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Electrophysiological correlates of abused drugs

Relation to natural rewards

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The addictive consequences of abused substances depend upon activation of neurons in reward centers of the brain. Investigations aimed at determining the underlying basis for substance abuse have resulted in breakthroughs related to drug actions on normal neural processes; for example, the singular role of dopamine as the basis for drug addiction has been revised to include effects that, with other transmitter systems, produce changes in target neuronal firing that are different from those previously assumed, including "reward value" at the neuronal and systems levels and changes in the significance of pursued stimuli as a function of motivational state, context, effort, salience, and cognitive demand. Studies comparing these factors directly show differences between the actions of abused substances and less potent food-related rewards. Characterization of the change in reward-encoding processes for drug and natural rewards has provided insight into how abused substances gain control over behavior. This report explores how abused drugs alter neuron firing in reward-sensitive brain regions and how those alterations effect drug-seeking activity in animals and humans.

Keywords: reward encoding; dopamine mediation; reward value; cocaine versus juice rewards

Introduction

The neurobiological consequences of drugs that are abused in society have been investigated from several different perspectives,[15,77] but a major underlying factor not extensively studied in a formal manner is the nature of the drug's reward "value" for maintaining behaviors in relation to other types of motivational stimuli.[8,21,41] Reward value can represent the significance of the goal for which a subject is working and depends on several factors, including the context in which the reward is administered.[20,57,69,73,74] Reward value can be encoded by at least three different parameters: (1) magnitude,[14,19,44] (2) probability of occurrence,[23,64,65,67,76] and (3) quality, that is, incentive or saliency.[2,13,60,81] The last parameter distinguishes natural rewards from drugs that are abused, such as cocaine, which has presumably higher incentive value and therefore results in addictive behavior.[38,40,45,56,68]

Understanding the relevance of alterations in normal, reward-related brain activity during drug-seeking behavior in animals or humans represents an important objective for the control of substance abuse.[54] A prominent view supported by recent findings maintains that drug seeking engages motivation-based brain circuits including dopamine (DA) reward pathways that are activated by natural (food related) rewards.[15,33,39] It is therefore possible to gain insight into the neural changes related to drug addiction, relapse, and abstinence by monitoring activity in the reward circuits of the brain in animals actively engaged in drug-seeking behaviors.[8,9,16,31,54,77] Such investigations can provide insight into the encoding processes associated with stimuli that represent drug versus appetitive rewards if determined within the same behavioral context. Factors important to understand include (1) whether different neurons in reward-specific brain regions encode different features (i.e., events)

when drugs versus appetitive rewards are delivered, (2) whether populations of task-specific cells show similar segregated firing patterns with respect to the type of reward for a given behavior, and finally (3) whether cells in these regions show more robust firing on drug- versus nondrug-rewarded contexts even though task-specific firing correlates are the same.

Effects of abused substances on brain reward processes

How abused substances affect normal brain function has been a topic of investigation over many years.[18,25] These questions can be addressed with a high degree of precision by comparing cognitive processes that are affected in addicted subjects with similar processes in nonusers.[78] Resolution of these issues is important because addiction produces alterations in decision making, impulsivity, and context assessment in humans.[34,36,68] Therefore, it is relevant to investigate the effects of drug seeking and drug exposure on similar cognitive processes in animal models. As indicated, one facet of human drug seeking that is considered important is reward value and its influence in initiating and maintaining addictive behavior.[24,42] Recently several investigations have assessed this variable directly in rodent and primate models, which is critical for assessing what brain processes are altered by drugs of abuse.[5,9,27,46,80]

Although the behavioral effects of addiction may be the same behaviorally, it is important to determine whether all drugs that are abused and produce drug seeking, affect similar brain processes. An area of the brain directly involved, the basal ganglia, is a region where these factors converge to provide a substrate for altered performance related to the differential reward values of drug versus appetitive reinforcement.[31,39,41] The brain circuitry that most likely underlies establishment of associative connections between motivational stimuli and goal-directed behavior are excitatory glutamatergic connections between cortex and the nucleus accumbens (NAc; ventral striatum [VStr]), used by both ventral and dorsal cortico-striatal loops to select the appropriate behavioral response.[63] These circuits are modified by midbrain DA inputs to the NAc in a manner that increases the likelihood that certain goal-directed behaviors will occur in future encounters with the same context and motivational stimuli.[11,22,42,61,62]

