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Endogenous estrogen is not associated with cognitive performance before, during, or after menopause

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Abstract

Objective: In a population-based sample of women (45, 50, or 55 years old), behavioral data and blood serum were collected concurrently, enabling us (1) to investigate cognitive differences among premenopausal, perimenopausal, and postmenopausal groups of women and (2) to evaluate the relationship between blood estrogen levels and cognitive performance.

Design: Groups of premenopausal (n = 129), perimenopausal (n = 58), and postmenopausal (n = 55) women were tested on tasks assessing episodic and semantic memory, verbal fluency, visuospatial performance, and face recognition. Blood serum was collected concurrently for analyses of estrogen levels.

Results: With inclusion of controls for age and education, results showed that there were no differences in cognitive performance among premenopausal, perimenopausal, and postmenopausal groups of women. In addition, there were no associations between blood estrogen levels and cognitive performance.

Conclusions: These results do not support the hypothesis that estrogen or menopausal status affects cognitive performance in middle-aged women.

Key Words: Memory – Estrogen – Hormones – Menopause – Aging – Cognition.

In the search for biological factors influencing cognition, estrogen has been proposed as a likely candidate. Indeed, there are plausible mechanisms to support the neurobiological role of estrogen in cognition.[1,2] Although the evidence supporting an influence of estrogen on cognition is compelling, the behavioral findings are less convincing.

One line of research has focused on the influence of estrogen on cognition in premenopausal women, with investigation of cognitive performance in relation to the normal fluctuations in endogenous estrogen levels associated with the menstrual cycle. A number of studies have shown that cognitive performance varies as a function of menstrual cycle phase.[3-7] These studies typically have suggested that estrogen has an inhibitory influence on the right hemisphere, resulting in decreased performance on visuospatial tasks. In contrast, estrogen is thought to have a facilitating effect on tasks at which women typically excel, such as articulation, manual speed, and coordination. As a result, women perform at a higher level on these tasks in the midluteal phase of the menstrual cycle. However, these effects are not always found.[8-10]

A second line of research has focused on the effect of hormone therapy (HT) on cognitive functions. Results from observational epidemiological and cohort investigations, as well as from clinical trials, have largely demonstrated beneficial effects of HT treatment. For example, Gleason et al[11] (see also LeBlanc et al[12]) found that 18 of 26 studies reported beneficial effects and 7 studies reported no effects, whereas investigators for the Women's Health Initiative have reported harmful effects of HT on cognition.[13] A difference in the compounds used, with estradiol resulting in positive outcomes and conjugated equine estrogens having unreliable effects, is one way of explaining the discrepancy in results. However, there are numerous other reasons for inconsistencies in results, including background differences between the groups of users and nonusers, in the cognitive tasks assessed, and lack of assessment of circulating estrogen levels in the participating women, thereby indicating a lack of control of compliance.

A third line of research has focused on the relation between endogenous levels of estrogen and cognition in menopausal women, with some studies failing to find an association[14-16] and others reporting a positive association.[17,18] The lack of association between estrogen and cognition in some of these

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studies could be a result of methodological problems surrounding the timing of blood sampling. For example, serum was collected for hormonal analysis either 4 to 5 years,[14] 5 months,[18] or 2 years[16] before cognitive testing was performed.

Because endogenous estrogen levels drop at menopause, the brain is deprived of the trophic effects of estrogen, thereby presenting an opportunity to study the effects of estrogen on brain and behavior. Previous studies examining the potential cognitive changes associated with menopause in a cross-sectional design showed that the menopausal transition was accompanied by cognitive decline; however, when controls for age and education were added, these effects disappeared.[19] Longitudinal investigations have replicated the results and failed to find the expected negative effects of the menopausal transition on cognitive abilities,[20] with the exception of verbal fluency.[21] However, as in most studies investigating the potential effects of estrogen, actual blood hormone values were not assessed.

Taken together, the findings in the existent literature make it difficult to draw any conclusions about the potential effects of estrogen on cognition at present. Part of the confusion is due to the vast differences among studies in design, cognitive abilities assessed, age, education, and health status of the participants, as well as methodological problems surrounding the studies. Thus, additional well-controlled studies, with blood hormone sampling concurrent with cognitive testing, and participants drawn from the general population are needed.

