Supplement 1

Supplemental Methods

Animals

Male Sprague Dawley rats (*n* = 17, Harlan Sprague Dawley, Indianapolis, IN) aged 90-120 d and weighing 260-350 g were used as subjects and individually housed with a 12:12 light:dark cycle. All experiments were conducted between 9:00 am and 5:00 pm. Bodyweights were maintained at no less than 85% of pre-experimental levels by food restriction (10-15 g of Purina laboratory chow each day, in addition to approximately 1 g of sucrose consumed during daily sessions). This regimen was in place for the duration of behavioral testing, except during the post-operative recovery period when food was given ad libitum. All procedures were approved by the Institutional Animal Care and Use Committee.

Behavioral training

All training occurred in custom experimental chambers (Med Associates, St Albans, VT) equipped with two retractable response levers, two corresponding cue lights, one reward receptacle, a house light, and a white noise generator. Lever pressing behavior in all rats was initially reinforced on a continuous schedule of reinforcement (fixed ratio 1, FR1) on two levers, such that every response on either lever resulted in the delivery of a 45 mg sucrose pellet to a centrally located food receptacle. A maximum of 100 reinforcers (50 per lever) were available per session (with 1 session per day). After stable responding developed (at least 5 sessions), rats were transferred to a multiple schedule task in which reward delivery was contingent on operant responses in 90 discrete trials per session. Each trial was initiated randomly after a variable time interval, with an average of 20 s between trials. Distinct cue lights (located above two response levers) were illuminated for 5 s before lever extension to signal which lever was active (i.e.,

which lever produced reinforcement; see Figure 1). Response levers were available for 15 s unless response requirements were completed, in which case the levers were retracted and the reward was delivered. On 60 forced-choice trials, one cue was presented alone and only a response on the corresponding lever was reinforced. On these trials, responses made on the uncued lever (termed "errors") resulted in the termination of the houselight for the remainder of the trial period and the absence of sucrose delivery for that trial. On another 30 free-choice trials, both cues were presented simultaneously, allowing a choice between both options. During the acquisition of this task, the response cost and the reward delay of each option was identical (an FR1 schedule of reinforcement; no reward delay).

Training occurred over 25 initial sessions. In order to produce an effort disparity between response options for the effort-based decision task, the required fixed ratio on one lever (termed the "high cost" option) was gradually increased from 1 to 16 (FR1 to FR16) according to the following schedule: Sessions 1-11, FR1; Session 12, FR2; Session 13, FR4; Sessions 14-16, FR8; Sessions 17-20, FR12; Sessions 21-25, FR16 (see Figure S1A). The fixed ratio on the other lever (termed the "low cost" option) remained the same throughout training. Likewise, in order to produce a disparity in reward delay between response options in the delay-based decision task, reward delay (the time interval between the behavioral response and reward delivery) was gradually increased for one option (termed the "delayed reward" option) according to the following schedule: Sessions 1-11, 0 s; Session 12, 1 s; Session 13, 2 s; Sessions 14-16, 3 s; Sessions 17-20, 4 s; Sessions 21-25, 5 s. The reward delay on the other lever (the "immediate reward" option) was held constant at 0 s throughout training and electrochemical recording.

This design was advantageous for three reasons. First, it allowed animals to learn the predictive associations fully before effort requirements were altered, meaning that cost-based

decisions and learning rates were not confounded. Second, it ensured that initial biases in response allocation did not contribute to electrochemical results. Third, it allowed full characterization of how behavioral preference changed as a function of effort and reward delay. In this task, the ability to discriminate between cues was necessary for better-than-chance performance on forced-choice trials. Therefore, the number of errors served as a convenient behavioral measure of cue discrimination. As each cue predicted different effort requirements and preceded the opportunity to respond, this design enabled direct comparison of both cue-related and response-related nucleus accumbens (NAc) dopamine (DA) signals. Response allocation on free-choice trials was used to evaluate behavioral preference on the basis of value.

Surgery

After behavioral training, rats were surgically prepared for voltammetric recordings as described previously (1). After establishing an anesthetic plane with ketamine hydrochloride (100 mg/kg, intramuscular) and xylazine hydrochloride (20 mg/kg, intramuscular), rats were placed in a stereotaxic frame. A guide cannula (Bioanalytical Systems, West Lafayette, IL) was positioned dorsally to the core or shell subregions of the NAc (1.3 mm anterior, 1.3 mm lateral from bregma). An Ag/AgCl reference electrode was placed contralateral to the stimulating electrode in the left forebrain. Stainless steel skull screws and dental cement were used to secure all items. A bipolar stimulating electrode was placed dorsally to the ventral tegmental area (VTA) (5.2 mm posterior, 1.0 mm lateral from bregma and 7 mm ventral from the dural surface). A detachable micromanipulator containing a glass-sealed carbon-fiber electrode (75−100 μm exposed tip length, 7 μm diameter, T-650; Amoco, Greenville, SC) was inserted into the guide cannula, and the electrode was lowered into the NAc. The bipolar stimulating electrode was then lowered in 0.2 mm increments until electrically evoked dopamine release was detected at the

carbon-fiber electrode in response to a stimulation train (60 biphasic pulses, 60 Hz, 120 μA, 2 ms per phase). The stimulating electrode was then fixed with dental cement and the carbon-fiber electrode was removed.

