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# Emotional memory in oral contraceptive users : Negative stimuli are more forgettable

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**Emotional memory in oral contraceptive users: Negative stimuli are more forgettable**

# Emotional memory in oral contraceptive users: Negative stimuli are more forgettable

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**Abstract**

Recent research suggests oral contraceptive use is associated with altered memory for emotional story information, blunted stress hormone responses to emotional stimuli, and altered structure or function of the amygdala and hippocampus. This study examined the extent to which oral contraceptives influence relative recall of: (a) the spatial location of emotional versus neutral stimuli, and (b) positive versus negative emotional stimuli. Participants (58 oral contraceptive users, 40 nonusers, and 37 men) completed an emotional spatial memory test and were evaluated on short-term recall and long-term (one week) recall. There was no evidence for group differences in recall of the locations of emotional versus neutral stimuli. However, oral contraceptive users remembered relatively more positive than negative items compared to nonusers and men on the spatial memory test.  This effect was driven by oral contraceptive users recalling fewer negative items than free-cyclers. The results indicate that hormonal contraceptives may decrease immediate recall of negative emotional stimuli.

**Keywords**

Oral contraceptives, emotional memory, spatial memory, emotional valence, recall, hormones

**Emotional Memory in Oral Contraceptive Users: Negative Stimuli are More Forgettable**

**Introduction**

Research indicates that hormones can affect cognition and mood, and menstrual cycle phase has also been linked with cognition and mood (see reviews in Erlanger, Kutner, & Jacobs, 1999; Romans, Clarkson, Einstein, Petrovic, & Stewart, 2012; Steiner, Dunn, & Born, 2003). Studies have suggested three other relevant findings. (a) Emotional images elicit different levels of activity in the hippocampus and amygdala at low versus high hormone times in the menstrual cycle (Andreano & Cahill, 2010). (b) Oral contraceptives (OCs) can influence mood (see reviews in Kurshan & Epperson, 2006; Oinonen & Mazmanian, 2002). (c) OCs may influence amygdala and hippocampal structure and function (e.g., Lisofsky, Riediger, Gallinat, Lindenberger, & Kuhn, 2016). Recent reviews of the effects of OCs on cognition (Gogos, Wu, Williams, & Byrne, 2014; Warren, Gurvich, Worsley, & Kulkarni, 2014) suggest that, while experimental designs have been weak, OCs may improve verbal memory, associative learning, and spatial attention. However, little is known about the effects of OCs on emotional memory. Given that approximately 82% of women between the ages of 15 and 44 in the United States take OCs during their lifetime (Mosher & Jones, 2010) and that emotional side effects are a common complaint (Rosenberg & Waugh, 1998; Sanders, Graham, Bass, & Bancroft, 2001), there is a need to understand possible effects of OCs on emotional memory. Research in this area also contributes to understanding of general hormonal mechanisms in memory, emotion, and emotional memory.

Nielsen, Ertman, Lakhani, and Cahill (2011) found that OC use was associated with altered memory for an emotional story. Women using OCs exhibited enhanced memory of gist (central information), but not story details, in an emotional story condition compared with a neutral story condition. Given that participants were exposed to only the emotional or the neutral story, the findings require replication using a within-subjects design whereby women's memory for both emotional and neutral information is tested.

Subsequent studies further suggest that OCs may affect memory for emotional information. One study examined the effects of OC use on long-term (one-week) recall of positive, negative, and neutral images as a function of a woman's stress hormone responses (Nielsen, Segal, Worden, Yim, & Cahill, 2013). OC users showed blunted stress hormone responses compared to nonusers but no overall group difference in memory for any emotional stimuli. Weak interactions between OC use, stress hormone response (yes/no), and valence of the stimuli (positive or negative) on long-term (one-week) recall of the images suggest that OC users and nonusers may differ

in their ability to recall positive or negative stimuli depending on their cortisol responses. Six other studies found

that OCs may influence emotional learning or memory (i.e., Drexler, Merz, Hamacher-Dang, & Wolf, 2016;

Graham & Milad, 2013; Merz et al., 2012; Nielsen, Ahmed, & Cahill, 2014; Petersen, Patihis, & Cahill, 2014;

Zsido, 2014). However, only two studies appear to have looked at whether OCs affect spatial memory (Postma et al.,

1999; Lisofsky et al., 2016), and no published studies have examined the relationship between OC use and memory

for the location of emotional stimuli, relative memory for the location of emotional versus neutral stimuli, or relative

memory for positively- and negatively- valenced stimuli (but see Nielsen, Segal, et al., 2013 for a study using

images).

There is evidence that OCs may affect brain structure and activity that is of potential relevance to emotions

and memory.  OC users show:  (a) decreased gray matter volume in the left amygdala/anterior parahippocampal

gyrus in (Lisofsky et al., 2016), (b) decreased bilateral amygdala reactivity in response to negatively valenced

emotional stimuli (Peterson & Cahill, 2015), (c) increased regional grey matter volumes in the prefrontal cortices,

pre- and postcentral gyri, parahippocampal and fusiform gyri and temporal regions (Pletzer, Kronbichler, Nuerk, &

Kerschbaum, 2014), and (d) localized decreases in cortical thickness in areas such as the lateral orbitofrontal cortex

and posterior cingulate cortex (Peterson, Touroutoglou, Adreano, & Cahill, 2015). Another study found that OC

users with a history of OC-related negative mood side effects show reduced left insula reactivity in BOLD responses

to an emotion processing task when compared to placebo users after 21 days of OC use (Gingnell et al., 2013).

Women with a history of OC-induced adverse mood side effects also showed the following changes when re-

exposed to OC use: lower reactivity to emotional faces in the left insula, left middle frontal gyrus, and bilateral

inferior frontal gyri compared to similar women exposed to placebo.  Thus, recent research suggests neurobiological

changes in OC users that could affect memory for emotional information.

