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Cellular Mechanisms Underlying Reinforcement-Related Processing in the Nucleus Accumbens: Electrophysiological Studies in Behaving Animals

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CARELLI, R. M. AND S. A. DEADWYLER. *Cellular mechanisms underlying reinforcement-related processing in the nucleus accumbens: Electrophysiological studies in behaving animals.* PHARMACOL BIOCHEM BEHAV **57**(3) 495–504, 1997.—Numerous investigations have implicated the nucleus accumbens (NA) as an important neural substrate involved in mediating reinforcement-related processing. Electrophysiological studies in behaving animals enable a direct examination of cellular mechanisms underlying this process via characterization of NA activity at critical times during responding for food, water, or drug reward. Electrophysiological studies are reported that examined the activity of NA neurons during water- and cocaine-reinforced responding in rats. These studies reveal that some NA neurons exhibit changes (increases or decreases) in firing rate synchronized to the response-contingent delivery of water or cocaine. Furthermore, the sampled population of NA neurons exhibited less synchronized cell firing during the response for cocaine than for the water reward. NA activity during cocaine self-administration was explicitly coupled to the behavioral state of the animal and was markedly influenced by the stimulus context in which the drug was delivered. These findings are discussed with respect to the dynamic properties of NA activity and its importance as an underlying cellular substrate mediating reinforcement-related events in the behaving animal. © 1997 Elsevier Science Inc.

Electrophysiology Cocaine self-administration Nucleus accumbens Behavior Dopamine Reinforcement

NUMEROUS investigations have indicated that the nucleus accumbens (NA) is an important neural substrate for maintaining reinforced behaviors. One widely held contention is that the NA functions to integrate limbic information related to motivation, memory, and associated motor activity (2,13,29,32). The anatomic organization of the NA clearly supports this view, because the NA receives input from limbic structures including the basolateral amygdala (4,50,54), subiculum (4,16,17,54), ventral tegmental area (VTA) (16,54), and prefrontal (prelimbic) cortex (4,28,54), and sends efferent projections to several structures involved in motor processing, such as the ventral pallidum and associated regions (16,18,55).

Studies on appetitive and drug-reinforced operant responding also support a crucial role for the NA, in particular the dopaminergic projection from the VTA to the NA, in reinforcement-related behaviors. The NA has been shown to be crucially involved in mediating operant responding for "natural" reinforcers such as food and water (20,21,27,39,46,53) and for drugs of abuse such as cocaine (12,24,25,38,46). In addition, recent studies implicate a role of the NA in "incentive motivation," in which environmental stimuli, through their association with a primary reinforcer, alter the motivational state of the animal and influence behavior (13,37).

Despite overwhelming evidence linking the NA with reinforcement-related events, little is understood regarding underlying cellular mechanisms mediating this process. One means of determining this process is via electrophysiological recordings in behaving animals, the advantage of which is that it enables a characterization of NA cell firing at critical times during operant responding. Such studies provide potential insight into the neurobiological mechanisms underlying the rewarding properties of "natural" reinforcers such as food and water, and how drugs of abuse such as cocaine may affect this system and lead to drug addiction. Here, we discuss electro-

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physiological evidence that illustrates the rather dynamic properties of NA neurons as a function of the behavioral state of the animal and/or the environmental context associated with reward.

CHARACTERIZATION OF ACCUMBENS CELL FIRING DURING WATER VS. COCAINE REINFORCEMENT

NA neurons exhibit similar changes (increases and/or decreases) in firing rate during water reinforcement and cocaine self-administration sessions in rats (5,8,9,33) and monkeys (1,3,40). We have previously reported that a subset of recorded NA neurons (25%) exhibit one of three types of neuronal firing patterns synchronized to either water- or cocaine-reinforced responding in rats (5,8). Examples of these patterned discharges are shown in Fig. 1. Note that NA neurons exhibited increased firing immediately prior to the response (PR cells) or an increase or decrease in firing rate after the response (RF_E or RF_I, respectively) (5). Similarities in neuronal firing patterns were observed relative to the water- or cocaine-reinforced response despite differences in overall behavioral response rates and the occurrence of cocaine-induced stereotypy during self-administration sessions. These findings support the notion that a subset of NA neurons discharge in relation to movements associated with both drug and water rewards.

It is possible that these changes in NA firing rates may instead be associated with concomitant motoric activity, such as locomotion and limb movements, involved in the response. This important issue was tested and rejected in several studies

