



Research report

Inadequate early social experience increases the incentive salience of reward-related cues in adulthood

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ABSTRACT

The mechanisms by which childhood abuse and/or neglect become risk factors for the development of drug addiction, problem gambling, and other disorders of behavioral inhibition are unknown. The loss of behavioral inhibition is often triggered by reward-related cues that acquire incentive salience. This study examined whether inadequate early-life social experience in rats affects the incentive salience of reward-related cues. Rats were deprived of early-life social experience with the mother and litter through artificial-rearing (AR). A group of AR rats (AR + STM) received additional tactile stimulation that mimicked maternal licking, a critical component of rat maternal care. Control rats were maternally reared (MR). The incentive salience attributed to a food cue was measured in adult rats using a conditioned approach task, where a conditional stimulus (CS; lever) was paired with food delivery, and in a conditional reinforcement task. The dependent measures were approach towards the CS (sign-tracking) versus approach towards the place of food delivery (goal-tracking) and instrumental responding for the CS. AR rats made significantly more sign-tracking responses than MR rats. AR rats also made more instrumental responses when reinforced with the CS. AR + STM rats' responses were intermediate to MR and AR rats. Thus, inadequate early-life social experience enhanced the incentive salience of a reward-related cue in adulthood. Replacement of maternal licking partially reversed this effect. These results highlight a potential link between early-life social adversity and susceptibility to disorders of behavioral inhibition.

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1. Introduction

Adverse social experiences in childhood, such as abuse or neglect, are known risk factors for the development of drug addiction and problem gambling [1–5]. One prominent feature of addictions is the inability to inhibit approach behavior in the presence of contextual cues associated with drug use or gambling [6–10]. Pairing of cues such as sights, sounds, and smells with reward can result in the attribution of incentive motivational value (incentive salience) to the cues themselves [11]. Through this process previously neutral cues can be transformed into attractive and desired incentives that motivate behavior [11,12]. Reward-related cues can acquire greater incentive salience for some individuals than for others [7,13]. In rats, repeated pairing of a conditional stimulus (CS; e.g., illuminated lever) with delivery of food reward

(unconditional stimulus; US) results in two distinctive approach responses. Sign-tracking rats preferentially approach the lever (CS) and chew and gnaw on it vigorously. Goal-tracking rats preferentially approach the site of food delivery during CS presentation. Some rats switch between both types of behavior. The preferential attraction of sign-tracking rats to the CS has been related to processes underlying the loss of inhibitory control in individuals susceptible to addiction [7,14].

Sign-tracking rats are more susceptible than goal-tracking rats to cocaine-cue induced reinstatement of drug-seeking following extinction [15]. Similarly, rats that were repeatedly isolated from the mother and littermates exhibit increased self-administration of cocaine in adulthood [16,17]. Sign-tracking rats also show less sensitivity to the acute locomotor-activating effects of cocaine than goal-tracking rats, but greater sensitization following repeated treatment with cocaine [18]. Likewise, early social isolation increases sensitivity to the locomotor effects of psychostimulants [19–21]. Furthermore, sign-tracking rats exhibit increased impulsive action and reduced impulsive choice [22], also a characteristic of rats that were socially isolated as neonates [23].

Social isolation may alter primary associative processes involved in behavior regulation. In rats, monkeys and humans,

Abbreviations: AR, artificial rearing; MR, maternal rearing; AR + STM, artificial rearing plus stimulation; CS, conditional stimulus; US, unconditional stimulus; PCA, Pavlovian conditioned approach; PND, post-natal day; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid.

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there are cognitive-behavioral effects of inadequate early social experience including decreased ability to change ineffective or disruptive behaviors and difficulty in inhibiting responses [24–27]. These “disorders of inhibition” either co-occur or are possibly part of the substrate of social behavioral problems associated with inadequate early social experience. These considerations raised the question of whether inadequate early social experience in rats would affect the propensity to approach reward cues in adulthood.

We reared rat pups in complete social isolation from the mother and littermates using artificial rearing (AR) [28–30]. This approach allows for complete experimental control of the social interactions of developing rats and enables the study of specific components of social and other environmental stimuli important during early development [31]. We hypothesized that AR would increase the incentive salience attributed to reward-related cues. That is, AR rats would exhibit (a) more CS-directed responses (sign-tracking) on a Pavlovian conditioned approach (PCA) task and (b) more instrumental responses for the presentation of a CS [13]. Since the effects of AR are presumed to be attributable to the lack of social stimulation rather than differences in nutrition and sensory deprivation per se, we included a condition in which rats received tactile stimulation to mimic maternal licking. Previous studies indicate that administering this type of stimulation during the time of rearing can partially reverse some of the effects of AR [19,29].

2. Materials and methods

2.1. Subjects

The subjects were 120 male Sprague-Dawley rats born to 42 primiparous dams. The dams were obtained from Charles River (St. Constant, Quebec, Canada). After mating dams were housed individually in clear Plexiglas cages (L 43 × W 22 × H 21 cm), lined with woodchip bedding (“Beta Chip”, NEPCO) with free access to water and lab chow (“5012 Rat Diet”, PMI Inc). Housing rooms were maintained at a 22 ± 1 °C and 40–50% humidity. Lights were off between 2000 and 0800 h. All procedures were performed in accordance with the guidelines set by the Canadian Council on Animal Care and were approved by the University of Toronto at Mississauga Local Animal Care Committee.

