Multimodal MRI Characterization of Pregnancy-Related Structural and Functional Brain Reorganization

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War.

COI: The authors do not have any conflicts of interest related to the content of this presentation.

This research protocol was reviewed and approved by the USUHS institutional animal care and use committee (IACUC) in accordance with all applicable Federal regulations governing the protection of animals in research.

Synopsis

- **Context & Motivation: Military personnel** experience postpartum mood and anxiety disorders at significantly **higher rates** (26% vs. 10–15% in civilians) due to operational stress, deployments, and relocations.
- **Neural Adaptation:** Pregnancy triggers major neuroanatomical shifts—including reduced gray matter volume/cortical thickness and increased white matter integrity/CSF volume—which may impact long-term cognition and mood (1-4).
- **Objective:** Establish rodent model of pregnancy, quantify maternal brain changes not limited to anatomical, but microstructural and functional as well.
- **Approach:** Perform longitudinal T_2weighted, diffusion tensor imaging (DTI), and resting-state functional MRI (rsfMRI) scans on primiparous and nulliparous rodent models to map volumetric, structural, and functional network changes after pregnancy.

References:
1. Hoekzema, E. et al. Nat Commun 13, 6931 (2022). 2. Lotter, L.D et al. Neuropsychopharmacol. 49, 1809–1818 (2024). 3. Pritschet, L et al. Nat Neurosci 27, 2253–2260 (2024). 4. Martínez-García, M et al. Brain sciences, 11(2), 168.

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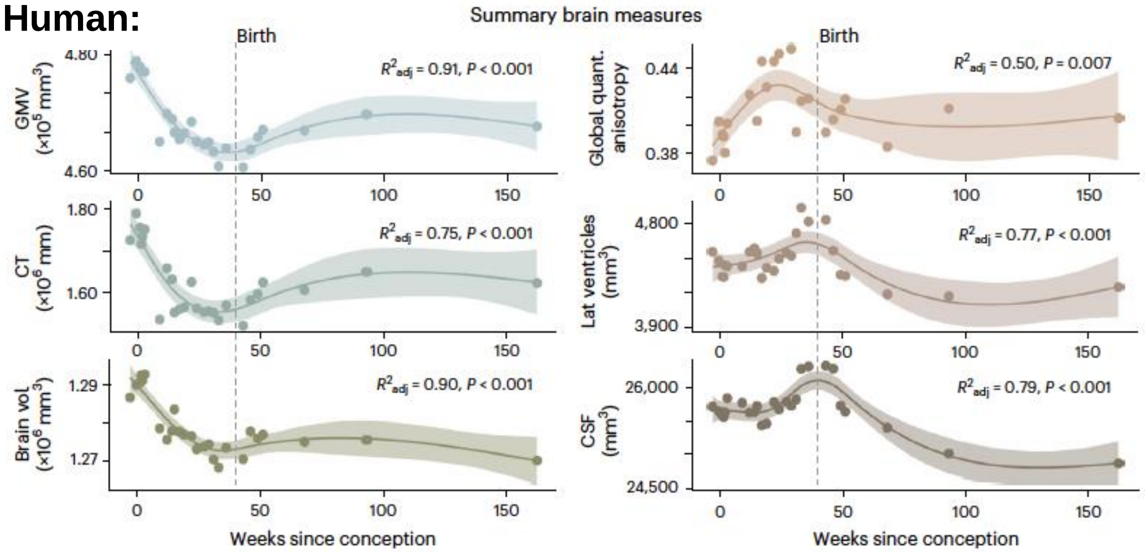
Introduction: Volumetrics and DTI

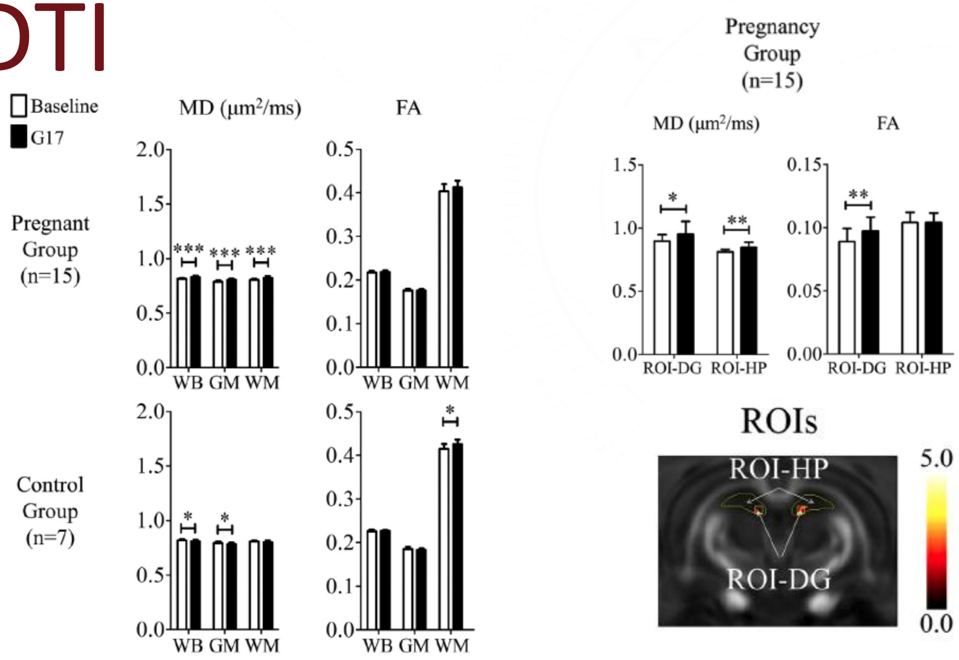
Human:



GMV, CT and total brain volume decreased throughout pregnancy, with a slight recovery postpartum. Global QA, lateral ventricle and CSF volumes displayed nonlinear increases across gestation, with a notable rise in the second trimesters before dropping sharply postpartum.

Figure: Pritschet, L et al. Nat Neurosci 27, 2253–2260 (2024). doi.org/10.1038/s41593-024-01741-0

Rodents:



The comparison of the tissue structural changes in the global brain between the BL and G17 in the pregnancy and control groups and the results of the voxel-based analysis followed by multiple testing in MD (a) and FA (b) of the pregnancy group.

Figure: Chan, RW et al. PLoS One. 2015 10(12): e0144328. doi: 10.1371/journal.pone.0144328

Human Findings:

- Pregnancy is associated with structural reductions primarily centered on areas including the bilateral superior temporal sulcus, temporo-parietal junction, precuneus, posterior cingulate cortex, and medial prefrontal cortex.
- There were **no statistically significant differences observed in white matter microstructure metrics** (Fractional Anisotropy (FA), Mean Diffusivity (MD), Axial Diffusivity (AD), or Radial Diffusivity (RD)) when comparing pre-pregnancy and post-pregnancy scans of women who became pregnant.

