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Evidence of estrogen modulation on memory processes for emotional content in healthy young women

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ABSTRACT

Purpose: It is well accepted that emotional content can affect memory, interacting with the encoding and consolidation processes. The aim of the present study was to verify the effects of estrogens in the interplay of cognition and emotion.

Methods: Images from the International Affective Pictures System, based on valence (pleasant, unpleasant and neutral), maintaining arousal constant, were viewed passively by two groups of young women in different cycle phases: a periovulatory group (PO), characterized by high level of estrogens and low level of progesterone, and an early follicular group (EF), characterized by low levels of both estrogens and progesterone. The electrophysiological responses to images were measured, and P300 peak was considered. One week later, long-term memory was tested by means of free recall.

Findings: Intra-group analysis displayed that PO woman had significantly better memory for positive images, while EF women showed significantly better memory for negative images. The comparison between groups revealed that women in the PO phase had better memory performance for positive pictures than women in the EF phase, while no significant differences were found for negative and neutral pictures. According to the free recall results, the subjects in the PO group showed greater P300 amplitude, and shorter latency, for pleasant images compared with women in the EF group.

Conclusion: Our results showed that the physiological hormonal fluctuation of estrogens during the menstrual cycle can influence memory, at the time of encoding, during the processing of emotional information.

1. Introduction

The physiological changes of sex hormone levels in the course of reproductive life expose women to periods of vulnerability, specifically related to these variations, such as the premenstrual phase, pregnancy, puerperium, and menopause. These hormonal fluctuations affected neural activity, and many authors have described the modulation of a broad spectrum of cognitive functions by estrogens in physiological as well as pathological conditions (Henry and Sherwin, 2012; Pompili et al., 2012; Poromaa, 2014). Therefore, it is not surprising that the modulatory role of female sex hormones, with particular emphasis on learning and memory, and emotions, represents one of the most exciting areas of research in women's health (Andreano et al., 2008; Ferree et al., 2011; Gasbarri et al., 2012; Nielsen et al., 2013; Dolcos et al., 2014; Toffoletto et al., 2014).

Estrogens can modulate cognitive activities and emotions, as the brain is an important target organ for estrogens (McEwen and Alves, 1999). Their two nuclear receptors (ERs), ERα and ERβ can be found in rodents, humans, and non-human primates in many cerebral areas involved in learning and memory, and emotion, such as amygdala, hippocampal formation (HF) and cerebral cortex (McEwen and Alves, 1999), providing an opportunity to modulate functioning of these regions and the processes they sub-serve (for a review see Frick, 2013).

It is well known that HF serves a critical role in the formation of new memories of a declarative nature (Squire and Zola, 1996; Squire, 2004), and much evidence suggests that estrogens exert a significant influence particularly in this area. HF shows dramatic morphological, electrophysiological and chemical changes across the estrous/menstrual cycle (Woolley, 1998; González-Burgos et al., 2005; Protopopescu et al., 2008; Spencer et al., 2008; Kato et al., 2013). ERs are located in CA1, CA3, and dentate gyrus, and behaviors relying on intact HF function are sensitive to estro-

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gens. Moreover, in humans, the amygdala, another important area of estrogen action, can affect hippocampus-based memory, modulating memory storage during encoding of arousing stimuli (Phelps, 2004). In fact, studies on humans, using brain imaging techniques, showed that the amount of long-term explicit recall of emotionally significant material is strictly correlated with amygdala activity during encoding (Cahill et al., 1996; Hamann et al., 1999; Kensinger and Schacter, 2005).

Most of the studies on the relationship between cognition and estrogens has been conducted on animals, utilizing models mimicking post-menopausal conditions, ovariectomized, and ovariectomized treated with estrogen replacement rodents and non-human primates, providing convincing evidence that ovariectomy and estradiol treatment can affect cognitive functions (Lacreuse et al., 2000; Daniel et al., 2006). Behavioral studies also suggest that memory performance may fluctuate, for intact animals, across the estrous cycle (Lacreuse et al., 2001; Pompili et al., 2010).

In humans, most of the research has been conducted on menopausal women, treated or not-treated with hormone replacement therapy (HRT). A smaller number of studies have been carried out under physiological conditions, showing that some cognitive abilities can fluctuate across the menstrual cycle, and can correlate with serum estrogen levels, in particular working memory (Gasbarri et al., 2008; Hampson and Morley, 2013), visual, verbal, and spatial functions (Phillips and Sherwin, 1992; Schöning et al., 2007; Mordecai et al., 2008; Hampson et al., 2014). Therefore, despite fluctuations associated with the estrous/menstrual cycle being modest, due to low hormonal changes compared to exogenous treatment, this is an area of potential interest documenting that the physiological range of estrogen levels can still influence specific aspects of cognition in gonadally intact female subjects.

