

Visual-spatial cognition in women with polycystic ovarian syndrome: the role of androgens

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Submitted on April 13, 2013; resubmitted on July 22, 2013; accepted on July 25, 2013

STUDY QUESTION: Are women with polycystic ovary syndrome (PCOS) better at three-dimensional mental rotation than other women?

SUMMARY ANSWER: Women with PCOS scored significantly higher on a mental rotation task than a female control group.

WHAT IS KNOWN ALREADY: PCOS is a condition characterized by elevated testosterone levels. Some researches have found that three-dimensional mental rotation task performance is positively correlated with testosterone levels.

STUDY DESIGN, SIZE, DURATION: This cross-sectional study was conducted between June 2006 and January 2009. The participants were 69 women with PCOS and 41 controls recruited from five gynaecology clinics in London. The control group consisted of non-PCOS women of comparable subfertility to PCOS group. These groups sizes gave roughly 80% power to detect moderate effect sizes for the main statistical test.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Participants were recruited at London gynaecology clinics. The women were aged between 18 and 43. PCOS was diagnosed based on the Rotterdam criteria. Controls were women who experienced some degree of subfertility. Blood samples from participants were frozen for up to 4 months until being assayed by direct electrochemiluminescence. The mental rotation task was undertaken electronically. Some questionnaires and other tasks were completed as control measures.

MAIN RESULTS AND THE ROLE OF CHANCE: Women with PCOS scored significantly higher than controls: median (range) 3.00 (0–9) and 2.00 (0–8), respectively ($U = 1147.500$, $N_1 = 69$, $N_2 = 41$, $P < 0.047$). Within the PCOS group, circulating levels of testosterone were significantly positively correlated with three-dimensional scoring ($r_s = 0.376$, $n = 56$, $P < 0.002$), whereas estradiol was significantly negatively correlated with three-dimensional scoring ($r_s = -0.473$, $n = 29$, $P < 0.010$). In the control group, the relationship between sex hormones and mental rotation was non-significant. Other factors, including general intelligence and social class, did not account for these findings. A subgroup analysis comparing hyperandrogenic PCOS cases, non-hyperandrogenic PCOS cases and controls, in which age and body mass index were controlled for using ANCOVA, found a non-significant difference in three-dimensional scoring between the three groups ($F = 1.062$, d.f. = 1, 73, $P < 0.351$).

LIMITATIONS, REASONS FOR CAUTION: The small number of women in the control group meant that correlations were underpowered in this group.

WIDER IMPLICATIONS OF THE FINDINGS: This study is the first to find a benefit of PCOS in visuospatial cognition, and the first to find a link between visuospatial cognition and sex hormones in PCOS. The fact that the correlations went in the opposite direction in the PCOS group compared with the controls might suggest the influence of increased prenatal exposure to androgen in PCOS.

STUDY FUNDING/COMPETING INTEREST(S): The assays for this study were funded by the Department of Psychology, City University London. All authors report no conflicts of interest.

Key words: mental rotation / testosterone / estradiol / polycystic ovary syndrome

Introduction

There is some evidence to support the generalization that males, on average, score higher than women on some types of visuospatial tasks, especially three-dimensional mental rotation, whereas females, on average, score higher than men on some types of verbal tasks. Several authors have found a positive correlation between circulating levels of testosterone and mental rotation ability in men and women (Aleman *et al.*, 2004) and indeed a sex difference in mental rotation ability can be seen from as early as 4 months old (Moore and Johnson, 2008). In women, although estradiol is beneficial for some verbal abilities (Sherwin, 2012), it has been associated with poorer three-dimensional performance (Kozaki and Yasukouchi, 2008). Functional magnetic resonance imaging during a three-dimensional task has found that in general, men show activation of parietal areas, whereas women show activation of frontal areas, suggesting that men perform the three-dimensional task intuitively, whereas women rely on a more effortful approach (Weiss *et al.*, 2003).

Twin studies (Heil *et al.*, 2011) and studies of females exposed to elevated prenatal androgens (Hines *et al.*, 2003) suggest that the sex difference in mental rotation ability is due to the organisational effects of testosterone. Prenatal exposure to testosterone permanently alters the cortical networks related to cognitive abilities (Schoning *et al.*, 2007) and the distribution of androgen receptors in parts of the brain involved in spatial processing, such as the hippocampus (Young and Chang, 1998).

