How Oral Contraceptive Use Impacts Brain Morphology: Preliminary Findings of a Population Neuroimaging Study

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Abstract

Oral contraceptives (OCs) are used by over 100 million women worldwide. They contain synthetic hormones which may alter brain structure and function; however, only a few small-scale neuroimaging studies have examined their effects on the brain thus far. Taking a big data approach, the Jacobs Lab at UCSB launched a database which pairs structural brain scans with reproductive health histories. Preliminary findings from the database found that, compared to never users, OC users had an increase of grey matter volume (GMV) in an area of the brain called the cerebellum (n=48). In this replication study, participants showed similar results (n=24).

Introduction

Access to contraception has dramatically improved economic advancement, educational attainment, and health outcomes for women across the globe. Reproductive autonomy allows women to forgo the health risks associated with pregnancy as well as to pursue higher education – one of the many reasons why the Centers for Disease Control and Prevention (CDC) named family planning one of the 10 major public health advancements of the 20th century (Centers for Disease Control, 1999). Unsurprisingly, many women today rely on birth prevention; 65% of women aged 15-49 and 73.7% of women aged 40-49 in the United States were using contraception in 2015-2017 (Hatcher et al., 2018). However, even with such a large population of chronic users, there continues to be a need for research on how contraceptives influence human physiology. This would better allow the millions of women across the globe to make more informed decisions on their reproductive health.

The main form of hormonal birth control is the oral contraceptive (OC), which contains synthetic forms of the ovarian hormones estrogen and progesterone. These hormones inhibit the production of the messengers responsible for triggering ovulation: follicle-stimulating hormone (FSH) and luteinizing hormone (LH). This change in the hormonal milieu is responsible for the desired effects of the pill; however, hormones travel through the blood and maintain the homeostasis of many organ systems beyond just reproduction. One major site for these receptors is the brain. Although ample evidence has shown that certain brain regions are sensitive to fluctuations in ovarian steroid hormones, the impact of OC use on the brain is still not completely clear - even after 50 years of being on the market (Pletzer and Kerschbaum, 2014).

The first oral contraceptive pill, Enovid, was developed in the 1950s before much was elucidated about the role of sex hormones in reproduction or the impact of hormones on the body in general. It contained dramatically higher doses of estrogen and progesterone needed for contraceptive purposes. As a consequence, it was discovered during clinical trials that its use was associated with deadly conditions such as thrombosis and pulmonary embolism (McWilliam et al., 1963). In almost every decade since OCs were released in 1960, there has been progress in advancing its formulation, such as reduced hormone levels and alternative administration routes. To continue to improve and expand the available contraceptive options on

the market, we need to shift attention towards a serious gap in the literature: how OC use impacts the central nervous system (CNS).

A large body of literature demonstrates that major endocrine events, such as puberty and menopause, impact CNS function. For example, during the pubertal transition, a steady decrease in grey matter volume (GMV: a type of brain tissue comprised of neuronal cell bodies) is observed in the frontal and parietal cortex of the brain, alongside marked changes in behavior and emotion (Schulz and Sisk, 2016). During menopause, the decline in ovarian hormone production is associated with CNS changes such as 'brain fog,' reduced hippocampal volume, and poorer performance on memory tasks (Hampson E., 2018; Leranth et al., 2002; Jacobs et al., 2016).

Beyond these large-scale endocrine events, there is now increasing evidence that smaller fluctuations in hormone concentrations can significantly impact the same circuits. For example, as estrogen concentrations rose across the menstrual cycle, women performed better on a verbal fluency task (measured by quickly recalling words in a semantic category) and worse on a mental rotation task (measured by the ability to identify rotated 3D objects) (Maki et al., 2002). Therefore, it is possible that these circuits are modified in women who do not experience a natural cycle - one subset being the hundreds of millions of women who use OCs.

Of the handful of neuroimaging studies which have begun examining OC use, there have been conflicting results. One study found that compared to never users, women using OCs had significantly larger GMVs in certain brain regions (prefrontal cortex, parahippocampal gyri, and fusiform gyri; Pletzer et al., 2010). Other researchers have found a decrease in the amygdala and parahippocampal gyrus volume after just three months of OC use (Lisofsky et al., 2016). These differences in findings are likely due to divergent study design (within versus between subjects), relatively small sample sizes, and the fact that critical factors of OC use (e.g., age of initiation, duration of use, and formulation) were not fully controlled for. These discrepancies call for a large-scale neuroimaging database, which accounts for the many variables concerning reproductive health history.

