

Persistent coding of outcome-predictive cue features in the rat nucleus accumbens.

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Acknowledgments: We thank Nancy Gibson, Martin Ryan and Jean Flanagan for animal care, and Min-Ching Kuo and Alyssa Carey for technical assistance. This work was supported by Dartmouth College (Dartmouth Fellowship to JMG and JEC, and start-up funds to MvdM) and the Natural Sciences and Engineering Research Council (NSERC) of Canada (Discovery Grant award to MvdM, Canada Graduate Scholarship to JMG).

Conflict of Interest: The authors declare no competing financial interests.

1 Abstract

2 The nucleus accumbens (NAc) has been shown to be important for learning from feedback, and biasing and
3 invigorating behavior in response to outcome-predictive cues. NAc encodes outcome-related cue features
4 such as the magnitude and identity of reward. However, not much is known about how features of cues
5 themselves are encoded. We designed a decision making task where rats learned multiple sets of outcome-
6 predictive cues, and recorded single-unit activity in the NAc during performance. We found that coding of
7 various cue features occurred alongside coding of expected outcome. Furthermore, this coding persisted both
8 during a delay period, after the rat made a decision and was waiting for an outcome, and after the outcome
9 was revealed. Encoding of cue features in the NAc may enable contextual modulation of ongoing behavior,
10 and provide an eligibility trace of outcome-predictive stimuli for updating stimulus-outcome associations to
11 inform future behavior.

¹² Introduction

¹³ Theories of nucleus accumbens (NAc) function generally agree that this brain structure contributes to moti-
¹⁴ vated behavior, with some emphasizing a role in learning from reward prediction errors (RPEs) (Averbeck &
¹⁵ Costa 2017; Joel, Niv, & Ruppin 2002; Khamassi & Humphries 2012; Lee, Seo, & Jung 2012; Maia 2009;
¹⁶ Schultz 2016; see also the addiction literature on effects of drug rewards; Carelli 2010; Hyman, Malenka,
¹⁷ & Nestler 2006; Kalivas & Volkow 2005) and others a role in the modulation of ongoing behavior through
¹⁸ stimuli associated with motivationally relevant outcomes (invigorating, directing; Floresco, 2015; Nicola,
¹⁹ 2010; Salamone & Correa, 2012). These proposals echo similar ideas on the functions of the neuromod-
²⁰ ulator dopamine (Berridge, 2012; Maia, 2009; Salamone & Correa, 2012; Schultz, 2016), with which the
²¹ NAc is tightly linked functionally as well as anatomically (Cheer et al., 2007; du Hoffmann & Nicola, 2014;
²² Ikemoto, 2007; Takahashi, Langdon, Niv, & Schoenbaum, 2016).

²³ Much of our understanding of NAc function comes from studies of how cues that predict motivationally rel-
²⁴ evant outcomes (e.g. reward) influence behavior and neural activity in the NAc. Task designs that associate
²⁵ such cues with rewarding outcomes provide a convenient access point eliciting conditioned responses such as
²⁶ sign-tracking and goal-tracking (Hearst & Jenkins, 1974; Robinson & Flagel, 2009), pavlovian-instrumental
²⁷ transfer (Estes, 1943; Rescorla & Solomon, 1967) and enhanced response vigor (Nicola, 2010; Niv, Daw,
²⁸ Joel, & Dayan, 2007), which tend to be affected by NAc manipulations (Chang, Wheeler, & Holland 2012;
²⁹ Corbit & Balleine 2011; Flagel et al. 2011; although not always straightforwardly; Chang & Holland 2013;
³⁰ Giertler, Bohn, & Hauber 2004). Similarly, analysis of RPEs typically proceeds by establishing an associa-
³¹ tion between a cue and subsequent reward, with NAc responses transferring from outcome to the cue with
³² learning (Day, Roitman, Wightman, & Carelli, 2007; Roitman, Wheeler, & Carelli, 2005; Schultz, Dayan, &
³³ Montague, 1997; Setlow, Schoenbaum, & Gallagher, 2003).

³⁴ Surprisingly, although substantial work has been done on the coding of outcomes predicted by such cues
³⁵ (Atallah, McCool, Howe, & Graybiel, 2014; Bissonette et al., 2013; Cooch et al., 2015; Day, Wheeler,

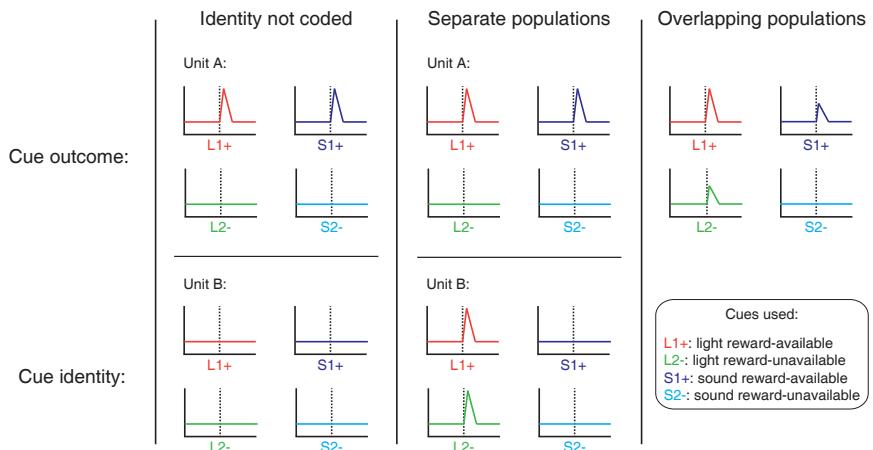
36 Roitman, & Carelli, 2006; Goldstein et al., 2012; Hollerman, Tremblay, & Schultz, 1998; Lansink et al.,
37 2012; McGinty, Lardeux, Taha, Kim, & Nicola, 2013; Nicola, 2004; Roesch, Singh, Brown, Mullins, &
38 Schoenbaum, 2009; Roitman et al., 2005; Saddoris, Stamatakis, & Carelli, 2011; Setlow et al., 2003; Sugam,
39 Saddoris, & Carelli, 2014; West & Carelli, 2016), much less is known about how outcome-predictive cues
40 themselves are encoded in the NAc (but see; Sleezer, Castagno, & Hayden, 2016). This is an important issue
41 for at least two reasons. First, in reinforcement learning, motivationally relevant outcomes are typically
42 temporally delayed relative to the cues that predict them. In order to solve the problem of assigning credit
43 (or blame) across such temporal gaps, some trace of preceding activity needs to be maintained (Lee et al.,
44 2012; Sutton & Barto, 1998). For example, if you become ill after eating food X in restaurant A, depending
45 on if you remember the identity of the restaurant or the food at the time of illness, you may learn to avoid
46 all restaurants, restaurant A only, food X only, or the specific pairing of X-in-A. Therefore, a complete
47 understanding of what is learned following feedback requires understanding what trace is maintained. Since
48 NAc is a primary target of DA signals interpretable as RPEs, and NAc lesions impair RPEs related to timing,
49 its activity trace will help determine what can be learned when RPEs arrive (Hamid et al., 2015; Hart,
50 Rutledge, Glimcher, & Phillips, 2014; Ikemoto, 2007; McDannald, Lucantonio, Burke, Niv, & Schoenbaum,
51 2011; Takahashi et al., 2016). Similarly, in an economic framework, in order to maximize utility a rational
52 agent selects the offer with the largest subjective value (Samuelson, 1947). NAc has been implicated as
53 containing representations of this domain-general subjective value (Bartra, McGuire, & Kable, 2013; Levy
54 & Glimcher, 2012; Peters & Büchel, 2009; Sescousse, Li, & Dreher, 2015), and having representations of
55 an offer alongside its subjective value could be one way in which the two are linked.

56 Second, for ongoing behavior, the relevance of cues typically depends on context. In experimental set-
57 tings, context may include the identity of a preceding cue, spatial or configural arrangements (Bouton, 1993;
58 Holland, 1992; Honey, Iordanova, & Good, 2014), and unsignaled rules as occurs in set shifting and other
59 cognitive control tasks (Cohen & Servan-Schreiber, 1992; Floresco, Ghods-Sharifi, Vexelman, & Magyar,
60 2006; Grant & Berg, 1948; Sleezer et al., 2016). In such situations, the question arises how selective, context-
61 dependent processing of outcome-predictive cues is implemented. For instance, is there a gate prior to NAc

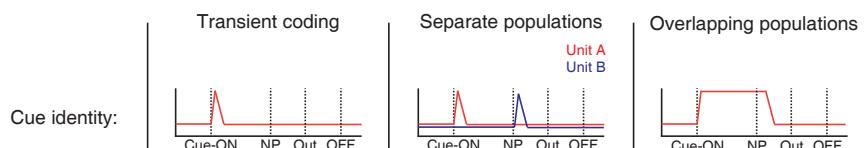
62 such that only currently relevant cues are encoded in NAc, or are all cues represented in NAc but their current
63 values dynamically updated (FitzGerald, Schwartenbeck, & Dolan, 2014; Goto & Grace, 2008; Sleezer et
64 al., 2016). Representation of cue identity would allow for context-dependent mapping of outcomes predicted
65 by specific cues.

66 Thus, both from a learning and a flexible performance perspective, it is of interest to determine how cue
67 identity is represented in the brain, with NAc of particular interest given its anatomical and functional po-
68 sition at the center of motivational systems. We sought to determine whether cue identity is represented in
69 the NAc, if cue identity is represented alongside other motivationally relevant variables, such as cue value,
70 and if these representations are maintained after a behavioral decision has been made (Figure 1). To address
71 these questions, we recorded the activity of NAc units as rats performed a task in which multiple, distinct
72 sets of cues predicted the same outcome.

A Presence of cue feature coding



B Persistence of cue feature coding



C Quantification of coding across units and time epochs

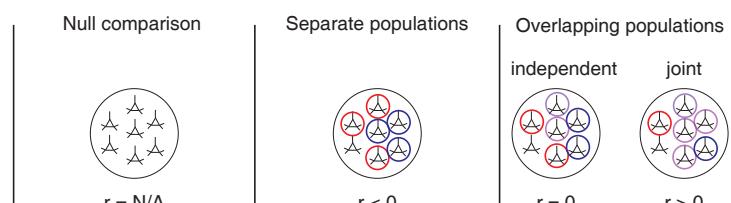


Figure 1: Schematic of potential coding strategies for cue identity (light, sound) and cue outcome (reward-available, reward-unavailable) employed by single units in the NAc across different units (A) and in time (B).

A: Displayed are schematic PETHs illustrating putative responses to different cues under different hypotheses of how cue identity and outcome are coded. Left panel: Coding of cue identity is absent in the NAc. Top: Unit A encodes a motivationally relevant variable, such as expected outcome, similarly across other cue features, such as cue identity or physical location. Hypothetical plot is firing rate across time. L1+ (red) signifies a reward-available light cue, S1+ (navy blue) a reward-available sound cue, L2- (green) a reward-unavailable light cue, S2- (light blue) a reward-unavailable sound cue. Dashed line indicates onset of cue. Bottom: No units within the NAc discriminate their firing according to cue identity. Middle panel: Coding of cue identity occurs in a separate population of units from encoding of motivationally relevant variables such as expected outcome or subsequent vigor. Top: Same as H1, with unit A discriminating between reward-available and reward-unavailable cues. Bottom: Unit B discriminates firing across stimulus modalities, depicted here as firing to light cues but not sound cues. Right panel: Coding of cue identity occurs in an overlapping population of cells with coding of other motivationally relevant variables. Hypothetical example demonstrating a unit that responds to outcome-predictive cues, but firing rate is also modulated by cue identity, firing most for the reward-available light cue.