Elevated testosterone is one of the diagnostic criteria for polycystic ovary syndrome (PCOS) and women with PCOS often have mildly elevated levels of testosterone. Given the findings of research on testosterone and three-dimensional mental rotation ability, it is perhaps surprising that the only two studies of three-dimensional ability in women with PCOS have found no significant difference compared with controls (Schattmann and Sherwin, 2007; Barnard *et al.*, 2007).

The aim of the present study is to assess the relationship between sex hormones and performance on the three-dimensional mental rotation task in women with PCOS.

Materials and Methods

Participants

Participants, selected from gynaecology clinics in central London, were examined by a gynaecologist or an endocrinologist. Women aged between 18 and 45 were included.

PCOS group

The PCOS group consisted of women diagnosed using the Rotterdam criteria (The Rotterdam ESHRE/ASRM, 2003) for a previous study (Barry *et al.*, 2011). Of the 69 women, 19 had serum total testosterone levels elevated beyond the normal range for women aged 18–40 years old (>2.90 nmol/l for the assay used). Women were excluded from this study if they showed signs of other endocrine disorders, such as congenital adrenal hyperplasia, Cushing's syndrome, menopause or androgen secreting tumours. Diagnosis and medication use were confirmed from hospital records. There were 10 women were taking medications to alleviate symptoms of androgen excess (seven taking the oral contraceptive pill (OCP), and three taking an anti-androgen). Smoking and drinking levels per week, height and weight and other relevant variables were recorded.

Control group

The control group consisted of 41 women with fertility problems not associated with PCOS, recruited from the clinics reported previously (Barry

et al., 2011). These women were chosen as a control group in order to control for any effects of subfertility on the outcomes. The fertility problems in this group were caused in most cases by tubal disease or male factor, or were unexplained. Only women who did not qualify for PCOS diagnosis by the Rotterdam criteria were included in the control group, and none of the women had polycystic ovaries on ultrasound scan. None of the control group women were taking OCPs or anti-androgens. All other exclusion criteria were the same as for the PCOS group. None of the women in either group had a condition that might affect three-dimensional scoring, apart from the hypothesized association with PCOS.

Measures

Three-dimensional mental rotation task

Peters *et al.* (1995) created a classic puzzle-like measure, in which a stimulus object is placed alongside four target objects. Two of the target objects are the same as the stimulus object but shown from a different angle; the other two target objects are distracters. Participants are required to identify the two target objects that are the same as the stimulus object in order to gain a point. The present study presented 12 sets of these objects to participants electronically, either on the researcher's laptop or on the participant's computer at home. The task was time-limited automatically to 3 min.

Vocabulary task

Based on Ekstrom *et al.* (1976), 18 words were presented with multiple-choice responses, time-limited to 4 min. This provides a brief assessment of verbal intelligence and acts as a control measure for the three-dimensional task; if the vocabulary score and three-dimensional score are correlated, then they may both simply be reflecting general intelligence rather than independent cognitive abilities.

Hand preference inventory

Five Likert-scaled items adapted from Bryden (1982) measured preference for right hand or left hand use for five everyday tasks, for example, writing.

Socioeconomic classification

Socioeconomic classification (SEC) was assessed using the Office for National Statistics' NS-SEC classes and collapses three-class hierarchy.

Hormone measures

For women who had a regular menstrual cycle, blood samples were taken during days 2–6 of the cycle. Blood samples from participants were centrifuged and frozen for up to 4 months until being assayed using the Roche Elecsys system 1010/2010 Modular E170, a direct electrochemiluminescence (ECLIA) methodology (Roche Diagnostics, Indianapolis, USA). The reference interval for testosterone in women aged between 18 and 40 are 0.22–2.90 nmol/l and for estradiol in the follicular phase, the reference interval is 90–716 pmol/l. The inter-assay coefficient of variation is $<20\%$ for both hormone assays. In the present study, 'testosterone' refers to total testosterone in nmol/l and 'estradiol' to total estradiol in pmol/l.