Fast-scan cyclic voltammetry

Following surgery, animals were allowed one week to recover pre-surgery body weight. Food restriction was then resumed to ensure motivation during behavioral performance. Dopamine concentration changes during behavior were assessed using fast-scan cyclic voltammetry, as described previously (1). Briefly, dopamine changes during behavior were assessed using a new carbon-fiber electrode, which was placed in the micromanipulator and lowered into the NAc core or shell. The potential of the carbon-fiber electrode was held at −0.4 V versus the Ag/AgCl reference electrode. Voltammetric recordings were made every 100 ms by applying a triangular waveform that drove the potential to +1.3 V and back at a rate of 400 V/s. The application of this waveform causes oxidation and reduction of chemical species that are electroactive within this potential range, producing a change in current at the carbon-fiber. Following equilibration in the brain (typically 20-30 minutes to reduce current drift at the electrode), dopamine release was electrically evoked by stimulating the VTA using a range of stimulation parameters (2-24 biphasic pulses, 20-60 Hz, 120 μA, 2 ms per phase) to ensure that carbon-fiber electrodes were placed close to release sites. The position of the carbon-fiber was secured at the site of maximal dopamine release. Electrochemical recordings were made continuously with 100 ms temporal resolution during a single behavioral session. VTA stimulation was repeated following the experiment to verify electrode stability and ensure that the location of the electrode could still support dopamine release.

Signal identification and separation

After in vivo recordings, dopamine release evoked by VTA stimulation of unexpected reward delivery was used to identify naturally occurring dopamine transients using methods described previously (2, 3). Stimulation of the VTA leads to two well-characterized electrochemical events: an immediate but transient increase in DA and a delayed but longer-lasting basic pH shift. To separate these signals, a training set was constructed from representative, background-subtracted cyclic voltammograms for dopamine and pH. This training set was used to perform principal component regression on data collected during the behavioral session. Principal components were selected such that at least 99% of the variance in the training set was accounted for by the model. All data presented here fit the resulting model at the 95% confidence level. After use, carbon-fiber electrodes were calibrated in a solution of known DA to convert observed changes in current to differential concentration.

Data analysis

All behavioral events (cue onset and offset, lever presses, lever extension/retraction, and reward delivery) occurring during training and electrochemical recording were recorded. Effects of response effort or reward delay on choice allocation during training (Figure S1) were evaluated using a two-way repeated measures ANOVA of mean choice probability as a function of cost, with Bonferroni post-hoc tests used to correct for multiple comparisons. Response latencies (distance between lever extension and first lever press) on low cost vs. high cost and immediate vs. delayed reward trials during recording sessions were compared using paired two-tailed *t*-tests.

Phasic changes in extracellular DA concentration during the task were assessed by aligning DA concentration traces to relevant behavioral events (specifically, cue presentations,

lever extension, and reward delivery). Individual data were smoothed using a Gaussian filter (kernel width = 3 bins). Group increases or decreases in NAc dopamine concentration were evaluated separately for each trial type and for each event using a one-way repeated measures ANOVA with Dunnett's correction for multiple comparisons. This analysis compared the baseline mean dopamine concentration to each data point (100 ms bin) obtained within 2.5 s following an event. The effects of increased effort or delay on dopamine concentration were assessed using paired, two-tailed *t*-tests. Comparisons were performed separately for data collected in the core and shell of the NAc and for data collected during different tasks. Forced-choice trials and free-choice trials were analyzed separately. For comparison of dopamine signals on free-choice trials, animals that never selected the low-value option were removed to allow for proper statistical comparison and ensure that results were not biased. For all trial types, only rewarded trials were included in analyses. Reward delays on high cost trials in the effort-based decision experiment were compared to the imposed delay on delayed reward trials using a one-sample, two-tailed *t*-test (with comparison to the hypothetical mean of 5.0 s). Comparison of differential cue-evoked dopamine signals between experiments was performed using unpaired, two-tailed *t*-tests. All analyses were considered significant at $\alpha = 0.05$. Statistical and graphical analyses were performed using Graphpad Prism and Instat (Graphpad Software, Inc.) and Neuroexplorer for Windows version 4.034 (Plexon, Inc.).

Histological verification of electrode placement

Upon completion of each experiment, rats were deeply anesthetized with a ketamine/xylazine mixture (100 mg/kg and 20 mg/kg, respectively). In order to mark the placement of electrode tips, a 50−500 μA current was passed through a stainless steel electrode for 5 seconds. Transcardial perfusions were then performed using physiological saline and 10%

formalin, and brains were removed. After post-fixing and freezing, 50 μm coronal brain sections were mounted on microscope slides. The specific position of individual electrodes was assessed by visual examination of successive coronal sections. Placement of an electrode tip within the NAc was determined by examining the relative position of observable reaction product to visual landmarks (including the anterior commissure and the lateral ventricles) and anatomical organization of the NAc represented in a stereotaxic atlas (4). For two animals in the effort experiment, separate recordings were performed in the NAc core and shell during different behavioral sessions. For three animals in the delay experiment, separate recordings were performed in the NAc core during different behavioral sessions in which the electrode was lowered to a new location.

