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ORIGINAL ARTICLE

Cognitive performance in healthy women during induced hypogonadism and ovarian steroid addback

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Abstract Gynecology clinic-based studies have consistently demonstrated that induced hypogonadism is accompanied by a decline in cognitive test performance. However, a recent study in healthy asymptomatic controls observed that neither induced hypogonadism nor estradiol replacement influenced cognitive performance. Thus, the effects of induced hypogonadism on cognition might not be uniformly experienced across individual women. Moreover, discrepancies in the effects of hypogonadism on cognition also could suggest the existence of specific risk phenotypes that predict a woman's symptomatic experience during menopause. In this study, we examined the effects of induced hypogonadism and ovarian steroid replacement on cognitive performance in healthy premenopausal women. Ovarian suppression was induced with a GnRH agonist (Lupron) and then physiologic levels of estradiol and progesterone were reintroduced in 23 women. Cognitive tests were administered during each hormone condition. To evaluate possible practice effects arising during repeated testing, an identical battery of tests was administered at the same time intervals in 11 untreated women. With the exception of an improved performance on mental rotation during estradiol, we observed no significant effects of estradiol or progesterone on measures of attention, concentration, or memory compared with hypogonadism. In contrast to studies in which a decline in cognitive performance was observed in women receiving ovarian suppression therapy for an underlying gynecologic condition, we confirm a prior report demonstrating that short-term changes in gonadal steroids have a limited effect on cognition in young, healthy women. Differences in the clinical characteristics of the women receiving GnRH agonists could predict a risk for ovarian steroid-related changes in cognitive performance during induced, and possibly, natural menopause.

Keywords Estradiol · Hypogonadism · Progesterone · Cognition

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Introduction

The nature and magnitude of the effects of declining ovarian hormone secretion and the onset of menopause on cognitive performance remain controversial. The plausibility of the capacity of ovarian steroids to regulate cognitive performance in women is supported by two types of evidence: (1) a multitude of studies in animals documenting the manifold neuroregulatory actions of ovarian steroids (Diaz Brinton 2009; Dumitriu et al. 2010; Gibbs 2010; Kelly and

Ronnekleiv 2009; Korol and Kolo 2002; McEwen 2010; Wise et al. 2005) and (2) neuroimaging studies in humans demonstrating the modulatory effects of ovarian steroids on brain activation patterns in regions implicated in the function of a wide range of cognitive domains (Berman et al. 1997; Eberling et al. 2000; Goldstein et al. 2005; Maki and Resnick 2000; Protopopescu et al. 2005; Rasgon et al. 2005; Resnick et al. 1998; van Wingen et al. 2007; Yaffe et al. 1998). Nonetheless, several recent randomized clinical trials, including the Women's Health Initiative (WHI), have demonstrated that estrogen therapy has no direct effect on cognitive performance in older postmenopausal women (Espeland et al. 2004; Hogervorst et al. 2002; Lethaby et al. 2008; Low and Anstey 2006; Mulnard et al. 2000; Rapp et al. 2003; Yaffe et al. 2006). In fact, the WHI findings suggest that estradiol increases the risk of cognitive disorders (Shumaker et al. 2003; Shumaker et al. 2004). These findings have been replicated in younger perimenopausal women (Maki et al. 2007), who frequently report a decline in cognitive function during the perimenopause (Gold et al. 2000; Mitchell and Woods 2001) (although actual performance deficits have not been observed to accompany these cognitive complaints in perimenopausal women (Fuh et al. 2006; Henderson et al. 2003; Kok et al. 2006). In contrast to the randomized controlled trials of estrogen therapy, observational studies more consistently report that estrogen therapy in young perimenopausal women has long-term beneficial effects on cognitive function and affords a small reduction in the risk of dementia (Bagger et al. 2005; Henderson et al. 2005; MacLennan et al. 2006; Whitmer et al. 2011; Yaffe et al. 1998; Zandi et al. 2002). The remaining evidence suggesting a significant effect of estradiol on cognitive function, to a large degree, is derived from clinic-based studies of hypogonadal women in whom surgical oophorectomy was performed (Phillips and Sherwin 1992; Sherwin 1988) or a GnRH agonist was administered to suppress ovarian function as part of a treatment for an underlying gynecologic condition (Craig et al. 2007, Craig et al. 2008a, b; Grigorova et al. 2006; Palomba et al. 2004; Sherwin and Tulandi 1996; Varney et al. 1993). Although the specific cognitive function that is reported to decline during hypogonadism varies across studies, a decline in some aspect of cognitive performance is consistently observed during induced hypogonadism (and in some studies, a subsequent improvement in performance after estradiol therapy). Nonetheless, in contrast to the majority of clinic-based studies, a recent study by Owens et al. (2002) reported that 4 months of GnRH agonist-induced ovarian suppression had no effect on cognitive performance measures in 16 asymptomatic healthy premenopausal women. Thus, despite employing an identical hormonal manipulation (i.e., GnRH agonist-induced hypogonadism) and administering similar cognitive tests, the findings in the Owens et al. study (2002) are ostensibly at variance with numerous studies in which a decline in at least one aspect of cognitive performance was observed.

