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PCOS, GRAY MATTER VOLUMES AND BMI

## Structural imaging of the brain reveals decreased total brain and total gray matter volumes in obese but not in lean women with polycystic ovary syndrome compared to body mass index-matched counterparts

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### Abstract

**Purpose:** To detect differences in global brain volumes and identify relations between brain volume and appetite-related hormones in women with polycystic ovary syndrome (PCOS) compared to body mass index-matched controls.

**Methods:** Forty subjects participated in this study. Cranial magnetic resonance imaging and measurements of fasting ghrelin, leptin and glucagon-like peptide 1 (GLP-1), as well as GLP-1 levels during mixed-meal tolerance test (MTT), were performed.

**Results:** Total brain volume and total gray matter volume (GMV) were decreased in obese PCOS compared to obese controls ( $p < 0.05$  for both) whereas lean PCOS and controls did not show a significant difference. Secondary analyses of regional brain volumes showed decreases in GMV of the caudate nucleus, ventral diencephalon and hippocampus in obese PCOS compared to obese controls ( $p < 0.05$  for all), whereas lean patients with PCOS had lower GMV in the amygdala than lean controls ( $p < 0.05$ ). No significant relations were detected between structural differences and measured hormone levels at baseline or during MTT.

**Conclusion:** This study, investigating structural brain alterations in PCOS, suggests volumetric reductions in global brain areas in obese women with PCOS. Functional studies with larger sample size are needed to determine physiopathological roles of these changes and potential effects of long-term medical management on brain structure of PCOS.

### Keywords

Appetite, brain imaging, ghrelin, glucagon-like peptide-1, obesity, polycystic ovary syndrome

### History

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### Introduction

Polycystic ovary syndrome (PCOS), the most common reproductive endocrinopathy in women of childbearing age, is closely related with obesity and metabolic dysfunction [1]. A similar increase in the prevalence of PCOS and obesity generated thoughts that these disorders might have a cause and effect relationship [2].

Obesity is a global epidemic, closely related with diseases causing an increase in morbidity and mortality [3]. Despite fast-food restaurants and presentation of food in large portions, not everybody to become obese could be related to individual differences in eating behavior and susceptibility to environmental factors [4]. Food intake is controlled centrally by two complementary systems which are known as homeostatic and hedonic systems. The homeostatic system is responsible for creating balance according to energy demands of the body and controlled mainly by hypothalamus [5]. The hedonic system is responsible for reward-related food intake and it is closely related with amygdala, striatum, insula and orbitofrontal cortex (OFC) [6].

Those areas related with homeostatic and hedonic systems are important parts of gray matter in the central nervous system (CNS). These systems are also closely related with hormones, most well-known being an adipocyte-derived hormone leptin, which informs the brain about long-term energy stores. Ghrelin and glucagon-like peptide-1 (GLP-1) are among other members of these systems and they are responsible for providing information about short-term energy status [5,6].

Neuroimaging is a widely used technique in obesity research in order to understand neurological basis of appetite and body weight [7]. By using cranial magnetic resonance imaging (MRI), global and regional volume measurements could be performed [8]. Alterations of the complex relationship between neuronal and hormonal systems in disorders such as PCOS and obesity may cause a tendency to weight gain. Major areas involved in appetite regulation, eating behavior and energy balance are hypothalamus, insula, OFC, ventral striatum (nucleus accumbens), dorsal striatum (putamen and nucleus caudatus), amygdala and hippocampus [9]. These regions are also important to include receptors of appetite hormones or to show signal changes due to hormonal effects by using functional MRI (fMRI) techniques [9,10]. Hypothalamus, nucleus caudatus, putamen, nucleus accumbens, amygdala and hippocampus were shown to have receptors of leptin, GLP-1 and ghrelin or show signal change in fMRI with stimulation with these hormones [11–14]. Overall, appetite and

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regulation of food intake is detected centrally by the hypothalamus and reward-related areas and peripherally by adipose tissue and gastrointestinal system. Understanding alterations of these mechanisms in PCOS might provide novel therapies.

Most of the studies suggest decreased total brain and total gray matter volume (GMV) in obesity and type 2 diabetes suggesting a decline in cognition and other brain functions [15–18]. Increased GMV is associated with increased brain activity whereas reduced GMV is associated with deficient function [19]. Detecting whether there are alterations in brain volumes in women with PCOS might provide further understanding in appetitive responses in women with PCOS.

In this study, we hypothesized that total brain and total GMVs are different in women with PCOS compared to healthy women and these differences are related to body mass index (BMI) and appetite-related hormones such as leptin, ghrelin and GLP-1.

