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Review

Reward, memory and substance abuse: functional neuronal circuits in the nucleus accumbens

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Abstract

The firing patterns of neurons in the nucleus accumbens (NA) are examined and discussed with respect to different types of rewards and reward conditions. Comparisons and contrasts between individually identified NA neuron responses to cocaine self-administration and water reinforcement are presented with an emphasis on the fact that the same neurons do not respond in a phasic manner to both types of rewards. However, the phasic firing patterns, even though segregated for each reinforcer, are quite similar, suggesting that the method of differentiation between rewarding stimuli in the NA is by sorting cell populations into distinct ensembles or networks for each type of reinforcer. These neural networks appear to be ‘tuned’ to respond to particular associative behavioral contexts that couple response execution to reward delivery, and in the process acquire a reciprocity to firing within reward contexts. This maintains the specificity of each reinforcer for the response and associated stimuli that produce it and, makes it possible to attach different NA networks to different reinforcing circumstances. Comparisons of cocaine and water reinforced NA cell firing patterns during rapid switching between these two reinforcers suggests that the networks are negatively coupled and mutually inhibit each other to maintain accurate encoding of immediately experienced, as well as expected (i.e. future) reward contingencies.

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Keywords: Nucleus accumbens; Cell recording; Reward, memory and substance abuse

Contents

1. Introduction	703
2. Methods	704
3. Results and discussion	704
3.1. Do drugs of abuse activate a reward system in the nucleus accumbens?	704
3.2. How are rewards partitioned in the nucleus accumbens?	706
3.3. Role of other brain areas in nucleus accumbens reward circuits	707
References	710

1. Introduction

Drugs are abused because they have high reward and incentive value and under most circumstances are selected over more natural types of reinforcers. There are several current views as to why substances which are abused acquire this ability to control behavior and become preferred over other reinforcing agents [21,28,29,44]. Many of these suppose that changes take place in ‘neuronal reward pathways’ that have either dopaminergic and/or glutamatergic synaptic processes. Current evidence

supports the notion that synapses or other cellular processes are altered by the direct action of these abused agents on pharmacological substrates such as receptors, transporters, and other gene/protein pathways [13,50]. What has not been explored extensively is the dynamics of neuronal firing that determines why drugs are selected over other types of rewards. In this brief review we will examine and compare the underlying functional dynamics of circuitry involved in supporting drug seeking vs other types of reinforced behavior. The purpose is to identify systems that have similar functional characteristics and to understand in more detail how such systems partition different reinforcers, i.e. drugs vs appetitive, into different functional circuits in the nucleus accumbens (NA).

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2. Methods

Animals were treated in accordance with the regulations established by the Guide for the Care and Use of Laboratory Animals (NIH). Male Sprague–Dawley rats (Harlan, Indianapolis, IN) weighing between 300 and 350 g were used as subjects. Rats were single-housed in cages within temperature-regulated rooms (22–23 EC) with artificial lighting provided on a 0700–1900 h cycle with experiments performed during the light phase. Body weights were maintained at 85–90% of ad libitum via regulation of water intake. Rats were implanted with jugular catheters [34] under xylazine hydrochloride (Rompun[®]; 10 mg kg⁻¹, i.m.) and ketamine hydrochloride (Ketaset[®]; 100 mg kg⁻¹, i.m.). The catheters were routed subcutaneously to the back and attached to a syringe-coupling assembly, and a swivel system that allowed intravenous infusions of cocaine from a syringe pump. Animals were allowed to recover from surgery for 1 week and then trained to self-administer cocaine (0.2 ml; 0.16–0.33 mg inf⁻¹) dissolved in heparinized saline (5 U ml⁻¹). Experiments were conducted in Plexiglas chambers housed in sound-proof metal cubicles containing two symmetrically placed retractable levers (14 cm, center-to-center) and cue lights mounted on the wall approximately 6.5 cm above the levers on either side of a water trough. Animals were initially trained to depress one of the two levers underneath the cue light. Drugs were delivered over a time period of 6.3 s followed by a 15 s time-out period, when the lever was inactive. Rats were trained to respond for water on the lever opposite the drug lever. House lights were turned on during water delivery and the cue light over the water lever flashed. Sessions consisted of alternating the availability of the levers as a function of a prescribed number of cocaine or water rewards, which alternated between cocaine and water reinforcement 2–3 times per session. The number of water and cocaine rewards per session varied between 8–60 and 3–30, respectively.

