Sex Steroids Modify Working Memory

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Abstract

■ In the last ten years, numerous mechanisms by which sex steroids modify cortical function have been described. For example, estrogen replacement improves verbal memory in women, and animal studies have shown effects of estrogen on hippocampal synaptogenesis and function. Little is known about sex steroid effects on other aspects of memory, such as frontal lobe-mediated working memory. We examined the relationships between working memory and sex steroid concentrations and whether sex steroid supplementation would modify age-related loss of working memory in older men and women. Before hormone supplementation, working memory, tested with the Subject Ordered Pointing Test (SOP), was worse in older subjects than younger subjects, and there was no evidence of gender differences at either age. Testosterone supplementation improved working memory in older men, but a similar enhancement of working memory was not found in older women supplemented with estrogen. In men, testosterone and estrogen effects were reciprocal—with better working memory related to a higher testosterone to estrogen ratio. These results suggest that sex steroids can modulate working memory in men and can act as modulators of cognition throughout life. ■

A wealth of studies now describe the modifiability of cognition by sex steroids (estrogen and testosterone) in humans. However, the effects of sex steroids on cognition have not, in general, been examined in a cognitive neuroscience framework. That is, studies have not focussed on determining which component cognitive processes are those affected by sex steroids or the underlying neural systems and neurobiological bases for hormone effects. In this study, we examined the relationships between sex steroids and working memory in both younger and older subjects and discuss the findings in relation to the neural system and neurobiological mechanisms that may underlie the effects.

Age-related declines in both working and long-term memory are common and occur even in healthy people (Howieson, Holm, Kaye, Oken, & Howieson, 1993; Light, 1991; Salthouse, 1990; Craik & McDowd, 1987). Recently, behavioral studies have shown that sex steroids can modify memory in aging. Older women on postmenopausal estrogen replacement show improved verbal memory on story or word-list recall tasks (Kampen & Sherwin, 1994; Sherwin, 1988). Women on estrogen replacement show greater longevity (Henderson, Paganini-Hill, & Ross, 1991) and are at less risk for Alzheimer's Disease (Barrett-Connor & Kritz-Silverstein, 1993). Data from studies using animal models suggest that estrogen can modify synaptic number and efficacy in the hippocampus (Woolley & McEwen, 1992; Woolley & McEwen, 1993; Woolley, Weiland, McEwen, & Schartzkroin, 1997) and it is presumed this underlies the effects of estrogen on memory in women. The effects of sex steroids in men and on other forms of memory, such as frontal lobe-mediated working memory, have received much less attention.

Working memory is the ability to ''hold in mind'' and flexibly manipulate information over brief periods of time in order to make a response (Goldman-Rakic & Friedman, 1991; Baddeley, 1986). Damage to the prefrontal cortex (Brodmann's areas 46 and 9) in humans and nonhuman primates (Petrides, 1995) impairs working memory performance. Functional neuroimaging studies show prefrontal activation during working memory tasks (Courtney, Ungerleider, Keil, & Haxby, 1997; McCarthy et al., 1994; Cohen et al., 1993; Cohen et al., 1997; Petrides, Alivisatos, Meyer, & Evans, 1993). The prefrontal cortex is particularly vulnerable to atrophy with aging (Raz, Gunning, Head, Dupuis, & Acker, 1998; Raz et al., 1997; Cowell et al., 1994; Salat, Kaye, & Janowsky, 1999); and at least, in part, it is these age-related changes in prefrontal function which underlie the loss of working memory in older people (Boone, Miller, & Lesser,1993; Daigneault & Braun, 1993). In this study, we used the Subject Ordered Pointing Test (SOP; Petrides, 1994) to examine working memory. This task was chosen because its prefrontal-neural basis has been well described in human and animal lesion studies and

with functional neuroimaging (Petrides et al., 1993; Petrides, 1994).

