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Abstract

Co-release of the inhibitory neurotransmitter GABA and the neuropeptide substance-P (SP) from single axons is a conspicuous feature of the basal ganglia, yet its computational role, if any, has not been resolved. In a new learning model, co-release of GABA and SP from axons of striatal projection neurons emerges as a highly efficient way to compute the uncertainty responses that are exhibited by dopamine (DA) neurons when animals adapt to probabilistic contingencies between rewards and the stimuli that predict their delivery. Such uncertainty-related dopamine release appears to be an adaptive phenotype, because it promotes behavioral switching at opportune times. Understanding the computational linkages between SP and DA in the basal ganglia is important, because Huntington’s disease is characterized by massive SP depletion, whereas Parkinson’s disease is characterized by massive DA depletion.
At the core of the brain’s action-selection system are the basal ganglia (BG), disorders of which produce Parkinson’s Disease (PD) and Huntington’s Disease (HD). The BG’s principal input zones, known collectively as the striatum, receive masses of fibers from the neocortex. The striatum in turn sends masses of fibers to BG output zones, including two adjacent compartments of the substantia nigra (SN). The substantia pars reticulata (SNr) contains highly active inhibitory neurons whose selective pauses release actions; and the substantia nigra pars compacta (SNc) contains moderately active dopamine (DA) neurons whose bursts and pauses are implicated in reward-related learning and performance. Of the two compartments, only the SNc projects massively to the striatum, thus closing an internal loop. In PD, a large proportion of the DA neurons in SNc die off, and this depletes the striatum of the DA needed for normal voluntary behavior. Fibers running directly from medium spiny projection neurons (MSPNs) of the striatum to the SN release both the inhibitory transmitter GABA and a neuropeptide, substance-P. In HD, degeneration of striatal MSPNs leads to loss of around 70% of the SP in the SNc, and 90% in SNr.

Despite the importance of the striatum-nigra loop, the computational role of some basic features remains uncertain. What computational benefits, if any, accrue when striatonigral synapses release both the fast-acting neurotransmitter GABA and the slower-acting neuropeptide, SP? The SP-rich fibers are distributed along the rostrocaudal extent of the SNr but are restricted to the ventral part of the SNc, from which DA neurons extend their dendrites into SNr. This pattern is similar across rodents, cats and primates, and it mirrors another: the distribution of type-one neurokinin receptors (NKRs) – the predominant type of SP-sensitive neurokinin receptors in humans – is highest on the DA neurons in the ventral part of the SNc. No consensus exists regarding the computational function(s) of these patterns.

One clue is the observation that some components of the spiking patterns of DA neurons can be regarded as reward prediction error (RPE) signals, i.e., signals of the unexpected occurrence or unexpected omission of rewards, and of cues that predict reward. The DA neurons respond rapidly to unexpected rewards with a phasic burst. The system adapts whenever a reward consistently follows a preceding conditioned stimulus (CS) after a fixed interval: the phasic burst appears to "transfer" from the (now expected) time of reward delivery to the (unexpected) time of CS onset. The amount of the "transfer" depends on the expectation of reward, \[ R = |R| \times p(R|CS), \] that is, the conditional probability, \( p(R|CS) \), that a reward of magnitude \( |R| \) follows the CS.

Recently, Fiorillo et al. reported a new reward-related component of DA neurons’ spiking behavior, which they called an uncertainty response. This DA signal component ramps up during the interval from CS onset to the expected time of reward if the reward schedule is probabilistic. The signal depends on two factors, the conditional probability, \( p(R|CS) \), and the amount of reward that is at risk. The maximal uncertainty response is observed if \( p(R|CS) = 0.5 \), but it disappears if \( p(R|CS) = 0.0 \) or \( 1.0 \). A \( p(R|CS) \) of 0.75 or 0.25 yields an intermediate-sized response. Thus, this component (Figures 1A and 2A) is a non-monotonic function of \( p(R|CS) \). This contrasts with the phasic DA signal component, the degree of transfer (from time of reward to time of CS onset) of which is a monotonic function of expected reward, \[ R = |R| \times p(R|CS). \] Therefore, the DA signal exhibits at least two learned, reward-related components. Both are functions of \( p(R|CS) \) and \( |R| \), but the uncertainty response is a non-monotonic function of conditional probability \( p(R|CS) \).
whereas the phasic response to CS onset is a monotonic function of expected reward, $\hat{R} = |R| \times p(R|CS)$.

