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Supporting Online Material

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 Materials and Methods

Figs. S1 and S2
 References

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Adaptive Coding of Reward Value by Dopamine Neurons

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It is important for animals to estimate the value of rewards as accurately as possible. Because the number of potential reward values is very large, it is necessary that the brain's limited resources be allocated so as to discriminate better among more likely reward outcomes at the expense of less likely outcomes. We found that midbrain dopamine neurons rapidly adapted to the information provided by reward-predicting stimuli. Responses shifted relative to the expected reward value, and the gain adjusted to the variance of reward value. In this way, dopamine neurons maintained their reward sensitivity over a large range of reward values.

In order to select the action associated with the largest reward, it is critical that the neural representation of reward has minimal uncertainty. A fundamental difficulty in representing the value of rewards (and many other stimuli) is that the number of possible values has no absolute limits. By contrast, the representational capacity of the brain is limited, as exemplified by its finite number of neurons and the limited number of possible spike outputs of each neuron. If a neuron's limited outputs were allocated evenly to represent the large, potentially infinite number of possible reward values, then that neuron's activity would allow for little if any discrimination between rewards. However, a neuron's discriminative capacity can be improved if the neuron has access to information indicating that some reward values are more likely to occur than others and if it can allocate most of its spike outputs to representing the most probable values. Conditioned, reward-predicting stimuli could provide such information for neurons, as they do in a more general way for behavior (1–3). Here we investigate how dopamine neurons adapt to the information about reward value contained in predictive stimuli. These neurons play a major role in

reward processing (4–7) and respond to rewards and reward-predicting stimuli (8–11).

We presented distinct visual stimuli that specified both the probability and magnitude of otherwise identical juice rewards to monkeys well trained in a Pavlovian procedure (12). Standard procedures were employed to extracellularly record the activity of single dopamine neurons of midbrain groups A8, A9, and A10 in two awake Macaque monkeys (12). We report data for all recorded neurons that displayed electrophysiological characteristics typical of dopamine neurons (wide impulses at low rates) (12, 13). In an attempt to accurately portray the whole population of dopamine neurons, we did not select neurons on the basis of their modulation by a reward event.

The expected value of future rewards (the sum of possible reward magnitudes, each weighted by its probability) is thought to be an important variable determining choice behavior (14–17). To test this, we trained an animal with a set of five distinct visual stimuli presented in pseudorandom alternation. Each stimulus indicated the probability that a specific liquid volume would be delivered 2 s after stimulus onset. Anticipatory licking before liquid delivery was elicited by the smallest positive expected liquid volume tested (0.05 ml at probability $p = 0.5$) and increased with expected liquid volume, suggesting that the animals had learned to use the stimuli to predict liquid delivery and that the larger liquid volumes corresponded to larger reward values (Fig. 1A). The transient

activation of dopamine neurons increased monotonically with the expected liquid volume associated with each stimulus (Fig. 1, B and C). For example, the stimulus predicting 0.15 ml at $p = 1.0$ elicited significantly greater neural activation than the stimulus predicting the same magnitude reward at $p = 0.5$, but less activation than the stimulus predicting 0.50 ml at $p = 0.5$. The activation of dopamine neurons also increased with the combination of magnitude and probability when the stimuli predicted that either of two nonzero magnitudes would occur with equal probability (Fig. 1C, animal B).

To investigate whether individual neurons might be preferentially sensitive to probability or magnitude, we took independent measures of sensitivity to magnitude and probability in each neuron ($n = 57$ neurons). There was a positive correlation ($R^2 = 0.23$, $P < 0.005$), indicating that those neurons that were most sensitive to reward magnitude were also most sensitive to probability (Fig. 1D). Thus, it appears that dopamine neurons encode a combination of magnitude and probability, as expressed, for example, by the expected reward value, rather than distinguishing between the two.

Having examined responses to reward-predicting stimuli of differing values, we investigated the extent to which dopamine neurons discriminated between different volumes of unpredicted liquid. We delivered three distinct liquid volumes (0.05, 0.15, and 0.50 ml) in pseudorandom alternation with a variable intertrial interval (18) and in the absence of any explicit predictive stimuli. Both individual dopamine neurons (43 of 55 neurons tested; $P < 0.01$, Wilcoxon test) and the population as a whole (55 neurons) showed greater activation for the large than for the small liquid volume (Fig. 2). Thus, the activation of dopamine neurons increased with the reward value of unpredicted liquids, similar to the responses to reward-predicting visual stimuli.

