Sexual experience enhances cognitive flexibility and dendritic spine density in the medial prefrontal cortex

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ABSTRACT

The medial prefrontal cortex is important for cognitive flexibility, a capability that is affected by environmental conditions and specific experiences. Aversive experience, such as chronic restraint stress, is known to impair performance on a task of cognitive flexibility, specifically attentional set-shifting, in rats. Concomitant with this performance decrement, chronic stress reduces the number of dendritic spines on pyramidal neurons in the medial prefrontal cortex. No previous studies have examined whether a rewarding experience, namely mating, affects cognitive flexibility and dendritic spines in the medial prefrontal cortex of male rats. To test this possibility, we exposed adult male rats to sexual receptive females once daily for one week, assessed attentional set-shifting performance, and then analyzed their brains for changes in dendritic spines. We found that sexual experience improved performance on extradimensional set-shifting, which is known to require the medial prefrontal cortex. Additionally, we observed increased dendritic spine density on apical and basal dendrites of pyramidal neurons in the medial prefrontal cortex, but not the orbitofrontal cortex, after sexual experience. We also found that sexual experience enhanced dendritic spine density on granule neurons of the dentate gyrus. The ventral hippocampus sends a direct projection to the medial prefrontal cortex, raising the possibility that experience-dependent changes in the hippocampus are necessary for alterations in medial prefrontal cortex structure and function. As a first attempt at investigating this, we inactivated the ventral hippocampus with the GABA agonist muscimol, after each daily bout of sexual experience to observe whether the beneficial effects on cognitive flexibility were abolished. Contrary to our hypothesis, blocking hippocampal activity after sexual experience had no impact on enhanced cognitive flexibility. Taken together, these findings indicate that sexual experience enhances medial prefrontal cortex dendritic spine density and cognitive flexibility but that these effects may not require continual input from the hippocampus.

1. Introduction

Chronic stress diminishes performance on tasks of cognitive flexibility in both humans and experimental animals (Diamond, 2013; Holmes & Wellman, 2009; Liston et al., 2006; Ohman, Nordin, Bergdahl, Slunga Birgander, & Stigsdotter, 2007). In rats, stress results in a decrease in performance on the extradimensional set-shifting phase of the attentional set-shifting task (ASST), a task that requires the medial prefrontal cortex (mPFC) (Barense, Fox, & Baxter, 2008; Bissonette, Powell, & Roesch, 2013; Dailey, Cardinal, & Robbins, 2004; Liston et al., 2006). Stress also produces a decrease in dendritic spine density on layer 2/3 pyramidal neurons of the mPFC (Liston et al., 2006). Conversely, we have shown that postpartum maternal rats exhibit improved cognitive flexibility along with increased dendritic spine density on layer 2/3 pyramidal neurons of the mPFC (Leuner & Gould, 2010). Although caring for pups has a strong hedonic component for maternal rats (Wansaw, Pereira, & Morrell, 2008), it is generally accepted that parenting is a complex experience with mixed emotional valence (Leuner, Glasper, & Gould, 2010a). Furthermore, it is possible that the enriching aspects of caregiving, as opposed to its specific rewarding properties, produce the positive effects of the postpartum experience on mPFC structure and function. Since environmental enrichment is known to both enhance cognitive function (Frick & Benoit, 2010; Mora-Galgaleos et al., 2014) and increase dendritic spine density (Gelfo, De Bartolo, Giovine, Petrosini, & Leggio, 2009; Hu, Bergström, Brink, Rönnbäck, & Dahlqvist, 2010), this explanation is plausible. To date, no studies have addressed the question of whether a purely hedonic experience, such as mating in male rats (Agmo & Berenfeld, 1990), is sufficient to enhance cognitive flexibility and dendritic spine density in the mPFC.
The mPFC receives both direct and indirect projections from the ventral hippocampus (Goto & Grace, 2008; Jay, Glowinski, & Thierry, 1989; Jay & Witter, 1991; Swanson, 1981). Like the mPFC, both the function and structure of the hippocampus are sensitive to experience. A large body of literature has shown that chronic stress both impairs performance on cognitive tasks known to require the hippocampus and diminishes hippocampal dendritic architecture (McEwen, 2005). By contrast, several experiences with a rewarding component, including those that appear to be predominantly rewarding, such as mating (Camacho, Sandoval, & Paredes, 2004; Coolen, Fitzgerald, Yu, & Lehman, 2004; Pfaus, Kippin, & Centeno, 2001; Tenen, Wilson, Zhang, Pitchers, & Coolen, 2008), running (Belke & Wagner, 2005; Greenwood et al., 2011), and intracranial self-stimulation (Ikeda, Moss, Fowler, & Niki, 2001; Sanchis-Segura & Spanagel, 2006), have been shown to enhance dendritic spine density in the hippocampus (Edale, Redila, & Christie, 2005; Leuner, Glasper, & Gould, 2010b; Shankaranarayana Rao, Raju, & Meti, 1999; Stranahan, Khalil, & Gould, 2007). Taken together, these results raise the possibility that experience-dependent changes in the hippocampus may initiate similar changes in the mPFC. To investigate the effects of a rewarding experience on mPFC function and structure, we tested whether male rats with repeated sexual experience exhibit enhanced cognitive flexibility using an ASST paradigm. Given the direct projections from ventral hippocampus to mPFC (Verwer, Meijer, Van Uum, Witter, & Menno, 1997), as a first attempt to determine whether ventral hippocampal activation is necessary for experience-dependent changes in mPFC function, we investigated whether inactivation of the hippocampus, by use of the GABA agonist muscimol (Hobin, Ji, & Maren, 2006; Maren, 2014; Maren & Holt, 2004), after sexual experience would block its beneficial effects on cognitive flexibility. Here, we show that the rewarding experience of mating improves cognitive flexibility during ASST performance, while also enhancing dendritic spine density in the mPFC. Contrary to our hypothesis, hippocampal muscimol infusion after sexual experience was not sufficient to prevent enhanced cognitive flexibility.