Several potential confounds could account for discrepancies across studies including the small effect sizes of the changes in cognitive outcomes measured, the presence of practice effects after repeated testing, and differences in baseline cognitive performance in the women prior to induced hypogonadism. Additionally, the clinical characteristics of the samples also obviously differed between a selected sample of healthy women in the Owens study compared with women receiving treatment for a gynecologic condition who constituted the majority of the clinic-based studies. The difference between the cognitive effects of induced hypogonadism in healthy women (observed by Owens et al. (2002)) compared with those in studies of gynecological clinic-based samples, therefore, could suggest a substrate of risk for a woman to experience a cognitive decline during an induced or natural menopause. Moreover, confirmation of these differences could identify subgroups of women who are differentially sensitive to changes in ovarian steroids and inform animal studies in which the mechanisms underlying these differences could be explored.

As part of a larger study investigating the effects of ovarian steroids on brain function and behavior, we had the opportunity to evaluate cognitive performance in a sample of premenopausal women who were healthy and free of gynecologic disease. To further examine the effects of ovarian steroids on measures of cognitive function in these women, we administered a battery of cognitive tests under conditions of GnRH agonist-induced ovarian suppression and then repeated testing after replacement with physiologic levels of estradiol (E) and progesterone (P), respectively. We, therefore, had the opportunity to ask the following questions: first, do some cognitive tasks elicit hormone-related changes in performance in healthy women. Second, do E and P mediate distinct changes in cognitive test performance in these women?

Methods

Subject selection

Lupron-treated group (GnRH agonist-induced hypogonadism and hormone replacement)

Subjects were 23 women (mean ± SD age=35±7 years) recruited through advertisements in the hospital newsletter (Table 1). All were medication free, and all were screened for the absence of significant medical and gynecologic illness through history, physical examination, and laboratory tests. All subjects were administered the Structured Clinical

Table 1 Baseline demographics in women treated with Lupron (n=23) and untreated controls (n=11)

	Lupron-treated group	Untreated control group
Age[a]	35.0 (6.7)	33.8 (10.5)
No. of years of education[a]	16.2 (1.8)	17.5 (1.6)
Racial distribution	21W/2AA	6W/1AA/4A
MC phase during first test session	9 follicular/14 luteal	5 follicular/6 luteal
BDI scores[a]	5.4 (9.4)	0.3 (0.5)

Values are mean (SD) unless otherwise indicated

[a] Lupron-treated women did not differ in age, years of education, or baseline BDI scores from the untreated control group (p>.05 for all comparisons)

Interview for DSM-III-R (Spitzer et al. 1990) to confirm the absence of current Axis I psychiatric illness. The protocol was approved by the National Institute of Mental health (NIMH) Intramural Research Review Board, and written informed consents were obtained from all subjects. All women completed an average of 16.2±1.8 years of education.

Untreated control group

To examine for possible practice effects arising during the repeated testing that we performed in this protocol, we recruited a group of 11 healthy women who served as an unmedicated [i.e., eugonadal] comparison group (mean ± SD age=33.8±10.5 years). They received the same medical and psychiatric screening as the participants who received Lupron, and all were medication free and had no medical, gynecologic, or psychiatric illness, current or past. All women completed an average of 17.5±1.6 years of education.

Protocol

Hormone manipulation group

Women received depot Lupron (leuprolide acetate, TAP Pharmaceuticals, Chicago, IL, USA), 3.75 mg by intramuscular (IM) injection every 4 weeks for 5–6 months (Table 2). Lupron alone was administered for the first 8–12 weeks. Subjects then received, in addition to Lupron, 17 beta E (0.1 mg/day) by skin patch (Ciba Geigy, Rariton, NJ, USA) or P suppositories (200 mg bid) (NIH CC Pharmacy, Bethesda, MD, USA) for 5 weeks each. The two "addback" regimens were separated by a 1−2 week washout period. Subjects were administered both patches and suppositories (active or placebo, depending upon the treatment phase) daily throughout the entire addback period to ensure the double-blind was maintained. The order of receiving E and P was randomly assigned and counterbalanced. During the last week of E, all subjects additionally received 1 week of P suppositories to precipitate menses (Fig. 1).

Cognitive testing was performed: at baseline prior to study (randomly across the menstrual cycle), after 6 weeks of Lupron alone (hypogonadal), and after 3 to 4 weeks of hormone replacement (Lupron plus E and Lupron plus P) (Table 3). Mood symptoms were monitored by the Beck Depression Inventory (BDI) (Beck et al. 1961), and the presence and severity of hot flushes were measured by a daily self-rating scale (Endicott et al. 1981). All women were paid for their participation according to National Institutes of Health (NIH) guidelines.

Untreated control group

The women who served as controls for this study did not receive Lupron at any time point and did not receive any hormone therapy but received the same battery of tests at similar time intervals as those in the main treatment protocol.

Blood samples were drawn at the time of testing in all women. The samples were centrifuged, and aliquots of serum or plasma were frozen at −20 °C until the time of assay. Plasma levels of E and P (Abraham et al. 1971; Jiang and Ryan 1969) and total T (Furuyama et al. 1970) were analyzed by radioimmunoassay.

