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Sign tracking and goal tracking are characterized by distinct patterns of nucleus accumbens activity

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Manuscript title: Sign tracking and goal tracking are characterized by distinct patterns of nucleus accumbens activity

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Abstract

During Pavlovian conditioning, if a cue (e.g., lever extension) predicts reward delivery in a different location (e.g., a food magazine), some individuals will come to approach and interact with the cue – a behavior known as sign tracking (ST) – and others will approach the site of reward, a behavior known as goal tracking (GT). In rats, the acquisition of ST vs. GT behavior is associated with distinct profiles of dopamine release in the nucleus accumbens (NAc), but it is unknown whether it is associated with different patterns of accumbens neural activity. Therefore, we recorded from individual neurons in the NAc core during the acquisition, maintenance, and extinction of ST and GT behavior. Even though NAc dopamine is specifically important for the acquisition and expression of ST, we found that cue-evoked excitatory responses encode the vigor of both ST and GT behavior. In contrast, among sign trackers only, there was a prominent decrease in reward-related activity over the course of training, which may reflect the decreasing reward prediction error encoded by phasic dopamine. Finally, both behavior and cue-evoked activity were relatively resistant to extinction in sign trackers, as compared with goal trackers, although a subset of neurons in both groups retained their cue-evoked responses. Overall, the results point to the convergence of multiple forms of reward learning in the NAc.

Significance Statement

An individual's tendency to interact with a cue that predicts reward – known as sign tracking – has been linked with impulsivity and addiction-related behaviors. Here, we show that, during learning, sign tracker rats – as compared with goal tracker rats, who preferentially interact with the site of reward – display different profiles of neuronal activity in the nucleus accumbens

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(NAc). The evolution of NAc activity is uniquely linked to the acquisition of sign tracking, but not goal tracking; however, after learning, NAc activity reflects the vigor of both behaviors. These findings imply that sign tracking and goal tracking result from different learning processes and engage distinct neural circuits that partially overlap in the NAc.

Introduction

Cues that are associated with rewards, such as food or drugs, can acquire motivational value – often referred to as incentive salience (Berridge 2004) – and thereby come to exert a powerful influence over behavior. Notably, there is considerable variation among individuals in their propensity to assign incentive salience to a cue (Robinson et al. 2014). For example, in a Pavlovian conditioned approach protocol, if a cue (e.g., extension of a lever) predicts reward in a different location (e.g. a sugar pellet delivered to a food magazine), some rats will preferentially approach and interact with the lever – a behavior known as sign tracking (ST; Hearst and Jenkins 1974). In contrast, other rats will approach the site of reward delivery, a behavior known as goal tracking (GT; Boakes 1977). A predisposition towards ST has been linked with measures of impulsivity (Flagel et al. 2010; Lovic et al. 2011), and susceptibility to drug-taking, addiction and relapse (Saunders and Robinson 2013; Tomie et al. 2008).

Both sign tracking and goal tracking require associative learning about a cue – i.e., learning that a cue predicts reward – but only sign trackers are thought to ascribe incentive salience to the cue. Consistent with this idea, a lever cue is more effective as a conditioned reinforcer (Robinson and Flagel 2009) and at reinstating reward-seeking behavior (Yager and Robinson 2010) among sign trackers than among goal trackers. In fact, it has been proposed that ST and GT behaviors result

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from different forms of learning: one linking the cue with an explicit representation of the outcome (goal tracking), and one linking the cue with the motivational properties of the outcome (sign tracking; Clark et al. 2012; Huys et al. 2014; Lesaint et al. 2014). Supporting this theory, sign-tracking behavior, compared with goal tracking, is resistant to changes in the cue-outcome relationship, including reward devaluation (Cleland and Davey 1982; Morrison et al. 2015; although see Derman et al. 2018) and extinction (Ahrens et al. 2015).

Many studies have shown that mesolimbic structures such as the nucleus accumbens (NAc) – and especially dopamine therein – play an essential role in conditioned approach, including sign tracking. Lesions of the NAc core impair Pavlovian conditioned approach and produce deficits in the acquisition and expression of sign tracking (Cardinal et al. 2002; Chang et al. 2012; although see Chang and Holland 2013); moreover, NAc dopamine depletion (Parkinson et al. 2002) or receptor blockade (Flagel et al. 2011; Saunders and Robinson 2012) reduce ST while affecting GT minimally or not at all. Similarly, injection of amphetamine into the NAc increases ST but not GT (Singer et al. 2016). Furthermore, both sign tracker and goal tracker individuals exhibit phasic dopamine release in the NAc in response to reward-predictive cues; however, only sign trackers show increasing dopamine release in response to the cue and decreasing dopamine release in response to the reward over the course of training (Flagel et al. 2011). This finding implies that acquisition of ST, but not GT, requires a form of learning that depends on the reward-prediction error encoded by mesolimbic dopamine.

Although sign trackers and goal trackers exhibit different characteristic profiles of NAc dopamine release (Flagel et al. 2011), it is unclear whether and how these differences impact NAc neuronal activity supporting these different forms of learning. In order to address this question, we recorded the activity of individual neurons in the NAc core during the acquisition,

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maintenance, and extinction of sign-tracking and goal-tracking behaviors. Studies using instrumental tasks have shown that cue-evoked firing in the NAc encodes both the reward associations of the cue and the vigor of the subsequent locomotor response (McGinty et al. 2013; Morrison et al. 2017). Therefore, we hypothesized that NAc activity would reflect the vigor of both sign-tracking and goal-tracking behaviors. Alternatively, robust differences in the representation of the locomotor properties of sign tracking vs. goal tracking might indicate a preferential role for NAc activity in promoting one of these behaviors.

At the same time, we anticipated that different patterns of task-related activity would emerge in sign tracker vs. goal tracker individuals, reflecting the different learning processes – a dopamine-dependent form of learning resulting in sign tracking, and a dopamine-independent form of learning resulting in goal tracking – that have been predicted to converge in the NAc (Clark et al. 2012; Lesaint et al. 2014). On the other hand, if we did not find such a dissociation, it would raise new questions regarding the functional relevance of differences in NAc dopamine release during the acquisition of sign tracking and goal tracking.

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Materials and methods

All animal procedures were performed in accordance with the [Author University] animal care committee's regulations.

Subjects. Subjects were 8 male Long-Evans rats obtained from Charles River Laboratory weighing 275-300 g upon arrival. Rats were pair-housed until surgery (see below) on a 12 h light/dark cycle (lights on at 7:00 pm). All experiments were performed during the dark phase. After arrival, rats were allowed to acclimate to the housing colony for 7 d. They were then habituated to human contact and handling over at least 2 sessions prior to surgery and the start of behavioral training. Subjects were provided with water *ad libitum* throughout and food *ad libitum* until 2 d before the start of training, when they were placed on a restricted diet of 15 g of chow per day. Rats were weighed regularly, and, if necessary, provided with extra food to maintain a minimum of 90% of pre-restriction body weight.

Implantation of electrode arrays. Using standard aseptic procedures, we implanted custom-constructed fixed electrode arrays bilaterally targeted at the NAc core (coordinates in mm from bregma: AP = +1.4, ML = ± 1.5, DV = -7.0 from dura). Recording arrays comprised 8 Teflon-insulated tungsten wires (A-M Systems) hand-cut to achieve an impedance of 90-110 MΩ and mounted in a circular pattern (diameter ~1 mm). Animals were anesthetized with isoflurane (4% for induction, 1-2% for maintenance) and treated with ketoprofen (5 mg/kg) for pain relief, as well as acetaminophen in their drinking water for 3 d following surgery. Animals were allowed to recover for at least 7 d prior to food restriction and the start of behavioral training.

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144 *Histology*. After completion of data collection, animals were deeply anesthetized using chloral
145 hydrate (400 mg/kg) and direct current (75 μA) passed through each of the electrodes in the
146 array for 10 s. Animals were then transcardially perfused with saline followed by 10% buffered
147 formalin; brains were removed and placed in formalin. Brains were sunk in 30% sucrose for at
148 least 3 d before sectioning on a cryostat (60 μm slices), followed by staining with cresyl violet.
149 Placement of electrode arrays was confirmed via light microscope.
150
151 *Apparatus and behavior*. All training and experiments took place in a standard operant chamber
152 (Coulbourn Instruments) equipped with a house light, a speaker for auditory cues, and a pellet
153 dispenser connected to a food magazine recessed into the side wall. The magazine was equipped
154 with an infrared photo-detector unit to detect entries and exits. Two retractable levers were
155 installed on either side of the magazine, although only one lever (counterbalanced among
156 subjects) was used for each subject. White cue lights were present above each lever. The
157 behavioral task was controlled by Coulbourn software (GraphicState 3.0).
158
159 Rats were trained using a Pavlovian conditioned approach procedure similar to those used
160 previously (Morrison et al. 2015; Tunstall and Kearns 2015). Each training session began with
161 illumination of the house light. Rats were initially trained over 2 sessions to retrieve sugar pellets
162 (45 mg, Bio-Serv) from the magazine, with each session consisting of 50 rewards delivered on a
163 variable interval schedule averaging 60 s. During the second magazine training session, rats were
164 habituated to the recording apparatus (see below).
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Following magazine training, subjects completed 7 consecutive daily acquisition sessions on the Pavlovian conditioned approach (PCA) task. Neuronal recording took place on all seven days. The PCA task consisted of 25 trials separated by an intertrial interval selected from a truncated exponential distribution averaging 60 s. Each trial was initiated by the presentation of the cue: lever extension accompanied by a brief auditory stimulus (1 s, 500 Hz intermittent tone) and flashing of the corresponding cue light (5 Hz). After 8 s, the lever retracted, the cue light extinguished, and the reward was delivered into the magazine. No action was required for reward to be delivered.