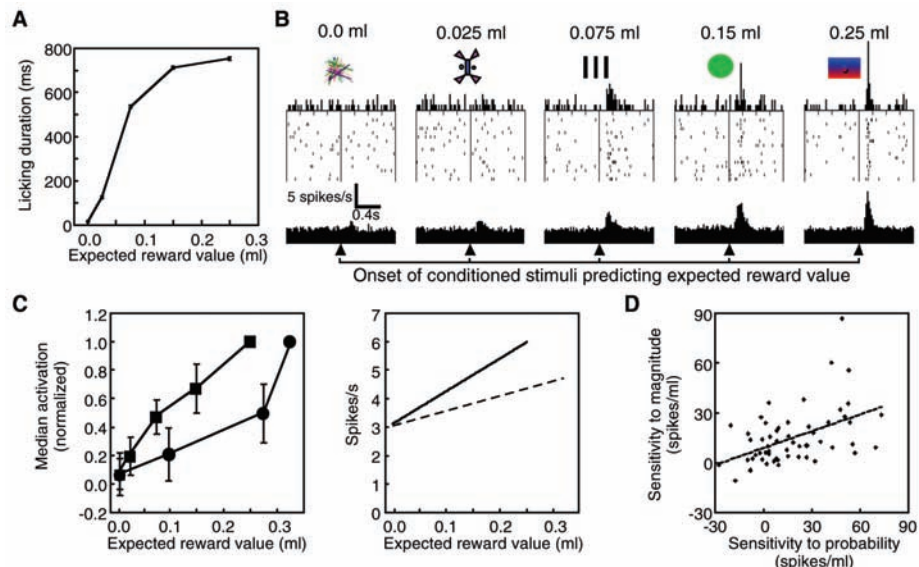
Although these results suggest that dopamine neurons encode the reward value in a monotonically increasing fashion, past work indicates that they do not represent absolute value. Rather, they appear to encode value as a prediction error by representing at each moment in time the difference between the

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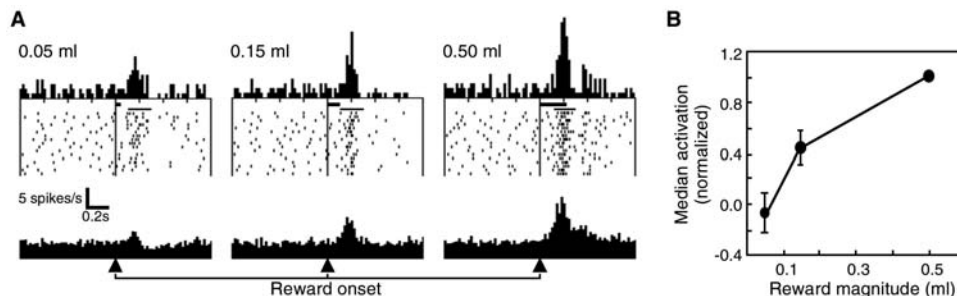
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Fig. 1. Behavioral and neuronal responses to conditioned stimuli increase with expected reward value. **(A)** Anticipatory licking responses during the 2-s delay between the conditioned stimuli and liquid delivery. Each point shows the mean (\pm SEM) of at least 1835 trials (animal A) and is significantly different from all other points (*t* tests). Similar results were obtained from animal B, although the mean licking durations varied over a smaller range. **(B)** Single-neuron (top) and population responses (bottom) ($n = 57$ neurons) from the experiment in (A). Visual conditioned stimuli with their expected magnitude of reward are shown above the rasters. Expected values (probability \times magnitude) were, from left to right, 0 ml (1.0 probability \times 0.0 ml magnitude), 0.025 ml (0.5 \times 0.05 ml), 0.075 ml (0.5 \times 0.15 ml), 0.15 ml (1.0 \times 0.15 ml), and 0.25 ml (0.5 \times 0.50). Bin width is 10 ms in histograms of all figures. **(C)** (Left) Population responses as a function of expected liquid volume. Measurements were taken 90 to 180 ms (animal A) and 110 to 240 ms (animal B) after the onset of visual stimuli. The median (\pm 95% confidence intervals) percent change in firing rates within the population was calculated after normalization of responses within each neuron to the response evoked after onset of the stimulus associated with the largest expected value. This stimulus elicited a median activation of 167% in animal A ($n = 57$ neurons) and 40% in animal B ($n = 53$ neurons). For animal A (squares), stimuli indicated probability and magnitude as in (B). For animal B (circles), one stimulus was never followed by liquid, whereas each of the other three stimuli was associated with two volumes of equal probability (0.05 or 0.15 ml, 0.05 or 0.50 ml, and 0.15 or 0.50 ml). In each animal, the population of neurons discriminated among each expected value tested, except for 0.0 versus 0.025 ml in animal A. (Right) An alternative analysis, illustrating the sensitivity (spikes/s/ml) of a typical dopamine response to expected liquid volume. For each individual neuron,



