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Medial Prefrontal Cortex Lesions in the Female Rat Affect Sexual and Maternal Behavior and Their Sequential Organization

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Temporal sequences of sexual and maternal behaviors in female rats and their correlation with each other and with performance on a sensory-motor gating response inhibition task assessed by prepulse inhibition (PPI) were investigated following medial prefrontal cortex (mPFC) lesions. Following excitotoxic mPFC ($n = 10$) or sham ($n = 9$) lesions, sexual behaviors across the ovarian cycle were scored. After mating and parturition, maternal interactions were scored until pups reached postnatal Day 10. After resumption of the ovarian cycle, the female rats were tested for PPI. Compared with sham lesions, mPFC lesions impaired proceptive behaviors and some maternal behaviors (e.g., pup retrieval, pup licking) but did not affect others (e.g., nest building, pup mouthing). Lesions disrupted temporal sequences of solicitations (number of male orientations followed, within 4 s, by a level change) and pup retrievals (number of pup retrievals followed, within 5 s, by another retrieval). These sequential behavior patterns were significantly correlated with each other and with PPI. However, when PPI effects were partialled out, group differences were less strong, but persisted. This study demonstrated that mPFC manipulations affect actions rich in sequential structure in response to biologically relevant stimuli.

Keywords: species-typical behavior, prefrontal cortex, prepulse inhibition, temporal organization, motor activity

Sexual and maternal behavior in the female rat consists of several stereotyped components, regulated by similar and overlapping mechanisms: by odors (Edwards & Warner, 1972; Fleming & Rosenblatt, 1974a, 1974b; Kolunie & Stern, 1995; Lumia, Meisel, & Sachs, 1981; McGinnis, Lumia, & McEwen, 1985; Williams, Goldman, McGinnis, Possidente, & Lumia, 1991), by ovarian hormones (Bridges, 1984; Leon, Numan, & Moltz, 1973; Moltz, Lubin, Leon, & Numan, 1970; Pfaff, 1970, 1982), and by subcortical brain systems consisting of the medial preoptic area, ventromedial hypothalamus, bed nucleus of stria terminalis, amygdala, septal area, and periaqueductal gray (Fleischer & Slotnick, 1978; Gray & Brooks, 1984; Lonstein & Stern, 1998; Numan, Fleming, & Levy, 2006; Simerly, 2002). Most research on reproductive behaviors has focused on deficits or facilitatory effects following neural manipulations. Very few studies have investigated the complex decision making needed for these behaviors.

In rodents, the medial prefrontal cortex (mPFC) has been studied extensively within the context of cognition and has been shown to contribute to decision making, monitoring, attentional selection, self-control, task switching, and sequencing of behavior (Dalley, Cardinal, & Robbins, 2004). These abilities, collectively referred to as executive functions, are particularly important in open-ended, unstructured, or dynamic environments. In rats, lesions of the mPFC produce deficits in cognitive tasks (Kolb, 1990; Uylings, Groenewegen, & Kolb, 2003). These deficits are reflected in alterations in visual attention (Broersen & Uylings, 1999), attentional shifts (Birrell & Brown, 2000), and sequential ordering of motor responses (Kolb, 1990), as well as response inhibition (Broersen & Uylings, 1999) and self-control (Winstanley, Theobald, Dalley, Cardinal, & Robbins, 2005). The role of the mPFC in individual features of executive function (e.g., attention, attentional shifts, response inhibition) has been studied. The mPFC's role in the organization of the sequential execution of sexual and maternal behavior has received little attention, although the mPFC has been implicated in both of these reproductive behaviors (Agmo, Villalpando, Picker, & Fernandez, 1995; Balfour, Brown, Yu, & Coolen, 2006; Hernandez-Gonzalez, Navarro-Meza, Prieto-Beracoechea, & Guevara, 2005; Stamm, 1955).

Sexual and maternal activities of the female rat involve naturally occurring behavioral patterns with well-organized behavioral sequences in time. During a sexual testing bout, a sexually responsive female rat will respond to a male with a series of proceptive behaviors. These behaviors include anogenital investigations, hopping, darting, and ear wiggling (Beach, 1976; Emery & Moss, 1984; Erskine, 1989), as well as a rapid sequence of approach toward, orientation to, and withdrawal from the male (i.e., solicitation; McClintock & Adler, 1978; Pfaus, Smith, & Coopersmith, 1999). Sexually active male rats find these behaviors attractive and will respond by performing mounts, intromissions, and ejaculations. During a maternal testing bout, a maternally responsive female exposed to pups will approach, sniff, and retrieve the pups to a previously built nest. Females then engage in pup licking,

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especially of the anogenital region. During this time, the female may adopt a nursing posture or simply hover over the litter. Intermittently, these females engage in other behaviors, such as nest building and explorative behavior (Numan et al., 2006). Both sexual and maternal behaviors occur in dynamic environments and involve the execution of complex, organized sequences of behavior.

The present study examined temporal sequences of sexual and maternal behaviors following mPFC lesions. We assessed whether observed sequential deficits in one behavioral system (e.g., sexual) could be correlated to deficits in another behavioral system (e.g., maternal) within the same rat. Another question examined in the present study was whether disruptions in temporal sequencing of behaviors would be reflected in deficits in sensorimotor gating (i.e., the ability to filter out irrelevant information; Norris & Blumenthal, 1996; Yee, 2000) and activity levels. Sensorimotor gating can be measured using prepulse inhibition (PPI) of the acoustic startle response (Swerdlow, Braff, & Geyer, 2000; Swerdlow, Geyer, & Braff, 2001). PPI is the reduction in amplitude of the acoustic startle response (e.g., fast twitch of body or facial muscles) to an intense stimulus by a preceding weak, nonstartling stimulus (Yee, 2000). The reduction or inhibition of the startle response observed after the presentation of a nonstartling stimulus is thought to be due to a momentary inhibitory sensorimotor "gate" that serves to protect the earliest stages of information processing (Hoffman & Ison, 1980; Swerdlow et al., 1995, 2000, 2001). Previously, Lovic and Fleming (2004) showed that PPI and an attentional set-shifting task were correlated to maternal behaviors (e.g., licking pups). Attention to irrelevant cues in a dynamic environment may disrupt a behavioral sequence by an inability of the rat to inhibit an inappropriate response during that sequence. The ability to respond to certain stimuli and filter out other information is central to all types of attention.

In addition to PPI testing, we assessed rats' activity levels (in activity boxes) to investigate whether disruptions in temporal organization of sexual and maternal behavior were affected by potential hyperactivity following mPFC lesions. In summary, the present study investigated the role of the mPFC in the execution of sexual and maternal behaviors and assessed whether these deficits were associated with impairments in sensorimotor gating and overactivity.

Method

Subjects

Twenty-three female Sprague–Dawley rats (weighing 250–300 g), from nine litters (no more than 3 rats from any given litter were placed into a group) born in the University of Toronto at Mississauga animal vivarium, were used in the study. The rats at this facility were originally obtained from Charles River Farms in St. Constant, Quebec, Canada. The rats were housed in Plexiglas cages (26 cm wide × 38 cm long × 21 cm high) with ad libitum access to food and water. The room temperature and humidity were maintained at 22 °C and 40–50%, respectively. Lights were off from 8 p.m. to 8 a.m.

Surgery, Perfusion, and Histology

Prior to mating, rats were randomly given sham ($n = 9$) or neurotoxic lesions ($n = 14$) of the mPFC under sodium pentobarbital (65 mg/kg) anesthesia. For the lesioned group, *N*-methyl-D-aspartate (NMDA) was used to produce bilateral cell body lesions in each of the areas. A neurotoxic dose was obtained by dissolving 10 mg of NMDA into 1 ml of 0.1 M phosphate buffer (pH = 7.4) (Salazar, White, Lacroix, Feldon, & White, 2004). For the sham group, the phosphate buffer vehicle was used. To infuse the NMDA or vehicle, polyethylene tubing (PE-20; Becton Dickinson, Sparks, MD) was attached to a 10-μl glass syringe mounted to an infusion pump (Model 22; Harvard Apparatus, South Natick, MA). Attached to the opposite end of the tubing was a 33-gauge single-barrel injection cannula (Plastics One; Roanoke, VA), 30 mm in length. The injection cannula and the portion of tubing were filled with NMDA solution (or vehicle), and the rest of the tubing was filled with water, an air bubble separating the two. There were two infusion sites in each hemisphere. The injection cannula was positioned (2 mm per 60 s) stereotaxically (flat skull) 0.6 mm lateral to the midline on either side of bregma; 3.2 and 2.2 mm anterior to bregma; and 1.3 and 3.7 mm ventral to dura, according to Paxinos and Watson (1986). A volume of 1 μl per side of NMDA or vehicle solution was infused at a rate of 0.25 μl/min per side. The injection cannula was left in the guide for 5 min after the infusions to ensure full absorption into the brain.