A recent characterization proposed by Joel *et al.*[35] of this role for primary structures in the basal ganglia is cast in the format of an "Actor–Critic" (A/C) scenario for dorso–ventral striatal interactions from which accrues appropriate pairing of behavioral outcomes with sensory inputs.[71] The model assumes that reward prediction and assessment are the role of the VStr, which then "critiques" or modifies the motor output of the dorsal striatum (DStr) in a manner consistent with effective "temporal prediction" of reward arrival.[72] Although not universally acknowledged,[63] recent reports have indicated definite distinction between DStr and VStr processing,[3,44] as well as their roles in controlling substance abuse.[6] Nearly all the schemes proposed cite the VStr as the major brain area for the "registration" or determination of reward value and cite the DStr as the output of the system to motor processes. Evidence supports this claim from several perspectives, including firing rate differences during programmed movements,[26] anticipatory firing to reward onset,[2,13,54] and importantly, recent demonstrations that reward value is encoded selectively by DStr and VStr as well as in other brain regions in nonhuman primates (NHPs).[5,19,32,48,59,67]

Role of dopamine in altering efficacy of rewards

Drugs that are abused release DA in multi-innervated brain regions, including striatum, and have direct access to reward circuitry,[10,18,23,33] which can redirect motivational stimuli to drug seeking and abuse.[45,70] The suspected process underlying drug addiction is the alteration in DA function in terms of release, transporters, and receptors,[9,41,43,50,53,58] which can also result in altered glutamatergic synaptic input to striatal neurons.[40] However, the basis for DA control of *differential* firing changes in separate brain regions, as stipulated for instance in the A/C model of striatal reward encoding (previous section), has yet to be fully understood.

Recent investigations in brain slices by Hjelmstad[30] have shown fundamental differences between the presynaptic effects of DA on neurotransmission in the DStr and VStr and that the effects are more than simply reducing the probability of release of

excitatory (glutamate) and inhibitory (GABA) transmitters. The investigation pointed out that in the NAc inhibition by DA is mediated by D1 (DA) receptors, whereas in DStr (pallidum and caudate), D2 receptors are responsible for inhibition. Also, despite inhibiting glutamate release, DA can effect excitation in the NAc, because the inhibition of GABA release by DA persisted throughout trains of excitatory synaptic inputs, which was not the case for suppression of glutamate release. Hence, unexpectedly, DA produced a *net excitation* in the NAc that increased during trains of excitatory inputs.[30] Unlike the NAc, DA does not inhibit synaptic transmission in the same manner in the DStr during trains of excitatory stimuli.[51] Although frequency dependent, the inhibition by DA is due to the slowing of recovery from synaptic depression[4] rather than differential effects on GABA neurons. It was concluded, therefore, that the frequencies of input to the NAc and DStr produce different degrees of synaptic inhibition (i.e., release) in a manner that is dependent upon the *pattern* of excitation.[30] This agrees with findings from iontophoretic application of psychostimulants in behaving animals in that actions of these drugs with respect to provoking increased motor responding are not totally dependent on DA release or inhibition, but rather the modulation of glutamate and GABA action on striatal neurons.[54] Given these observations, a net result under conditions of increased release of DA is the "sculpting" of excitation-produced synaptic potentiation during events that trigger inputs to the VStr and DStr.[47] In the A/C scenario stated earlier, such pattern-specific differentiation would influence how precisely the DStr output corresponds to the predictions of temporal associations established by VStr neurons.[72] Support for such a hypothesis is also provided by investigations showing a close relationship between NAc cell firing and simultaneous DA release during intracranial self-stimulation.[12] Using voltammetry, these investigations showed that NAc shell neurons fired simultaneous with DA release in the same area but that maintained increases in firing exhibited by these cells occurred in the absence of sustained increases in DA release. In addition, as pointed out by Cheer *et al.*,[12] such firing specificity may depend upon the type of task involved as well as the nature of reinforcement or reward obtained due to either NAc shell or NAc core neurons responding to task-specific patterns of DA release.

