Does polycystic ovary syndrome affect cognition? A functional magnetic resonance imaging study exploring working memory

Remi S. Soleman, M.Sc.,[a,b,d,g] Baudewijntje P. C. Kreukels, Ph.D.,[a,b,g] Dick J. Veltman, Ph.D., M.D.,[c,g] Peggy T. Cohen-Kettenis, Ph.D.,[a,b,g] Peter G. A. Hompes, Ph.D., M.D.,[d] Madeleine L. Drent, Ph.D., M.D.,[f,g] and Cornelis B. Lambalk, Ph.D., M.D.[d,e,g]

[a] Department of Medical Psychology, [b] Center of Expertise on Gender Dysphoria, [c] Department of Psychiatry, [d] Department of Obstetrics and Gynecology, [f] Department of Internal Medicine, Section of Endocrinology, VU University Medical Center, Amsterdam, the Netherlands; [g] Neuroscience Campus Amsterdam, Amsterdam, the Netherlands; and [e] Department of Obstetrics and Gynecology, Center for Reproductive Medicine of the University of Ghent, Ghent, Belgium

Objective: To study effects of overexposure to androgens and subsequent antiandrogenic treatment on brain activity during working memory processes in women with polycystic ovary syndrome (PCOS).
Design: In this longitudinal study, working memory function was evaluated with the use of functional magnetic resonance imaging (MRI) in women with PCOS before and after antiandrogenic treatment.
Setting: Department of reproductive medicine, university medical center.
Patient(s): Fourteen women with PCOS and with hyperandrogenism and 20 healthy control women without any features of PCOS or other hormonal disorders.
Intervention(s): Antiandrogenic hormone treatment.
Main Outcome Measure(s): Functional MRI response during a working memory task.
Result(s): At baseline women with PCOS showed more activation than the control group within the right superior parietal lobe and the inferior parietal lobe during task (all memory conditions). Task performance (speed and accuracy) did not differ between the groups. After antiandrogenic treatment the difference in overall brain activity between the groups disappeared and accuracy in the high memory load condition of the working memory task increased in women with PCOS.
Conclusion(s): Women with PCOS may need additional neural resources during a working memory task compared with women without PCOS, suggesting less efficient executive functioning. This inefficiency may have effects on daily life functioning of women with PCOS. Antiandrogenic treatment appears to have a beneficial effect on this area of cognitive functioning.
Clinical Trial Registration Number: NTR2493. (Fertil Steril® 2016;105:1314–21. ©2016 by American Society for Reproductive Medicine.)
Key Words: PCOS, working memory, functional MRI, cognition

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/solemanr-pcos-cognition-mri/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Received November 16, 2015; revised January 8, 2016; accepted January 25, 2016; published online February 12, 2016.
R.S.S. has nothing to disclose. B.P.C.K. reports grants from Foundation for Gynaecological Research and Education (SWOG), Neuroscience Campus Amsterdam, Hersenstichting Nederland, The Hague, and Fonds Nuts-Ohra, Amsterdam. D.J.V. has nothing to disclose. P.T.C.-K. has nothing to disclose. P.G.A.H. reports grants from Hersenstichting and Nuts-Ohra Fund, Ferring, and Merck Serono; and personal fees from Ferring. M.L.D. has nothing to disclose. C.B.L. reports grants from Hersenstichting, Nuts-Ohra Fund, Ferring, Merck Serono, and Auxogyn; and personal fees from MSD and Ferring.
Supported by the Foundation for Gynaecological Research and Education (SWOG), Amsterdam; Neuroscience Campus, Amsterdam; Hersenstichting Nederland, The Hague and Fonds Nuts-Ohra, Amsterdam, all in the Netherlands.
Reprint requests: Cornelis B. Lambalk, Ph.D., M.D., Department of Obstetrics and Gynecology, VU University medical center, PO Box 7057, Amsterdam 1007 MB, The Netherlands (E-mail: cb.lambalk@vumc.nl).

Fertility and Sterility® Vol. 105, No. 5, May 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.01.034

Polycystic ovary syndrome (PCOS) is a common cause of infertility, menstrual irregularity, and hirsutism. According to the Rotterdam criteria (1), patients are diagnosed with PCOS when two of the three following symptoms are present: [1] oligoamenorrhea, [2] clinical/biochemical signs of hyperandrogenism not associated with adrenal hyperplasia and androgen-producing tumors, and [3] polycystic ovaries (PCOs). Five to 10% of women fulfill

these criteria for PCOS (2). Although not all women with PCOS suffer equally from symptoms, such as hirsutism and acne, about 70% of these women do have clinical/biochemical signs of hyperandrogenism. These physical signs, together with infertility problems, make this syndrome a burden for patients.

