in firing. This approach permitted the assessment of firing change magnitudes and directionalities, enabling comprehensive, objective analyses of firing rate trends across subregions and between time bases.

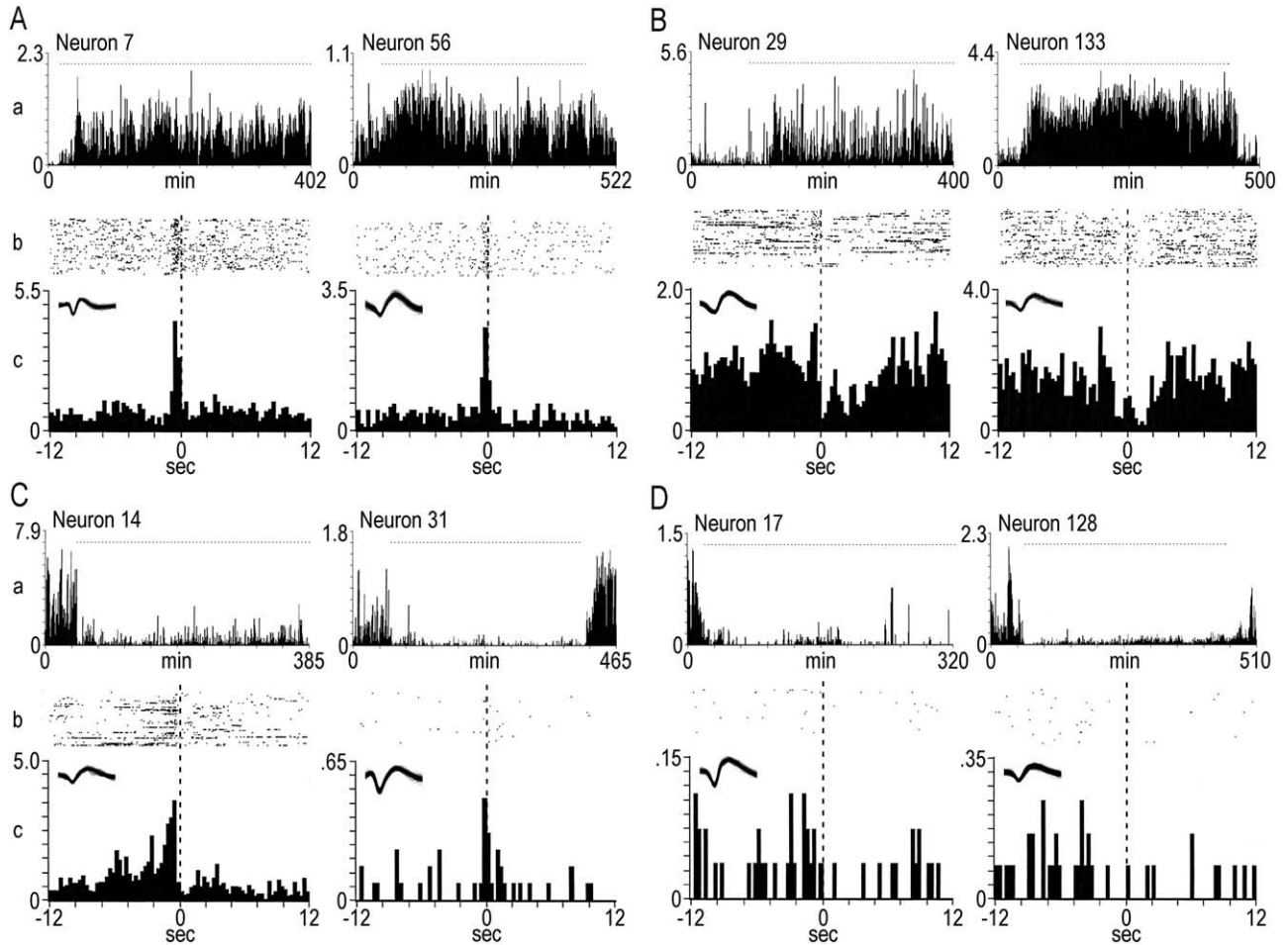


Fig. 3. Examples of neurons exhibiting different combinations of tonic and phasic firing patterns during cocaine self-administration. For each panel (A, B, C, D) single unit recordings from each schedule are presented: an example from S^D -controlled cocaine self-administration (left column), and an example from FR1 cocaine self-administration (right column). Each column subsection (a, b, c) depicts a different temporal representation of data from the same neuron as follows: (a) Tonic strip chart depicting average firing rate (impulses/s) (y axis) as a function of time (minutes) (x axis) during the cocaine self-administration session. Horizontal dotted line above strip chart denotes the time period during which cocaine-reinforced lever pressing occurred. For the FR1 self-administration experiment, a 60 min post-drug period, when the lever was removed, followed the cocaine self-administration period. (b) Phasic rasters: neuronal discharges are displayed for individual trials, shown chronologically from the bottom row to the top row of each raster. (c) Phasic PETHs depicting average firing rate (impulses/s) (y axis) during seconds proximal to the cocaine-reinforced lever press. Dotted vertical line at time 0 represents the cocaine-reinforced lever press, and corresponds directly to the time scale of the raster display above it. For each PETH, the inset depicts the corresponding neuronal waveform. (A) Two neurons exhibiting both a tonic increase in firing during the cocaine self-administration period and a phasic increase in firing in the seconds proximal to the lever press. (B) Two neurons showing