Rodents Findings:

- Pregnancy is associated with global tissue structural changes, including a general increase in diffusivities (MD, AD, and RD) in the whole brain, grey matter, and white matter during pregnancy.
- These increases in diffusivity were interpreted as reflecting microscopic tissue changes facilitating water movement, such as cell shrinkage and increased extracellular space.
- FA was observed to have a tendency to increase in the whole brain and significantly in the white matter (DG hippocampus) during pregnancy.

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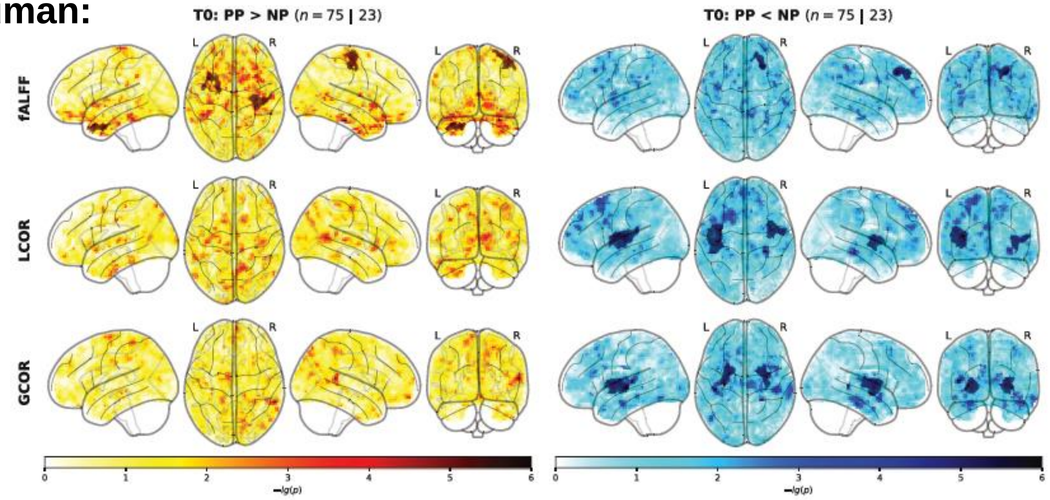
Introduction: resting state fMRI

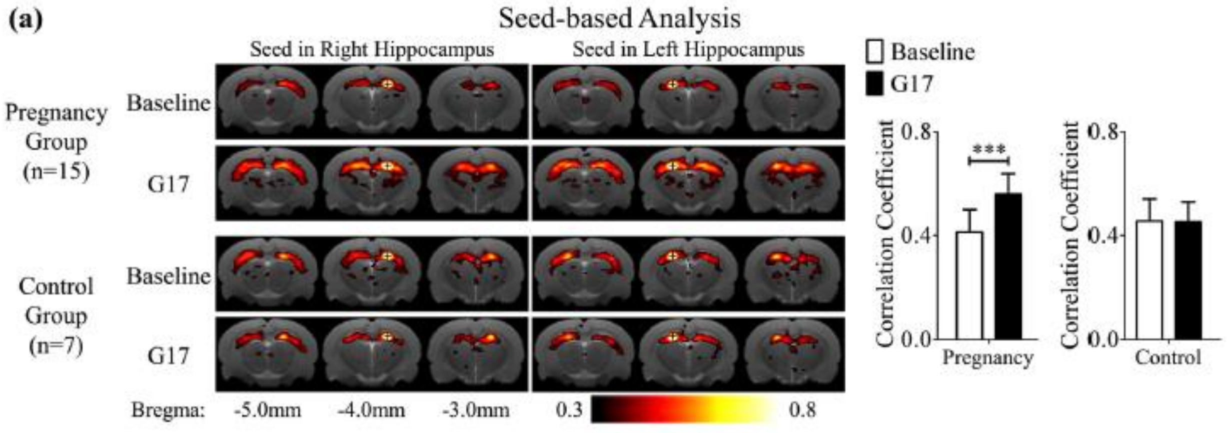
Human:



Clusters of differing local activity (fALFF), local connectivity (LCOR), and global connectivity (GCOR) in the nulliparous and one-week postpartum groups.

Figure: Lotter LD et al. Neuropsychopharmacol. 49, 1809–1818 (2024). doi.org/10.1038/s41386-024-01880-9

Rodents:



The mean correlation coefficient maps of rsfMRI obtained using seed based analysis (SBA) with seeds (crosses) in the right or left dorsal hippocampus.

Figure: Chan, RW et al. PLoS One. 2015 10(12): e0144328. doi: 10.1371/journal.pone.0144328

Human Findings:

- Intra-regional (local) activity (fALFF) and connectivity (LCOR) changes in widespread neocortical regions persisted throughout the 6-month study period. Initially reduced inter-regional (global) connectivity (GCOR) of subcortical areas, particularly the putamen, normalized to control levels within approximately 6-9 weeks postpartum.
- Spatial colocalization analyses suggested that the distribution of postpartum rsfMRI changes across the brain was associated with the distribution of various hormone and neurotransmitter receptors. The transient global connectivity changes seemed generally associated with hormone levels, especially progesterone.

Rodents Findings:

- Using rsfMRI, researchers found that bilateral connectivity in the hippocampus became stronger during pregnancy in rats compared to control rats.
- Independent component analysis (ICA) also identified bilateral primary and secondary somatosensory networks in rats, but these networks did not show significant connectivity strength changes during pregnancy
- There was a correlation between structural changes (specifically, fractional anisotropy increase in the dorsal dentate gyrus as measured by DTI) and the increase in bilateral hippocampal rsfMRI connectivity in the pregnant rat group during pregnancy.