2.2. Pup rearing conditions

On the day of parturition (post-natal day – PND 0) litters were culled to 12 pups (~7 male and 5 female pups). On PND 5 two male pups from each litter were removed, underwent cheek cannulation and were reared artificially thereafter (AR; see below). The remaining pups were left in the litter undisturbed until weaning, except for weekly cage changes. These pups were maternally reared (MR) and each litter contributed 1 male towards the control group (i.e., MR group).

Details of the cheek cannulation and AR procedures are described elsewhere [29,32]. Briefly, the cannulation procedure was performed following topical anesthesia of the cheek with lidocaine (EMLA). The cheek was then pierced to implant a polyethylene (PE10) cannula. Polysporin antibacterial cream was applied at the site of penetration. Following cannulation each AR pup was placed into a plastic cup (11 cm in diameter × 15 cm deep) lined with corn-cob bedding (Bed O’Cobs). The cups floated in a temperature controlled water bath (36 ± 1 °C). The tops of the cups were open to allow the cheek cannula to be attached to polyethylene (PE 50) tubing that was in turn connected to a syringe. Each syringe was filled with rat milk substitute formula (Messer diet; University of Iowa). The syringes were mounted on timer-controlled infusion pumps (Harvard Apparatus Syringe, PHD 2000). The pumps were programmed to deliver the formula for 10 min/h (24 h daily). Feeding via cheek cannulae began 1–2 h after the cannulation procedure. On the first day of artificial rearing pups were fed 33% of the mean body weight with the volume increasing by 2% per day up to 51%. Each morning the pups were removed from the cups, weighed, and had their cheek cannulae flushed with 0.1 ml of sterile water. New syringes were filled with fresh diet and the infusion pumps were programmed according to the pups’ new mean weight.

AR pups were randomly assigned to one of two tactile stimulation treatment groups. One group (AR) had their anogenital region stimulated twice per day (morning and evening) for 30–45 s with a warm, wet, pony-hair paintbrush. This was done to induce urination and defecation. Another group (AR + STM) had the same anogenital stimulation regimen as above, but in addition received maternal licking-like tactile stimulation all over the body with a dry pony-hair paintbrush for 2 min, 5 times per day. Thus, there were 3 rearing groups: AR ($n = 35$), AR + STM ($n = 42$), and MR ($n = 43$). Each litter contributed a maximum of 1 subject per group.

Feeding of AR pups via cheek cannulae ended on PND 17. Each pup was transferred from its cup into an individual small opaque cage (L 27 × W 17 × H 13 cm)

lined with woodchip bedding and supplied with a water bottle, regular rat chow, and milk formula mixed with powdered chow (“5012 Rat Diet”, PMI Inc). Daily weighing of AR pups continued until PND 21. All pups were weaned from their respective rearing conditions on PND 21. At this time, 1 male MR pup was selected from each original litter. All pups were weighed, ear notched for identification, and placed into clear cages (L 43 × W 22 × H 21 cm) lined with woodchip bedding and containing plastic enrichment tubes. All rats were housed with a cage mate from the same rearing condition. Rats were weighed weekly until PND 60. Behavioral testing began when rats were between 90 and 160 days old.

2.3. Pavlovian conditioned approach (PCA)

PCA procedures have been described elsewhere [33]. Briefly, a day prior to magazine training rats were given ~20 food pellets (45 mg banana flavored pellets; Bio-Serv) in their home cages. During a single magazine training session 25 pellets were delivered on a random interval (RI) 30 s schedule. All but 2 rats readily ate all the pellets following 1 session of magazine training. The remaining 2 rats ate all of the dispensed pellets during a second magazine training session (same day). No food restriction was used throughout this study. Over 5 subsequent daily sessions, rats were presented with 25 trials of CS-US pairing per day. The CS was an 8 s extension of an illuminated retractable lever presented on a variable interval (VI) 90 s schedule (range 30–150 s). Retraction of the lever was immediately followed by the delivery of the banana flavored sucrose pellet (US) into the food magazine (Paired condition). The delivery of the US was independent of the rat’s response. A subset of rats (AR = 6; AR + STM = 9; MR = 9) experienced the same stimuli, but the relationship between the CS and the US was not paired in time (Unpaired condition). In this condition the CS and US were presented on VI 90 s schedules that were independent of one another. The schedules were also constrained such that the US was never presented during CS presentation or within the 5 s period after CS presentation. All sessions lasted approximately 40 min.

Dependent measures included the total number of lever and magazine contacts during CS presentation, as well as the total number of magazine contacts during the inter-trial intervals (ITIs) when the CS was not available (non-CS magazine entries). As well, latencies to first contact the lever and the magazine during each CS presentation trial were computed. Each final latency measure was the mean of 25 trials in a session, with independent latency measures for lever and magazine contacts. The probabilities of contacting the lever and the magazine were also computed based on the number of CS presentation trials in a session where contact occurred divided by the total number of trials (25) in a session. Again, independent probability measures were computed for lever and magazine contacts.