both a tonic increase in firing over the course of cocaine self-administration and a phasic decrease in firing around the lever press. (C) Two neurons exhibiting both a tonic decrease in firing during the cocaine self-administration period and a phasic increase in firing proximal to the lever press. (D) Two neurons showing both a tonic decrease in firing over the course of cocaine self-administration and a phasic decrease in firing following the lever press.

Potential correlates of tonic and rapid phasic firing rate changes

Electrophysiological studies of NAcc neurons during cocaine self-administration have manipulated behavioral or pharmacological variables to systematically examine the nature of changes in firing rate on various time bases (Carelli and Deadwyler, 1996; Peoples et al., 1998; Carelli, 2000; Nicola and Deadwyler, 2000; Carelli and Ijames, 2001; Ghitza et al., 2003, 2004). It has been proposed that tonic firing patterns are influenced by pharmacological factors related to elevated levels of drug (Peoples et al., 1998). Evidence has been presented that in addition to drug effects, non-pharmacological factors related to pro-

cessing of instrumental responses are apparent in the tonic firing of a substantial number of NAcc neurons (Fabricatore et al., 1998).

Studies from this laboratory and others have investigated whether various factors influence firing rate changes in NAcc neurons within seconds of the cocaine-reinforced lever press (i.e. correlates of rapid-phasic patterns), including, but not limited to, the onset of a conditioned stimulus tone, processes related to the operant response, and pharmacological factors (Carelli and Deadwyler, 1996; Peoples et al., 1997; Carelli, 2000; Carelli and Ijames, 2001). In order to address these potential correlates of prepress rapid phasic firing patterns, several studies have examined