Estradiol may enhance memory due to its ability to facilitate dendritic spine growth and neuroplasticity in

the CA1 of the hippocampus (see reviews in Frankfurt & Luine, 2015; Frick, 2015).  Repeated exposure to estradiol

in female rodents modulates hippocampal neurogenesis and there is evidence of dose-dependent effects in brain

areas that play a role in working memory (hippocampus, prefrontal cortex), spatial reference memory

(hippocampus), and emotion (amygdala) (see review in Galea et al., 2008). OCs reduce endogenous levels of

estradiol and testosterone (which is aromatized to estradiol) and reduce variability in estradiol across the cycle

(Coenen et al., 1996; Fleischman et al., 2010; Gaspard et al., 1983; Kjeld, Puah, & Joplin, 1976). Thus, it is possible

that OCs could adversely affect memory. In addition, OCs reduce the cortisol response to stress (Kirschbaum & Hellhammer, 1995; Kirschbaum, Platte, Pirke, & Hellhammer, 1996; Kuhlmann & Wolf, 2005) and thus may also adversely affect memory in this way. However, convincing evidence of an adverse OC-memory effect has not been found.

Given evidence that OCs affect mood and may cause differential recall of emotional and neutral story information, it follows that there might also be adverse or differential effects of OCs on recall of emotional versus neutral spatial information, or on positively versus negatively valenced information. An adequately powered study without additional stressors or other factors that could influence mood (e.g., the possible influence of saliva sampling on mood) is needed to examine immediate and long-term recall of such emotional stimuli.

The present study compared the performance of OC users, nonusers, and men on an Emotional Spatial Memory test created for the present study. The relative recall of emotional versus neutral stimuli, and positive versus negative stimuli was examined and two hypotheses were tested. (1) OCs influence relative memory for the spatial location of recalled emotional versus neutral stimuli. (2) OCs influence relative memory for positively- and negatively-valenced stimuli. These hypotheses were nondirectional in nature as there was not enough consistent previous research to justify a directional hypothesis.

**Method**

*Participants*

The final sample consisted of 135 Canadian university students and community volunteers aged 16 to 35 (58 women currently using OCs, 40 nonusers, and 37 men). Their mean age was 20.16 ($SD = 3.82$), mean years of education was 13.88 ($SD = 1.44$), and 87.3% of the sample was of European decent. Participants in eligible psychology courses received course credit for participation. The University Research Ethics Committee approved the study.

Initially, 282 participants completed the screening questionnaire and met the inclusion criteria for the study. Of these, 150 and 147 participants completed the first and second laboratory sessions, respectively. The four main inclusion criteria (and number of relevant participants excluded) were: (a) age 16 to 35 ($n = 9$), (b) no history of brain injury or a diagnosed memory problem ($n = 13$), (c) no use of mood-altering medications, other than OCs (e.g. antidepressants, benzodiazepines) ($n = 37$), and (d) geographic location (i.e., must be living in the city to attend lab

sessions) ($n = 50$).  Five additional inclusion criteria were used for women: (e) no current pregnancy, lactation, or breast feeding ($n = 5$), (f) no hysterectomy or menopausal status ($n = 5$), (g) must have menstruated in the past two months ($n = 9$), (h) a regular menstrual cycle or provide enough menstrual cycle information to determine cycle day ($n = 18$), and (i) OC use for at least the past two months (for OC users) or no use of OCs for at least the past two months (nonusers) ($n = 8$).  Post-hoc exclusion criteria included: (a) not self-identifying as male or female ($n = 1$), (b) current high alcohol intake (i.e., five or more alcoholic drinks in the 24 hours prior to sessions) ($n = 4$), (c) a change in OC status between screening and laboratory sessions ($n = 1$), and (d) other hormonal contraceptive use (i.e., NuvaRing) ($n = 7$).  As in Nielsen et al. (2011), recruitment of OC users was targeted at monophasic users, with 76% of the OC users taking a monophasic OC.

*Measures and tests*

*Screening questionnaire*.  This questionnaire was used to evaluate the inclusion and exclusion criteria.  It included questions about demographics (e.g., age, sex, ethnicity), memory, OC use, menstrual cycle phase and other factors that could affect memory such as stress, sleep, alcohol and caffeine consumption, medications, and medical and psychological conditions.

*Emotional spatial memory test.*  This test of visuospatial memory was designed for the present study to assess: (a) memory for the location of visuospatial material with differing emotional valence, and (b) memory for stimuli with positive, negative, and neutral emotional valence.  The test materials consist of a tray containing 30 items (10 positive, 10 negative, and 10 neutral items), with one item found within each of the 30 sections of the tray.  The stimuli were selected through a pilot study (see Table 1 for emotional valence ratings of the stimuli).  In Laboratory Session I participants were instructed to carefully look at all items on the tray and "think about how each item makes you feel".  This instruction was given to enhance the emotional value of the stimuli and to provide participants with a common activity that maximized the likelihood that the items were attended to.  After 60 seconds a towel was placed over the tray and the tray was removed from the participant's view.  An immediate free recall test followed. Participants were asked to list as many items as they could remember (ST Item Recall).  To assess spatial memory, a second memory test was given where participants were presented with an identical empty tray and asked to indicate the location of each item they remembered (ST Spatial Memory).  In Laboratory Session II (one week later)

Table 1

Emotional Spatial Memory Test Stimuli: Emotional Valence Ratings in the Pilot Study and Main Study.