The neurobiological mechanism(s) by which sex steroids could affect cognition is not well understood. Recently, a host of new biological mechanisms have been described by which either testosterone or estrogen could differentially influence the function of particular cortical systems and, thus, particular cognitive processes. Here, we report the results of a double-blind placebo-controlled study of the role of sex steroids in the control of working memory, and whether sex hormones can modify age-related declines in working memory.

RESULTS

Aging and Sex Steroid Concentrations

Aging was associated with the expected changes in sex steroid concentrations (Vermeulen, 1991; Korenman, 1982; Table 1). In postmenopausal women, estradiol levels were more than tenfold lower, and free testosterone concentrations were on average 50% lower than in young women. Free testosterone levels were approximately 50% lower in older than younger men, but estradiol levels were similar. Steroid levels were increased in the supplemented older subjects at the time of the second test session (Table 1). Estrogen treatment significantly increased estradiol concentrations in the older women such that their levels did not differ from those of younger women ($p > .10$). Testosterone treatment in the older men resulted in a significant increase in circulating testosterone, as well as estradiol (presumably as a result of aromatization of testosterone to estradiol). Testosterone and estradiol levels in the supplemented older men were higher than that in younger men ($t_{23} > 5.80, p < .001$).

Age Effects on Working Memory

Before treatment, older subjects made more errors on the SOP than younger subjects ($F(1,73) = 11.31$, $p = .001$; see Figure 1), a finding similar to the age-related decline in working memory reported by others (Daigneault & Braun, 1993). No sex differences in performance were found in either the young or elderly ($F(1,73) = .59$, $p = .45$), and the performance of men and women was similarly affected by age (sex-by-age interaction $F(1,73) = .10$, $p = .76$). Younger men and women both improved in performance between the two test sessions ($F(1,43) = 28.4$, $p < .001$) without evidence of sex differences in this practice effect (interaction between sex and session ($F(1,43) = 1.14$, $p = .29$). In contrast, older men and women without sex steroid supplementation showed no improvement in performance across the two test sessions.

Sex Steroid Effects on Working Memory

Sex steroid supplementation resulted in a significant enhancement in performance in older men but not older women ($F(3,27) = 3.37$, $p = .03$; post hoc $t_9 = 4.81, p = .001$; Figure 2). In fact, the testosterone-supplemented older men performed approximately as well in the second session as younger men in the first test session (8.4 vs. 7.8 errors, respectively).

Analyses of the relationship between serum hormone levels in the second test session and working memory performance show that testosterone is related to better, but estrogen worse, working memory in men. Multiple regression analysis revealed that SOP performance was positively associated with testosterone levels ($t = 2.56$, $p = .02$) and negatively associated with age ($t = -3.45$, $p < .01$) and estradiol

Table 1. Hormone Levels

	Estradiol (pg/ml)[a]		*Free testosterone (pg/ml)*	
	Session 1	*Session 2*[b]	*Session 1*	*Session 2*[b]
Older men placebo, $N = 9$	23.5 (14.1–36.4)	26.2 (13.4–53.7)	12.3 (8.1–18.0)	16.6 (10.3–40.4)
Older men testosterone, $N = 10$	29.2 (6.3–68.6)	75.3 (19.9–133.9)	12.2 (9.5–14.1)	45.2 (15.3–54.1)
Older women placebo, $N = 7$	7.3 (4.9–19.9)	7.2 (4.9–19.9)	.81 (.54–1.30)	.81 (.54–1.20)
Older women estrogen, $N = 6$	12.7 (4.9–41.9)	64.0 (13.8–128.8)	.70 (.65–.80)	.64 (.54–.66)
Younger men, $N = 18$	23.6 (10.0–37.5)	26.7 (9.5–50.5)	26.5 (15.7–43.4)	24.2 (12.5–34.2)
Younger women, $N = 29$	126.3 (38.6–248.9)	108.1 (23.6–260.9)	1.40 (.65–3.40)	1.54 (.65–3.60)

Younger subjects did not have hormone supplementation.
[a]Estradiol levels are unavailable for one male and one female younger subject Session 2 only due to lipemic sample.
[b]Post-supplementation; testosterone for the older men and estrogen for older women, or placebo.

