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Modulation of spatial and response strategies by phase of the menstrual cycle in women tested in a virtual navigation task

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ABSTRACT

Different memory systems are employed to navigate an environment. It has been consistently shown in rodents that estrogen impacts multiple memory system bias such that low estradiol (E2) is associated with increased use of a striatal-mediated response strategy whereas high E2 increases use of a hippocampal-dependent spatial memory. Low E2 also enhances performance on a response-based task whereas high E2 levels improve learning on a spatial task. The purpose of the present cross-sectional study was to investigate navigational strategies in young, healthy, naturally cycling women. Participants were split into either an early follicular (i.e., when E2 levels are low), ovulatory (i.e., when E2 levels are high) or mid/late luteal (i.e., end of the cycle, when E2 levels decrease and progesterone levels rise) phase group, using self-reported date of the menstrual cycle. Serum hormone level measurements (E2, progesterone, testosterone) were used to confirm cycle phase assignment. Participants were administered a verbal memory task as well as a virtual navigation task that can be solved by using either a response or spatial strategy. Women tested in the ovulatory phase, under high E2 conditions, performed better on a verbal memory task than women tested during the other phases of the cycle. Interestingly, women tested in the mid/late luteal phase, when progesterone is high, predominantly used a spatial strategy, whereas the opposite pattern was observed in the early follicular and ovulatory groups. Our data suggest that the specific memory system engaged differs depending on the phase of the menstrual cycle and may be mediated by both E2 and progesterone, rather than E2 alone.

1. Introduction

Multiple memory systems can be engaged to solve a task and aid in navigating a complex environment. Different learning systems were first documented by Tolman and colleagues (1946) who showed that rats utilize different strategies to find their way in a maze (Tolman et al., 1946). Namely, several learning strategies can be used: one is response strategy, which is a strategy that relies on body turns at specific points in the environment forming stimulus-response associations, and the second is spatial strategy, which is allocentric, i.e. independent of the position of the observer and relies on forming stimulus–stimulus associations between landmarks in order to create a cognitive map of the environment. These systems are dissociable, they can be competitive, and rely on different brain regions to function optimally. The hippocampus is implicated in spatial memory (O'Keefe and Nadel, 1978) whereas the dorsal striatum (which includes the caudate nucleus) is crucial for response memory (Packard et al., 1989). In a series of seminal studies, spatial memory was significantly impaired when the hippocampal formation (fornix) was damaged and response memory was impaired when the dorsal striatum was damaged (McDonald and White, 1994, 1993). It has also been shown that rats initially use hippocampus-dependent spatial memory early on in a dual-solution maze task but this changes to striatum-dependent response memory with additional training, suggesting that the hippocampus and striatum have different temporal dynamics (Packard and McGaugh, 1996). There is some evidence that multiple memory system bias is influenced by dopamine (DA) levels in the dorsal striatum, such that DA enhances response learning and DA blockade within the dorsal striatum impairs response learning (Daniel et al.,

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2006; Quinlan et al., 2013). Thus, these memory systems are dissociable, such that as one is inactivated, other systems are engaged to navigate an environment (Packard and McGaugh, 1992; Packard and White, 1991; Packard et al., 1989).

Evidence for the existence of multiple memory systems has also been observed in humans; as in rodents, spatial memory is associated with fMRI activity and grey matter in the hippocampus whereas response memory is associated with the caudate nucleus (Bohbot et al., 2007, 2004; Iaria et al., 2003). Increased hippocampal volume is associated with navigational expertise (Maguire et al., 2000; Woollett and Maguire, 2011), and individuals with a damaged hippocampus were shown to have impaired spatial memory (Bohbot et al., 1998; Holdstock et al., 2000). Yet a damaged hippocampus does not impair the use of a response strategy to solve the task (Bohbot et al., 2004). Though multiple memory systems rely on specific brain structures, there exist individual differences in the type of strategies that are employed to navigate an environment. However, with time and practice, spatial learners tend to switch to the less cognitively demanding and faster response strategy. This has been observed in both humans (Iaria et al., 2003) and male rats (Chang and Gold, 2003; Packard and McGaugh, 1996). Switching from a spatial strategy to a response strategy with time and practice is observed in male rodents; female rats persist in using a spatial strategy when estradiol (E2) levels are high. This has been shown in naturally cycling rats (Korol et al., 2004; McElroy and Korol, 2005) as well as ovariectomized rats receiving E2 replacement (Davis et al., 2005; Hussain et al., 2013; Korol and Kolo, 2002; Quinlan et al., 2008).

