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.

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.
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 \((\text{testosterone/SHBG}) \times 100\) [45]. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as \([\text{fasting serum insulin (uIU/L)} \times \text{fasting serum glucose (mmol/L)})/100\) [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/m²) 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** | **Control Group** |
| \(n = 40\) | \(n = 40\) | \(P Value^a\) |
| **Age, y** | 27 ± 5 | 27 ± 4 | 0.67 |
| **BMI, kg/m²** | 31.3 ± 8.4 | 24.7 ± 4.9 | <0.01 |
| Proportion with normal weight | 15/40 (37.5) | 26/40 (65.0) | <0.01b |
| 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** | 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.

^aData 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/m²), overweight (BMI, 25.0–29.9 kg/m²), and obese categories (BMI, ≥30.0 kg/m²).

^cRefers 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...
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
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.

| Feature | Univariate Analysisa | Multivariate Analysisb |
|---------|----------------------|------------------------|
|         | 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, cm³  | −0.16 (0.15)         | NA                     | NA                   |
| Glucose control | HbA1c, % −4.90 (1.27)c | −4.09 (1.48)c          | −0.50 (0.60)        |

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

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

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.

Multivariate models included PCOS status and BMI as covariates and were only performed in the event of a significant main effect in univariate models, \( P < 0.05 \).

Significant main effect of a reproductive or metabolic feature or PCOS status on visuospatial ability, \( P < 0.05 \).
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 mech-
anism 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 collin-
eararity 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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