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Does the use of hormonal contraceptives affect the mental rotation performance?

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ABSTRACT

Oral contraceptive pill (OC) is one of the most popular form of contraception. Despite both behavioral and neuroimaging evidence of its significant impact on female brain and cognitive functions, much remains to be discovered regarding OCs targets in the brain and mechanisms of action. In the present study mental rotation performance was compared between women using anti-androgenic oral contraceptives ($n = 35$), naturally cycling (NC) women ($n = 33$) and men ($n = 29$). On average, OC users were less accurate than NC women and men. Men performed the task more accurately than NC women, but the difference reached significance only in the highest angular disparity condition (150 deg). The response time was positively related with progesterone level while accuracy was negatively related with 17ß-estradiol level, in NC, but not OC women. The comparison of slope and intercept values (parameters relating response time to angular disparity) revealed the main result of present study: OC users exhibited significantly lower slope compared to men and NC women, but there were no differences in intercept between groups. These results suggest that OC users instead of using rotation in mind strategy implemented some alternative method(s). We conclude that lower performance accuracy of OC users could be related to a less efficient performance strategy.

1. Introduction

During the last decades oral hormonal contraceptives (OCs) became one of the most popular form of contraception. While there is an increasing amount of data about significant effect of hormonal contraceptives on brain structure (e.g. Petersen et al., 2015; Pletzer et al., 2015) and functions (e.g. Armbruster et al., 2017; Beltz et al., 2015; Cicinelli et al., 2011; Egan and Gleason, 2012; Gogos, 2013; Graham and Milad, 2013; Griksiene and Ruksenas, 2011; Kerschbaum et al., 2017; Kuhlmann and Wolf, 2005; Marecková et al., 2014; Mordecai et al., 2017; Nielsen et al., 2013; Petersen et al., 2014; Pletzer et al., 2014b; Wharton et al., 2008), some studies are demonstrating no impact (e.g. Islam et al., 2008; Rosenberg and Park, 2002). With such ambiguous findings it is natural that recent papers reviewing the effects of hormonal contraceptives on cognition highlight a need for more studies in this area (Giatti et al., 2016; Gogos et al., 2014; Pletzer and Kerschbaum, 2014).

Spatial abilities (including mental rotation) play an important role in human intelligence. Mental rotation is a hypothetical psychological operation in which a mental image is rotated around some axis (Zacks, 2008), characterized as one of the cognitive functions demonstrating the most consistent sex differences and sensitivity to the effect of sex hormones in humans (for a review see Hamson et al., 2016; Pletzer, 2014). Namely, male excel at the behavioral level in the form of shorter response time and/or higher accuracy (Astur et al., 2004; Boone and Hegarty, 2017; Halari et al., 2006; Noreika et al., 2014; Parsons et al., 2004; Roberts and Bell, 2003; Simić and Santini, 2012). Furthermore, sex and/or sex steroids related differences are evident in the brain activity evaluated by functional magnetic resonance imaging (Hugdahl et al., 2006; Jordan et al., 2002; Schöning et al., 2007; Thomsen et al., 2000; Weiss et al., 2003) and electroencephalography (Desrocher et al., 1995; Jaušovec, 2012; Yu et al., 2009). Changes in mental rotation performance and/or in mental rotation related brain activity have been demonstrated in various conditions related to altered levels of fluctuating sex steroids. Studies evaluating mental rotation performance during women menstrual cycle reported a decrease of accuracy with an increase of estradiol (Hampson et al., 2014; Hausmann et al., 2000) and slower response time when progesterone was higher (Courvoisier et al., 2013; Noreika et al., 2014). Whereas, androgens have been shown to improve the performance of both women (Aleman et al., 2004; Hausmann et al., 2000) and men (Hooven et al., 2004). Moreover, it has been demonstrated that individuals with complete androgen insensitivity syndrome (a male karyotype but a female phenotype) (van Hemmen et al., 2016) and male-to-female transsexuals after cross-sex

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hormone treatment (Carrillo et al., 2010) show a female-like neural activation pattern during mental rotation, providing evidence that sex differences in regional brain function during mental rotation reflect gonadal hormone exposure. On the other hand, results of some studies denied contribution of sex steroids to sex differences in mental rotation e.g. (Gordon and Lee, 1993; Puts et al., 2010).