2.4. PCA Index (Paired condition)

In order to directly compare responses towards the lever with responses towards the magazine a PCA Index was calculated for each rat based on the number, latency, and probability of lever and magazine contacts during CS presentation. Difference scores for the three dependent variables were compiled to obtain a total PCA score for each testing session. The following formula was used to compute this PCA score: $[\text{response bias (lever contacts – magazine contacts)} / (\text{lever contacts} + \text{magazine contacts}) + \text{probability (lever contact probability – magazine contact probability)} + \text{contact latency (lever contact latency – magazine contact latency)}] / (8 \text{ s}) / 3$. Scores were between –1 and +1.

A final PCA Index was obtained by averaging scores from the last two sessions (4 and 5), when the rate of increase in responding began to plateau. Rats with a PCA Index of less than –0.5 were designated as goal-trackers (GT; twice as likely to direct behavior towards the magazine than the CS lever), whereas rats with the PCA index above +0.5 were designated as sign-trackers (ST; twice as likely to direct behavior towards the CS lever than the magazine). Rats with a PCA Index between –0.5 and +0.5 were designated as intermediates (IG).

2.5. Conditional reinforcement

One day after the last PCA session all rats underwent the conditional reinforcement test during which they made instrumental responses (nose pokes) for the presentation of the CS (i.e., the illuminated lever). The food magazine was removed and the illuminated lever was positioned in its place. Two nose poke ports (2 cm diameter; 2 cm above the floor), equipped with photocells, were added, one on each side of the lever. Nose poke responses into one of the ports (Active) resulted in the presentation of the lever CS for 4 s, whereas responses into the other port (Inactive) were inconsequential. This session lasted 40 min and no food pellets were delivered during this time. The difference in the number of nose pokes between Active and Inactive ports and the number of lever contacts were the dependent measures.

2.6. Data analyses

Repeated measures ANOVA was used to assess differences between rearing groups in performance on the PCA test. Following a significant interaction, simple effects were analyzed using one-way ANOVA. One-way ANOVA was also used to compare differences between rearing groups in performance on the conditional reinforcement test. Significant group differences were followed by a Tukey HSD

post-hoc test to compare individual groups. Statistical analyses were conducted using SPSS 17.0 (SPSS Inc., Chicago, IL), with the rejection level set at $p < 0.05$.

3. Results

3.1. PCA Paired condition

In the PCA Paired condition retraction of the illuminated lever (CS) was immediately followed by the delivery of food pellets (US).

3.1.1. Lever directed behaviors

Fig. 1 shows the number, latency, and probability of lever contacts during the CS presentation over 5 PCA training sessions. As shown in Fig. 1A, the number of lever contacts increased significantly over sessions (main effect of session: $F_{(4, 372)} = 50.8$, $p < 0.0001$). There were also significant rearing group differences (main effect of rearing: $F_{(2, 93)} = 5.2$, $p < 0.01$). AR rats made more lever contacts overall than MR rats ($p < 0.01$). AR+STM rats did not differ significantly from the other groups. There was no significant interaction between the effects of rearing and session.

As shown in Fig. 1B, the latency to contact the lever significantly decreased over sessions (main effect of session: $F_{(4, 372)} = 63.1$, $p < 0.0001$). There were also significant rearing group differences (main effect of rearing: $F_{(2, 93)} = 4.6$, $p = 0.05$). AR rats contacted the lever more rapidly than MR rats ($p < 0.05$). AR+STM rats did not differ significantly from the other groups (interaction NS).

As shown in Fig. 1C, the probability of lever contacts significantly increased over sessions (main effect of session: $F_{(4, 372)} = 66.9$, $p < 0.0001$). There were also significant rearing group differences (main effect of rearing: $F_{(2, 93)} = 4.7$, $p < 0.05$). AR rats had a greater probability of contacting the lever than MR rats ($p < 0.05$). AR+STM rats did not differ significantly from the other groups (interaction NS).

3.1.2. Magazine directed behaviors

As shown in Fig. 1D–F, there were significant changes over sessions in the number of magazine contacts during the CS presentations (main effect of session: $F_{(4, 372)} = 5.5$, $p < 0.005$), the latency to contact the magazine following CS onset (main effect of session: $F_{(4, 372)} = 11.0$, $p < 0.0001$), and the probability of magazine contact during CS presentations (main effect of session: $F_{(4, 372)} = 8.5$, $p < 0.0001$). However, there were no significant rearing group differences or interactions in any of these measures. The number of magazine contacts during the ITIs (between CS presentations) significantly decreased over sessions (main effect of session: $F_{(4, 372)} = 145.8$, $p < 0.0001$), but there were no rearing group differences or significant interaction (data not depicted).

3.2. PCA Unpaired condition

In the PCA Unpaired condition the illuminated lever and the food pellets were presented independently of each other. Fig. 2 depicts lever and magazine directed responses of rats in the Unpaired condition. There were no significant differences across sessions or between rearing groups on any lever directed responses and no rearing group by session interactions (Fig. 2A–C).

