

Early-Life Maternal Separation and Social Isolation Produce an Increase in Impulsive Action but Not Impulsive Choice

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Early life environment, events, and context, such as mother–offspring relationship, can have profound effects on future behavior and physiology. We investigated the effects of long-term maternal and social separation, through artificial rearing, on adult impulsivity. Rats were maternally reared (MR) or artificially reared (AR) and half of the AR rats were provided with replacement somatosensory stimulation intended to simulate maternal licking. There are at least 2 forms of impulsivity and we compared rats on 1 test of impulsive action (differential reinforcement of low rates of responding—DRL-20s) and 2 tests of impulsive choice (delay discounting and fixed consecutive number schedule—FCN). We found that AR rats are more action impulsive; however, this effect can be reduced by maternal licking-like stimulation. In contrast, AR rats did not display an increase in impulsive choice. Overall, these experiments show that early life maternal and social separation have different effects on the 2 forms of impulsivity.

Keywords: development, impulsivity, isolation, maternal, social

Mammalian brain and behavior are plastic as both can be altered by experience. This plasticity is particularly evident during early stages of development when young mammals are usually in the care of their parent(s) (Cirulli, Berry, & Alleva, 2003; Hofer, 1994; Kaffman & Meaney, 2007; Pryce & Feldon, 2003). Our objective was to assess how early life experiences, in the form of maternal and social separation, influence adult impulsivity. In rats, several “separation” paradigms have been developed to assess the importance of the mother, litter, and nest environment to biobehavioral development (Hall, 1998; Kaffman & Meaney, 2007; Pryce & Feldon, 2003). We recently adopted an artificial rearing paradigm as a method of studying the impact of early life factors on several adult behaviors and neurophysiological outcomes. Artificial rearing involves complete separation of rat pups from their mother, siblings, and the nest so that after the first 2 postnatal days (PND) of life, pups are reared alone and without the usual forms of

stimulation provided by the mother in the nest context (Gonzalez, Lovic, Ward, Wainwright, & Fleming, 2001).

Compared to maternally reared (MR) rats, artificially reared (AR) rats show deficits in adult maternal (Gonzalez et al., 2001; Lovic & Fleming, 2004; Lovic, Palombo, & Fleming, 2011) and sexual behavior (Akbari, Budin, Parada, & Fleming, 2008) and also display deficits in social memory (Lévy, Melo, Galef, Madden, & Fleming, 2003; Melo et al., 2006). When examined on social behavior and attentional set shifting AR rats, compared to MR rats, tend to be more active (Burton, Lovic, & Fleming, 2006; Lovic, Fleming, & Fletcher, 2006) and show less inhibition (Lovic & Fleming, 2004). For example, during the assessment of social learning, AR rats frequently failed to inhibit responses toward normally “neutral” minor environmental stimuli, often at the expense of attending to a social conspecific. In a similar manner in the attentional set shifting task, AR rats tended to respond more rapidly when making choices and frequently failed to inhibit responses toward the first (sometimes incorrect) stimulus (Lovic & Fleming, 2004). Some of these effects can be partially or completely reversed by providing AR pups with maternal licking-like stimulation. These observations led us to hypothesize that AR rats are more impulsive than MR rats.

Impulsivity is characterized by rapid decision making, premature actions, and reduced tolerance of delay of gratification (Dalley, Everitt, & Robbins, 2011). Impulsivity has recently received much attention in the context of several disorders such as drug addiction (Belin, Mar, Dalley, Robbins, & Everitt, 2008; de Wit, 2009; Jentch & Taylor, 1999; Olmstead, 2006; Perry & Carroll, 2008). Although progress has been made on elucidating the neural mechanisms of impulsivity (see Dalley et al., 2011; Pattij & Vanderschuren, 2008), virtually nothing is

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known about how early life social and environmental factors influence adult impulsivity.

Impulsivity is not a unitary "trait" as there is at least two behaviorally, neuroanatomically, and pharmacologically dissociable forms of impulsivity: impulsive action and impulsive choice (Dalley et al., 2011; Dellu Hagedorn, 2006; de Wit, 2009; Evenden, 1999; Winstanley, Dalley, Theobald, & Robbins, 2004). Our aim was to assess the effects of early life maternal and social separation, through artificial rearing, on these two different forms of impulsivity. Based on observations from our previous studies, we hypothesized that AR rats would be more impulsive than MR rats and that maternal licking-like stimulation, provided to some AR pups, would reverse the effects associated with artificial rearing.

Experiment 1: The Effects of Artificial Rearing on Impulsive Action (DRL-20s)

Impulsive action refers to situations in which an individual fails to inhibit responses. The individual does not have to make a choice between different contingencies; rather, the correct response has to be withheld until the timing is correct as acting prematurely will not be rewarded (Dalley et al., 2011; Olmstead, 2006). Differential reinforcement of low rates of responding (DRL) is one of several operant schedules of reinforcement that can be used to measure impulsive action (Dalley et al., 2011). On a DRL schedule, rats are rewarded for making operant responses after a specific (minimum) length of time has elapsed (e.g., 20 s). Premature responses reset "waiting times" and do not produce any reward (Fletcher, 1995; Peterson, Wolf, & White, 2003). The first experiment examined the ability of AR rats to acquire responding on a DRL-20s schedule. If AR rats are more impulsive they should have lower efficiency ratios (responses:reinforcers) and show reduced interresponse times.

Method

Subjects. Twenty-nine male (AR-MIN, $n = 7$; AR-MAX, $n = 8$; MR, $n = 14$) and 31 female (AR-MIN, $n = 7$; AR-MAX, $n = 8$; MR, $n = 16$) Sprague-Dawley rats (derived from eight litters) were used in this experiment. All rats were born at University of Toronto Mississauga animal vivarium. Rats at this facility were originally obtained from Charles River Farms (St Constant, Quebec, Canada). At the time of weaning, rats were same-sex pair-housed in medium-size Plexiglas cages (W 26 × L 38 × H 21 cm), lined with woodchips and ad lib access to rat Purina Chow food (unless otherwise specified) and water. The room temperature and humidity were maintained at 22 °C and 40 to 50%, respectively. Lights were off 2000 to 0800. All of the experiments reported here were approved by the Local Animal Care Committee (University of Toronto Mississauga).

Apparatus. Testing was carried out in 12 modular operant conditioning chambers (28 × 21 × 21 cm; Med Associates, St. Albans, VT), housed inside sound attenuated cubicles, and outfitted with a lever (4.5 cm long; 6 cm above the grid floor), a food pellet dispenser, food magazine, and a white house light located on

the wall opposite the dispenser. The apparatus was controlled by Med Associates software and a Dell computer.

Procedures.

Artificial rearing.

Groups and treatments. Dams gave birth, and on the day of parturition (PND 0) litters were culled to 7 to 8 males and 7 to 8 females. On PND 2, six pups (three males and three females) were removed from the nest and two pups of each sex were implanted with a cheek cannula and raised artificially (AR groups). The other two pups (one male and one female) were sham-operated (MR-SHAM group) and returned to their mother. In addition, one male and one female sibling were designated as controls (MR-CON group). Siblings that received cheek cannula implants were randomly assigned to one of two conditions: (1) artificially reared with minimal maternal licking-like stimulation (AR-MIN group) and (2) artificially reared with "maximal" maternal licking-like stimulation (AR-MAX group; see below). Therefore, four groups of rats for both sexes were tested: AR-MIN, AR-MAX, MR-SHAM, and MR-CON. MR-SHAM and MR-CON rats were not statistically different from one another and were combined into one group—mother reared (MR; see Statistical Analyses section below).

