Journal of Neuroscience Research 95:251–259 (2017)

Sex, Age, and Sex Hormones Affect Recall of Words in a Directed Forgetting Paradigm

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During the course of serious discussion, an unexpected interruption may induce forgetting of the original topic of a conversation. Sex, age, and sex hormone levels may affect frequency and extension of forgetting. In a list-method directed forgetting paradigm, subjects have to learn two word lists. After learning list 1, subjects receive either a forget or a remember list 1 cue. When the participants had learned list 2 and completed a distraction task, they were asked to write down as many recalled items as possible, starting either with list 1 or list 2 items. In the present study, 96 naturally cycling women, 60 oral contraceptive users, 56 postmenopausal women, and 41 young men were assigned to one of these different experimental conditions. Forget-cued young subjects recall fewer list 1 items (list 1 forgetting) but more list 2 items (list 2 enhancement) compared with remember-cued subjects. However, forget-cued postmenopausal women showed reduced list 1 forgetting but enhanced list 2 retention. Remember-cued naturally cycling women recalled more list 1 items than oral contraceptive users, young men, and postmenopausal women. In forget-cued follicular women, salivary progesterone correlated positively with recalled list 2 items. Salivary 17β-estradiol did not correlate with recalled list 1 or list 2 items in either remember- or forget-cued young women. However, salivary 17β-estradiol correlated with item recall in remember-cued postmenopausal women. Our findings suggest that sex hormones do not globally modulate verbal memory or forgetting, but selectively affect cue-specific processing.

Key words: cognitive aging; estrogen; learning and memory; estradiol

INTRODUCTION

Statements like "What did we talk about before we were interrupted?" or "I forgot what I was going to say" are familiar to all of us. Despite the fact that we cannot recall conversation-relevant items after an interruption, they are not erased. A brief cue retrieves conversation-related items from our memory, indicating that these items have been disconnected from the context. One way to assess the effects of context on forgetting is to compare the recall of items following a cue to remember or to forget memorized items. Standardized experiments on directed forgetting have delineated distinct cognitive and neural processes associated with enhanced encoding and impaired retrieval of items (Bäuml et al., 2010; Pastötter et al., 2016). Several lines of evidence indicate that sex hormones are involved in verbal memory. In postmenopausal women, a decline in verbal memory has been associated with permanently lowered circulating estradiol (Sherwin, 2006). Of specific interest for the present study, expression profile of estrogen receptors in hippocampus and prefrontal cortex (Bixo et al., 1995; McEwen, 2002) may overlap with brain areas activated in directed forgetting processes (Hanslmayr et al., 2011).

In a list-method directed forgetting paradigm, participants have to learn two word lists. Encoding of list 1 is followed by a forget list 1 or remember list 1 cue. Encoding of list 2 is followed by list 2 as well as list 1 recall

SIGNIFICANCE

Changes in the hormonal milieu across the menstrual cycle or menopausal transition may affect forgetting. In a directed forgetting paradigm, subjects receive a cue to either remember or forget list 1 items but remember list 2 items. Forget-cued young women and men recall fewer list 1 but more list 2 items compared with remember-cued young subjects. Forget-cued postmenopausal women show reduced list 1 forgetting but also show list 2 enhancement. In forget-cued young women, progesterone correlates positively with recalled list 2 items. In remember-cued postmenopausal women, 17β-estradiol correlates with recalled items.

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Received 1 April 2016; Revised 19 September 2016; Accepted 28 September 2016

Published online 7 November 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jnr.23973

(Geiselman et al., 1983). While it is generally accepted that a single forget cue enhances forgetting of precue information and improves encoding of postcue information, there is debate as to whether single-mechanism or two-mechanism models best describe precue information forgetting and postcue information enhancement (Sahakyan and Delaney, 2003; Pastötter and Bäuml, 2010; Pastötter et al., 2012). Single-mechanism models postulate that changes in list 2 enhancement are directly linked to changes in list 1 forgetting (for review, see Bäuml et al., 2010). The selective rehearsal account assumes that list 2 enhancement and list 1 forgetting in forget-cued individuals are due to selective rehearsal of list 2 items (Bjork, 1972). The retrieval inhibition account emphasizes that active inhibition reduces accessibility of list 1 item memory representations in forget-cued individuals (Bjork, 1989). Consequently, selective suppression of list 1 context minimizes interference with list 2 items and improves list 2 item retrieval. In the context change account, a forget instruction prompts participants to shift their mental activity from list 1 to list 2. Accordingly, list 2 recall is improved because list 1 lacks mental cues but list 2 maintains mental cues (Sahakyan and Kelley, 2002). Two-mechanism accounts postulate dissociation between list 1 forgetting and list 2 enhancement. At the behavioral level, list 2 enhancement in recall can be present but list 1 forgetting be absent, and vice versa (Pastötter and Bäuml, 2010). As another dissociation between the two effects, list 2 enhancement can be present in recall and item recognition, whereas list 1 forgetting can be present in recall but be absent in item recognition (Pastötter et al., 2016). Further, electrophysiological, fMRI, and endocrinological studies support two-mechanism accounts. An increase in alpha power during list 2 encoding correlates with list 2 enhancement, whereas a reduction in alpha phase coupling correlates with list 1 forgetting (Bäuml et al., 2008). A combined EEG–fMRI study revealed that a decrease in beta power in the left inferior prefrontal cortex improves semantic encoding (Hanslmayr et al., 2011). Further, in forget-cued young men, low testosterone associates with successful list 2 encoding but not with list 1 forgetting (Sterzer et al., 2015). Taken together, these experimental findings support the two-factor account suggested by Pastötter and colleagues, according to which a list 1 forget cue independently inhibits retrieval of list 1 items and enhances encoding of list 2 items (Pastötter et al., 2012; see also Sahakyan and Delaney, 2003).