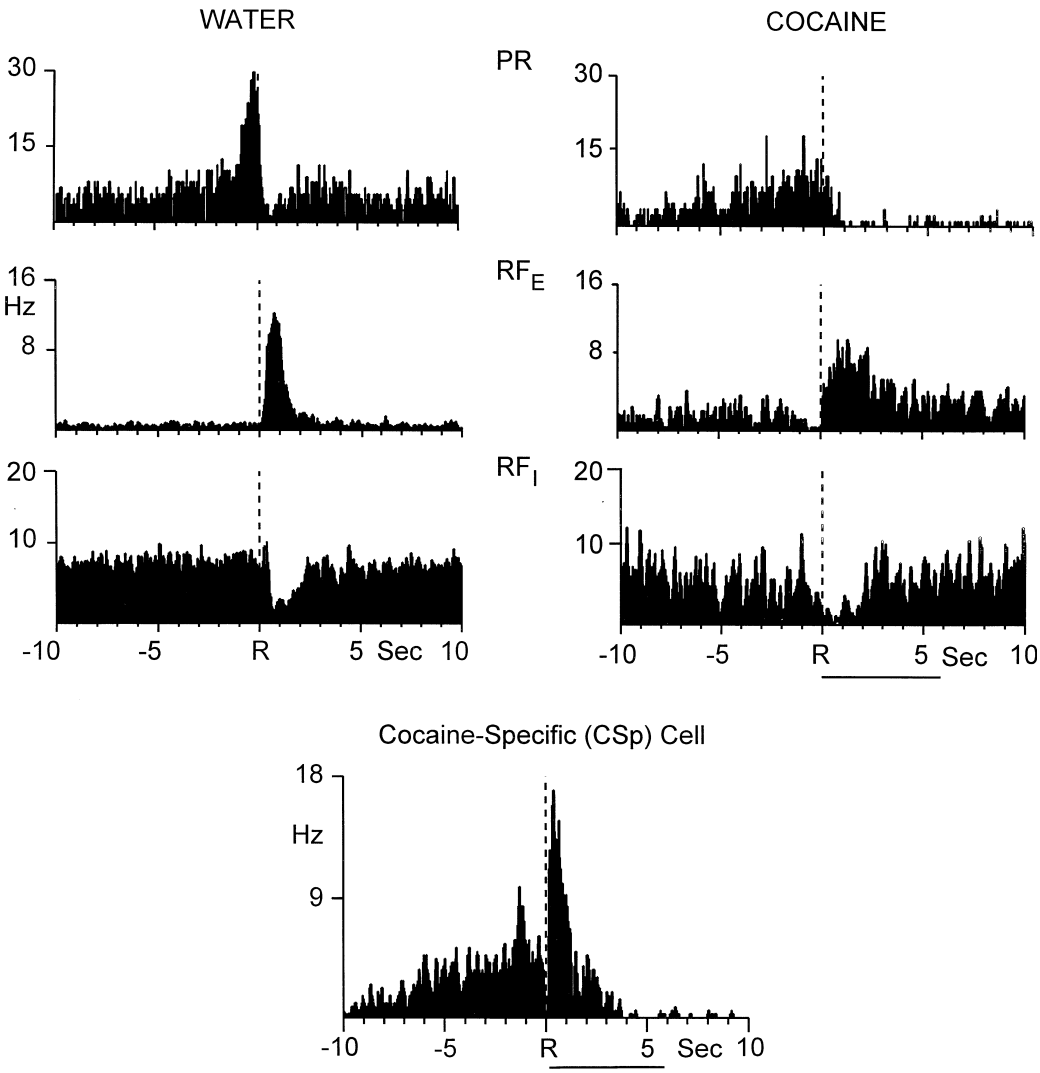

FIG. 1. Perievent histograms (PEHs) showing three similar types of neuronal firing patterns relative to the reinforced response for water (left) and cocaine (right). Firing patterns were characterized by increased activity immediately before the response (termed preresponse, PR cell), and increased (termed reinforcement-excitation, RF_E cell) or decreased (termed reinforcement-inhibition, RF_I cell) firing immediately following the response. The bottom PEH shows the NA neuronal firing pattern observed only during cocaine self-administration (termed cocaine specific, CSp cell) characterized by the same three features of response-related activity observed in the other three types shown above. Reinforced response is indicated by "R" at the dashed line. Cocaine delivery (0.33 mg/infusion, 5.8 s) is indicated by the horizontal line below the PEHs for cocaine.

(8,9,26,40). We reported a dissociation between NA patterned discharges that occurred prior to the cocaine-reinforced response and the execution and maintenance of unreinforced lever-press responses using higher ratio schedules of reinforcement (8). Chang and coworkers reported that a subset of NA neurons were activated during "orienting" movements toward the lever prior to completion of the cocaine-reinforced response but not during similar movements within the interresponse interval (9). Furthermore, Schultz and coworkers reported that NA cell firing preceding reward was prolonged within the session when reward delivery was delayed, even though electrophysiologically monitored arm movements remained unchanged (40). These findings indicate that the differential NA patterned discharges illustrated in Fig. 1 were not related solely to motor activity associated with the lever press.

DIFFERENCES IN NA CELL FIRING DURING WATER VS. COCAINE REINFORCEMENT

Because NA neurons exhibit the same general classes of neuronal firing patterns with two very different reinforcers (water vs. cocaine), it is equally important to characterize any difference in NA cell firing between water- and cocaine-reinforcement conditions. The most dramatic disparity was the detection of a fourth type of neuron found to be "cocaine-specific" (CSp) because it was observed exclusively during cocaine self-administration sessions and never in water-reinforcement sessions (5,6,8). As shown in Fig. 1 (bottom), an important feature of CSp cell firing was that it incorporated all of the features observed in the other three NA cell types (Fig. 1, top). This finding suggests the intriguing possibility that cocaine may alter NA synaptic circuitry such that some of the other cell types (PR, RF_E, and/or RF_I) may discharge in the combined CSp pattern.

An alternative explanation is that a completely different set of NA neurons with CSp characteristics discharge during cocaine self-administration sessions and not during responding for "natural" reinforcers such as food or water (5,6). This latter interpretation is supported by the recent studies of Bowman and coworkers (3), who examined the activity of NA neurons in monkeys performing a reaction time task for either juice or cocaine reinforcement. Results indicated that although similar "anticipatory" and postresponse changes in NA cell firing rate were observed under both reinforcement conditions, the *same* NA neuron exhibited differential activity relative to delivery of cocaine vs. juice. These differences in neural firing may reflect a cellular mechanism by which the NA distinguishes between qualitatively different reinforcers.

The composite perievent histograms (PEHs) in Fig. 2 show NA cell firing averaged over all PR, RF_E, and CSp neurons, and also reveal important differences with respect to NA cell firing during responding for water vs. cocaine reinforcement. Most notable is the pronounced attenuation in NA response-related activity in the cocaine-reinforcement condition. Specifically, the population of NA neurons (PR, RF_E, CSp cells) exhibited a pronounced decrease in peak (maximal) firing rates at the time of the reinforced response for cocaine (bottom) vs. water (top). This reduction in NA cell firing may reflect any of several differences between reinforcement contexts, including: a) a greater dispersal and/or fragmentation in NA activity relative to the response during cocaine self-administration sessions, b) a cocaine-induced inhibition in NA cell firing, and/or c) a cocaine-induced change in neural correlation with response topography, suggesting that NA cell firing was not as synchronized to the response. The same data were therefore regraphed and aligned relative to each cell's peak (maximum) firing rate in the same analysis time period during water reinforcement (PR, RF_E cells) and cocaine self-administration (PR, RF_E, CSp cells) sessions. The PEHs in the top portion of Fig. 3 show that peak firing rates for both reinforcer conditions were elevated, however the peak increase in activity during cocaine self-administration shown in Fig. 3 (top) was significantly lower than for water reinforcement [$t(48) = 3.22$, $p < 0.01$], supporting findings that cocaine "blunts" NA cell firing even though it continues to discharge during the analysis epoch (19,36,43–45).

The basis for this attenuation in NA activity appears to be that NA cell firing is less synchronized to the reinforced response during cocaine vs. water reward. The vertical lines above each PEH in Fig. 3 indicate where in time the behavioral response occurred relative to peak neural activity during different trials. During water reinforcement sessions (top, left), the distribution of the responses ranged from approximately 3 s before to 2 s following peak cell firing. In contrast, the distribution of responses during cocaine self-administra-

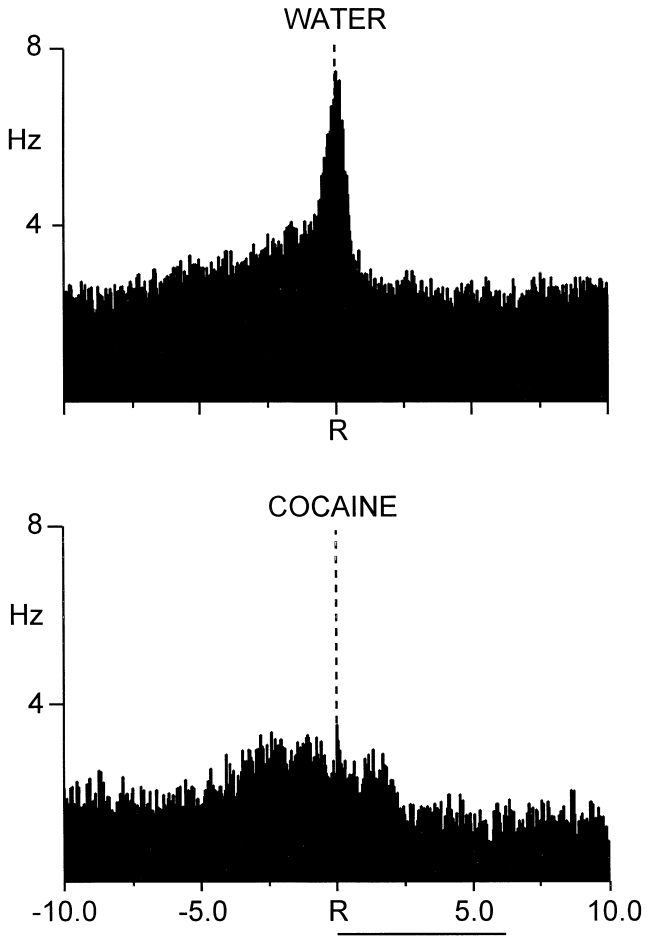

FIG. 2. Composite PEHs showing NA activity averaged across all cells exhibiting patterned excitatory discharges and displayed relative to the water-reinforced (top) or cocaine-reinforced (bottom) response (indicated by "R" at the dashed line). PEH for water includes PR and RF_E cells ($n = 27$). PEH for cocaine includes PR, RF_E, and CSp cells ($n = 40$). Cocaine delivery (0.33 mg/infusion, 5.8 s) is indicated by the horizontal line below the cocaine PEH.

