

Differences Between Accumbens Core and Shell Neurons Exhibiting Phasic Firing Patterns Related to Drug-Seeking Behavior During a Discriminative-Stimulus Task

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Ghitza, Udi E., Anthony T. Fabbriatore, Volodymyr F. Prokopenko, and Mark O. West. Differences between accumbens core and shell neurons exhibiting phasic firing patterns related to drug-seeking behavior during a discriminative-stimulus task. *J Neurophysiol* 92: 1608–1614, 2004. First published May 19, 2004; 10.1152/jn.00268.2004. The habit-forming effects of abused drugs depend on the mesocorticolimbic dopamine system innervating the nucleus accumbens (NAcc). To examine whether different NAcc subterritories (core and medial shell) exhibit a differential distribution of neurons showing phasic firing patterns correlated with drug-seeking behavior, rats were trained to self-administer cocaine, and activity of single NAcc neurons was recorded. In the presence of a discriminative-stimulus (S^D) tone, a single lever press produced an intravenous infusion of cocaine (0.35 mg/kg), terminated the tone, and started an intertone interval ranging from 3 to 6 min. Lever presses during this intertone interval had no programmed consequences. In addition to evaluating neuronal firing patterns associated with cocaine-reinforced presses, we also evaluated firing patterns associated with unreinforced lever presses to allow interpretation of firing free of factors other than the instrumental response (such as tone-off and onset of the pump signaling drug infusion). Core neurons exhibited a greater change in firing than medial shell neurons both in the seconds preceding the reinforced and unreinforced lever press response and in the seconds following the unreinforced response. Core and medial shell neurons exhibited similar changes in firing during the seconds following the cocaine-reinforced press. The differential distribution of neurons exhibiting phasic changes in firing preceding the lever press suggests that the physiological activity of core neurons may play a greater role than that of medial shell neurons in processes related to the execution of conditioned drug-seeking responses.

INTRODUCTION

The nucleus accumbens (NAcc) and its inputs from the ventral tegmental area (VTA) are components of the mesocorticolimbic dopamine (DA) system, which is necessary in the activation of drug-seeking behavior in response to various drugs of abuse or stimuli previously paired with drug (Koob and Bloom 1988; Roberts et al. 1980; Wise and Bozarth 1987; Wise and Rompre 1989; Zito et al. 1985). Mesencephalic dopaminergic and limbic-cortical glutamatergic inputs converge in the NAcc, which sends prominent projections via ventral pallidum to somatomotor and autonomic effector sites. This pattern of connectivity supports the hypothesis proposed by Nauta et al. (1978) and Mogenson et al. (1980) that the NAcc is a “limbic motor” interface and a neural substrate for appetitive behavior.

The NAcc can be differentiated into “core” and “shell” based on differences in connectivity, neurochemistry, and function (Brog et al. 1993; Corbit et al. 2001; Heimer et al. 1991; Zaborszky et al. 1985). For instance, prefrontal cortical afferents differentially project to the core and shell. The shell receives preferential innervation from the infralimbic and ventromedial prefrontal cortex (Berendse et al. 1992a). In contrast, the core receives preferential innervation from the dorsal prefrontal cortex and, like the dorsal striatum, is more closely connected with structures linked to somatomotor function (Berendse et al. 1992a).

Studies of NAcc function have shown that, in animals self-administering cocaine, NAcc neurons exhibit rapid-phasic changes in firing that occur within seconds of the cocaine-reinforced instrumental response (Carelli and Deadwyler 1996, 1997; Carelli et al. 1993; Chang et al. 1994; Peoples et al. 1997). Peoples et al. (1997) showed that many of these rapid-phasic firing patterns are eliminated during noncontingent drug delivery, providing evidence that these firing patterns are not pharmacological correlates, and that, in many cases, instrumental drug-seeking responses are necessary for them to occur.

We previously observed a paucity of rapid-phasic firing patterns in the medial shell (Uzwiak et al. 1997), but the small sample size precluded a direct statistical core versus shell comparison. This study sampled adequate numbers of core and shell recordings to permit subterritorial-specific statistical comparisons.

