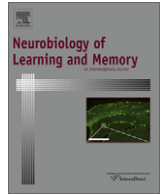




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## Hormonal contraception usage is associated with altered memory for an emotional story

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### ABSTRACT

Substantial evidence now documents sex-related influences on the neurobiology of emotional memory. Robust sex influences exist, for example, on the amygdala's role in emotional memory formation, as well as on retention of central information (gist) and detail for an emotional event. Evidence also suggests that the well-documented effects of stress hormones on memory depend upon sex hormone levels. Since hormonal contraception alters sex hormone levels, and must by extension alter sex/stress hormone interactions in memory, we examined whether the use of hormonal contraception also alters memory for an emotional story. Two groups of healthy female subjects—one naturally cycling, one using hormonal contraception—viewed either a brief, emotionally arousing story, or a closely matched, but more emotionally neutral story. Each subject's eye movements and pupil dilation changes were recorded as they viewed the story. Additionally, saliva samples were taken throughout the experimental session to examine salivary alpha-amylase, a biomarker for norepinephrine. A surprise free recall test one week later measured story memory in all subjects. Naturally cycling women exhibited enhanced memory of story details, but not of central information (gist), in the emotional compared with neutral story conditions. In contrast, women using hormonal contraception exhibited enhanced memory of gist, but not story details, in the emotional compared with neutral story conditions. Analysis of eye movements made while watching the stories indicated that the differences in memory could not be attributed either to a differential attention focus or to the degree of arousal induced by the stories in the two groups. These findings suggest that the use of hormonal contraception alters memory for an emotional event, perhaps by altering sex/stress hormone interactions in memory formation. They also suggest that further investigation of the mnemonic effects of these very widely used treatments is warranted.

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### 1. Introduction

Since the introduction of hormonal contraception in 1960, its effects on cognition and memory have remained largely unexplored. Studies have shown that hormonal contraception suppresses levels of endogenous estrogen and progesterone. The synthetic estrogen and progestins in hormonal contraception inhibit gonadotropin-releasing hormone (GnRH) via negative feedback, preventing both the mid-cycle surge of luteinizing hormone (LH) and subsequently, ovulation (Rapkin, Morgan, Sogliano, Biggio, & Concas, 2006). Inhibition of GnRH in turn suppresses endogenous levels of estrogen and progesterone, likely disrupting sex/stress hormone interactions, cognitive performance, and memory.

Though the literature on the cognitive effects of hormonal contraception is relatively limited, recent studies have indicated that hormonal contraception may indeed have structural and functional consequences on brain function. Pletzer et al. (2010) showed that use of hormonal contraception was related to significant differences in gray matter volume. Behaviorally, hormonal contraception has been associated with improved performance on a verbal memory task (Mordecai, Rubin, & Maki, 2008), and two studies have demonstrated that hormonal contraception use was associated with facilitated acquisition of classical conditioning responses (Beck et al., 2008; Holloway, Beck, & Servatius, 2011).

Hormonal contraception also has been shown to alter the reactivity of the different stress axes. In the case of the sympathetic stress response to acute maximal exercise, Otterstetter et al. (1999) showed that post-exercise concentrations of norepinephrine were significantly lower in women on oral contraceptives as compared to naturally cycling women. Research on hormonal contraceptives and the hypothalamic–pituitary–adrenal axis has shown that women using hormonal contraception generally show reduced cortisol responses to physical and psychosocial stressors

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(Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999), which in turn may influence memory (Kuhlmann & Wolf, 2005). For example, Kuhlmann and Wolf (2005) found that cortisol impaired verbal retrieval in naturally cycling women, but not in those using hormonal contraception. Given the evidence for sex/stress hormone interactions in emotional memory (Andreano, Arjomandi, & Cahill, 2008), and that the use of hormonal contraception should alter such interactions, we examined how memory for an emotional story differed in women using hormonal contraception (HC) compared with naturally cycling (NC) women.

