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Effects of hormonal contraceptives on mental rotation and verbal fluency

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Mood

Summary Cognitive abilities, such as verbal fluency and mental rotation, are most sensitive to changes in sex steroids but poorly studied in the context of hormonal contraceptive usage. Therefore, we investigated the performance of mental rotation and verbal fluency in young (21.5 ± 1.8 years) healthy oral contraceptive (OC) users (23 women) and non-users (20 women) during the follicular, ovulatory and luteal phases of the menstrual cycle. Salivary 17β -estradiol, progesterone and testosterone levels were assayed to evaluate hormonal differences between groups and the phases of the menstrual cycle. To assess the effects of progestins having androgenic/anti-androgenic properties, OC users were subdivided into the third and new generation OC users. In addition, positive and negative affects as factors possibly affecting cognitive performance were evaluated.

Salivary 17β -estradiol and progesterone levels were significantly lower in hormonal contraception users. Level of salivary testosterone was slightly lower in the OC users group with significant difference only during ovulatory phase. Naturally cycling women performed better on verbal fluency task as compared to OC users. Subjects who used the third generation (androgenic) OCs generated significantly fewer words as compared to new generation (anti-androgenic) OC users and non-users. The third generation OC users demonstrated significantly longer RT in MRT task as compared to non-users. The MRT, verbal fluency and mood parameters did not depend on the phase of menstrual cycle. The parameters of the PANAS (Positive and Negative Affect Schedule) scales did not differ between OC users and non-users.

Our findings show that hormonal contraception has an impact on verbal and spatial abilities. Different performances between users of oral contraceptives with androgenic and anti-androgenic properties suggest an essential role for the progestins contained in OCs on cognitive performance.

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Introduction

Oral contraceptives, one of the most popular methods of reversible contraception, act centrally (mainly at the hypothalamic level) and peripherally (Benagiano et al.,

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2009) to inhibit follicular growth, reduce overall endogenous sex steroid levels and prevent monthly hormonal fluctuations (Gordon and Lee, 1993; van Heusden and Fauser, 1999). Changes in cognitive functions have been reported as a result of the long-term suppression of endogenous sex steroids in transsexuals (Slabbekoorn et al., 1999), after surgical menopause (Farrag et al., 2002), or due to aging (Sherwin, 2006; Matousek and Sherwin, 2010). However, the level of sex steroids can be suppressed by the use of hormonal contraceptives, and the data about the effect of this relatively short-term and reversible change on cognitive functions are sparse and contradictory (Gordon and Lee, 1993; Rosenberg and Park, 2002; Mordecai et al., 2008; Wharton et al., 2008; Griksiene and Ruksenas, 2009).

Cognitive abilities in verbal fluency and mental rotation (MRT) are gender-specific and are most sensitive to the effects of changes in sex steroid levels (Sherwin, 2003; Weiss et al., 2003). On a verbal fluency task, women mostly outperform men (Weiss et al., 2003; Halari et al., 2006; Hausmann et al., 2009) (but for critical review see Wallentin, 2009), whereas on mental rotation tasks, men perform better than women on average (Gouchie and Kimura, 1991; Moffat and Hampson, 1996; Weiss et al., 2003; Peters et al., 2006; Halari et al., 2006; Kozaki and Yasukouchi, 2009; Jansen and Heil, 2010). There are studies reporting that the performance on verbal and spatial tests depends on the phase of menstrual cycle; verbal fluency improves during the high estrogen and progesterone phases, whereas visuospatial skills are enhanced during low estrogen and progesterone phases (Hampson, 1990; Hausmann and Gunturkun, 2000; Maki et al., 2002). Studies of the effects of sex hormone on spatial and verbal performance demonstrate a negative estradiol correlation and a positive testosterone correlation with mental rotation performance (Hausmann et al., 2000; Maki et al., 2002; Aleman et al., 2004), a positive estradiol correlation with verbal fluency (Maki et al., 2002), and no relationship between testosterone and verbal fluency (Moffat and Hampson, 1996; Slabbekoorn et al., 1999; Hausmann et al., 2009). In addition, there are studies reporting a curvilinear relationship between testosterone (*T*) concentration and spatial abilities in men and women; men with comparatively low *T* levels performed better on spatial tasks than men with higher *T* levels, and women with high *T* concentrations were superior to those with low *T* levels (Gouchie and Kimura, 1991; Moffat and Hampson, 1996; Ostatnikova et al., 2002). However, there are studies reporting no relationship between spatial and verbal performance and sex steroid levels in men, women, or both (Yang et al., 2007; Hausmann et al., 2009; Puts et al., 2010).

