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Conditioned approach behavior of SHR and SD rats during Pavlovian conditioning

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ABSTRACT

Individual differences in reward-related learning are relevant to many behavioral disorders. Sensory cues that predict reward can become incentive stimuli that adaptively support behavior, or alternatively, cause maladaptive behaviors. The spontaneously hypertensive rat (SHR) expresses a genetically determined elevated sensitivity to delay of reward, and has been extensively studied as a behavioral model for attention deficit hyperactivity disorder (ADHD). We investigated reward-related learning in the SHR, comparing them to Sprague-Dawley (SD) rats as a reference strain. A standard Pavlovian conditioned approach task was used, in which a lever cue was followed by reward. Lever presses could occur while the lever was extended, but had no effect on reward delivery. The behavior of both the SHRs and the SD rats showed that they learnt that the lever cue predicted reward. However, the pattern of behavior differed between the strains. During lever cue presentation, SD rats pressed the lever more often and made fewer magazine entries than SHRs. When lever contacts that did not result in lever presses were analyzed, there was no significant difference between SHRs and SDs. These results suggest that the SHRs attributed less incentive value to the conditioned stimulus than the SD rats. During the presentation of the conditioned cue, cue directed responses are called sign tracking responses, whereas responses directed towards the food magazine are called goal tracking responses. Analysis of behavior using a standard Pavlovian conditioned approach index to quantify sign and goal tracking tendencies showed that both strains had a tendency towards goal tracking in this task. However, the SHRs showed a significantly greater goal tracking tendency than the SD rats. Taken together, these findings suggest that attribution of incentive value to reward predicting cues is attenuated in SHRs, which might explain their elevated sensitivity to delay of reward.

1. Introduction

Sensory cues that predict reward can become incentive stimuli that powerfully control behavior [1]. Such learning is usually highly adaptive. For example, incentive stimuli promote approach to food sources and act as secondary reinforcers to motivate persistent behavior when reward is infrequent or delayed. On the other hand, the incentive value of reward cues can also lead to maladaptive behavior such as impulsivity and drug seeking [2]. Individual differences in reward-related learning are thus relevant to many behavioral disorders. In particular, altered sensitivity to reward has been described in attention deficit hyperactivity disorder (ADHD) [3-6]. Experimentally, the association of sensory cues with rewards can be measured using Pavlovian conditioned approach (PCA) behavior [7]. Here we investigated PCA behavior of the spontaneously hypertensive rat (SHR), a congenic strain proposed as an animal model for components of ADHD behavior [8,9] that exhibits genetically determined altered sensitivity to reward [8,10].

The SHR was originally developed as a genetic animal model for hypertension [11]. During selective breeding for hypertension, some distinct behavioral characteristics became fixed in the SHR genome [12-15]. These characteristics include altered responses to reinforcement [16,8,17], impulsivity [18-24] and inattention [19,8,9,25], which have led to its use as a behavioral model of ADHD [26,25,23,27–29]. Of particular relevance to their reward-related behavior, SHRs show a higher sensitivity to delay of reinforcement than comparison strains, evident in a steeper delay of reinforcement gradient [30,16,8,17] and a

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stronger preference for immediate over delayed reward [21,31,32].

The higher sensitivity to delay of reward in the SHR, relative to comparison strains, may be due to underlying differences in their attribution of incentive properties to reward-predicting cues. Normally, when reward is delayed, a cue that has acquired incentive properties can act as a conditioned reinforcer and bridge delays between cues and rewards [33-35]. This bridging effect reduces the impact of delay on learning. Conversely, failure of reward-predicting cues to develop incentive properties would be expected to cause increased sensitivity to delay of reward due to the absence of this bridging effect. Thus, reduced attribution of incentive value to reward predicting cues in the SHRs might explain their increased sensitivity to delay of reward. Here, we investigated the attribution of incentive salience to a lever cue that predicted food reward in SHRs, using SDs as the reference strain for comparison.

Differences in the attribution of incentive value to reward predicting cues causes different patterns of response to the cues. In PCA studies, the reward predicting cue is presented in one location and the reward is delivered in another. When the cue acquires incentive value, animals approach and interact with it, a behavioral pattern defined as sign tracking [36]. In sign tracking behavior, interaction with the cue by touching or gnawing on it occurs, even when those actions have no effect on subsequent food delivery [37]. Thus, sign tracking behavior is an indication that a reward-predicting cue has developed incentive properties. Conversely, approaching and interacting with the reward location during the cue presentation has been defined as goal tracking [38]. Goal tracking is an indication that the cue has less incentive value than the reward location. Knowledge of sign tracking and goal tracking behavior of the SHR may help explain their increased sensitivity to delay of reinforcement. If the increased sensitivity to delay of reinforcement in the SHR is caused by reduced incentive properties of reward-predicting cues, then the SHR should exhibit less sign tracking behavior than comparison strains.