This study involved a novel approach using discriminative-stimulus (S^D)-controlled cocaine self-administration (Ghitza et al. 2003) to determine whether core neurons exhibit greater rapid-phasic changes in firing within seconds of instrumental drug-seeking than medial shell neurons. We examined rapid-phasic changes in firing in the seconds surrounding both reinforced and unreinforced presses. Unlike previous electrophysiological studies, this study used an S^D tone that predicted cocaine availability and that triggered drug-seeking and drug-taking behavior. This design provides an animal model for human drug-taking behavior precipitated by exposure to drug-predictive environmental stimuli (Ghitza et al. 2003) that commonly prompt relapse to drug use in drug abusers.

METHODS

Surgery

In 19 male (280–350 g) Long-Evans rats (Charles River, Raleigh, NC), a catheter was surgically implanted in the jugular vein. An array

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of 16 microwires (50 μm diam of each uninsulated wire tip; California Fine Wire, Grove City, CA) 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).

Cocaine self-administration sessions

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 intravenous infusion of cocaine (0.35 mg/kg infusion), terminated the tone, and started an intertone interval (3–6 min). If lever pressing did not occur during the 2-min tone presentation period, the tone was terminated and an intertone interval began. Timing of tones was programmed to approximate the timing of spontaneous self-infusions of the same dose that rats exhibit in a fixed-ratio 1 (FR1) schedule of reinforcement. Further details concerning the cocaine self-administration session are described in a previous report (Ghitza et al. 2003). Two to 4 wk of self-administration training preceded a 3- to 4-wk period of drug abstinence during which the subjects were withdrawn from self-administration. Two rats received 1 wk of self-administration training, and for two others, 2 wk of abstinence followed training. These four rats were included in the study because behavioral analyses indicated that they exhibited typical cocaine self-administration behavior consistent with that of the other subjects. Single unit activity of core and shell neurons was recorded over one to three recording sessions during the second or third week of cocaine self-administration training (when animals maintained stable cocaine self-administration), during extinction sessions, and during reinstatement sessions. The procedures used for electrophysiological recording and waveform discrimination are described in previous reports (Peoples and West 1996; Peoples et al. 1999b).

Extinction and reinstatement sessions

Following a 3- to 4-wk period of drug abstinence, one to three extinction sessions were conducted as described previously (Ghitza et al. 2003). In this study, a test of reinstatement of cocaine self-administration was conducted on the day after the final extinction session. This test of reinstatement was conducted in a subset of subjects ($n = 9$) to assess whether the subjects would engage in reinstatement of cocaine self-administration.

Histology

The histological procedures used to verify the location of each recorded neuron were described in a previous report (Ghitza et al. 2003). Briefly, the location of each wire was marked 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 anterior-posterior (A-P) position. Neurons recorded by particular wires were histologically confirmed to be located in either the NAcc core or shell subterritories (Fig. 1) by eliminating all lesion centers within 150 μm of any border.

NAcc subterritories were defined, and subterritorial distribution of phasic firing was analyzed in two ways. An analysis was conducted wherein subterritories were defined as in the three subterritory classification of Zahm and Brog (1992), in which neurons were localized to shell, core, or rostral pole. In a separate analysis, the subterritorial distribution of phasic firing was assessed 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.