B: Displayed are schematic PETHs illustrating potential ways in which cue identity signals may persist over time. Left panel: Cue-onset triggers a transient response to a unit that codes for cue identity. Dashed lines indicate time of a behavioral or environmental event. 'Cue-ON' signifies onset of cue, 'NP' signifies when the rat holds a nosepoke at a reward receptacle, 'Out' signifies when the outcome is revealed, 'OFF' signifies when the cue turns off. Middle and right panel: Coding of cue identity persists at other time points, shown here during a nosepoke hold period until outcome is revealed. Coding can either be maintained by a sequence of units (middle panel) or by the same unit as during cue-onset (right panel).

Figure 1: (Previous page.) **C:** Displayed are a schematic pool of NAc units, representing the different outcomes for each of the analyses. R values represent the correlation among recoded beta coefficients (see text for analysis details). Left panel: Cue identity is not coded (A: left panel), or is only transiently represented in response to the cue (B: left panel). Middle panel: A negative correlation ($r < 0$) suggests that cue identity and cue outcome are represented by specialized populations of units (A: middle panel), or cue identity is represented by distinct units among different points in a trial (B: middle panel). Red circles represents coding for one cue feature or epoch, blue circles for the other cue feature or epoch. Right panel: Cue identity and cue outcome (A: right panel), or cue identity at cue-onset and nosepoke (B: right panel) are represented by overlapping populations of units, shown here by the purple circles. The absence of a correlation ($r = 0$) suggests that the overlap of cue identity and cue outcome, or cue-onset and nosepoke coding, is expected by chance and the two populations are independent from one another. A positive correlation ($r > 0$), suggests a higher overlap than expected by chance, and that the two populations are jointly coded. Note: The same hypotheses apply to other information-containing aspects of the environment when the cue is presented, such as the physical location of the cue, as well as other time epochs within the task, such as when the animal receives feedback about an approach.

73 Results

74 Behavior

75 Rats were trained to discriminate between cues signaling the availability and absence of reward on a square
76 track with four identical arms for two distinct set of cues (Figure 2). During each session, rats were pre-
77 sented sequentially with two behavioral blocks containing cues from different sensory modalities, a light and
78 a sound block, with each block containing a cue that signalled the availability of reward (reward-available),
79 and a cue that signalled the absence of reward (reward-unavailable). To maximize reward receipt, rats should
80 approach reward sites on reward-available trials, and skip reward sites on reward-unavailable trials (see Fig-
81 ure 3A for an example learning curve). All four rats learned to discriminate between the reward-available
82 and reward-unavailable cues for both the light and sound blocks as determined by reaching significance ($p <$
83 .05) on a daily chi-square test comparing approach behavior for reward-available and reward-unavailable
84 cues for each block, for at least three consecutive days (range for time to criterion: 22 - 57 days). Mainte-
85 nance of behavioral performance during recording sessions was assessed using linear mixed effects models
86 for both proportion of trials where the rat approached the receptacle, and trial length. Analyses revealed
87 that the likelihood of a rat to make an approach was influenced by whether a reward-available or reward-

88 unavailable cue was presented, but was not significantly modulated by whether the rat was presented with a
89 light or sound cue (Percentage approached: light reward-available = 97%; light reward-unavailable = 34%;
90 sound reward-available = 91%; sound reward-unavailable 35%; cue identity $p = .115$; cue outcome $p < .001$;
91 Figure 3B). A similar trend was seen with the length of time taken to complete a trial (Trial length: light
92 reward-available = 1.85 s; light reward-unavailable = 1.74 s; sound reward-available = 1.91 s; sound reward-
93 unavailable 1.78 s; cue identity $p = .106$; cue outcome $p < .001$; Figure 3C). Thus, during recording, rats
94 successfully discriminated the cues according to whether or not they signaled the availability of reward at
95 the reward receptacle.

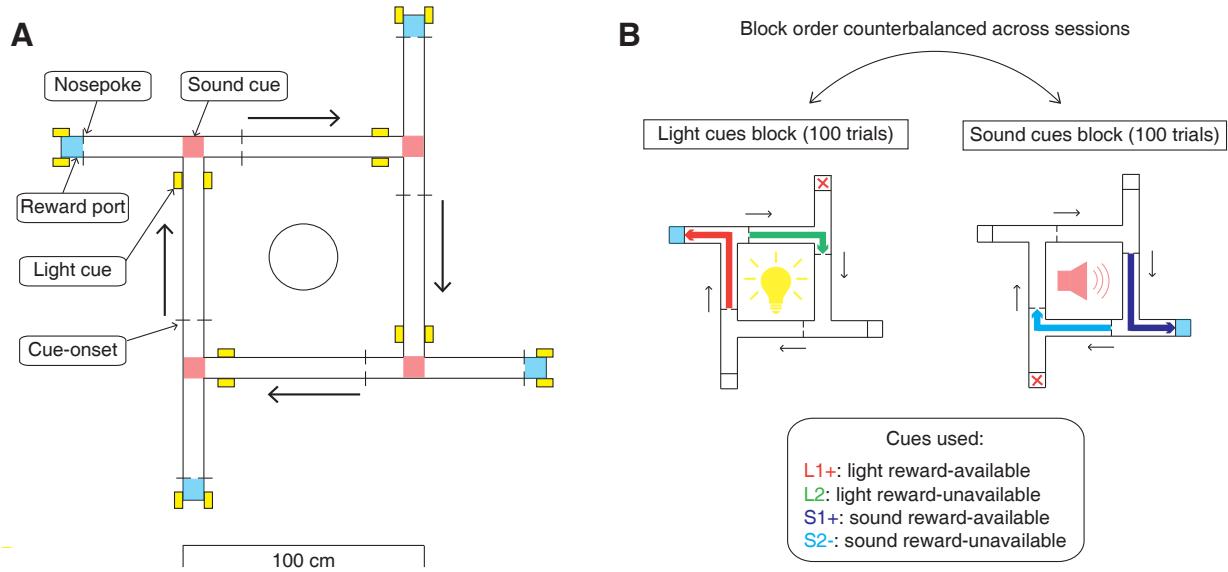


Figure 2: Schematic of behavioral task. **A:** To scale depiction of square track consisting of multiple identical T-choice points. At each choice point, the availability of 12% sucrose reward at the nearest reward receptacle (light blue fill) was signaled by one of four possible cues, presented when the rat initiated a trial by crossing a photobeam on the track (dashed lines). Photobeams at the ends of the arms by the receptacles registered Nosepokes (solid lines). Rectangular boxes with yellow fill indicate location of LEDs used for light cues. Speakers for tone cues were placed underneath the choice points, indicated by magenta fill on track. Arrows outside of track indicate correct running direction. Circle in the center indicates location of pedestal during pre- and post-records. Scale bar is located beneath the track. **B:** Progression of a recording session. A session was started with a 5 minute recording period on a pedestal placed in the center of the apparatus. Rats then performed the light and sound blocks of the cue discrimination task in succession for 100 trials each, followed by another 5 minute recording period on the pedestal. Left in figure depicts a light block, showing an example trajectory for a correct reward-available (approach trial; red) and reward-unavailable (skip trial; green) trial. Right in figure depicts a sound block, with a reward-available (approach trial; navy blue) and reward-unavailable (skip trial; light blue) trial. Ordering of the light and sound blocks was counterbalanced across sessions. Reward-available and reward-unavailable cues were presented pseudo-randomly, such that not more than two of the same type of cue could be presented in a row. Location of the cue on the track was irrelevant for behavior, all cue locations contained an equal amount of reward-available and reward-unavailable trials.

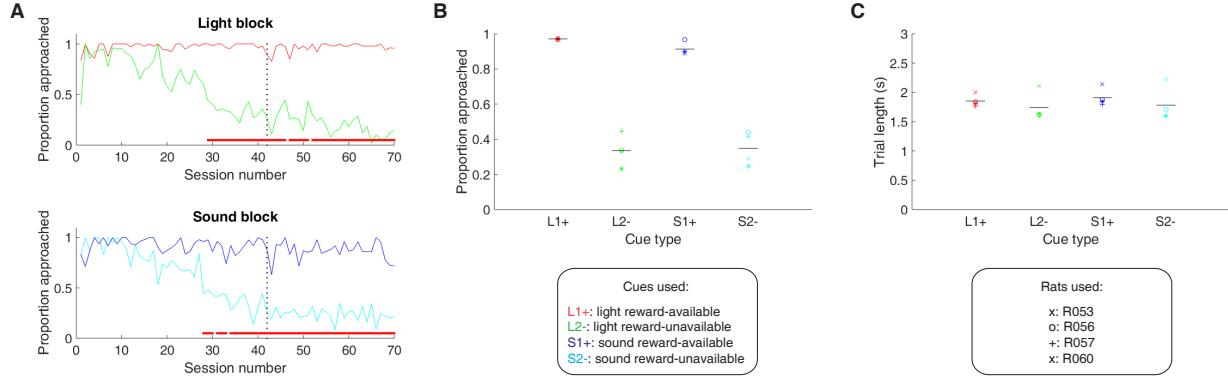


Figure 3: Performance on the behavioral task. **A.** Example learning curves across sessions from a single subject (R060) showing the proportion approached for reward-available (red line for light block, navy blue line for sound block) and reward-unavailable trials (green line for light block, light blue line for sound block) for light (top) and sound (bottom) blocks. Fully correct performance corresponds to an approach proportion of 1 for reward-available trials and 0 for reward-unavailable trials. Rats initially approach on both reward-available and reward-unavailable trials, and learn with experience to skip non-rewarded trials. Red bars indicate days in which a rat statistically discriminated between reward-available and reward-unavailable cues, determined by a chi square test. Dashed line indicates time of electrode implant surgery. **B-C:** Summary of performance during recording sessions for each rat. **B:** Proportion approached for all rats, averaged across all recording sessions. Different columns indicate the different cues (reward-available (red) and reward-unavailable (green) light cues, reward-available (navy blue) and reward-unavailable (light blue) sound cues). Different symbols correspond to individual subjects; horizontal black line shows the mean. All rats learned to discriminate between reward-available and reward-unavailable cues, as indicated by the clear difference of proportion approached between reward-available (~90% approached) and reward-unavailable cues (~30% approached), for both blocks (see Results for statistics). **C:** Average trial length for each cue. Note that the time to complete a trial was comparable for the different cues.

96 **NAc units encode behaviorally relevant and irrelevant cue features**

97 **Single unit responses discriminate cue features:**

98 We sought to address which parameters of our task were encoded by NAc activity, specifically whether the
99 NAc encodes aspects of motivationally relevant cues not directly tied to reward, such as the identity and
100 location of the cue, and whether this coding is accomplished by separate, independent, or joint populations
101 (Figure 1A). To do this we recorded a total of 443 units with > 200 spikes in the NAc from 4 rats over 57
102 sessions (range: 12 - 18 sessions per rat) while they performed a cue discrimination task (Table 1). Units that
103 exhibited a drift in firing rate over the course of either block were excluded from further analysis, leaving
104 344 units for further analysis. The activity of 133 (39%) of these 344 units were modulated by the cue, with
105 more showing a decrease in firing ($n = 103$) than an increase ($n = 30$) around the time of cue-onset (Table 1).
106 Within this group, 24 were classified as FSIs, while 109 were classified as SPNs. Upon visual inspection, we
107 observed several patterns of firing activity, including units that discriminated firing upon cue-onset across
108 various cue conditions, showed sustained differences in firing across cue conditions, had transient responses
109 to the cue, showed a ramping of activity starting at cue-onset, and showed elevated activity immediately
110 preceding cue-onset, for example (Figure 4).