2. Materials and methods

2.1. Experimental animals

Young adult male and ovariectomized (OVX) female Sprague Dawley rats (2–3 months of age; Taconic, Germantown, NY) were acclimated to the colony for 5 d before initiation of experiments, where they were provided unlimited access to food and water and maintained on a reverse 12:12 light:dark cycle (lights on 1900 h). Males were housed 3/cage (except following surgery in Experiment 2), while OVX were individually housed. Prior to and throughout ASST testing, male rats were maintained on a restricted diet of 15–20 g of food per day to reach ~ 85% of ad libitum body weight, which took 3–4 days on average to reach. Rats housed together were included in the same experimental group. All procedures were approved by the Princeton University IACUC (protocol #1756, approved July 2009) and followed the National Research Council’s Guide for the Care and Use of Laboratory Animals.

2.2. Experiment 1

2.2.1. Sexual experience paradigm

Sexual receptivity was induced in OVX rats by subcutaneous injection of estradiol (.75 mg/gm body weight in sesame oil) 48 h and progesterone (1.5 mg/gm body weight in sesame oil) 3 h before pairing with a male. Naïve male rats were placed in a novel cage with a non-receptive female (n = 13) or a sexually-receptive female (n = 11) for 7 consecutive days, during the dark cycle (1300–1600 h). Males were allowed to engage in sexual behavior for 30 min, starting from the first intromission and were then returned to their home cages. Exposures were monitored and videotaped in the dark under red light illumination and daily sexual behavior was monitored for mounts, intromissions, and ejaculations (Glasper & Gould, 2013; Hull & Domínguez, 2007; Leuner et al., 2010b).