Previous studies mainly focused on the endocrine effects of hyperandrogenism on hirsutism and infertility in women with PCOS. Clinical symptoms of PCOS, like hirsutism and acne, are the result of a hormonal imbalance in androgen levels (3). In addition, prenatal hormone levels, in particular those of androgens, may play a role in the development of PCOS (4). These hormonal influences ask the question whether elevated levels of androgens in women with PCOS will affect brain function as well. It is known that sex differences in cognition are, at least partially, an effect of sex steroids and changes in hormonal levels are associated with shifts in cognitive performance (5, 6). However, only a few studies investigated cognition in women with PCOS (7–9). Barnard et al. (7) compared cognition in an internet-based study in 221 women with PCOS (with and without antiandrogenic treatment) and 442 controls and found a significantly longer reaction time on an attention control task (arrow flanker task), a higher number of errors in a word recognition task, and a slower reaction time during a spatial location test. No differences were found in mental rotation and speed of word recognition between women with PCOS and control women. Women with PCOS undergoing antiandrogenic treatment showed a faster reaction time on the flanker task than women with PCOS without any hormonal treatment. Barnard et al. (7) concluded that antiandrogenic treatment enhances this aspect of cognitive performance. However, even with antiandrogenic treatment women with PCOS performed worse on the arrow flanker task than control women. Schattmann and Sherwin (8) investigated cognition in women with PCOS associated with high T levels, hypothesizing that the cognitive profile of women with PCOS and hyperandrogenism would be more masculine. The women with PCOS and hyperandrogenism were found to perform significantly worse on female-favoring tasks such as verbal fluency, verbal memory, manual dexterity, and visuospatial working memory than control women, but they did not show enhanced performance on male-favored tasks. These results suggest that androgens compromise performance on female-favoring tasks in women with PCOS. Another study (9) investigated cognitive functioning (visuospatial abilities, verbal abilities, and perceptual speed) in women with PCOS after manipulation of T. Hormonal treatment to suppress the level of free T did not result in changes in most of the cognitive functions, except for verbal fluency, which appeared to improve.

A key executive function is working memory, which includes temporal storage and manipulation of information and is needed for multiple processes of cognition such as language, perceptual speed, verbal and visual memory, and planning. Compromised working memory broadly affects cognitive functioning and therefore also quality of life (QoL) and psychological well-being. Neuroimaging studies have shown a strong involvement of the frontal and parietal lobes (10, 11). Previous studies have demonstrated a female advantage in accuracy of verbal working memory tasks. Also, men tend to show bilateral activation or right-sided dominance during the completion of this task, whereas women predominantly show left-sided activation (12). There are indications that menstrual cycle pattern-dependent E_2 levels relate to working memory (13, 14). It is, however, unclear whether changes in androgen levels affect working memory processes as well (15–17).

The aim of the present study was to investigate differences in working memory, as measured by the so-called N-back task (see Materials and Methods section) between women with and without PCOS and the effects of antiandrogen treatment. With the use of functional magnetic resonance imaging (MRI), women with PCOS were, before and during antiandrogenic treatment, compared with control women without PCOS with respect to working memory performance and its neural correlates. We hypothesized that women with PCOS and hyperandrogenism would demonstrate a more masculine pattern (i.e., worse performance and right-sided dominance in brain activity in the parietal and frontal lobe during the completion of the N-back task) when compared with control women without PCOS. We furthermore hypothesized that antiandrogen treatment would result in a more feminine pattern in women with PCOS.

MATERIALS AND METHODS

Subjects

From September 2010 until November 2012, 14 women with PCOS (1) with clinical and/or biochemical signs of hyperandrogenism and twenty women without PCOS were included in the study. Women with PCOS were recruited at the VU University Medical Center in Amsterdam after they were diagnosed with PCOS based on hyperandrogenism, oligomenorrhea, and 12 or more follicles in one or both ovaries.

The controls were recruited at the campus of the VU University in Amsterdam with the use of flyers. They had a regular menstrual cycle of no longer than 35 days and no signs of hyperandrogenism or polycystic ovaries (PCOs).

Participants were excluded from the study if they had received any kind of sex steroid treatment in the past or used hormonal contraceptives 3 months before the start of the study. Participants with psychiatric, neurological, or endocrine disorders, which could lead to deviant test results, were excluded from the study as well. Both groups were tested during a period within the menstrual cycle when influence of a previous cycle or forthcoming ovulation was likely to be negligible. To control for the effects of hormonal fluctuations during the menstrual cycle, we examined all women without PCOS in the early follicular phase (days 1–5) to ensure that the findings could not be explained by progestagenic activity. We investigated the women with PCOS in a menstrual cycle phase in which estrogen (E) levels are low and comparable with the control group (days 11–17) (18). According to van Hooff et al. (19) an oligomenorrheic menstrual cycle can be divided into five phases in which the third phase (days 15–22) is called a specific oligomenorrheic phase: a potentially stable period before ovulation.

This study was approved by the ethics committee of the VU University Medical Center Amsterdam, The Netherlands and all participants gave written informed consent. This study is also registered as a clinical trial (http://www.trialregister.nl; NTR2493). After the approval of the ethics committee and the systematic approach to recruitment, the participants tended to be insufficient and needed an optimization. After the optimization of this systematic approach, this study was registered as a clinical trial and recruitment was started. Consequently, this study started with a delay of 3 months.

Procedure

Participants completed two test sessions with a maximum interval of 16 weeks. Women with PCOS started after the first test session with an antiandrogenic treatment (cyproterone acetate, 25 mg/d orally) combined with a hormonal oral contraceptive (OC) (2 mg cyproterone acetate and 35 mg ethinyl E_2 (EE)/d, orally). The control group did not receive any treatment (Supplemental Fig. 1, available online).