Supplemental Results

Changes in behavioral preference during training

Behavioral preference on free-choice trials changed as a function of imposed response cost and reward delay during training (repeated measures ANOVAs, effect of cost; $p < 0.0001$ for both comparisons). In the effort-based decision task, rats preferred the low cost option over the high cost option when the high cost was 4, 8, or 16 lever presses (Bonferroni *post hoc* tests, all p's < 0.01; Figure S1B). Likewise, in the delay-based decision task, rats preferred the immediate reward option over the delayed reward option when the imposed delay was 4 and 5 seconds (Bonferroni *post hoc* tests, both p's < 0.01; Figure S1B).

Response latencies on high and low value trials

Behavioral discrimination between response options on the basis of effort was also evident in the response latency on the recording day, with significantly faster responses on the

low cost option (paired *t*-test, $t = 3.822$, df = 13, $p = 0.0024$; Figure S1C). Likewise, on free-choice trials, animals exhibited significantly faster response times on trials in which the low cost option was selected than on trials in which the high cost option was selected (analysis limited to animals that selected the high cost option; paired *t*-test, $t = 3.321$, df = 8, $p = 0.0105$). Thus, animals behaved similarly when they selected the low or high cost option regardless of whether choices were free or forced, indicating that high cost choices on free choice trials were not simply accidental. There was no significant difference in response latency on immediate and delayed reward forced-choice or free-choice trials (paired *t*-test, $p > 0.2$ for each comparison).

Core and shell differences in dopamine signaling

In another group of animals where dopamine release was recorded from the nearby NAc shell ($n = 7$ sessions from 7 animals; effort task only), cue-evoked dopamine signals did not significantly encode future reward value ($t = 1.803$, df = 6, $p = 0.12$; Figure S4). This subregion difference was not attributable to the differences in behavioral performance between animals during core and shell recording sessions (*t*-test comparisons for choice allocation, number of errors, number of rewards, all *p*'s > .10), suggesting that value signals (at least with respect to effort) are not as robust in the NAc shell.

Laterality of value signals

Although all recording sites were located in the right nucleus accumbens, there were no differences in cue selectivity of dopamine responses based on whether the low value option was contralateral or ipsilateral to the recording site (unpaired *t*-test, $t = 0.9861$, df = 12, $p = 0.3436$).

Supplemental Discussion

These present results are consistent with aspects of a recent report which revealed that both reward cost and reward magnitude are encoded by rapid NAc dopamine transmission (5). However, these findings also differ in important ways. First, the previous report found that effort encoding was only present in dopamine signals early in experience with a specific contingency. In contrast, our findings demonstrate that dopamine signals still encode reward cost after even prolonged training, and are therefore in a position to affect decisions between familiar response options. Secondly, the present experiment separately examined both reward delay and effort, thereby revealing that these two parameters are dissociably reflected in cue-evoked dopamine signals. Finally, by examining both forced and free choice trials, these results reveal a critical distinction between how dopamine may contribute to decisions that only involve one option and decisions that involve competing response options. Thus, these data provide new insights into cost-based decision making and call for a reassessment of how the mesolimbic dopamine system contributes to cost evaluation.

The role of NAc dopamine in effort-based decision making has received much attention, with a number of studies revealing two related yet dissociable deficits following dopamine depletion or antagonism in the NAc. First, in fixed choice tasks in which animals can only gain reinforcement on one response lever, dopamine blockade produces robust decreases in response rates, even when reinforcement rates are held constant (6-8). Secondly, in tasks that allow animals to choose between multiple sources of reinforcement that come with different costs, dopamine manipulation alters the relative allocation of responses (9, 10). Specifically, although animals normally prefer to pay higher costs for larger magnitude rewards, this preference rapidly switches to lower cost, smaller rewards when NAc dopamine receptors are blocked. Importantly,

such effects are not attributable to impaired reward processing or decreased reward sensitivity, as NAc dopamine depletion does not change positive hedonic reactions to rewarding stimuli, and mice that completely lack dopamine still exhibit normal reward preferences (11, 12). Taken together, these findings suggest that increases in dopamine may be acting as an "activator" to help animals overcome particularly high costs to obtain better rewards (8, 13). In the present task, identical rewards were provided for both high and low value response options, making it easier to determine whether dopamine signaling was encoding effort and reward delay. However, given that operant responses in the present task were not associated with phasic increases in dopamine levels, it is possible that the rate-decreasing effects of NAc dopamine depletions operate through another aspect of dopaminergic transmission. A candidate mechanism is tonic release of dopamine, which has been used successfully in free-operant models of behavior to explain how NAc dopamine depletions could impact response vigor and response rate (14). One possibility is that tonic dopamine levels increase before or during the behavioral session, and that these changes serve to prime or enable reward seeking, especially when it is attended by high costs (15). In contrast, phasic dopamine release events may influence moment-to-moment decisions between rewarding alternatives that differ in their delay or effort. The present findings suggest that this may be achieved via differential dopamine release for cues that predict low vs. high cost requirements. In this way, information about both the cost and benefits of future rewards could be relayed to striatal circuits to either facilitate or strengthen choices that involve the same reward but lower costs.