## Materials and methods

A total of 40 subjects participated in this study. Ten lean and 10 obese PCOS patients were enrolled who presented to the Endocrinology and Metabolism or Gynecology and Obstetrics Clinics of Hacettepe University. Ten lean and 10 obese healthy women volunteered to be in the study comprised the control groups. Controls had no menstrual irregularities, hirsutism or any disease and did not use any medication. Ovarian ultrasonography and hormonal evaluation were performed to exclude the diagnosis of PCOS in both lean and obese control groups. PCOS diagnosis was made according to Androgen Excess and PCOS Society (AE-PCOS Society) criteria [20]. Biochemical and clinical hyperandrogenism, oligo-anovulation and polycystic ovaries were defined as previously described [21]. Obesity was defined as having BMI  $\geq 30$  kg/m<sup>2</sup> and being lean was considered to have a BMI between 18.5 and 25 kg/m<sup>2</sup> [3]. All women diagnosed with PCOS had biochemical and/or clinical hyperandrogenism. Oligo-anovulation was present in 70% of lean PCOS group and 80% of obese PCOS group, whereas polycystic ovaries were present 100% of lean PCOS group and 70% in obese PCOS group. Women with any other endocrine disorder were excluded. Being smoker or ex-smoker, left-handed, less than a high school graduate and having psychiatric disorder were other exclusion criteria. Four groups were studied according to their BMI values and their diagnosis of PCOS, as lean control, lean PCOS, obese control and obese PCOS.

Measurement of the waist, hip and neck circumference, as well as weight and height was performed in all subjects. Total fat mass, fat-free mass and total body water were measured using a Bioelectrical Impedance Segmental Body Analysis Monitor (TANITA, BC-418 MA type, Tokyo, Japan). Measurements were taken in kilograms and percentages. Basal metabolic rate was calculated through bioimpedance analysis prediction method [22]. All subjects were studied at baseline, during the follicular phase (days 2–5) of the menstrual cycle. All measurements were made after 8 h of fasting. For endocrine and metabolic evaluation; total testosterone (T), dehydroepiandrosterone sulfate (DHEAS), sex hormone binding globulin (SHBG), fasting insulin, fasting glucose, fasting lipid profile [triglycerides (TG), high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL)], as well as alanine aminotransferase, creatinine and complete blood count, were studied. Free androgen index (FAI = [T(mmol/l)/SHBG (nmol/l)]  $\times$  100), homeostasis model assessment index-insulin resistance (HOMA-IR = [fasting insulin (uU/ml)  $\times$  fasting plasma glucose (mg/dl)]/405) and total cholesterol (total cholesterol = [LDL + HDL + (TG/5)]) were calculated from the formulas.

Every individual's perception of satiety was measured on a subjective satiety scale (from very hungry to very full) [23].

Mixed-meal tolerance test (MTT) was performed with Abbott standard oral enteral solution (Abbott Ensure plus; Abbott Laboratories, Columbus, OH). After an overnight fast, a standardized mixed meal was given as breakfast within 5 min. Blood samples were taken at 0, 15, 30, 45, 60, 90, 120 and 180 min to measure fasting levels of leptin and ghrelin and fasting and meal stimulated levels of GLP-1. Subjects completed a scale to assess subjective satiety before and during MTT before each venous sampling. Physical activity and additional food consumption were not allowed during testing.

Venous blood samples were obtained and centrifuged within 2 h, and serum was stored at  $-80^{\circ}\text{C}$ . T and insulin concentrations were measured by chemiluminescent immunoassay kits (Roche Diagnostics GmbH, Mannheim, Germany). Intra- and interassay coefficients of variation for T were both  $<5\%$  and for insulin  $\leq 4.3\%$  and  $\leq 3.4\%$ , respectively. The concentration of DHEAS was determined by chemiluminescent immunoassay (Immulate 2000; Siemens Healthcare Global Eschborn, Germany) and SHBG was measured by immunoradiometric assay (ZenTech, Angleur, Belgium) with both intra- and interassay coefficients of variation  $<10\%$ . TG, LDL and HDL concentrations were measured by using enzymatic calorimetric kits with intra- and interassay coefficients of variation of  $<10\%$  and plasma glucose concentration was determined by the glucose oxidase method (Olympus AU 2700; Beckman Coulter, Inc., Pasadena, CA). Detection of serum leptin levels was performed using ELISA method (Boster Immunoleader, EK0437, Pleasanton, CA) with intra- and interassay coefficients of variation  $<10\%$ . Serum ghrelin levels were measured with ELISA method (Human Ghrelin (total) ELISA, Millipore Total Ghrelin-EGZRT-89K, St. Charles, MO) with intra- and interassay coefficients of variation  $<10\%$ . GLP-1 concentrations were also detected with ELISA method (Millipore, EZGLP1T-36K, St. Charles, MO) with an intraassay coefficient of variation 1% and interassay coefficient of variation  $<12\%$ .