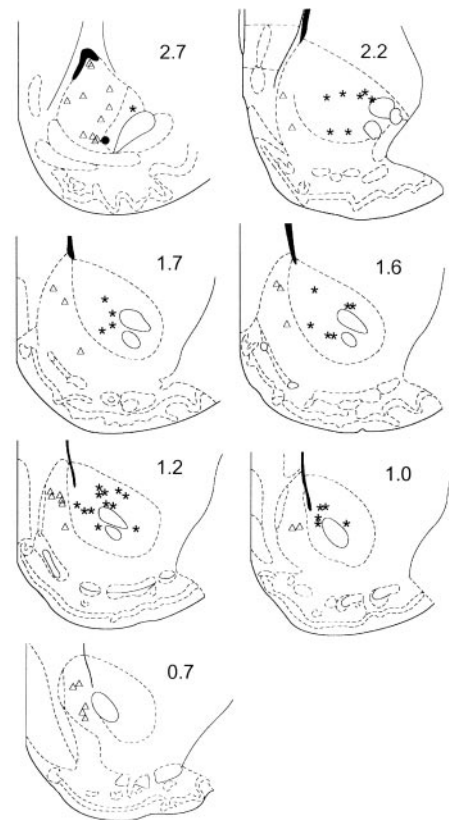


FIG. 1. Histologically verified microwire tip placement. Rat atlas plates representing the nucleus accumbens (NAcc) in serial coronal sections (Paxinos and Watson 1997). Number at top right of each plate represents anterior-posterior (A-P) distance from bregma. Core/shell differences in prepress or postpress firing were identical using the Zahm and Brog (1992) or the Jongen-Relo et al. (1994) approaches. Shell and core are demarcated here and in all figures as defined by Paxinos and Watson (1997). Histologically confirmed NAcc microwire tip placements are designated by triangles (shell) or asterisks (core). In the rostral pole, a core/shell border neuron is designated by a filled circle. Fifteen of the neurons in this study yielded a minority of the single unit recordings of 70 neurons reported previously (Ghitza et al. 2003). In that study, there were no significant differences in the relative magnitude of discriminative-stimulus (S^D) tone-evoked activity along the rostral-caudal axis of the medial shell that was sampled.

Construction of peri-event time histograms

Rapid-phasic changes in firing that occurred within seconds of the instrumental drug-seeking response were determined by constructing rasters and peri-event time histograms (PEHs) that display neuronal discharges within the 6 s before and after each lever press. Cocaine-reinforced and unreinforced lever presses were used as the drug-seeking responses (nodes) around which all histograms were constructed. In separate PEHs, unreinforced lever presses were used to ensure that changes in firing were also evaluated in the absence of factors coincident with the delivery of drug. For each neuron, one histogram was constructed, either from a drug self-administration or extinction session. Obtaining histograms from either type of session was justified as follows: 1) previous data have shown that these instrumental response related firing patterns are not pharmacological correlates, and their occurrence in many cases depends on drug-seeking behavior whether or not drug is delivered (Peoples et al. 1997); 2) analysis of 10 neurons recorded in both self-administration and extinction revealed no difference between the two types of session in each neuron's histogram appearance or $B/(A + B)$ values (see next paragraphs) calculated from histograms (Figs. 4C and 5C); and 3) an equivalent proportion of core and shell neurons were recorded under cocaine self-administration and extinction conditions to ensure that

neurons from each NAcc subregion were equally represented under each condition.

Using these histograms, the magnitude of changes in firing was standardized and calculated for all NAcc neurons. Accumbens neurons that exhibited rapid changes in firing related to the instrumental response did not exhibit these changes in firing prior to -3 s before the lever press. Therefore the period between -6 to -3 s prior to each lever press served as the baseline period.

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 change in firing relative to baseline. Histograms were constructed around only lever press nodes that were separated by >6 s from other lever presses. A was equal to the mean firing rate of the neuron during the *baseline* time window (-6 to -3 s) 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 used to rule out any spurious fluctuations in spontaneous activity and yet to be sensitive enough to detect even 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 and Ijames 2001; Carelli et al. 2000).

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 (-6 to -3 s before each lever press). 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.

Thus prepress firing was separated from postpress firing for purposes of interpreting their possible correlations with behavior, although some neurons exhibit changes in firing both before and after the lever press (Peoples et al. 1997).

Some neurons failed to exhibit a change of 20%, but to include them in the analysis, along with all other neurons, 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 (1 prepress and 1 postpress firing window).

