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ORIGINAL INVESTIGATION

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Cortisol and memory retrieval in women: influence of menstrual cycle and oral contraceptives

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Abstract *Rationale:* Studies in rodents observed that the effects of stress on memory are modulated by gonadal hormones. In animals and humans, stress and cortisol treatment impairs memory retrieval. *Objectives:* To investigate if the acute impairing effect of cortisol on memory retrieval in women is influenced by endogenous or exogenous gonadal steroids. *Methods:* Three groups of women were studied: women during mensis (n=13), women in the luteal phase (n=14), and women using oral contraceptives (OCs; n=20). In a double-blind crossover fashion, they received cortisol (30 mg) or placebo 1 h prior to memory retrieval testing. *Results:* Overall cortisol led to a significant impairment of memory retrieval. Further exploratory analysis using t tests showed that both groups of naturally cycling women were significantly impaired (p<0.05), while no effect was apparent in the OC users (p=0.29). *Conclusions:* The current results could suggest that OC use is associated with a reduced sensitivity of the brain to acute cortisol elevations. In contrast, menstrual-cycle-associated changes in estradiol and progesterone concentrations appear to have no strong influence on this acute cortisol effect. The underlying neurobiological mechanisms of these behavioral findings remain to be elucidated.

Keywords Stress · Cortisol · Estrogens · Progestins · Memory · Hippocampus · Humans

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Introduction

Several psychiatric disorders are more prominent in women than in men (e.g., depression), and it has been suggested that these differences might be mediated in part by sex steroids (Studd and Panay 2004; Young 1998). However, animal studies have also observed a wide variety of neuroprotective properties of estrogens. For example, estrogens protect the brain against free radicals and ischemia-induced damage (McEwen and Alves 1999). Moreover, estrogens stimulate spine development and neurogenesis in the hippocampus (Gould et al. 2000; McEwen and Alves 1999). In addition, there are interdependent effects between the gonadal hormones and the hormones of the hypothalamus–pituitary–adrenal (HPA) axis.

Several studies in animals and humans report on modulation of cognitive performance by stress (Lupien and Lepage 2001; Roozendaal 2002; Wolf 2003). These effects are mediated by the multiple-stress-associated neuroendocrine changes, which consist of increased levels of corticotrophin releasing factor, increased levels of adrenocorticotrophin, and, finally, increased levels of cortisol or corticosterone. In addition, enhanced release of catecholamines (epinephrine and norepinephrin) might also influence cognition (see, for recent reviews, Croiset et al. 2000; Roozendaal 2002).

Pharmacological studies with glucocorticoids (GCs) suggest that these hormones can also be independent of stress modulate memory (Lupien and Lepage 2001; Wolf 2003). These effects are different depending on the investigated memory phases (learning, consolidation, and retrieval). Based on findings in rats, it has been suggested that GCs enhance memory consolidation but impair delayed memory retrieval (Roozendaal 2002). Studies in humans also found impairing effects of acute cortisol treatment on delayed memory retrieval (de Quervain et al. 2000, 2003; Kuhlmann et al. 2005a; Wolf et al. 2001a). Even more pronounced negative effects on declarative memory appear to occur after prolonged cortisol treatment (McAllister-Williams and Rugg 2002; Newcomer et al. 1999). Animal as well as human neuroimaging studies show that the hip-

pocampus (and surrounding medial temporal lobe structures) mediate the cortisol effect on memory retrieval (de Quervain et al. 2003; Roozendaal 2002). However, prefrontal structures like the cingulate gyrus might also contribute to this effect (Hsu et al. 2003).

Before reviewing the evidence for interdependent effects of gonadal hormones and GCs on memory, we will first briefly describe the impact of estrogens and progestins on the cortisol stress response. During mensis, levels of estradiol and progesterone are low, whereas the luteal phase is characterized by elevated levels of both hormones, especially progesterone (Franz 1988). Oral contraceptives (OCs) containing synthetic ethinylestradiol and a synthetic progestin inhibit ovulation and cause low levels of natural estradiol and progesterone (Likis 2002). Ethinylestradiol, however, has a high biological efficiency in the brain and the body (Oge et al. 2003). For example, oral ethinylestradiol treatment suppresses experimental autoimmune encephalomyelitis in mice more powerful than the natural 17β-estradiol (Subramanian et al. 2003).

