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### Authors

Sakhai, Samuel A  
Saxton, Katherine  
Francis, Darlene D

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Samuel A. Sakhai<sup>1</sup>  
 Katherine Saxton<sup>2</sup>  
 Darlene D. Francis<sup>3,4</sup>

<sup>1</sup>Department of Psychology  
 University of California at Berkeley  
 3210 Tolman Hall MC 1650, Berkeley CA  
 94720  
 E-mail: ssakhai@berkeley.edu

<sup>2</sup>Department of Biology  
 Santa Clara University  
 Santa Clara CA

<sup>3</sup>Helen Wills Neuroscience Institute  
 University of California at Berkeley  
 3210 Tolman Hall MC 1650, Berkeley CA  
 94720

<sup>4</sup>School of Public Health  
 University of California at Berkeley  
 3210 Tolman Hall MC 1650, Berkeley CA  
 94720

# The Influence of Early Maternal Care on Perceptual Attentional Set Shifting and Stress Reactivity in Adult Rats

**ABSTRACT:** Stress influences a wide variety of outcomes including cognitive processing. In the rat, early life maternal care can influence developing offspring to affect both stress reactivity and cognitive processes in adulthood. The current study assessed if variations in early life maternal care can influence cognitive performance on a task, the ability to switch cognitive sets, dependent on the medial prefrontal cortex. Early in life, offspring was reared under High or Low maternal Licking conditions. As adults, they were trained daily and then tested on an attentional set-shifting task (ASST), which targets cognitive flexibility in rodents. Stress-sensitive behavioral and neural markers were assayed before and after the ASST. High and Low Licking offspring performed equally well on the ASST despite initial, but not later, differences in stress axis functioning. These results suggest that early life maternal care does not impact the accuracy of attentional set-shifting in rats. These findings may be of particular importance for those interested in the relationship between early life experience and adult cognitive function. © 2015 Wiley Periodicals, Inc. *Dev Psychobiol*

**Keywords:** maternal programming; cognition; HPA axis; stress; training; medial prefrontal cortex; rat

## INTRODUCTION

Stressful experiences influence a wide variety of health outcomes, both mental and physical. One potent regulator of the stress, or hypothalamic–pituitary–adrenal (HPA) axis, is exposure to compromised or challenging early-life experiences, which can set the stage for individual differences in adult phenotypes. Abuse or neglect early in childhood influences a variety of outcomes later in adulthood including stress-reactivity, psychiatric morbidity and mortality (e.g., increased incidence of depressive symptoms and anxiety), and memory impairments (Anda et al., 2006; Bernet &

Stein, 1999; Brown, Cohen, Johnson, & Smailes, 1999; Hildyard & Wolfe, 2002; Valentino, Toth, & Cicchetti, 2009). Patients with anxiety and depressive disorders often show deficits in cognitive domains, including prefrontal-dependent cognitive tasks such as the Wisconsin Card Sort Test (Austin, Mitchell, & Goodwin, 2001; Merriam, Thase, Haas, Keshavan, & Sweeney, 1999).

Developing mammals are also influenced by more subtle changes in the early-life period. In humans, the quality of early caregiving is a major environmental determinant of both HPA reactivity and broader neurodevelopmental processes (Ainsworth, 1979; Anda et al., 2006; Bernet & Stein, 1999; Byrd-Craven, Auer, Granger, & Massey, 2012; Egeland & Sroufe, 1981; Enlow, Egeland, Blood, Wright, & Wright, 2012; Grossmann, Grossmann, & Waters, 2006; Hildyard & Wolfe, 2002; Hunter, Minnis, & Wilson, 2011). For instance, low levels of maternal care are correlated with increased risk of depression among offspring in adulthood (Parker, 1993). In the laboratory rat, differ-

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ences in the quality of care pups receive from dams have large effect on later adult phenotypes. Offspring reared in Low maternal care (i.e., licking; L) litters exhibit increased anxiety-like phenotypes, diminished HPA-negative feedback capacity in response to an acute stressor, and decreased expression of glucocorticoid receptors (GR) in the hippocampus relative to rats reared under High maternal care conditions later as adults (Champagne, Francis, Mar, & Meaney, 2003; Francis, Champagne, Liu, & Meaney, 1999; Liu et al., 1997; Weaver et al., 2004). All rat dams provide adequate care to their offspring, however, the quality of care is important to later neuroendocrine and behavioral outcomes (Akers et al., 2008).

The prefrontal cortex (PFC), a region of the brain central to cognitive flexibility and executive functioning (Arnsten, 2009; Birrell & Brown, 2000; Dalley, Mar, Economidou, & Robbins, 2008; DeSteno & Schmauss, 2008; Goldman-Rakic, 1995; Hauber & Sommer, 2009; McEwen & Morrison, 2013; Wallis, Anderson, & Miller, 2001), is highly susceptible to environmental experience, particularly during early life (Cook & Wellman, 2004; Dias-Ferreira et al., 2009; Evans & Schamberg, 2009; Hackman & Farah, 2009; Mizoguchi et al., 2000; Radley et al., 2008; Watson, Kirby, Kelleher, & Bradley, 1996). For instance, prenatal and postnatal maternal stress in rodents results in alterations in PFC development, which can then influence behavior in adulthood (Green et al., 2011; McEwen & Morrison, 2013; Muhammad, Carroll, & Kolb, 2012; Quirk, Garcia, & González-Lima, 2006). Similarly, early life maternal care is capable of shifting  $\alpha$ -1 GABAA receptor mRNA expression in the rodent mPFC as well as stress-induced dopamine release; potentially contributing to observed alterations in adult anxiety behavior and sensorimotor gating in High and Low offspring (Caldji, Diorio, & Meaney, 2000; Caldji, Francis, Sharma, Plotsky, & Meaney, 2000; Zhang, Chretien, Meaney, & Gratton, 2005). However, it is not clear if changes in maternal care are capable of altering behaviors dependent on the mPFC despite alterations in structural and functional neuronal plasticity.