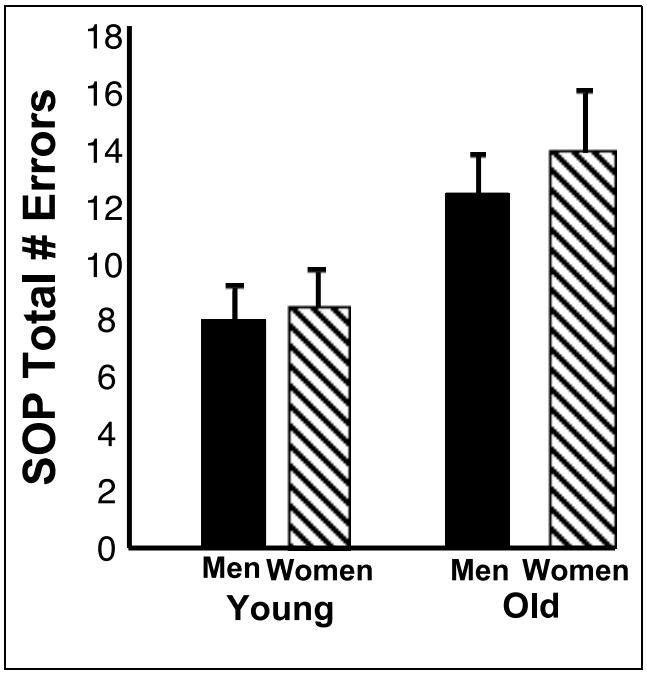

Figure 1. Performance (number of errors) on the SOP in men and women in Session 1, before hormone supplementation in the older subjects. Older subjects made more errors than younger subjects, suggesting an age-related decrement in performance; however, no sex differences in performance were found. Brackets show standard error of the mean.

levels ($t = -2.27$, $p = .03$) in men. Similar results were found when the data from older men was analyzed alone. The ratio of serum estradiol to testosterone was related to errors in SOP performance ($R = .61$, $p < .001$).

In older women, estrogen supplementation did not affect performance. However, the multiple regression analysis revealed that testosterone concentrations were negatively related to working memory performance in older women ($t = -2.30$, $p = .05$). When considered in all women, estradiol/testosterone ratio was positively related to working memory performance ($R = .31$, $p = .05$); however, when each group was considered individually, neither sex steroid was significantly related to performance in women (all $p > .15$).

The enhancement of performance in the supplemented older men was not due to awareness of their treatment, as the subjects did not accurately predict their assigned treatment group at the end of the study. In addition, the effects of testosterone supplementation in men was not due to a general enhancement of mood, as there were no significant changes on any subscale or the total score on the Profile of Mood States (POMS; $t < 1.80$, $p > .10$). In addition, there were no differences between the placebo- and testosterone-treated group in mood ratings from Session 1 to Session 2 ($t < 1.10$, $p > .10$).

DISCUSSION

Working memory is considered a critical, ''gateway'' cognitive function. The ability to maintain information in mind and flexibly manipulate or update it is a hallmark feature of most mental abilities. Thus, subtle modulation of working memory could affect a wide range of cognitive abilities. Our data suggest that sex steroids can modulate working memory in men throughout life. Testosterone supplementation enhanced working memory performance in older men and was positively related to working memory performance in younger men. Estrogen may inhibit working memory in men as shown by the negative relationship between working memory and estrogen in men in the multiple regression analysis. While younger subjects showed improvement in performance with repeated testing, older subjects did not. Testosterone supplementation in men resulted in an improvement in performance that was even larger than the practice effects found in younger subjects. From these data, we cannot be certain whether the improvements are due to better working memory within a session or savings across sessions (e.g., long-term memory). Inspection of the

