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Evaluation of Cognitive Functioning and Laterality in Women with Polycystic Ovary Syndrome

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What is known on this subject?

There are very few studies on cognitive functions in polycystic ovary syndrome (PCOS). Although there are various studies on spatial perception and manual skills, the test for spatial perception, line splitting task, used in our study was not utilized in previous studies. Again, studies on hand preference are severely limited.

What this study adds?

This is the first study to address the effect of hormones on lateralization through motor functions and attention in PCOS. The findings of this study primarily reveal an alteration in spatial attention, independent of hormones, in PCOS. However, it revealed that dehydroepiandrosterone also had a significant effect, although mild.

ABSTRACT

Objective: To investigate potential differences in laterality and cognitive performance between women with polycystic ovary syndrome (PCOS) and healthy individuals.

Material and Methods: Thirty women with PCOS and thirty-four healthy controls were recruited. Beck depression inventory, state and trait anxiety inventory (STAI), hand preference questionnaire, line splitting task (LBT), finger tapping, Rey auditory verbal learning test (RAVLT), and Stroop Test were administered to the patient and control groups. In addition, blood levels of androgens were measured.

Results: Although the depression score in the PCOS group was higher than the control group ($p=0.048$), there was no significant difference in the STAI scores ($p>0.05$). Stroop scores were found to be significantly lower in the PCOS group ($p=0.007$, $p=0.043$, $p=0.017$). The evaluation of Stroop interference scores and RAVLT scores revealed significant differences in RAVLT 1, RAVLT 2, and RAVLT 8 recognition sub-scores between groups ($p=0.003$, $p=0.002$, $p=0.038$, $p=0.010$ respectively). The absolute rate of right-handedness was statistically lower in the PCOS group ($p=0.04$). Only LBT values of absolute right-handed subjects (Hand Preference Questionnaire Score: 13) were involved to compare spatial distribution of attention between the groups. It seems that the bisection judgement bias of the PCOS group shifted slightly to the right ($p=0.025$). A significant interaction was found between LBT scores and dehydroepiandrosterone levels ($p<0.05$).

Conclusion: Several cognitive domains and laterality seem to be affected in PCOS.

Keywords: Brain laterality, cognitive functioning, polycystic ovary syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is a complex hormonal condition marked by elevated androgen levels, irregular or absent ovulation, and the presence of multiple cysts on the ovaries (1). Endocrinologic and androgenic disturbance might lead to psychological and mood disorders (1).

Cognitive differences between the sexes have always been of interest and may be due to gender differences (2,3). However, the effects of sex differences both in functional cerebral asymmetry and cognitive functioning have not been resolved yet (3). It has also been demonstrated that exposure to prenatal testosterone may have an effect on cognitive functions (2,4,5). However, there are many results regarding the effects of hyperandrogenism on cognitive functions in adulthood. It is generally accepted that women have higher scores on verbal and fine motor tasks than men. Men have higher scores on mathematical abilities and spatial tasks than women, as indicated by research (3). However, data are limited and unclear. Moreover, a factor such as depression affects cognitive functions. Depression may be common in patients with PCOS (6).

In this study, we aimed to assess whether the laterality and cognitive performance of patients with PCOS are different from those of the healthy control group.

Material and Methods

This study enrolled 30 women diagnosed with PCOS and 34 healthy controls from the outpatient clinic of a university hospital. The diagnosis of PCOS was established according to the Rotterdam criteria (2003). Cases of congenital adrenal hyperplasia, androgen-producing neoplasms, and Cushing's syndrome were excluded (7). It was preferred that the patients be at least high school graduates.

The exclusion criteria include systemic diseases, including renal, cardiovascular, and liver diseases, and endocrinopathies such as thyroid disease and diabetes mellitus. Moreover, patients using oral contraceptives and other hormonal drugs within the last 6 months were also excluded.

Modified-Ferriman-Gallwey score (FGS) was used to evaluate clinical hirsutism (8). The study protocol was approved by the Kırıkkale University Institutional Review Board (approval no: 2009/183; approval date: 29.06.2009), and written informed consent was obtained from all participants prior to enrollment.

Laboratory Measurements

A basal hormonal profile was obtained between 2 and 5 days of a spontaneous or progesterone-induced menstrual cycle, if necessary. A Venous blood sample was taken between 08:00-09:00 A.M. after an overnight fasting period of 8-10 hours, after that all samples were stored at -20 °C until analysis.