There were significant changes over sessions in the number of magazine contacts during CS presentation (main effect of session: $F_{(4, 84)} = 6.1$, $p < 0.001$), the latency to contact the magazine following CS onset (main effect of session: $F_{(4, 84)} = 6.3$, $p < 0.001$), and the probability of magazine contact during CS presentations (main effect of session: $F_{(4, 84)} = 6.1$, $p < 0.001$). There were also significant rearing group \times session interactions for measures of latency ($F_{(8, 84)} = 2.8$, $p < 0.01$) and probability ($F_{(8, 84)} = 2.8$, $p < 0.005$). AR rats had significantly lower latencies to contact the magazine than AR+STM and MR rats during session 5 ($p < 0.05$; Fig. 2E). AR rats

also had a significantly lower probability of magazine contact than the other two rearing groups during session 1 ($p < 0.05$) and a significantly higher probability of magazine contact than MR rats during session 5 ($p < 0.05$; Fig. 2F).

The number of magazine contacts during the ITI decreased significantly over sessions (main effect of session: $F_{(4, 356)} = 9.9$, $p < 0.0001$), but there were no significant differences between rearing groups or significant interactions (data not depicted).

3.3. PCA Index (Paired condition)

As shown in Fig. 3A, the PCA scores increased significantly over sessions (main effect of session: $F_{(4, 372)} = 34.9$, $p < 0.0001$). That is, overall there was an increase in attraction to the lever CS in comparison to the magazine. The overall difference in the PCA scores between rearing groups approached significance (main effect of rearing: $F_{(2, 93)} = 3.0$, $p = 0.057$; interaction NS).

As shown in Fig. 3B, there was a significant difference between rearing groups in the final PCA Index, computed as the mean of PCA scores from sessions 4 and 5 (main effect of rearing: $F_{(2, 93)} = 3.6$, $p < 0.05$). The Index of AR rats was significantly greater than the Index of MR rats ($p < 0.05$). AR+STM rats did not differ significantly from the other groups (interaction NS).

Fig. 4 illustrates the distribution of rats from each rearing group over the entire range of the PCA Index and the percentage of rats from each group displaying sign-tracking, goal-tracking, and intermediate phenotypes. Chi Square analyses were performed to compare the frequency distribution of the phenotypes in each AR group with that of the control MR group. The distribution of the phenotypes differed significantly between AR and MR rats ($\chi^2_{(2, N=63)} = 6.3$, $p < 0.05$). AR+STM and MR rats did not differ.

3.4. Conditional reinforcement

In the conditional reinforcement test rats were reinforced with the presentation of the lever when they poked their nose into the Active port, but not into the Inactive port. Fig. 5A shows the mean difference in nose pokes into the Active minus the Inactive port (conditional reinforcement score). For rats in the Paired condition, rearing groups differed significantly in the conditional reinforcement score (main effect of rearing: $F_{(2, 93)} = 4.3$, $p < 0.05$). MR rats had significantly lower conditional reinforcement scores compared to AR rats ($p < 0.05$). AR+STM rats did not differ significantly from the other groups. For rats in the Unpaired condition, there were no significant differences between rearing groups in the conditional reinforcement score.

Fig. 5B show the number of lever contacts during the conditional reinforcement test. Only rearing groups in the Paired condition significantly differed in the number of lever contacts (main effect of rearing: $F_{(2, 93)} = 6.2$, $p < 0.005$). MR rats made significantly fewer lever contacts compared to both AR rats ($p < 0.01$) and AR+STM rats ($p < 0.05$).

4. Discussion

Early social isolation of rats increased the incentive motivational value (incentive salience) attributed to a food cue in adulthood, as indicated by two measures. (1) The food cue was more attractive to AR rats, in that they approached and engaged it more avidly than MR rats. (2) The food cue was a more effective conditional reinforcer in AR rats. Thus, early-life social experience in rats affects the extent to which reward-related cues acquire incentive motivational properties in adulthood.

The behavior of AR rats in this study is not explained by spontaneous attraction to a neutral stimulus or a general (non-specific) enhancement of approach behavior. AR rats made more contacts