the number of impulses after stimulus onset was plotted as a function of expected magnitude, and a line was fit. The lines shown are the median lines of each population of neurons (animal A, solid line, spikes/s = $11.5 \times$ magnitude + 3.1, $R^2 = 0.51$; animal B, spikes/s = $5.2 \times$ magnitude + 3.0, $R^2 = 0.69$). **(D)** Positive correlation between the sensitivity of individual neurons to reward probability and magnitude ($R^2 = 0.23$, $P < 0.005$). For the data from animal A in (C), responses in each neuron ($n = 57$ neurons) are plotted both as a function of expected value, as determined both by reward probability (0.15 ml at $p = 0.0, 0.5$, and 1.0) and by liquid volume (0.05, 0.15, and 0.50 ml at $p = 0.5$). A line was fit in each case, and the slopes provided independent estimates of the sensitivity of that neuron to reward probability and magnitude. For each neuron, the slopes are plotted against each other.

Fig. 2. Neural discrimination of liquid volume. **(A)** (Top) Rasters and histograms of activity from a single dopamine neuron. (Bottom) Population histograms of activity from all neurons tested ($n = 55$ neurons). Three volumes of liquid were delivered in pseudorandom alternation in the absence of any explicit predictive stimuli. The inter-trial interval ensured that the expected volume at any given moment was low (18). Thick horizontal bars above the rasters indicate the time of reward delivery, and thin horizontal bars indicate the single standard time window that was used for measuring the magnitude of all responses in all neurons, as summarized in (B). Similar windows were used for all analyses and plots (supporting text). **(B)** Neural response as a function of liquid volume. Median (\pm 95% confidence intervals) percentage



change in activity for the population of neurons ($n = 55$ neurons) was calculated for responses to each volume after normalization in each neuron to the response after delivery of 0.5 ml, which itself elicited a median activation of 159% above baseline activity.

reward value (the sum of current and future rewards) and its expected value (before observation of current sensory input). Recent work demonstrates that, when signaling prediction errors, dopamine neurons are able to use contextual information in addition to information from explicitly conditioned stimuli (19). In the experiments shown in Figs. 1 and 2, all visual stimuli and liquid volumes were delivered in a context in which the expected reward value at each moment in time was low and invariant across trial types because of the inter-trial interval (18). In our next set of experiments, we delivered differ-

ent volumes of liquid in the presence of explicit predictions indicated by conditioned stimuli, allowing us to systematically vary the expected value and range of reward. Consistent with past work, a reward occurring exactly at the expected value (0.15 ml) elicited no response. However, when liquid volume was unpredictably smaller (0.05 ml) or larger (0.50 ml) in a minority of trials, dopamine neurons were suppressed or activated, respectively, compared to both the prestimulus baseline and the response to the expected volume delivered in the majority of trials ($P < 0.01$, Mann-Whitney test) (Fig. 3,

A and B). In an additional experiment, one stimulus predicted that either the small or medium volume would be delivered with equal probability, whereas another stimulus predicted either the medium or large volume with equal probability. In both cases, delivery of the larger of the two potential volumes elicited an increase in activity, whereas the smaller volume elicited a decrease (Fig. 3C). Thus, the identical medium volume had opposite effects on activity depending on the prediction ($P < 0.01$ in 19 of 53 neurons, Mann-Whitney; $P < 0.0001$ for the population of 53 neurons, Wilcoxon test) (Fig. 3D). These

results show how dopamine neurons process reward magnitude relative to a predicted magnitude and that a reward outcome that is positive on an absolute scale can nonetheless suppress the activity of dopamine neurons.

