Dysglycemia, Not Altered Sex Steroid Hormones, Affects Cognitive Function in Polycystic Ovary Syndrome

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Context: Polycystic ovary syndrome (PCOS) is a complex endocrine condition characterized by multiple reproductive and metabolic abnormalities. Because individual reproductive and metabolic abnormalities modulate working memory in the general population, there is growing interest in whether cognitive function is dually and negatively affected in PCOS.

Objective: To examine the association of reproductive and metabolic features with cognitive function in women with and without PCOS.

Design: An observational, cross-sectional study was conducted at an academic clinical research center in North America between 2006 and 2009. Common tests of working memory (*i.e.*, manual dexterity, perceptual speed, and visuospatial ability) were performed by women with PCOS (n = 40) and control subjects (n = 40). Markers of sex steroid hormones, ovulatory function, and cardiometabolic health were also assessed.

Results: Reduced visuospatial ability was observed in women with PCOS compared with control subjects ($P < 0.01$). Reduced visuospatial ability was linked to higher levels of hemoglobin A1c in the entire study cohort, independent of body mass index or PCOS status. No associations were observed between visuospatial ability and reproductive features, after controlling for confounding variables.

Conclusion: Our findings support a role for glycemic control, and not PCOS *per se*, in cognitive dysfunction in women of reproductive age. Additional studies are needed to understand the short- and long-term effects of dysglycemia on brain health in women with PCOS, given their increased propensity for metabolic comorbidities, compared with control subjects.

Freeform/Key Words: polycystic ovary syndrome, cognition, androgens, glycated hemoglobin A

Polycystic ovary syndrome (PCOS) is characterized by reproductive and metabolic disturbances, including altered concentrations of sex steroid hormones, ovulatory dysfunction, obesity, dysglycemia, insulin resistance, hypertension, dyslipidemia, and inflammation [1–6]. Reproductive and metabolic disturbances individually modulate cognitive function in the general population. Therefore, there is growing interest in whether the abnormal endocrine milieu can uniquely influence cognitive outcomes in women with PCOS [7–13].

Abbreviations: AFC, antral follicle count; BMI, body mass index; CRP, C-reactive protein; FAI, free androgen index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; PCOS, polycystic ovary syndrome.

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There is reasonable evidence to suggest that sex steroid hormones exert activational effects on cognitive function [14]. Androgen and estrogen receptors are abundant in the hippocampus, a region of the brain closely involved with working memory [15, 16]. Observational studies have demonstrated that women perform better than men on tests of manual dexterity and perceptual speed but worse on tests of visuospatial ability [17]. Sex-specific advantages have been linked to higher circulating concentrations of estradiol in women, compared with testosterone in men [14]. Changes in cognitive function have also been detected with physiologic [18, 19] and pathologic variations in sex steroid hormones [20], as well as during interventional studies of hormone replacement [21] and gender reassignment [22]. Such findings have led to the notion that hyperandrogenism and hyperestrogenism might enable male- and female-advantage cognitive task performance in PCOS [7, 8, 11, 13].

Previous studies have reported mixed evidence regarding sex steroid hormones and cognitive function in women with PCOS. Barry *et al.* [11] have described increased visuospatial ability in hyperandrogenic phenotypes compared with control subjects and associated male-advantage performance with elevations in total testosterone. However, other groups have found similar visuospatial ability, but reduced verbal memory and manual dexterity, in women with PCOS [7, 8]. Deficits have been linked to androgen status [7], albeit antiandrogen therapy has not yielded consistent improvements in female-advantage performance [10, 23]. Some authors have responded to the conflicting data with an appreciation that sex steroid hormones may represent one of many factors contributing to cognitive differences in PCOS and that additional studies are needed to understand any potential relationships [7, 8, 13].

Studies that focus on metabolic risk factors may be especially important. There is accumulating epidemiological and experimental evidence that insulin resistance contributes to the development of dementia in aging adults [24]. Insulin receptors and transporters are widely expressed in the brain, owing to the hormone's critical roles in energy balance, reproduction, and cognition [25]. Peripheral insulin resistance impairs neural insulin dynamics and leads to cerebral glucose hypometabolism [26], neuroinflammation [27], white matter abnormalities [28], brain atrophy [29], and cognitive decline [24]. Obesity, hypertension, dyslipidemia, and inflammation have also been linked to poor working memory, but the effects independent of insulin resistance remain unknown [30–32]. Interestingly, previous studies have described both cerebral glucose hypometabolism [12] and altered white matter microstructure in women with PCOS [9]; however, relationships between systemic metabolic disturbances and cognitive outcomes have not been explored.

Ultimately, the extent to which the spectrum of reproductive and metabolic disturbances in PCOS can influence cognitive outcomes is unclear. Such investigations are critical to inform patients about the long-term consequences of PCOS and to guide the selection of adequate therapies across the lifespan. Our objective for the current study was to examine the association of reproductive and metabolic features with cognitive function in women with and without PCOS. We hypothesized that the dual burden of reproductive and metabolic abnormalities would be linked to deficits in cognitive function in PCOS.