During the first test (baseline session), participants completed a structured interview to collect data on age, education, use of medication, and medical history. The session continued with a physical examination to perform anthropometric measurements, after which blood samples were collected.

Next, participants underwent a neuropsychological assessment of approximately 1 hour. At the end of this session, several questionnaires were administered and the participants were prepared for an MRI scan.

Before the MRI scan, participants received task instructions outside the scanner. Subsequently, the participants underwent MRI scanning, which took 1 hour to complete. The procedure of the second session was similar to the first session except that different (but comparable) versions of the neuropsychological and functional MRI tasks were used to control for learning effects. Due to an unforeseen MRI scanner upgrade during the project five women with PCOS and four control women only took part in the first testing session.

Instruments

The computerized letter N-back task is developed to investigate the neural basis of working memory processes. The participants were given several stimuli that should be stored and manipulated to respond correctly. Working memory capacity is reflected by performance accuracy and speed. The participants performed a letter variant of the N-back task with increasing levels of difficulty. The task measures a complex form of working memory and has often been used in functional MRI studies to evaluate working memory. Successful completion of this task requires several aspects of working memory, as described by Baddeley (20). During the task, letters were successively presented on a screen divided into blocks of 20 stimuli. At the beginning of each block participants were instructed [1] to press the button when the letter "X" appeared (0-Back); [2] to press the button when two of the same letters appeared directly after each other (1-Back); [3] to press the button when two of the same letters appeared with one random letter in between (2-Back); [4] to press when two of the same letters appeared with two random letters in between (3-Back). Blocks were presented in pseudorandom order, and each stimulus was presented for 1 second with a stimulus interval of 1 second. To estimate intelligence quotient, participants completed the Dutch version of the National Adult Reading Test (21) and screening for psychological distress was done with the use of Hospital Anxiety and Depression scale. This questionnaire assesses self-reported psychological burden on two symptom scales: anxiety and depression (22).

MRI Acquisition

Imaging acquisition was performed on a whole-body 3T MR (SignaHDXt, General Electric), located in the VU University Medical Center in Amsterdam, with the use of a SENSE 8-channel head coil. During the task, echo-planar images were obtained using an axial T_2*-weighted gradient echo sequence. Repetition time (TR) = 2,100 milliseconds, echo time (TE) = 30 milliseconds, matrix size = 96 × 96, number of slices = 40, with a sequential ascending slice order.

Anatomical imaging included a sagittal three-dimensional gradient-echo T_1-weighted sequence. The settings used for anatomical imaging were: TR = 7.8 seconds, TE = 3.0 milliseconds, matrix size = 256 × 256, voxel size = 1 × 1 × 1 mm, and number of slices = 170 slices.

Hormonal Assays

Estradiol was measured by a competitive fluorescence immunoassay (PerkinElmer) with a lower limit of detection of 20 pmol/L and an interassay coefficient of variation (CV) of <10%. For T and DHEAS a RAI (Siemens Medical Solutions Diagnostics) was used with a lower limit of detection of 1 nmol/L and an interassay CV of <7% and a lower limit of detection of 0.2 μmol/L and an interassay CV of <9%. Both LH and FSH were measured by commercially available fluorescence immunometric assays (Abbott Laboratories). The lower limit of detection was 2 nmol/L for both LH and FSH. Progesterone was measured with a competitive fluorescence immunoassay (Abbott Laboratories) with a lower limit detection of 2 nmol/L and an interassay CV of <5%. The levels of sex hormone-binding globulin (SHBG) and PRL were measured with an fluorescence immunometric assay (Siemens Medical Solutions Diagnostics) with a lower limit of detection of 2 nmol/L and an interassay CV of <4% and a lower limit of detection of 0.05 U/L and an interassay CV of <6%. Androstenedione (A) was measured by radioimmunoassay (Webster) with a lower limit of detection of 0.5 nmol/L and an interassay CV of <9%. Finally, TSH was measured with an electrochemilluminescence immunoassay (Roche Diagnostics) with a lower limit of detection of 0.005 mU/L and an interassay CV of <3%. The free androgen index (FAI) was calculated by the total T divided by the SHBG level multiplied by 100.

Statistical Analyses

Statistical parametric mapping 8 (http://www.fil.ion.ucl.ac.uk/spm) and a standard software suite of MATLAB (the

Mathworks Inc.) were used for the functional MRI analyses. Images were manually reoriented and the origin was set to the anterior commissure. Slice timing was used to correct for differences in acquisition time, followed by realignment to correct for possible movements in the scanner. The echo planar images were coregistered to the T_1 anatomical image, which was segmented and normalized to a standard brain space defined by the Montreal Neurological Institute. Finally, images were smoothed using an 8-mm full-width half-maximum Gaussian filter.