111 To characterize more formally whether these cue-evoked responses were modulated by various aspects of the
112 task, we fit a forward selection stepwise generalized linear model (GLM) to each cue-modulated unit. Fitting
113 GLMs revealed that a variety of task parameters accounted for a significant portion of firing rate variance in
114 NAc cue-modulated units (Figure 5, Table 1). Notably, there were units that discriminated between whether
115 the rat was performing in the light or sound block (28% of cue-modulated units, accounting for 6% of
116 variance on average), which arm the rat was currently on (38% of cue-modulated units, accounting for 6%
117 of variance on average), and whether the rat was engaged in the common portion of a reward-available or
118 reward-unavailable trial (26% of cue-modulated units, accounting for 4% of variance on average), suggesting
119 that the NAc encodes features of reward-predictive cues in addition to expected outcome (Figure 4). To

120 determine whether overlap of coding of cue features was different than expected by chance we correlated
121 recoded beta coefficients from the GLMs. This revealed that cue identity was coded by an independent
122 population of units from both cue identity ($r = -.018$; $p = .840$) and cue location ($r = .107$; $p = .220$), as
123 determined by non-significant correlations, but that cue identity and cue location were encoded by a joint
124 population ($r = .221$; $p = .011$), as signified by a significant positive correlation. Additionally, a sliding
125 window GLM centered on cue-onset revealed that cue identity and cue location contributed to the activity of
126 a significant proportion of cue-modulated units throughout this epoch, whereas an increase in units encoding
127 cue outcome became apparent after cue-onset (Figure 5D). Together, these findings show that various cue
128 features are represented in the NAc, that cue modality is coded in an independent population from cue
129 outcome and cue location, and that cue outcome and cue location are coded in a joint population (Figure 1).

Task parameter	Total	\uparrow MSN	\downarrow MSN	\uparrow FSI	\downarrow FSI
All units	443	155	216	27	45
<i>Rat ID</i>					
R053	145	51	79	4	11
R056	70	12	13	17	28
R057	136	55	75	3	3
R060	92	37	49	3	3
Analyzed units	344	117	175	18	34
Cue modulated units	133	24	85	6	18
<i>GLM aligned to cue-onset</i>					
Cue identity	37	7	21	1	8
Cue location	50	13	27	3	7
Cue outcome	34	10	18	0	6
Approach behavior	31	8	18	1	4
Trial length	25	5	18	0	2
Trial number	32	11	12	1	8
Previous trial	5	0	5	0	0
<i>GLM aligned to nosepoke</i>					
Cue identity	66	14	36	2	14
Cue location	66	14	40	3	9
Cue outcome	42	8	29	0	5
<i>GLM aligned to outcome</i>					
Cue outcome	10	0	6	0	4

Table 1: Overview of recorded NAc units and their relationship to task variables at various time epochs.

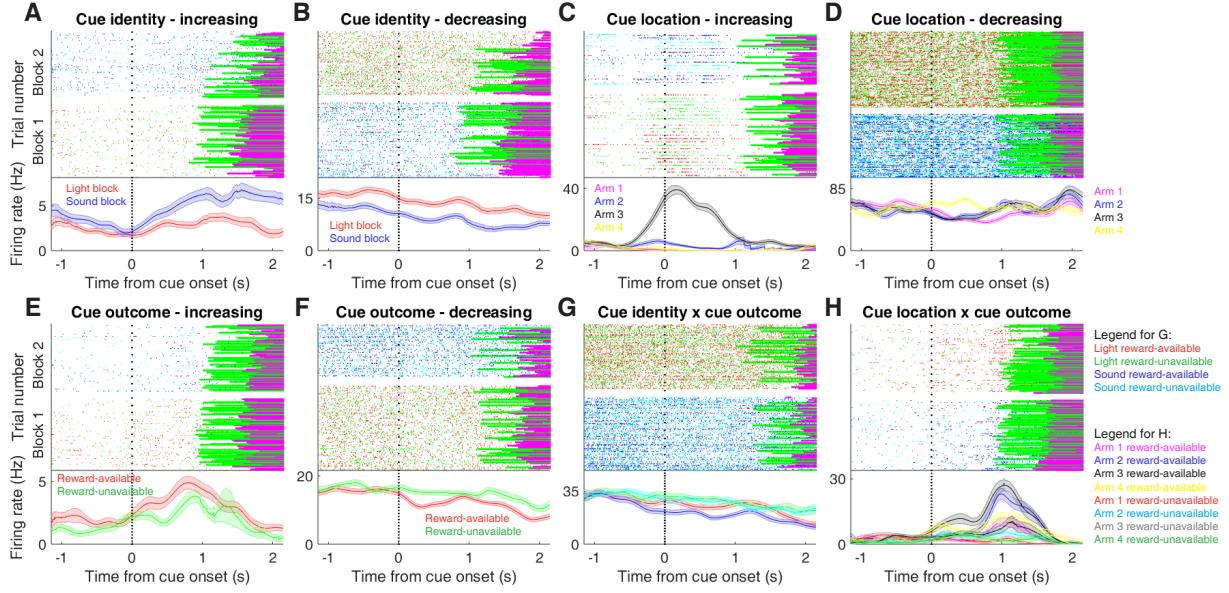


Figure 4: Examples of different cue-modulated NAc units influenced by various task parameters. **A:** Example of a cue-modulated NAc unit that showed an increase in firing following the cue, and encoded cue identity. Top: rasterplot showing the spiking activity across all trials aligned to cue-onset. Spikes across trials are color-coded according to cue type (red: reward-available light; green: reward-unavailable light; navy blue: reward-available sound; light blue: reward-unavailable sound). Green and magenta bars indicate trial termination when a rat initiated the next trial or made a nosepoke, respectively. White space halfway up the rasterplot indicates switching from one block to the next. Dashed line indicates cue onset. Bottom: PETHs showing the average smoothed firing rate for the unit for trials during light (red) and sound (blue) blocks, aligned to cue-onset. Lightly shaded area indicates standard error of the mean. Note this unit showed a larger increase in firing to sound cues. **B:** An example of a unit that was responsive to cue identity as in A, but for a unit that showed a decrease in firing to the cue. Note the sustained higher firing rate during the light block. **C-D:** Cue-modulated units that encoded cue location, each color in the PETHs represents average firing response for a different cue location. **C:** The firing rate of this unit only changed on arm 3 of the task. **D:** Firing decreased for this unit on all arms but arm 4. **E-F:** Cue-modulated units that encoded cue outcome, with the PETHs comparing reward-available (red) and reward-unavailable (green) trials. **E:** This unit showed a slightly higher response during presentation of reward-available cues. **F:** This unit showed a dip in firing when presented with reward-available cues. **G-H:** Examples of cue-modulated units that encoded multiple cue features. **G:** This unit integrated cue identity and outcome. **H:** An example of a unit that integrated cue identity and location.

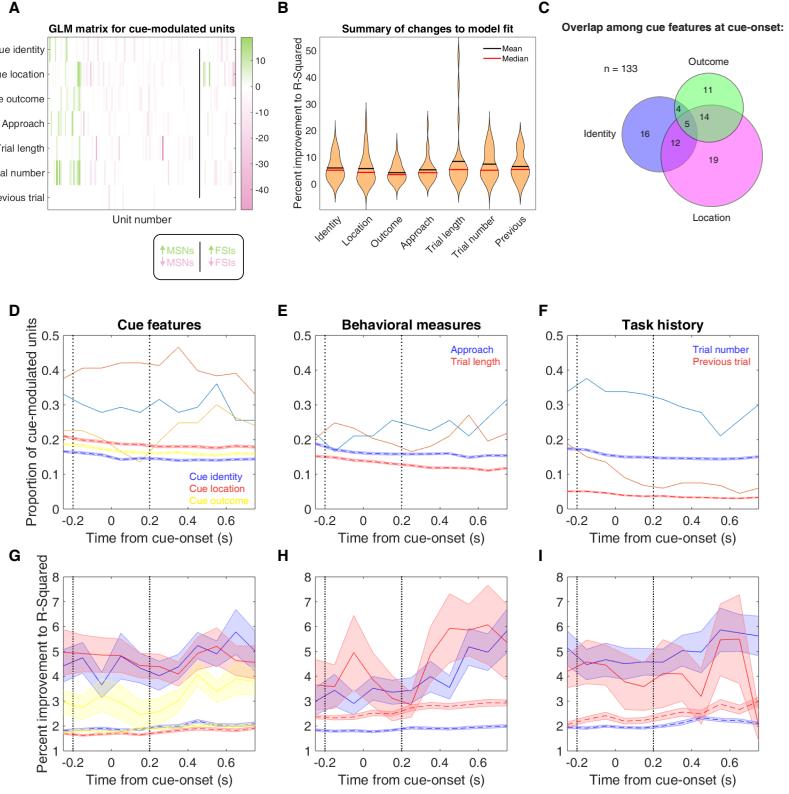


Figure 5: Summary of influence of various task parameters on cue-modulated NAc units after cue-onset. **A:** GLM matrix illustrating the contribution of various task parameters to NAc unit firing rates. A stepwise GLM was fit to each unit that showed evidence of cue modulation by a Wilcoxon signed-rank test. Each row represents a given task parameter, and each column corresponds to a single unit. Colors indicate how much of the firing rate variance an individual predictor contributed to the model, as measured by differences in R-squared between the final model and the model minus the predictor of interest. Ordering from left to right: MSNs that increased firing in response to the cue (green, left of line), MSNs with a decreasing response (red, left of line), FSIs with an increasing response (green, right of line), FSIs with a decreasing response (red, right of line). Darker shades indicate more firing rate variance explained by a given predictor. Black line indicates separation of MSNs and FSIs. Scale bar indicates range of improvements to model fit for units with an increasing (green) and decreasing (red) response to the cue. **B:** Violin plots demonstrating changes in R-squared values with the addition of each of the individual predictors. The mean, median, and distribution of changes in R-squared values is plotted for each of the seven task parameters used in the GLM. **C:** Venn diagram illustrating the number of cue-modulated units encoding cue identity (blue circle), cue location (green circle), cue outcome (pink circle), as well as the overlap among units that encoded multiple cue features. **D-F:** Sliding window GLM illustrating the proportion of cue-modulated units influenced by various predictors around time of cue-onset. **D:** Sliding window GLM (bin size: 500 ms; step size: 100 ms) demonstrating the proportion of cue-modulated units where cue identity (blue solid line), cue location (red solid line), and cue outcome (yellow solid line) significantly contributed to the model at various time epochs relative to cue-onset. Dashed colored lines indicate the average of shuffling the firing rate order that went into the GLM 100 times. Points in between the two vertical dashed lines indicate bins where both pre- and post-cue-onset time periods were used in the GLM. **E:** Same as D, but for approach behavior and trial length. **F:** Same as D, but for trial number and previous trial. **G-I:** Average improvement to model fit. **G:** Average percent improvement to R-squared for units where cue identity, cue location, or cue outcome were significant contributors to the final model for time epochs surrounding cue onset. Shaded area around mean represents the standard error of the mean. **H:** Same as G, but for approach behavior and trial length. **I:** Same G, but for trial number and previous trial.