After the behavioral data were collected, rats were killed by an overdose of sodium pentobarbital (120 mg/kg ip) and perfused intracardially with ice-cold phosphate-buffered saline (300 ml) followed by ice-cold 4% paraformaldehyde in 0.1 M phosphate buffer (300 ml). Brains were removed, postfixed in fresh 4% paraformaldehyde for 4 hr, blocked, and stored overnight in 30% sucrose at 4 °C. The brains were frozen using dry ice and sliced into coronal sections (30 μm) using a cryostat. These sections were mounted on gel-coated slides, stained in cresyl violet, cover slipped, and examined under a microscope to confirm placements. Only rats with bilateral lesions encompassing more than 50% of the mPFC were included in statistical analysis. Rats with unilateral lesions, lesions greater than the desired area, lesions less than 50% of the desired area, or misplaced lesions were not included.

Procedure

Sexual behavior testing. One week after surgeries, determination of the ovarian phase began and then continued throughout the sexual tests. At 9 a.m. (4 hr prior on sexual test days), vaginal smears were performed. An eyedropper (o.d. 5 mm) with approximately 500 μl distilled water was inserted into the vagina; the water was ejected and then sucked back into the eyedropper. The water was placed onto a glass slide and analyzed under a microscope. Changes in vaginal epithelial cell morphology were used to indicate the phase of the ovarian cycle (see Freeman, 1994). Rats began sexual testing after the determination of one full estrous cycle and during metestrus.

Female rats were given seven daily 1-hr sexual tests with copulating male rats in Plexiglas bilevel chambers (60 cm wide × 60 cm high × 20 cm deep) during the middle third of the rats' dark circadian cycle (Pfaus, Mendelson, & Phillips, 1990; Pfaus et al., 1999). The female was placed into the chamber for a 5-min acclimation period prior to the sexual test. Each acclimation period and test was videotaped, and the first 35 min were scored subsequently using a computerized event recorder customized for female sexual behavior (Cabilio, 1996).

The frequencies of proceptive behaviors were scored as in Pfaus et al. (1999) for each of the phases of the ovarian cycle (i.e., metestrus, diestrus, proestrus, and estrus). The behaviors included (a) solicitation, a headwise orientation followed by a runaway from one level of the chamber to another; (b) hops and darts, quick short runs in front of the male on the same level; (c) pacing, defined as level changes between interactions with the male; and (d) anogenital investigation, sniffing the genital area of the stimulus male. The frequencies of rejection responses (i.e., any incidents of aggressive behavior; see Barnett, 1963) and the number and magnitude (see Pfaus et al., 1999) of lordosis behavior were scored. In addition, appetitive behavior was assessed as the number of level changes observed during the 5 min prior to male access in the bilevel chamber.

Only the data from the first full estrous cycle (during testing) were included for analysis. When a phase lasted across two tests, a mean frequency score was generated. If pregnancy did not occur within the seven sexual tests, females were mated for an additional week in their home cage.

Maternal behavior testing. Twenty-one days after the initial access to males, females were placed in a large observation cage and given two shredded paper towels as nest-building material. On the day of pup birth (considered postnatal day [PND] 0 for births that occurred before 5 p.m.), dams' litters were culled to four male and four female pups. On PNDs 1, 3, 5, 7, and 9 (i.e., five trials), the pups were removed from the nest, weighed, and 10 min later placed in the corner diagonally opposite the nest. The observations began immediately following the return of the pups to the cage. Observations were recorded using a computer-based event recorder (Behavioral Evaluation Strategy and Taxonomy [BEST] software; Educational Consulting Inc., Las Vegas, NV) during the middle third of the rats' dark circadian cycle. During maternal observations, the following latencies, frequencies, and durations (when appropriate) of behaviors were recorded: pup mouthing, pup licking (anogenital or body), lactating postures (i.e., low and high crouch, hovering over pups), pup sniffing, nest building, exploratory behavior (i.e., rearing on hind legs while sniffing air), and self-grooming. Additional analysis was performed on the weight of the litter, latency to retrieve the first pup, and latency to retrieve the last pup (a score of 600 s was given to a female that did not retrieve all pups to the nest). This 10-min maternal testing procedure typically induces dams to retrieve and lick pups; however, other maternal behaviors were assessed as well, because mPFC lesions may result in atypical maternal behaviors.

Locomotor activity testing. Twenty-four hours after the last day of maternal testing, pups were permanently removed from their mothers and subjects were tested for locomotor activity. Rats were given three trials (daily) of 1-hr testing in Plexiglas activity chambers (22 cm wide $\times$ 44 cm long $\times$ 30 cm high). Two arrays of 16 infrared photocells, spaced 2.5 cm apart with two rows, 2 cm (bottom) and 12 cm (top) above the cage floor, were mounted on the outside of the cage, extending lengthwise along the cage. The beams were interfaced with a PC equipped with a computerized event recorder customized for the activity chambers (Center for Addiction and Mental Health, Toronto, Ontario, Canada). Rats could not see but could hear each other. The numbers of bottom beam cuts (reflecting locomotor activity) and top beam cuts (reflecting rearing) were calculated.

Acoustic startle response and PPI testing. Two weeks after the last day of maternal testing, rats were tested in a single-unit acoustic startle apparatus (MED Associates, St. Albans, VT). The acoustic startle cubicle (55 cm length $\times$ 51 cm width $\times$ 31 cm height) was sound attenuated and equipped with a ventilation fan and red house light. A grid floor animal holder (16.5 cm length $\times$ 7.6 cm width $\times$ 8.9 cm height) was mounted on top of the startle platform, which detected and transduced motion of the rat. Background noise and startle stimuli were delivered through two Radio Shack supertweeters located at the base of the back wall. The delivery of acoustic stimuli was controlled by a PC equipped with Windows-based Startle Reflex Software (Version 3.35; MED Associates). The signal was digitized, rectified, and recorded.

On test day, rats were placed in the grid floor holder and secured to the startle platform. The session started with a 7-min acclimatization period, with a 70-dB background noise level that continued throughout the test session. The rats were given four pulses of 120 dB, 10 kHz, 30 ms long in order to establish baseline startle responses. Next, rats were given 90 trials each. These trials consisted of 15 startle trials (120-dB, 10-kHz tone, 30 ms long), 60 prepulse with startle trials that assessed PPI (15 for each of four prepulse intensities), 12 prepulse-alone trials (3 for each prepulse intensity), and 3 no-stimulus trials. The PPI trials consisted of prepulses of 72, 76, 80, and 84 dB (10 kHz, 20 ms long), followed by startle pulses of 120 dB. The interval between the onset of the prepulse and pulse was 100 ms. The trials were presented in a pseudorandom fashion and in an identical manner for all rats. The startle apparatus was cleaned with 70% alcohol between rats. PPI was calculated according to the equation (1 – [startle amplitude on prepulse with startle trials / startle amplitude on prepulse-alone trials]) $\times$ 100 = percentage of inhibition.

Statistical Analysis

Only data from rats that satisfied the criterion set for acceptable lesion placements were used in statistical analysis. For sexual behavior, a 2 (lesion vs. sham) $\times$ 4 (day of ovarian cycle) repeated measures analysis of variance (ANOVA) was performed for the frequency of sexual behaviors and magnitude of the lordosis responses. For maternal behavior, a 2 (lesion vs. sham) $\times$ 5 (trial) repeated measures ANOVA was performed on each of the latencies, frequencies, and durations of maternal behaviors, as well as litter weight, latencies to retrieve first and last pups, and number of pups retrieved to nest site during the test. For the activity measure, a 2 (lesion vs. sham) $\times$ 3 (trial) repeated measures ANOVA was performed for the number of bottom and top beam cuts. For PPI, a 2 (lesion vs. sham) $\times$ 4 (prepulse intensity) repeated measures ANVOA was performed for the average percentage of inhibition. Post hoc Tukey's honestly significant difference (HSD) tests followed each significant interaction and main effect, when appropriate ($p < .05$). Appropriate variance corrections were made.

To investigate the organization of behavioral patterns, we performed sequential analysis with the BEST program on solicitations for sexual behavior and retrieval of pups for maternal behavior. Explanations of how scores were generated and analyzed are provided in the *Results* section. To investigate the relationship between the sequential analysis scores and PPI, we performed correlations.

Results

Histology

Lesioned rats that did not reach criteria for inclusion had either lesions greater than the desired area ($n = 1$) or lesions less than 50% of the desired area ($n = 3$) and were not used for analysis. In rats with acceptable lesion sites ($n = 10$), shrinkage was observed along the midline. This was pronounced toward the caudal levels of the mPFC and extended to the infralimbic area (see Figure 1). All sham-operated rats were included for analysis ($n = 9$).

Sexual Behavior

Appetitive level changes. The ANOVA revealed a day effect, $F(3, 51) = 5.57$, $p < .005$. Post hoc analysis showed that for all rats the number of level changes increased during proestrus compared with estrus and metestrus and level changes were increased during diestrus compared with estrus (Figure 2).

