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Original Research Article

Exploring EEG Biomarkers of Cognitive Dysfunction in Polycystic Ovary Syndrome

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Abstract:

Polycystic Ovary Syndrome (PCOS) and its associated cognitive dysfunction represent significant health burdens among women of reproductive age; however, reliance on traditional hormonal markers limits diagnostic precision. This analytical cross-sectional study investigated subclinical neurocognitive changes using electroencephalography (EEG) to establish novel, objective neurophysiological biomarkers in PCOS. The study comprised 55 cases and 55 healthy controls. The mean age of individuals in PCOS group is 26.5±4.8 and the mean age of individuals in control group is 26.0±5.5. The mean BMI in both the groups is near similar (PCOS=27.4±5.2 , control=27.6±6.0). In COWAT (Controlled Oral Word Association Test) Women with PCOS showed significantly lower verbal fluency scores compared to controls with a significant difference between the groups (P=0.01*). This indicates mild cognitive impairment in the PCOS group. Parietal theta power is significantly reduced in PCOS participants compared to controls, suggesting altered cognitive, as theta activity is often linked to working memory and attention (P=0.04*), whereas other parameters of EEG (Electro-Encephalo-Gram) did not show strong evidence of differences between PCOS and controls. No statistically significant alterations in relative EEG power or ratios between PCOS and control groups were found. However, trends such as slightly higher theta/alpha ratio in PCOS may indicate subtle cognitive changes. Lower theta/beta ratio in PCOS (especially at Fz) could relate to frontal cognitive processing, but further studies with larger samples are needed.

Keywords: EEG, PCOS, Neurocognition.

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Introduction

Polycystic ovary syndrome (PCOS), a common endocrine and metabolic disorder, is related to hyperandrogenism and anovulation [1]. Polycystic ovary syndrome (PCOS) is a prevalent and distressing disorder of largely unknown aetiology. Although PCOS defined by ovarian dysfunction, accumulating evidence supports a critical role for the brain in the ontogeny and pathophysiology of PCOS [2].

Its prevalence is about 10% among women of the reproductive age group in western world [3], whereas in India the pooled prevalence of PCOS was close to 10% using Rotterdam's criteria and AES criteria, while it was 5.8% using the NIH criteria [4].

Apart from hormonal alterations polycystic ovary syndrome is associated with behavioural alterations. Studies reported that women with PCOS are at a higher risk of depression [5, 6]. On the other hand, the risk of mood and anxiety disorder is significantly higher in PCOS women, and they may show symptoms of generalized anxiety disorder, social phobia, and panic disorder [7]. Data showed that memory dysfunction and cognitive deficits might occur in PCOS patients due to alteration in brain structures [8].

Many studies suggested a widespread decline in cognitive performance, which is reflected in terms of episodic memory, executive, and attentional function in PCOS. When women with PCOS underwent diffusion tensor magnetic resonance imaging (MRI) and assessment of cognitive function, the cognitive performance of PCOS subjects was less than that of the controls despite the same educational status when their executive function and episodic memory were assessed [9]. In contrast, in another study, the mental rotation task exhibited significantly higher scores in PCOS women than in control healthy women, which was found to be positively correlated with the increased level of testosterone [10].

Besides, very few studies, so far, have attempted to address the cognitive aspect of the disease objectively. There are few reports that use objective techniques, such as electroencephalography (EEG) and event-related potential (ERP) to substantiate the cognitive alteration in PCOS.

From the EEG, Electrophysiological index - the Theta-Beta Ratio (TBR), will be extracted which are frequency bands that provide an index of oscillatory activity associated with cognitive load recorded from participants while they were engaged in a semantic coordination task [11]. TBR is altered in other disorders like ADHD [Attention Deficit Hyperactivity Syndrome], Alzheimer's disease, lewy's disease [12,13]. Age group of these diseases is unlikely to affect our study.

Most of the studies are focused on the subjective assessment methods, evaluating the associated comorbidities, that is, diabetes, and hypertension or assessing the hormonal influence.