In a population-based sample of women (45, 50, or 55 years old), behavioral data and blood serum were collected concurrently, enabling us (1) to investigate potential cognitive differences among premenopausal, perimenopausal, and postmenopausal groups of women and (2) to evaluate the relationship between blood serum estrogen levels and cognitive performance. If estrogen has a positive effect on cognition, we would expect women with substantially higher levels of estrogen to perform at a superior level than with women with lower levels of estrogen, taking potential differences in age and education into account.

METHODS

Participants

Participants in the present study were community-dwelling women aged 45, 50, and 55 years taken from the population-based Betula study on memory, health, and aging.[22,23] The Betula study is based on a longitudinal sequential design using 5-year retest intervals, with participants belonging to one of four samples: S1, S2, S3, or S4. Data were recorded during the third wave of data collection between 1998 and 2000. The Regional Ethical Review Board in Umeå, Sweden, approved the study. Persons with a severe visual or auditory handicap, mental retardation, or dementia and persons whose native language was not Swedish were excluded from the sample. All women who gave written consent to participate completed a medical examination, blood sampling, and a health interview. Participants completed questionnaires on social and economic issues and critical life events and had an extensive examination of cognitive functions lasting 1.5 to 2 hours. For the majority of the participants, the health examination and cognitive testing were performed on the same day. Blood sampling was done in conjunction with the cognitive testing.

Women were asked to complete a questionnaire on topics of pregnancy, menopausal status, and hysterectomy, and to give the approximate dates for any of these events they had experienced. Several questions required responses on use of exogenous hormones, including dates of use and name of the HT used. Women were placed in the premenopausal group if they stated that they had not yet reached the transitional period or menopause. Women were placed in the perimenopausal group if they stated that they were in the transitional period. The group of postmenopausal women consisted of participants who claimed to have passed menopause naturally. In addition, women who had passed menopause as a result of hysterectomy with bilateral oophorectomy (n = 13) and women with bilateral oophorectomy (n = 2) were placed in the postmenopausal group. All women claiming to be HT users were excluded from the analyses. There were 129 premenopausal, 58 perimenopausal, and 55 postmenopausal women included in the current study.

Cognitive tasks

Participants were tested during two sessions taking place on the same day, each lasting between 1.5 and 2 hours. The present analyses were based on 11 measures of episodic memory, 1 semantic memory task, 1 verbal fluency task, 1 visuospatial task, and 1 face recognition task. The scores were *z*-transformed to allow for comparison. In addition, the 11 measures of episodic memory (stemming from 4 tasks) were *z*-transformed and averaged to provide a composite score reflecting episodic memory performance. Detailed descriptions of the cognitive tasks can be found elsewhere.[22,24]

Episodic memory

Free recall, cued recall, and recognition of a subject-performed task and a verbal task were assessed. In these tasks, participants were presented with two lists of 16 verb-noun sentences, each denoting a simple action (eg, lift the book). For the subject-performed task, participants were requested to enact each sentence using the specified object. The verbal task list was studied without enactment. Participants were asked to freely recall the sentences. The nouns of the sentences were dividable into semantic categories (eg, fruits or musical instruments). Cued recall was assessed in two different ways: one condition with the semantic category names serving as cues and one condition in which participants completed an incomplete sentences (ie, "Lift the ___"). For recognition, participants were presented with nouns from each list of sentences, randomly interspersed with distractor nouns, and were asked

to make yes/no recognition judgments. Correctly recognized minus incorrectly recognized nouns constituted the score.

To study word recall under conditions of focused and divided attention, four word lists, each comprising 12 unrelated nouns, were read aloud. The concurrent task was to sort a deck of playing cards into one red and one black pile. Card sorting was performed during both the study and the test, during the study only, or during the test only. In the fourth condition, no card sorting was performed during either the study or the test. The last episodic measure, memory of activities, was administered at the end of the testing session. In this task, participants were asked to incidentally recall all the tasks they had performed during the test session.