Neither the uncertainty response nor its functional dependencies were predicted to appear in single trial data by basal ganglia models proposed to explain learned RPE responses of DA neurons(10; 11; 12). Based on the temporal difference (TD) model of RPE signal genesis, Niv et al.(12) proposed that the uncertainty responses reported by Fiorillo et al.(8) should be seen as averaging artifacts explicable in terms of hypothesized “slowly back-propagating” RPEs. There are two problems with this interpretation. First, measured DA signals taken to be RPEs do not “back propagate”, i.e, do not slide through intermediate times to the time of the CS over the course of learning. Rather, they “jump”, in the sense that they abruptly appear and begin to grow at the time of the CS, while they shrink at the time of the expected reward, as learning progresses (7; 8; 9; 10). Second, the ramp-like uncertainty responses of DA neurons appear robustly within a single behavioral trial(13), hence are not an averaging artifact. Thus, the TD-based interpretation (12) does not explain the DA neuron data. To be successful, an alternative model must explain single-trial uncertainty responses and how they emerge from computations performed by verifiable elements of the neural substrate. We now present a model within which co-release of SP and GABA in SNC enables efficient computation of uncertainty.

The MSPNs of the striatum are all GABAergic and are distributed across two compartments: matrix and patch. The MSPNs whose degeneration in HD leads to 70%-90% depletion of SP in the SN are rich in the calcium buffering protein, calbindin (CB)(14). These CB+ MSPNs mostly inhabit striatal matrix compartments(15; 16), whereas the MSPNs that lack CB mostly inhabit striatal patch compartments(16). In the primate SNr and SNC, most SP fibers originate from striatal MSPNs(17). Thus, the primary sources of SP in the SN are striatal matrix MSPNs, not patch MSPNs. Furthermore, natural release of SP in SNC depends on MSPN activity(18). Although SP fibers in the SN conspicuously synapse on GABAergic SNr neurons(2; 19; 20), Bolam and Smith(20) reported that SP fibers also synapse on dendrites of SNC DA neurons, whose dendrites extend ventrally into SNr. Pinnock and Dray(19) reported that SP release does not interact with the release of other transmitters, such as the GABA that is co-released by matrix MSPNs via axon terminals in SN. Local application of SP in the SN increases DA neuron activity(21), and such SP-induced excitation in the SNC has a slow onset and prolonged duration compared with phasic DA responses(19). In summary, SP released by MSPNs of the striatal matrix exerts a prolonged excitatory effect on DA neurons in ventral SNC.

A computational local-circuit model proposed by Brown et al.(10) implied the monotonic relationship between phasic DA signals and $p(R|CS)$. In that model, learning at cortico-striatal synapses onto matrix MSPNs in ventral striatum mediates phasic excitation of DA neurons in SNC at CS onset, whereas patch MSPNs learn to inhibit DA neurons at the expected time of reward delivery after CS onset. After learning, model DA neurons burst at CS onset, but the burst that would otherwise be induced at the time of reward delivery is "cancelled" by timed inhibitory input (as required for the "transfer" noted above). In the model, the cortico-striatal synaptic weights that mediate such learning reflect experienced reward magnitudes, because the size of the phasic DA “teaching signals” that scale weight increments/decrements depend on reward magnitude(7). Moreover, because each delivery of reward yields a DA burst that induces a weight increment,
whereas each omission of an expected reward yields a pause in DA firing that induces a weight decrement(22; 23), the synaptic weights also track the conditional probability of reward. Thus, the Brown et al.(10) modelpredicted that the strength of cortico-striatal synapses is a monotonic function of expected reward, $\hat{R} = |R| \times p(R|CS)$, and thus of conditional probability (Figure 1B), consistent with later physiological observations(8; 9). Given that transmitter release from striatonigral terminals is dependent on synaptically driven activity of the MSPNs(21), the released amounts of SP and GABA should be monotonic functions of expected reward value, $\hat{R} = |R| \times p(R|CS)$, hence of the conditional probability $p(R|CS)$.

The uncertainty, $U(x)$, of an event $x$ can be defined as the joint probability of the occurrence, $p(x)$, and absence, $(1-p(x))$, of that event. Thus: $U(x) = p(x) \times (1-p(x))$. Since $0 \leq p(x) \leq 1$, this relation implies that the uncertainty will be maximal if the probability of occurrence of an event is equal to the probability of its absence, and that $U(x)$ is a non-monotonic function of $p(x)$, with minima ($= 0$) at $p(x) = 0$ and $p(x) = 1$, and a maximum at $p(x) = 0.5$. Thus, the uncertainty associated with a reward, given a CS, can be written as a non-monotonic function of the conditional probability of the reward given the CS: $U(R|CS) = p(R|CS) \times (1-p(R|CS))$. This contrasts with the monotonic dependence of MSPN activity, and transmitter release, on $p(R|CS)$.