Cheek cannula implants and artificial rearing. Following local anesthesia (Lidocaine) cheek cannula were implanted. The implantation of cheek cannula lasted less than 1 min. MR-SHAM rats were treated in an identical fashion to AR rats, except that cannula were not implanted and pups were returned to their nests. Following implantation of the cannula, each pup was housed individually in a plastic cup (11 cm in diameter × 15 cm deep), which fitted into a second, weighted cup. Both cups floated in a temperature controlled water aquarium (~ 36 °C). The housing cups contained corn-cob bedding (1/4"; Bed O'Cobs, The Andersons, Maumee, Ohio) and cups' tops remained open to allow cheek cannula tubing to emerge and connect to nearby syringes containing milk formula (Messer diet; see Gonzalez et al., 2001). The infusion of milk formula was executed by timer-controlled infusion pumps (Harvard Apparatus Syringe, PHD 2000, Harvard Apparatus Canada, St. Laurent, Quebec, Canada). The pumps were programmed to infuse the diet for 10 min every hour, 24 hr daily. The amount of milk formula the pumps delivered was based on a specific fraction of pups' mean weight. Pups were initially given formula in a volume equal to 33% of their body weight and this volume was increased by 1% each day.

Every morning the pups were disconnected from the pumps, removed from the cups, weighed and had their tubing flushed with 0.1 ml of distilled water. New syringes, containing fresh formula, were set up and the pump's infusion rate was reprogrammed according to the pups' mean body weight. AR-MIN rats were stimulated twice a day (30 s each; morning and evening) with a warm, wet, camel-hair paintbrush, to stimulate urination and defecation. Only the pups' anogenital region was stimulated. AR-MAX rats were stimulated eight times a day (2 min of body stimulation) in addition to two regular anogenital stimulations (30 s each). Stimulations were carried out from the first day of artificial rearing to PND 16. On PND 18/19 AR rats were removed from their cups, placed in mouse cages (22 cm × 15 cm × 10 cm; on top of heating pads) and provided with milk formula, regular rat chow, and the mixture of formula and chow. They were kept in these cages until weaning. On PND 21, AR rats were pair-housed

with nonexperimental, mother-reared social partners with whom they remained for the remainder of the experiment. Experimental MR rats were weaned from their mother and paired together (MR-SHAMs and MR-CONs). Rats were left undisturbed until adulthood (PND 60+).

DRL schedule. Adult rats (PND 90+) were gradually reduced to 85 to 90% of their free-feeding weight and subsequently trained to make lever responses for food (45 mg food pellets; Bio-Serv, Frenchtown, New Jersey) on a fixed ratio (FR)-1 schedule (30-min sessions) over a 7-day period. All rats had three or four successful FR-1 schedule sessions (100 lever responses in 30 min) prior to being switched to a DRL-20s schedule. On the DRL-20s schedule (30-min sessions), rats were reinforced if at least 20 s had elapsed since their previous response. Premature responses reset the “waiting period” and were not rewarded. Testing was carried out over 18 days. Sessions began with the illumination of the house light and insertion of the lever into the chamber. The first response was always reinforced. For each session the following measures were collected: (a) number of responses, (b) number of reinforcers earned, (c) percent efficiency ([number of reinforcers earned/number of responses made] $\times$ 100), and (d) mean interresponse time.

Data analyses. MR-SHAM and MR-CON groups were not statistically different from each other on any measures of interest. Thus, these groups were combined into one mother-reared (MR) group. However, to not inflate statistical power, data from MR-CON and MR-SHAM rats (siblings within a litter) were averaged and used as a single data point. Data for each of the four measures of interest were averaged across 3 days (six blocks of 3 days each) and analyzed using repeated-measures analysis of variance (ANOVA; Group $\times$ Sex $\times$ Block). Scheffé post hoc tests were used to assess group differences. Significant interactions were followed by one-way ANOVAs assessing group differences for specific blocks/bins. The level for achieving statistical significance was $p < .05$. All analyses for this and the subsequent experiments were done using SPSS 18.0.

Results

Number of responses. There were marginal overall group differences, $F(2, 42) = 2.8, p = .07$. As can be seen in Figure 1(a, b), rats showed a reduction in the number of responses over successive test blocks, $F(5, 210) = 177.2, p < .001$. In addition, female rats made fewer responses than male rats (151.6 vs. 174.9/block), $F(1, 42) = 5.36, p < .05$. There were no significant interactions.

Number of reinforcers earned. As can be seen in Figure 1(c, d) there were significant group differences, $F(2, 42) = 3.5, p < .05$, and post hoc analyses indicated that AR-MIN rats earned fewer reinforcers than MR rats ($p < .05$). AR-MAX rats were not significantly different from either of the two groups. Rats earned more pellets over successive blocks, $F(5, 210) = 87.1, p < .001$, and female rats earned more reinforcers than male rats (32.5 vs. 26.5/block), $F(1, 53) = 6.6, p < .05$. There were no significant interactions.

Efficiency. As shown in Figure 2(a, b) there were significant overall group differences in efficiency, $F(2, 42) = 4.4, p < .05$. Post hoc analyses revealed that AR-MIN rats were significantly less efficient than MR rats ($p < .05$). AR-MAX rats were not

Differential Reinforcement of Low Rates of Responding (DRL-20s)

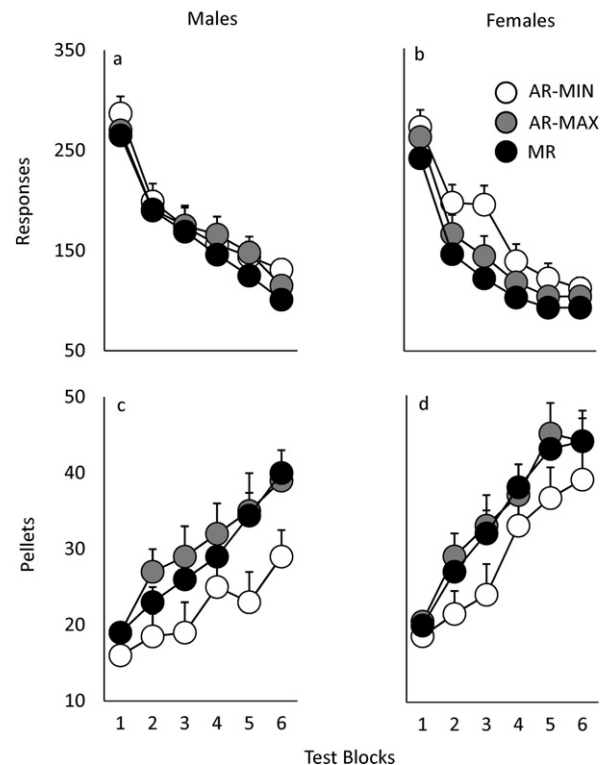


Figure 1. The figure depicts mean (+ SEM) number of responses for (a) male and (b) female rats. Female rats made fewer responses than male counterparts ($p < .05$). Lower panels depict the mean (+ SEM) number of reinforcers earned by (c) male and (d) female rats. Female rats earned more reinforcers than male rats and AR-MIN rats earned fewer reinforcers than MR rats ($ps < .05$). DRL-20s = differential reinforcement of low rates of responding–20 s; AR-MIN = artificially reared with minimal maternal licking-like stimulation; AR-MAX = artificially reared with maximal maternal licking-like stimulation; MR = maternally reared.

significantly different from either one of the groups. Moreover, efficiency increased across successive blocks of testing, $F(10, 210) = 113.96, p < .001$, and there were marginal sex differences, $F(1, 45) = 3.55, p = .067$. There was a significant Block $\times$ Group interaction, $F(10, 210) = 2.21, p < .05$, and this interaction was followed by one-way ANOVAs and post hoc tests assessing group differences during individual blocks. Compared to MR rats, AR-MIN rats were less efficient at earning pellets during Blocks 2, 3, 5, and 6 ($ps < .05$). AR-MAX rats were not significantly different from either one of the groups.

mIRTs. Mean interresponse times (mIRTs) significantly differed between groups, $F(2, 42) = 3.99, p < .05$, and post hoc analyses indicated that AR-MIN rats had significantly shorter mIRTs than MR rats ($p < .05$). AR-MAX rats were not significantly different from either one of the groups. There was a main effect of block and a significant Group $\times$ Block interaction, $F(10, 210) = 2.2, p < .05$. One-way ANOVAs and post hoc tests revealed that, compared to MR rats, AR-MIN rats had significantly shorter mIRTs during Blocks 2, 5, and 6 ($ps < .05$). AR-MAX rats were not significantly different from either one of the groups.