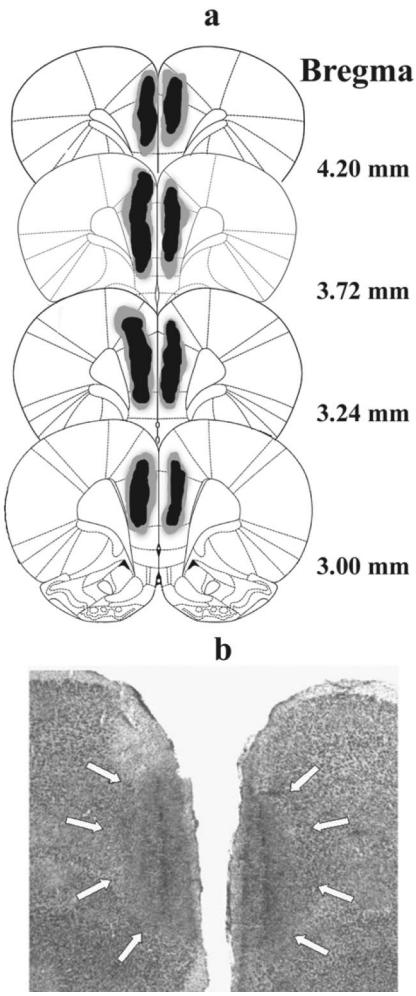

Figure 1. Schematics of lesions for the medial prefrontal cortex (mPFC). (a) Lesions drawn in dark and light intensity are representative of the largest and smallest (respectively) lesion sizes and at four different locations anterior to bregma, according to Paxinos and Watson (1986). (b) A photomicrograph of a representative mPFC lesion shows the medial aspect of the frontal cortex at 3.50 mm anterior to bregma. There was clear shrinkage along the midline of the cortex as indicated by the arrows.

Level changes. There was a significant interaction, $F(3, 51) = 5.24$, $p < .005$, and a main effect of day, $F(3, 51) = 16.91$, $p < .001$. Post hoc analysis indicated that although on proestrus all rats performed more level changes compared with any other day of the cycle, lesioned rats performed significantly fewer level changes during proestrus compared with the sham rats (Figure 2). The groups did not differ on any other day of the cycle.

Solicitations. The ANOVA detected a significant interaction, $F(3, 51) = 5.45$, $p < .005$; day effect, $F(3, 51) = 14.00$, $p < .001$; and group effect, $F(1, 17) = 5.56$, $p < .05$. Post hoc analysis indicated that on proestrus all rats performed more solicitations compared with any other day of the cycle and lesioned rats performed significantly fewer solicitations compared with the sham rats (Figure 2). The groups did not differ on any other day of the cycle.

Hops and darts. The ANOVA revealed a significant interaction, $F(3, 51) = 4.55$, $p < .01$; day effect, $F(3, 51) = 11.54$, $p < .001$; and group effect, $F(1, 17) = 4.24$, $p < .05$. Post hoc analysis found that the lesioned rats performed significantly fewer hops and darts on proestrus compared with the sham rats. The groups did not differ on any other day of the cycle. On proestrus, all rats performed more hops and darts compared with any other portion of the cycle (Figure 2).

Anogenital investigation. The ANOVA revealed a significant day effect, $F(3, 51) = 4.56$, $p < .01$. During proestrus all rats had increased anogenital investigations compared with other days of the cycle (Figure 2).

Lordosis. The mean percentage of lordosis response (i.e., lordosis quotient = number of lordosis/male mounts $\times$ 100) was used for analysis. The ANOVA revealed a significant day effect, $F(3, 51) = 12{,}086.55$, $p < .001$. During proestrus all rats had increased lordosis responses compared with any other day, with no group differences (Figure 2). There were no significant differences found for the magnitude of the lordosis response.

Defensive behavior. No significant differences were found.

Sequential analysis of solicitations. The sham-operated female rats began solicitational patterns by approaching the male rats. When in close proximity to the male, the female would orientate her head toward the male and quickly (i.e., within 1–3 s) dart away to another level. The male typically responded by chasing the female from level to level until he mounted her. Similar to the sham females, lesioned females would approach and orientate their head toward the male. However, unlike the sham females, the headwise orientation performed by lesioned females was rarely followed by a quick dart (i.e., within 3 s) away from the male to another level. Alternatively, the lesioned females would engage in hopping, darting, anogenital investigation, or an incomplete level change, thus breaking the solicitational pattern. This break resulted in male mounts rather than male pursuit of the female. The lesioned female would respond by lordosis or a single dart to another level.

To assess group differences in the execution of solicitational patterns, we recorded the number of headwise orientations followed, within 4 s, by a level change for each rat on proestrus. This frequency number was divided by the total frequency of solicitations made on that day and multiplied by 100, yielding a sequential solicitation score. If no solicitations were observed, the rat was

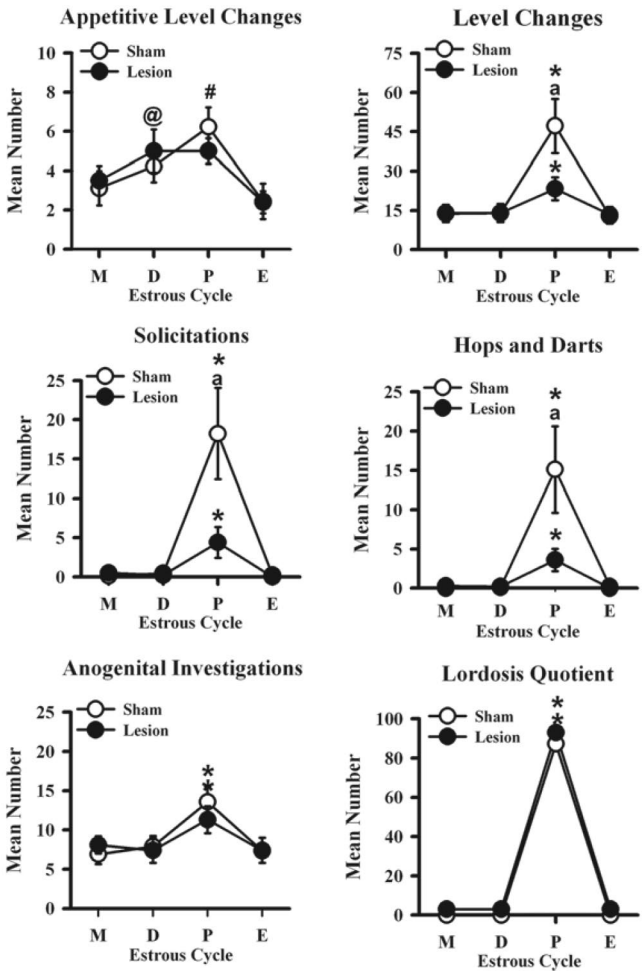

Figure 2. Frequency ($M \pm SEM$) of several sexual behaviors after either sham surgery or medial prefrontal lesion surgery for each phase of the estrous cycle (M = metestrus; D = diestrus; P = proestrus; E = estrus). $^{@}p < .05$ for day difference from only E (groups collapsed); $^{\#}p < .05$ for day difference from M and E (groups collapsed); $^{*}p < .05$ for day difference from D, M, and E; $^{a}\ p < .05$ for group difference on any given day.

excluded from the analysis ($n = 1$ per group). The sequential solicitation scores were then analyzed with an independent-groups t test. The analysis found that lesioned females had significantly fewer executions of this behavioral pattern (headwise orientations toward the male followed within 4 s by a level change) than did sham rats, $t(15) = 12.07$, $p < .001$ (see Figure 3).

Maternal Behavior

Litter weight. The ANOVA for the litter weight showed only a significant day effect $F(4, 68) = 998.47$, $p < .001$. Post hoc analysis revealed that from day to day, both groups significantly increased litter weight (Figure 4).

Retrieval. The ANOVA performed on the number of pups retrieved during the tests and latencies to retrieve the first and last pups showed that there were significant group effects for each, $F(1, 17) = 4.81$, $p < .05$; $F(1, 17) = 9.41$, $p < .01$; and $F(1, 17) = 24.84$, $p < .001$, respectively. Post hoc analysis on individual

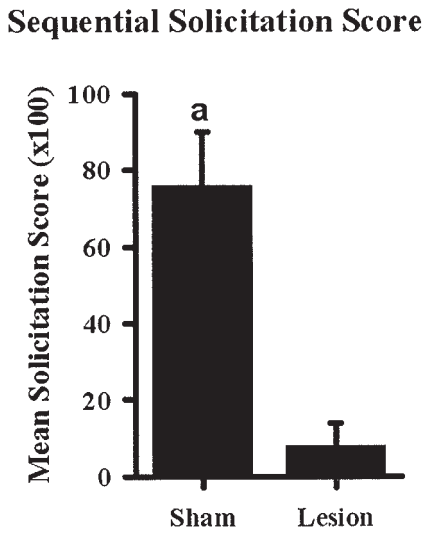

Figure 3. Solicitations ($M \pm SEM$). Scores reflect the ratio of orientations toward male rats followed within 4 s by a level change to the total number of solicitations, scored during proestrus after sham and lesion surgery. $^{a}\ p < .05$ for group difference.

means revealed that on PNDs 1 and 7 the lesioned rats retrieved significantly fewer pups than the sham rats, and on all days the lesioned rats took significantly longer to retrieve the first and last pups to the nest site (Figure 4).