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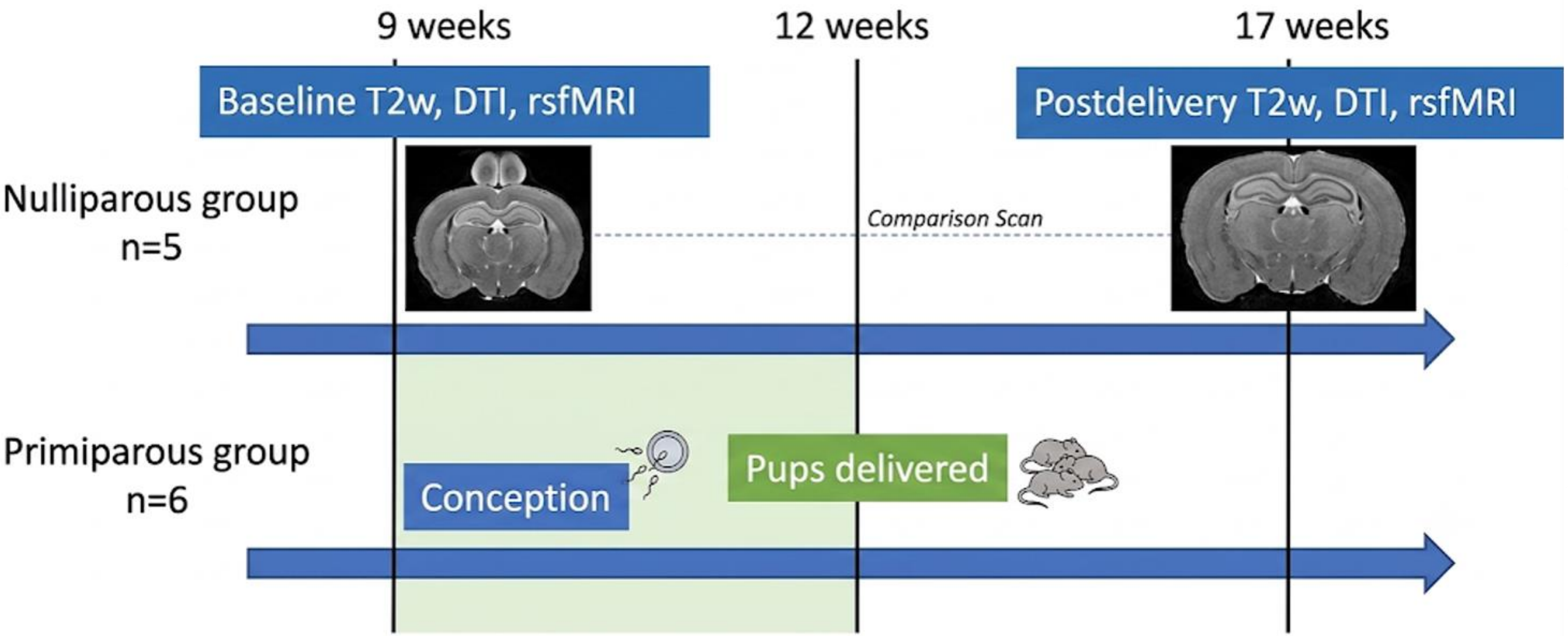
Methods: Experimental timeline



*All procedures were approved by the USUHS Institutional Animal Care and Use Committee.

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Methods: MRI acquisition parameters

7T Bruker BioSpec 70/20 (ParaVision 6.0.1) — Approved USUHS IACUC Protocol — Mouse Brain Multimodal Imaging

Equipment Note: All scans performed on a 7T Bruker BioSpec 70/20 scanner running ParaVision 6.0.1 under approved USUHS IACUC protocols.

3D T2W RARE — Scan: 60 min

PURPOSE & SEQUENCE

Target	Brain Volumetry
Sequence	3D RARE (Fat Supp)
RARE Factor	8
Averages (NA)	1

TIMING & BANDWIDTH

TR	2500 ms
Effective TE	30 ms
Bandwidth	36 kHz

SPATIAL RESOLUTION

FOV	16 × 14 × 12 mm^3
Isotropic Voxel	125 × 125 × 125 μm^3

High-contrast isotropic anatomical reference for volumetric registration and template building.

2D DTI-EPI — Scan: 15 min

DIFFUSION PARAMETERS

Target	Microstructure / FA
Sequence	2D Single-Shot EPI
Directions	4 b0 + 30 non-collinear
b-values	800, 1600 s/mm^2
Diffusion Timing	δ = 6 ms, Δ = 12 ms

TIMING & GEOMETRY

TR / TE / NA	3500 ms / 30 ms / 4
FOV / Matrix	14×12.6×16mm / 80×72×32
Voxel Size	175 × 175 × 500 μm^3
Partial-FT / BW	96×60×49 / 300 kHz

Dual b-value diffusion tensor scheme for robust FA, MD, AD, and RD quantification via RESTORE.

rsfMRI GE-EPI — Scan: 15 min

FUNCTIONAL PROTOCOL

Anesthesia	Isoflurane + Medetomidine
Sequence	Single-Shot GE-EPI
Volumes	400 frames
Sampling TR	2000 ms (2.0 s)

TIMING & RESOLUTION

Echo Time (TE)	16 ms
FOV	25.6 × 25.6 mm^2
Matrix Size	64 × 64
Slice Thickness	0.75 mm

Optimized for resting-state BOLD functional connectivity networks and graph theoretical analysis.

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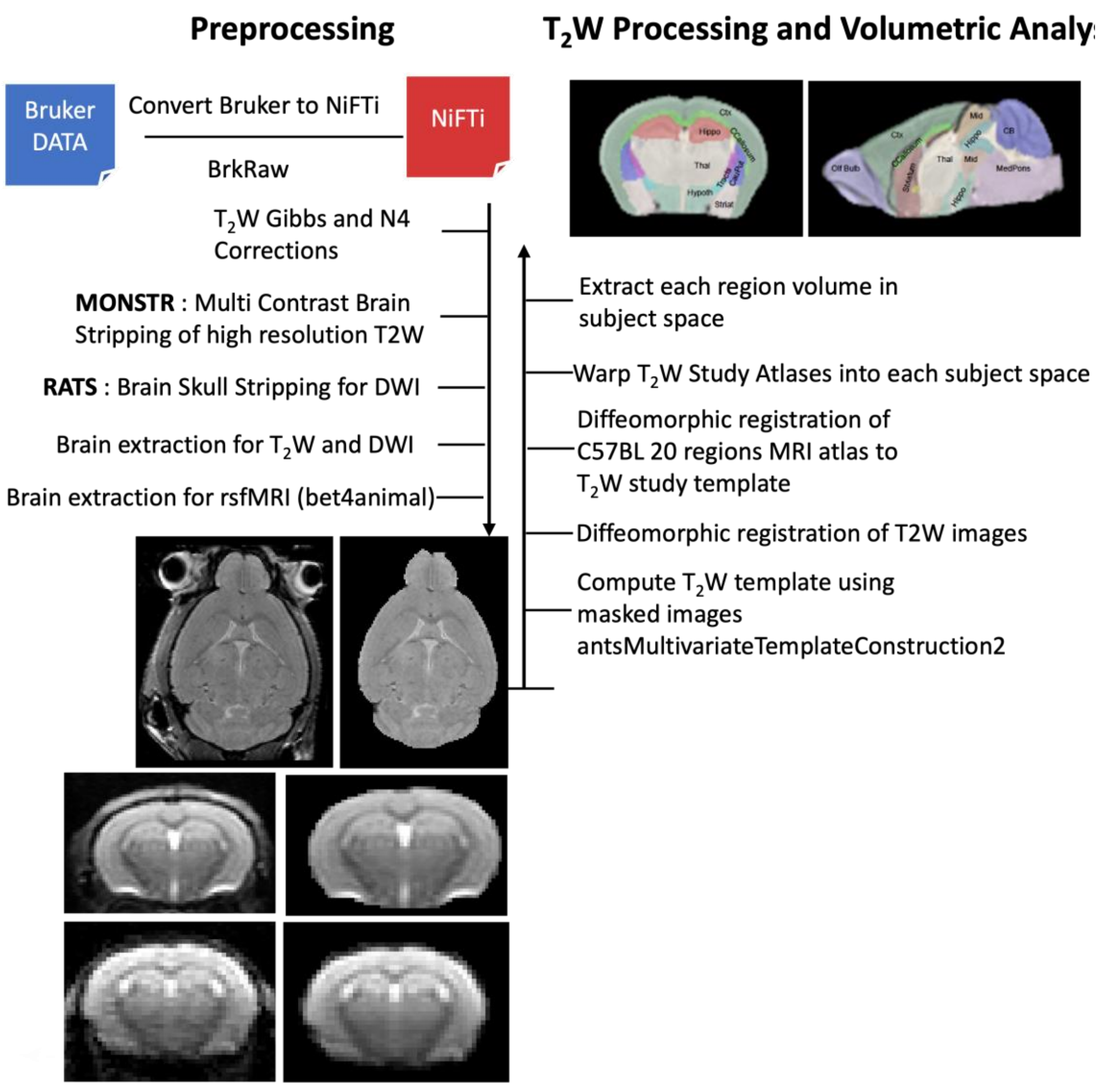
Methods: MRI Post Processing and Analysis