Trained animals were anesthetized with xylazine hydrochloride (Rompun[®]; 10 mg kg⁻¹, i.m.) and ketamine hydrochloride (Ketaset[®]; 100 mg kg⁻¹, i.m.). Prefabricated arrays of eight Teflon-coated stainless steel microwires (40 μm) separated by 0.5 mm and containing a silver ground wire (NB Labs, Denison, TX) were lowered into the NA using predetermined stereotaxic coordinates (AP: +1.6 mm from bregma; ML 1.5 mm and DV: 6.5–7.5 mm from skull surface) [37]. The electrodes were attached to a connector (Microtech, PA) that was embedded in dental cement and affixed to the skull with screws.

Animals were allowed to recover from surgery for 1 week before resumption of testing on the multiple (cocaine/water) schedule with initiation of recording. Animals were attached to a flexible recording cable which allowed them to move freely during the session. A Multi-Neuron Acquisition Processor (MAP, Plexon Inc, TX) provided on line computer-controlled digital processing of neural signals. Extracellular action potentials

were isolated (1–4 neurons per electrode) and counted separately as a function of waveform, monitored from session-to-session. Data analysis consisted of assessment of single session strip charts and single or multi-session perievent histograms (PEHs) constructed from a temporal interval which bracketed the lever press. Individual session PEHs were averaged and analyzed with conventional ANOVA and Newman–Keuls post hoc tests to determine statistical differences in firing rates compared to baseline activity in the absence of lever pressing behavior. The above assessment of cell types only included data from rats trained to press for cocaine and water on either lever. All electrodes were determined to be in the NA in either the shell, core or rostral pole [37].

3. Results and discussion

3.1. Do drugs of abuse activate a reward system in the nucleus accumbens?

What is it that drugs share in common, at the neural activity level, with other natural reinforcers? This question seems simple from an operational viewpoint since it can be easily demonstrated that animals will seek drugs and self-administer them much like natural rewards [3,22,23]. However, drug taking is not, in many respects, like eating, drinking, etc. and there are many ways in which drugs and natural rewards differ in their actions at the pharmacological and behavioral levels [19,24]. Much of the research that has been done in this regard has focused on examining the effects of various manipulations of the mesolimbic structures on drug vs food-reinforced behavior [1,22,23]. However, at the level of the neuronal firing presumably mediating these behaviors ‘on line’, it is important to know how much these processes differ. In other words, within structures like the NA that are shown to be critical for maintaining and even the reinstatement of drug-seeking behavior [18], are there similarities in the manner in which behaviors associated with the acquisition of food and drugs initiate neuronal firing? The answer, not surprisingly, is yes, and in fact there are remarkable similarities between the two conditions. Although this observation provides some degree of satisfaction, it also reveals a paradox that needs to be resolved not only at the systems level but also with respect to individual neurons and synapses [50].

If one records from neurons in the NA during either appetitive (water) or drug-reinforced responding, it is clear that there are similar types of neurons that fire in with the same patterns irrespective of which reinforcer is in effect. Fig. 1 illustrates what has been shown in earlier reports [7,8] comparing water and cocaine reinforcement. Both reinforcers evoke phasic firing patterns (but on different time scales) and have segregated neuron populations with respect to encoding the various