Licking. The ANOVA for the latency, frequency, and duration of licking found significant group effects for each, $F(1, 17) =$

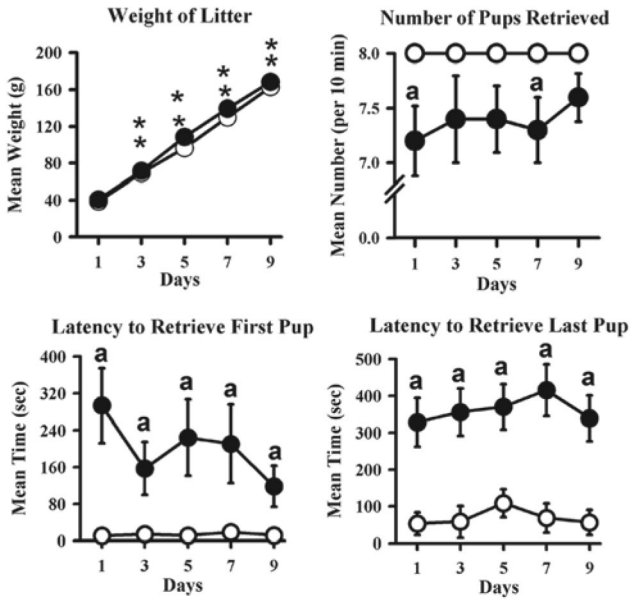

Figure 4. Mean ($\pm SEM$) litter weight, number of pups retrieved during a test, and latencies to retrieve first and last pups for sham (open circles) and medial prefrontal lesion (closed circles) operated dams at Postnatal Days 1–9. Collapsed across the days, there were significant group differences ($p < .05$) for all measures except litter weights. $^{*}p < .05$ for difference from prior day; $^{a}\ p < .05$ for group difference on any given day.

63.91, $p < .001$; $F(1, 17) = 8.60$, $p < .01$; and $F(1, 17) = 5.96$, $p < .05$, respectively. Lesioned rats had shorter latencies, had lower frequencies, and spent less time engaged in pup licking compared with the sham rats (Figure 5). Post hoc analysis on the individual means found that compared with the sham rats, the lesioned rats had significantly shorter latencies to lick pups on all days and significantly lower frequencies and shorter durations of licking bouts by PND 9. There was also a significant day effects for latency, frequency, and duration, $F(4, 68) = 3.10$, $p < .05$; $F(4, 68) = 6.05$, $p < .01$; and $F(4, 68) = 6.74$, $p < .001$, respectively. All rats increased licking behavior across days (Figure 5).

Lactating postures. No differences were found for high and low crouch postures, as very few rats (independent of group) were observed to engage in these behaviors. The ANOVA found a significant group effect for latency to hover and duration of hovering, $F(1, 17) = 14.48$, $p < .001$, and $F(1, 17) = 5.18$, $p < .05$, respectively. Compared with shams, lesioned rats took longer to begin and spent less time hovering over pups (Figure 5). There also was a significant day effect for frequency and duration of hovering, $F(4, 68) = 7.47$, $p < .001$, and $F(4, 68) = 3.53$, $p < .05$, respectively. All rats showed increased frequency and duration of hovering across the days (Figure 5). Post hoc analysis on individual means revealed that lesioned rats compared with sham rats had a greater latency to hover over pups on PND 1.

Nest building. The ANOVA for latency, frequency, and duration spent nest building showed a day effect for each, $F(4, 68) = 23.16$, $p < .001$; $F(4, 68) = 4.21$, $p < .005$; and $F(4, 68) = 5.57$, $p = .001$, respectively, with all rats increasing in latency to nest

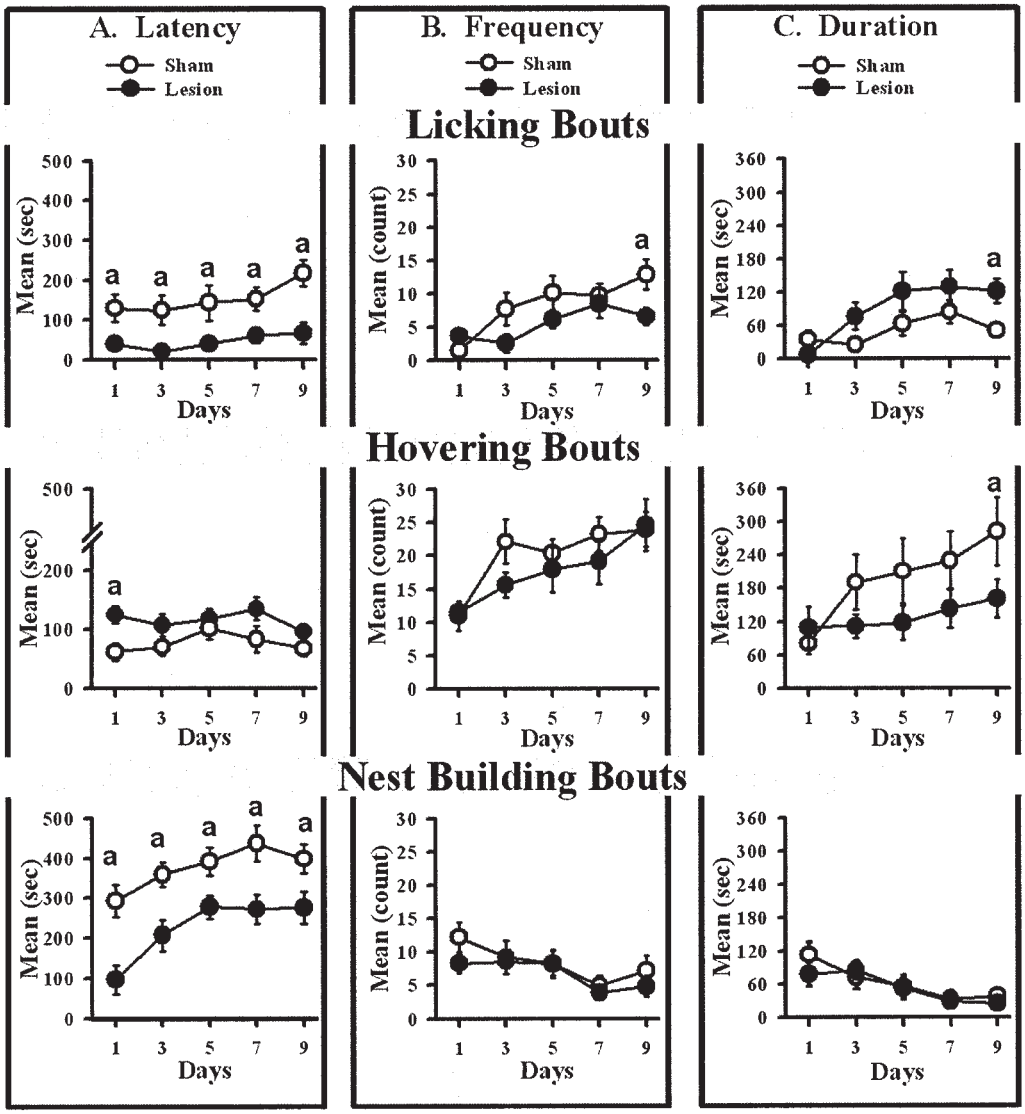

Figure 5. Mean (± *SEM*) latencies (A), frequencies (B), and durations (C) of several maternal behaviors after either sham or medial prefrontal lesion surgery at Postnatal Days 1–9. Collapsed across the days, there were significant group differences ($p < .05$) for licking bout latency, frequency, and duration; hovering bout latency and duration; and nest-building bout latency. [a] $p < .05$ for group difference on any given day.

build and decreasing in frequency and duration of nest-building bouts over days (Figure 5). Post hoc analysis showed that on any given day, the lesioned rats compared with the sham rats had significantly shorter latencies to engage in nest building.

Sequential analysis of pup retrieval. The typical pup-retrieval pattern seen in the sham rats began with a quick approach and sniff of the litter. Shortly after (i.e., 1–10 s after the initial pup sniff), retrieval was initiated. After the first pup was placed in the nest, the rat retrieved the next pup within seconds (i.e., 5–15 s), rarely engaging in other behaviors (except for pup sniff) between retrievals. This pattern of retrieval continued until the last pup was in the nest. Once the pups were in the nest, the sham rat engaged in exploratory and grooming behavior intermingled with licking and hovering bouts before settling over the pups. In contrast, the lesioned rats approached, sniffed, and withdrew from the pups. These rats, during the period between pup withdraw and first retrieval, would engage in many other behaviors (e.g., exploration, nest building, grooming, pup sniffing, pup mouthing). Once the first pup was in the nest, the rat would typically hover over and lick the pup before she would begin the pup approach–withdraw–retrieval pattern again. These rats typically would not settle over the pups during the 10-min test.