In a subset of subjects (n = 7), rats were subsequently retrained for one day, followed by an extinction procedure, which was identical to the PCA task except that no reward was delivered. The lag between the last acquisition session and retraining/extinction ranged from 5 to 14 days. No substantive differences in behavior or neural responses were seen in the groups that underwent extinction earlier vs. later, so data were combined for subsequent analysis.

Electrophysiology. We recorded neuronal activity throughout task acquisition, maintenance, and extinction using Plexon hardware and software. Rats were connected to a light-weight headstage and a motorized commutator that allowed free movement. Voltages were bandpass filtered between 220 Hz and 6 kHz, amplified 500x, and digitized at 40 kHz. Putative spikes were time-stamped and stored in segments of 1.4 ms, followed by sorting (Offline Sorter, Plexon) using principal component analysis and visual inspection of waveform clusters in 3D feature-based space. Only units with a peak amplitude >75 μV, as signal-to-noise ratio exceeding 2:1, and fewer than 0.1% of interspike intervals <2 ms were analyzed. We verified isolation of single

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189 units by inspecting autocorrelograms, as well as cross-correlograms for those units recorded on
190 the same electrode.
191
192 *Analysis of behavior*. All analyses were carried out using custom-written programs in Matlab.
193 We quantified the degree to which rats engaged in sign tracking and goal tracking by calculating
194 a PCA index (Meyer et al. 2012; Morrison et al. 2015), which comprises the average of three
195 ratios: (1) a probability index, which compares the probability of lever deflection vs. magazine
196 entry during the 8 s cue, calculated as ($P_{lever} - P_{magazine}$), (2) a bias index, which compares the
197 average number of lever deflections and magazine entries per cue, calculated as (#lever –
198 #magazine)/(#lever + #magazine), and (3) a latency index, which compares the average latency
199 from cue onset to lever deflection vs. latency from cue onset to magazine entry, calculated as
200 (magazine latency – lever latency)/(cue length). For trials in which a behavior was not
201 performed, the latency for that behavior was defined as the cue length (8 s). All of these indices,
202 including the PCA index, range from -1.0 to +1.0, with more positive numbers for animals that
203 preferentially sign track (interact with the lever) and more negative numbers for animals that
204 preferentially goal track (interact with the magazine). Sign trackers were operationally defined as
205 those subjects with PCA index greater than the mean PCA index on the final day of training; all
206 other subjects were categorized as goal trackers.
207
208 Two subjects (both goal trackers) were not included in the data set for the first day of training
209 because a software error rendered the recording inaccessible. One subject was not included in the
210 data set for the last day (day 7) of training because no neurons could be isolated during that

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session; for the same reason, this subject did not undergo extinction and was therefore not included in the extinction data set.

Analysis of neural activity. To identify neurons with excitatory responses to the cue, we used a Poisson distribution to approximate the baseline firing rate of each recorded cell during the 1 s prior to cue onset. Cue-excited neurons were identified as such by the presence of three consecutive 10 ms bins within the 500 ms after cue onset in which firing rate exceeded the 99.9% confidence interval of the baseline distribution. We also examined whether the cue response was primarily excitatory or inhibitory by calculating the mean Z-score relative to baseline in 10 ms bins over the 200 ms or 400 ms following cue onset. If this value was negative for both bins, the neuron was excluded from analysis. Finally, we excluded from analysis a handful of neurons with baseline firing rates too low (< 0.5 Hz) to ensure isolation throughout the session.

Responses to reward delivery were identified in a similar manner to cue responses, except that the Poisson distribution was fit to firing rate during the 1 s prior to reward delivery. Excitatory and inhibitory responses were identified by the presence of three consecutive 10 ms bins within the 500 ms after reward delivery in which firing rate exceeded the upper 99.9% confidence interval or was less than the lower 99.9% confidence interval, respectively.

To evaluate whether individual neurons remained stable across sessions, we first identified a subset of candidate units that were present on all seven training days, and then applied a simple waveform similarity analysis (Kennedy and Shapiro 2009). Briefly, for each neuron's waveform,

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we calculated the daily average voltage deflection at peak and trough, and computed the Pearson's correlation coefficient (r) for peak and trough across days. Units with $|r| > 0.9$ and $p < 0.05$ were considered stable. Because many recorded neurons did not meet these criteria, and many more were not present for all seven days of recording, we did not perform analyses that would rely on neuronal stability (other than the examples shown in Extended Data Fig. 5-1).

Peristimulus time histograms (PSTHs) for individual neurons were calculated in 10 ms bins and are shown smoothed with a 5-bin moving average. Population PSTHs were also calculated in 10 ms bins and normalized relative to a 1 s pre-cue baseline before averaging across neurons. The average activity was smoothed for display using a 5-bin moving average.

Analyses were performed on firing rates from a 500 ms window following cue onset or reward delivery unless otherwise specified. In cases where an alternate window of 1 s was used, results did not qualitatively differ when data were reanalyzed using a 500 ms window. In some cases, we used ROC analysis to generate an "index" to compare two distributions of firing rates. For these indexes, which are derived from the area under the ROC curve, a value of 0.5 indicates that the two distributions are indistinguishable. To generate *P* values for individual indexes, we performed permutation tests by randomly reshuffling the data 1000 times.

Within extinction sessions, we identified cue-excited neurons that decreased their cue-related activity over the course of the session using a 1-way ANOVA with trial number as a continuous variable. If the *P* value was < 0.01 for firing rate in either a 200 ms or 500 ms window after cue onset and activity decreased over the course of the session, the neuron was categorized as an

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257 “extinguishing” cell. Only one cell significantly increased its activity over the course of the
258 session and was excluded from further analysis. The remaining neurons were categorized as
259 “non-extinguishing” cells.

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Results

We used fixed electrode arrays to record from individual neurons in the NAc core while rats (n = 8) acquired and performed a Pavlovian conditioned approach (PCA) task similar to others that have been used to study sign-tracking and goal-tracking behavior (e.g., Meyer et al. 2012; Morrison et al. 2015; Tunstall and Kearns 2015). In this task, sign tracking (ST) is represented by lever presses and goal tracking (GT) is represented by entries into a food magazine. We quantified individual rats' propensity towards ST and GT behavior by calculating a PCA index (Meyer et al. 2012) that ranges from -1.0 (all goal tracking, no sign tracking) to +1.0 (all sign tracking, no goal tracking). On the last day of training (day 7), subjects exhibited a wide range of ST and GT behavior; however, all rats performed some degree of goal tracking, resulting in a PCA index distribution that was negatively skewed (Fig. 1A). Therefore, we divided subjects into "sign trackers" (STs) and "goal trackers" (GTs) based on whether each individual's PCA index on the last day of training was above or below the mean. This definition categorized as STs only those subjects with an appreciable degree of interaction with the lever. Indeed, we observed that operationally defined STs behaved in a qualitatively different manner from GTs, with marked orienting towards the lever and sniffing, biting, and gnawing behaviors directed towards the lever.

In agreement with previous studies (e.g., Morrison et al. 2015), sign trackers' PCA index steadily increased over the course of training while that of goal trackers stayed the same or decreased slightly (Fig. 1B). This was largely driven by a robust increase in the number of lever presses by sign trackers (Fig. 1C) while all subjects' magazine entries during the cue remained relatively

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stable (Fig. 1D), with only a small increase in entries for goal trackers and decrease in entries for sign trackers over the 7 sessions.

NAc cue-evoked activity encodes the vigor of subsequent sign-tracking and goal-tracking behavior

We recorded from 122 individual neurons on the final day of training; recording locations based on histological reconstruction are shown in Figure 2. Of these neurons, approximately half (58/122; 47.5%) exhibited excitatory responses evoked by cue onset, consistent with prior reports from studies using instrumental tasks (McGinty et al. 2013; Morrison et al. 2017; Morrison and Nicola 2014). Of these, 15 cells were recorded from sign tracker individuals (n = 3) and 43 from goal tracker individuals (n = 4). One subject did not contribute to data from the final day of training because no cells could be isolated during that session. There were no obvious differences in firing characteristics in cells recorded from sign trackers vs. goal trackers; their baseline firing rates were statistically identical ($p = 0.7$, Wilcoxon rank sum test).