The prediction that SHRs should exhibit less sign tracking behavior than comparison strains contrasts with expectations based on studies showing that impulsive behavior is associated with a tendency to attribute incentive properties to cues predicting reward [39]. Several studies have shown evidence of various forms of impulsivity in the SHR [18-24], suggesting that, contrary to our prediction, SHRs might be expected to show increased sign tracking. However, the PCA behavior of the SHR remains to be tested experimentally. Although the effects of reinforcement on operant and instrumental learning in the SHR have been extensively studied [30,16,9,25,40], relatively few studies have investigated Pavlovian conditioned responses in the SHR. Bucci et al. [41] used a Pavlovian conditioning task in which a visual stimulus was paired with food reward and found that SHRs and Wistars learnt to associate the light with food reward. However, approach to the visual stimulus was not measured.

In the present study, the PCA behavior of SHRs was investigated using a standard Pavlovian conditioning procedure with a retractable lever as the conditioned stimulus (CS) and sucrose pellets as the reward. Lever presses were recorded as a measure of interaction with the CS, but had no effect on reward delivery. Lever contact without lever pressing was also measured using touch-detection circuitry, to record approach behavior that involved less vigorous interaction with the lever than a lever press. Magazine entries before and during the CS were recorded as a measure of goal tracking. To provide a comparison with other studies of sign and goal tracking, an established PCA index was calculated from the lever press and magazine entries [7]. Sprague Dawley (SD) rats were used as the comparison strain because the PCA index has been determined for large numbers of SD rats providing normative data for comparison [7,42].

2. Material and methods

2.1. Subjects

Subjects in the main study were 19 SHR and 20 SD male rats (Charles River, Japan). An additional 4 SHR and 5 SD rats were used in exploratory studies reported as supplementary data. Rats were pair-housed and placed on a 12-hr reverse light/dark cycle. Lights were off from 9:00 am to 9:00 pm. Behavioral testing was performed during the dark cycle between 9:30 am and 4:30 pm. All procedures were approved by the Committee for Care and Use of Animals at Okinawa Institute of Science and Technology (ACUC protocol #2021–330).

2.2. Behavioral apparatus

Pavlovian conditioned approach training was conducted in standard operant boxes (Med Associates) that contained a food magazine, one retractable lever, and a house light. The food magazine was located at the center of one wall and the lever was located on the same wall, to the left or right of the food magazine. Rats were randomly allocated to boxes with right or left placed levers. The lever required a ~15 g force to depress and operate the microswitch that registered a lever press. Capacitative touch-sensing circuitry was added to levers to detect contact with the lever that did not result in a lever press, defined as a "lever contact". Lever presses, lever contacts, and magazine entries were recorded.

2.3. Habituation

Rats underwent 5 days of handling by the experimenter and habituation to the room in which the operant boxes were housed. During the last two days of habituation the animals were provided with 7 banana-flavored food pellets (Bio-Serv, #F0024) in their home cage to familiarize them with the reinforcers to be used in the study.

2.4. Magazine training

Rats completed three days of magazine training. Ten minutes before a magazine training session, rats were placed in their operant boxes. During these ten minutes, house lights remained off, the lever was retracted, and no food was delivered. In each magazine training session, 25 banana-flavored pellets were delivered into the food magazine on a variable interval 30-second schedule (20–40 s range). During these sessions, magazine entries were recorded. During magazine training, rats' access to food was limited to the hour after the training session. At all other times animals had free access to food. All rats successfully collected 25 pellets on the last day of the magazine training and therefore they proceeded to the Pavlovian conditioned approach training. At the beginning of PCA training rats were five weeks old.

2.5. Pavlovian conditioned approach training

After magazine training, rats underwent 11 daily sessions of PCA training. Each session consisted of 25 trials in which a lever was presented for 8 s then retracted. Immediately after lever retraction, a reward pellet was delivered into the food receptacle by operation of the mechanical feeder. Trials were separated by a 90 s variable interval (range = 50 −130 s). During the 8 s of lever cue presentation, the number and duration of magazine entries, lever presses, and lever contacts were recorded. The number and duration of magazine entries were also recorded during the 8 s before lever cue presentation.

2.6. Behavioral measures

2.6.1. Cue-directed responses

Cue-directed responses (lever contacts and lever presses) were

counted during the 8 s cue presentation. In a pilot study we observed that SHRs performing a similar task often contacted the lever in ways that did not result in a lever press. Lever contacts without lever pressing might indicate learning of the cue-reward association without the cue acquiring sufficient incentive value to energize a lever press. Lever contacts that did not result in lever depression were used as a measure of learning that the cue predicted reward, and lever presses brought about by more vigorous interaction with the cue served as an indicator of the incentive value attached to the cue [43]. To determine the number of "lever contacts that did not result in a lever press" we counted only those contacts in which there was no lever depression during the contact period.

2.6.2. Magazine entries

Magazine entries were measured during the 8 s interval prior to cue presentation (baseline) and during the 8 s cue presentation.