In order to evaluate structural brain differences, MRI was performed in all participants on a 1.5 T system equipped with 8-channel phase-array head coil system (Magnetom Symphony Tim, Siemens, Erlangen, Germany). Imaging protocol applied whole brain sagittal 3D T1-weighted (W) magnetization prepared recalled gradient-echo (MPRAGE) (TR/TE/TI; 1910/3.5/1100 ms, BW: 130, Slice thickness: 1 mm, FOV: 195\*260, matrix: 192p\*256, number of slices: 176) and T2-W axial turbo spin-echo (TR/TE; 5890/117, BW: 130, SL: 5/0.75, FOV: 220\*220, matrix: 359\*448s, number of slices: 25) sequences. Following the acquisition of the data, these images were reviewed by an experienced neuroradiologist and MRI physician who were blind to subject status. For total brain volume analysis, we used Freesurfer version 5.3.0 (Boston, MA) (<http://surfer.nmr.mgh.harvard.edu/>) volumetric segmentation including the removal of non-brain tissue, using an automated algorithm to segment the whole brain (including caudate nucleus, ventral diencephalon, hippocampus and amygdala), motion correction and cortical surface reconstruction [24]. For the automated segmentation and labeling of subcortical brain regions, a standard atlas, Talairach atlas was used and the images were smoothed with Gaussian blurring kernels. The automated segmentation trades on an affine rigid linear transformation and defines the location of neighboring structures. Each region was normalized with intracranial volume. The relation between these measurements and basal levels of leptin and ghrelin as well as basal and stimulated levels of GLP-1 were investigated with Spearman's correlation analysis.

## Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics for Mac version 20 (IBM Corp. Released 2011, Armonk, NY).

Table 1. Clinical, hormonal and biochemical characteristics and brain volumetric measurements of PCOS patients and control women.

	Lean			Obese		
	PCOS median, (min–max)	Control median, (min–max)	<i>p</i>	PCOS median, (min–max)	Control median, (min–max)	<i>p</i>
Age	20 (18–25)	26.5 (25–40)	<0.01	28.5 (18–34)	32 (20–39)	NS
Height (m)	1.61 (1.51–1.68)	1.63 (1.55–1.70)	NS	1.58 (1.55–1.77)	1.65 (1.54–1.74)	NS
Weight (kg)	55.1 (48.7–67)	54.2 (47.9–68.9)	NS	89.7 (77–123.6)	103.6 (85.5–125.9)	NS
BMI (kg/m <sup>2</sup> )	21.0 (18.6–24.9)	20.5 (19.1–24.8)	NS	34.2 (30.8–44.3)	38.2 (30.8–47.5)	NS
Waist circumference (cm)	68.5 (61–82)	65.5 (60–70)	NS	103.5 (90–130)	108 (91–130)	NS
Waist/hip ratio	0.73 (0.65–0.81)	0.70 (0.64–0.73)	0.023	0.84 (0.79–1.12)	0.83 (0.74–0.93)	NS
Neck circumference (cm)	30.0 (28–35)	30.5 (28–33)	NS	38 (34–41)	38 (35–41)	NS
Fat mass (%)	22.8 (13.5–33.6)	22.2 (16–29.6)	NS	43.2 (38–51.4)	43.4 (35.5–52.6)	NS
BMR (kcal)	1306 (1226–1504)	1265 (1193–1495)	NS	1589 (1472–2092)	1792 (1618–2006)	NS
Fasting plasma glucose (mg/dl)	84.5 (82–93)	88 (74–101)	NS	100 (84–115)	97 (79–110)	NS
Insulin (μIU/ml)	7.1 (5.1–11.1)	4.4 (2–9.6)	0.029	19.2 (10.6–27.7)	15 (9–26.9)	NS
HOMA-IR	1.5 (1.0–2.3)	1.04 (0.4–1.95)	0.029	4.4 (2.6–7.2)	3.3 (1.8–6.3)	NS
Leptin 0 min (ng/ml)	12.4 (2.9–52)	7.4 (5–38.6)	NS	41.6 (23.6–61)	45.9 (18.9–65)	NS
Ghrelin 0 min (pg/ml)	319 (234–594)	353 (204–1104)	NS	245 (204–359)	221 (202–279)	NS
GLP-1 0 min (pM)	25.5 (18.2–65.1)	34.2 (20.4–43.7)	NS	57.6 (10.8–73.1)	50.7 (34–66.8)	NS
GLP-1 AUC	6516 (3583–10 380)	7125 (4144–9866)	NS	9739 (3104–21 620)	11145 (7728–16 070)	NS
Satiety Index AUC	735 (315–1110)	750 (210–1005)	NS	851 (353–1230)	619 (293–1118)	NS
Total brain volume (cm <sup>3</sup> )	1090 (998–1249)	1104 (1040–1201)	NS	1027 (972–1121)	1091 (984–1296)	0.023
Total gray matter volume (cm <sup>3</sup> )	634 (563–724)	636 (579–680)	NS	601 (538–665)	636 (551–739)	0.048