To that end, the UCSB Brain Imaging Database was created to systematically examine OC use. The database houses a collection of standard magnetic resonance image (MRI) sequences from the majority of participants who are scanned at the University's Brain Imaging Center. The participants' scans are then matched with an online Qualtrics questionnaire, which asks extensive questions regarding reproductive health history and hormone use. A preliminary analysis from the first 100 database participants (resulting in a final sample size of 48 women with no prior pregnancies, no history of hormone use other than OC, and other exclusionary criteria) revealed significantly greater GMV in the cerebellum of OC users relative to women who had never used OC. The present study aimed to test the replicability of these results with a new cohort of database participants (n=24).

General Overview

Subjects

Subjects were recruited from the pool of all participants scanned at the UCSB Brain Imaging Center (BIC). Participants from any research project who had an MRI were invited to participate in this ancillary study. It consisted of a 10-minute online Qualtrics questionnaire, and all participation was voluntary. This study was IRB approved and allowed for the collection of de-identified data from all BIC participants.

In this replication, a total of 56 subjects completed the questionnaire. Thirty-two subjects were eventually excluded for previous pregnancies, other hormone use, endocrine disorders, head trauma, low-quality MRI images, or any psychiatric/mood disorders. This yielded a final sample of 24 women (aged 18-24). Women were divided into groups of current OC users and women who had never used OC. In keeping with the discovery dataset analyses, in this replication study, "OC Users" and "Never-Users" were matched for age, age of menarche (puberty), and BMI (see table 1).

Table 1. Participant demographics for both cohorts.

	Old Cohort (2017)		Current Replication	
	Never Users	OC Users	Never Users	OC Users
N	24	24	12	12
Age	21 ± 2	21 ± 2	20 ± 1	21 ± 3
BMI (kg/m²)	21 ± 2	22 ± 3	24 ± 5	23 ± 3
Age of Menarche	13 ± 2	13 ± 2	12 ± 1	12 ± 1
Age of Initiation	-	18 ± 2	-	17 ± 2
Duration (Months)	-	41 ± 24	-	32 ± 16

MRI analysis (for replication purposes)

Data was acquired with a Siemens 3T Prisma MRI scanner. The participant's T1 scan, a high-resolution structural image taken at the

beginning of all fMRI studies, was matched with their corresponding questionnaire data. The images went through preprocessing, where they were normalized to an average brain template and segmented into the different tissues - gray matter, white matter, and CSF (cerebrospinal fluid). Bias correction removed intensity non-uniformities and images were smoothed with an 8 mm kernel. This was done in a Matlab program called SPM12 using the Computational Anatomy Toolbox (CAT12).

Analyses were performed in SPM12 to compare the GMV between OC users and never users (2-sample t-test). To assess if there was an effect of duration of use on GMV, 'months of use' was entered as a covariate of interest in an analysis of OC users (multiple regression). To correct for variations in head size, total intracranial volume (TIV) was included as a covariate of no interest in all analyses. Results were corrected for multiple comparisons, $p < 0.05$.

Results

Current OC Users versus Never Users

In the original cohort, greater cerebellar GMV was observed in current OC users compared to never users (□p □_FDR < 0.05; see Figure 1). In concordance with these previous findings, a whole-brain 2-sample t-test of the current cohort revealed significantly greater GMV in the cerebellum of current users compared to never users (□p □_(FWE)= 0.041; see Figure 2). According to the Stoodley et al. (2009) cerebellar mapping, where the cerebellum is divided into lobules (regions), this cluster is located in the posterior cerebellum in lobule VI (MNI x, y, z = 3, -17, -75; k_(E)= 451 voxels (a measure of three-dimensional space), extending bilaterally.

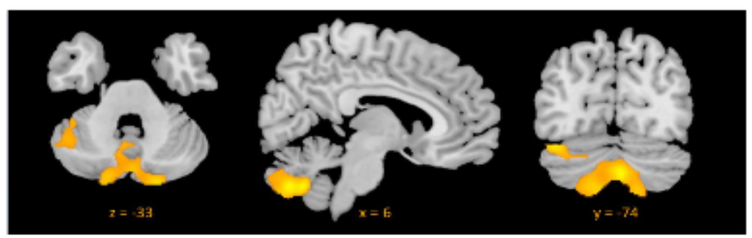

Figure 1. Regions (in yellow) from the 2017 cohort where the increase in regional GMV for 'Current OC Users' compared to 'Never OC Users' was observed (p_(FDR)< 0.05).