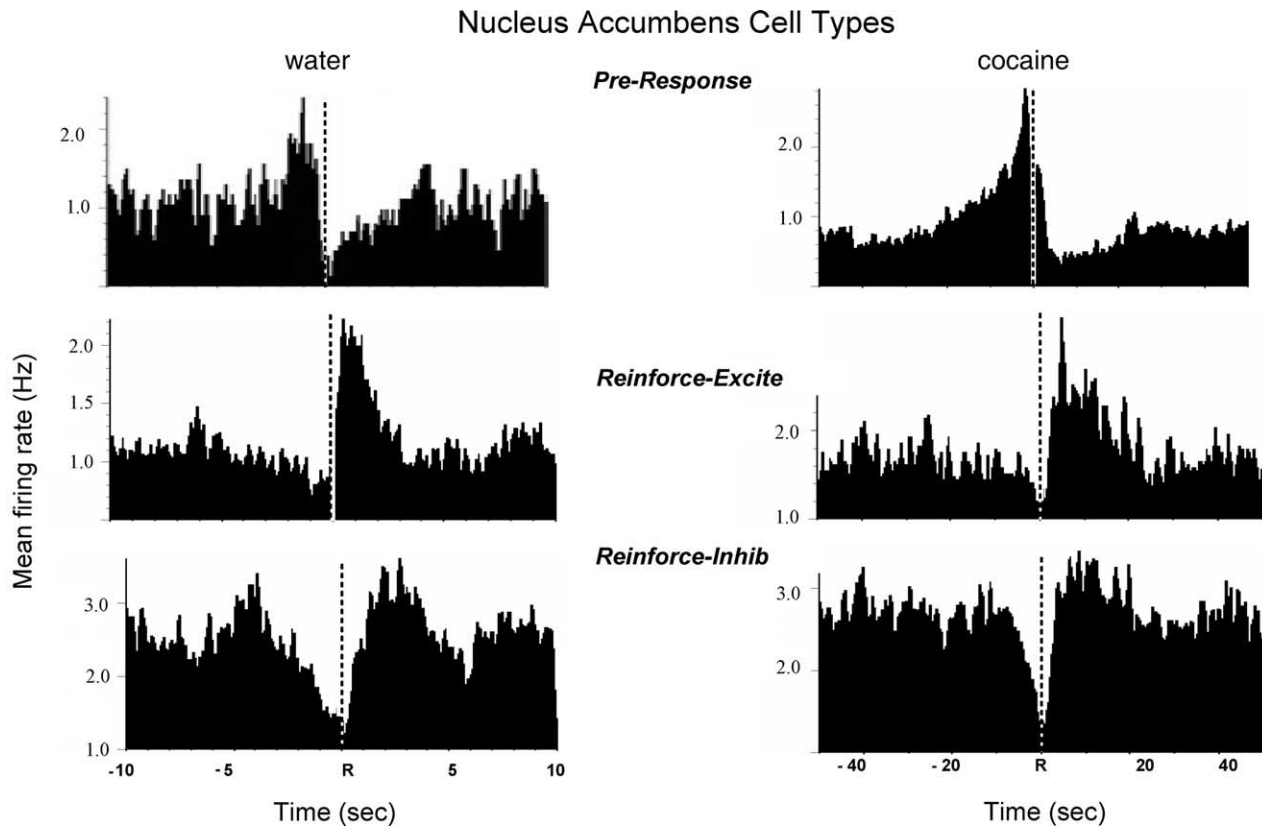


Fig. 1. Three different types of nucleus accumbens (NA) discharge patterns recorded during water or cocaine (self-administration) reinforcement series in the same sessions. Left: averaged and normalized perievent histograms (PEHs) of three different NA cell firing patterns to water reinforcement obtained on a FR1 lever press schedule. Right: three different NA cells with the same type of cell firing patterns (PEHs) to cocaine delivery. Note difference in time base showing different time courses but similar firing tendencies of the three different cell types under each reward condition. *Pre-Response* cells show significant increased firing before the lever press and reduction following reward delivery at 'R'. *Reinforce-Excite* cell type increases firing following response at reward delivery. *Reinforce-Inhib* cells are inhibited during response 'R' and reward delivery. Bin width 250 ms. Firing rate normalized by number of trials.

topographies of the reinforced behavioral response. The firing patterns of NA neurons indicate that the nature of the reward per se, as operationally defined (i.e. delivered following a contingent response), is not the principal variable that activates NA cells. Rather NA cell firing patterns appear to be regulated by both the acquisition and delivery or consumption of the reinforcer [8,14]. This suggests that the neuronal firing that occurs in the NA is 'tuned' to approaching and registering the rewarding circumstance irrespective of the particular substance that is delivered contingent on a prescribed behavioral event [11].

In many respects the behavioral state signified by such firing is more appropriately defined by the concept of 'drive' rather than reinforcement in the psychological sense, since firing is initiated in these neurons long before there are indications of overt movements toward the lever [10,38]. Firing rate 'ramps up' linearly in *Pre-Response* cells until response execution and then abruptly subsides as a separate population *Reinforce-Excite* cells become activated [10,38]. Such temporal encoding is quite precise amongst these two NA populations [11,40].

There is even a strong suggestion of a functionally specific inhibitory interneuron (*Reinforce-Inhib* cells in Fig. 1) that may control the transition in firing between the other two types of NA neurons [8,10]. Thus NA cells encode: (1) a process that is initiated and maintained until reward seeking is complete (*Pre-Response* cells) and (2) a mirror image process that signifies that the behavioral response was successful and reward was obtained (*Reinforce-Excite* cells, Fig. 1). The inverse temporal relationships and behavioral specificity of the firing in these two neuronal populations suggests the processes are coupled and mutually interact to 'bridge' the interval from initiation of reward seeking to its completion by signaling behaviorally contingent reward delivery (Fig. 2). When motivation is high it is likely that such NA circuits are active and that these firing patterns are distinct with sharp cutoffs between *Pre-Response* and *Reinforce-Excite* cells (Fig. 1). From this perspective drugs (cocaine) are rewarding because they activate NA neurons in the same manner as natural reinforcers by setting up similar temporal firing patterns related to the behaviors required to obtain them.