AUC: area under the curve; BMI: body mass index; BMR: basal metabolic rate; GLP-1: glucagon-like peptide-1; HOMA-IR: homeostasis model assessment index-insulin resistance; NS: non-significant; PCOS: polycystic ovary syndrome.

Numeric variables were summarized as median and minimum and maximum values. Categorical variables were evaluated with cross table analysis and shown numerically with a percentage. Mann–Whitney U test was used for all pairwise comparisons. The area under the curve (AUC) for SI results and GLP-1 measurements were calculated using the trapezoidal formula. The correlation between volumes of the specified structures and hormonal measurements were detected using Spearman's correlation coefficient. Because of the statistical difference of age in lean PCOS and control groups, the age-adjusted statistical analysis was performed in all comparisons of these two groups.  $p < 0.05$  was considered statistically significant. Power analysis suggested that 10 people per study group achieved 95.02% power to detect a standardized effect size of 0.45 between groups, in the total brain volume (cm<sup>3</sup>) with  $\alpha = 0.05$ . Power calculation was conducted with the NCSS-PASS software (Kaysville, UT).

## Results

### Baseline characteristics of study groups

Anthropometric measurements, body composition properties and hormonal and biochemical parameters are presented in Table 1.

Although all women were in childbearing age, the mean age of lean PCOS group was lower than lean controls ( $p < 0.01$ ) (Table 1). There were no difference between lean PCOS and lean control groups in terms of height, weight, BMI and waist and neck circumference, but lean PCOS group had a significantly higher waist/hip ratio than the lean control group ( $p = 0.023$ ), (Table 1). TANITA measurements were similar between two groups. T, DHEAS and FAI values, as well as modified Ferriman–Gallwey (mF-G) score, were higher ( $p < 0.01$  for all), whereas SHBG levels were lower ( $p < 0.01$ ) in lean PCOS compared to controls. There were no differences between two groups in terms of lipid profile and fasting glucose values but fasting insulin values were higher in lean PCOS group ( $p = 0.029$ ) (Table 1).

Obese PCOS group and obese controls had similar anthropometric measurements (Table 1). T, FAI, DHEAS and mF-G scores were significantly higher in obese PCOS group ( $p < 0.01$  for all), whereas SHBG, lipid profile, fasting glucose and insulin levels were similar in both groups.

### Comparison of volumetric measurements

When obese PCOS and obese controls were compared, total brain volume (brain segmentation volume without ventricles) and total GMV were found to be significantly lower in obese PCOS group compared to obese controls ( $p = 0.023$  and  $p = 0.048$ , respectively) (Table 1). Additionally, reduced volume was also observed in left ventral diencephalon ( $p = 0.018$ ), left nucleus caudatus ( $p = 0.043$ ) and left and right hippocampus in obese PCOS group ( $p = 0.015$  and  $p = 0.042$ , respectively).

In the lean groups, the age-adjusted statistical analysis revealed no statistically significant difference in total brain volume and total GMV, however, lean women with PCOS had significantly lower GMV in left amygdala compared to controls ( $p = 0.028$ ).

### Comparison of basal and meal stimulated hormone levels, satiety and determination of correlation with volumetric measurements

No significant differences were detected between lean PCOS and lean control groups and between obese PCOS and obese control groups in terms of basal serum leptin, ghrelin and GLP-1 levels (Table 1). Meal stimulated GLP-1 levels were similar in obese PCOS and healthy obese groups ( $p = 0.822$ ). Even though there was a tendency for reduced levels of GLP-1 toward the end of the test in lean PCOS compared to lean controls this difference did not reach statistical significance.

Lean PCOS and lean control groups and obese PCOS and obese control groups did not differ when AUC calculations of SI values were considered ( $p = 0.985$  and  $p = 0.579$ , respectively) (Table 1).