Serum follicle-stimulating hormone, luteinizing hormone, and estradiol levels were measured using a chemiluminescent enzyme immunometric assay on an Immulite analyzer, with a commercial kit provided by Diagnostic Products Corporation. Serum dehydroepiandrosterone sulfate (DHEAS) and total testosterone levels were assessed using chemiluminescence immunoassays (Elecsys 1010/2010 kit, Roche Diagnostics GmbH, Mannheim, Germany). Free testosterone and androstenedione levels were measured by enzyme immunoassay (EIA) (Diagnostics Systems Laboratories Inc., Webster, TX, USA). Sex hormone-binding globulin (SHBG) levels were also determined using EIA (BioSource Inc.). 17-hydroxyprogesterone levels were measured by enzyme-linked immunosorbent assay on a spectrophotometer (BioTek Instruments Inc., USA) using EIA kits from DSL (Diagnostic Systems Laboratories Inc., USA). The Free Androgen Index (FAI) was calculated using the following formula:

FAI: T (nmol/L) x100/ SHBG (nmol/L)

Evaluation of Cognitive Functions and Severity of Depression and Anxiety

In this study, the following tests were applied to all participants.

1. Beck depression inventory (BDI): Depression was scored using the Beck depression scale (9).

2. State and trait anxiety inventory (STAI): STAI 1 and STAI 2 were used to identify chronic anxiety lasting more than 1 year (10).

3. Hand preference questionnaire (HPQ): The hand preference scale was developed by Chapman and Chapman (11). The Turkish validity and reliability study was conducted by Nalçaci et al. (12). This questionnaire was developed to assess which hand is predominantly used in the performance of different actions carried out in daily life. It is a 13-question survey. The right hand was scored as 1, the left hand as 3, and a "both of them" response scored 2, thus hand preference was scored as a continuous value between 13 and 39 points. Therefore, as the score increases, there is a shift from right to left (12).

4. Finger tapping test: Motor speed was evaluated with the finger tapping test. The finger tappingtest test is a fast and reliable test used in the evaluation of fine motor movement. This test, all participants were instructed to press a button as quickly as possible using the index finger of the right hand,

followed by the left hand, for 20 seconds each. The procedure was repeated twice (right, left) (13).

5. Line bisection task (LBT): Spatial distribution of attention was evaluated using LBT. LBT is a simple and reliable test for assessing the spatial distribution of attention (14). In LBT, participants were requested to draw the midpoint of 10 different lines of different lengths, ranging from 9 cm to 18 cm, each extending by 1 cm. The deviation of the line from the midpoint was calculated and included in the analysis. Here, after a reliable test, right hand dominant individuals generally have a very slight right neglect, known as pseudo-neglect. The right hemisphere is responsible for managing attention.

6. Rey auditory verbal learning test (RAVLT): RAVLT is a neuropsychological test designed to assess verbal memory, also providing rich data on multiple memory processes. When applying this test, two lists of 15 words each were used (list A and list B). In the first 5 repetitions, the words in list A were read in the same order with gaps of approximately 1 second, and when the reading was finished, the person was asked to remember the words read (Rey 1-5) (total count of words remembered in the first trial indicates immediate verbal memory). Trials 1 and 5 show the learning performance. In the sixth application, list B was read and the patient was instructed to memorize the words in this list (Rey 6). List B in the sixth application is the interference list, which is expected to have a disruptive effect on remembering the words in list A. After this interference trial, the participant is immediately asked to recall the words from list A, which she heard five times previously (Rey 7). After 20 minutes, the participant is asked to recall the words in list A again (Rey 8). This application provides information about the "delayed recall" task. Then they were asked to identify the original words from list A within a set of 50 words, including 15 target words from list A, 15 distractor words from list B, and 20 entirely new words. The last application is the recognition application (15).

7. Stroop Test: Stroop Test includes 3 cards. Word (W), color (C), and colored word (WC). In the first condition, the person reads the words directly. In the second, she says the names of the colors in the list. In the third, she reads the word list printed with a different ink color than the written word, during which the Stroop effect is observed. The Stroop effect is characterized by a slower response time when the individual is obliged to say the color of the ink instead of reading the word itself, compared to plain reading (16,17). The following formula was used to calculate the Stroop interference scores of the participants.

