

Endogenous Estradiol and Testosterone Levels Are Associated with Cognitive Performance in Older Women and Men

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Relatively few studies have investigated the relationship between endogenous sex steroid levels and cognition in older people and the reported results have been inconsistent. A number of experimental hormone replacement studies have suggested that estrogen replacement in older women enhances cognition, especially verbal memory. In contrast, little research has been done focusing on men. In the current study the association between endogenous sex steroids (estradiol and testosterone) and cognition was investigated in 38 healthy older women (mean age 68 years) and 30 healthy older men (mean age 69 years). Five cognitive tests measuring verbal memory, spatial memory, verbal fluency, mental rotation, and susceptibility to interference were administered. Results revealed that in women higher estradiol levels as well as testosterone levels were associated with better verbal memory (paired associates and estradiol; $r = .38$, $P < 0.05$; paired associates and testosterone; $r = .33$, $P < 0.05$). Moreover estradiol, but not testosterone was associated with less susceptibility to interference (Stroop color word test; $r = -0.34$, $P < 0.05$). In men the only significant association was a negative correlation between testosterone and verbal fluency ($r = -0.38$, $P < 0.05$). The associations observed in this small study support the notion that estradiol is protecting verbal memory and possibly also frontal lobe mediated functions in older women. In contrast to the positive findings in women endogenous sex steroids do not appear to be closely linked to better cognition in older men. © 2002 Elsevier Science (USA)

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INTRODUCTION

Levels of the gonadal sex steroids estradiol and testosterone decrease with aging in women and men. Estradiol concentrations drop sharply in women after menopause, while in men a more gradual decline of free as well as total testosterone occurs (Sternbach, 1998). Basic neuroscience research has demonstrated multiple genomic and nongenomic estradiol effects in the central nervous system (CNS) in areas known to be important for cognitive performance (McEwen *et al.*, 1997; 1998; McEwen and Alves, 1999; Rubinow and Schmidt, 1996; Sternbach, 1998). Testosterone on the other hand can influence cognitive performance directly by acting on the androgen receptor, or after being converted to estradiol in the CNS (Rubinow and Schmidt, 1996; Sternbach, 1998).

Experimental human studies in young subjects and clinical observations suggest that gonadal steroids especially modify verbal and spatial skills where gender differences are apparent (Hampson, 1995; Kimura and Hampson, 1994). Epidemiological studies in postmenopausal women have observed that women on hormone replacement therapy (HRT) are often superior in neuropsychological test performance, even though the magnitude and the specificity of the results vary sometimes drastically between different studies (Hogervorst *et al.*, 2000; LeBlanc *et al.*, 2001; Yaffe *et al.*, 1998b). In addition HRT seems to reduce the risk for dementia in postmenopausal women, even though the findings are again inconsistent (Hogervorst *et al.*, 2000; LeBlanc *et al.*, 2001; Yaffe *et al.*, 1998b). Direct evidence for estradiol effects on brain structures relevant to human cognition has been derived from functional neuroimaging studies (Berman *et al.*, 1997; Maki and Resnick, 2000; Resnick *et al.*, 1998; Shaywitz *et al.*, 1999). Experimental placebo controlled studies testing

the effects of estradiol on cognitive performance reported a specific enhancement of verbal memory (Phillips and Sherwin, 1992; Sherwin and Tulandi, 1996; Wolf *et al.*, 1999) or a more global improvement (Duka *et al.*, 2000; Sherwin, 1988). However several other studies, which did not test verbal declarative memory failed to find beneficial effects (Ditkoff *et al.*, 1991; Janowsky *et al.*, 2000; Polo-Kantola *et al.*, 1998). Surprisingly few studies have investigated whether or not endogenous estradiol and testosterone levels are associated with cognitive performance in healthy older women not taking estrogens. Two studies observed no associations between endogenous estradiol levels and cognition (Polo-Kantola *et al.*, 1998; Yaffe *et al.*, 1998a); however, none of these studies included tests of verbal declarative memory. Studies investigating the potency of estradiol levels to predict cognitive decline resulted in mixed findings. One study observed no association between estradiol levels and cognitive performance assessed several years later (Yaffe *et al.*, 1998a), another study found that higher testosterone levels (but not higher estradiol levels) were associated with better cognition (Barrett-Connor and Goodman-Gruen, 1999), while a third study found that higher nonprotein bound estradiol levels were associated with a lower risk of cognitive decline (Yaffe *et al.*, 2000). In addition, two studies observed that more global measures of life-long estrogen exposure were associated with enhanced cognitive performance and a reduced risk of cognitive decline (Smith *et al.*, 1999; Yaffe *et al.*, 1999). Of special relevance for the current paper is a recent study in older women where the authors used a broad range of neuropsychological tests and measured several sex steroids (Drake *et al.*, 2000). The authors reported that higher estradiol levels were associated with better verbal memory but poorer visual memory. Higher testosterone levels in this study were surprisingly associated with superior verbal fluency (Drake *et al.*, 2000).