For the first-level analyses, task conditions were modeled using boxcar regressors convolved with a canonical hemodynamic response function. Next, contrast images containing weighted parameter estimates reflecting task load were entered into second-level analyses of variance to assess main effects for task load as well as group by task interaction effects. Between-group analysis was carried out with the use of analysis of variance (ANOVA) to evaluate main ($P<.05$), family-wise error corrected and interaction effects ($P<.05$), small volume corrected for a priori defined brain areas (bilateral parietal lobes and bilateral prefrontal lobes), created using 20-mm diameter spheres centered around the peak voxels identified for the main effect across groups, which is orthogonal with respect to these interaction effects (23). Within-group analyses were carried out with the use of a pairwise comparison between the first and second session with the use of a paired sample *t* test.

Performance and questionnaire data were scored according to standard criteria and analyzed with the Statistical Package for the Social Sciences (SPSS), version 20. Independent sample *t* tests and ANOVAs of variance were used for the analyses of between-group differences in performance, questionnaire, and sociodemographic data. However, if assumptions for homogeneity of variance were violated, the groups were compared with nonparametric Kruskal-Wallis tests and post hoc testing with Mann-Whitney *U* tests. A between-group analysis was carried out for each group for the sample characteristics and performance data with the use of an unpaired two-sample *t* test. A paired *t* test was carried out to analyze within-group differences. Statistical tests were considered to be significant at $P<.05$.

To examine the influence of androgen levels on brain activity a regression analysis was performed with Statistical Parametric Mapping 8. Testosterone, A, and FAI were defined as predictors and BOLD response as dependent variable for both sessions separately. Not all participants completed both sessions. Five women with PCOS and four women without PCOS completed the first session only. Comparisons between the first and second session were done for the 25 subjects who completed both sessions.

RESULTS

Sample

Thirty-four women participated in the study: 14 women with PCOS and hyperandrogenism (mean age, 29.3 years, SD = 5.6 years) and 20 women without PCOS (mean age, 25.5 years, SD = 6.2 years). There were no significant differences in age, intelligence quotient, or depression scores between the two groups. Nine women with PCOS (mean age = 29.3 years, SD = 5.6 years) and 16 women without PCOS (mean age, 25.6 years, SD = 6.2 years) completed both sessions. Comparing participants with and without PCOS who completed both sessions showed no differences between the groups in age or intelligence quotient either.

TABLE 1

Sample characteristics.

	PCOS	Controls	
Characteristic	**N = 14**	**N = 20**	***P* value**
Age, y (±SD)	29.3 (5.6)	25.6 (6.2)	.1
Range	20.3–40.8	18.8–42.7	
Estimated IQ (±SD)	103.1 (10.0)	102.6 (9.0)	.9
Range	84–119	93–126	
Body mass index session 1			
BMI, kg/m^2 (±SD)	25.8 (5.6)	24.5 (3.0)	.4
Range	16.9–40.5	20.7–31.1	
Body mass index session 2			
BMI, kg/m^2 (±SD)	25.7 (3.9)	23.7 (2.1)	.1
Range	18.1–29.7	20.8–27.4	
HADS session 1			
Depression scale (±SD)	3.9 (4.5)	1.7 (1.6)	.1
Range	0–13	0–6	
Anxiety scale (±SD)[b]	6.8 (3.2)	3.6 (1.8)	<.01[c]
Range	3–13	1–8	
HADS session 2	N = 9	N = 16	
Depression scale (±SD)	4.1 (5.4)	1.8 (2.4)	.3
Range	0–15	0–8	
Anxiety scale (±SD)	6.4 (4.0)	4.4 (1.8)	.1
Range	3–13	2–7	
Hormonal levels session 1	**N = 14**	**N = 20**	
A (±SD)	9.1 (3.9)	6.1 (2.9)	.01[c]
DHEAS (±SD)	6.5 (3.3)[a]	4.8 (1.9)	.73
LH (±SD)	11.0 (5.8)	4.0 (1.5)	<.01[c]
FSH (±SD)	5.4 (1.3)	5.4 (1.6)	.97
PRL (±SD)	0.2 (0.1)	0.2 (0.1)	.90
P (±SD)	2.6 (1.9)[a]	4.1 (9.4)	.64
E_2 (±SD)	216.1 (114.3)	147.1 (75.5)	.04[c]
T (±SD)	1.6 (0.7)[a]	1.1 (0.11)	.02[c]
SHBG (±SD)	35.3 (16.8)	47.4 (14.3)	.03[c]
FAI (±SD)	6.2 (4.6)	2.5 (0.9)	.01[c]
TSH (±SD)	1.9 (1.1)	2.1 (1.3)	.64
Hormonal levels session 2	**N = 9**	**N = 16**	
A (±SD)	4.1 (1.3)	6.3 (3.5)	.04
DHEAS (±SD)	4.7 (2.1)	5.4 (2.3)	.44
LH (±SD)	0.5 (0.8)	4.4 (2.0)	<.01
FSH (±SD)	1.2 (1.2)	5.6 (1.6)	<.01
PRL (±SD)	0.2 (0.1)	0.4 (0.2)	.03
P (±SD)	<2.0	<2.0	–
E_2 (±SD)	32.0 (7.9)	127.6 (37.9)	<.01
T (±SD)	<1	1.1 (0.2)	–
SHBG (±SD)	186.9 (99.4)	53.6 (18.0)	<.01
FAI (±SD)	0.6 (0.2)	2.2 (1.0)	<.01
TSH (±SD)	2.0 (1.1)	2.2 (1.4)	.72

Note: Session 1 = 6.6 (2.9), session 2 = 6.4 (4.0), *P*= .8 (average session1 (±SD), average session 2 (±SD), *P* value). A = Androstenedione; BMI = body mass index; FAI = free androgen index; HADS = Hospital Anxiety and Depression scale; IQ = intelligence quotient; PCOS = polycystic ovary syndrome; SHBH = sex hormone-binding globulin.