130 **Population level averages reveal characteristic response profiles:**

131 We observed a variety of single unit response profiles around the time of cue onset (Figure 4). To investigate
132 whether these firing rate patterns were related to what cue features were encoded, we plotted the population
133 level averages for units that were modulated by each feature. To do this, we normalized firing activity for
134 each unit that was modulated by a given cue feature, such as light block, then generated the cue-onset aligned
135 population average firing rate for each of the cue features (Figure 6). Overall, this analysis revealed that cells
136 that showed an increase upon cue presentation had stronger responses for the preferred cue condition (Figure
137 6A,C,E). Interestingly, units that were classified as decreasing in response to the cue showed a biphasic
138 response at the population level, with a small peak at a time in alignment with entry into the arm, followed by
139 a sustained dip after cue-onset (Figure 6B,D,F). Units that were modulated by cue identity showed a stronger
140 increase in response to the preferred task block, as well as a higher tonic firing rate to the preferred task block,
141 most notably in units that decreased in firing rate to the cue (Figure 6A,B). Units that were modulated by cue
142 location showed a graded response to locations of decreasing preference, with peak firing occurring around
143 cue-onset (Figure 6C,D). Units that were modulated by cue outcome showed a ramping of activity after
144 cue-onset for their preferred cue type. Additionally, units that exhibited a decrease in firing in response to
145 the cue and whose activity was modulated by cue outcome, showed a sustained discriminatory response to
146 reward-available and reward-unavailable cues that extended beyond cue-onset (Figure 6F). Together, these
147 visualizations of the averaged population responses revealed nuanced differences in the way NAc units are
148 modulated by cue conditions across cue features.

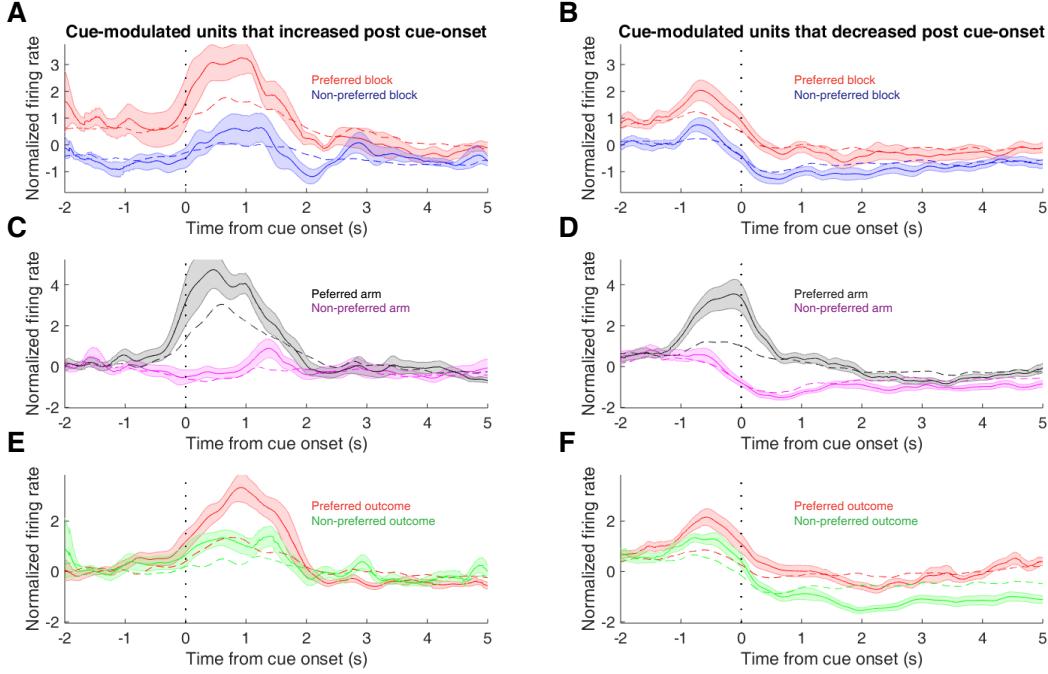


Figure 6: Population-level averages of cue feature sensitive NAc units. **A:** Average smoothed normalized (z-score) activity for cue-modulated units where cue identity was a significant predictor in the GLM, aligned to cue-onset. Activity is plotted for preferred stimulus block (red) and nonpreferred stimulus block (blue). Dashed vertical line indicates onset of cue. Dashed color lines indicate the result of shuffling the identity of the units used for this average 1000 times. Lightly shaded area indicates standard error of the mean. Note larger increase to preferred stimulus block over nonpreferred stimulus block. Black lines indicate the average of 1000 rounds of random sampling of units from the non-drifting population for the preferred and non-preferred blocks. **B:** Same as A but for units that decreased in firing. Note population level activity reveals units classified as decreasing in response to cue show a biphasic response at the population level, with a transient increase around the time the rat starts on the arm, followed by a minimum after cue onset. Also, note the sustained difference in firing between the two blocks. **C-D:** Same as A-B for cue location. Activity is plotted for most preferred arm (black) and least preferred arm (magenta). **E-F:** Same as A-B for cue outcome. Activity is plotted for preferred expected outcome (red), and nonpreferred outcome (green). Note the larger increase to the cue representing the units preferred outcome (E), and the sustained decrease to the nonpreferred outcome (F).

149 **NAc units dynamically segment the task:**

150 Given the varied time courses and response profiles of NAc units to various aspects of the cue, the NAc
151 may be computing a temporally evolving state value signal (Pennartz., 2011). If this is the case, then the
152 recruitment of NAc units should vary alongside changes in the environment. To look at the distribution of
153 responses throughout our task space and see if this distribution is modulated by cue features, we z-scored
154 the firing rate of each unit and plotted the normalized firing rates of all units aligned to cue-onset and sorted
155 them according to the time of peak firing rate (Figure 7). We did this separately for both the light and sound
156 blocks, and found a nearly uniform distribution of firing fields in task space that was not limited to alignment
157 to the cue (Figure 7A). Furthermore, to determine if this population level activity was similar across blocks,
158 we also organized firing during the sound blocks according to the ordering derived from the light blocks.
159 This revealed that while there was some preservation of order, the overall firing was qualitatively different
160 across the two blocks, implying that population activity distinguishes between light and sound blocks. To
161 control for the possibility that any comparison of trials would produce this effect, we did a within block
162 comparison, comparing half of the trials in the light block against the other half. This comparison looked
163 similar to our test comparison of sound block trials ordered by light block trials. Additionally, given that the
164 majority of our units showed an inhibitory response to the cue, we also plotted the firing rates according to
165 the lowest time in firing, and again found some maintenance of order, but largely different ordering across
166 the two blocks, and the within block comparison (Figure 7D). To further test this, we divided each block into
167 two halves and looked at the correlation of the average smoothed firing rates across various combinations
168 of these halves across our cue-aligned centered epoch. A linear mixed effects model revealed that within
169 block correlations (e.g. one half of light trials vs other half of light trials) were higher and more similar
170 than across block correlations (e.g. half of light trials vs half of sound trials) suggesting that activity in
171 the NAc discriminates across various cue conditions (within block correlations = .383 (light), .379 (sound);
172 across block correlations = .343, .338, .337, .348; within block vs. within block comparison = $p = .934$;
173 within block vs. across block comparisons = $p < .001$). This process was repeated for cue location (Figure
174 7B,E; within block correlations = .369 (arm 1), .350 (arm 2); across block correlations = .290, .286, .285,

.291; within block vs. within block comparison = $p = .071$; within block vs. across block comparisons = $p < .001$) and cue outcome (Figure 7C,F; within block correlations = .429 (reward-available), .261 (reward-unavailable); across block correlations = .258, .253, .255, .249; within block vs. within block comparison = $p < .001$; within block vs. across block comparisons = $p < .001$), showing that NAc segmentation of the task is qualitatively different even during those parts of the task not immediately associated with a specific cue, action, or outcome, although the within condition comparison of reward-unavailable trials was less correlated than reward-available trials, and more similar to the across condition comparisons, potentially due to the greater behavioral variability for the reward-unavailable trials.

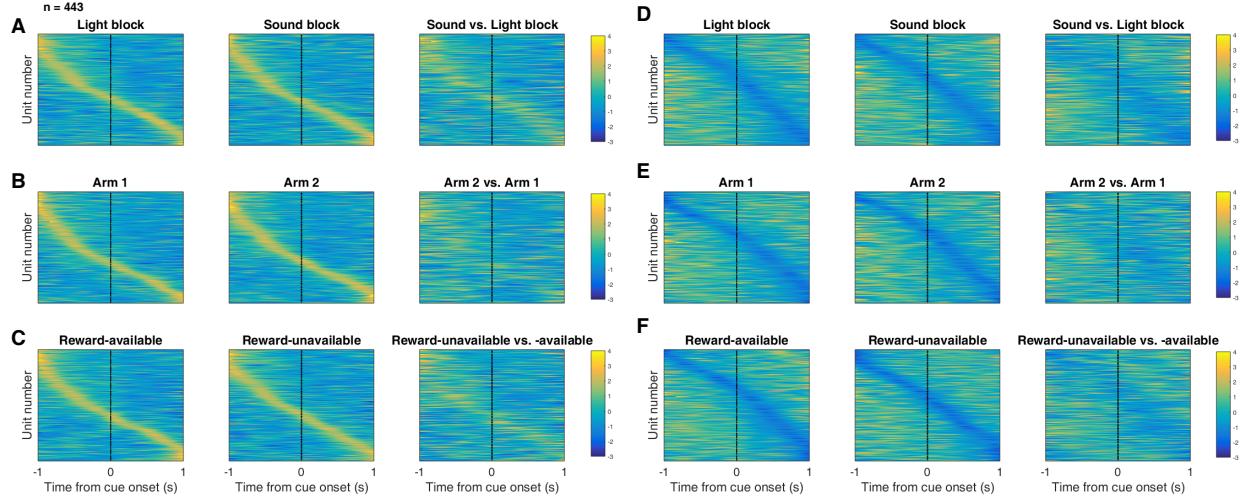


Figure 7: Distribution of NAc firing rates across time surrounding cue onset. Each panel shows normalized (z-score) firing rates for all recorded NAc units (each row corresponds to one unit) as a function of time (time 0 indicates cue onset), averaged across all trials for a specific cue type, indicated by text labels. **A-C:** Heat plots aligned to normalized peak firing rates. **A, left:** Heat plot showing smoothed normalized firing activity of all recorded NAc units ordered according to the time of their peak firing rate during the light block. Each row is a units average activity across time to the light block. Dashed line indicates cue onset. Notice the yellow band across time, indicating all aspects of visualized task space were captured by the peak firing rates of various units. **A, middle:** Same units ordered according to the time of the peak firing rate during the sound block. Note that for both blocks, units tile time approximately uniformly with a clear diagonal of elevated firing rates. **A, right:** Unit firing rates taken from the sound block, ordered according to peak firing rate taken from the light block. Note that a weaker but still discernible diagonal persists, indicating partial similarity between firing rates in the two blocks. A similar pattern exists for within-block comparisons suggesting that reordering any two sets of trials produces this partial similarity, however correlations within blocks are more similar than correlations across blocks (see text). **B:** Same layout as in A, except that the panels now compare two different locations on the track instead of two cue modalities. As for the different cue modalities, NAc units clearly discriminate between locations, but also maintain some similarity across locations, as evident from the visible diagonal in the right panel. Two example locations were used for display purposes; other location pairs showed a similar pattern. **C:** Same layout as in A, except that panels now compare reward-available and reward-unavailable trials. **D-F:** Heat plots aligned to normalized minimum firing rates. **D:** Responses during different stimulus blocks as in A, but with units ordered according to the time of their minimum firing rate. **E:** Responses during trials on different arms as in B, but with units ordered by their minimum firing rate. **F:** Responses during cues signalling different outcomes as in C, but with units ordered by their minimum firing rate. Overall, NAc units "tiled" experience on the task, as opposed to being confined to specific task events only. Units from all sessions and animals were pooled for this analysis.