To evaluate group differences between core and shell neurons from different animals, planned comparisons using a one-tailed Mann-Whitney U test with an α level of 0.01 to reduce type I error (Castellan and Siegel 1988) were conducted between these groups of neurons to assess differences in the magnitude of their lever press-related activity. Since the firing patterns of core and shell neurons from different animals are independent, the matched pairs of each Mann-Whitney U test were statistically independent. One-tailed tests were used to test the hypotheses that the magnitude of prepress- and postpress-related activity around the unreinforced lever press was greater in the accumbens core than in the shell. In addition, to test whether or not any core and shell differences exist during S^D -triggered drug-taking behavior, one-tailed tests were used to compare magnitude of prepress and postpress firing around the cocaine-reinforced response across core and shell subterritories.

The dependent variable in this study was magnitude of lever press-related activity, measured as the absolute value of the difference between 0.5 (no change from baseline) and the $B/(A + B)$ value. This standardized measure of magnitude of lever press-related firing was

applied to all neurons. Mann-Whitney U tests were conducted because these data did not exhibit a normal distribution. Note that although $B/(A + B)$ values themselves exhibit nearly a normal distribution (Figs. 2 and 3), they are not measures of magnitude per se.

To calculate effect size estimates for the nonparametric tests, the raw data were transformed into rank values for which the partial η^2 statistic was calculated as described by Morse (1999). Mann-Whitney U tests were conducted to evaluate core and shell differences using both the NAcc subterritorial designations of Zahm and Brog (1992) and Jongen-Relo et al. (1994).

Analysis of durations of prepress or postpress firing

For neurons that exhibited little or no change in firing around the lever press, analyses of onset or offset of a response were not possible. Therefore, to obtain a valid measure of duration, only neurons that exhibited at least a twofold change in such firing were subjected to these particular analyses. Duration of prepress or postpress firing was defined as the difference between the onset and the offset of the firing window.

RESULTS

Behavior

Animals learned to discriminate the S^D tone, shown by the tone's ability to selectively induce lever pressing in extinction

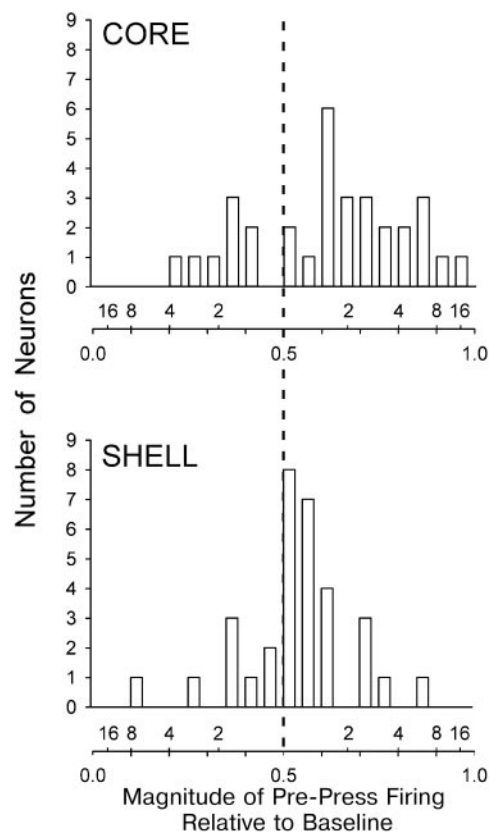


FIG. 2. Magnitude of prepress change in neural activity as a function of NAcc region. Magnitude of prepress change in neural activity of each neuron is expressed as $B/(A + B)$ value (bottom of the x-axis), where B is mean firing rate (impulses/s) in the *firing window* prior to the unreinforced lever press, and A is mean firing rate in the -6 to -3 s preceding the lever press (*baseline firing window*). Top of the x-axis indicates twofold, fourfold, etc. increases above, or decreases below, baseline value. Dashed vertical line at 0.5 value indicates no change from baseline. Magnitude of prepress changes in firing was significantly greater for core neurons than for shell neurons ($P = 0.0005$). Note the greater prevalence of substantial increases (>0.5) in firing of core, relative to shell, neurons.