References: BrkRaw/bruker: Lee SH et al., BrkRaw v0.3.3 (Version 0.3.3). doi.org/10.5281/zenodo.3877179; MONSTR: Roy S et al. Neuroimage. 2017 146:132-147. doi: 10.1016/j.neuroimage.2016.11.017; RATS: Ipek O. J Neurosci Methods. 2014 15:221:175-82. doi: 10.1016/j.jneumeth.2013.09.021; Atlas: Ma Y et al. Front Neuroanat. 2008 2:1. doi:10.3389/neuro.05.001.2008
TORTOISE: Pierpaoli C et al., 2010 ISMRM 18th annual meeting, abstract #1597 ; Irfanoglu MO et al. 2017 ISMRM 25th annual meeting, abstract #3540.

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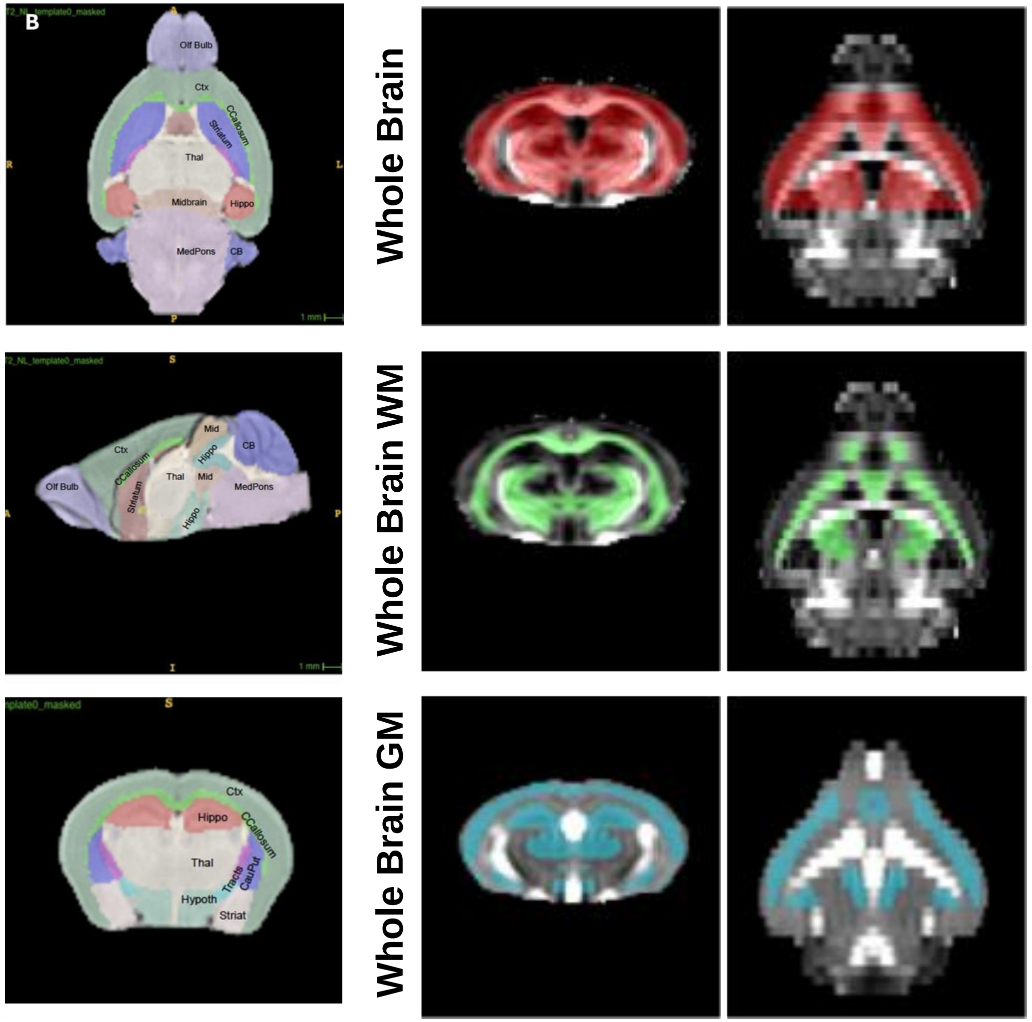
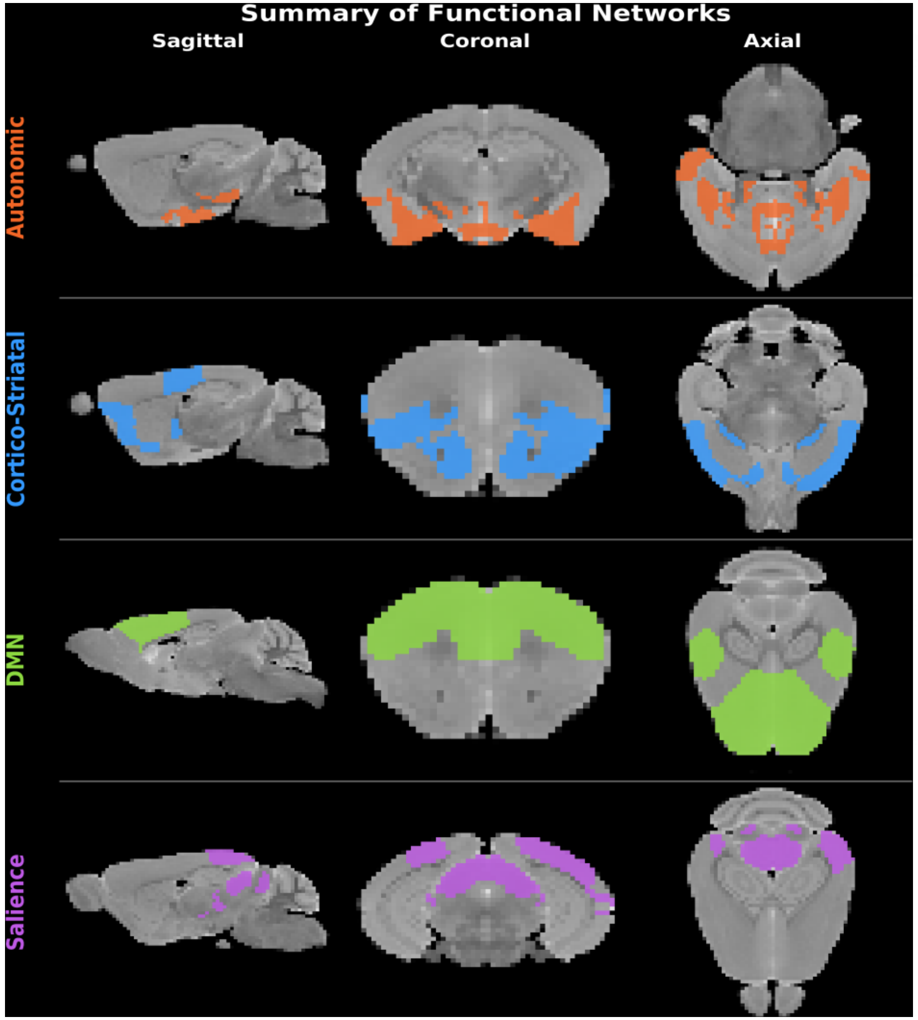
Results: Volumetric analysis