tion sessions (top, right) occurred within a notably wider range (5 s before to 5 s after peak neural activity). This greater dispersal in NA cell firing relative to the cocaine-reinforced response was attributed primarily to differences in type PR activity across the two reinforcer conditions. Figure 3 (bottom) shows the peak-aligned activity of only PR cells during water (left) and cocaine (right) reinforcement sessions. Note the wider distribution of reinforced responses for cocaine. Therefore, the altered distribution of behavioral responses relative to peak NA activity (Fig. 3, top) appears to be accounted for by differences in type PR NA cell firing. This finding may be attributed to the longer interinfusion interval (INT) and the occurrence of stereotypy during cocaine self-administration sessions, or possibly may indicate that NA neurons differentially encode information related to "expectation" of different types of reward (3).

COMPLEMENTARY PATTERNS OF NA CELL FIRING

An important feature of NA cell firing was the temporal specificity and complementary manner with which the cells discharged relative to the reinforced response for cocaine or water. For example, Fig. 1 shows that the peak increase in the type PR cell firing was followed by an abrupt decline in activity. The decreased activity of the PR cell coincided with the peak firing of the RF_E cell type immediately after response completion. Likewise, the phasic inhibitory period in RF_I cell firing corresponded to the time period during which RF_E activity was maximal. These findings show that the different NA firing patterns "bridge" discrete temporal intervals during the execution of the behavioral response for reward. This important aspect of NA cell firing is illustrated further in Fig. 2. Note that despite differences in overall firing rates between the two reinforcer conditions (drug vs. water), the different types of NA cells form a population discharge pattern encompassing response initiation, completion, and reinforcement delivery. This process may reflect a general functional property of the striatum (both dorsal and ventral regions), because Schultz and colleagues reported that populations of dorsal striatal neurons encode the entire sequence of juice-reinforced responding during a Go-NoGo task in monkeys (41).

Given this complementary firing property of different types of NA cells, it was important to determine the extent to which such linkages were maintained over the entire INT. A recent report by Peoples and West (33) showed that a subset of NA neurons exhibit cyclic alterations in firing rate with periodicities on the order of minutes, which correspond roughly to the cocaine interinfusion (i.e., response) interval. Some NA

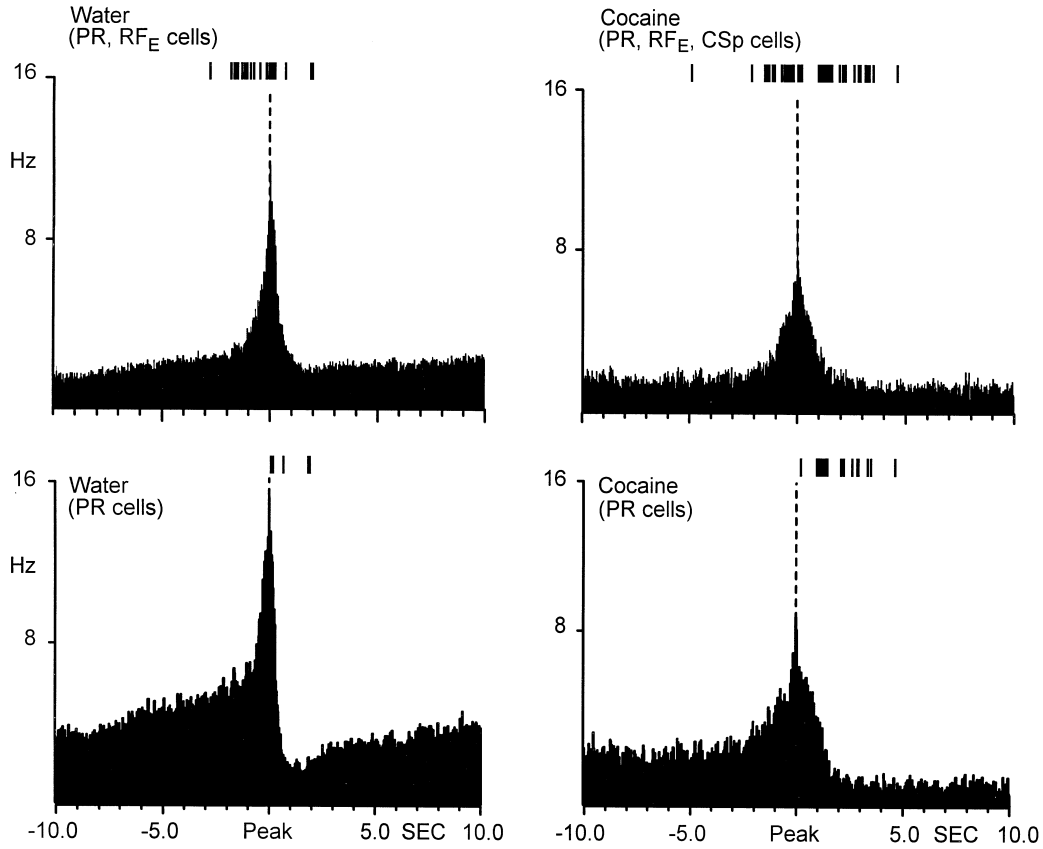

FIG. 3. Top: Composite PEHs showing averaged firing of PR and RF_E cells (water reinforcement, left) or PR, RF_E, and CSp cells (cocaine self-administration, right), aligned relative to each cell's maximum increase in the firing rate (indicated by "Peak" at the vertical line). Bottom: Composite PEHs showing the same display format as above but including only PR cells. The vertical tick marks above each PEH indicate the distribution of reinforced responses relative to the peak firing rate for each cell included in the PEHs.

neurons showed cyclic changes in firing that terminated with increases at the time of the response (like PR cells), whereas others showed 180° differences in firing tendency across the same interresponse interval with response correlates like RF_E cells. Recent analysis of data from our laboratory supports the Peoples and West (33) finding. We have observed long-term cyclic changes in activity of NA cells classified by our original criteria (Carelli and Deadwyler, in prep.). Figure 4 shows the activity of four NA neurons (classified as PR, RF_E, RF_I, and CSp cell types) synchronized to the response but summed over temporal intervals (20 min) encompassing the entire INTs during self-administration sessions. Tick marks above each PEH indicate the slightly nonsynchronized preceding (left) and subsequent (right) behavioral responses as they occurred in relation to the summed neural activity timed locked to the response at "0" min (indicated by "R"). Note that neurons exhibited substantial cyclic increases (PR, RF_E, and CSp cells) or decreases (RF_I cell) in firing rates corresponding to the time period between responses. Furthermore, the timing of the peak (maximal) cyclic change was phase shifted in time across the four different cell types despite similarities in the timing of behavioral responses (Fig. 4). Preliminary findings also indicate that another subset of NA cells, which did not meet short interval classification criteria, displayed long-term cyclic changes in firing rate during the INT. This latter finding suggests that a larger population of NA cells engage in cell firing (either on a long or short time interval basis) related to the execution of the cocaine-reinforced response.

