Progesterone & Interhemispheric Decoupling:
Dense Sampling and Intrinsic Functional Connectivity Approach

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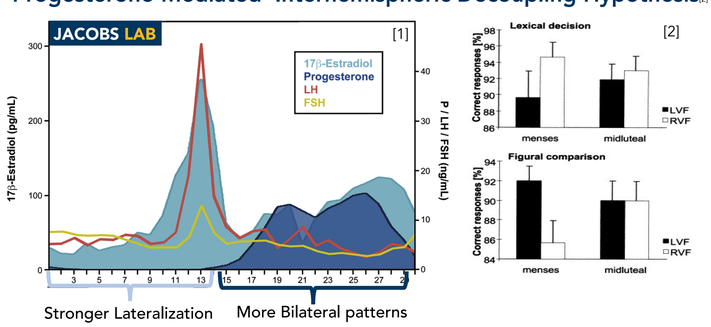
Introduction

- Functional & structural asymmetries are well-known yet poorly understood features of the human brain.
- Brain is an endocrine organ and sex hormones can shape its structure & function [1].

➢ To what extent are sex hormones related to functional and structural asymmetries?

Progesterone-Mediated Interhemispheric Decoupling Hypothesis[2]



Different **behavioral** lateralization patterns were observed for low versus high progesterone [2], and authors have argued that progesterone can alter interhemispheric interaction.

In this study, we have tested whether progesterone levels alter interhemispheric functional coupling, using a dense-sampling, deep-phenotyping approach, capturing natural progesterone fluctuations vis-a-vis tightly-controlled hormonal suppression.

Methods

Data: Resting-state fMRI and blood samples of a healthy adult female (age 23) for 30 consecutive days: once while naturally-cycling and again one year later while using an oral contraceptive, which selectively suppressed circulating Progesterone [1].

Functional Connectivity: Coherence estimated between 400 cortical + 32 subcortical regions; prior to further analysis, applied either simple FDR threshold or additional proportional threshold (top 50% to top 5% of edges, in 5% increments).

Community Detection: performed using Multi-Resolution Consensus Clustering (MRCC) [3].

Laterality Estimates: 'Laterality Indices' (LI) computed both at the level of functional communities/modules and at the level of edge strengths (i.e. intra- vs. interhemispheric edges).

Modularity LI:
Quantifies the degree to which a given functional community spans both hemispheres: ranges from -1 (all LH) to +1 (all RH)—however, used absolute values for analysis here to capture general lateralization patterns.

Edge LI:
Quantifies the ratio of total intra-hemispheric vs total inter-hemispheric connectivity (i.e. is more weight represented in edges *within* each hemisphere or *between* the two hemispheres).

Analyzed using Bayesian generalized Linear models (RStan), considering LIs as a function of natural progesterone fluctuations *or* as contrasted between natural cycle and hormonal suppression.

Bayesian efficient multiple kernel learning also used to train/test a model that distinguishes natural cycle from hormonal suppression based on multivariate patterns of connectivity—MKL approach allows us to identify the importance of edge laterality (intra- vs interhemispheric) in driving the prediction.

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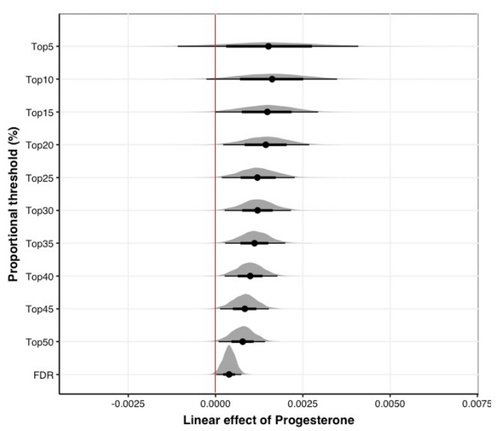
Results

Edge Analysis

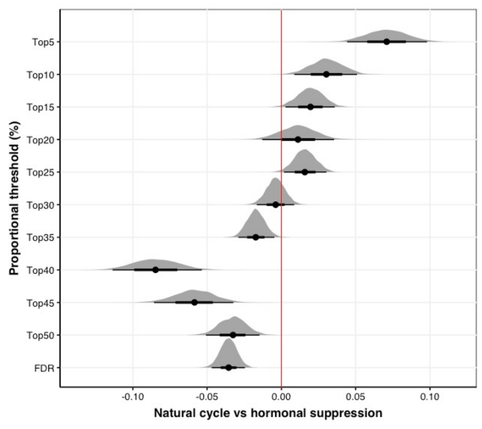
by Progesterone Fluctuation



- Higher Progesterone generally predicts higher Edge LI.
- Higher values of Edge LI indicates intra-hemispheric connectivity > inter-hemispheric