Having in mind the importance of sex steroids on mental rotation, it is possible that performance on this task might be altered in OC users whose hormonal balance is changed markedly. Although some previous studies demonstrated differences between OC users and naturally cycling (NC) women (Griksiene and Ruksenas, 2011; Wharton et al., 2008), others found no such differences (Islam et al., 2008; Rosenberg and Park, 2002). Inconsistencies across studies may have been caused by various methodological issues such as sample size, treating all OCs users as one group without the respect to the type of OC, the use of tasks that are differently sensitive to sex steroids, lack of hormone measures as well as different intellectual abilities among others (Beltz et al., 2015). Accounting for the heterogeneity of OCs is one of the most common differences between studies that demonstrated the effect of OCs on mental rotation, and those that did not. Most combined OCs contain ethinyl estradiol and various progestins. All progestins bind to the progesterone receptors, but they also modulate the activity of other steroid hormones (androgen, estrogen, glucocorticoid, and mineralocorticoid) receptors by preventing the activation or inducing the transactivation of a steroid receptor. Depending on agonistic or antagonistic effect of progestins on androgen receptors they can be grouped into androgenic (e.g. levonogestrel, desogestrel, gestodene) and antiandrogenic (e.g. chlormadinone acetate, dienogest, drospirenone) compounds (Africander et al., 2011; Giatti et al., 2016; Schneider, 2003; Sitruk-Ware, 2006). Within these groups, androgenic as well as antiandrogenic properties may differ depending on the affinity of the particular progestin to androgen receptors. For example, gestodene, desogestrel and norgestimate have been shown to have lower androgenic effect as compared to levonogestrel (Hammond et al., 2001; Stanczyk and Archer, 2014). In studies where no effect of OCs on mental rotation was demonstrated women were not separated according to the pills used (estradiol dose, progestin androgenity and dose, constant or changing amount of hormones across the active pill phase etc.) (Gordon and Lee, 1993; Islam et al., 2008; Rosenberg and Park, 2002). Whereas in the studies showing an impact of OCs on mental rotation, the dose of ethinyl estradiol (Beltz et al., 2015) and androgenity of progestins (Griksiene and Ruksenas, 2011; Wharton et al., 2008) were shown as significant factors. Wharton et al. (2008) results revealed the highest mental rotation performance accuracy in women who used the most androgenic OCs (containing second generation progestins) and the lowest accuracy in women who used antiandrogenic OCs. We, in our previous study (Griksiene and Ruksenas, 2011), demonstrated lower accuracy in antiandrogenic OC users but only in a more difficult task condition (higher angular disparity between figures in pair). Moreover, the study by Beltz et al. focusing on the effect of ethinyl estradiol, showed that monophasic OC users, taking OCs that contain androgenic progestins, outperformed NC women in mental rotation (Beltz et al., 2015).

This is in line with findings demonstrating an association between sex steroids and mental rotation results in females (Aleman et al., 2004; Hampson et al., 2014; Hausmann et al., 2000). The distinction between effects of androgenic and antiandrogenic progestins is even more important due to the increasing usage of the new generation progestins (at least in Europe) (Pletzer and Kerschbaum, 2014) with most of them (drospirenone, dienogest, nomegestrol acetate etc.) exerting an antiandrogenic activity (Sitruk-Ware, 2006).

The complexity of mental rotation process is another potent source for inconsistencies between mental rotation studies investigating the effect of sex hormones. Mental rotation involves several distinct and functionally independent subprocesses. For example, to complete the classical Shepard and Metzler (1971)'s task, which requires participants to decide if one object is a rotated version of another or it's a mirror image, subjects must: (i) create mental representation of an object, (ii) mentally rotate; (iii) compare the two objects; (iv) decide whether the objects are the same or different; (v) give a motor response (Karádi et al., 2001). Therefore, the precision of interpreting such results may be increased by applying of a method which enables to isolate measures of mental rotation ability (step “ii” above) from the other abilities involved in the task. To achieve this, authors of some previous mental rotation studies (e.g. Cohen and Kubovy, 1993; Hirschfeld et al., 2013; Hooven et al., 2004) used a linear regression of the response time (RT) on the angle of rotation. In such analysis, the slope of the regression shows the average change in RT per additional degree of rotation, i.e. represents the rotation process (Hooven et al., 2004). Whereas, the intercept of the regression indexes show the RT for the 0° orientation, i.e. point where regression line crosses y axis and represents the efficiency of all other processes used to perform the task (Hirschfeld et al., 2013; Hooven et al., 2004). The comparison of an individual and group slope and intercept values should reveal if the differences between subjects and/or groups are due to the differences in rotation itself or in other processes related to the task. Based on these measures, the strategies used to perform the task (rotation in mind vs other (e.g. analytical)) could be inferred.

In this study, we compared mental rotation performance between women using antiandrogenic OCs with NC women and included a group of men to control the sex effect. We implemented a 3D mental rotation paradigm with two sequentially presented figures rotated with respect to each other (similar to used in Cohen and Kubovy, 1993). To evaluate the task performance we measured performance accuracy (ACC) and RT. Afterwards we calculated RT slope and intercept. Our hypothesis was related to the antiandrogenic properties of hormonal contraceptives. Based on previous knowledge about the effect of sex steroids on mental rotation performance, we anticipated to confirm previously discovered negative effect of antiandrogenic OCs on mental rotation performance (i.e. lower accuracy) and to expand the knowledge about this effect by assessing parameters related to the different mental rotation subprocesses. Based on these results we expected to reveal dominating strategies used by distinct participant groups to perform the task.

2. Methods

2.1. Participants

69 female and 30 male healthy right-handed volunteers with no history of mental illness or neurological disorders, with normal or corrected-to-normal vision and body mass index between 18 and 28 kg/m^2 participated in the study. Naturally cycling (NC, $n = 34$) women, oral contraceptives users (OC, $n = 35$) and men were recruited through advertisements at the University and on social networks. Only women with a regular menstrual cycle (ranging from 26 to 34 days) and not using hormonal contraceptives for at least three months were recruited for the NC group. NC women participated in experiments in the early and mid follicular ($n = 13$) and luteal ($n = 21$) phase of their menstrual cycle as the reference points of low and high 17β-estradiol and progesterone levels respectively. However, retrospective analysis of salivary 17β-estradiol and progesterone levels for some women did not correspond to the expected menstrual cycle phase (see Section 3.1. Hormones in Results for mean values and Table in Supplement B for individual data). Therefore, for the data analyses, we decided not to divide NC women into follicular and luteal phase sub-groups, but rather to evaluate the relationships between the concentrations of sex hormones and performance results. Since the individual performance characteristics of women whose progesterone level did not correspond to the expected mid-luteal phase were compatible with other NC women (all $p \geq 0.21$), their results were included in further analyses.

OC group consisted of women using antiandrogenic monophasic