No significant correlations were found between volume reduction of brain areas and fasting leptin, ghrelin, GLP-1 and meal stimulated GLP-1 levels.

## Discussion

Our study indicates that obese women with PCOS have a lower total brain and total GMVs than age- and BMI-matched obese controls. Most studies suggest decreased total brain and total GMV in obesity and type 2 diabetes [15–18], although not all

agree [8,25]. Those reporting differences frequently involved men and women with older age (from 45 up to 75) [15,17,18]. Taki et al. [17] showed decreased total brain volumes in obese men but not in women and linked this finding to different fat distribution patterns of men and women, with visceral fat predominating in men and subcutaneous fat predominating in women. Increased visceral fat is associated with increased risk of metabolic syndrome and women with PCOS are known to be prone to increase visceral fat [26]. Castellano et al. [27] showed similar total brain volumes in lean women with PCOS compared to BMI-matched healthy counterparts, consistent with our findings in lean women with PCOS. Our results suggest that when obesity is accompanied with PCOS, decreased brain volume could be observed at early ages that is usually observed in older patients with obesity and/or diabetes.

Although our primary aim was to detect total brain volumetric differences, we have also made secondary analyses related with regional brain volumes taking into account previous data including diabetes and obesity studies. We have found volumetric reductions in some gray matter areas related with appetite and appetite-related behavior in obese women with PCOS when compared to obese controls such as; left ventral diencephalon (includes hypothalamus), left nucleus caudatus and bilateral hippocampus. These areas are involved in appetite regulation, eating behavior and energy balance and are also important to include receptors of appetite hormones or to show signal changes due to hormonal effects by using fMRI techniques [9,10]. Generally, it could be inferred that structural and functional differences in brain regions related with sensory processing, pleasure, memory and inhibitor control could cause an increase in food consumption in obese individuals. Also, metabolic changes seen in obesity could trigger undesirable changes in brain tissue [28]. Hypothalamus, nucleus caudatus and hippocampus volumes were reported to be inversely correlated with BMI [8,29,30]. Also, hippocampal volumes were shown to be decreased in patients with type 2 diabetes [16]. In the presence of both obesity and PCOS, food intake and appetite regulation may be altered more evidently through homeostatic and hedonic systems. We have also observed reduced GMV in left amygdala in our lean PCOS group compared to lean controls. Lower amygdala volume was reported to be associated with altered reward susceptibility, which could increase the risk for future weight gain [31]. However, we were not able to explain the reason of volumetric differences not seen bilaterally but on one side. To the best of our knowledge, no convincing explanation is available in the literature, although there are studies finding different results for the left and right regions [32,33]. Although we have found statistically significant regional volumetric differences in both groups, these secondary results can only be taken as hypothesis generating preliminary findings for women with PCOS.

In our study, we have also looked at whether brain structural differences in PCOS are linked to satiety, measured by a visual analog scale and hormonal alterations. SI was similar between the groups and did not correlate with structural differences. Basal leptin, ghrelin and GLP-1 were not significantly different in PCOS patients compared to their BMI-matched healthy counterparts. Meal stimulated GLP-1 levels were similar in obese PCOS and healthy obese groups whereas there was a tendency to reduced levels of GLP-1 toward the end of the test in lean PCOS compared to lean controls. Nevertheless, we have failed to detect any significant correlation between hormone levels and structural alterations in brain regions. There are no studies in PCOS looking at structural or functional changes in brain and alterations in the appetite-related gut and adipose hormones. Leptin was reported to be positively associated with hypothalamus volumes in obese individuals [32]. Peripheral levels might not reflect central levels

of hormones in the CNS or tissue levels [34], also potentially other hormones that have not been measured in our study such as peptide YY, cholecystokinin, gastric inhibitory peptide might be involved in linking gut-brain axis in PCOS.

Limitations of our study include the relatively small sample size, which might have precluded us to detect minor differences between the groups. Also, the cross-sectional design of our study does not allow us to interpret whether our findings are cause or consequence of obesity and PCOS. Finally, the volumetric analysis is not able to give detailed information about the micro-architectural structure of brain regions.

In conclusion, we have observed a reduction in total brain volume and total GMV, as well as gray matter reductions in some appetite-related areas. These alterations did not show any association with basal peripheral levels of leptin, ghrelin and GLP-1 and meal stimulated GLP-1 levels. Further studies with larger sample size are needed to assess the functional relevance of structural alterations in brain regions of PCOS.

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### Declaration of interest

The authors report no conflicts of interest.

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