Differential Reinforcement of Low Rates of Responding (DRL-20s)

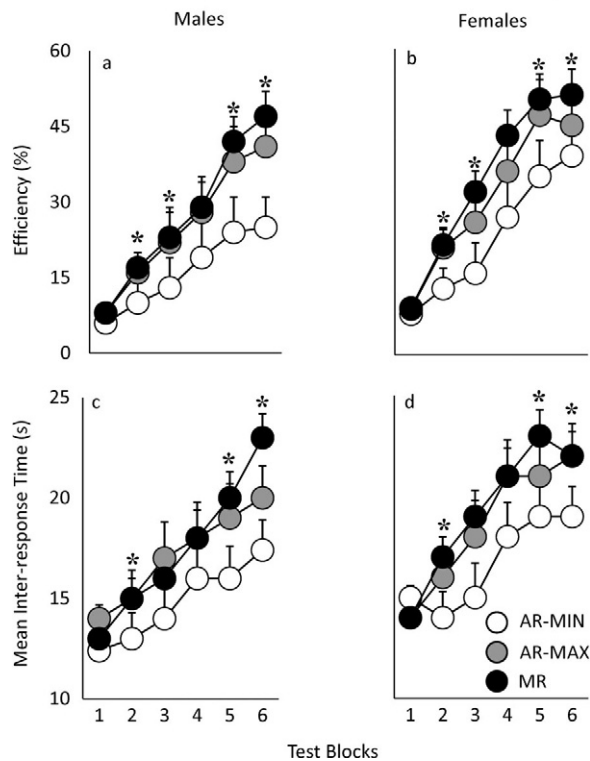


Figure 2. Mean (+ SEM) percent efficiency for (a) male and (b) female rats. AR-MIN rats had lower efficiency levels than the MR rats. *AR-MIN rats were less efficient than MR rats during Blocks 2, 3, 5, and 6 ($ps < .05$). Lower panels depict mean interresponse times (mIRTs; + SEM) for (c) male and (d) female rats. *AR-MIN rats had shorter mIRTs than MR rats during Blocks 2, 5, and 6 ($ps < .05$). DRL-20s = differential reinforcement of low rates of responding–20 s; AR-MIN = artificially reared with minimal maternal licking-like stimulation; AR-MAX = artificially reared with maximal maternal licking-like stimulation; MR = maternally reared.

Distribution of responses across time bins. Responses changed across 2-s bins, $F(19, 798) = 2.41, p < .001$, and there were significant group differences, $F(2, 42) = 3.64, p < .05$. In addition, there was a significant Group $\times$ Bin interaction, $F(38, 798) = 2.41, p < .01$, and a Sex $\times$ Bin interaction, $F(19, 798) = 3.48, p < .01$. These significant interactions were followed up by one-way ANOVAs assessing group differences during individual bins. Analyses indicated that AR-MIN rats made more responses during Bins 4 through 8 ($ps < .05$). AR-MAX rats were not significantly different from either one of the groups during these bins. As depicted in Figure 3, AR-MIN rats showed both a leftward and upward shift in distribution of their responses. In other words they made more responses and these responses were made during early bins (i.e., prior to the expiration of the waiting period).

Brief Discussion

We asked whether variation in the early life environment, namely maternal and artificial rearing, would produce changes in

adult impulsive action. We found that AR-MIN rats are more action impulsive on the DRL-20s schedule as exemplified by lower efficiency ratios, shorter mIRTs, and greater number of responses during the waiting period (Bins 4 to 8).

AR-MIN rats made more responses during Bins 4 to 8, well before the 20-s waiting period elapsed. This pattern of results suggests that AR-MIN rats are more behaviorally disinhibited (i.e., they make more responses) and that they have altered subjective perception of time (i.e., their peak responding is shifted to the left). Providing AR rats with maternal licking-like stimulation reduced these effects as AR-MAX rats were not significantly different from MR rats. These findings are further discussed in the General Discussion (see below).

Experiment 2: The Effects of Artificial Rearing on Impulsive Choice (Delay Discounting)

Impulsive choice refers to situations in which an organism is faced with action choices, each leading to distinct outcomes (Dalley et al., 2011). In the delay discounting choice procedure an individual is presented with a choice between a smaller immediate reward and a larger delayed reward. A larger reward is preferred

Differential Reinforcement of Low Rates of Responding (DRL-20s)

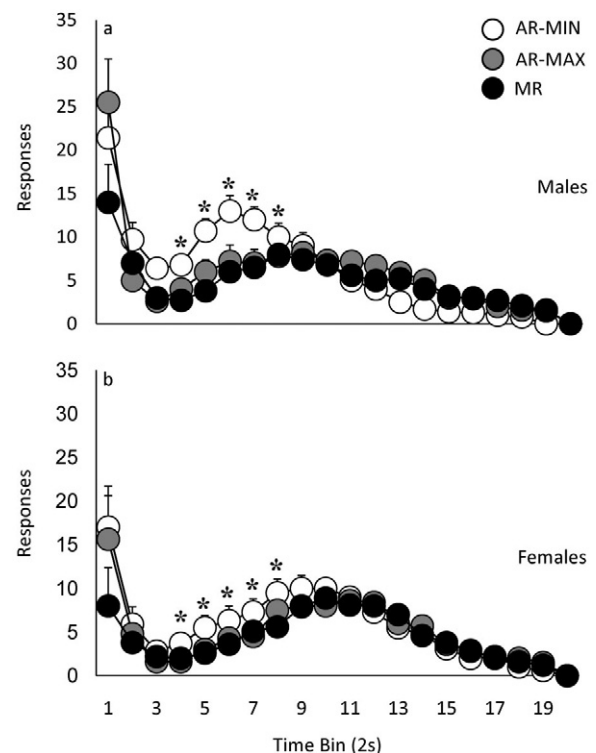


Figure 3. Depiction of mean (+ SEM) number of lever responses across 20 (2 s) bins during sixth block of testing for (a) male and (b) female rats. *AR-MIN rats, compared to MR rats, made more responses during Bins 4 to 8 ($ps < .05$). DRL-20s = differential reinforcement of low rates of responding–20 s; AR-MIN = artificially reared with minimal maternal licking-like stimulation; AR-MAX = artificially reared with maximal maternal licking-like stimulation; MR = maternally reared.

when the delay to its delivery is equal to that of the smaller reward. However, as the delay to the delivery of the larger reward increases, individuals tend to shift their preference toward the smaller immediate reward, and impulsive individuals make this shift more rapidly (Cardinal, 2006; Ho, Mobini, Chiang, Bradshaw, & Szabadi, 1999; Reynolds, de Wit, & Richards, 2002). This experiment examined whether AR rats differed from MR rats on a test on impulsive choice.

Method

Subjects. Twenty-six male (AR-MIN, $n = 7$; AR-MAX, $n = 7$; MR, $n = 12$) and 28 female (AR-MIN, $n = 7$; AR-MAX, $n = 8$; MR, $n = 13$) Sprague-Dawley rats (derived from eight litters) were used. Rats were assigned to the same conditions as in the previous experiment.

Apparatus. Operant conditioning chambers were the same as in the previous experiment except that the magazine was flanked by two retractable levers.

Procedures.

Delay discounting. Testing was carried out over 61 test days and divided into distinct stages.

Fixed ratio training. Adult rats were gradually reduced to 85 to 90% of their free-feeding weight and trained to press the left and right lever (alternate days) for food (45 mg food pellets; Bio-Serv, Frenchtown, New Jersey) on a FR-1 schedule for 7 consecutive days. Each session lasted 30 min or until rats made 100 lever responses. Rats were considered trained if they made 100 lever presses on 2 consecutive days (1 day each on the left and right lever).

Choice training—No delays to larger reward. Testing, based on procedures used by others (e.g., Cardinal et al., 2001), was done across five blocks of 12 trials each—composed of two forced and 10 choice trials. Sessions started in the dark and rats had to nose poke in the food magazine to trigger the illumination of the house light and presentation of one (forced trials; first two trials within a block; see below) or both levers (10 choice trials within the block). When both levers were extended, rats had a response choice. Responding resulted in the retraction of both levers and a delivery of either one or four pellets, depending on lever choice. Each subsequent trial was signaled by the illumination of the house light and rats had 10 s to nose poke in the magazine to initiate the presentation of one or both levers (forced and choice trials, respectively). Each trial was 100 s long and the entire session lasted 100 min. The purpose of this phase of testing was to assess whether rats could discriminate between the two levers (i.e., smaller and larger reward) and whether they preferred the larger reward. The preference criterion was at least 85% selection of the larger reward across 2 consecutive days. Rats were tested in this manner for 5 days (see Results).