183 **Encoding of cue features persists until outcome:**

184 In order to be useful for credit assignment in reinforcement learning, a trace of the cue must be maintained
185 until the outcome, so that information about the outcome can be associated with the outcome-predictive
186 cue. To test whether representations of cue features persisted post-approach until the outcome was revealed,
187 we fit a GLM to the post-approach firing rates of cue-modulated units aligned to the time of nosepoke into
188 the reward receptacle. This analysis showed that a variety of units still discriminated firing according to
189 various cue features, but not other task parameters, showing that NAc activity discriminates various cue
190 conditions well into a trial (Table 1, Figures 8,9). Additionally, these units were a mix between most of the
191 units that encoded cue features at cue-onset (observed overlap greater than expected by chance according
192 to chi-square tests), and those that did not previously have a cue feature as a predictor (29, 48, and 30
193 out of 133 cue-modulated units encoded both time points for cue identity, cue location, and cue outcome,
194 respectively). Population level averages for units that increased to cue-onset showed a ramping up of activity
195 that peaked upon nosepoke, whereas units that decreased to cue-onset showed a gradual reduction of firing
196 activity that reached a minimum upon nosepoke (Figure 10). Additionally, a peak is seen for preferred
197 cue outcome in decreasing units at 1 second post cue-onset when reward was received, demonstrating an
198 integration of expected and received reward (Figure 10F). Furthermore, aligning normalized peak firing rates
199 to nosepoke onset, revealed a clustering of responses around outcome receipt for all cue conditions where the
200 rat would have received reward (Figure 11), in addition to the same trend of higher within- vs across-block
201 correlations for cue identity (Figure 11A,C; within block correlations = .560 (light), .541 (sound); across
202 block correlations = .487, .481, .483, .486; within block vs. within block comparison = p = .112; within
203 block vs. across block comparisons = p < .001) and cue location (Figure 11B,E; within block correlations
204 = .474 (arm 1), .461 (arm 2); across block correlations = .416, .402, .416, .415; within block vs. within
205 block comparison = p = .810; within block vs. across block comparisons = p < .001), but not cue outcome
206 (Figure 11C,F; within block correlations = .620 (reward-available), .401 (reward-unavailable); across block
207 correlations = .418, .414, .390, .408; within block vs. within block comparison = p < .001; within block
208 vs. across block comparisons = p < .001). To determine whether coding of cue features persisted after

209 the outcome was revealed, a GLM was fit to the firing rates of cue-modulated units at the time of outcome
210 receipt, during which the cue was still present. Fitting a GLM revealed 10 units (8%) where cue outcome
211 accounted for an average of 32% of firing rate variance (Table 1, data not shown). An absence of cue identity
212 or cue location coding at this level of analysis was observed, but looking at the data more closely with a
213 sliding window GLM revealed that cue identity, cue location, and cue outcome were encoded throughout
214 time epochs surround cue-onset, nosepoke hold, and outcome receipt, suggesting that the NAc maintains a
215 representation of these cue features once the rat receives behavioral feedback for its decision (Figure 9E-J).

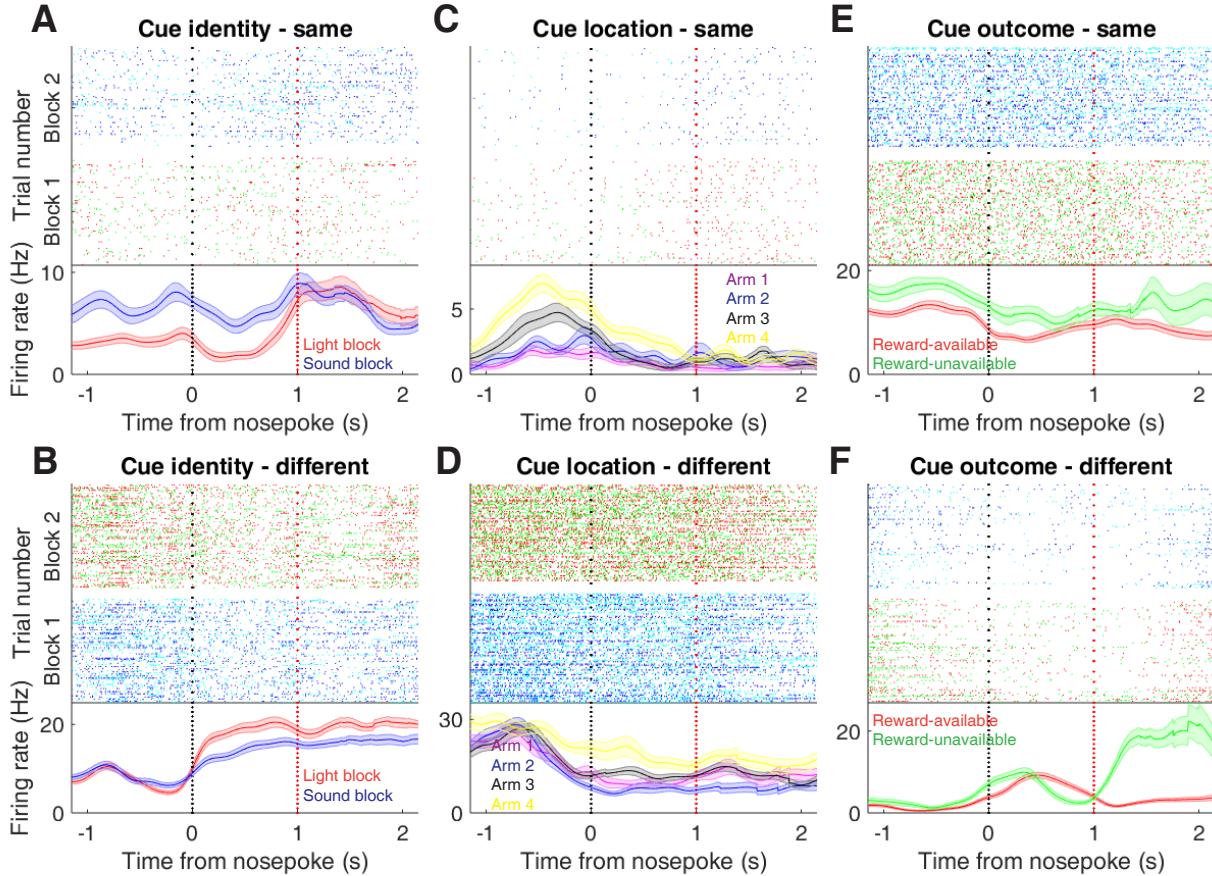


Figure 8: Examples of cue-modulated NAc units influenced by various task parameters at time of nosepoke. **A:** Example of a cue-modulated NAc unit that encoded cue identity at both cue-onset and during nosepoke hold. Top: rasterplot showing the spiking activity across all trials aligned to nosepoke. Spikes across trials are color coded according to cue type (red: reward-available light; green: reward-unavailable light; navy blue: reward-available sound; light blue: reward-unavailable sound). White space halfway up the rasterplot indicates switching from one block to the next. Black dashed line indicates nosepoke. Red dashed line indicates receipt of outcome. Bottom: PETHs showing the average smoothed firing rate for the unit for trials during light (red) and sound (blue) blocks, aligned to nosepoke. Lightly shaded area indicates standard error of the mean. Note this unit showed a sustained increase in firing to sound cues during the trial. **B:** An example of a unit that was responsive to cue identity at time of nosepoke but not cue-onset. **C-D:** Cue-modulated units that encoded cue location, at both cue-onset and nosepoke (C), and only nosepoke (D). Each color in the PETHs represents average firing response for a different cue location. **E-F:** Cue-modulated units that encoded cue outcome, at both cue-onset and nosepoke (E), and only nosepoke (F), with the PETHs comparing reward-available (red) and reward-unavailable (green) trials.

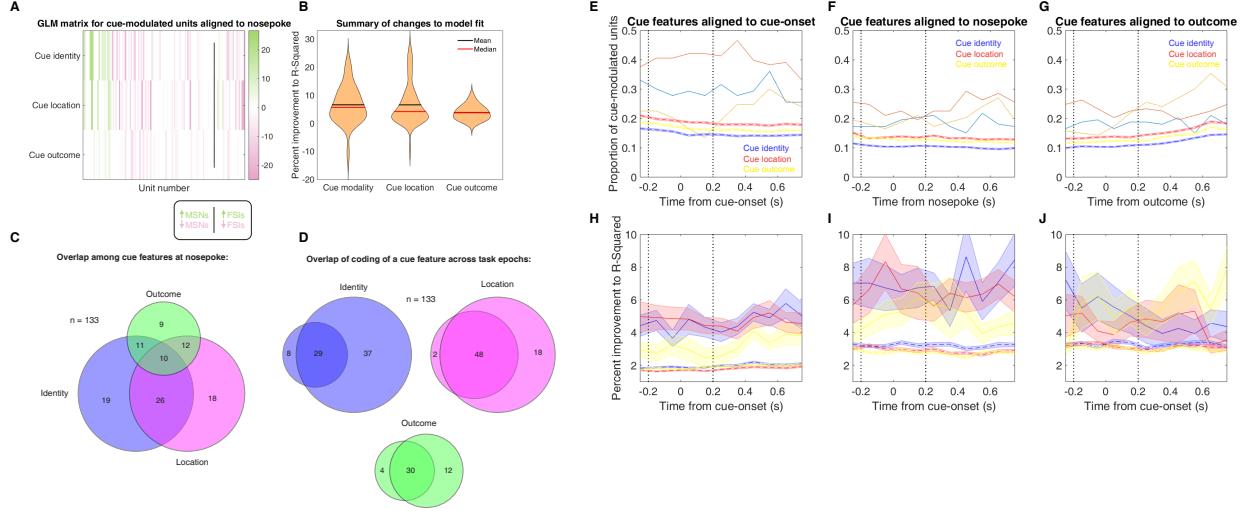


Figure 9: Summary of influence of various task parameters on cue-modulated NAc units during nosepoke. **A:** GLM matrix illustrating the contribution of various task parameters to NAc unit firing rates. A stepwise GLM was fit to each unit that showed evidence of cue modulation by a Wilcoxon signed-rank test. Each row represents a given task parameter, and each column corresponds to a single unit. Colors indicate how much of the firing rate variance an individual predictor contributed to the model, as measured by differences in R-squared between the final model and the model minus the predictor of Interest. Ordering from left to right: MSNs that increased firing in response to the cue (green, left of line), MSNs with a decreasing response (red, left of line), FSIs with an increasing response (green, right of line), FSIs with a decreasing response (red, right of line). Darker shades indicate more firing rate variance explained by a given predictor. Black line indicates separation of MSNs and FSIs. **B:** Violin plots demonstrating changes in R-squared values with the addition of each of the individual predictors. The mean, median, and distribution of changes in R-squared values is plotted for each of the three task parameters that were significant predictors in the GLM. **C:** Venn diagram illustrating the number of cue-modulated units encoding cue identity (blue circle), cue location (green circle), cue outcome (pink circle), as well as the overlap among units that encoded multiple cue features. **D:** Venn diagram illustrating the number of cue-modulated units encoding cue identity, cue location, and cue outcome during cue-onset (left circle), during nosepoke hold (right circle), and during both epochs (overlap). **E-G:** Sliding window GLM illustrating the proportion of cue-modulated units influenced by various predictors around time of cue-onset (E), nosepoke (F), and outcome (G). **E:** Sliding window GLM (bin size: 500 ms; step size: 100 ms) demonstrating the proportion of cue-modulated units where cue identity (blue solid line), cue location (red solid line), and cue outcome (yellow solid line) significantly contributed to the model at various time epochs relative to cue-onset. Dashed colored lines indicate the average of shuffling the firing rate order that went into the GLM 100 times. Points in between the two vertical dashed lines indicate bins where both pre- and post-cue-onset time periods were used in the GLM. **F:** Same as E, but for time epochs relative to nosepoke where the rat waited for the outcome. **G:** Same as E, but for time epochs relative to receipt of outcome after the rat got feedback about his approach. **H-J:** Average improvement to model fit. **H:** Average percent improvement to R-squared for units where cue identity, cue location, or cue outcome were significant contributors to the final model for time epochs relative to cue-onset. Shaded area around mean represents the standard error of the mean. **I:** Same as H, but for time epochs relative to nosepoke. **J:** Same H, but for time epochs relative to receipt of outcome.