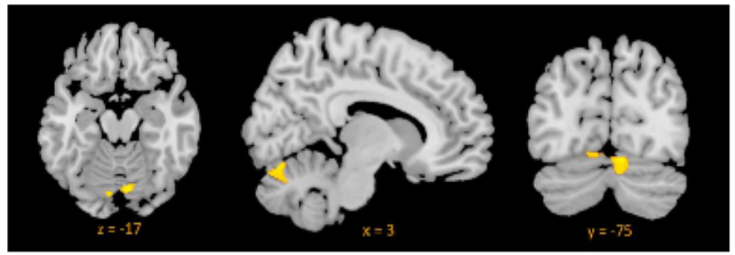

Figure 2. Regions (in yellow) from current replication where the increase in regional GMV for 'Current OC Users' compared to 'Never OC Users' was observed (p_(FWE)= 0.041).

Duration of Use in Current Users

In the 2017 cohort, the duration of OC use (months) was associated with changes in GMV in the cerebellum (p_(FDR)< 0.05) (see Figure 3). The current replication did not find an effect on the duration of use (p_(FDR)> 0.05).

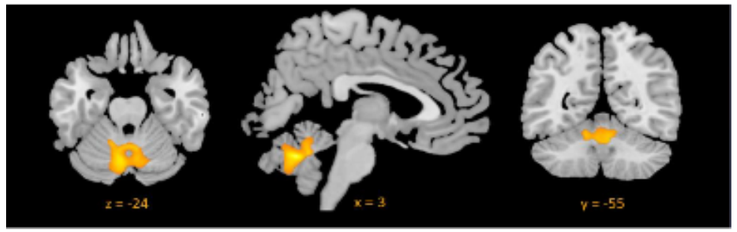

Figure 3. Regression analysis from the 2017 cohort showing an impact of 'Duration of Use' on increase in regional GMV (p_(FDR)< 0.05). Areas with significant change are highlighted in yellow.

Discussion

We consider the present analysis to have replicated the initial findings as we also observed greater cerebellar GMV in OC users relative to never users. However, the two cohorts revealed GMV differences in distinct regions of the cerebellum. The initial findings were located in lobules IX and VIIB (MNI x, y, z = 6, -33, -74) while the current cohort's effects can be observed in lobule V and VI (MNI x, y, z = 3, -17, -75). In both cohorts, the effects were observed bilaterally. The regional differences are likely due to the small sample size of the replication cohort and will be re-examined with

greater power once larger cohorts are amassed.

As the database continues to grow, checking in (even with small cohorts) can provide valuable insight to which brain regions are particularly sensitive to hormonal fluctuations. These insights inspire behavioral/ cognitive research topographically targeted to the known functions of those affected areas. According to a meta-analysis of functional topography in the cerebellum by Stoodley & Schmahmann (2009), the brain regions that displayed significant differences in the current replication have been functionally implicated for working memory tasks. In the right lobule, this area extends from (6, − 78, − 26) to (18, − 70, − 18), and in the left lobule it extends from (− 14, − 88, − 20) to (− 8, − 72, − 12). The region observed in the current study falls in a similar area with a peak at (3, -75, -17) and sub-peaks at (8, -75, -17) and (14, -71, -23). The hypothesis that OC use may impact working memory performance is supported by work from Mordecai et al. (2008), which showed an increase in working memory performance for OC users during their active pill phase versus their inactive pill phase.

Summary

This study contributes to an emerging body of work, indicating that OC use modulates brain structure (Lisofsky et al., 2016; Pletzer et al., 2010). Although an increase in grey matter was observed with OC use, it is difficult to make conclusions on how this change relates to behavior and cognitive ability. While some evidence suggests that GMV in the cerebellum is positively correlated with performance on topographically significant tasks, it is not always that simple (Ramanoël et al., 2018). More volume does not necessarily equate a positive effect; grey matter reduction is sometimes beneficial, representing specialization or maturation. This can be observed during the onset of menses (puberty), where many cognitive functions are enhanced, yet a marked decrease in GMV is observed (Peper et al., 2011).

Thus, in order to fully understand the implications of synthetic hormone administration, there is a strong need for systematic population level studies, which account for the many factors associated with OC use, including the age of initiation, duration of use, and pill formulation. This imaging database initiative continues to expand, with researchers at UC Berkeley now administering the questionnaire to their MRI participants in hopes of using big data to answer these long overdue questions. With implications for half of the population, viewing neuroscience through a women's health lens and further establishing the effects of OC on the brain is a global public health issue.

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About the Author

Margaret Hayes, a Biopsychology major and student researcher, uses magnetic resonance imaging (MRI) to examine the effects of hormones on the brain. She is passionate about advancing public health, and plans to continue onto graduate school with a focus on behavioral neuroscience.