The present results suggest that dopamine signals in the NAc core reflect the value of the best available action under choice situations. This is consistent with a recent study in which VTA dopamine neurons were recorded during a decision making task in which animals chose between

rewards of different magnitudes or different temporal delays (16). However, our results appear to be inconsistent with another report in which substantia nigra dopamine neurons were recorded as monkeys chose between two options that were rewarded at different probabilities (17). In this study, dopamine neuron activity reflected the value of the upcoming choice, rather than the value of the best available option. Although the present results appear to contradict this finding, it is important to note that several methodological differences may also explain this discrepancy, such as the nature of cues used, the species involved, and the task design (e.g., blocked trials vs. intermixed trials). Most importantly, we would note that whereas most of the dopaminergic input into the NAc arises from the VTA, the majority of dopaminergic substantia nigra projections terminate in the dorsal striatum (18, 19). Since our dopamine recordings were made in the NAc, it remains possible that the action value signals reported by Morris *et al.*, (17) could only be detected in the dorsal striatum, which is more closely linked to the execution of specific actions. In fact, such an arrangement would be entirely consistent with studies that selectively implicate the NAc in cue-reward associations and the dorsal striatum in response-reward associations (20-24). Moreover, several recent studies have reported key subregion differences between the firing patterns of dopamine neurons located in the VTA and substantia nigra in response to environmental cues and other stimuli (25-27), indicating dopamine neuron firing is not completely homogenous. Thus, the present results do not necessarily refute the idea that dopamine neurons in the substantia nigra could signal action value instead of the value of the best available action.

Emerging evidence suggests that cost-based decision making is regulated by a complex brain circuit, which includes the anterior cingulate cortex (ACC), basolateral amygdala (BLA), NAc core, and dopamine release within the NAc core (28). Precisely why dopamine disruption in

the NAc alters choice behavior on cost-related tasks remains a question for open investigation. However, the difference in cue-evoked NAc core dopamine signals reported here may indicate one substrate for dopamine's role in cost-based decision making. Dopamine release is thought to modulate synaptic plasticity through a number of mechanisms within the NAc (29), determining which glutamatergic inputs drive NAc output. Thus, cue-evoked release of dopamine would presumably engage synaptic plasticity mechanisms to strengthen coincidently active glutamatergic inputs onto NAc neurons, which provide cue-specific, context-related, and outcome-specific information related to those cues. This idea is supported by evidence that interrupting dopamine transmission alters cue-evoked neuronal responses in the NAc and impairs behavioral responses to reward-paired cues (30). It follows that cues which evoke greater release of dopamine, such as those that predict lower cost or immediate rewards, would facilitate certain inputs over time and across repeated experiences, allowing them to exhibit enhanced control over NAc output and motivated behavior.