| Item | Participants Indicating a Positive, Negative, or Neutral Rating (%) (Pilot Study) | Mean (SD) (Pilot Study) | Mean (SD) (Main Study) |
|---|---|---|---|
| Skull | 93.34% negative | 1.47 (0.83) | 2.15 (0.98) |
| Spider | 93.33% negative | 1.47 (1.06) | 1.98 (1.01) |
| Bat | 86.67% negative | 1.80 (1.08) | 2.38 (1.03) |
| Rat | 86.67% negative | 1.67 (0.72) | 2.27 (1.00) |
| Payment Due Notice | 86.67% negative | 1.73 (0.70) | 1.65 (0.91) |
| Gun | 80.00% negative | 1.53 (0.83) | 2.05 (1.03) |
| Handcuffs | 80.00% negative | 1.73 (0.96) | 2.34 (0.94) |
| Pin/Needle | 80.00% negative | 1.93 (0.70) | 2.46 (0.81) |
| Tombstone | 80.00% negative | 1.53 (0.99) | 1.83 (1.05) |
| Knife | 73.34% negative | 1.67 (1.05) | 1.95 (0.95) |
| Button | 80.00% neutral | 3.13 (0.64) | 3.16 (0.65) |
| Paper Clip | 80.00% neutral | 3.07 (0.46) | 3.13 (0.61) |
| Pen Cap | 80.00% neutral | 2.80 (0.41) | 2.93 (0.51) |
| Rubber Elastic | 80.00% neutral | 2.93 (0.46) | 3.06 (0.50) |
| Twist Tie | 80.00% neutral | 2.93 (0.46) | 2.99 (0.53) |
| Bobby Pin | 73.33% neutral | 3.33 (0.62) | 3.34 (0.64) |
| Key | 73.33% neutral | 3.33 (0.62) | 3.26 (0.64) |
| Thread | 73.33% neutral | 3.07 (0.70) | 3.22 (0.64) |
| Toothpick | 73.33% neutral | 2.87 (0.52) | 2.89 (0.57) |
| Clothes Peg | 60.00% neutral | 3.00 (0.93) | 3.03 (0.61) |
| Heart | 100% positive | 4.80 (0.41) | 4.02 (0.75) |
| Present | 100% positive | 4.80 (0.41) | 4.28 (0.64) |
| Rainbow | 100% positive | 4.80 (0.41) | 4.30 (0.65) |
| Winking Face | 100% positive | 4.53 (0.52) | 4.29 (0.77) |
| Bow | 93.34% positive | 4.40 (0.63) | 4.39 (0.65) |
| Cake Slice | 93.34% positive | 4.40 (0.63) | 4.20 (0.73) |
| Happy Face | 93.34% positive | 4.60 (0.63) | 4.33 (0.61) |
| Peace Sign | 93.34% positive | 4.40 (0.63) | 4.07 (0.77) |
| Birthday Candle | 93.33% positive | 4.47 (0.64) | 4.23 (0.73) |
| Flower | 93.33% positive | 4.53 (0.64) | 4.48 (0.63) |

Note: $N = 15$ for columns 2 and 3 (Pilot Study); $N = 135$ for column 4 (Main Study). Response options ranged from 1 (*very negative*) to 3 (*neutral*) to 5 (*very positive*).

participants were asked to recall all items they saw on the tray during session I (LT Item Recall) and to indicate the location of each item on the tray (LT Spatial Memory). ST and LT spatial memory scores (i.e., the number of items that were correctly recalled and their exact location identified) and the total number of correctly recalled positive and negative items were calculated for both ST and LT recall. The spatial memory scores were further broken down by emotional or neutral valence of the stimuli.

*Attention Test.* The Choice Reaction Time for Single Digits test from the California Computerized Assessment Package (CalCap) (Miller, 1990) was used to assess for any group differences in complex attention during the study. Participants are to press a key as soon as they see a specific number on the screen, requiring a simple element of working memory, selective attention, and inhibition. Internal consistency is quite high ($r = .81$ to $.96$) (Miller, 1990). The d prime scores or the discriminability index from the Choice Reaction Time test was used as an index of attention and the ability to accurately discriminate target stimuli from distracter stimuli.

*Positive and negative affect schedule (PANAS).* The PANAS consists of 20 adjectives that describe affective states (10 negative affect (NA) and 10 positive affect (PA) items; Watson, Clark, & Tellegen, 1988). Participants indicated the extent to which they currently felt each affective adjective. Response options ranged from 1 (*very slightly or not at all*) to 5 (*extremely*). Coefficient alphas for the PA and the NA subscales are .89 and .87, respectively (Watson et al., 1988). The PANAS was completed three times (start of laboratory session I (baseline measure), end of laboratory session I (after viewing the emotional stimuli), and during laboratory session II) to assess affect level and reactivity in response to the emotional stimuli.

*Procedure*

*Recruitment and screening.* Participants in the "Hormones and Cognition" study provided informed consent, completed the Screening Questionnaire, and were selected for Laboratory Session I based on the above inclusion criteria. For women, sessions were scheduled based on menstrual cycle phase using information provided in the screening and laboratory questionnaires. Actual cycle days of testing were later confirmed using date of the next menstrual period (e.g., Hatta & Nagaya, 2009; Protopopescu et al., 2008). Individual men were booked on the same days as individual women in order to yoke the men's testing days with women's and minimize testing day sex

differences.  Women were tested in one of three phases (i.e., menstrual, periovulatory, or luteal) and the proportion

of women in the three phases did not differ between the OC user and nonuser groups, $X^2$ (2, $N$ = 98) = 1.761, $p$ =

.415. Both sessions were scheduled in the laboratory between the hours of 12:00 and 18:00, as in previous studies

(e.g., Nielsen et al., 2011).

*Laboratory questionnaires I and II.*  These questionnaires were similar and contained questions about factors

theoretically relevant to memory (e.g., sleep, alcohol and caffeine consumption, tobacco use, medications, fatigue,

boredom, and interest).

*Laboratory session I.*  Participants completed Laboratory Questionnaire I (including the PANAS), the Emotional

Spatial Memory test (exposure and ST recall), the attention test, and the PANAS a second time.

*Laboratory session II.*  One week later, participants returned for the last phase of the study. LT recall was tested for

the Emotional Spatial Memory test, and then the Laboratory Questionnaire II and the PANAS were also completed.