Cognitive tests

Cognitive tests were selected to assess performance in the following cognitive domains: verbal and visual memory, visuospatial ability, verbal fluency and articulation, motor speed and dexterity, and attention and concentration. General ability was evaluated employing components of the Wechsler adult intelligence scale (WAIS-R) (Wechsler 1981) and the Wide range achievement test-revised (WRAT-R) (Jastak and Wilkinson 1984). The selection of cognitive tests was limited

Table 2 Plasma hormone levels in women treated with Lupron (n=23) and untreated controls (n=11)

Lupron-treated group	Baseline	Hypogonadal	E replaced	P replaced
Estradiol (pg/ml)	84.3 (64.1)	18.9 (9.7)	108.9 (64.9)	16.4 (6.0)
Progesterone (ng/ml)	2.8 (4.3)	0.4 (0.2)	0.4 (0.3)	14.1 (7.6)
Untreated control group	Test # 1	Test # 2	Test # 3	Test # 4
Estradiol (pg/ml)	115.2 (72.1)	114.7 (77.6)	88.6 (57.7)	112.1 (75.8)
Progesterone (ng/ml)	2.2 (3.8)	3.9 (4.3)	4.8 (6.1)	4.0 (6.1)

Conversions—E: pg/ml×3.67=pmol/L; P: ng/ml×3.18=nmol/L

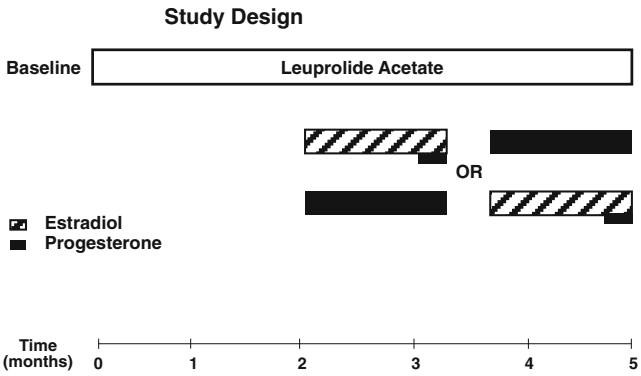

Fig. 1 All women received 3.75 mg of depot Lupron (leuprolide acetate, TAP Pharmaceuticals, Chicago, IL, USA) by IM injection every 4 weeks for 5–6 months. The first injection of Lupron was administered during the follicular phase between days 2 and 6 after the onset of menses. Lupron alone was administered for the first 8–12 weeks. All women then received, in addition to Lupron, 17 beta estradiol (0.1 mg/day) (E) by skin patch (Alora, Watson Pharmaceuticals, Salt Lake City, UT, USA) or progesterone suppositories (200 mg bid) (P) (NIH CC Pharmacy, Bethesda, MD, USA) for 5 weeks each. The two replacement regimens were separated by a 1–2 week washout period. Subjects were administered both patches and suppositories (active or placebo, depending upon the treatment phase) daily throughout the entire replacement period to ensure the double-blind was maintained. During the last week of E, all women received 1 week of active P suppositories in addition to E to precipitate menses. All women received prepackaged 1-week unit-dose supplies of suppositories that were formulated and coded (weeks 1–5) by the NIH CC Pharmacy Department

by the repeated measures design of this study, since subjects were tested on four separate occasions. We, therefore, selected cognitive tests (e.g., paragraph memory) in which at least four separate forms were available (Table 4).

Statistical analysis

First, data from the Lupron-treated women (i.e., hormone manipulation protocol) were analyzed by analysis of variance with repeated measures (ANOVA-R; SYSTAT, SPSS, Chicago, IL, USA). In these women, test scores at each time point were compared by ANOVA-R, with hormone condition (baseline vs. hypogonadal vs. E replacement vs. P replacement) as the within-subjects variable. Complete data sets were present for all tests except for four (i.e., Line Orientation, Digit span, Fragmented Pictures, and Mental Rotation) in which two women treated with Lupron in each test had unusable data during one hormone condition. If the ANOVAs were significant, we performed post hoc comparisons of cognitive test performance during hormone replacement compared with hypogonadal and baseline conditions and, additionally, compared the cognitive performance during hypogonadism with baseline.

The principle focus of this study was whether significant changes in cognitive test performance could be observed during the pharmacologically induced hormone conditions. The repeated testing in this protocol could give rise to practice effects that mistakenly could be attributed to an effect of a specific hormone condition. Additionally, the testing in this protocol occurred in a partially fixed order with the first and second testing sessions occurring during baseline and hypogonadism, respectively. Given the partially fixed order of our study, in a second analysis, we performed ANOVAs on the cognitive data from both the Lupron-treated women and the untreated controls, who were tested at the same approximate time intervals as in women receiving Lupron and hormone replacement. These data were analyzed with Group (Lupron-treated and untreated controls) as the between-subjects factor and time (i.e., hormone condition in Lupron-treated women and time in the untreated women). The absence of a significant main or interaction between group and time/hormone condition would be consistent with a practice effect in that test measure. ANOVAs were performed on both the cognitive test scores at each test phase and the change in test scores between sessions. By so doing, we could effectively identify many of the ostensible hormone condition-related changes in cognitive function that were simply a product of repeated testing (i.e., practice effects).