Are normal reward brain circuits activated by exposure to abused substances?

An important issue concerning the control of substance abuse by therapeutic agents is whether normal reward processes will be altered by such treatments. It is an important concern if the brain reward circuitry conditioned by nondrug (normal) rewards is activated or "hijacked," during substance abuse. A recent review indicates that certain brain regions are vulnerable to psychostimulants in rats, NHPs, and humans; however, such vulnerability may be dose, context, or even age dependent.[37] As summarized earlier, it is well established that striatal systems are involved in most instances because of the abused drugs action on DA release and reuptake (previous two sections). However, a direct test of whether normal (appetitive) rewards and drugs activate the same reward neurons has not been extensively investigated. To make this distinction the same behavioral context is required, in which some trials are rewarded by appetitive rewards and other trials with the same behavioral requirements are rewarded by administration of an abused drug.

The rewarding efficacy of psychostimulants, such as cocaine, has been implicated as a basis of their abuse potential. However, few investigations have translated the motivation promoted by drug seeking in self-administration paradigms to other types of reward contexts in which the same psychostimulant drugs are made contingent as "rewards" for successful task performance. Delimiting the conditions under which drugs can support conditioned responding in new or relearned behavioral contexts provides a comparison of the differences in "strengths" (i.e., value) of appetitive, food-related rewards versus drugs that support self-administration in animal models of addiction. It is clear that sensitization to abused substances affects acquisition and performance of new and learned behaviors in animals and in humans[68,70]; however, if drugs are provided as rewards for successful performance, they act in a manner that can affect cognitive processes (such as associative learning) in the same way as rewards with nonaddictive properties. By directly comparing the effects on neuronal processes under these two conditions, one can gain insight into how drugs gain control over existing brain reward circuitry and the subsequent conditionally "captured" behavioral responses that lead to drug acquisition.

To investigate this relationship directly, appetitive- versus drug-rewarded VStr neuron firing rates were compared in four NHPs trained to move a cursor on a computer projection screen[28] while performing a simple GoNogo task. Selection of a *Target* image by moving the cursor on to the image (Go response) or avoiding a *Nogotarget* image by withholding the cursor from the image (Nogo response), produced either an appetitive (juice) reward or intravenous delivered drug (cocaine). On trials where drug was the designated reward, intravenous cocaine (0.03–0.09 mg/kg/injection) was infused via peristaltic pump contingent on correct performance.[17,52] Both types of trial were presented randomly during the session and the type of impending reward on a given trial was signaled to the animal by (1) the color of a "start ring image" that began each trial and (2) different color *Target* and *Nogotarget* images on juice versus drug trials.[52]

Phasic increases in VStr neuron discharges occurred on both types of signaled reward trial (juice and cocaine). However, the distribution of firing across the population of VStr cells and features of the task in which firing occurred was unexpected, and indicated an underlying scheme for reward classification by striatal neurons not previously described. Figure 1 illustrates the classification system for VStr neurons ($n = 192$) recorded in the GoNogo task in which poststimulus time histograms of mean firing rates were segregated into six distinct subcategories for juice- or drug (cocaine)-rewarded trials. Cells were initially classified in terms of each trial event: *Target*, *Nogotarget*, and *Reward Delivery* (operation of juice solenoid or initiation of infusion pump), on either juice - (left) or cocaine - (right) rewarded trials. In addition, a further subclassification of *Only* or *Both* (top and bottom row of Fig. 1, respectively) indicates whether the cell fired (1) on *only* a cocaine-*or* juice-rewarded trial (20–30% of total cells) or (2) on *both* types of trial cocaine *and* juice, irrespective of reward type (50% of total cells). Figure 1 shows that in each of the three event subcategories, cocaine trials produced a higher firing rate than juice trials, even though each type of trial was presented randomly within the session. In this regard, even cells that showed increased firing to either trial type (*Both* in Fig. 1) also showed higher firing rates on cocaine- versus juice-rewarded trials, indicating that the same VStr cells showed differential firing to the *same conditioned stimulus* as a function of the type of signaled reward. The categorized firing of VStr cells to stimuli signaling or associated with delivery of cocaine versus juice rewards was therefore independent of the type of motor output because *Target* images prompted the animal to actively move the cursor into the image anywhere on the screen while on *Nogotarget* trials to withhold responding by not moving the cursor into the image.