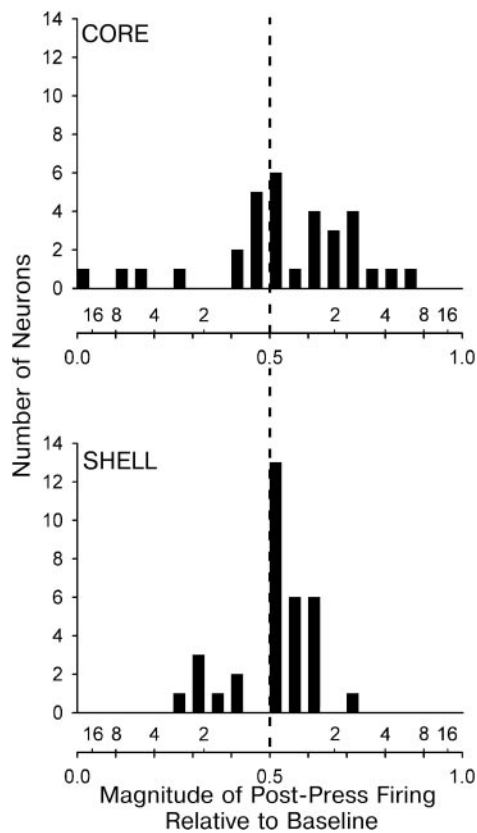


FIG. 3. Magnitude of postpress change in neural activity as a function of NAcc region. Magnitude of postpress (unreinforced) change in neural activity of each neuron is expressed as $B/(A + B)$ value (details as in Fig. 2). Magnitude of postpress changes in firing was significantly greater for core neurons (typically increases) than for shell neurons ($P = 0.0015$).

(Ghitza et al. 2003). However, during late conditioning sessions, the high rate of lever pressing in the absence of the tone (mean of 6 ± 1.5 unreinforced lever presses/min) suggests that lever pressing was not exclusively under programmed stimulus control, but likely was controlled by internal factors such as blood level of drug (Yokel and Pickens 1974). On the final training session, the mean percentage of tone presentations during which rats lever pressed was $96.2 \pm 2.1\%$. By the end of tone discrimination training, all rats self-administered levels of cocaine that remained stable throughout the session at ~ 2 – 3 mg/kg calculated blood level of drug; this drug level was lower than that observed in a FR1 schedule (Peoples et al. 1997, 1999a). During the reinstatement session, all rats engaged in reinstatement of drug-seeking behavior and maintained a 2 – 3 mg/kg calculated blood level of drug. Behavioral data of these animals during extinction were described in a previous report (Ghitza et al. 2003).

Differences in magnitude of lever press-related firing across NAcc regions

Single neuron activity is reported only for histologically confirmed NAcc microwire tip placements (Fig. 1). Fifteen of the neurons in this study yielded a small portion of the single unit recordings from 70 neurons reported previously (Ghitza et al. 2003). Two analyses of subterritorial differences in firing were conducted, one based on the two subterritory classifica-

tion by Jongen-Relo et al. (1994) and the other based on the three subterritory classification of Zahm and Brog (1992). The first analysis, based on the two subterritory classification, indicated that baseline firing rate did not significantly differ between core (mean = 1.05 impulses/s) and medial shell neurons (mean = 0.82 impulses/s; $z = -1.678$, $P = 0.047$; 1-tailed Mann-Whitney test).