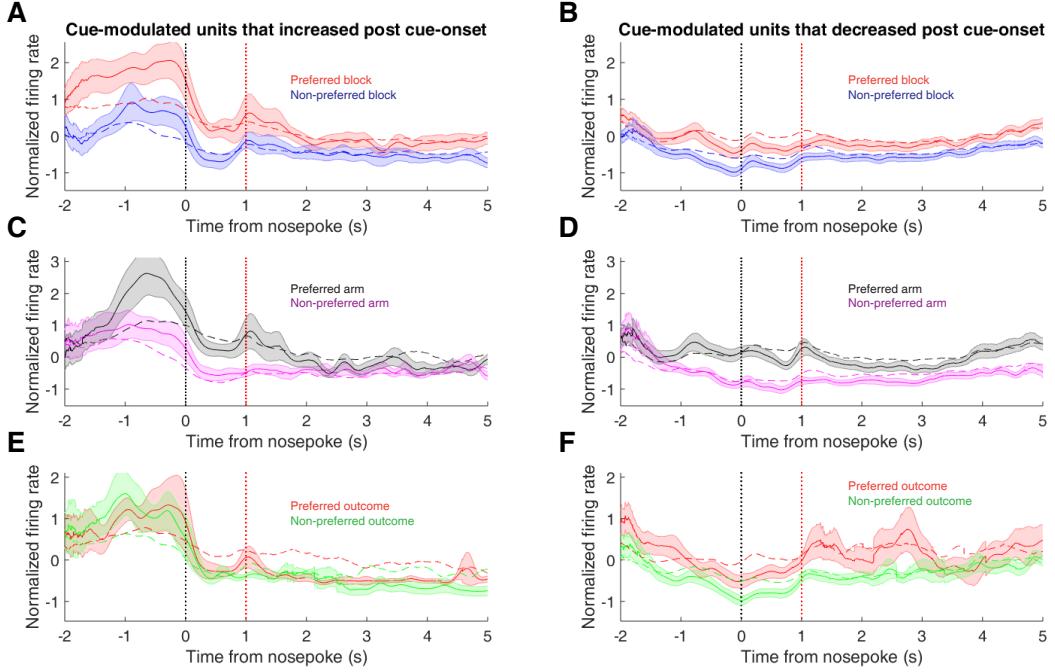


Figure 10: Population-level averages of cue feature sensitive NAc units during a nosepoke. **A:** Average smoothed normalized (z-score) activity for cue-modulated units where cue identity was a significant predictor in the GLM, aligned to nosepoke with reward delivery occurring 1 s after nosepoke. Activity is plotted for preferred stimulus block (red) and nonpreferred stimulus block (blue). Black vertical dashed line indicates nosepoke. Red vertical dashed line indicates reward delivery occurring 1 s after nosepoke for reward-available trials. Dashed color lines indicate the result of shuffling the identity of the units used for this average 1000 times. Lightly shaded area indicates standard error of the mean. Note larger increase leading up to nosepoke to preferred stimulus block over nonpreferred stimulus block. **B:** Same as A but for units that decreased in firing. Note the sustained difference in firing between the two blocks. **C-D:** Same as A-B for cue location. Activity is plotted for most preferred arm (black) and least preferred arm (magenta). **E-F:** Same as A-B for cue outcome. Activity is plotted for preferred expected outcome (red), and nonpreferred outcome (green). Note the peak after outcome receipt for preferred outcome in decreasing units (F).

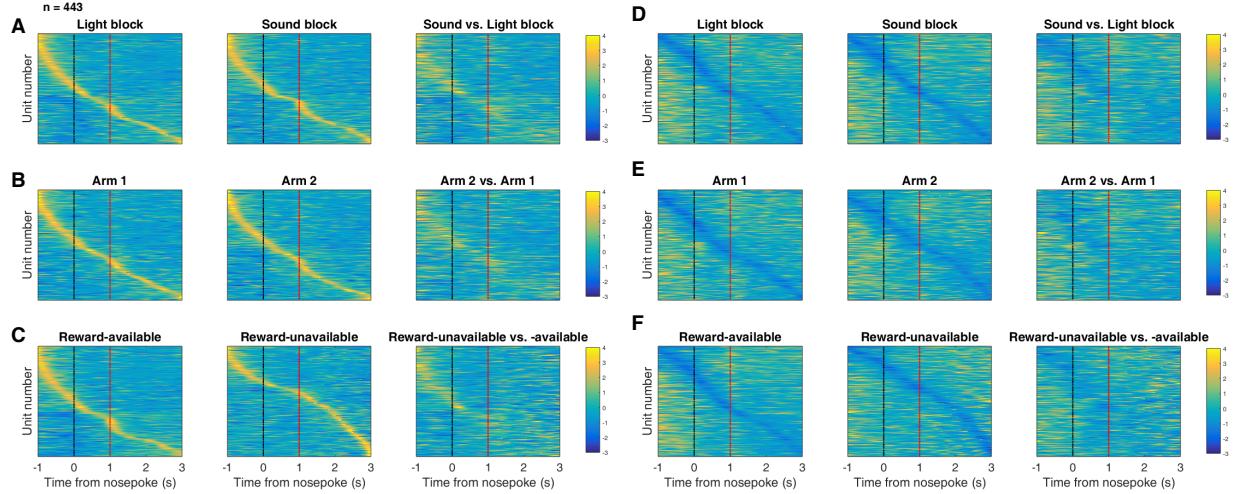


Figure 11: Distribution of NAc firing rates across time surrounding nosepoke for approach trials. Each panel shows normalized (z-score) firing rates for all recorded NAc units (each row corresponds to one unit) as a function of time (time 0 indicates nosepoke), averaged across all approach trials for a specific cue type, indicated by text labels. **A-C:** Heat plots aligned to normalized peak firing rates. **A**, far left: Heat plot showing smoothed normalized firing activity of all recorded NAc units ordered according to the time of their peak firing rate during the light block. Each row is a units average activity across time to the light block. Black dashed line indicates nosepoke. Red dashed line indicates reward delivery occurring 1 s after nosepoke for reward-available trials. Notice the yellow band across time, indicating all aspects of visualized task space were captured by the peak firing rates of various units. **A**, middle: Same units ordered according to the time of the peak firing rate during the sound block. Note that for both blocks, units tile time approximately uniformly with a clear diagonal of elevated firing rates, and a clustering around outcome receipt. **A**, right: Unit firing rates taken from the sound block, ordered according to peak firing rate taken from the light block. Note that a weaker but still discernible diagonal persists, indicating partial similarity between firing rates in the two blocks. A similar pattern exists for within-block comparisons suggesting that reordering any two sets of trials produces this partial similarity, however correlations within blocks are more similar than correlations across blocks (see text). **B:** Same layout as in A, except that the panels now compare two different locations on the track instead of two cue modalities. As for the different cue modalities, NAc units clearly discriminate between locations, but also maintain some similarity across locations, as evident from the visible diagonal in the right panel. Two example locations were used for display purposes; other location pairs showed a similar pattern. **C:** Same layout as in A, except that panels now compare correct reward-available and incorrect reward-unavailable trials. The disproportionate tiling around outcome receipt for reward-available, but not reward-unavailable trials suggests encoding of reward receipt by NAc units. **D-F:** Heat plots aligned to normalized minimum firing rates. **D:** Responses during different stimulus blocks as in A, but with units ordered according to the time of their minimum firing rate. **E:** Responses during trials on different arms as in B, but with units ordered by their minimum firing rate. **F:** Responses during cues signalling different outcomes as in C, but with units ordered by their minimum firing rate. Overall, NAc units “tiled” experience on the task, as opposed to being confined to specific task events only. Units from all sessions and animals were pooled for this analysis.

216 **Discussion**

217 The main result of the present study is that NAc units encode not only the expected outcome of outcome-
218 predictive cues, but also the identity of such cues. Importantly, this identity coding was maintained on
219 approach trials both during a delay period where the rat held a nosepoke until the outcome was received, and
220 immediately after outcome receipt (H2 and H3 in Figure 1B). Units coding for cue identity showed partial
221 overlap with those coding for expected outcome (H3 in Figure 1A). Units that coded different cue features
222 (identity, outcome, location) exhibited different temporal profiles as a whole, although across all recorded
223 units a tiling of task structure was observed such that all points within our analyzed task space was accounted
224 for by the ordered peak firing rates of all units. Furthermore, this tiling differed between various conditions
225 with a cue feature, such as light versus sound blocks. We discuss these observations and their implications
226 below.

227 **Cue identity:**

228 Our finding that NAc units can discriminate between different outcome-predictive stimuli with similar moti-
229 vational significance (i.e. encodes cue identity) expands upon an extensive rodent literature examining NAc
230 correlates of conditioned stimuli (Ambroggi, Ishikawa, Fields, & Nicola, 2008; Atallah et al., 2014; Bis-
231 sonette et al., 2013; Cooch et al., 2015; Day et al., 2006; Dejean et al., 2017; Goldstein et al., 2012; Ishikawa,
232 Ambroggi, Nicola, & Fields, 2008; Lansink et al., 2012; McGinty et al., 2013; Nicola, 2004; Roesch et al.,
233 2009; Roitman et al., 2005; Saddoris et al., 2011; Setlow et al., 2003; Sugam et al., 2014; West & Carelli,
234 2016; Yun, Wakabayashi, Fields, & Nicola, 2004). Perhaps the most comparable work in rodents comes
235 from a study that found distinct coding for an odor when it predicted separate but equally valued rewards
236 (Cooch et al., 2015). The present work is complementary to such *outcome identity* coding as it shows that
237 NAc units encode *cue identity*, both separately and integrated with the reward it predicts (H2 and H3 in Fig-
238 ure 1A). Similarly, Setlow et al. (2003) paired distinct cues with appetitive or aversive outcomes, and found
239 separate populations of units that encoded each cue. Once again, our study was different in asking how

240 distinct cues encoding the same anticipated outcome are encoded. Such cue identity encoding suggests that
241 even when the biological relevance of these stimuli is similar, NAc dissociates their representations at the
242 level of the single-units. A possible interpretation of this coding of cue features alongside expected outcome
243 is that these representations are used to associate reward with relevant features of the environment, so-called
244 credit assignment in the reinforcement learning literature (Sutton & Barto, 1998). A burgeoning body of
245 human and non-human primate work has started to elucidated neural correlates of credit assignment in the
246 PFC, particularly in the lateral orbitofrontal cortex (Akaishi, Kolling, Brown, & Rushworth, 2016; Asaad,
247 Lauro, Perge, & Eskandar, 2017; Chau et al., 2015; Noonan, Chau, Rushworth, & Fellows, 2017). Given
248 the importance of cortical inputs in NAc associative representations, it is possible that information related to
249 credit assignment is relayed from the cortex to NAc (Cooch et al., 2015; Ishikawa et al., 2008).

