Functional Connectivity Varies with Menstrual Hormones, Anxiety, and Stress

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Cognitive and Affective Neuroscience of Psychopathology

INTRODUCTION

- Menstrual phase and cyclical hormone changes have been linked to functional and volumetric changes in the brain.[1,2]
- Oral contraceptives (OC) reduce endogenous hormone levels by introducing synthetic hormones, typically ethinylestradiol and a progestin.
  - The resulting lower estrogen and progesterone levels are comparable to the follicular phase of an active menstrual cycle.
- Two key cycling hormones, estrogen and progesterone, have complex relationships with anxiety.[3]
- Anxiety, marked by biased processing toward threat, is increasingly conceptualized as having multiple dimensions accompanied by differing connectivity patterns.
- These dimensions may interact differentially with cyclical hormonal changes to affect anxiety-related regional brain functional connectivity.

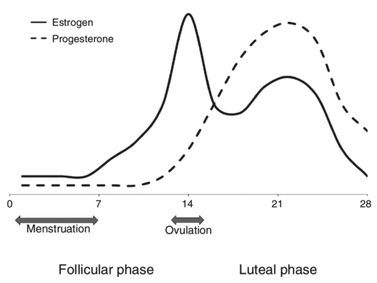


Image from Handy et al., 2022

- The present analysis examined internalizing measures and neural connectivity in a 2back working memory task as a function of hormonal cycling status and phase to identify any interaction between internalizing and menstrual hormones.

METHODS

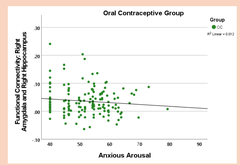
- Sample: 1200-subject release of the Human Connectome Project
  - Healthy subjects, ages 21-36
- Subjects selected for present study had:
  - Active and regular (25-30 day) menstrual cycles
  - No reported menstrual or hormonal disorders or medications
- Phases derived from reported last menstruation start, with day 15 overlap discarded
- Luteal phase n=80; Follicular phase n=160; OC n=150
- Anxious arousal score measured by the NIH toolbox Somatic Fear measure
- Anxious apprehension score estimated as the residual after regressing anxious arousal from the NIH Toolbox Fear Affect measure

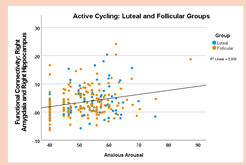
HUMAN Connectome PROJECT

Imaging

- HCP subjects completed a 2back working memory task in a Siemens 3T scanner (see Barch et al., 2013 for imaging details).
  - Stimuli were places, neutral faces, body parts, and tools.
- Connectivity for present study extracted using Python and nilearn and nibabel libraries
  - ROIs identified a priori and defined per Yale Brain Atlas
  - Connectivity measured as within-subject timecourse correlation, transformed to Fisher's z
  - Cycle phase group and anxiety scores predicted functional connectivity via hierarchical linear regression
    - ΔR^2 assessed main effects and interactions
- Connectivity assessed during 2back condition across all blocks
- FDR Benjamini/Hochberg correction applied to p-value vector

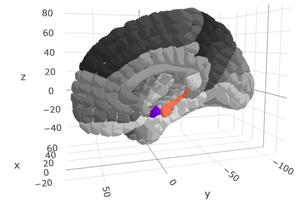
RESULTS





In the oral contraceptive group, higher anxious arousal predicted lower connectivity, whereas in the active cycling group higher anxious arousal predicted higher right amygdala-hippocampus connectivity.

- Contrast 1: Cycling Group v Oral Contraceptive Group
  - Full model including anxious arousal and group showed a small to medium effect size (4% of the variance).
  - Higher anxious arousal was associated with higher functional connectivity, but not group, when group was added second.
  - Their interaction also contributed unique variance.
  - Stress x group interaction was also significant.
- Contrast 2: Luteal Group vs Follicular Group
  - Full model including anxious arousal and stress was marginally significant.
  - Anxious arousal again predicted right amygdala-hippocampus connectivity.
  - Anxiety x group interaction did not approach significance.
  - Stress x group interaction was significant, but not overall model.
- Contrast 3: Luteal Group vs Oral Contraceptive Group
  - Results resembled those for the full sample (Contrast 1), with significant effects for the full model and anxious arousal x group interaction.
  - Stress-related findings were nonsignificant.



Contrast	Predictors	R^2	ΔR^2	F, t	p	df
1. Cycling group vs oral contraceptive group	**Full model**	**0.039**		**5.226**	**0.041**	**3, 385**
	Anx. Aros added first		**0.011**	**2.046**	**0.041**	**1, 387**
	Group added next		0.000	0.013	.989	1, 386
	Anx. Aros*Group interaction		**0.028**	**3.375**	**<0.001**	**1, 385**
	Full model	**0.024**		**3.138**	**0.025**	**3, 385**
	Stress added first		0.000	0.428	0.669	1, 387
	Group added next		0.000	0.009	0.993	1, 386
	Stress*Group interaction		**0.024**	**3.038**	**0.003**	**1, 385**
2. Luteal group vs Follicular group	Full model	0.017		2.234	0.084	3, 385
	Anx. Aros added first		**0.011**	**2.046**	**0.041**	**1, 387**
	Group added next		0.000	-0.041	0.967	1, 386
	Anx. Aros*Group interaction		0.006	1.584	0.114	1, 385
	Full model	0.017		2.206	0.087	3, 385
	Stress added first		0.000	0.428	0.669	1, 387
	Group added next		0.001	-0.212	0.832	1, 386
	Stress*Group interaction		**0.016**	**2.527**	**0.012**	**1, 385**
3. Luteal group vs oral contraceptive group	**Full model**	**0.027**		**3.582**	**0.014**	**3, 385**
	Anx. Aros added first		**0.011**	**2.046**	**0.041**	**1, 387**
	Group added next		0.000	-0.033	0.973	1, 386
	Anx. Aros*Group interaction		**0.016**	**-2.551**	**0.011**	**1, 385**
	Full model	0.009		1.188	0.314	3, 385
	Stress added first		0.000	0.428	0.669	1, 387
	Group added next		0.001	-0.115	0.908	1, 386
	Stress*Group interaction		0.008	-1.835	0.067	1, 385

CONCLUSIONS

- Anxious arousal, but not anxious apprehension, showed a distinct relationship with right amygdala-hippocampus connectivity that differed between individuals with an active menstrual cycle and those taking oral contraceptives.
- Actively cycling individuals did not show phase-specific (luteal vs. follicular) differences, suggesting that homeostatic mechanisms buffer possible impact of hormone fluctuations on connectivity.

Results highlight the need to account for menstrual hormone status in neuroimaging studies and to differentiate dimensions of anxiety to better understand their effects in reproductive-age and adolescent populations.

- Oral contraceptive use, which stabilizes hormone levels, was linked to a connectivity pattern opposite that of active cycling, indicating that endocrine context critically shapes neural manifestations of anxious arousal.
- These findings suggest that menstrual hormones moderate the extent to which anxiety alters threat-related limbic circuitry.

Limitations include:
- Tasks and measures not pre-selected for optimal relevance to present issues
- A within-subject would be preferable for menstrual cycle studies.
- Limited variation in psychopathology due to a non-clinical population

Further analyses will address:
- Functional connectivity at rest and in other tasks in HCP dataset
- Multi-region measures of functional connectivity using graph theory

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Citations:
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