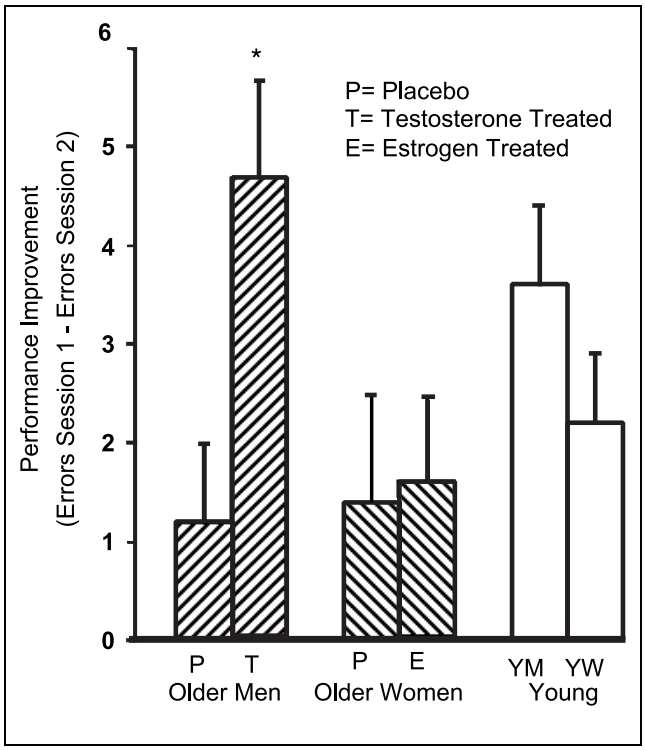

Figure 2. Change in performance after a month of placebo or hormone supplementation (older subjects; striped bars) or no treatment (younger subjects). Older men on testosterone supplementation showed an improvement in performance (fewer errors). Younger subjects showed the expected improvement on the task due to practice; whereas older subjects, without hormone supplementation or with estrogen supplementation, did not. Brackets show standard error of the mean.

data suggests similar slopes of the error curve from the 6-item to the 12-item card sets for both the placebo and treated groups, with the treated group having fewer errors than the placebo group on each card set. From this, it is not possible to disentangle a performance improvement due to savings across session from enhanced working memory within a session. On the other hand, if testosterone had a more general effect of preserving learned information across sessions, we might expect testosterone effects on all measures. This was not found in this study nor a previous double-blind placebo-controlled study of testosterone effects on cognition (Janowsky, Oviatt, & Orwoll, 1994). Therefore, we suspect the improvement in performance in this study is working memory specific. We do not know if there is a critical or threshold level of steroid concentration for these effects.

The effects of estrogen and testosterone on working memory in women is less clear. Older women on estrogen supplementation did not show an improvement in performance, although the supplementation did not raise estrogen levels as high as testosterone levels were raised in the men. Thus, it is not known whether even greater supplementation would result in improved working memory in older women. In general, it appeared that estrogen and testosterone have opposite effects in women than men; however, the effects were much weaker and should likely be considered tentative.

Working memory is mediated, in part, by the prefrontal cortex; thus, our results suggest that testosterone can modify the function of the prefrontal cortex in men. The neurobiological mechanism for this is not known. Sex steroids have two established functions in the central nervous system: participation in brain organization during neural development, and activation of sexual behavior at maturity (McEwen, 1991a, b; Phoenix, Goy, Gerall, & Young, 1959). The traditionally described mechanism for sex steroid action is that they bind to specific intracellular genomic receptors and influence transcription of proteins (for review, see Brown, 1994). For example, the hypothalamus is rich in estrogen and androgen receptors and these hormones influence sexual behavior throughout life. Androgens can modify the development of the prefrontal cortex in rats and monkeys (Kolb & Stewart, 1995; Bachevalier & Hagger, 1991; Goldman & Brown, 1975), but our data suggest that testosterone continues to play a modulatory role in the function of the prefrontal cortex, particularly working memory, throughout life. Mechanisms for androgen effects in adulthood in cortex include effects via genomic receptors distributed throughout cortex (Simerly, 1993). It is also possible that the effects described are not mediated through androgen receptors but through the aromatization of testosterone to estrogen and then a subsequent effect via estrogen receptors and/or on synaptic morphology or function. For instance, estrogen affects one class of serotonin receptors in frontal cortex in the rat (Sumner & Fink, 1995). Of note, however, is that testosterone receptors upregulate with androgen exposure but estrogen receptors downregulate with estrogen exposure. Thus, even with aromatization, testosterone and estrogen may have opposite effects. In addition, there is a significant decline in nuclear estrogen receptors (estrogen receptor α) in prefrontal cortex in adulthood as opposed to during development (McEwen, 1991a, b; Michael, Rees, & Bonsall, 1989) making it less likely that aromatized testosterone is working via estrogen receptors in prefrontal cortex. Thus, there are multiple mechanisms by which sex steroids could differentially affect men and women.