It has previously been observed that cue-evoked excitations in the NAc encode the vigor – including latency and speed – of subsequent approach to a target during instrumental tasks, as well as information about whether the target is associated with a reward (McGinty et al. 2013; Morrison et al. 2017). Because the NAc is also essential for Pavlovian conditioned approach (Day and Carelli 2007) – and for sign-tracking behavior in particular (Cardinal et al. 2002; Chang et al. 2012) – we examined whether NAc cue-evoked activity similarly encodes the vigor of approach in a Pavlovian context, and whether this encoding differs for sign-tracking vs. goal-tracking behavior. Indeed, we noted that many individual neurons responded more strongly to

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the cue when the subsequent behavior was faster or more vigorous. For example, Figure 3A,B shows a neuron recorded in a sign tracker subject that had stronger cue-evoked firing when the cue was followed by a lever press with short latency; Figure 3C,D shows a different neuron – from a goal tracker subject – that had stronger cue-evoked firing when the cue was quickly followed by a magazine entry.

In order to quantify this effect throughout the population, we calculated a "vigor index" using ROC analysis (see Materials and Methods) that compared the magnitude of cue-evoked excitations on trials with relatively short latency vs. long latency to action. A vigor index greater than 0.5 indicates higher firing when the subsequent action occurred with shorter latency; an index less than 0.5 indicates higher firing when the subsequent action occurred with longer latency. When evaluated on a cell-by-cell basis, the distribution of the vigor index for latency to first action (either lever press or magazine entry) was significantly shifted to the right of 0.5 (Fig. 3E, Wilcoxon signed rank test, $p = 0.02$), indicating stronger neural responses prior to short-latency actions. Notably, the vigor of goal tracking was encoded more robustly than that of sign tracking: when the vigor index was calculated for latency to magazine entry, the resulting distribution was significantly shifted from 0.5 (Fig. 3F; $p < 0.001$), whereas the vigor index for latency to lever press was not different from 0.5 when evaluated across the whole population of neurons (Fig. 3G; $p = 0.22$). This was the case for sign tracker and goal tracker subjects considered separately as well as together.

We next examined whether NAc neural activity is related to the expression of sign-tracking and/or goal-tracking behavior on a trial-by-trial basis. To do so, we calculated the Spearman's

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rank correlation coefficient (rho) for each cell between firing rate (500 ms window after cue onset) and the magnitude or latency of behavior over the last two days of training (50 trials). Many individual correlations were significant (Extended Data Fig. 3-1), especially among goal trackers, who exhibited neural activity that was positively correlated with the vigor of magazine entry and negatively with the vigor of lever pressing. The average Spearman's rho for each behavioral measure is shown in Figure 3H. Overall, neurons recorded in goal trackers had significantly larger correlation coefficients for most behaviors, including latency to first magazine entry ($p = 0.007$, Wilcoxon rank sum test), as well as lever press number and latency ($p < 0.001$ for each), but, interestingly, not number of magazine entries ($p = 0.75$). Meanwhile, the activity of neurons recorded in sign trackers – although they sometimes varied with behavior on an individual basis (Extended Data Fig. 3-1) – did not show correlations that were significantly different from zero, on average ($p > 0.2$ for all measures, Wilcoxon sign rank test).

Overall, even though sign tracking and goal tracking are thought to represent the output of separate learning processes that engage different neural circuits (Lesaint et al. 2014), the vigor of each behavior – and, surprisingly, goal-tracking even more than sign-tracking – is represented by a subset of cue-excited neurons in the NAc. This is consistent with the proposed role of the NAc as a node of interaction for multiple brain systems that promote approach towards a reward-associated target (Clark et al. 2012; Nicola 2010).

NAc activity evolves differently in sign tracker and goal tracker individuals over the course of behavior acquisition

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Although it has been established that ST and GT individuals develop distinct patterns of NAc dopamine release over the course of learning (Flagel et al. 2011), it remains unclear whether and how this corresponds with differences in the activity of single neurons. Therefore, we next asked how NAc activity changes with respect to task events during early and late stages of acquisition of ST and GT behavior.

Starting with the first day of training on the PCA task, we found clear differences between sign trackers and goal trackers in the evolution of NAc activity. We recorded from 64 individual neurons in 6 subjects during day 1 of training; of these, 33 cells (51.6%) exhibited cue-evoked excitatory responses, 16 of which were recorded from sign tracker subjects and 17 from goal trackers. In most cases, cue-evoked excitations were present on the very first training trial. In order to examine how neural responses changed over the course of the session, we divided the session into "early trials" (trials 1-12) and "late trials" (trials 13-25). On a population level, there was no significant difference in firing in the 500 ms after cue onset during early vs. late trials in either sign trackers ($p = 0.08$, Wilcoxon rank sum test) or goal trackers ($p = 0.37$; Fig. 4A,B). Moreover, cue-evoked activity was slightly higher in sign trackers than in goal trackers during early trials ($p = 0.01$, Wilcoxon rank sum test), and indistinguishable between the two groups during later trials ($p = 0.5$).

In contrast, in sign trackers only, there was a significant decrease in firing in the 500 ms following reward delivery during the first half vs. the second half of trials ($p < 0.001$, Wilcoxon rank sum test; Fig. 4C). In goal trackers, on the other hand, population-level reward-related activity remained stable over the course of the training session ($p = 0.18$; Fig. 4D). Similarly,

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373 during the first half of trials, reward-related activity was slightly higher in sign trackers than in
374 goal trackers ($p = 0.02$, Wilcoxon rank sum test); however, during the second half of trials,
375 reward-related activity in sign trackers decreased to a level significantly below that of goal
376 trackers ($p = 0.006$). This pattern was also apparent when we examined reward-related responses
377 on a trial-by-trial basis: median reward-evoked firing during the first 5 trials of the session was
378 significantly greater than firing during the last 5 trials in sign trackers ($p < 0.001$, Wilcoxon rank
379 sum test; Fig. 4E) but not in goal trackers ($p = 0.07$; Fig. 4F).
380
381 In order to quantify this effect on a cell-by-cell basis, we calculated a "learning index" based on
382 ROC analysis (see Materials and Methods) that compared the magnitude of cue-evoked
383 responses (Fig. 4G,H) or reward-evoked responses (Fig. 4I,J) during the first half and second
384 half of trials. A learning index value greater than 0.5 indicates higher firing during early trials –
385 i.e., decreasing activity over the course of the session – while an index less than 0.5 indicates
386 higher firing during late trials: i.e., increasing activity over the course of the session. Among sign
387 trackers, the median learning index for cue-evoked activity was not different from 0.5 ($p = 0.82$,
388 Wilcoxon signed rank test), whereas the median for reward-evoked activity was significantly
389 greater than 0.5 ($p < 0.001$), indicating that a substantial proportion of individual neurons
390 showed decreasing reward-related responses over the course of the session. Among goal trackers,
391 on the other hand, the median learning index for cue-evoked activity (Fig. 4H) was slightly less
392 than 0.5 ($p = 0.01$), reflecting a small increase in firing in the 1 s following the cue, but the
393 median learning index for reward-related activity was not different from 0.5 ($p = 0.29$).
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Consistent with the above results, we found that the learning index for reward-related activity was markedly higher in sign trackers than in goal trackers ($p < 0.001$, Wilcoxon rank sum test); in contrast, the learning index for cue-related activity was slightly higher in sign trackers ($p = 0.05$), which can be entirely attributed to the small increase in cue-evoked activity among goal trackers over the first day of training. Finally, an individual subject's relative degree of sign-tracking vs. goal-tracking behavior on the last day of training – represented by the PCA index – was significantly correlated with the learning index for reward-related activity observed in cells recorded from that subject ($r^2 = 0.34$, $p < 0.001$; Fig. 4K). Thus, during the first training session, cue-evoked activity showed only minor changes or no changes in both sign trackers and goal trackers, whereas reward-related activity exhibited a significant decrease over the course of the session in sign trackers only – a decrease that was markedly more robust in those individuals with the greatest tendency to sign track later on.

It has been shown that, among outbred rats with a propensity for sign tracking, cue-evoked NAc dopamine release increases, and reward-evoked dopamine release decreases, over the course of 6 days of training (Flagel et al. 2011). The same was not true of outbred rats that were categorized as goal trackers. In light of this finding, we wished to examine whether NAc cue- and/or reward-evoked neuronal activity differs between sign trackers and goal trackers on the last day of training – in parallel with dopamine release – and whether these groups show differences in the evolution of their task-related neuronal firing over the full course of training.

We found that, after behavior was fully established, sign trackers and goal trackers showed only minor differences in cue-evoked firing, but diverged markedly in their response to reward.