There is ample evidence that women and men differ in their response to stress and pharmacologic HPA challenge tests (for a recent review, see Kudielka and Kirschbaum 2005). Vice versa, the actions of stress hormones within the central nervous system appear to be modulated by sex and sex steroids (Bisagno et al. 2003; Conrad et al. 2004; Shors 2004; Wood et al. 2001). In humans, male participants display higher cortisol level after psychosocial stress than female participants (Kudielka and Kirschbaum 2005). Besides sex, the menstrual cycle influences HPA reactivity. Women in the luteal phase have comparable saliva cortisol stress responses to men, but women in follicular phase and women using OCs show lower increases. The latter study population has elevated corticosteroid-binding globulin levels, which may account for the blunted free cortisol stress response (Kirschbaum et al. 1999). The negative feedback regulation of the HPA also varies across the menstrual cycle. Cortisol levels after dexamethasone treatment were lower in the follicular phase than during the luteal phase, demonstrating a reduced feedback sensitivity at times of high estradiol and progesterone levels (Altemus et al. 1997). This fits to the observed enhanced free cortisol stress response in women during the luteal phase (Kirschbaum et al. 1999). With respect to women using OCs, one study observed a higher GC sensitivity of proinflammatory cytokines after stress exposure in this group when compared to free cycling women. It has been suggested that this could be a compensatory mechanism for the blunted free cortisol stress response of OC users (Rohleder et al. 2003).

Most importantly to the present study, there is also evidence that stress affects memory differently in males and females, and that gonadal steroids are partially responsible for this. Animal studies show opposite effects of acute stress in female and male rats. Spatial memory is only impaired by acute or chronic stress in male but not in female rats (Conrad et al. 2004; Luine 2002). In contrast, the acquisition of the conditioned eyelid response is impaired by acute stress in female but not in male rats (Wood and Shors 1998). Similarly, hippocampal-dependent trace conditioning is worse after stress in females but not in males. The authors of the latter study found a correlation between corticosterone level and conditioning performance in male rats only (Wood et al. 2001). These results are similar to observations made in the human. A correlation between cortisol levels after stress and memory appears to occur only in men but not in women (Wolf et al. 2001b).

Not only sex influences the stress effects on memory, but also the stage of the estrus cycle plays a role. For example, only rats which were trained during high-estrogen levels show better memory after chronic stress (Bowman et al. 2001). Likewise, working memory which depends on the prefrontal cortex was impaired by a pharmacologic stressor in female animals at times of high-estradiol levels only (Shansky et al. 2004).

Taken together even though these results are far from conclusive, they demonstrate that in rodents, gonadal hormones appear to interact with the effects of stress on memory. Since previous studies in rodents observed sex and menstrual cycle differences in how stress effects memory, we were interested to test whether or not gonadal hormones modulate the effects of the stress hormone cortisol on memory retrieval in healthy young women.

Materials and methods

Forty-seven young healthy female students participated in this study. Twenty of them were using monophasic OCs with an ethinylestradiol concentration between 0.02 and 0.035 mg and a progesterone derivative. The remaining subjects were naturally cycling (regular cycle between 26 and 32 days). Fourteen of them were tested in the luteal phase (4th to 8th days before the onset of the new menstrual cycle) and 13 of them were tested in the mensis (2nd to 4th days of bleeding). Each subject was tested twice (placebo and cortisol) in the same menstrual cycle phase with a between-treatment interval of one menstrual cycle (26–32 days). Subjects taking OCs were tested between the 7th and 14th days after the intake of their first monthly pill.

None of the women had acute or chronic diseases or were taking medications. Subjects were not obese (BMI< 25, BMI: weight in kg/height in m^2) and were between 20 and 34 years old (24.81±0.59 (Mean±SE)). The three groups did not differ significantly in age or BMI. There were also no differences in personality scores assessed with the NEO Five-Factor Inventory (Borkenau and Ostendorf 1993).

The study was approved by an ethic committee, and subjects provided written informed consent before they took part at the examination. The experimental design was identical to a previous study conducted with women in the first half of the menstrual cycle only (Kuhlmann et al. 2005a). There was no overlap between the current and the past study population.

In a double-blind crossover placebo-controlled fashion, participants received either three pills with each containing

10 mg hydrocortison (Hoechst, Germany) or three placebo pills. Treatment order was randomized. Upon arrival (between 10:00 and 11:00 A.M.), the participants learned a list containing 15 neutral and 15 negative words (see below). Four hours later, they received cortisol (30 mg) or placebo. After a delay of 1 h (between 3:00 and 4:00 P.M.), subjects were led to a separate testing room and were informed that the memory testing would start soon. They filled out a mood questionnaire (see below), followed by a free and cued recall of the word list (details below). Thereafter, working memory and attention was assessed (details below).