Peoples and West (33) speculated that the "progressive" changes in NA activity that occurred during the INT of cocaine self-administration sessions may be related to systematic changes in NA dopamine levels relative to each cocaine infusion. Support for this notion is provided by microdialysis studies showing fluctuations in NA dopamine levels between lever-press responses over a time course similar to that of the long-term changes in neural activity (33,48). Peoples and West hypothesized that the changes in NA neuronal firing rates during the INT may reflect a neural mechanism that translates declining NA dopamine levels into drug-seeking behavior (33). This is a very provocative and plausible interpretation of the long-term cyclic variations in NA activity. However intriguing, though, such assumptions need to be backed by accurate assessment of the neurobehavioral correlates that occur within such long analysis intervals in order to rule out possible motivational and/or behavioral contaminants. Specifically, it is possible that the changes in neural activity averaged across these long time epochs (Fig. 4) may reflect behavioral factors not under rigorous experimental control. Shorter analysis epochs avoid these contaminants to a greater extent. Cyclic NA cell firing assessed over *6- or 7-min* INTs during cocaine self-administration sessions could reflect: a) locomotion to and from the lever, b) cyclical exploratory movements around the chamber, and/or c) cyclical patterns of stereotypic behavior well known to be induced by the cumulative effects of cocaine infusions during the session. For this reason, accurate interpretation of the basis of such cyclic patterns of NA activity must await more detailed assessments of behavioral correlates over these long analysis periods.

DYNAMIC PROPERTIES OF NA CELL FIRING

The findings described above indicate that drugs of abuse such as cocaine are capable of altering the activity of NA neurons, and provide insight into the cellular mechanisms underlying this process in the behaving animal. However, another important aspect of NA cell firing observed in behaving animals was the ability of these neurons to modify activity depending upon the environmental context and/or behavioral state of the animal. For example, Chang and coworkers demonstrated that response-related activity was not exhibited by NA cells during acquisition sessions, but developed gradually over days after the animals acquired stable lever pressing behavior for cocaine (9). In addition, NA neurons have been shown to exhibit abrupt changes in firing rate when the magnitude of a liquid reinforcer was altered (26,40).

Recent investigations in our laboratory also illustrate that NA cell firing is modifiable and explicitly coupled to the be-

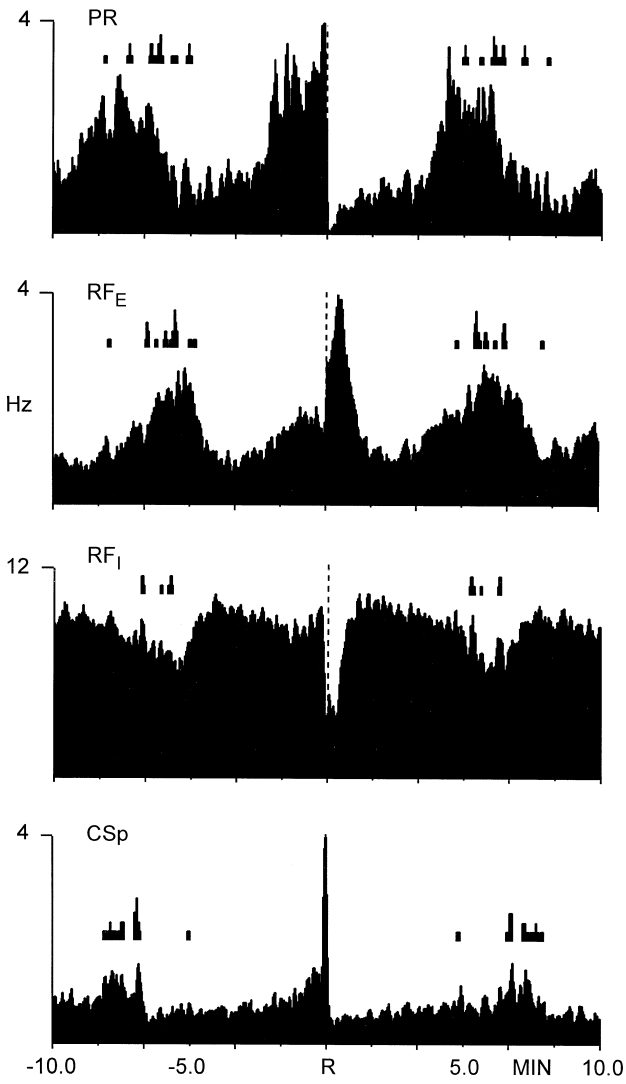

FIG. 4. PEHs showing the activity of four NA neurons (type PR, RF_E, RF_I, and CSp) displayed within an extended analysis time interval (20 min) during different cocaine (0.33 mg/infusion) self-administration sessions. Reinforced responses are indicated by "R" at the dashed vertical lines. Tick marks above each PEH indicate preceding (left) and subsequent (right) lever-press responses. Fourteen trials are shown for each neuron. Mean interinfusion intervals (min): 6.39 ± 0.27 (PR), 6.37 ± 0.10 (RF_E), 6.20 ± 0.30 (RF_I), 7.01 ± 0.27 (CSp).

havioral state of the animal during cocaine self-administration sessions in rats. Specifically, NA patterned discharges were not present during initial trials of the cocaine self-administration session, but instead "emerged" after a few trials in correspondence to an abrupt transition from high (load-up) to low behavioral response rates (6,8). In a series of experiments, we demonstrated that transitions in behavioral responding and NA activity could be systematically prolonged within the self-administration session, in a dose-dependent manner, by decreasing the dose of cocaine. Figure 5 shows an NA cell that exhibited a delay in onset of type PR patterned cell firing as an inverse function of dose of cocaine. In each case, the delay in the onset of PR activity was accompanied within a single trial by the transition from high to low behavioral response rates (arrows). The number of trials to transitions in behavioral responding and NA cell firing was also prolonged at a given dose of cocaine by pretreatment with the dopamine D_1 receptor antagonist SCH 23390, similar to decreasing the dose of cocaine (6).

These findings suggest that the rapid transitions in behavioral responding and NA cell firing at the early stages of cocaine self-administration sessions may be linked to dopamine levels in the NA which increase in relation to cumulative doses of cocaine delivered at short time intervals (5,6,8). This notion is consistent with microdialysis and voltammetry studies reporting significant increases in NA dopamine levels during cocaine self-administration sessions in rats (15,21,23,34,35,47,48). This was further substantiated by recent studies showing that the load-up phase could be eliminated following experimenter-controlled preinjection of cocaine before the start of the session (Carelli and Deadwyler, in prep.).

The cocaine-related increased levels of dopamine in the NA may function to "sculpt out" the patterned discharges of NA cells by suppressing non-response-related NA background firing. Support for this notion is shown in Fig. 6. The PEHs show the activity of two NA neurons during 19 load-up trials averaged across four sessions (left) vs. the same number of trials immediately following the load-up phase (right). During the load-up phase, both NA cells exhibited relatively high nonspecific firing rates with little phasic relation to the response. However, following the load-up phase (as defined by the change in response rate), neuron 1 (top right) exhibited a dramatic shift to type PR cell firing and neuron 2 (bottom right) exhibited a transition to CSp activity. In both cases, the onset of patterned activity was coupled to a reduction in background firing rates.