2.6.3. PCA index

For comparison with previous studies that used a PCA index, we used the formula from Meyer et al. [7] to compute a PCA index based on three measures: response bias, probability difference, and lever and magazine latency as follows:

2.6.4. Response bias (R)

The number of lever presses, *l*, minus the number of magazine entries, *m*, during the cue presentation divided by the sum of lever presses and magazine entries (Eq. 1):

$$R = \frac{(l - m)}{l + m} \tag{1}$$

2.6.5. Probability difference (P)

The number of trials with a lever press, *N(l)*, minus the number trials with a magazine entry, *N(m)*, divided by the total number of trials in the session, *N(s)* (Eq. 2):

$$P = \frac{N(l) - N(m)}{N(s)} \tag{2}$$

2.6.6. Latency measure (L)

The latency to enter the food magazine after cue onset, *f*, minus the latency to the first lever press, *p*, divided by the cue duration (8 s) (Eq. 3):

$$L = \frac{f - p}{8} \tag{3}$$

The overall PCA index (*I*) was calculated from the mean of response bias, probability difference, and latency measures (Eq. 4):

$$I = \frac{R + P + L}{3} \tag{4}$$

Rats were classified using the average of the PCA index on days 10 and 11, as sign trackers (scores from +0.5 to +1), intermediate responders (scores between +0.5 and −0.5), or goal trackers (scores from −1 to −0.5).

2.7. Statistical analysis

Prior to undertaking statistical analyses, data distributions were checked using Kolmogorov-Smirnov and Shapiro-Wilk tests for normality, and QQ plots. Non normally distributed data were subject to square root transformations to provide closest approximation to normally distributed data.

Two-way ANOVA with strain as the between-subject factor and session as the within-subject factor were used to analyze the development of a cue-directed conditioned response. The Greenhouse-Geisser correction was used to correct for violation of the sphericity assumption.

Three-way ANOVA (with Greenhouse-Geisser correction) conducted on magazine entries with session and period (cue vs. baseline) as within-subject factors and strain as the between-subject factor was used to confirm magazine directed conditioned response.

The PCA index was separately calculated to classify rats as sign trackers, goal trackers, or intermediate responders to permit comparison with previous literature [7,42]. The SD and SHR PCA index scores were compared using two-way ANOVA (Greenhouse-Geisser correction) with strain as the between-subject factor and session as within-subject factor. This was followed by an analysis of simple main effects (Bonferroni adjustment). Two-way ANOVA (Greenhouse-Geisser correction) was separately performed on measures of probability and latency of lever presses and magazine entries across the 11 sessions with session as the within-subject factor and strain as the between-subject factor. Stable PCA index scores were obtained by taking the average performance across days 10 and 11. The SD and SHR groups were compared using the Mann-Whitney test, because the PCA index scores were not corrected by data transformation.

3. Results

We first compared the lever press behavior of the SHRs and SD rats during Pavlovian conditioning. As shown in Fig. 1A, during presentation of the lever cue preceding reward delivery – the CS – the SD rats made more lever presses than the SHRs. Statistical analysis (two-way ANOVA) showed significant main effects of both Strain ($F(1, 37) = 4.824$; $p = 0.0344$) and Session ($F(3.334, 123.4) = 11.29$; $p < 0.0001$). The Strain x Session interaction was not significant ($F(10, 370) = 1.702$; $p = 0.0785$). The topography of the lever pressing response was similar in both strains. Fig. 1B shows the timing of lever presses during the CS, averaged over sessions 10 and 11. In both strains the rate of lever pressing peaked 2–3 s after the onset of the CS. Both SHRs and SDs made fewer lever presses during later segments of the cue presentation, with

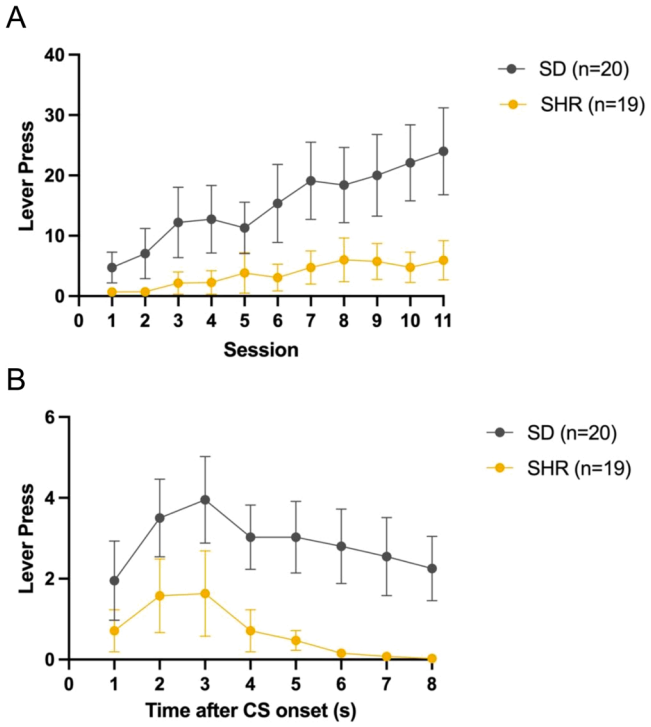

Fig. 1. Acquisition of Pavlovian conditioned approach toward lever CS by SHR and SD rats. A. Lever presses during CS across the 11 sessions. B. Lever presses during each second of CS, average of sessions 10 and 11. Comparison of SD (black filled circles, n = 20) and SHR (yellow filled circles, n = 19). Data are group averages ± SEM.