Although these results suggest that dopamine responses shift relative to the predicted reward magnitude, it is not known how their activity scales with the difference between actual and expected reward. To this end, we analyzed the dopamine responses at the time of the reward in the experiment shown in Fig. 1. Each of three distinct visual stimuli, presented on pseudorandomly alternating trials, predicted that one of two potential liquid volumes would be delivered with equal probability. Animals discriminated behaviorally between the three reward-predicting stimuli (Fig. 1A). Confirming the data described above, the larger of the two volumes always elicited an increase in activity at the time of the reward, and the smaller a decrease. However, the magnitude of activation or suppression appeared to be identical in each case, despite the fact that the absolute difference between actual and expected volume varied over a 10-fold range (Fig. 4, A and B). Thus, the responses of dopamine neurons did not appear to scale according to the absolute dif-

ference between actual and expected reward. Rather, the sensitivity or gain of the neural responses appeared to adapt according to the discrepancy in volume between the two potential outcomes.

To document this result further, we plotted the median neural responses as a function of liquid volume and drew a straight line to connect the data points representing the larger and smaller outcomes after each visual stimulus (Fig. 4C). The slope of these lines provided an estimate of the neurons' gain or sensitivity with respect to liquid volume. When the discrepancy was large, the sensitivity of dopamine neurons was low, and when the discrepancy was small, sensitivity was high. As a result of this adaptation, the neural responses discriminated between the two likely outcomes equally well, regardless of their absolute difference in magnitude. The present data are not sufficient to determine precisely to which aspect of the reward prediction the neuron's sensitivity adapted, but further analysis provided limited evidence that sensitivity adapted to the discrepancy between potential liquid volumes (such as the difference or variance) rather than to their expected value (12) (fig. S2).

Our results suggest that the activity of dopamine neurons carries information on the

magnitude of reward. In representing reward magnitude, neural activity displayed two forms of adaptation that depended on the prediction that was in place at the time of the reward. First, the activity increased or de-

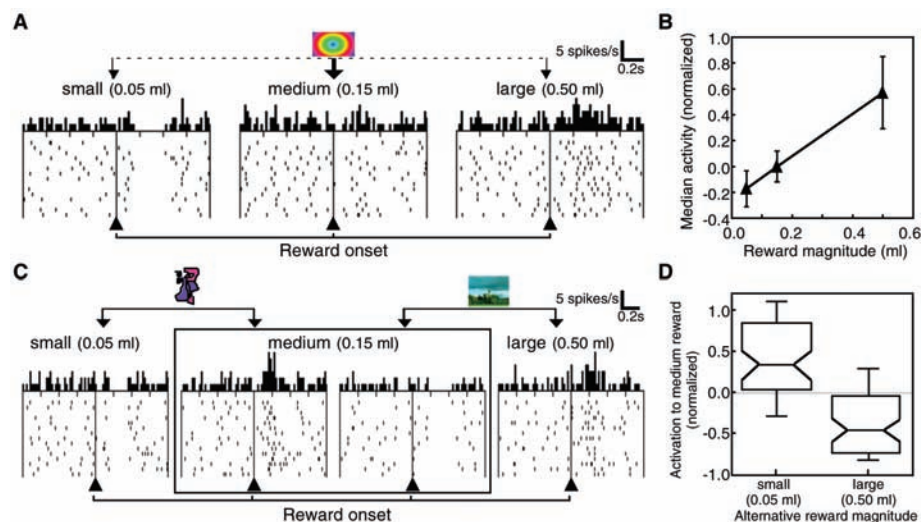


Fig. 3. Bidirectional dopamine responses to reward outcomes reflect deviations from predictions. (A) A single conditioned stimulus was usually followed by an intermediate volume of liquid (0.15 ml) that elicited no change in the neuron's activity (center). However, on a small minority of trials, smaller (0.05 ml) or larger (0.50 ml) volumes were unpredictably substituted, and neural activity decreased (left) or increased (right), respectively. Neural responses to the large liquid volume were relatively long-lasting (supporting online text). (B) Median responses ($\pm 95\%$ confidence intervals) from the population as a function of liquid volume for the experiment in (A) (12 neurons from animal A, 17 neurons from animal B). Responses in each neuron were normalized to the response after the unpredicted delivery of liquid (0.15 ml) in a separate block of trials and in the absence of any explicit reward-predicting stimulus. (C) Responses of a single neuron to three liquid volumes, delivered in the context of two different predictions. One stimulus predicted small or medium volume with equal probability, whereas another stimulus predicted medium or large volume. The medium volume activated the neuron in one context, but suppressed activity in the other. (D) Population responses ($n = 53$ neurons, animal B) to medium reward in the experiment in (C). The plot shows the median, the $\pm 95\%$ confidence intervals (notches corresponding to obtuse angles), the 25th and 75th percentiles (boundaries corresponding to right angles), and the 10th and 90th percentiles (bars). In each neuron, percentage change in activity was normalized to the response to unpredicted liquid (0.15 ml, which elicited a median increase in activity of 97%).