Several secondary analyses evaluated potential confounds in the data. First, the ANOVA-R in the women was repeated with each of the following as a between-subjects variable: (1) phase of menstrual cycle (i.e., follicular (n=15) vs. luteal (n=8) during baseline testing and (2) hormonal milieu during baseline testing (i.e., plasma levels of P≥2 ng/ml and/or E≥70 pg/ml (n=10) vs. plasma levels of P<2 ng/ml and E<70 pg/ml (n=13)). These two analyses examined the potential impact of baseline hormonal status on the observed performance across the different hormone conditions. Second, eight women reported the presence of premenstrual symptoms (PMS) prior to study entry. Thus, ANOVA-R analyses were repeated in the asymptomatic women without PMS (n=15) to ensure that the pattern of cognitive performance across each hormonal state was not confounded by the inclusion of women reporting PMS (either due to differences in symptomatology at baseline or differences in response characteristics during hormone replacement). Further, due to baseline differences in BDI scores between women with and without reported PMS, the ANOVA-R analyses were repeated with baseline BDI scores as a covariate. Third, in the Lupron-treated women, we examined the effects of age as a covariate in the first set of ANOVAs. Fourth, in the Lupron-treated women, we examined the effect on test scores of the order of receiving estradiol or progesterone first during the replacement phase of the study. Finally, several studies (LeBlanc et al. 2001; Maki et al. 2008; Yaffe et al. 1998), but not all (LeBlanc et al. 2007), suggest an interaction between E's observed

Table 3 Cognitive performance scores in Lupron-treated women (n=23) at baseline (eugonadal), during hypogonadism and during hormone replacement, and untreated controls (n=11) tested at similar time intervals —(mean ± standard deviation). Reported scores are not adjusted for educational levels

Testing session:	Study sjs: Controls:	Eugonadal Time #1	Hypogonadal Time #2	E replaced Time #3	P replaced Time #4
Memory:					
Paragraph memory (Kramer et al. 1988; Lezak Deutsch 1995; Wechsler 1981)					
Immediate (% of paragraph)	Study sjs	57.0 (19.5)	64.0 (16.1)	64.3 (18.5)	67.5 (12.7)
	Controls	62.4 (18.9)	64.7 (17.3)	72.4 (17.2)	72.5 (15.8)
Delay (% of paragraph)	Study sjs$^{\#\#}$	48.4 (18.6)	57.3 (20.3)	58.1 (18.5)	63.0 (14.7)
	Controls$^{\#}$	53.7 (14.3)	55.5 (15.5)	68.5 (13.0)	68.2 (17.2)
Spatial ability:					
Mental rotation (Shepard and Metzler 1971; Vandenberg and Kuse 1978)					
Total (number correct)	Study sjs	12.3 (4.5)	11.7 (5.3)	13.8 (4.9)	13.8 (4.7)
	Controls$^{\#}$	9.2 (3.9)	10.8 (4.4)	13.4 (5.6)	13.5 (5.8)
Adjusted (number correct)	Study sjs$^{\#}$	8.8 (5.5)	8.3 (5.7)$^{\circ}$	11.1 (6.1)	10.4 (6.0)
	Controls	6.4 (4.6)	7.5 (5.7)	9.9 (7.7)	9.3 (7.5)
Money road map (Money 1976)					
Time up (s)	Study sjs$^{\#\#\#}$	23.0 (10.5)	20.0 (6.0)	17.3 (4.3)	16.2 (3.4)
	Controls$^{\#}$	29.5 (16.5)	26.2 (11.9)	23.4 (12.7)	22.5 (8.9)
Time total (s)	Study sjs$^{\#\#\#}$	58.0 (23.9)	50.3 (18.3)	45.2 (12.8)	41.3 (10.4)
	Controls$^{\#}$	69.2 (36.0)	59.9 (28.5)	55.0 (24.2)	53.6 (22.4)
Porteus maze (Porteus 1959)					
Immediate (s)	Study sjs$^{\#}$	50.7 (29.2)	40.4 (13.8)	36.3 (14.9)‡	37.0 (17.2)$^{\updownarrow}$
	Controls	52.4 (39.1)	54.5 (42.1)	39.9 (26.5)	48.0 (33.5)
Verbal fluency:					
Verbal fluency (Benton and Hamsher 1976)					
Number of words generated	Study sjs$^{\#\#}$	40.4 (7.9)	44.2 (9.9)	44.2 (11.8)	45.8 (10.4)$^{\updownarrow}$
	Controls	41.5 (9.5)	42.2 (9.8)	44.6 (11.9)	44.0 (10.3)
Stroop color naming (Stroop 1935)					
Number of words read	Study sjs$^{\#}$	52.2 (6.2)	52.7 (6.3)	53.2 (6.2)	54.3 (5.4)
	Controls$^{\#}$	49.0 (5.7)	48.0 (6.4)	51.4 (5.9)	50.5 (6.0)
Motor speed and dexterity:					
Purdue peg board (Spreen and Strauss 1991)					
Dominant (number of pegs)	Study sjs$^{\#}$	14.9 (1.2)	15.4 (1.1)	15.4 (1.2)	15.9 (1.3)$^{\updownarrow}$
	Controls	15.2 (1.9)	15.7 (1.7)	15.8 (1.9)	16.2 (0.9)
Grooved pegboard (Harley et al. 1980)					
Dominant hand (s)	Study sjs$^{\#}$	56.9 (7.8)	58.4 (7.0)	58.1 (9.9)	61.3 (5.5)
	Controls$^{\#}$	58.2 (8.7)	60.3 (6.7)	64.5 (6.2)	61.9 (5.0)
Finger tapping (Kløve 1963; Reitan and Wolfson 1993; Spreen and Strauss 1991)					
Dominant (number of taps)	Study sjs$^{\#\#}$	55.7 (7.0)	55.1 (7.3)	55.9 (7.8)	58.5 (7.2)
	Controls$^{\#}$	57.2 (6.5)	55.6 (7.3)	60.9 (8.5)	61.6 (7.3)
Attention and concentration:					
Digit span (Wechsler 1981)					
Number of correct responses (backward)	Study sjs$^{\#}$	5.4 (1.1)	6.0 (1.2)†	5.9 (1.2)	5.9 (0.8)
	Controls	5.8 (1.6)	6.1 (1.5)	6.4 (1.2)	6.5 (1.3)
Trail making (Kløve 1963; Reitan 1958; Reitan and Wolfson 1993)					
Form A (s)	Study sjs	21.1 (6.2)	19.2 (3.9)	19.7 (4.3)	19.1 (5.0)
	Controls$^{\#}$	26.4 (10.5)	22.0 (6.3)	21.8 (9.4)	19.7 (7.4)