*Data reduction and analyses.* For the emotional spatial memory test, emotional : neutral spatial memory scores

[number of emotional items recalled and located / number of neutral items recalled and located] and positive :

negative item memory scores [number of positive items recalled / number of negative items recalled] were

computed using both ST and LT memory scores.

Two main sets of analyses were carried out using multivariate analysis of covariance (MANCOVA) to

examine group differences in (a) emotional : neutral ST and LT spatial memory scores (Hypothesis 1), and (b) ST

and LT positive: negative item recall scores from the Emotional Spatial Memory test (Hypothesis 2). Follow-up

ANCOVAs were conducted where justified in order to examine group differences on the individual memory scores.

For all analyses, a significance level of $p$ < .05 was chosen.  Pillai's trace criterion was used to evaluate multivariate

significance and Bonferroni adjustment was used for follow-up pairwise comparisons.  All means reported are

untransformed unadjusted means, unless otherwise indicated and figures represent adjusted means and their standard

errors.

**Results**

*Data Screening/ Statistical Considerations*

*Assessing univariate assumptions.* All distributions were reasonably normally distributed. As some outliers in each group (i.e. z scores > │3.29│; Tabachnik & Fidell, 2001) represented true data points, each analysis was run twice, both with and without outliers. As findings were similar for all analyses, the analyses reported below include outliers. As an additional control for possible violations of statistical assumptions, significant parametric analyses were followed up with nonparametric tests (i.e., Kruskal-Wallis analysis of ranks and Mann-Whitney *U* tests), which require that fewer normality assumptions be met.

*Examination of Group Equivalency*

The three groups were examined for equivalency on demographic, cognitive, and substance use variables using univariate ANOVAs and chi-square tests (see Tables 2 and 3). Group differences were found for diagnosis of an attention problem (men more likely than OC users ($p = .026$) and nonusers ($p = .046$)); typical alcohol use (lower in nonusers than both OC users ($p = .046$) and men ($p = .013$)); and caffeine consumption in the 24 hours prior to the first laboratory session (higher in nonusers than OC users ($p = .037$)). The three groups did not differ on attention scores, $F(2, 132) = 0.547$, $p = .580$. Given general population sex differences in ADHD (American Psychiatric Association, 2013) and that there was no evidence of a difference in attention during the lab session, diagnosis of an attention problem was not used as a covariate in the main analyses. However, given that both typical alcohol use (see review in Zeigler et al., 2005) and caffeine consumption prior to the first lab session (see review in Ruxton, 2008) could affect memory, these two variables were used as covariates in the main analyses.

*Main Analyses*

Means and standard deviations for the raw scores used in the main analyses are provided in Table 4 (see Table 4).

*Hypothesis 1.* The overall multivariate examination of group differences in ST and LT emotional: neutral spatial memory scores was nonsignificant, $F(4, 252) = 0.181$, $p = .948$. The univariate ANCOVAs also did not reveal any

Table 2

Examination of Group Equivalency between Nonusers, Oral Contraceptive (OC) users, and Men: Means (and SDs).

| Variable | Nonusers | OC users | Men |
|---|---|---|---|
| | *n* = 40 | *n* = 58 | *n* = 37 |
| | Mean (SD) | | |
| Age (years) | 20.95 (5.42) | 19.60 (2.70) | 20.22 (3.24) |
| Education (years) | 13.43 (0.98) | 13.97 (1.54) | 14.27 (1.59) |
| Typical drug use score | 1.41 (0.90) | 1.31 (0.66) | 1.19 (0.46) |
| Typical alcohol use score * | 7.54 (5.99)[x] | 11.74 (8.77) | 13.11 (9.48) |
| Sess. 2 Sleep (hours) [a] | 8.20 (1.40) | 8.14 (1.60) | 8.42 (2.01) |
| Sess. 2 Fatigue | 1.65 (0.98) | 1.49 (0.80) | 1.25 (0.77) |
| Sess. 2 Interest | 2.15 (0.77) | 2.02 (0.77) | 2.09 (0.70) |
| Attention Score (CalCap) | 0.99 (0.01) | 0.99 (0.02) | 1.00 (0.10) |

Note: [a] data refers to experience during the past 24 hours. [x] this group differed from the other two groups. The groups differed on typical alcohol use, $F(2, 130) = 4.807$, $p = .010$.
* $p < .05$.

Table 3

Examination of Group Equivalency between Nonusers, Oral Contraceptive (OC) users, and Men: Frequencies (Percentages).

| Variable | Nonusers $n = 40$ | OC users $n = 58$ | Men $n = 37$ |
|---|---|---|---|
| Diagnosis of attention problem * | | | |
| Yes | 0 (0.0%) | 0 (0.0%) | 3 (8.1%) |
| No | 40 (100.0%) | 58 (100.0%) | 34 (91.9%) |
| Tobacco use | | | |
| Yes | 2 (5.0%) | 1 (1.7%) | 1 (1.7%) |
| No | 38 (95%) | 57 (98.3%) | 36 (97.3%) |
| Sess. 1 alcohol use [a] | | | |
| Yes | 4 (10.3%) | 3 (5.2%) | 4 (10.8%) |
| No | 35 (89.7%) | 55 (94.8%) | 33 (89.2%) |
| Sess. 1 caffeine use [a] * | | | |
| Yes | 16 (40.0%) | 10 (17.2%) | 10 (27.0%) |
| No | 24 (60.0%) | 48 (82.8%) | 27 (73.0%) |
| Sess. 1 Drug use [a] | | | |
| Yes | 2 (5.0%) | 0 (0.0%) | 0 (0.0%) |
| No | 38 (95.5%) | 58 (100.0%) | 37 (100.0%) |
| Sess. 2 alcohol use [a] | | | |
| Yes | 3 (7.5%) | 4 (7.0%) | 5 (14.7%) |
| No | 37 (31.1%) | 53 (93.0%) | 29 (85.3%) |
| Sess. 2 caffeine use [a] | | | |
| Yes | 15 (37.5%) | 12 (21.1%) | 9 (25.0%) |
| No | 25 (62.5%) | 45 (78.9%) | 27 (75.0%) |
| Sess. 2 Drug use [a] | | | |
| Yes | 2 (5.1%) | 1 (1.8%) | 0 (0.0%) |
| No | 37 (94.9%) | 56 (98.2%) | 36 (100.0%) |