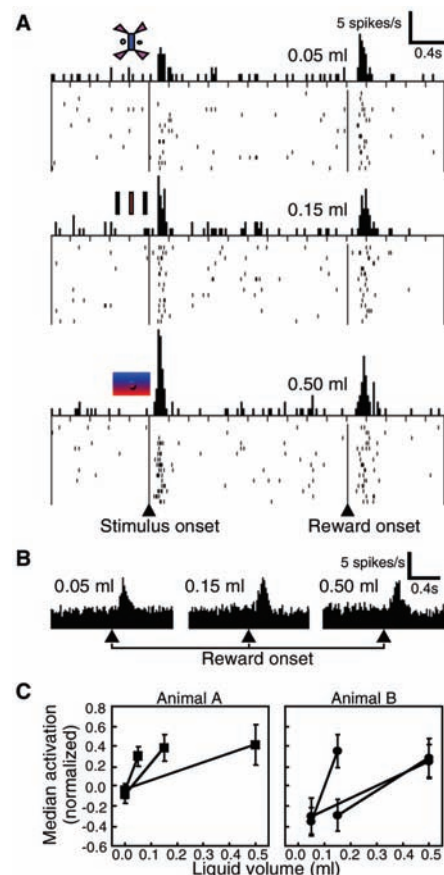


Fig. 4. Neural sensitivity to liquid volume adapts in response to predictive stimuli. (A) Activity of a single neuron showing nearly identical responses to three liquid volumes spanning a 10-fold range. Each of three pseudorandomly alternating visual stimuli (shown at left) was followed by one of two liquid volumes at $p = 0.5$ (top, 0.0 or 0.05 ml; middle, 0.0 or 0.15 ml; bottom, 0.0 or 0.5 ml). Responses after onset of visual stimuli increased with their associated expected reward values. Only rewarded trials are shown. (B) Population histograms for different liquid volumes from the experiment in (A) (57 neurons, animal A). (C) Each line connects responses occurring in the context of a specific conditioned stimulus, and its slope provides a measure of gain or sensitivity. Each point represents the median ($\pm 95\%$ confidence intervals) response of the population taken after normalizing the percentage change in activity in each neuron to the response after unpredicted liquid (0.15 ml) delivered in a separate block of trials (which elicited an activation of 266% above baseline in animal A, $n = 57$ neurons, and 97% in animal B, $n = 53$ neurons). (Left) The experiment in (A) and (B). (Right) The same experiment, but performed in animal B with two nonzero liquid volumes per conditioned stimulus at equal probability ($p = 0.5$) (stimulus 1: 0.05 versus 0.15 ml, stimulus 2: 0.15 versus 0.5 ml, stimulus 3: 0.05 versus 0.5 ml).

creased depending on whether the reward outcome was larger or smaller, respectively, than an intermediate reference point such as expected value. A second, unanticipated form of adaptation was the change in sensitivity or gain of neural activity that appeared to depend on the range of likely reward magnitudes (Fig. 4). Thus, the larger of two potential rewards always elicited the same increase in activity and the smaller of the two elicited the same decrease in activity, regardless of absolute magnitude. The identical responses to liquid volumes spanning a 10-fold range were not due to an insensitivity of the dopamine neurons, which were capable of greater activations (Fig. 4C, note normalization of data points) and discriminated well among these same liquid volumes when delivered in the absence of explicit predictive stimuli (Fig. 2). Rather, the gain of neural activity with respect to liquid volume appeared to adapt in proportion to the range or standard deviation of the predicted reward outcomes, so that neural discrimination between the two reward outcomes that were most probable from the animal's perspective was robust regardless of their absolute difference in magnitude.

The efficiency and accuracy with which neural activity can code the value of a stimulus (such as liquid volume) can be greatly increased if neurons make use of information about the probabilities of potential reward values. Neural activity can then be devoted to representing probable values at the expense of improbable values. Our evidence suggests that the transient dopamine response to conditioned stimuli may carry information on expected reward value, and previous work shows that the more sustained activity of dopamine neurons reflects a measure of reward uncertainty such as variance (10). If the system possesses prior information consisting of the expected value and variance of reward, then this information need not be represented redundantly at the time of re-

ward. Discarding this old information may be achieved by subtracting the expected value from the absolute reward value and then dividing by the variance. Analogous normalization processes appear to occur in early visual neurons (20–22). It is not known to what extent the normalization processes observed in dopamine neurons are actually performed in dopamine neurons as opposed to their afferent input structures (23). Because the new information is by definition precisely the information that the system needs to learn, the activity of dopamine neurons would be an appropriate teaching signal (24).

