Research Article

Independent Association Of Luteinizing Hormone, But Not Testosterone, With Attention-Domain Cognitive Performance In Women With Polycystic Ovary Syndrome: A Case-Control Study

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Abstract

Background
Cognitive dysfunction in polycystic ovary syndrome (PCOS) has been variably reported and the hormonal correlates of attention-domain performance are poorly characterized.
Aim
To compare performance on the Attention subdomain of the Addenbrooke's Cognitive Examination-III (ACE-III) and digit span between women with PCOS and controls, and to explore independent hormonal predictors of attention-domain performance after adjustment for metabolic, dyslipidaemic and inflammatory confounders.
Methods
This cross-sectional case-control study was conducted in 65 women with PCOS (Rotterdam criteria) and 65 age-matched controls, between 18 and 35 years old. The ACE-III Attention subdomain score and digit span were obtained. During the early follicular phase serum free testosterone, estrogen, LH and FSH were measured. Group comparisons were performed using Mann Whitney U test. Independent hormonal predictors were identified using multiple robust linear regression adjusted for age, BMI, dyslipidaemia, and hs-CRP.
Results
The ACE-III Attention subdomain score was significantly higher in PCOS than controls (18 [16–18] vs. 17 [15–18], p=0.034), but scaled digit span did not significantly differ (p=0.579). Adjusted regression showed LH to be significantly and positively associated with ACE-III Attention score (β=0.027, 95% CI 0.008 to 0.045, p=0.006) but significantly and negatively associated with scaled digit span (β=-0.030, 95% CI -0.048 to -0.013, p=0.001). Testosterone was not associated significantly.
Conclusion
LH was the independent hormonal correlate of attention-domain performance, with opposite directions of association between two different attention-related measures. This isolated, directionally-inconsistent finding warrants cautious hypothesis-generating interpretation, and suggests gonadotropin signalling as an under-investigated target for attention domain research in PCOS.

Keywords: Polycystic ovary syndrome, luteinizing hormone, attention, cognitive function, testosterone.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age, characterized by hyperandrogenism, oligo-anovulation and polycystic ovarian morphology. [1] Besides reproductive manifestations, PCOS has been associated with insulin resistance, dyslipidaemia, chronic low-grade inflammation and increased luteinizing hormone (LH), and an increasing amount of literature has examined whether these perturbations translate into measurable effects on cognitive function. [2,3]

However, results on cognition in PCOS have been extremely inconsistent. In a 30-year prospective study of the CARDIA cohort, Huddleston et al. reported that women with PCOS had significantly lower scores on measures of attention, verbal learning, and memory at midlife, as well as reduced white matter integrity on brain imaging. [4] Similarly, Redkar and Khan reported that women with PCOS were significantly slower on focused-attention and divided-attention trials, relative to controls using experimental reaction-time paradigms. [5] In contrast, Barry et al. found that women with PCOS did better than controls on a three-dimensional mental rotation task, an effect that was positively correlated with circulating testosterone. [6] This discrepancy may be partly due to variation in the sensitivity and specificity of the cognitive instruments used, and few studies have explored the attention domain using both a brief screening subscale and a dedicated psychometric measure within the same cohort, in addition to a multivariable-adjusted hormonal analysis.

Therefore, we aimed to compare performance on the ACE-III Attention subdomain and digit span tests between women with PCOS and controls, and to determine which hormonal parameters were independently associated with performance on the attention domain after adjustment for age, BMI, dyslipidaemia, depression and inflammation.

Materials and Methods

Study Population and Design

The study was case-control and cross-sectional, and included 65 women with PCOS diagnosed according to Rotterdam criteria (presence of at least two of the following: oligo/anovulation, clinical or biochemical hyperandrogenism, polycystic ovarian morphology on ultrasound) and 65 age-matched women without PCOS, aged 18-35 years. Participants were recruited by consecutive sampling after approval of the institutional ethics committee (IHEC-II/0328/23 dated 23.03.2023) and written informed consent.

Inclusion and Exclusion Criteria

Inclusion criteria were women with age 18–35 years and, for the PCOS group, diagnosis by Rotterdam criteria. Exclusion criteria were other endocrinological or neurological disorders, medication likely to affect study endpoints in the preceding 2 months, pregnancy or lactation, and clinically evident depression.