SHRs making fewer lever presses than SDs overall, reducing to zero towards the end of the CS. Two-way ANOVA with Greenhouse-Geisser correction on square-root transformed data of lever presses for sessions 10 and 11 showed significant effects of Strain ($F(1, 37) = 8.157$; $p = 0.0070$) and Time after CS onset ($F(2.714, 100.4) = 5.916$; $p = 0.0014$). The Strain x Time interaction was not significant ($F(7, 259) = 1.027$; $p = 0.4122$). Thus, the SDs exhibited a higher conditioned lever pressing response rate than the SHRs, but both strains showed a similar temporal pattern of responses.

We also measured the number of lever contacts that did not end in a lever press (Fig. 2A). A two-way ANOVA (Greenhouse-Geisser correction) on the foregoing measure showed no significant effect of Strain ($F(1, 37) = 0.001129$; $p = 0.9734$), Session ($F(3.183, 117.8) = 1.342$; $p = 0.2632$), or Strain x Session interaction ($F(10, 370) = 1.519$; $p = 0.1303$). Both SHRs and SDs made fewer lever contacts during later segments of the cue presentation (Fig. 2B) and this tendency was more pronounced in the SHRs. Two-way ANOVA with Greenhouse-Geisser correction on non-press lever contacts during sessions 10 and 11 showed a significant Strain x Time interaction ($F(7, 259) = 4.055$; $p = 0.0003$) and a main effect of Time ($F(2.101, 77.72) = 18.21$; $p < 0.0001$). Thus, SHR and SD rats made a similar number of non-press lever contacts but the SHR made more non-press lever contacts than the SD in the first few seconds of the CS, as confirmed by analysis of simple main effects (Time after CS onset x Strain, $F(1,37) = 7.640$; $p = 0.0088$; Time after CS onset $F(1, 37) = 26.82$; $p < 0.0001$; Strain, $F(1, 37) = 1.549$; $p = 0.2211$).

The effect of the cue on magazine entries was assessed by comparing the number of magazine entries during the 8 s interval immediately prior to lever extension – which we term "baseline" – with the number of magazine entries during the CS. Relative to baseline, the SHRs showed an increase in magazine entries during the CS, while the SDs showed a decrease in magazine entries (Fig. 3A). A three-way ANOVA (Greenhouse-Geisser correction) was performed on the magazine entries measures with Session and Period (cue versus baseline period) as within-subject factors and Strain as the between-subject factor. The Session x

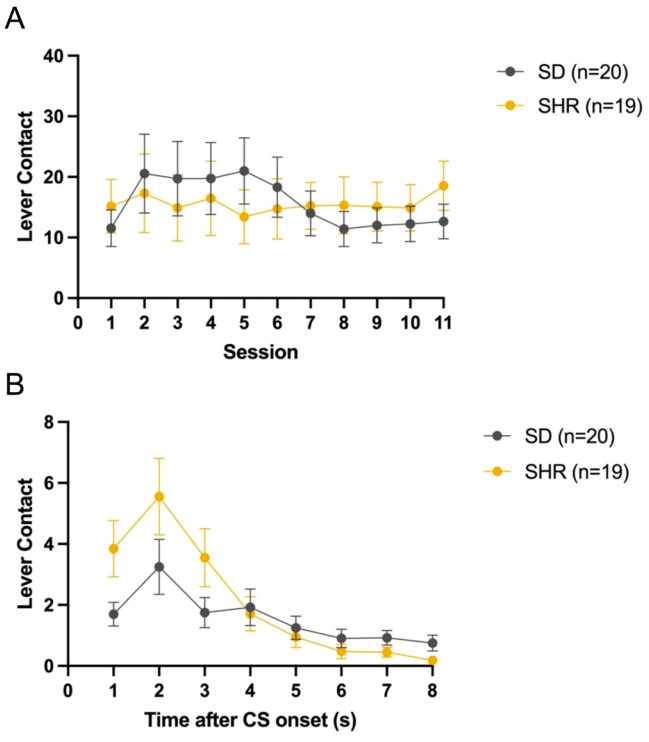

Fig. 2. Lever contacts not resulting in lever presses in SD and SHR rats. A. Lever contacts during CS across the 11 sessions. B. Lever contacts during each second of CS, average of sessions 10 and 11. Data are group averages ± SEM.