In non-human primates, early experiences, both mild and severe, are also capable of altering stress responsivity, pre-frontal glucocorticoid expression, pre-frontal cortex volume, monoamine metabolism, and cognitive behaviors dependent on the pre-frontal cortex (Feng et al., 2011; Lyons, Afarian, Schatzberg, Sawyer-Glover, & Moseley, 2002; Lyons, Yang, Mobley, Nickerson, & Schatzberg, 2000; Parker, Buckmaster, Lindley, Schatzberg, & Lyons, 2012; Patel, Katz, Karssen, & Lyons, 2008; Pryce, Dettling, Spengler, Spaete, & Feldon, 2004; Schneider et al., 1998; Spinelli et al., 2009). It has become increasingly clear that early life stressors can augment PFC

development in humans as well. For example, children from impoverished backgrounds exhibit diminished activity in PFC activity as measured by EEG (Kishiyama, Boyce, Jimenez, Perry, & Knight, 2009). Damaged or compromised cognitive function is associated with low academic achievement, lower IQ, and deficits in memory and attention (Pechtel & Pizzagalli, 2011).

Converging evidence, across species, demonstrates the influence early-life experiences can have on executive function. In the current study, we predict that rats reared under low maternal conditions will have impaired executive function as measured by a perceptual attentional set-shifting task (ASST). We also predict that Low L offspring will differ in stress reactivity profiles, and potentially, that these stress profiles may influence executive functioning compared to High L animals.

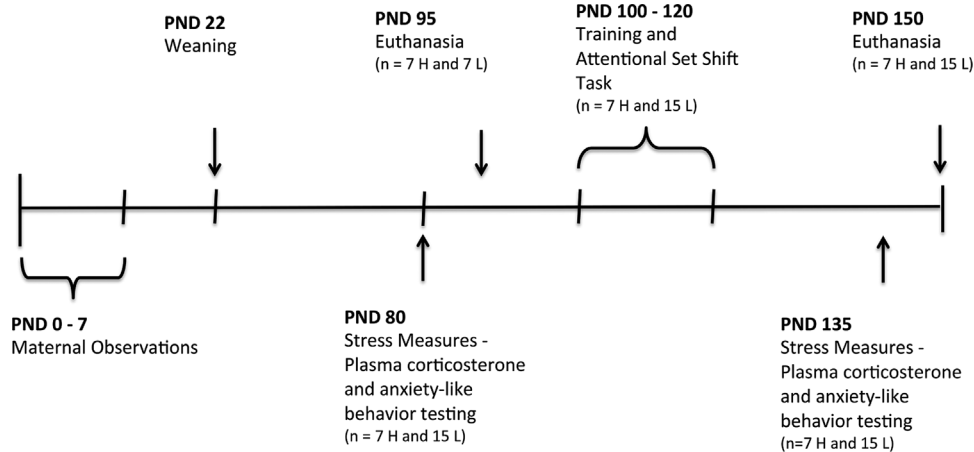
## MATERIALS AND METHODS

### Animals and Housing

Male rats used in the study were born in our home colony, generated from Long Evans rats purchased from Charles River Breeding Laboratories (Wilmington, MA). Female Long-Evans rats were bred in-house at UC Berkeley, allowed to give birth and maternal behaviors recorded as described below. Dams gave birth within 5 days of each other. Animals were weaned on post-natal Day (PND) 22, and pair housed in polypropylene cages (27.8 × 17.5 × 13.0 cm) and left undisturbed until adulthood (PND 80) upon which they were assessed on several stress sensitive tasks. On PND 95, a subset of animals was euthanized for post-mortem measures. From PND 100 to 120, remaining animals were trained and tested for cognitive flexibility (ASST task described below). On PND 135, following ASST training and testing, animals were again assessed on a battery of stress-sensitive tasks and then euthanized (~ on PND 150). Please see Figure 1 for the experimental timeline. Temperature was kept constant at 20 ± 2°C and relative humidity was maintained 50 ± 5%. Rats were maintained on a 12-hr light-dark cycle (lights on 07:00 to 19:00 hr), housed on wood pulp bedding, and allowed access to food (Purina Rat Chow, Purina Mills, St. Louis, MO) and tap water ad libitum, except during ASST testing. Two weeks prior to ASST, animals were maintained on a restricted diet of 20 g of food per day and maintained to 85% of their original starting weight to ensure motivation to complete the task. Care of rats was carried out in accordance with the standards and practices of the UC Berkeley Animal Care and Use Committee.

### Observations of Maternal Behavior

Observations of maternal behavior were performed, with slight modification, as previously described in Sakhai, Kriegsfeld, and Francis (2011). Female rats were bred and permitted to give birth. Maternal observations were performed the day



**FIGURE 1** Experimental timeline (PND—postnatal day).

following birth, beginning on PND 1 and continued until PND 7. Each litter was observed for 5 hr a day at the following times: 06:00–08:00, 12:00–13:00, and 18:00–20:00. This observation schedule was selected as rats are crepuscular and maternal care is most active surrounding lights on and lights off. During each session, litters were observed and maternal behaviors recorded every 2 min. Maternal licking was expressed as a percentage of the total number of observations performed for each litter. High and Low L litters were assessed as those falling one SD above or below the mean frequency of maternal licking, respectively. Offspring were weaned, pair housed with same sex littermates, and left undisturbed until adulthood.

### PFC-Dependent Set-Shifting Behavior

In adulthood, animals were trained on an mPFC-dependent ASST ( $n=7$  High and  $n=15$  Low); the overall maternal L distribution skewed low L (which is consistent across studies), leading to unequal group numbers. The ASST is a rodent version of the Wisconsin Card Sorting Test, a neuropsychological task used to assess PFC function in humans (Robinson, Lehman, Stilson, & Donald, 1980). It necessitates an intact mPFC, requiring animals to shift between varying response rules, and is thought to be a measure of cognitive flexibility and executive functioning (Birrell & Brown, 2000; Ng, Noblejas, Rodefer, Smith, & Poremba, 2007). As animals must learn one set of rules and behavioral actions before testing, the ASST requires extensive training and handling to test mPFC set-shifting integrity (Birrell & Brown, 2000; McAlonan & Brown, 2003). Testing protocol and equipment was modified from Birrell and Brown (2000).