After applying SP in SNc, Reid et al.(24) observed that striatal DA release, which depends on SNc cell activation, was maximal at intermediate SP concentrations, and lower at low and high SP concentrations (Figure 1C). This non-monotonic dose-dependence of striatal DA release on SP level in SN has been replicated (25; 26). Such reports are consistent with a multiplicative interaction between an excitatory and an inhibitory effect of SP on DA cells. Reid et al.(24) suggested that the non-monotonic action of SP could be an effect of two SP fragments, SP$_1$–7 and SP$_6$–11, which, respectively, can be shown to facilitate and inhibit DA neuron firing (Figure 1C).

However, two recent reports suggest that SP excites SNc DA cells with a linear dose-dependence(27; 28). If the latter holds true for all physiologically relevant SP doses, then the observed non-monotonic dependence of DA neurons’ uncertainty responses on $p(R|CS)$ would require some mechanism that cooperates with SP release. The most likely mechanism is GABAergic input to DA neurons, because GABA release should shunt the excitatory effect of SP on DA neurons in SNc. The co-release of GABA and SP from individual striatonigral terminals of matrix MSPNs appears to be the most efficient way possible$^1$ to achieve the non-monotonic dependence of the uncertainty response on $p(R|CS)$. Similar multiplicative dendritic interactions between transmitters of opposing valence have been implicated by theoretical and experimental studies of cortical pyramidal neurons(e.g., 31).

To show that the learning process and transmitter co-release noted above can cooperate to compute the observed non-monotonic function, let $M$ denote the activation level of matrix SP-

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$^1$However, further bases may exist. Bolam and Smith(20) reported that some GABAergic terminals that are not immunoreactive for SP also synapse on the dendrites of DA neurons in SNc, and suggested that some of these terminals arise from GABAergic neurons of SNr. This is consistent with Mendez et al.(30), who observed that GABAergic cells in the SNr, which are also recipients of SP terminals, make synaptic contacts with the dendrites that DA cells of the SNc extend ventrally into SNr. Moreover, Whitty et al.(6) reported that NKRI mRNAs were found in some non-pigmented (i.e., non-DA) cells of the ventral SN. Thus, GABAergic neurons of SNr that become excited by high SP release may also shunt the excitatory effect of SP on SNc DAergic cell dendrites.
MSPNs in response to a CS. Let SP and GABA release from corresponding striatonigral terminals be approximated by $[M - \Gamma]^+$, and the effects of SP and GABA on nigral DA cell dendrite by $\alpha[M - \Gamma]^+$ and $\beta[M - \Gamma]^+$, respectively. Here, $\Gamma$ is a fixed non-negative threshold and $\alpha$ and $\beta$ are scaling constants. Furthermore, the GABA release level will shunt SP’s excitatory effect at the SNc DA neuron’s dendrite. Let the net signal $S$ resulting from this interaction be approximated as $S = \alpha[M - \Gamma]^+ (1 - \beta[M - \Gamma]^+)$, where the former term represents the primary excitatory effect, and the latter represents the shunting effect. This equation implies a maximum net excitation if $\alpha[M - \Gamma]^+ = (1 - \beta[M - \Gamma]^+)$, zero excitation if $\alpha[M - \Gamma]^+ = 0$ or $\beta[M - \Gamma]^+ = 1$, and net inhibition if $\beta[M - \Gamma]^+ > 1$. Now assume, without loss of generality, that $\beta = \alpha$, $0 \leq \alpha[M - \Gamma]^+ \leq 1$. That is, let the normalized effects of SP and GABA on DA cells be equivalent. Given the result from Brown et al.(10), that corticostriatal synaptic weights are a monotonic function of $\hat{R} = |R| \times p(R|CS)$, it follows that MSPN activation to the CS is $M \sim |R| \times p(R|CS) \sim p(R|CS)$ (up to a constant), so

$$S = \alpha[M - \Gamma]^+ (1 - \alpha[M - \Gamma]^+) \sim p(R|CS) \times (1 - p(R|CS)) \sim U(R|CS) \quad (1)$$

up to a constant that is determined by the reward magnitude $|R|$, and the parameters $\alpha$ (= $\beta$) and $\Gamma$. Note that the implicit dependence of the net signal, $S$, on reward magnitude, $|R|$, is consistent with the Fiorillo et al.(8) report that the magnitude of the uncertainty response (at least for the $p = 0.5$ case), depends monotonically on the reward magnitude. Next we model sustained DA neuron spiking rate in the simplest realistic way, with a differential equation for a bounded leaky integrator,