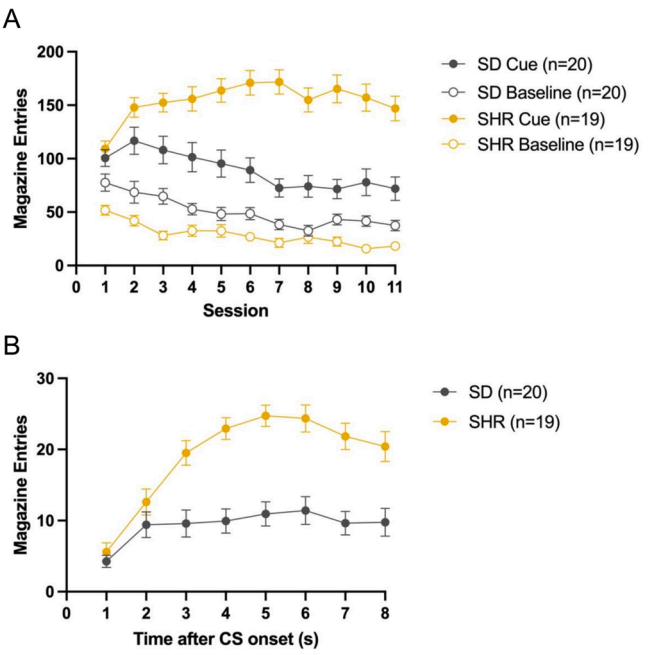

Fig. 3. Acquisition of Pavlovian conditioned approach to magazine by SHR and SD rats A. Group average number of magazine entries during (Cue), and before (Baseline), the CS across the 11 sessions, for SHR and SD. B. Group average number of magazine entries during each 1 s interval of the CS, average of sessions 10 and 11.

Strain x Period interaction ($F(10, 370) = 6.117$; $p < 0.0001$) was significant. Separately, Strain x Period interaction ($F(1, 37) = 67.15$; $p < 0.0001$), Session x Period interaction ($F(2.621, 96.96) = 8.589$); $p < 0.0001$), and Session x Strain interactions ($F(10, 370) = 5.437$; $p < 0.0001$) were significant as were the main effects of Strain ($F(1, 37) = 7.783$; $p = 0.0083$), Session ($F(4.912, 181.7) = 5.196$; $p = 0.0002$), and Period ($F(1.000, 37.00) = 241.0$; $p < 0.0001$). These results indicate that SHR also learnt that the CS predicts reward: the increase in magazine entries by the SHRs during the CS across sessions, relative to the Baseline, shows that the CS evoked approach to the reward location.

The pattern of magazine entries by the SHRs during the CS period was different from the SDs, and showed an increase in magazine entries at later times after CS onset (Fig. 3B). Two-way ANOVA with Greenhouse-Geisser correction on magazine entries during sessions 10 and 11 showed a significant Strain x Time interaction ($F(7, 259) = 10.81$; $p < 0.0001$) with significant effects of Strain ($F(1, 37) = 22.17$; $p < 0.0001$) and Time after CS onset ($F(2.925, 108.2) = 35.99$; $p < 0.0001$).

To quantify animals' goal and sign tracking tendencies, we used a PCA index used in previous studies of sign and goal tracking behavior in rats [7]. We first separately computed the component measures of the PCA index: response bias; probability difference; and latency score; and compared these measures between strains (Fig. 4A–C). The response bias measure showed significant Session by Strain interaction ($F(10, 370) = 2.952$; $p = 0.0014$). Inspection of Fig. 4A reveals that the response bias of the SD increased more over sessions than that of the SHR. There were a significant main effects of Strain ($F(1, 37) = 8.355$; $p = 0.0064$) and Session ($F(2.882, 106.6) = 5.835$; $p = 0.0012$).

The probability difference measure also showed significant Strain x Session interaction ($F(10, 370) = 3.743$; $p < 0.0001$) and significant main effects of Strain ($F(1, 37) = 14.46$; $p = 0.0005$) and Session ($F(3.034, 112.3) = 7.497$; $p = 0.0001$). As shown in Fig. 4B, the SD gradually shifted away from the magazine and toward the lever, while the SHRs responses remained directed toward the magazine.

Lastly, for the latency score there was a significant Session x Strain interaction ($F(10, 370) = 2.897$; $p = 0.0017$). As shown in Fig. 4C, the