Statistical analysis

Kolmogorov–Smirnov tests and Levene's equality of variance tests were used to determine the normality of data distribution; non-normal distributions were analysed using nonparametric tests (Spearman's rho for correlations or a Mann–Whitney *U*-test to analyse group differences). Distributions that passed normality testing were analysed using parametric tests (analysis of covariance, ANCOVA). Categorical data were analysed using χ^2 or Fisher's exact test. The software package SPSS version 20 for Windows was used for these statistical analyses. The Fisher's *Z*-test was used to compare the magnitude of bivariate correlation coefficients. Where a directional hypothesis

was made and supported by the findings, *P* values are stated as one tailed. The threshold for statistical significance was $P < 0.05$.

Analyses were carried out on the main two main groups (69 women with PCOS and 41 controls) and then further divided into three groups (14 hyperandrogenic PCOS, 37 non-hyperandrogenic PCOS and 27 controls). For the main between-groups comparison of three-dimensional mental rotation score, the group sizes gave 81% power to detect a moderate effect size (Cohen's $d = 0.5$) using Mann–Whitney *U*-test, with alpha at 0.05. The groups sizes for correlations (56 women with PCOS and 32 controls) gave 74% power to detect a moderate correlation (Pearson's $r = 0.3$) in the PCOS group and 52% power to detect a moderate correlation in the control group, with alpha at 0.05. For the further subgroup analysis of the three groups using ANCOVA, post-hoc power was 48%. Power was estimated using G*Power Version 3.1.6 software (Buchner et al., 1997).

Ethical approval

This study was done with the approval of London Multicentre Research Ethics Committee (MREC) and the Local Research Ethics Committees (RECs) of participating clinics. Written informed consent was given by all the patients prior to the start of the study.

Results

The PCOS group consisted of 69 women, aged between 18 and 38, who completed the three-dimensional mental rotation task. Of these, 56 women gave blood samples for the assessment of hormones and 19 women were biochemically hyperandrogenic, having serum total testosterone levels elevated beyond the normal range for women aged 18–40 years old (>2.90 nmol/l for the assay used). When categorized by phenotype, 40% showed evidence of clinical and/or biochemical hyperandrogenism, 23% were oligo- or anovulatory, and 37% had both clinical and/or biochemical hyperandrogenism and were oligo- or anovulatory. The control group consisted of 41 women, aged between 24 and 43, who completed the three-dimensional mental rotation task. Of these, 32 gave blood samples for the assessment of hormones and 2 women with biochemically elevated testosterone levels (>2.90 nmol/l) were excluded from the subgroup analysis of women with hyperandrogenic PCOS.

Background variables

Table 1 shows that, as expected, the PCOS group had significantly higher testosterone levels than the controls, and larger body mass index (BMI). The PCOS group were also significantly younger, with a median age of 29 compared with 35 in the control group. Age was not significantly correlated with three-dimensional scoring in either group. There were no significant differences for any of the other background variables (ethnicity, socioeconomic class, handedness). There was no statistically significant difference in vocabulary scores between PCOS and control women and no correlation between vocabulary scores and three-dimensional mental rotation scores in either group. Comparing the 10 women who were taking OCPs or anti-androgens for PCOS to the other women with PCOS, there was no significant difference in testosterone levels ($t = -0.979$, d.f. = 63, $P < 0.331$) or three-dimensional mental rotation scores ($t = 1.287$, d.f. = 64, $P < 0.203$).

Three-dimensional mental rotation score

The PCOS group scored significantly higher than the control group on the three-dimensional mental rotation task: PCOS group median

(range) 3.00 (0–9); control group 2.00 (0–8) and this difference was statistically significant ($U = 1147.500$, $N_1 = 69$, $N_2 = 41$, $P < 0.047$, one tailed). Comparing the three groups (hyperandrogenic PCOS, non-hyperandrogenic PCOS and controls), the hyperandrogenic PCOS group had a mean (SD) score of 4.00 (1.52), the non-hyperandrogenic PCOS group scored 2.97 (2.10) and the controls scored 3.11 (2.20) (Fig. 1). Comparing the three groups using ANCOVA, there was not a statistically significant difference in three-dimensional scoring ($F = 1.472$, d.f. = 1, 83, $P < 0.235$), but post-hoc tests using Fisher's least significant difference test found that the hyperandrogenic PCOS group scored significantly higher than the control group ($P < 0.05$, one tailed). Controlling for age and BMI using ANCOVA, there was not a statistically significant difference between the three groups ($F = 1.062$, d.f. = 1, 73, $P < 0.351$). Post-hoc tests were not possible with ANCOVA because of insufficient degrees of freedom.