2.2.2. Attentional set-shifting task

Beginning on the 5th day of the experiment, male rats were habituated, shaped, and tested on an ASST paradigm. For non-mated rats, this occurred after 4 consecutive days of pairing with a non-receptive female. For mated rats, this occurred 4 days after pairing with a receptive female, 30 min after the 1st intromission for Experiment 1 or 20 min after the muscimol infusion in Experiment 2. Rats were trained to dig for a food reward (1/3 of a FrootLoop®) and made discriminations based on digging container texture or digging medium (see Table 1). ASST testing occurred in a Plexiglas box (50 × 40 × 30 cm) divided into three areas: a starting/holding area (16 × 40 × 30 cm) with a sliding door separating it from two choice areas (34 × 20 × 30 cm), each containing a digging container (internal diameter and depth, 10 cm). Textures covering the digging containers were made from various materials, including velvet, sandpaper, and smooth cloth. ASST habituation, shaping, and testing occurred over 3 d. Habituation to the task occurred on Day 1. Digging containers were half-filled with corn cob bedding and a food reward was placed on top. Rats were transferred to the starting area and the sliding door was lifted, allowing access to both containers. When both rewards were consumed, the rat was returned to the starting area and the containers were rebaited for two more trials. If the rat failed to retrieve both rewards within 5 min, the trial was terminated and repeated until 3 successful retrievals were achieved. On Day 2, rats were shaped to dig for a food reward buried within both containers and then trained on both texture and medium simple discriminations (SD). Shaping was performed in four stages, with the food reward; (1) placed on top, (2) placed under a thin layer of cob, (3) buried under ~2 cm of cob, and (4) buried under ~4 cm of cob. The first three shaping stages consisted of 3 trials each, while the last shaping stage consisted of 6 trials to ensure reliable digging. If rats failed to retrieve both rewards within 2 min, the trial was repeated. If five consecutive no-dig trials occurred, shaping was terminated and continued on the following day. Immediately after successful shaping, rats were trained to locate the reward based on either digging medium or texture to a criterion of six consecutive correct trials. The order of the SDs and rewarded stimuli (+stimuli) was determined randomly and represented equally across rats. These stimuli were never used again. On Day 3, rats were assessed on a series of 5 discriminations. For all trials, rats were given access to both containers, but only one was baited with a food reward. To eliminate the strategy of using odor to find the reward, all media included a small amount of powdered food reward. The left–right positioning of the baited container across

Table 1

<table>
<thead>
<tr>
<th>Exemplars used.</th>
<th>Medium pairs</th>
<th>Texture pairs</th>
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<tbody>
<tr>
<td>Ribbon vs. crinkled paper strips</td>
<td>Waxed paper vs. fine sand paper</td>
<td></td>
</tr>
<tr>
<td>Gravel vs. plastic beads</td>
<td>Velvet vs. reversed velvet</td>
<td></td>
</tr>
<tr>
<td>Sawdust vs. sand</td>
<td>Yellow fuzzy vs. reversed yellow fuzzy</td>
<td></td>
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</tbody>
</table>

The exemplars within a dimension were always presented in pairs and were randomized, so that no two rats received the same discriminations. However, all shifts were performed by controls and sexually-experienced rats (Experiment 1) and saline and muscimol treated rats (Experiment 2).
trials was randomized. In the first 4 trials of each discrimination, rats were allowed to recover the reward even if it initially dug in the incorrect container; however, an error was recorded. This was to maintain responding on the task and to ensure sampling of both stimuli. After the first 4 trials, the rat was not permitted to recover the reward after making an error and was returned to the starting/holding area and a new trial commenced. Trials were terminated after 2 min if the rat failed to dig and these trials were marked as errors. If 5 consecutive no-dig trials occurred, the test was terminated and continued on the following day. Average duration of ASST was 120 min.

On day 4 of the sexual experience paradigm, ASST testing started with a simple discrimination (SD) in which the rat discriminated between two textures or two digging media, one of which predicted the food reward (+stimulus; see Table 2). Containers were filled with a neutral medium (corn cob bedding) if the SD involved texture or containers were untextured if the SD involved medium. Next, in a compound discrimination (CD), a new dimension was introduced, but the + stimulus remained the same as in the SD. After that, an intradimensional shift (IDS) involving two new exemplars from each stimulus dimension was introduced, but the relevant dimension remained the same. The IDS was then reversed (REV) such that the formerly – stimulus became the +stimulus. Finally, in the extradimensional shift (EDS), two new exemplars from each dimension were introduced and the formerly irrelevant dimension became relevant. A rater blind to the experimental conditions performed behavioral testing. Fewer trials to criterion indicated improved performance on the ASST.

