Research report

# Dopamine gating of glutamatergic sensorimotor and incentive motivational input signals to the striatum

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**Abstract**

Dopamine (DA) neurons of the substantia nigra (SN) and ventral tegmental area (VTA) respond to a wide category of salient stimuli. Activation of SN and VTA DA neurons, and consequent release of nigrostriatal and mesolimbic DA, modulates the processing of concurrent glutamate inputs to dorsal and ventral striatal target regions. According to the view described here, this occurs under conditions of unexpected environmental change regardless of whether that change is rewarding or aversive. Nigrostriatal and mesolimbic DA activity gates the input of sensory, motor, and incentive motivational (e.g. reward) signals to the striatum. In light of recent single-unit and brain imaging data, it is suggested that the striatal reward signals originate in the orbitofrontal cortex and basolateral amygdala (BLA), regions that project strongly to the striatum. A DA signal of salient unexpected event occurrence, from this framework, gates the throughput of the orbitofrontal glutamate reward input to the striatum just as it gates the throughput of corticostriatal sensory and motor signals needed for normal response execution. Processing of these incoming signals is enhanced when synaptic DA levels are high, because DA enhances the synaptic efficacy of strong concurrent glutamate inputs while reducing the efficacy of weak glutamate inputs. The impairments in motor performance and incentive motivational processes that follow from nigrostriatal and mesolimbic DA loss can be understood in terms of a single mechanism: abnormal processing of sensorimotor and incentive motivation-related glutamate input signals to the striatum.
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## 1. Overview

Dopamine (DA) neurons of the substantia nigra (SN) and ventral tegmental area (VTA) respond to unexpected reward events [102]. However these cells respond to a wide category of salient stimuli [57,99]-unexpected rewards are one member of this category. While it has been suggested that reward stimuli may be unique in producing a phasic DA response and that other arousing stimuli may produce only gradual DA elevations [102], this assumption is not made here. Novel, intense, rewarding, aversive, and conditioned rewarding and aversive stimuli all produce increases in forebrain DA activity [57,99]. It is assumed here that these DA responses to salient and arousing events signal neither the pleasantness nor the unpleasantness of the event. Activation of SN and VTA DA neurons, and consequent release of nigrostriatal and mesolimbic DA to dorsal and ventral striatal target regions, modulates the processing of concurrent glutamate inputs [26,41,67,88]; as argued below, this occurs under conditions of unexpected environmental change. The question of how DA transmission within the dorsal and ventral striatum influences behavioral processes may reduce, then, to the questions of 1) the organismic and environmental conditions that lead to elevated nigrostriatal and mesolimbic DA activity, 2) the nature of the information carried by glutamate inputs to striatal neurons, and 3)

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the manner in which glutamate inputs to the striatum are modulated by DA activity.

The nucleus accumbens, ventromedial caudate-putamen and olfactory tubercle are referred to collectively as ventral striatum [49]. In this paper, the term ventral striatum is often employed in place of the term nucleus accumbens to emphasize that DA is likely to play a similar modulatory role within its various striatal target sites (but see [83]), and that the different behavioral results following from DA activity within specific regions of the dorsal and ventral striatum reflect the different types of information carried by glutamate inputs projecting to distinct striatal regions. The processing of this information is facilitated under conditions of elevated DA activity, that is, under conditions of salient/ arousing environmental change.

If DA neurons become activated during conditions of salient environmental change and not exclusively during conditions of reward obtainment, DA may still play an important role in appetitive conditioning but it is unlikely to provide a neurochemical reward code. If an animal is trained to associate a conditioned stimulus (CS) and/or a behavioral response with food reward, DA may play an important role in the formation of the CS–reward or response–reward association [10,35,58,109], but, according to the view described here, DA does not itself provide a reward signal that imbues a CS with incentive value. Instead, environmentally elicited elevations in mesolimbic and nigrostriatal DA activity gate the input of reward signals to the striatum, just as they gate the throughput of sensorimotor signals to the striatum. As suggested below, striatal reward signals are likely to originate in the orbitofrontal cortex and basolateral amygdala (BLA), regions that contain neurons sensitive to reward magnitude [84,95,106,115] and that project strongly to the striatum [37,47,63].