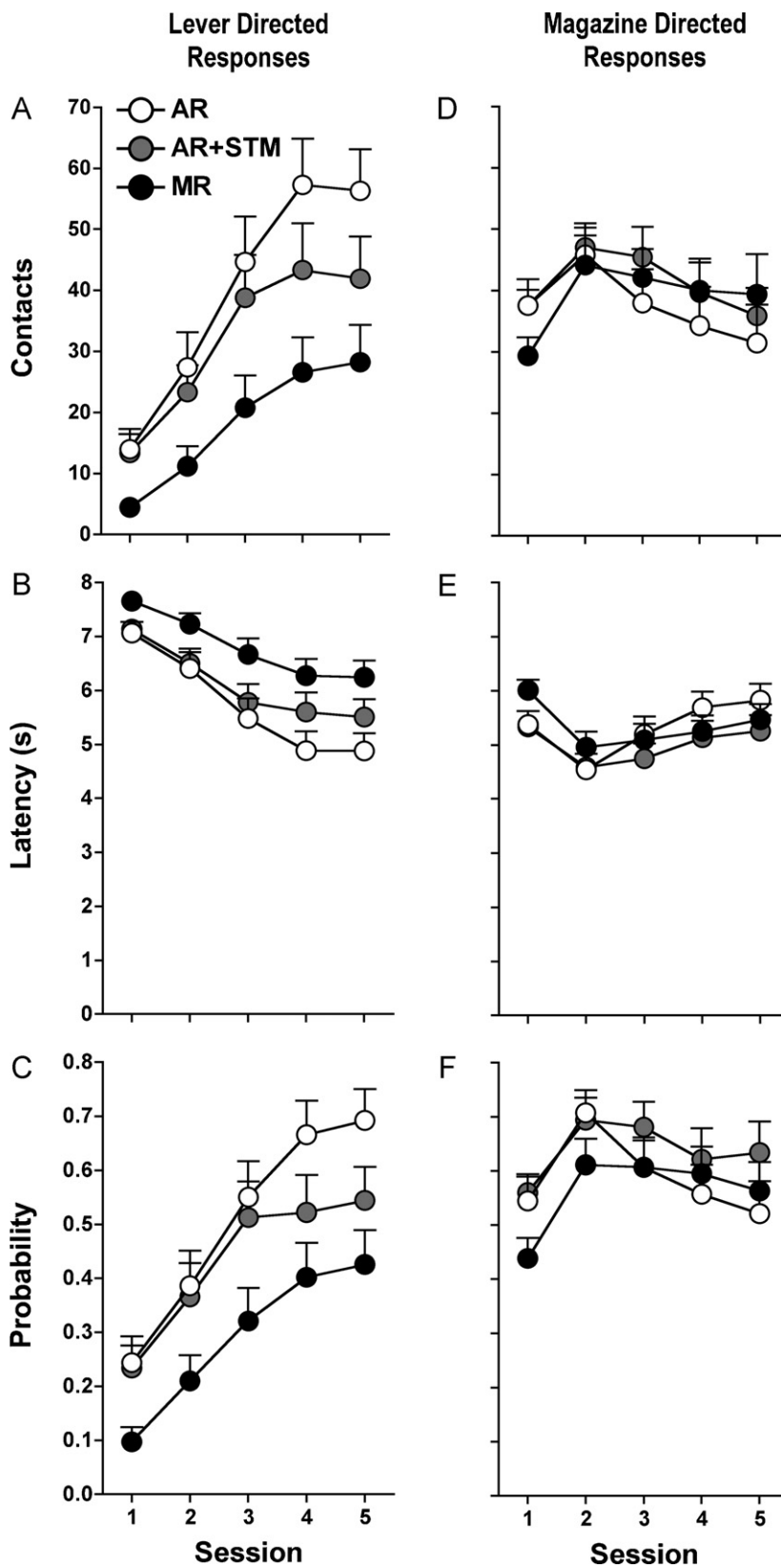


Fig. 1. Pavlovian conditioned approach (PCA) responses directed towards the lever (A–C) and the magazine (D–F) during CS presentation. The CS was paired with US delivery (Paired condition). Overall, AR ($n = 29$) rats made significantly more lever contacts and contacted the lever with a higher probability and lower latency than MR ($n = 34$) rats ($p < 0.05$). AR + STM ($n = 33$) rats did not differ significantly from the other groups. There were no significant group differences in magazine directed responses. Data represent means \pm SEM.