Based on the rat literature, it is clear that E2 levels modulate the use of memory systems; however, little is known about if and how this occurs in humans. It has been observed that E2 is associated with changes in cognition in women; for example, E2 has been linked with improved verbal memory (Maki et al., 2002; Mordecai et al., 2008; Rosenberg and Park, 2002) whereas it is associated with impaired performance on mental rotation tasks (Hampson, 1990; Hausmann et al., 2000). Hippocampal volume changes across the menstrual cycle in women, i.e., high endogenous E2 levels are associated with an increase in hippocampal grey matter (Protopescu et al., 2008). In addition, it has previously been found that estrogen receptors are present in the human hippocampus (Osterlund et al., 2000a,b). Thus, E2 could be structurally altering the hippocampus and binding to estrogen receptors within this brain area to promote spatial memory.

Progesterone (P) has been shown to be associated with both enhanced (Maki et al., 2001; Natale et al., 2001) and disrupting (Freeman et al., 1992) effects on verbal memory in women. It is important to note that the majority of studies that are focused on hormones and cognition in women, are carried out with a postmenopausal sample, taking hormone replacements. These samples of women typically receive progestin with their hormone treatments that include E2, thus, very few studies have focused on the effects of P in isolation. P has been shown to increase hippocampal spine density when administered with E2, but these spine densities decrease more rapidly than when E2 is administered alone (Woolley and McEwen, 1993). P receptor function is dependent on induction of E2 receptors (Lydon et al., 1995), which suggests that many of the effects linked to P are also underscored by E2 action. Furthermore, E2 and P are often studied separately so the interaction between the two hormones, and how this can potentially affect cognitive function, is not well understood. E2 and P seem to work in concert to affect hippocampal function and, possibly, multiple memory system bias.

Low levels of testosterone (T) produced by the ovaries have also been found in some areas of the female brain, and can be converted into E2 (Davis and Tran, 2001; Vierhapper et al., 1997). Androgen receptors are also located in the hippocampus (Beyenburg et al., 2000), which indicates that T could be exerting an effect on hippocampus-dependent tasks, such as allocentric spatial memory. T has been shown to influence cognitive abilities in cycling women (Hausmann et al., 2000) and spatial cognition is affected by diurnal changes in testosterone levels in women, such that T is correlated with enhanced performance on a visuo-spatial task (Moffat and Hampson, 1996) and shorter latencies in finding a hidden platform in a virtual water maze task (Burkitt et al., 2007). Another study also demonstrated that performance on a virtual water maze task in women is affected by the interaction between T function and androgen receptor sensitivity (Nowak et al., 2014). These studies suggest that testosterone could also be playing a role in multiple memory system bias.

In the current study, young, naturally cycling women were tested on the 4 on 8 virtual maze (4/8 VM), a dual-solution navigation task in which they could utilize either a spatial or response strategy to complete the experiment. Estradiol peaks towards the end of the follicular phase (ovulation) and then rises and plateaus across the luteal phase. The menstrual cycle is also marked by changes in P levels such that they are low throughout the follicular phase while they peak and plateau in the luteal phase, before dropping at the onset of menstruation (for review, see Ref.: Hussain et al., 2014; Mihm et al., 2011). E2 levels are higher in the ovulatory phase compared to the early follicular phase, which is marked by low E2 levels throughout menstruation. Based on animal studies, it was hypothesized that women tested during the ovulatory phase, when E2 levels peak, would be more likely to use a spatial strategy and utilize more landmarks to navigate whereas those tested in the early follicular phase, when E2 and P levels are low, would use a response strategy more often. Furthermore, it was expected that the ovulatory phase would be associated with a higher number of errors and trials required to reach criterion, since spatial strategies are more cognitively demanding and are associated with increased errors on the 4/8 VM (Iaria et al., 2003).

In addition, a battery of standard neuropsychological tests that measure verbal and visuo-spatial memory was administered in order to test whether these functions change across the menstrual cycle; according to the existing literature, we would expect high E2 levels to be associated with enhanced verbal memory (Maki et al., 2002; Mordecai et al., 2008; Rosenberg and Park, 2002) whereas low E2 would be related to enhanced performance on a visuo-spatial task (Hampson, 1990; Hausmann et al., 2000). Finally, an IQ test as well as questionnaires measuring perceived stress and quality of sleep were carried out in order to ensure that participants tested in the early follicular, ovulatory, and mid/late luteal phase of the menstrual cycle are similar in terms of cognitive function, stress levels, and sleep quality.

2. Methods

2.1. Participant characteristics

A total of 45 healthy, right-handed, regularly cycling (i.e., a menstrual cycle lasting between 25 and 34 days) women were tested (age: $M = 30.31$; $SD = 3.38$; range = 23-36; see Fig. 1 for the study outline). All participants underwent a screening questionnaire over the phone to determine whether they were eligible to participate in this study. Participants who reported a history of psychological or neurological illness, drug or alcohol abuse, had been pregnant within the past two years, currently breastfeeding, or had taken contraceptive medication within three months of testing were excluded. Participants had, on average, 16.67 years of education ($SD = 2.76$) and a mean sleep score of 0.90 ($SD = 0.15$; sleep score = average number of hours of sleep over the past week/ideal number of hours of sleep for the individual). See Table 1 for all participant demo-