It is known that conditioning of a CS to a reward outcome requires that the reward be unexpected. To the degree that an animal is surprised by presentation of the unconditioned stimulus (US), conditioning to a preceding CS is enhanced [62,73]. As proposed here, the role of mesolimbic DA in appetitive conditioning is not to tell the striatal cells that a reward has occurred, but to signal to these cells that an important unexpected event has occurred. DA and corticostriatal glutamate terminals often synapse upon common dendritic spines on striatal target neurons [15]. It is proposed that the DA signal of an unexpected event and the amygdala/orbitofrontal glutamate reward signals converge upon common dendritic spines on striatal target neurons. Processing of these incoming signals is enhanced when synaptic DA levels are high, because DA enhances the synaptic efficacy of strong concurrent glutamate inputs while reducing the efficacy of weak glutamate inputs (see below). According to this view, nigrostriatal and meso-

limbic DA neurons are activated under conditions of salient environmental change, and DA gates the throughput of concurrent cortical and limbic inputs to the striatum carrying information about sensorimotor and incentive motivation-related events.

## 2. DA neurons respond to salient unexpected events

Among the attributes that may imbue an event with salience are 1) novelty, 2) primary and conditioned reward properties, 3) primary and conditioned aversive properties, and 4) physical characteristics such as high intensity and fast rise-time. VTA DA neurons, i.e. those that give rise to mesolimbocortical DA pathways, respond to each of these types of salient events [57]. Single-unit recordings have demonstrated that VTA DA neurons show phasic elevations in activity in response to novel events [72], unexpected rewards [72,79], conditioned predictors of reward [72,79], primary and conditioned aversive stimuli [46,66] but see [80], and high intensity auditory and visual events with neither conditioned reward nor aversive properties [59].

While DA neurons are activated by unexpected stimulus presentation, these neurons are not activated by the absence of an expected event; they are inhibited under this condition [102]. Schultz [103] notes that this finding makes it unlikely that heightened attentional states are directly associated with the phasic DA response, since attentional systems are likely to be recruited similarly by the presence of an unexpected event and the absence of an expected event. On the other hand, one cannot rule out the possibility that distinct neurochemical systems may promote attentional states a) when an unexpected event occurs, and b) when an expected event fails to occur. If DA serves to promote attention, its role would be restricted to the former case.

Striatal DA activity is known to modulate the processing of concurrent glutamate inputs [27,52,67]. As described below, the informational nature of these glutamate inputs differs within particular striatal regions. The psychological correlate to DA modulation of striatal glutamate inputs may depend upon the nature of the glutamate input subject to DA modulation, and may, therefore, differ according to striatal region. While there may be subjective states (attentional, affective, etc) that correlate with elevations in DA activity within particular striatal target sites, the present paper does not attempt to characterize the subjective nature of these states.

VTA and SN DA responses have a rapid onset. The cells show phasic increases in activity 50–100 ms after the onset of a salient sensory event [59,105,111]. Redgrave et al. [96] make the incisive observation that the midbrain DA neurons respond to a visual event before the animal has had the opportunity to make a visual

saccade, and therefore, before the animal has foveated the stimulus. The visual saccade has a latency of 180–200 or 80–110 ms for express saccades [82]. Whatever the nature of the information that elicits VTA DA firing to a visual event, it appears to be relatively low-level (pre-attentive) information (although the DA response may be modulated by top–down influences prior to the eliciting event). DA neurons are activated by an unexpected change in environmental stimulus conditions, but the precise nature of that environmental change is largely undetermined at the time that the midbrain DA neurons respond.

These single-unit findings are consistent with the large body of data from microdialysis and voltammetry studies that show that levels of DA release within the prefrontal cortex and nucleus accumbens are elevated under both appetitive [13,32,51] and aversive conditions [13,75,110,113]. A primary aim below is to provide a framework that accounts both for the promiscuous DA response to salient events [57,99] and for the large body of evidence showing that DA disruptions attenuate the impact of rewards (and punishers) on several aspects of behavior and learning [1,29,35,38,58,60,76,100,129]. As described below, DA may be considered a gatekeeper of glutamatergic information flow to the striatum.