### 2.2.3. Golgi-impregnation

On the last day of the ASST, all rats were deeply anesthetized with sodium pentobarbital and brains were rapidly removed from the skull, rinsed with dH₂O, blocked into small sections containing the prefrontal cortex and hippocampus, and immersed in Golgi-Cox impregnation solution using the FD Rapid GolgiStain™ Kit (FD Neurotechnologies, Columbia, MD). Brains were left undisturbed in the dark for 2 weeks and then reacted using the GolgiStain Kit and light protected for 10 days at 4 °C. Coronal sections (125 μm thickness) were cut on a vibrating microtome, immediately mounted onto slides and allowed to dry overnight in the dark. Slides were then rinsed in dH₂O and dehydrated in increasing concentrations of EtOH (50%, 75%, 95%, and 100%) for 5 min each. Slides were then cleared in Citrisolv for 5 min and coverslipped under Permount.

### 2.2.4. Dendritic spine analysis

Pyramidal neurons in layer 2/3 of the mPFC and the orbitofrontal cortex (OFC), as well as pyramidal cells of the CA1 region and granule cells of the dentate gyrus (DG) of the hippocampus from rats in Experiment 1, were analyzed at 100X using a BX-60 Olympus microscope equipped with a motorized stage and attached to a computer with Stereoinvestigator software (Microbrightfield, Burlington, VT). Neurons were considered for analysis if they were fully impregnated. On selected pyramidal neurons, five apical and five basal dendritic segments (each 10–25 μm long) meeting the following criteria were randomly chosen and analyzed for dendritic spine density: (1) on secondary or tertiary dendrites; (2) ≥50 μm away from the cell body for apical dendrites and 30 μm for basal dendrites; and (3) predominantly in one focal plane. Only spines extending away from the shaft were counted. A similar analysis was used on DG granule cells, with proximal segments defined as 0–50 μm from the cell body and distal segments between 50 μm to the tip of the process. An individual blind to the experimental conditions performed all analyses.

### 2.2.5. Statistical analysis

ASST trials and errors to criterion were analyzed via two-way ANOVA. When appropriate, Bonferroni post hoc comparisons were applied. Dendritic spine density was analyzed using two-tailed, unpaired Student’s t-tests.

### 2.3. Experiment 2

#### 2.3.1. Cannulae placement

In Experiment 2, rats were anesthetized with sodium pentobarbital and implanted bilaterally with guide cannulae (26 gauge; Plastics One, Roanoke VA) directed at the ventral hippocampus (±5.0 mm lateral to bregma; −6.3 mm posterior to bregma; −5.0 mm ventral to dura). To fix the cannulae to the skull, jeweler’s screws and dental acrylic were used. Dummy cannulae (33 gauge; Plastics One) were inserted into the guide cannulae to prevent clogging. Rats were allowed to recover for at least 1 week. Following 1 week, food deprivation in preparation for the ASST began (see methods above). During this period, the dummy cannulae were repeatedly changed to prevent the guide cannulae from clogging, while also allowing the rats to habituate to daily handling associated with intracranial infusions.

#### 2.3.2. Sexual experience paradigm

Naïve male rats were placed individually in a novel cage during their active period (1300 h) with a sexually-receptive female rat (see above) and allowed one intromission after which they were removed from the cage and subjected to ventral hippocampal infusion.

#### 2.3.3. Hippocampal inactivation

Immediately after each daily intromission, dummy cannulae were removed and the internal infusion cannulae, made via 33 gauge internal cannulae (Plastics One), were inserted. Rats were infused bilaterally with either sterile saline solution (0.9%; n = 7) or muscimol (1 mg/ml; n = 4) for 1 min, for a total infusion volume of 0.25 μl/hemisphere. This dose and duration of infusion has been shown to inactivate the ventral hippocampus but not surrounding brain regions (Hobin et al., 2006; Maren & Holt, 2004). After the infusion was complete, the infusion cannulae remained in place for 1 min to allow the infused solution to diffuse away from the cannulae tip. Following this, dummy cannulae were replaced and rats were returned to their home cages.