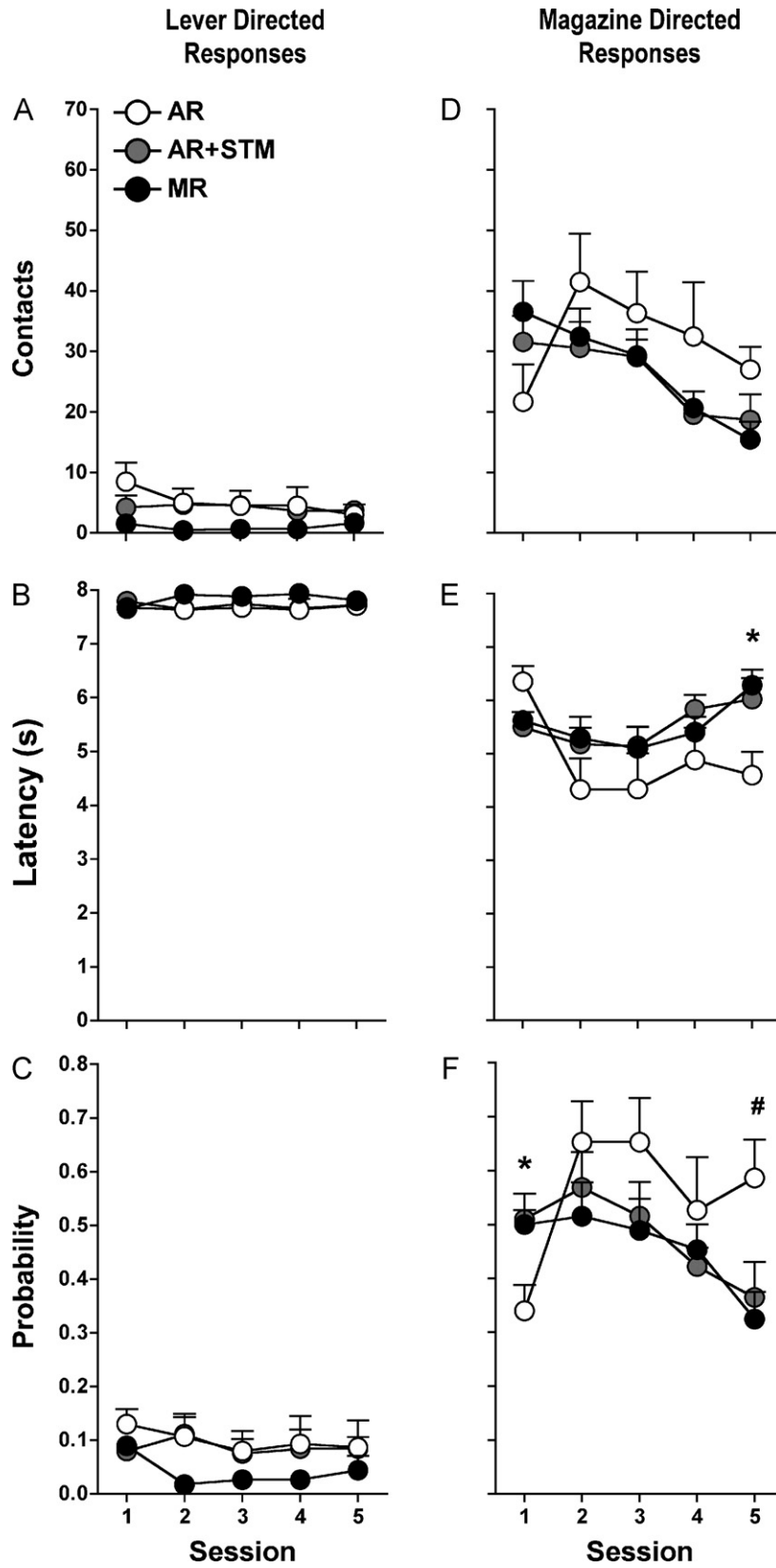


Fig. 2. Pavlovian conditioned approach (PCA) responses directed towards the lever (A–C) and the magazine (D–F) during CS presentation. The CS and US were delivered independently of one another (Unpaired condition). Unlike the Paired condition (Fig. 1), there were no significant differences between rearing groups on any lever directed responses. Groups differed in magazine directed responses during sessions 1 and 5. (*) AR ($n=6$) significantly different than AR+STM ($n=9$) and MR ($n=9$), $p < 0.05$. (#) AR significantly different than MR, $p < 0.05$. Data represent means \pm SEM.

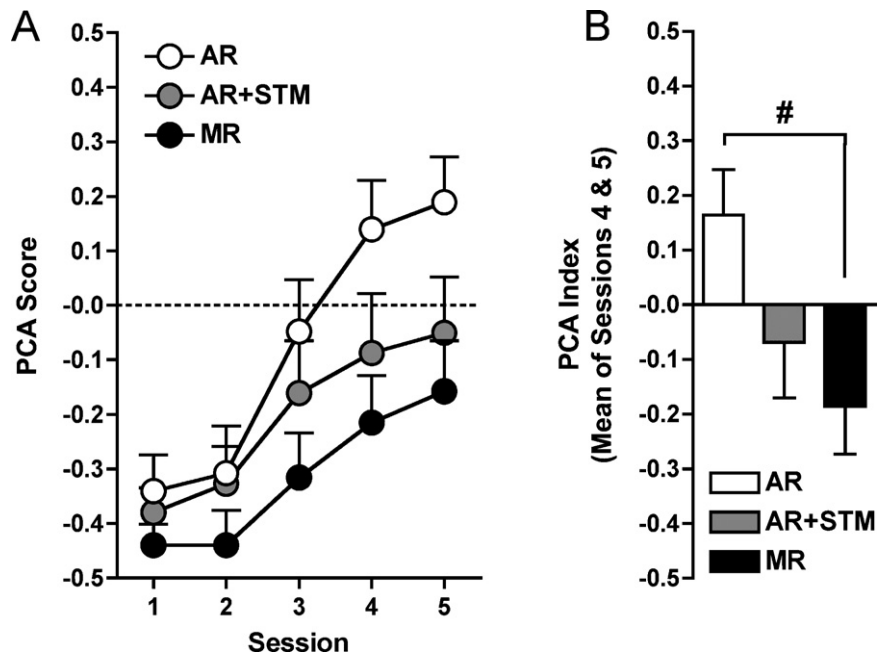


Fig. 3. Comparison of lever versus magazine directed responses of rats in the Paired condition. (A) The differences in the number, latency, and probability of lever and magazine contacts during CS presentation were used to compute a Pavlovian conditioned approach (PCA) score for each session. The PCA score increased significantly over 5 conditioning session ($p < 0.001$), indicating that rats responded more towards the lever than the magazine as conditioning progressed. (B) The final PCA Index was based on the mean of PCA scores from the last two sessions. The PCA Index was positive for AR rats ($n = 29$) and negative for MR rats ($n = 34$), indicating that by the end of conditioning AR rats made more lever directed than magazine directed responses, and vice versa for MR rats. There was a significant difference in the PCA Index between AR and MR rats ($\#p < 0.05$). AR+STM rats ($n = 33$) did not differ significantly from the other groups. Data represent means \pm SEM.

with the lever and contacted it with higher probability and shorter latency compared to MR rats. When the same lever was presented independently of food delivery (Unpaired condition), both AR and MR rats displayed minimal lever-directed responses. This indicates that rats were not attracted to the lever unless it was paired with food. Thus, the difference in lever attraction between rearing groups was dependent on the lever–food relationship. Furthermore, differences between rearing groups in PCA were only observed for lever-directed and not magazine-directed responses.