Only few investigations tested the effects of testosterone on cognition in elderly men and again the findings have been inconsistent. Two replacement studies by Janowsky *et al.* observed beneficial effects on spatial cognition or visual working memory (Janowsky *et al.*, 1994, 2000). A third recent study observed beneficial effects of long term testosterone treatment on spatial as well as verbal memory, the latter effect being interpreted by the authors as resulting from the testosterone induced increase in estradiol levels (Cherrier *et al.*, 2001). A study from our laboratory found impaired verbal fluency after acute testosterone treatment, while no other beneficial effects on

memory or mental rotation skills could be detected (Wolf *et al.*, 2000). One epidemiological study observed that higher testosterone levels in older men were a predictor of better cognitive performance assessed several years later (Barrett-Connor *et al.*, 1999).

In order to further investigate the relationship between endogenous sex hormone concentrations and cognitive performance in older healthy subjects the present analysis was undertaken. It was of special interest whether there are gender differences in the observed hormone-cognition relationships. The current report therefore contains sex hormone as well as cognitive data from older women and men tested with the same cognitive tests (see below).

SUBJECTS AND METHODS

Baseline hormone and cognitive data from participants of two recent estradiol (women) and testosterone (men) replacement studies were analysed (Wolf *et al.*, 1999; 2000). Thirty-eight healthy elderly postmenopausal women (age: 68.0 ± 1.0 year (\pm SEM)) and 30 healthy elderly men (age: 69.0 ± 1.3) recruited by newspaper advertisements, participated in the study. All subjects were healthy and high functioning individuals who lived independently in the community. They underwent a comprehensive medical examination and subjects with psychiatric, neurological, endocrine, cardiovascular, other chronic diseases, or medicated with psychoactive drugs, sex steroids, or glucocorticoids were excluded from participation. The study was approved by the local ethics committee and all subjects gave written informed consent.

Participating women had reached menopause at a mean of 17.4 ± 1.3 years (\pm SEM) before entering the study (range: 7 to 40 years). None of the women were currently on hormone replacement therapy. Women and men did not differ in age or body mass index (BMI; women: 24.9 ± 0.5 ; men: 24.7 ± 0.4). Typical for an elderly German sample men had significantly more years of formal education (women: 8.7 ± 0.6 ; men: 12.0 ± 0.8).

Biochemical Analyses

Estradiol and total testosterone levels were measured from blood samples, taken after cognitive testing, using commercially available RIA's (estradiol: Biermann, Bad Nauheim, Germany; total testosterone: RIA, IBL, Hamburg, Germany). Free testosterone (RIA: Biermann, Bad Nauheim, Germany) was as-

sessed in men only. Intra- and interassay coefficient were below 10% for all assays. The sensitivity of the RIAs was as follows (estradiol: 8 pg/ml; total testosterone: 0.08 ng/ml; free testosterone: 0.15 pg/ml). According to our experience, the lower detection limits for these kits provided by the manufacturers are rather conservative; reliable measurements can also be achieved at lower steroid levels.

Cognitive Tests

Subjects participated in five cognitive tests assessing verbal as well as spatial memory, executive control, verbal fluency, and mental rotation. Testing was performed in the early afternoon (between 2:00 and 5:00 p.m.). The tests were selected based on previous findings in the literature showing effects of sex steroids on verbal and spatial skills and/or verbal and spatial memory. All tests were part of standardized German test batteries. The tests were presented in the order of their description.

Semantic memory (verbal fluency). Subjects had one minute to generate as many words as possible to a given first letter, thereafter a second letter was introduced with another one minute test period. The total number of produced words was used as test score (Horn, 1983).

Spatial memory (city map task). Subjects were asked to memorize (within 2 min) a route marked in a city map. Immediate as well as delayed recall (after the mental rotation task, approximately 10 min later) was assessed by letting the subject draw the learned route into an unmarked map. The number of correctly chosen roads was used as test score (Baeumler, 1974). In order to reduce the number of performed correlations a single test score was created by combining the immediate and delayed recall score (see (Craft *et al.*, 1999)).