1. Materials and Methods

A. Study Population

The current study involved secondary analysis of a larger case-control study [33–37]. Participants were women from the original study who provided complete cognitive data sets; information about the evaluations of most of the women was reported in previous publications [33–37]. Women with (n = 40) and without (n = 40) PCOS were recruited from the general population. PCOS was diagnosed by the combined presence of oligomenorrhea and hyperandrogenism [38]. Oligomenorrhea was judged on the basis of self-report of menstrual cycles >35 days apart [39]. Thresholds for hyperandrogenism were based on the 95th percentiles for modified hirsutism score (≥7) and serum total testosterone concentration

(≥4.41 nmol/L) in an internal reference cohort. Control subjects had regular menstrual cycles (21 to 35 days) and no hyperandrogenism. Exclusion criteria were abnormalities in circulating concentrations of cortisol, prolactin, or thyroid-stimulating hormone; use of medications known to affect study end points in the 2 months prior to participation; and pregnancy or lactation. The original study was approved by the University of Saskatchewan Biomedical Research Ethics Review Board, and all participants provided written, informed consent [33–37].

B. Measurement of Cognitive Function

Control subjects were evaluated during the early follicular phase of the menstrual cycle. Women with PCOS were evaluated at a random time when no dominant follicles or active corpora lutea were observed in the ovaries. Seventeen women with PCOS (43%) were evaluated during prolonged periods of oligomenorrhea, wherein their self-reported last menstrual periods had occurred ≥90 days before the study assessments.

Cognitive end points were quantified using tests of working memory, including manual dexterity [40], perceptual speed [41], and visuospatial ability [42]. Participants were asked to complete two test sessions with a minimum interval of 4 weeks. However, some women did not return for the second session (n = 12) and those that did had improved scores on two of the three tests, suggesting a learning effect over time. Therefore, the current study only included scores from the first test session.

Manual dexterity was assessed with the Purdue pegboard task [40], which required participants to insert round metal pegs into a row of 25 consecutive holes as quickly as possible. Participants were asked to complete three trials: one using their self-reported dominant hand, one using their self-reported nondominant hand, and a third using both hands. During the bimanual trial, participants were asked to use both hands simultaneously to fill two adjacent rows of holes. The score for each uni- or bimanual trial was the time to complete the task in seconds. Perceptual speed was assessed with the identical pictures task [41], which required participants to match a given picture to one of five pictures in a row. Participants were prompted with 48 pictures and asked to match as many as possible in 90 seconds. The score for the task was the number of correctly matched pictures. Participants earned one point for each correct item and lost one-quarter point for each incorrect item. Possible scores ranged from −12 to 48 points. Visuospatial ability was assessed with the mental rotation task [42], which required participants to mentally rotate a two-dimensional picture to match two of four identical alternatives. Participants were prompted with 12 pictures. Participants earned one point for each correct item and lost one point for each incorrect item. Possible scores ranged from 0 to 24 points.

C. Measurement of Reproductive and Metabolic Features

Clinical reproductive end points were quantified using a semistructured interview to gauge menstrual cycle history, physical examination to rate modified hirsutism score [43], and transvaginal ultrasound scan to assess ovarian morphology [34, 44]. Ultrasound images of the ovaries were evaluated offline for antral follicle count (AFC) and mean ovarian volume [34, 44]. Clinical metabolic end points were quantified using standard anthropometry and vital signs assessment.

Blood samples were collected after fasting to measure biochemical markers of reproductive (*i.e.*, total testosterone, SHBG, androstenedione, estradiol, progesterone, LH, FSH) and metabolic status [*i.e.,* fasting glucose, HbA1c, fasting insulin, triglycerides, high-density lipoprotein (HDL), C-reactive protein (CRP), cortisol] [35–37]. Briefly, total testosterone was measured by isotope-dilution liquid chromatography–tandem mass spectrometry. Intra- and interassay coefficients of variation for total testosterone were <5% [37]. SHBG, androstenedione, estradiol, progesterone, LH, FSH, insulin, and cortisol were measured by two-site chemiluminescent immunoassay. Glucose, triglycerides, HDL, and CRP were measured by colorimetry or nephelometry. HbA1c was measured by high-performance liquid

chromatography. Overall, intra- and interassay coefficients of variation for the reproductive and metabolic analytes were <8% [35–37], despite readings for some analytes (*e.g.*, fasting insulin) having higher values than reported by others [3]. The free androgen index (FAI) was calculated as (testosterone/SHBG) × 100) [45]. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as [fasting serum insulin (uIU/L) × fasting serum glucose (mmol/L)]/100 [46].