Animals were first trained to retrieve a food reward by digging in small terra-cotta pots (6 cm diameter  $\times$  5 cm height) filled with medium (e.g., type of bedding). Pots carried two types of information salient to the animal to receive reward—medium type or odor. Animals were trained to dig for reward using information from a single dimension (i.e., odor). The number of errors, perseveration effects, and time to complete the task was assessed before and after the

dimension shift occurred. Animals then had to attend to the new relevant dimension of the stimulus (i.e., medium). See Table 1 for the order of discriminations for the ASST.

**Initial Training and Simple Discrimination.** Starting on PND 100, animals were handled daily for  $\sim 5$  min per day for 10 days in preparation for ASST testing. After initial handling, animals were trained to dig to retrieve a food reward over 7 days. A minimum of 20 consecutive digs was used as a threshold of learning. For two consecutive days, animals were then trained on a simple discrimination (SD) in which they learned to respond to a specific odor cue to receive a reward. Testing continued until six consecutive correct trials were made. Rats were allowed to approach and sniff the pot or climb over it; however, if medium was displaced by digging or by sniffing, the response was recorded. All rats were trained on the same discriminations, in similar order. Exemplars, medium and odor, were not used again during testing. See Table 2 for a list of exemplars.

**Training Experience and ASST Testing.** During the SD, rodents learned that one odor is relevant and rewarded. In the next stage of the task, the compound discrimination (CD), stimuli were made more complex. Odor continued to remain the rewarded dimension while animals had to discount extraneous information regarding the medium. The first of three reversals (R1) followed the CD, in which animals learned that the previously correct exemplar was now incorrect within the same dimension (i.e., odor remained the relevant dimension; however, the previously rewarded odor exemplar was now irrelevant). Animals had to learn to switch learned odor associations to receive reward. For both the intra-dimensional (ID) and extra-dimensional shift (ED), new exemplars were used for the relevant and irrelevant dimensions. For the ID, odor was reinforced as the relevant dimension using new stimuli, solidifying odor-reward associations. For the ED, animals were required to shift rule contingencies with the previously relevant dimension (odor) no longer being rewarded, that is, the medium was now rewarded. Testing was counterbalanced to minimize order

**Table 1. Order of Discriminations for Attentional Set Shift Task**

| Training Discriminations     | Dimensions |            | Exemplar Combinations |       |
|------------------------------|------------|------------|-----------------------|-------|
|                              | Relevant   | Irrelevant | +                     | –     |
| Simple (SD)                  | Odor       | Medium     | <b>O1</b>             | O2    |
| Testing Discriminations      | Dimensions |            | Exemplar Combinations |       |
|                              | Relevant   | Irrelevant | +                     | –     |
| Simple (SD)                  | Odor       | Medium     | <b>O3</b>             | O4    |
| Compound (CD)                | Odor       | Medium     | <b>O3/M1</b>          | O4/M2 |
|                              |            |            | <b>O3/M2</b>          | O4/M1 |
| Reversal (Rev 1)             | Odor       | Medium     | <b>O4/M1</b>          | O3/M2 |
|                              |            |            | <b>O4/M2</b>          | O3/M1 |
| Intra-dimensional shift (ID) | Odor       | Medium     | <b>O5/M3</b>          | O6/M4 |
|                              |            |            | <b>O5/M4</b>          | O6/M3 |
| Reversal (Rev 2)             | Odor       | Medium     | <b>O6/M3</b>          | O5/M4 |
|                              |            |            | <b>O6/M4</b>          | O5/M3 |
| Extra-dimensional shift (ED) | Medium     | Odor       | <b>M5/O7</b>          | M6/O8 |
|                              |            |            | <b>M5/O8</b>          | M6/O7 |
| Reversal (Rev 3)             | Medium     | Odor       | <b>M6/O7</b>          | M5/O8 |
|                              |            |            | <b>M6/O8</b>          | M5/O7 |

Example of stimulus combination pairs for attentional set shift task. The correct exemplar, which the rat must choose, is shown in bold, with an irrelevant exemplar paired. On each discrimination, a new set of exemplars was used. Odor remained the relevant dimension until the extra dimensional shift, upon which the medium became relevant and the odor irrelevant. (Modified from Birrell & Brown, 2000).

effects. In total, each animal received 20 days of consecutive training ranging from 5 min for handling sensitization to 3 hr of cognitive stimulation on testing day.

### Anxiety-Like Behavior

Between 10:00 and 13:00, beginning on PND 80 and again after ASST training ( $n=7$  High and  $n=15$  Low), animals were tested in two stress-sensitive behavioral tasks: the Open-Field and the Light-Dark Box Test (Archer, 1973; Hall, 1934). Animals were tested on non-consecutive days.

**Open Field.** To assess anxiety-like behavior, animals were exposed to an open field. The open field consisted of a large circular polypropylene arena 140 cm in diameter, 61 cm in height. Each animal was placed in the open-field for 5 min and subsequent behaviors recorded. Frequency of crosses between the outer arena (14 cm width) and the interior inner arena (112 cm diameter) and amount of time spent in the inner-arena of the open field was quantified from video.

**Table 2. Examples of Exemplar Stimulus Pairs Used**

| Odor Pairs               | Medium Pairs                      |
|--------------------------|-----------------------------------|
| Vanilla vs. cranberry    |                                   |
| Pine vs. strawberry      | Moss vs. felt                     |
| Honey dew vs. cinnamon   | Styrofoam vs. shredded sand paper |
| Lavender vs. pomegranate | Shredded paper vs. plastic beads  |

**Light-Dark Box.** Similar to the open field, the light-dark box is used to assess anxiety-like behavior in rodents. The light-dark box consists of two contiguous rectangular arenas (76 × 40 cm) joined by an entrance (10 × 10 cm). One arena, the light box, is open and exposed, while the second arena is dark and sheltered providing a less aversive space for the animal. Animals were initially placed within the dark chamber and given 5 min of exploration time. Latency to emerge from the dark box and time spent in the light box was recorded by an experimenter blind to group conditions.