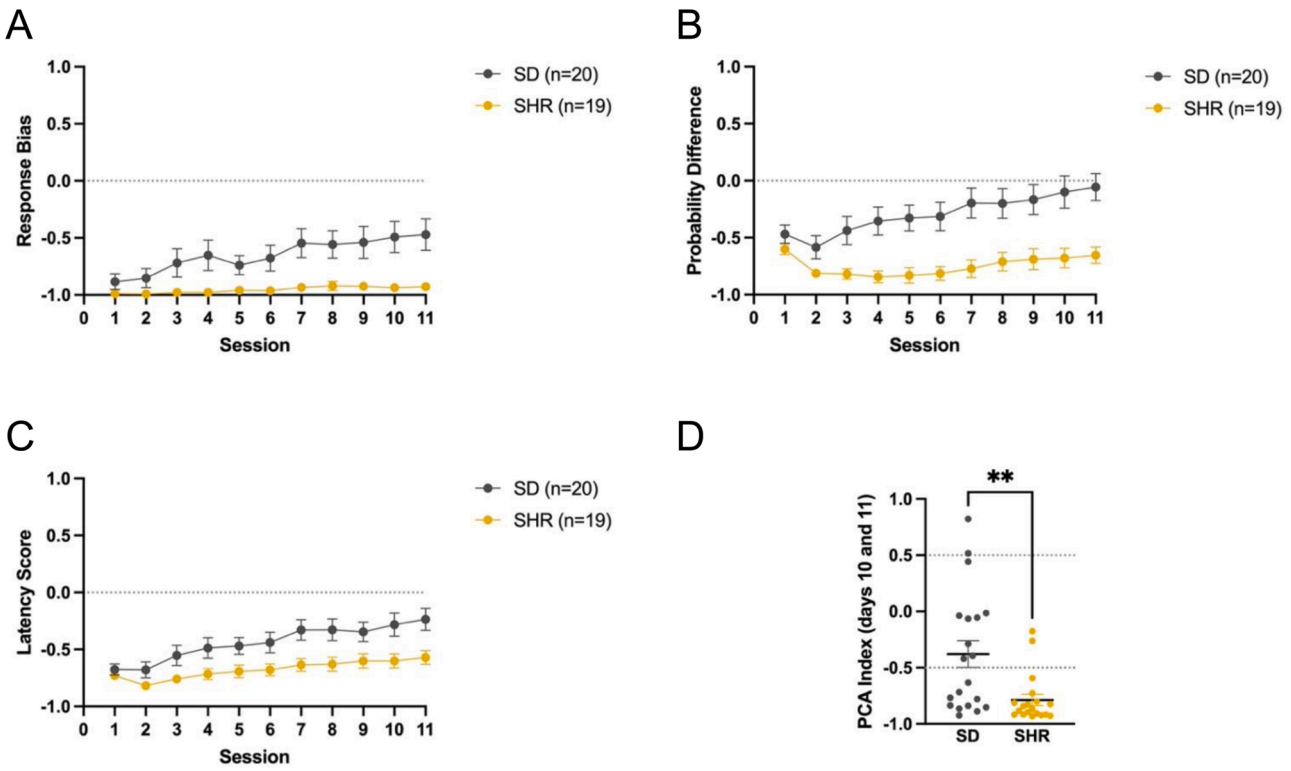

Fig. 4. Derivation of PCA index. A. Response bias across sessions. B. Probability difference across sessions. C. Latency score across sessions. D. PCA Index for SHR and SD rats derived from A – C, average of sessions 10 and 11.

SD responded to the lever cue with a lever press earlier over sessions. There were significant main effects of Strain ($F(1, 37) = 6.996$; $p = 0.0119$) and Session ($F(3.323, 122.9) = 20.72$; $p < 0.0001$).

Thus, SHRs and SDs were significantly different in the development of all three measures over sessions. Previous studies used averages of the three PCA measures over the final two sessions – the terminal PCA index – for classifying animals' sign and goal tracking tendencies. The terminal PCA index (days 10 and 11) indicated that among the SDs, 10 could be categorized as goal trackers, 8 as intermediate responders, and 2 as sign trackers (Fig. 4D). Among the SHRs, 17 could be categorized as goal trackers, 2 as intermediate responders, and 0 as sign trackers. The difference in terminal PCA index measure between SHR and SD rats was statistically significant (Mann-Whitney test, $p = 0.0019$). Based on the cut points used in previous studies [7], and indicated by dotted lines on Fig. 4D, there were more goal trackers among the SHRs than among the SDs, although there was a high proportion of goal trackers in both groups.

To check whether differences in unconditioned activity between the SHR and SD might account for the differences in lever press, lever contact, or magazine entry, additional exploratory control groups of SHR and SD rats were exposed to a non-conditioning schedule in which the time of reward delivery and lever cue was randomized so that the lever cue did not predict reward. Statistical analysis (two-way ANOVA) of unconditioned lever press activity in the control groups during the lever cue showed a significant Session by Strain interaction ($F(10, 70) = 2.401$; $p = 0.0163$); a significant main effect of Session ($F(4.433, 31.03) = 8.796$; $p < 00001$) and non-significant effect of Strain ($F(1,7) = 0.8079$; $p = 0.3986$). Inspection of Supplementary Fig 1 A reveals that the lever pressing of SHRs increased slightly over sessions. This unconditioned increase in lever press, however, does not explain why SHRs did not lever press in the conditioned group. In the same unconditioned groups, for lever contacts that did not result in lever presses (Supplementary Fig 1B) there was no significant Session by Strain interaction ($F(10, 70) = 1.436$; $p = 0.1831$), a non-significant main effect of Session ($F(4.236, 29.65) = 1.909$; $p = 0.1320$); and a non-significant effect of Strain ($F(1, 7) = 0.8757$; $p = 0.3805$). Similarly, for magazine entries during the lever cue (Supplementary Fig 1 C), there was no significant Session by Strain interaction ($F(10, 70) = 1.559$; $p = 0.1373$); a significant main effect of Session ($F(2.292, 16.04) = 6.52$; $p = 0.0068$); and a non-significant effect of Strain $F(1, 7) = 0.005051$; $p = 0.9453$). Thus, the difference in PCA behavior between the two strains was not due to differences in unconditioned lever pressing or magazine entry.