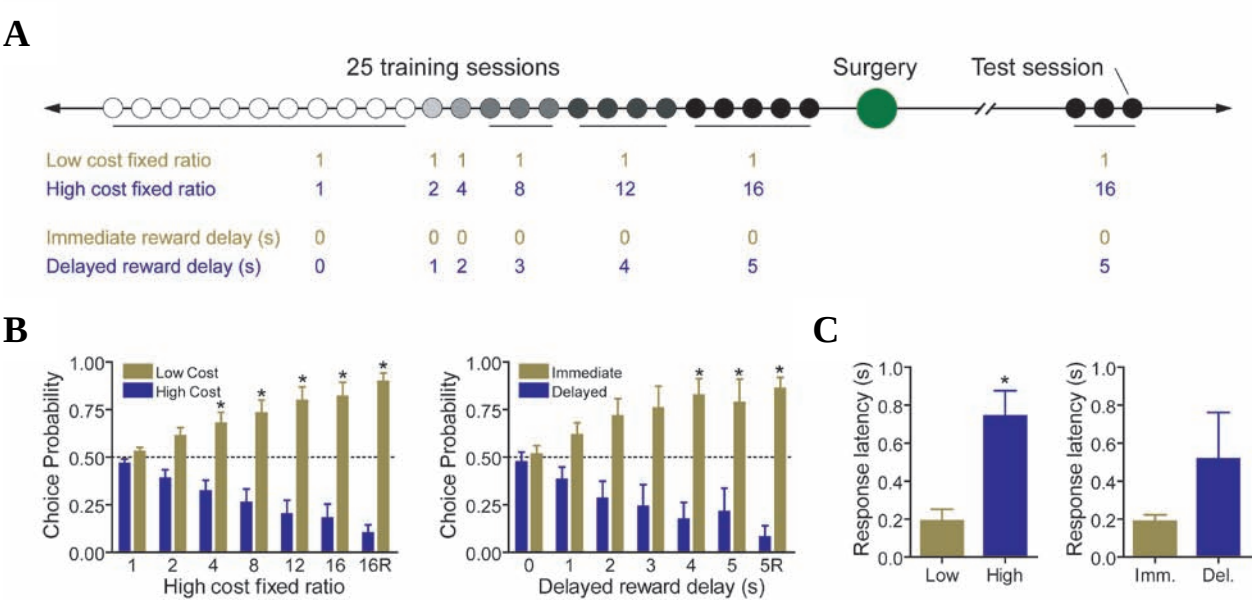

Figure S1. (**A**) Experimental timeline. Animals received 25 total training sessions before surgical implantation of guide cannula above the NAc (each circle = 1 session). At least 3 additional training sessions occurred after surgery, and dopamine concentration was recorded during the task. Animals acquired the task in the absence of a difference in response cost or reward delay for each option. Numbers below circles indicate number of responses required to produce reinforcement on low and high cost trials for each session (effort-based decision task) or time (in seconds) from the behavioral response to the reward delivery (delay-based decision task). Required response costs and imposed reward delays were gradually increased for high cost and delayed reward trials across training. (**B**) Choice probability (free-choice trials only) as a function of the response cost (effort task, left panel) and reward delay (delay task, right panel) imposed on high cost and delayed reward trials, respectively. Dashed line indicates indifference point. Choice allocation shifted as a function of response cost and reward delay (two-way repeated measures ANOVA, $p < 0.05$). Asterisks indicate ratios at which preference for the low-cost option was significant (Bonferroni *post hoc* tests, $p < 0.05$). 16R and 5R denotes choice preference during recording sessions. (**C**) Response latencies for forced choice trials in effort (left) and delay (right) tasks. Animals took longer to initiate responding on high cost trials than low cost trials (paired *t*-test, $p = 0.014$). There was no significant difference between response latencies on the delay task ($p = 0.22$).

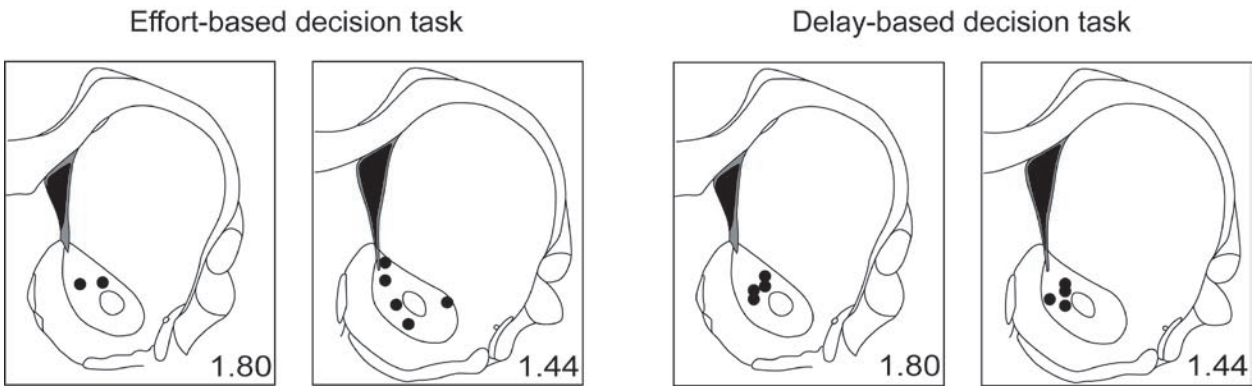

Figure S2. Coronal diagram illustrating confirmed location of carbon-fiber electrodes within the NAc core for effort and delay based decision tasks. Number in lower right corner indicates location anterior to bregma, in mm.