The behavioral gender and sex steroid-driven differences in spatial and verbal performance were confirmed by functional imaging studies where sex-specific brain activation during mental rotation (Schoning et al., 2007) and verbal fluency (Halari et al., 2006; Rumberg et al., 2010) tasks was demonstrated.

Whereas most of the studies conducted in this area have focused on differences between genders or phases of menstrual cycle, few studies have investigated hormonal contraception-related changes in verbal and spatial task performance (Gordon and Lee, 1993; Rosenberg and Park, 2002; Mordecai et al., 2008; Wharton et al., 2008). Gordon and Lee (1993) did not find significant differences in

performance of verbosequential and visuospatial tests among OC users and non-users. Other authors have reported that OCs enhance verbal memory in the midluteal cycle phase (Rosenberg and Park, 2002; Mordecai et al., 2008) but do not affect verbal fluency (Mordecai et al., 2008) or visuospatial abilities (Rosenberg and Park, 2002; Mordecai et al., 2008). Wharton et al. (2008) did not find any differences in MRT performance between OC users and non-users but demonstrated an effect of OC generation on MRT performance.

Almost all of the currently used combined OC pills contain the same estrogen compound, ethinyl estradiol (Amy and Tripathi, 2009), that, in most cases, is in the so-called "low-dose" form (on average, 30–35 µg) or "ultra-low-dose" form (on average 20–25 µg) (Batur et al., 2003). The progestins used in the currently available combined OCs are divided into so-called generations: first-generation (no longer available for the prevention of pregnancy), second-generation (e.g., levonorgestrel, norethindrone), third-generation (e.g., gestodene, desogestrel and norgestimate) and the new-generation (e.g., drospirenone) (Glasier, 2006; Benagiano et al., 2009). The classification of contraceptives into generations is controversial. There is an opinion that classification lacks scientific rationale and could obscure the fact that each of the progestins have unique biological properties (Carr, 1998). An alternative opinion is that such classification is clearly defined (Glasier, 2006; Benagiano et al., 2009), helps to group OCs having similar properties and makes the comparison of results obtained from different studies easier. First to third generation progestins are testosterone-derived, bind to the androgen receptors and have varying degrees of androgenic activity. The most selective are the third-generation progestins that were developed with structural modifications to lower their androgenic activity. New generation progestins, for example the spironolactone-derived drospirenone, have anti-mineralocorticoid and anti-androgenic properties (Rowlands, 2003; Batur et al., 2003). Because of the androgenic activity of earlier generation pills and the opposite anti-androgenic activity of the new generation pills, opposite effects on gender specific and sex steroid sensitive mental rotation and verbal fluency tasks may be observed. For example, Wharton et al. (2008) reported that second generation OC users were better on mental rotation task (MRT) performance compared with the third, new generation OC users and non-users. The new generation OC users performed poorly on the MRT in comparison to the second and third generation OC users as well as to non-users. As no difference in MRT performance was observed when compared all OC users and non-users, these authors suggested that the effects were masked by a combination of high and low androgenic progestins in the same analysis.

In the present study, we investigated the influence of hormonal contraceptive use on mental rotation and verbal fluency abilities. For this purpose, the performance of mental rotation and verbal fluency was investigated in OC users and non-users during three phases of the menstrual cycle. To assess the effects of the progestins having androgenic/anti-androgenic properties, OC users were subdivided into third (androgenic) and new (anti-androgenic) generation OC users. In addition, mood was evaluated as a factor that could affect cognitive performance. We hypothesized that OC users would perform worse on the verbal fluency task and the

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