Verbal memory (paired associates). Six word pairs of unrelated words were read to the subject (one word per second). Immediate as well as delayed recall (after the delayed spatial memory recall, approximately 10 min later) was tested by presenting the first word of each pair as a cue. If the subject could not recall the word, the whole pair was read to the subject again. In each recall condition every pair was tested twice (Oswald and Fleischmann, 1994). In order to reduce the number of performed correlations a single test score was created by combining the immediate and delayed recall score (see (Craft *et al.*, 1999)).

Color word test (Stroop). The tests employ three cards. The first card contains color words (printed in

black) which must be read as quickly as possible. The second card contains colored quadrants, which must be named as quickly as possible. The third card depicts color words, this time printed in a different color (e.g., the word 'RED' is printed in blue). The task of the subject is to name the color of the word, thereby repressing the impulse to read the word aloud. For each card the time needed to read or name the items was assessed and the difference between cards 3 and 2 was used as "interference score" (Oswald and Fleischmann, 1994; Stroop, 1935). Higher test scores reflect stronger interference and therefore poorer performance.

Mental rotation. Five copies of a specific letter or number were presented on a piece of paper. Each item was rotated to different degrees from the normal horizontal position, in addition one item in each line was flipped horizontally. This item had to be marked by the subject. The subject was given two minutes to complete as many items as possible (Horn, 1983).

Mood Assessment

An adjective checklist was used to assess elevated vs depressed mood. Test scores in this questionnaire vary between five and zero with five indicating maximum agreement with the "positive" end of the scale (Steyer *et al.*, 1994).

Statistics

Estradiol and testosterone levels were normally distributed in women and men according to Shapiro-Wilks' *W* test. All additional analyses were therefore performed with the raw hormone data and parametric tests. First, the association between sex steroids, age and body mass index (BMI) were analyzed using Pearson correlations. Thereafter the relationship between sex steroids and cognitive test performance was analyzed separately for men and women using Pearson correlations. As a next step age was controlled using partial correlations. As a final step age and years of education were controlled, again using partial correlations.

RESULTS

Sex Steroids

Four women had nondetectable estradiol levels. The estradiol variable used for the correlational analysis

TABLE 1a

Association between Cognitive Performance and Sex Steroid Concentrations in Elderly Women ($n = 38$)

| | Estradiol | Testosterone |
|-----------------|--------------|--------------|
| Verbal fluency | $r = .22$ | $r = .07$ |
| Verbal memory | $r = .38^*$ | $r = .33^*$ |
| Spatial memory | $r = .09$ | $r = .05$ |
| Stroop | $r = -.34^*$ | $r = -.22$ |
| Mental rotation | $r = -.01$ | $r = -.07$ |

* $p < 0.05$; Pearson's correlations.

was set to 0.9 pg/ml, which is half the distance between zero and the lowest estradiol level assessed with the assay. It should be noted that identical results as presented below were obtained if these four women were excluded from the entire analysis. Elderly women had significantly lower testosterone (women: 0.37 ± 0.03 (ng/ml); men: 3.6 ± 1.2 (ng/ml)) and estradiol (women: 12.1 ± 1.4 (pg/ml); men: 28.9 ± 2.4 (pg/ml)) levels than elderly men. Free testosterone was assessed in men only (13.3 ± 0.9 (pg/ml)). As expected, total and free testosterone were highly correlated ($r = 0.79$). Estradiol levels were significantly correlated with testosterone levels in both sexes (women: $r = 0.56$, $P < 0.05$; men: $r = .45$, $P < 0.05$). In women estradiol but not testosterone levels were positively correlated with BMI ($r = 0.36$, $P < 0.05$), but not with age ($r = -0.19$, $P = 0.25$). In contrast testosterone but not estradiol levels were negatively associated with age ($r = -0.40$, $P < 0.05$), while no association was apparent with BMI in men.

Cognitive and Mood Data

Elderly women and men did not differ in their performance in any of the five cognitive tasks (data not shown). They also did not differ on average in mood ratings; both groups rated their mood as good to high (mean: 4.3 out of a possible of 5 points). Age was significantly correlated with increased interference in the stroop test in men ($r = 0.66$), but not women ($r = 0.26$). In addition age was negatively associated with spatial memory in men ($r = -0.49$), and with verbal fluency in women ($r = -0.32$). None of the other possible age-performance associations were significant.

Association between Cognitive Performance and Sex Steroids

The associations between sex steroids and cognitive performance are presented in Table 1a for women and

TABLE 1b

Association between Cognitive Performance and Sex Steroid Concentrations in Elderly Men ($n = 30$)

| | Estradiol | Testosterone |
|-----------------|------------|--------------|
| Verbal fluency | $r = -.25$ | $r = -.38^*$ |
| Verbal memory | $r = -.24$ | $r = -.24$ |
| Spatial memory | $r = -.32$ | $r = .05$ |
| Stroop | $r = .18$ | $r = -.26$ |
| Mental rotation | $r = -.28$ | $r = .02$ |

* $p < 0.05$; Pearson's correlations.