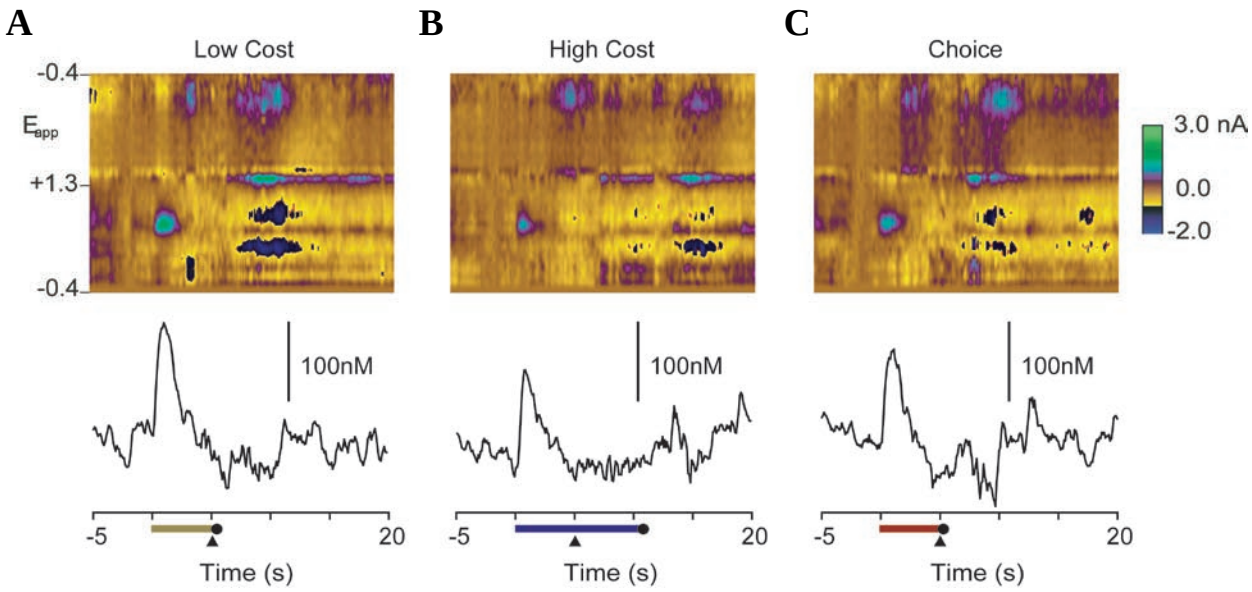

Figure S3. Representative electrochemical data collected during individual behavioral trials. (**A**) Two-dimensional representation (color plot) of electrochemical data collected during a single low cost trial (top) and corresponding dopamine concentration trace (bottom). The applied voltage (ordinate) is plotted during a 25 s window aligned to cue onset (horizontal gold bar beginning at time-point zero, abscissa). Changes in current at a carbon-fiber electrode located in the NAc are encoded in color. The black triangle denotes lever extension, whereas the black circle marks reward delivery. Dopamine is visible as a green-encoded spike in current at cue onset in the color plot. (**B**) Color plot and dopamine trace from a high cost trial. Blue bar denotes cue presentation. All other conventions follow panel A. Here, cue presentation is prolonged and reward delivery delayed due to the FR16 requirement. (**C**) Color plot and dopamine trace on choice trial, when both cues were presented. Here, the animal selected the low cost option. Red bar denotes cue presentation; all other conventions follow panel A. All cues evoked dopamine release in the NAc.

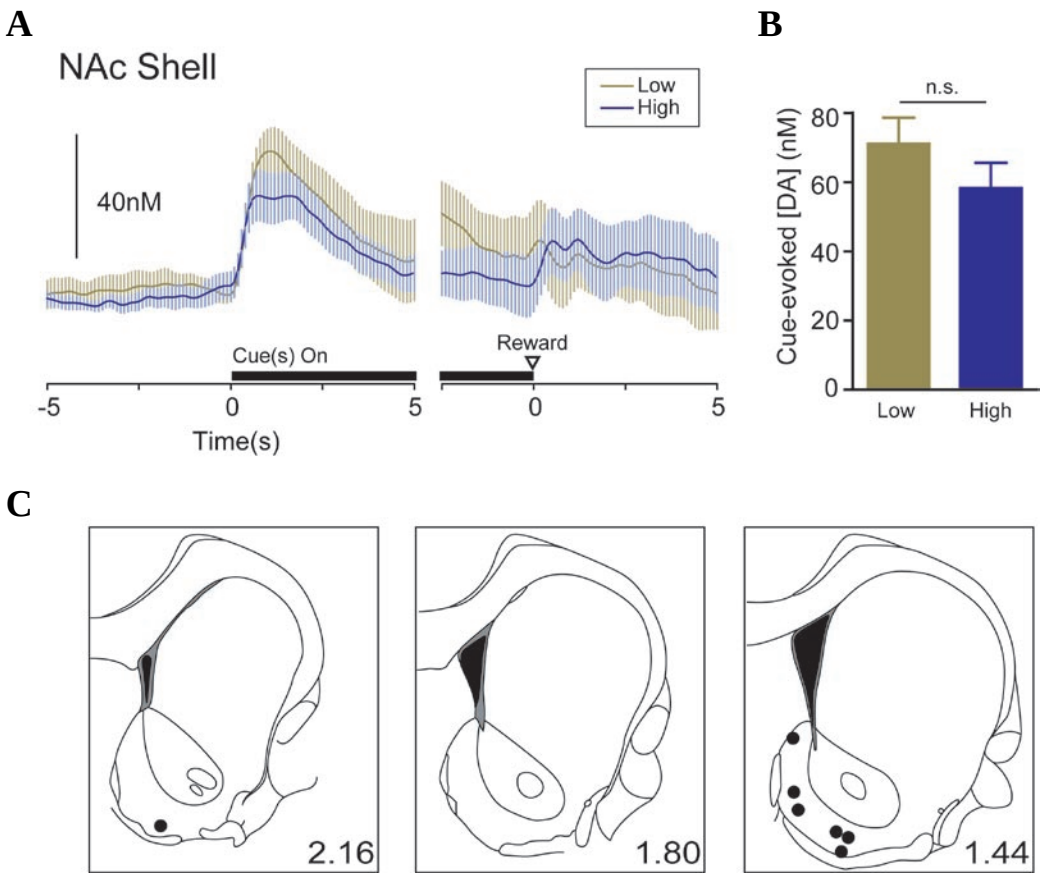

Figure S4. Cue-evoked dopamine signal in the NAc shell does not significantly encode reward cost. (**A**) Mean (solid lines) ± SEM (shaded lines) change in dopamine concentration during each trial type for electrode placements in the NAc core (n = 7). Aligned to cue onset (black bar, left panel) and reward delivery (inverted triangle, right panel). Both cues evoked significant increases in dopamine concentration (repeated measures ANOVAs, $p < 0.05$). Reward delivery did not change dopamine concentration. (**B**) Peak cue-evoked dopamine signal (mean ± SEM) across for low and high cost trial types for NAc shell electrode placements. There were no differences in the magnitude of dopamine released in response to low cost, high cost, and choice cues within the NAc shell (repeated measures ANOVA, $p > 0.05$). (**C**) Confirmed location of carbon-fiber electrodes within the NAc shell (n = 7). Units indicate coronal placement anterior to bregma. n.s., not significant

