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Research Report

Differential effects of androgenic and anti-androgenic progestins on fusiform and frontal gray matter volume and face recognition performance

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ABSTRACT

Effects of oral hormonal contraceptives (OC) on human brain structure and behavior have only recently become a focus of research. Two explorative reports observed larger regional gray matter (GM) volumes in OC users within the prefrontal cortex, ACC and fusiform gyri, as well as parahippocampal gyri, hippocampus and cerebellum. These studies did however not control for the androgenicity of the progestin compound of OC, did not take into consideration how long OC users had been on their OC, and did not control for age differences between the OC group and the naturally cycling group. We compared 20 naturally cycling women during their early follicular cycle phase to 18 users of OC containing androgenic progestins and 22 users of OC containing anti-androgenic progestins. When controlling for age, we found that in users of anti-androgenic progestins relative GM volumes within the bilateral fusiform gyri, fusiform face area (FFA), parahippocampal place area (PPA) and cerebellum, were significantly larger than in naturally cycling women, while in users of androgenic progestins, relative as well as absolute volumes within the bilateral middle and superior frontal gyri were significantly smaller compared to naturally cycling women. These morphological changes were related to performance in a face recognition task. Face recognition performance was significantly better in users of anti-androgenic progestins compared to the other groups and significantly related to absolute as well as relative GM volumes in the FFA and PPA. Total GM volume, as well as absolute GM volumes within the bilateral fusiform gyri, FFA, hippocampus, parahippocampus, PPA, middle frontal gyri and ACC were significantly larger, the longer the duration of OC use, particularly in users of androgenic progestins. Morphological differences between active and inactive pill phase were observed in users of androgenic progestins. These findings suggest differential effects of androgenic and anti-androgenic progestins on human brain structure.

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1. Introduction

Oral hormonal contraceptives (OC) have been used for over 50 years now by over 100 million women worldwide (Petitti, 2003). Over the years adverse side effects on women's health and mood have been studied extensively and several generations of progestin compounds have been developed with the aim to reduce these side effects (e.g. Darney, 1995; Sitruk-Ware, 2006). Some of these effects have been attributed to androgenic actions of older generation progestins, which were derived from 19-nortestosterone (Sitruk-Ware, 2006). The most common second generation progestin was Levonorgestrel with clear androgenic side effects (e.g. Knopp et al., 2001). Several third generation progestins were developed in order to achieve androgenic neutrality. Those include Desogestrel, Norgestimat and Gestodene (Knopp et al., 2001; Kuhl, 1996). Both Desogestrel and Norgestimat are however quickly metabolized to 3-keto-Desogestrel and Levonorgestrel, respectively, which both excert androgenic actions (Kuhl, 1996). Newer progestins, such as Dienogest and Drospirenone have on the contrary been demonstrated to bind specifically to progesterone receptors and excert anti-androgenic actions (e.g. Sitruk-Ware, 2006).

While metabolic and emotional side effects of OC have been heavily investigated (e.g. Wiegratz and Kuhl, 2006), the effects on brain structure and function have largely been ignored. This is surprising given the fact that 19-nortestosterone is a widely-used (e.g. Brueggemeier, 2006) anabolic androgenic steroid and side effects of anabolic androgenic steroid abuse on brain structure and function have been discussed (see Scaccianoce et al., 2013 for a review).

Only a small number of studies reported behavioral effects of OC on cognitive tasks. For example, OC have been found to enhance verbal memory (Mordecai et al., 2008) as well as recognition working memory during sleep deprivation (Wright and Badia, 1999). However, verbal reaction times are slower in OC users compared to non-users (Garrett and Elder, 1984) and non-significant effects were reported for other measures of verbal abilities, like verbal fluency (Mordecai et al., 2008) or a verbosequential task (Gordon and Lee, 1993). OC have also been found to enhance mental rotation performance (Wright and Badia, 1999; Wharton et al., 2008), although other studies report non-significant effects on visuospatial tasks (Gordon and Lee, 1993; Mordecai et al., 2008). Furthermore, OC users differ from naturally cycling women in an emotional memory paradigm (Nielsen et al., 2011). Alterations of brain activation patterns due to OC use have been observed in verbal (Rumberg et al., 2010) and numerical tasks (Pletzer et al., 2014).

In 2010 we were able to publish the first report of hormonal contraceptive dependent effects on brain structure (Pletzer et al., 2010). In a small explorative study we found that users of oral hormonal contraceptives had significantly larger regional gray matter volumes in the lateral and medial prefrontal cortex, anterior cingulate cortex (ACC), as well as the parahippocampal and fusiform gyri and cerebellum. Thus hormonal contraceptives in this study did affect both regions typically larger in women, e.g. the prefrontal cortex and regions typically larger in men, e.g. the cerebellum (e.g. Pletzer et al., 2010; Goldstein et al., 2001; Good et al., 2001). DeBondt et al. (2013) were able to replicate the effect on the fusiform gyri and ACC, as well as the superior frontal gyrus, but did not report any differences between OC users and non-users in the cerebellum.

There are several methodological issues that arise when studying effects of OC use in a between-subjects design that have not been captured in these first exploratory studies.

First, neither of these studies did control for androgenicity of the progestin compound used in OC. Hence inconsistencies may arise from different composition of the OC group.

Second, one question that has not previously been addressed is the question of reversibility of hormonal contraceptive dependent changes. If some effects on the brain are long-lasting, the duration of OC use in the OC group as well as the duration of previous OC use in the group of naturally cycling women may also affect the detectability of differences.

Third, the duration of OC use and sampling in naturally cycling and OC users is naturally confounded with age. Women who have used the pill for a longer period of time are likely older than those having used the pill for only a short period of time. Also, OC are used more commonly by younger women and women who decide to not use OCs are often older. While the women participating in these previous studies have been of approximately the same age, several of the areas, in particular the prefrontal cortex, that have been affected by OC use are also affected by normal aging (e.g. Sowell et al., 2003).

The aims of the present study were (i) to dissociate the impact of androgenic vs. anti-androgenic progestin compounds in brain structural differences between OC users and non-users, (ii) attempt to dissociate effects of synthetic progestins from the effects of ethinylestradiol, and (iii) to explore the reversibility of hormonal contraceptive dependent effects while controlling for age.

Furthermore, the morphological differences between OC users and non-users have to our best knowledge not been related to behavioral differences. As two previous studies (Pletzer et al., 2010; DeBondt et al., 2013) found OC dependent differences in the fusiform and parahippocampal gyri, we chose a face recognition task, to investigate, whether differences in GM volumes within these areas, were reflected in performance.

2. Results

2.1. *Comparison of naturally cycling women and OC users—Total and regional GM volumes and face recognition performance*

Controlling for age ($F_{(1,56)}=11.42$, $p<0.001$), total GM volumes did not differ significantly between naturally cycling women and each of the OC groups, i.e. anti-androgenic and androgenic ($F_{(2,56)}=0.96$, $p=0.39$). Note however, that as in our previous study, OC users, in particularly users of anti-androgenic compounds had non-significantly smaller total GM volumes than naturally cycling women. Face recognition performance was however significantly affected by group ($F_{(2,56)}=3.47$, $p<0.05$) with users of antiandrogenic progestins outperforming naturally cycling women ($p_{posthoc}<0.10$) and users of androgenic progestins ($p_{posthoc}<0.05$). Results are summarized in Fig. 1.