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**Table 2**

<table>
<thead>
<tr>
<th>Dimensions</th>
<th>Relevant</th>
<th>Irrelevant</th>
<th>Exemplar combinations</th>
</tr>
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<tbody>
<tr>
<td>SD Medium (M)</td>
<td>Texture (T)</td>
<td>M1</td>
<td>M2</td>
</tr>
<tr>
<td>CD Medium</td>
<td>Texture</td>
<td>M1/T1</td>
<td>M2/T2</td>
</tr>
<tr>
<td>IDS Medium</td>
<td>Texture</td>
<td>M3/T3</td>
<td>M4/T4</td>
</tr>
<tr>
<td>REV Medium</td>
<td>Texture</td>
<td>M3/T4</td>
<td>M4/T3</td>
</tr>
<tr>
<td>EDS Texture</td>
<td>Medium</td>
<td>T5/M5</td>
<td>T5/M6</td>
</tr>
</tbody>
</table>

Example of discrimination order for a rat shifting from digging medium to texture. Half of the rats shifted from digging medium to texture, while the other half shifted from texture to digging medium. The correct exemplar is indicated in bold and was paired with either exemplar from the irrelevant dimension. Exemplar presentation and assignment of exemplars into + and – stimuli were randomized.
2.3.4. Attentional set-shifting task

Twenty min after the drug infusion (Hobin et al., 2006; Maren, 2014; Maren & Holt, 2004), male rats were tested on an ASST, as described above (Fox, Barense, & Baxter, 2003; Liston et al., 2006). After ASST testing, rats were transcardially perfused and their brains were cut on a vibrating microtome for verification of cannula placement. Brains from this study were not stained for Golgi because the tissue damage caused by the cannula precluded cannula placement. Brains from this study were not stained for Golgi because the tissue damage caused by the cannula precluded cannula placement. Brains from this study were not stained for Golgi because the tissue damage caused by the cannula precluded cannula placement. Brains from this study were not stained for Golgi because the tissue damage caused by the cannula precluded cannula placement.

2.3.5. Statistical analysis

ASST trials and errors to criterion were analyzed via two-way ANOVA. When appropriate, Bonferroni post hoc comparisons were applied.

3. Results

3.1. Mating selectively enhances performance on ASST

Mating resulted in a reduction in the number of trials to criterion compared to controls on the EDS phase of the ASST \( (F_{4, 88} = 5.514, p < 0.001) \) (Fig. 1), the phase of this task that requires the mPFC. No significant difference in errors to criterion was observed between sexually-experienced rats and controls during the EDS phase of the set-shifting task \( (p > 0.05) \). Discrimination learning (SD and CD), IDS, and REV were similar between controls and sexually-experienced males in trials and errors to criterion. For the control group, more trials to reach criterion were needed during the EDS phase than in the SD phase \( (F_{4, 64} = 6.261, p < 0.01) \) and more errors were made during the EDS phase than during the SD phase \( (F_{4, 64} = 5.304, p < 0.01) \).

3.2. Mating increases dendritic spine density in the medial prefrontal cortex and the dentate gyrus, but not in the orbitofrontal cortex or CA1 region

Mating was associated with enhanced dendritic spine density of Golgi-impregnated pyramidal neurons in layer 2/3 of the mPFC (Fig. 2). Compared to controls, mated rats had more dendritic spines on apical \( (t_{8} = 2.615, p < 0.05) \) and basal \( (t_{8} = 2.706, p < 0.05) \) dendrites of mPFC pyramidal cells. No change in OFC dendritic spine density was observed on either apical \( (t_{8} = 0.220, p > 0.05) \) or basal \( (t_{8} = 0.099, p > 0.05) \) dendrites. In the hippocampus, which projects to the mPFC (Groenewegen, Wright, & Uylings, 1997) and is known to be sensitive to sexual experience (Glasper & Gould, 2013; Leuner et al., 2010b; Spritzer, Weinberg, Viala, & Galea, 2009), DG granule cells exhibited an increase in dendritic spine density in distal \( (t_{9} = 3.433, p < 0.01) \) but not proximal \( (t_{9} = 1.277, p > 0.05) \) segments (Fig. 2). By contrast, no changes were observed in dendritic spine density on apical \( (t_{8} = 0.332, p > 0.05) \) or basal dendrites \( (t_{8} = 0.325, p > 0.05) \) of CA1 pyramidal cells with sexual experience.