To evaluate group differences in the execution of retrieval patterns, for each rat we counted the number of pup retrievals followed, within 15 s, by another pup retrieval, yielding a sequential retrieval score. For each maternal testing day, the sequential retrieval score could range from 0 to 7. In addition, extraneous behaviors displayed during the delay were analyzed. From immediately after pups were given to dams until the last pup was in the nest, the frequency and duration of exploring, grooming, nest building, and pup sniffing, licking, mouthing, and hovering were scored.

A repeated measures ANOVA (Group × Day) performed on the sequential retrieval scores detected a significant group effect, $F(1, 17) = 17.21$, $p < .001$. Tukey's HSD test conducted on the individual means ($p < .05$) revealed that lesioned rats had significantly fewer retrievals occurring within 15 s of each other than did sham rats during PNDs 3–9 (see Figure 6).

A repeated measures ANOVA (Group × Days) was performed on the extraneous behaviors (summed for each day) displayed during retrieval delays. There was a significant group effect for frequencies and durations, $F(1, 17) = 27.06$, $p < .001$, and $F(1, 17) = 21.62$, $p < .001$, respectively. Tukey's HSD test conducted on the individual means ($p < .05$) found that lesioned rats engaged in significantly greater frequencies and durations of these extraneous behaviors during retrieval delays than did sham rats on all test days (Figure 7, right side).

In investigating the individual behaviors (summed across the test days), we found that for each behavior except pup sniffing (i.e., exploring, grooming, nest building, and pup licking, mouthing, and hovering), the lesioned rats performed significantly greater frequencies and durations of each behavior, as evaluated with a series of independent-group t tests (Bonferroni correction, all ps $< .05$) (Figure 7, left side). From Figure 7, it can be seen that regardless of group affiliation, the rats engaged in similar proportions of frequencies and duration of each individual behavior during the retrieval delays.

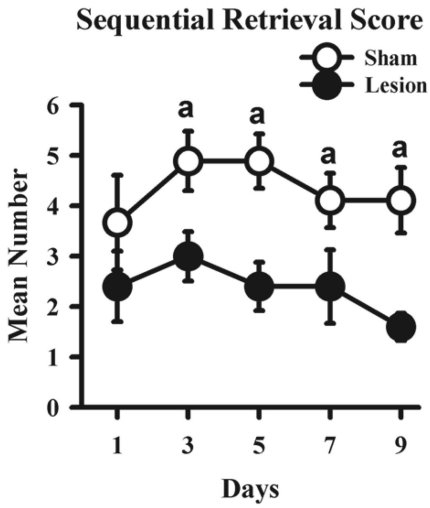

Figure 6. Frequency ($M \pm SEM$) of retrievals occurring within 15 s of each other (range of scores, 0–7) after either sham or medial prefrontal lesion surgery at Postnatal Days 1–9. Collapsed across the days, there was a significant group difference ($p < .05$). [a] $p < .05$ for group difference on any given day.

PPI

A repeated measures ANOVA (Group × Prepulse Intensity) indicated that there was a significant Group × Prepulse Intensity interaction, $F(3, 51) = 2.81$, $p < .05$. Tukey's HSD test conducted on the individual means ($p < .05$) revealed that at 72 dB, lesioned rats had lower levels of PPI compared with sham rats (Figure 8). Also, the lesioned rats had significantly lower levels of PPI at 72 dB compared with any other intensity. In addition, both main effects were significant: For group, $F(1, 17) = 8.80$, $p < .01$, lesioned rats had lower levels of PPI when intensities were collapsed; for prepulse intensity, $F(3, 51) = 6.71$, $p < .001$, all rats showed greater levels of PPI at higher intensity levels (see Figure 8).

Activity

The ANOVA for bottom and top beam cuts revealed a significant trial effect, $F(2, 36) = 21.43$, $p < .001$, and $F(2, 36) = 14.83$, $p < .001$, respectively. All rats showed declined activity over trials, with no significant group differences on locomotor (bottom beam cuts) and rearing (top beam cuts) activities (Figure 9).

Correlational Analysis of Sexual Behaviors, Maternal Behaviors, Activity, and PPI Data

Partial correlations (controlling for group) were performed on sequential solicitation scores, sequential retrieval scores (summed across days), and percentage of PPI at each of the intensities (i.e., 72, 76, 80, 84 dB). Only at the lowest intensity were significant correlations found between PPI scores and sequential scores. Table 1 indicates that at the lowest intensity (i.e., 72dB) the PPI scores were significantly correlated (positively) with both sequential solicitation and sequential retrieval scores. Table 1 also shows that sequential solicitation and retrieval scores were significantly correlated (positively) with each other. When partial correlations were

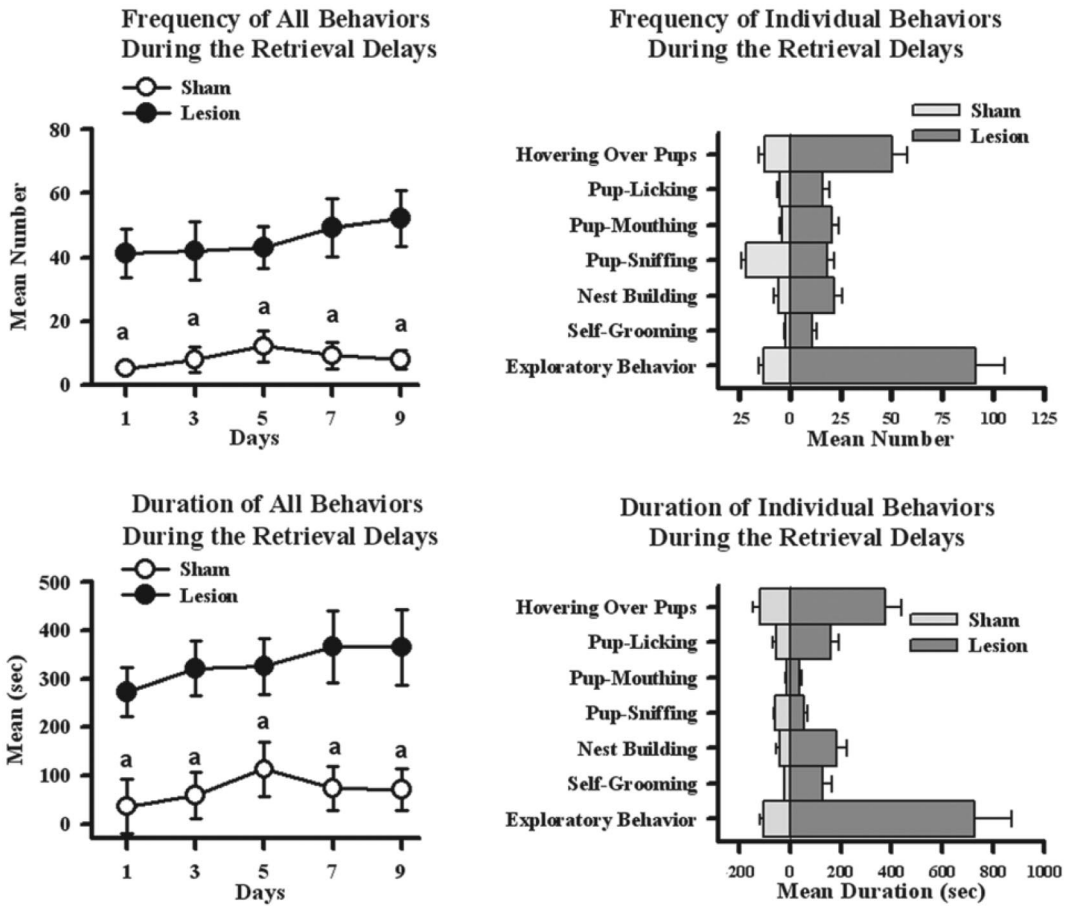

Figure 7. Frequencies and durations ($M \pm SEM$) of all behaviors displayed during retrieval delays for each postnatal day (left-side panels; [a] $p < .05$ for group difference on any given day) and individual behaviors (summed across days) displayed during the retrieval delay (right-side panels; groups significantly differed on all behaviors except pup sniffing, $p < .05$). Retrieval delay started immediately after pups were given to dams and finished when the last pup was in the nest.

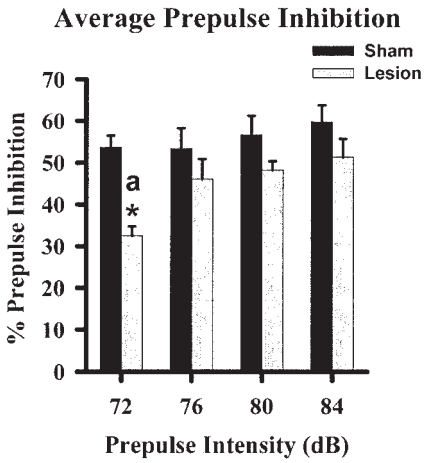

Figure 8. Percentage ($M \pm SEM$) of prepulse inhibition of acoustic startle after either sham or medial prefrontal lesion surgery at four intensities. Collapsed across the days, there was a significant group difference ($p < .05$). [*] $p < .05$ for intensity difference from 76, 80, and 84 dB; [a] $p < .05$ for individual group difference.

performed on PPI and the frequency of behaviors performed during the pup-retrieval delays (summed across days), no significant correlations were found.

