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Functional neuroimaging of emotional processing in women with polycystic ovary syndrome: a case-control pilot study

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Abstract

Objective—To evaluate emotional processing in women with insulin-resistant polycystic ovary syndrome (IR-PCOS) and its relationship to glucose regulation and the mu-opioid system.

Design—Case-control pilot.

Setting—Tertiary referring medical center.

Patient(s)—Seven women with IR-PCOS and five non-insulin-resistant controls, aged 21–40 years, recruited from the general population.

Intervention(s)—Sixteen weeks of metformin (1,500 mg/day) in women with IR-PCOS.

Main Outcome Measure(s)—Assessment of mood, metabolic function, and neuronal activation during an emotional task using functional magnetic resonance imaging (fMRI), and mu-opioid receptor availability using positive emission tomography (PET).

Result(s)—We found that insulin-resistant PCOS patients [1] had greater limbic activation during an emotion task than controls (n = 5); [2] trended toward decreased positive affect and increased trait anxiety; [3] after metformin treatment, had limbic activation that no longer differed from controls; and [4] had positive correlations between fMRI limbic activation during emotional processing and mu-opioid binding potential.

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Conclusion(s)—Patients with IR-PCOS had greater regional activation during an emotion task than the controls, although this resolved with metformin therapy. Alterations in mu-opioid neurotransmission may underlie limbic system activity and mood disorders in IR-PCOS.

Clinical Trial Registration Number—NCT00670800.

Keywords

Emotion; functional magnetic resonance; insulin resistance; imaging (fMRI); mu-opioid neurotransmission; polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS), a common endocrine disorder affecting approximately 10% of reproductive aged women, is characterized by hyperandrogenism and menstrual disorders (1, 2). Women with PCOS are at increased risk for mood and metabolic disorders, with insulin resistance (IR) found in up to 70% of women with PCOS (3, 4). A recent study by Rassi et al. (5) showed that up to 60% of women with PCOS met the diagnostic criteria for major depression, bipolar disorder, and/or anxiety disorder. Although that study did not report the prevalence of insulin resistance in their study population, women with diabetes mellitus were excluded. The relationship between PCOS and mood disorders is likely complex, and the pathogenesis is poorly understood.

Neurotransmitters, including opioids, mediate the neuromodulatory effects of insulin; animal studies have demonstrated β -endorphin immunoreactivity in up to 90% of cells with insulin receptors (6, 7). Hyperinsulinemia increases oxidative stress and induces an inflammatory state, compromising neuronal and glial survival, which may be associated with the affective symptoms seen in mood disorders (8). Several studies have found an increased incidence of type 2 diabetes in depressed individuals (9), and insulin-resistant individuals show decreased cortical excitation in response to insulin (10). Other central effects of insulin resistance include altered catecholamine reuptake, turnover, and transport (11). Also, common pathways exist for insulin signaling and pharmacotherapy of certain mood disorders, with insulin-sensitizing drugs alleviating mood symptoms in insulin-resistant and diabetic individuals (10, 12).

Altered central endogenous mu-opioid receptor mediated neurotransmission may underlie the relationship between insulin metabolism and mood. Opioid system dysfunction and metabolic disorders, conditions that are associated with PCOS, have been independently linked to mood disorders. Kennedy et al. (13) detected altered mu-opioid neurotransmission in depressed women as compared with healthy control women. We recently reported that women with insulin-resistant PCOS (IR-PCOS) had greater mu-opioid receptor binding potential than control women in the nucleus accumbens, bilaterally, and the left amygdala, which resolved after treatment with metformin (14).

Our current study evaluates emotional processing and its relationship to the opioid system and glucose regulation in women with IR-PCOS. Functional magnetic resonance imaging (fMRI) activation patterns during an emotional processing task were compared between non-IR controls and women with IR-PCOS, both at baseline and after treatment with an insulin-sensitizing drug, metformin. Functional MRI activation patterns were additionally correlated to mu-opioid receptor binding potential using positron emission tomography (PET) in conjunction with [^{11}C]carfentanil, a selective mu-opioid receptor radiotracer. We hypothesized that [1] fMRI activation patterns would differ between the women with IR-PCOS and the non-IR controls in emotion processing regions, [2] treatment with metformin would improve mood measures and normalize activation patterns, and [3] fMRI activation patterns would be associated with mu-opioid receptor availability in limbic brain regions.