Ma atlas labels overlaid on Ma T2w template



Resting state networks in anesthetized rats on the Waxholm atlas space



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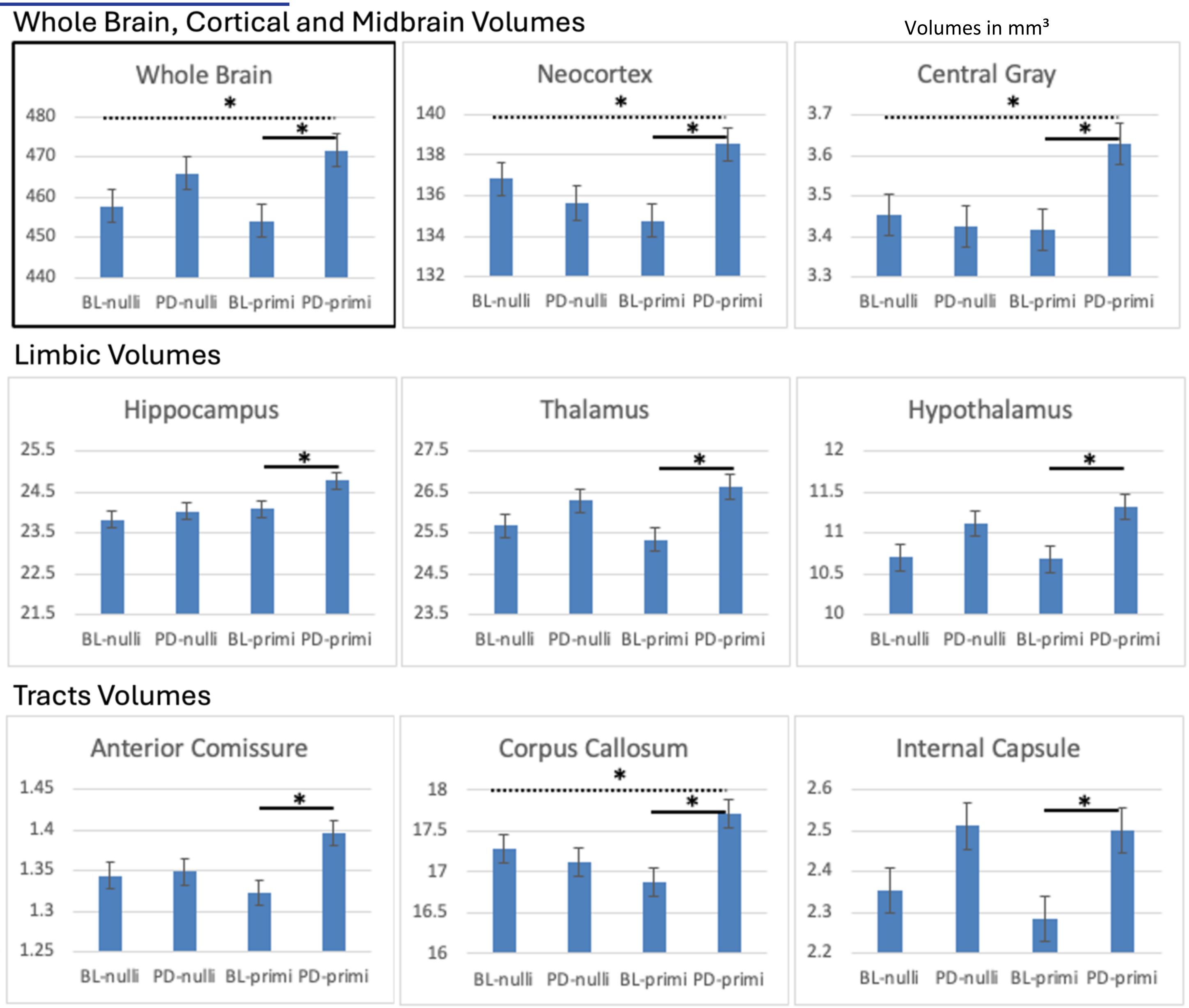
Results: Volumetric analysis



Numerous gray matter regions—including neocortex and central gray—exhibited **pregnancy-induced volume increases**.

This contrasts with human studies that typically report gray matter reductions (during pregnancy and birth).

