Neurobiology of Learning and Memory 110 (2014) 55–63

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Menstrual-cycle dependent fluctuations in ovarian hormones affect emotional memory

Janine Bayer *, Heidrun Schultz, Matthias Gamer, Tobias Sommer

Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Germany

ARTICLE INFO

Article history:
Received 15 August 2013
Revised 23 January 2014
Accepted 25 January 2014
Available online 31 January 2014

Keywords:
Functional imaging
Dual process
Estrogen
Progesterone
Emotional memory
Menstrual cycle

ABSTRACT

The hormones progesterone and estradiol modulate neural plasticity in the hippocampus, the amygdala and the prefrontal cortex. These structures are involved in the superior memory for emotionally arousing information (EEM effects). Therefore, fluctuations in hormonal levels across the menstrual cycle are expected to influence activity in these areas as well as behavioral memory performance for emotionally arousing events. To test this hypothesis, naturally cycling women underwent functional magnetic resonance imaging during the encoding of emotional and neutral stimuli in the low-hormone early follicular and the high-hormone luteal phase. Their memory was tested after an interval of 48 h, because emotional arousal primarily enhances the consolidation of new memories. Whereas overall recognition accuracy remained stable across cycle phases, recognition quality varied with menstrual cycle phases. Particularly recollection-based recognition memory for negative items tended to decrease from early follicular to luteal phase. EEM effects for both valences were associated with higher activity in the right anterior hippocampus during early follicular compared to luteal phase. Valence-specific modulations were found in the anterior cingulate, the amygdala and the posterior hippocampus. Current findings connect to anxiolytic actions of estradiol and progesterone as well as to studies on fear conditioning. Moreover, they are in line with differential networks involved in EEM effects for positive and negative items.

1. Introduction

Estradiol (E2) and progesterone (P4) modulate neuronal plasticity in a variety of brain areas, where most evidence accumulated so far for hormonal effects in the amygdala, the hippocampus and the prefrontal cortex (Foy et al., 1999; Hao et al., 2006; McEwen & Woolley, 1994; Murphy & Segal, 1996; Tang et al., 2004). These cellular effects of E2 and P4 stimulated research about hormonal influences on various cognitive and emotional functions. Consistent with their opponent effects on hippocampal neurotransmission, E2 exerts beneficial effects on memory that are reversed by P4 (Bimonte-Nelson, Francis, Umphlet, & Granholm, 2006; Gibbs, Gabor, Cox, & Johnson, 2004; Harburger, Bennett, & Frick, 2007). However, hormonal influences differ across brain regions, with E2 stimulating neural transmission for instance in the hippocampus while decreasing neuronal excitability in the amygdala (Foy et al., 1999; Womble, Andrew, & Crook, 2002). Moreover, E2 and P4 act opponent on some cellular processes in the hippocampus but exert conjoint neuroprotective effects in the prefrontal cortex (Djebaili, Hoffman, & Stein, 2004; Foy, Akopian, & Thompson, 2008; Hill, Chua, Jones, Simpson, & Boon, 2009; Kritzer & Kohama, 1998). The superior memory formation for emotionally arousing information, i.e. the emotional enhancement of memory (EEM), depends upon the interplay between all these structures. Therefore, predictions concerning hormonal influences on this memory function are less straightforward (for a review, see Dolcos, Denkova, & Dolcos, 2012).

Prefrontal areas, the hippocampus and the amygdala contribute differentially to the EEM, i.e. to distinct aspects and at different stages of emotional memory formation. When an emotional stimulus is encountered, a network between the amygdala and cortical areas rapidly initiates emotional processing and the allocation of attentional resources (Davis & Whalen, 2001; Pessoa, 2008). A prefrontal-parietal network then mediates the elaborate cognitive processing of stimulus valence (Canli, Zhao, Desmond, Glover, & Gabrieli, 1999; Dolcos, LaBar, & Cabeza, 2004; Kensinger & Schacter, 2006; Mickley & Kensinger, 2008). After the initial processing, emotional arousal leads to enhanced hippocampal consolidation of arousing stimuli via the amygdala and increased noradrenergic neurotransmission (Huff, Miller, Deisseroth,

* Corresponding author at: Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany. Fax: +49 40 7410 59955.

E-mail addresses: j.bayer@uke.de (J. Bayer), h.schultz@uke.de (H. Schultz), m.gamer@uke.de (M. Gamer), t.sommer@uke.de (T. Sommer).

http://dx.doi.org/10.1016/j.nlm.2014.01.017
1074-7427/

Moorman, & LaLumiere, 2013; McGaugh, 2004; Roozendaal, Nguyen, Power, & McGaugh, 1999; Strange & Dolan, 2004). Consequently, the effect of emotional arousal on memory requires a consolidation-delay between encoding and retrieval (Schwarze, Bingel, & Sommer, 2012; Sharot, Verfaellie, & Yonelinas, 2007).