Materials and Methods

Beginning in January 2008, we screened 21 women (10 with IR-PCOS and 11 control women) from the general population in southeast Michigan for possible enrollment in the pilot case-control study. We included only women who were healthy, right-handed, nonsmokers between 21 and 40 years of age, with no history of significant medical comorbidities (including depression or diabetes). Participants were excluded if they had contraindications to fMRI, were pregnant within 6 months of the start of the study, had a history of substance abuse, used centrally acting medications or corticosteroids, or if they had used hormones within 2 months of the start of the study. We used the National Institutes of Health (NIH) criteria of menstrual irregularity and hyperandrogenism for the PCOS diagnosis because a higher metabolic risk has been seen with these diagnostic criteria (2, 15). Insulin resistance was defined as a homeostasis model assessment (HOMA2)–Glycemia (mmol/L) $\times$ Insulinemia (μ IU/mL)/22.5–sensitivity of $\geq 60\%$. Non-PCOS controls had regular menstrual cycles with no clinical or laboratory evidence of hyperandrogenism and a HOMA2 sensitivity of $\geq 80\%$.

After we had screened 21 women, 14 women (7 IR-PCOS and 7 control) were enrolled in the study. Three women were excluded for metabolic testing results (one IR-PCOS and two controls), and four women were excluded for abnormal neuropsychiatric screens (two IR-PCOS and two controls). Two controls were excluded from the analysis for insulin resistance, and one woman with IR-PCOS was excluded from the PET analysis for incomplete imaging data.

We used the Beck Depression Inventory (BDI) (16) and the State-Trait Anxiety Inventory (STAI) (17) to measure depressive and anxiety symptoms, respectively. To assess the affective state, we used the Positive and Negative Affect Schedule (PANAS) (18) and the Profile of Mood States (POMS) (19).

The study procedures were approved by the University of Michigan institutional review board and the Radiation Safety Review Committee (HUM00008330), and written informed consent was obtained from all participants. We obtained medical histories and performed physical examinations (including assessing body mass index [BMI], a potential confounder) for each woman. We also measured each woman's levels for fasting glucose, insulin, 2-hour 75-g dextrose oral glucose tolerance test (OGTT) (potential predictors), free and total testosterone (T) (potential confounders), dehydroepiandrosterone sulfate (DHEAS), lipids, blood count, thyroid-stimulating hormone (TSH), electrolytes, and liver enzymes.

To assess outcomes, the women underwent one (controls) or two (women with IR-PCOS) fMRI and PET scans with [^{11}C]carfentanil, during the follicular phase if they were cycling. The PET scan (HR $^{+}$ scanner; Siemens) was in three-dimensional mode (reconstructed full-width/half-maximum resolution, approximately 5.5 mm in plane and 5.0 mm axially), with the septa retracted and scatter correction, during which 28 frames of increasing duration (from 30 seconds to 10 minutes) were collected.

The specific mu-opioid receptor radiotracer [^{11}C]carfentanil was administered in subpharmacologic tracer quantity (10–15 mCi, less than 0.03 $\mu\text{g/kg}$ total mass) via an antecubital intravenous line (50% in initial bolus, and the remainder continuously infused to achieve constant plasma concentrations). We synthesized [^{11}C]carfentanil at high specific activity ($> 2,000$ Ci/mmol [the conversion factor for 1 Ci is 3.7×10^{10} Bq]) by the reaction of [^{11}C]methyl iodide and a normethyl precursor. The mu-opioid receptor binding potential, B_{max}/K_d , where B_{max} = receptor concentration and K_d = receptor affinity for the radiotracer, was used to measure receptor availability (binding potential, BP). Functional MRIs were

acquired axially with a 3T scanner (GE Healthcare) with a spoiled gradient recalled three-dimensional volumetric acquisition (repetition time, 9.6; echo time, 3.3; inversion recovery preparation, 200 ms; flip angle, 17°; bandwidth, 15.63; 24-cm field-of-view; 1.5-mm slice thickness; 106-110 slices; 256×256 matrix; 2 excitations). The T1-weighted fMRI images were coregistered to the International Consortium for Brain Mapping/Montreal Neurological Institute template (20).