Hormonal, inflammatory and metabolic assay

Fasting venous blood samples were obtained on day 3–4 of the menstrual cycle (early follicular phase). Serum free testosterone, estrogen, LH and follicle-stimulating hormone (FSH) were measured by chemiluminescent immunoassay. Anthropometric covariates (BMI, waist circumference) and blood pressure were measured with standardized equipment. High sensitivity immunoturbidimetric assay was used to determine hs-CRP. Dyslipidaemia status was determined by fasting lipid profile.

Cognitive Assessments

Attention domain function was evaluated using two complementary measures: (i) the Attention/Orientation subdomain of the Addenbrooke's Cognitive Examination-III (ACE-III; maximum score 18), a brief screening test that includes orientation and simple attention items, and (ii) the digit span test (forward and backward), a specific psychometric test for attention span and working memory, scored as the length of forward span, the length of backward span, and an age-scaled composite score.

Statistical Analysis

Normality was assessed by the Shapiro–Wilk test. The Mann–Whitney U test was used to compare non-normally distributed variables between groups. Independent hormonal predictors of ACE-III Attention and scaled digit span scores were identified by multiple robust linear regression with free testosterone, estrogen, LH and FSH entered simultaneously and adjusted for age, BMI, dyslipidaemia status, and hs-CRP. A p-value <0.05 was considered statistically significant. Analyses were conducted using SPSS Version 27.0

Results

A total of 130 women (65 PCOS, 65 controls) were included. Baseline demographic and hormonal characteristics of this cohort, including the significantly higher free testosterone (0.70 vs. 0.45 ng/mL, $p<0.001$) and BMI ($p<0.001$) in the PCOS group, have been reported in detail elsewhere from this parent study.

Group Comparison of Attention-Domain Measures

ACE-III Attention subdomain score was significantly higher in women with PCOS than in controls. Digit span parameters, including the scaled digit span score, did not differ significantly between groups (Table 1, Figure 1).

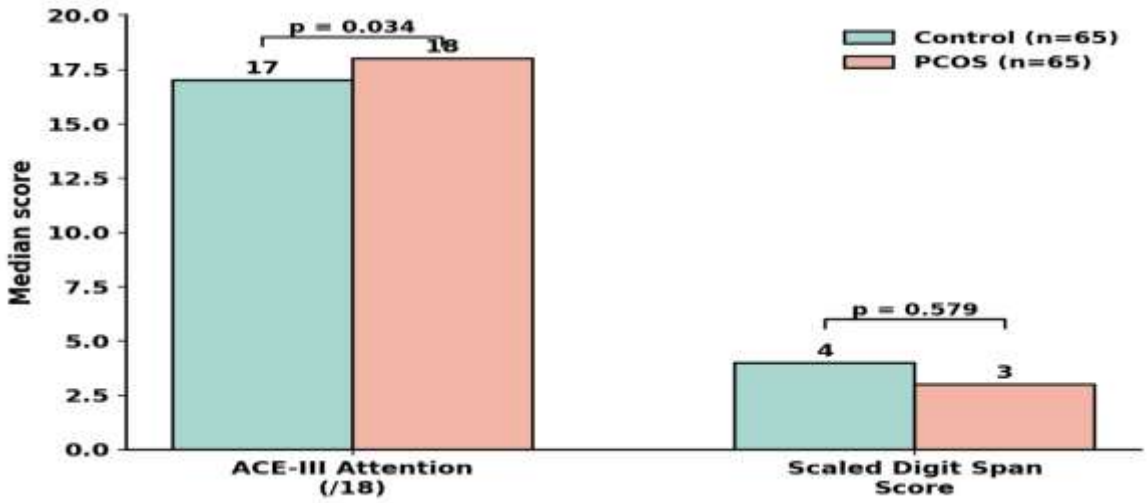
Table 1. Comparison of ACE-III Attention subdomain and digit span scores between groups

Variable	Control (n=65) Median (IQR)	PCOS (n=65) Median (IQR)	p-value
ACE-III Attention subdomain (/18)	17 (15–18)	18 (16–18)	0.034
Forward digit span length	6 (5–7)	6 (5–7)	0.937
Backward digit span length	5 (4–6)	4 (4–5)	0.236

Scaled digit span score	4 (2–5)	3 (2–4)	0.579

Mann–Whitney U test.