Semantic memory

A vocabulary task was used to assess semantic memory. The task was to choose a synonym for the target word among five alternatives.

Verbal fluency

A composite score was determined on the basis of two fluency measures. In one task, participants were asked to generate words starting with the letter "A." In another task, they were asked to generate five-letter words starting with "M." For each task, 1 minute was given to generate as many words as possible.

Visuospatial abilities

To assess visuospatial abilities, the Block Design task from the Wechsler Adult Intelligence Scale–Revised[25] was used. Scoring was based on standardized procedures.

Face recognition

At the encoding step, 16 faces were presented. The presentation time was 8 seconds for each picture. At the recognition step, 32 faces in total (16 old and 16 new) were presented, and the participants were asked to give a yes/no recognition judgment for each face. The score was correctly recognized minus incorrectly recognized faces.

Hormone measures

After serum was obtained, it was frozen and stored at −80°C. A solid-phase fluoroimmunoassay (AutoDELFIA Estradiol assay, Wallac Oy, Turku, Finland) was used. The intra- and interassay coefficients of variations are 3.6% and 4.0%, respectively, and the assay has a sensitivity of less than 10.6 pmol/L. Analyses were performed in the Clinical Chemistry Laboratory at Karolinska Hospital in Stockholm, Sweden. A more detailed description of the hormone analyses can be found elsewhere.[26]

Statistical analysis

The statistical analyses were done in six steps. First, analyses of variance (ANOVAs) were computed to assess demographic differences among the three groups (ie, premenopausal, perimenopausal, and postmenopausal). Second, the effect of age on cognitive performance was analyzed in separate ANOVAs. Third, a multivariate analysis of covariance (MANCOVA) was computed to investigate the three groups' cognitive ability. Altogether 241 participants were included in the MANCOVA. One premenopausal woman was excluded from this analysis because of missing data. Age and years of education were used as covariates. Measures of cognitive abilities were examined as a function of menopausal group in the univariate *F* tests in the MANCOVA. Contrast analyses were computed to investigate differences between any two groups of women. In the fourth step, 19 women were removed because their estradiol hormone value was atypical (premenopausal, n = 10; perimenopausal, n = 1; postmenopausal, n = 8),[27] and the analyses were repeated. Next,

TABLE 1. *Descriptive statistics*

	Premenopausal	Perimenopausal	Postmenopausal	P^a
n	129	58	55	
Age, y	46.6 (2.6)	51.6 (3.1)	53.8 (2.5)	<0.01
Education, y	14.4 (2.9)	13.2 (3.7)	12.0 (3.7)	<0.01
Stress[b]	2.6 (2.4)	1.9 (1.7)	1.9 (1.6)	0.03
Depression scale[c]	13.3 (4.1)	13.6 (4.1)	14.1 (5.0)	0.59
Feeling healthy, %[d]	74.4	75.9	72.7	0.93
BMI, kg/m^2	25.5 (3.8)	25.9 (3.5)	27.1 (4.4)	0.04
Smoking, %	16.3	24.1	18.2	0.35
Alcohol, %				
Beer (l/mo)	1.2 (1.4)	0.8 (1.3)	0.5 (0.8)	<0.01
Wine (cL/mo)	101.0 (88.5)	91.7 (91.6)	116.0 (157.8)	0.49
Hard liquor (cL/mo)	5.3 (8.7)	6.2 (11.0)	5.2 (14.5)	0.84
Medications, n	0.19 (0.76)	0.07 (0.32)	0.20 (0.65)	0.46
Menopause symptoms[e]	0.2 (0.7)	1.4 (1.0)	0.0 (0.0)	<0.01
Estradiol, pmol/L	355.9 (324.9)	162.9 (178.9)	89.5 (93.1)	<0.01

Data are mean (SD). cL, centiliters.
[a]Significant ($P < 0.05$) difference between groups.
[b]Stress score,[24] where 0 = no stress at all and 10 = feeling stressed all the time.
[c]Depression scale score[25] ranged from 0 to 60, with a larger number indicating a higher frequency of reported depressive symptoms.
[d]Feeling healthy, percentage answering "yes" when asked "Do you feel healthy?".
[e]Menopause symptoms indicate mean number of symptoms reported.

partial correlations were computed in the full sample to further investigate the association between hormones and each of the dependent cognitive measures. Age and years of education were used as covariates. Finally, the above analyses were repeated after splitting the groups by age. No covariates were entered in these analyses.