Analyses: —ANOVA: hormone condition $^{\#}p<0.05$, $^{\#\#}p\leq0.01$, $^{\#\#\#}p\leq0.001$; —Bonferroni t: eugonadal vs. hypogonadal $^{\dagger}p<0.05$; eugonadal vs. E replaced $^{\ddagger}p<0.01$; eugonadal vs. P replaced $^{\updownarrow}p<0.01$; hypogonadal vs. E replaced $^{\circ}p<0.05$; Otherwise p=NS

Table 4 Cognitive tests administered to Lupron-treated women and the untreated control group

1) Rey complex figure (Corwin and Bylsma 1993)

A figure is presented to the subject, who is asked initially to copy the figure. Scores reflect the amount of the figure (divided into 18 components) accurately copied, with each component rated on a scale from zero to two (copy). The maximum score for the 18 components in the picture is 36. After a 1- to 1 1/2-h delay, the subject is asked to draw the figure from memory, and the figure is scored in a manner identical to that for the original copy (delay)

2) Paragraph memory: logical memory test (Green and Kramer 1983; Talland 1965; Wechsler 1987)

A paragraph is read to the subject, who is asked to recall as much of the paragraph as possible (immediate). After a 1- to 1 1/2-h delay, the subject is asked to recall the paragraph (delay). Each paragraph ranges from 20 to 25 sections and the final score represents a percentage of the paragraph recalled correctly. Two paragraphs were derived from each of the Wechsler adult intelligence scale (Wechsler 1981) and the California Discourse Memory Test (Kramer et al. 1988; Lezak Deutsch 1995). The administration of paragraphs was counterbalanced

Spatial ability

3) Line orientation (Benton et al. 1976, 1983)

A series of 15 cards is presented, and the subject is asked to match the angle of orientation of two lines on the card with those numbered within a spectrum of lines on the reference card shown. Scores represent the number of correct paired (both line pointing to the left and line pointing to the right matched correctly; maximum score=15) (pairs) and single matches (only one of the paired lines being matched correctly; maximum score=30) (singles)

4) Mental rotation: figure rotation (Shepard and Metzler 1971; Vandenberg and Kuse 1978)

A series of geometrically complex objects are presented to the subject, who is asked to identify two matches from a group of four similar objects (two of which are the original objects rotated in space). A 24-item test is administered. Scores include both the number of correct matches (total) as well as the number of matches that are adjusted for errors (adjusted)

5) Embedded figures: hidden figures (Spreen and Benton 1969)

Scores reflect the number of seconds to outline a given shape that is embedded in a more complex series of distracting lines (average time for best three of four figures (best) and for all four figures (all))

6) Money road map (Money 1976)

A map in which the subject is required to report to the examiner the sequence of turns (left or right) involved in a specified route going up to the top of the map and then coming down to the bottom of the map. Scores represent the number of seconds going up (time up), the number of seconds for the return trip (time total), the number of errors going up (errors up), and the number of errors going down (errors down)

7) Porteus maze (Porteus 1959)

Subjects are required to find the route to exit from the center of a maze. Scores consist of the number of seconds and the number of errors (wrong directional decisions) made prior to exiting the maze (immediate). After a 1- to 1 1/2-h delay, the same maze is presented to the subject, and both the seconds and the number of errors made in exiting are scored (delay)

Verbal fluency and articulation

8) Verbal fluency (Benton and Hamsher 1976)

Subjects are asked to generate words beginning with a specific letter within a 60-s time period for each of three letters (e.g., F, A, and S). The score represents the combined number of words generated in 3 min for the three letters

9) Stroop color naming (Stroop 1935)

Subjects are presented with a list of words consisting of the names of three colors (red, green, and blue) in different order. The score represents a *T*-score reflecting the number of words correctly spoken in 45 s. (We did not employ this test as a measure of perceptual interference)

Motor speed and dexterity

10) Purdue pegboard (Spreen and Strauss 1991)

Scores represent the number of pegs inserted with the dominant hand alone (dominant), the nondominant hand alone (nondominant), both hands (both), and an assembly task in which the pegs must be inserted in a particular order along with a washer and a collar (assembly)

11) Grooved pegboard (Harley et al. 1980)