HC and NC women watched either a brief, narrated emotionally arousing story or a closely matched, but more emotionally neutral story, both adapted from our previous research (Cahill, Prins, Weber, & McGaugh, 1994); each story consisted of the same 11 slides, but they differed in the emotionally arousing elements of the narratives associated with slides 5–8 or “phase 2.” Previous work from our laboratory has indicated there to be significant sex-related influences on memory for central story information (gist) versus peripheral details of these stories (Cahill & van Stegeren, 2003; Cahill, Gorski, Belcher, & Huynh, 2004). In general, men exhibited enhanced memory for gist, but not details of an emotional story whereas women exhibited enhanced emotional memory for details, but not gist (Cahill & van Stegeren, 2003; Cahill et al., 2004).

Because of these previous sex-related findings, we specifically examined whether memory for gist and peripheral story details differed in the HC and NC women when they received a surprise free recall test for the story one week later. Eye-tracking technology allowed us to determine both eye movements (an index of attention) and pupil dilation (an index of arousal) while subjects viewed the story. On the basis of extensive prior research with this “three-phase” story paradigm, we anticipated that any effects of hormonal contraceptive status on emotional memory would be most evident in recall from the most emotional story phase, phase 2.

## 2. Materials and methods

### 2.1. Participants

Seventy-two female undergraduate and graduate students from the University of California, Irvine between the ages of 18–35 participated in this study, which was approved by the university's Institutional Review Board. The subjects received either course credit or payment for their participation in the study. Participants were asked to refrain from alcohol, caffeine, and cardiovascular exercise for 24 h prior to each experimental session to control for outside influences that could affect baseline salivary alpha-amylase levels. To avoid contamination of salivary samples, participants were asked to fast 1 h prior to each experimental session as well as refrain from brushing teeth within the hour before their appointment.

Of the participants, 35 were naturally cycling women (NC) and 37 were women currently on a combined hormonal contraception regimen (HC) for at least 1 month. All naturally cycling women had regular menstrual cycles indicated by self-report. One NC woman was excluded due to her inability to provide salivary samples, and two NC women were excluded because they did not return for the second experimental session. Two HC women were excluded because their method was either unknown or progesterone only, and one HC woman did not return for the second experimental session. The final analyses included data from 32 NC women and 34 HC women. Of the HC women, 29 took monophasic drugs, five used triphasic pills. All the HC women were on drugs that contained ethinyl estradiol, and the content of this synthetic estrogen varied between 0.015 mg and 0.035 mg/dose.

### 2.2. Procedures

All experimental sessions were conducted between the hours of 12:00 and 18:00 to control for the effects of circadian rhythm on salivary alpha amylase levels. During the first experimental session, participants filled out a screening questionnaire and three cognitive assessments including the Autism Spectrum Questionnaire (AQ), the Toronto Alexithymia Scale (TAS-20), and the Mehrabian test. The AQ was implemented to as a biological index of “extreme maleness” since males in the general population score higher on the AQ than do females (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001; Baron-Cohen, 2002), whereas the TAS-20 was given to measure the participants' ability to express and identify with emotional event (Parker, Bagby, Taylor, Endler, & Schmitz, 1993). The Mehrabian was implemented to assess levels of trait anxiety (Mehrabian, 1994).

Fifteen minutes after their arrival, participants provided a 1-mL saliva sample using the “passive drool” collection method. Following the baseline saliva sample, participants moved into the eye-tracking room where they underwent a 9-pt. calibration on the iViewX RED III eye-tracking system (SensoMotoric Instruments). A second 1-mL saliva sample was taken immediately after the calibration period.

Participants then viewed either a brief, narrated story containing emotionally arousing elements or one containing only neutral elements. Each version of the story was composed of 11 slides, and the images on the slides were identical between the two versions of the story. The stories were also identical in the narratives associated with slides 1–4 or “phase 1” and similar in those associated with slides 9–11 or “phase 3” of the slideshow. However, the stories were quite different in the narratives associated with slides 5–8 or “phase 2;” in this part of the story, the emotional version contained emotionally arousing elements unlike the neutral version of the story.

As they viewed the story, their chin rested comfortably on a platform to minimize head movements and allow the iViewX RED III eye-tracking system to track eye movement and pupil diameter changes. Immediately after the slide show, participants provided a third 1-mL saliva sample. Additional samples were taken 10 and 20 min after termination of the slide show.