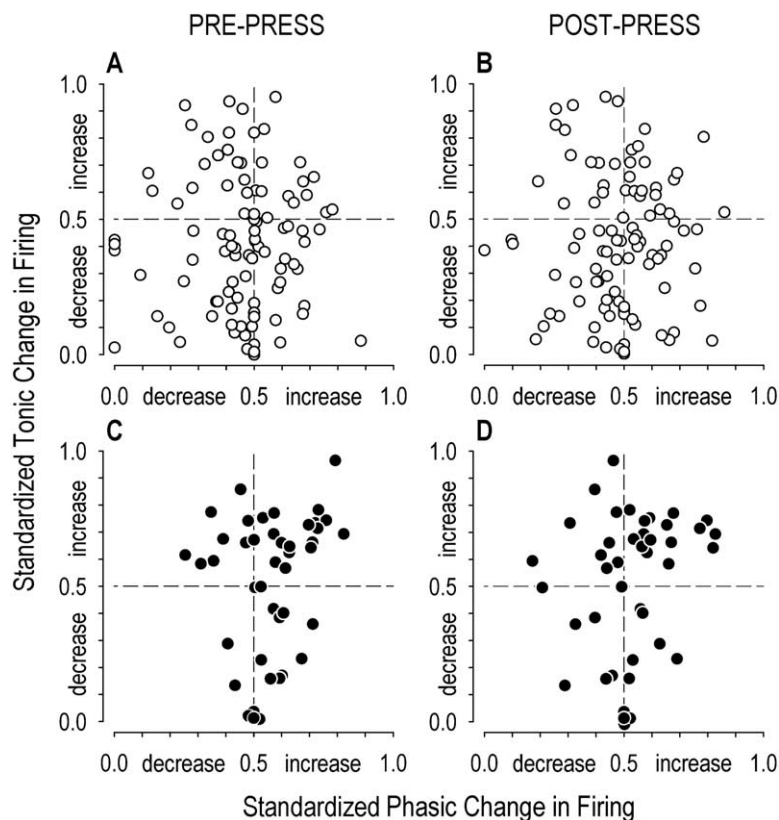


Fig. 4. Relative magnitude of tonic change in firing versus magnitude of phasic lever-press change in firing. Relative magnitude of firing rate change (calculated using $B/(A+B)$) for phasic (plotted on abscissa) and tonic (plotted on ordinate) time bases. Dashed lines at 0.5 represent no change in firing rate. Each open or filled circle represents a single shell or core neuron, respectively. (A) In shell neurons, no relationship exists between tonic firing changes and pre-press firing changes. (B) In shell neurons, no relationship exists between tonic changes and post-press changes. (C) For core neurons, tonic firing rate changes compared with pre-press phasic firing changes. Note that core neurons that exhibited a tonic increase were more likely to show robust pre-press changes in firing than core neurons that exhibited a tonic decrease. This is evidenced in the upper two quadrants by more firing rate change values located farther from the vertical dashed line. (D) Change in tonic firing as compared with change in post-press phasic firing is depicted for core neurons. Core neurons that showed tonic increases were more likely than those that showed tonic decreases to exhibit greater magnitude post-press changes in firing. However, this relationship was weaker than that between pre-press patterns and tonic patterns for core neurons.

firing rate changes in the seconds preceding reinforced presses by evaluating unreinforced lever presses, in which factors such as drug delivery and exteroceptive (e.g. tone, light) cues are absent. Using a partial reinforcement schedule (Carelli and Deadwyler, 1996), a contingent/non-contingent infusion schedule (Peoples et al., 1997), or an S^D -controlled self-administration schedule (Ghitza et al., 2004) rapid phasic firing rate changes in NAcc neurons during the seconds preceding the lever press were shown to reflect processes related to the performance of instrumental responding, and not to drug fluctuations or exteroceptive cues.

Whereas pre-press firing rate changes precede the infusion and its accompanying cues, thus mitigating these factors as likely contributors to rapid phasic patterns leading up to the lever press, post-press analyses will require closer inspection of these factors. Post-press firing occurs on unreinforced trials in a substantial number of neurons (Peoples et al., 1997) and may contribute to evaluation of response outcome by core neurons (see below) (Ghitza et al., 2004). However, post-press firing changes have also

been shown in response to cues, whose onset is coincidental to the onset of cocaine delivery (Carelli and Deadwyler, 1996; Carelli, 2000). While pharmacological factors are ruled out in both cases, further study is required regarding the contribution of cues versus instrumental processing to post-press firing rate changes.

Accumbens neurons exhibited a broad range of magnitudes and all combinations of tonic and rapid-phasic firing rate changes (Figs. 3 and 4). This diversity indicates that the directionality of a neuron's tonic firing rate change during the self-administration phase of the experiment is likely independent of the directionality of its phasic change in firing proximal to the lever press: neurons that exhibited tonic increases and phasic *decreases* (Fig. 3B) in firing around the lever press and neurons that exhibited tonic decreases and phasic *increases* (Fig. 3C) in firing around the lever press exemplify the likelihood of multiple influences on firing rate. Support for this comes from the aforementioned evidence that pharmacological factors cannot be ruled out as a major influence on tonic patterns, while rapid phasic responsivity is temporally incompatible with a