The subject is timed while inserting pegs in each of the grooved openings on the board. The scores consist of *T*-scores reflecting the time required for completion with the dominant (dominant) and nondominant (nondominant) hands

12) Finger tapping (Kløve 1963; Reitan and Wolfson 1993; Spreen and Strauss 1991)

Numbers of taps by dominant and nondominant index fingers in 10 s are counted and averaged over three trials

Attention/concentration

13) Digit span (Wechsler 1981)

Number of correct digits repeated (both forward and backward) after a list of digits has been read to the subject

14) Symbol digit modalities (Smith 1982)

Subjects are presented with a group of digits that are paired with matching symbols. The subject is presented with a series of symbols and must provide the corresponding digit of the pair from the sheet containing the correct match. Subjects are allowed 90 s to complete the task. The scores represent the number of correct written (written) and oral (oral) responses, as well as the number of correct pair matching from memory (recall).

15) Trail making test (Benton et al. 1983; Kløve 1963; Reitan and Wolfson 1993)

Scores represent the number of seconds required to connect points (numbers and letters) on a sheet of paper. Both the A and the B forms were administered

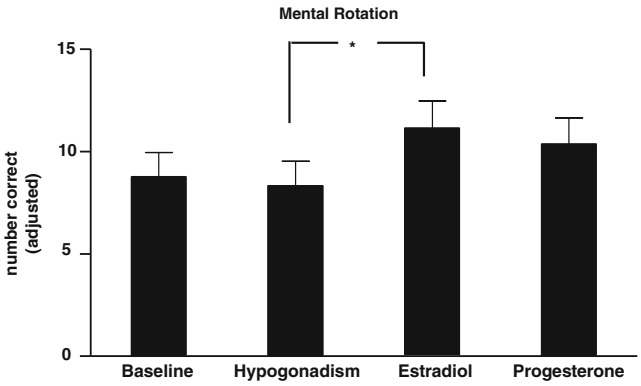

Fig. 2 Performance scores (number of correct responses adjusted for errors) on the mental rotation test during baseline (eugonadal), Lupron-induced hypogonadism, and estradiol- and progesterone-replaced conditions (mean + SEM). ANOVA-R demonstrated a significant effect of hormone condition in the group receiving Lupron and hormone replacement that was not identified in the medication-free comparison group. Post hoc testing identified a significant improvement in the performance on the mental rotation test during estradiol replacement compared with hypogonadism ($^{*}p<.05$). However, there were no significant differences between baseline (eugonadal) and hypogonadism or between progesterone and either hypogonadism or baseline conditions

effects on verbal memory and hot flush-induced sleep disturbance. Thus, we examined differences (ANOVA-R) in the severity of self-ratings of hot flushes and disturbed sleep (on the days of cognitive testing) between women whose performance on selected tests improved and those whose performance declined from baseline to hypogonadism as well as from hypogonadism to E replacement. Age, baseline BDI scores, and years of education in the Lupron-treated women and the untreated control group were compared with Student's *t* test.

Results

Lupron-treated women did not differ in age or years of education from the untreated control group (p=ns). Baseline BDI scores were nonsignificantly higher in the Lupron-treated women compared with the untreated control group (Student's $t_{30}=1.7$, p=ns) due to the presence of several women with PMS in the Lupron-treated group (see below).

Effects of hormone condition on cognitive test performance

In the first analysis of only the data from the Lupron-treated women, ANOVA-Rs were significant for several cognitive tests (Table 3); however, with only a few exceptions (listed below), identical differences in test performances also were observed in the comparison subjects who remained eugonadal throughout the study. Thus, the potential differences across hormone conditions in the Lupron-treated women were, in large part, effects related to the repeated administration of these tests on performance scores. Significant effects across hormone conditions that were not also present in the comparison group were observed in the following tests: (1) mental rotation test (adjusted), (2) Porteus maze (immediate seconds), (3) verbal fluency (number of words), (4) Purdue peg board (dominant hand), and (5) digit span. Post hoc testing examining these significant differences showed that performance in the adjusted mental rotation test was significantly better during E compared with hypogonadism. Other comparisons on this measure were not significant after correction for multiple comparisons (Fig. 2). The remainder of the significant paired comparisons reflected significant differences between one of the hormone conditions and baseline. Specifically, performance scores were significantly better during P compared with baseline conditions in the Porteus maze, verbal fluency, and the Purdue peg board. Additionally, performance scores in the Porteus maze were significantly better during E compared with baseline. Finally, performance in the digit span was significantly better during hypogonadism compared with baseline (Table 3 and Supplemental Table 1).

The analysis of change scores showed a similar pattern of effects with no significant treatment group by test session interactions, with the exception of two test scores. First, in the scores of both dominant and nondominant finger tapping, we identified a significant interaction that reflected an improved performance in the untreated controls during their second test compared with their first test that was not observed in women receiving Lupron. Second, in the symbol digit written test, the women receiving no medication performed better during test session 3 compared with the other times, whereas women receiving Lupron did not show substantial differences across time points.

When the women reporting PMS were excluded from the analyses, a similar pattern of effects (both nonsignificant and significant) were observed with the 15 asymptomatic women, although fewer test scores showed significant differences due to the reduced sample size. Finally, in the Lupron-treated women, there were no significant main or interactive effects with age on any test score nor was there a significant effect of the order of receiving estradiol or progesterone first during the replacement phase of the study.