One week later, participants returned and provided one 1-mL saliva sample after a 15 min acclimation period. A surprise free recall test for slide recall and associated story elements was administered shortly after the saliva sample. During the test, subjects were asked to write a brief phrase identifying each slide they remembered as well any elements of the story they could recall that were associated with each remembered slide. After completing the test, subjects were debriefed and compensated with either course credit or payment.

### 2.3. Scoring of recall performance

Correct recall of a slide was credited if the identifying phrase used by the subject could unambiguously be attributed to a specific slide. Slide descriptions not clearly linked to a picture in the slide show were not counted. The vast majority of responses unambiguously identified a particular slide. A scoring template derived from our previous work with these stories (Cahill & van Stegeren, 2003; Cahill et al., 2004) was used to score recalled story elements as concerning either the “gist” or “details” of the story. In these previous studies, “gist” was defined by a consensus of  $\frac{3}{4}$  independent judges as “any story element that could not be changed or altered without changing the fundamental story line” (Cahill & van Stegeren, 2003). Gist items were derived from both the narrative and slides and the number that could be recalled varied by slide. Examples of gist items from the scoring template for phase

2 of the emotional version include “mother,” “son,” “boy hit by a runaway car,” and “the boy is taken to a nearby hospital.”

“Details” were defined as all other recalled elements and the number of details that could be recalled differed by slide (Cahill & van Stegeren, 2003). Examples of detail items from the scoring template for phase 2 of the emotional story include “hospital – light brown,” “parked car in background,” and “boy post-surgery.”

Of the slides that were correctly recalled, the associated story elements were scored as either a “gist” or “detail” if the story element corresponded to a “gist” or “detail” item on the scoring template. Most of the story elements listed by the subjects (82.4%) were classifiable by this method as either “gist” or “detail.” Recall performance was scored by two independent judges. Agreement between the two judges was 91%. The relatively few cases of disagreement were decided by a third independent judge.

#### 2.4. Eye movements and pupil dilation

Fixation duration and pupil dilation were measured using the iViewX RED III eye-tracking software at a sampling rate of 60 Hz. We selected these measures for analysis because fixation time has been used as an index of attention and visual processing (Dalton et al., 2005), and pupil dilation is considered a reliable measure of arousal (Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; Einhauser, Stout, Koch, & Carter, 2008). Standard analysis procedures were used (Gilzenrat et al., 2010; Einhauser et al., 2008). Fixation and pupil dilation data for each participant were exported using the eye-tracking analysis software program BeGaze (SensoMotoric Instruments). Eye movement events (fixations, saccades, blinks) for the duration of each slide (approximately 15 s) were exported. Fixation time % was determined by adding the time of each fixation event within a slide and dividing the total fixation time by the total time of the slide; this was determined for each slide (data not shown) and each phase.

In order to examine whether HC and NC women visually explored the slides differently, we conducted an area of interest (AOI) analysis on two of the most emotional and visually complex slides of phase 2 of the emotional story (Poole & Ball, 2005). We selected seven AOIs between the two slides. Within each AOI, we examined the number of glances (entries) the subject made into the area as well as the number of fixations made upon entry.

To assess pupil dilation, we collected approximately 415–425 data points over the course of the first 10 s of each slide, which allowed determination of the average pupil dilation both 1 sec prior to the onset of the narration (baseline), and within the first 2 sec following the end of the narration (response to slide). This approach was necessary because in this paradigm, the visual images in both the emotional and neutral stories were identical (Cahill et al., 1994). The emotional response to each slide is determined by the narrative description of the slide. Thus the most appropriate method for assessing an arousal response to each slide is to assess pupil dilation before and after the slide’s narration.

#### 2.5. Saliva samples

Saliva samples were immediately frozen for a minimum of 24 h to allow mucins to precipitate. On the day of the alpha-amylase assay, they were then thawed and centrifuged at 2080g for 15 min to extract particulates from saliva. Clear supernatant was decanted into microtubes.

