



## Testosterone influences spatial strategy preferences among adult male rats

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### ABSTRACT

Males outperform females on some spatial tasks, and this may be partially due to the effects of sex steroids on spatial strategy preferences. Previous work with rodents indicates that low estradiol levels bias females toward a striatum-dependent response strategy, whereas high estradiol levels bias them toward a hippocampus-dependent place strategy. We tested whether testosterone influenced the strategy preferences in male rats. All subjects were castrated and assigned to one of three daily injection doses of testosterone (0.125, 0.250, or 0.500 mg/rat) or a control group that received daily injections of the drug vehicle. Three different maze protocols were used to determine rats' strategy preferences. A low dose of testosterone (0.125 mg) biased males toward a motor-response strategy on a T-maze task. In a water maze task in which the platform itself could be used intermittently as a visual cue, a low testosterone dose (0.125 mg) caused a significant increase in the use of a cued-response strategy relative to control males. Results from this second experiment also indicated that males receiving a high dose of testosterone (0.500 mg) were biased toward a place strategy. A third experiment indicated that testosterone dose did not have a strong influence on the ability of rats to use a nearby visual cue (floating ball) in the water maze. For this experiment, all groups seemed to use a combination of place and cued-response strategies. Overall, the results indicate that the effects of testosterone on spatial strategy preference are dose dependent and task dependent.

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### Introduction

It is now well established that men outperform women on certain spatial tasks (Voyer et al., 1995). These include mental rotation of objects (Kaufman, 2007; Parsons et al., 2004), judgment of line angles (Cherney et al., 2008), route learning (Holding and Holding, 1988; Postma et al., 2004), and maze navigation (Astur et al., 1998; Moffat et al., 1998). Similarly, male rats have better spatial learning and memory abilities than females based on performance in the Morris water maze (Harris et al., 2008; Jonasson et al., 2004; Markowska, 1999; Roof and Stein, 1999) and the radial-arm maze (Gibbs and Johnson, 2008; Luine and Rodriguez, 1994; Seymoure et al., 1996).

One underlying cause of this sex difference seems to be that the two sexes use different strategies to solve spatial tasks. A *place strategy* involves using knowledge about the positions of environmental cues relative to a goal and relative to one's own position to locate the goal (Packard and McGaugh, 1996; Schmidt et al., 2009). A *response strategy* involves using stimulus–response relationships to locate a goal (Packard

and McGaugh, 1996; Schmidt et al., 2009). We will use the term *motor-response strategy* to refer to the use of proprioceptive stimuli (e.g., turn to the left or turn to the right in the T-maze) and the term *cued-response strategy* to refer to the use of stimuli proximal to the goal (e.g., visible goal platform in the water maze). Many studies with rodents involving localized brain lesions have demonstrated that the use of a place strategy relies on the hippocampus, whereas the use of response strategies (both motor-response and cued-response) relies on the dorsal striatum (Devan et al., 1996; McDonald and White, 1993; Packard and McGaugh, 1996; Pearce et al., 1998). Because both the motor-response strategy and the cued-response strategy rely on a functional striatum (McDonald and White, 1994; Packard and McGaugh, 1996), we consider these different types of response strategy to be functionally similar. When solving spatial tasks, men preferentially use a place strategy involving Euclidian cues, whereas women preferentially use a response strategy involving local landmarks (Cherney et al., 2008; Dabbs et al., 1998; Lawton, 1994; Silverman and Choi, 2006). This sex difference in preferred strategy seems to be because men are better able than women to employ a place strategy (Goyette et al., 2012; Sandstrom et al., 1998).

Experiments with rats generally support the findings of human studies. In the Morris water maze, female rats show a strong bias for using local landmarks to find the escape platform (Jonasson et al., 2004; Kanit et al., 1998, 2000), whereas males seem to rely more

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heavily on extra-maze cues than do females (Sava and Markus, 2005). Males outperformed females in the water maze when a place strategy was needed to solve the task, but no sex difference was observed when response strategies (local cues or a turn bias) could be used to solve the task (Blokland et al., 2006). Additionally, in a task that required rats to switch between place and response strategies, females performed more errors than males when they had to switch from a response strategy to a place strategy (Schmidt et al., 2009).

Interestingly, Kanit et al. (2000) found that unlike adult rats, juveniles did not show a sex difference in spatial strategy preference. This suggests that the sex difference in spatial strategy preference may be due to the activational effects of sex steroids. The effects of estrogens on spatial strategies have been extensively tested using female rats (Korol, 2004). The estrus cycle influences strategy preference, with females in proestrus (high estradiol) showing a bias toward a place strategy and females in estrus (low estradiol) showing a bias toward a response strategy (Korol et al., 2004; McElroy and Korol, 2005; Pleil and Williams, 2010; Sava and Markus, 2005). Similarly, high or low doses of estradiol given to ovariectomized females cause a bias toward a place strategy or a response strategy, respectively (Quinlan et al., 2008). Females given estradiol replacement performed better than ovariectomized females without estradiol on tasks requiring a place strategy, whereas for tasks requiring a response strategy females without estradiol performed better than females given estradiol (Davis et al., 2005; Korol and Kolo, 2002). One study found that ovariectomized females relied more heavily on local landmarks (stimulus–response strategy) in the water maze than did females with relatively low circulating levels of estradiol (Daniel and Lee, 2004). Finally, intra-hippocampal infusions of estradiol improved place learning in females rats (Zurkovsky et al., 2007), whereas intra-striatal infusions of estradiol impaired motor-response learning (Zurkovsky et al., 2007, 2011). Overall, these results indicate that increasing a female's estradiol levels improves her ability to use a place strategy but impairs her ability to use a response strategy.

