

COMMENTARY

MESOLIMBOCORTICAL AND NIGROSTRIATAL DOPAMINE RESPONSES TO SALIENT NON-REWARD EVENTS

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Abstract—While it has previously been assumed that mesolimbic dopamine neurons carry a reward signal, recent data from single-unit, microdialysis and voltammetry studies suggest that these neurons respond to a large category of salient and arousing events, including appetitive, aversive, high intensity, and novel stimuli. Elevations in dopamine release within mesolimbic, mesocortical and nigrostriatal target sites coincide with arousal, and the increase in dopamine activity within target sites modulates a number of behavioral functions. However, because dopamine neurons respond to a category of salient events that extend beyond that of reward stimuli, dopamine levels are not likely to code for the reward value of encountered events.

The paper (i) examines evidence showing that dopamine neurons respond to salient and arousing change in environmental conditions, regardless of the motivational valence of that change, and (ii) asks how this might shape our thinking about the role of dopamine systems in goal-directed behavior. © 2000 IBRO. Published by Elsevier Science Ltd.

Key words: attention, reinforcement, aversive, voltammetry, single-unit dialysis, salient arousal.

CONTENTS

1. NIGROSTRIATAL AND MESOLIMBOCORTICAL DOPAMINE NEURONS RESPOND TO SALIENT ENVIRONMENTAL CHANGE	651
1.1. Dopamine responses to appetitive events	652
1.2. Dopamine responses to novel events	652
1.3. Dopamine responses to aversive events	652
1.3.1. Single-unit versus neurochemical data.	652
1.3.2. Strong versus mild aversive events.	653
1.3.3. The onset versus offset of aversive events.	653
1.4. Dopamine responses to salient events without primary or conditioned motivational properties	653
2. DOPAMINE RELEASE WITHIN NIGROSTRIATAL, MESOLIMBIC AND MESOCORTICAL TARGET SITES	653
3. DO DOPAMINE NEURONS REPORT A “PREDICTION ERROR” OR A “REWARD PREDICTION ERROR”?	654
4. IMPLICATIONS FOR BEHAVIORAL FUNCTION	654
ACKNOWLEDGEMENTS	654
REFERENCES	654

1. NIGROSTRIATAL AND MESOLIMBOCORTICAL DOPAMINE NEURONS RESPOND TO SALIENT ENVIRONMENTAL CHANGE

According to traditional views, nigrostriatal dopamine (DA) neurons, originating in the substantia nigra (SN) and projecting to the dorsal striatum,²⁵ play a role in the expression of motor acts,^{12,34} while mesolimbic DA neurons, originating in the ventral tegmental area (VTA) and projecting largely to the nucleus accumbens and other ventral striatal regions²⁵ play a role in reinforcement or incentive motivational processes.^{13,22} From these views, it might have been expected that nigrostriatal DA neurons would fire in relation to specific motor acts, and that mesolimbic DA neurons would respond specifically to the presentation of reward stimuli. However, single-unit studies show that DA neurons within the SN do not respond to phasic bodily movements,^{68,71} nor do DA neurons within the VTA respond exclusively to reward stimuli.³⁶ It has previously been noted that

mesolimbic DA activity plays a role in behavioral responses to both appetitive and aversive stimuli, and that “reward signal transmission” fails to appropriately characterize DA’s behavioral role.^{9,43,62,65} In accordance with this view, the present paper examines evidence showing that mesolimbic, mesocortical and nigrostriatal DA neurons respond to the presentation of salient and arousing environmental stimuli, a category of events that includes but extends beyond that of rewards.

When considering the behavioral function of nigrostriatal and mesolimbocortical DA systems, it is helpful to ask: (i) under what environmental conditions are the systems activated; and (ii) what are the behavioral consequences of that activation? Sections 1–3 of this paper focus on the former question, and answer that nigrostriatal, mesolimbic, and mesocortical DA neurons are activated by salient and arousing environmental stimuli. Section 4 addresses the latter question. If DA release within nigrostriatal, mesolimbic, and mesocortical target sites increases in response to salient environmental change, how should this influence our thinking about the role of these DA systems in goal-directed behavior?