#### 2.6. Salivary alpha-amylase measurement

Alpha-amylase levels were measured in the collected saliva samples using Salimetrics (State College, PA) enzyme kinetic assay kits. A microtiter plate incubator was pre-heated to 37 °C; 11-mL of

alpha-amylase chromagenic substrate (2-chloro-p-nitrophenol linked with maltotriose) was placed in the reagent warming trough provided by Salimetrics and heated to 37 °C for 20 min. Saliva samples were diluted (1:200) with Salimetrics diluents (phosphate buffered solution containing a non-mercury preservative). 8-μL of each diluted sample were transferred to a 96-well microtiter plate along with eight microliters of pre-diluted Salimetrics high and low controls. The controls were used for calibration of the assay. 320-μL of the pre-heated substrate were added to each well using a multichannel pipette. The plate was then placed in a microtiter plate mixer and mixed at 500–600 RPM for 1 min. The plate was immediately transferred to a microplate reader and read at 405 nm. The plate was then mixed at 500–600 RPM for 2 min and read immediately at 405 nm. The enzymatic action of alpha-amylase on the substrate yields 2-chloro-p-nitrophenol, which can be spectrophotometrically measured at 405 nm. The amount of alpha-amylase present in the sample is directly proportional to the increase in absorbance at 405 nm.

In both sessions, a total of six saliva samples were collected at various times before and after story viewing because our previous work involving longer sets of emotional stimuli (Segal & Cahill, 2009) suggested that analysis of salivary alpha-amylase (an indicator of noradrenergic activation) (Chatterton, Wogelsong, Lu, Ellman, & Hudgens, 1996; van Stegeren, Rohleder, Everaerd, & Wolf, 2006) might be useful in detecting noradrenergic activation in response to viewing the emotional story. No significant effects were detected with respect to the salivary alpha-amylase changes associated with the story (data not shown), suggesting that the salivary alpha-amylase method is not sensitive enough to detect noradrenergic activation in this relatively brief emotional story paradigm.

### 3. Results and discussion

Considering first the total recall of all slides in the emotional and neutral stories, a two-way ANOVA with emotional story content and hormonal contraception status (NC versus HC) as independent factors revealed that both NC ( $n = 32$ ) and HC ( $n = 34$ ) women recalled significantly more slides from the emotional than neutral stories ( $F_{(1,63)} = 12.6, P = .0007$ , see Fig. 1). The main effect of contraceptive status was non-significant ( $F_{(1,63)} = 1.38, P = .24$ ) as was the interaction effect of emotion x contraceptive status ( $F_{(1,63)} = .06, P = .81$ ). As predicted on the basis of earlier work with this story paradigm, the enhancement of total slide recall was driven by enhanced slide recall in the emotional component of the emotional story, phase 2. A two-way ANOVA with emotion and

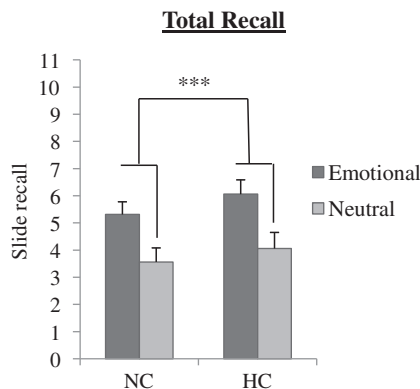


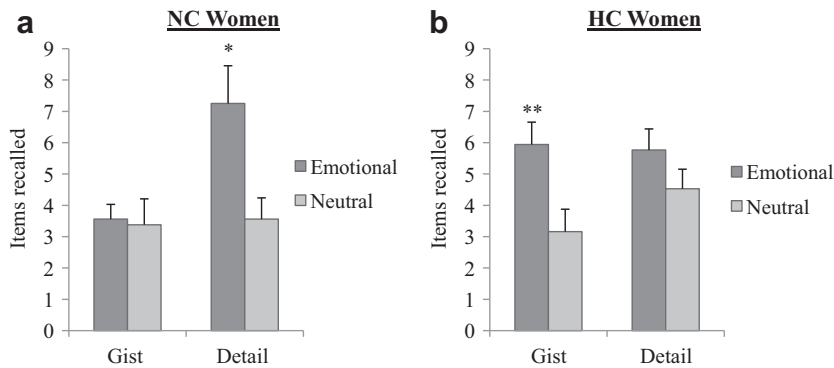
Fig. 1. Total slide recall in NC and HC women. A two-way ANOVA revealed a main effect of emotion on total slide recall in both NC and HC women ( $n = 32$  NC women,  $n = 34$  HC women; three asterisks,  $P < .001$ ). Values are means  $\pm$  s.e.m.