Stroop interference = WC- [(WxC)/(W+C)]

Statistical Analysis

All statistical analyses were conducted using SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation. The Kolmogorov-Smirnov test was applied to assess data normality, confirming a normal distribution ($p>0.05$). Given the homogeneity of variances, parametric tests were employed. Group comparisons for STAI and BDI scores, as well as for mean hand preference scores, were performed using the Student's t-test. Nominal variables were analyzed using the chi-square test. An ANCOVA test was applied to examine the effect of PCOS and related hormones on cognitive test performance. For all implementations of RAVLT, individual groups were compared by Student's t-test. All analyses were performed two-tailed and $p<0.05$ was considered statistically significant.

Results

Table 1 presents the demographic and clinical profiles of the study groups. No statistically significant differences were observed in mean age or educational attainment between groups ($p=0.066$ and $p=0.188$, respectively). As anticipated, the PCOS group exhibited significantly higher body mass index and FGS values compared to controls ($p=0.006$ and $p<0.001$, respectively).

The blood parameters and hormone values of the groups are also presented in Table 1. Among these parameters, free testosterone and FAI showed statistically higher levels; however, 17-OH progesterone showed a borderline statistically significant elevation ($p=0.002$, $p=0.006$, and $p=0.050$, respectively). As expected, SHBG levels were found to be statistically lower in the PCOS group ($p<0.05$).

Cognitive test results are shown in Table 2. In the PCOS group, the depression scale indicated borderline significance. There was no difference between the groups in terms of STAI (anxiety) ($p>0.05$).

HPQ: No significant difference was observed when the participants were compared according to the groups in terms of the hand preference scores ($p=0.540$). To understand the effect of hormones on hand preference, the ANCOVA test was performed using DHEAS and free testosterone as covariates, group as a constant factor, and hand preference as an independent variable. Accordingly, although no effect of free testosterone on hand preference was observed, DHEA had a significant effect [$F(1.60)=0.364$, $p=0.433$; $F(1.60)=3.923$, $p=0.05$, respectively]. The Absolute right-handedness rate was statistically lower in the PCOS group ($p=0.04$).

Table 1. General characteristics and blood parameters of all participants

	PCOS (n=30) Mean ± SD	Control (n=34) Mean ± SD	p
Age (years)	22.7±2.24	24.2±3.81	0.066
Education			0.188
High school	8	7	
College student	16	13	
University graduate	6	14	
BMI (kg/m^2)	22.9±3.64	20.7±2.45	0.006
FGS	8.87±3.49	5.71±2.29	<0.001
Hb (gr/dL)	12.92±1.16	13.08±1.33	0.626
FSH (mIU/mL)	5.38±1.52	6.024±2.30	0.198
LH (mIU/mL)	9.14±3.74	9.76±10.38	0.851
LH/FSH	1.82±1.02	1.98±4.41	0.847
E_2 (pg/mL)	64.88±65.40	77.59±73.31	0.470
T testosterone (ng/mL)	0.560±0.29	0.456±0.26	0.131
F testosterone (pg/mL)	2.71±2.12	1.33±0.68	0.002
17-OH progesteron (ng/mL)	1.57±1.20	1.089±0.56	0.050
Androstenedione (ng/mL)	3.58±1.69	2.91±1.96	0.147
DHEAS (µU/dL)	290.39±167.13	226.48±67.96	0.058
SHBG (nmol/L)	34.21±20.65	46.29±25.94	0.045
FAI	2.59±2.2	1.24±0.8	0.06
Insulin (µU/mL)	11.80±6.47	9.82±4.48	0.166
T cholesterol (mg/dL)	167.33±37.75	158.94±33.38	0.349
LDL (mg/dL)	90.67±31.53	83.21±28.85	0.327
HDL (mg/dL)	56.13±9.16	60.16±12.12	0.143

PCOS: Polycystic ovary syndrome, BMI: Body mass index, FGS: Ferriman-Gallwey score, Hb: Hemoglobin, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, DHEAS: Dehydroepiandrosterone sulfate, SHBG: Sex hormone-binding globulin, FAI: Free androgen index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, SD: Standard deviation

Table 2. Cognitive tests results

Cognitive tests	PCOS (n=30) Mean ± SD	Control (n=34) Mean ± SD	p
BDI	10.07±6.878	6.74±6.307	0.048
STAI-1	56.67±13.904	58.68±11.502	0.529
STAI-2	54.50±9.504	56.41±8.968	0.411
HPQ	15.50±4.67	14.76±4.86	0.540
Absolute right hand	36%	64%	0.04
Right hand 1 (tapping)	78.33±8.8	84.35±7.9	0.006
Right hand 2	79.27±9.8	84.03±7.3	0.03
Left hand 1	67.40±78.7	70.44±77.8	0.145
Left hand 2	67.63±9.9	69.68±6.7	0.148
LBT_{mean} (mm)	-0.04±0.20	0.039±0.19	0.108
LBT_{mean} (mm)* 13 cut-off	-0.096±0.21 (n=14)	0.042±0.15 (n=25)	0.025
Rey 1	7.07±1.660	8.44±1.926	0.003