Note: [a] data refers to experience during the past 24 hours. The groups differed on diagnosis of an attention problem, $X^2$ (2, $N = 135$) = 8.127, $p = .017$; typical alcohol use, $F(2, 130) = 4.807$, $p = .010$; and caffeine consumption in the 24 hours prior to session 1, $X^2$ (2, $N = 135$) = 6.274, $p = .043$.
* $p < .05$.

Table 4

Unadjusted Means and Standard Deviations for Raw Scores and Ratio Scores on the Emotional Spatial Memory Test and the Positive and Negative Affect Schedule.

| Measures | Nonusers $n = 39$ | OC users $n = 57$ | Men $n = 34$ |
|---|---|---|---|
| **Emotional Spatial Memory Test** | | | |
| Emotional : Neutral ST | 3.25 (1.54) | 3.52 (1.99) | 3.46 (2.40) |
| Emotional : Neutral LT | 2.70 (1.53) | 2.74 (1.65) | 3.03 (1.81) |
| Positive : Negative ST** | 0.78 (0.24) | 0.97 (0.44)[x] | 0.76 (0.28) |
| Positive : Negative LT | 0.83 (0.35) | 0.92 (0.42) | 0.80 (0.44) |
| Negative Item ST* | 5.97 (1.61)[y] | 5.17 (1.84)[y] | 5.67 (1.35) |
| Positive Item ST | 4.28 (1.72) | 4.48 (1.43) | 3.92 (1.57) |
| **Positive and Negative Affect Schedule[a]** | | | |
| Mean PA[b] | 26.92 (7.15) | 25.41 (6.02) | 28.39 (6.33) |
| Mean NA[b]** | 15.48 (5.96)[x] | 13.40 (2.77) | 12.56 (2.60) |
| PA Range[b] | 7.04 (0.67) | 5.91 (0.54) | 6.61 (0.69) |
| NA Range[b]* | 5.59 (5.48)[y] | 4.29 (4.25) | 2.97 (2.21)[y] |
| Lab 1 NA before | 14.28 (5.73) | 13.02 (2.79) | 12.91 (3.23) |
| Lab 1 NA after* | 15.75 (7.14)[x] | 13.41 (4.12) | 12.89 (3.30) |
| Lab 2 NA** | 16.42 (7.58)[y] | 13.76 (4.44) | 11.89 (2.49)[y] |

Note: While data reported here are unadjusted for covariates, all analyses controlled for typical alcohol use and caffeine consumption. ST = Short-Term, LT = Long-Term.
[a]$N$s ranged from 122 to 133 for MANCOVA and ANCOVA analyses. Affect scores were calculated from the Positive Affect (PA) and Negative Affect (NA) subscales. [b]Computed across the three measures. [x] group differences exist between the indicated group and the other two groups. [y] group differences exist between the two indicated groups.
* $p < .05$
** $p < .01$

group effects in ST, $F(2, 126) = 0.031$, $p = .969$, or LT, $F(2, 126) = 0.251$, $p = .778$, recall ratios for the spatial

memory test.

*Hypothesis 2.*  A significant multivariate group effect was found for the ratio of positive to negative item recall on

the Spatial Memory test, $F(4, 252) = 2.628$, $p = .035$.  A follow-up ANCOVA revealed a significant univariate

group effect for positive to negative item STM recall, $F(2, 126) = 5.39$, $p = .006$.  Pairwise comparisons indicated

that OC users had a higher ratio, reflecting relatively higher recall of positive than negative items compared to both

nonusers ($p = .021$) and men ($p = .022$).  No significant difference in the ratio of positive to negative item recall was

found for LTM, $F(2, 126) = 1.276$, $p = .283$.  However, the direction of the means suggested that the pattern of LT

recall was in the same direction with OC users having the largest ratio of positive to negative item recall compared

to nonusers and men (see Figure 1 for an illustration of both ST and LT positive to negative item ratios).

To examine whether group differences in ST recall of either positive or negative stimuli were driving the

above findings, two ANCOVAs were conducted on these scores. ST recall of negative items significantly differed

between groups, $F(2,128) = 3.824$, $p = .024$, with OC users recalling fewer negative items than nonusers ($p = .020$).

Although ST recall of positive items did not differ significantly between groups,

$F(2,128) = 1.748$, $p = .178$, the pattern of the means was consistent with the negative item ratio effect (see Figure 2).

Non-parametric tests corroborated the above significant findings.  A Kruskal-Wallis analysis of ranks

evaluating differences among the three groups in the ratio of positive to negative STM item recall was significant, $X^2$

$(2, N = 135) = 8.58$, $p = .014$.  Pairwise comparisons using the Mann-Whitney $U$ test were consistent with the above

findings of higher positive to negative item recall in OC users compared to nonusers ($p = .041$) and men ($p = .006$).

A Kruskal-Wallis analysis of ranks evaluating differences among the three groups (OC users, nonusers, and men) on

short-term recall of negative items was nonsignificant but suggested a trend, $X^2$ $(2, N = 135) = 5.06$, $p = .080$.