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Abbreviations: DA, dopamine; SN, substantia nigra; VTA, ventral tegmental area.

1.1. Dopamine responses to appetitive events

Nucleus accumbens DA levels are elevated during appetitive behaviors, including feeding,^{33,53,59,80} drinking,⁸² and copulation.^{18,51,56,57} Dorsal striatal DA elevations have also been observed during these appetitive behaviors,^{18,48,56,82} although the elevations are generally of a smaller magnitude than those observed within the accumbens. Single-unit responses to food and to conditioned stimuli signaling food delivery have been observed in DA neurons within the VTA and SN,^{45,54,55} sites of origin for the mesolimbic and nigrostriatal DA pathways, respectively.²⁵ These findings, in themselves, are consistent with a DA/reward view. However, the increased accumbens DA concentrations that are observed during feeding sessions are not closely tied to food consumption itself, but to locomotor or exploratory behavior associated with certain feeding schedules.⁵³ This latter finding raises the possibility that increases in DA activity that are observed during reward-related behaviors might reflect something other than reward consumption.

It is possible to present food reward in a manner which is salient and arousing, or to present it in a less-salient manner. DA neurons respond to food delivery in the former, but not the latter condition. VTA and SN DA neurons reliably respond to food when the time of delivery is unpredictable.⁵⁴ DA elevations are generally absent when the food is presented in a predictable manner.⁵⁴ The DA response to a reward stimulus appears to require that its presentation be surprising. This again suggests that DA neurons may be responding to something other than reward *per se*. Finally, when a conditioned stimulus, e.g., a light, has come to predict food delivery, DA neurons become less responsive to the food, and respond instead to presentation of the light.⁴⁵ This may reflect a shift of incentive value from the food to the light. Alternatively, this may reflect an increase in the salience of the light as it comes to predict food, and a decrease in the salience of the food, as its presentation becomes less surprising.

1.2. Dopamine responses to novel events

Another class of salient and arousing events are novel stimuli. If DA neurons respond to stimulus salience, one would predict that DA neurons should respond to novel events. Microdialysis fails to detect DA elevations following exposure to a novel environmental chamber.^{18,56} However, because novel stimuli are subject to habituation, methods that detect phasic changes in DA neuronal activity with better temporal resolution, such as single-unit electrophysiology and voltammetry, are most likely to detect DA responses to novel events.

Single-unit studies show midbrain DA responses to the novel opening of a door compartment of a behavioral apparatus prior to appetitive conditioning, when the animals react to the door opening with target-directed saccades.⁴⁵ DA neuronal responses to this event are no longer seen after the ocular reaction has habituated. Consistent with these findings, novelty-induced increases in DA release have been observed within the accumbens shell using fast-scan voltammetry.⁶⁰ Mesolimbic DA neurons, then, respond to novel events. These elevations might reflect an animal's expectation of possible reward whenever a novel circumstance is encountered; alternatively, these DA responses may reflect the salience

and arousal value of the novel event, regardless of reward expectation.

1.3. Dopamine responses to aversive events

If DA neurons respond to arousing and salient events, and not only to reward-related stimuli, they should also respond to arousing 'aversive' events and to salient sensory stimuli without primary or conditioned motivational properties. In fact, microdialysis and voltammetry studies have shown elevations in DA release in response to aversive events such as foot shock,^{70,83} a conditioned signal for foot shock,⁸³ tail shock,^{1,39} tail pinch,⁴⁶ restraint stress,^{20,37,76} and administration of anxiogenic drugs.^{7,52} Single-unit responses to aversive stimuli have been observed in VTA⁴¹ and SN¹⁶ DA neurons. However, in a recent single-unit study, DA responses to aversive or conditioned aversive stimuli were rarely observed.⁵⁵ The current debate over the nature of DA responses to aversive events involves data obtained using single-unit, dialysis, and voltammetry techniques; data which are not always in agreement. Some important differences between single-unit and neurochemical (dialysis and voltammetry) measurement techniques are discussed below.