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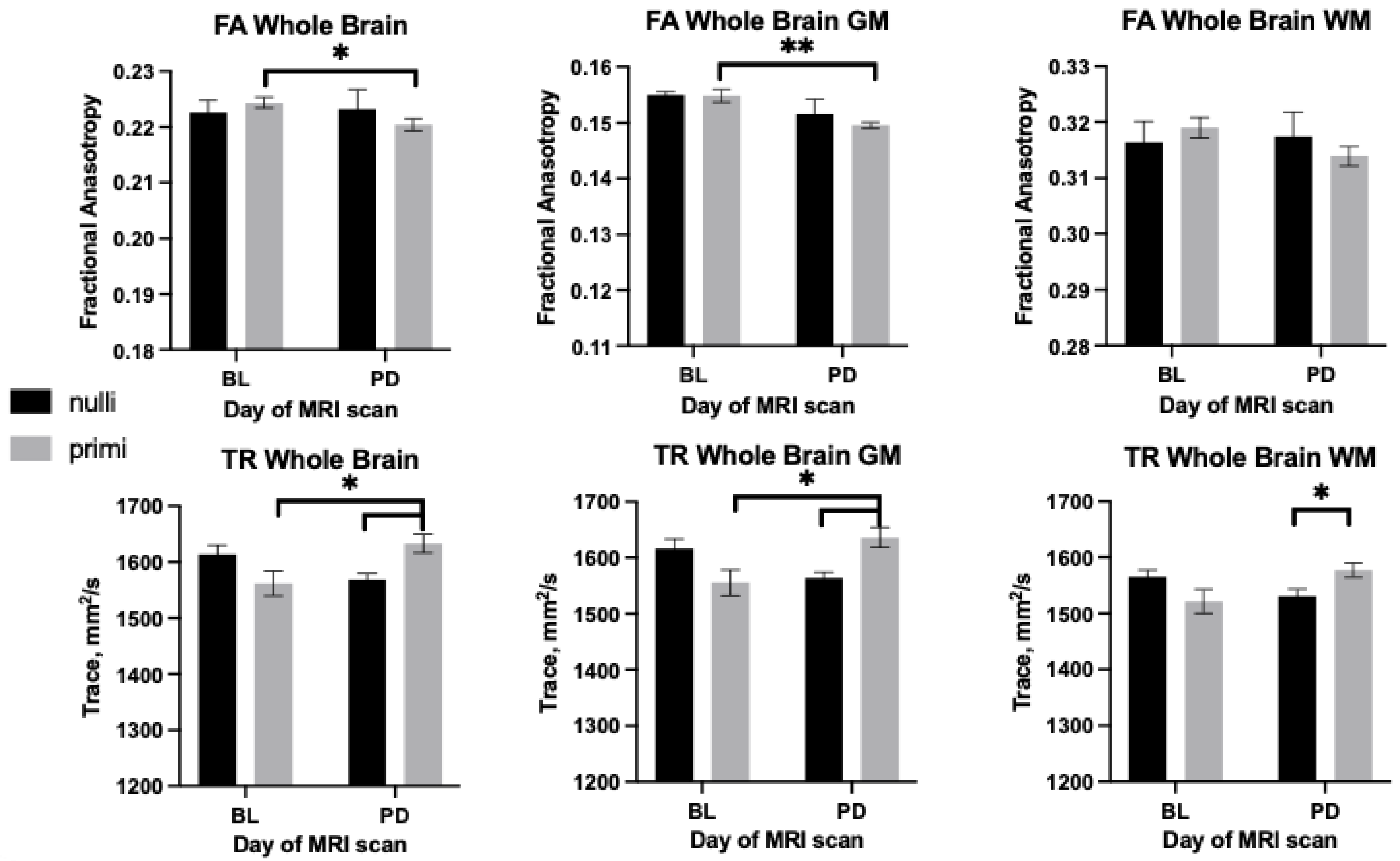
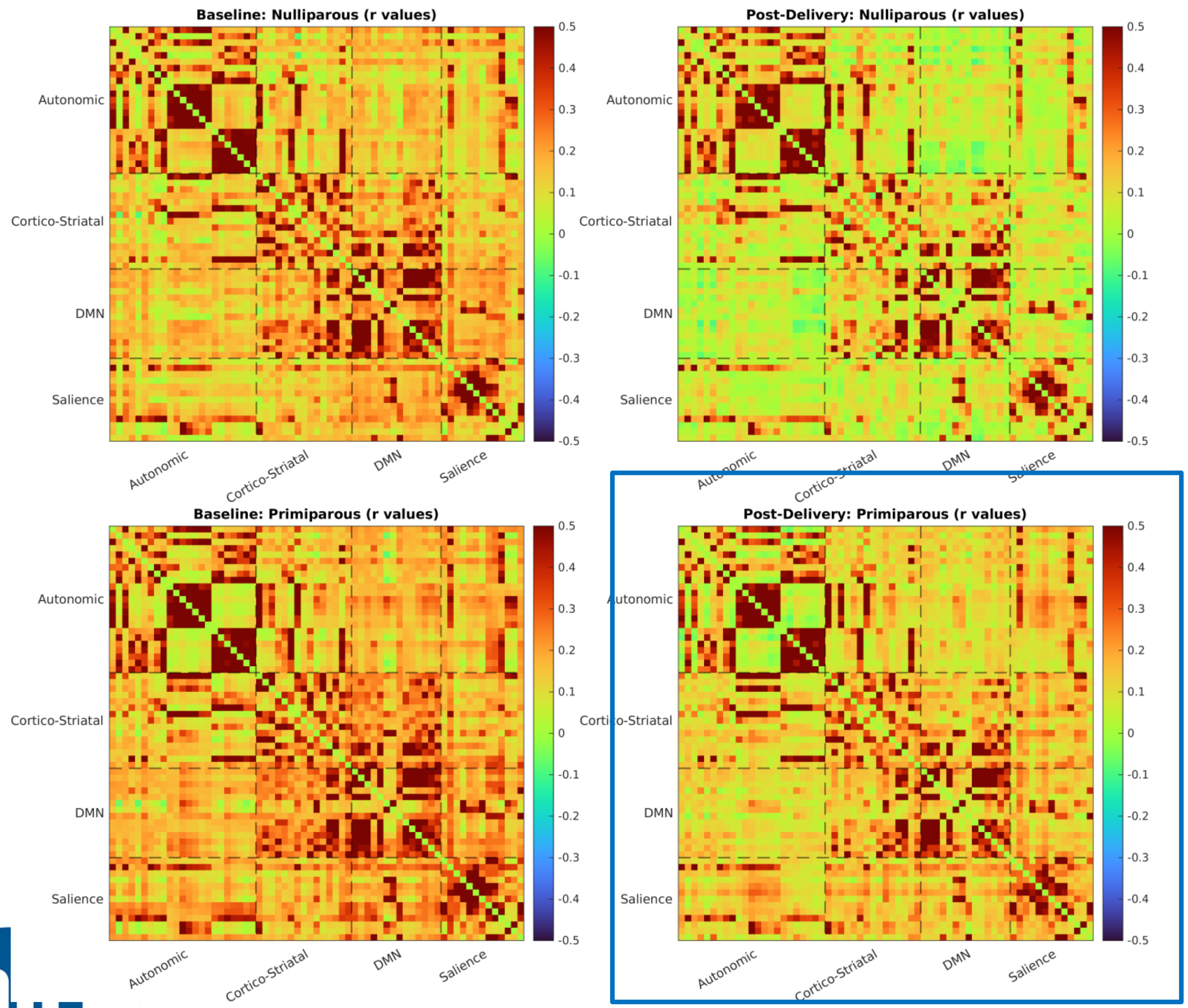
Results: Diffusion Tensor Imaging (DTI)



The fractional anisotropy, (FA) - reduction in gray matter and whole brain values.

Trace, reflecting total diffusivity, was elevated—indicating increased extracellular space or reduced cellularity.

Results: Seed-based resting-state functional MRI (rsfMRI)



Network covariance profiles across groups and maternal states: 65 regions of interest (ROIs) 4 networks: autonomic, cortico-striatal, DMN, salience network. Positive correlations (warm colors; red/orange) to negative correlations (cool colors; blue).

Robust positive correlations within cortico-striatal and DMN regions, paired with mild negative correlations between autonomic and DMN network regions.

Across timepoints, these 2 groups showed similar pattern however primiparous PD showed more pronounced correlations as compared to nulliparous PD.