## 3. DA selectively promotes the processing of strong glutamate inputs to the striatum

If DA is a gatekeeper for glutamate input to the striatum, it is a selective gatekeeper that, within dorsal and ventral striatal regions, enhances the impact of strong input signals while dampening the impact of weaker signals [26,27,67,88]. Cells in the dorsal and ventral striatum undergo transitions from a state of hyperpolarization (ca. −80 mV), far below the cell's action potential threshold, to a less polarized state (ca. −60 mV), within close range of action potential threshold [88,92,127,128]. While in the former 'down' state, the cells are unlikely to fire, even when an excitatory input signal is received. While in the less polarized 'up' state, an input signal can elicit an action potential [86,125]. Activation of the D1 receptor enhances the evoked response of medium spiny striatal output neurons to excitatory signals when the striatal neuron is in a relatively depolarized state (ca. −60 mV) at the time of the excitatory input. However, when the striatal cell is in a strongly hyperpolarized state (ca. −80 mV), D1 receptor activation attenuates the cell's response to an incoming excitatory signal [52]. These findings suggest that DA enhances the efficacy of excitatory inputs to those striatal cells that are in the up state, and to reduce the efficacy of excitatory inputs to cells that are in the down state at the time that DA binds to the D1 receptor on the striatal neuron [89]. These actions would be expected to produce a selective amplification of striatal cells receiving strong and/or convergent excitatory synaptic inputs at the time of the D1 receptor activation while discouraging the participation of other less active synapses [44,88].

An input filtering action of DA is further supported by the observation that DA, acting at the D1 receptor, facilitates glutamate actions at NMDA receptors [26,27,69,70]. D2 receptor activity attenuates glutamate actions at non-NMDA receptors [26,70]. Since the non-NMDA glutamate activity is necessary before the NMDA receptor can become activated, this selective amplification of the NMDA response should selectively boost already-strong input signals, as might be expected when the striatal cell receives converging excitatory input from a large number of cortical cells [44]. (A full understanding of DA's modulatory role in the striatum will also require consideration of presynaptic DA/glutamate interactions [40,43,91,119]. While this paper does not attempt to integrate this important and complex literature into the current discussion, it will be of interest in the future to determine whether and how these presynaptic interactions might contribute to a selective gating function). As described above, and noted by others, DA appears to amplify the activity of neurons receiving strong corticostriatal input (and, within the accumbens, cells receiving coincident input from frontal and hippocampal regions [86]) while filtering-out activity at weakly-activated synapses [27,33,48,67,88,120,124]. A disruption in striatal DA activity may, therefore, interfere with corticostriatal information processing either by disrupting the transmission of strong input signals, or by permitting the transmission of weak signals that would not normally be permitted to compete for basal ganglia processing beyond the level of the striatum.

## 4. DA activity gates the throughput of sensorimotor and incentive motivational inputs to the striatum

The dorsal striatum receives glutamate inputs [42,77] from virtually all sensory and motor regions of the cerebral cortex [64,68,71,78,107]. Neurons in the dorsolateral striatum (putamen) fire in relation to the movement of particular body parts [5,23,30,31,81,121], and in some cases particular joints [2,5,31]. Some putamen cells show activity during the preparation of a movement [2,53]. In some of these neurons, the neuronal activity during movement preparation is tied to the nature of the limb movement (e.g. flexion vs. extension movement of the elbow). In other neurons the preparatory response is tied to the desired outcome of the movement (e.g. bring the cursor to a given location on the screen) regardless of the specific muscles involved in producing that outcome [4]. Striatal neurons (within the caudate) have

also been shown to respond to visual and auditory stimuli [54], and to fire in relation to visual saccades toward a particular direction [53].

Individual striatal neurons appear to receive a convergence of distinct types of information across sensory modalities. Some putamen neurons have both visual and tactile receptive fields, with the visual response restricted to stimuli in proximity to the tactile field [45]. For other striatal neurons, movement-related neuronal responses are restricted to conditions when a particular outcome of the movement is expected [56,108]. Anterior regions of the caudate, putamen, and ventral striatum contain cells that respond to arm movements-but only when the animal expects to receive food reward as a result of the movement. These cells show very little activity tied to the arm movement when the animal expects to receive only a sound as a result of the movement. Further, this type of striatal cell shows little activity when the animal expects to receive reward and no movement is called for. A robust neural response requires the conjunction of movement preparation and an outcome expectation. Other striatal neurons respond to an arm movement only when the animal expects to receive an auditory stimulus as an outcome of the movement, rather than primary reward [56].

A striking property of the striatal response is, therefore, the convergence of information regarding sensory input, motor requirements, and outcome expectations. This convergence is often observed in the response properties of individual striatal neurons, which appear capable of representing the conjunction of two or more conditions. It has been previously noted that the medium spiny neurons of the dorsal and ventral striatum are among the most densely spined neurons in the brain, making these cells well designed to integrate information from different sources [49].