D. Statistical Analysis

Statistical analyses were performed with JMP Pro 12 (SAS Institute, Cary, NC). The threshold for significance was set at $P < 0.05$. Descriptive statistics are presented as mean ± SD or proportions. Normality was ascertained with histograms or residual plots, and skewed data were log-transformed prior to analysis. Demographic and diagnostic features were compared between groups using independent samples *t* tests (continuous variables) or Fisher exact tests (categorical variables). Cognitive, reproductive, and metabolic end points were compared between groups using univariate and multivariate linear regression. PCOS status was designated as the independent variable. In the event of a significant main effect in the univariate models (*i.e.*, PCOS status, $P < 0.05$), potential differences between groups were reassessed with multivariate analysis. Body mass index (BMI) was included in multivariate models because of the increased prevalence of overweight and obesity (*i.e.*, BMI ≥ 25.0 kg/m^2) in the PCOS group versus the control group (Table 1), as well as evidence that BMI affects cognitive, reproductive, and metabolic outcomes in women with and without PCOS [30, 47].

In the event of a continued significant main effect in the multivariate models (*i.e.* PCOS status after accounting for BMI, $P < 0.05$), associations of reproductive and metabolic features with cognitive task scores were examined using univariate and multivariate linear regression. The feature was designated as the independent variable. In the event of a significant main effect in the univariate models, potential associations were reassessed using multivariate analysis, with BMI and PCOS status included as covariates. Features used to diagnose PCOS in the current study (*i.e.*, menstrual cycle length, modified hirsutism score, and total testosterone) were not considered, because of their collinearity with PCOS status. In this study, we explored a battery of potential predictors of cognitive deficits in PCOS.

Table 1. Demographic and Diagnostic Characteristics of Study Subjects

	PCOS Group (n = 40)	Control Group (n = 40)	*P* Value[a]
Age, y	27 ± 5	27 ± 4	0.67
BMI, kg/m^2	31.3 ± 8.4	24.7 ± 4.9	<0.01
Proportion with normal weight	15/40 (37.5)	26/40 (65.0)	<0.01[b]
Proportion with overweight	3/40 (7.5)	7/40 (17.5)	—
Proportion with obesity	22/40 (55.0)	7/40 (17.5)	—
Menstrual cycle length, d[c]	114 ± 101	29 ± 3	<0.01
Modified hirsutism score	12 ± 6	3 ± 2	<0.01
Proportion with clinical signs of HA	35/40 (87.5)	0/40 (0.0)	<0.01
Total T, nmol/L	3.6 ± 1.5	2.7 ± 0.7	0.02
Proportion with HA by total T	11/40 (27.5)	0/40 (0.0)	<0.01
FAI, %	13 ± 8	5 ± 2	<0.01
Proportion with HA by FAI	20/40 (50.0)	0/40 (0.0)	<0.01

Data are presented as mean ± SD or no./total (%).

Abbreviations: —, comparison between individual categories was not performed; HA, hyperandrogenism; T, testosterone.

[a]Data were assessed with independent samples *t* tests or Fisher exact tests. $P < 0.05$ was considered statistically significant.

[b]*P* value reflects a comparison across normal weight (BMI, ≤24.9 kg/m^2), overweight (BMI, 25.0–29.9 kg/m^2), and obese categories (BMI, ≥30.0 kg/m^2).

[c]Refers to the average self-reported interval between menses in the year before study enrollment.

Therefore, *a priori* sample size calculations were not performed and corrections for multiple hypothesis testing were not applied.

2. Results

A. Participant Characteristics

Demographic and diagnostic features of women with (n = 40) and without PCOS (n = 40) are presented in Table 1. The two groups were similar in age ($P = 0.67$), but women with PCOS had higher BMI than did control subjects ($P < 0.01$). By design, women with PCOS were also distinguished from control subjects by longer menstrual cycles, higher modified hirsutism scores, and higher serum levels of total and free androgens ($P < 0.05$ for all). Most women with PCOS met the criteria for hyperandrogenism based on clinical signs of androgen excess (Table 1).

B. Cognitive Function

Cognitive task scores are compared between groups in Table 2. In univariate models, PCOS status was associated with visuospatial ability, as judged by the mental rotation task ($P < 0.01$). PCOS status remained independently associated with lower mental rotation task scores after adjustment for BMI ($P = 0.02$). There was no evidence of an independent effect of PCOS status on manual dexterity (Purdue pegboard task) or perceptual speed (identical pictures task; $P > 0.05$ for all; Table 2).

C. Associations of Reproductive and Metabolic Features With Cognitive Function

Reproductive and metabolic features are compared between groups in Table 3. In univariate models, PCOS status was associated with FAI, AFC, ovarian volume, systolic blood pressure, and levels of LH, HbA1c, fasting insulin, HOMA-IR, triglycerides, HDL, and CRP ($P < 0.05$ for all). PCOS status remained independently associated with higher FAI, AFC, ovarian volume, and HbA1c after adjustment for BMI ($P < 0.01$ for all). Results of multivariate models were not tabulated for fasting insulin, HOMA-IR, HDL, or CRP, because of collinearity between the metabolic features and BMI (Table 3).