One possible interpretation of these findings is that elevated levels of NA dopamine may define the patterned discharges of NA neurons in the behaving animal by changing the susceptibility of these neurons to excitatory synaptic inputs (6,31). Recent iontophoresis studies by Kiyatkin and Rebec in awake behaving animals support this contention (22). Those authors demonstrated that iontophoretic application of glutamate during prolonged dopamine application in the NA decreased background firing rates and increased the signal-to-noise ratio of NA cells. The overall effect was an enhancement in the relative magnitude of the glutamate-induced neural excitation of NA cells. This finding is consistent with previous studies showing similar neuromodulatory actions of catecholamines in the NA (51,52) and cerebellum (49). It is therefore possible that the spontaneous shifts in NA cell firing at the start of cocaine self-administration sessions in rats may also reflect a dopamine-mediated "enhancement" of NA cells to other convergent excitatory afferents during behavioral responding for cocaine reward.

ASSOCIATIVE PROPERTIES OF NA CELL FIRING DURING COCAINE SELF-ADMINISTRATION

To date, few if any investigations have addressed the issue of the cellular basis of conditioning or associative factors during cocaine self-administration. To address this issue, we examined the activity of NA neurons during response-dependent cocaine delivery vs. experimenter-controlled (response independent) cocaine infusion (7,8). As in all prior studies, cocaine delivery was paired with a tone–houselight stimulus complex that remained on for 14 s following drug delivery. Once behavioral responding was stable, random deliveries of the same dose of cocaine were given as "probe" trials during the INT in the absence of the stimulus. The PEHs in Fig. 7

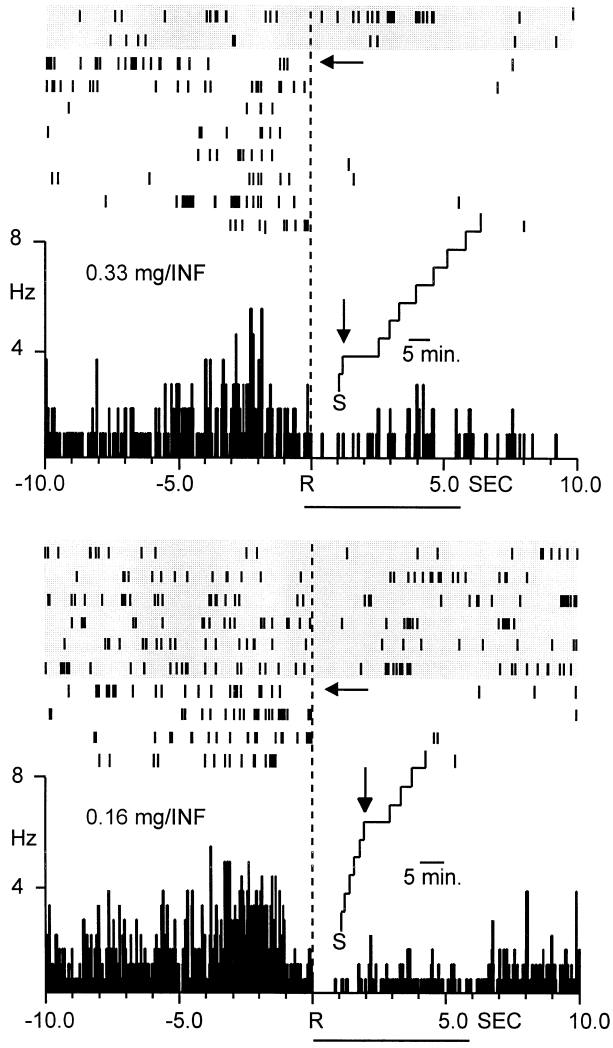

FIG. 5. PEHs showing the activity of the same NA neuron during different self-administration sessions in which the animal responded for either 0.33 (top) or 0.16 (bottom) mg/infusion cocaine. During each session, the NA neuron exhibited activity unrelated to the reinforced response during the load-up phase (shaded area in rasters) then shifted to patterned type PR activity (arrows at rasters), corresponding to a shift from high to low response rates (arrows at records). "R" is the reinforced response. The start of the session (trial 1) in each record is indicated by "S".

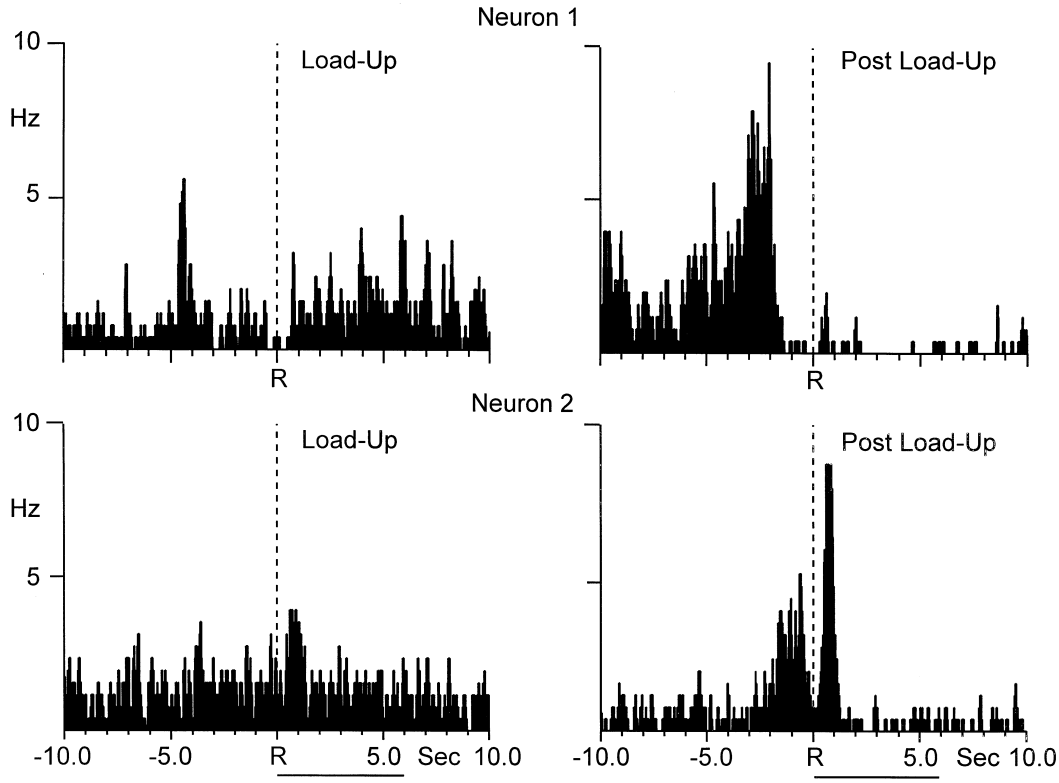

FIG. 6. PEHs showing the activity of two NA neurons during load-up trials (left) vs. the same number of trials immediately following the load-up phase (right). Each neuron exhibited non-response-related discharges and relatively high background firing rates during the load-up phase, then shifted to either type PR (neuron 1) or CSp (neuron 2) activity coupled to a reduction in background neural activity following load-up responding. "R" is the reinforced response. Cocaine delivery (0.33 mg/infusion, 5.8 s) is indicated by the horizontal lines below the bottom PEHs.