Comparison of conditioned (experiment) and unconditioned (control) groups (Supplementary Figs 2) showed that both groups of conditioned rats made more magazine entries during the cue period than the controls: for SD rats magazine entries showed a significant effect of Group ($F(1, 23) = 6.023$; $p = 0.0221$) and Session ($F(2.945, 67.72) = 4.757$; $p = 0.0048$) but no Session by Group interaction ($F(10, 230) = 0.6510$; $p = 0.7689$).

For SHR magazine entries, comparison of experiment and control groups showed a significant effect of Group ($F(1, 21) = 30.97$; $p < 0.0001$) and Session by Group interaction ($F(10, 210) = 2.430$; $p = 0.0093$) but no significant effect of session ($F(4.121, 86.53) = 0.5833$; $p = 0.6805$). This indicates that the SHRs in the experimental group made more magazine entries during the cue period than the controls.

To check whether motivation for food reward was similar in the two strains in the main study, food collection latency and magazine entries during the last session of magazine training of the experimental groups were compared. There was no significant difference in food collection latency (Supplementary Fig 3 A, $t = 1.548$; $p = 0.1290$. Welch's t-test). There was a significantly smaller number of magazine entries by the SHR than the SD during magazine training (Supplementary Fig 3B, $t = 2.320$; $p = 0.0257$, Welch's t-test). Although this might indicate a difference in motivation for food reward, the smaller number of magazine entries by the SHR compared to the SD cannot explain the larger number of magazine entries that occurred during the CS period after conditioning.

4. Discussion

We found that SHR and SD rats differed in the way they responded to a reward-predicting lever cue – the CS – that preceded reward delivery. Both SHR and SD rats learnt conditioned approach responses. However, during the CS the SD rats interacted vigorously with the lever, pressing it more than the SHRs. Conversely, the SHRs made more magazine entries than the SD during the CS. These results suggest that both SHR and SD rats learnt that the CS predicted reward, but the CS developed more incentive value in the SD rats than the SHR as a result of conditioning. Consistent with this finding, transformation of the data into a standard PCA index indicated that the SHRs had a greater tendency toward goal tracking than sign tracking. The SD rats also had a tendency toward goal tracking, but significantly less than the SHRs. To the best of our knowledge, this is the first publication investigating the goal and sign tracking tendencies of SHRs.

Previous work has shown lower rates of lever pressing by SHRs than comparison strains in an autoshaping paradigm ([44–46]) and reduced habit learning in an T-maze task [47]. These behavioral characteristics of the SHR have been interpreted as deficits in learning. Here we show, however, that the SHR made more magazine entries during the CS than during the baseline period prior to the CS, indicating that they had successfully learnt that the CS predicted reward delivery. The magazine entries made by the SHR increased in frequency towards the end of the CS interval, indicating a scallop-like anticipation of reward similar to that seen in SHRs on a fixed interval schedule [14,9,48]. In addition, the conditioned group of SHRs made more magazine entries than a non-conditioned control group of SHRs in which the lever cue and the reward occurred at random intervals. These findings indicate that the SHR were not impaired in learning, and in particular, learnt that the CS predicted reward.

Compared to the SDs, the SHRs showed a smaller increase in lever presses during the CS over sessions. When lever contacts that did not result in lever presses were analyzed, the effect of session was not significant, and the interaction was also not significant. This implies that non-press lever contacts were a baseline response, not a conditioned response. The lower rate of lever pressing by the SHRs suggests that the SHRs allocate less physical effort and display less action vigor during their interaction with the lever. Previous work has shown that a CS that develops incentive properties energizes ongoing instrumental actions in the Pavlovian-to-instrumental task [49,50]. Such cues may also enhance physical effort even if the effort does not have any instrumental consequences [43]. The smaller number of lever presses by the SHR thus indicates that the lever did not energize their cue-directed behavior as much as it energized the cue-directed behavior of the SD rats. Thus, the SHRs attributed lesser incentive properties to the lever CS relative to the SDs, even though they learnt that the CS predicted reward.

Although various forms of hyperactivity have been described in the SHR [51-53,14,25], a general increase in activity cannot explain the current findings. Previous work has shown that the SHR is more active than comparison strains on a fixed interval schedule of reinforcement, producing more lever presses than SD and other strains during the fixed interval and also during time out [9,48]. Such general increase in lever press activity cannot explain the lower rates of lever pressing in the present study. Conversely, in an open field test the SHR was less active than the SD [52] or Wistar rats [41]. Taken together with our finding that the SHRs had fewer magazine entries before cue presentation than the SDs, although SHRs tend to produce more exploratory behavior than Wistar Kyoto rats [54], a general increase in activity cannot explain the SHRs' higher rates of magazine entry during the CS. Consistent with our findings, in a previous Pavlovian conditioning study in which the CS was a tone, SHR rats spent less time inside the magazine prior to cue presentation than a comparison strain [41]. Thus, the present findings of differences between the SHR and the SD in lever presses and magazine entries in the PCA task are more likely to be caused by differences in the acquisition of incentive value of the CS, rather than a general increase in activity.