Figure 1. Median ACE-III Attention subdomain and scaled digit span scores by group



Note: Bars show median values; brackets indicate p-values from the Mann–Whitney U test.

Adjusted Hormonal Predictors of Attention-Domain Performance

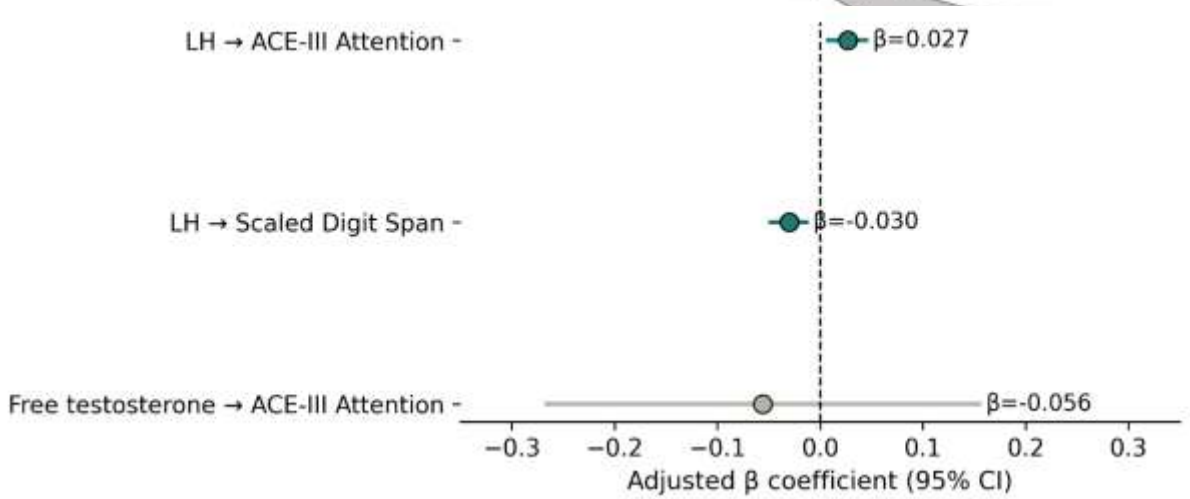
On multiple robust linear regression adjusting for age, BMI, dyslipidaemia, and hs-CRP, LH was the only hormone significantly and independently associated with ACE-III Attention score, and this association was positive. Free testosterone, estrogen, and FSH were not significantly associated with ACE-III Attention score after adjustment. In the equivalent adjusted model for scaled digit span, LH was again the only significant independent predictor, but the association was negative — opposite in direction to its association with ACE-III Attention (Table 2, Figure 2).

Table 2. Multiple robust linear regression: hormonal predictors of ACE-III Attention and scaled digit span scores

Outcome	Predictor	Adjusted β	95% CI	p-value
ACE-III Attention	Free testosterone	-0.056	-0.266 to 0.155	0.603
ACE-III Attention	LH	0.027	0.008 to 0.045	0.006
Scaled digit span	Free testosterone	-0.065	-0.273 to 0.142	0.535
Scaled digit span	LH	-0.030	-0.048 to -0.013	0.001

Adjusted for age, BMI, dyslipidaemia, and hs-CRP. Estrogen and FSH were included in the model but did not reach significance for either outcome (not shown).

Figure 2. Adjusted β coefficients and 95% confidence intervals for hormonal predictors of attention-domain outcomes



Note: Green markers indicate statistically significant associations (p<0.05); grey markers indicate non-significant associations. Dashed line represents no effect (β=0).