The results shown in Figure 1 confirm prior findings in NHPs showing differential striatal cell firing to cocaine versus appetitive rewards[8] and provide additional insight into the underlying basis for the distinction. In addition, some clues as to how drugs that are abused may access normal reward circuitry to provoke drug-seeking behavior are also revealed. The fact that a smaller proportion of VStr cells were partitioned into the classifications that fired only on one type of reward trial (20–30% of total cells) also agrees with the earlier report by Bowman *et al.*[8] This suggests that segregation was not complete because most cells were responsive to both types of signaled reward (Fig. 1, *Both*). Ironically, however, for the same VStr neurons that fired to both types of rewards, signaled cocaine rewards produced greater increased firing for all task events. The preceding demonstration points to an important assessment of cocaine actions on neuronal processing of rewards in this important brain region, namely, that cocaine appears to be processed in the same manner as other incentives used in response-contingent paradigms. From this perspective intravenous cocaine delivery, even though physically quite distinct from the oral consumption of juice in this paradigm, appeared to be processed by VStr neuronal populations in nearly the same manner (Fig. 1, blue line). The fact that abused substances like cocaine can "tap into" existing reward systems exhibited by VStr cell firing shows an apparent process by which drugs gain control over the behaviors associated with their administration.[15,29,37]

Summary: critical neural substrates for control of drug actions

The results in Figure 1 provide additional insight into the dynamics and ability of abused substances to control behavioral responding in the same manner as appetitive rewards. Findings suggest that many functional properties related to drug seeking in the brain mimic those for other types