Moreover, the existing research findings are conflicting mainly with reference to confounding factors and the selection of control groups. Early identification of cognitive impairment can help in enhancing the outcomes of the target population.

Therefore, the present study aimed to assess objectively as well as subjectively the functional changes in neural, cognitive, and psychological aspects in PCOS patients who have not yet developed any associated comorbidities.

Aim: To assess the neurocognitive effects among individuals with polycystic ovary syndrome.

Objectives

1. To assess the neurocognitive effects among individuals with polycystic ovary syndrome by using controlled oral word association test
2. To evaluate the possible changes in neurocognition technically by electroencephalogram (EEG) among individuals with polycystic ovary syndrome

Material and Method

Study Population: Women of reproductive age group who are old diagnosed with PCOS

Study Design: Cross-sectional study.

Sample Size: In a study conducted by Kabilan S, et al.,

$$n = \frac{z^2 * \hat{p}(1-\hat{p})}{\epsilon^2}$$

Where, n is the required sample size.

Z is the standard normal deviate, which is equal to 1.96 at 95% confidence interval.

p is the prevalence in the population of the factor under study.

ϵ = Absolute precision taken as 10%

p = 3.5%

n= 104, cases = 52, controls = 52

Although the total study population was estimated to be 104, a slightly larger sample of 110 participants was collected, comprising 55 cases and 55 controls.

Since the sample size exceeds the required number, this is acceptable and does not pose any methodological concerns.

Time frame to address the study: 1 month

Inclusion Criteria:

- Age: 18 – 35 years
- Gender: females
- Diagnosed as PCOS according to Rotterdam's criteria
- Women who give consent for the study
- Women who are educated (degree holders)
- Women diagnosed with PCOS who are not under treatment

Exclusion Criteria:

- Comorbidities affecting hormonal axis: fibroid uterus, AUB [abnormal uterine bleeding]
- Diabetes mellitus
- Hypertension
- Thyroid disease
- Neurological disorders in which Theta /Beta ratio is altered

Definition of Case: Reproductive age group individual who obeys Rotterdam's criteria

Definition of Control: Reproductive age group individual who does not obey Rotterdam's criteria

Rationale: Specific EEG patterns especially electrophysiological index - the Theta-Beta Ratio

(TBR) reflect underlying neural dysfunctions associated with cognitive deficits.

Methodology: It is an analytical cross-sectional study which includes college going females, age 18 to 35 years who are falling under the Rotterdam's criteria and individuals who are not falling under this criterion were considered as control group. We had recruited 55 individuals with PCOS and same number of control group. Investigations were conducted in the "Clinical Physiology Laboratory" of Department of Physiology, Government Medical College, and Vizianagaram as well as in government general hospital, Vizianagaram, Andhra Pradesh. All subjects received the comprehensive explanations of the study in prior (Subject Information Sheet, SIS) and written informed consent form (Subject Informed Consent Form, SICF) was obtained from all the subjects. The study adhered to Good Clinical Practices (GCP) guidelines. The details of the Subject Information Sheet (SIS), Subject Informed Consent Form (SICF) are given in detail in the annexures attached below (Annexures I, II, III, IV, V, VI and VII respectively).

Rotterdam's criteria: According to the Rotterdam consensus, polycystic ovarian syndrome (PCOS) is defined by the presence of two of three of the following criteria: oligo-anovulation, hyperandrogenism and polycystic ovaries (≥ 12 follicles measuring 2-9 mm in diameter and/or an ovarian volume > 10 mL in at least one ovary) [14]. Details were enclosed in annexures III.