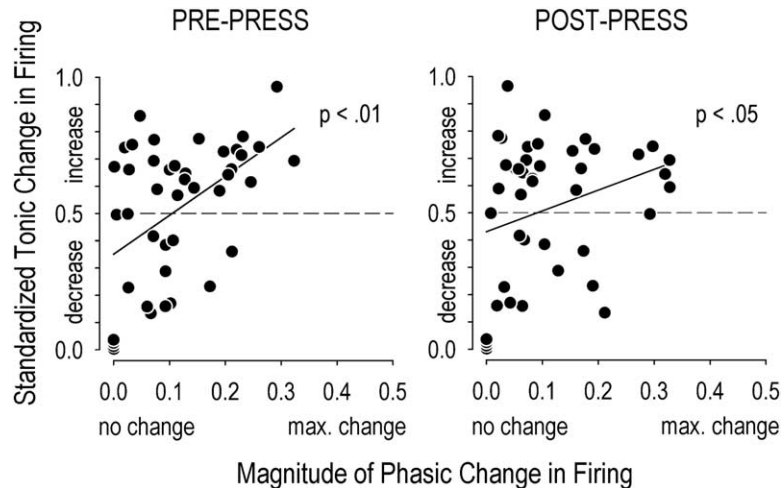


Fig. 5. Core neuron firing: tonic change (magnitude and direction) versus phasic change (magnitude only). Each dot represents a single core neuron. Left: Change in tonic firing compared with change in pre-press phasic firing for core neurons, expressed as a linear correlation. Magnitude of tonic change in firing is expressed as $B/(A+B)$ value on y axis. For pre-press phasic firing, a variant of that measure, $B/(A+B) - 0.5$, is depicted on the x axis (this is a standardized measure of the magnitude of phasic change in firing, irrespective of directionality). On this x axis scale, 0 represents no change in firing from baseline, and as changes in firing increase in magnitude, values approach 0.5 (maximum change). Dashed horizontal line (y axis value = 0.5) represents no tonic firing rate change. Core neurons that showed tonic increases were more likely than those that showed tonic decreases to exhibit greater magnitude pre-press phasic changes in firing. Right: Change in tonic firing compared with change in post-press phasic firing, expressed as a linear correlation. Core neurons that showed tonic increases were more likely than those that showed tonic decreases to exhibit greater magnitude post-press phasic changes in firing.

direct pharmacological effect. Interestingly, signaling related to appetitive responding cannot be discounted from influencing firing rate change on either time base (see above). Thus, the net effect of factors which determine a particular neuron's tonic firing pattern is likely distinct from the specific factors which influence its rapid phasic pattern, as evidenced by the substantial number of neurons that exhibited opposite signs in firing rate change between time bases (Fig. 4, upper left and lower right quadrants of each panel).

Both tonic decreases and increases are exhibited by NAcc neurons in which rapid phasic firing rate changes occur

Although reduced firing is the most common tonic pattern exhibited by NAcc neurons during cocaine self-administration (Peoples et al., 1998; Fabricatore et al., 2001), it is not the most common tonic pattern exhibited by neurons that show rapid-phasic firing patterns; in fact, the latter are more common among tonic increase neurons than among tonic decrease neurons. A recent study (Peoples and Cavanaugh, 2003) concluded that a common neurophysiological mechanism mediating cocaine-reinforced drug-taking behavior is an increase in signal-to-background ratio (S:B) of NAcc neurons by evaluating the *minority* of 'lever-press' (i.e. rapid-phasic) neurons that exhibit tonic decreases. The authors suggest that phasic firing ('signal') is less sensitive than tonic firing ('background') to cocaine's presumed inhibitory effect, on the basis of enhanced S:B among tonic decrease neurons that show rapid-phasic increases.

Their study proposes a *common* mechanism based on only a selected subset of rapid phasic neurons, those

exhibiting tonic decreases. When data from all NAcc neurons are analyzed, no particular tonic firing pattern predominates among neurons that fire phasically at the time of drug-taking (Figs. 3, 4A and 4B). Indeed, neurons that exhibit tonic firing decreases and rapid phasic increases constitute only one combination within a spectrum of firing patterns exhibited by NAcc neurons during cocaine self-administration, any of which may reflect greater or lesser degrees of DA-modulated gating of information related to drug taking. Moreover, in the core, a greater degree of phasic responsivity was found for neurons which exhibited tonic *increase* patterns.

In addition, since the 'background' (i.e. baseline) period for rapid phasic increase neurons occurs during the self-administration phase of the experiment (the same period which operationally defines tonic change), enhanced S:B in their study apparently is a consequence of the data subset—signal merely appears enhanced for these rapid-phasic increases because baselines were lowered by the selective evaluation of tonic decrease neurons. The notion that any particular group of accumbal neurons exhibits changes in signal/background differentially from any other can be addressed only by a comprehensive analysis of all combinations of tonic and rapid phasic patterns (Fig. 4 and previous studies: Peoples et al., 1998; Ghitza et al., 2001).