One other possibility is that the effects of testosterone on working memory described here could be due to actions on the striatal dopamine system with secondary effects on prefrontal function (van Hartesveldt & Joyce, 1986; Goldman & Nauta, 1977). Estradiol modulates dopamine-mediated striatal sensorimotor function despite the fact that there are few or no estrogen receptors in the striatum (Becker & Beer, 1986; Becker, Snyder, Miller, Westgate, & Jenuwine, 1987). If testosterone acts via aromatization to estrogen then it can act through the modulation of calcium channels at the neural membrane in striatum to increase dopamine (Mermelstein, Becker, & Surmeier, 1996). We recently showed that estrogen can modify sequential movement in women and this is likely due to estrogen's effect on dopamine in basal ganglia (Jennings, Janowsky, & Orwoll 1998).

Estrogen replacement in older women apparently causes a specific enhancement of long-term verbal memory (Kampen & Sherwin, 1994; Sherwin, 1988), and several studies using animal models suggest these mnemonic effects result from estrogen-induced changes in both the number and function of synapses in the hippocampus and temporal cortex (Woolley et al., 1997). To date, the kinds of estrogen-induced changes in long-term memory, or medial temporal lobe synaptic organization, have not been reported to occur with testosterone, and our data suggest that estrogen does not have the same effects on memory functions of the prefrontal cortex as it does on hippocampally mediated memory.

It is clear that sex steroids modulate cognition in adulthood (Hampson & Kimura, 1988; Hampson & Kimura, 1992). Previous reports have focused on aspects of cognition in which there are sex differences in performance. For instance, men tend to be advantaged on tasks that require mental rotation (for review, see Halpern, 1986) and performance on mental rotation tasks varies across the menstrual cycle in young women (Hampson, 1990). However, there is no reason to presume that the effects of sex steroids are necessarily limited to tasks tapping cognitive domains for which there are sex differences. The data we report here is on a task for which sex differences in performance have not been identified, and men and women performed simi-

larly, regardless of age. Nevertheless, our finding of relationships between sex steroid levels and working memory and the improved performance in older men in response to testosterone administration indicate that gonadal steroids can modulate working memory. The complex interactions between sexual dimorphisms in brain systems and circulating sex steroids require further evaluation.

Aging has profound effects on cognition with particular effects on working memory. To our knowledge, this is the first study to demonstrate that these effects can be modified by sex steroids in men. Additional data are needed to better understand the effects of testosterone administration on cognition, as well as on a variety of other functional correlates of aging. It is premature to suggest testosterone as a potential cognitive enhancer for older men. The positive and negative effects of chronic testosterone on a variety of other organ systems require further study.

In sum, these data, and the recent findings of both genomically mediated and neuromodulatory mechanisms for hormone action, suggest that sex steroids may affect multiple neural systems and, thus, have the potential to modify many cognitive processes throughout life. Furthermore, sex steroids may act on aspects of cognition, and brain systems, that are not obviously sexually dimorphic. Therefore, sex steroid replacement or supplementation in the aged may have pleiotropic effects on cognition. We expect that sex steroid replacement will have different effects in men and women and could either enhance or decrease selected aspects of cognition, depending on the neurobiological mechanism underlying the cognitive effect.