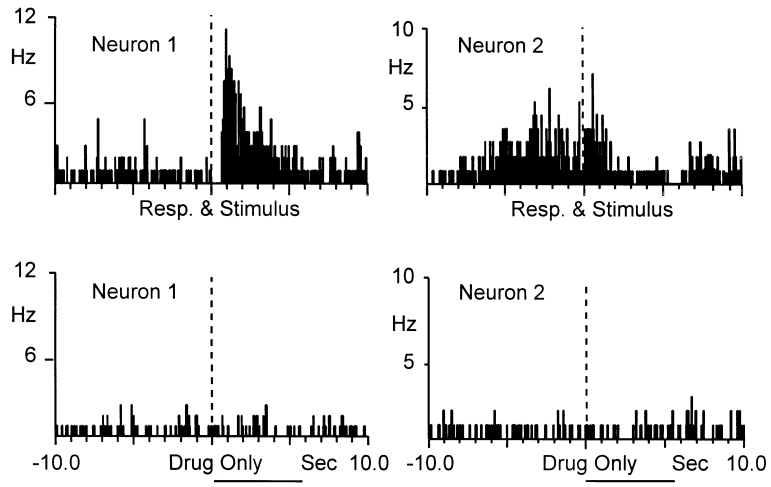

FIG. 7. PEHs showing the activity of two NA neurons during response-dependent (top) vs. response-independent (bottom) cocaine delivery. NA cells exhibited type PR (neuron 1) or CSp (neuron 2) activity relative to the cocaine-reinforced response paired with a tone–houselight (20 s) stimulus (indicated by "Resp. & Stimulus" at the dashed line), but no change in firing rate during response-independent delivery of the same dose of cocaine (indicated by "Drug Only" at the dashed line). Cocaine delivery (0.33 mg/infusion) is indicated by the horizontal lines below bottom PEHs. Twenty trials in each PEH.

show the activity of two NA neurons recorded during response-dependent (top) vs. response-independent (bottom) cocaine delivery. Neuron 1 (type RF_E) exhibited a robust increase in cell firing following the cocaine-reinforced response (top); however, the same neuron exhibited no change in firing rate above baseline levels during response-independent delivery of the same dose of cocaine (bottom). Likewise, neuron 2 exhibited the typical CSp cell firing pattern relative to the reinforced response (top), which was absent when the same dose of cocaine was delivered in a response-independent manner (bottom). These findings suggest that the patterned discharges exhibited by NA neurons were not directly controlled by a pharmacological action of cocaine but instead appear to be at least partially maintained by stimuli that have been paired with response-dependent cocaine delivery.

Ongoing investigations are examining the influence on NA cell firing of the stimulus previously paired with cocaine delivery when presented alone (7). Stimulus "probes" (without cocaine) were randomly presented by the computer to well-trained rats during the INT of the cocaine self-administration session. The PEHs in Fig. 8 show the activity of a CSp neuron relative to response-dependent cocaine infusion paired with the tone–houselight stimulus (top) vs. response-independent stimulus-only "probes" (bottom). Note that the neuron exhibited increased firing immediately before and after the reinforced response, characteristic of type CSp activity (top). In addition, the same neuron exhibited excitatory discharges in relation to stimulus "probes" (bottom), but no change in firing rate relative to response-independent cocaine-only "probes" delivered in the absence of the stimulus (not shown). These findings indicate that the patterned discharges of NA cells during cocaine-reinforced responding are controlled to a large extent by the stimulus paired with drug delivery, rather than the drug itself. Activation of NA cell firing during stimulus presentation most likely represents a conditioned response of this population of neurons as opposed to a generalized stimulus-evoked discharge because such patterned activity was not observed during the load-up phase despite the presence of the stimulus paired with the drug [see above and (6)].

We have speculated that this observation may have important implications with regard to human drug addiction (7). It has been reported that stimuli associated with cocaine-taking behavior, such as environmental cues or drug paraphernalia, are strong elicitors of drug "craving" and lead to relapse following a period of drug abstinence in humans (10,11,30). Little is understood, however, regarding the neural processes mediating stimulus-evoked craving in humans, although recent studies suggest a potential involvement of the amygdala and related structures (including the NA) in this process (10). The finding that a subset of NA neurons exhibit increased activity during presentation of stimuli previously paired with cocaine is consistent with this notion. In addition, these findings illustrate the importance of examining "associative" factors in determining underlying neurobiological mechanisms mediating reinforcement-related processing in the NA.

It has also been proposed that the process by which stimuli elicit "craving" in humans is likely related to conditioned associations between stimuli paired with drug-taking behavior and cocaine (30,42). However, further investigations are needed to determine the precise relationship between stimulus control in drug-seeking behavior and NA cell firing. For example, it will be important to determine whether the same stimulus can function as a secondary reinforcer and support responding in the absence of cocaine (37). It will also be important to determine whether elevated levels of dopamine in the NA are involved in mediating the conditioned activation of NA cell firing, because microdialysis and voltammetry studies show that presentation of conditioned stimuli previously paired with cocaine delivery significantly increase dopamine levels in the NA (14,15). Further understanding of the relationship between "associative" factors and NA cell firing in the behaving animal will provide insight into the role of this structure in mediating information processing related to reward.

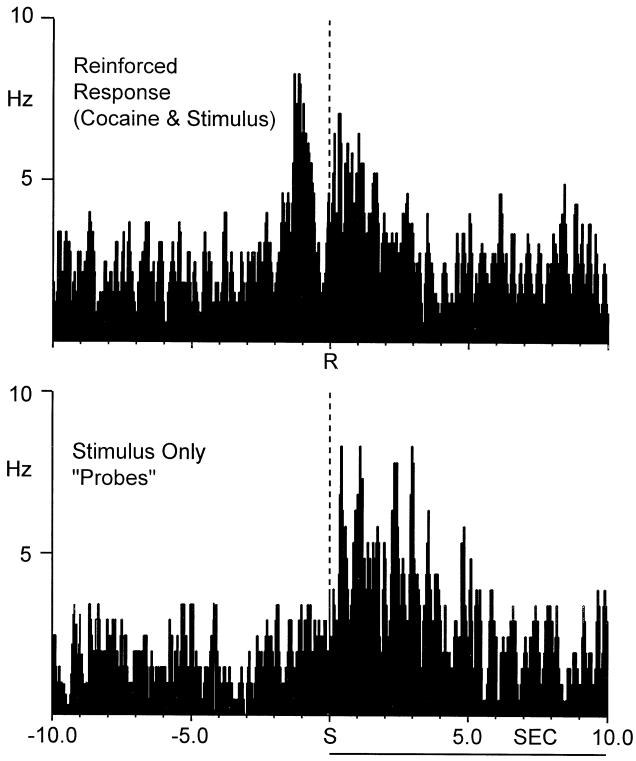

FIG. 8. PEHs showing the activity of the same cocaine-specific (CSp) NA cell relative to the cocaine-reinforced (0.33 mg/infusion) response paired with the tone–houselight stimulus (top) or stimulus-only "probes" (bottom). Horizontal line below bottom PEH indicates tone-houselight stimulus (20 s total; 10 s shown). The reinforced response is indicated by "R". Stimulus "probes" are indicated by "S". Twenty trials in each PEH.