contraception status as independent factors showed that both NC and HC women recalled significantly more phase 2 slides from the emotional compared with neutral stories. ( $F_{(1,63)} = 18.6$ ,  $P < .0001$ ). The main effect of HC was non-significant ( $F_{(1,63)} = .8441$ ,  $P = .36$ ) as was the interaction effect of emotion  $\times$  HC ( $F_{(1,63)} = 1.15$ ,  $P = .29$ ). The same analysis for phases 1 and 3 revealed no significant main effects or interactions.

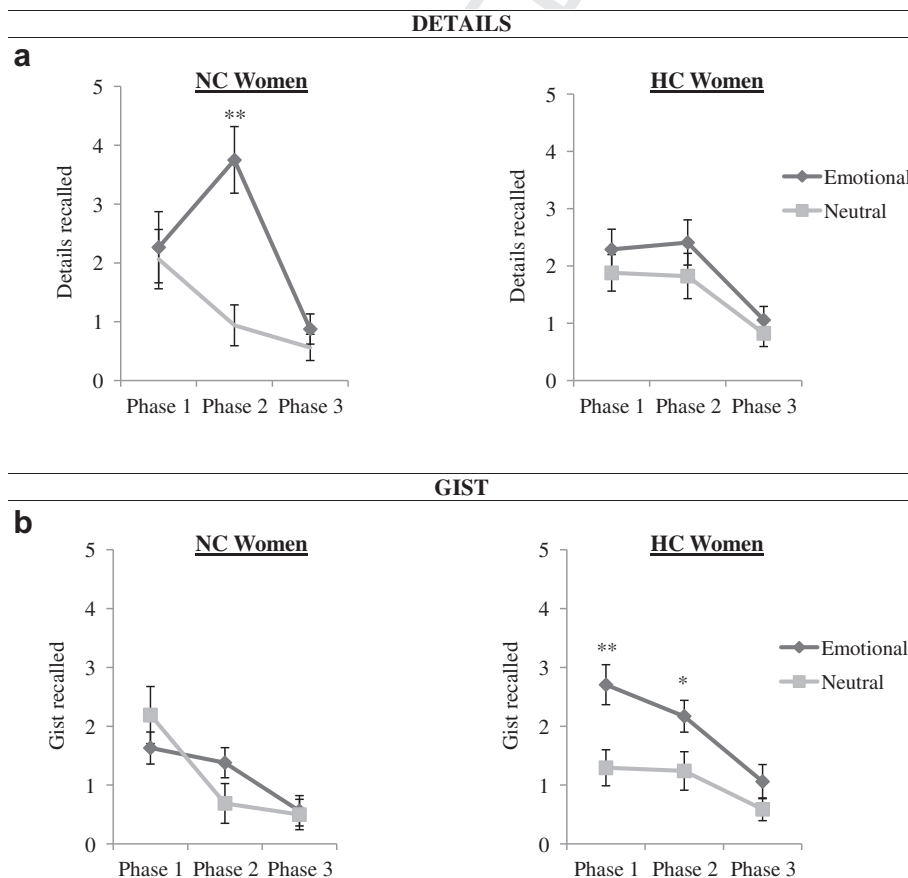
Although NC and HC women displayed equivalent total slide recall, they exhibited substantially different memory for gist and

detail information from the emotional story. NC women ( $n = 16$  per condition) recalled significantly more details ( $F_{(1,30)} = 7.1$ ,  $P = .012$ ) from the emotional ( $M = 7.25$ ,  $SD = 4.82$ ) compared with neutral ( $M = 3.56$ ,  $SD = 2.71$ ) story. However, NC women recalled the gist no differently ( $F_{(1,30)} = .039$ ,  $P = .85$ , see Fig. 2a) in the emotional ( $M = 3.56$ ,  $SD = 1.89$ ) as compared to the neutral ( $M = 3.38$ ,  $SD = 3.30$ ) condition.