Core neurons ($n = 31$) exhibited a greater prepress change in firing than medial shell neurons in the seconds preceding the unreinforced lever press ($n = 31$; $z = -3.28$, $P = 0.0005$; 1-tailed Mann-Whitney U test; Fig. 2). Analysis of effect size revealed a partial η^2 value of 0.171, which is greater than the minimum value (0.14) considered to be a large effect size (Cohen 1988). Moreover, core neurons exhibited a greater postpress change in firing than medial shell neurons in the seconds following the unreinforced lever press ($z = -3.01$, $P = 0.0015$; 1-tailed Mann-Whitney U test; Fig. 3). The partial η^2 value (0.141) indicated a large effect size. In general, the magnitude of both prepress and postpress changes in firing rate, particularly increases, were greater for core than medial shell neurons (Figs. 2 and 3). Core neurons also exhibited greater prepress changes in firing than medial shell neurons during the seconds preceding the cocaine-reinforced lever press ($z = -3.244$, $P = 0.0005$; 1-tailed Mann-Whitney U test), particularly increases. The partial η^2 value (0.280) indicated a large effect size.

The second analysis was based on the three subterritory classification, in which the accumbens core and shell were caudal to the rostral pole. During the seconds surrounding the unreinforced lever press, core neurons ($n = 30$) exhibited greater prepress ($z = -2.718$; $P = 0.0035$; 1-tailed Mann-Whitney U test) and postpress ($z = -2.441$; $P = 0.0075$; 1-tailed Mann-Whitney U test) changes in firing than medial shell neurons ($n = 20$). Core neurons also exhibited greater prepress changes in firing than medial shell neurons during the seconds preceding the cocaine-reinforced lever press ($z = -2.695$, $P = 0.003$; 1-tailed Mann-Whitney U test).

In contrast, core neurons did not exhibit a greater postpress change in firing than medial shell neurons during the seconds following the cocaine-reinforced lever press using the two subterritory classification ($z = -0.176$, $P = 0.436$; 1-tailed Mann-Whitney U test) or the three subterritory classification ($z = -0.230$, $P = 0.417$; 1-tailed Mann-Whitney U test). At the instant of the cocaine-reinforced lever press, the pump signals onset of the cocaine infusion, and tone offset occurs. The lack of a subterritorial difference in postpress firing following the cocaine-reinforced lever press may reflect the presence of either or both of these events accompanying the reinforced response.

Duration of NAcc lever press-related neural activity

The mean durations of pre- and postpress changes in firing were evaluated for neurons that exhibited at least a twofold change relative to baseline. The mean duration of NAcc prepress changes in firing was 1.45 ± 0.2 s. The mean onset of the prepress firing change was 1.55 s prior to the lever press, and the mean offset was 0.1 s prior to the press. The mean duration of NAcc postpress changes in firing was 2.27 ± 0.5 s (Figs. 4 and 5). The mean onset of the postpress change in firing was