Associations of reproductive and metabolic features with visuospatial ability are reported in Table 4. Of the three reproductive features that differed between women with and without PCOS (Table 3), only FAI was associated with mental rotation task score ($P = 0.03$), yet significance was lost after adjustment for BMI ($P = 0.53$). Conversely, HbA1c was negatively associated with mental rotation task score before and after adjustment for BMI ($P < 0.01$ for

Table 2. Associations of PCOS With Cognitive Task Scores

	PCOS Group (n = 40)	Control Group (n = 40)	Univariate Analysis	Multivariate Analysis
	Mean ± SD		PCOS Status β (SE)	
Purdue pegboard, sec				
Dominant hand	49 ± 5	48 ± 5	0.83 (0.58)	NA
Nondominant hand	52 ± 5	52 ± 4	0.25 (0.54)	NA
Both hands	61 ± 7	58 ± 6	1.40 (0.72)	NA
Identical pictures	38 ± 7	38 ± 8	0.23 (0.83)	NA
Mental rotation	6 ± 3	9 ± 5	−1.34 (0.48)[a]	−1.24 (0.53)[a]

Cognitive task score was designated as the outcome variable. PCOS status was designated as the independent variable. Multivariate models included BMI as a covariate and were only performed in the event of a significant main effect in univariate models, $P < 0.05$.

Abbreviation: NA, not assessed, because of the absence of a significant main effect in univariate models.

[a]Significant main effect of PCOS status on cognitive task score, $P < 0.05$.

Table 3. Associations of PCOS With Reproductive and Metabolic Features

	PCOS Group (n = 40)	Control Group (n = 40)	Univariate Analysis	Multivariate Analysis
	Mean ± SD		PCOS Status β (SE)	
Sex steroid hormone				
FAI, %	13 ± 8	5 ± 2	0.39 (0.06)[a,b]	0.20 (0.06)[a,b]
ANSD, nmol/L	11.7 ± 5.3	11.0 ± 6.2	0.05 (0.05)[b]	NA
Estradiol, pmol/L	187.3 ± 96.8	146.1 ± 94.7	0.14 (0.06)[a,b]	0.13 (0.07)[b]
Progesterone, pmol/L	2.2 ± 0.7	2.0 ± 0.5	0.03 (0.03)[b]	NA
Ovulatory function				
Antral follicle count	84 ± 28	40 ± 21	0.41 (0.05)[a,b]	0.46 (0.06)[a,b]
Mean OV, cm^3	11 ± 3	8 ± 3	0.21 (0.04)[a,b]	0.22 (0.05)[a,b]
LH, IU/L	6.3 ± 2.9	4.9 ± 1.8	0.73 (0.30)[b]	0.69 (0.36)
FSH, IU/L	5.1 ± 1.8	5.3 ± 1.5	−0.13 (0.20)	NA
Glucose control				
Fasting glucose, mmol/L	4.9 ± 0.5	4.8 ± 0.3	0.02 (0.01)[b]	NA
Hemoglobin A1c, %	5.3 ± 0.4	4.9 ± 0.3	0.19 (0.04)[b]	0.15 (0.05)[a]
Insulin sensitivity				
Fasting insulin, pmol/L	83.9 ± 60.8	35.8 ± 19.4	0.36 (0.08)[a,b]	NR
HOMA-IR	2.7 ± 2.2	1.0 ± 0.6	0.39 (0.09)[a,b]	NR
Blood pressure, mm Hg				
Systolic	115 ± 9	111 ± 9	2.18 (1.00)[a]	1.03 (1.05)
Diastolic	74 ± 8	72 ± 7	0.01 (0.01)[b]	NA
Lipids, mmol/L				
Triglycerides	1.3 ± 1.0	0.8 ± 0.4	0.23 (0.06)[a,b]	0.08 (0.06)[b]
HDL	1.3 ± 0.3	1.5 ± 0.3	−0.10 (0.04)[a]	NR
Stress/inflammation, nmol/L				
CRP	36.8 ± 37.9	7.5 ± 9.6	0.71 (0.13)[a,b]	NR
Cortisol	193.1 ± 100.3	219.4 ± 76.1	−0.10 (0.05)[b]	NA

The reproductive or metabolic feature was designated as the outcome variable. PCOS status was designated as the independent variable. Multivariate models included BMI as a covariate and were only performed in the event of a significant main effect in univariate models, $P < 0.05$.

Abbreviations: ANSD, androstenedione; NA, not assessed due to the absence of a significant main effect in univariate models; NR, not reported due to collinearity between the feature and BMI; OV, ovarian volume; WC, waist circumference.

[a]Significant main effect of PCOS status on the reproductive or metabolic feature, $P < 0.05$.

[b]The outcome variable was log-transformed prior to analysis due to skewed residuals. Effect sizes were not back transformed for data presentation.

both). Overall, there was no evidence of an independent effect of BMI or PCOS status on visuospatial ability in any of the multivariate models ($P > 0.10$ for all; Table 4).

3. Discussion

In this study, we expanded on previous research by comprehensively examining associations between the abnormal endocrine milieu and cognitive outcomes in PCOS. We observed reduced visuospatial ability, as judged by scores on the mental rotation task, in women with PCOS compared with control subjects. We also identified a link between reduced visuospatial ability and higher levels of HbA1c in our entire study cohort, independent of BMI or PCOS status.