[a] Number of measurements is different. DHEAS: n = 13; T: n = 13; P: n = 9.

[b] A paired sampled *t* test showed no significant difference between the first and second session within the group of women with PCOS.

[c] Significantly different.

Soleman. Does PCOS affect working memory?. Fertil Steril 2016.

During the first session, anxiety scores (Hospital Anxiety and Depression scale) were significantly higher in women with PCOS than in control women (P=.04; Table 1). No significant differences were found for depression scores or for anxiety and depression scores between the two groups during the second session (Table 1). A paired sample t test did not show any significant differences between the first and second session within the two groups with regard to anxiety and depression.

Hormonal Levels

At baseline, women with PCOS showed significantly higher levels of A, LH, E_2, T, and FAI than control women (Table 1). The level of SHBG was significantly lower in women with PCOS. None of the other hormonal levels differed significantly between the groups (Table 1).

During the second session the women with PCOS showed significantly lower levels of A, LH, FSH, E_2, FAI compared with the control group (Table 1). Only the levels of SHBG were increased in the group of women with PCOS compared with the control group. A within-group comparison showed no differences between the first and second session for the control group. The participants with PCOS showed significant differences between the two sessions for all hormone levels, except for DHEAS (P=.44) and T (P=.16).

Performance Data

At both sessions, no reaction time differences were found between the two groups on the N-back task. During the first session, the number of errors did not differ between the groups, but during the second session women with PCOS made fewer errors while completing the 3-Back condition than control women (P=.012; Table 2).

Functional MRI Data

Main effect of N-back task. Because differences in anxiety scores were found between the groups, anxiety was added as a covariate. During both sessions and for both groups, performance of the N-back task was associated with bilateral activation in the dorsolateral prefrontal lobe, insula, parietal lobe, cerebellum, and in the superior medial prefrontal lobe (Table 3 and Fig. 1).

Group comparisons: N-back task. During the first session women with PCOS showed more activation than controls while completing the task in the superior temporal lobe, the superior parietal lobe, and the inferior parietal lobe (Table 3 and Fig. 1). During the second session, no significant differences were found between the two groups while performing the N-back task.

Regression Analyses

A multivariate regression analysis revealed no correlation between the levels of A, T, FAI, and E_2, and brain activity in the superior temporal lobe, the superior parietal lobe, and the inferior parietal lobe during the first session.

Session One versus Session Two

Control women showed no significant difference in brain activation between the first and the second session. Women with PCOS showed a similar activation pattern for both sessions (main effect). However, during the second session women with PCOS showed decreased activation in the bilateral superior parietal lobes compared with the first session (Table 3).

TABLE 2

Performance data N-back task.

	Session 1			Session 2		
Data	**PCOS (N = 14)**	**Controls (N = 20)**	***P* value**	**PCOS (N = 9)**	**Controls (N = 16)**	***P* value**
Reaction time						
0-Back	428.0 (52.7)	410.4 (61.4)	.4	367.9 (136.2)	404.7 (45.0)	.3
Range	336–529	304–546		22–480	324–489	
1-Back	468.1 (71.8)	459.8 (79.4)	.7	383.4 (151.6)	464.3 (83.5)	.1
Range	366–630	326–633		0–511	342–622	
2-Back	535.1 (104.3)	522.8 (96.4)	.7	494.4 (109.9)	534.3 (66.4)	.3
Range	405–764	384–684		344–665	422–644	
3-Back	570.8 (89.3)	582.0 (102.4)	.7	589.0 (154.3)	751.0 (392.7)	.3
Range	385–765	404–773		323–820	329–1,865	
No. of errors						
0-Back	0.1 (0.3)	0.2 (0.4)	.5	0.0 (0.0)	0.1 (0.3)	.5
Range	0–1	0–1		0	0–1	
1-Back	0.6 (1.2)	0.2 (0.4)	.2	0.0 (0.0)	0.6 (1.1)	.06
Range	0–4	0–1		0	0–4	
2-Back	1.7 (1.4)	1.5 (1.7)	.7	0.8 (0.7)	1.6 (1.4)	.07
Range	0–4	0–5		0–2	0–4	
3-Back	4.3 (2.4)	3.5 (2.2)	.3	2.4 (1.4)	4.4 (2.2)	.01
Range	1–8	0–9		1–6	1–8	

Note: PCOS = polycystic ovary syndrome.

Soleman. Does PCOS affect working memory?. Fertil Steril 2016.

TABLE 3

Regions with significantly increased brain activity during linear increased load weighed contrast.