The emotional processing task performed during the fMRI involved pictures that had been previously rated by a normative female sample (21). The pictures were chosen with affective content rated as negative or neutral. The pictures were viewed through radiofrequency-shielded goggles and were presented in a blocked design in 4 runs with 48 pictures/run. The women rated the pictures as unpleasant or neutral by pressing one of two buttons on a response pad. Subsequently, the IR-PCOS patients were treated with metformin (500 mg titrated to 1,500 mg daily over 2 weeks). We repeated the fMRI, PET scan with [^{11}C]carfentanil, and OGTT in women with IR-PCOS after 4 months of metformin treatment.

The fMRI and PET images were analyzed using SPM parametric imaging software (Wellcome Cognitive Neurology) and SPSS (SPSS Inc.). Initial whole-brain two-sample tests were performed in SPM to determine the regions that were statistically significantly different ($P < .05$, not corrected for multiple comparisons) between controls and pre-metformin IR PCOS groups in either the PET or fMRI t test analyses. Two regions were identified based on statistically significant differences in whole-brain fMRI analysis (the left prefrontal cortex and the right ventral anterior cingulate). Two additional regions were identified based on statistically significant differences in the whole-brain PET analysis: left nucleus accumbens, $-6, -4, -12$, cluster size $2,808 \text{ mm}^3$ ($P = .003$); and left amygdala, $-26, -8, -24$, cluster size 656 mm^3 (uncorrected $P = .013$) (14).

For data analyses, individual data were deidentified, and references to the specific treatment were omitted from the subject code before the preparation of the statistical models. The fMRI data were then extracted bilaterally from these regions for subsequent analyses in SPSS, and the group comparisons were performed using unpaired (control vs. IR-PCOS) or paired (before vs. after metformin) t tests. We performed two-tailed Pearson correlations to assess the relationship between fMRI activation with mood and metabolic measures and fMRI activation with mu-opioid binding availability. $P < .05$ was considered statistically significant, $P < .1$ was used to assess trends.

Results

Demographic and Clinical Parameters

Mean $\pm$ standard deviation (SD) age of women with IR-PCOS was $26.1 (\pm 3.5)$ years (Table 1). The women with IR-PCOS had oligomenorrhea (cycle length, >35 days) and a higher BMI, weight, waist circumference, and total and free T levels compared with controls. Compared with the controls, the women with IR-PCOS had higher fasting insulin and HOMA 2 IR as well. The women with IR-PCOS trended toward a decreased positive affect (mean PANAS score 24 ± 7.3 controls vs. 15.7 ± 6.7 IR-PCOS; $P = .07$) and increased trait anxiety (mean STAI score 29.8 ± 5 controls vs. 38.3 ± 8.5 IR-PCOS; $P = .08$) at baseline, which correlated with the fasting insulin ($R = -0.51$, $P = .06$; $R = 0.54$, $P = .07$, respectively) and HOMA 2 IR ($R = -0.51$, $P = .06$; $R = 0.54$, $P = .07$, respectively). Although all seven women with IR-PCOS completed the metformin treatment protocol, the improvements in their affect and anxiety measures after metformin treatment did not reach statistical significance.

Functional MRI Activation during Negative Emotional Processing

Before metformin treatment, greater regional activation during the presentation of negative emotional pictures (as compared with the neutral pictures) was seen in women with IR-PCOS compared with controls in the left prefrontal cortex (MNI coordinates [x, y, z; mm]: 10, 54, 4; cluster size 9,488 mm³; $Z = 3.19$; uncorrected $P = .001$; mean -0.09 ± 0.12 controls vs. 0.12 ± 0.07 IR-PCOS, $P = .01$) and ventral anterior cingulate, with bilateral extension (MNI coordinates: 6, 26, 4; cluster size 6,128 mm³; $Z = 3.19$; $P = .001$; left: mean -0.09 ± 0.09 controls vs. 0.01 ± 0.04 IR-PCOS, $P = .05$; right: mean -0.13 ± 0.03 controls vs. 0.02 ± 0.05 IR-PCOS, $P < .01$) (Fig. 1). Treatment with metformin did not statistically significantly alter the limbic activation in women with IR-PCOS compared with their baseline measures (Fig. 2). However, differences in activation between the controls and the baseline of women with IR-PCOS in these specific regions were no longer statistically significant after metformin treatment. Although the results did not reach statistical significance, we did observe a positive correlation between HOMA2 IR and fMRI activation in the right nucleus accumbens during emotional processing ($R = 0.53$, $P = .1$) (Supplemental Fig. 1, available online) and a negative correlation with HOMA2 insulin sensitivity and fMRI activation in the same region ($R = -0.57$, $P = .07$). We observed no correlation between BMI and fMRI activation.