Table 1b for men. Since the correlations with free versus total testosterone revealed almost identical results, it was decided only to present the data for total testosterone.

In women, higher estradiol as well as higher testosterone levels were positively associated with verbal memory (see Fig. 1). If immediate and delayed recall were analyzed separately it was detected that the associations were very similar (estradiol and immediate recall: $r = 0.38$; estradiol and delayed recall: $r = 0.35$; testosterone and immediate recall: $r = 0.36$; testosterone and delayed recall: $r = 0.28$). In addition to the association with verbal memory higher estradiol levels were also associated with better stroop performance (less induced interference). No significant association was observed with verbal fluency, spatial memory, or mental rotation.

If the correlations were controlled for age almost identical results were obtained (estradiol and verbal memory: $r = .36$, $P < 0.05$; testosterone and verbal

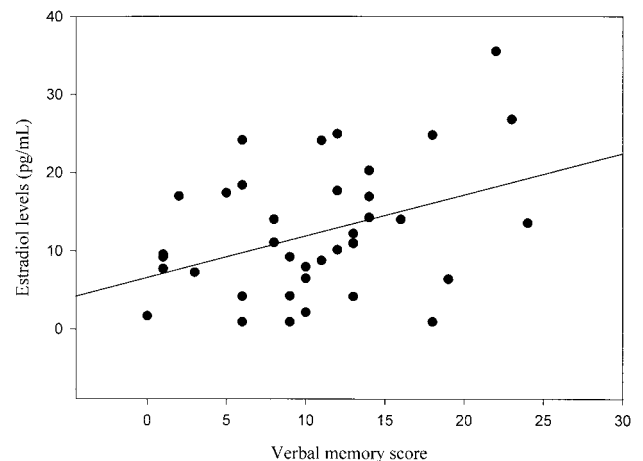


FIG. 1. Positive association between endogenous estradiol levels and verbal memory (paired associates) in older women ($n = 38$).

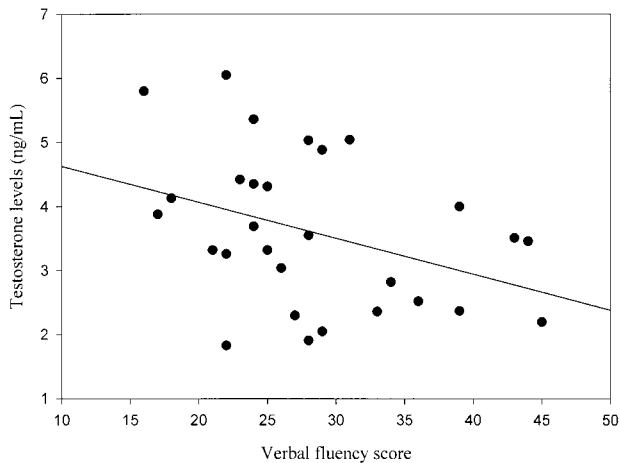


FIG. 2. Negative association between endogenous total testosterone levels and verbal fluency in older men ($n = 30$).

memory: $r = .33$, $P < 0.05$), except that the association between estradiol and the Stroop became a non significant trend ($r = -0.30$, $P = 0.07$). If the correlations were additionally controlled for years of formal education, then the association between estradiol and stroop was further reduced ($r = -0.26$, $P = 0.12$). However, the associations between estradiol as well as testosterone and verbal memory remained significant (estradiol: $r = 0.33$, $P = 0.05$; testosterone: $r = 0.33$, $P = 0.05$).

Since the detection limit of the estradiol RIA used in the study was 8 pg/ml, we performed an additional set of analyses including only those women, who had estradiol levels greater than 8 pg/ml ($n = 25$). The association between estradiol and verbal memory was almost identical and still significant ($r = 0.44$, $P < 0.05$), while the association between estradiol and stroop performance became non significant in this smaller sample.

In men no positive association between sex steroids and cognition could be detected (see Table 1b). Only higher testosterone levels were significantly negatively associated with verbal fluency (see Fig. 2). Similar results were obtained when free testosterone levels were used ($r = -0.34$, $P = 0.06$). If the correlations were controlled for age almost identical results were obtained. If the correlations were in addition also controlled for years of formal education, then the negative association between testosterone and verbal fluency became a non significant trend ($r = -0.35$, $P = 0.07$).