Estradiol's strong role in regulating spatial strategies suggests that testosterone may also have activational effects on spatial strategies. In support of this idea, androgen receptors have been found in both the hippocampus and striatum of male rats (Feng et al., 2010; Kerr et al., 1995; Li et al., 1997; Xiao and Jordan, 2002). Although recent literature reviews have concluded that elevated circulating testosterone levels do not consistently improve spatial ability in men (Puts et al., 2010; Ulubaev et al., 2009), some human studies have shown that testosterone improves mental rotation ability (Christiansen and Knusmann, 1987; Hooven et al., 2004; Silverman et al., 1999), route-learning (Choi and Silverman, 2002), and performance on a block design task (Thilers et al., 2006). Among male rats, the effects of testosterone have been shown to differ between working and reference memory. Working memory is a form of short-term memory that involves storage of information from a particular task only for as long as it is useful to complete that task, and reference memory refers to the long-term storage of memories that are used from one task to the next (Olton and Papas, 1979). Numerous studies have shown that castrating male rats impairs their spatial working memory (Daniel et al., 2003; Gibbs and Johnson, 2008; Hasegawa and Mochizuki, 2009; Kritzer et al., 2001; Spritzer et al., 2008), and some studies have shown that testosterone replacement restores spatial working memory (Bimonte-Nelson et al., 2003; Kritzer et al., 2001; Spritzer et al., 2011b). In contrast, most studies to date indicate that testosterone has no effect on spatial reference memory (Hodosy et al., 2010; Naghdi et al., 2005; Sandstrom et al., 2006; Spritzer et al., 2008), but a few have demonstrated testosterone-induced improvements in reference memory (Khalil et al., 2005; Spritzer et al., 2011b).

Only two studies to date have specifically addressed the effects of testosterone on spatial strategies used by male rats (Gibbs, 2005; Hawley et al., 2012). Gibbs (2005) observed no differences in strategy preference among castrated, intact, and testosterone-implanted male rats and none of the groups showed a significant bias toward a particular

strategy. Hawley et al. (2012) found that intact males had a significant bias toward a place strategy, and castration had no significant effect on this bias. In combination, these two studies suggest that testosterone does not have activational effects that influence spatial strategy preference. However, some evidence indicates that the effects of testosterone on spatial memory are dose dependent (Naghdi et al., 2001; Spritzer et al., 2011b), and the effects of testosterone may also be task dependent (Spritzer et al., 2008, 2011b). For the current study, we tested three different physiological doses of testosterone and used three different maze tasks to assess learning strategy.

The overarching goal of the current study was to clarify the activational effects of testosterone on the spatial strategy preference of male rats. Our three experiments assessed bias for three slightly different types of response strategies, and estradiol has been previously shown to influence female strategy preferences for all three tasks. Experiment 1 employed a dual-solution T-maze in which the motor-response strategy involved learning to turn either to the right or left (proprioceptive cues). For this task, high estradiol and low estradiol levels bias females toward place and motor-response strategies, respectively (Korol et al., 2004; Quinlan et al., 2008). Experiments 2 and 3 both involved versions of the Morris water maze that could be solved using either a place strategy or a cued-response strategy. The distinction between the two experiments is that for Experiment 2 the goal platform itself could be used as a cue, whereas for Experiment 3 a floating ball near the platform was the only proximal cue. Females show a strong bias toward a cued-response strategy in the visible-platform version of the water maze, and this bias does not emerge until after puberty (Kanit et al., 2000). For the floating-ball task, ovariectomy caused a strong bias toward a cued-response strategy relative to estrogen-replaced females (Daniel and Lee, 2004). Given the previous results for females on these tasks and the fact that testosterone can be aromatized to estradiol in the male brain (Shibuya et al., 2003), we predicted that castration would bias males toward a response strategy and that testosterone replacement would bias them toward a place strategy. As an alternative hypothesis, the limited data for male rats suggested that we might instead observe no effects of testosterone on spatial strategy preferences (Gibbs, 2005; Hawley et al., 2012).

## Methods

### Subjects

Adult male Long-Evans rats (approximately 60 days old) were obtained from Charles River Laboratories (St. Constant, Quebec, Canada). For all experiments, rats were individually housed in opaque polypropylene cages (21 × 42 × 21 cm) with Tek-Fresh Bedding (Harlan Laboratories, Indianapolis, IN, USA). Animals had free access to water and a soy-protein-free rodent diet (Harlan Teklad Diet 2020X), except during food restriction for rats tested on the T-maze. The housing and testing rooms were temperature controlled (21 ± 1 °C) with a 12:12 h light/dark cycle (lights on at 0700 h). All animal procedures were approved by the Middlebury College Animal Care and Use Committee and were carried out in accordance with ethical guidelines set by the National Institutes of Health.

All subjects were bilaterally castrated 7–8 days after they arrived in the animal facility. Surgeries were performed with aseptic technique under isoflurane anesthesia (3.5–4.0% in oxygen during induction, 2.0–2.5% in oxygen during maintenance). The analgesic Ketofen (5 mg/kg body mass, s.c.) was administered just before surgery. Immediately after surgery, topical antibiotic (vetriyopolycin) and analgesic (2.5% lidocaine, 2.5% prilocaine) were applied to the incision area. Each testis was excised through a small incision at the posterior end of the scrotum and ligated with chromic gut suture material (Ethicon, Somerville, NJ, USA). The muscular sheath was closed with chromic gut sutures, and the skin layer was closed with ethilon sutures (Ethicon). For Experiments 2 and 3, the rats were castrated over two

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