Delay discounting. Each block of 12 trials began with two forced trials—one trial for each of the two levers/reward sizes. This was followed by 10 choice trials in which rats had a choice between earning a smaller or larger reward. The delay to a larger reward was increased across five blocks from 0 to 5, 10, 20, and then 40 s. Rats were tested for 30 days in this manner and the criterion for termination of testing was stable performance across 3 consecutive days (i.e., no significant change in preference; repeated-measures ANOVA).

Delay discounting—No delays to larger reward. This testing was identical to procedures used above (Delay discounting training—No delays across blocks section). Testing lasted 8 days and the criterion was stable performance (at least 85% preference for the larger reward across 2 days).

Reversal of smaller and larger reward levers with no delays to larger reward. This testing was identical as with other sessions with no delay (see above) to the larger reward except that larger and smaller reward associations with the left and right levers were reversed. That is, if the left lever was associated with smaller reward it was now associated with the larger reward and vice versa.

Data analyses. After statistical tests confirmed no differences, MR-CON and MR-SHAM rats were combined into one group—MR. Larger reward preference (%) was the main dependent variable. Data were analyzed using repeated-measures ANOVA (Group $\times$ Sex $\times$ Delay) and when appropriate followed by Scheffé post hoc tests. In cases of significant interactions between sex and other variables, data were analyzed separately for males and females. Significant Group $\times$ Delay interactions were followed by one-way ANOVAs assessing group differences at different delays to larger reward. The level of statistical significance was $p < .05$.

Results

No delays across blocks. Repeated-measures ANOVA (averaged data for the last 2 days of a 5-day test period) indicated that groups were not significantly different, that there were no changes across blocks of trials and that there were no interactions. All groups showed a greater than 90% preference for the larger reward across all blocks (data not depicted).

Delay discounting. Rats were tested until their responses were stable across 3 days. Stability was assessed using repeated-measures ANOVA (data for individual delay intervals across 3 days). If there were no significant day effects, we considered the rats' performances stable. Stability was achieved by Day 30 of testing. Next, data were averaged across the last 3 days of testing and analyzed using repeated-measures ANOVA (Group $\times$ Sex $\times$ Delay). Initial analyses indicated significant delay effects, $F(4, 144) = 176.3$, $p < .001$, significant group differences, $F(2, 36) = 5.04$, $p < .05$, a significant Group $\times$ Sex interaction, $F(2, 36) = 5.05$, $p < .05$, and a significant Group $\times$ Sex $\times$ Delay interaction, $F(8, 144) = 2.7$, $p < .05$ (Figure 4a, b). To further examine group differences, without sex effects, we ran another set of repeated-measures ANOVAs (Group $\times$ Delay) separately for male and female rats.

Analyses of male rats' data indicated significant delay effects, $F(4, 72) = 93.2$, $p < .001$, significant group differences, $F(2, 18) = 10.5$, $p < .001$, and a significant Group $\times$ Delay interaction, $F(2, 18) = 3.7$, $p < .05$. These overall group differences were followed by post hoc tests. AR-MIN rats, compared to MR and AR-MAX rats, showed a significantly higher preference for larger reward across the delays greater than 0 s ($p < .001$; Figure 4a). AR-MAX rats were not significantly different from the MR rats. Significant Group $\times$ Delay interaction was followed by one-way ANOVAs assessing group differences for individual delays. Significant group differences were found within Blocks 2 to 5 (all $ps < .05$). Post hoc analyses indicated that AR-MIN rats were

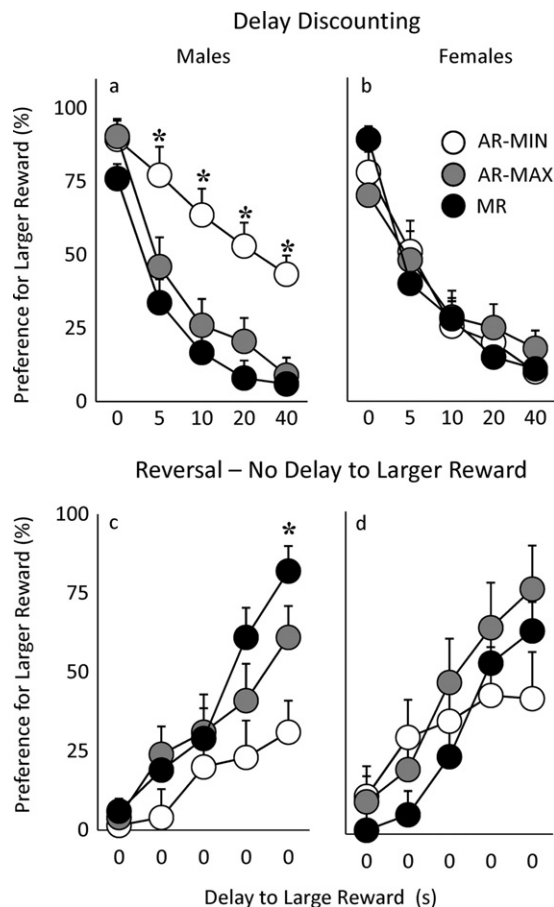


Figure 4. Large reward preference (+ SEM) across five delays for (a) male and (b) female rats. AR-MIN rats, compared MR rats, had higher preference for large reward (male rats). * Compared to (male) MR and AR-MAX rats, AR-MIN (male) rats showed a significantly higher larger reward preference during all delays to larger reward. Lower panels depict larger reward preference (+ SEM) for (c) male and (d) female rats during the first reversal session (left and right lever associations with the smaller and larger reward reversed). * Significant group differences between AR-MIN and MR rats ($p < .05$). AR-MIN = artificially reared with minimal maternal licking-like stimulation; AR-MAX = artificially reared with maximal maternal licking-like stimulation; MR = maternally reared.

significantly different from the MR and AR-MAX rats across all of these delays (i.e., Blocks 2 to 5; all $ps < .05$; Figure 4a). For female rats, we found significant delay effects, $F(4, 72) = 83.7$, $p < .001$, but no significant group differences or a significant Group $\times$ Delay interaction (Figure 4b).

No delays across blocks. Following delay discounting testing, rats were tested again with no delays to the larger reward across the blocks. In a similar manner to initial testing with no delays to the larger reward, rats' preferences for the larger reward stabilized relatively rapidly (within 7 days). All groups showed over 90% preference for the larger reward (data not depicted).

No delays to larger reward—Reversal of lever associations with the smaller and larger reward. Rats were tested over 4 days but because we were interested in assessing how quickly rats modify their responses (as they do within a single test session) we

were primarily concerned with the first session of reversal testing. Data were analyzed separately for male and female rats using repeated-measures ANOVA (Group $\times$ Block).

Analyses of male rats' performances revealed a significant block effect, $F(4, 72) = 30.42$, $p < .001$, marginal overall group differences, $F(2, 18) = 2.86$, $p = .08$, and a significant Group $\times$ Block interaction, $F(4, 72) = 2.41$, $p < .05$. This interaction was followed by one-way ANOVAs for individual blocks. Compared to MR rats, AR-MIN rats' choice for the larger reward was significantly lower during the last block of the session ($p < .05$; see Figure 4c). AR-MAX rats did not differ from AR-MIN or MR rats.

For female rats, there was a significant block effect, $F(4, 72) = 39.82$, $p < .001$ (Figure 4d), and a significant Group $\times$ Block interaction, $F(8, 72) = 2.78$, $p < .01$, but there were no overall group differences. Significant Group $\times$ Block interaction was followed by one-way ANOVAs for individual blocks. Groups were not significantly different at any block of the session.