Correlations between Mood and Neuroimaging

In the control and the baseline of women with IR-PCOS, the measures of mood and behavior correlated with the neuroimaging data (Table 2). In the controls and the baseline of women with IR-PCOS, we obtained a positive correlation between mu-opioid receptor availability and PANAS positive affect score in the right amygdala ($R = 0.67$, $P = .02$). In the left nucleus accumbens, the controls and the baseline of women with IR-PCOS showed a positive correlation between mu-opioid receptor availability and a PANAS negative affect score ($R = 0.85$, $P < .01$), the STAI trait anxiety score ($R = 0.7$, $P = .02$), and a BDI depression score ($R = 0.64$, $P = .04$). With fMRI, activation of the right amygdala during emotional processing correlated positively with a PANAS negative affect score ($R = 0.64$, $P = .03$) and a BDI depression score ($R = 0.69$, $P = .02$).

Correlations between PET and Functional MRI

To address the behavioral implications of increased regional brain activation and mu-opioid receptor availability in general, we correlated PET and fMRI regional findings in the controls and the baseline of women with IR-PCOS. We observed a positive correlation between mu-opioid receptor availability in the right amygdala and fMRI activation in the interconnected right ventral anterior cingulate ($R = 0.63$, $P = .05$). We also obtained a positive correlation between mu-opioid receptor availability in the left ventral anterior cingulate and fMRI activation in the left nucleus accumbens ($R = 0.7$, $P = .02$). When we evaluated the study and control subjects separately, we found no statistically significant correlations between the mood measures and neuroimaging measures.

Discussion

Our is the first study to use neuroimaging methods to evaluate the association between emotional processing and insulin resistance in women with PCOS. We found trends in the baseline differences in metabolic and mood measures between women with IR-PCOS and the healthy controls. During emotional processing, we saw differences in the regional activation of the prefrontal cortex and anterior cingulate between the women at baseline IR-PCOS and the control women. Although we did not see any statistically significant correlation between fMRI activation and glucose regulatory measures, both the fMRI activation and mu-opioid receptor availability correlated with measures of affect and

depression. A difference in regional limbic activation during emotional processing was found between the controls and the women with IR-PCOS at baseline, before the metformin treatment. No regional activation differences were seen between the controls and the women with IR-PCOS after metformin treatment. Finally, we found relationships between mu-opioid receptor availability with fMRI limbic activation during emotional processing. These data suggest that mu-opioid neurotransmission may contribute to the alterations in emotion regulation and mood that are frequently reported by women with PCOS.

Limbic and paralimbic brain regions, including the prefrontal cortex, anterior cingulate, amygdala, and ventral basal ganglia/nucleus accumbens, are involved in the integration and regulation of emotionally relevant information, including salient, rewarding, and nonrewarding events, and are centrally implicated in the regulation of motivated behavior. Although there is substantial variation across studies, depending on the experimental paradigms employed and the samples under study, depression has been associated with a dysregulation of emotion response and regulation circuitry (22, 23). We found greater activation with emotional processing in the left prefrontal cortex and bilateral ventral anterior cingulate in women with IR-PCOS as compared with controls. These regions are centrally involved in the integration of cognitive and emotional information, and the left dorsolateral prefrontal cortex is a common target for repetitive transcranial magnetic stimulation in individuals with treatment-resistant depression (24).

In a meta-analysis of fMRI during emotional processing, Fitzgerald et al. (25) described greater activation in the prefrontal cortex in depressed individuals compared with controls in two out of five studies. The ventral anterior cingulate is additionally involved with attention, motivation, and modulating emotional responses. Engels et al. (26) found greater activation in the anterior cingulate cortex with emotional processing in individuals with depression and anxiety. Using PET data, Mayberg et al. (27) found differential anterior cingulate glucose metabolism and antidepressant drug response in hospitalized patients with unipolar depression. We correlated negative affect and depression with limbic activation during emotional processing, so the alterations in limbic activation may be associated with the increased prevalence of mood disorders observed in PCOS women.