Brain region	MNI coordinates x	y	z	t	*P* value	Number of voxels
Main effect						
Main effect: session 1						
Frontal mid R	36	14	49	14.97	<.001	557
Frontal mid L	−27	8	49	14.26	<.001	163
Insula L	−30	23	−2	9.11	<.001	73
Insula R	30	23	−2	7.86	<.001	48
Frontal superior medial	6	23	43	9.88	<.001	106
Parietal lobe L	−30	−55	37	11.70	<.001	429
Parietal lobe R	45	−46	37	13.21	<.001	322
Cerebellum L+R	−33	−61	−35	10.59	<.001	534
Main effect difference: session 1 vs. session 2						
Session 1 > session 2						
Parietal lobe L	−36	−49	49	8.21	<.001	73
Parietal lobe R	27	−43	34	6.76	<.001	86
Session 2 > session 1						
No differences						
Group differences						
PCOS > controls						
Superior temporal lobe L	−51	2	−8	3.68	<.001	14
Superior temporal lobe R	51	5	−11	3.89	<.001	39
Postcentralis R	63	−19	37	4.14	<.001	117
Superior parietal lobe R	45	−43	58	3.68	<.001	13
Superior parietal lobe L	−36	−49	55	3.46	.001	25
Inferior parietal lobe L	−54	−25	37	3.53	.001	69
Inferior parietal lobe R	48	−34	49	3.36	.001	24
Precentralis L	−30	2	43	3.84	<.001	34
Controls > PCOS						
No differences						

Note: All brain regions were marked as significant at $P<.05$ family-wise error-corrected for main effects and $P<.05$ small volume-corrected. L = left; PCOS = polycystic ovary syndrome; R = right.

Soleman. Does PCOS affect working memory?. Fertil Steril 2016.

DISCUSSION

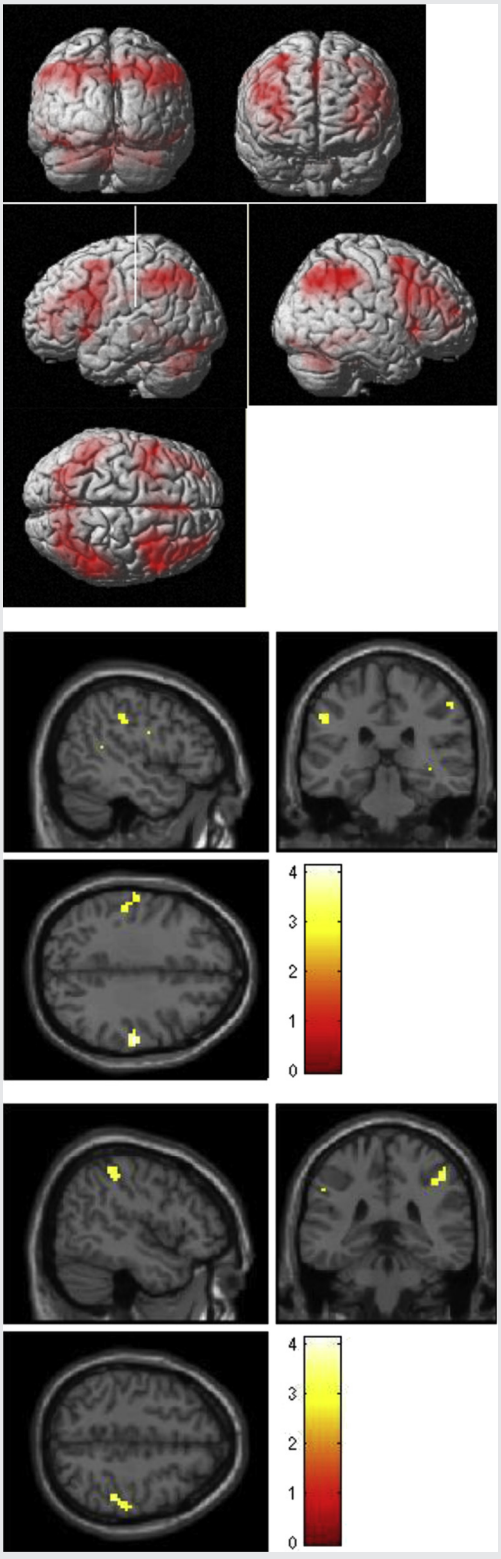
We found that women with PCOS differed in brain activation in the parietal lobe (superior and inferior) and in the temporal lobe (superior) than control women, but not in performance (number of errors and reaction time) during a working memory task. Hormonal levels of A, E_2, T, and FAI differed between the groups, but did not correlate with brain activity in the regions of interest. After antiandrogenic treatment differences in brain activity between the two groups were no longer observed.

The N-back task is a complex working memory task requiring substantial effort to complete the task successfully. The task includes interpretation, storage, and rehearsal of the letters, matching the present letter with previous letters, temporal ordering of the letters, inhibition of irrelevant letters, and response processes (24). Our results suggest that women with PCOS need more neural resources than control women, as reflected by increased brain activity in the parietal lobe while performing similarly to control women.

