Impact of oral hormonal contraceptives on the CNS: Developing a population neuroimaging study

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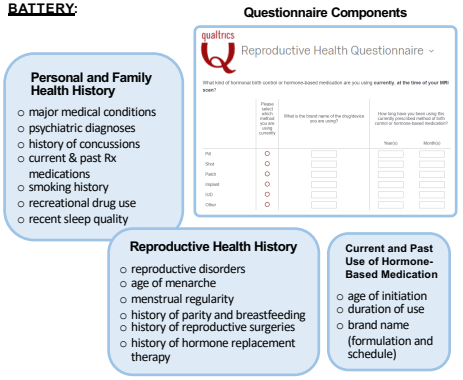
INTRODUCTION

- Combined hormonal oral contraception (OC) is used by >100 million women worldwide.[1]
- OC use suppresses the endogenous production of sex steroid hormones.[2]
- Two decades of rodent and nonhuman primate studies have established sex hormones' role in shaping synaptic morphology in cortical and subcortical brain regions at the microstructural level. [3,4,5,6]
- Whether long-term ovarian hormone suppression has consequences at the gross level of regional brain morphology in humans is unclear, but emerging evidence from two small-scale human studies raises the possibility.[7,8]
- OC use varies across multiple dimensions (e.g., age of initiation, duration of use, hormone formulation, schedule). This multifactorial problem would benefit from a large-scale imaging dataset that captures normal variability in OC use among women.
- We launched the UCSB Brain Imaging Database that leverages the activity of the campus-wide neuroimaging community. Multimodal brain imaging data from standard MR sequences (high resolution T1, T2, DSI and resting state) are pooled and participants' neuroimaging data is paired with a comprehensive battery of demographic/clinical/reproductive health data.
- Target n=1000. Here we present data from a discovery dataset of the first 100 database participants as a proof of concept and hypothesis-generator.
- We begin by asking three questions:
  1. **Does regional gray matter volume (rGMV) differ between current OC users vs. never-users?**
  2. **Does duration of OC use impact rGMV?**
  3. **Does OC use impact sex differences in rGMV?**

METHODS

PARTICIPANTS: 150 men and women (ages 18-33) from the UCSB Brain Imaging Database. Participants were excluded for previous parity, psychiatric/mood disorder, substance use, or low-quality MPRAGE, yielding a sample of 48 women (24 current OC users and 24 never-users, matched on age, education age of menarche and BMI) and 27 age-matched men.

BATTERY:



Demographic Characteristics. Groups were matched on age, BMI and (in females) age at menarche.

	Female		Male
	Current User	Never User	
n	24	24	27
Age	21 ± 2	21 ± 2	21 ± 2
Age at Menarche	13 ± 2	13 ± 2	--
Age of Initiation	18 ± 2	--	--
Duration of Use (Months)	41 ± 24 (9 – 84)	--	--
BMI (kg/cm^2)	21 ± 2	22 ± 3	22 ± 3

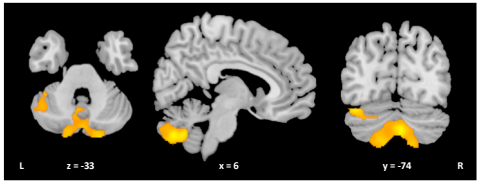
± SD (Range)

MRI ANALYSES: T1-weighted MPRAGE MRI data were acquired with a Siemens 3T Prisma scanner. Data were preprocessed in SPM12 using the Computational Anatomy Toolbox (CAT12). Preprocessing followed standard parameters. T1 images were normalized to an MNI template, segmented into gray matter, white matter and CSF. Bias correction removed intensity non-uniformities. Statistical analysis was performed in SPM12 to compare whole brain GMV between Current and Never-Users (2-sample *t*-test); months of OC use was entered as a covariate to assess the relationship between duration of use and GMV in Current Users. Sex Differences in GMV were assessed using 2-sample *t*-tests. Total intracranial volume (TIV) was included as a covariate of no interest in all analyses. Analyses were corrected for multiple comparisons using an FDR corrected threshold of $p < 0.05$. To estimate the most likely cytoarchitectonic areas covered by significant clusters, we used the maximum probability map within the SPM Anatomy Toolbox.[9]

RESULTS

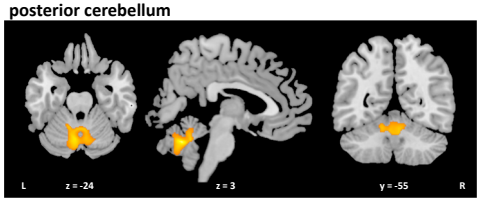
Effects of OC Use on Gray Matter Volume

Current OC users have greater GMV than Never-Users in bilateral posterior cerebellum



cluster-level p<.05, FDR corrected

Duration of OC use correlates with greater GMV in posterior cerebellum

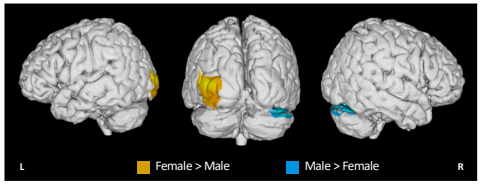


cluster-level p<.05, FDR corrected

Based on the initial success of the UCSB database, we are now broadening the initiative to include UC Berkeley's Brain Imaging Center (scan volume = 1000 participants/year), thus moving toward our goal of a UC-wide brain imaging database that fosters collaboration across campuses and further escalates the sample size that users can draw upon (n=10,000 participants/year).

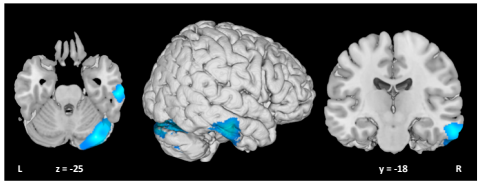
Effects of OC Use on Sex Differences

Sex differences in GMV between Males and all Females



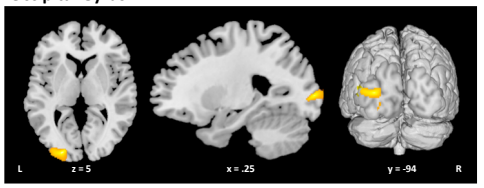
cluster-level p<.05, FDR corrected

Males have greater GMV than Never-Users in Cerebellum & Inferior Temporal Gyrus



cluster-level p<.05, FDR corrected

Current OC Users have greater GMV than Males in Middle Occipital Gyrus



cluster-level p = .057, FDR corrected

CONCLUSIONS

- Whole brain analyses (FDR-corrected) revealed greater cerebellar GMV in OC users compared to never-users.
- Duration of OC use (9-84 mos) was positively correlated with greater cerebellar GMV.
- Sex differences in regional gray matter volume observed between Males and Never-Users were obscured in Current OC Users.
- Results are being tested for replication in additional cohorts.

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