Brief Discussion

In this study we assessed AR and MR rats on impulsive choice. We examined their preference specifically for the larger reward and shift from the larger reward to the smaller reward as the delay to the larger reward increased. We found that (male) AR-MIN rats, compared to MR and AR-MAX rats, showed a greater tendency to select the larger delayed reward across all delay intervals. This suggests that AR-MIN rats were better able to tolerate the delay to the larger reward and are, therefore, less choice impulsive. Our findings of reduced impulsive choice in maternally deprived rats are similar to those of Hellemans, Nobrega, and Olmstead (2005), who reported a decrease in impulsive choice in adult rats isolated during the early postweaning period. This suggests that both, pre- and postweaning isolation produce similar behavioral profiles in adulthood (i.e., a reduction in impulsive choice).

However, it also is possible that the specifics of the task did not allow us to accurately assess tolerance of delayed reward. In our version of the delay discounting choice procedure (similar to most other published studies with delay discounting; e.g., Uslander & Robinson, 2006; Winstanley, Theobald, Cardinal, & Robbins, 2004), the delay to the larger reward started at 0 s during the first block of testing and increased to 40 s over the subsequent blocks. All rats showed a high preference for the larger reward during the first block within a session. Over the next several blocks, MR rats discounted the value of the large reward much more rapidly than the AR-MIN rats (AR-MAX rats were similar to MR rats). It can be argued that this switch in preference could depend on several factors, including attention to changes in the larger reward properties (i.e., the delay) and the ability to disengage from previously preferred responses (i.e., behavioral flexibility).

To test the possibility that AR-MIN rats are less able to assess changes in stimulus properties and switch their behavior accordingly, we tested the same rats again with no-delays to the larger reward but with left and right lever-reward associations reversed. As can be seen in Figure 4c, all groups showed a near 0% preference for the larger reward during the first block of reversal testing. This was expected as rats responded almost exclusively on the lever that was previously associated with the larger reward but currently corresponded to the selection of the smaller reward.

However, by the fifth block MR rats showed a high (~80%) preference for the larger reward, while the AR-MIN rats chose the larger reward in less than 30% of the trials. This finding shows that MR rats were able to relatively rapidly switch their behavior within a session. On the other hand the rate of change for AR-MIN rats was significantly slower. Overall, this finding suggests that AR-MIN rats are less able to modify their behavior when contingencies are changed. These findings are consistent with our observations of AR-MIN rats' slower reversal learning in the attentional set shifting task (Lovic & Fleming, 2004).

These data suggest that AR rats are not necessarily less impulsive (choice), but that they are less likely to switch their preferential responding (see also General Discussion). Although these findings are informative, it is not entirely clear what the nature of the deficit in AR rats is with respect to impulsive choice. To further elucidate the relationship between AR and impulsive choice we conducted the next experiment.

Experiment 3: The Effects of Artificial Rearing on Impulsive Choice (FCN8)

To provide clarity regarding the effects of AR on impulsive choice, a separate set of rats were tested on the fixed consecutive number (FCN) operant schedule (only male rats). On this schedule rats have a choice of responding on two levers; however, the schedule requires that rats respond on one (chain) lever a number of times (e.g., on FCN8, at least eight responses) before a single response on the other (reinforcement) lever will produce a reward (food pellet) delivery. Impulsive rats tend to have shorter chain lengths and thus sometimes fail to obtain rewards (Dellu-Hagedorn, 2006; Evenden, 1998). Based on all the findings from the previous experiment we predicted that AR rats would not be less impulsive than MR rats. That is, we predicted that AR-MIN rats' chain lengths would not be significantly different from those of MR rats.

Method

Subjects. Thirty-three male Sprague-Dawley (AR-MIN, $n = 8$; AR-MAX, $n = 8$; MR, $n = 17$) rats (derived from nine litters) were used in this study. Rats were assigned to the same conditions as in the previous two experiments.

Apparatus. Operant conditioning chambers were outfitted in the same manner as in Experiment 2.

Procedures.

FR training. Adult rats were gradually reduced to 85 to 90% of their free-feeding weight and were subsequently trained to make lever responses for food (45 mg food pellets; Bio-Serv; Frenchtown, New Jersey) on a FR-1 schedule (30-min sessions). Rats were tested with the left and right levers on alternate days. Learning criteria were at least 100 lever responses, during a 30-min session, on 2 consecutive days.

FCN training. Following FR-1 training rats were tested on a FCN1 schedule (1 day) and a FCN3 schedule (6 days). Each 45-min session was initiated with the illumination of the house light and extension of both levers into the operant chamber. Rats had to make at least one (FCN1) or three (FCN3) responses on the (chain) lever and then respond once on the (reinforcement) lever to get rewarded (one pellet). Once the rats' performance stabilized

(no significant changes across 3 days) they were switched to a FCN8 schedule.

FCN8. FCN8 testing was identical to FCN1 and FCN3 testing except that rats had to make at least eight responses on the chain lever before a single response on the reinforcement lever resulted in the delivery of a food pellet. Rats were tested over 20 days. The main dependent variables were: (a) number of chain lever responses; (b) number of reinforcement lever responses; (c) number of pellets earned; (d) number of chains (the number of times rats made at least one response on the chain lever before responding on the reinforcement lever); (e) time to complete the chain; and (f) average chain length (the average number of responses made on the chain lever before a response was made on the reinforcement lever), which was our measure of impulsivity (see Dellu-Hagedorn, 2006; Evenden, 1998). Shorter chains were indicative of an increase in impulsivity.

Data analyses. As with the two previous experiments (see above) MR-SHAM and MR-CON groups were combined into one group—MR. Data for each of the six dependent variables was averaged across 4 days (for a total of five blocks) and analyzed using repeated-measures ANOVA (Group $\times$ Block). Scheffé post hoc test was used to assess group differences. Significant interactions were followed by one-way ANOVAs and post hoc tests. The level for achieving statistical significance was $p < .05$.

Results

Chain lever responses. As can be seen in Figure 5a there was an overall increase in the number of chain lever responses across the blocks of testing, $F(4, 100) = 24.387, p < .001$. There were no overall group differences but there was a significant Block $\times$ Group interaction, $F(8, 100) = 2.038, p < .05$. One-way ANOVAs revealed overall group differences for Blocks 4, $F(2, 27) = 4.18, p < .05$, and 5, $F(2, 27) = 5.54, p < .05$, and post hoc tests indicated that AR-MAX rats made significantly more responses than MR rats during these last two blocks of testing ($ps < .05$).

Reinforcement lever responses. There was no overall change in the number of responses made on the reinforcement lever; however, there were significant group differences, $F(2, 25) = 7.38, p < .01$, and post hoc analyses revealed that AR-MAX group, compared to MR group, made significantly more responses on the reinforcement lever ($p < .01$; see Figure 5b). There were no significant interactions.

Number of pellets earned. The number of pellets earned increased over successive test blocks, $F(4, 100) = 59.34, p < .001$. There were no overall group differences but there was a significant Group $\times$ Block interaction, $F(8, 100) = 2.18, p < .05$. One-way ANOVAs revealed no significant group differences for any of the blocks (see Figure 5c).

Number of chains. There was an overall increase in the number of chains generated across blocks, $F(4, 92) = 5.6, p < .001$, and there were significant groups differences, $F(2, 23) = 6.2, p < .01$, as well as a significant Group $\times$ Block interaction, $F(8, 92) = 2.06, p < .05$. Post hoc analyses revealed that AR-MAX, but not AR-MIN rats, created more chains across sessions compared to the MR rats ($p < .05$; see Figure 5d). Significant Group $\times$ Block interaction was followed by one-way ANOVAs for the number of chains during individual blocks of testing. Groups were significantly different during Blocks 3, $F(2, 26) = 8.06, p < .01$; 4, $F(2,$