The following tests and questionnaires were used:

Memory for words

A word list, (with two parallel versions available) containing 15 negative and 15 neutral words, was presented to the subjects on a piece of paper (Kuhlmann et al. 2005a). There were no differences between neutral and negative words or between the two lists with respect to word frequency or word length. Subjects were given 2 min to learn the list with immediate free recall being tested. This procedure was directly repeated leading to two learning trials.

In the afternoon (5 h after initial learning 1 h after oral cortisol or placebo treatment), delayed free recall of the wordlist presented in the morning was tested. In order to account for within- and between-subject variance in initial learning, free recall performance in the afternoon was expressed as the percentage of words remembered in relation to the second (and last) learning trial in the morning (Kuhlmann et al. 2005a).

Immediately after free recall, cued recall was assessed by presenting the first two letters of each learned word in a random order on a piece of paper.

Working memory (digit-span test)

A series of numbers with increasing length were read to the subjects. They had to repeat the digits in the same order or in reversed order. Each length was tested twice. One point was given for each correctly repeated set (Wechsler 1987).

d2 test of attention/psychomotor speed

Out of a series of d's and p's with one or two lines above and/or beneath each letter, the participants had to mark as quickly and correctly as possible the d's with two lines. The test score was calculated by the number of correctly marked letters minus the number of errors (Brickenkamp 1994).

Mood assessment

An adjective checklist for the assessment of good vs bad mood, awake vs tired, and calm vs restless was used. Each scale contains eight adjectives (Steyer et al. 1994).

Hormone analysis

Saliva was collected using Salivette collection devices (Sarstedt, Nümbrecht, Germany). Samples were taken before treatment, 60 min (immediately before cognitive testing) and 90 min after treatment. Free cortisol was measured using an immunoassay (IBL, Hamburg, Germany). For the measurement of estradiol and progesterone, an additional saliva sample was obtained in the morning of each study day. Subjects filled a small tube with saliva. Cotton-swab-based sampling was avoided because it might lead to incorrect results for some sex steroids (Shirtcliff et al. 2001). Estradiol and progesterone concentrations were analyzed by an independent laboratory using commercially available radioimmunoassay kits adopted for the analysis of salivary samples (DSL, Sinsheim, Germany). The sensitivity of the progesterone assay is 10 ng/dl (Groschl et al. 2001), and the sensitivity of the estradiol assay is 0.25 pg/ml (Shirtcliff et al. 2000). Inter- and intra-assay variance was below 12% for both assays.

Statistical analysis

Data were analyzed using analysis of variance (ANOVAs) with three groups (mensis, luteal phase, OC use) or two groups (normally cycling vs OC use) as grouping factor and treatment (cortisol vs placebo) as within-subject factor. In addition, exploratory *t* tests were conducted within each of the three groups separately. The specific analyses are described in each of the following result paragraphs.

In addition, we calculated the effect sizes for the cortisol effect on retrieval for each of the three studied groups in order to give the reader the possibility to evaluate the size of the treatment effect and to allow comparison with a recently published meta-analysis (Het et al. 2005). We used the formula from Hedges and Olkin (1985) in order to create the effect size (g_{Hedges}), which is defined as the difference between the mean of the experimental group $\left(\overline{X}_{\text{EG}}\right)$ and the placebo control group $\left(\overline{X}_{\text{CG}}\right)$ standardized by the pooled standard deviation (S_{pooled}). Calculation was performed using the free meta-analytic software program META (Schwarzer 1989). According to Cohen (1988), an effect size of 0.20 can be classified as small, 0.50 can be classified as moderate, and 0.80 can be classified as large.