Mood symptoms and hot flushes

No significant changes in BDI scores were observed across hormonal conditions. However, since we observed higher BDI scores at baseline prior to study entry in the eight women reporting PMS compared to controls, baseline BDI scores were included as a covariate. The pattern of results did not differ from that observed in the original analysis. Women experienced a significant increase in the severity of

hot flushes during the hypogonadal state: all women reported hot flushes during hypogonadism, and none of the women reported hot flushes at baseline. For those tests in which the literature suggests an effect of estradiol that could interact with symptoms (e.g., paragraph memory and mental rotation test), differences in self-reports of the severity of hot flushes or disturbed sleep did not distinguish the women whose performance worsened from those whose performance improved during hypogonadism or hormone replacement.

Discussion

In this study, we did not replicate previous reports that GnRH agonist (Lupron)-induced ovarian suppression was accompanied by a decline in measures of cognitive performance. Nor did we observe an estradiol-related improvement in cognitive test performance (Grigorova et al. 2006; Kampen and Sherwin 1994; Resnick et al. 1997; Sherwin and Tulandi 1996). In particular, we observed no changes in measures of attention, concentration, or memory function (either verbal or visual). The majority of differences in cognitive performance in women were also observed in the untreated control subjects over time. These differences in cognition, then, are unlikely due to the effects of gonadal steroids but rather are "practice effects" due to the repeated administration of these tests. Indeed, significant differences across hormone conditions that were not mirrored in the comparison group reflected either improvements during E or P replacement compared with baseline (i.e., the first test session) with no improvement compared with hypogonadism (when both E and P levels were suppressed), or in the digit span test, a significant improvement during hypogonadism compared with baseline that was maintained during estradiol and progesterone replacement. One test, the digit span, did show a difference between baseline and hypogonadism; however, the change in performance reflected an improvement (not a decline) in performance scores during hypogonadism. Moreover, the improved scores during hypogonadism were virtually identical to those seen during gonadal steroid replacement, rendering an uncompelling role for changing gonadal steroid levels in the performance scores. An analysis of change scores across test sessions also failed to show specific effects of hormone condition, and differences from the untreated control group were observed in only two tests, both of which reflected changes in the untreated controls not the women receiving Lupron. The only test scores that improved during E compared with hypogonadism (i.e., adjusted scores of the mental rotation test) also were better (albeit not significantly so) during P compared with hypogonadism and during E compared with baseline. The better performance on mental rotation during E compared with baseline is not consistent with a specific effect of E on performance, since similar plasma E levels were observed during E and baseline. These data, therefore, also suggest the absence of a specific effect of E levels on mental rotation performance. Nonetheless, a previous study reported a significant improvement in mental rotation performance scores in postmenopausal women after 3 weeks of estrogen therapy (Duka et al. 2000). Our findings are consistent with the one prior study in healthy asymptomatic young women, in whom cognitive testing was performed after 4 months of GnRH agonist-induced ovarian suppression (Owens et al. 2002). While the effects of E (or P) on cognitive function may vary with age (Rapp et al. 2002), our data and those of Owens et al. (2002) suggest that changes in the secretion of neither E nor P substantially alter cognitive function in younger women, at least over the several weeks of exposure in this protocol.

Previous studies examining the effects of E replacement in older hypogonadal (postmenopausal) women identified positive effects on measures of verbal and visual memory in some (Joffe et al. 2006; Kampen and Sherwin 1994; Maki et al. 2001; Resnick et al. 1997) but not all studies (Berman et al. 1997; Keenan et al. 2001; LeBlanc et al. 2001; Shaywitz et al. 1999). Additionally, several neuroimaging studies have identified changes in brain activity corresponding to changes in ovarian steroid hormone secretion (Berman et al. 1997; Goldstein et al. 2005; Protopopescu et al. 2005; Shaywitz et al. 1999; Smith et al. 2006; van Wingen et al. 2007). We were unable to identify significant declines in performance scores during hypogonadism, in tests of attention or verbal or visual memory, or improvements during E replacement in this study. Two meta analyses (LeBlanc et al. 2001; Yaffe et al. 1998) suggested that the beneficial effects of E on cognition are restricted to symptomatic hypogonadal women. Nonetheless, the severity of hot flushes and disturbed sleep did not distinguish those women in our study whose performance on the paragraph memory improved from hypogonadism to E replacement and those whose performance declined. Our finding that individual self-reports of neither hot flushes nor disturbed sleep impact cognitive performance are consistent with two recent reports in symptomatic peri- and postmenopausal women (LeBlanc et al. 2007; Maki et al. 2008); however, in one of these studies (Maki et al. 2008), objective measures of hot flushes suggested that the number of objective hot flushes (which exceeded the numbers recorded by self-report) was associated with declines in verbal memory performance. Thus, it is possible that had we employed objective measures of the numbers of hot flushes experienced by each woman, we might be able to better distinguish those women who experienced an improvement in verbal memory between the hypogonadal- and estradiol-replaced testing sessions. In our study, we also were limited in the choice of testing measures due to the repeated measures design (e.g., four