3.3. Ventral hippocampal muscimol infusion does not affect performance during the ASST in sexually experienced rats

Bilateral infusion of muscimol into the ventral hippocampus did not alter discrimination learning (SD and CD), or performance during IDS, REV, or EDS shifting (trials to criteria: \( F_{4, 36} = 2.013, p > 0.05 \)); errors to criteria: \( F_{4, 36} = 2.327, p > 0.05 \). Sexually-experienced rats infused with muscimol did not differ in trials to criterion \( (p > 0.05) \) or errors to criterion \( (p > 0.05) \) on any phase of the attentional set-shifting task, compared to saline-injected rats with sexual experience (Fig. 3).

4. Discussion

Our results show that sexual experience enhances performance on the EDS phase of the ASST, a task that depends on an intact mPFC (Birrell & Brown, 2000). Concomitant with these findings, we observed increased dendritic spine density of both apical and basal dendrites of pyramidal neurons in the mPFC of adult male rats after sexual experience and ASST testing. Consistent with previous results, we found that sexual experience alone increased the density of dendritic spines of granule cells within the dentate gyrus of the hippocampus (Glasper & Gould, 2013; Leuner et al., 2010b). Although all of the rats we examined in the present study were exposed to both sexual experience and ASST training, raising the possibility of interacting effects between both experiences, the previously published results on sexual experience alone in the hippocampus argue against this possibility. The ability of sexual experience and ASST to increase dendritic spine density was not universal in that no such changes were observed in pyramidal cells of the orbitofrontal cortex or CA1 region. Despite the fact that sexual experience did increase dendritic spine density on at least one population of hippocampal neurons, the granule cells, and that neurons from the ventral hippocampus project directly to the mPFC (Jay & Witter, 1991; Swanson, 1981), inactivation of this afferent structure did not prevent mating-induced enhancements in cognitive flexibility.

Our findings showing enhanced cognitive flexibility along with enhancements in dendritic spine density of pyramidal neurons of the mPFC with sexual experience are consistent with several studies examining the influence of other types of experience on this neuron type. Previous work has shown that postpartum maternal rats display enhanced cognitive flexibility along with increases in

Fig. 1. (A) Mean number of trials to criterion in virgin males \((n = 13)\) and sexually-experienced males \((n = 11)\) on each stage of discrimination in the attentional set-shifting task. There were no significant differences between the two groups in the acquisition of the task (simple discrimination (SD) or compound discrimination (CD)), the intradimensional shift (IDS) or on reversal learning (REV) but sexually-experienced rats showed enhanced performance on the extradimensional shift (EDS). (B) Errors to criterion were not significantly different between groups. Bars represent mean ± SEM. *p < 0.001.
Studies have also shown that restraint stress produces diminished cognitive flexibility along with decreases in dendritic spine density on mPFC pyramidal neurons (Liston et al., 2006). Taken together, these findings suggest a positive relationship between performance on tasks of cognitive flexibility and dendritic spine density on layer 2/3 mPFC pyramidal neurons. Since these results are correlational, it remains unclear whether there is a causal link between these two sets of effects. If such a causal link exists, at least two possibilities exist. First, it is possible that experience changes dendritic spine numbers, which in turn influence the function of the region. Specifically, improvements in ventral hippocampal structure may induce changes in the mPFC, which in turn improve ASST performance. Given that dendritic spines are primary sites of excitatory synapses that are influenced by experience (Bourne & Harris, 2008; Yuste, 2013), this scenario seems plausible. Second, it is possible that experience alters the activity of neurons in the mPFC, either in a negative or positive way, which in turn affects neuronal structure. That is, sexual experience may increase mPFC neuronal activity, which, in turn, may stimulate neuronal growth. The finding that sexual experience increases immediate early gene expression, a proxy for neuronal activation, in both naïve and experienced males (Pitchers et al., 2013) is consistent with this possibility. Although, again, it is unclear whether such increases in neuronal activation occur before or after dendritic spine growth.