Table 2. Continued

Cognitive tests	PCOS (n=30) Mean ± SD	Control (n=34) Mean ± SD	p
Rey 2	9.97±2.428	11.56±1.521	0.002
Rey 3	11.50±41.697	12.24±1.653	0.084
Rey 4	12.97±1.691	12.79±1.452	0.662
Rey 5	12.53±2.161	13.35±1.368	0.081
Rey 6	6.57±1.775	7.12±1.855	0.231
Rey 7	12.30±1.860	12.79±2.086	0.324
Rey 8	11.73±2.57	12.94±1.984	0.038
Rey recognition	13.67±1.863	14.65±0.646	0.010
Stroop 1	99.5±13.33	108.79±13.07	0.007
Stroop 2	71.10±12.25	77.53±12.63	0.043
Stroop 3	43.90±8.39	49.24±8.95	0.017
Stroop interference	2.96±6.04	4.26±7.22	0.44

**Data obtained from individuals with a Handedness Questionnaire Score of 13, indicating absolute right-handedness. PCOS: Polycystic ovary syndrome, BDI: Beck depression inventory, STAI: State and trait anxiety inventory, HPQ: Hand preference questionnaire, LBT: Line splitting task, SD: Standard deviation*

Finger tapping test: Repeated measures ANCOVA was also applied for the finger tapping test and it revealed a significant main group effect [F(1.61)=4.606, p=0.036]. Accordingly, the control group performed more finger taps than the PCOS group. At the same time, the hand preference effect was also detected [F(1.61)=72.796, p<0.001]. Finally, as expected, an interaction between right hand and hand preference was determined [F(1.61)=15.381, p<0.001].

LBT: In the LBT, there was no significant difference between the groups in terms of the mean distance from the center. However, due to the possibility that hand preference has an effect on the spatial distribution of attention in PCOS, absolute right-handed (Hand Preference Questionnaire Score: 13) individuals were included in the comparison between the groups to eliminate this effect, and the Student's t-test was used. In this analysis, 14 patients remained in the patient group and 25 in the control group. Accordingly, a significant difference was found between the groups in terms of distance from the center (p=0.025). In the ANCOVA test, free testosterone and DHEAS were treated as covariates, the LBT as the dependent variable, and the group as the independent variable. According to this, a significant main group effect and a significant DHEA effect were detected [F(1.60)=6.303, p=0.015], [F(1.60)=6.814, p=0.011, respectively].

RAVLT: Since each subgroup test of RAVLT differs, each subgroup test was compared between groups separately with a Student's t-test. In these comparisons, there was a significant difference was observed between the groups in Rey 1, Rey 2, Rey 8, and Rey recognition practices, with p values of (p=0.003, p=0.002, p=0.038, and p=0.010, respectively). In all these applications, the performance of the control group was better (Figure 1).