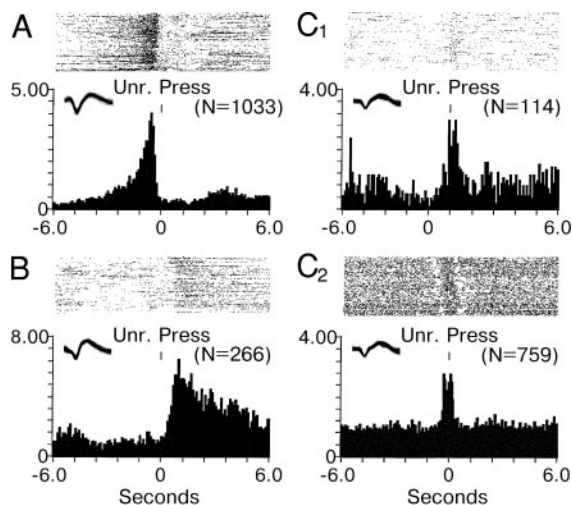


FIG. 4. Examples of prepress and postpress changes in firing in NAcc core neurons. *A*: example of a core neuron exhibiting an increase in firing prior to the unreinforced lever press (denoted by Unr. Press at time 0). This change in firing was the most common among prepress firing patterns. The ordinate of each peri-event time histogram displays average firing rate (impulses/s); *N* denotes the number of unreinforced lever presses the animal made during the course of the experimental session. Trials are shown chronologically from the bottom row to the top row of each raster. All axes are labeled similarly in Figs. 4 and 5. Overlaid waveforms in Figs. 4 and 5 represent the neurons whose activity is depicted in the histograms. Histograms were constructed around only unreinforced lever press events that were separated by >6 s from other lever presses. *B*: example of a NAcc core neuron exhibiting a postpress increase in firing. Among core neurons, this change in firing was the most common among postpress firing patterns. *C*₁ and *C*₂: example of a single core neuron (meeting all criteria of Peoples et al. 1999a) exhibiting similar firing patterns in both extinction and reinstatement as evidenced by similar $B/(A + B)$ values (0.64 for *C*₁ and 0.66 for *C*₂) under both conditions. The greater number of discharges in the raster of *C*₂ than in the raster of *C*₁ reflects the greater number of unreinforced lever presses made by the animal during reinstatement (*C*₂) than during extinction (*C*₁).

0.2 s following the lever press, and the mean offset was 2.47 s following the press.

DISCUSSION

Extracellular recordings of single NAcc core and medial shell neurons during drug-seeking behavior revealed subterritorial differences in firing rate changes that occurred within seconds of the drug-seeking response. With respect to unreinforced lever presses, core neurons exhibited greater prepress as well as postpress changes in firing rate than medial shell neurons. These firing patterns were unrelated to factors coincident with drug delivery because the responses were executed *in the absence of drug delivery* and the discriminative stimulus (S^D) tone that signaled cocaine availability. Interestingly, an analysis of cocaine-reinforced lever presses also revealed that the magnitude of prepress changes in firing rate was greater for core neurons than for medial shell neurons. The prepress changes exhibited predominantly by core neurons were typically increases in firing rate, and may reflect either a motoric or a planning component of drug-seeking behavior. These firing rate changes were correlated with the execution of both conditioned cue-induced and unreinforced drug-seeking responses.

The postpress firing rate changes that were observed in this study following unreinforced lever presses are intriguing because they occurred *in the absence of drug delivery* or any

exteroceptive cues (e.g., tone, light, pump) that accompanied infusions in previous studies (Carelli and Deadwyler 1996; Carelli et al. 1993; Chang et al. 1994; Peoples et al. 1997). Carelli (2000) has previously shown that postpress firing changes occur in response to conditioned stimuli predictive of drug delivery. The present changes in firing rate that followed unreinforced lever presses in core neurons cannot be mediated by cue-related neural processing and therefore may reflect qualitatively different processes. Perhaps the animal evaluates reward-outcome information immediately after pressing, which, via a core-associated network, influences subsequent instrumental behavior (Corbit et al. 2001). The prelimbic cortex may be an additional component of this circuitry and may be involved in retrieving information about this reward-outcome relationship (Corbit and Balleine 2003).

Dissociation of NAcc core and shell function in addiction-related neuronal processes

The present differences between NAcc subterritories related to the execution of drug-seeking behavioral responses may be attributed to their distinct connectivity. The core receives inputs from the dorsal prelimbic cortex and projects preferentially to the dorsolateral ventral pallidum (Brog et al. 1993; Gorelova and Yang 1997; Pinto and Sesack 2000). The dorsolateral ventral pallidum projects via the subthalamic nucleus and substantia nigra pars reticulata to the ventromedial (VM) motor thalamic nucleus (Zahm 1999); it also projects to the mesencephalic locomotor region (Mogenson and Yang 1991). This neural circuit is thus closely aligned with somatomotor portions of the basal ganglia (Brog et al. 1993; Heimer et al. 1991). Recent evidence indicates that the core, along with the dorsal prefrontal cortex and ventral tegmental area (VTA), may

