



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.

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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; Dalley, 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-Gallegos 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.

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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; Tenk, 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 (Eadie, 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 & Dominguez, 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
Exemplars used.

Medium pairs	Texture pairs
Ribbon vs. crinkled paper strips	Waxed paper vs. fine sand paper
Gravel vs. plastic beads	Velvet vs. reversed velvet
Sawdust vs. sand	Yellow fuzzy vs. reversed yellow fuzzy

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).

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