Adaptation appears to be a nearly universal feature of neural activity. There is substantial evidence, particularly from the early visual system, that adaptation contributes to the efficient representation of stimuli (20–22, 25–28). We have extended the principles of efficient representation to the study of reward. Reward is central to processes underlying behavior, such as reinforcement learning and decision-making, and consideration of limitations and efficiency in the neural representation of reward may yield insights into these processes.

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Supporting Online Material

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Material and Methods

The individual animals, the basic design of the experiments and the electrophysiological techniques for extracellularly recording from dopamine neurons were identical to those previously reported (10). All procedures were performed in Fribourg, complied with the Swiss Animal Protection Law and were supervised by the Fribourg Cantonal Veterinary Office.

Experimental design. Two adult female *Macaca fascicularis* monkeys were mildly fluid deprived. They were trained in a Pavlovian procedure in which distinct visual stimuli predicted specific amounts of sweetened liquid (0.00 ml, 0.05 ml over 40 ms, 0.15 ml over 100 ms, or 0.50 ml over 240 ms) with specific probabilities ($P = 0.0, 0.5, \text{ or } 1.0$) (Fig. S1). We used not more than two rewards per stimulus, which allowed us to explore several stimuli with different reward conditions during the limited testing period with each neuron. We assume the frequency and amount of liquid to provide reasonable approximations of the animals' estimates of the probability and magnitude of reward. Stimuli were chosen to have similar physical salience but to be easily discriminated. To aid discrimination, each stimulus was presented at a unique location on the computer monitor. Liquid was delivered via a computer-controlled solenoid valve from a spout in front of the animal's mouth. The onset of liquid delivery occurred 2 s after the onset of visual stimuli, and offsets of visual stimuli and liquid flow coincided. Licking behavior was monitored with an infrared detector. 'Unpredicted' liquid, not signaled by any immediately preceding stimulus, was delivered to each neuron in a separate block of trials. The inter trial interval

(from reward to next conditioned stimulus or reward) averaged 9 s, consisting of a fixed 4 s plus an exponentially distributed interval with a mean of 5 s.

The computer that controlled behavior did not deliver liquid in a completely random manner. To prevent long streaks in which a stimulus was repeatedly followed by the same reward outcome, the program insured that the actual frequencies would precisely match the assigned probabilities after 8 consecutive trials of a specific visual stimulus. The 'counter' was reset if the experimenter interrupted the recording for more than a few seconds.

Although it would seem to be difficult given the intermixed trial types, it would be possible in principle for an animal to learn this structure and thereby reduce its uncertainty about reward. Previously published analysis of behavior and neural data suggests that the animals did not learn to take advantage of this structure (10).

Training consisted of 100–200 trials of each stimulus per day, five days per week, for about five weeks. Recordings began only after substantial pretraining (5-8 days and 600–1500 trials of each type) and emergence of discriminative conditioned licking responses during the stimulus and preceding the time of reward.

Electrophysiological Recordings. As previously described (S1, 8-11), dopamine neurons in the substantia nigra and ventral tegmental area were identified solely by their discharge characteristics, including low basal firing rates (0.1 – 8.0 Hz) and long duration, initially negative or positive waveforms (1.5 – 5.0 ms, high-pass filtered at 100 Hz and -3 dB). Prior studies in primates have shown that ventral midbrain neurons having these properties are antidromically activated by stimulation of the striatum, and their firing is suppressed by systemic administration of the dopamine D2 receptor agonist apomorphine

(S1). These characteristics are similar to those of identified dopaminergic neurons in other mammalian species (e.g. S2, S3, S4).

Recording sites. Recording sites were marked with small electrolytic lesions and reconstructed from 40 μm thick, stereotaxically oriented coronal brain sections, stained with cresyl violet or antibodies to tyrosine hydroxylase. Recording sites overlapped substantially with those described in a previous report which shows plots of neuronal positions relative to regions of dense tyrosine hydroxylase staining (10). Planes of recorded neurons ranged from 5.5 to 10.5 mm anterior to the interaural line.