This indicates that AR rats showed enhanced responding towards the lever only and did not show a general enhancement in PCA responses towards both the lever and the magazine.

In addition to exhibiting more lever-directed responses, AR rats were also more likely to exhibit a sign-tracking phenotype and less likely to exhibit a goal-tracking phenotype in comparison to MR rats. Rats identified as sign-trackers primarily exhibited lever-directed PCA responses, with minimal magazine-directed PCA responses, and vice versa for rats identified as goal-trackers

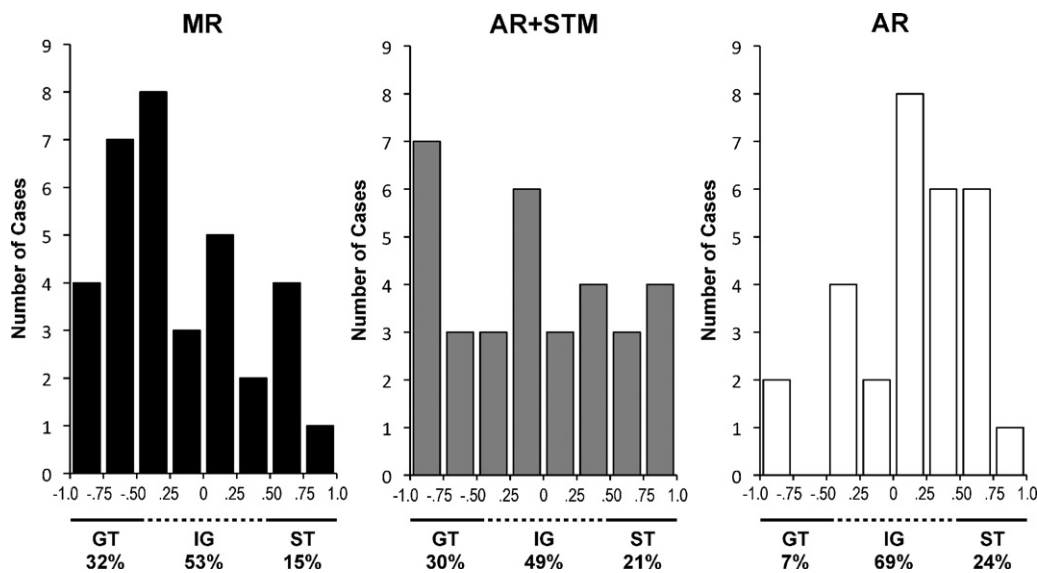


Fig. 4. The frequency distribution of rats according to their Pavlovian conditioned approach (PCA) Index. Rats with a PCA Index of less than -0.5 were designated as goal-trackers (GT; twice as likely to direct behavior towards the magazine than the CS lever), whereas rats with the PCA index above $+0.5$ were designated as sign-trackers (ST; twice as likely to direct behavior towards the CS lever than the magazine). Rats with a PCA Index between -0.5 and $+0.5$ were designated as the intermediate group (IG). The percentage of rats in each rearing group that exhibited the ST, GT, and IG phenotypes is displayed below the graphs. The within-group distribution of these phenotypes differed significantly between the AR ($n = 29$) and MR ($n = 34$) groups ($p < 0.05$), but not between the AR+STM ($n = 33$) and MR groups.