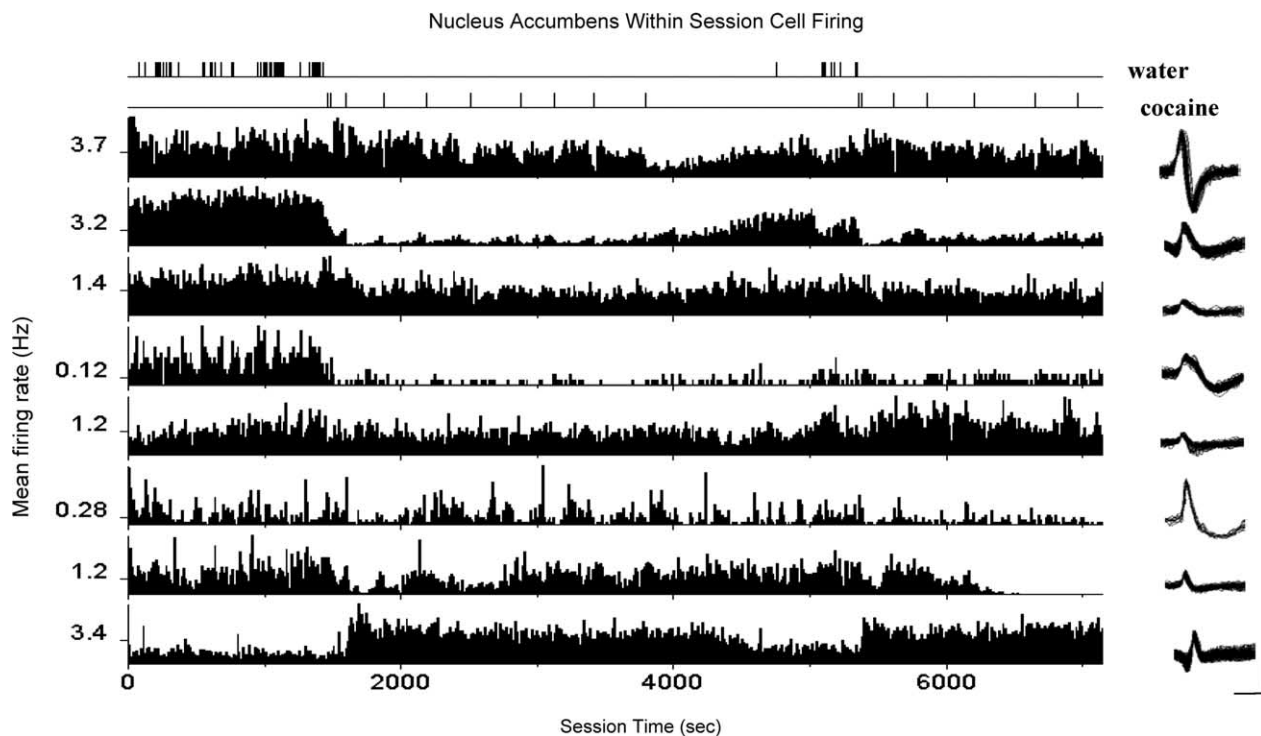


Fig. 2. Within-session fluctuations in firing tendencies of eight different simultaneously recorded NA neurons from a single animal. Top two traces indicate delivery of water and cocaine (second trace) on two separate levers. Each line is a separate continuous strip chart firing record of a single NA cell throughout a single session. Note differences in discharge tendencies across the session correlated with either water or cocaine reward delivery (upper two traces). Waveforms of each NA cell are depicted at the right of each strip chart recording. Mean firing rates are indicated by variable height bars and y-scale of each strip chart at left. Waveform calibration 100 μ V, 1 ms.

3.2. How are rewards partitioned in the nucleus accumbens?

However, as reported by Carelli and co-workers [11,12], and as shown below, the synchronized temporal firing patterns of NA neurons are occurring in completely different cell populations. Substantial numbers of cells can be shown to fire in nearly a reciprocal manner with different functional cell types switching on and off as the type of reinforcer changes within the session (Fig. 2). Fig. 3 shows two examples of reciprocally activated water and cocaine neurons recorded simultaneously in the same animals. In both cases it is clear that cocaine-related neurons show decreased firing when cells associated with water reward begin to fire and that the reverse is the case for cocaine responding. That such encoding is truly distinct is shown in Fig. 4 where 23 different cells categorized as *Pre-Response* cells across different animals and sessions showed nearly the same firing correlate during cocaine self-administration. However, those same cells showed no correlation or consistent phasic firing related to responding for the water reward during the same session (right column of Fig. 4).