Data analysis. Statistical analysis of neural activity followed our previously described methods (8, 10). Typically, at least 15 trials of each trial type were performed per neuron; the minimum accepted trial number for analysis was 7. Average firing rates were measured in standard time windows (see below) and divided by the average rate in a 1 s control period immediately preceding event onset to calculate the percent change in impulse rate. These values were normalized by dividing them by the response to an analogous event (either a visual stimulus or liquid delivery) recorded in the same neuron. Normalized percent changes were used for both statistical analysis and graphical display. The 95% confidence intervals were calculated in the same manner as in the preceding report (10), multiplying the appropriate t-value by the interquartile range and dividing by 1.075 times the square root of the number of observations (S5). Activity in the standard time windows was compared to the 1 s control activity using a Wilcoxon matched-pairs, signed rank test on normalized counts in each trial with each neuron ($p < 0.01$). We employed the Mann-Whitney test for assessing the discrimination between different trial types within single neurons ($p < 0.01$) and the Wilcoxon test for comparing responses within

populations of neurons. The Bonferroni method was used to correct for multiple comparisons.

Standard time windows were fixed across trial types and across neurons, and were chosen so as to capture most of the period in which neural activity changed. Following onset of visual stimuli, the windows were 90-180 ms for monkey A and 110-240 ms for monkey B. For responses following liquid onset, or visual stimulus offset in the case of no reward, the window was 120-320 ms in both monkeys. Peak dopamine responses are typically delayed by about 150 – 200 ms after an error event. A single window was chosen to capture both the periods of suppression and excitation.

A particular time window of 250–400 ms was employed for the specific experiment shown in figure 3A, B, because responses were spread over a longer duration due to prolonged liquid flow with unexpectedly higher volumes. In many past experiments in our laboratory, the animals were able to predict that at a particular moment in time, a drop of a known volume of liquid either would or would not be delivered. A particular volume of liquid always corresponds to a particular duration of liquid flow, so that if a particular volume is expected, then the onset of liquid flow can be used to predict its overall duration. Thus the prediction error, and the dopamine response, is time locked to the onset and does not continue for the duration of the liquid flow. In some of the present experiments however, and particularly that shown in figure 3A, B, both the theoretical prediction error and the dopamine response are spread out over time. In figure 3A, the activation can be seen to be particularly sustained in response to 0.5 ml of liquid flowing for 240 ms. Most other neurons tested in this experiment showed similarly long-lasting responses. In principle, the positive error signal in this case would begin only after 120 ms, since the

expected liquid volume lasts only for 120 ms, and would continue until 240 ms when liquid flow stops. The negative error signal to the small reward (0.05 ml over 40 ms) in this experiment would not be expected to begin until 40 ms.

Additional analysis of data shown in Figure 4

The sensitivity or gain of the neural responses as a function of liquid volume adapted according to the prediction made by the visual stimulus, so that responses appeared to be equivalent regardless of their absolute magnitude (Fig. 4). We considered two hypotheses concerning what aspect of the prediction evoked the adaptation. First, the adaptation in sensitivity may have consisted of normalization to some measure of the discrepancy between likely outcomes, such as the range or standard deviation. Alternatively, normalization could have occurred to the expected value. The experiments were not originally designed to discriminate between these two possibilities, and in the experiment depicted in figure 4C left, expected value and range perfectly covaried. However, in the experiment of figure 4C right, the two varied in a partially independent manner across visual stimuli, and therefore this data set provided an opportunity to compare the two hypotheses. The neural responses of figure 4C right were replotted after normalizing the abscissa by either the difference (range) in potential volumes (Fig. S2 top) or by expected liquid volume (mean) (Fig. S2 bottom). The observation that neural responses in all three conditions appeared to be identical could be explained by the fact that all pairs of reward outcomes were exactly one range apart (Fig. S2 top). By contrast, when liquid volume is expressed in units of the mean, the difference between pairs of reward outcomes ranged from 1.00 to 1.64 means (Fig. S2 bottom), and yet neural responses appeared insensitive to this discrepancy. This did not appear to be due to saturation of the response, since