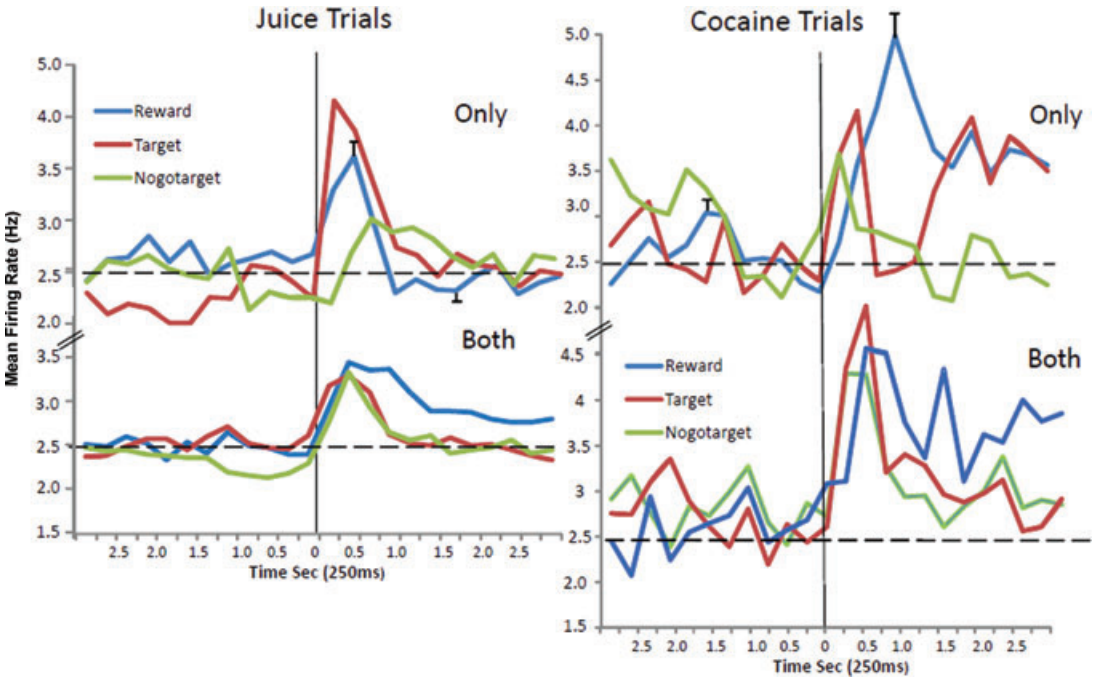

Figure 1. **Poststimulus time histograms (PSTHs) of mean firing rates of ventral striatal (VStr) neurons on cocaine- versus juice-rewarded trials in a GoNogo task. Firing is segregated on the basis of trial events ("Go" *Target* presentation, red line; *Nogotarget* presentation, green; delivery of *Reward*, blue) and selectivity for one (*Only*) or either (*Both*) type of reward. Juice trials (left): *Both* (lower): PSTHs constructed from VStr cells that fired on both juice - and cocaine - rewarded trials show mean firing rates on juice trials to each event indicated by the solid vertical line (0.0-s time): *Target* (red line, $n = 80$ cells), *Nogotarget* (green, $n = 62$), and delivery of *Reward* (blue, $n = 86$ cells). *Only* (upper): PSTHs show mean firing rates to same events from a different set of VStr cells that fired exclusively on juice-rewarded trials. *Target* (red, $n = 48$ cells) or *Nogotarget* (green, $n = 68$) presentation; delivery of *Reward* (blue, $n = 47$ cells). Cocaine trials: *Both* (lower): PSTHs of mean firing rate from the same VStr cells shown at left (juice trials) depict activation by each event on trials in which cocaine was the reward. *Only* (upper): PSTHs of mean firing rate from a different set of VStr cells that fired exclusively (*Only*) on cocaine-rewarded trials to the indicated events (solid line, 0.0-s time); *Target* (red, $n = 40$ cells), *Nogotarget* (green, $n = 29$ cells), and delivery of *Reward* (blue, $n = 43$ cells). Error bars (± standard error of the mean) on *Reward* events indicate overall range of variation across all cells and conditions. (In color in *Annals* online.)**

of reinforcement.[49,66] Mesolimbic DA pathways are involved in the reinforcing actions of cocaine as well as natural rewards that reinforce food seeking and other species-specific behaviors.[7] Repeated cocaine administration depletes DA, producing hedonic dysfunction.[38] As a further complication the VStr is less responsive to DA suppression after chronic exposure to cocaine,[1,50] whereas cells recorded from the frontal cortex show reduced activity after repeated cocaine exposure.[70] Cocaine inhibition of DA uptake promotes modification of the probability of DA release in the striatum[10,75] and provides a mechanism through which cocaine could noncontingently interact with cue-related stimuli to enhance the saliency of reward-related activity involving DA synapses.[9,13,14,56] This could account for several factors associated with cocaine addiction in humans, including persistence in drug seeking[24,66,68] as well as associated craving for cocaine that accompanies even moderate periods of abstinence.[55,79] Whatever the basis for induction and maintenance of drug seeking in humans, the evidence presented in Figure 1 points to the ability of these types of compounds to activate existing brain reward processes in such a way as to make responding for these agents "transparent" to the circuitry

that normally controls motivational components of reward-guided behavior. If effective therapeutic agents are to be developed to control the drug addiction process, one means of increasing effectiveness might be to co-administer compounds that selectively inhibit key elements in the aforementioned reward circuits during exposure to abused substances.

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Conflicts of interest

The author declares no conflicts of interest.

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