Our results showing that repeated sexual experience increases cognitive flexibility and dendritic plasticity in young adult rats adds to the increasing literature on reward-induced enhancements in prefrontal cortex neuroplasticity. Not surprisingly, given its interconnectedness with reward-related brain regions, including the ventral tegmental area, the mPFC is activated by conditioned place preference testing, intracranial self-stimulation, and self-administration of addictive drugs and other rewarding treatments (reviewed in Tzschentke, 2000). The enhanced performance during the EDS stage of the ASST among sexually experienced rats suggests that the rewarding properties of sexual experience might alter the function and structure of the mPFC similarly to other rewarding experiences. This raises the possibility that there may be a common mechanism promoting this enhancement in neuroplasticity. One possible candidate is activation of the mesolimbic dopamine system, as studies have shown that pharmacologic activation of dopamine receptors increases, while pharmacologic blockade of dopamine receptors decreases, dendritic spine density in the medial prefrontal cortex (Ferrario et al., 2005; Frankfurt, Salas-Ramirez, Friedman, & Luine, 2011; Frost, Page, Carroll, & Kolb, 2010).

Research in rodents has shown that the mPFC participates in cognitive function via its influence on the hippocampus, midbrain dopamine neurons, and the nucleus accumbens (Brooks, Sarter, & Bruno, 2011; Floresco, Ghods-Sharifi, Vexelman, & Magyar, 2006; Klanker, Feenstra, & Denys, 2013; Tseng, Chambers, & Lipska, 2009). Enhancement of function in either the hippocampus or the midbrain may be critical for the benefits observed following the rewarding experience of mating. The hippocampus, specifically the ventral portion, is important for the functional development and regulation of the prefrontal cortex–nucleus accumbens circuit (Flores et al., 2005; Lipska, 2004; Lipska & Weinberger, 2002). Despite these developmental and neuroanatomical connections, infusion of muscimol into the ventral hippocampus did not prevent mating-induced enhancement of performance on the ASST. These results may suggest that experience-dependent improvements in cognitive flexibility do not depend on the ventral hippocampus, but instead rely on modifications to dopamine signals within the nucleus accumbens that are critical for reinforcement learning. Alternatively, or in addition, improvements in cognitive flexibility may be due to increases in dendritic spine density within the mPFC. It should be noted, however, that inputs from the ventral hippocampus may be necessary for sexual experience-induced improvements in cognitive flexibility but that the time of
hippocampal inactivation was not of long enough duration in our study. Future studies will be necessary to determine whether blocking ventral hippocampal activation for the entire time between sexual experience bouts, or even during sexual experience, results in prevention of the beneficial effects of sexual experience on cognitive flexibility.

Taken together with previous work, the present findings suggest that a relatively brief exposure to a basic rewarding experience, namely sexual experience, is sufficient to alter structural plasticity in the hippocampus (Gasper & Gould, 2013; Leuner et al., 2010b; present report) and mPFC (present report), as well as cognitive function on tasks that require the hippocampus (Gasper & Gould, 2013) and those that require the mPFC (present report). Collectively, these findings raise questions about the degree to which laboratory control animals have brains that reflect those of animals living in natural environments. Given that typical laboratory control conditions are devoid of experiences that occur regularly in the wild, such as mating, the laboratory baseline may more accurately reflect a state of deprivation. Indeed, the wide range of conditions that are sufficient to enhance structural plasticity and function in the hippocampus and mPFC strongly suggest that any such experience may help to restore a baseline that more accurately reflects that of wild living animals. It should be emphasized, however, that the present study examined only a relatively brief period of sexual experience (7 days) in animals that were born, raised and lived as adults for a time in standard laboratory conditions. Short-term sexual experience does not come close to mimicking the circumstances of animals living in the wild. It thus remains unknown whether laboratory experiences that induce plasticity do so with any specificity and whether they reflect the myriad of environmental cues that undoubtedly shape the wild living brain.

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References