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Indeed, on the final day of training, there was no significant difference on a population level between sign trackers and goal trackers in firing in the 1 s window after cue onset ($p = 0.52$, Wilcoxon rank sum test; Fig. 5A). In contrast, activity in the 1 s following reward delivery was significantly diminished in sign trackers relative to goal trackers ($p < 0.001$; Fig. 5B). The majority of cue-excited cells were also excited by reward (38 out of 58); of the remaining cue-excited cells, 8 were reward-inhibited and 12 had no significant response to reward delivery. Some of these 20 cells may have decreased their reward response over the course of training; consistent with such decreases being more prevalent in sign trackers, a disproportionate number of these were found in sign trackers, although the disparity was just short of reaching significance ($p = 0.07$, chi square test).

We next assessed how task-related activity, on a population level, evolved over the full course of training. Examining activity in a 1 s window following either cue onset or reward delivery (Fig. 5C), we found that subjects' cue-evoked excitatory responses remained stable, on average, between Day 1 and Day 7 of training (sign trackers, $p = 0.31$; goal trackers, $p = 0.22$, Wilcoxon rank sum test). In contrast, reward-related firing decreased significantly among both sign trackers and goal trackers (both, $p < 0.001$) from Day 1 to Day 7, with a more dramatic decrement in activity averaging -55% in sign trackers (compared to -26% in goal trackers). Although we had no definitive way to assess whether the same cells were recorded from day to day, we used a simple waveform similarity analysis (see Materials and Methods), to identify a small number of individual neurons that appeared to be stable across all seven days. Two representative examples – one each from a sign tracker and a goal tracker – are shown in Extended Data Figure 5-1. The activity of these two neurons reflects the same trends as the overall population average. Overall,

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these data support the observation that reward-related activity – but not cue-related activity – in the NAc core decreases in prominence over the course of training – a decrease that is more robust in sign trackers than in goal trackers and that is apparent whether activity is sampled at an early or late stage of training.

Distinct patterns of NAc cue-evoked activity and behavior during extinction among sign tracker and goal tracker individuals

It has previously been shown that sign-tracking behavior, compared to goal-tracking behavior, is relatively impervious to changes in the cue-outcome relationship, including both reward devaluation (Morrison et al. 2015) and extinction (Ahrens et al. 2015). Because it is thought that NAc activity plays an important role in promoting Pavlovian approach (Cardinal et al. 2002; Day and Carelli 2007; Morrison and Nicola 2014), including sign tracking, we next asked whether NAc cue-evoked excitations "extinguish" in concert with behavior in the current task. We therefore exposed a subset of subjects (n = 7; 3 sign trackers and 4 goal trackers) to a single extinction session following the completion of training on the PCA task; the extinction procedure was identical to the PCA task except that no rewards were delivered. We chose to carry out the extinction session on a separate day from training in order to ensure that the subject's behavioral state was comparable to previous sessions (i.e., by removing the possible confounds of satiety, boredom, or fatigue.) During extinction, we recorded from 78 individual neurons, of which 53 (68.0%) exhibited cue-evoked excitatory responses – 17 from subjects categorized as sign trackers and 36 from goal trackers.

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463 We found that many individual neurons in the NAc indeed exhibit reductions in cue-evoked
464 firing over the course of an extinction session; in some cases, the cue-evoked excitation is
465 entirely absent by the end of the session. Intriguingly, however, other individual neurons, often
466 within the same subject, exhibit no apparent decrease in cue-evoked firing over the course of
467 extinction. To quantify this phenomenon, we used a one-way ANOVA with trial number as a
468 continuous factor (see Materials and Methods) to categorize neurons as "extinguishing" or "non-
469 extinguishing." Figure 6A,B shows a representative example of two neurons – one extinguishing
470 cell (Fig. 6A) and one non-extinguishing cell (Fig. 6B) – recorded in the same subject during the
471 same extinction session. We found no difference in the proportion of extinguishing and non-
472 extinguishing cells among sign trackers and goal trackers: sign trackers contributed a total of 8
473 extinguishing and 9 non-extinguishing cells, whereas goal trackers contributed 16 extinguishing
474 cells and 19 non-extinguishing cells ($p = 0.93$, chi square test). One cell showed a significant
475 increase in cue-evoked firing and was not included in subsequent analyses.
476
477 Although the proportions of distinct neuronal response profiles were not different in sign trackers
478 vs. goal trackers, population cue-evoked activity across the extinction session was greater among
479 sign trackers than goal trackers in extinguishing cells ($p = 0.02$, Wilcoxon rank sum test; Fig.
480 6C) but not in non-extinguishing cells ($p = 0.23$; Fig. 6D) during the peak of excitation (0-300
481 ms after cue onset). If the tail of the excitation was included (0-500 ms or 0-1 s after cue onset),
482 sign trackers exhibited greater average activity over the course of extinction among both cells
483 types (all cases, $p < 0.001$). We hypothesized that this activity profile might result from a more
484 gradual extinguishing of cue-evoked excitations among sign trackers than among goal trackers.
485 Supporting this notion, when we examined average cue-evoked firing (0-500 ms after cue onset)

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in 5-trial bins over the course of the extinction session (Fig. 6E), we observed that activity among extinguishing cells (solid lines) in sign trackers and goal trackers is initially indistinguishable (bin 1: $p = 1$, Wilcoxon rank sum test) but then trends higher in sign trackers during trials 6-10 (bin 2: $p = 0.09$) before converging again. The same was not true for non-extinguishing cells (dashed lines in Fig. 6E). Thus, sign trackers exhibit a delayed extinction of cue-evoked activity relative to goal trackers that is mainly driven by a slower decline in activity among the subpopulation of extinguishing cells.

This slower decline in cue-evoked activity among sign trackers was paralleled by a more gradual decrease in sign-tracking behavior compared to goal-tracking behavior, as has been reported previously (Ahrens et al. 2015). Compared with magazine entries in goal trackers, the number of lever presses in sign trackers remains elevated later into the extinction session, as shown in Figure 6F (bin 2: $p = 0.1$, bin 4: $p = 0.1$, Wilcoxon rank sum test); similarly, after starting out indistinguishable, the latency to first lever press after cue onset among sign trackers trends lower than latency to first magazine entry among goal trackers during trials 6-10 of extinction (bin 2: $p = 0.1$; Fig. 6G). Although the relatively small number of subjects precludes strong statistical conclusions about behavior, it is clear that the largest differences we observed in sign-tracking vs. goal-tracking behavior occur at the same time as the largest differences in the decline of cue-evoked neural activity, consistent with the finding that cue-evoked firing encodes the vigor of both sign tracking and goal tracking.

In order to draw a more direct connection between the activity of individual cells and the extinction of behavior, we next examined the trial-by-trial correlation (Spearman's rho) between

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firing rate in the 500 ms following cue onset and sign-tracking vs. goal-tracking behaviors. Many individual correlations were significant (see Extended Data Fig. 6-1), especially for goal-tracking behavior, which exhibited a larger dynamic range among subjects. Figure 6H shows the average correlation coefficient for the intensity (i.e., number) and latency of each behavior among sign trackers (blue) and goal trackers (magenta). Overall, neurons recorded in sign trackers had significantly higher correlation coefficients with sign-tracking behavior (number of lever presses: $p = 0.03$, Wilcoxon rank sum test; latency to first lever press: $p < 0.001$), compared with neurons recorded in goal trackers. This finding held true when one goal tracker subject with zero lever presses was excluded. Conversely, neurons recorded in goal trackers had significantly higher correlation coefficients with goal-tracking behavior (number of magazine entries: $p = 0.002$; latency to first magazine entry: $p = 0.02$) than neurons recorded in sign trackers, even though all subjects – including sign trackers – displayed some degree of goal-tracking behavior during the extinction session.

Thus, among the subset of cells that extinguished their cue-evoked excitations during extinction, this activity decreased in concert with the subject's predominant behavior – whether sign tracking or goal tracking – during the course of the session. This is consistent with the finding that many cue-evoked excitations reflect the vigor of the immediate subsequent action, whether lever press or magazine entry, on the final day of training (see Fig. 3). Overall, these data support the hypothesis that the separable learning processes that produce sign tracking and goal tracking converge in the NAc to promote both forms of approach.

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Discussion

Individual animals show a wide range of behavior on a task in which a lever cue predicts the delivery of a reward in a separate location. Some animals are prone to transfer incentive salience to the cue, resulting in sign-tracking behavior (Hearst and Jenkins 1974) – approach and/or interaction with the lever – whereas others animals are goal trackers: they tend to approach and/or interact with the site of reward rather than the cue (Boakes 1977). The NAc plays an essential role in conditioned approach behaviors, including sign tracking (Cardinal et al. 2002; Chang et al. 2012; although see Chang and Holland 2013). In particular, dopamine release in the NAc is required for the acquisition and expression of sign-tracking, but not goal-tracking, behavior (Flagel et al. 2011; Fraser and Janak 2017; Parkinson et al. 2002; Saunders and Robinson 2012).