250 A different possible function for cue identity coding is to support contextual modulation of the motivational
251 relevance of specific cues. A context can be understood as a particular mapping between specific cues and
252 their outcomes: for instance, in context 1 cue A but not cue B is rewarded, whereas in context 2 cue B
253 but not cue A is rewarded. Successfully implementing such contextual mappings requires representation of
254 the cue identities. Indeed, Sleezer et al. (2016) recorded NAc responses during the Wisconsin Card Sorting
255 Task, a common set-shifting task used in both the laboratory and clinic, and found units that preferred firing
256 to stimuli when a certain rule, or rule category was currently active. Further support for a modulation of
257 NAc responses by strategy comes from an fMRI study that examined BOLD levels during a set-shifting task
258 (FitzGerald et al., 2014). In this task, participants learned two sets of stimulus-outcome contingencies, a
259 visual set and an auditory set. During testing they were presented with both simultaneously, and the stimulus
260 dimension that was relevant was periodically shifted between the two. Here, they found that bilateral NAc
261 activity reflected value representations for the currently relevant stimulus dimension, and not the irrelevant
262 stimulus. The current finding of separate, but overlapping, populations of units encoding cue identity and
263 expected outcome, suggests that the fMRI finding is generated by the combined activity of several different
264 functional cell types.

265 Our analyses were designed to eliminate several potential alternative interpretations to cue identity coding.
266 Because the different cues were separated into different blocks, units that discriminated between cue identi-
267 ties could instead be encoding time or other slowly-changing quantities. We excluded this possible confound
268 by excluding units that showed a drift in firing between the first and second half within a block. However, the
269 possibility remains that instead of or in addition to stimulus identity, these units encode a preferred context,
270 or even a macroscale representation of progress through the session. Indeed, encoding of the current strategy
271 could be an explanation for the sustained difference in population averaged firing across stimulus blocks
272 (Figure 6), as well as a potential explanation for the differentially tiling of task structure across blocks in the
273 current study (Figure 7).

274 A different potential confound is that between outcome and action value coding. We discriminated between
275 these possibilities by analyzing error trials, where the rat approached reward (left turn) after presentation of
276 the reward-unavailable cue. Units that were modulated by the expected outcome of the cue maintained their
277 specific firing patterns even during error trials, as expected from outcome value coding but not action value
278 coding. Additionally, NAc signals have been shown to be modulated by response vigor (McGinty et al.,
279 2013); to detangle this from our results we included trial length (i.e. latency to arrival at the reward site) as a
280 predictor in our GLMs, and found units with cue feature correlates independent of trial length.

281 An overall limitation of the current study is that rats were never presented with both sets of cues simultane-
282 ously, and were not required to switch strategies between multiple sets of cues. Thus, it is unknown to what
283 extent the cue identity encoding we observed is behaviorally relevant, although extrapolating data from other
284 work (Sleeker et al., 2016) suggests that cue identity coding would be modulated by relevance. NAc core
285 lesions have been shown to impair shifting between different behavioral strategies (Floresco et al., 2006),
286 and it is possible that selectively silencing the units that prefer responding for a given modality or rule would
287 impair performance when the animal is required to use that information, or artificial enhancement of those
288 units would cause them to use the rule when it is the inappropriate strategy.

289 **Encoding of position:**

290 Our finding that cue-evoked activity was modulated by cue location is in alignment with several previous
291 reports (Lavoie & Mizumori, 1994; Mulder, Shibata, Trullier, & Wiener, 2005; Strait et al., 2016; Wiener
292 et al., 2003). The NAc receives inputs from the hippocampus, and the communication of place-reward in-
293 formation across the two structures suggests that the NAc tracks locations associated with reward (Lansink
294 et al., 2008; Lansink, Goltstein, Lankelma, McNaughton, & Pennartz, 2009; Lansink et al., 2016; Pennartz,
295 2004; Sjulson, Peyrache, Cumpelik, Cassataro, & Buzsáki, 2017; Tabuchi, Mulder, & Wiener, 2000; van der
296 Meer & Redish, 2011). NAc units can also signal progress through a sequence of cues and/or actions (Atal-
297 lah et al., 2014; Berke, Breck, & Eichenbaum, 2009; Khamassi, Mulder, Tabuchi, Douchamps, & Wiener,
298 2008; Lansink et al., 2012; Mulder, Tabuchi, & Wiener, 2004; Shidara, Aigner, & Richmond, 1998). Given
299 that the current task was pseudo-random, it is possible that the rats learned the structure of sequential cue
300 presentation, and the neural activity could reflect this. However, this is unlikely as including a previous trial
301 variable in the analysis did not explain a significant amount of firing rate variance in response to the cue for
302 the vast majority of units. In any case, NAc units on the present task continued to distinguish between differ-
303 ent locations, even though location, and progress through a sequence, were explicitly irrelevant in predicting
304 reward. We speculate that this persistent coding of location in NAc may represent a bias in credit assignment,
305 and associated tendency for rodents to associate motivationally relevant events with the locations where they
306 occur.

307 **Implications:**

308 Maladaptive decision making, as occurs in schizophrenia, addiction, Parkinson's, among others, can re-
309 sult from dysfunctional RPE and value signals (Frank, Seeberger, & O'Reilly, 2004; Gradin et al., 2011;
310 Maia & Frank, 2011). This view has been successful in explaining both positive and negative symptoms in
311 schizophrenia, and deficits in learning from feedback in Parkinson's (Frank et al., 2004; Gradin et al., 2011).
312 However, the effects of RPE and value updating are contingent upon encoding of preceding action and cue

313 features, the eligibility trace (Lee et al., 2012; Sutton & Barto, 1998). Value updates can only be performed
314 on these aspects of preceding experience that are encoded when the update occurs. Therefore, maladaptive
315 learning and decision making can result from not only aberrant RPEs but also from altered cue feature en-
316 coding. For instance, on this task the environmental stimulus that signaled the availability of reward was
317 conveyed by two distinct cues that were presented in four locations. While in our current study, the location
318 and identity of the cue did not require any adjustments in the animals behavior, we found coding of these
319 features alongside the expected outcome of the cue that could be the outcome of credit assignment compu-
320 tations computed upstream. Identifying neural coding related to an aspect of credit assignment is important
321 as inappropriate credit assignment could be a contributor to conditioned fear overgeneralization seen in dis-
322 orders with pathological anxiety such as generalized anxiety disorder, post traumatic stress disorder, and
323 obsessive-compulsive disorder (Kaczkurkin et al., 2017; Kaczkurkin & Lissek, 2013; Lissek et al., 2014),
324 and delusions observed in disorders such as schizophrenia, Alzheimer's and Parkinson's (Corlett, Taylor,
325 Wang, Fletcher, & Krystal, 2010; Kapur, 2003). Thus, our results provide a neural window into the process
326 of credit assignment, such that the extent and specific manner in which this process fails in syndromes such
327 as schizophrenia, obsessive-compulsive disorder, etc. can be experimentally accessed.

328 Methods

329 Subjects:

330 A sample size of 4 adult male Long-Evans rats (Charles River, Saint Constant, QC) from an apriori deter-
331 mined sample of 5 were used as subjects (1 rat was excluded from the data set due to poor cell yield). Rats
332 were individually housed with a 12/12-h light-dark cycle, and tested during the light cycle. Rats were food
333 deprived to 85-90% of their free feeding weight (weight at time of implantation was 440 - 470 g), and water
334 restricted 4-6 hours before testing. All experimental procedures were approved by the the University of Wa-
335 terloo Animal Care Committee (protocol# 11-06) and carried out in accordance with Canadian Council for

336 Animal Care (CCAC) guidelines.

337 **Overall timeline:**

338 Each rat was first handled for seven days during which they were exposed to the experiment room, the
339 sucrose solution used as a reinforcer, and the click of the sucrose dispenser valves. Rats were then trained
340 on the behavioral task (described in the next section) until they reached performance criterion. At this point
341 they underwent hyperdrive implantation targeted at the NAc. Rats were allowed to recover for a minimum
342 of five days before being retrained on the task, and recording began once performance returned to pre-
343 surgery levels. Upon completion of recording, animals were glosed, euthanized and recording sites were
344 histologically confirmed.

345 **Behavioral task and training:**

346 The behavioral apparatus was an elevated, square-shaped track (100 x 100 cm, track width 10 cm) containing
347 four possible reward locations at the end of track “arms” (Figure 2). Rats initiated a *trial* by triggering a
348 photobeam located 24 cm from the start of each arm. Upon trial initiation, one of two possible light cues
349 (L1, L2), or one of two possible sound cues (S1, S2), was presented that signaled the presence (*reward-*
350 *available trial*, L1+, S1+) or absence (*reward-unavailable trial*, L2-, S2-) of a 12% sucrose water reward
351 (0.1 mL) at the upcoming reward site. A trial was classified as an *approach trial* if the rat turned left at the
352 decision point and made a nosepoke at the reward receptacle (40 cm from the decision point), while trials
353 were classified as a *skip trial* if the rat instead turned right at the decision point and triggered the photobeam
354 to initiate the next trial. A trial is labeled *correct* if the rat approached (i.e. nosepoked) on reward-available
355 trials, and skipped (i.e. did not nosepoke) on reward-unavailable trials. On reward-available trials there
356 was a 1 second delay between a nosepoke and subsequent reward delivery. *Trial length* was determined by
357 measuring the length of time from cue onset until nosepoke (for approach trials), or from cue onset until
358 the start of the following trial (for skip trials). Trials could only be initiated through clockwise progression

359 through the series of arms, and each entry into the subsequent arm on the track counted as a trial.

360 Each session consisted of both a *light block* and a *sound block* with 100 trials each. Within a block, one cue
361 signaled reward was available on that trial (L1+ or S1+), while the other signaled reward was not available
362 (L2- or S2-). Light block cues were a flashing white light, and a constant yellow light. Sound block cues
363 were a 2 kHz sine wave and a 8 kHz sine wave whose amplitude was modulated from 0 to maximum by
364 a 2 Hz sine wave. Outcome-cue associations were counterbalanced across rats, e.g. for some rats L1+ was
365 the flashing white light, and for others L1+ was the constant yellow light. The order of cue presentation
366 was pseudorandomized so that the same cue could not be presented more than twice in a row. Block order
367 within each day was also pseudorandomized, such that the rat could not begin a session with the same block
368 for more than two days in a row. Each session consisted of a 5 minute pre-session period on a pedestal (a
369 terracotta planter filled with towels), followed by the first block, then the second block, then a 5 minute post-
370 session period on the pedestal. For approximately the first week of training, rats were restricted to running
371 in the clockwise direction by presenting a physical barrier to running counterclockwise. Cues signaling the
372 availability and unavailability of reward, as described above, were present from the start of training. Rats
373 were trained for 200 trials per day (100 trials per block) until they discriminated between the reward-available
374 and reward-unavailable cues for both light and sound blocks for three consecutive days, according to a chi-
375 square test rejecting the null hypothesis of equal approaches for reward-available and reward-unavailable
376 trials, at which point they underwent electrode implant surgery.