Discussion

This study found that women with PCOS scored modestly higher than controls on the ACE-III Attention subdomain, a finding that did not replicate on the more targeted digit span measure. This pattern sits against a predominant and, notably, very recent body of literature reporting attentional impairment rather than enhancement in PCOS. Huddleston et al., in a 30-year prospective analysis of the CARDIA cohort, found that women with PCOS scored significantly lower on attention, verbal learning, and memory at midlife, alongside reduced white matter integrity on brain imaging — the first report of its kind linking PCOS to measurable brain health changes in later life.[4] More directly relevant to attention specifically, Redkar and Khan used experimental reaction-time paradigms (Flanker's task for focused attention and Posner's cueing task for divided attention) in 173 women and found that those with PCOS were significantly slower on focused-attention trials than controls, with a smaller but consistent deficit on divided attention.[5] Our conflicting ACE-III finding is an outlier and should be taken with caution instead of confirmatory weight, supporting a more consistently reported direction of effect in PCOS in two separate reports published in 2024 and 2025 respectively.

A plausible biological candidate for cognitive enhancement, where it has been reported, is androgen exposure: higher circulating testosterone has previously been linked to superior performance on visuospatial and attentional tasks in both PCOS and non-PCOS populations.[6] However, our adjusted regression findings argue against a simple androgen-driven explanation: free testosterone, although significantly elevated in PCOS at the univariate group level, was not independently associated with ACE-III Attention score once age, BMI, dyslipidaemia, and hs-CRP were accounted for. LH, by contrast, remained significantly and independently associated with attention score after the same adjustment, suggesting that gonadotropin signalling, rather than androgen exposure per se, may be more directly relevant to the attention-domain finding in this cohort.

Using resting-state functional MRI, Lai et al. demonstrated that plasma LH level was specifically related to right frontal lobe activity in women with PCOS, a region central to attentional and executive control networks, providing a neuroanatomical substrate through which LH — independent of androgen status — could plausibly influence attention-related task performance.[7] This adds mechanistic weight to our observation that LH, rather than testosterone, was the hormone independently associated with attention in this cohort.

At the same time, the direction of this association warrants caution. A separate and substantial body of work, largely from the reproductive-aging and Alzheimer's disease literature, has consistently linked elevated peripheral LH to declines, not improvements, in cognitive and memory performance: Casadesus et al. demonstrated that experimentally increased LH was associated with impaired working memory in animal models,[8] and this has since been extended in review to a broader association between elevated LH, impaired neuroplasticity, and cognitive decline in aging women.[9] Our own data are, in fact, consistent with this predominant direction for the digit span outcome, where higher LH was significantly associated with poorer, not better, scaled digit span performance in the same adjusted model. The co-occurrence of a positive LH–attention association on ACE-III alongside a negative LH–digit span association within the same cohort and the same regression framework is itself a notable internal inconsistency, and reinforces the broader point that findings

from brief screening subscales should not be generalised to broader attentional or working-memory function without corroboration from dedicated, validated psychometric tools.

Two further aspects of our data argue for particular caution in interpreting the ACE-III finding. First, the effect size was modest (a one-point median difference on an 18-point subscale) and the p-value close to the conventional significance threshold. Second, the ACE-III Attention/Orientation subdomain combines temporal-spatial orientation items with brief attention tasks, and it is possible that the observed group difference reflects orientation-related items rather than attention per se — a limitation not shared by the digit span test, which isolates attention span and working memory more precisely.

Limitations

This study is cross-sectional and cannot establish causality between LH and attention-domain performance. The ACE-III Attention subdomain has coarse granularity relative to dedicated psychometric attention paradigms (e.g., Flanker, Posner cueing tasks), which may partly explain the direction-inconsistent findings reported here. Replication using validated, task-based attention paradigms, with concurrent androgen and gonadotropin measurement, is needed to determine whether these isolated findings reflect a genuine subgroup effect or measurement artefact.

Conclusion

In this cohort, LH — not free testosterone — was the independent hormonal correlate of attention-domain performance, with a plausible neuroanatomical basis in LH-related frontal lobe activity, though the direction of this association differed between the ACE-III Attention subdomain and the digit span test. This direction-inconsistent, isolated observation warrants cautious, hypothesis-generating interpretation rather than confirmatory weight, and highlights gonadotropin signalling as an underexplored avenue for future attention-domain research in PCOS.

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