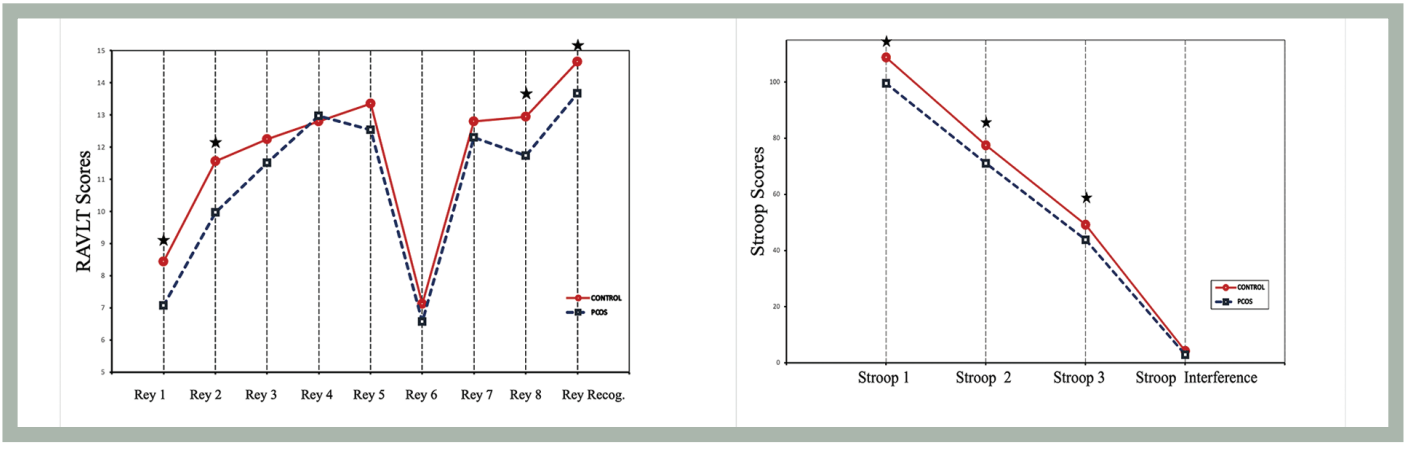

Figure 1. Demonstration of RAVLT and Stroop values in patients and control groups
★: p<0.05, RAVLT: Rey auditory verbal learning test, PCOS: Polycystic ovary syndrome

Stroop Test: In order to compare the groups in terms of Stroop Test performances, the number of words read for each of the 3 tests (word, color, color-word card) was analyzed using the Student's t-test separately (Table 2). As a result of the comparison of the groups, it was observed that the PCOS group performed significantly worse in all the 3 cards (p=0.007, p=0.043, p=0.017 respectively) (Figure 1). However, when the Stroop interference score was calculated, it was revealed that the groups did not differ in their capacity to resist the interference of the dominant response (p=0.44).

Discussion

Women with PCOS have elevated serum levels of testosterone, androstenedione, and DHEAS (1,18). In this study, patients with PCOS displayed higher plasma levels of androgens than controls, as expected.

While a borderline level of depression was observed in the PCOS group, in this study, no change was observed in anxiety tests. Moreover, no relationship was observed between depression and other cognitive functions and lateralization in this study. Although Barnard et al. (2) stated that depression impairs cognitive functions, Sukhapure et al. (19) showed that depression and anxiety do not impair cognitive functions, similar to our study. We think that depression is mild and does not affect cognitive disorders; occurs through different mechanisms. Soyupek et al. (18) found that the presence of depression in particular negatively affected hand function. There was no change in hand strength and dexterity in patients with PCOS in their study. In their study, hand dexterity was evaluated with the grooved pegboard test (18). In our study, the HPQ was used. There was no difference in the hand questionnaire scores between the two groups, but the absolute right-handedness rate was lower in the polycystic patient group. The rate of individuals who performed all tasks using their right hand was lower among patients with PCOS compared to controls. No statistically significant effects of androgens on handedness were observed, and only DHEA-S was found to be borderline effective (p=0.05). When we evaluated fine motor speed performance in PCOS, PCOS patients exhibited significantly slower finger tapping performance in the right hand than the control group. The low scores observed on the left hand in the PCOS group did not reach statistical significance.

There are limited studies in the literature on cognitive functioning and cerebral asymmetry in PCOS (2,4,20). Sex-related differences in cognitive functioning are thought to be influenced by variations in androgen and estrogen levels (2). In a study by Barnard et al. (2), individuals with PCOS were assessed using mental rotation, spatial rotation, and word recognition tasks, alongside the evaluation of the impact of anti-androgen treatment. While performance in spatial and mental rotation tasks did not significantly differ, participants exhibited reduced speed and accuracy in word recognition. Anti-androgen therapy showed only limited improvement in certain cognitive functions. The findings suggested that PCOS does not lead to a masculinized cognitive profile (2). Sukhapure et al. (19) showed that cognitive functions change with testosterone. Similarly, we have seen in our study that DHEA may be important in some cognitive functions (19). Franik et al. (21) also found that free testosterone was associated with verbal psychomotor speed. Androstenedione level showed a negative correlation with executive functions. 17-OH-P levels had a positive effect on phonological verbal fluency scores (21). Another study reported reduced performance among individuals with PCOS in cognitive domains typically favoring females, including verbal fluency, verbal memory, and fine motor skills. In contrast, no significant differences were identified in cognitive tasks generally associated with male advantage, such as mental rotation, spatial visualization, spatial perception, and perceptual speed (4). The same authors later showed in a prospective randomized study that anti-androgen and estrogen treatment improved verbal tests. However, most cognitive tests could not be corrected with this pharmacological treatment. It was also stated that these tests could not be easily corrected with hormonal treatment (22). Contrary to all these studies, Barry et al. (20) found that patients with PCOS had an advantage over other women in visuospatial cognition, and this was positively correlated with testosterone. Although we found in our study that many cognitive functions were affected and decreased in patients with PCOS, only spatial distribution of attention (LBT) may be related to DHEA in the PCOS group with absolute right-handedness. Rees et al. (23) evaluated cognitive function and white matter microstructure with diffusion tensor magnetic resonance imaging. Cognitive performance decreased in the PCOS group. It was also stated that the white matter microstructure may be affected by insulin androgens, and this relationship in PCOS may differ from that in the control group (23).