In the present study, we report both similarities and key differences between sign trackers and goal trackers in their patterns of NAc activity during the acquisition, maintenance, and extinction of sign-tracking and goal-tracking behavior. Cue-evoked excitations in the NAc encoded the vigor of the subsequent behavioral response, whether it was sign tracking or goal tracking, among subsets of recorded neurons. Meanwhile, although cue-evoked activity remained relatively stable over the course of training in all subjects, reward-evoked activity showed a marked decrease in sign trackers, but not goal trackers. Finally, during an extinction session, a subset of cue-excited neurons ("extinguishing cells") decreased their activity in concert with behavior – a decrease that was more closely linked to lever presses among sign trackers, and to magazine entries among goal trackers. However, we observed an additional subset of NAc neurons ("non-extinguishing cells") that did not decrease their cue-evoked activity over the course of behavioral extinction.

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554

555 *Convergence of multiple forms of reward learning in the NAc*

556 Consistent with prior studies using both Pavlovian tasks (e.g., Day et al. 2006) and instrumental
557 tasks (e.g., McGinty et al. 2013), we found that a large proportion of NAc neurons (averaging
558 ~58%) exhibit excitatory responses to cues that are associated with reward. These cue-evoked
559 excitations have been shown to encode the vigor of subsequent locomotor responses – e.g.,
560 approach to a reward-associated lever – including such factors as latency and speed, as well as
561 the probability that a behavioral response will occur at all (McGinty et al. 2013; Morrison et al.
562 2017; Morrison and Nicola 2014). Interestingly, this encoding is much more prominent during
563 tasks that require taxic approach – i.e., in which the cue elicits a novel action sequence – rather
564 than praxic approach, in which the cue elicits one of a limited subset of possible actions
565 (McGinty et al. 2013). Indeed, NAc activity, as well as dopaminergic function, is specifically
566 required for taxic but not praxic approach tasks (Nicola 2010).

567 Both sign-tracking and goal-tracking behavior require taxic approach towards a reward-
568 associated target – either the lever or the food magazine – so, in that regard, we might expect that
569 the vigor of both behaviors would be represented in NAc cue-evoked activity. Indeed, we found
570 that many individual neurons have stronger cue-evoked firing when the subsequent behavioral
571 response, whether lever press or magazine entry, occurred with shorter latency. In fact, despite
572 the special importance of the NAc for the acquisition and expression of Pavlovian conditioned
573 approach – including sign tracking (Cardinal et al. 2002) – the relationship of cue-evoked firing
574 to the vigor of goal tracking (represented by latency to enter the food magazine) was particularly
575 strong relative to sign tracking. This might be a consequence of the larger dynamic range of
576 goal-tracking behavior both within subjects and between subjects: goal tracking was present in

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577 all subjects to some degree, whereas sign-tracking behavior was exhibited by only the subset of
578 subjects categorized as sign trackers.

579 It is important to note that the essential role of the NAc – especially NAc dopamine release – in
580 sign tracking is not incompatible with a role for accumbens neuronal activity in goal tracking.
581 Although few studies have directly compared the impact of loss of NAc function on sign
582 tracking vs. goal tracking, it has been shown that lesion (Parkinson et al. 1999) or reversible
583 inactivation (Blaiss and Janak 2009) of the NAc core impairs the expression of goal-tracking
584 behavior – at least to a moderate extent – during Pavlovian conditioning tasks in which goal
585 tracking is the primary response. Notably, however, inactivation of the NAc does not impair the
586 initial acquisition of goal-tracking behavior (Blaiss and Janak 2009). In contrast, a number of
587 studies have shown that a functional NAc is necessary for the acquisition of sign tracking and
588 other forms of Pavlovian conditioned approach (Chang et al. 2012; Dalley et al. 2005; Di Ciano
589 et al. 2001; but see Chang and Holland 2013). The idea that the NAc is specifically involved in
590 the acquisition of sign tracking, but plays a role in the expression of both sign tracking and goal
591 tracking, is in line with our finding that the learning processes underlying sign tracking vs. goal
592 tracking are reflected by differently evolving activity patterns in the NAc.

593 Finally, the current evidence that NAc cue-evoked activity promotes the vigor of both sign
594 tracking and goal tracking supports the notion that the NAc functions as a node of interaction
595 between different forms of reward learning (Clark et al. 2012; Lesaint et al. 2014). Mounting
596 evidence indicates that sign tracking arises from a dopamine-dependent form of learning that
597 results in the transfer of incentive value from reward to cue and is relatively independent of the
598 sensory characteristics of the outcome, at least under some conditions (Clark et al. 2012; Flagel
599 et al. 2011; Huys et al. 2014; Morrison et al. 2015; although see Derman et al. 2018). Goal

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tracking, on the other hand, is thought to arise from a dopamine-independent form of learning that incorporates sensory characteristics of the outcome, as it is profoundly sensitive to manipulations of outcome value (Morrison et al. 2015) or cue-outcome relationship (Ahrens et al. 2015; Beckmann and Chow 2015). These disparate learning processes appear to converge in the accumbens, supporting the idea that a key function of the NAc is to invigorate approach towards reward-associated targets (Morrison and Nicola 2014), regardless of the source of the stimulus-reward association.

Relationship of NAc single-unit activity to phasic dopamine release

It has been shown that sign trackers and goal trackers – whether selectively bred "high responders" and "low responders," or outbred rats – exhibit different characteristic patterns of NAc dopamine release during training on a PCA task comparable to the one used here. Using fast-scan cyclic voltammetry, Flagel et al. (2011) found that, on average, sign trackers showed increased dopamine release in response to the cue, and decreased dopamine release in response to the reward, over the course of six training sessions. Goal trackers, on the other hand, showed relatively stable levels of dopamine release in response to the cue and reward throughout training. These results implied that sign trackers, but not goal trackers, were utilizing the reward prediction error encoded by phasic dopamine (Waelti et al. 2001) as a teaching signal, consistent with the notion that sign tracking, but not goal tracking, is a manifestation of dopamine-dependent reinforcement learning.

In the current study, we demonstrate that the differences between sign trackers and goal trackers in patterns of NAc dopamine release are at least partially reflected by the task-related activity of

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single neurons in the NAc. Over the course of training – even during the very first training session – sign tracker individuals exhibit a marked decrease in neuronal firing evoked by reward delivery, whereas goal tracker individuals do not. This finding mirrors the decrease in reward-evoked NAc dopamine release seen in sign trackers, but not goal trackers, during learning (Flagel et al. 2011), and supports the idea that, among sign trackers only, the motivational value of the reward undergoes a transfer from the reward itself to the predictive cue.

On the other hand, in contrast to the increase in cue-evoked phasic dopamine seen in sign trackers (Flagel et al. 2011), we observed little to no change in neural activity in response to the reward-predictive lever cue. Among goal trackers only, there was a small increase in cue-evoked activity over the course of the first training session; but there was no significant difference in population activity between the first and last sessions for either sign trackers or goal trackers. There are at least two possible reasons for this discrepancy. The first is that, in the current study, operationally defined sign trackers all performed an appreciable amount of goal tracking behavior in addition to sign tracking. Indeed, sign trackers executed more magazine entries than goal trackers during the first two days of training (see Fig. 1D), and their level of goal tracking stayed relatively stable throughout training, even as their sign-tracking behavior increased. Because cue-evoked excitations represent the vigor of goal tracking more robustly than that of sign tracking in the current data set, it is perhaps not surprising that sign trackers' cue-evoked firing remained stable throughout the acquisition period.

Second, Flagel et al. (2011) find that, among outbred sign trackers, the increase in cue-evoked phasic dopamine release is relatively modest compared with the robust decrease in reward-evoked dopamine release. This is consistent with our finding of a strong decrease in reward-evoked firing among sign trackers along with a small, non-significant increase in cue-evoked

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645 firing. It has been shown that activation of D1 and/or D2 dopamine receptors in the NAc
646 enhances cue-evoked excitatory responses (du Hoffmann and Nicola 2014), so we might expect
647 that sign trackers' increase in cue-evoked dopamine release over the course of training would
648 result in increased cue-evoked neuronal activity. However, any additional firing resulting from a
649 small increase in phasic dopamine release – i.e., as part of a dopamine-dependent learning
650 process – may be rendered undetectable by the already-strong cue-evoked excitation, perhaps
651 resulting from a concurrent non-dopamine-dependent process, that promotes vigorous goal
652 tracking responses.

653 Indeed, it is important to note that goal trackers, as well as sign trackers, exhibit dopamine
654 release in response to reward predictive cues, even though acquisition of goal tracking behavior
655 does not depend on NAc dopamine (Flagel et al. 2011; Saunders and Robinson 2012). This
656 observation is consistent with the idea that phasic mesolimbic dopamine release plays a dual
657 role: invigorating action directed towards reward-associated targets in addition to facilitating
658 simple forms of reinforcement learning (Berke 2018; Guitart-Masip et al. 2012; Ko and Wanat
659 2016; Syed et al. 2016). Although the precise relationship between sub-second dopamine release
660 and neuronal firing in target regions has been difficult to determine, we would speculate that the
661 cue-evoked excitations we observe in both sign trackers and goal trackers more strongly reflect
662 the former function of dopamine – action invigoration – whereas the decreasing reward-evoked
663 responses observed in sign trackers reflect the latter function, reinforcement learning.

