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Resting Regional Cerebral Blood Flow Across Men, Naturally-Cycling Women, and Women using Oral Contraceptives Measured by [^{15}O]-Water Positron Emission Tomography

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INTRODUCTION

- Regional cerebral blood flow (rCBF) is an index of neural function that exhibits robust sex differences[1], as well as abnormalities in several neuropsychiatric diseases wherein sex differences occur, including schizophrenia[2,3].
- It is hypothesized that the observed sex differences in resting cerebral blood flow could reflect important brain-endocrine interactions. However, in certain situations, the hormonal milieu is modified with exogenous hormone use, commonly via oral contraceptives (OCs).
- Importantly, over 100 million women worldwide use oral contraceptives[4], and it remains unexplored how this hormonal manipulation might modulate rCBF.
- To address this knowledge gap, we used the gold standard [^{15}O]-water positron emission tomography to evaluate rCBF at rest across three hormonally distinct populations: men, naturally-cycling women, and women using oral contraceptives.

METHODS

Participants:

- 134 healthy participants between the ages of 18 and 50 underwent resting PET scans at the NIH Clinical Center (Table 1).
  - Of the naturally-cycling women, 19 were in the follicular phase, 19 were in the luteal phase, and 6 were in between (self-reported).

Group	N	Age (Mean ± SD)
Men	65	36.65±7.03
Naturally-Cycling Women	44	33.51±9.06
Women Using Oral Contraceptives	25	29.79±6.25

Table 1. Sample size and age distribution of participants across the three groups.

Neuroimaging Acquisition:

- Participants were instructed to lie still in the scanner and rest with their eyes closed.
- Two resting emission frames, following intravenous administration of 12 mCi [^{15}O]-water, were obtained six minutes apart on a HRRT PET scanner.

Neuroimaging Analysis:

- PET data were analyzed using SPM5[5].
- The images were reconstructed, realigned, anatomically normalized to an average template, globally normalized and smoothed using a 10mm Gaussian smoothing kernel.
- After preprocessing, the resting scans of each participant were averaged to enter group level analysis.
- A whole-brain voxel-wise one-way ANCOVA analysis was conducted to test for differences in rCBF across the three groups (p = 0.001, uncorrected), including age as a covariate of no interest.
- Post-hoc two-sample t-tests were performed and Bonferroni corrected to p=0.002.

RESULTS

- We found widespread resting rCBF differences distributed across the brain for the main effect of group (p=0.001, uncorrected).
  - Post-hoc analyses revealed that men have greater resting rCBF than both naturally cycling women and women using OCs in frontal cortical regions, as well as the insula (Figures 1A, 1B, 1C, & 1D). Compared with men, both naturally cycling women and women using OCs exhibited greater resting rCBF in subcortical regions (Figures 1E & 1F) (p=0.002, Bonferroni corrected).
  - There were no significant differences between naturally-cycling women and women using OCs in this analysis.

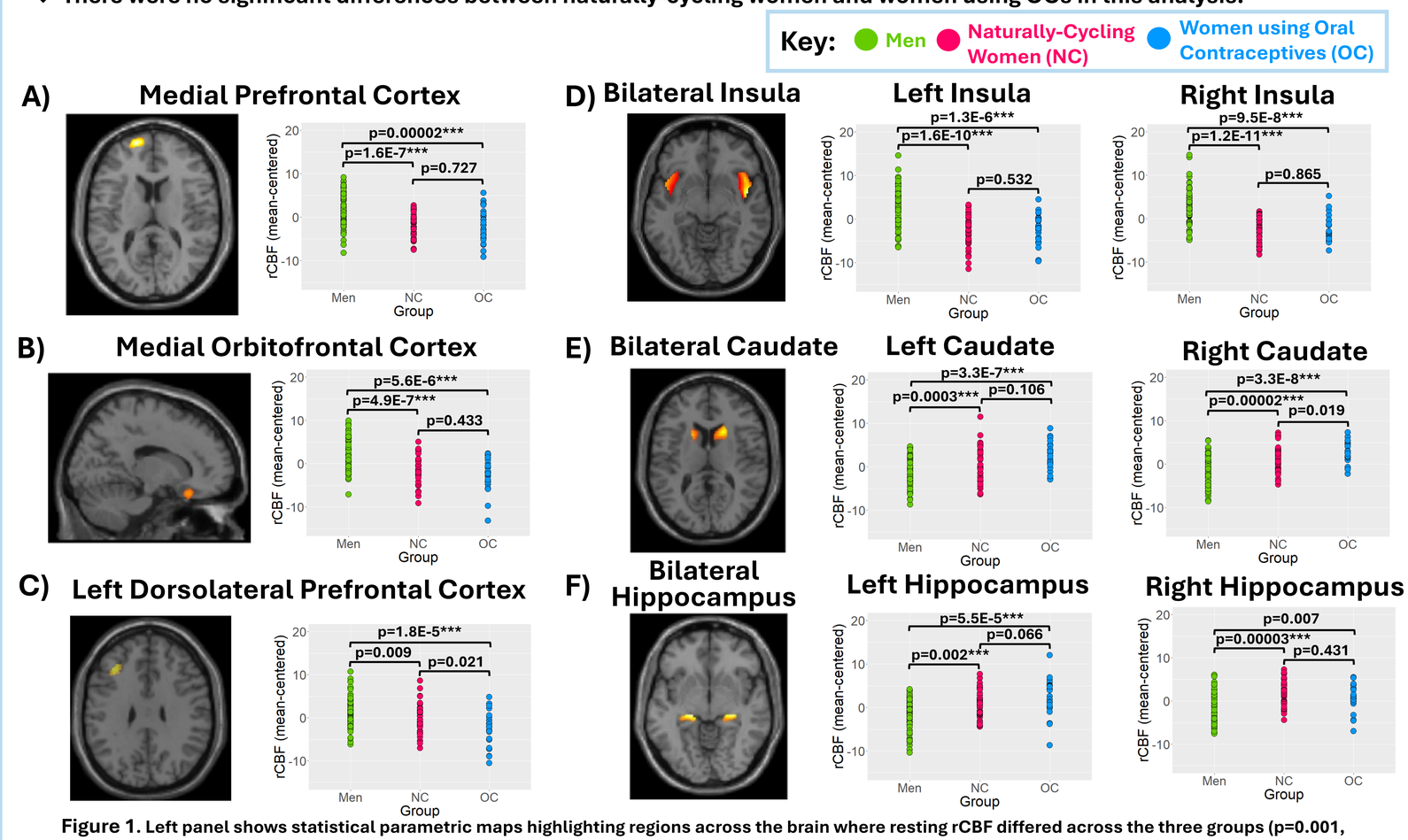

Figure 1. Left panel shows statistical parametric maps highlighting regions across the brain where resting rCBF differed across the three groups (p=0.001, uncorrected). Right panel shows dot plots displaying the mean-centered resting rCBF values for the local maximum voxel in each region separated by group. Brackets display results from post-hoc two-sample t-tests Bonferroni corrected at p=0.002. *** - p(Bonferroni)=0.05.

CONCLUSIONS

- Our results demonstrate resting rCBF differences between men and women in brain regions rich with hormone receptors, including prefrontal cortex and hippocampus.
- In these preliminary analyses, we observed greater rCBF in men compared with women in frontal cortical and insular areas, while women showed greater rCBF in subcortical areas. However, we did not find resting rCBF differences in our sample based on oral contraceptive use.
- Future analyses will explore the effects of menstrual cycle phase and specific hormonal formulation on resting regional cerebral blood flow in healthy adults.

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