The fact that the two distinct NA cell populations have the same functional correlates (Fig. 1) is not a problem since the cells fire synchronously to different events (i.e. delivery of cocaine vs water). Thus, the two populations have

essentially non-overlapping temporal firing domains and are unlikely to ‘miscode’ events related to the procurement of the appropriate reinforcer as determined by the associated stimulus context and specific behavioral outcomes [1,43,48]. This ‘segregation’ of populations of NA neurons for different reinforcers suggests that the two circuits are never simultaneously engaged. Fig. 4 illustrates the paradox alluded to earlier. Since the same population of cells that respond to one reinforcer (cocaine) do not fire in the same synchronous manner when other reinforcers are in effect (see Fig. 2), what controls the activation and suppression of these apparently independent neuron populations? In fact, no cells were recorded that responded with either: (1) the same temporal firing characteristic to both reinforcers (Figs. 1 and 3), or (2) phasic firing to more than one reinforcing event. Rather, it appears that different reinforcers ‘sculpt out’ different connections within a pool of common NA neurons, such that individual circuits with the same firing characteristics will be independently activated under a restricted set of conditions dependent upon both the type and magnitude of reward [1,17,22,42].

Hence, there may not be a common reward circuit in the NA [23,31], instead different neuronal networks in the NA may control the anticipation and registration of different reinforcers as they are behaviorally established. It therefore appears that drugs like cocaine that are self-administered,