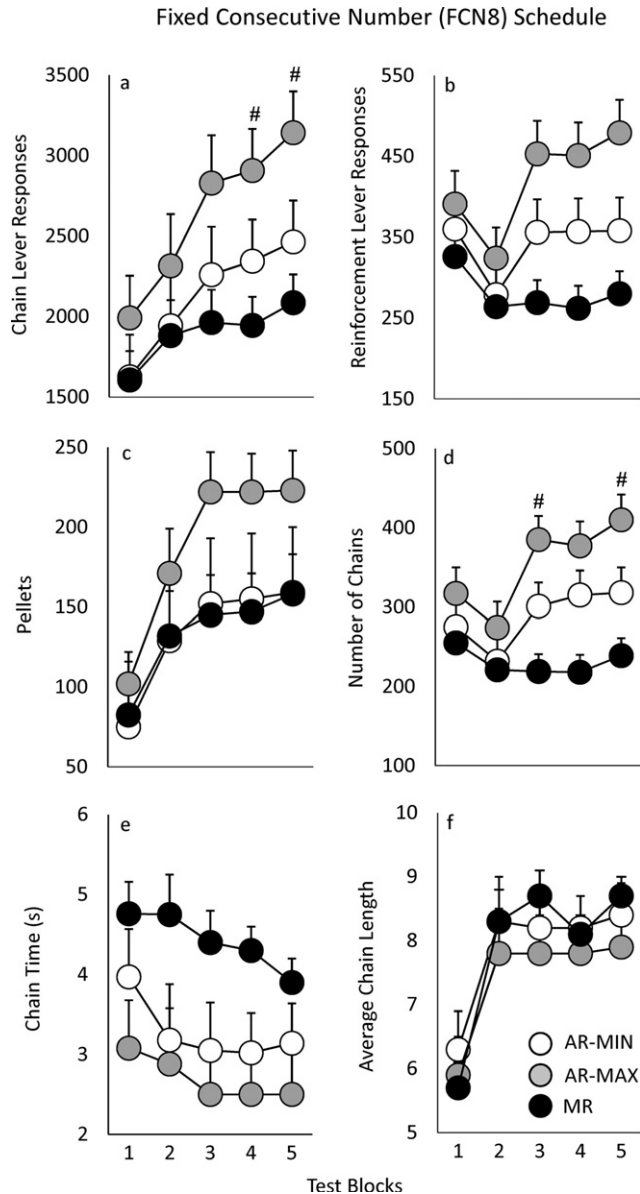


Figure 5. The figure depicts means (+ SEM) for different FCN8 measures across five blocks of testing. (a) Number of responses made on the chain lever. #AR-MAX rats made significantly more responses than MR rats during the last two blocks of testing ($p < .05$). (b) Number of responses made on the reinforcement lever. AR-MAX rats made significantly more responses on the reinforcement lever than MR rats. (c) Number of pellets earned. (d) Number of chains. #AR-MAX rats executed significantly more chains during blocks 3 and 5 of testing ($p < .05$), compared to MR rats. (e) Time to complete chains across different groups. Overall, AR-MAX rats were significantly faster than MR rats at completing their chains. (f) Average chain length for different rearing groups. AR-MIN = artificially reared with minimal maternal licking-like stimulation; AR-MAX = artificially reared with maximal maternal licking-like stimulation; MR = maternally reared.

26) = 7.53, $p < .01$; and 5, $F(2, 26) = 9.2$, $p < .01$. Post hoc analyses revealed that MR rats were significantly different from AR-MAX rats during Blocks 3 and 5, ($p < .05$; see Figure 5d).

Time to complete the chains. As can be seen in Figure 5e there was an overall decrease in time taken to complete the chains, $F(4, 100) = 5.5$, $p < .001$. Groups differed significantly, $F(2, 25) = 4.02$, $p < .05$, and post hoc analyses revealed that AR-MAX rats, compared to MR rats, were significantly faster at completing the chains ($p < .05$). There were no significant interactions.

Average chain length. Rats' chain lengths were our measure of impulsivity. As can be seen in Figure 5f there was an increase in chain length over successive blocks, $F(4, 92) = 35.66$, $p < .001$. However, there were no significant group differences or interactions.

Brief Discussion

Consistent with our predictions, we did not see any evidence of altered impulsivity in AR-MIN rats. Their behavior was in general similar to those displayed by MR rats. We suggested in the previous experiment that AR-MIN rats might be showing persistent larger delayed reward preference because of their perseverative tendencies to respond on one of the levers. One question that is raised from these observations is: If the AR-MIN rats show perseverative responding, as we suggested in the delay discounting experiment, why are they not showing perseverative responding on the FCN8 schedule? One of the key differences is that in the delay discounting choice procedure each lever is associated with a reward delivery—either smaller or larger. However, all rats, including AR-MIN rats, make significantly more responses early in the test session almost exclusively on the larger delayed reward lever (excluding forced trials). On the contrary, in the current experiment more responses are made on the chain lever but these responses are not directly associated with reward delivery. Hence, this operant schedule does not have confounds inherent in the delay discounting operant schedule, at least in the version of the delay discounting operant schedule that we used.

Compared to MR rats, AR-MAX, but not AR-MIN rats, made more responses on both, the chain and the reinforcement lever, made more chains and did so faster. However, despite this, AR-MAX rats were not more impulsive. Their average chain length did not significantly differ from chain lengths displayed by MR rats. Thus, despite being more active, AR-MAX rats did not prematurely interrupt their sequences on the chain lever.

General Discussion

The experiments reported here extend the findings previously reported from our laboratory relating to the effects of artificial rearing on attention, learning, and naturally occurring behaviors (maternal and sexual behavior; e.g., Lovic & Fleming, 2004; Lovic et al., 2006). We asked whether early life maternal and social separation would have an effect on adult impulsive behavior. We report here that artificially reared rats (AR-MIN) tend to show greater levels of impulsive action but not impulsive choice. These effects can be reversed or ameliorated by providing artificially reared rats with maternal licking-like stimulation (AR-MAX group).

We found that AR-MIN, but not AR-MAX rats, are less efficient at earning rewards on the DRL-20s schedule as they made more premature responses. That is, AR-MIN rats made more responses before the waiting period had elapsed (Bins 4–8; see Figure 3). Conversely, on the delay discounting schedule, male AR-MIN rats were less

impulsive as they preferred the larger delayed reward significantly more than did the MR or AR-MAX rats. However, AR-MIN rats were also slower to modify their behavior when we switched the association between left and right levers and smaller and larger rewards. Hence, they showed reduced behavioral flexibility. To further explore impulsive decision making, or choice, we tested a separate set of rats on the FCN8 schedule. AR and MR groups did not differ on a measure of impulsivity in this task—their average chain lengths were of similar values. Overall, we conclude that maternal and social deprivation, achieved through artificial rearing, increases adult displays of impulsive action but not impulsive choice.

Next, we discuss possible psychological and neurobiological mechanisms that may account for these differences between MR and AR-MIN rats on two forms of impulsivity. One psychological mechanism involves differential attribution of incentive salience to an instrumental manipulandum (i.e., a lever) between AR-MIN and MR rats. Cues or conditioned stimuli associated with rewards can be attributed with incentive salience. That is, through associative (Pavlovian) processes cues might become attractive, potent energizers of behavior and effective conditional reinforcers (Cardinal, Parkinson, Hall, & Everitt, 2002; Lovibond, 1983). However, it also is possible that instrumental manipulanda, such as a lever, can be attributed with incentive salience (Lovic, Saunders, Yager, & Robinson, *in press*) making the lever more attractive and thus resulting in greater approach toward and contact with the lever (i.e., make more lever responses). This possibility might explain differences between AR-MIN and MR rats during both, the DRL-20s and delay discounting testing. Successful performance on the DRL-20 schedule requires that rats refrain from approaching and making frequent contacts with the lever. If AR-MIN rats attribute greater incentive salience to the lever during the DRL-20s testing, they are more likely to approach it and make contact with it. In a similar manner in the delay discounting procedure, AR-MIN rats might attribute greater salience to the lever associated with the larger reward and be more likely to approach it and respond on it even when this responding produces a delay in reward delivery (later blocks of delay discounting testing). This also would explain why the AR-MIN rats are slower to reverse their preference between the left and right lever during the reversal choice procedure.

Although we do not have direct evidence of differential (AR-MIN versus MR) attribution of incentive salience to the lever, two recent studies lend weight to our hypothesis. Rats that tend to attribute incentive salience to a food-cue also tend to be more impulsive on tests of impulsive action but are less impulsive on a test of impulsive choice (Lovic et al., *in press*). That is, rats that attribute greater incentive salience to a reward-cue show similar behavior as AR-MIN rats. Furthermore, in a recent study it has been reported that AR-MIN rats, compared to MR rats, attribute greater incentive salience to a food-cue; that is, they approach the cue (lever) more readily and the cue is a more potent reinforcer of new behavior for AR-MIN rats than MR rats. AR-MAX (or AR-STIM) rats show intermediate (to AR-MIN and MR rats) levels of attribution of incentive salience (Lomanowska et al., 2011).