Table 1 Levels of cortisol and gonadal hormones in the three groups for the two treatment conditions (mean±SE)

Test	Treatment	Luteal group	Mensis group	OC group
Cortisol level in mmol/l baseline	Placebo	10.36±2.26	7.82±1.30	8.05±0.59
	Cortisol	7.30±1.01	9.61±1.84	8.17±0.93
Cortisol level, pretesting	Placebo	7.32±0.50	7.34±1.59	6.22±0.46
	Cortisol	154.32±27.08	175.25±37.32	186.71±18.85
Cortisol level, posttesting	Placebo	5.21±0.25	6.46±1.22	6.66±0.53
	Cortisol	152.80±25.35	165.26±16.77	207.67±20.26
Estradiol level in pg/ml	Placebo	1.58±0.21	1.47±0.33	1.45±0.37
	Cortisol	2.06±0.39	1.81±0.42	0.94±0.21
Progesterone level in pg/ml	Placebo	34.00±5.29	15.93±3.67	23.07±7.45
	Cortisol	44.25±6.28	20.43±6.90	27.51±7.77

For statistical analyses, see Results

Results

Cortisol levels

Results revealed a treatment-induced cortisol increase (see Table 1). ANOVA with the two repeated measurement factors treatment (cortisol vs placebo) and time (baseline, +60 min, +90 min) and the between-subject factor group (mensis, luteal phase, OCs) revealed a significant treatment by time interaction (F=103.29; p<0.01) in the absence of a treatment by time×group interaction (F=0.83; p<0.50). Bonferroni-adjusted paired t tests showed significantly elevated cortisol levels at 60 and 90 min after cortisol treatment. No differences were apparent at baseline.

Sex steroid levels

Sex steroid levels of the three groups at the two testing days are also presented in Table 1. Only concentrations of the cortisol day were analyzed, because we assumed potential modulating effects of estradiol and progesterone at this treatment day. ANOVA with the three groups as the between-subject factor displayed a significant main effect of group for estradiol (p<0.01) and progesterone (p<0.03). Post-hoc analysis indicated significantly lower estradiol level for the OC women than that for the luteal women and mensis women. Women in the luteal phase tended to have higher progesterone levels than women in mensis and had significantly higher levels than those using OCs. Almost identical results were obtained when both days were averaged.

Cortisol effect on memory retrieval

Cortisol led to a significant reduction in free recall of words in the entire study population. Subjects under cortisol recalled 73.89±1.54% while recalling 80.26±1.74% under placebo (t(46)=3.46; p<0.01). Exploratory follow-up analysis using t tests showed that retrieval for emotional words was significantly impaired (73.03±2.18% vs 79.18±2.20; t(46)=2.19; p<0.05), whereas, for neutral words, a nonsignificant trend was apparent (75.61±2.25% vs 81.18±2.71; t(46)=1.88; p<0.10).

Influence of menstrual cycle or OCs

Initial learning in the morning did not differ between the three groups (see Table 2). Separate analysis for the three groups using t tests displayed a cortisol-induced retrieval impairment for the mensis group (t(12)=2.90; p<0.01) and for the luteal group (t(13)=2.22; p<0.05). In contrast to these significant results, no effect was observed for women using OCs (t(19)=1.10; p=0.29; see Fig. 1).

An ANOVA with the between-group factor group (mensis, luteal, OC) and the within-subject factors treatment, and treatment order displayed a main effect of treatment (F(1,43)=15.30; p<0.01) and a nonsignificant treatment by

Table 2 Cognitive test performance of the three groups during the placebo and the cortisol treatment day (mean±SE)

Test	Treatment	Luteal group	Mensis group	OC group
Word list: initial learning	Placebo	21.79±1.04	20.00±1.03	20.00±0.87
(2nd trial in the morning)	Cortisol	22.14±0.84	20.00±1.00	20.90±0.86
Cued recall	Placebo	17.64±1.21	15.77±1.20	15.75±0.94
	Cortisol	16.64±1.89	16.38±1.11	16.30±1.08
Digit span, forward	Placebo	8.42±0.54	8.00±0.51	9.00±0.28
	Cortisol	8.71±0.50	8.53±0.51	9.15±0.24
Digit span, backward	Placebo	7.28±0.34	7.69±0.41	7.40±0.31
	Cortisol	7.00±0.44	7.08±0.42	7.10±0.30
Attention	Placebo	174.00±11.83	171.23±12.60	194.30±9.75
(correct hits minus errors)	Cortisol	179.57±14.45	172.38±12.57	191.30±9.87