In contrast, HC women ( $n = 17$  per condition) exhibited no enhancement of memory for details ( $F_{(1,32)} = 1.8$ ,  $P = .19$ ) in the



**Fig. 2.** Total gist and detail item recall in NC and HC women. (a) NC women exhibited an effect of emotion for detail retention but not for gist ( $n = 32$  NC women; asterisk,  $P < .05$ , one-way ANOVA). Values are means  $\pm$  s.e.m. (b) HC women exhibited an effect of emotion for gist retention but not for details ( $n = 34$  HC women; two asterisks,  $P < .01$ , one-way ANOVA). Values are means  $\pm$  s.e.m.



**Fig. 3.** Recall of detail and gist items by story phase in NC and HC women. (a) NC women exhibited an effect of emotion on detail retention in phase 2 ( $n = 32$ ; two asterisks,  $P < .01$ , one-way ANOVA) whereas HC women did not ( $n = 34$ ) exhibit an effect of emotion on detail retention. Values are means  $\pm$  s.e.m. (b) HC women exhibited an effect of emotion on gist retention in phases 1 and 2 ( $n = 34$ ; two asterisk,  $P < .01$ ; asterisk,  $P < .05$ , one-way ANOVA, respectively), whereas NC women ( $n = 32$ ) did not exhibit an effect of emotion on gist retention. Values are means  $\pm$  s.e.m.

emotional ( $M = 5.76, SD = 2.77$ ) versus the neutral ( $M = 4.53, SD = 2.58$ ) conditions, but showed a significant enhancement of memory for gist ( $F_{(1,32)} = 7.83, P = .008$ , see Fig. 2b) from the emotional ( $M = 5.94, SD = 2.95$ ) story compared to the neutral ( $M = 3.18, SD = 2.93$ ).

We next examined which story phase was driving the overall enhancements for gist in the HC women, and detail in the NC women. For NC women ( $n = 16$  per cell), the emotional enhancement for detail memory was driven by recall from the emotionally-charged phase 2 ( $F_{(1,30)} = 17.9, P = .0002$ , see Fig. 3a). No significant enhancements of detail recall were seen for phases 1 and 3, nor were any significant enhancements for recall of gist seen in NC women in any story phase (Fig. 3b). For HC women ( $n = 17$  per cell), emotionally enhanced recall of gist was driven by phase 1 ( $F_{(1,32)} = 9.50, P = .0042$ ) and phase 2 ( $F_{(1,32)} = 4.86, P = .0347$ , see Fig. 3b). No difference in recall of gist between the emotional versus neutral stories was detected for phase 3, nor was any difference in recall of story details detected for HC women in any story phase (Fig. 3a).

We next examined differences in gist and detail memory in HC and NC women specifically during phase 2 of the emotional story. A one-way ANOVA revealed that HC women ( $M = 2.18 \pm .27, SD = 1.13$ ) recalled significantly more gist items in phase 2 of the emotional story ( $F_{(1,32)} = 4.53, P = .04$ ; see Fig. 4a) as compared to NC women ( $M = 1.38 \pm .26, SD = 1.02$ ). A second one-way ANOVA revealed that NC women ( $M = 3.75 \pm .57, SD = 2.27$ ) recalled significantly more detail items in phase 2 of the emotional story ( $F_{(1,32)} = 3.84, P = .05$ ; see Fig. 4b) than did HC women ( $M = 2.41 \pm .39, SD = 1.62$ ).

Finally, to better understand the nature of the recall differences, we assessed the subjects' scores on the AQ, TAS-20, and Mehrabian. Three separate one-way ANOVAs were used. NC women ( $M = 16.4 \pm 0.87$ ) did not differ significantly from HC women ( $M = 16.0 \pm 0.97$ ) on the AQ. On the TAS-20 and the Mehrabian, NC women ( $M = 42.8 \pm 1.76$  and  $M = 2.6 \pm 1.9$ , respectively) and HC women ( $M = 43.6 \pm 1.92$  and  $M = 2.7 \pm 1.7$ , respectively) also exhibited no significant differences.

