

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

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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.

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Key Words: PCOS, working memory, functional MRI, cognition

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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.

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