In our study, the LBT test, in which we evaluated spatial perception in PCOS patients, was not statistically different from controls. The LBT test was statistically significantly shifted more to the left only in the absolute right-handed group, indicating that the pseudo-neglect state of the right brain is

more common in the absolute right-handed group. Moreover, the spatial distribution of attention (LBT) may be related to DHEA in the PCOS group with absolute right handedness. When we looked at the literature, we could not find any study on the LBT in the PCOS.

The effects of DHEA on the human brain have not yet been clarified. DHEA is found in higher concentrations in the human brain than in the plasma and is actually a neurosteroid, synthesized *de novo* in the brain. It modulates the effects of various receptors in the brain, such as the γ-aminobutyric acid type A receptor, the N-methyl-D-aspartate receptor, and the sigma subtype 1 receptor (24). Davis et al. (25) also found that cognitive functions increased in women with high DHEA sulfate levels in their study. In our study, the effect of DHEAS was observed, especially in the absolute right-handed group.

In this study, PCOS patients performed significantly worse on the RAVLT test than controls in the first and second repetitions. According to these test results, immediate verbal memory is impaired in patients with PCOS. However, the learning curve associated with repetitions did not show statistically significant differences. It has also been observed that recognition in long "delayed recall" tasks is impaired in patients with PCOS. The worse performance of Rey recall scores compared to controls also indicates a difference in priming. Although language, which is a cognitive domain that strongly displays laterality, is affected by PCOS, it is difficult to say that lateralization is different in PCOS patients. This indicates that PCOS patients may have problems with attention, but they are not different from controls in terms of verbal memory. Similarly, the literature indicates that verbal learning studies using different tests show that verbal learning may be impaired in PCOS patients (4,22). Again, in a literature evaluation where both the RAVLT and the Stroop Test were performed, it was observed, similar to our study, that both tests were negatively affected in patients with PCOS (26).

The Stroop Test is a neurocognitive test that measures frontal lobe functions such as information processing speed, selective attention skills, and the ability to inhibit cognitive interference. Interestingly, in this study, PCOS patients read fewer words on all 3 cards, but there was no significant difference between the groups in terms of the Stroop interference score. That is, although their reading speed is slow, their ability to resist interference, which is an executive function, does not differ from the control group.

Study Limitations

A primary limitation of this study is the small sample size within the patient cohort.

Conclusion

This is the first study to address the effect of hormones on lateralization through motor and attention in PCOS. The findings of this study primarily reveal a change in spatial attention in PCOS independent of hormones. However, it also revealed that DHEA also had a significant effect, albeit mildly.

Tests assessing cognitive functions vary greatly among patients with PCOS. However, studying subgroups in patients with PCOS may provide more accurate information. In our study, patients with absolute right hands had different results than other patients.

In the present study, interpreting findings as a whole showed us that there would be a general slowness in PCOS that has been suggested by slower finger tapping performance in the absolutely right-handed group and slower reading in the Stroop Test.

Immediate verbal memory and word recall were also significantly lower in patients with PCOS. There is no robust evidence to claim that PCOS is a clinical condition where laterality is affected according to the LBTs.

There are not enough data to show that androgens affect cognitive functions in PCOS. Further studies are needed regarding the effectiveness of DHEA in this regard.

Ethics

Ethics Committee Approval: The study protocol was approved by the Kırıkkale University Institutional Review Board (approval no: 2009/183; approval date: 29.06.2009).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment.

Footnotes

Authorship Contributions

Concept: N.S., O.M.K., R.A.B., Design: N.S., O.M.K., Data Collection or Processing: R.A.B., Analysis or Interpretation: N.S., O.M.K., Literature Search: N.S., O.M.K., R.A.B., Writing: N.S., O.M.K., R.A.B.

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