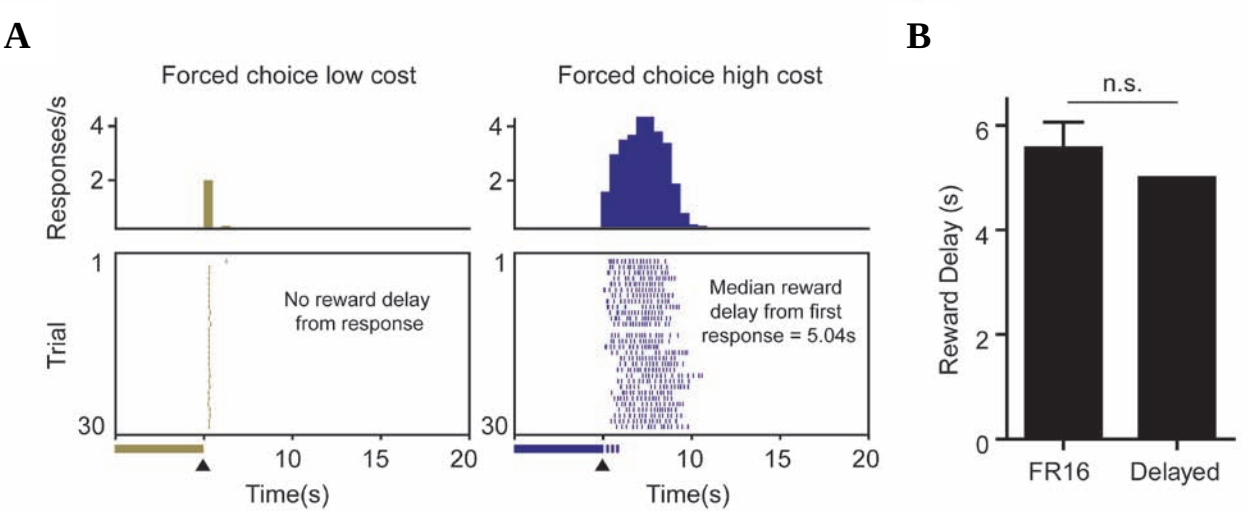

Figure S5. Increased effort requirement leads to implicit reward delay. (**A**) Left panel, histogram and raster plot representing timing of behavioral responses on low cost trials relative to cue presentation (gold bar). Data are aligned to cue onset (time zero). For raster plot, each tick represents a single response. Rewards were delivered immediately after response. Right panel, histogram and raster plot representing timing of behavioral responses on high cost trials, relative to cue presentation (blue bar). Here, rewards were delivered after completion of 16 responses, leading to a longer delay between the first response and reward delivery. (**B**) Mean (± SEM) reward delay associated with high cost (FR16) completion in effort task and 5 s delay imposed on delayed reward trials in delay task. Reward delays did not significantly differ (one-sample *t*-test, comparison with hypothetical 5 s mean, $p = 0.29$). n.s., not significant

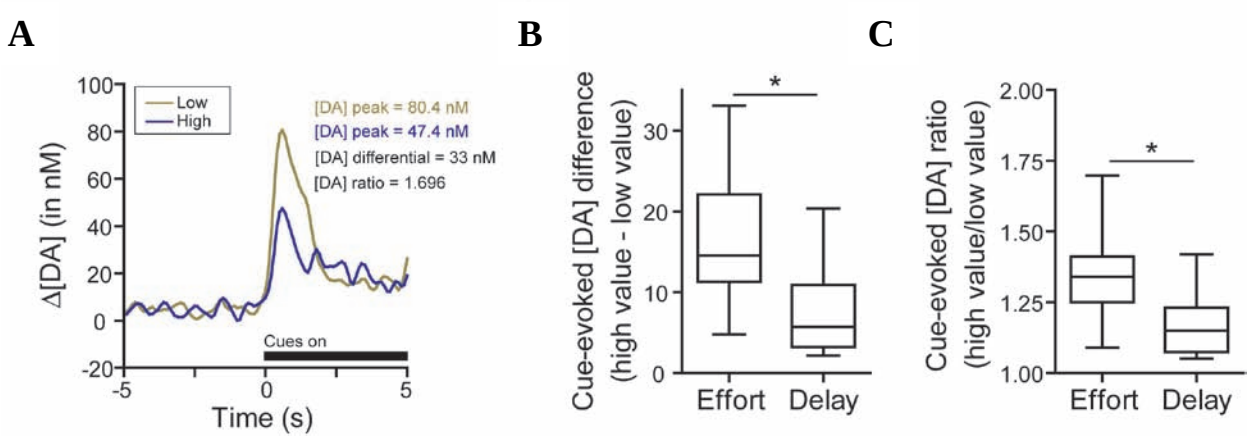

Figure S6. Separate contribution of effort and delay to selective dopamine signals. (**A**) Mean dopamine traces for high and low cost trials for a representative animal, aligned to cue onset. The low cost cue evoked a peak of 80.4 nM in dopamine concentration, whereas the high cost cue evoked a dopamine peak of 47.4 nM. The difference (low cost minus high cost) in this signal was 33 nM and the ratio (low cost/high cost) was 1.646. (**B**) Box plots representing the difference in cue-evoked dopamine signals. The difference in high value and low value dopamine signals was significantly greater in the effort task than in the delay task (unpaired *t*-test, $p = 0.038$). (**C**). Box plots representing the ratio between cue-evoked dopamine signals. The ratio of high value:low value dopamine signals was significantly greater in the effort task than in the delay task (unpaired *t*-test, $p = 0.048$).