For statistical analyses, see Results

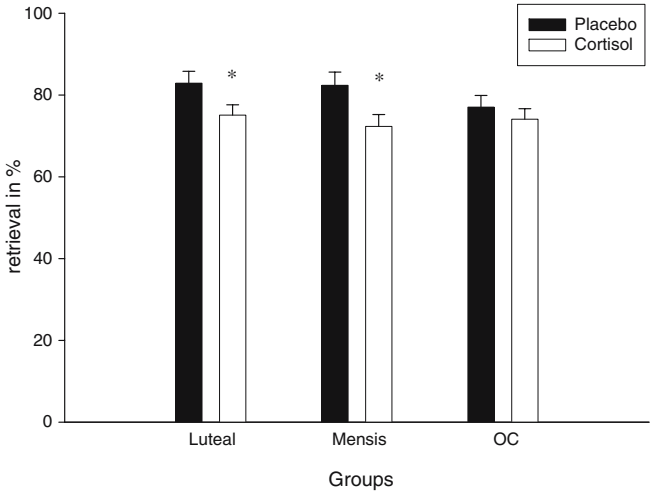

Fig. 1 Effects of cortisol (30 mg) treatment on delayed free recall of words in the luteal, mensis, and OC group. Performance is presented as percentage of words remembered from the learning trial. *$p<0.05$ in paired t tests

group interaction ($F(2,43)=1.77$; $p=0.18$). Treatment order had no main effect ($F(1,41)=0.48$; $p=0.49$), and did not interact with treatment ($F(1,41)=0.13$; $p=0.72$) or the treatment by phase interaction ($F(2,41)=1.44$; $p=0.25$).

Since the effects for the two naturally cycling groups were very similar, we computed another ANOVA with the between-group factors—OCs ($n=20$) vs naturally cycling ($n=27$) and the repeated measurement factors—treatment and treatment order. This analysis revealed a significant main effect of the treatment ($F(1,43)=10.50$; $p<0.01$) and a nonsignificant trend for a group by treatment interaction ($F(1,43)=2.62$; $p=0.11$). Treatment order had again no main effect ($F(1,43)=0.22$; $p=0.64$) and did not interact with the treatment ($F(1,43)=0.01$; $p=0.94$) or the treatment by group interaction ($F(1,43)=0.90$; $p=0.35$).

Effect size analysis

In addition to the t test and ANOVA analysis, effect sizes were computed in order to allow an estimation of the size of the observed cortisol effects for each of the three groups separately. The effect size (g_{Hedges}) was −0.88 for the mensis group and −0.73 for the luteal group. Both values are within the range of large effect according to Cohen (1988). In contrast, the effect size for the OC group was −0.24, which can be classified as small.

Other cognitive tests and mood

Results are displayed in Table 1. Cortisol had no significant effects on the cued recall, digit span, or attention (all p's>0.10). Cortisol also did not affect mood (data not shown). There were no significant differences between the three groups on any of the cognitive measures displayed in Table 2 on the placebo day (all p's>0.26).

Discussion

The present study examined systematically for the first time the effects of cortisol on memory retrieval in naturally cycling women and women using OCs. Overall results show a significant impairment of memory retrieval by cortisol, which is in line with previous work (de Quervain et al. 2000; Kuhlmann et al. 2005a; Wolf et al. 2001a). Interestingly, only the free cycling women (mensis and luteal phase) were significantly affected by GCs. Between those two groups, no difference was apparent. Animal and human studies have documented that the cortisol-induced retrieval impairment is mediated by the hippocampus (de Quervain et al. 2003; Roozendaal 2002). Thus, the current observation of a cortisol-induced retrieval impairment in the luteal phase appears to argue against a reduced GC sensitivity of the female hippocampus during times of high endogenous progesterone levels. Previous human studies had observed that women in the luteal phase showed a reduced sensitivity to dexamethasone (Altemus et al. 1997) and an enhanced HPA stress response (Kudielka and Kirschbaum 2005). These effects might be mediated by different brain structures (e.g., pituitary and hypothalamus).