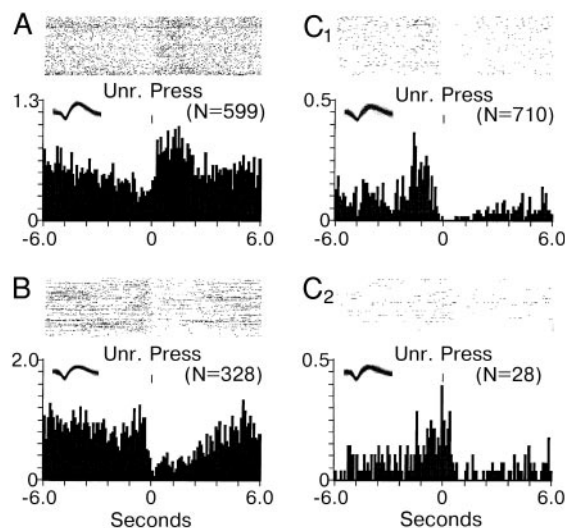


FIG. 5. Examples of prepress and postpress changes in firing in NAcc shell neurons. *A*: example of a shell neuron exhibiting an increase in firing following the unreinforced lever press (denoted by Unr. Press). *B*: example of a shell neuron exhibiting a postpress decrease in firing, which was the most common among shell postpress firing patterns. *C*₁ and *C*₂: example of a single shell neuron (meeting all criteria of Peoples et al. 1999a) exhibiting similar firing patterns around the unreinforced lever presses in both extinction (*C*₂) and reinstatement (*C*₁) as evidenced by similar $B/(A + B)$ values under both conditions (0.27 for *C*₁ and 0.32 for *C*₂, both values reflecting a postpress decrease in firing; 0.67 for *C*₁ and 0.71 for *C*₂, both values reflecting a prepress increase in firing).

be part of a somatomotor-related circuit involved in the execution of drug-seeking responses (Cornish and Kalivas 2000; McFarland and Kalivas 2001; McFarland et al. 2003).

In contrast, the medial shell exhibits a pattern of connectivity consistent with that of the extended amygdala (Alheid and Heimer 1988; Brog et al. 1993; Heimer et al. 1991). Recent evidence suggests that the shell may be involved in processing learned information regarding the motivational significance of reward-related S^D (Ghitza et al. 2003). Since the onset of the S^D -evoked firing patterns preceded movement onset and since these firing patterns occurred even in the absence of movement, they were not correlated with the execution of drug-seeking responses per se. Instead, these firing patterns may encode the motivational salience of the S^D , as evidenced by the firing rate changes that shell neurons exhibited to the reward-predictive S^D , but that were typically absent following presentation of a stimulus with no reward-predictive value.

During exposure to an S^D predictive of unconditioned stimulus (US) availability, a circuit that includes the medial shell and its input from the basolateral amygdaloid complex and VTA may play a role in attributing incentive salience to a rewarding US. This neural representation persists across extended drug abstinence, may play a role in the maintenance of drug dependence, and can render drug abusers vulnerable to relapse long after initial drug withdrawal (Ghitza et al. 2003; Robinson and Berridge 1993, 2003).

The medial shell projects via the ventromedial ventral pallidum and the mediodorsal thalamus to the dorsal prefrontal cortex that innervates the core (Brog et al. 1993; Heimer et al. 1991; Usuda et al. 1998; Zahm and Heimer 1990). Moreover, the medial shell projects to parts of the VTA that innervate the core and adjacent regions of the dorsal striatum (Berendse et al. 1992b; Brog et al. 1993; Haber et al. 2000; Otake and Nakamura 2000; Zahm 2000). Thus shell processing could ultimately modulate core output via feed-forward information from this medial-shell associated neural circuitry (Haber et al. 2000; Pennartz and Kitai 1991; Zahm 2000). Interestingly, the medial shell has been shown to be involved in dopamine-mediated potentiation of the ability of conditioned stimuli to trigger instrumental actions (Wyvell and Berridge 2000), perhaps via its feed-forward output to core-associated somatomotor circuitry. This distinct connectivity of NAcc subterritories together with our data showing S^D -related firing in medial shell (Ghitza et al. 2003) versus instrumental response-related firing in core (this study) provide a neurophysiological basis for functionally distinct but integrative involvement of core and medial shell in addiction and relapse. Such neurophysiological processes may mediate the motivational impetus, on exposure to drug-predictive stimuli, to seek and take drugs.

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GRANTS

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