### HPA Measures

**Plasma Corticosterone.** Tail blood was collected from two subsets of High and Low offspring, before and after training experience ( $n=7$  High and  $n=15$  Low). Blood samples were collected similarly across both time points between 07:00 and 10:00. To assess basal corticosterone values, animals were removed from home cage and tail bled within 2 min. For stress values, animals underwent 15 min of restraint stress, and blood rapidly collected. Upon completion of acute restraint stress, animals were released to home cage and blood collected every 30 min for four recovery time points. Plasma was extracted from blood and frozen at  $-20^{\circ}\text{C}$  until assayed using corticosterone enzyme immunoassay (Enzo Life Sciences, Ann Arbor, MI). Prior to analysis of data, one animal was removed due to insufficient volume of blood sample.

**Glucocorticoid Receptor Western Blot.** To assess alterations in HPA physiology, before and after training experience (before:  $n=7$  High and  $n=7$  Low; after:  $n=7$  High and  $n=15$  Low), two subsets of High and Low offspring were

assayed for glucocorticoid receptor (GR) protein expression in the frontal cortex and hippocampus via Western blot. Hippocampus was removed and frontal cortex dissection was restricted to infralimbic, prelimbic, and anterior cingulate cortices. Protein was extracted and blotted against polyclonal rabbit anti-GR at 1:2000 (Santa Cruz Biotechnology, Santa Cruz, #sc-1004) and mouse anti-actin at 1:10,000 (Sigma-Aldrich, St. Louis, #A1978). See Sakhai, Preslik, and Francis (2013) for a more detailed protocol.

### Data Analysis

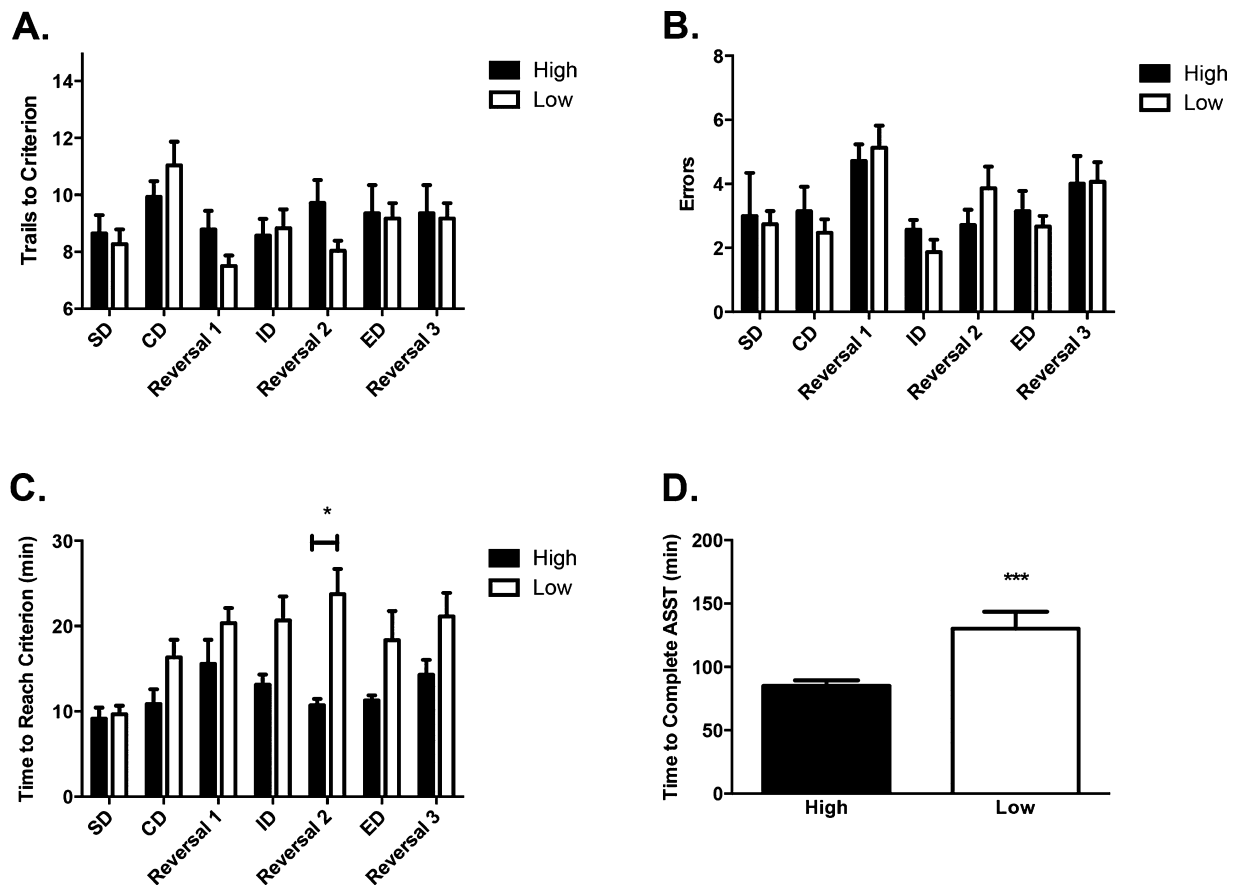
Prior to analysis of behavioral data, a D'Agostino—Pearson omnibus test for normality was conducted. If data did not pass normality, a Mann–Whitney U-test was used to account for a non-Gaussian distribution. Otherwise, data were analyzed by a Student's *t*-test. Plasma corticosterone and ASST performance were analyzed by repeated measures analysis of variance (ANOVA). The ANOVA for ASST performance included one within-subjects factor (stage: SD, CD, Rev1, ID, Rev2, ED, Rev3), one between-subjects factor (group: high

maternal care, low maternal care), and their interaction. A Šidák–Bonferroni multiple comparisons posttest was used to assess groups across conditions. Results were considered statistically significant when  $p < .05$ . Data were also analyzed to assess within litter and within cage effects.