Sex hormones and mental rotation scores

In the PCOS group, there was a significant positive correlation between testosterone and three-dimensional mental rotation scores ($r_s = 0.376$, $n = 56$, $P < 0.002$, one tailed) as well as a negative correlation between estradiol and three-dimensional mental rotation score ($r_s = -0.473$, $n = 29$, $P < 0.010$, one tailed). In the control group, there was a non-significant negative correlation between testosterone and three-dimensional scores ($r_s = -0.278$, $n = 33$, $P < 0.117$, two tailed) as well as a non-significant positive correlation between estradiol and three-dimensional rotation scores ($r_s = 0.303$, $n = 26$, $P < 0.133$, two tailed). Fisher's *Z*-tests found that these correlations for testosterone were significantly stronger in the PCOS group than in the control group ($Z = 4.046$, $P < 0.0001$, two tailed) and estradiol ($Z = 5.488$, $P < 0.0001$, two tailed).

Discussion

This is the first paper to report significant correlations between sex hormones (testosterone and estradiol) and mental rotation ability in women with PCOS. This is also the first paper to report a significant difference in mental rotation scoring between women with PCOS and other women.

A weakness of this study is that the statistical tests tended to be underpowered. For example, correlations in the control group achieved 52% power instead of 80%. The statistical power was lower due to the smaller number of women in the control group and the control group correlations may have been significant had the group size been larger. However, low power does not explain the large difference between the strength of the correlations between the groups nor why the direction of correlation was different in each group. One might speculate that these differences might have their origins in prenatal androgenization in PCOS (see discussion below).

It could be argued that a further weakness of the study is that the commonly used electrochemiluminescence method lacks the sensitivity to accurately detect testosterone below 10 nmol/l, and that instead tandem mass spectrometry should have been used (Rosner et al., 2007). Most studies of sex hormones and mental rotation have not used tandem mass spectrometry to measure testosterone, and the present study is in this tradition. However, it should be born in mind that in women with PCOS, testosterone measured using standard assay methodology shows a strong correlation ($r = 0.67–0.79$) with

Table 1 Demographic and other background variables in women with PCOS compared with control women.

Variable	PCOS (n = 69) ^a	Controls (n = 41) ^a	Test statistic
Total testosterone (T, nmol/l)	2.10 (0.20–5.80)	1.10 (0.40–4.20)	529.500 ^{*b}
Total estradiol (E2, pmol/l)	164.00 (57–1042.0)	137.00 (48–1503.00)	443.000
Age	29 (18–38)	35 (24–43)	346.500 ^{**b}
BMI	25.00 (19.00–51.00)	21.68 (18.24–50.15)	661.500 ^{*b}
Socioeconomic class			
Professional	22 (58%)	16 (42%)	3.053 ^c
Intermediate occupation	8 (44%)	10 (56%)	
Routine/manual	19 (65%)	10 (35%)	
Handedness			
Right	29 (76%)	9 (24%)	1.111 ^c
Left	4 (57%)	3 (43%)	
Ethnicity			
White	31 (52%)	29 (48%)	2.391 ^a
Non-White	20 (69%)	9 (31%)	

PCOS, polycystic ovary syndrome; BMI, body mass index.

^aNumbers vary slightly depending on whether information on all variables was available.

^bMann–Whitney *U*-test.

^c χ^2 -test.

* $P < 0.001$, ** $P < 0.001$. Significance values are two tailed.