Core versus shell differences in tonic and rapid-phasic firing patterns and their inter-relationships during cocaine self-administration

Drugs of abuse and natural rewards both activate the mesocorticolimbic DA system (Bowman et al., 1996; Di Chiara, 1998; Lee et al., 1998, 1999; Di Chiara et al., 1999; Carelli et al., 2000; see Kelley and Berridge, 2002; Salam-

one et al., 2003 for review). Evidence suggests that drugs manipulate this system such that excessive motivation to self-administer drugs is elicited upon exposure to drug-conditioned stimuli previously paired with drug availability (Stewart et al., 1984; Robinson and Berridge, 1993, 2000, 2003). Studies of accumbal function suggest that the core and shell are differentially involved in such behavior. Shell firing may encode the motivational salience of reward-related, contextual stimuli (Ghitza et al., 2003; Sellings and Clarke, 2003) while core neurons have been shown to fire in relation to the instrumental response (Ghitza et al., 2004). Given that the shell projects to the core via feed-forward circuitry (Zahm, 2000), connectivity exists such that shell cue-related output to core could facilitate an instrumental drug-seeking response.

Consistent with the above findings, core neurons in the present study exhibited greater magnitude pre-press phasic increases in firing than shell neurons. Moreover, core neurons exhibited greater tonic increases in firing than medial shell neurons. While shell neurons did not exhibit any predictive relationship between tonic and phasic firing patterns, core neurons did: tonic increase neurons exhibited greater magnitude rapid-phasic firing patterns than tonic decrease neurons. This bias toward enhanced phasic activity among core neurons that exhibit tonic increases may reflect particular sensitivity of these neurons to excitatory limbic afferent signaling. The distinct tendency of core to exhibit increased excitation, coupled with its dichotomous firing outputs (i.e. tonic decreases without rapid phasic responses or tonic increases with rapid phasic responses), may provide clues as to the information projected to discrete targets, each of which may encode a separate component of core's influence on instrumental responding.

Potential mechanisms in the gating of information to targets of core neurons

Cocaine self-administration behavior depends on elevated DA levels in the NAcc (Ritz et al., 1987; for review see Wise and Bozarth, 1987; Wise et al., 1995). Convergent evidence suggests that DA elevates the activity of strongly activated medium spiny neurons (MSNs) while suppressing that of weakly activated MSNs in the NAcc and striatum (reviewed in Nicola et al., 2000; O'Donnell, 2003). Elevated DA transmission during cocaine self-administration may gate the activity of MSNs in the accumbens core. Specifically, core neurons in the present study that tended to exhibit excitatory responses (tonic and phasic increases) may have responded to enhanced DA levels with elevated activation while core neurons that tended to exhibit tonic decreases may have responded to enhanced DA levels with reduced activation. This differential activation may be the result of either a particular convergence of excitatory inputs onto the recorded neuron or perhaps the differential expression of DA receptor subtypes which have been shown to affect up-state duration, and thus action potential likelihood.

An alternative mechanism by which information may be gated to core targets is via lateral inhibition, which has

been demonstrated in NAcc and striatal MSNs (Marco et al., 1973; Park et al., 1980; Lighthall and Kitai, 1983; Shi and Rayport, 1994; Taverna et al., 2004). Excitatory afferents from different cortico-limbic areas may compete to influence firing of interconnected core neurons. A tonic increase core neuron encoding rapid-phasic information related to drug-taking may laterally inhibit neurons so that they fail to encode such information (i.e. tonic decrease neurons), thereby resolving potentially competing afferent signals to ensure unconflicted output to target structures. Enhanced rapid-phasic processing associated with compulsive drug-taking behavior may subvert the normal functioning of core circuitry resulting in a hyper-sensitive cortico-striato-pallidal throughput.

Any neurophysiological process which is positioned to be corrupted by chronic drug exposure may account for dysfunction in the circuitry of normal reward processing. While it is unlikely that either of the above proposed mechanisms functions exclusively in the development of drug addiction, they each describe a process by which pathologically enhanced phasic responsivity in the core may occur over time. Such neural adaptations may heighten the vulnerability of drug addicts to engage in continued drug seeking behavior, especially upon exposure to stimuli or contexts associated with drug availability.

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