664 Finally, we found that, among both sign trackers and goal trackers, the large majority of cue-
665 excited NAc neurons also exhibit excitatory responses to reward delivery. This result stands in
666 apparent contrast with the frequently reported finding that consummatory actions are
667 accompanied by inhibition of neuronal activity in the NAc (Nicola et al. 2004; Roitman et al.

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668 2010; Taha and Fields 2005; Wan and Peoples 2006). Although a small subset of NAc neurons
669 encode the value of a reward via excitatory responses during consumption (Taha and Fields
670 2005), we believe it is more likely that the brief excitations we observe are occurring prior to
671 actual consumption. Rather, they may be related to the sight and/or sound of the sucrose pellet
672 dropping into the food magazine – i.e. by cues conveying the information that reward has been
673 delivered – rather than to the hedonic experience of sucrose consumption or to consummatory
674 actions such as chewing. Indeed, although we did not track consummatory behavior in the
675 current study, excitations associated with reward delivery were often followed by inhibitions,
676 which were likely associated with pellet consumption. Notably, this profile of reward-related
677 NAc activity roughly corresponds, in both direction and scale, to the time course of NAc
678 dopamine release in response to delivery of a sucrose pellet following a reward-predictive cue
679 (McCutcheon and Roitman 2018).

680

681 *Divergent profiles of NAc activity during behavioral extinction*

682 Previous studies have shown that sign-tracking behavior is relatively resistant to extinction,
683 compared with goal-tracking behavior, both within subjects (Beckmann and Chow 2015) and
684 between subjects (Ahrens et al. 2015). This is likely the result of sign trackers' tendency to
685 attribute incentive salience to the cue, resulting in continued cue-directed actions even in the
686 absence of reward. In support of this idea, a lever cue is much more effective as a conditioned
687 reinforcer in sign trackers than in goal trackers (Robinson and Flagel 2009), indicating that the
688 cue has been imbued with motivational value. On the other hand, sign trackers and goal trackers
689 do not differ in their rates of instrumental extinction (Ahrens et al. 2015; Yager and Robinson

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690 2010), implying that sign trackers' dopamine-dependent learning system is selectively and
691 preferentially engaged during Pavlovian conditioning.

692 In the current study, we confirm that sign-tracking behavior (among sign trackers) extinguishes
693 more slowly than goal tracking (among goal trackers). Further, we demonstrate that the cue-
694 evoked excitatory responses of many neurons in the NAc decrease, or extinguish, in concert with
695 behavior: these extinguishing cells decrease their firing more rapidly in goal trackers than in sign
696 trackers, on average. Finally, we show that the decreasing cue-evoked response is more closely
697 associated with decrements in lever pressing among sign trackers, and with decrements in
698 magazine entry among goal trackers. All of these findings are consistent with the notion that
699 NAc cue-evoked excitations invigorate approach towards reward-associated targets – regardless
700 of the source of the association or the specific form of the conditioned response – and that a
701 reduction in NAc firing elicited by a cue will increase the latency and decrease the probability of
702 a behavioral response to that cue (Morrison et al. 2017).

703 Although no study, to our knowledge, has compared dopamine release in sign trackers and goal
704 trackers during extinction, our observation that NAc activity gradually extinguishes when reward
705 is no longer available is consistent with the finding that cue-evoked phasic dopamine release
706 decreases over the course of Pavlovian extinction (Sunsay and Rebec 2014). At least among
707 extinguishing cells in the NAc, it is likely that dopamine release acts as a gating mechanism
708 permitting both cue-evoked firing and, as a result, behavioral responding to the cue (du
709 Hoffmann and Nicola 2014). This gradual decrease in both dopamine release and cue-evoked
710 NAc firing could provide a neural substrate for the kind of "unlearning" process of extinction
711 posited by traditional reward prediction error models of reinforcement learning (Rescorla and
712 Wagner 1972; Schultz et al. 1997).

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713 On the other hand, it is now widely recognized that extinction involves more than unlearning:
714 phenomena such as reinstatement and spontaneous recovery demonstrate that the original cue-
715 reward association is not forgotten and may be retrieved in a different context or after the
716 passage of time (Todd et al. 2014). Consistent with this idea, in addition to extinguishing cells,
717 we observed almost equal numbers of non-extinguishing cells: NAc neurons with cue-evoked
718 excitatory responses that do not decrease over the course of behavioral extinction. The
719 proportions of these cells did not differ between sign trackers and goal trackers, whose different
720 rates of behavioral extinction might be better explained by divergent reductions in cue-evoked
721 firing among extinguishing cells only. Rather, non-extinguishing cells might constitute part of
722 the neural circuitry that maintains a latent representation of the cue-reward relationship following
723 extinction. Interestingly, their cue-evoked responses appear to be resistant to the decrease in
724 phasic dopamine release that accompanies extinction (Sunsay and Rebec 2014). Further
725 investigations will be necessary to determine whether these non-extinguishing cells differ from
726 extinguishing cells in characteristics such as dopamine receptor or transporter expression, and/or
727 participate in anatomically separable circuits. If so, extinguishing and non-extinguishing cells
728 could provide a novel neural substrate for the simultaneous new learning and maintenance of
729 prior associations that characterizes extinction (Pan et al. 2008; Todd et al. 2014).

730 Overall, we observed both similarities – such as robust encoding of food magazine-directed
731 behavior – as well as key differences between sign trackers and goal trackers in NAc neuronal
732 activity patterns, including a decrease in reward-related activity specific to sign trackers that
733 appears to reflect reward prediction error signals encoded by phasic dopamine. Indeed, these
734 findings highlight the widely varying extent to which phasic dopamine, as a signal, is reflected in
735 the neuronal activity of target structures. This is certainly true of NAc cue-evoked activity during

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736 extinction, which broadly reflects decreases in phasic dopamine release, but also includes non-
737 extinguishing cells that do not decrease their activity in concert with dopamine release and
738 behavior. Ultimately, understanding how differences in dopamine release are translated into
739 neural activity will provide insight into how and why different individuals – e.g. sign trackers
740 and goal trackers – engage different learning systems (Clark et al. 2012; Huys et al. 2014;
741 Lesaint et al. 2014) when cues in the environment predict reward.

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883 their propensity to attribute incentive salience to food cues. *Behav Brain Res* 214: 30-34, 2010.

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886 **Figure legends**

887 **Figure 1.** Sign tracker and goal tracker individuals differed mainly in their level of interaction
888 with the lever cue. **(A)** PCA index (see Methods) for all subjects measured during the last
889 training session (day 7). Arrowhead, mean PCA index. Blue, subjects categorized as sign
890 trackers; magenta, goal trackers. **(B-D)** PCA index (**B**), total lever presses (**C**), and total
891 magazine entries during the cue (**D**) over all 7 days of training for sign trackers (blue) and goal
892 trackers (magenta). Error bars, SEM.
893
894 **Figure 2.** Histological reconstruction of recording locations in NAc core. Panels are coronal
895 atlas sections (Paxinos and Watson 2007) showing the location of electrode tips derived from
896 electrolytic lesions and/or electrode tracks. Numbers are distance in millimeters from bregma.
897
898 **Figure 3.** The vigor of both sign-tracking and goal-tracking behavior may be represented in NAc
899 firing. **(A,B)** Example of a neuron with stronger cue-evoked excitation when the cue is followed
900 by a lever press with shorter **(A)** rather than longer **(B)** latency. **(C,D)** Example of a neuron with
901 stronger cue-evoked excitation when the cue is followed by a magazine entry with shorter **(C)**
902 rather than longer **(D)** latency. Left panels, action latency < 50^{th} percentile; right panels, action
903 latency ≥ 50^{th} percentile. Trials are shown in chronological order with earliest on top. Blue dots,
904 cue onset; magenta triangles, magazine entries; cyan triangles, lever presses. **(E-G)** On the
905 population level, representation of latency to magazine entry (i.e., goal tracking) predominates.
906 **E**, Vigor index for latency to first action after cue onset. Median index is greater than 0.5 ($p =$
907 0.02, Wilcoxon). **F**, Vigor index for latency to magazine entry. Median index is greater than 0.5
908 ($p < 0.001$, Wilcoxon). **G**, Vigor index for latency to lever press. Distribution not different from

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0.5 ($p = 0.22$, Wilcoxon signed rank text). All panels, blue indicates significant vigor index ($p < 0.05$, permutation test); arrowhead indicates median. **(H)** Average Spearman's rank correlation coefficient (rho) between cue-evoked neural activity in the 500 ms following cue onset and the indicated behavioral measure for sign trackers (blue) and goal trackers (magenta). From left to right: number of lever presses ($p < 0.001$, Wilcoxon rank sum test), number of magazine entries ($p = 0.75$), latency to first lever press ($p < 0.001$), latency to first magazine entry ($p = 0.007$).