We found that the artificial rearing procedure produces opposing effects on two forms of impulsivity and these findings are not unique. Increased dopamine tone, via injections of the dopamine

releaser amphetamine, produces similar effects—an increase in impulsive action and a decrease in impulsive choice (Cole & Robbins, 1987; Fletcher, Rizos, Noble, & Higgins, *in press*; Robbins, 2002; Winstanley, Dalley, Theobald, & Robbins, 2003). We previously found that AR rats show greater novelty- and amphetamine-induced locomotor activity suggesting that AR-MIN rats might be hyperdopaminergic (Lovic et al., 2006). Although we do not have direct evidence of altered dopamine levels in the rats used in this study, two independent studies show that AR rats have elevated baseline dopamine levels (*in vivo*) in the nucleus accumbens (Akbari, Budin, Chatterjee, Maheu, & Fleming, 2010). This is consistent with other studies showing that maternal deprivation produces enduring effects on *in vivo* dopamine output (Hall, Wilkinson, Humby, & Robinson, 1999), dopamine profile (Matthews, Dalley, Matthews, Tsai, & Robbins, 2001), dopamine receptors (Brake, Zhang, Diorio, Meaney, & Gratton, 2004), and dopamine-mediated behaviors (Brake et al., 2004).

There are two other significant findings from the current study. First, AR-MAX rats were not different from the MR rats during DRL-20s, delay discounting, or reversal no-delays testing. This indicates that maternal licking-like stimulation has a significant effect on brain mechanisms mediating impulsive behavior. These reversal or ameliorating effects of somatosensory stimulation are concordant with our previous observations of stimulation reversing the effects of artificial rearing. These effects are also concordant with the studies showing that maternal licking has a beneficial effect on other biobehavioral systems such as the stress response (see Kaffman & Meaney, 2007; Meaney et al., 2000). Simulations of maternal licking, using a paintbrush, increase several hormones and growth factors necessary for normal development (Kuhn & Schanberg, 1998). Second, artificial rearing seems to differentially affect male and female rats (DRL-20s and delay discounting choice procedure). This might be due to the fact that male rats are “preprogrammed” to receive greater levels of maternal care than female rats and absence of maternal care, as with artificial rearing, could be more detrimental to male rats. Indeed, under normal nest conditions mother rats spend more time caring for male pups than their female counterparts (Moore & Moralli, 1979).

Impulsivity has recently received considerable attention in the context of drug addiction research (Belin et al., 2008; Jentch & Taylor, 1999; Perry & Carroll, 2008). Increased impulsive action is associated with compulsive drug taking in rats (Belin et al., 2008). Adverse social experiences in childhood, such as abuse or neglect, are risk factors for the development of drug addiction (Koss et al., 2003; Wilsnack, Vogeltanz, Klassen, & Harris, 1997). For example, adults reporting childhood victimization are at significantly greater risk for drug abuse compared to individuals who do not report such experiences (Enoch et al., 2010; Widom, Weiler, & Cottler, 1999). However, psychological and physiological mechanisms by which early life adverse events increase adult susceptibility to addictions remain unknown. Our findings might be relevant in deconstructing this relationship. Given that early life adversity produces an increase in impulsivity and given that impulsivity is predictive of compulsive drug taking, perhaps impulsivity is a mediating factor between early life adversity and addiction vulnerability. Our findings are relevant to human instances of maternal and social deprivation as well. They are particularly relevant to cases of institutionalized care, which is sometimes associated with extremely impoverished conditions (e.g., Roma-

nian orphans). Many of the children described in the Romanian orphan studies spent their early life period in institutionalized care but are often adopted into families later on. Several studies have shown that these children show persistent changes in behavior, long after they leave the institutions. Although these individuals have been described as having attentional deficits and increased hyperactivity and impulsivity (Chugani et al., 2001), the exact effects of early adversity are still poorly understood.

References

- Akbari, E. M., Budin, R., Chatterjee, D., Maheu, M., & Fleming, A. S. (2010, September). *Maternal deprivation produces alterations in the androgen and dopamine systems and results in deficits in masculine sexual behavior. Partial reversal with maternal 'licking-like' stimulation during the deprivation period*. Paper presented at the Parental Brain conference, Edinburgh, Scotland.
- Akbari, E. M., Budin, R., Parada, M., & Fleming, A. S. (2008). The effects of early isolation on sexual behaviour and c-fos expression in naïve male Long-Evans rats. *Developmental Psychobiology*, 50, 298–306.
- Belin, D., Mar, A. C., Dalley, J. W., Robbins, T. W., & Everitt, B. J. (2008). High impulsivity predicts the switch to compulsive cocaine-taking. *Science*, 320(5881), 1352–1355.
- Brake, W. G., Zhang, T. Y., Diorio, J., Meaney, M. J., & Gratton, A. (2004). Influence of early postnatal rearing conditions on mesocorticolimbic dopamine and behavioural responses to psychostimulants and stressors in adult rats. *European Journal of Neuroscience*, 19, 1863–1874.
- Burton, C., Lovic, V., & Fleming, A. S. (2006). Early adversity alters attention and locomotion in adult Sprague-Dawley rats. *Behavioural Neuroscience*, 120, 665–675.
- Cardinal, R. N. (2006). Neural systems implicated in delayed and probabilistic reinforcement. *Neural Networks*, 19, 1277–1301.
- Cardinal, R. N., Parkinson, J. A., Hall, J., & Everitt, B. J. (2002). Emotion and motivation: The role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience and Biobehavioral Reviews*, 26, 321–352.
- Cardinal, R. N., Pennicott, D. R., Sugathapala, C. L., Robbins, T. W., & Everitt, B. J. (2001). Impulsive choice induced in rats by lesions of the nucleus accumbens. *Science*, 292(5526), 2499–2501.
- Chugani, H. T., Behem, M. E., Muzik, O., Juhasz, C., Nagy, F., & Chugani, D. C. (2001). Local brain functional activity following early deprivation: A study of postinstitutionalized Romanian orphans. *NeuroImage*, 14, 1290–1301.
- Cirulli, F., Berry, A., & Alleva, E. (2003). Early disruptions of the mother-infant relationship: Effects on brain plasticity and implications for psychopathology. *Neuroscience and Biobehavioral Reviews*, 27, 73–82.
- Cole, B. J., & Robbins, T. W. (1987). Amphetamine impairs the discriminative performance of rats with dorsal noradrenergic bundle lesions on a 5-choice serial reaction time task: New evidence for central dopaminergic-noradrenergic interactions. *Psychopharmacology*, 91, 458–466.
- Dalley, J. W., Everitt, B. J., & Robbins, T. W. (2011). Impulsivity, compulsivity and top-down cognitive control. *Neuron*, 69, 680–694.
- Dellu-Hagedorn, F. (2006). Relationship between impulsivity, hyperactivity and working memory: A differential analysis in the rat. *Behavioural and Brain Functions*, 28, 2–10.
- de Wit, H. (2009). Impulsivity as a determinant and consequence of drug use: A review of underlying processes. *Addiction Biology*, 14, 22–31.
- Enoch, M. A., Hodgkinson, C. A., Yuan, Q., Shen, P. H., Goldman, D., & Roy, A. (2010). The influence of GABRA2, childhood trauma, and their interaction on alcohol, heroin, and cocaine dependence. *Biological Psychiatry*, 67, 20–27.
- Evenden, J. L. (1998). The pharmacology of impulsive behaviour in rats, II: The effects of amphetamine, haloperidol, imipramine, chlordiazepoxide and other drugs on fixed consecutive number schedules (FCN 8 and FCN 32). *Psychopharmacology*, 138, 283–294.
- Evenden, J. L. (1999). Varieties of impulsivity. *Psychopharmacology*, 146, 348–361.
- Fletcher, P. J. (1995). Effects of combined or separate 5, 7-dihydroxytryptamine lesions of the dorsal and median raphe nuclei on responding maintained by a DRL 20s schedule of food reinforcement. *Brain Research*, 675(1–2), 45–54.
- Fletcher, P. J., Rizzo, Z., Noble, K., & Higgins, G. A. (in press). Impulsive action induced by amphetamine, cocaine and MK801 is reduced by 5-HT(2C) receptor stimulation and 5-HT(2A) receptor blockade. *Neuropharmacology*. Advance online publication. doi: 10.1016/j.neuropharm.2011.02.025
- Gonzalez, A., Lovic, V., Ward, G. R., Wainwright, P. E., & Fleming, A. S. (2001). Intergenerational effects of complete maternal deprivation and replacement stimulation on maternal behaviour and emotionality in female rats. *Developmental Psychobiology*, 38, 11–42.
- Hall, F. S. (1998). Social deprivation of neonatal, adolescent, and adult rats has distinct neurochemical and behavioural consequences. *Critical Reviews in Neurobiology*, 12, 129–169.
- Hall, F. S., Wilkinson, L. S., Humby, T., & Robbins, T. W. (1999). Maternal deprivation of neonatal rats produces enduring changes in dopamine function. *Synapse*, 32, 37–43.
- Hellems, K. G., Nobrega, J. N., & Olmstead, M. C. (2005). Early environmental experience alters baseline and ethanol-induced cognitive impulsivity: Relationship to forebrain 5-HT1A receptor binding. *Behavioural Brain Research*, 159, 207–220.
- Ho, M.-Y., Mobini, S., Chiang, T.-J., Bradshaw, C. M., & Szabadi, E. (1999). Theory and method in the quantitative analysis of “impulsive choice” behaviour: Implications for psychopharmacology. *Psychopharmacology*, 146, 362–373.
- Hofer, M. A. (1994). Early relationships as regulators of infant physiology and behaviour. *Acta Paediatrica*, 397, 9, 18.
- Jentch, J. D., & Taylor, J. R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: Implications for the control of behaviour by reward-related stimuli. *Psychopharmacology*, 146, 373–390.
- Kaffman, A., & Meaney, M. J. (2007). Neurodevelopmental sequelae of postnatal maternal care in rodents: Clinical and research implications of molecular insights. *Journal of Child Psychology and Psychiatry*, 48, 224–244.
- Koss, M. P., Yuan, N. P., Dightman, D., Prince, R. J., Polacca, M., Sanderson, B., & Goldman, D. (2003). Adverse childhood exposures and alcohol dependence among seven Native American tribes. *American Journal of Preventive Medicine*, 25, 238–244.
- Kuhn, C. M., & Schanberg, S. M. (1998). Response to maternal separation: Mechanisms and mediators. *International Journal of Developmental Neuroscience*, 16, 261–270.
- Lévy, F., Melo, A. I., Galef, B. G., Madden, M., & Fleming, A. S. (2003). Complete maternal deprivation affects social, but not spatial, learning in adult rats. *Developmental Psychobiology*, 43, 177–191.
- Lomanowska, A. M., Lovic, V., Rankine, M. J., Mooney, S. J., Robinson, T. E., & Kraemer, G. W. (2011). Inadequate early social experience increases the incentive salience of reward-related cues in adulthood. *Behavioural Brain Research*, 220, 91–99.
- Lovibond, P. F. (1983). Facilitation of instrumental behavior by a Pavlovian appetitive conditioned stimulus. *Journal of Experimental Psychology: Animal Behavior Processes*, 9, 225–47.
- Lovic, V., & Fleming, A. S. (2004). Artificially-reared female rats show reduced prepulse inhibition and deficits in the attentional set shifting task-reversal of effects with maternal-like licking stimulation. *Behavioural Brain Research*, 148, 209–219.
- Lovic, V., Fleming, A. S., & Fletcher, P. J. (2006). Early life tactile stimulation changes adult rat responsiveness to amphetamine. *Pharmacology, Biochemistry and Behaviour*, 84, 497–503.