Our main finding is a group difference in brain activation within the parietal lobe. Although the parietal lobe is involved in several cognitive processes (25), for the current paradigm the parietal lobe is likely to be involved in the storage of working memory contents and attentional processes (24). As mentioned previously, visual information needs to be interpreted and stored before manipulation. Previous studies suggest that the parietal region mediates as a storage buffer (10). Todd and Marois (25) suggest that the parietal lobe may act as a storage place for the representation of visual scenes, whereas the frontal/prefrontal cortex is involved in the consolidation and/or maintenance of this storage. As mentioned by Markett et al. (26) attentional processes play an important role in working memory, and a network including the anterior cingulate cortex and the parietal lobe is likely involved in attentional processes. Specifically, the posterior parietal cortex has been implicated in sustained attention, which is critical for adequate N-back performance (27). Arguably, reduced efficiency in one or more underlying processes of working memory may lead to the need for compensatory parietal activity. Although this may not be observed in daily life performance of women with PCOS, their resources may be continuously challenged due to suboptimal processing.

Differences between the groups may be associated with the excessive amount of androgens in women with PCOS. Although hormonal levels were not significantly correlated with brain activation, it is still likely that androgens do play a role in the differences between groups. It may be that there are already differences in brain functions and structure in women with PCOS independent of current hormonal levels. Abbot and colleagues (4) reported that in animal studies excessive androgen exposure prenatally may result in remarkable phenotypical similarities to women with PCOS,

FIGURE 1



Top: Main effect in brain activity during the N-back task. Threshold: $P<.05$ family-wise error corrected. *Middle, Bottom*: Colored bars depicting the z-scores. Brain areas with increased activation in women with polycystic ovary syndrome (PCOS) before start of treatment compared with control women during the N-back task (PCOS > controls). *Difference in brain activation within left inferior parietal lobe and superior parietal lobe right. Threshold: $P<.05$ small volume correction.

Soleman. Does PCOS affect working memory? Fertil Steril 2016.

suggesting a fetal origin for this syndrome, which may also have effects on the organization of the brain. During the second session, all women with PCOS had undergone suppression of their androgen levels for a period of 16 weeks. After treatment, the women with PCOS showed better performance both before treatment and compared with controls during the second session. Furthermore, differences with controls in brain activity had disappeared. The principal component of the antiandrogenic treatment was the lowering of ovarian androgen levels by pituitary suppression of gonadotropin secretion in combination with the administration of EE and cyproterone acetate. Although the lowering of androgenic effects is a plausible explanation for our observations, a potential direct role of EE, cyproterone acetate, or the combination of both cannot be ruled out. With the available data it is difficult to identify a specific hormone alteration that may be responsible for our findings. Future research should clarify what the effects are of the various sex steroids.

In our sample, women with PCOS showed a significantly higher level of anxiety than control women. Psychological distress and QoL in women with PCOS has previously been investigated, and a systematic review concluded that PCOS has a negative impact on the overall health-related QoL (28). It should be noted that in Europe approximately 40% of the women with PCOS have obesity (29) and especially these weight concerns together with fertility problems may have a negative effect on QoL (28). Although symptoms, such as hirsutism, acne, or infertility, may affect psychological functioning and QoL, suboptimal brain functioning may also be associated with less psychological well-being.

Strengths and Limitations

Although 5%–10% of women suffer from PCOS, most women have some form of treatment such as hormonal contraceptives or do not want to receive any form of hormonal treatment because they try to conceive. It appeared to be difficult to include women fulfilling both the criteria for PCOS with hyperandrogenism (clinical and/or biochemical) and without hormonal treatment. Therefore, our patient group was relatively small.

To correct for baseline differences in levels of Es, we attempted to schedule test sessions in such a way that participants' E levels were comparable. Yet, the levels were still slightly higher in women with PCOS. However, a regression analysis did not show a direct relation between E levels and our results.

Although several other studies investigated different aspects of PCOS, brain functioning and performance of working memory was never studied before. This study investigated working memory in brain activity and performance for the first time.

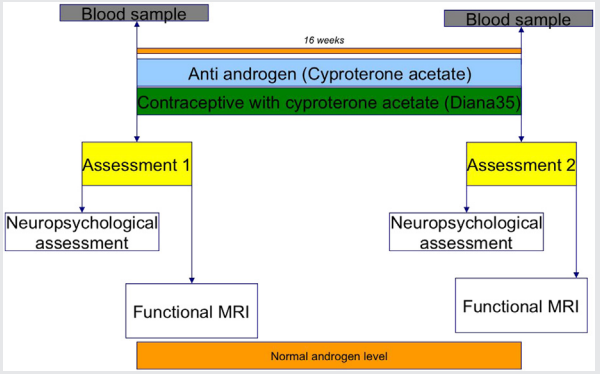
A strength of our study is that we examined both performance and neural processing during a demanding task in women with PCOS. Because working memory is one of the basic cognitive functions, suboptimal processing may lead to deficits in higher order functions. We have furthermore shown that antiandrogenic treatment, which is very commonly applied in these patients, appears to normalize working memory processing. Future research should include more highly demanding tasks to challenge the efficiency of working memory processes and elucidate the relationship between these vulnerable aspects of their brain functioning and their psychological well-being.

Acknowledgments: The authors thank Mieke Staphorsius for her help in recruitment and testing the participants of the study. Furthermore, Ted Korsen and Ton Schweigman, for their technical support during functional MRI scanning and finally, we would like to acknowledge Annemieke Heijboer for her help describing the different hormonal assays.