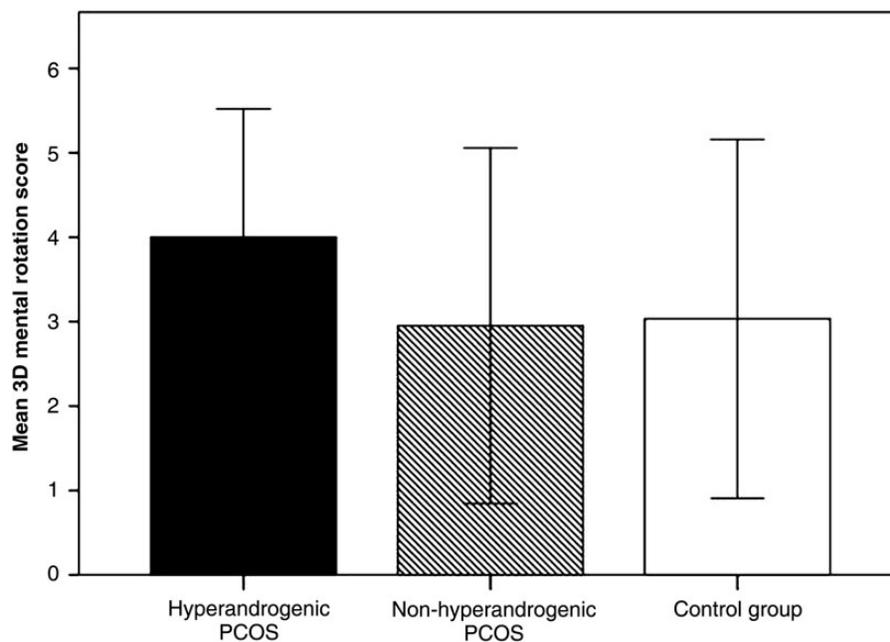


Figure 1 Mean three-dimensional mental rotation score in the hyperandrogenic PCOS group (total testosterone > 2.90 nmol/l), non-hyperandrogenic PCOS group (total testosterone < 2.90 nmol/l) and control group. The error bars show ± 1 SD.

testosterone measured using liquid chromatography mass spectrometry (Legro *et al*, 2010), thus we might infer that for practical purposes the electrochemiluminescence method used in the present study (and in many other studies) is adequate, though perhaps not ideal, for the purposes of this study.

Another possible weakness is that the women in the control group were not completely healthy as they were subfertile, and many did not have normal menstrual functioning. However, this group was healthy apart from experiencing fertility problems, and was considered a good comparison group because they were comparable to the PCOS group

in terms of their experiences of fertility problems (Barry *et al.*, 2011), thus controlling for any confounding effects (e.g. psychological distress) associated with fertility problems. Thus, although the control group was not a healthy control group, they were a suitable comparator for the PCOS group.

Although these findings are consistent with previous research of sex hormones in non-PCOS populations, they contrast with the two previous studies of PCOS (Schattmann and Sherwin, 2007; Barnard *et al.*, 2007) which reported null findings. This discrepancy might be explained by methodological differences between the present study and these two previous studies. Schattmann and Sherwin had a small sample (22 PCOS and 22 controls), used a bespoke diagnosis of PCOS (a variation of the NIH criteria) and, unlike the present study, gave participants 25% longer to complete the task than that described by Peters *et al.* (1995). Likewise, the task used by Barnard *et al.* (2007) was different to Peters *et al.* in that the participants of Barnard *et al.* were presented with one instead of four alternative figures. Furthermore, Barnard *et al.* did not measure testosterone or estradiol, so were unable to test for a relationship between cognitive performance and hormone levels. In contrast, Aleman *et al.* (2004) found a link between testosterone and three-dimensional mental rotation scoring in healthy women; the present study did not find such a relationship in the control group, possibly because Aleman *et al.* induced an improvement in three-dimensional scoring by administering 0.5 mg of testosterone to their participants, whereas the design of the present study was observational and the testosterone level in the control group was within the normal range.

The fact that differences in mental rotation ability have been reported in male and female infants, and in girls exposed to prenatal androgen (Hines *et al.*, 2003), suggests that mental rotation ability is due to the organisational effect of androgen on prenatal neurological development. Androgens such as testosterone have been linked to sexually dimorphic behaviours through such changes in brain morphology (Mendrek *et al.*, 2011). Prenatal exposure to testosterone is believed to permanently alter the cortical networks within the brain, directly affecting the cognitive abilities controlled by these brain regions (Weiner *et al.*, 2004; Schoning *et al.*, 2007). Organisational influences of testosterone might also be responsible for the distribution of androgen receptors in parts of the brain involved in spatial processing, such as the hippocampus (Young and Chang, 1998). As well as these prenatal organisational effects of testosterone, it is likely that post-natal sex differences in testosterone levels (e.g. in adult men and women) reinforce gender differences in cognition by causing temporary activational changes in brain function (Schattmann and Sherwin, 2007).