Partial correlations (controlling for group) were performed on activity measures (bottom and top beam cuts were summed for each trial) and sequential solicitation and retrieval scores (summed across days). No significant correlations were found on any given activity trial. Similarly, no significant partial correlations were found between activity measures (on any trial) and PPI (at any given dB) or behaviors performed during retrieval delays.

Covariate Analysis of Sexual and Maternal Behavior Data

To investigate the influence of PPI and activity levels on group differences in sexual and maternal behavior, we performed analyses of covariance by partialing out PPI and activity levels. With PPI (summed across the prepulse intensities) and activity (total beam cuts summed across the trials) scores as the covariates, one-way analyses of covariance comparing the groups (lesion vs.

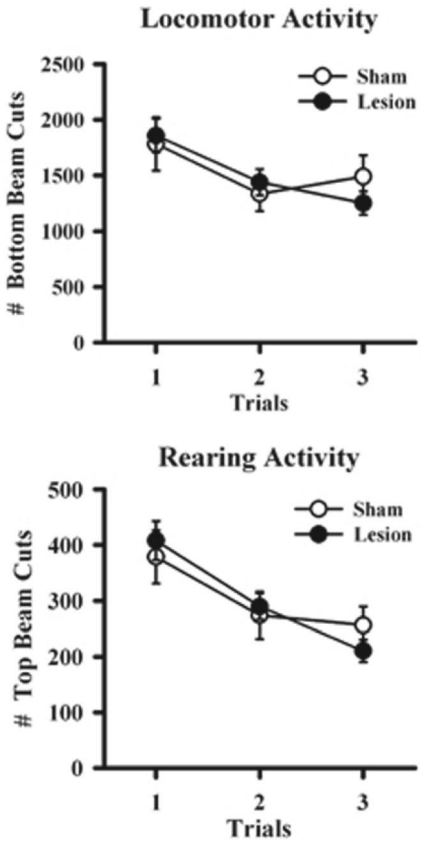

Figure 9. Frequency ($M \pm SEM$) of bottom (locomotor activity) and top (rearing activity) beam cuts after sham and medial prefrontal lesion surgery across three trials. There were no individual group differences (though there was a significant trial effect, as described in the *Results*).

sham) on the frequencies of proestrus sexual behaviors and the frequencies and durations of maternal behaviors (each summed across the 5 days) were performed. The group effects are presented in Table 2.

Table 1
Correlations Between Sexual Behavior, Maternal Behavior, and Prepulse Inhibition (PPI)

Measure	Prepulse intensity				Retrieval score
	72 dB	76 dB	80 dB	84 dB	
Solicitation scores					
r (14)	.523*	−.351	.224	−.089	.745*
p	.003	.141	.371	.725	<.001
Retrieval scores					
r (16)	.672*	−.342	−.035	.192	
p	.002	.339	.891	.940	

Note. Table shows partial correlations (controlling for surgery groups) on sequential solicitation scores, sequential retrieval scores (summed across days), and percentage of PPI at each of the intensities. At the lowest intensity, solicitation and retrieval scores correlated with PPI. Solicitation and retrieval scores were highly correlated.
* $p < .05$.

Table 2
Covariate Analysis of Sexual and Maternal Behaviors

Variable	F(1, 15)	p
Sexual behaviors		
Appetitive level changes	0.03	.87
Level changes	5.08	.04*
Solicitations	4.36	.05*
Hops and darts	1.05	.32
Anogenital investigations	1.25	.28
Lordosis	0.35	.57
Defensive behaviors	2.36	.15
Sequential solicitational score	10.34	.006*
Maternal behaviors		
Latency to retrieve first pup	7.50	.02*
Latency to retrieve last pup	14.32	.002**
Licking bouts		
Frequency	6.50	.02*
Duration	3.03	.10
Hovering bouts		
Frequency	4.50	.05*
Duration	5.86	.03*
Nest-building bouts		
Frequency	8.14	.01*
Duration	4.28	.06
Sequential retrieval score	9.50	.008*

Note. Group differences in sexual and maternal behavior continued to exist when prepulse inhibition (PPI) and activity were partialed out. The table shows statistics for analysis of variance with the covariates of PPI (summed across the prepulse intensities) and activity scores (total beam cuts summed across the trials). F values correspond to group differences.
* $p < .05$. ** $p < .01$.

For sexual behaviors, the group differences in frequency of level changes, solicitations, and sequential solicitations remained significant ($p < .05$) after partialing out PPI and activity data, although the significance level decreased. Furthermore, the above finding that lesioned rats performed significantly fewer hops and darts ($p < .05$) was not found after partialing out PPI and activity data (*ns*).

For maternal behaviors, after partialing out PPI and activity data, there were significant ($p < .05$) group differences in the latencies to retrieve first and last pups; frequency of licking, hovering, and nest building; sequential pup retrievals; and duration of hovering. When these covariates were added to the analysis, the group difference in the duration of licking pups became nonsignificant (i.e., from $p < .05$) and the group differences became less significant for the latencies to retrieve first and last pups and frequency of licking pups.

Discussion

Lesions of the mPFC impaired sexual and maternal behaviors. These lesions had disruptive effects on the latency, frequency, duration, and sequential execution of sexual and maternal behaviors. In addition, lesions of the mPFC had disruptive effects on PPI. Impairments of sexual behavior, maternal behavior, and PPI could not be explained by differences in locomotor activity, as (a) groups did not differ on activity levels (on any given trial) and activity habituation rates and (b) activity measures could not be correlated with sexual behavior, maternal behavior, or PPI measures. Impairments of sexual and maternal behavior could in part be explained by PPI deficits: Reproductive behaviors correlated

with PPI, and partialing out PPI data reduced or eliminated the significant group differences between lesioned and sham-operated animals. However, deficits following mPFC lesions in sexual and maternal behaviors persisted even when PPI levels were factored out.

mPFC lesions did not affect the development of reproductive behaviors across days. Regardless of group affiliation, rats displayed increased sexual behaviors during proestrus compared with the rest of the cycle, and there were no significant Group × Day interactions for maternal behaviors. However, lesions of the mPFC attenuated the frequency and duration of several sexual and maternal behaviors. The behaviors most sensitive to mPFC lesions appear to be those requiring the completion of a complex behavioral sequence that occurs while female rats interact with conspecifics (i.e., males or pups). For example, on the proestrus day of sexual testing, the number of level changes performed during the 5-min period prior to male access (i.e., appetitive level changes) did not differ between groups. However, the sham rats performed more level changes (i.e., paced level changes) when the male was present. Thus, mPFC lesions appear to have affected level changes only when the male was present. During proestrus, lesioned rats demonstrated decreased solicitations and hops and darts, whereas the frequency of anogenital investigations, self-grooming, and lordosis behavior were unaffected. Paced level changes, solicitations, and hops and darts require the female not only to orientate the behavior toward the male but also to complete the behavioral sequence in the presence of the responding male. Anogenital investigations and self-grooming require little interaction with the male, and the execution of these behaviors is not complex compared with other behaviors (e.g., solicitations). Although lordosis is a response to male tactile cues, the behavior is considered reflexive (see Pfaff, 1980). Thus, for sexual behavior mPFC lesions affect behaviors that are more complex and interactive (i.e., paced level changes, solicitations, hops and darts) compared with those behaviors that are not as complex or interactive (i.e., appetitive level changes, self-grooming, lordosis).

Similar to their effects with sexual behaviors, mPFC lesions produced deficits in the more complex and/or interactive maternal behaviors. In the lesioned group, deficits were observed in pup retrievals and licking behavior. Pup retrieval and licking require a complex behavioral pattern during interaction with pups. There were no group differences for pup mouthing, pup sniffing, nest building, sniffing air, and self-grooming. Thus, some maternal behaviors have no group differences after mPFC lesions, and other behaviors become sensitive after the manipulation.

In addition to the differences between sham and lesioned rats in frequencies and durations of sexual and maternal behaviors, there were group differences in the successful execution of a behavior. The present study investigated the execution of two behavioral sequences (as described in the *Sequential analysis* sections in the *Results*): solicitations (sexual) and pup retrievals (maternal). The finding that the sequential solicitation and retrieval scores were significantly correlated, even when the groups were partialed out, and that mPFC lesions impaired both sequences suggests that these behaviors most likely require similar resources. Solicitations and pup retrievals are goal-directed behaviors that involve responses performed in an adequate spatial orientation and temporal sequence. In addition, both are motorically active behaviors that precede and contribute to the success of female-initiated mating or nursing, respectively, and hence form part of the appetitive aspects of sexual and maternal behaviors. Thus, the mPFC may mediate aspects of appetitive behaviors.