Association between Mood and Sex Steroids

No significant association between the two sex steroids and the mood measurement could be detected in either sex (correlation coefficients < 0.20).

DISCUSSION

The main finding of this analysis is that in healthy older women endogenous estradiol and testosterone levels were associated with better verbal memory performance. Moreover estradiol levels were also (but weaker) related to better performance in the Stroop test. Together with recent findings by other laboratories (Drake *et al.*, 2000; Yaffe *et al.*, 2000), the current results indicate that variations within the low range of estradiol levels observed in the postmenopausal period exert a modulatory effect on cognitive function. It has to be noted that the majority of estradiol levels observed in the post menopause is derived from extraglandular conversion of adrenal androgen precursors (Burger, 1996).

Our findings in women support a recently published study, where higher estradiol levels were also associated with better verbal memory performance (Drake *et al.*, 2000). In contrast to those previous findings by Drake *et al.* (2000), testosterone levels, which were highly correlated with estradiol levels, were also associated with better verbal memory in our study. The present study failed to find evidence for a negative association between estradiol and nonverbal or spatial memory or a positive association between testosterone and verbal fluency. Differences in the tests used to assess these cognitive functions as well as differences in mean age might explain these discrepancies. In addition, the small sample sizes, possibly leading to a lack of power, as well as the use of multiple comparisons, possibly leading to alpha error accumulation, must be considered. Moreover, this study like previous studies used only a single blood sample for the determination of estradiol levels. It has been reported that time of day has little effects on estradiol concentrations in postmenopausal women (Panico *et al.*, 1990), however there seems to be an influence of lifestyle variables (Cauley *et al.*, 1989) and a relatively low stability of the measurement over time (Cauley *et al.*, 1991).

A positive association between estradiol and Stroop performance (a measure of frontal lobe mediated inhibitory control) has not been reported previously. Frontal lobe mediated tasks are often not responsive to

estradiol treatment (Ditkoff *et al.*, 1991; Janowsky *et al.*, 2000; Polo-Kantola *et al.*, 1998); however, two recent replacement studies reported beneficial effects on frontal lobe mediated tasks in healthy older women (Duka *et al.*, 2000) and patients with Alzheimer's disease (Asthana *et al.*, 1999).

The present study does not provide any evidence for a beneficial effect of higher endogenous sex steroids in older men. While the older men had as expected higher testosterone and estradiol levels than the elderly women, no associations between these sex steroids and cognitive functions were observed. Our findings therefore do not support the notion that older men might benefit from higher endogenous estradiol levels as previously suggested (Carlson and Sherwin, 2000). However the hypothesis of Carlson and Sherwin was mostly based on findings in the digit span test, a test not used in the current study. The absence of correlations between sex steroids and cognitive performance in older men also seems to be in conflict with positive effects of testosterone replacement on spatial cognition and visual working memory (Janowsky *et al.*, 1994; Janowsky *et al.*, 2000) as well as verbal and spatial memory (Cherrier *et al.*, 2001). However, it is in line with a negative study investigating the effects of long-term testosterone replacement on several neuropsychological tests (Sih *et al.*, 1997).

Interesting relationships between the current analysis on endogenous sex steroid levels and cognitive performance and our two recent replacement studies (Wolf *et al.*, 1999; 2000) became apparent. In women, two weeks of transdermal estradiol replacement lead to enhanced verbal memory performance in those subjects showing a strong treatment induced estradiol increase (Wolf *et al.*, 1999). Similarly in the current analysis, a positive association between endogenous estradiol levels and verbal memory was observed. In addition, the present analysis observed a negative association between testosterone and verbal fluency and verbal fluency was indeed negatively affected by an acute high dose of testosterone in these subjects (Wolf *et al.*, 2000). The observed positive association between estradiol and verbal memory in women and the negative association between testosterone and verbal fluency in men could suggest that in older subjects sex steroid replacement modulates those cognitive test performances, where associations with the endogenous sex steroid levels are apparent at baseline. This hypothesis needs to be substantiated by future studies.

In sum, the present small study in healthy educated subjects provides further evidence for a protective role

of estrogen on verbal memory as suggested by Sherwin (Sherwin, 1997) and supported by recent prospective observational data (Maki *et al.*, 2001). The current results document that the variations observed within the low postmenopausal estradiol range are related to verbal memory functions. This finding argues against a "floor effect" in post menopause. The present observations, together with a recent report that higher endogenous unbound estradiol levels are associated with a decreased risk of future cognitive decline (Yaffe *et al.*, 2000), suggest that estradiol replacement in older women with low endogenous estradiol levels might be an especially promising venue for future intervention studies.

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