Several authors have found a positive correlation between circulating levels of testosterone and mental rotation ability in men and post-menopausal women, indicating an activational effect of testosterone. In a study of post-menopausal women, Stangl *et al.* (2011) found that the administration of dehydroepiandrosterone (DHEA) significantly improved performance on a mental rotation test. In healthy young women, one small study found that the administration of testosterone improved mental rotation scores (Aleman *et al.*, 2004). However, this apparent benefit may be to some degree the result of a practice effect, because participants only performed better when they experienced a placebo condition first, during which they did the three-dimensional task. Furthermore, the serum testosterone levels in the study by

Aleman *et al.* were not measured, so correlations between testosterone and three-dimensional scores were not possible.

The modest difference in three-dimensional scoring between the PCOS and control group in the present study was unlikely to be due to a difference between the groups in general intelligence because there was no significant difference in vocabulary test performance between women with PCOS and the controls, and no correlation between vocabulary score and three-dimensional mental rotation scores in either group. Although the scoring was highest in the hyperandrogenic PCOS group, the scores were similar to the norm score of 4.1 for female Bachelor of Arts students based on 12 sets of the Peters *et al.* (1995) three-dimensional objects, and the inter-group differences became non-significant when age and BMI were controlled.

The significantly stronger correlations between sex hormones and mental rotation ability in the PCOS group compared with controls could suggest a greater activational effect of sex hormones in the PCOS group. This effect could, in theory, be the result of organisational effects of prenatal exposure to testosterone in PCOS, altering brain morphology. In view of the evidence that prenatal androgen excess programmes the metabolic and reproductive derangements of PCOS, it is possible that the participants in our study experienced such exposure *in utero*. The finding of differences in communication and focus of attention in the children of hyperandrogenic women with PCOS is compatible with an organisational effect of androgens on brain development (Palomba *et al.*, 2012). It is possible that prenatal hyperandrogenic exposure might programme for adult hyperandrogenism via altered adult hypothalamic–pituitary–gonadal functioning, without altering prenatal brain development, thus higher three-dimensional mental rotation scores might be the result of an activational effect of testosterone that has prenatal/organisational origins. The fact that the non-hyperandrogenic PCOS group scored similarly to the control group might suggest that these women were either not exposed to a hyperandrogenic prenatal environment, or that they experienced a weaker exposure that resulted neither in altered brain development nor hyperandrogenism in adulthood. It is therefore reasonable to speculate that for some women with PCOS, prenatal exposure to testosterone increases the expression of androgen receptors in those regions associated with visuospatial ability (cortical areas, the hippocampus and parietal lobe). A greater number of receptors would mean that those regions of the brain are more efficient in the uptake of circulating testosterone, thus women with PCOS, who often have higher circulating testosterone, and possibly more androgen receptors in relevant areas due to prenatal exposure to testosterone, would use circulating testosterone more efficiently in these areas when engaging in a mental rotation task. It has recently become possible to assess the distribution (Garg *et al.*, 2008) and degree of activity (Evans *et al.*, 2011) of androgen receptors non-invasively with positron emission tomography (PET) technology; future researchers should consider using this technique to investigate mental rotation ability in women with PCOS.

The results of this study are novel and demonstrate an area in which women with PCOS are advantaged, rather than disadvantaged, compared with their peers who do not have this syndrome. It could be argued that the existence of such factors, together with 'thrifty genes' favouring energy conservation, may explain the ability of PCOS, a condition of impaired reproduction, to withstand evolutionary pressures.

Acknowledgements

The authors thank the consultants and other helpful staff at the participating clinics for facilitating recruitment and sample collection: Ms Diana Hamilton-Fairley, Guys and St. Thomas Hospital, London; Dr Gerard Conway, University College London Hospital, London; Ms Davinia White, St Mary's Hospital, London; and Mr Paul Serhal, Centre for Reproductive and Genetic Health, Eastman Dental Hospital, London. We also thank Professor Melissa Hines of the University of Cambridge for her advice, and the Senior Analyst Programmer at City University London, Peter Barr, for excellent technical support.

Authors' roles

J.B. designed the study and protocol. J.B. and P.J.H. recruited participants to the study. J.B. and H.P. conducted the literature review, statistical analysis and wrote the first draft of the paper. All authors contributed to the writing and approval of the final version.

Funding

The assays for this study were funded by the Department of Psychology, City University London.

Conflict of interest

None declared.

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