*Supplementary Analyses*

*OC use and mood/affect.*  Scores on the PANAS (i.e., means and range scores for PA and NA) were examined to see

if group differences in affect level or variability existed over the three measures of affect across the two laboratory
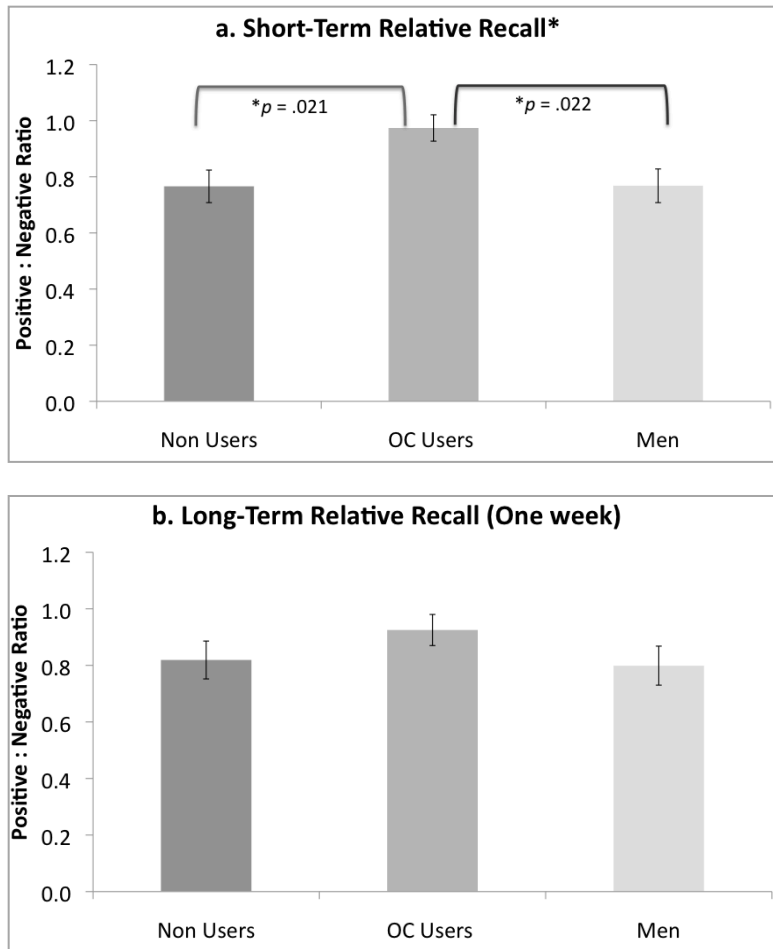
Figure 1

Group Differences Between Nonusers, Oral Contraceptive (OC) users, and Men in the Ratio of Positive to Negative Items Recalled on the Emotional Spatial Memory Test. Higher ratios reflect relatively better recall of positive versus negative stimuli. (a) OC users had significantly larger positive to negative item ratios than nonusers ($p = .021$) and men ($p = .022$) for ST item recall, $F(2, 126) = 5.39$, $p = .006$. (b). No group differences were found in positive to negative ratios for LT item recall, $F(2, 126) = 1.276$, $p = .283$. Error bars represent $\pm 1$ SEM. * $p < .05$
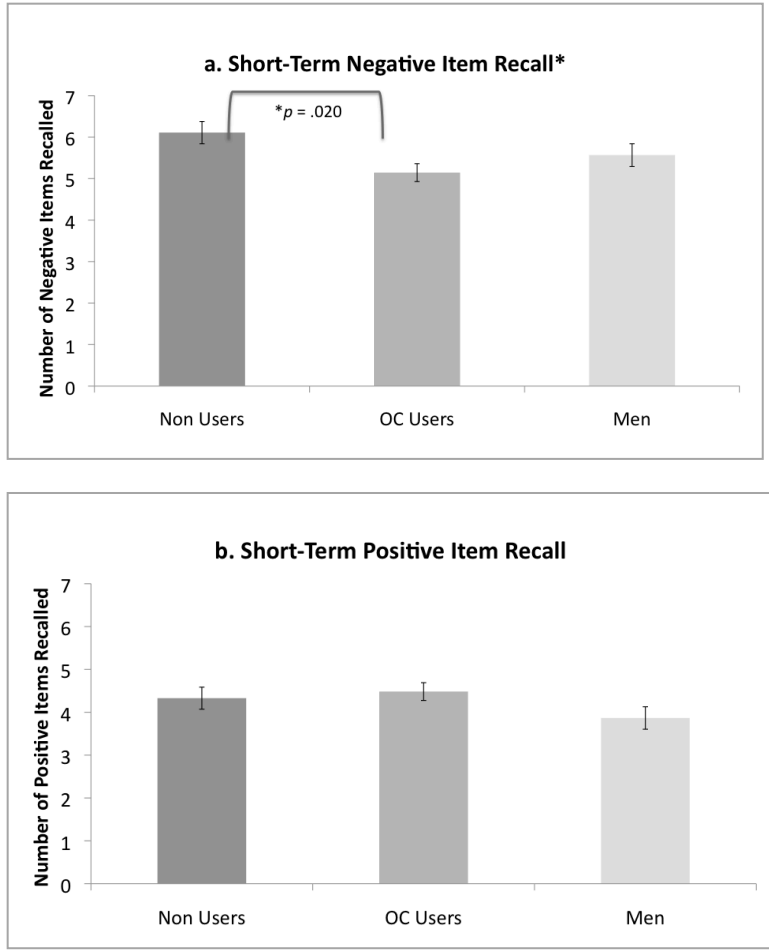
Figure 2

ST Recall of Negatively- and Positively-Valenced Stimuli on the Emotional Spatial Memory Test as a function of Group (Non users, Oral contraceptive (OC) users, Men). (a) There was a group difference in recall of negative items, $F(2,128) = 3.824$, $p = .024$. OC users recalled significantly fewer negative items than nonusers. (b) No group differences were found for recall of positive items, $F(2,128) = 1.748$, $p = .178$. Error bars represent ±1 SEM. * $p <$ .05

sessions (see bottom panel of Table 4 for means and SDs). MANCOVAs were conducted and the same covariates from the main analyses were used.