SUMMARY AND UNRESOLVED ISSUES

The findings described above reveal several important properties of NA cell firing patterns in the behaving animal, and provide insight into the underlying synaptic and cellular mechanisms mediating reinforcement-related activity in this structure. Specifically, NA neurons exhibit discrete patterns of activity that become rapidly synchronized to the response that produces drug and appetitive reward. Importantly, these effects are dissociable from the motoric aspects of the goal-directed behavior. In addition, NA cell types exhibit complementary firing patterns that bridge the individual events in the reinforced response. The net result of this cellular organization is that the population of NA neurons encodes a large portion of the temporal domain comprising initiation and completion of the reinforced response. Studies also revealed that NA cell firing is capable of exhibiting a high degree of plasticity relative to either the behavioral state of the animal or the environmental context associated with cocaine reinforcement.

The spontaneous transitions in cell firing observed at the start of cocaine self-administration sessions suggest a change in firing related to NA dopamine levels. Furthermore, studies showing the powerful influence of conditioned stimuli on eliciting NA cell firing suggest that associative factors play a major role in drug self-administration.

These findings, however, leave several unresolved issues with respect to the underlying cellular organization of the NA and how activation of this structure influences behavior. For example, investigations need to determine the precise role of conditioning in the acquisition and maintenance of reinforced responding for cocaine; and to determine how this associative process may differ in animals responding for natural reinforcers such as food and water. Likewise, it will be important to determine whether the spontaneous shifts in NA cell firing observed at the start of the self-administration session are unique to cocaine reinforcement, and whether similar types of neural changes coupled to behavior might occur in other reinforcement circumstances. Because numerous investigations implicate an important role of NA dopamine in both drug and appetitive reward (12,20,21,24,25,27,38,39,46,53), it is critical to examine how this transmitter modulates NA cell firing in the behaving animal with respect to: a) interactions between NA neurons, and b) alterations in the underlying synaptic circuitry of the NA.

Anatomic and electrophysiological studies show that the NA receives convergent afferents from several different limbic structures involved in processing information related to memory [i.e., hippocampus (4,16,17,54)], motivation [i.e., basolateral amygdala (4,50,54)], and higher "associative" functions [i.e., prelimbic cortex (4,28,54)]. It has been proposed, therefore, that the NA functions to integrate information across each of these dimensions and translates or "gates" the appropriate behavioral responses necessary for rewards based on such integrated information (26,29,31,32,37,40). The present findings support and expand this view by showing that the activation of NA neurons in the behaving animal is not simply dependent upon a single critical event (i.e., reinforcer type or specific motor response). Instead, the optimal conditions for synchronizing cell firing with behavior appear to involve a convergence of several motivation-related events that provide a neural "representation" in the NA of the contexts that are appropriate for different goal-directed behaviors.

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REFERENCES

1. Apicella, P.; Ljungberg, T.; Scarnati, E.; Schultz, W.: Responses to reward in monkey dorsal and ventral striatum. Exp. Brain Res. 85:491–500; 1991.
2. Beninger, R. J.: The role of dopamine in locomotor activity and learning. Brain Res. Rev. 6:173–196; 1983.
3. Bowman, E. M.; Aigner, T. G.; Richmond, B. J.: Neural signals in the monkey ventral striatum related to motivation for juice and cocaine rewards. J. Neurophysiol. 75:1061–1073; 1996.
4. Brog, J. S.; Salyapongse, A.; Deutch, A. Y.; Zahm, D. S.: The patterns of afferent innervation of the core and shell in the "accumbens" part of the ventral striatum: Immunohistochemical detection of retrogradely transported fluoro-gold. J. Comp. Neurol. 338: 255–278; 1993.
5. Carelli, R. M.; Deadwyler, S. A.: A comparison of nucleus accumbens neuronal firing patterns during cocaine self-administration and water reinforcement in rats. J. Neurosci. 14:7735–7746; 1994.
6. Carelli, R. M.; Deadwyler, S. A.: Dose-dependent transitions in nucleus accumbens cell firing and behavioral responding during cocaine self-administration sessions in rats. J. Pharmacol. Exp. Ther. 277:385–393; 1996.
7. Carelli, R. M.; Deadwyler, S. A.: Dual factors controlling the activity of nucleus accumbens cell firing during cocaine self-administration. Synapse. 24:308–311, 1996.
8. Carelli, R. M.; King, V. C.; Hampson, R. E.; Deadwyler, S. A.: Firing patterns of nucleus accumbens neurons during cocaine self-administration in rats. Brain Res. 626:14–22; 1993.
9. Chang, J. Y.; Sawyer, S. F.; Lee, R. S.; Woodward, D. J.: Electrophysiological and pharmacological evidence for the role of the nucleus accumbens in cocaine self-administration in freely moving rats. J. Neurosci. 14:1224–1244; 1994.
10. Childress, A. R.; Mozley, D. P.; Fitzgerald, J.; Reivich, M.; Jaggi, J.; O'Brien, C. P.: Regional blood flow during cue-induced cocaine craving. College on Problems of Drug Dependence, Fifty-Seventh Annual Scientific Meeting; 1995:27.
11. Ehrman, R. N.; Robbins, S. J.; Childress, A. R.; O'Brien, C. P.: Conditioned responses to cocaine-related stimuli in cocaine abuse patients. Psychopharmacology 107:523–529; 1992.
12. Ettenberg, A.; Pettit, H. O.; Bloom, F. E.; Koob, G. F.: Heroin and cocaine intravenous self-administration in rats: Mediation by separate neural systems. Psychopharmacology 78:204–209; 1982.
13. Everitt, B. J.; Robbins, T. W.: Amygdala–ventral striatal interactions in reward-related processes. In: The amygdala: Neurobiological aspects of emotion, memory and mental dysfunction. New York: Wiley-Liss, Inc.; 1992:401–429.
14. Fontana, D. J.; Post, R. M.; Pert, A.: Conditioned increases in mesolimbic dopamine overflow by stimuli associated with cocaine. Brain Res. 629:31–39; 1993.
15. Gratton, A.; Wise, R. A.: Drug- and behavior-associated changes in dopamine-related electrochemical signals during intravenous cocaine self-administration in rats. J. Neurosci. 14:4130–4146; 1994.
16. Groenewegen, H. J.; Berendse, H. W.; Meredith, G. E.; Haber, S. N.; Voorn, P.; Walters, J. G.; Lohman, A. H. M.: Functional anatomy of the ventral, limbic system-innervated striatum. In: Willner, P.; Scheel-Kruger, J., eds. The mesolimbic dopamine system: From motivation to action. New York: John Wiley & Sons; 1991:19–59.
17. Groenewegen, H. J.; Vermeulen-Van Der Zee, E.; Te Kortschot, A.; Witter, M. P.: Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of *Phaseolus vulgaris* leucoagglutinin. Neuroscience 23:103–120; 1987.
18. Heimer, L.; Zahm, D. S.; Churchill, L.; Kalivas, P. W.; Wohltmann, C.: Specificity in the projection patterns of accumbal core and shell in the rat. Neuroscience 41:89–125; 1991.
19. Henry, D. J.; White, F. J.: The persistence of behavioral sensitization to cocaine parallels enhanced inhibition of nucleus accumbens neurons. J. Neurosci. 15:6287–6299; 1995.
20. Hernandez, L.; Hoebel, B. G.: Feeding and hypothalamic stimulation increase dopamine turnover in the accumbens. Physiol. Behav. 44:599–606; 1988.
21. Kiyatkin, E. A.; Gratton, A.: Electrochemical monitoring of extracellular dopamine in nucleus accumbens of rats lever-pressing for food. Brain Res. 652:225–234; 1994.
22. Kiyatkin, E. A.; Rebec, G. V.: Dopaminergic modulation of glutamate-induced excitations of neurons in the neostriatum and nucleus accumbens of awake, unrestrained rats. J. Neurophysiol. 75:142–153; 1996.
23. Kiyatkin, E. A.; Stein, E. A.: Fluctuations in nucleus accumbens