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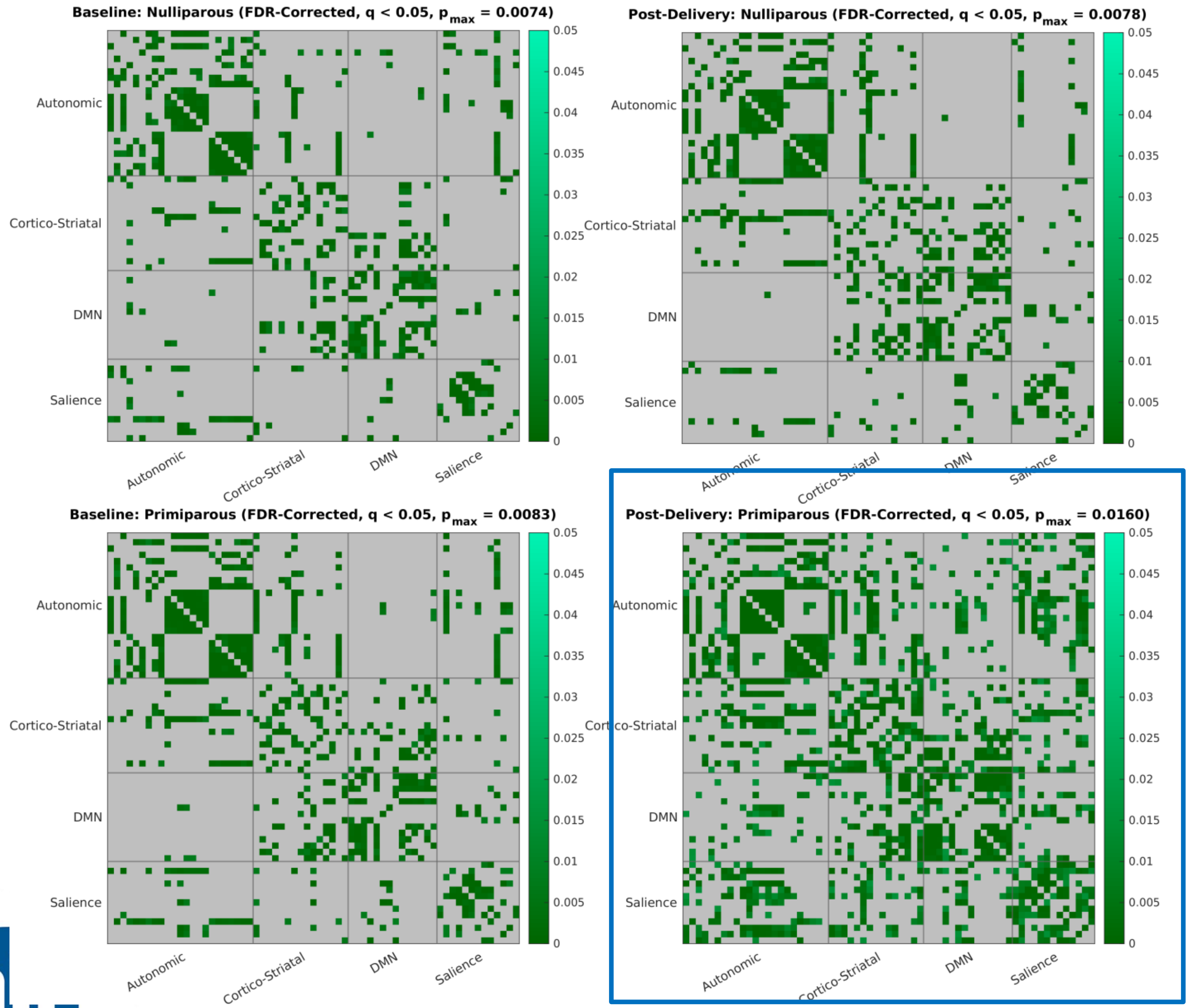
Results: Seed-based resting-state functional MRI (rsfMRI)



Statistical Thresholding and Significance Filtering: Matrices depicting significant seed-seed connections determined by one sample Student's t-tests ($p < 0.05$, FDR corrected).
(dark green; $p \approx 0$) to (light green/white; $p \approx 0.05$).

Post-Delivery: Primiparous cohort exhibited a massive, highly significant increase in network density and integration suggesting a parity-induced priming of neural network resilience through:

- **Enhanced Inter-Network Communication**
- **Preserved Intra-Network Coherence**

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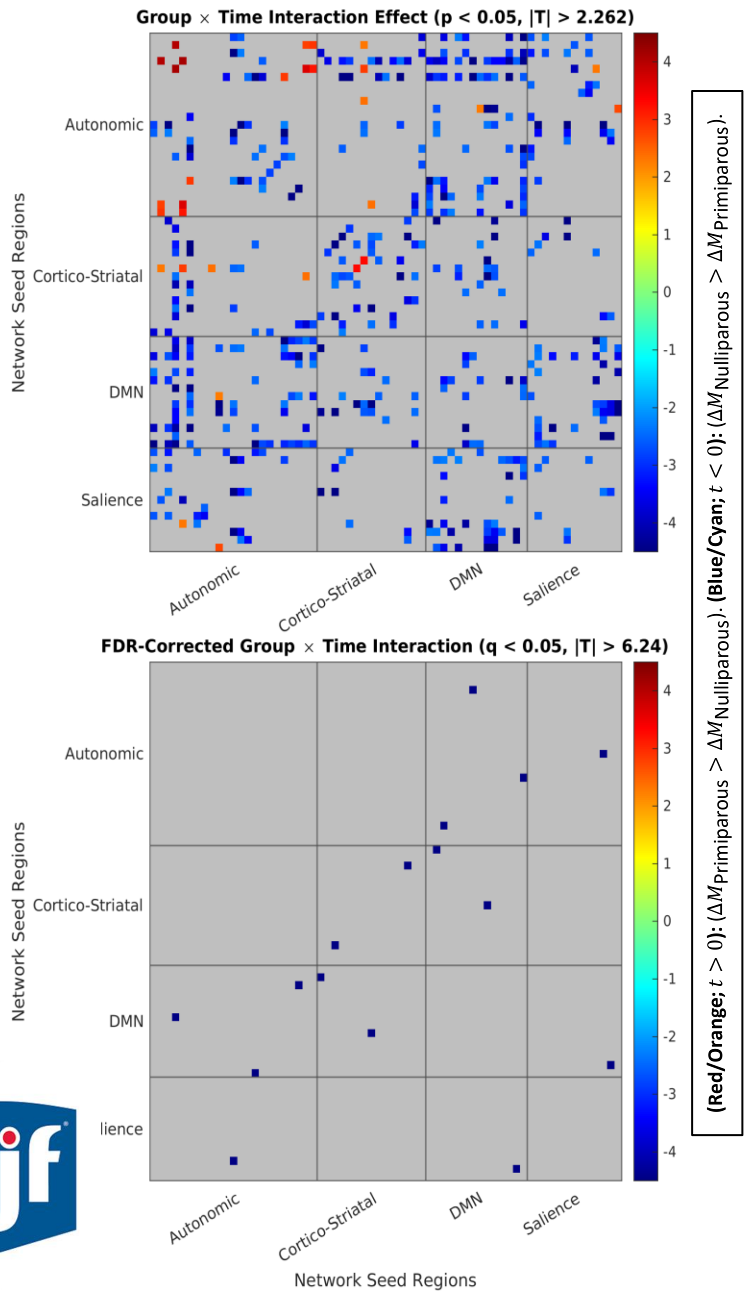
Results: Seed-based resting-state functional MRI (rsfMRI)



1. Reward Preservation: Nucleus Accumbens Right (ACB_R) -- Infralimbic Area Left (ILA_L).
Primiparous: Coupling maintained (Delta = -0.0026) | **Nulliparous:** Steep drop (Delta = -0.1870).
Function: Sustains pup-reward motivation.

