Hormones and Behavior 63 (2013) 759–765

Contents lists available at SciVerse ScienceDirect

Hormones and Behavior

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

Acute pre-learning stress and declarative memory: impact of sex, cortisol response and menstrual cycle phase

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ARTICLE INFO

Article history:
Received 27 March 2012
Revised 14 March 2013
Accepted 17 March 2013
Available online 12 April 2013

Keywords:
Pre-learning stress
HPA axis
Salivary cortisol
TSST
Sex differences
Menstrual cycle

ABSTRACT

This study explores the influence of pre-learning stress on performance on declarative memory tasks in healthy young adults in relation to sex and menstrual cycle phase. The sample was composed of 119 students (32 men and 87 women) from 18 to 25 years of age. The women were tested in different hormonal stages (30 in follicular phase, 34 in luteal phase, and 23 using oral contraceptives). The participants were exposed to the Trier Social Stress Test (TSST) or a control condition. Afterwards, their memory performance was measured using a standardized memory test (Rey's Auditory Verbal Learning Test). In the control condition, all groups of women recalled more words than men, but these differences disappeared in the group exposed to TSST because men's performance on the memory test improved, but only to the level of women. In addition, our data suggest that in women the relationship between cortisol and memory can be modulated by sex hormone levels, since in luteal women a negative relationship was found between memory performance and peak cortisol level. These results confirm that sex differences need to be considered in the relationship between pre-learning stress and memory performance.

Introduction

The relationship between stress and declarative memory has been widely studied, although with contradictory results. Several studies have indicated that declarative memory can be impaired when subjects are exposed to stress before learning (Payne et al., 2006; Smeets et al., 2006), while others have found no effect (Elzinga et al., 2005; Wolf et al., 2001b) or even an enhancing effect of stress on declarative memory performance (Domes et al., 2002; Nater et al., 2007; Schwabe et al., 2008). This discrepancy has been explained by diverse factors, such as the memory phase under investigation (acquisition, consolidation or retrieval) and the time of testing (morning vs afternoon), among others (Het et al., 2005).

There is a body of literature suggesting that the release of cortisol is mainly involved in the effects of acute stress on memory performance (de Kloet et al., 1999; Het et al., 2005; Lupien and McEwen, 1997). Some studies have shown that stress-induced cortisol increase was negatively related to declarative memory performance when stress was applied prior to learning (Kirschbaum et al., 1996; Wolf et al., 2001b). In contrast, Nater et al. (2007) found the opposite result: high cortisol responders to stress actually had better recall on declarative memory performance than low cortisol responders. Along the same lines, Joels et al. (2006) proposed that cortisol released around the time of learning facilitates ongoing learning processes and, thus, would predict memory-enhancing effects of stress experienced shortly before learning.

Previous studies suggest that sex influences the cortisol response to stress. In animal studies, ACTH (adrenocorticotropic hormone) and corticosterone levels in response to stress have been shown to be consistently greater in females compared to males (Armario et al., 1995; Handa et al., 1994). However, in human studies on this issue, some research employing standardized acute laboratory stressors has shown significantly larger stress-induced salivary cortisol-concentrations in men compared to women (Kajantie and Phillips, 2006; Kudielka et al., 2009), but other studies found no sex differences in the cortisol response to laboratory stress (Kelly et al., 2008). In addition, the cortisol response in women seems to depend on the different menstrual cycle phases. Women in the luteal phase displayed a similar stress-induced cortisol response to that of men, but higher concentrations than women in the follicular phase and those taking oral contraceptives (Kajantie and Phillips, 2006; Kirschbaum et al., 1999; Kudielka and Kirschbaum, 2005).

Whether there is an effect of sex on the impact of the stress-induced cortisol response on declarative memory among young people remains unknown. To our knowledge, few studies have investigated this issue, and the results have not been conclusive. Some studies about the effect of pre-learning stress on memory in young subjects have shown that memory performance was negatively associated with cortisol response to a stressor only for men, while there

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0018-506X/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.yhbeh.2013.03.013

was no such association for women tested in the luteal phase (Wolf et al., 2001b). The reason for this sex difference is unclear, although there has been speculation about the potential beneficial effects of female sex hormones (Wolf, 2006) and about sex differences in the cortisol response to stress (Kudielka and Kirschbaum, 2005). In a more recent study, only women using oral contraceptives were included in order to avoid the menstrual cycle effect. The results of this study showed that there were no differences between men and women in cortisol response, and no significant effect of sex was found on free recall (Schwabe et al., 2008). Both studies included men and women, but without taking into account the effect of the different phases of the menstrual cycle, a factor that should be considered when studying the impact of sex on the cortisol response to acute stress (Bouma et al., 2009; Hidalgo et al., 2012; Kirschbaum et al., 1996, 1999; Kudielka and Kirschbaum, 2005). Moreover, because the effect of cortisol on memory may differ depending on the levels of estrogen and progesterone circulating in different phases in the menstrual cycle, findings showing no relationship between stress hormones and memory in women may have resulted from combining women in hormonally distinct phases into a single group (Andreano et al., 2008).