1.3.1. Single-unit versus neurochemical data. Single-unit studies of DAergic neurons record the time of occurrence of individual action potentials, and typically generate peri-event time histograms depicting the relationship between neuronal discharge and the occurrence of a sensory or behavioral event.^{36,38,45,69} On the other hand, microdialysis and voltammetry techniques estimate concentrations of extracellular DA within target regions, such as the neostriatum, nucleus accumbens, or prefrontal cortex. Single-unit electrophysiology possesses the attribute of millisecond time resolution of neuronal events, allowing the detection of phasic neuronal responses to environmental events, responses that might not be observable under the (generally) 10-min sampling rate of microdialysis or even under the faster (seconds) resolution of voltammetry.

However, single-unit recordings cannot reveal the final amount of DA released into the extracellular space within terminal regions. The quantity of DA released is known to reflect the influence of a number of factors, including action potential occurrence,⁷⁷ presynaptic neuronal inputs¹⁵ and activity at release-modulating autoreceptors at the nerve terminal.²⁹ The precise time of DA action potential occurrence is measurable using single-unit electrophysiology, but assessment of the final amount of DA release to target regions requires dialysis or voltammetry.

One explanation for the consistently observed DA response to aversive events using dialysis and voltammetry, but not using single-unit methods, is that stress-induced elevations in DA activity result primarily from presynaptic enhancement of DA release by glutamate acting at receptor sites on the DA terminal, rather than from elevated rates of action potential discharge at DA cell bodies. It is known, for instance, that glutamate and other excitatory amino acid inputs to the striatum and nucleus accumbens are capable of enhancing presynaptic DA release.^{27,63} However, there is evidence to suggest that elevated rates of DA neuronal firing, rather than presynaptic factors, may be largely responsible for the DA response to aversive events.^{16,39,41,85} Striatal DA elevations produced by tail-pinch, for instance, are not attenuated

by infusion of glutamate receptor antagonists into DA terminal sites, but are abolished following tetrodotoxin-induced blockade of action potential propagation along DA axons.^{39,85}

An alternative explanation for the consistent observation of DA responses to aversive events using neurochemical, but not single-unit, methods is that DA responses to aversive events may be gradual rather than phasic.⁶⁹ A gradual DA response to stress might be difficult to detect using single-unit methods that typically look for changes in action potential likelihood within hundreds of milliseconds after an event has occurred. Further research is needed to characterize precise temporal relationships between the occurrence of aversive events and DA neuronal activation.

1.3.2. Strong versus mild aversive events. The question of whether aversive events produce a DA response (phasic or gradual) appears to depend upon the strength of the aversive event. It has been suggested that elevations in DA activity occur in response to strong, but not mild, aversive stimuli.^{14,65} Indeed, mesolimbic and nigrostriatal DA activity is not increased by air puffs to the arm,⁵⁵ the taste of hypertonic saline,⁵⁵ gentle handling¹⁴ or mild tail pinch.^{14,57} DA activity is, however, elevated in response to stronger aversive events such as footshock,⁷⁰ tail shock,^{1,14,39,58} tail prick,⁴¹ cold ice bath,⁴⁰ prolonged restraint,^{20,37} and anxiogenic drugs.^{7,52} Regardless of the degree to which the DA response to aversive events is gradual or phasic, impulse-dependent or due to presynaptic factors, elevations in DA neuronal firing are generally absent during the presentation of mild aversive stimuli, but are seen in response to strong aversive events that produce greater behavioral activation and/or arousal. This generalization appears to account for a very large number of findings, using a number of different aversive stimuli, and involving dialysis, electrochemical detection, and single-unit recording of DA activity.

1.3.3. The onset versus offset of aversive events. Still, in defense of the view that DA provides a reward signal to target regions, one might suggest that elevations in DA release to aversive events reflect the rewarding or negative reinforcing consequences of aversive event offset. Indeed, neurochemical techniques often lack the temporal resolution to distinguish responses to the onset versus the offset of a brief aversive event. However, even when aversive conditions are present throughout an entire microdialysis sampling period, DA elevations are observed; that is, DA elevations are seen prior to the offset of the aversive event.^{11,37,58} DA responses to aversive events are therefore not a response to aversive event offset, but instead, reflect important changes in environmental conditions, even if those changes are of an aversive nature.