$$\frac{1}{\tau} \frac{d}{dt} D = -D + (1 - D) [I + S] \quad (2)$$

where input $S$ is given by equation (1), constant intrinsic input $I$ controls the baseline DA neuron firing rate in the absence of input $S$, and $\tau$ is the time constant. The simulated equilibrium (Figure 1D) and dynamic responses (Figure 2B) capture the main properties of the physiological data reported by Fiorillo et al.(8) (Figures 1A and 2A). Unlike the Niv et al.(12) proposal, this model details a local circuit basis that supports robust, single-trial, uncertainty responses that exhibit the correct dependence on $p(R|CS)$ and that do not depend on hypothetical back-propagation of RPE signals.

Simulations with an extended striato-nigral model (Tan and Bullock, submitted) demonstrate two additional features. First, variations of intrinsic parameters of the striatal circuit model readily produce the kind of between-monkey differences in the amplitude of the non-monotonic function that are visible in Figure 1A. Second, learned phasic responses can co-exist with learned uncertainty responses in single DA neurons (Figure 2C). Approximately 50% of recorded DA neurons responded to a predictive stimulus with a reliable phasic activation, whereas 9% responded with a reliable sustained activation, and 18% responded with both (C. Fiorillo, pers. comm.). All three types emerge in the model from differences in afferentation that arise naturally across the SN. The rarest type, according to the model, is a DA neuron that is contacted by the SP-rich fibers that engender uncertainty responses but not by the distinct fibers that excite phasic bursts.
In this model, it is the co-release of GABA and SP that enables genesis of sustained DA responses related to the uncertainty in the CS-reward contingency. Because of the co-release, different aspects of a CS-reward contingency, notably the anticipated timing and uncertainty, could be learned and reflected in the DA signal of the SNc by a circuit that requires half the cells and fibers that would otherwise be needed. Besides being more efficient, the co-release phenotype is also inherently more precise than a dual-path solution, which could not ensure as perfect a correlation between the two release processes(32).

Adjusting striatal DA release to reflect learned uncertainty may have profound effects on action selection, because DA promotes behavioral switching. Uncertainty arises whenever a formerly applicable reinforcement contingency no longer applies, and the animal’s internal estimate of \( p(R|CS) \) begins declining (? ? ). It is then adaptive to switch one’s orienting behavior in search of a more predictive cue, and one’s instrumental behavior in search of a more effective strategy. It is especially useful to seek alternatives before negative experiences with the current one fully erode the synaptic weights that favor it, because the cue or strategy will often regain currency at a later time. While promoting switches to new behavior, the DAergic uncertainty response may thus also help protect old learning from being completely eroded during short-term reversals of contingencies. Consistent with the predictions of the co-release model, adaptation to such reversals is impaired in advanced HD patients(33). In summary, uncertainty-dependent sustained DA release between cue onset and reward onset/omission (either of which resolves the uncertainty) can emerge from local computations using known BG signals, and appears to be an adaptive phenotype when considered in the context of action selection.

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References


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Figure 1: Basal ganglia computations during probabilistic schedules of reward. (A) Sustained uncertainty responses (% above baseline) of dopamine neurons in the SNc of four monkeys were a non-monotonic function of the conditional probability, $p(R|CS)$, of receiving a reward ($|R| = 0.15$ ml juice) after a conditioned stimulus, CS (data plot reprinted with permission from Fiorillo et al., 2003). (B) During simulated training with different expected reward values ($\hat{R} = |R| \times p(R|CS)$), the model learns corticostriatal synaptic weights that discriminate among expected reward values. Black, gray and white squares show the synaptic weights attained after training with reward magnitudes, $|R|$, of 0.05, 0.15 and 0.50, respectively. (C) Dose-response curves for the maximal effects on striatal DA levels produced by SP$_{1-7}$, SP$_{6-11}$, or SP injected into the SNr (data reprinted with permission from Reid et al., 1990). (D) Sustained activity (% above baseline) of model dopamine neurons as a function of reward probability, after training with reward magnitude $|R| = 0.15$. 
Figure 2: Responses of dopamine neurons under probabilistic reward schedules. (A) Data, reprinted with permission from Fiorillo et al., 2003. Note the sustained ramp component when $p(R|CS)=.5$. Also note the initial phasic burst increases as $p(R|CS)$ increases from 0.0 to 1.0. (B) Model dopamine neurons’ simulated sustained responses, after training with analogous probabilistic reward schedules. (C) Model dopamine cells responding with both a phasic burst and a sustained activation, after learning.