Various studies have suggested that the mPFC plays a major role in the modulation of sequential behaviors and in the spatial orientation of motivated behaviors (Kolb & Cioe, 2003; Kolb, Sutherland, & Whishaw, 1983; Sutherland, Kolb, & Whishaw, 1982). The mPFC receives highly processed sensory information from visual, auditory, and somatosensory regions (Groenewegen & Uylings, 2000) and has been implicated in the integration of motor action with sensory information (Kolb & Cioe, 2003; Mogenson, Jones, & Yim, 1980). Impairments to the mPFC may affect the integration of motor actions with sensory information and result in deficits of sequential execution and spatial orientation of motivated behaviors. Thus, the greater is the complexity or interaction required for the execution of a behavioral sequence, the greater will be the need for the integration of motor and sensory information. Impairments of the more complex or interactive sexual and maternal behavior following mPFC lesions may reflect impairments of the integration of motor actions with sensory information.

Possible sensory feedback deficits after mPFC lesions may have produced sexual and maternal deficits. Reproductive behaviors require sensory feedback. For example, vaginocervical stimulation induces estrous abbreviation in female rats (Bennett, Blasberg, & Blaustein, 2001, 2002; Coopersmith, Candurra, & Erskine, 1996; Lodder & Zeilmaker, 1976), increases return latencies during paced mating (Erskine, 1989; Yang & Clemens, 1997), and increases production of immediate early genes (reviewed in Pfaus & Heeb, 1997). Similarly, somatosensory feedback has been shown to be important for maternal behavior. During lactation, obstruction of the infraorbital nerve innervating the skin of the upper lip, nose, snout, whiskers, and mucous membrane of the mouth produce deficits in retrieval, licking of pups, and nursing behavior (Kenyon, Cronin, & Keeble, 1983; Stern, 1996; Stern & Johnson, 1990; Stern & Kolunie, 1989, 1991). Thus, sensory feedback systems mediate both reproductive behaviors.

The sensory feedback system may contribute to inhibiting the intrusion of extraneous actions into an otherwise programmed sequence. mPFC lesions may have interrupted the feedback system, thus increasing extraneous behaviors displayed during the execution of a behavioral pattern. In the present study we found that compared with sham-operated rats, mPFC-lesioned rats had (a) decreased solicitational and pup-retrieval sequences and (b) increased levels of extraneous behaviors during retrieval delays. It has been hypothesized that successful completion of goal-directed behaviors is optimized by inhibition of competing cognitive or motor processes (see Dellu-Hagedorn, 2006). For example, the impaired retrieval pattern may be reflective of the dam's inability to inhibit responses following that retrieval, thus leading her to engage in other behaviors prior to the next retrieval. Similarly, impairments to the solicitational pattern may be reflective of the female's inability to inhibit responses following orientation toward the male.

One way that mPFC lesions may have disrupted the integration of motor and sensory information is through the ability to gate out irrelevant stimuli. PPI was shown to be sensitive to mPFC manipulations and to correlate with reproductive behaviors, and when PPI was factored out of the behavioral analysis, some group

differences decreased. PPI is thought to be reflective of central attentional inhibitory processes. Disruptions to central inhibitory processes, as presumably occurs after mPFC lesions, would result in increased occurrences of extraneous behaviors during the execution of a behavioral pattern, as observed in the present study. However, impairments to the central inhibition processes that may have occurred in our study can play only a small role in disruptions in the integration of motor and sensory information. After the variance due to PPI and activity levels was partialed out, the group differences in some sexual and maternal behaviors continued to exist.

Conclusions

Despite the mPFC's effects on PPI, deficits in sexual and maternal behaviors continue to be observed in mPFC-lesioned rats. During sexual and maternal testing, it was observed that lesions did not eliminate any single behavior or change the development of the behavior over days; however, the execution of the behaviors appeared disorganized. All rats displayed similar behaviors on nonproestrus days; exhibited increased sexual behavior on proestrus day; experienced similar periods of impregnation, gestation, and parturition; and had comparable litter size, pup attrition rate, and litter weight gain. Furthermore, rats engaged in similar proportions of specific behaviors (see Figure 7, left panel) during the retrieval delays. Together these results suggest that the lesions did not profoundly affect the function of sexual and maternal behavior. If the function of sexual and maternal behavior is to ensure pregnancy and pup survival, respectively, then the behavioral deficits following mPFC lesions did not affect these functions. However, in an environment that is much more dynamic (e.g., involving competition with other females, sexually sluggish males, foraging while lactating, protecting offspring), deficits produced by mPFC lesions may have a profound effect on the outcome of pregnancy and pup survival. For example, female rats that solicit less may receive no ejaculation from a sexually sluggish male, and pups not retrieved to a nest site in a timely manner may be attacked by a predator. Impairments to the mPFC processes do not affect the unified function of these behaviors in the laboratory; however, in a more naturalistic setting, breaking a behavioral pattern can have unfavorable consequences.

References

Agmo, A., Villalpando, A., Picker, Z., & Fernandez, H. (1995). Lesions of the medial prefrontal cortex and sexual behavior in the male rat. *Brain Research, 696,* 177–186.

Balfour, M. E., Brown, J. L., Yu, L., & Coolen, L. M. (2006). Potential contributions of efferents from medial prefrontal cortex to neural activation following sexual behavior in the male rat. *Neuroscience, 137,* 1259–1276.

Barnett, S. A. (1963). *The rat: A study in behaviour.* Oxford, England: Aldine.

Beach, F. A. (1976). Sexual attractivity, proceptivity, and receptivity in female mammals. *Hormones and Behavior, 64,* 803–812.

Bennett, A. L., Blasberg, M. E., & Blaustein, J. D. (2001). Sensory cues mediating mating-induced potentiation of sexual receptivity in female rats. *Hormones and Behavior, 40,* 77–83.

Bennett, A. L., Blasberg, M. E., & Blaustein, J. D. (2002). Mating stimulation required for mating-induced estrous abbreviation in female rats: Effects of repeated testing. *Hormones and Behavior, 42,* 206–211.

Birrell, J. M., & Brown, V. J. (2000). Medial frontal cortex mediates perceptual attentional set shifting in the rat. *Journal of Neuroscience, 20,* 4320–4324.

Bridges, R. S. (1984). A quantitative analysis of the roles of dosage, sequence, and duration of estradiol and progesterone exposure in the regulation of maternal behavior in the rat. *Endocrinology, 14,* 930–940.

Broersen, L. M., & Uylings, H. B. (1999). Visual attention task performance in Wistar and Lister hooded rats: Response inhibition deficits after medial prefrontal cortex lesions. *Neuroscience, 94,* 47–57.

Cabilio, S. (1996). Rodent sex behavior scoring program [Unpublished computer software program]. Concordia University, Montreal, Quebec, Canada.

Coopersmith, C., Candurra, C., & Erskine, M. S. (1996). Effects of paced mating and intromissive stimulation on feminine sexual behavior and estrus termination in the cycling rat. *Journal of Comparative Psychology, 110,* 176–186.

Dalley, J. W., Cardinal, R. N., & Robbins, T. W. (2004). Prefrontal executive and cognitive functions in rodents: Neural and neurochemical substrates. *Neuroscience Biobehavioral Reviews, 28,* 771–784.

Dellu-Hagedorn, F. (2006). Relationship between impulsivity, hyperactivity and working memory: A differential analysis in the rat. *Behavioral Brain Function, 2,* 10.

Edwards, D. A., & Warner, P. (1972). Olfactory bulb removal facilitates the hormonal induction of sexual receptivity in the female rat. *Hormones and Behavior, 7,* 823–828.

Emery, D. E., & Moss, R. L. (1984). Lesions confined to the ventromedial hypothalamus decrease the frequency of coital contacts in female rats. *Hormones and Behavior, 18,* 313–329.

Erskine, M. S. (1989). Solicitation behavior in the estrous female rat: A review. *Hormones and Behavior, 23,* 473–502.

Fleischer, S., & Slotnick, B. M. (1978). Disruption of maternal behavior in rats with lesions of the septal area. *Physiology & Behavior, 21,* 189–200.

Fleming, A. S., & Rosenblatt, J. S. (1974a). Olfactory regulation of maternal behavior in rats: I. Effects of olfactory bulb removal in experienced and inexperienced lactating and cycling females. *Journal of Comparative and Physiological Psychology, 86,* 221–232.

Fleming, A. S., & Rosenblatt, J. S. (1974b). Olfactory regulation of maternal behavior in rats: II. Effects of peripherally induced anosmia and lesions of the lateral olfactory tract in pup-induced virgins. *Journal of Comparative and Physiological Psychology, 86,* 233–246.

Freeman, M. E. (1994). The neuroendocrine control of the ovarian cycle of the rat. In E. Knobil & J. D. Neill (Eds.), *The physiology of reproduction* (Vol. 2, pp. 613–658). New York: Raven Press.

Gray, P., & Brooks, P. J. (1984). Effect of lesion location within the medial preoptic–anterior hypothalamic continuum on maternal and male sexual behaviors in female rats. *Behavioral Neuroscience, 98,* 702–711.