There were no significant group differences in mean PA level, $F(2,117) = 1.829$, $p = .165$, or range, $F(2,128) = 0.896$, $p = .411$. Thus, no further analyses were done on PA scores.

Mean NA level differed between groups, $F(2,121) = 5.201$, $p = .007$, with nonusers having higher NA than OC users ($p = .014$) and men ($p = .002$). There was also a group difference in NA variability, $F(2,128) = 3.457$, $p = .034$. Nonusers had a larger range in NA than men ($p = .029$), but did not differ from OC users ($p = .393$). There were no group differences in NA level, $F(2,121) = 1.237$, $p = .294$, at the beginning of laboratory session I, but the groups differed in NA level at the end of that session, $F(2,121) = 4.363$, $p = .015$. Nonusers had significantly higher negative affect than both OC users ($p = .039$) and men ($p = .024$), suggesting that viewing the emotional stimuli was associated with subsequently greater NA in nonusers. In laboratory session II, NA level also differed between groups, $F(2,121) = 5.890$, $p = .004$. Nonusers had higher NA than men ($p = .003$) and showed a nonsignificant trend toward higher NA than OC users ($p = .099$).

*Re-examination of hypothesis 2 using negative affect as a covariate.* Given that OC use could affect emotional responses to the stimuli (e.g., a blunting in the NA response) which could affect relative recall of positive or negative stimuli, the significant analyses from hypothesis 2 were re-run with NA level at the end of laboratory session I included as an additional covariate. Statistically adjusting for NA did not change the results. The significant univariate group effect held for ST recall of positive to negative stimuli, $F(2, 121) = 4.776$, $p = .010$. OC users ($M = 0.97$, $SD = 0.36$) significantly differed from men ($M = 0.76$, $SD = 0.36$; $p = .021$) but the difference with nonusers reduced to a strong trend ($M = 0.79$, $SD = 0.37$; $p = .060$). The group difference in ST recall of negative items remained significant, $F(2,123) = 3.382$, $p = .037$. OC users ($M = 5.16$, $SD = 1.65$) recalled significantly fewer negative items than nonusers ($M = 6.10$, $SD = 1.71$; $p = .011$). Thus, this group difference was even stronger after controlling for NA, and group differences in affect could not account for the current findings.

**Discussion**

*Summary*

The present study did not find any evidence that OC users, nonusers, and men differ on recall of emotional versus neutral spatial location information. However, for ST recall of positive and negative stimuli, OC users had a higher positive to negative item recall ratio than nonusers and men, and OC users recalled fewer negative items than nonusers. Emotional group differences (i.e., higher negative affect in nonusers after viewing emotional stimuli) could not account for the findings.

*No evidence that OCs influence emotional versus neutral spatial memory*

There was no evidence to suggest that OCs influence memory for emotional versus neutral spatial stimuli. This is the first study to examine if OC use is associated with altered relative recall of emotional and neutral spatial information. Postma et al. (1999) found that OC use did not yield any main or interaction effects in their study on spatial memory but did find that there was a spatial memory advantage in the nonmenstrual compared with the menstrual phase in both the OC user and nonuser groups. While two other studies have suggested links between OC use and visuospatial ability (e.g., mental rotation) (Egan & Gleason, 2012; McCormick & Teillon, 2001), neither of these studies looked at visuospatial memory or spatial memory for emotional versus neutral stimuli.

*Evidence of an OC-related emotional memory valence effect*

OC users recalled relatively more positive than negative items, and significantly fewer negative items than nonusers, immediately after viewing the visual stimuli in the Emotional Spatial Memory test. No effect was found for LT recall. This appears to be the first study to examine whether OC use is associated with differential relative ST recall of information with positive versus negative emotional valence. These findings suggest that OC use may decrease immediate recall of items with a negative valence. While nonusers experienced higher negative affect levels than OC users and men after viewing the emotional stimuli, group differences in negative affect could not explain the group differences in memory.

Two other studies examined the effects of OCs on LT recall of emotional stimuli. Nielsen, Segal, and colleagues (2013) examined LT recall of positive, negative and neutral stimuli and did not find a simple effect of OC use. This is consistent with the current findings for LT recall. However, a recent study found that OC users subjected to a psychosocial stress test prior to the LT recall of emotional word pairs recalled fewer negative words compared to positive or neutral words (Mordecai et al., 2017). Also, performance was unrelated to cortisol. Overall, the research suggests that the effect of OCs on recall of negative stimuli may: (a) apply to both ST and LT recall of

negative stimuli, (b) apply to both verbal and nonverbal stimuli, (c) be more prominent in stressful situations, and (d) be unrelated to cortisol.

While comparisons between samples can be difficult, the tendency for OC users to recall relatively less negative, and more positive, information may be similar to the positive memory bias found in older individuals by Charles, Mather, and Carstensen (2003). While one can only speculate about mechanisms, it is worth noting that both OC users and older individuals (aged 65 to 80) have lower endogenous gonadal steroid hormone levels than the groups they were compared to in these studies (i.e., nonusers and younger individuals aged 18 to 29).