METHODS

Subjects

Eighteen younger men, nineteen older men, thirty younger women, and thirteen older postmenopausal women participated in the study (Table 2). Subjects were recruited via advertisements in a university newsletter, a senior adult newsletter, and radio and newspaper advertisements. Health questionnaires (Cornell Medical Index, 1974) and laboratory testing (multichemistry battery, complete blood count) were used to exclude volunteers with conditions known to affect cognitive, neurological or gonadal function. In older men, measures of serum prostate-specific antigen (PSA) and a manual prostate examination were normal. Older women had a normal breast and gynecological exam within the past year, and younger women had normal menstrual function (normal hormone levels and menstrual cycle 25–35 days in length). Serum levels of estradiol and free testosterone were within sex and age-specific normal ranges in all subjects. Older and younger subjects had similar levels of education and performance on the vocabulary subtest of the WAIS-R (Wechsler, 1981) as an index of intellectual functioning ($p > .10$; Table 1). The relationship between sex steroids and performance on a variety of other cognitive measures in the younger subjects has been reported elsewhere (Janowsky, Chavez, Zamboni, & Orwoll, 1998; Jennings et al., 1998). Participants were aware that this was a study of the role that sex steroids play on cognition, although they were not aware of specific hypotheses regarding the effects of hormones on the cognitive measures studied. Each subject received compensation of $10/hr for his or her participation in the study.

The study was approved by the Institutional Review Board of Oregon Health Sciences University. All subjects gave written informed consent for the study.

Procedure

In older subjects, working memory performance was tested before and after sex steroid supplementation. Using a double blind procedure, half of the older subjects were randomly assigned to receive either hormone supplementation (.625 mg/day conjugated estrogen taken orally for older women, and 150 mg testosterone enanthate/week (Tenover, 1992) by intramuscular injection for older men) or placebo for 1 month following the first test of memory performance. The second test of memory occurred within 2 days of the last testosterone injection or in the last week of estrogen supplementation. In young subjects, memory was tested twice approximately 1 month apart (with no hormone supplementation). In younger women, tests

Table 2. Subject Characteristics—Means; Ranges in Parentheses

	Older men placebo N = 9	*Older men testosterone N = 10*	*Older women placebo N = 7*	*Older women estrogen N = 6*	*Younger men*[a] *N = 18*	*Younger women*[a] *N = 29*
Age	67.4 (64–71)	67.5 (61–75)	69.1 (61–74)	69.0 (65–73)	28.5 (23–34)	30.0 (25–34)
Education	15.3 (11–18)	16.6 (10–25)	13.9 (12–19)	16.0 (12–21)	16.0 (14–19)	16.4 (12–24)
WAIS-R vocabulary	55.7 (36.0–64.0)	55.7 (39.0–68.0)	56.6 (50.0–64.0)	54.0 (36.0–64.0)	58.2 (43.0–64.0)	56.8 (42.0–66.0)

[a]Younger subjects did not have hormone supplementation.

were scheduled in the midluteal phase of the menstrual cycle (6–10 days before menses). All test sessions were in the morning. Serum was obtained immediately before both test sessions to determine sex steroid levels (estradiol and free testosterone). Serum sex steroid levels were analyzed by the Clinical Research Center Laboratory at Oregon Health Science University by radioimmunoassay (Diagnostic Products, Los Angeles, CA). All samples from each subject were analyzed in the same assay. The interassay mean coefficients of variation were 8.0% for estradiol assays, and 11.0% for free testosterone assays.

Stimuli and procedures for the working memory task (SOP) were performed as in a previous report (Petrides & Milner, 1982). Briefly, the subjects were presented with stacks of cards, (6, 8, 10, or 12 cards/set). Each card showed a regular array of abstract drawings, but the drawings were in a different spatial arrangement on each card (Figure 3). The subject was to touch one drawing on each card in any order, but not touch the same drawing on subsequent cards in the set. Subjects erred when they touched a drawing that had been touched on a previous card in the set. Therefore, the subject had to remember previous drawings touched while planning a future response. Subjects repeated each 6, 8, 10, and 12 card set three times. The total number of errors across all card sets was the measure of interest. The examiner explained the task, then showed the subjects on two consecutive practice cards what would be the correct responses. Subjects were instructed to do the task at their own pace, and to try to not go too quickly or too slowly.