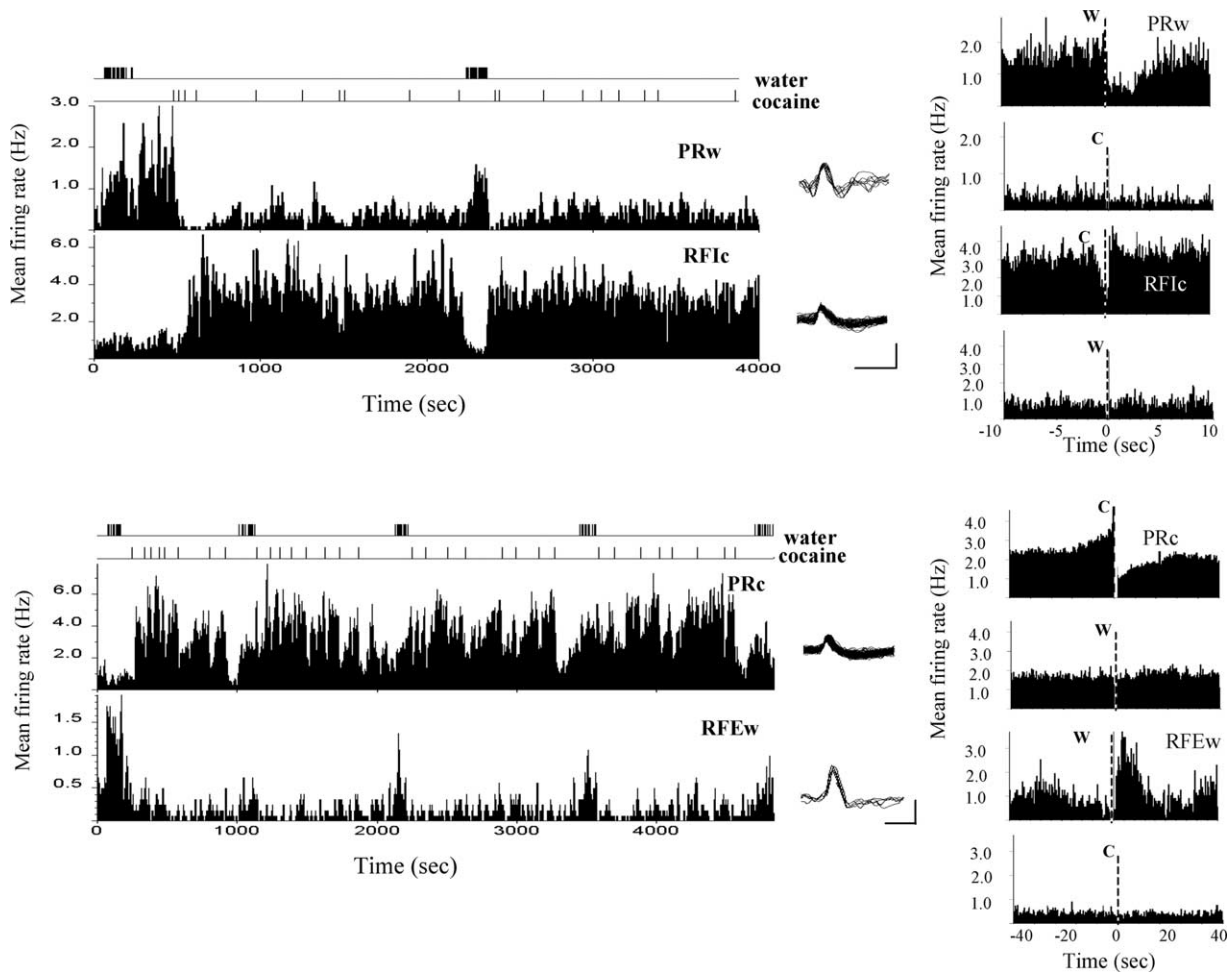


Fig. 3. Within-session changes in different NA cell types. Upper: strip chart record of *Water Pre-Response* cell and *Cocaine Reinf-Inhib* cell recorded simultaneously within the same session. Individual event PEHs are shown at right for each lever press. Bottom: similar illustration for simultaneously recorded *Cocaine Pre-Response* cell and *Water Reinf-Excit* cell. Upper two traces in each strip chart show occurrences of lever presses for water and cocaine. Waveforms are shown at right of strip chart record. Calibration 1 ms and 100 μ V.

are no different than other reinforcers in that they can usurp independent populations of NA cells specifically engaged during the associative process [21,24,49,51].

3.3. Role of other brain areas in nucleus accumbens reward circuits

In the above scheme it is clear that the NA contains a well defined rubric for representing different types of reward conditions. By allocating different circuits to different reinforcers, NA cell populations effectively segregate critical aspects of motivational specificity, thereby decreasing the likelihood of the wrong behavior occurring during inappropriate reward conditions. However, in 'real-time' these circuits must be switched on and off in accordance with what can be relatively rapid changes in behavioral circumstances and consequences. What are the factors that control activation of the water or cocaine NA cell populations? It is likely that other brain regions interrelated with the NA, i.e. ventral tegmental area and prefrontal cortex, play a major role in this process [3,9,26,27,46].

Clearly major influences are the dopaminergic projections from ventral tegmental dopamine cells [35,36,25]. The firing properties of dopamine neurons have been well characterized in non-human primates with respect to when and how they are activated under different reward conditions [2,4,45,47]. In the rat similar analyses have been made of these cells with regard to their susceptibility to change following acute and chronic exposure to cocaine [5,32,50]. Because of the distinctly different NA populations that emerge during cocaine self-administration, it is likely that NA circuit formation may be provoked initially by increased levels of dopamine, but sustained later by the consequence of long-term changes in local NA synaptic connections [16,53].

NA firing can be utilized as a measure of the degree to which dopaminergic inputs control NA circuit operations under conditions of drug seeking. Nicola and Deadwyler [34], using a progressive ratio schedule, demonstrated that NA cell firing was closely tied to the time of the last cocaine reinforcer. As the time interval (due to progressively increased schedule demand) was systematically increased