Both attentional and arousal processes in the subjects during initial story viewing (assessed with eye-tracking technology) were very similar. As an index of attention, we determined the average fixation time for the four slides constituting phase 2, in which emotional elements occurred in the emotional story. NC ( $n = 16$ ) and HC ( $n = 17$ ) women spent equivalent percentages of time fixated on the slides in phase 2 of the emotional story ( $F_{(1,31)} = 1.2, P = .28$ , see Fig. 5a). In addition to fixation time, we examined whether the subjects explored the slides similarly in the emotional condition as indicated by the number of glances and subsequently, fixations, made in the specified AOIs (Poole & Ball, 2005). No significant differences between NC ( $n = 16$ ) and HC ( $n = 17$ ) women were detected on either measure in any of the AOIs (data not shown).

Pupillary dilation indicated arousal to the emotional components (phase 2) of the emotional story (Koss, 1986; Rajkowski, Kubiak, & Aston-Jones, 1993; Aston-Jones & Cohen, 2005). NC and HC women showed equivalent average pupil dilation in response to phase 2 slides of the emotional story ( $F_{(1,31)} = .057, P = .81$ , see Fig. 5b). Collectively, the eye movement and dilation findings suggest that the differences in retention observed between NC and HC women cannot be explained by any potential

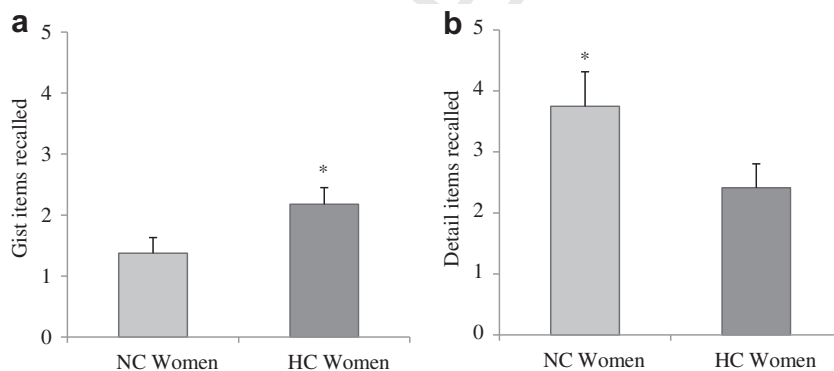


Fig. 4. Recall of gist and detail items in phase 2 of the emotional story in NC and HC women. a, HC women ( $n = 17$ ) recalled significantly more gist items (one asterisk,  $P = .05$ , one-way ANOVA) than NC women ( $n = 16$ ) b, NC women ( $n = 16$ ) recalled significantly more detail items (one asterisk,  $P < .05$ , one-way ANOVA) than HC women ( $n = 17$ ). Values  $\pm$  s.e.m.

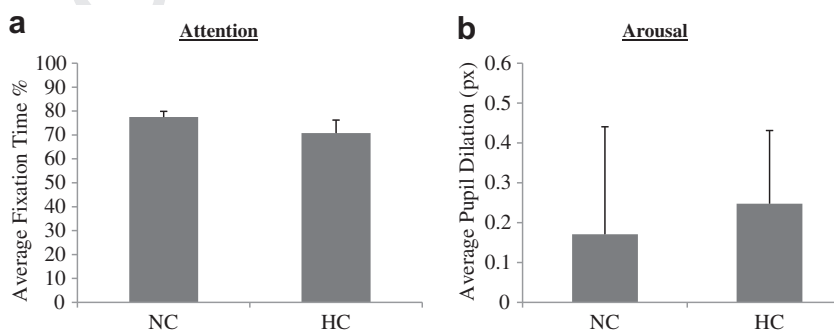


Fig. 5. Attention and arousal in phase 2 of the emotional story. (a) No significant differences in average fixation time between NC and HC women ( $n = 16$  and  $n = 17$ , respectively;  $P \gg 0.1$ , one-way ANOVA). Values  $\pm$  s.e.m. b, No significant differences in pupil dilation change between NC and HC women ( $n = 16$  and  $n = 17$ , respectively;  $P > 0.1$ , one-way ANOVA). Values  $\pm$  s.e.m.

effects of hormonal contraception either on the attentional focus of the women while they viewed the emotional story, or in the degree of arousal the story induced.