- Lovic, V., Palombo, D. J., & Fleming, A. S. (2011). Impulsive rats are less maternal. *Developmental Psychobiology*, 53, 13–22.
- Lovic, V., Saunders, B. T., Yager, L. M., & Robinson, T. E. (in press). Rats prone to attribute incentive salience to reward cues are also prone to impulsive action. *Behavioural Brain Research*. Advance online publication. doi: 10.1016/j.bbr.2011.04.006
- Matthews, K., Dalley, J. W., Matthews, C., Tsai, T. H., & Robbins, T. W. (2001). Periodic maternal separation of neonatal rats produces region- and gender- specific effects on biogenic amine content in postmortem adult brain. *Synapse*, 40, 1–10.
- Meaney, M. J., Diorio, J., Francis, D., Weaver, S., Yau, J., Chapman, K., & Seckl, J. R. (2000). Postnatal handling increases the expression of cAMP-inducible transcription factors in the rat hippocampus: The effects of thyroid hormone and serotonin. *Journal of Neuroscience*, 20, 3936–3935.
- Melo, A. I., Lovic, V., Gonzalez, M., Madden, M., Sinopoli, K., & Fleming, A. S. (2006). Maternal and littermate deprivation disrupts maternal behaviour and social-learning of food preference in adulthood: Tactile stimulation, nest odor, and social rearing prevent these effects. *Developmental Psychobiology*, 48, 209–219.
- Moore, C. L., & Moralli, G. A. (1979). Mother rats interact differently with male and female offspring. *Journal of Comparative Physiological Psychology*, 93, 677–684.
- Olmstead, M. C. (2006). Animal models of drug addiction: Where do we go from here? *Quarterly Journal of Experimental Psychology (Colchester)*, 59, 625–653.
- Pattij, T., & Vanderschuren, L. J. (2008). The neuropharmacology of impulsive behaviour. *Trends in Pharmacological Science*, 29(4), 192–199.
- Perry, J. L., & Carroll, M. E. (2008). The role of impulsive behaviour in drug abuse. *Psychopharmacology*, 200, 1–26.
- Peterson, J. D., Wolf, M. E., & White, F. J. (2003). Impaired DRL 30 performance during amphetamine withdrawal. *Behavioural Brain Research*, 143, 101–108.
- Pryce, C. R., & Feldon, J. (2003). Long-term neurobehavioural impact of the postnatal environment in rats: Manipulations, effects and mediating mechanisms. *Neuroscience and Biobehavioural Reviews*, 27(1–2), 57–71.
- Reynolds, B., de Wit, H., & Richards, J. B. (2002). Delay of gratification and delay discounting in rats. *Behavioural Processes*, 59, 157–168.
- Robbins, T. W. (2002). The 5-choice serial reaction time task: Behavioural pharmacology and functional neurochemistry. *Psychopharmacology*, 163, 363–380.
- Uslaner, J. M., & Robinson, T. E. (2006). Subthalamic nucleus lesion increase impulsive action and decrease impulsive choice—Mediation by enhanced incentive motivation? *European Journal of Neuroscience*, 24, 2345–2354.
- Widom, C. S., Weiler, B. L., & Cottler, L. B. (1999). Childhood victimization and drug abuse: A comparison of prospective and retrospective findings. *Journal of Consulting and Clinical Psychology*, 67, 867–880.
- Wilsnack, S. C., Vogeltanz, N. D., Klassen, A. D., & Harris, T. R. (1997). Childhood sexual abuse and women's substance abuse: National survey findings. *Journal of Studies On Alcohol*, 58(3), 264–271.
- Winstanley, C. A., Dalley, J. W., Theobald, D. E., & Robbins, T. W. (2003). Global 5-HT depletion attenuates the ability of amphetamine to decrease impulsive choice on a delay-discounting task in rats. *Psychopharmacology*, 170, 320–331.
- Winstanley, C. A., Dalley, J. W., Theobald, D. E., & Robbins, T. W. (2004). Fractioning impulsivity: Contrasting effects of central 5-HT depletion on different measures of impulsive behaviour. *Neuropsychopharmacology*, 29, 1331–1343.
- Winstanley, C. A., Theobald, D. E., Cardinal, R. N., & Robbins, T. W. (2004). Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. *Journal of Neuroscience*, 24, 4718–4722.

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