➢ More intra-hemispheric connectivity with more Progesterone

Natural Cycle vs. Oral Contraceptive

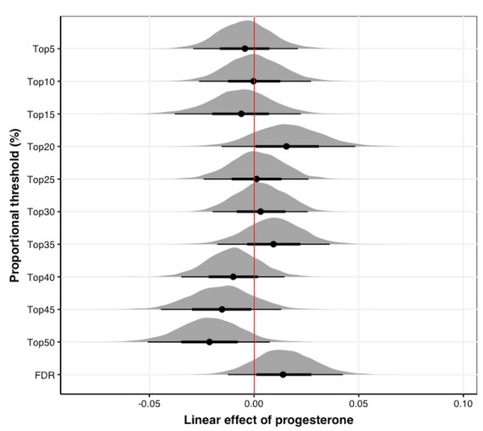


- Positive differences: OC > natural cycle.
- Negative differences: natural cycle > OC.
- Greater Edge LI indicates intra-hemispheric connectivity > inter-hemispheric.

➢ Highly threshold-dependent—OC data show stronger Edge LI at more stringent thresholds.

Modularity Analysis

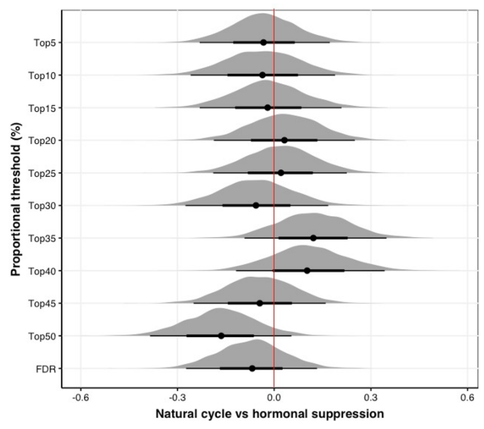
by Progesterone Fluctuation



- No clear association between progesterone fluctuations and Module LI across any threshold.

➢ Progesterone did not predict more laterality or more bilaterality of the modules.

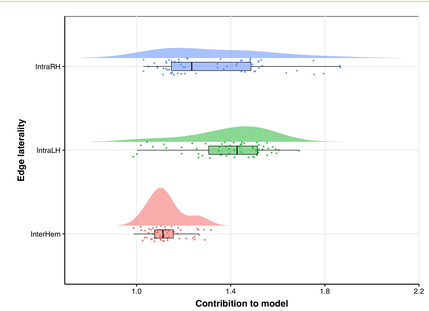
Natural Cycle vs. Oral Contraceptive



- Again, no clear association between hormonal status and Module LI across any threshold.

➢ Laterality of Modules did not differ between natural cycle and OC.

MKL Classifier Highlights Importance of Intra-Hemispheric Connectivity



- Cross-validated model distinguished between connectivity during natural cycle and OC (balanced accuracy = 93.33%).
- Inspection of kernel weights suggests that intra-hemispheric connectivity (particularly LH) had strongest contributions to model—potentially indicative of global shifts in intra-LH connectivity?

Discussion

Intra-hemispheric connectivity seems to be associated with Progesterone fluctuations, but the laterality of community partitions (functional modules) is not.

Limitations Intra- and inter-hemispheric connectivity is analyzed globally rather than focusing on specific networks and homotopic regions. It would be interesting to check connectivity differences within these networks specifically.

Except during the luteal phase, progesterone levels are typically low in natural cycle. It would be interesting to subset the data to compare high progesterone period with OC.

Hypothesized **mechanism behind** Progesterone – Interhemispheric Decoupling: higher Progesterone can increase the inhibitory response to GABA, this can reduce cortico-cortical transmission, and this can lead to interhemispheric decoupling, and that would lead to less inter-hemispheric inhibition, which then results in lesser functional asymmetries [2]. However, this assumes interhemispheric inhibition to be the central process in generating asymmetries. (i.e., **greater interhemispheric coupling** leading to **higher inhibition** leading to **higher lateralization,** which is an ongoing debate. Recent studies showed reduced connections between lateralized regions compared to nonlateralized (not increased connection due to inhibiting each other.) [4].

Higher Progesterone predicted more intra-hemispheric connectivity than inter-hemispheric. Overall laterality of the modules in whole brain was not associated with progesterone levels.

References

[1] Pritschet, L., Santander, T., Taylor, C. M., Layher, E., Yu, S., Miller, M. B., ... & Jacobs, E. G. (2020). Functional reorganization of brain networks across the human menstrual cycle. NeuroImage, 220, 117091.
[2] Hausmann, M., & Güntürkün, O. (2000). Steroid fluctuations modify functional cerebral asymmetries: the hypothesis of progesterone-mediated interhemispheric decoupling. Neuropsychologia, 38(10), 1362-1374.
[3] Jeub, L. G., Sporns, O., & Fortunato, S. (2018). Multiresolution consensus clustering in networks. Scientific reports, 8(1), 1-16.
[4] Karolis, V. R., Corbetta, M., & Thiebaut de Schotten, M. (2019). The architecture of functional lateralisation and its relationship to callosal connectivity in the human brain. Nature communications, 10(1), 1-9.