1.4. Dopamine responses to salient events without primary or conditioned motivational properties

Strong evidence that DA neuronal responses are elicited by event salience, rather than incentive value, is the finding that DA neurons within the SN respond to salient auditory, visual, somatosensory and olfactory stimuli with neither primary nor conditioned reward or aversive properties.^{16,32,72,73} One might imagine that these sensory responses are restricted to SN DA neurons since this system is implicated in sensory motor processes.^{12,78} However, VTA DA neurons also respond to

non-appetitive events like loud clicks and bright flashes of light,³⁶ that is, to events whose salience derives from physical sensory characteristics such as rapid onset and high intensity, and not from conditioned reward properties. Further, these salient events cause VTA DA cells to fire in burst mode,^{28,36} an activity mode associated with disproportionately large increases in DA release at target sites.³¹ Nigrostriatal and mesolimbocortical DA neurons, then, appear to respond to sensory stimuli that are rewarding or aversive, conditioned predictors of rewarding or aversive outcomes, novel, or simply of high intensity. A large category of salient and arousing events appears capable of driving SN and VTA DA neurons.

2. DOPAMINE RELEASE WITHIN NIGROSTRIATAL, MESOLIMBIC AND MESOCORTICAL TARGET SITES

Aversive events increase DA activity both within the nucleus accumbens^{7,37,52,76,79,83} (but see Refs 6 and 8) and within the prefrontal cortex.^{1,6,37,74,75,79} Similarly, appetitive events elevate DA levels both in the accumbens^{4,5,33,49,59} and in the prefrontal cortex.^{4,14,74} On the other hand, detectable elevations in DA levels within the dorsal striatum are often absent following appetitive^{14,49} and aversive³⁷ events (but see Refs 1 and 8). One cannot rule out the possibility that specific regions within DA target sites respond differentially to events of differing motivational value, and there is some evidence in support of this possibility.^{6,8,49} However, a large research literature suggests that salient and arousing events elevate mesolimbic, mesocortical, and to a lesser degree nigrostriatal, DA activity regardless of the motivational valence of the event.

Using an identical stressor, the magnitude of the observed increase in DA utilization relative to baseline levels is greatest in the prefrontal cortex, less in the accumbens, and least in the neostriatum.¹ Why are large elevations in DA concentration most likely to be observed within the prefrontal cortex? First, there is evidence to suggest that prefrontal DA release may be most strongly elevated during early stages of conditioning, while accumbens DA release may occur predominantly during later stages of conditioning, when conditioned responding emerges.⁷⁹ Therefore, the apparent volatility in prefrontal DA levels compared to those in other target regions may reflect the fact that DA responses to appetitive and aversive events are often measured during initial exposure to the event, that is during periods when prefrontal responses are likely to be greatest. Second, high levels of prefrontal DA activity may reflect a relative lack of autoreceptor and other feedback regulatory mechanisms within the prefrontal cortex,¹⁷ mechanisms that act to prevent wide fluctuation in extracellular DA concentrations within other DA target regions.^{26,84}

Single-unit recordings of DA neurons in the SN and VTA, sites of origin for the nigrostriatal and mesolimbocortical systems, show that cells originating in these regions are similarly activated by salient environmental stimuli.^{36,45,73} It is therefore likely that DA neurons projecting to the striatum, accumbens, and prefrontal cortex all respond to salient sensory events with a burst of action potential discharge, but that the magnitude of the resulting increase in extracellular DA concentration with the prefrontal cortex, accumbens, and dorsal striatum, depends upon presynaptic influences at the nerve terminal and the efficiency of feedback regulatory

mechanisms. Efficient regulatory mechanisms within the striatum^{26,84} may prevent long-term fluctuations in extracellular DA concentrations in this region.