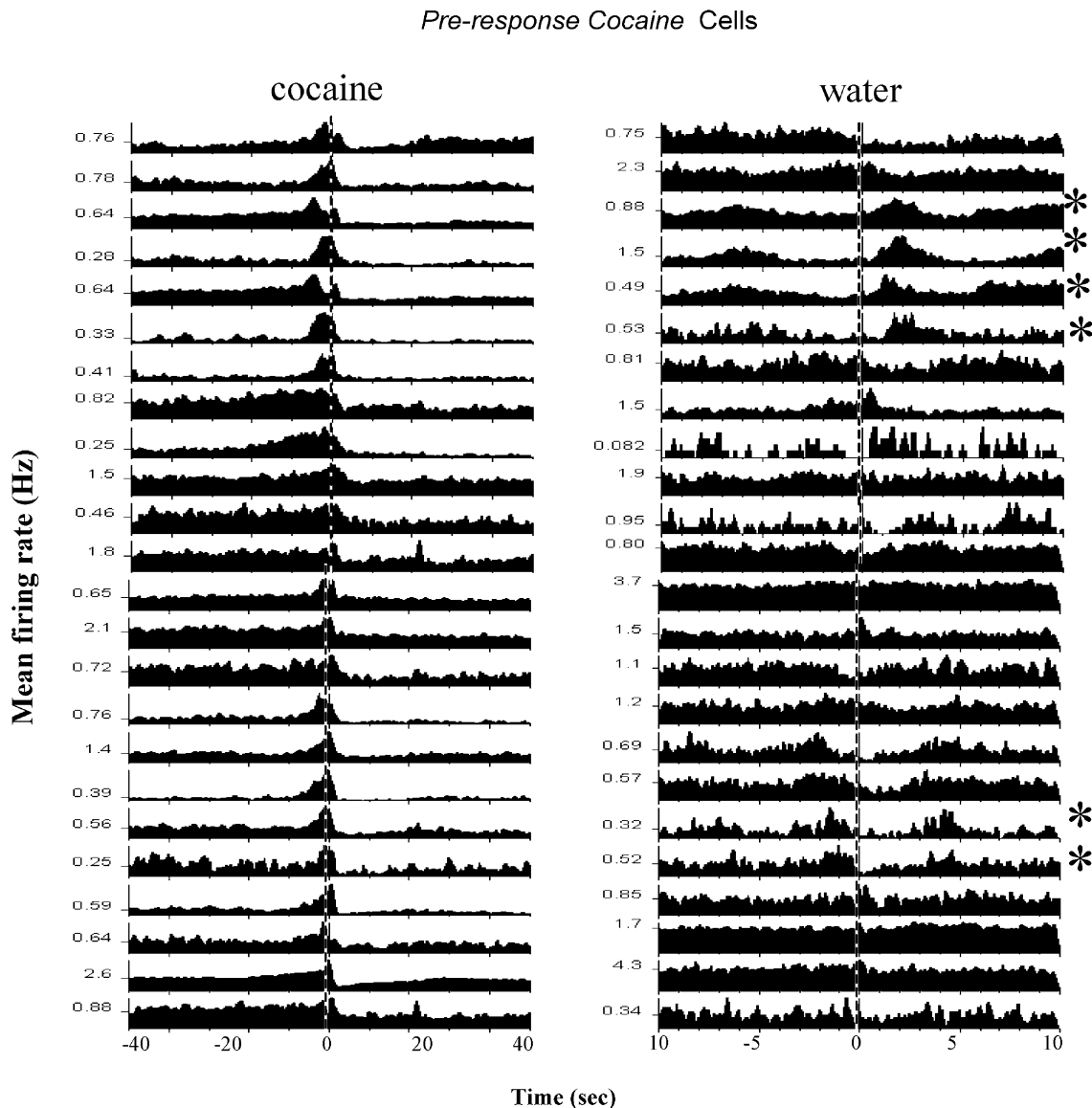


Fig. 4. Comparison of cocaine- and water-reinforced lever presses for 23 different cells meeting classification as *Cocaine Pre-Response* cells. Left: PEHs for cocaine lever responding. Right: PEHs of same neurons for water lever responding within the same sessions. Note similar phasic firing patterns across all 23 cells when cocaine is self-administered and lack of similar phasic firing when water was the reinforcer for the same neurons. NA neurons were recorded across eight different animals under the same within-session alternating reward conditions (see Figs. 2 and 3).

between cocaine reinforcements, background firing rates of NA neurons increased until behavioral responding ceased (breakpoint). NA cell firing rates at breakpoint were associated with pre-session (i.e. prior to cocaine infusion) levels, which in some cases was an order of magnitude higher than phasic within-session firing. Another finding that implicates dopamine as a permissive in the formation and expression of reinforcer-specific NA circuits is the fact that the emergence of the phasic firing patterns themselves (Figs. 1–4) is dependent on the level of dopamine achieved by the pattern of cocaine delivery during the session [9,10]. Finally, Phillips et al. [41] using voltammetric measures of dopamine efflux, demonstrated that in animals self-administering cocaine, small sub-second increments in dopamine were discernible in the NA. These investigators showed that

if cues were presented that had previously been paired with drug, the cues themselves were capable of rapidly releasing small amounts of dopamine. If dopamine release is regulated by situational events it, together with convergent activation via frontal cortical projections, may provide the basis for how cue–reward associations are established in the NA [15,20].

The above findings provide a rational underpinning for the firing patterns of NA neurons to different reward circumstances. We have suggested previously that such patterns reflect the differential actions of cocaine vs food deprivation on the propensity of NA neurons to fire either in synchrony with the delivery of reward or asynchronously when that particular reward is no longer appropriate or expected (Figs. 3 and 4). These factors make it important to