RESULTS

Demographic characteristics

First, ANOVAs were computed to examine potential differences among the groups of women (ie, premenopausal, perimenopausal, and postmenopausal) in age, education, stress level,[28] depressive symptoms,[29] feeling healthy, body mass index, smoking, beer consumption, wine consumption, hard liquor consumption, number of medications affecting cognitive ability, menopausal symptoms, and estradiol. There were significant differences among the groups in age, education, body mass index, alcohol consumption, and estradiol level. The postmenopausal group had the lowest levels of estrogen, the fewest years of education, and the lowest alcohol consumption (beer drinking). See Table 1 for means, SDs, and *P* values.

Cognitive performance

Second, separate ANOVAs indicated that there were significant effects of age on episodic memory ($P < 0.01$), semantic memory ($P = 0.02$), verbal fluency ($P = 0.01$), and visuospatial ability ($P < 0.01$). In line with what was expected from earlier research,[30] the youngest age group performed at the highest level and the oldest age group at the lowest level. The effect of age on face recognition performance was nonsignificant ($P = 0.68$). Another factor well known to affect cognitive performance is years of education.[31] Third, because there were educational differences among the groups of premenopausal, perimenopausal, and postmenopausal women, age and education were entered as covariates in the MANCOVA, conducted to examine the effect of menopausal status on cognitive performance (episodic memory, semantic memory, verbal fluency, visuospatial ability, and face recognition). The MANCOVA revealed that there was no effect of menopausal status on overall cognitive performance ($P = 0.35$). However, both age ($P < 0.05$) and education ($P < 0.001$) affected overall cognitive performance.

Fourth, to evaluate the effect of menopause on each of the cognitive variables, the univariate *F* tests from the MANCOVA were examined. These analyses were statistically nonsignificant: episodic memory ($P = 0.83$), semantic memory ($P = 0.21$), verbal fluency ($P = 0.14$), visuospatial ability ($P = 0.38$), and face recognition ($P = 0.43$). Post hoc contrast analyses showed that there were no significant differences between any two groups. Estimated means and SEs are presented in Table 2.

To avoid missing potential differences among the three groups, women were removed from a second set of analyses if their estradiol values were atypical for the expected group (ranges based on Greenspan and Strewler[27]). In the premenopausal group, participants were removed if their estradiol levels were below 73 pmol/L (n = 10). One woman was excluded from the perimenopausal group because she had an out-of range value (ie, 1,040 pmol/L). In the postmenopausal group, eight individuals were excluded because they had an estradiol value greater than 110 pmol/L. The above analyses were repeated on the reduced sample. However, the same pattern of results was obtained.

Fifth, partial correlations were computed in the full sample to specifically examine the associations between estrogen levels and cognitive performance. Again, age and education were covaried. These associations were nonsignificant: episodic memory, $r = 0.019$ ($P = 0.77$); semantic memory, $r = -0.012$ ($P = 0.86$); verbal fluency, $r = 0.015$ ($P = 0.81$); visuospatial performance, $r = 0.014$ ($P = 0.83$); and face recognition, $r = 0.013$ ($P = 0.84$).

Finally, to control for potential cohort effects, ANOVAs were computed within each age group (ie, 45, 50, and 55 years) as a function of menopausal status, with each of the cognitive measures as dependent variables (Table 3). No covariates were used. A comparison of the cognitive performances among the 45-year-old premenopausal (n = 92), perimenopausal (n = 5), and postmenopausal (n = 2) women indicated that there were no differences among the groups in episodic memory ($P = 0.76$), semantic memory ($P = 0.39$), verbal fluency ($P = 0.22$), visuospatial performance ($P = 0.59$), and face recognition ($P = 0.85$). A similar pattern of data was found for the 50-year-old premenopausal (n = 33), perimenopausal (n = 30), and postmenopausal (n = 9) women: episodic memory ($P = 0.18$), semantic memory ($P = 0.93$), verbal fluency ($P = 0.10$), visuospatial performance ($P = 0.96$), and face recognition ($P = 0.52$). There were no differences among the groups of 55-year-old premenopausal (n = 3), perimenopausal (n = 23), and postmenopausal (n = 44) women: episodic memory ($P = 0.52$), semantic memory ($P = 0.38$), verbal fluency ($P = 0.25$), visuospatial performance