We describe poorer performance on a male-advantage cognitive task in PCOS. We appreciate that our findings add to already mixed evidence in the field [7, 8, 11]. Barnard *et al.* [8] and Schattmann and Sherwin [7] reported similar scores on tests of visuospatial ability between women with and without PCOS, and Barry *et al.* [11] reported higher scores on the mental rotation task in women with PCOS. Lower scores in the present versus previous studies might be explained by differences in our control groups. We recruited women with

Table 4. Associations of Reproductive and Metabolic Features With Visuospatial Ability in Women With and Without PCOS

	Univariate Analysis[a]	Multivariate Analysis[b]	
	Feature β (SE)	Feature β (SE)	PCOS Status β (SE)
Sex steroid hormones			
FAI, %	−0.17 (0.08)[c]	−0.07 (0.11)	−1.02 (0.62)
Ovulatory function			
Antral follicle count	−0.03 (0.02)	NA	NA
Mean OV, cm^3	−0.16 (0.15)	NA	NA
Glucose control			
HbA1c, %	−4.90 (1.27)[c]	–4.09 (1.48)[c]	−0.50 (0.60)

Abbreviation: NA, not assessed due to the absence of a significant main effect in univariate models.
[a]Univariate models were only performed in the event of a significant main effect of PCOS on cognitive task scores (Table 2) and reproductive or metabolic features (Table 3) after adjustment for BMI. Visuospatial ability (as judged by mental rotation task score) was designated as the outcome variable. The reproductive or metabolic feature was designated as the independent variable.
[b]Multivariate models included PCOS status and BMI as covariates and were only performed in the event of a significant main effect in univariate models, $P < 0.05$.
[c]Significant main effect of a reproductive or metabolic feature or PCOS status on visuospatial ability, $P < 0.05$.

regular menstrual cycles to serve as control subjects. Barry *et al.*, for example, obtained control subjects from a patient population with irregular menstrual cycles and seeking fertility treatment [11]. If sex steroid hormones exert activational effects on cognitive function [14], then it is reasonable to suspect that any differences in hormone secretion across ovulatory disorders [48] could yield differences in cognitive outcomes. Barry *et al.* might have identified lower scores on the mental rotation task in PCOS had the composition of their control group had been more like ours.

Our findings of similar performance on female-advantage cognitive tasks between women with and without PCOS are also inconsistent with previous studies [7, 8]. Barnard *et al.* [8] reported lower scores on tasks measuring reaction time and word recognition in PCOS, and Schattmann and Sherwin [7] reported lower scores on the controlled word association, category fluency, and Purdue pegboard tasks. The discrepancies might be explained by differences in the criteria that were used to diagnose PCOS. We used the National Institutes of Health criteria [38], which identify patients solely on the basis of the presence of oligo-anovulation and hyperandrogenism [49]. Barnard *et al.* [8] administered an online survey and relied on self-reported diagnoses. A lack of biochemical data to corroborate the diagnoses might have led to the misclassification of some healthy control subjects as having PCOS. Likewise, Schattmann and Sherwin [7] used nonstandard diagnostic criteria, which might have led to the evaluation of a broad range of ovulatory disorders [48]. As a result, our study might have been better positioned to capture differences in female-advantage performance between women with and without PCOS. The discrepancies between studies might also be explained by the use of different tests of working memory. By administering different tests, we and others [7, 8] evaluated diverse behavioral abilities within the domains of manual dexterity and perceptual speed. The distinction is notable, because female-advantage performance varies at the intertest and interindividual levels [50]. Modulation of cognitive function by sex steroid hormones may also be less likely to manifest on "easier" tests, like the Purdue pegboard and identical pictures tasks [7, 51]. Taken together, it is challenging to draw conclusions regarding the effect of PCOS on manual dexterity or perceptual speed.

Our finding of a link between reduced visuospatial ability and higher levels of HbA1c builds on similar evidence from the general population [52, 53] and cohorts with diabetes mellitus [54, 55]. Namely, a negative association between working memory and HbA1c has been documented in children [55] and adults with diabetes mellitus [54]. The relationship is moderate

[56] but appears to emerge within the normal range of HbA1c [52, 53]. Poorer long-term glycemic control might also accelerate the age-related cognitive decline [57, 58]. The mechanism whereby dysglycemia impairs working memory is likely complex [24] and mediated by age, visceral adiposity, and/or sex steroid hormones [32, 42, 59]. In the current study, the relationship between visuospatial ability and dysglycemia occurred independently of BMI and PCOS status. However, we propose that evidence of lower mental rotation task scores in PCOS was, in part, explained by differences between groups in HbA1c. Therefore, there might be a potential cognitive benefit of lifestyle intervention, regardless of BMI, given that changes in dietary intake and physical activity improve glycemic control in women with PCOS [39, 60].