Correlative and endocrine intervention studies identified a link between estradiol and episodic memory in premenopausal as well as postmenopausal women. Women treated with a gonadotropin-releasing hormone agonist to suppress release of ovarian sex hormones show impaired verbal episodic memory compared with their baseline performance. Crucially, only agonist-treated women receiving estrogens recover to their baseline memory scores (Sherwin and Tulandi, 1996). Comparable observations have been made in reproductive-age women following surgery-induced menopause. Only women receiving estrogen therapy maintained their verbal memory performance, whereas women not receiving estrogens showed impaired verbal memory (Sherwin, 2006). In postmenopausal women, some studies describe a positive association between verbal episodic memory performance and estradiol (Drake et al., 2000; Wolf and Kirschbaum, 2002; Hogervorst et al., 2004; Yaffe et al., 2007), while other studies failed to find an association (Henderson et al., 2003; Espeland et al., 2013; Gleason et al., 2015). Onset of estrogen therapy in postmenopausal women seems to be crucial. Only women starting estrogen replacement with menopause show improvement in episodic memory (Sherwin, 2005, 2006).

If estradiol level predicts verbal performance in healthy premenopausal women, menstrual cycle phases with high estradiol or use of contraceptives containing synthetic estrogens are associated with improved verbal performance. However, among the small number of studies on verbal memory in naturally cycling women, only a few studies are in line with this prediction (Rosenberg and Park, 2002; Protopopescu et al., 2008). Most studies do not describe differences in verbal performance across menstrual cycle phases (for review, see Sundström Poromaa and Gingnell, 2014). For example, whereas Maki and colleagues describe a positive correlation between estradiol and verbal fluency (Maki et al., 2002), Griksiene and Ruksenas did not find a correlation between estradiol and verbal fluency (Griksiene and Ruksenas, 2011). Ethinylestradiol, the most common synthetic estrogen in combined oral contraceptives, is less metabolized compared with estradiol and does not bind to sex hormone–binding globulin, but it does bind to estrogen receptors (for review, see Stanczyk et al., 2013). Accordingly, during the active pill phase, ethinylestradiol is maintained at an elevated level. However, similar to endogenous 17β-estradiol, studies on verbal performance in women using ethinylestradiol-containing oral contraceptives are inconsistent. Mordecai and colleagues (2008) describe improved verbal memory in the active compared with inactive pill phase. Yet, Rosenberg and Park (2002) did not find differences in verbal working memory performance between the active and inactive phase in women using oral contraceptives. Gogos (2013) reports that oral contraceptive users and naturally cycling women in the midluteal phase of the menstrual cycle (high in 17β-estradiol and progesterone) show similar performances in their short-term and long-term verbal memory.

In the present study, we asked whether differences in sex, age, or salivary sex hormone concentrations correlate with performance in word recall in a list-method directed forgetting paradigm. This paradigm allows not only quantification of verbal memory but also assessment of the context of a memory trace. In directed forgetting, a forget cue does not affect the irrelevant memory trace itself but, rather, the item–context binding by recruitment of inhibitory processes (Bäuml et al., 2010). Thus, any factor that modulates these inhibitory processes in item–context binding could affect item recall at the behavioral or neural level.