Metabolic dysregulation may correlate with regional limbic neuronal activation during emotional processing. Although it was not statistically significant, insulin sensitivity had a negative correlation with right nucleus accumbens activation and insulin resistance a positive correlation with right nucleus accumbens activation during emotional processing. Similarly, Kumar et al. (28) found smaller gray matter volumes in the orbitofrontal cortex on magnetic resonance imaging (MRI) in type 2 diabetics as compared with controls after controlling for age, intracranial volume, and whole-brain gray matter volume. The right nucleus accumbens is part of an interconnected limbic network that includes the amygdala, anterior cingulate, and orbitofrontal cortex, modulating emotion and cognition, and may provide a link between hyperinsulinemia and the mood disorders seen in PCOS women.

To better understand the previously reported differences in limbic mu-opioid receptor availability between IR-PCOS and control women (14), we evaluated the impact of these mu-opioid system alterations on mood measures and emotional processing. We found correlations between depression and negative affect with mu-opioid receptor availability in the right amygdala and left nucleus accumbens. Similarly, when comparing patients with the diagnosis of major depression compared with healthy controls, Kennedy et al. (13) found greater mu-opioid system activation during sadness induction in several brain regions, including the right nucleus accumbens and amygdala bilaterally, which was consistent with the involvement of this neurotransmitter system in the regulation of stress responses and

affective state. Differences in endogenous opioid neurotransmission in these regions may be tied to the predisposition to the development of mood disorders seen in IR-PCOS.

We also found relationships between mu-opioid receptor availability in vivo and fMRI neuronal activation during emotional processing between the left amygdala and the ventral anterior cingulate region, as well as between the ventral anterior cingulate cortex and the nucleus accumbens. These are heavily interconnected regions involved in the response and regulation of emotionally salient stimuli and mood states. Functional connectivity alterations between prefrontal regions and the amygdala have been reported in mood disorders (29). Alterations in the regulatory capacity of mu-opioid neurotransmission in these regions as observed in women with IR-PCOS is likely to impact emotion regulation and may cause a predisposition to pathologic mood states.

The strengths of this pilot study include the prospective, intrasubject design and the inclusion of a control group, while the limitations are the small sample size and lack of placebo control. Due to the small sample size, we were unable to correct for possible confounding variables such as obesity and hyperandrogenism. However, we found no statistically significant change in BMI of the women with IR-PCOS after metformin therapy, and the BMI did not correlate with fMRI activation in any limbic region. Also, as only the women with IR-PCOS received metformin therapy, we cannot rule out that the differences seen between the controls and the women with IR-PCOS after therapy were related to the medication and not to changes in insulin metabolism. Future studies including more women and randomization of the insulin-sensitizing agent would further delineate the relationship between emotional processing, mu-opioid system, and insulin resistance in women with PCOS.

We describe a relationship between neuronal activation during emotional processing in limbic, appetite, and mood-regulating regions that is associated with alterations in mu-opioid receptor availability in women with IR-PCOS. Although further study is required to understand the complex relationship between metabolic dysfunction and the mood disorders seen in PCOS, this pilot study provides strong initial evidence of altered metabolic-opioid-emotion regulation system interactions in women with IR-PCOS. Our results suggest that insulin-opioid interactions may contribute to both the behavioral and the reproductive pathologies of PCOS, which should be explored in comprehensive, larger-scale studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Functional MRI limbic activation with emotional processing in women with IR-PCOS at baseline ($n = 7$) and after metformin ($n = 7$) and in control women ($n = 5$). Images were collected from a whole brain t test analysis of pre-metformin-control subtraction images, at a viewing threshold of $P < .01$. *Student's t test (IR-PCOS at baseline vs. controls). **Student's t test (IR-PCOS after metformin vs. controls). †Paired t test (IR-PCOS before and after metformin).

Figure 2. Functional MRI limbic activation with emotional processing in women with IR-PCOS at baseline and after metformin administration. *Dark gray:* IR-PCOS at baseline. *Light gray:* IR-PCOS after metformin.