## RESULTS

### Maternal Observations

Dams naturally differed in frequency of licking directed at pups over the first week post-partum. A maternal care score was generated by calculating the frequency of maternal licking observed relative to the total number of observations performed over the entire observation period. Anogenital licking scores ranged from 3.3 to 11.9% with a mean of 6.8% (SD of 1.7%) across litters. Litters that fell  $\pm 1$  SD away from the mean in each cohort were used in the remainder of the



**FIGURE 2** Offspring attention set-shifting behavior. The number of (A) trials to criterion and (B) errors on each component of the attentional set-shifting task across maternal care conditions ( $p > .05$ ). (C) Animals reared by a Low L mother spend significantly more time to reach criterion on the second reversal of the ASST ( $p < .05$ ). (D) Low L animals spend  $\sim 35\%$  more time to complete the task in its entirety ( $p < .05$ ) than High L animals. SD, simple discrimination; CD, compound discrimination; R, reversal, ID, intra-dimensional shift; ED, extra-dimensional shift.

study ( $n = 5$  High and 6 Low L litters). For each of the dependent variables, no within litter or within cage effects were observed,  $p > .05$ .

### Attentional Set-Shifting Task

High and Low L animals did not differ across groups in set-shifting performance on the ASST (Fig. 2A and B). Trials to criterion differed significantly by Stage of the ASST (e.g., SD, CD, R1, ID etc.),  $F(6, 120) = 6.26$ ,  $p < .001$ , but neither the effect of Maternal care nor the interaction were significant,  $F(1, 120) = .69$ ,  $p = .416$  and  $F(6, 120) = .52$ ,  $p = .790$ , respectively. Similarly, errors differed significantly by Stage,  $F(6, 120) = 4.29$ ,  $p < .001$ , but neither Maternal care nor the interaction were significant,  $F(1, 120) = .02$ ,  $p = .879$  and  $F(6, 120) = .59$ ,  $p = .735$ , respectively.

Remarkably, animals reared by Low L mothers take ~35% more time to complete the ASST task than High L offspring,  $U(20) = 7.5$ ,  $p < .001$  (Fig. 2C). Although there is no significant interaction between Stage of the ASST and Maternal care in time to completion,  $F(6, 120) = 1.74$ ,  $p = .118$ , main effects of Maternal care,  $F(1, 120) = 5.13$ ,  $p = .0347$  and Stage of ASST,  $F(6, 120) = 4.73$ ,  $p < .001$  are significant (Fig. 2D). Šidák-Bonferroni post-hoc tests show Low L animals spend significantly more time than High animals to complete the second reversal of the ASST  $t(140) = 3.36$ ,  $p < .05$ . This trend was also observed, although not significantly, with the CD, R1, ID, ED, and R3. Importantly because animals must be food restricted to ensure proper motivation on the ASST, there were no absolute differences in weight before or after food restriction between groups,  $F(1, 20) = .004$ ,  $p = .952$ .

### Pre-Training Stress Phenotype

#### Behavior.

**Open field.** As adults, High animals spent significantly more time exploring the inner arena of the open field than Low animals before training on the ASST,  $U(20) = 19.50$ ,  $p = .018$  (Fig. 3A). More time exploring the inner area of this arena is interpreted as lower levels of anxiety in these animals.

**Light-dark box.** High animals spent significantly more time exploring the light arena of the Light-Dark box before training,  $U(20) = 16.50$ ,  $p = .008$  (Fig. 3B). Similar to the open field, greater time exploring the exposed arena of a light-dark box apparatus suggests lower levels of anxiety.

#### HPA Measures.

**Plasma corticosterone.** Prior to training experience, High and Low animals significantly differed in HPA

reactivity to an acute stressor. The main effect of Maternal care was significant,  $F(1, 118) = 10.68$ ,  $p = .001$ , as was the main effect of Time,  $F(5, 118) = 16.99$ ,  $p < .001$ . The interaction of these two factors was not significant,  $F(5, 118) = 1.159$ ,  $p = .334$ . Post-hoc testing shows that Low animals displayed a significantly higher corticosterone peak 30 min after restraint stress than High animals  $t(119) = 2.93$ ,  $p < .05$  (Fig. 3C). Integrated corticosterone values (area-under-the curve) across the 2-hr period was significantly higher in Low L offspring as well, showing that Low L animals are exposed to higher overall amounts of corticosterone compared to High animals,  $t(20) = 2.12$ ,  $p = .046$  (Fig. 3D). Intra-assay and inter-assay variability for corticosterone ELISA was 3.4 and 7.8%, respectively.

**Glucocorticoid Receptor Expression.** Hippocampal glucocorticoid receptor expression was significantly different between High and Low animals before ASST testing, with High L exhibiting significantly more GR expression,  $U(11) = 3$ ,  $p = .008$  (Fig. 3E). However, glucocorticoid receptor expression in the frontal cortex did not differ across groups,  $U(13) = 28$ ,  $p = .999$  (Fig. 3F).