For comparison with previous studies, we calculated a PCA index [7, 42] that has been used to quantify variations in PCA behavior along a single dimension ranging between goal tracking and sign tracking. The PCA index measures the relative propensity to engage with the lever or the magazine during presentation of the CS. On this measure we found that the SHRs had a greater tendency toward goal tracking than SD rats.

The SD rat was used as the comparison strain in the present study in part because normative data from numerous SD rats has been collected during conditioned approach behavior, providing a reference for comparison with the SHR. Although the Wistar-Kyoto (WKY) strain has been advocated as a normotensive control for the SHR in behavioral studies [55], biological variability and behavioral characteristics of the WKY make interpretation of differences between the SHR and WKY problematic. The SHR was originally derived from a Wistar (WI) colony maintained at the University of Kyoto, Japan [56,57]. To provide a normotensive control for the SHR, the WKY strain was developed by inbreeding of the original Kyoto WI strain [56]. However, as this did not occur until a decade after the SHR was developed, and the breeding stock of WKY was released before the strain was fully inbred, there is significant biological variation between SHR and WKY [58] and within the WKY strain [59,60]. The WKY rats have behavioral characteristics that make them very different from other common rat strains [61]. They show impaired acquisition on DRL tasks compared to SD and SHR [62], hypoactivity in open field tests, high anxiety [63] and depressive behavior [64,65]. These behavioral characteristics make them unsuitable as a comparison strain in the current study. On the other hand, our use of an established PCA index that has been extensively tested on SD rats allowed us to compare behavior in the present study with normative data [7,42].

It is difficult to draw general conclusions about the SHR phenotype from a comparison of only two strains. Normative data on sign tracking and goal tracking behavior, like that for the SD, is not yet available for other rat strains. One study of PCA behavior in Wistar rats, which might be considered to be a distant background strain for the SHR, has shown that they do not have the same tendency toward goal tracking as the SHR but do exhibit similar intermediate behavior similar to that shown by the SD rats in the present study [66]. However, different conclusions might be made if the SHR were compared with a different reference strain such as the WKY. Thus, the current study can only conclude that the SHR has a greater tendency toward goal tracking than the SD. Additional studies with other comparison strains would be required to draw more general conclusions about the SHR phenotype.

The SDs in our study showed a greater tendency to goal tracking than has been reported in other studies of PCA behavior in the SD. Differences in sign and goal tracking between SDs obtained from different breeders have been reported. In particular, a sample of rats acquired from Charles River contained more goal trackers than sign trackers [42]. The rats in the present sample were from Charles River Japan, so it is possible that the greater than expected tendency to goal tracking in the SD is due to genetic or environmental factors. Subtle differences in the task may also affect the propensity to sign tracking and goal tracking. For example, longer inter-trial intervals promote increased sign tracking [67-69]. However, in the current study the inter-trial intervals were similar to those used in previous studies. Another potentially important variable concerns the lever used as a cue. In previous studies, the lever was illuminated when it was extended [7,42]. This may have increased the salience of the cue, compared to the non-illuminated cue in the present study. Lastly, a goal tracking tendency in the SDs only reduces the chance of observing a true increase in goal tracking in the SHRs compared to the SDs (due to a ceiling effect). Despite the increased chance of a false negative, we found that SHRs exhibit more goal tracking than SDs.

The SHR has been proposed as an animal model for ADHD. Therefore, our finding that SHRs have a greater tendency toward goal tracking than SD rats raises the question of whether children with ADHD would

show a similar tendency. In humans with ADHD, functional MRI studies of striatal responses – thought to indicate dopaminergic activity [70] – have shown reduced striatal responses to reward predicting cues [71,3,72] and increased responses to reward delivery [3]. In rodents, a decreased striatal dopamine response to reward predicting cues and increased response to reward delivery has been associated with goal tracking behavior [73]. To date, however, studies of sign tracking and goal tracking have not been reported in children with ADHD, and further work is needed to investigate possible differences in these behaviors.

Our data indicates that SHRs have a greater tendency toward goal tracking than SD rats. Although we have speculated that the greater sensitivity of the SHR to reward delays, compared to the SD rat, may be due to reduced incentive properties of reward-predicting cues, it is possible that the goal tracking tendency is independent of the sensitivity to reward delays. Several other behavioral traits have been described in the SHR and our study did not show a specific correlation of goal tracking tendency with sensitivity to reward delays. Additional studies would be required to determine whether there is any causal relationship between goal tracking and sensitivity to reward delays in the SHR.

CRediT authorship contribution statement

Bozena Silic: Conceptualization, Investigation, Data curation, Formal analysis, Writing – original draft. **Mayank Aggarwal**: Conceptualization, Writing – review & editing. **Kavinda Liyanagama**: Software, Data curation. **Gail Tripp**: Conceptualization, Writing – review & editing, Supervision. **Jeffery R. Wickens**: Funding acquisition, Conceptualization, Writing – review & editing, Supervision.

Data availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2023.114348.

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