TABLE 2. *Estimated measures of cognitive performance as a function of menopause status, controlling for age and years of education*

	Premenopausal (n = 128)	Perimenopausal (n = 58)	Postmenopausal (n = 55)	*P*
Episodic memory	0.002 (0.06)	−0.023 (0.075)	0.040 (0.092)	0.83
Semantic memory	−0.062 (0.097)	0.200 (0.122)	−0.025 (0.149)	0.21
Verbal fluency	−0.064 (0.101)	0.221 (0.126)	−0.054 (0.154)	0.14
Visuospatial ability	−0.082 (0.107)	0.170 (0.134)	0.025 (0.163)	0.38
Face recognition	−0.049 (0.112)	0.160 (0.140)	−0.038 (0.172)	0.43

Data are standardized mean (SE).

TABLE 3. *Measures of cognitive performance by group and age*

	Premenopausal	Perimenopausal	Postmenopausal	r^a
45 year olds, n	92	5	2	
Estrogen level	341.6 (289.9)	155.5 (111.4)	412.0 (299.8)[b]	
Episodic memory	−0.010 (0.627)	0.195 (0.176)	−0.033 (0.540)	−0.046
Semantic memory	−0.038 (1.025)	0.481 (0.385)	0.540 (0.000)	−0.058
Verbal fluency	−0.018 (0.113)	0.083 (0.371)	0.640 (0.510)	0.163
Visuospatial task	−0.024 (0.999)	0.173 (1.160)	0.653 (0.771)	0.056
Face recognition	−0.016 (1.023)	0.178 (0.696)	0.274 (0.681)	0.106
50 year olds, n	33	30	9	
Estrogen level	416.2 (415.0)	212.7 (220.9)	105.4 (78.18)	
Episodic memory	0.058 (0.090)	−0.009 (0.459)	0.264 (0.638)	0.035
Semantic memory	−0.044 (1.169)	0.023 (0.844)	0.089 (0.873)	−0.035
Verbal fluency	0.080 (0.477)	0.588 (0.588)	−0.351 (0.320)	0.103
Visuospatial task	−0.018 (1.049)	−0.006 (1.037)	0.089 (0.745)	−0.067
Face recognition	−0.136 (1.096)	0.153 (0.866)	0.005 (1.077)	−0.111
55 year olds, n	3	23	44	
Estrogen level	111.7 (92.5)	99.6 (93.4)	71.7 (50.8)	
Episodic memory	0.262 (0.294)	−0.063 (0.476)	0.015 (0.499)	0.003
Semantic memory	0.148 (1.155)	0.226 (0.874)	−0.128 (1.052)	0.202
Verbal fluency	0.052 (0.212)	0.146 (0.569)	−0.080 (0.495)	0.129
Visuospatial task	−0.852 (0.770)	0.327 (1.006)	−0.113 (0.989)	0.145
Face recognition	0.834 (0.236)	0.099 (1.004)	−0.108 (1.010)	−0.051

Data are standardized mean (SE).
[a]Correlation coefficients between estrogen level and measures of cognitive performance.
[b]Based on values from two women, one with an unusually high estrogen value.

($P = 0.07$), and face recognition ($P = 0.25$). More important, correlations within each age group did not reveal significant associations between estrogen level and any of the cognitive measures. Means, SEs, and correlation coefficients are presented in Table 3.