The main limitation of the current study was that our cohorts differed by PCOS status and BMI. We attempted to control for an effect of obesity by including BMI in our multivariate regression analysis and exercising caution when interpreting models that showed collinearity between metabolic features and BMI. We believe our approach was sufficient to identify a link between visuospatial ability and HbA1c, because others have also shown that the relationship is independent of BMI [53]. However, we appreciate that our unmatched cohorts made it impossible to explore the complete contribution of PCOS-related endocrine features to cognitive outcomes. Future studies should intentionally match cohorts for BMI, perhaps by recruiting normal weight and obese women with and without PCOS, to ascertain the independent effect(s) of obesity versus PCOS. Furthermore, it should be noted that our biochemical and cognitive tests did not always occur on the same day. Coordinating the availability of technicians and facilities to a single time was challenging and resulted in the need for us to perform assessments over several days. Some women with irregular menses were also, consequently, in sporadic luteal phases during the first cognitive test session. Although we standardized our biochemical assessments to the follicular phase and confirmed that menstrual cycle phase did not affect cognitive outcomes, we understand that an ideal study design would have involved the collection of all end points on the same day.

In conclusion, we observed reduced visuospatial ability in women with PCOS compared with control subjects. Reduced visuospatial ability was linked to higher levels of HbA1c in our entire study cohort, suggesting a role for glycemic control and not PCOS, *per se*, in the modulation of cognitive outcomes in women of reproductive age. Additional studies are needed to understand the short- and long-term effects of dysglycemia on brain health in women with PCOS, given their increased propensity for metabolic comorbidities, compared with control subjects [2].

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Additional Information

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Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References and Notes

1. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2012;**18**(6): 618–637.
2. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2010;**16**(4):347–363.
3. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocr Rev*. 2012;**33**(6):981–1030.
4. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, Lobo R, Norman RJ, Talbott E, Dumesic DA. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. *J Clin Endocrinol Metab*. 2010;**95**(5): 2038–2049.
5. Franks S, Stark J, Hardy K. Follicle dynamics and anovulation in polycystic ovary syndrome. *Hum Reprod Update*. 2008;**14**(4):367–378.
6. Stener-Victorin E, Holm G, Labrie F, Nilsson L, Janson PO, Ohlsson C. Are there any sensitive and specific sex steroid markers for polycystic ovary syndrome? *J Clin Endocrinol Metab*. 2010;**95**(2): 810–819.
7. Schattmann L, Sherwin BB. Testosterone levels and cognitive functioning in women with polycystic ovary syndrome and in healthy young women. *Horm Behav*. 2007;**51**(5):587–596.
8. Barnard L, Balen AH, Ferriday D, Tiplady B, Dye L. Cognitive functioning in polycystic ovary syndrome. *Psychoneuroendocrinology*. 2007;**32**(8-10):906–914.
9. Rees DA, Udiawar M, Berlot R, Jones DK, O'Sullivan MJ. White matter microstructure and cognitive function in young women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2016;**101**(1): 314–323.
10. Soleman RS, Kreukels BPC, Veltman DJ, Cohen-Kettenis PT, Hompes PGA, Drent ML, Lambalk CB. Does polycystic ovary syndrome affect cognition? A functional magnetic resonance imaging study exploring working memory. *Fertil Steril*. 2016;**105**(5):1314–1321.e1.
11. Barry JA, Parekh HS, Hardiman PJ. Visual-spatial cognition in women with polycystic ovarian syndrome: the role of androgens. *Hum Reprod*. 2013;**28**(10):2832–2837.
12. Castellano CA, Baillargeon JP, Nugent S, Tremblay S, Fortier M, Imbeault H, Duval J, Cunnane SC. Regional brain glucose hypometabolism in young women with polycystic ovary syndrome: possible link to mild insulin resistance. *PLoS One*. 2015;**10**(12):e0144116.
13. Barry JA, Qu F, Hardiman PJ. An exploration of the hypothesis that testosterone is implicated in the psychological functioning of women with polycystic ovary syndrome (PCOS). *Med Hypotheses*. 2018; **110**:42–45.
14. Hamson DK, Roes MM, Galea LA. Sex hormones and cognition: neuroendocrine influences on memory and learning. *Compr Physiol*. 2016;**6**(3):1295–1337.
15. Spencer JL, Waters EM, Romeo RD, Wood GE, Milner TA, McEwen BS. Uncovering the mechanisms of estrogen effects on hippocampal function. *Front Neuroendocrinol*. 2008;**29**(2):219–237.
16. Ulubaev A, Lee DM, Purandare N, Pendleton N, Wu FC. Activational effects of sex hormones on cognition in men. *Clin Endocrinol (Oxf)*. 2009;**71**(5):607–623.
17. Halpern D, Lamay M. The smarter sex: a critical review of sex differences in intelligence. *Educ Psychol Rev*. 2000;**12**(2):229–246.
18. Hampson E. Estrogen-related variations in human spatial and articulatory-motor skills. *Psychoneuroendocrinology*. 1990;**15**(2):97–111.
19. Hampson E, Morley EE. Estradiol concentrations and working memory performance in women of reproductive age. *Psychoneuroendocrinology*. 2013;**38**(12):2897–2904.
20. Karlsson L, Gezelius A, Nordenström A, Hirvikoski T, Lajic S. Cognitive impairment in adolescents and adults with congenital adrenal hyperplasia. *Clin Endocrinol (Oxf)*. 2017;**87**(6):651–659.
21. Sherwin BB. Estrogen and cognitive functioning in women: lessons we have learned. *Behav Neurosci*. 2012;**126**(1):123–127.
22. Slabbekoorn D, van Goozen SH, Megens J, Gooren LJ, Cohen-Kettenis PT. Activating effects of cross-sex hormones on cognitive functioning: a study of short-term and long-term hormone effects in transsexuals. *Psychoneuroendocrinology*. 1999;**24**(4):423–447.