Methods – Recording protocols:

1. Controlled oral word association test [15] questionnaire was provided to all the study population and details were attached in annexures.
2. All baseline anthropometric and physiological variables, including height, weight, BMI were recorded.
3. Blood parameters such as serum lipids - triglycerides were assessed.
4. EEG recoding: After an initial 15-minute rest period, EEG recording begins while the subject remains awake, relaxed, and with eyes closed for 20 minutes. Subsequently, offline re-referencing of the EEG data was performed, followed by visual inspection to identify and exclude artifacts such as eye blinks and gross body movements. The absolute power (expressed as 10 log10 $\mu V^2/Hz$) of alpha (8–12 Hz), beta (13–35 Hz), and theta (4–7 Hz) bands are calculated. In addition, the theta/alpha ratio (TAR) and theta/beta ratio (TBR) are derived. The relative power of alpha, beta, and theta waves are also measured at frontal (Fz) and parietal (Pz) electrode sites, using Cz as the reference [16].

Statistics: The collected data was imported and systematically categorized in Ms. Excel. Subsequently, the data undergo analysis to compute descriptive statistics (mean and SD). Further, the data is analysed for normality and statistical significances was calculated using T test. All these statistical analyses were done using SPSS Software latest version 24.

Results

Table 1: Mean distribution of anthropometric and neurocognitive variables among cases and controls

Age	**Mean±SD**
Pcos	26.5±4.8
Control	26.0±5.5
BMI	
Pcos	27.4±5.2
Control	27.6±6.0
COWAT	
Pcos	32.3±4.6
Control	34.2±3.8
P Value	0.01*

Women with PCOS showed significantly lower verbal fluency scores compared to controls. This may indicate mild cognitive impairment in the PCOS group.

Table 2: Mean distribution of serum cholesterol among cases and control group

Study Population	**TG**	**HDL**	**TG/HDL**
PCOS	141±20.7	35.4±8.5	4.2±1.2
Control	138±22.1	35.8±7.7	4±1.1
P value	0.2	0.3	0.1

Although TG and TG/HDL ratio were slightly higher in PCOS, and HDL slightly lower, these variations did not reach statistical significance. [However, the trend toward higher TG/HDL ratio in PCOS may indicate a possible increased cardiometabolic risk that could become significant in larger sample sizes or in longitudinal studies.]

Table 3: Absolute Power ($10\log_{10}\mu V^2/HZ$) of EEG Waves and Their Ratios at Fz and Pz Electrode Location

	Alpha		Beta		Theta		Theta/AlphaRatio		Theta/Beta Ratio	
EEG Parameters	**Fz**	**Pz**	**Fz**	**Pz**	**Fz**	**Pz**	**Fz**	**Pz**	**Fz**	**Pz**
PCOS	4.85±1.5	5.44±1.7	3.02±1.1	3.56±1.3	5.72±1.7	6.38±1.9	1.36±0.7	1.31±0.6	2.27±1.2	2.16±1.2
Control	4.46±1.5	5.39±1.6	3.06±1.1	3.48±1.3	5.84±1.5	7.01±1.8	1.49±0.7	1.43±0.6	2.22±1.2	2.36±1.2
P Value	0.09	0.43	0.42	0.38	0.35	0.04*	0.18	0.14	0.41	0.19

Parietal theta power is significantly reduced in PCOS participants compared to controls, suggesting altered cognitive, as theta activity is often linked to working memory and attention (P=0.04*), whereas other parameters did not show strong evidence of differences between PCOS and controls.

Table 4: Relative Power of EEG Parameters and Their Ratios

	Alpha		Beta		Theta		Theta/Alpha Ratio		Theta/Beta Ratio	
EEG Parameters	**Fz**	**Pz**	**Fz**	**Pz**	**Fz**	**Pz**	**Fz**	**Pz**	**Fz**	**Pz**
PCOS	0.24 ±0.08	0.25 ±0.08	0.17 ±0.07	0.18 ±0.07	0.3 ±0.12	0.29 ±0.11	1.45 ±0.91	1.33 ±0.77	2.15 ±1.64	1.93 ±1.26
Control	0.24 ±0.08	0.25 ±0.08	0.16 ±0.08	0.18 ±0.07	0.29 ±0.11	0.28 ±0.1	1.34 ±0.73	1.3 ±0.82	2.53 ±2.0	1.95 ±1.51
P Value	0.29	0.48	0.31	0.45	0.46	0.24	0.24	0.42	0.13	0.46

No statistically significant alterations in relative EEG power or ratios between PCOS and control groups. However, trends such as slightly higher theta/alpha ratio in PCOS may indicate subtle cognitive changes. Lower theta/beta ratio in PCOS (especially at Fz) could relate to frontal cognitive processing, but further studies with larger samples are needed.