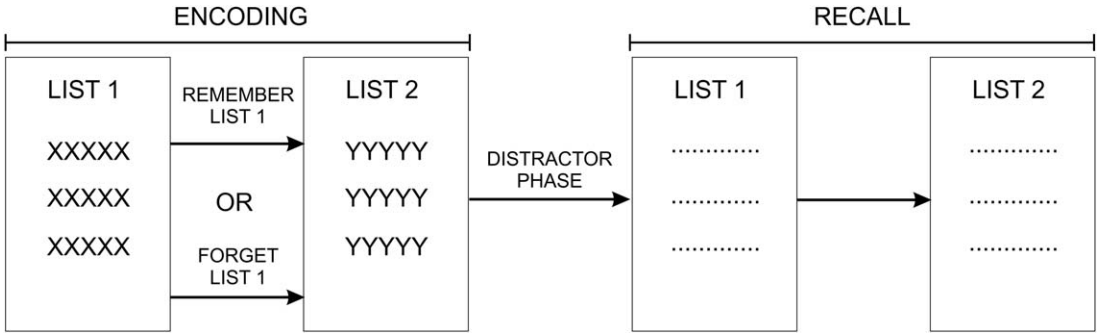

Fig. 1. Schematic diagram of the experimental paradigm. The list-method directed forgetting paradigm consists of a study (encoding), distraction, and test phase (recall). In the study phase, participants have to learn two word lists containing 12 words in each list. Each word is visualized on the computer screen one-by-one for 2 sec. Immediately after learning list 1 items, participants receive either a "remember list 1" or a "forget list 1" cue. All participants have to memorize list 2 items. After presentation of list 2 items, participants are asked to count backward aloud in threes from a three-digit number to prevent rehearsal of list items (distraction phase) for 30 sec. Finally, participants are asked to write down list 1 as well as list 2 items separately. List order of recall is mandatory. This means that randomly half of the participants are asked to start with list 1 and the other half to start with list 2 items. At the beginning of the experiment, subjects are instructed (1) to memorize list 1 and list 2 items and (2) to be aware that there is a 50% chance of receiving either a remember or forget cue after learning list 1 items. Note that for analyses of the experiments, participants are grouped according (1) to the cue ("remember" or "forget") in the encoding phase and (2) to the list order in the recall phase (recall either list 1 or list 2 items first) (see Table II). Only list items recalled first (either list 1 or list 2) are used for analyses (see Pastötter et al., 2012). As the main focus in list-method directed forgetting studies is on the cue, but not on the comparison between list 1 and list 2 items, list order was not changed in the encoding phase.

MATERIALS AND METHODS

Participants

Ninety-six naturally cycling women (mean age: 25.55; range 18–39 years), 60 women using oral contraceptives (mean age: 22.83; range 18–28 years), 56 postmenopausal women (mean age: 67; range 54–82 years), and 41 young men (mean age: 23.29; range 18–28 years) participated in the present study. Naturally cycling women reported a regular menstrual cycle. We used a calendar-based method to estimate the menstrual cycle position. Tests were scheduled during the early follicular phase (2–5 days after onset of menses) and luteal phase (5–10 days before the next expected menses). In addition, salivary 17β-estradiol and progesterone were quantified to verify the menstrual cycle position. Women using oral contraceptives were studied in the active phase, but not during the pill break. Women on hormonal contraceptives used different brands of combination pills (Aliane, Alisma, Balanca, Belara, Belinda, Bilinda, Diane Mite, Lamuna, Lenea, Liberel Mite, Meliane, Midane, Mirelle, Selina Mite, Triodena, Valette, Yirala, Yris Mite). The oral combination contraception products contained ethinylestradiol (15–40 μg per pill) but differed in their progestin compound (chlormadinone acetate, cyproterone acetate, desogestrel, dienogest, drospirenone, gestodene, levonorgestrel). Except Triodena (triphasic), all brands are monophasic oral contraceptives. None of the young adults reported use of medications. Most young adults were recruited from the University of Salzburg. Of the 56 postmenopausal women, 4 women took herbal drugs and 20 women took drugs to counterbalance hypofunction of the thyroid (Thyrex or Euthyrox). In the present study, we did not discriminate between early and late menopausal women. None of the young participants and postmenopausal women reported neurological or psychiatric diseases. All participants gave consent to participate in the study. The study was approved by the local research ethics board. Some data on directed forgetting in young men have been published in a short communication (Sterzer et al., 2015).

Experimental Procedure

We used a list-method directed forgetting paradigm as described by Pastötter and colleagues (2012). For experimental details, see Figure 1. Participants were assigned to one of four experimental conditions (Fig. 1) and were tested only once. The order of conditions was counterbalanced across subjects.

Estradiol and Progesterone Immunoassay

Saliva was collected in centrifuge tubes and stored until use at −20 °C. Salivary 17β-estradiol and progesterone were measured using an ELISA kit according to the recommendations of the provider (Demeditec Diagnostics GmbH, Germany).

Statistical Analyses

Normal distribution of data was evaluated using Shapiro-Wilk test as well as Kolmogorov-Smirnov test with Lilliefors correction. Because some of the data in the present study did not meet normality assumptions of an ANOVA test, we used nonparametric tests. Group characteristics, including sex, menstrual cycle phase, use of oral contraceptives, and age were estimated using the Kruskal-Wallis H-test. For pairwise, nonparametric comparison or independent samples, we used the two-tailed Mann-Whitney *U*-test (unless otherwise

TABLE I. Salivary 17β-Estradiol and Progesterone Concentrations

	17β-estradiol (pg/ml)	Progesterone (pg/ml)
Follicular women	3.70 ± 3.10 2.33 (0.66–14.21) (n = 46)	71.06 ± 45.94 73.20 (6.1–176.08) (n = 39)
Luteal women	4.02 ± 3.10 2.55 (1.09–11.91) (n = 46)	141.31 ± 59.11⋆ 128.04 (55.77–271.37) (n = 35)
Oral contraceptive users	5.08 ± 4.01 2.71 (0.15–16.17) (n = 60)	n.d.
Postmenopausal women	2.86 ± 1.17 2.61 (0.62–5.36) (n = 48)	n.d.

Note: Sex hormone concentrations are given as mean ± SD (first line) and median (minimum–maximum) (second line). Salivary 17β-estradiol did not differ significantly across naturally cycling women, women using oral contraceptives, and postmenopausal women. Salivary progesterone level was significantly larger in luteal than in follicular women ($P < 0.001$, two paired-samples t-test). According to the Shapiro-Wilk test and Kolmogorov-Smirnov test with Lilliefors correction, salivary 17β-estradiol as well as salivary progesterone concentrations followed a normal distribution in follicular women. Criteria for a normal distribution were satisfied in postmenopausal women if four outliers (> 7.0 pg/ml) were excluded, as well as for salivary progesterone levels in luteal women if four outliers (> 300 pg/ml) were removed. In luteal women and oral contraceptive users, distribution of salivary 17β-estradiol level was skewed. n.d. indicates not determined. ⋆$P < 0.001$ (two paired-samples t-test).

mentioned). The theoretical error accumulation due to multiple pairwise comparisons in our study was 0.19 at most. Forgetting ratio was calculated by dividing the number of list 1 items recalled by forget-cued subjects by the number of list 1 items recalled by remember-cued subjects. Enhancement ratio was calculated by dividing the number of list 2 items recalled by forget-cued subjects by the number of list 2 items recalled by remember-cued subjects. Because forgetting and enhancement ratios were calculated between participants, listing of recalled items was sorted by number of recalled list items. Thus, ratios were calculated between subjects showing similar performance in recall of list items. Associations between salivary sex hormone levels and number of recalled words in remember- and forget-cued individuals were evaluated using a Spearman correlation. Statistical analyses were conducted in SPSS for Windows, Version 23.

RESULTS

Salivary 17β-Estradiol and Progesterone

Mean and median values of salivary 17β-estradiol and progesterone in women are summarized in Table I. Salivary 17β-estradiol did not differ significantly across the groups (follicular women, luteal women, women using oral contraceptives, postmenopausal women). Salivary progesterone was significantly elevated in luteal compared with follicular women ($P < 0.001$).

List 1 Forgetting

Forget-cued young subjects showed list 1 forgetting as well as list 2 enhancement (Table II and Figure 2). Significant differences in recall of list 1 items between remember- and forget-cued subjects were observed in follicular and luteal women as well as in young men ($P < 0.005$). Interestingly, postmenopausal women did not differ between remember and forget conditions. Accuracy of recalled list 1 items across groups (young and postmenopausal women, young men) revealed significant group differences in remember-cued, but not forget-cued subjects. Compared with remember-cued postmenopausal women, remember-cued young women and men showed a significantly better recall of list 1 items ($P < 0.005$, Mann-Whitney U-test for independent samples). In addition, follicular as well as luteal women showed a superior performance in list 1 recall compared with men ($P < 0.005$). Further, women using oral contraceptives showed a trend toward impaired list 1 recall compared with women not using oral contraceptives ($P = 0.067$, one-tailed Mann-Whitney U-test).

To compare list 1 forgetting across young participants, we analyzed the ratio of recalled list 1 items in forget-cued subjects to recalled list 1 items in remember-cued subjects (forgetting ratio). A nonparametric test revealed significant group differences ($P = 0.044$). Pairwise comparisons between men and follicular women, luteal women, and women using oral contraceptives showed significant differences ($P < 0.03$). Pairwise comparisons between follicular women, luteal women, and women using oral contraceptives did not reveal significant differences in their forgetting ratio. Thus, young men were more sensitive to a forget cue than young women.

List 1 item recall and salivary 17β-estradiol levels did not correlate in remember-cued follicular and luteal women. However, remember-cued postmenopausal women showed a correlation between list 1 item recall and salivary 17β-estradiol levels. When list 1 items were recalled first, the direction was negative ($r = -0.648$, $P < 0.05$, $N = 14$). When list 1 items were recalled last, the direction of the association was positive ($r = +0.470$, $P < 0.05$, $N = 14$). Forget-cued follicular, luteal, and postmenopausal women did not show a correlation between salivary 17β-estradiol and number of recalled list 1 items. Neither follicular nor luteal women exhibited a correlation between progesterone and number of recalled list 1 items.

List 2 Enhancement

Forget-cued subjects recalled more list 2 items than did remember-cued subjects (Table II, Figure 3). Forget list 1 cue improved list 2 recall in young men ($P < 0.005$) as well as in follicular women and postmenopausal women ($P < 0.05$). Compared with remember-cued follicular

TABLE II. Recall of List 1 and List 2 Items (in %)

List 1				
Cue	Remember		Forget	
List order	First	Last	First	Last
Follicular women	49.27 ± 16.07★‡ 45.80 (33.30–83.30) (*n* = 12)	33.32 ± 22.48 25.00 (8.30–75.00) (*n* = 12)	29.13 ± 16.48 29.15 (8.30–66.67) (*n* = 12)	29.14 ± 18.97 25.00 (0.00–58.30) (*n* = 12)
Luteal women	51.35 ± 17.34★‡ 58.30 (25.00–75.00) (*n* = 12)	31.91 ± 20.05 29.15 (0.00–66.67) (*n* = 12)	27.06 ± 12.87 25.00 (0.00–50.00) (*n* = 12)	19.42 ± 9.63 20.80 (8.30–33.30) (*n* = 12)
Oral contraceptive users	41.11 ± 20.28★‡ 33.33 (16.67–91.67) (*n* = 15)	30.00 ± 19.62 33.33 (0.00–66.67) (*n* = 15)	23.33 ± 12.6 16.66 (8.33–50.00) (*n* = 15)	22.22 ± 18.54 16.66 (0.00–58.33) (*n* = 15)
Postmenopausal women	16.01 ± 8.89 16.66 (0.00– 25.00) (*n* = 14)	16.61 ± 10.81 20.75 (0.00–33.30) (*n* = 14)	16.62 ± 17.87 16.66 (0.00–50.00) (*n* = 14)	7.71 ± 7.61 8.30 (0.00–25.00) (*n* = 14)
Young men	37.09 ± 13.62★† 33.30 (16.60–58.30) (*n* = 11)	24.96 ± 13.04 20.80 (8.30–50.00) (*n* = 10)	15.72 ± 18.83 8.30 (0.00–58.30) (*n* = 9)	22.71 ± 11.23 25.00 (0.00–41.60) (*n* = 11)

List 2				
Cue	Remember			Forget
List order	First	Last	First	Last
Follicular women	45.10 ± 21.17★† 41.60 (8.30–100.00) (*n* = 12)	38.17 ± 29.19 41.60 (0.00–83.30) (*n* = 12)	55.53 ± 18.23 50.00 (33.30–100.00) (*n* = 12)	33.30 ± 15.48 4.46 (8.30–58.30) (*n* = 12)
Luteal women	46.51 ± 28.09★ 50.00 (8.30–91.60) (*n* = 12)	35.38 ± 23.60 33.30 (8.30–75.00) (*n* = 12)	53.45 ± 22.33 50.00 (25.00–100.00) (*n* = 12)	38.16 ± 16.83 37.45 (8.30–66.67) (*n* = 12)
Oral contraceptive users	39.44 ± 19.02★ 41.67 (8.33–83.33) (*n* = 15)	32.77 ± 18.76 33.33 (0.00–75.00) (*n* = 15)	48.33 ± 16.43 50.00 (25.00–66.67) (*n* = 15)	28.89 ± 16.02 33.33 (0.00–66.67) (*n* = 15)
Postmenopausal women	12.46 ± 12.00† 8.30 (0.00–33.33) (*n* = 14)	13.05 ± 15.19 8.30 (0.00–50.00) (*n* = 14)	21.96 ± 10.12 25.00 (8.30–41.67) (*n* = 14)	21.37 ± 18.10 16.66 (0.00–66.67) (*n* = 14)
Young men	31.62 ± 21.46★† 25.00 (8.30–75.00) (*n* = 10)	40.09 ± 26.78 41.60 (0.00–83.00) (*n* = 11)	50.75 ± 14.18 50.00 (25.00–75.00) (*n* = 11)	38.87 ± 17.69 33.30 (8.30–66.67) (*n* = 9)

Note: Recalled items given as mean ± SD (first line) and median (minimum–maximum) (second line). Only the list recalled first (list 1 or list 2) was used for comparisons (see Fig. 1). Nonparametric tests were used to estimate differences across groups and cue condition. *n* indicates number of participants. ★$P < 0.005$ compared with postmenopausal women (differences across age groups); †$P < 0.05$ and ‡$P < 0.005$ compared with forget list 1 condition (differences between cue conditions).

women, luteal women, women using oral contraceptives, and young men, remember-cued postmenopausal women showed impaired list 2 item recall (Table II, Figure 3) ($P < 0.005$).

We compared list 2 enhancement across young participants by analyzing the ratio of recalled list 2 items in forget-cued subjects to recalled list 2 items in remember-cued subjects (enhancement ratio). Pairwise, two-tailed Mann-Whitney *U*-test between men vs. follicular women, luteal women, as well as oral contraceptive–using women, revealed significant differences ($P < 0.04$). Enhancement ratio did not differ when comparing follicular with luteal women, and oral contraceptive–using women with follicular and luteal women.

Spearman rank-order correlation did not reveal an association between salivary 17β-estradiol level and list 2 item recall in remember- as well as in forget-cued follicular women, luteal women, oral contraceptive–using women, and postmenopausal women. However, salivary progesterone correlated positively with recalled list 2 items in forget-cued follicular women (+0.647 and $P = 0.05$; $N = 10$).

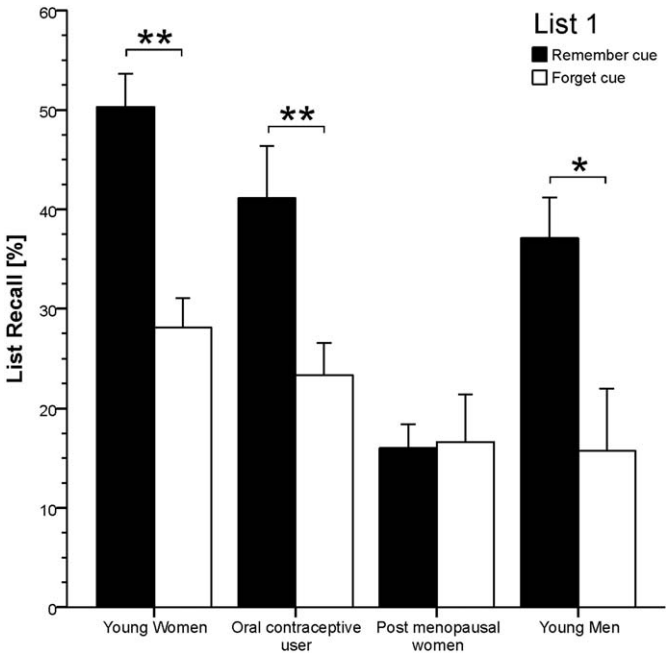

Fig. 2. List 1 forgetting. A forget cue leads to forgetting of previously encoded list 1 items in young subjects, but not in postmenopausal women. Because the item recall did not differ significantly between follicular and luteal women, we combined their results in a single group. Participants included young women having a natural menstrual cycle ($n = 24$), oral contraceptive users ($n = 15$), postmenopausal women ($n = 14$), and young men (remember cue: $n = 11$; forget cue: $n = 9$). $\star P < 0.05$; $\star\star P < 0.005$. Mean ± SEM.

DISCUSSION

List 1 forgetting as well as list 2 enhancement differs quantitatively across naturally cycling women, consumers of oral contraceptives, postmenopausal women, and young men. While a forget cue in young subjects is associated with list 1 forgetting as well as list 2 enhancement, a forget cue in postmenopausal women is associated with list 2 enhancement, but not with list 1 forgetting. List 1 forgetting is higher in forget-cued young men compared with forget-cued young women. Further, remember-cued naturally cycling women score higher in list 1 recall compared with women using oral contraceptives, postmenopausal women, and young men. In forget-cued naturally cycling women, progesterone but not 17β-estradiol correlates with list 2 recall. The most likely interpretation regarding age differences and hormonal correlation findings is that two independent mechanisms are responsible for list 1 forgetting and list 2 enhancement. Beyond the interpretation of the mechanism of directed forgetting, our study indicates that sex and sex hormones may affect these mechanisms differently.

17β-Estradiol, Progesterone, and Word Recall

Salivary 17β-estradiol concentrations do not reliably reflect the secretory profile of 17β-estradiol across the menstrual cycle. Whereas serum 17β-estradiol shows a preovulatory as well as luteal phase peak, salivary 17β-estradiol shows only a transient preovulatory increase, but not the expected increase in the luteal phase (Lu et al., 1999; Chatterton et al., 2005). Thus, some studies quantifying salivary 17β-estradiol do not identify significant differences across the menstrual cycle phase (e.g., Andreano and Cahill, 2010; Lobmaier et al., 2015; present study). In contrast to 17β-estradiol, salivary progesterone level reliably distinguishes between follicular and luteal women (e.g., Andreano and Cahill, 2010; present study).

Previous studies have associated menstrual cycle phase or sex hormone level with verbal performance. Some studies identified an increased verbal fluency or verbal memory in the midluteal phase, when 17β-estradiol and progesterone are elevated (Maki et al., 2002; Sherwin, 2012), and verbal working memory in the middle of the menstrual cycle, when 17β-estradiol is elevated (Rosenberg and Park, 2002). However, in a free verbal recall test, Mordecai and colleagues (2008) do not report on a difference in performance between the early follicular and midluteal phase. Similarly, the present study does not find differences in item recall between early follicular and luteal women. Menstrual cycle phase differences in verbal performance could relate to sex hormone levels. Whereas Maki and colleagues describe a positive correlation between serum estradiol and verbal fluency (Maki et al., 2002), Griksiene and Ruksenas do not find a correlation between verbal fluency scores and salivary 17β-estradiol (Griksiene and Ruksenas, 2011). Interestingly, even within a single study, estradiol correlates with some

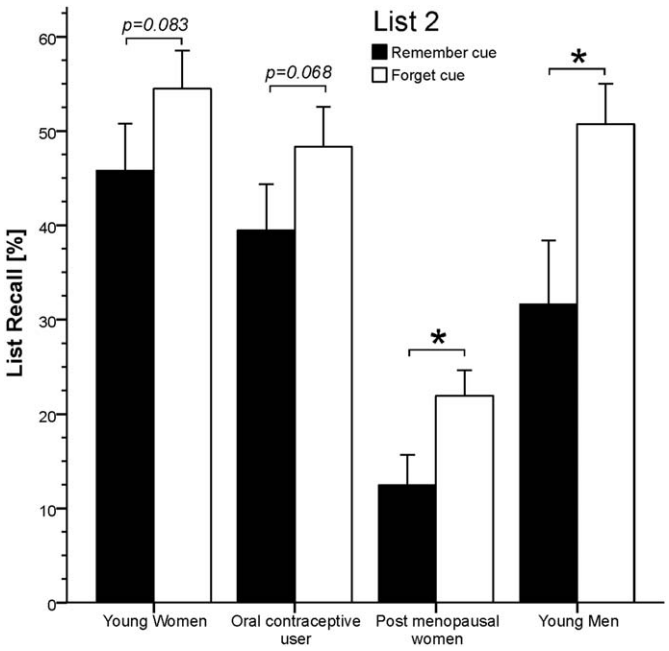

Fig. 3. List 2 enhancement. Forget list 1–cued subjects show improved recall of list 2 items. Participants included young women having a natural menstrual cycle ($n = 24$), oral contraceptive users ($n = 15$), postmenopausal women ($n = 14$), and young men (remember cue: $n = 10$; forget cue: $n = 11$). Mean ± SEM; $\star P < 0.05$.

verbal performances, like phonemic fluency (generating as many words as possible that begin with a certain letter), but not with others, like rhyme fluency (Maki et al., 2002). Furthermore, a previous study failed to find an association between verbal recall and serum 17β-estradiol (Craig et al., 2008). Comparably, we do not find a correlation between salivary 17β-estradiol and recalled items in young women. Interestingly, even when performance does not relate to menstrual cycle phases or sex hormone level, menstrual cycle phase–related or sex hormone–related differences have been found in brain activity. For example, Craig and colleagues (2008) did not find an association between 17β-estradiol and verbal recall, but they describe a positive correlation between estradiol and brain activation during successful verbal encoding. Comparably, despite small behavioral differences in number tasks between follicular and luteal women, we found strong differences in the corresponding brain activity using fMRI (Pletzer et al., 2011, 2013). In addition to 17β-estradiol, progesterone may affect word recall. Freemann and colleagues (1992) have shown that exogenous application of very high concentrations of progesterone impairs free recall of words, whereas in the present study, we identified a positive correlation between progesterone and word recall. However, the main difference between these studies is that in Freeman and colleagues' study women received a supraphysiological concentration of progesterone, whereas in the present study endogenous progesterone level was used. Comparably, Ertman and colleagues (2011) describe a positive correlation between emotional memory and endogenous progesterone regardless of the menstrual cycle phase. Taken together, these studies indicate that even when an association between sex hormone level and performance fails or is small, it still could be detected in the corresponding brain activity. Thus, women could maintain cognitive performance at a stable level across menstrual cycle by changing neural activity across the menstrual cycle.

As synthetic sex hormones used in oral contraceptives have a higher affinity to receptors as well as a longer half-life time compared with endogenous sex hormones (Coelingh Bennink, 2004; Stanczyk et al., 2013), they may take hormone-related changes in neural structure and behavior to the extreme. Performance in the list-method directed forgetting paradigm differs between oral contraceptive users and naturally cycling women. (1) Remember-cued oral contraceptive users recall fewer list 1 and list 2 items compared with remember-cued naturally cycling women. (2) Although statistically not significant, forget-cued oral contraceptive users recall fewer list 1 items than naturally cycling women. (3) Performance of women using oral contraceptives is between those of naturally cycling women and men. These findings may indicate a superiority of naturally cycling women in verbal performance in the list-method directed forgetting paradigm. Further, they suggest that the use of oral contraceptives induces in women male-like performance, such as impaired recall of words in the remember condition compared with naturally cycling women, but also maintenance of female-like performance, such as improved recall of words in the forget condition compared with men. Male-like performance in women using oral contraceptives has also been observed in an emotional memory paradigm. While men recall the gist of an emotional story, naturally cycling women recall details of the story (Cahill et al., 2004). Critically, women using oral contraceptives show an impairment in recall of details compared with naturally cycling women (Nielsen et al., 2011). Recently, we described a number-bisection task in which women using oral contraceptives show a similar performance to that of naturally cycling women, but male-like brain activity as demonstrated using fMRI (Pletzer et al., 2014). Is the similarity in performance and brain activity between women using oral contraceptives and young men related to activation of androgen receptors? In favor of activation of androgen-related effects, we observed in a previous study different effects of androgenic and anti-androgenic progestins on brain structure and behavior. Oral contraceptives containing androgenic progestins are associated with smaller bilateral middle and superior frontal gyri, whereas anti-androgenic progestins are associated with an increased volume in some temporal areas compared with naturally cycling women (Pletzer et al., 2015). Further, women using oral contraceptives containing anti-androgenic progestins show a lower error rate in face recognition compared with women having a natural menstrual cycle (Pletzer et al., 2015). However, chronic 17β-estradiol treatment in ovariectomized rats impairs working memory in a prefrontal cortex–dependent task (Wang et al., 2009; Neese et al., 2010). Thus, whether the consequences of synthetic hormones in women using oral contraceptives are due to chronically elevated ethinylestradiol or activation of androgen receptors due to androgenic progestins is not resolved yet.

The reduction in verbal performance along with a decrease in estrogen in natural menopause women as well as in reproductive-age women with surgically induced menopause is commonly seen (Sherwin, 2005; Yaffe et al., 2007; Maki, 2015). Interestingly, women who received estrogen after surgery maintained performance in short- and long-term verbal memory (Sherwin, 2005). Further, in older women, endogenous estradiol is positively correlated with word recall (Drake et al., 2000; Wolf and Kirschbaum, 2002). Comparably, we determined that, in remember-cued postmenopausal women, 17β-estradiol correlates with number of recalled items. However, the direction of the association depends on list order of recall. When list 1 items are recalled first, 17β-estradiol correlates negatively with performance, but when list 1 items are recalled last, 17β-estradiol correlates positively with performance. These data strongly suggest that changes in the hormonal milieu along the menopausal transition are related to verbal performance and that 17β-estradiol is among the most critical hormones related to word recall. Further, impairment in verbal memory may become visible only if 17β-estradiol is permanently below the physiological 17β-estradiol range of reproductive-age women.

List 1 Forgetting in Forget-Cued Subjects Declines with Age

The classical finding in list-method directed forgetting experiments is that forget-cued subjects recall more list 2 items (list 2 enhancement) and fewer list 1 items (list 1 forgetting) compared with remember-cued subjects (see Bäuml et al., 2010). However, forget-cued older subjects show a decline in list 1 forgetting but maintain the expected list 2 enhancement (Aslan et al., 2013; present study). Because the study by Aslan and colleagues does not differentiate between elder women and men, the reduction in list 1 forgetting reported in the present study is presumably not due to sex but to aging. The inhibition-deficit account theory relates poorer memory performance in older adults—specifically, retrieval of information from working memory—with malfunction of inhibitory mechanisms (Hasher and Zacks, 1988). These authors suggest that inhibitory mechanisms limit access of irrelevant information to working memory. Further, Gazzaley and colleagues (2005) show that age-related decline in working memory is related to deficits in suppression of irrelevant information, but not in enhancement of relevant information. While in Gazzaley and colleagues' study the participants knew *before* the task which items are relevant or irrelevant, in the present study participants received the forget cue *after* presentation of list 1 and had to mark list 1 items as irrelevant in forget-cue conditions. Despite these differences in the schedule of cueing of irrelevant information, visual working memory studies as well as list-method directed forgetting support the view that age-related impairment in working memory is associated with the suppression of irrelevant information. If inhibitory mechanisms are impaired, irrelevant information will enter the working memory and causes competition between relevant and irrelevant information at retrieval. The electrical signature of functional inhibition in cognitive processes is alpha oscillations ($\sim$ 10 Hz) (Klimesch, 2012). In young adults, Bäuml and colleagues (2008) found that forget list 1–cued participants showed during list 2 encoding an increase upper alpha power, which was associated with list 2 encoding, and a decrease in upper alpha coupling, which was associated with list 1 forgetting. EEG-studies on aging-related deficits in working memory identified neural correlates of impaired top-down processes. The electrophysiological differences between young and elderly subjects occur as soon as 100 msec (P1 amplitude, N1 latency) after stimulus onset (Gazzaley et al., 2008). Although Gazzaley and colleagues' study did not find an association between alpha oscillations and decline in working memory, the frequency-dependent segregation in lower and upper alpha may indicate that the functional significance of alpha oscillations is concealed in the alpha power identified in that study (Gazzaley et al., 2008).

By using a list-method directed forgetting paradigm, we found that forget-cued young subjects reveal list 1 forgetting as well as list 2 enhancement, whereas postmenopausal women show reduced list 1 forgetting but reveal list 2 enhancement. In forget-cued follicular women, progesterone correlates positively with recalled list 2 items. 17β-estradiol does not correlate with recalled list 1 or list 2 items in young women, but correlates with recalled list 1 items in remember-cued postmenopausal women. Our findings indicate that sex hormones do not globally modulate verbal memory or forgetting, but selectively affect cue-specific processing. Thus, progesterone may enhance the inhibitory mechanism in item–context binding in forget-cued young women.

ACKNOWLEDGMENTS

We thank Dr. Karin Oberascher for her expert technical assistance in hormone quantification.

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