DISCUSSION

The main purpose of the current study was to examine potential cognitive differences among premenopausal, perimenopausal, and postmenopausal groups of women and to evaluate the relationship between serum blood estrogen levels and cognitive performance in these groups. To not miss potential effects of estrogen levels on cognitive performance, we conducted a number of statistical analyses. Our results were straightforward; there were no differences among the three groups of women in episodic and semantic memory, verbal fluency, visuospatial ability, or face recognition performance. In addition, we found no evidence of a relationship between serum blood estrogen levels and cognitive performance. The implication of these findings will be discussed.

Few studies have investigated cognitive performance before, during, and after menopause, and none have had access to actual serum blood levels of estrogen.[19-21] Our results are in line with those of previous cross-sectional studies on menopausal status and cognition, indicating that the transition into menopause is not accompanied by cognitive decline when controls for age and education are included.[19] Similarly, the results from two longitudinal studies[20,21] indicated that menopausal status was unrelated to cognitive decline.[21] Although there was some uncertainty about the participating women's estradiol levels in these studies, it is clear that the existent literature indicates no or little effect of menopausal status on cognition in and around menopause.

A large number of published studies indicate that estrogen plays an important role in cognition.[3,12,32-34] Yet our data suggest that the substantial difference in estrogen levels in and around menopause does not affect cognitive performance significantly. To explain the discrepancies in results, we could hypothesize that the long-term deprivation of estrogen, rather than the short-term fluctuations before, during, and after menopause, may influence cognitive performance. If this hypothesis is correct, effects from the endogenous decline in estrogen may not become evident until years later.[35] In support of such an interpretation are the longitudinal studies[36] and randomized trials[37] indicating that HT may have a positive effect on cognition when treatment is started at a relatively early age, which suggests that cognitive performance is maintained if estrogen levels remain constant. However, once estrogen levels have dropped and have remained low for a longer time period, HT has no or possibly even a negative effect on cognitive performance in older women.[38,39] Longitudinal studies investigating the long-term outcomes of the menopausal transition with concurrent measures of blood hormone levels and cognition are therefore warranted.

In general, it is methodologically difficult to conclude that a factor has no effect on an outcome, and we acknowledge that there may be weak associations in the present study that were not detected because of limited statistical power. To avoid missing potentially small, but reliable, effects, we used a number of statistical analyses. For example, we stratified the groups by age, thereby eliminating the confounding factors of age and education on our results, and the pattern of results remained the same. However, it should be noted that a consequence of the stratification procedure was small sample sizes, which decreased the statistical power to detect differences among the groups. Nevertheless, the group

comparisons, the associations between cognitive performance and estrogen levels, and the analyses stratified on age all indicated that the transition from premenopause to perimenopause is not associated with cognitive decline.

Several strengths of the study increase our confidence in the findings. For example, we assessed blood serum estrogen levels, allowing us to examine the direct association between estrogen levels and cognitive performance. In addition, participants were tested on a wide variety of cognitive tasks, making it less likely that reliable effects of menopause on cognition were missed. Nonetheless, some limitations of the study need to be addressed. The classification of women as premenopausal, perimenopausal, or postmenopausal was based on self-reports. Such a procedure may be unreliable. However, the assessment of blood serum estrogen levels enabled us to validate self-reported menopausal status and to remove individuals with atypical estrogen values from parts of the statistical analyses. The same pattern of results was obtained. Furthermore, we used a cross-sectional study design in which we excluded HT users, thereby possibly excluding those with the most severe menopausal symptoms and/or memory complaints, which could result in an overestimation of the postmenopausal women's memory performance. However, because the same pattern of results was obtained for all measures of cognition, such a selection bias is not likely to have occurred. Finally, a cross-sectional design can detect only between-group differences; hence, changes within individuals over time can be missed. Thus, we acknowledge that further longitudinal studies examining potential cognitive changes across the menopausal transition are warranted.

CONCLUSIONS

The current study, based on cross-sectional data, suggests that there is no effect of menopausal status on cognitive performance once the confounding effect of age is taken into account. In support of this finding is the lack of association between cognitive performance and blood serum estrogen levels. Although our results and those of previous studies indicate that the severe drop of estrogen around menopause has no effect on cognitive performance, longitudinal research with concurrent assessment of hormone levels would be valuable to further investigate the relationship between estrogen and cognitive decline in relation to menopause.

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