Discussion

The incidence of PCOS has increased, resulting in higher disability-adjusted life-years [17]. Sanchez-Garrido et al, stated that underlying pathophysiological mechanisms contributing to the development of PCOS are multifactorial; PCOS is more than one reproductive disorder [18]. In the present study it was found that PCOS might be linked to neurocognitive changes.

According to Van Duinkerken et al and Sutin et al, poor cognitive performance has been observed in individuals with PCOS. However, the exact pathophysiological mechanisms underlying the association between PCOS and cognitive dysfunction remain unknown. PCOS and cognitive dysfunction have been proposed to share common risk factors. PCOS symptoms and comorbidities, such as infertility, appearance changes, cosmetic problems, metabolic disturbances, and sleep problems, could pose the greatest threat to psychological distress in females with PCOS, while psychological distress and cognitive dysfunction are linked together [19,20], which is aligning with the current study observations where Women with PCOS showed significantly lower verbal fluency scores compared to controls. This may indicate mild cognitive impairment in the PCOS group.

Along with psychological distress, metabolic conditions can contribute to the loss of cognitive function [20]. Guicciardi et al observed that metabolic impairment can affect different aspects of cognitive function, such as executive functioning, visuospatial abilities, and processing speed [21]. Sanchez-Garrido et al and Kim et al, stated that Insulin resistance, a prevalent metabolic perturbation in PCOS [18], connects metabolic syndromes with cognitive impairment [22]. Notably, metabolic disturbances caused by PCOS have discernible effects on metabolic tissues such as the brain [18]. Moreover, brain structure is affected by sex hormone fluctuations. Insulin resistance and hyperandrogenism may result in structural and functional brain disturbances [23]. However our study couldn't define whether insulin resistance, high blood sugars and high serum androgen levels association with PCOS which will be explored in our future studies.

The Controlled Oral Word Association Test (COWAT) a highly specific clinical neuropsychological test that measures verbal fluency, which yielded low scores in cases when compared to control with a significant statistical difference between the groups [p=0.01*]. A study conducted by Neethu Showkath et al, used MoCA score for assessing cognition which is provides brief and comprehensive cognitive information, they found significant statistical difference between the groups. They also assessed psychological status of the study group with State-Trait Anxiety Inventory and Beck Depression Inventory.

When objectively mapping brain activity at rest, we found distinct differences between individuals with PCOS and the control group. The two groups showed significantly different spatial distributions

in their EEG brainwave power. Parietal theta power is significantly reduced in PCOS participants compared to controls, suggesting altered cognitive, as theta activity is often linked to working memory and attention (P=0.04*), whereas other parameters did not show strong evidence of differences between PCOS and controls. Neethu Showkath et al, found significant differences between among the EEG parameters in both absolute and relative power.

Conclusion

Polycystic Ovary Syndrome (PCOS) is linked to objective neurocognitive changes, extending its impact beyond a purely reproductive disorder. Women with PCOS exhibited signs of mild cognitive impairment, evidenced by significantly lower verbal fluency scores and a marked reduction in resting-state parietal theta power, suggesting altered working memory and attention networks. These cognitive deficits likely arise from a multifactorial interplay between psychological distress and metabolic disturbances. While literature implicates insulin resistance and hyperandrogenism in these brain alterations, further research is required to definitively isolate these metabolic and hormonal drivers. Ultimately, these findings underscore the importance of recognizing cognitive dysfunction as a key component of the PCOS clinical profile.

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