Under conditions of reduced nigrostriatal DA transmission, input signals are less likely to produce a response in the striatal neuron. DA depletion within the dorsal striatum, for example, reduces the responsiveness of striatal neurons to auditory, visual and tactile stimuli [6,98,101,122]. Prior to DA depletion, approximately 22% of neurons sampled from the dorsolateral caudate of the cat responded to tactile stimulation of the face; only 6% showed such tactile responses after MPTP-induced DA depletion [101]. Prior to DA depletion, 7% of neurons in this region responded to auditory events; less than 1% did so after the DA loss.

DA depletion similarly reduces the movement-related activity of striatal cells [48,118,122]. The reduced striatal response to sensory and motor inputs following striatal DA loss is not a consequence of baseline reductions in striatal activity. Reductions in DA transmission reduce the response of the cells to phasic input while increasing the baseline activity of most striatal cells [98]. An increase in striatal DA, on the other hand, suppresses striatal baseline firing rates, but does not suppress phasic activation of the cells, thereby increasing signal-to-noise ratios in corticostriatal transmission [67]. This DA-mediated enhancement in the processing of strong relative to weak corticostriatal inputs is consistent with a DA role in the selective gating of inputs to the striatum [17,41,112,123].

The ventral striatum receives input largely from basal amygdala, prefrontal cortex, hipposcampus, and other limbic-related brain regions [49,50,63,94]. Reward-related neurons are found in both the dorsal and ventral striatum, but they are more frequently found in the ventral striatum [7]. These cells respond to both the anticipation [55,104] and presentation of reward stimuli [7,16,55], and show activity levels that reflects the appetitive value of the reward [7,104]. The striatum also contains cells responsive to aversive stimuli [122,126]. However, distinct populations of striatal neurons may respond to appetitive and aversive events [126].

The sustained striatal neuronal response during reward anticipation has a pattern (gradual build up of activity as the time of expected reward approaches) and duration (often > 2 s) that closely mirrors the pattern and duration of activity in orbitofrontal reward neurons [106]; these response properties are not similar to those seen in midbrain DA neurons which show phasic activity (100 s of ms) tightly bound to the time of an unpredicted reward [106] or other salient events [59,111]. It is suggested here that the reward response seen in the striatal cell is driven by input from the orbitofrontal cortex (and possibly the BLA), and that striatal DA gates these reward inputs, just as DA gates the throughput of other types of strong inputs to the striatum.

The orbitofrontal cortex contains a population of neurons that respond specifically to reward value [106,114–117]. The response of these cells to one of several food rewards corresponds to the animal's preference for that reward [115]. Damage to the orbitofrontal cortex reduces the ability of reward contingencies to influence behavior [61], and produces deficits in the assignment of reward value to conditioned stimuli [34]. Humans with damage to this region have difficulty making judgements regarding the rewarding/punishing outcome of their actions [8]. Functional magnetic resonance imaging studies reveal distinct orbitofrontal regions that respond to rewards and punishments, and within these distinct regions, the magnitude of brain activation is correlated with the magnitude of the reward or punishment [85]. The orbitofrontal cortex sends dense projections to the nucleus accumbens core [47], and to a striatal region just above the dorsal boundary of the nucleus accumbens [37].

A second candidate source of reward input to the striatum is the BLA, which projects to all parts of the striatum except for an anterior dorsolateral sector [63]. The BLA contains neurons that are sensitive to food reward magnitude [95]. Following lesions of the BLA, conditioned stimuli associated with reward lose their ability to control operant behavior [19,20,97]. The projections from the BLA to the striatum widely overlap striatal projections from the VTA [63]. In accordance with the view that DA gates the processing of these reward-related inputs, amygdala-mediated conditioned reinforcement processes have been shown to depend upon intact ventral striatal DA transmission [39].

It has previously been suggested that the amygdala and orbitofrontal cortex send reward signals to the striatum [93,106]. Under conditions of surprising event occurrence, DA may facilitate the processing of these signals, and permit their throughput to downstream basal ganglia structures. One prediction from this view is that ventral striatal DA loss will not attenuate all aspects of reward processing. Cells in the orbitofrontal cortex, for example, may continue to respond to the incentive value of reward events under conditions of mesoaccumbens DA loss. The orbitofrontal region of the cortex projects to a number of cortical and subcortical regions [24] which may continue to receive normal reward signals following striatal DA depletion. Salamone and colleagues have shown that ventral striatal DA depletion reduces the ability of food reward to energize animals' behavioral response systems, while leaving some other aspects of reward processing intact [100]. Similarly, the euphoric effects of amphetamine, even at high neuroleptic doses, appear to survive DA antagonist challenge [18].