Groenewegen, H. J., & Uylings, H. B. (2000). The prefrontal cortex and the integration of sensory, limbic and autonomic information. *Progress in Brain Research, 126,* 3–28.

Hernandez-Gonzalez, M., Navarro-Meza, M., Prieto-Beracoechea, C. A., & Guevara, M. A. (2005). Electrical activity of prefrontal cortex and ventral tegmental area during rat maternal behavior. *Behavioral Processes, 70,* 132–143.

Hoffman, H. S., & Ison, J. R. (1980). Reflex modification in the domain of startle: I. Some empirical findings and their implications for how the nervous system processes sensory input. *Psychological Reviews, 87,* 175–189.

Kenyon, P., Cronin, P., & Keeble, S. (1983). Role of the infraorbital nerve in retrieving behavior in lactating rats. *Behavioral Neuroscience, 97,* 255–269.

Kolb, B. (1990). Prefrontal cortex. In B. Kolb & R. C. Tees (Eds.), *The cerebral cortex of the rat* (pp. 437–458). Cambridge, MA: MIT Press.

Kolb, B., & Cioe, J. (2003). Recovery from early cortical damage in rats: IX. Differential behavioral and anatomical effects of temporal cortex

lesions at different ages of neural maturation. *Behavioral Brain Research, 144,* 67–76.

Kolb, B., Sutherland, R. J., & Whishaw, I. Q. (1983). A comparison of the contributions of the frontal and parietal association cortex to spatial localization in rats. *Behavioral Neuroscience, 97,* 13–27.

Kolunie, J. M., & Stern, J. M. (1995). Maternal aggression in rats: Effects of olfactory bulbectomy, ZnSO4-induced anosmia, and vomeronasal organ removal. *Hormones and Behavior, 29,* 492–518.

Leon, M., Numan, M., & Moltz, H. (1973, March 9). Maternal behavior in the rat: Facilitation through gonadectomy. *Science, 179,* 1018–1019.

Lodder, J., & Zeilmaker, G. H. (1976). Role of pelvic nerves in postcopulatory abbreviation of behavioral estrus in female rats. *Journal of Comparative and Physiological Psychology, 90,* 925–929.

Lonstein, J. S., & Stern, J. M. (1998). Site and behavioral specificity of periaqueductal gray lesions on postpartum sexual, maternal, and aggressive behaviors in rats. *Brain Research, 804,* 21–35.

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. *Behavioral Brain Research, 148,* 209–219.

Lumia, A. R., Meisel, R. L., & Sachs, B. D. (1981). Induction of female and male mating patterns in female rats by gonadal steroids: Effects of neonatal or adult olfactory bulbectomy. *Journal of Comparative and Physiological Psychology, 95,* 497–511.

McClintock, M. K., & Adler, N. T. (1978). Induction of persistent estrus by airborne chemical communication among female rats. *Hormones and Behavior, 11,* 414–418.

McGinnis, M. Y., Lumia, A. R., & McEwen, B. S. (1985). Increased estrogen receptor binding in amygdala correlates with facilitation of feminine sexual behavior induced by olfactory bulbectomy. *Brain Research, 334,* 19–25.

Mogenson, G., Jones, D. L., & Yim, C. Y. (1980). From motivation to action: Functional interface between the limbic system and the motor system. *Progress in Neurobiology, 14,* 69–97.

Moltz, H., Lubin, M., Leon, M., & Numan, M. (1970). Hormonal induction of maternal behavior in the ovariectomized nulliparous rat. *Physiology & Behavior, 5,* 1373–1377.

Norris, C. M., & Blumenthal, T. D. (1996). A relationship between inhibition of the acoustic startle response and the protection of prepulse. *Psychobiology, 24,* 160–168.

Numan, M., Fleming, A. S., & Levy, F. (2006). Maternal behavior. In J. D. Neill (Ed.), *Knobil and Neill's physiology of reproduction* (3rd ed., pp. 1921–1993). New York: Raven Press.

Paxinos, G., & Watson, C. (1986). *The rat brain in stereotaxic coordinates* (2nd ed.). San Diego, CA: Academic Press.

Pfaff, D. W. (1970). Nature of sex hormone effects on rat sexual behavior: Specificity of effects and individual patterns of response. *Journal of Comparative and Physiological Psychology, 73,* 349–358.

Pfaff, D. W. (1980). *Estrogens and brain function: Neural analysis of a hormone controlled mammalian reproductive behavior.* New York: Springer-Verlag.

Pfaff, D. W. (1982). Neurobiological mechanisms of sexual motivation. In D. W. Pfaff (Ed.), *The physiological mechanisms of motivation* (pp. 287–317). New York: Springer-Verlag.

Pfaus, J. G., & Heeb, M. M. (1997). Implications of immediate-early gene induction in the brain following sexual stimulation of female and male rodents. *Brain Research Bulletin, 44,* 397–407.

Pfaus, J. G., Mendelson, S. D., & Phillips, A. G. (1990). A correlational and factor analysis of anticipatory and consummatory measures of sexual behavior in the male rat. *Psychoneuroendocrinology, 15,* 329–340.

Pfaus, J. G., Smith, W. J., & Coopersmith, C. B. (1999). Appetitive and consummatory sexual behaviors of female rats in bilevel chambers. *Hormones and Behavior, 35,* 224–240.

Salazar, R. F., White, W., Lacroix, L., Feldon, J., & White, I. M. (2004). NMDA lesions in the medial prefrontal cortex impair the ability to inhibit responses during reversal of a simple spatial discrimination. *Behavioral Brain Research, 152,* 413–424.

Simerly, R. B. (2002). Wired for reproduction: Organization and development of sexually dimorphic circuits in the mammalian forebrain. *Annual Review of Neuroscience, 25,* 507–536.

Stamm, J. S. (1955). The function of the median cerebral cortex in maternal behavior of rats. *Journal of Comparative and Physiological Psychology, 48,* 347–356.

Stern, J. M. (1996). Trigeminal lesions and maternal behavior in Norway rats: II. Disruption of parturition. *Physiology & Behavior, 60,* 187–190.

Stern, J. M., & Johnson, S. K. (1990). Ventral somatosensory determinants of nursing behavior in Norway rats: I. Effects of variations in the quality and quantity of pup stimuli. *Physiology & Behavior, 47,* 993–1011.

Stern, J. M., & Kolunie, J. M. (1989). Perioral anesthesia disrupts maternal behavior during early lactation in Long–Evans rats. *Behavioral and Neural Biology, 52,* 20–38.

Stern, J. M., & Kolunie, J. M. (1991). Trigeminal lesions and maternal behavior in Norway rats: I. Effects of cutaneous rostral snout denervation on maintenance of nurturance and maternal aggression. *Behavioral Neuroscience, 105,* 984–997.

Sutherland, R. J., Kolb, R., & Whishaw, I. Q. (1982). Spatial mapping: Definitive disruption by hippocampal or medial frontal cortical damage in the rat. *Neuroscience Letters, 31,* 271–276.

Swerdlow, N. R., Braff, D. L., & Geyer, M. A. (2000). Animal models of deficient sensorimotor gating: What we know, what we think we know, and what we hope to know soon. *Behavioral Pharmacology, 11,* 185–204.

Swerdlow, N. R., Geyer, M. A., & Braff, D. L. (2001). Neural circuit regulation of prepulse inhibition of startle in the rat: Current knowledge and future challenges. *Psychopharmacology (Berlin), 156,* 194–215.

Swerdlow, N. R., Lipska, B. K., Weinberger, D. R., Braff, D. L., Jaskiw, G. E., & Geyer, M. A. (1995). Increased sensitivity to the sensorimotor gating-disruptive effects of apomorphine after lesions of medial prefrontal cortex or ventral hippocampus in adult rats. *Psychopharmacology (Berlin), 122,* 27–34.

Uylings, H. B. M., Groenewegen, H. J., & Kolb, B. (2003). Do rats have a prefrontal cortex? *Behavioural Brain Research, 146,* 3–17.

Williams, G. W., Goldman, J., McGinnis, M. Y., Possidente, B., & Lumia, A. R. (1991). Effects of ovarian hormones on sexual receptivity, proceptivity, and motivation in olfactory bulbectomized females rats. *Physiology & Behavior, 50,* 751–755.

Winstanley, C. A., Theobald, D. E. H., Dalley, J. W., Cardinal, R. N., & Robbins, T. W. (2005). Double dissociation between serotonergic and dopaminergic modulation of medial prefrontal cortex during a test of impulsive choice. *Cerebral Cortex, 13,* 1–9.

Yang, L. Y., & Clemens, L. G. (1997). Function of intromissions and intromission-return latency of female rats during paced sexual behavior. *Physiology & Behavior, 61,* 889–894.

Yee, B. K. (2000). Cytotoxic lesion of the medial prefrontal cortex abolishes the partial reinforcement extinction effect, attenuates prepulse inhibition of the acoustic startle reflex and induces transient hyperlocomotion, while sparing spontaneous object recognition memory in the rat. *Neuroscience, 95,* 675–689.

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