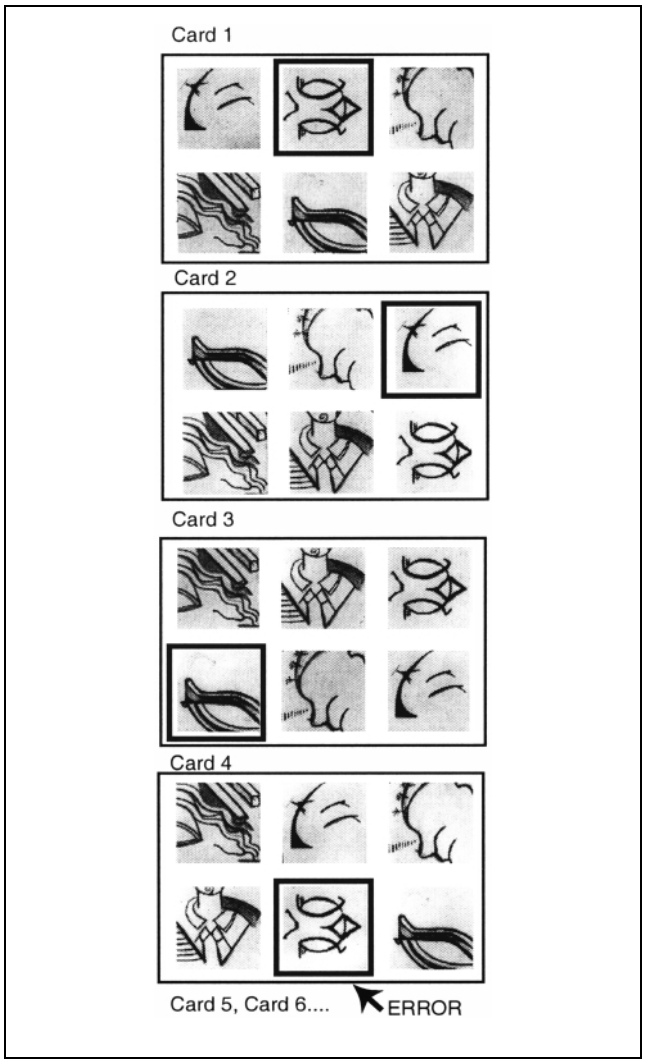

Figure 3. Example stimuli from the SOP working memory task. Darkly outlined figures are examples of possible responses. Choices for cards 1–3 are correct responses. Repeating a previously chosen figure is an error (Card 4).

In order to insure that cognitive changes were not due to nonspecific effects of hormone administration on mood, the POMS (McNair, Lorr, & Droppleman, 1971) scale was administered in each session. The standard manner of administration and scoring was used. The scale asked the subject to rate how they were feeling in the last week and responses were categorized into six subscales (tension-anxiety, depression, anger, vigor, fatigue, and confusion). In addition, subjects in the placebo and hormone groups were asked to assess whether they thought they were on hormone or placebo using a five-point Likert scale (surely on hormone, maybe on hormone, no idea, maybe on placebo, surely on placebo).

Statistical Analysis

Performance (total errors) for young and old men and women in each session was assessed with factorial repeated measures analysis of variance (ANOVA) with session as the repeated measure. A one-way ANOVA on the difference in number of errors (Session 1–Session 2) with post hoc Tukey test was used to assess which groups showed a significant change in performance from the first to second session. The relationships between sex steroids and performance were assessed with Pearson *R* correlations and with multiple regression using age, estradiol and free testosterone as factors in the model. Significance levels were calculated with two-tailed tests.

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