responses to unpredicted volumes of 0.15 ml in the same neurons were about twice as large (Fig. S2). In order to statistically compare the two normalization procedures, we compared the slopes for each pair of reward outcomes (Fig. S2). The slopes did not differ from one another after normalizing by the range (Fig. S2 top) ($p > 0.2$ for all three comparisons, Wilcoxon paired sample test, $n = 53$), but the slope corresponding to liquid volumes of 0.05 and 0.50 was significantly less than either of other two after normalizing by the mean (Fig. S2 bottom) ($p < 0.001$). To directly compare the effect of normalization by range versus mean on the slopes, the difference between the slope for the 0.05–0.50 ml pair and the mean of the other two slopes was divided by the mean slope. This ratio was calculated in each neuron after normalization to the mean, and again after normalization to the range, and was significantly greater after normalization by the mean ($p < 0.0001$, $n = 53$, Wilcoxon paired sample test). This analysis suggests that normalization by the range could account for the identical responses, whereas normalization by the mean or expected value would not in itself appear to be fully sufficient to account for the identical responses. Although the present evidence on this point is limited, it suggests that normalization by the range provides the more parsimonious explanation. As the range perfectly covaried with the standard deviation in all the present experiments, the observed adaptation appeared to occur relative to the standard deviation, which is an accepted measure of uncertainty. Furthermore, past experiments indicate that the sustained, delay-period activity of dopamine neurons may represent the standard deviation or some other measure of uncertainty. Studies on motion-sensitive neurons of the fly suggest that they possess information about the standard deviation and use it for normalization in a manner analogous to what we observe in dopamine neurons (21, 22).

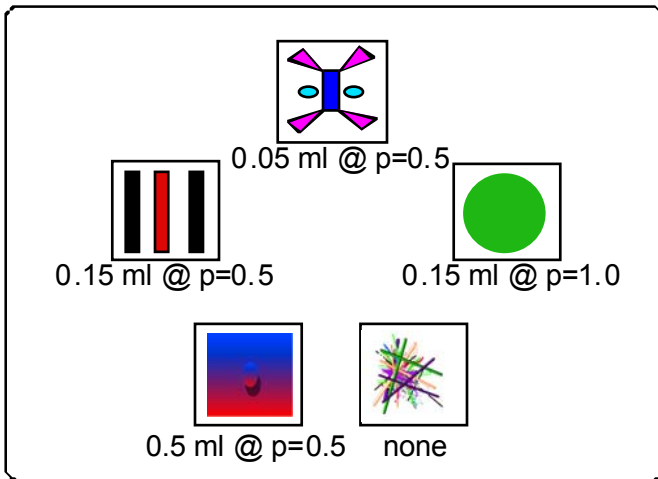


Fig. S1 Visual stimuli indicated probabilities of various liquid volumes. One stimulus was presented in each trial on a computer monitor directly in front of the animal. Each stimulus was always presented in the same unique location. The particular stimuli illustrated here were used in animal A in the experiments illustrated in figures 1 and 4. A particular image was never used in more than one experiment in an individual animal. Different images were used in Animal B.

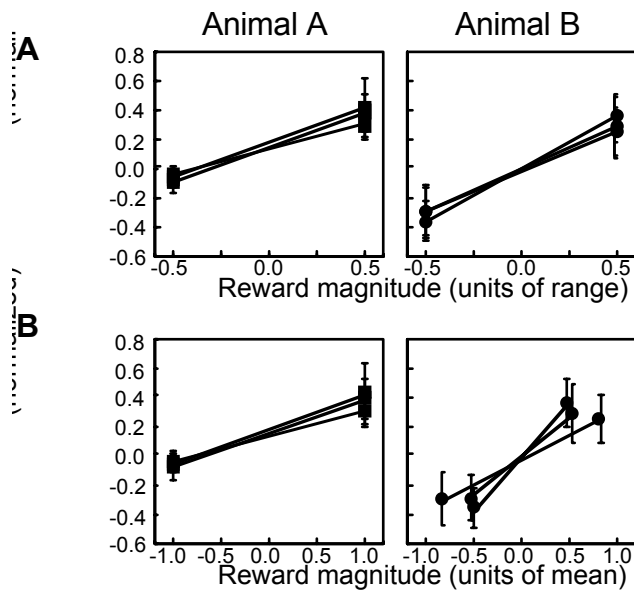


Fig. S2. Adaptation of neural sensitivity to liquid volume following reward-predicting stimuli. Same data as in figure 4C, but replotted after normalizing the abscissa by either the range of potential liquid volumes predicted by a visual stimulus (top), or by the expected value (mean) indicated by a visual stimulus (bottom). Each line connects a pair of points representing the two potential reward outcomes predicted by a distinct visual stimulus. Each point represents the median response ($\pm 95\%$ confidence intervals) of the population taken after normalizing to the response following unpredicted reward recorded in the same neuron (0.15 ml; median activation of 266% in animal A, $n = 57$, and 97% in animal B, $n = 53$). The lesser variation of the slopes in panel A suggests that dopamine neurons or their inputs may normalize the liquid volumes by range or standard deviation rather than expected value or mean.

References and Notes

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