In previous studies conducted in our laboratory, we analyzed the influence that endogenous fluctuation of estrogens can exert on the performance of tasks utilized to assess spatial memory in rats (Pompili et al., 2010), and working memory in young women (Gasbarri et al., 2008), finding significant differences in performances during estrous/menstrual phases. The purpose of this study was to elucidate the role of estrogens in the interplay of cognition and emotion: we hypothesized that estrogens could have an effect on memory encoding of emotional stimuli, when the stimulus is encountered for the first time. In order to analyze this effect, we used event-related potentials (ERPs), and then measured, using a behavioral task, the long-term retrieval of the stimuli, evaluating the correlation between ERPs and the memory of a specific stimulus. To this aim, we compared P300 brain responses to brief presentations of emotional and neutral pictures from the International Affective System (IAPS) in women during two different phases of the menstrual cycle, early follicular, characterized by low levels of both estrogens and progesterone, and periovulatory phase, characterized by high levels of estrogens and low levels of progesterone. We chose these two phases to avoid the interference of progesterone. Many studies, investigating the effects of emotion on retrieval activity by means of ERP methods, have found that emotional content tends to produce an overall enhancement in ERP correlates of retrieval memory (Gasbarri et al., 2007). To our knowledge, only few researchers have investigated the correlation between P300, menstrual cycle and emotional stimuli, showing a significant increase of P300 amplitude during the luteal phase, with high levels of progesterone, in response to emotional pictures, such as male models and babies (Johnston and Wang, 1991; Wang and Johnston, 1993), while Fleck and Polich (1988) did not find any differences in the P300 components in response to auditory stimuli, as a function of the menstrual cycle.

2. Methods

2.1. Participants

Fifty-eight young women volunteers, aged 21–27 (mean age 23.4 ± 2.2), and all students at the University of L'Aquila, were recruited for this study. They were initially screened in a standardized interview, to check for any health problems and to evaluate the regularity of their menstrual cycle. We selected only those subjects, 46, naturally cycling and with a cycle length from 26 to 30 days. Participants were all right-handed, had normal or corrected-to-normal vision, and were not suffering from any neurological disorders. Exclusion criteria included any form of hormonal contraceptive within the last 4 months, chronic illness, and psychiatric disorders (including premenstrual syndrome). Moreover, they had not been pregnant or lactating during the last 12 months.

During the screening interview, data regarding last menstrual period were collected, and subjects were subdivided into two groups, corresponding to early follicular (EF: 1th–4th day of the cycle) and periovulatory (PO: 12th–16th day of the cycle) phases. To assess ovarian function and verify the cycle phase, we used salivary measures of estradiol and progesterone as a non-invasive method.

All tests began at 10.00 h and the salivary samples were collected prior to the experiment. The final sample included 38 women, 20 in EF phase and 18 in PO phase. It was predicted that subjects in the PO group would show high levels of estrogens (>5 pg/ml) and low levels of progesterone (<110 pg/ml), while the EF group would show low levels of both estrogens (< 2 pg/ml) and progesterone (< 85 pg/ml).

Eight subjects from the initial of 46 (3 in EF group, and 5 in PO group), were not included in data analyses because the sex hormone levels were outside the expected range at the time of testing. Therefore, we chose only those individuals with characteristics closely adapted to our study. We conducted all experiments in accordance with the Declaration of Helsinki, and we carried out all procedures with adequate understanding of the subjects, who read and signed an informed consent before taking part in this research.

2.2. Endocrine measures

Salivary levels of estradiol and progesterone are believed to accurately represent the biologically active fraction in general circulation. Therefore, we measured salivary hormone concentrations using a kit of competitive enzymatic immunoassay, to verify the cycle phase (Salimetrics, State College, PA, USA). Monitoring these hormones in saliva has several advantages: collection techniques are less invasive than venipuncture, and research assistants or subjects can easily collect saliva samples with minimal training. For test principle, saliva sample assays, and data analysis, see Gasbarri et al., 2008.

2.3. Stimuli

The stimuli materials consisted of a set of 150 pictures[1] selected from the IAPS (Lang et al., 2008), according to the valence dimension (50 pleasant, 50 unpleasant, and 50 neutral). The IAPS is a widely used method for investigating emotion in the laboratory, and each picture had been rated on arousal and valence using 1–9 point scales. The choice of images was realized in order to define unequivocally pleasant [7.6 (SD: 0.61)], unpleasant [2.4 (SD: 0.59)] and neutral [4.9 (SD: 0.59)] valence levels, while maintaining the same arousal levels for each category [neutral: 5 (SD: 0.45); pleasant: 5 (SD: 0.49); unpleasant 5.1 (SD: 0.46)]. We excluded images

[1] The IAPS slide numbers were as follows: