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SHORT COMMUNICATION

Intentional updating in episodic memory: Low testosterone associates with enhanced memory updating

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Abstract

OBJECTIVES: Although there is consensus that sex hormones modulate memory, we have an incomplete understanding of their role in remembering and forgetting. Humans continuously update memory, forgetting old, out-of-date information and encoding new, more relevant information. Updating processes can be studied with the list method of directed forgetting.

METHODS: In the list method of directed forgetting task, subjects study two lists of items and, after study of list 1, are asked to either forget or remember the list for an upcoming memory test. Free testosterone level was quantified from saliva samples. Directed forgetting and saliva testosterone were evaluated in young men (aged between 18 and 28 years).

RESULTS: Following a forget cue, recall of list-1 items was reduced and recall of list-2 items was enhanced. However, only recall of list-2 items was associated with free testosterone level. Following a forget cue, participants with low testosterone levels showed higher recall of list-2 items than participants with high testosterone levels.

CONCLUSION: The selective association between testosterone level and list-2 recall is consistent with two-mechanism accounts of memory updating, where the forgetting effect is due to impaired retrieval and the enhancement effect to improved encoding. On the basis of this view, the present results indicate that low testosterone levels are associated with improved binding of the newly encoded memories to their context cue.

INTRODUCTION

Forgetting irrelevant out-of-date information – like a friend's old home address – and enhancing access to more relevant, newer information – like the friend's current home address – is the scaffold for the efficient use of our memory. In episodic memory, memory updating has been studied using the directed-forgetting paradigm (Bjork 1970; for reviews, see Bäuml, *et al.* 2010; MacLeod 1998; Sahakyan *et al.* 2013). In the list method of this task, subjects are cued to forget a previously learned item list and to learn a new list of items instead. Such cuing typically leads to impaired memory for the first list (list 1) and enhanced memory for the second (list 2), relative to control condition in which subjects are asked to keep both item lists in mind.

Although originally explained by a single mechanism, like inhibition or context change (e.g., Geiselman *et al.* 1983; Sahakyan & Kelley 2002), more recently the two effects of the forget cue in directed forgetting [DF] have been attributed to different mechanisms. Sahakyan and Delaney (2003), for instance, proposed that list-1 forgetting arises from impaired access to the list-1 context due to a mental context change between the study of lists, and list-2 enhancement from more elaborate encoding of list-2 items, due to a change in forget-cued participants' encoding strategy. Alternatively, Pastötter and Bäuml (2010) suggested that list-1 forgetting is due to inhibition-induced impaired access to the list-1 context, and list-2 enhancement arises from improved encoding of list-2 primacy items, as is reflected in the reset-of-encoding hypothesis. This hypothesis claims that encoding efficacy decreases with an increase of study material, i.e., decreases from list-1 encoding to list-2 encoding, but a forget cue can reset encoding efficacy, making the encoding of list-2 items comparable to the encoding of list-1 items. Despite some differences in detail, two-mechanism accounts agree on the view that list-1 forgetting reflects impaired retrieval of list-1 items and list-2 enhancement (partly) reflects improved encoding of list-2 items. By reporting a number of experimental dissociations between the two effects of the forget cue, the results of numerous studies are consistent with this two-factor account of updating in episodic memory (see Pastötter *et al.* 2014).

Although there is now considerable knowledge on the cognitive (Pastötter *et al.* 2012; Sahakyan & Delaney 2003) and the neurocognitive mechanisms (e.g., Bäuml *et al.* 2008; Hanslmayr *et al.* 2012) mediating memory updating in the DF task, not much is yet known about whether hormones modulate DF. Correlative observations as well as experiments indicate that testosterone or its metabolites are associated with memory performance in experimental animals and men. Testosterone decline and memory impairment occur in parallel during aging in men (Barrett-Connor *et al.* 1999, Moffat *et al.* 2002), androgen deprivation therapy in prostate cancer patients (Beer *et al.* 2006; Bussiere *et al.* 2005), and orchiectomy in rodents and non-human primates (for review see Janowsky 2006). In animal studies, testosterone substitution improves memory performance following orchiectomy (for review see Janowsky 2006). However, testosterone substitution revealed inconsistent results in elderly men. Depending on the study, testosterone substitution improves (Cherrier *et al.* 2002), impairs (Maki *et al.* 2007), or has no effect (Vaughan *et al.* 2007) on verbal memory performance. However, in young, healthy men improved performance is associated with low endogenous testosterone levels (Gouchie & Kimura 1991). Although forgetting is about equally important as remembering, to the best of our knowledge, there are no studies on the association between testosterone and forgetting in healthy young men.

Here we examined whether endogenous levels of free testosterone associated with individuals' memory updating as it is studied in DF. In particular, we investigated whether free testosterone levels are related to both aspects of the updating process, i.e., the forgetting of the irrelevant information and the enhancement of the relevant information, or are selectively related to just one of the two factors.

MATERIAL AND METHODS

Subjects

48 healthy male students at the University of Salzburg, all German native-speakers (Austrians or Germans) ranging in age between 18 and 28 years participated in the study. Participants reported no history of neurological or psychiatric disease. Three men were excluded from the study, due to anti-allergic medication, antihypertensive drugs, or insulin use, and three subjects were excluded because of deliberately neglecting the instructions of the supervisor. Participants were asked to avoid smoking or drinking coffee at least one hour before the experiment. Each subject gave informed consent to participate in the present study. The University of Salzburg committee for ethics approved the study.

Directed forgetting task (DF) Task

The DF task contains an encoding phase, in which two item lists – list-1 and list-2 – were presented, an intermediate distractor phase, and a test phase for list-1 and list-2 items (Geiselman *et al.* 1983; Pastötter & Bäuml 2010; Sahakyan & Kelley 2002). Each of the two lists consisted of twelve unrelated German nouns. List-1 contained: Polster (pillow), Kurve (turn), Kette (chain), Richter (judge), Fleck (spot), Lunge (lung), Wald (forrest), Honig (honey), Stall (barn), Drucker (printer), Stube (parlor) , Rand (edge). List-2 contained: Treppe (stairs), Wunde (lesion), Sessel (chair), Brunnen (well), Radio (radio), Hebel (lever), Rüstung (armament), Zaun (fence), Brett (plank), Spalte (cleft), Tonne (barrel), Knall (bang). The words were taken from the prior study by Pastötter *et al.* (2012).

Before beginning of the experiment, participants were asked to memorize list-1 and list-2 items and were prepared that after presentation of list-1 items there is a 50% chance that they are instructed to forget list-1 items. During the encoding phase, each noun was displayed on a computer screen for two seconds. Nouns were presented on a computer screen without an interval between the nouns. After presentation of all list-1 items, participants were either cued to keep these items in mind for an upcoming memory test or to forget list-1 items. Each subject was asked to memorize the subsequent list-2 items. The intermediate distractor phase consisted of counting backwards aloud in steps of three starting from a three-digit number for 30 seconds. In the final test phase, participants were asked to write down list-1 items, regardless of the cue provided after presentation of list 1, and list-2 items on separate sheets of paper. In remember cue as well as forget cue conditions, 50% of the participants started recall with list-1 items, and 50% started recall with list-2 items. The test phase for each list lasted 60 seconds. Participants were tested individually. To minimize variations due to circadian rhythm, all experiments were performed in the afternoon (1 p.m. – 5 p.m.). All experiments were performed in February and March, 2014, and were supervised by the same person (first author).

Salivary testosterone assay

Saliva samples were collected in polypropylene centrifuge tubes about three minutes before and after the experiment. Samples were kept frozen at –20 °C in a freezer until quantification of free testosterone. Before quantification, samples were centrifuged. Saliva testosterone was measured using Demeditec Salivary Testosterone ELISA kit according to the recommendations of the provider (Demeditec Diagnostics GmbH). Free testosterone levels reported are the average of duplicate samples run in the same assay.

Statistical analysis

Correct recall of list-1 and list-2 items, respectively, were used to estimate recall performance. For statistical analysis of recall performance we used a between subject univariate analysis of variance (ANOVA) with factors for cuing condition (remember vs. forget) and task (order of list recall). Post-hoc analysis was performed with t-tests. Statistical analysis was performed by using PASW Statistics 18 (SPSS).

RESULTS

Free testosterone levels

Basal free testosterone level before the task was (in pg/mL) between 15 and 114 with a mean ± SD of 76±23 and the free testosterone level after the task was (in pg/mL) between 13 and 124 with a mean ± SD 71±27 (N=42). The difference in free testosterone level before and after the directed forgetting paradigm was statistically not significant.

Recall performance

When list 1 was recalled first, the forget cue impaired recall of list-1 items relative to the remember condition (15% vs. 37%; $t_{(18)}$=–2.953, p=0.009). In addition, when list 2 was recalled first, the forget cue enhanced recall of list-2 items relative to the remember condition (51% vs. 32%; $t_{(19)}$=2.427, p=0.025). In line with prior DF work, the effect of the forget cue on list-2 recall was absent when list-2 was recalled last (e.g., Pastötter & Bäuml 2010; Sahakyan & Delaney 2003). The effect of the forget cue on list-1 was alsoabsent when list-1 was recalled last.

Relation between free testosterone level and recall performance

Concentrations of saliva testosterone were significantly correlated with list-2 recall in the forget condition, with testosterone being negatively linked to number of correctly recalled list-2 items (Table 1). No significant correlation arose in the remember condition. Correlations in the two cuing conditions differed significantly from each other (Z=–2.11, p=0.035, r=0.405). In both the remember condition and the forget condition, concentrations of saliva testosterone and list-1 recall were unrelated, and the two (non-significant) correlations did not differ significantly from each other (Z=0.59, p=0.555, r=0.031). For tested-last lists, no correlations between testosterone level and recall performance arose.

DISCUSSION

Consistent with prior DF studies, presentation of the forget cue after list-1 study reduced recall of the (irrelevant) list-1 items and enhanced recall of the (relevant) list-2 items (e.g., Geiselman *et al.* 1983). More important, individuals' testosterone level was related to performance in this task. In the forget conditions, high recall of list-2 items is associated with low testosterone levels, whereas low recall of list-2 items is associated with high testosterone levels. No relation arose between testosterone levels and recall of list-1 items. On the basis of the view that, in DF, list-1 forgetting reflects the action of a retrieval mechanism and list-2 enhancement the action of an encoding mechanism (e.g., Pastötter &

Tab. 1. Correlations between free testosterone and recall.

CONDITION	RECALL FIRST	
	LIST-1	LIST-2
Forget cue	$r_{(7)}$=-0.242; p=0.530	$r_{(9)}$=-0.656; p=0.028
Remember cue	$r_{(9)}$=-0.514; p=0.106	$r_{(8)}$=0.297; p=0.404

List recall correlated with saliva free testosterone collected before the experiment. Using testosterone collected after the experiment revealed similar results.

Bäuml 2010; Sahakyan & Delaney 2003), the present results indicate that, in memory updating, testosterone may influence the encoding of the newly acquired (relevant) information but has no major influence on the reduced accessibility of the old (irrelevant) information. The findings thus confirm the proposal that, in memory updating, the forgetting of the irrelevant information and the enhancement of the relevant information is mediated by different mechanisms (see also Pastötter *et al.* 2012).

Testosterone modulates connectivity between distant brain areas. In humans, testosterone administration reduces functional connectivity between amygdala and orbitofrontal cortex (van Wingen *et al.* 2010), but activates connectivity between amygdala and brainstem areas (Hermans *et al.* 2008). Most interestingly, in resting EEG recordings, men having low endogenous testosterone show delta – beta coupling in the prefrontal cortex, whereas men having high endogenous testosterone do not show a significant delta – beta coupling (Miskovic & Schmidt 2009). In an fMRI study, an increased activity in the amygdala as well as an increased recall of neutral images is associated with a high endogenous testosterone level (Ackermann *et al.* 2012). At the cellular level, androgens modulate GABAergic receptor activity (Oberlander *et al.* 2012), the main component of physiological inhibition in the brain (Mann & Paulsen 2007). As our findings indicate that increasing endogenous testosterone levels are associated with binding of the newly encoded relevant items to their context (list) cue, endogenous testosterone level-dependent weakening of selective neural networks may represent a physiological mechanism in DF.

Studies on the correlation between verbal memory performance and endogenous testosterone level as well as with testosterone substitution in elderly men report either on improvement, impairment, or no effect in individuals with higher testosterone (Alexander *et al.* 1998; Barrett-Connor *et al.* 1999; Cherrier *et al.* 2002; Maki *et al.* 2007; Martin *et al.* 2007; Moffat *et al.* 2002). In one study, cognitive performance was compared between men receiving the progestin, levonorgestrel, to suppress testosterone release and men receiving levonorgestrel and testosterone (Cherrier *et al.* 2002). This study reported that a levonorgestrel-induced decrease in verbal memory in men is compensated by co-administration of testosterone (Cherrier *et al.* 2002). In contrast, another study does not find improvement in verbal memory when testosterone is supplemented in an induced hypogonadism model using the GnRH agonist, Depot-Lupron (Young *et al.* 2010). In young men (aged 18–27 years), testosterone does not correlate with verbal articulation (measuring time to say tongue twisters) and vocabulary (select the word most similar in meaning to the stimulus word among five alternatives) (Gouchie & Kimura 1991). Interestingly, young men with low endogenous testosterone level score better in spatial and mathematical tasks compared to men with higher testosterone levels (Gouchie & Kimura 1991). Moffat and Hampson describe a negative quadratic relation between salivary testosterone and spatial cognition (Moffat & Hampson 1996). Furthermore, Yonker and colleagues describe that independent of age (35 to 80 year old men), men with low level of testosterone score higher is spatial visualization tasks than men with higher level on testosterone (Yonker *et al.* 2006). Notably, in the present study, young male participants with low testosterone show improved recall of correct items compared to participants with higher testosterone levels. Whereas some studies report an improvement in cognitive tasks in individuals with low endogenous testosterone (Gouchie & Kimura 1991, Yonker *et al.* 2006) others report an improvement in individuals with high endogenous testosterone (Ackermann *et al.* 2012). Whether this difference is related either to activation of androgen receptors by testosterone or an activation of a testosterone metabolites remains to be evaluated.

In addition to androgen receptors, the brain contains aromatase, an enzyme metabolizing testosterone to estradiol (for review see Celec *et al.* 2015). Accordingly, correlative studies demonstrating an association between testosterone and behavior may actually show estradiol-dependent effects. A study by Cherrier and colleagues describes the consequences of testosterone application in absence or presence of an aromatase inhibitor to hypogonadal men on verbal memory (Cherrier *et al.* 2005). Interestingly, these authors describe that testosterone alone improves verbal memory scores, but co-applications of testosterone and aromatase inhibitor fail to improve memory. Further, men with mild cognitive impairments receiving estrogens show enhanced verbal memory in comparison to those not receiving estrogens (Sherwin *et al.* 2011). In line with these observation, a study on visual memory in healthy young men reports that estradiol levels, but not testosterone levels correlate positively with visual memory (Kampen & Sherwin 1996).

In conclusion, the present results indicate a selective association with testosterone and updating processes in episodic memory. Further, similar to spectral coupling of resting brain oscillations, where low but not high testosterone is associated with delta – beta coupling (Miskovic & Schmidt 2009), memory improvement for the relevant new information, is associated with low endogenous testosterone. Thus, endogenous testosterone or one of its metabolites may at least partially modulate memory performance by coupling of distinct brain oscillations.

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Competing interests

All authors declare no conflicts of interest.

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