REFERENCES

1. Rotterdam, ESHRE & ASRM-Sponsored, PCOS. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–7.
2. Franks S. Polycystic ovary syndrome. N Engl J Med 1995;333:853–61.
3. Randall VA. Androgens and hair growth. Dermatol Ther 2008;21:314–28.
4. Abbott DH, Padmanabhan V, Dumesic DA. Contributions of androgen and estrogen to fetal programming of ovarian dysfunction. Reprod Biol Endocrinol 2006;4:17.
5. Crucian GP, Berenbaum SA. Sex differences in right hemisphere tasks. Brain Cogn 1998;36:377–89.
6. Weiss EM, Deisenhammer EA, Hinterhuber H, Marksteiner J. [Gender differences in cognitive functions]. Fortschr Neurol Psychiatr 2005;73:587–95.
7. Barnard L, Balen AH, Ferriday D, Tiplady B, Dye L. Cognitive functioning in polycystic ovary syndrome. Psychoneuroendocrinology 2007;32:906–14.
8. Schattmann L, Sherwin BB. Testosterone levels and cognitive functioning in women with polycystic ovary syndrome and in healthy young women. Horm Behav 2007;51:587–96.
9. Schattmann L, Sherwin BB. Effects of the pharmacologic manipulation of testosterone on cognitive functioning in women with polycystic ovary syndrome: a randomized, placebo-controlled treatment study. Horm Behav 2007;51:579–86.
10. Smith EE, Jonides J. Storage and executive processes in the frontal lobes. Science 1999;283:1657–61.
11. Tamnes CK, Walhovd KB, Grydeland H, Holland D, Ostby Y, Dale AM, et al. Longitudinal working memory development is related to structural maturation of frontal and parietal cortices. J Cogn Neurosci 2013;25:1611–23.
12. Speck O, Ernst T, Braun J, Koch C, Miller E, Chang L. Gender differences in the functional organization of the brain for working memory. Neuroreport 2000;11:2581–5.
13. Joseph JE, Swearingen JE, Corbly CR, Curry TE Jr, Kelly TH. Influence of estradiol on functional brain organization for working memory. Neuroimage 2012;59:2923–31.
14. Grigorova M, Sherwin BB, Tulandi T. Effects of treatment with leuprolide acetate depot on working memory and executive functions in young premenopausal women. Psychoneuroendocrinology 2006;31:935–47.
15. Young LA, Neiss MB, Samuels MH, Roselli CE, Janowsky JS. Cognition is not modified by large but temporary changes in sex hormones in men. J Clin Endocrinol Metab 2010;95:280–8.
16. Cherrier MM, Asthana S, Plymate S, Baker L, Matsumoto AM, Peskind E, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. Neurology 2001;57:80–8.
17. Cherrier MM, Matsumoto AM, Amory JK, Johnson M, Craft S, Peskind ER, et al. Characterization of verbal and spatial memory changes from moderate to supraphysiological increases in serum testosterone in healthy older men. Psychoneuroendocrinology 2007;32:72–9.
18. De Boer J, Lambalk C, Hendriks H, van Aken C, van der Veen E, Schoemaker J. Growth hormone secretion is impaired but not related to insulin sensitivity in non-obese patients with polycystic ovary syndrome. Human Reprod 2003;19:504–9.
19. van Hooff MH, van der Meer M, Lambalk CB, Schoemaker J. Variation of luteinizing hormone and androgens in oligomenorrhoea and its implications for the study of polycystic ovary syndrome. Hum Reprod 1999;14:1684–9.
20. Baddeley A. Working memory. New York: Oxford University Press; 1986.
21. Nelson HE Jr. National adult reading test (NART). 2nd ed. Windsor, UK: NFER Nelson; 1991.
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
23. Kriegeskorte N, Simmons WK, Bellgowan PS, Baker CI. Circular analysis in systems neuroscience: the dangers of double dipping. Nat Neurosci 2009;12:535–40.
24. Jonides J, Lauber E, Minoshima S, Koeppe RA. Verbal working memory load affects regional brain activation as measured by PET. J Cogn Neurosci 1997;9:462–75.
25. Todd JJ, Marois R. Capacity limit of visual short-term memory in human posterior parietal cortex. Nature 2004;428:751–4.
26. Markett S, Reuter M, Montag C, Voigt G, Lachmann B, Rudorf S, et al. Assessing the function of the fronto-parietal attention network: insights from resting-state fMRI and the attentional network test. Hum Brain Mapp 2013;35:1700–9.
27. Malhotra P, Coulthard EJ, Husain M. Role of right posterior parietal cortex in maintaining attention to spatial locations over time. Brain 2009;132:645–60.
28. Jones GL, Hall JM, Balen AH, Ledger WL. Health-related quality of life measurement in women with polycystic ovary syndrome: a systematic review. Hum Reprod Update 2008;14:15–25.
29. Balen AH, Conway GS, Kaltsas G, Techatrasak K, Manning PJ, West C, et al. Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. Hum Reprod 1995;10:2107–11.

SUPPLEMENTAL FIGURE 1



Study design. MRI = magnetic resonance imaging.

Soleman. Does PCOS affect working memory? Fertil Steril 2016.