The current study was designed to examine the effects of pre-learning stress on declarative memory performance, and we hypothesized a memory-enhancing effect of stress applied shortly before learning (Joels et al., 2006). In order to investigate the impact of stress on specific processes of memory performance, we employed the Rey Auditory Verbal Learning Test (RAVLT; Miranda and Valencia, 1997). This test provides several memory indicators, such as immediate and delayed recall, and it has been shown to be sensitive to cognitive deficits associated with corticosteroid elevations in corticosteroid-treated patients (Brown et al., 2004) and with salivary cortisol levels (Fox et al., 2009). In addition, the RAVLT can also be sensitive to sex differences, since differences in memory performance between middle-aged women and men have been found using this measure (Almela et al., 2011).

According to previous studies with young people (Kirschbaum et al., 1992, 1995a,b; Uhart et al., 2006), we expected to find a higher cortisol response to stress in men than in women. Therefore, we hypothesized that the impact of stress on memory would be different in young men and women. To test this hypothesis, we included men, women in the luteal and follicular phases, and women using hormonal contraception.

In a between-subjects design, the participants were exposed to either the Trier Social Stress Test (TSST, Kirschbaum et al., 1993) or a control task, before learning a list of neutral words. Furthermore, this study evaluated self-reported state anxiety, using the Anxiety Inventory (STAI)-State, and positive and negative moods, using the mood questionnaire (PANAS), to investigate their impact on memory performance. As in the case of cortisol release after stress, some data indicate that negative mood can reduce working memory capacity (Eysenck and Derakshan, 2011), and elevated state anxiety has also been negatively associated with short-term memory capacity (Humphreys and Revelle, 1984) and working memory (Gass and Curiel, 2011).

Material and methods

Participants

A general health questionnaire was completed by an initial sample of 180 undergraduate students from the University of Murcia (Spain). On this questionnaire, participants were asked whether they suffered from any cardiovascular diseases, endocrine disorders or asthma, and whether they were habitual smokers (more than 10 cigarettes per day). If so, they were excluded from the study. In addition, the women had to be nulliparous, with no gynecological problems and regular menstrual cycles (24–36 days), or taking oral contraceptives. Of the initial sample, 61 students were finally not included for different reasons; 49 were not selected because of the exclusion criteria, and 12 subjects were eliminated due to several problems during the experimental procedure. Therefore, the final sample was composed of 119 voluntary participants who were single, had no known medical or psychological problems (32 men and 87 women), and ranged from 18 to 25 years of age. Their mean age was 19.33 years (S.D. = 1.77). The group submitted to the TSST was made up of 14 men, 17 women in the luteal phase (4th to 8th day before the onset of the new menstrual cycle), 14 in the follicular phase (5th to 8th day after the onset of the new menstrual cycle), and 12 taking oral contraceptives (monocyclic formulas). The subjects in the control group were 18 men, 17 women in the luteal phase, 16 in the follicular phase, and 11 taking oral contraceptives. The menstrual cycle phase was calculated using two estimation procedures (Espin et al., 2010). First, in order to establish the date of each subject's appointment, all the cycles were converted to a standard 28-day cycle, taking as reference points the day of onset of the last menstruation and the real length of the studied cycle (Rossi and Rossi, 1980). Second, to confirm the previous estimation and estimate the ovulation point, Basal Body Temperature (BBT) was recorded daily during two complete menstrual cycles by means of sublingual temperature, taken for 5 min before getting up. To analyze the BBT, the method of the "smoothed curve" (SMC) was used, as described by McCarthy and Rockette (1983, 1986).

The subjects were referred a few days before the experiment, so that they could be given a series of instructions to follow to participate in the study. The instructions were to abstain from excessive physical activity within 48 h of the experiment, any sports activities within 24 h, intake of alcohol and caffeine within 18 h, and eating 60 min before the study, and not sleep less than usual (7–8 h). Naturally cycling women were trained in the daily recording of their basal body temperature (BBT), and they were given a chart and a thermometer for this purpose. Participants were not evaluated during stressful periods (such as exam periods).

The study was conducted in accordance with the Declaration of Helsinki, and the protocol and conduct were approved by the University of Murcia Ethics Research Committee. All the participants received verbal and written information about the study and signed an informed consent form.

Questionnaires and scales

Mood

This was evaluated by the Spanish version (Sandín et al., 1999) of the PANAS (Positive and Negative Affect Schedule; Watson et al., 1988). This 20-item questionnaire assesses mood according to two dimensions: positive affect (PA: interested, excited, strong, enthusiastic, etc.) and negative affect (NA: distressed, upset, guilty, scared, etc.), with 10 items measuring each state. Participants were asked to complete the questionnaire based on how they felt at that particular moment. They responded using a 5-point Likert scale ranging from 1 (not at all) to 5 (extremely).

Anxiety

To assess the anxiety state, the Spanish version of the STAI (State Anxiety Inventory) form S was used (Spielberger et al., 1970). It consists of 20 phrases (e.g. "I feel at ease", "I feel upset"), with a 4-point Likert scale ranging from 0 (not at all) to 3 (extremely) to evaluate how the participants felt at the moment they gave the answer. The Spanish version of the scale had a Cronbach's alpha ranging from 0.90 to 0.93 (Seisdedos, 1988).

Memory

To measure declarative memory, the Spanish version of the RAVLT (Miranda and Valencia, 1997), consisting of different trials, was used