separate test forms were not available for the California Verbal Learning Test (CVLT)) (Keenan et al. 2001). Alternate measures may have been more sensitive to differences in hormone-induced changes in memory function. However, several methodologic differences may explain the discrepancies between our findings and those reporting E-related memory improvements. First, cross-sectional studies in E users and nonusers may reflect more enduring characteristics, such as education and general health, rather than the use of E replacement (Yaffe et al. 1998). Second, our younger sample permits no conclusion about potential age-related decline in verbal or working memory, which may be E-responsive (Rapp et al. 2002). Third, the healthy paid volunteers in this study were recruited from a local catchment area surrounding the hospital. Thus, it is possible that our selection process could have introduced a bias that resulted in a more motivated group of women whose performances would be different from the scores of women studied in the clinic-based studies of treatment-seeking women. Finally, the duration of hypogonadism in postmenopausal women would be considerably longer than in our study and may be associated with a differing responsivity to E (Tinkler et al. 2002).

Several previous reports examined the effects of GnRH agonist-induced hypogonadism, and in some E replacement, on cognition in younger women receiving treatment for uterine fibroids or endometriosis (Grigorova et al. 2006; Sherwin and Tulandi 1996). In contrast to our data, (Craig et al. 2007; Craig et al. 2008a, b; Palomba et al. 2004; Varney et al. 1993) the majority of these studies observed a significant decline in cognitive performances during hypogonadism compared with baseline, including measures of verbal memory, working memory, and visual recognition, and an improvement in several of these measures (e.g., verbal memory) in those women receiving E (but not in those receiving placebo) while on GnRH agonist. Our findings are consistent with those of Owens et al. (2002), who also studied asymptomatic healthy women at baseline and under conditions of GnRH agonist-induced ovarian suppression of 4 months duration and, in half of the women, after estradiol replacement. Both our study and that of Owens et al. (2002) observed numerous practice effects after repeated testing but no specific effects of either hypogonadism or estradiol replacement despite administering similar test measures as those administered in several gynecologic clinic-based studies. Together, our data and those of Owens et al. (2002) represent experience with over 30 healthy asymptomatic women (as well as eight women reporting PMS who were otherwise gynecologically normal) showing a consistent lack of effect on cognitive performance after a decisive hormone intervention (i.e., ovarian suppression). These findings in healthy asymptomatic women also stand in remarkable contrast to the otherwise uniform findings in multiple studies of a decline in cognitive performance in women treated with ovarian suppression for gynecologic illness.

These ostensibly discrepant findings could reflect important differences in the clinical characteristics of the samples that are associated with or are predictive of a decline in cognitive function during either the natural or induced menopause. Epidemiologic studies in women during the perimenopause would suggest that complaints of cognitive decline are not uniformly reported by women (Gold et al. 2000; Mitchell and Woods 2001), and some women, therefore, might be differentially vulnerable to the cognitive-impairing effects of declining ovarian steroids. For example, the presence of endometriosis or fibroids could be associated with a greater risk for cognitive decline under conditions of ovarian steroid withdrawal or suppression. Abnormalities of estrogen receptor function have been suggested to play a role in the pathophysiology of both of these conditions (Cavallini et al. 2011; Huhtinen et al. 2011; Li and McLachlan 2001; Wei et al. 2007), and obviously, both are treated, in part, by induced hypogonadism. Thus, it is possible that in women with endometriosis or uterine fibroids, estrogen signaling is abnormal at other tissue sites including the brain, perhaps accounting for the otherwise discrepant cognitive findings during GnRH agonist therapy. Alternately, the symptoms of a longstanding gynecologic condition could be accompanied by increased stress in these women. Chronic stress, in turn, could either diminish cognitive reserve or impair ovarian estradiol secretion prior to treatment sufficient to amplify the effects of GnRH agonist-induced hypogonadism on cognitive performance. Clearly, other factors could account for differences observed across studies including the baseline levels of cognitive performance prior to starting GnRH agonist. Finally, mood symptoms may impair performance and confound the effects of gonadal steroids on cognition. Mood symptoms, however, did not significantly differ between hypogonadal and hormone-replaced conditions. We did observe mood symptoms in women who reported PMS at baseline. Additional potential confounds related to the inclusion of women with PMS in this study include the documented efficacy of GnRH agonist treatment in PMS and observations of deficits in the retrieval of learned information that is menstrual cycle phase-independent in women with PMS (Keenan et al. 1992; Keenan et al. 1995). However, a similar pattern of results was observed in the asymptomatic women without PMS who were analyzed separately.

Conclusions

We did not find evidence that gonadal steroids regulate measures of cognitive function including verbal memory or visuospatial abilities in younger healthy women. Our data in women suggest that short-term changes in either E or P

do not substantially alter cognitive test performance in any of the domains measured, including those previously reported to change in the context of short-term E therapy (Kampen and Sherwin 1994) or across the menstrual cycle (Hampson and Kimura 1988). However, the discrepancies between data collected from gynecologic clinic-based samples and that from our study and that of Owens et al. (2002) suggest that, not surprisingly, the effects of E on the brain are not uniform across individuals. Such differences further suggest the existence of as yet undefined risk phenotypes that might predict an individual woman's symptomatic experience during the menopause and her possible response to estradiol therapy.

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Conflict of interest Dr. Keenan is a full salaried employee of Johnson and Johnson. None of the other authors report any potential conflicts of interest relevant to the information contained within this manuscript.

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