Extended Data Figure 3-1. Correlation of the activity of individual neurons with trial-by-trial sign-tracking and goal-tracking behavior. Distribution of Spearman's rank correlation coefficient (rho) relating cue-evoked neural activity (500 ms window) to number of lever presses (**A,B**), number of magazine entries (**C,D**), latency to first lever press (**E,F**), or latency to first magazine entry (**G,H**) for individual neurons recorded in sign trackers (**A,C,E,G**) or goal trackers (**B,D,F,H**) over the last two days of training. All panels, blue indicates significant correlation ($\alpha = 0.1$) and p-values indicate results of Wilcoxon signed rank test for median different from zero.

Figure 4. Sign trackers and goal trackers exhibit differences in NAc activity on the first day of training. **(A-D)** Population average normalized activity aligned on cue onset **(A,B)** or reward delivery **(C,D)** for sign tracker **(A,C)** and goal tracker **(B,D)** subjects. Blue and magenta solid lines, first half of trials (trials 1-12); cyan and pink dashed lines, second half of trials (trials 13-25). Shading, SEM. **(E,F)** Trial-by-trial normalized activity in response to reward delivery (1 s window) for sign trackers **(E)** and goal trackers **(F)**. Error bars, SEM. **(G-J)** Distribution of learning index for sign trackers **(G,I)** and goal trackers **(H,J)** derived from ROC analysis comparing the first half and second half of trials. Index > 0.5 indicates higher cue-evoked **(G,H)**

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or reward-evoked **(I,J)** activity during early trials. Blue represents index significantly different from 0.5 ($p < 0.05$, permutation test). Arrowheads indicate median. The median is significantly greater than 0.5 for reward-evoked activity in sign trackers only ($p < 0.001$, Wilcoxon signed rank test). **(K)** PCA index for behavior from the final day of training plotted against the learning index for reward-related neural activity (1 s window). Regression line in red.

Figure 5. Sign trackers exhibit an attenuated reward response on the last day of training. **(A,B)** Population average normalized activity aligned on cue onset **(A)** or reward delivery **(B)**. Shading, SEM. **(C)** Population-wide average neural activity in the 1 s following cue onset (dashed lines) or reward delivery (solid lines) on the first day of training (left) and the last day of training (right). Error bars, SEM. All panels: sign trackers in blue, goal trackers in magenta.

Extended Data Figure 5-1. Evolution of cue- and reward-related activity over the course of training in two example neurons. Two representative neurons with highly stable waveforms over the course of training (7 sessions) were selected for analysis, one from a sign tracker **(A,B)** and one from a goal tracker **(C,D)**. **(A,C)** Heat plots show activity related to the cue (left) or reward (right) during each of the 7 training sessions as average firing rates calculated in 10 ms bins with no smoothing. **(B,D)** Average firing rate over the 500 ms following cue onset (dashed lines) or reward delivery (solid lines) for the cells shown in **A** and **C**, respectively. Error bars, SEM.

Figure 6. In sign trackers, as compared to goal trackers, behavior and cue-evoked firing are resistant to extinction. **(A,B)** Two example neurons recorded during the same extinction session. Within the same subject, some NAc neurons extinguish their cue-evoked firing (as in **A**), and

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some do not (as in **B**). Trials are shown chronologically with the earliest trial on top. Blue dots, cue onset. **(C,D)** Population average activity during extinction sessions for extinguishing cells **(C)** and non-extinguishing cells **(D)**. Shading, SEM. **(E,F)** Average behavior during extinction sessions for sign trackers (blue; lever presses only) and goal trackers (magenta; magazine entries only). The number **(E)** and latency **(F)** of actions are averaged in 5-trial bins. **(G)** Cue-evoked neural responses in the 500 ms after cue onset for extinguishing cells (Ex.; solid lines) and non-extinguishing cells (N.Ex.; dashed lines). Activity is averaged in 5-trial bins. Blue, sign trackers; magenta, goal trackers. All panels, dagger indicates $p < 0.1$, Wilcoxon rank sum test. **(H)** Average Spearman's rank correlation coefficient (rho) between cue-evoked neural activity in the 500 ms following cue onset and the indicated behavioral measure for sign trackers (blue) and goal trackers (magenta). All comparisons between sign trackers and goal trackers are significant. From left to right: number of lever presses ($p = 0.03$, Wilcoxon rank sum test), number of magazine entries ($p = 0.002$), latency to first lever press ($p < 0.001$), latency to first magazine entry ($p = 0.02$).

Extended Data Figure 6-1. Correlation of the activity of individual neurons with behavioral extinction of sign tracking and goal tracking. Distribution of Spearman's rank correlation coefficient (rho) relating cue-evoked neural activity (500 ms window) to number of lever presses **(A,B)**, number of magazine entries **(C,D)**, latency to first lever press **(E,F)**, or latency to first magazine entry **(G,H)** for individual neurons recorded in sign trackers **(A,C,E,G)** or goal trackers **(B,D,F,H)** during an extinction session. All panels, blue indicates significant correlation ($\alpha = 0.1$), and p-values indicate results of Wilcoxon signed rank test for median different from zero.

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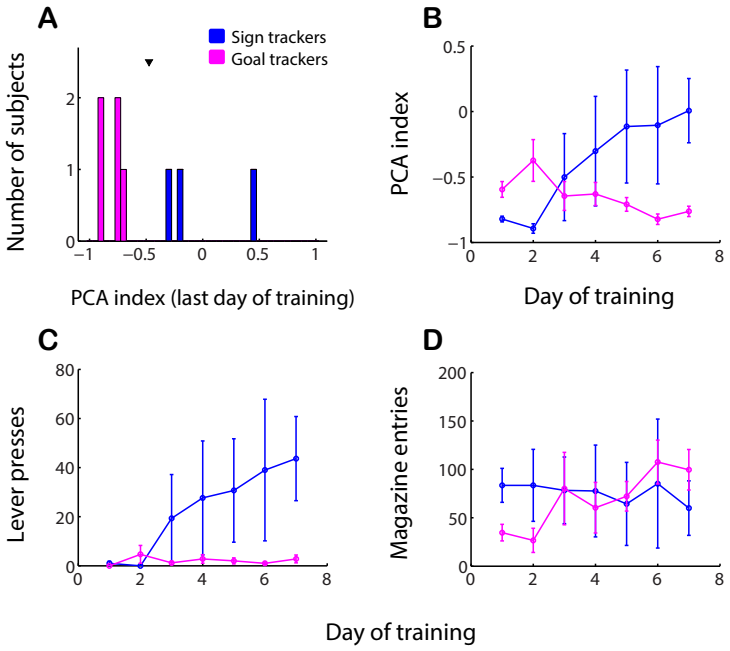

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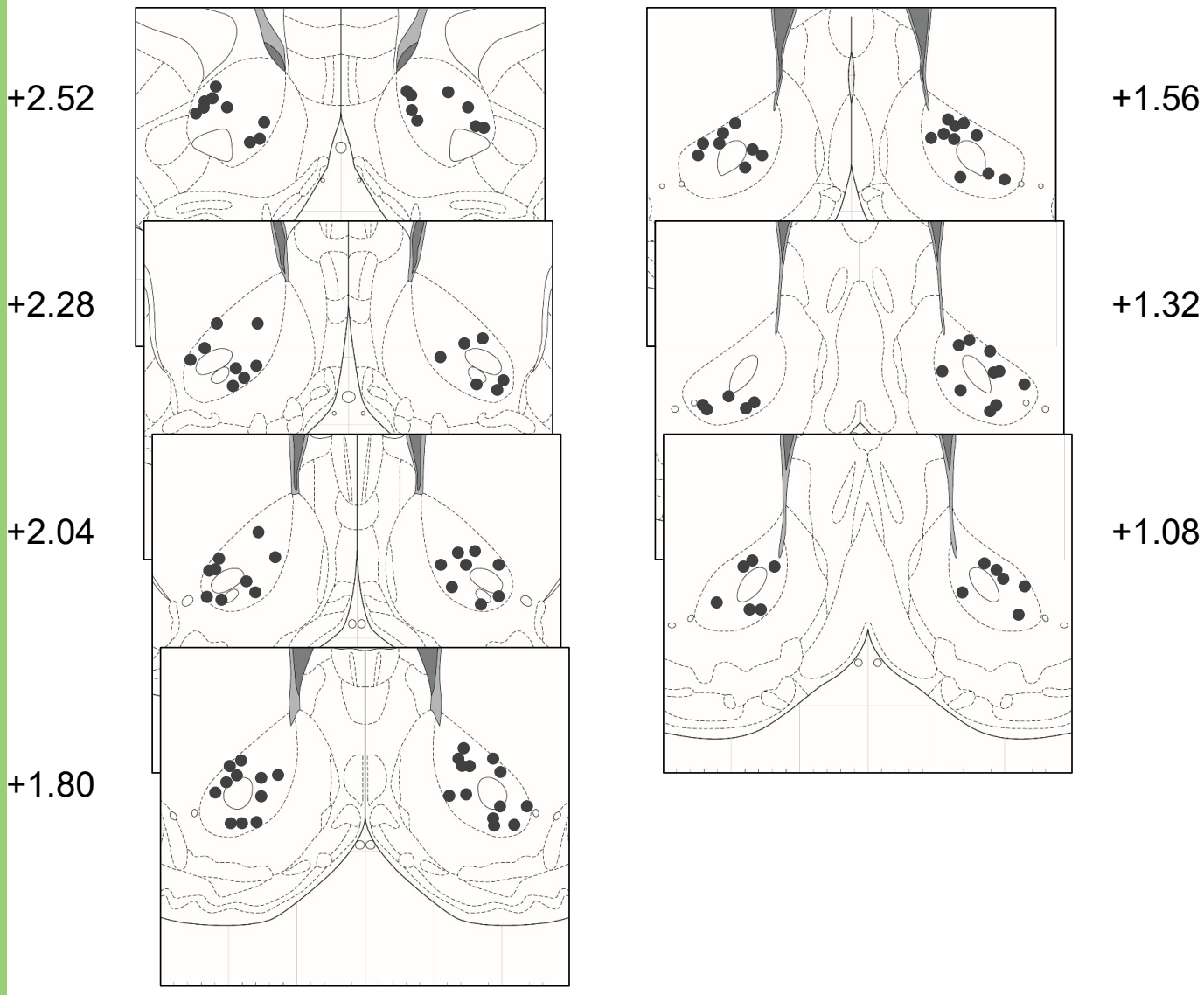