Table 1

Demographic and clinical measures (n = 5 controls, IR-PCOS = 7 patients).

	Control median (IQR)	IR-PCOS before metformin median (IQR)	P value control vs. before metformin ^a	IR-PCOS after metformin median (IQR)	P value before vs. after metformin ^{b,c}
Age (y)	26 (8)	25 (6)	.74		
Education (y)	16 (4)	17 (4)	.74		
Weight (lb)	123.7 (35.3)	203.9 (85.8)	.01	187.1 (98.6)	.50
BMI (kg/m ²)	23.0 (3.1)	35.3 (16.2)	.02	31.7 (15.4)	.11
Waist circumference (cm)	72.0 (13.5)	102.0 (27.6)	<.01	94.5 (27.6)	.18
Laboratory values					
Free T (pg/mL)	0.5 (0.2)	1.5 (0.9)	<.01		
Total T (ng/mL)	0.36 (0.32)	0.70 (0.51)	.07		
HDL (mg/dL)	76 (24)	47 (17)	.07		
Triglycerides (mg/dL)	72 (37)	74 (42)	.42		
Fasting insulin (mIU/mL)	8.1 (0.9)	14.4 (8.1)	<.01		
HOMA2 IR	1(0.2)	2.7 (0.6)	<.01		
PANAS					
Positive	26 (7)	16 (6)	.07	11 (8.5)	.65
Negative	0 (0)	2 (2.5)	.29	0 (3.5)	.95
POMS mood disturbance	-6 (8)	6 (23.5)	.17	2 (19.5)	.81
STAI					
State anxiety	29 (11)	31.5 (16.3)	.53	28 (6)	.97
Trait anxiety	30 (4)	38 (9)	.08	37 (15.5)	.23
Beck Depression Inventory	1 (0)	5 (4.5)	.12	6 (9)	.51

Note: BMI = body mass index; HDL = high-density lipoprotein; HOMA2 IR = homeostatic model assessment index for insulin resistance; IQR = interquartile range; IR-PCOS = insulin-resistant polycystic ovary syndrome; PANAS = Positive and Negative Affect Schedule; POMS = Profile of Mood States; STAI = State-Trait Anxiety Inventory; T = testosterone.

^aMann-Whitney test between controls and IR-PCOS patients before metformin treatment.

^bWilcoxon signed ranks test between IR-PCOS patients before and after metformin treatment.

^cPaired *t* test between IR-PCOS patients before and after metformin treatment.

Table 2

Correlation between mood symptoms and functional neuroimaging in IR-PCOS women at baseline (n = 7) and control women (n = 5).

Limbic region	Positive mood (PANAS) R (P value)	Negative mood (PANAS) R (P value)	Mood state (POMS) R (P value)	State anxiety (STAD) R (P value)	Trait anxiety (STAD) R (P value)	Depression (BDI) R (P value)
fMRI negative emotion limbic activation						
Right amygdala	0.08 (.82)	0.64 (.03)	0.54 (.84)	0.37 (.29)	0.60 (.07)	0.69 (.02)
Left amygdala	−0.30 (.36)	0.40 (.22)	0.56 (.07)	0.42 (.23)	0.41 (.24)	0.49 (.12)
Mu-opioid binding potential ND						
Right nucleus accumbens	0.13 (.71)	0.04 (.91)	−0.21 (.53)	0.02 (.10)	−0.23 (.52)	−0.09 (.79)
Left nucleus accumbens	0.28 (.40)	0.85 (<.01)	0.53 (.10)	0.57 (.08)	0.70 (.02)	0.64 (.04)
Right amygdala	0.67 (.02)	0.02 (.96)	−0.43 (.19)	0.13 (.72)	−0.44 (.21)	0.03 (.94)
Left amygdala	0.42 (.20)	0.37 (.26)	0.10 (.78)	0.24 (.50)	0.35 (.33)	0.36 (.28)

Note: fMRI = functional magnetic resonance imaging; IR-PCOS = insulin-resistant polycystic ovary syndrome; ND = non-displaceable; PANAS = Positive and Negative Affect Schedule; POMS = Profile of Mood States; STAI = State-Trait Anxiety Inventory; BDI = Beck Depression Inventory.