377 **Surgery:**

378 Surgical procedures were as described previously (Malhotra, Cross, Zhang, & Van Der Meer, 2015). Briefly,
379 animals were administered analgesics and antibiotics, anesthetized with isoflurane, induced with 5% in med-
380 ical grade oxygen and maintained at 2% throughout the surgery (0.8 L/min). Rats were then chronically
381 implanted with a “hyperdrive” consisting of 16 independently drivable tetrodes, either all 16 targeted for the
382 right NAc (AP +1.4 mm and ML +1.6 mm relative to bregma; Paxinos & Watson 1998), or 12 in the right

383 NAc and 4 targeted at the mPFC (AP +3.0 mm and ML +0.6 mm, relative to bregma; only data from NAc
384 tetrodes was analyzed). Following surgery, all animals were given at least five days to recover while receiv-
385 ing post-operative care, and tetrodes were lowered to the target (DV -6.0 mm) before being reintroduced to
386 the behavioral task.

387 **Data acquisition and preprocessing:**

388 After recovery, rats were placed back on the task for recording. NAc signals were acquired at 20 kHz with
389 a RHA2132 v0810 preamplifier (Intan) and a KJE-1001/KJD-1000 data acquisition system (Amplipex).
390 Signals were referenced against a tetrode placed in the corpus callosum above the NAc. Candidate spikes
391 for sorting into putative single units were obtained by band-pass filtering the data between 600-9000 Hz,
392 thresholding and aligning the peaks (UltraMegaSort2k, Hill, Mehta, & Kleinfeld, 2011). Spike waveforms
393 were then clustered with KlustaKwik using energy and the first derivative of energy as features, and manually
394 sorted into units (MClust 3.5, A.D. Redish et al., <http://redishlab.neuroscience.umn.edu/MClust/MClust.html>).
395 Isolated units containing a minimum of 200 spikes within a session were included for subsequent analysis.
396 Units were classified as fast spiking interneurons (FSIs) by an absence of interspike intervals (ISIs) > 2 s,
397 while medium spiny neurons (MSNs) had a combination of ISIs > 2 s and phasic activity with shorter ISIs
398 (Atallah et al., 2014; Barnes, Kubota, Hu, Jin, & Graybiel, 2005).

399 **Data analysis:**

400 *Behavior.* To determine if rats distinguished behaviorally between the reward-available and reward-unavailable
401 cues (*cue outcome*), we generated linear mixed effects models to investigate the relationships between cue
402 type and our behavioral variables, with *cue outcome* (reward available or not) and *cue identity* (light or
403 sound) as fixed effects, and the addition of an intercept for rat identity as a random effect. For each cue,
404 the average proportion of trials approached and trial length for a session were used as response variables.
405 Contribution of cue outcome to behavior was determined by comparing the full model to a model with cue

406 outcome removed for each behavioral variable.

407 *Neural data.* To investigate the contribution of different cue features (cue identity and cue outcome) on the
408 firing rates of NAc single units, we first determined whether firing rates for a unit were modulated by the
409 onset of a cue by collapsing across all cues and comparing the firing rates for the 1 s preceding cue-onset
410 with the 1 s following cue-onset. Single units were considered to be *cue-modulated* if a Wilcoxon signed-
411 rank test comparing pre- and post-cue firing was significant at $p < .01$. Cue-modulated units were then
412 classified as either increasing or decreasing if the post-cue activity was higher or lower than the pre-cue
413 activity, respectively.

414 To determine the relative contribution of different task parameters to firing rate variance (as in Figures 4-
415 5), a forward selection stepwise GLM using a Poisson distribution for the response variable was fit to each
416 cue-modulated unit. Cue identity (light block, sound block), cue location (arm 1, arm 2, arm 3, arm 4), cue
417 outcome (reward-available, reward-unavailable), behavior (approach, skip), trial length, trial number, and
418 trial history (reward availability on the previous 2 trials) were used as predictors, and the 1 s post-cue firing
419 rate as the response variable. Units were classified as being modulated by a given task parameter if addition
420 of the parameter significantly improved model fit using deviance as the criterion ($p < .01$). A comparison
421 of the R-squared value between the final model and the final model minus the predictor of interest was used
422 to determine the amount of firing rate variance explained by the addition of that predictor for a given unit.
423 To determine the degree to which coding of cue identity, cue location, and cue outcome overlapped within
424 units we computed Pearson's r on recoded beta coefficients from the GLM for the cue features. Specifically,
425 for all cue-modulated units, we coded a 1 if the cue feature was a significant predictor in the final model,
426 and 0 if it was not, and calculated Pearson's r comparing an array of the coded 0s and 1s for cue-modulated
427 units for one cue feature with a similar array for another cue feature. The NAc was determined as coding a
428 pair of cue features in a) a separate populations of units if there was a significant negative correlation ($r < 0$),
429 b) an independent overlapping population of units if there was no significant correlation ($r = 0$), and c) a
430 joint overlapping population of units if there was a significant positive correlation ($r > 0$). To investigate

431 more finely the temporal dynamics of the influence of task parameters to unit activity, we then fit a sliding
432 window GLM with the same task parameters using 500 ms bins and 100 ms steps, starting 500 ms before
433 cue-onset, up to 500 ms after cue-onset, and measured the proportion of units and average R-squared value
434 for a given time bin where a particular predictor contributed significantly to the final model. To control for
435 the amount of units that would be affected by a predictor by chance, we shuffled the trial order of firing rates
436 for a particular unit within a time bin, and took the average of this value over 100 shuffles.

437 To better visualize responses to cues and enable subsequent population level analyses (as in Figures 4, 6,
438 and 7), spike trains were convolved with a Gaussian kernel ($\sigma = 100$ ms), and peri-event time histograms
439 (PETHs) were generated by taking the average of the convolved spike trains across all trials for a given
440 task condition. For analysis of population-level responses for cue features (Figure 6), convolved spike trains
441 for all units where cue identity, cue location, or cue outcome explained a significant portion of firing rate
442 variance were z-scored. Within a given cue feature, normalized spike trains were then separated according
443 to the preferred and non-preferred cue condition (e.g. light vs. sound block), and averaged across units to
444 generate population-level averages. To account for separation that would result from any random selection
445 of units, unit identity was shuffled and the shuffled average for preferred and non-preferred cue conditions
446 was generated for 1000 shuffles.

447 To visualize NAc representations of task space within cue conditions, normalized spike trains for all units
448 were ordered by the location of their maximum or minimum firing rate for a specified cue condition (Figure
449 7). To compare representations of task space across cue conditions for a cue feature, the ordering of units
450 derived for one condition (e.g. light block) was then applied to the normalized spike trains for the other
451 condition (e.g. sound block). For control comparisons within cue conditions, half of the trials for a condition
452 were compared against the other half. To look at the correlation of firing rates of all units within and across
453 various cue conditions, trials for each cue condition for a unit were shuffled and divided into two averages,
454 and averages within and across cue conditions were correlated. A linear mixed effects model was run for
455 each cue condition to determine if correlations of firing rates within cue conditions were more similar than

456 correlations across cue conditions.

457 To identify the responsivity of units to different cue features at the time of a nosepoke into a reward re-
458 ceptacle, and subsequent reward delivery, the same cue-responsive units from the cue-onset analyses were
459 analyzed at the time of nosepoke and outcome receipt using identical analysis techniques (Figures 8, 9, 10,
460 and 11). To compare whether coding of a given cue feature was accomplished by the same or distinct pop-
461 ulation of units across time epochs, we ran the recoded coefficient correlation that was used to assess the
462 degree of overlap among cue features within a time epoch.

463 Given that some of our analyses compare firing rates across time, particularly comparisons across blocks,
464 we sought to exclude units with unstable firing rates that would generate spurious results reflecting a drift
465 in firing rate over time unrelated to our task. To do this we ran a Mann-Whitney U test comparing the
466 cue-evoked firing rates for the first and second half of trials within a block, and excluded 99 of 443 units
467 from analysis that showed a significant change for either block, leaving 344 units for further analyses.
468 All analyses were completed in MATLAB R2015a, the code is available on our public GitHub repository
469 (<http://github.com/vandermeerlab/papers>), and the data can be accessed through DataLad.

470 **Histology:**

471 Upon completion of the experiment, recording channels were glosed by passing $10 \mu A$ current for 10 sec-
472 onds and waiting 5 days before euthanasia, except for rat R057 whose implant detached prematurely. Rats
473 were anesthetized with 5% isoflurane, then asphyxiated with carbon dioxide. Transcardial perfusions were
474 performed, and brains were fixed and removed. Brains were sliced in $50 \mu m$ coronal sections and stained
475 with thionin. Slices were visualized under light microscopy, tetrode placement was determined, and elec-
476 trodes with recording locations in the NAc were analyzed (Figure 12).

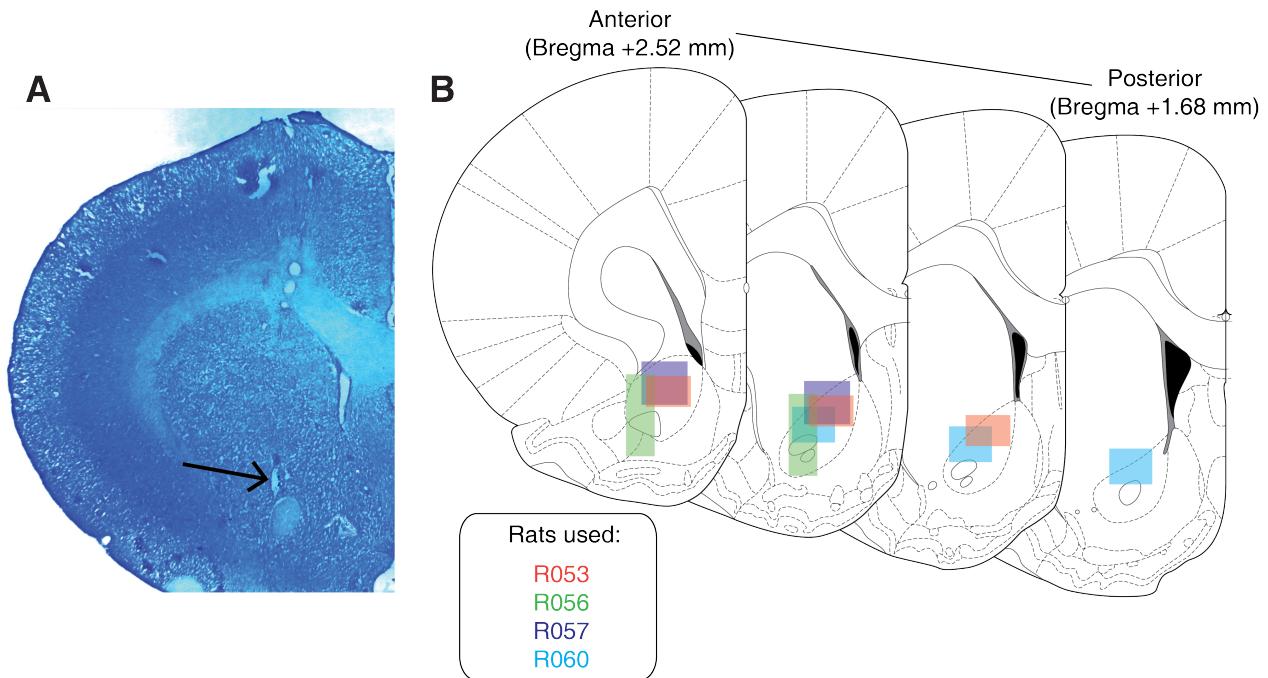


Figure 12: Histological verification of recording sites. Upon completion of experiments, brains were sectioned and tetrode placement was confirmed. **A:** Example section from R060 showing a recording site in the NAc core just dorsal to the anterior commissure (arrow). **B:** Schematic showing recording areas for all subjects.

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