Supplemental References

1. Day JJ, Roitman MF, Wightman RM, Carelli RM (2007): Associative learning mediates dynamic shifts in dopamine signaling in the nucleus accumbens. *Nat Neurosci* 10:1020-1028.
2. Heien ML, Johnson MA, Wightman RM (2004): Resolving neurotransmitters detected by fast-scan cyclic voltammetry. *Anal Chem* 76:5697-5704.
3. Heien ML, Khan AS, Ariansen JL, Cheer JF, Phillips PE, Wassum KM, Wightman RM (2005): Real-time measurement of dopamine fluctuations after cocaine in the brain of behaving rats. *Proc Natl Acad Sci U S A* 102:10023-10028.
4. Paxinos G, Watson C (2005): *The rat brain in stereotaxic coordinates*, Fifth ed. New York: Elsevier.
5. Gan JO, Walton ME, Phillips PE (2010): Dissociable cost and benefit encoding of future rewards by mesolimbic dopamine. *Nat Neurosci* 13:25-27.
6. Aberman JE, Salamone JD (1999): Nucleus accumbens dopamine depletions make rats more sensitive to high ratio requirements but do not impair primary food reinforcement. *Neuroscience* 92:545-552.
7. Aberman JE, Ward SJ, Salamone JD (1998): Effects of dopamine antagonists and accumbens dopamine depletions on time-constrained progressive-ratio performance. *Pharmacol Biochem Behav* 61:341-348.
8. Salamone JD, Correa M, Mingote S, Weber SM (2003): Nucleus accumbens dopamine and the regulation of effort in food-seeking behavior: implications for studies of natural motivation, psychiatry, and drug abuse. *J Pharmacol Exp Ther* 305:1-8.
9. Cousins MS, Atherton A, Turner L, Salamone JD (1996): Nucleus accumbens dopamine depletions alter relative response allocation in a T-maze cost/benefit task. *Behav Brain Res* 74:189-197.
10. Cousins MS, Salamone JD (1994): Nucleus accumbens dopamine depletions in rats affect relative response allocation in a novel cost/benefit procedure. *Pharmacol Biochem Behav* 49:85-91.
11. Cannon CM, Palmiter RD (2003): Reward without dopamine. *J Neurosci* 23:10827-10831.
12. Berridge KC (2006): The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl).*
13. Salamone JD, Correa M (2002): Motivational views of reinforcement: implications for understanding the behavioral functions of nucleus accumbens dopamine. *Behav Brain Res* 137:3-25.
14. Niv Y, Daw ND, Joel D, Dayan P (2007): Tonic dopamine: opportunity costs and the control of response vigor. *Psychopharmacology (Berl)* 191:507-520.
15. Cousins MS, Trevitt J, Atherton A, Salamone JD (1999): Different behavioral functions of dopamine in the nucleus accumbens and ventrolateral striatum: a microdialysis and behavioral investigation. *Neuroscience* 91:925-934.
16. Roesch MR, Calu DJ, Schoenbaum G (2007): Dopamine neurons encode the better option in rats deciding between differently delayed or sized rewards. *Nat Neurosci* 10:1615-1624.
17. Morris G, Nevet A, Arkadir D, Vaadia E, Bergman H (2006): Midbrain dopamine neurons encode decisions for future action. *Nat Neurosci* 9:1057-1063.
18. Ikemoto S (2007): Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. *Brain Res Rev* 56:27-78.

19. Haber SN, Fudge JL, McFarland NR (2000): Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci* 20:2369-2382.
20. Di Ciano P, Cardinal RN, Cowell RA, Little SJ, Everitt BJ (2001): Differential involvement of NMDA, AMPA/kainate, and dopamine receptors in the nucleus accumbens core in the acquisition and performance of pavlovian approach behavior. *J Neurosci* 21:9471-9477.
21. O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ (2004): Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* 304:452-454.
22. Yin HH, Knowlton BJ (2004): Contributions of striatal subregions to place and response learning. *Learn Mem* 11:459-463.
23. Balleine B, Killcross S (1994): Effects of ibotenic acid lesions of the nucleus accumbens on instrumental action. *Behav Brain Res* 65:181-193.
24. Yin HH, Ostlund SB, Balleine BW (2008): Reward-guided learning beyond dopamine in the nucleus accumbens: the integrative functions of cortico-basal ganglia networks. *Eur J Neurosci* 28:1437-1448.
25. Brischoux F, Chakraborty S, Brierley DI, Ungless MA (2009): Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *Proc Natl Acad Sci U S A* 106:4894-4899.
26. Matsumoto M, Hikosaka O (2009): Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature* 459:837-841.
27. Zhang D, Yang S, Jin GZ, Bunney BS, Shi WX (2008): Oscillatory firing of dopamine neurons: differences between cells in the substantia nigra and ventral tegmental area. *Synapse* 62:169-175.
28. Floresco SB, Onge JR, Ghods-Sharifi S, Winstanley CA (2008): Cortico-limbic-striatal circuits subserving different forms of cost-benefit decision making. *Cogn Affect Behav Neurosci* 8:375-389.
29. Nicola SM, Surmeier J, Malenka RC (2000): Dopaminergic modulation of neuronal excitability in the striatum and nucleus accumbens. *Annu Rev Neurosci* 23:185-215.
30. Yun IA, Wakabayashi KT, Fields HL, Nicola SM (2004): The ventral tegmental area is required for the behavioral and nucleus accumbens neuronal firing responses to incentive cues. *J Neurosci* 24:2923-2933.