### Post-Training Stress Phenotype

#### Behavior.

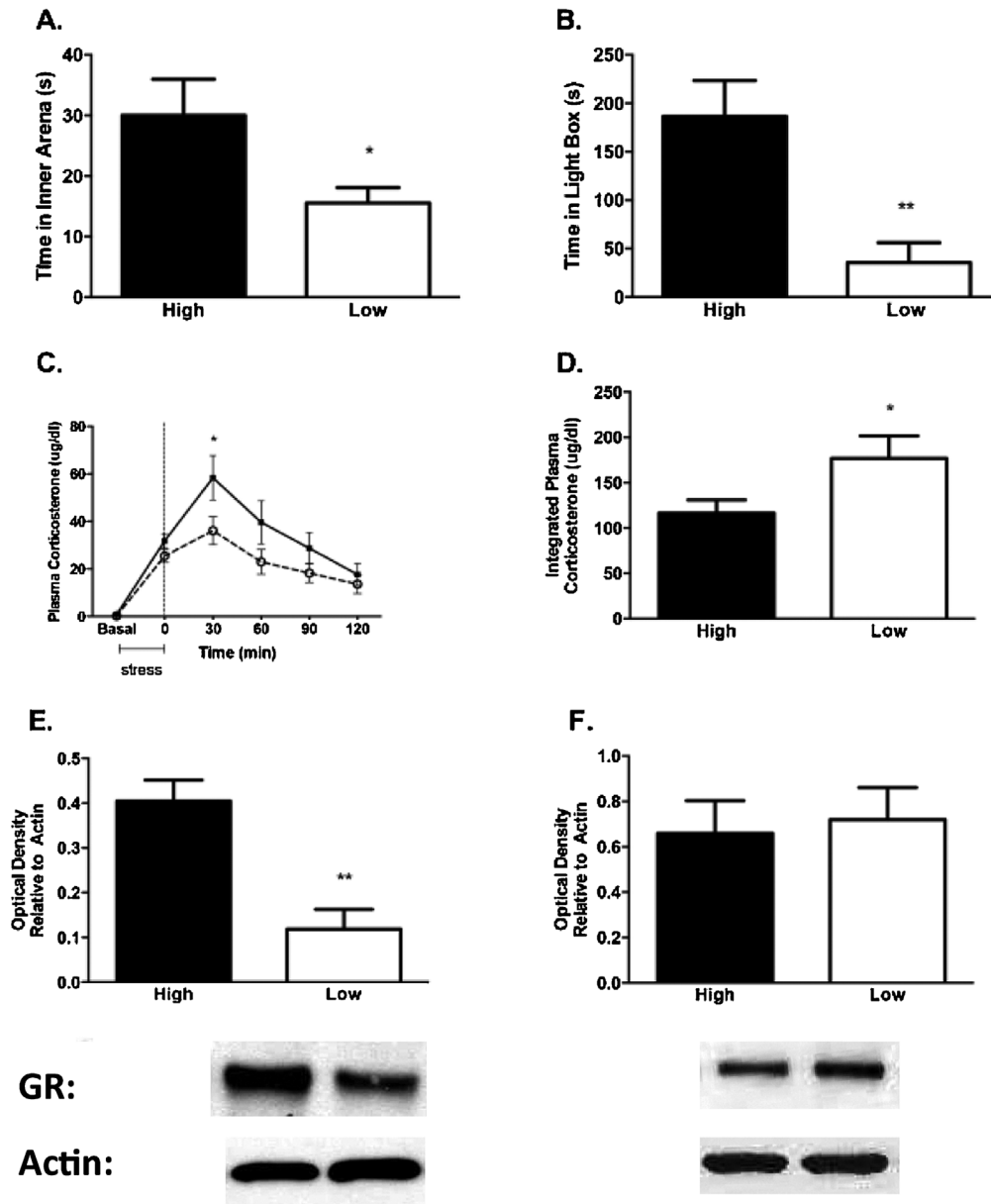
**Open field.** As adults, groups were no longer significantly different in the open field.  $U(20) = 42$ ,  $p = .479$  (Fig. 4A).

**Light-dark box.** High and Low animals spend equivalent time exploring the light arena of the Light-Dark box,  $U(20) = 40$ ,  $p = .535$  (Fig. 4B).

#### HPA Measures.

**Plasma corticosterone.** Plasma corticosterone values did not significantly differ between High L and Low L animals, main effect of maternal care,  $F(1, 114) = 1.35$ ,  $p = .247$  (Fig. 4C). Time, as a main effect, remained significant,  $F(5, 114) = 21.67$ ,  $p < .001$ . There was no interaction between Time and Maternal care,  $F(5, 114) = .99$ ,  $p = .427$ . Furthermore, integrated corticosterone values (area-under-the curve) over the 2-hr period were not significantly different across groups,  $U(19) = 37$ ,  $p = .539$  (Fig. 4D). Intra-assay variation for corticosterone ELISA was 3.2 and 8% inter-assay.

**Glucocorticoid Receptor Expression.** After ASST testing, glucocorticoid receptor expression in the hippocampus remained significantly different, with High L