Because the neostriatum is associated with sensory-motor processes and the execution of complex motor acts,^{2,10} it is not unreasonable to imagine that there is a benefit to tight control of basal DA levels within this region, which would permit phasic DA elevations to occur with some temporal precision, for example, to facilitate switching of response components of a behavioral act.⁴⁴ In contrast, because DA within the nucleus accumbens and other limbic target sites is associated with incentive motivational, behavioral or mood states^{3,22,62,65} and prefrontal DA modulates working memory function,³⁰ one might imagine that, within these regions, there is less need for DA fluctuations to occur with great temporal precision. To the contrary, one would imagine that DA modulation of these functions might instead call for a build-up of extracellular DA concentrations over a sustained period of time.

3. DO DOPAMINE NEURONS REPORT A "PREDICTION ERROR" OR A "REWARD PREDICTION ERROR"?

DA neurons signal the occurrence of events that were not expected to occur, and of events that occur at unexpected times.⁶⁹ Schultz has described this DA function as the reporting of a "reward prediction error". However the present analysis assumes a more general DA function in reporting "prediction error". The notion that DA specifically signals reward prediction error is based upon the findings that DA neurons (i) respond to unexpected food presentation, (ii) fail to respond to food presented at an expected time, and (iii) show suppressed activity when food fails to be delivered at a time when its delivery was expected (see Ref. 69 for review). These findings can be accounted for by the assumption that changes in DA activity reflect the computation: reward occurrence – reward expectation.⁶⁹ Because midbrain DA neurons rarely respond to aversive events such as airpuffs to the arm or saline to the mouth, it is possible that DA cells specifically report the occurrence of unexpected rewards.⁵⁵ However, as described in Section 1.3.2 above, DA activity appears to increase in response to strong and arousing aversive stimuli; responses to mild aversive events are less frequently observed. According to the present analysis, DA neurons are activated by a large category of arousing events that (as described above) include novel stimuli, unexpected rewards, aversive stimuli, high intensity visual and auditory events. DA activity is, on the other hand suppressed by events that are associated with reduced arousal or decreased anticipatory

excitement, including the actual consumption of food reward⁶¹ and the omission of expected reward.⁶⁹

4. IMPLICATIONS FOR BEHAVIORAL FUNCTION

The function of DA activity within specific brain sites has been examined with respect to a number of behavioral processes, including associative learning and reinforcement,^{19,42,81} temporal processing,⁴⁷ and other aspects of cognition.³ While consideration of the precise functional consequences of elevated DA transmission within its various forebrain target sites is beyond the scope of the present analysis, several general inferences regarding DA function may be made. First, while DA activity plays a role in reinforcement processes,^{21,23,35,81} this role is unlikely to involve either (i) a strengthening of stimulus–response connections, or (ii) a neurochemical signal of reward value. DA release increases, within forebrain target sites, in response to a large set of salient events that extend beyond that of reinforcing stimuli; it is therefore unlikely that DA elevations serve to increase the likelihood that a preceding response will reoccur under similar stimulus conditions. Similarly, DA transmission would provide an ambiguous signal of reward value.

DA neurons are activated under conditions of salient environmental change, conditions that require an organism to (i) become responsive to environmental stimuli, (ii) prepare for the possible output of high levels of behavioral activity, (iii) maintain a working memory representation of the just-encountered event (i.e. the event that caused DA neurons to release large quantities of DA into terminal regions). DA plays a role in each of these three behavioral functions. DA levels within the neostriatum, ventral striatum/accumbens, and prefrontal cortex modulate (i) motor responses to sensory inputs,^{50,64,78} (ii) the response energizing or response-maintaining effects of motivationally-relevant stimuli,^{24,66} and (iii) working memory processes,^{30,67} respectively. While a strong case can be, and has been, made for a DA-dependent reward teaching signal,⁶⁹ the present analysis suggests an alternative view: midbrain DA neurons are driven by a large category of salient environmental events, and the consequent elevation in DA activity within its various target sites mediate the effects of arousal on a number of behavioral functions that contribute to the successful execution of goal-directed behavior. DA activity, on the other hand, is unlikely to communicate reward value.

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