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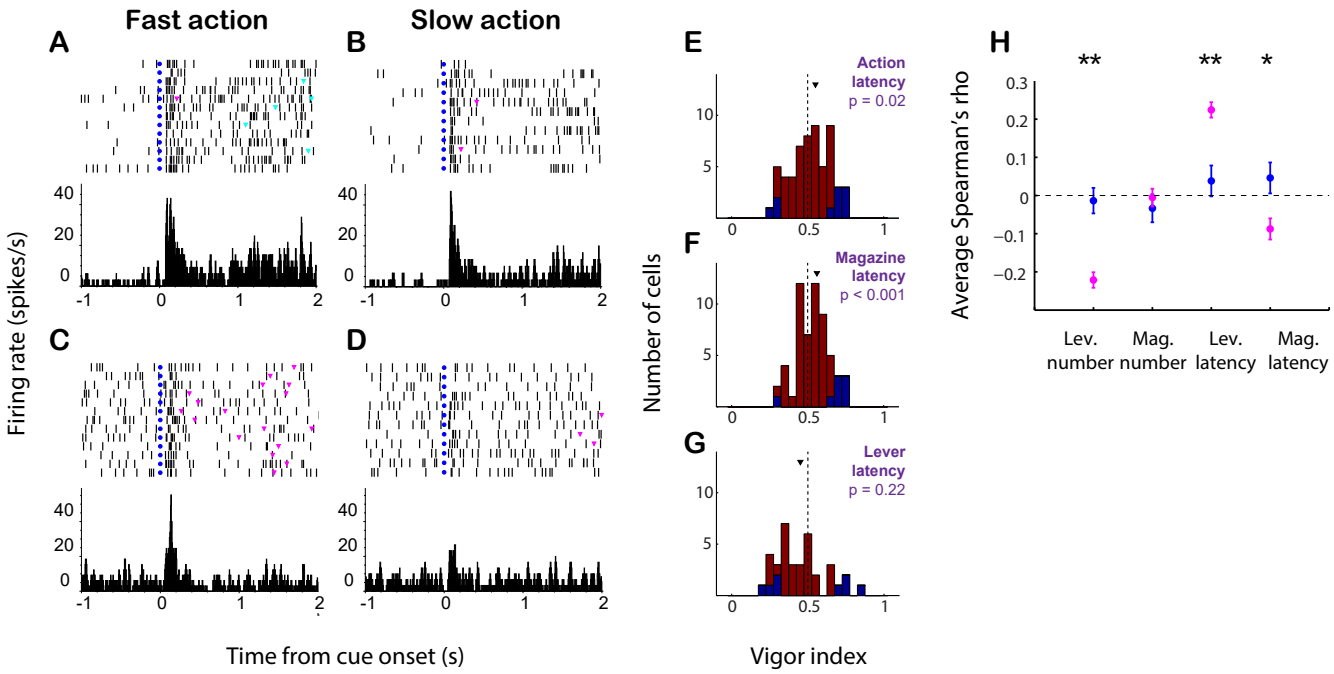

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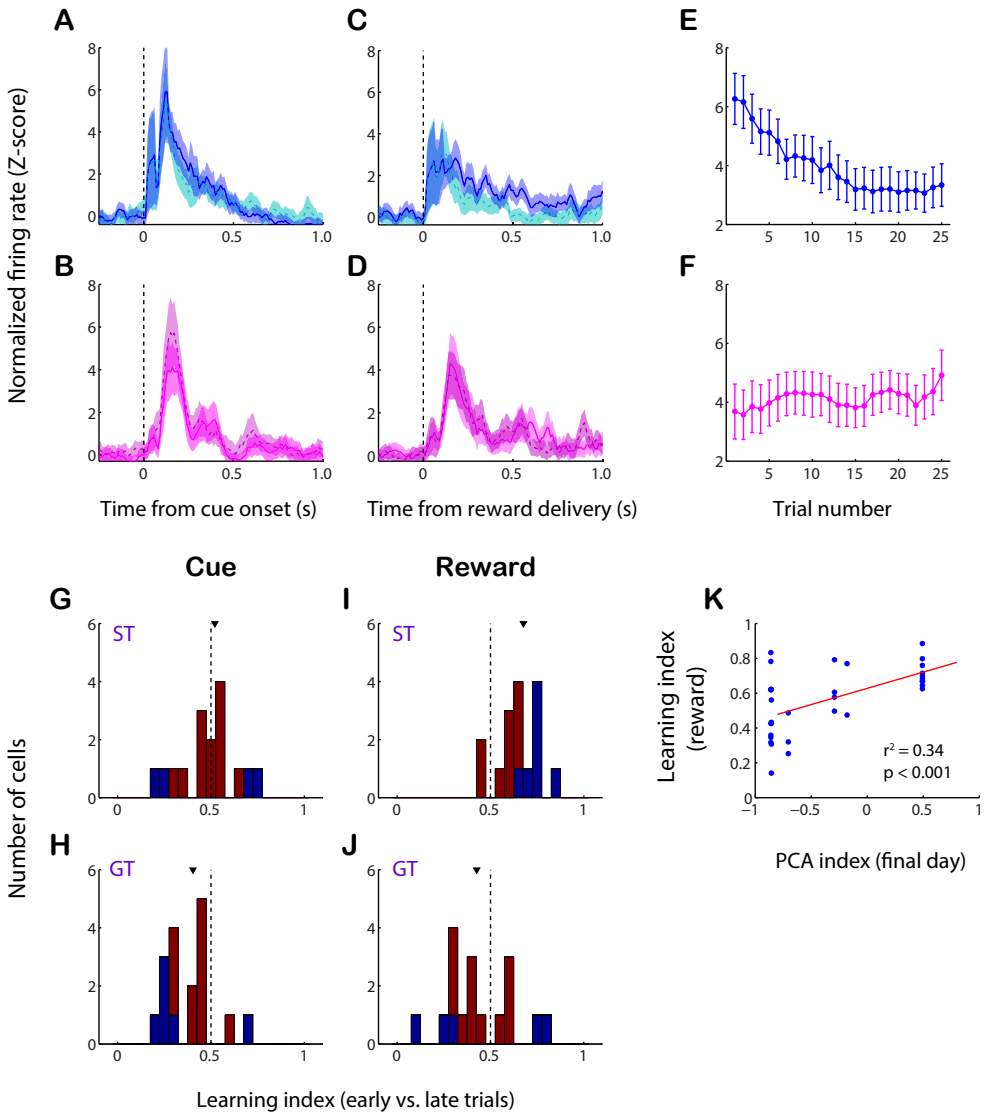

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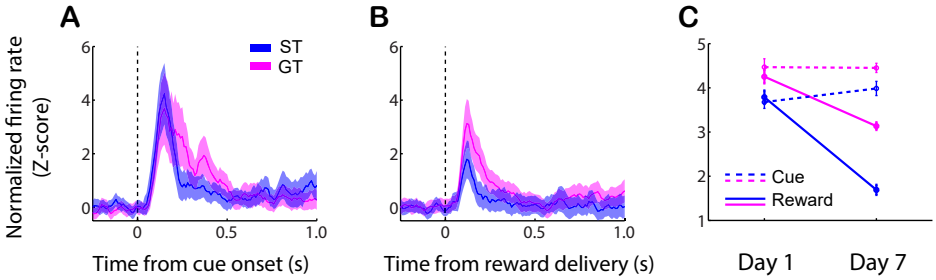

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