Given that this was not a randomized placebo design, we can only speculate about possible reasons why nonusers recalled significantly more negative items than OC users.  First, higher endogenous hormone levels in free cyclers (Gaspard et al., 1983) may selectively enhance memory for negative stimuli or OCs may dampen both endogenous hormone levels and memory for negative stimuli.  Such effects could be modulated through effects of estradiol on the prefrontal cortex, hippocampus, and amygdala as these are areas dense with estradiol receptors (Montague et al., 2008; Spencer et al., 2008). While previous research on memory and OCs has not typically considered the emotional valence of stimuli, the finding that nonusers had better recall of negative stimuli in the Emotional Spatial Memory test fits with other findings of better visual, visuospatial memory, or visuospatial working memory with higher estrogen levels (e.g. Hampson & Morley, 2013, Phillips & Sherwin, 1992; Solis-Ortiz & Corsi-Cabrera, 2008). While an estrogen enhancement effect for visuospatial memory could explain why nonusers have better recall, it is not clear why estrogen would selectively enhance recall of negative versus positive stimuli. One possibility is that there is greater adaptive value for periods of high estradiol to be associated with recall of negative stimuli versus positive stimuli (e.g., to help avoid noxious stimuli such as poisonous foods, aggressive men, or dangerous situations to maximize survival at ovulation or during pregnancy).  While this possibility is inconsistent with the findings of Gasbarri et al. (2008), a recent study suggests that high estradiol in pregnancy may enhance spatial working memory once mood is controlled (Hampson et al., 2015).

The lower more stable progesterone levels in OC users compared to nonusers across the menstrual cycle (Coenen et al., 1996; Fleischman et al., 2010; Paoletti et al., 2004) is a second potential explanation for the higher recall of negatively valenced items in nonusers.  Higher progesterone has been associated with enhanced activity in the amygdala when viewing negative stimuli (Andreano & Cahill, 2010; van Wingen et al., 2008), higher heart rate while viewing negative stimuli (Ossewaarde et al., 2010), and a higher frequency of spontaneous intrusive

recollections (SIRs) after viewing negative stimuli (Ferree, Kamat, & Cahill, 2011).  Thus, the possibility that lowered progesterone levels in OC users decreases memory for emotionally arousing stimuli, particularly negative stimuli, deserves further study.

Third, the lower cortisol levels or blunted cortisol response to stressors (or negatively-valenced stimuli) in OC users versus nonusers (e.g. Bonen et al. 1991; Kirschbaum et al., 1995; 1996; Rohleder et al., 2003) might also account for the lower recall of negative stimuli in OC users. Recent studies have suggested links between OC use, cortisol response, and effects of postlearning stress in emotional memory (Merz et al., 2012; Nielsen, Segal, et al., 2013; Nielsen et al., 2014).  One of these studies suggests that lower LT recall of negative stimuli and higher LT recall of positive stimuli is more likely to occur in OC users when such women are cortisol responders (Nielsen, Segal, et al., 2013). It is not clear if this would also apply to immediate recall. However, as noted above, one study found lower recall of negative words following stress in OC users was unrelated to cortisol (Mordecai et al., 2017).

Two final possible mechanisms involve the amygdala. First, decreased amygdala activity might play a role in the OC-related memory deficit for negative stimuli. This possibility is raised by evidence that OC users show decreased bilateral amygdala reactivity in response to negatively valenced emotional stimuli compared to nonusers (Peterson & Cahill, 2015).

Finally, a sex-related neurobiological explanation for lower recall of negative stimuli in OC users may relate to the finding that OC users show reduced gray matter in the left amygdala/anterior parahippocampal gyrus (Lisofsky et al., 2016). An OC-related left amygdala gray matter reduction may be relevant given that a systematic review by Baas, Aleman, and Kahn (2004) found that the left amygdala is more often activated than the right amygdala during emotional processing. Furthermore, Killgore and Yurgelun-Todd (2001) found that both sexes showed greater left amygdala activation for fearful faces, while happy faces produced greater right than left amygdala activation for males but not females. A recent meta-analysis also examined sex differences in brain activation to emotional stimuli (Stevens & Hamann, 2012). The majority of sex differences where women show lower activity than men have been observed for positive emotion, whereas the majority of sex differences where women show higher activity than men are observed for negative emotion.  Given that OC users' memory performance for negative stimuli was shifted towards male-like responses, and that men are more likely to show lower brain activity than women with negative emotions, the current finding of lower recall of negative stimuli in OC users may suggest an OC-related masculinization of brain structures involved in emotional memory.

*Strengths and Limitations*

The survivor effect (e.g., Kutner & Brown, 1972) is a potential limitation in any study on OC use without random assignment to groups.  Thus, the study is limited in fully demonstrating the effect of OCs on emotional memory because the OC users were 'surviving' self-selected users.  The findings may therefore suggest that women who choose to continue OC use (possibly due to fewer negative side effects, no side effects, or positive side effects) recall fewer negative stimuli than nonusers.

In terms of strengths, this is the first study to examine whether OCs affect relative recall of emotional versus neutral spatial information. Second, this is the first study to examine whether OCs affect memory for positively- and negatively-valenced stimuli independent of a stress-induction paradigm. Fourth, we included a number of methods to measure and control for group difference in other variables that could affect mood or memory.  Additional strengths include sample size, controls for menstrual cycle phase, and the inclusion of men.

*Conclusions and Future Directions*

Our findings suggest that OC users and nonusers who experience the same emotional stimuli, or an emotional event in the real world, may process and remember that information in different ways.  This could have implications for sex differences in symptoms of depression, anxiety, or post-traumatic stress. The lower retention of aversive or negative stimuli in OC users may suggest that OC use could lessen the risk or severity of these types of symptoms for some women.  Future studies should focus on replicating the current finding of reduced memory for negative stimuli in OC users, and examine possible mechanisms for such an effect.  If replicable, it will be important to determine whether the effect is due to an effect of OCs on encoding, consolidation, retrieval, or all three.  Future research in this area will increase understanding of the hormonal neurobiological mechanisms involved in emotional memory.

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The Authors declare that there is no conflict of interest.

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**Data Statement**

The dataset generated during the current study is available from the corresponding author on reasonable request.

**Role Of Authors**

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: both authors; Acquisition of data: first author; Analysis and interpretation of data: both authors; Drafting of the manuscript: both authors; Critical revision of the manuscript for important intellectual content: both authors; Statistical analysis: both authors; Administrative, technical, and material support: both authors; Study supervision: second author

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