In addition to reward-responsive neurons, the striatum also contains populations of neurons responsive to aversive inputs [122,126]. Disruptions in DA transmission are known to disrupt aversively motivated behaviors as well as appetitively-motivated behaviors (see [99,100] reviews). While the prior discussion proposes DA gating of reward inputs from the orbitofrontal cortex and amygdala, it is possible that DA may have symmetrical effects on inputs to the striatum carrying information about rewarding and aversive events. It should also be emphasized that while reward-responsive neurons are more often found in the ventral relative to the dorsal striatum [7], ventral striatal DA disruption interferes with some [36], but not all [28], aspects of reward processing. Reward-related responses are also found in the dorsal striatum [7,56], and dorsal striatal DA disruption attenuates some aspects of reinforcement [11]. DA modulates both the striatal response to current glutamate inputs [27,67,87] and long-term changes in synaptic strength of these inputs [21,22,65]. It will be of interest to determine how the functional consequences of these short- and long-term modifications differ with respect to striatal subregion.

## 5. Striatal plasticity: stimulus-response learning, salience assignment to synaptic inputs, and/or stimulus-response-outcome chunking

The prior discussion suggested that DA neurons are activated by salient environmental change and that elevations in synaptic DA activity within the striatum increase signal-to-noise ratios, permitting strong corticostriatal inputs privileged access to striatal outputs, by amplifying strong inputs and dampening the impact of weak (task-irrelevant) inputs. Further, it was noted that glutamate inputs to the striatum represent not only sensory and motor events, but also events coded on the basis of incentive value. As seen from this framework, both motoric and incentive motivational deficits following DA depletions result from disruption of signal-to-noise ratios at synapses carrying cortical and limbic inputs to the striatum. In the absence of normal DA activity, the striatum can neither process the appropriate sensory–motor signals, e.g. from sensory–motor cortex, nor process appropriate incentive motivational signals, e.g. from the orbitofrontal cortex and amygdala. A loss of normal signal-to-noise ratios within the striatum might in itself account for the disruptive effects of DA loss on the acquisition of reinforced behavior. If reinforcement involves long-term modifications in the strength of striatal input signals [9,102,124], then abnormalities in the relative strength of these inputs would prevent reinforcement of appropriate inputs. However, DA is also necessary for striatal plasticity [21,25]. DA's role in learning is, therefore, likely to include not only a selective gate-keeping function for glutamate inputs, but also a direct role in promoting plasticity of currently active synapses.

Schultz describes a model in which DA provides a teaching signal, reporting discrepancies between 'reward occurrence' and 'reward prediction' [102]. According to this view, phasic DA elevations occur in response to a reward outcome that was not fully predicted on the basis of a prior CS [102]. The phasic DA response increases the synaptic strength between currently active striatal input and output elements, increasing the future likelihood that the current set of corticostriatal inputs will activate striatal outputs [102]. If one imagines that the striatal outputs designate motor responses, and that the DA response signals unexpected reward, then, following DA-mediated strengthening of currently active corticostriatal synapses, the future arrival of the same pattern of corticostriatal inputs becomes more likely to elicit a particular pattern of motor outputs in the future. This scenario requires that phasic DA release occur exclusively to rewarding events, or to the offset of aversive

events. If DA neurons are similarly activated by the onset of aversive events, the scenario becomes less plausible, for it would lead to the strengthening of behavioral responses that lead to the onset of aversive consequences. While there is evidence to suggest that the DA response to reward events may be in some way distinct from the DA response to aversive events [14,74,80,102], other evidence suggests that the DA response to reward and aversive event onset is likely to be similar, given that the events are of comparable intensity or significance [46,57,66,99]. If DA neurons respond to surprising/arousing events, regardless of appetitive or aversive value, one would postulate that DA activation does not serve to increase the likelihood that a given behavioral response is repeated under similar input conditions; that is to say, the primary function of DA in striatal plasticity is unlikely to involve a strengthening of stimulus–response (S–R) connections.