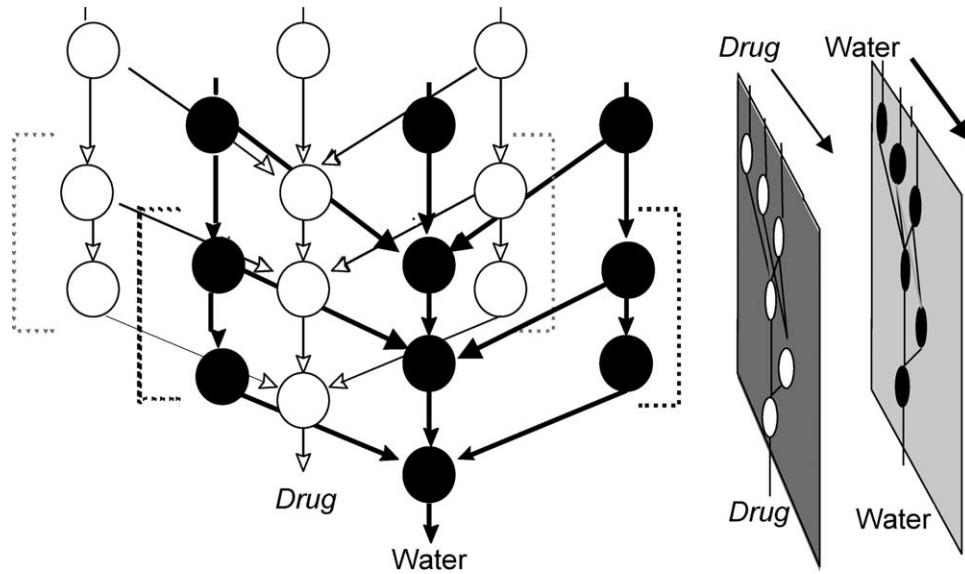


Fig. 5. Illustration of dual adjacent neural networks in nucleus accumbens for drug and water reward. The white (drug) network is presumed active when the animal self-administers cocaine, the black network is active when the animal is being reinforced with water. The dynamics of network connectivity allow individual NA neurons to have completely different firing correlates but exist adjacent to each other. The open and filled circles represent specific cell types in the network with indicated connections to other similar 'reinforcer-specific' cell types, symbolized by thin and thick arrows, respectively. The two networks operate independently as indicated by the side-by-side drug and water network panels at the right. The networks are considered to be mutually inhibitory in the sense that the output cells that control firing to cocaine are suppressed or not activated when the animal is responding for water.

understand the basis for the coherence in firing of NA cell populations and suggest that reward delivery is not the only factor controlling NA cell firing [6,30,33,48]. They also indicate that the local circuits formed within the NA have powerful convergent inputs from other brain regions [35].

The supposition that NA cells organize into isolated local circuits to encode different reinforcing events suggests that most of the presumed NA medium spiny neurons are interconnected functionally either through dis-inhibition or directly via oscillatory processes [25,38,40] with neurons that encode other reinforcers. Whether such reciprocity is controlled by intra- or extra-NA influences is to a large extent irrelevant, as it has been determined that NA neurons as close together as 100 μM can have totally different functional characteristics. This is illustrated by the model NA neuronal network configurations in Fig. 5. The side-by-side existence of independent circuits controlling the acquisition (*Pre-Response cells*) and registration (*Reinforce-Excite cells*) of water or drug reward as well as possible reciprocal inhibitory interneurons (*Reinforce-Inhib cells*) reflect the mode of segregation used to isolate distinct reinforcing circumstances. Once established, the different NA neuronal populations would not be capable of 'pattern completion' through the same networks (Fig. 5), since such circuits would be partitioned for specific behavioral/reinforcement events (i.e. cocaine or water, but not both, Fig. 3). The spontaneous fluctuations in firing rates across large numbers of simultaneously recorded NA neurons during the session suggest that such networks have become 'trained' to recognize patterns of inputs provoked by responding for different types of rewards [39]. Since it is

very unlikely that two different behaviors associated with acquisition of different rewards would be activated at the same time, the system appears to work as a means of sorting and segregating NA firing appropriate to particular circumstances. However, in the case of drugs that 'tap' into this organizational structure, there are violations of the learning rules that normally control connectivity within the NA. This self-organizing feature is observable in the 'load-up' or priming phase of cocaine self-administration [52] and reflects the emergence of NA circuit operation that persists long after the drug sessions have been terminated [10].

The nature of underlying processes controlling substance abuse and addiction are rapidly becoming known as the arsenal of methodologies available to investigate basic neural, cellular and genetic substrates increases. We are now approaching the difficult task of understanding how this large constellation of behavioral and neurobiological evidence provides the insight into why substances are abused in the human population. It is becoming obvious that many factors can control the direction and degree to which addictions develop. However, at this point effective therapeutic strategies realize the possibility that the local circuits in the NA that control drug taking may be different from those involved in other reinforcement processes.

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