The OC users showed no cortisol-induced retrieval impairment. A slightly (but not significantly) lower retrieval performance under placebo was apparent compared to that of the naturally cycling groups, which was not further reduced by cortisol. The three groups did not differ in initial learning performance in the morning. Moreover, the recall performance of the OC users was still very good (77%), which argues against a floor effect. Also, another study reported no differences in memory performance between free cycling women and women using OC (Wright and Badia 1999). Thus, our data could provide first evidence for a reduced 'central' GC sensitivity of women using OC. Of course, this initial observation awaits replication, especially since the computed ANOVAs revealed only a nonsignificant trend for a group (naturally cycling vs OC) by treatment interaction (see Results). This might reflect the small group sizes and the associated lack of power as well as the fact that in the OC group, the descriptive trend was in the same direction (less retrieval on the cortisol day) as in the other two groups. Additional analysis using effect size measures revealed that in both groups of the normally cycling subjects, the effect sizes were large (around 0.80; see Cohen (1988)). In a recent meta-analysis on the acute effects of cortisol on memory, we calculated an average negative effect size of cortisol on retrieval of −0.49 (Het et al. 2005). The results for the normally cycling women were therefore larger than those previously reported. In contrast, the average effect size for the OC group was only −0.24, which can be considered a small effect (Cohen 1988). This suggests that the effect of cortisol on retrieval is not absent in OC women but markedly reduced. While we cannot exclude the possibility that the missing effect in the OC group reflects a lack of power, it has to be stated that this group had the largest sample size ($n=20$) of the current study. In addition, a sam-

ple size of 20 is larger than the sample size used in most previous studies on this topic (see Het et al 2005).

In this study, a quasi-experimental design was used with respect to OC use since OC use vs naturally cycling was not assigned randomly. We cannot therefore, of course, exclude that some a priori group differences associated with the decision to use OCs might underlie our findings. At least, OC users did not differ from the other two groups in age, BMI, personality, mood, and performance in all the remaining tests.

Estradiol levels differed as expected between the two free cycling groups and the OC users. Similarly, the cortisol effects on memory differed between those groups, with only naturally cycling women showing a cortisol-induced memory impairment. We also had expected higher estradiol level in luteal phase than that in mensis phase (e.g. Hausmann et al. 2000; Fernandez et al. 2003) but failed to find the effect even though estradiol levels were slightly higher in the luteal group. One explanation might be that our study used a between-group design, while most previous menstrual cycle studies used a within-subject design, which might be better suited to detect cycle-associated changes in gonadal hormones. The women in luteal phase were tested in the mid to late luteal phase, which is characterized by a moderate estradiol elevation or even no elevation compared with the mensis. Shirtcliff et al. (2000) using the same assay reported during menses 1.33 pg/ml and for the mid to late luteal phase 1.44 pg/ml salivary estradiol. These results are very close to what we observed in our study. The highest level of estradiol is reached in the late follicular phase just before ovulation (Cumming 1990). It would be desirable to include a group of women in this cycle phase in future studies.

Progesterone levels were elevated in the luteal phase as expected. This apparently did not influence the cortisol effects, since mensis and luteal women did both show a significant large retrieval impairment after cortisol treatment. Therefore, our data might suggest that estrogens rather than progestins modulate the cortisol effect on memory. Women using OCs have low concentration of endogenous estradiol, but the OCs contain synthetic ethinylestradiol. We cannot, of course, solve the questions whether the low endogenous estradiol or the synthetic ethinylestradiol in the OC leads to the reduced retrieval impairment after cortisol. Future studies could investigate women using progestin-only agents in order to address this issue.

Studies in animals suggest that stress-induced changes in conditioning in males depend on changes in corticosterone concentration, whereas the impairment in females is independent of the presence of adrenal hormones and might be mediated by gonadal hormones (Wood et al. 2001). It therefore remains to be investigated whether or not similar effects like those observed in the present study employing a pharmacological approach are observable in women after psychosocial stress exposure (Kuhlmann et al. 2005b; Shors et al. 1999; Wood et al. 2001).

The effects of cortisol on memory retrieval were examined in two previous studies in men only (de Quervain et al. 2003; Wolf et al. 2001a). Both studies showed a significant impairment. Another study of de Quervain et al. (2000) tested female and male participants. No separate data analysis for both sexes was provided in the initial report, and it is unclear how many women were using OCs. The only study which examined only women was a previous study of our workgroup (Kuhlmann et al. 2005a), in which we tested naturally cycling women during the first half of their menstrual cycle (mensis and follicular phase combined). This study also observed a retrieval impairment by cortisol, which is in line with the current observations. To the best of our knowledge, there is no previous experiment which investigated cortisol modulated memory retrieval impairments in women selected for taking OCs.

In sum, this study replicates a negative effect of cortisol on memory retrieval. For the first time, the influence of gonadal hormones on this effect was investigated systematically in women. The results suggest that menstrual-cycle-associated changes in gonadal hormones have little influence on the effects of cortisol on memory. In contrast, OC users appear to be less sensitive to acute cortisol elevations. This finding, of course, awaits replication. The underlying neurobiological mechanisms remain to be elucidated in future animal and human experiments.

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