D1 receptor binding critically mediates both long-term potentiation and long-term depression at corticostriatal synapses [21]. If the DA signal does not stamp-in S–R connections, what aspect of learning might be subserved by DA-mediated corticostriatal plasticity? One possibility is that strengthening of particular corticostriatal inputs increases the likelihood that the current set of strong inputs to the striatum will receive downstream basal ganglia processing in the future, i.e. it increases the future salience of currently-active striatal inputs. According to this scenario, the nature of the required motor response is not determined at the level of the striatum, but at downstream structures, e.g. in anterior regions of the frontal cortex, and/or other recipients of corticostriatal–basal ganglia flow-through [3]. Elevations in DA activity, then, would increase the likelihood that task-relevant sensory-, motor-, and outcome-related inputs to the striatum receive basal ganglia processing in the future, and ultimately influence frontal regions, where response selection is designated. This differs from the S–R strengthening scenario, in that phasic DA elevations in response to the onset of an aversive event would not cause reinforcement of the injury-inducing behavior; rather it would increase the likelihood that the current set of striatal inputs is processed and responded to in the future. If the animal approaches an object and is bitten in the foot, an increase in DA activity would increase the salience of the currently-active set of corticostriatal inputs, i.e. it would increase the likelihood that this set of inputs receives striatal and downstream basal ganglia processing in the future. But because DA does not stamp-in S–R bonds, the animal is spared the misfortune of increasing the likelihood of emitting the previous response under similar input conditions.

Facilitation of the strengthening of corticostriatal synapses by a non-reward-specific DA signal could also promote certain types of associative learning. As noted above, striatal cells receive inputs reflecting sensory stimuli, responses (both those anticipated and emitted) and outcomes (both those expected and those that have occurred). The temporal properties of these responses (including the outcome responses) do not mirror those of midbrain DA neurons, and are, therefore, likely to originate from cortical and/or limbic sources (see Section 4 above). Further, it was noted that an individual striatal neuron often displays activity that reflects the conjunction of various input conditions. If DA promotes plasticity at currently active synapses, it could promote chunking of inputs [44] that include sensory, response, and outcome information. In cases where representations of responses and associated outcomes converge on a single striatal neuron [56], DA activity may promote the strengthening of these inputs under conditions when the outcome is not fully predicted by prior cues. As a result, future anticipatory activation of the outcome representation (originating, for example, in the orbitofrontal cortex) could activate striatal neurons associated with the appropriate response.

Neither the salience attribution nor the S–R-outcome chunking mechanisms require a unique DA response to reward events. On the other hand, if future research suggests that DA neurons do respond in a unique manner to rewards [80], for example if the phasic DA response to reward [72,102] differs in an important respect from the phasic DA responses to salient non-reward events, such as bright light flashes and loud clicks [59,111], then DA could serve to stamp-in S–R associations, i.e. to reinforce those behaviors that lead to a phasic DA response.

In summary, it is argued that SN and VTA DA neurons are activated by highly salient environmental events (see Section 2) and consequent DA release gates the basal ganglia processing of sensorimotor and incentive motivational glutamate inputs to the dorsal and ventral striatum (see Section 3). This view, like a DA/reward signal view, accounts for the disruptive effect of reduced DA transmission on incentive motivation [121,38,60,100,129]. However, in contrast to a DA/reward signal view, the present framework also accounts for (1) the promiscuous DA response to a wide range of salient and arousing stimuli [57], (2) the fact that disruptions in DA activity can impair animals' abilities to learn about aversive events [1,100], and (3) the observation that disruptions in DA activity impair some, but not all, aspects of reward processing [12,18,90,100]. From the present view, orbitofrontal and amygdala reward (and aversive) signals send projections to brain areas that are subject to DA modulation, but also to areas that are not subject to DA modulation, therefore, some (e.g. perceptual) aspects of reward processing occur independent of meso-

limbic and nigrostriatal DA activity [18]. Finally, the framework is parsimonious in that it assigns a single role to nigrostriatal and mesolimbic DA neurons: activation under conditions of salient environmental change, and consequent enhancement of glutamate signal-to-noise ratios within dorsal and ventral striatal target sites. Deficits in sensorimotor and incentive motivational processes after nigrostriatal and mesolimbic DA loss can be understood in terms of a single mechanism, i.e. disrupted processing of glutamate input signals to the striatum, signals that carry both sensory-motor and incentive motivational information.

## Acknowledgements

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