dopamine during cocaine self-administration behavior: An in vivo electrochemical study.Neuroscience 64:599–617; 1995.
24. Koob, G. F.: Drugs of abuse: Anatomy, pharmacology and function of reward pathways. Trends Neurosci. 13:177–184; 1992.
25. Koob, G. F.; Goeders, N. E.: Neuroanatomical substrates of drug self-administration. In: Liebman, J. M.; Cooper, S. J., eds. Neuropharmacological basis of reward. New York: Oxford University Press; 1988:214–263.
26. Lavoie, A. M.; Mizumori, S. J. Y.: Spatial, movement- and reward-sensitive discharge by medial ventral striatum neurons of rats. Brain Res. 638:157–168; 1994.
27. McCullough, L. D.; Salamone, J. D.: Involvement of nucleus accumbens dopamine in the motor activity induced by periodic food presentation: A microdialysis and behavioral study. Brain Res. 592:29–36; 1992.
28. McGeorge, A. J.; Faull, R. L. M.: The organization of the projection from the cerebral cortex to the striatum in the rat. Neuroscience 29:503–537; 1989.
29. Mogenson, G. J.: Limbic–motor integration. Prog. Psychobiol. Physiol. Psychiatry 12:117–169; 1987.
30. O'Brien, C. P.; Childress, A. R.; McLellan, A. T.; Ehrman, R.: Classical conditioning in drug-dependent humans. Ann. N.Y. Acad. Sci. 654:400–415; 1992.
31. O'Donnell, P.; Grace, A. A.: Synaptic interactions among excitatory afferents to nucleus accumbens neurons: Hippocampal gating of prefrontal cortical input. J. Neurosci. 15:3622–3639; 1995.
32. Pennartz, C. M.; Groenewegen, H. J.; Lopes Da Silva, F. H.: The nucleus accumbens as a complex of functionally distinct neuronal ensembles: An integration of behavioural, electrophysiological and anatomical data. Prog. Neurobiol. 42:719–761; 1994.
33. Peoples, L. L.; West, M. O.: Phasic firing of single neurons in the rat nucleus accumbens correlated with the timing of intravenous cocaine self-administration. J. Neurosci. 16:3459–3473; 1996.
34. Pettit, H. O.; Justice, J. B., Jr.: Dopamine in the nucleus accumbens during cocaine self-administration as studied by in vivo microdialysis. Pharmacol. Biochem. Behav. 34:899–904; 1989.
35. Pettit, H. O.; Justice, J. B., Jr.: Effect of dose of cocaine self-administration behavior and dopamine levels in the nucleus accumbens. Brain Res. 539:94–102; 1991.
36. Qiao, J. T.; Dougherty, P. M.; Wiggins, R. C.; Dafny, N.: Effects of microiontophoretic application of cocaine, alone and with receptor antagonists, upon the neurons of the medial prefrontal cortex, nucleus accumbens and caudate nucleus of rats. Neuropharmacology 4:379–385; 1990.
37. Robbins, T. W.; Cador, M.; Taylor, J. R.; Everitt, B. J.: Limbic–striatal interactions in reward-related processes. Neurosci. Biobehav. Rev. 13:155–162; 1989.
38. Roberts, D. C. S.; Koob, G. F.: Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats. Pharmacol. Biochem. Behav. 17:901–904; 1982.
39. Salamone, J. D.: The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. Behav. Brain Res. 61:117–133; 1994.
40. Schultz, W.; Apicella, P.; Scarnati, E.; Ljungberg, T.: Neuronal activity in monkey ventral striatum related to the expectation of reward. J. Neurosci. 12:4595–4610; 1992.
41. Schultz, W.; Romo, R.: Role of the primate basal ganglia and frontal cortex in the internal generation of movements. I. Preparatory activity in the anterior striatum. Brain Res. 91:363–384; 1992.
42. Stewart, J.: Neurobiology of conditioning to drugs of abuse. Ann. N.Y. Acad. Sci. 654:335–346; 1992.
43. White, F. J.: Electrophysiological basis of the reinforcing effects of cocaine. Behav. Pharmacol. 1:303–315; 1990.
44. White, F. J.: Electrophysiological effects of cocaine in the rat nucleus accumbens: Microiontophoretic studies. J. Pharmacol. Exp. Ther. 266:1075–1084; 1993.
45. White, F. J.; Wachtel, S. R.; Johansen, P. A.; Einhorn, L. C.: Electrophysiological studies of the rat mesoaccumbens dopamine system: Focus on dopamine receptor subtypes, interactions, and the effects of cocaine. In: Chiodo, L. A.; Freeman, A. S., eds. Neurophysiology of dopaminergic systems—Current status and clinical perspectives. New York: Lakeshore; 1987:317–365.
46. Wise, R. A.: Neural mechanisms of the reinforcing actions of cocaine. NIDA Res. Monogr. 50:15–33; 1984.
47. Wise, R. A.: In vivo estimates of extracellular dopamine and dopamine metabolite levels during intravenous cocaine or heroin self-administration. The Neurosciences 5:337–342; 1993.
48. Wise, R. A.; Newton, P.; Leeb, K.; Burnette, B.; Pocock, D.; Justice, J., Jr.: Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. Psychopharmacology 120:10–20; 1995.
49. Woodward, D. J.; Moises, H. C.; Waterhouse, B. D.; Hoffer, B. J.; Freedman, R.: Modulatory actions of norepinephrine in the central nervous system. FASEB J. 38:2109–2116; 1979.
50. Wright, C. I.; Beijer, A. V. M.; Groenewegen, H. J.: Basal amygdaloid complex afferents to the rat nucleus accumbens are compartmentally organized. J. Neurosci. 16:1877–1893; 1996.
51. Yim, C. Y.; Mogenson, G. J.: Response of nucleus accumbens neurons to amygdala stimulation and modification by dopamine. Brain Res. 239:401–415; 1982.
52. Yim, C. Y.; Mogenson, G. J.: Neuromodulatory action of dopamine in the nucleus accumbens: An in vivo intracellular study. Neuroscience 26:403–415; 1988.
53. Young, A. M. J.; Joseph, M. H.; Gray, J. A.: Increased dopamine release in vivo in nucleus accumbens and caudate nucleus of the rat during drinking: A microdialysis study. Neuroscience 48:871–876; 1992.
54. Zahm, D. S.; Brog, J. S.: Commentary: On the significance of subterritories in the accumbens part of the rat ventral striatum. Neuroscience 50:751–767; 1992.
55. Zahm, D. S.; Heimer, L.: Specificity in the efferent projections of the nucleus accumbens in the rat: Comparison of the rostral pole projection patterns with those in the core and shell. J. Comp. Neurol. 327:220–232; 1993.