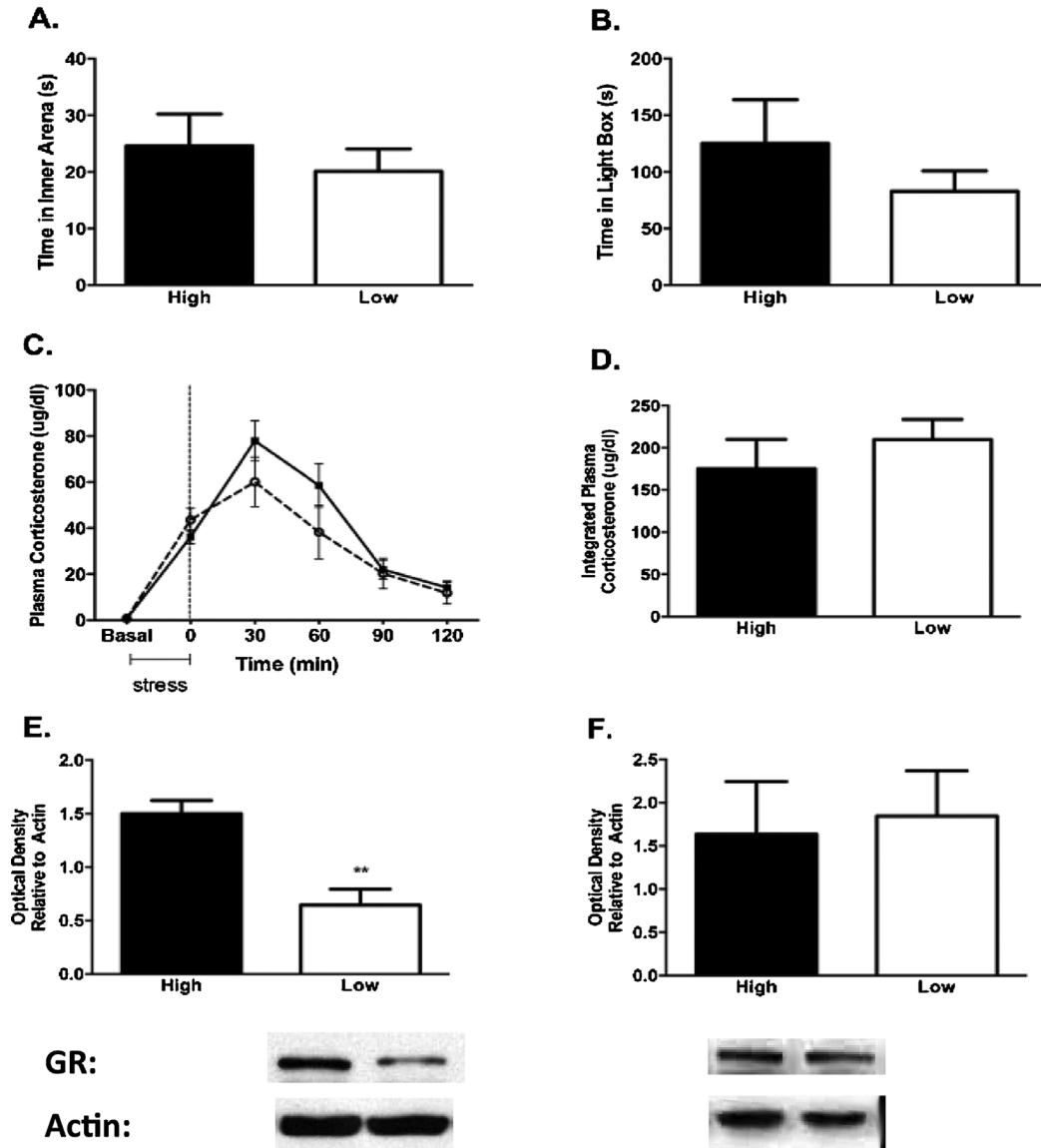
**FIGURE 3** Offspring behavior in adulthood prior to training-experience. (A) Open Field and (B) Light-Dark Box. Animals reared by a Low L mother spend significantly more time on behavioral indices of anxiety as indicated by the open field and light-dark box task ( $p < .05$ ). (C) When exposed to acute restraint stress, Low L animals exhibit significantly greater peak corticosterone profiles after 30-min recovery as well as (D) across the 120 min recovery period ( $p < .05$ ) assessed calculating the area under the curve (AUC). Basal corticosterone was not significant between groups. (E) Hippocampal glucocorticoid receptor protein levels were decreased in the Low LG animals compared to High L ( $p < .05$ ); however, (F) glucocorticoid receptor protein levels did not differ in the mPFC between groups.

offspring exhibiting more GR expression,  $U(14) = 6$ ,  $p = .005$  (Fig. 4E). Glucocorticoid receptor expression in the frontal cortex was not significantly different across groups,  $U(14) = 25$ ,  $p = .512$ , (Fig. 4F).

## DISCUSSION

We predicted that rats reared under reduced maternal conditions early in life, when tested later in adulthood,





**FIGURE 4** Offspring behavior in adulthood after ASST training-experience. (A) Open Field and (B) Light-Dark Box. Animals reared by Low or High L mothers did not differ in behavioral indices of anxiety as measured by the open field and light-dark box ( $p > .05$ ). (C) When exposed to acute restraint challenge, Low and High groups were no longer significantly different at either peak stress ( $p > .05$ ) or (D) across the 120-min recovery period ( $p > .05$ ). (E) Hippocampal glucocorticoid receptor protein levels remained reduced in the Low L group ( $p < .05$ ). (F) Glucocorticoid receptor protein levels also remained unchanged in the mPFC, compared to High L animals.

would exhibit impaired executive function in a rodent version of the Wisconsin Card Sorting Task, an attentional set-shifting task. Instead, we report here that both groups were capable of successfully performing the ASST task, regardless of maternal rearing condition. Performance was assessed as i) the number of

trials it took each animal to reach criterion and ii) the number of incorrect choices made by individual rats. This finding was unexpected given the known effects of variations in maternal care on adult cognitive function (Green et al., 2011; Liu, Diorio, Day, Francis, & Meaney, 2000; Muhammad et al., 2012). We did find

that adult rats reared under Low maternal licking conditions took significantly longer to complete the overall task relative to High L offspring. We also predicted that High and Low L offspring would differ in stress reactivity profiles when tested as adults. This hypothesis was confirmed as animals differed in stress reactivity profiles as adults. Interestingly, these group differences were not apparent after cognitive training/handling and testing.

We predicted that High L adult offspring would perform better than Low L offspring on the ASST, based on a variety of data from humans and rodents exhibiting a putative link between early life experiences and cognitive function (Meaney, 2010). These differences include variability between High and Low rat offspring in multiple physiological and behavioral domains, including hippocampal-dependent tasks, neuronal survival, HPA functioning and stress reactivity, sociality and reproductive behavior (Bredy, Grant, Champagne, & Meaney, 2003; Cameron et al., 2008; Champagne et al., 2008; Engert, Jooper, Meaney, Hellhammer, & Pruessner, 2009; Fish et al., 2004; Francis, Champagne, & Meaney, 2000; Liu et al., 2000; Sakhai et al., 2011; Starr-Phillips & Beery, 2014; Zhang et al., 2005). In humans, a correlation between early-life experiences and cognitive function also suggests a putative role for early-experiences in PFC development. In children, exposure to early-life trauma is associated with deficits in cognitive function (Enlow et al., 2012). Children exposed to child neglect, the most common form of maltreatment, also have deleterious effects on children's development including cognitive function. Compared to other maltreatment groups, emotionally neglected children have the largest decrease in scores on the Bayley Scales of Infant Development between 9 and 24 months old (Egeland & Sroufe, 1981). By kindergarten age, neglected children have the lowest scores of all maltreatment groups on tests of intellectual functioning and academic achievement (Hildyard & Wolfe, 2002).