23. Schattmann L, Sherwin BB. Effects of the pharmacologic manipulation of testosterone on cognitive functioning in women with polycystic ovary syndrome: a randomized, placebo-controlled treatment study. *Horm Behav*. 2007;**51**(5):579–586.
24. Blázquez E, Velázquez E, Hurtado-Carneiro V, Ruiz-Albusac JM. Insulin in the brain: its pathophysiological implications for states related with central insulin resistance, type 2 diabetes and Alzheimer's disease. *Front Endocrinol (Lausanne)*. 2014;**5**:161.
25. Gerozissis K. Brain insulin: regulation, mechanisms of action and functions [published correction appears in *Cell Mol Neurobiol*. 2003;**23**(4-5):873–874]. *Cell Mol Neurobiol*. 2003;**23**(1):1–25.
26. Baker L, Cross D, Minoshima S, Belongia D, Watson G, Craft S. Insulin resistance is associated with Alzheimer-like reductions in cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Arch Neurol*. 2011;**68**(1):51–57.
27. De Felice FG, Lourenco MV. Brain metabolic stress and neuroinflammation at the basis of cognitive impairment in Alzheimer's disease. *Front Aging Neurosci*. 2015;**7**(94):94.
28. Ryu SY, Coutu JP, Rosas HD, Salat DH. Effects of insulin resistance on white matter microstructure in middle-aged and older adults. *Neurology*. 2014;**82**(21):1862–1870.
29. Willette AA, Xu G, Johnson SC, Birdsill AC, Jonaitis EM, Sager MA, Hermann BP, La Rue A, Asthana S, Bendlin BB. Insulin resistance, brain atrophy, and cognitive performance in late middle-aged adults. *Diabetes Care*. 2013;**36**(2):443–449.
30. Prickett C, Brennan L, Stolwyk R. Examining the relationship between obesity and cognitive function: a systematic literature review. *Obes Res Clin Pract*. 2015;**9**(2):93–113.
31. van den Berg E, Kloppenborg RP, Kessels RP, Kappelle LJ, Biessels GJ. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: a systematic comparison of their impact on cognition. *Biochim Biophys Acta*. 2009;**1792**(5):470–481.
32. Yaffe K. Metabolic syndrome and cognitive disorders: is the sum greater than its parts? *Alzheimer Dis Assoc Disord*. 2007;**21**(2):167–171.
33. Lujan ME, Jarrett BY, Brooks ED, Reines JK, Peppin AK, Muhn N, Haider E, Pierson RA, Chizen DR. Updated ultrasound criteria for polycystic ovary syndrome: reliable thresholds for elevated follicle population and ovarian volume. *Hum Reprod*. 2013;**28**(5):1361–1368.
34. Christ JP, Willis AD, Brooks ED, Vanden Brink H, Jarrett BY, Pierson RA, Chizen DR, Lujan ME. Follicle number, not assessments of the ovarian stroma, represents the best ultrasonographic marker of polycystic ovary syndrome. *Fertil Steril*. 2014;**101**(1):280–287.e1.
35. Clark NM, Podolski AJ, Brooks ED, Chizen DR, Pierson RA, Lehotay DC, Lujan ME. Prevalence of polycystic ovary syndrome phenotypes using updated criteria for polycystic ovarian morphology: an assessment of over 100 consecutive women self-reporting features of polycystic ovary syndrome. *Reprod Sci*. 2014;**21**(8):1034–1043.
36. Christ JP, Vanden Brink H, Brooks ED, Pierson RA, Chizen DR, Lujan ME. Ultrasound features of polycystic ovaries relate to degree of reproductive and metabolic disturbance in polycystic ovary syndrome. *Fertil Steril*. 2015;**103**(3):787–794.
37. Lujan ME, Bloski TG, Chizen DR, Lehotay DC, Pierson RA. Digit ratios do not serve as anatomical evidence of prenatal androgen exposure in clinical phenotypes of polycystic ovary syndrome. *Hum Reprod*. 2010;**25**(1):204–211.
38. Zawadzki J, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens J, Haseltine F, eds. *Polycystic Ovary Syndrome*. Boston, MA: Blackwell Scientific; 1992:377–384.
39. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ; International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertil Steril*. 2018;**110**(3):364–379.
40. Tiffin J, Asher EJ. The Purdue pegboard; norms and studies of reliability and validity. *J Appl Psychol*. 1948;**32**(3):234–247.
41. Ekstrom R, French J, Harman H, Dermen D. *Manual for Kit of Factor-Referenced Cognitive Tests*. Princeton, NJ: Education Testing Service; 1976.
42. Vandenberg SG, Kuse AR. Mental rotations, a group test of three-dimensional spatial visualization. *Percept Mot Skills*. 1978;**47**(2):599–604.
43. Yildiz BO, Bolour S, Woods K, Moore A, Azziz R. Visually scoring hirsutism. *Hum Reprod Update*. 2010; **16**(1):51–64.
44. Lujan ME, Brooks ED, Kepley AL, Chizen DR, Pierson RA, Peppin AK. Grid analysis improves reliability in follicle counts made by ultrasonography in women with polycystic ovary syndrome. *Ultrasound Med Biol*. 2010;**36**(5):712–718.

45. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab*. 1999;**84**(10):3666–3672.
46. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*. 1999;**22**(9):1462–1470.
47. Lim SS, Norman RJ, Davies MJ, Moran LJ. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. *Obes Rev*. 2013;**14**(2):95–109.
48. Lauritsen MP, Pinborg A, Loft A, Petersen JH, Mikkelsen AL, Bjerge MR, Nyboe Andersen A. Revised criteria for PCOS in WHO Group II anovulatory infertility - a revival of hypothalamic amenorrhoea? *Clin Endocrinol (Oxf)*. 2015;**82**(4):584–591.
49. Lujan ME, Chizen DR, Pierson RA. Diagnostic criteria for polycystic ovary syndrome: pitfalls and controversies. *J Obstet Gynaecol Can*. 2008;**30**(8):671–679.
50. Leeners B, Kruger THC, Geraedts K, Tronci E, Mancini T, Ille F, Egli M, Röblitz S, Saleh L, Spanaus K, Schippert C, Zhang Y, Hengartner MP. Lack of associations between female hormone levels and visuospatial working memory, divided attention and cognitive bias across two consecutive menstrual cycles. *Front Behav Neurosci*. 2017;**11**:120.
51. Bimonte HA, Denenberg VH. Estradiol facilitates performance as working memory load increases. *Psychoneuroendocrinology*. 1999;**24**(2):161–173.
52. Sanz CM, Ruidavets JB, Bongard V, Marquié JC, Hanaire H, Ferrières J, Andrieu S. Relationship between markers of insulin resistance, markers of adiposity, HbA1c, and cognitive functions in a middle-aged population-based sample: the MONA LISA study. *Diabetes Care*. 2013;**36**(6):1512–1521.
53. Arnoriaga Rodríguez M, Blasco G, Coll C, Biarnés C, Contreras-Rodríguez O, Garre-Olmo J, Puig J, Gich J, Ricart W, Ramió-Torrentà L, Fernández-Real JM. Glycated hemoglobin, but not insulin sensitivity, is associated with memory in subjects with obesity. *Obesity (Silver Spring)*. 2019;**27**(6): 932–942.
54. Mansur RB, Lee Y, Zhou AJ, Carmona NE, Cha DS, Rosenblat JD, Bruins R, Kakar R, Rasgon NL, Lovshin JA, Wroolie TE, Sim K, Brietzke E, Gerstein HC, Rong C, McIntyre RS. Determinants of cognitive function in individuals with type 2 diabetes mellitus: A meta-analysis. *Ann Clin Psychiatry*. 2018;**30**(1):38–50.
55. He J, Ryder AG, Li S, Liu W, Zhu X. Glycemic extremes are related to cognitive dysfunction in children with type 1 diabetes: A meta-analysis. *J Diabetes Investig*. 2018;**9**(6):1342–1353.
56. Geijselaers SLC, Sep SJS, Stehouwer CDA, Biessels GJ. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. *Lancet Diabetes Endocrinol*. 2015;**3**(1):75–89.
57. Rawlings A, Sharrett A, Schneider A, Coresh J, Albert M, Couper D, Griswold M, Gottesman RF, Wagenknecht LE, Windham BG, Selvin E. Diabetes in midlife and cognitive change over 20 years: the Atherosclerosis Risk in Communities Neurocognitive Study. *Ann Intern Med*. 2014;**161**(11):785–793.
58. Lehtisalo J, Lindström J, Ngandu T, Kivipelto M, Ahtiluoto S, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Eriksson JG, Uusitupa M, Tuomilehto J, Luchsinger JA; Finnish Diabetes Prevention Study (DPS). Diabetes, glycaemia, and cognition-a secondary analysis of the Finnish Diabetes Prevention Study. *Diabetes Metab Res Rev*. 2016;**32**(1):102–110.
59. Bove R, Brick D, Healy B, Mancuso SM, Gerweck AV, Bredella MA, Sherman JC, Miller KK.. Metabolic and endocrine correlates of cognitive function in healthy young women. *Obes (Silver Spring)*. 2013; **21**(7):1343–1349.
60. Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. *Fertil Steril*. 2009;**92**(6):1966–1982.