#### 4. Conclusions

The present findings indicate that hormonal contraception usage alters memory for an emotional experience in healthy women. Since hormonal contraception has been shown to suppress levels of estrogen and progesterone, it is likely that sex/stress hormone interactions shown to affect both emotional memory and the amygdala were affected (Andreano & Cahill, 2010; van Wingen et al., 2008). Therefore, it is plausible that hormonal contraception usage alters emotional memory by disrupting normal sex/stress hormone interactions involved in memory formation.

Previous research identified sex differences in the retention of gist and detail from an emotional event (Cahill & van Stegeren, 2003; Cahill et al., 2004; Seidnitz & Diener, 1998). For example, Cahill and van Stegeren (2003) found that the beta-adrenergic antagonist propranolol impaired memory for the details of an emotional story in women but not in men, yet impaired memory for the gist of the same story in men but not in women. In general, women in these studies exhibited enhanced retention of details but not gist of an emotional event. The present findings regarding NC women are consistent with these previous findings, assuming that an appreciable number of the female subjects were not on hormonal contraception. At the same time, the present findings indicate that failure to account for hormonal contraceptive status in studies of emotional memory will likely produce inaccurate conclusions about the effects of emotion on recall of gist versus detail in women.

While this study's goal was to provide an initial assessment of how/whether hormonal contraception affected retention of an emotional event, the findings raise a number of important questions for future work. A caveat to this study is that it's limited in fully demonstrating the effect of hormonal contraception on emotional memory because the HC women were self-selected users. Therefore, the findings could potentially underestimate any mood or cognitive differences between NC and HC women (Mordecai et al., 2008) that could have influenced the memory results, though in this context, it is important to reiterate that the HC women in our study did not differ on any of the cognitive measures.

Another important issue that was not addressed in this study concerns menstrual cycle position in naturally cycling women. It is possible that the effects reported in the naturally cycling women will vary systematically according to the menstrual cycle stage a woman is in during one or both phases of testing. For future work, it will be important to study menstrual cycle effects in order to fully understand the mechanisms underlying the effects of sex hormone status on emotional memory.

In addition to studying menstrual cycle position, future work concerning the effects of sex hormone status on emotional memory should also examine men. Currently, we are conducting this study in men, and preliminary results indicate that their pattern of memory is similar to that of HC women (enhanced retention for gist, but not detail, from the emotional story). These preliminary findings with men are consistent with earlier work (Cahill & van Stegeren, 2003) and suggest that sex hormone status plays a critical role in emotional memory processes.

Another question for future work concerns the nature of the observed effects of hormonal contraception on memory for gist versus detail. As seen in Fig. 3, whereas hormonal contraception selectively blocked the enhancement in detail memory seen in phase 2 for NC women, it enhanced recall of gist for both story phases 1 and 2. As story phase 1 is identical for both the emotional

and neutral stories, the phase 1 effect suggests a retrograde effect on memory resulting from phase 2 arousal; which merits further exploration. Also, from these present findings, it is unknown whether the observed memory effects were the result of hormonal contraception altering encoding, retrieval, or both; this is an important direction for future work.

Our present findings demonstrate that hormonal contraception alters emotional memory. These findings, in conjunction with studies showing that hormonal contraception alters the acquisition of a classical conditioning response (Beck et al., 2008; Holloway et al., 2011), may have important clinical implications for understanding the influence of sex hormones on disorders related to learning and emotional memory. For example, many mood disorders, including clinical depression, anxiety disorders and PTSD disproportionately affect women (Breslau, Davis, Andreski, & Peterson, 1991; Breslau, Davis, Andreski, Peterson, & Schultz, 1997; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Studies have demonstrated that these disorders are related to learning and memory systems, and there is increasing evidence that sex hormones can influence these systems. Therefore, it may be important to investigate whether the manipulation of sex hormone levels via hormonal contraception can influence the development or treatment of these disorders. In addition to the potential clinical implications, there are a very large number of women on hormonal contraception worldwide, and this only magnifies the importance of exploring these outstanding issues for investigators of the brain's emotional memory mechanisms.

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