In laboratory rats, variations in maternal behavior are related to the development of individual differences in cognitive performance of offspring when tested later in adulthood. Specifically, spatial learning and memory is enhanced in adult offspring reared in a High L relative to Low L maternal condition (Bredy, Humpartzoomian, Cain, & Meaney, 2003; Bredy, Zhang, Grant, Diorio, & Meaney, 2004; Liu et al., 2000). This is a persistent effect that lasts into old age (Liu et al., 2000). As spatial learning and memory are hippocampal-dependent processes, it is not surprising that markers of hippocampal synaptic plasticity (synaptophysin and N-CAM) are significantly higher in High L rats when measured at PND 18 and at PND 90 (Bredy

et al., 2004; Liu et al., 2000). To our knowledge, there is no evidence that PFC-dependent cognitive tasks differ across rats reared under different maternal conditions. Current findings are consistent with this statement.

The difference in time it took for High and Low L animals to complete each stage of the ASST, with equivalent levels of accuracy across groups, was unexpected yet interesting. Time differences could reflect information-processing deficits, stress effects, possible differences in appetitive behaviors (reward and motivation) that may include differences in food rewards to achieve satiety. Variations in maternal care have been shown to influence most of these processes (with the exception of the latter). As all animals were food restricted to 80–85% of their body weight before the start of testing we believe they were all sufficiently motivated to complete the task. We believe that stress effects may confound performance on cognitive tasks (directly and indirectly); however, additional and more detailed experiments are required to specifically test this hypothesis.

An exciting finding is the convergence of stress phenotypes across High and Low L animals by the end of the testing period. Measures of stress-sensitive behaviors and hormones were measured prior to the training and administering of the ASST task and again after the task. Prior to cognitive training and testing, the High L offspring had greater exploration in the behavioral tasks and lower corticosterone levels following an acute stressor relative to Low L offspring. Following the ASST training and trialing period, High and Low L offspring stress phenotypes were no longer significantly different. In fact, both H and L animals displayed an increase in plasma corticosterone after training and handling. This rise may be due to the broad exposure of animals to HPA activating experiences. Our study was not designed to investigate training effects on amelioration of the stress response. It is possible that changes in corticosterone levels after the training regimen may be simply be occurring due to the passage of time (Brudieux, Ait Chaoui, & Rakoton-drazafy, 1995). We hypothesize, however, that one potential explanation for the observed changes in plasma corticosterone levels and amelioration of stress-sensitive behavioral and HPA differences across groups is the robust training, handling, and cognitive enrichment provided to all animals to implement the ASST task. Animals received, on average, ~25 min of handling per day for 20 consecutive days, ranging from 5 min to 3 hr of stimulation on testing day. In congruence with this hypothesis, previous animal studies have shown an ostensible reversal of the effects of early life experience by handling, training, and enrichment.

For example, mice handled in adulthood have been shown to reverse anxiety-like behavior incurred by the stress of solitary housing (Heredia, Torrente, Domingo, & Colomina, 2012). In rats, postnatal handling is capable of reversing the effects of prenatal stress both behaviorally and at the level of the HPA axis (DeNelsky & Denenberg, 1967; Maccari et al., 1995; Vallée et al., 1999; Weinstock, 1997). Environmental enrichment post-weaning is also capable of reversing the adult anxiogenic HPA and behavioral responses to stress generated by maternal separation models (Francis, Diorio, Plotsky, & Meaney, 2002; Whimbey & Denenberg, 1967). Quite relevantly, environmental enrichment during adolescence and early adulthood has been shown to eliminate deficits in cognitive function (assessed by Morris water maze learning and object recognition tasks; hippocampal dependent tasks) between High and Low L offspring. However, mechanisms of reversibility/compensation are not known (Bredy, Humpartzoomian, Cain, & Meaney, 2003). Collectively, these studies demonstrate that at the level of behavior, the long-term effects of early-life maternal care are, indeed, reversible. We would also like to note that with the current data set we have not established a causal relationship between quality of maternal care received and later adult cognitive function. To do this would require a different experimental design, which may include early postnatal cross-fostering of offspring across varying maternal conditions.

In the current study, we hypothesize that some measure of compensation is occurring in animals as a result of the training and handling regimen. Frontal cortex and hippocampal glucocorticoid receptor gene expression, which influence the magnitude and efficacy of the stress response, remained the same after handling/training enrichment relative to pre-training levels. Indeed, these findings suggest that alterations to hippocampal and frontal cortex GR expression may be resistant to subsequent environmental influences, maintaining the residues of early life experience. The scope of the proposed compensatory effect remains a matter of speculation, but the hippocampus and PFC are interesting sites for consideration due to their role in mediating and moderating the stress response.

We initially hypothesized that adult rats reared under low maternal conditions would be impaired on a PFC-dependent task relative to rats raised in high maternal care conditions. However, this turned out not to be the case. We do provide tentative evidence that stress-sensitive developmental effects in rats may be influenced by later handling/training. The most highly and consistently reported differences between High and Low L reared rats are related to stress-sensitive markers and behaviors. Low L rats, as adults, are more anxious,

fearful, and stress-reactive relative to High L animals. Here, we confirm reports that Low L offspring, as adults, are more stress-reactive compared to High L offspring; however, early life maternal care does not appear to impact mPFC-dependent set-shifting behavior in the rat. These findings may be of particular importance for those interested in the relationship between early life experiences and adult cognitive function.

## NOTES

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## FINANCIAL DISCLOSURE

The authors, Samuel A. Sakhai, Katherine Saxton, and Darlene D. Francis declare no financial or potential conflicts of interests in the investigation or publication of this work.

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