Because E2 and P4 affect cellular mechanisms in brain areas mediating initial processing but also encoding and consolidation of emotionally arousing information, it is conceivable that hormonal fluctuations modulate the EEM effect at various stages. In animal models, both hormones exert anxiolytic and antidepressant actions (Frye, Petralia, & Rhodes, 2000; Frye & Walf, 2004; Lund, Rovis, Chung, & Handa, 2005; Reddy, O'Malley, & Rogawski, 2005; Shirayama et al., 2011; Walf & Frye, 2006). Functional imaging in humans reveals that E2 and P4 change reactivity to emotional stimuli in the amygdala, the hippocampus and the medial prefrontal cortex (Derntl et al., 2008; Goldstein et al., 2005; Guapo et al., 2009; Ossewaarde et al., 2010; Sripada et al., 2013; van Wingen et al., 2007). Likewise, E2 enhances extinction of contextual and cued fear conditioning in both animal models and humans (Graham & Milad, 2013; Gupta, Sen, Diepenhorst, Rudick, & Maren, 2001; Markus & Zecevic, 1997; Milad, Igoe, Lebron-Milad, & Novales, 2009; Milad et al., 2006, 2010; Zeidan et al., 2011). Hormonal influences on declarative emotional memory have been investigated only in studies employing between-subject designs, in which women were Post Hoc grouped according to their hormonal states (Ertman, Andreano, & Cahill, 2011; Felmingham, Fong, & Bryant, 2012; Nielsen, Ahmed, & Cahill, 2013). In detail, Ertman et al. (2011) found better memory for negative images in the second half relative to the first half of the menstrual cycle and a positive relationship between P4 levels and recall of negative images. In contrast, Felmingham et al. (2012) did not detect significant differences in memory for negative images between a high- and a low-P4 group. Nielsen et al. (2013) showed that only women in the second, but not the first, half of the menstrual cycle recalled more details from an emotional than a neutral story. Memory performance in this study did not show significant relationships to P4 or E2 levels.

The current study aims to further explore how natural hormonal variations affect the superior consolidation of emotional arousing information within the same women. Therefore, functional neuroimaging was performed in healthy young women while encoding positive, negative and neutral pictures once during menstruation in the *early follicular phase,* where both hormones are low, and once in the middle of the *luteal phase* where the concentration of P4 is at its maximum and E2 reaches a second peak. These phases of relatively stable hormone levels were chosen to reduce the variance between women. Moreover, the chosen cycle phases avoid the effects of sharp increase and decrease in E2 and P4 on cognition but also of the luteinizing hormone that rises shortly before ovulation (Berry, Tomidokoro, Ghiso, & Thornton, 2008; Casadesus et al., 2007; Hausmann, Slabbekoorn, Van Goozen, Cohen-Kettenis, & Güntürkün, 2000). In order to assess the effects of hormones on arousal-stimulated consolidation rather than the initial processing of emotional stimuli, memory was tested two days after encoding. Memory accuracy was assessed by means of d-prime. Additionally, memory quality was examined by estimating the process parameters recollection and familiarity of a prominent dual-process recognition memory model using confidence ratings (Yonelinas, 2002). In this model, recollection represents the process of remembering an item together with contextual information, such as thoughts, feelings or other details of the learning context. As such, memory based on recollection is always accompanied by high confidence. Familiarity is the sense of having something encountered before, but without recollecting any further details. Familiarity can be accompanied by the full range of confidence levels. Arousal ratings were acquired from each subject on a 9-point Likert scale for target images and stimuli were grouped according to arousal ratings into either high (HA) or low arousing (LA). According to the goal of the study, analyses were primarily conducted on HA emotional and LA neutral stimuli. Menstrual cycle phases were verified by assessments of E2 and P4 in saliva.

2. Materials and methods

2.1. Subjects

Twenty-three healthy, naturally cycling female volunteers aged 19–33 years ($M = 26$, $SD = 3.25$) were each tested twice during their menstrual cycle; once during *early follicular* and once during the *luteal phase* in counterbalanced order. On average, the first and second measurement points were separated by 46.41 days ($SD = 20.54$). A telephone screening prior to the first test session ensured that no subject met criteria for premenstrual dysphoric disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders IV (American Psychiatric Association., 2000). All subjects reported to be free of neurological or psychiatric diseases, use of illicit drugs and central nervous system medication and did not smoke more than two cigarettes per week. Date of the last menstruation and length of the menstrual cycle ($M = 28.18$, $SD = 1.42$) were assessed during the first interview to determine adequate time points for testing. During the time period between the first contact and last testing, all subjects informed the experimenter about their menstruation dates. One subject was excluded due to menstrual cycle irregularities, leaving 22 subjects for further analysis.

Memory encoding inside the scanner was scheduled at day 0 to day 4 after onset of menstruation in the early follicular phase ($M = 1.52$, $SD = 1.34$) and at 5–11 days before estimated onset of next menstruation ($M = 8.14$, $SD = 2.08$) in the luteal phase. After encoding and a 10 min break, women performed a reward paradigm which is reported elsewhere (Bayer, Bandurski, & Sommer, 2013). Memory retrieval was conducted 2 days after the encoding session outside the scanner.

Participants received financial compensation for the time spent at the institute. All participants gave written informed consent according to the Declaration of Helsinki. Ethics approval was obtained from the ethics committee of the medical association of Hamburg.

2.2. Emotional memory-task

In total, 576 color photographs depicting positive, negative and neutral contents were used for the current study. Images were drawn from the 'International Affective Picture Set' (IAPS; Lang, Bradley, & Cuthbert, 1999) and internet search. All three valence categories contained an equal number of images showing animals and people. Moreover, image contents were kept as equal as possible across valence categories to equalize semantic coherence and complexity. Images with similar gist were grouped pair wise, so that each target image had a corresponding lure image. Two lists were created for every subject, each assigning stimulus pairs to cycle phases and determining which item of the stimulus-pairs would be a target or lure.

During each cycle phase, subjects encoded 144 stimuli spread over four runs inside the scanner. Stimuli were pseudo-randomized with the restriction that not more than three pictures of the same valence category were presented in a row. Participants were informed about the memory test 2 days later.

Each trial began with a fixation cross lasting for 3 s, followed by presentation of the image for 2 s. Next, the picture disappeared and