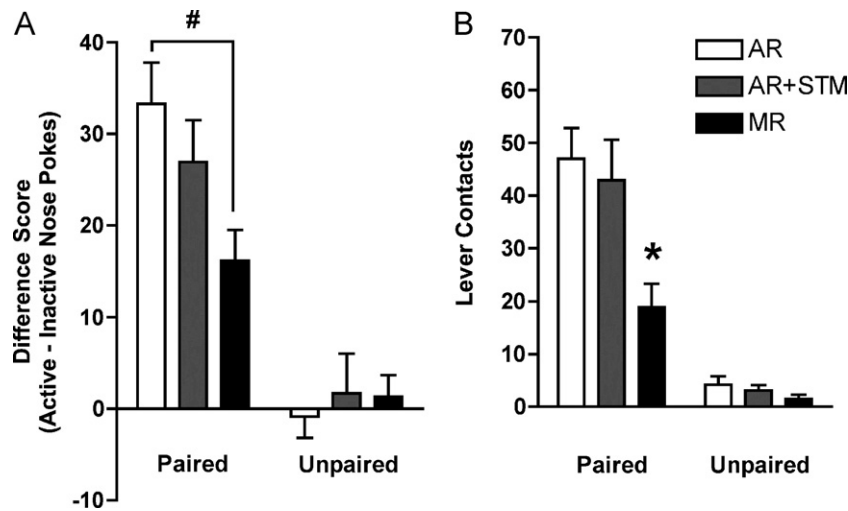


Fig. 5. Performance on the conditional reinforcement test. Data represent (A) the mean (\pm SEM) difference in nose pokes into the Active minus the Inactive port and (B) the mean (\pm SEM) number of lever contacts. Significant differences between rearing groups in both measures were observed in the Paired condition. (#) MR ($n = 34$) significantly lower than AR ($n = 29$), $p < 0.05$. (*) MR significantly lower than AR and AR + STM ($n = 33$), $p < 0.05$. Unpaired groups: AR, $n = 6$; AR + STM, $n = 9$; MR, $n = 9$.

[13]. This pattern of results indicates that the overall difference in lever-directed responses between rearing groups reflects the influence of two, albeit related, factors: more lever-directed responses in the AR group as a whole, and a shift in the proportion of rats that primarily expressed the sign-tracking versus the goal-tracking phenotypes in the AR group compared to the MR group.

Expression of conditioned approach responses requires the functional integrity of several structures spanning the mesocorticolimbic dopamine (DA) system, including the nucleus accumbens, amygdala, and prefrontal and cingulate cortex [34–39]. Sign-tracking rats differ from goal-tracking rats in DA receptor and synthetic enzyme mRNA expression [33,40]. Sign-tracking rats also have higher tissue levels of DA and 3,4-dihydroxyphenylacetic acid (DOPAC) in the nucleus accumbens and lower levels of DOPAC/DA turnover in the caudate putamen [40]. Recent evidence suggest that DA is not important for learning about the predictive nature of the cue, but is important for attribution of incentive salience to the cue. Blocking DA functioning prevents the acquisition and expression of sign-tracking, but not goal-tracking [41]. The differences in cue-directed responses observed between AR and MR rats may therefore be mediated by developmental alterations of the DA system.

There is direct and indirect evidence that AR rats, compared to MR rats, have alterations in DA functioning. AR rats are more sensitive to locomotor inducing effects of amphetamine [19,20]. In a series of microdialysis studies, AR rats showed higher basal NAcc DA levels and altered DA responses towards the presentation of naturally rewarding stimuli [42,43]. These findings are concordant with other studies examining the effects of early-life isolation on DA levels [44,45]. Another physiological correlate of sign-tracking behavior is an increase in the level of plasma corticosterone [7,40]. Early experience of intermittent social isolation has been shown to enhance the corticosterone response to restraint stress in later life [46]. Therefore, it is possible that increased expression of sign-tracking behavior in AR rats may be related to changes in hypothalamic–pituitary–adrenal axis responsiveness.

In this study the cue-directed responses of AR + STM rats were intermediate to those of AR and MR control rats. Previous studies show that some of the effects of AR can be partially reversed by administering replacement maternal licking-like tactile stimulation during the time of rearing [19,29]. Tactile stimulation is an important regulator of rat pup physiology [47,48] and is known

to promote healthy growth and development in human infants [47,49]. The current findings indicate that licking-like tactile stimulation received during early development in rats contributes to the expression of goal-directed responses. The amount of licking and grooming rat pups receive from the mother is also negatively correlated with the propensity to self-administer cocaine and alcohol in adulthood [50]. This effect may be mediated by differences in attraction to drug-related cues that trigger subsequent self-administration behavior [15]. In humans, reward-related cues can act as powerful incentives that instigate cravings and drug-seeking behavior in addicts and can lead to relapse in recovering addicts [51–53]. Therefore, the present results contribute to our understanding of how certain components of early social experience may influence vulnerability to the development of disorders of behavioral inhibition such as addiction. This may provide an important perspective for future research into the treatment and prevention of these disorders.

The results could also enhance our understanding of the cognitive effects of early social deprivation. Sign-tracking is distinctive because it demands attention and effort that is not reinforced. Sign-tracking may actually interfere with reinforcement. In certain circumstances it persists even when the consequence is missing the reinforcement [7,54,55]. Considering an example in humans and monkeys, inadequate early social experience may often be associated with unusual attachment behavior [26,56]. In children “indiscriminant friendliness” or “disinhibited social behavior” is an example [56,57]. It involves approaching and interacting in a familiar way (physical contact, hugging) with total strangers (seeking adult cues). In monkeys, it involves persistent attachment behavior directed at inanimate soft objects (seeking contact comfort cues). Neither of these behaviors leads to acquisition of parental care or food (US) – goals that are required for survival. Sign- versus goal-tracking could be an underlying mechanism. Beyond this, co-occurring problems caused by deprivation, and somewhat analogous across species, are persistent difficulties with attention and impulse control, over-activity, deficits in inhibitory control, problems with parent and peer relationships, and oppositional behavior [25,57–60]. Therefore, understanding the neural mechanisms of associative conditioning by which inadequate early social experience promotes or permits increases in sign- versus goal-tracking may have substantial implications for our understanding of the psychobiological basis of some developmental disorders.

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