2. Spatial-Memory Integration: Perirhinal Area (PERI) -- Posterior Parietal (PTLp) & Primary Motor (MOp).
Primiparous : Connectivity increased (Delta = +0.0084, +0.0101) | **Nulliparous :** Declined (Delta = -0.1440, -0.0742).
Function: Integrates object memory and spatial mapping for pup retrieval.

3. Sensory & Emotional Tuning: Olfactory & Amygdala Circuits
Regions: Piriform (PIR) --Orbital (ORB) & Basomedial Amygdala (BMA) --Anterior Cingulate (ACA).
Primiparous : Olfactory pruning (Delta = -0.3057) & limbic tuning (T = -25.5418).
Function: Refines sensory discrimination and emotional responses to pup cues.

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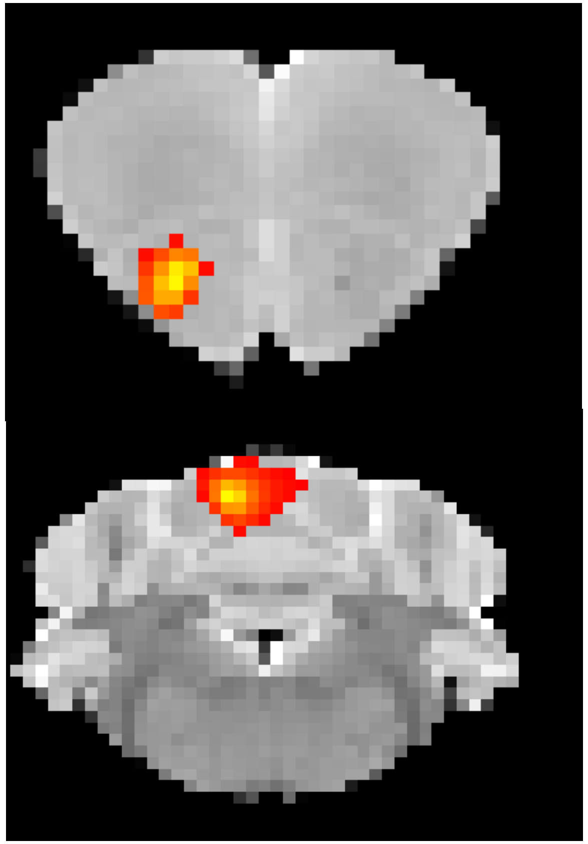
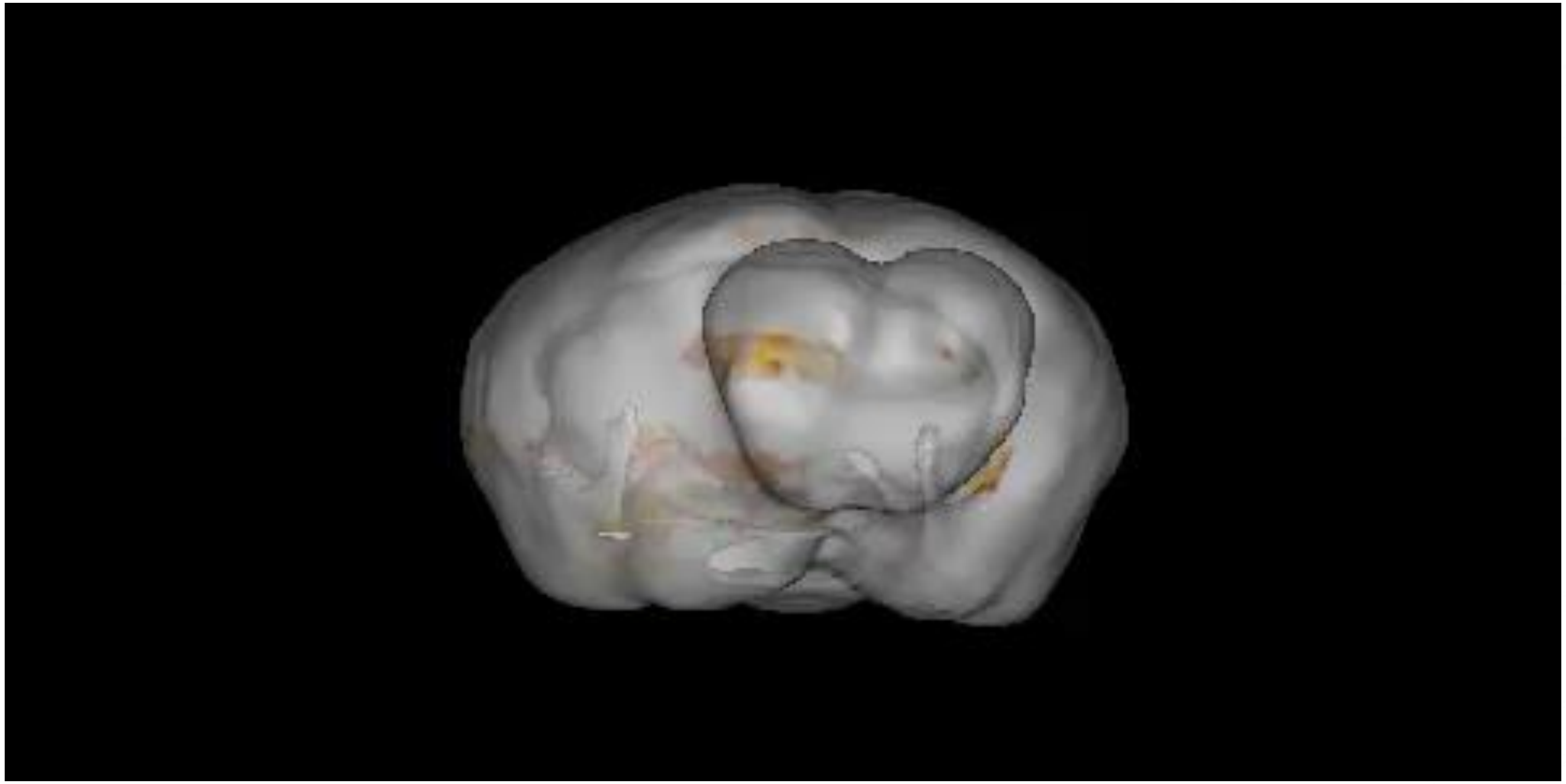
Results: Voxel-based resting-state functional MRI (rsfMRI)

(A) Time effect in Mothers ($\Delta_{Primi} > 0$)





Medullary Autonomic, Visceral Core, Arousal Hub : Post-weaning connectivity surge- Sets up **<u>central neuroendocrine, vagal, and autonomic infrastructure</u>** for lactation, oxytocin output, and maternal cardiovascular control.

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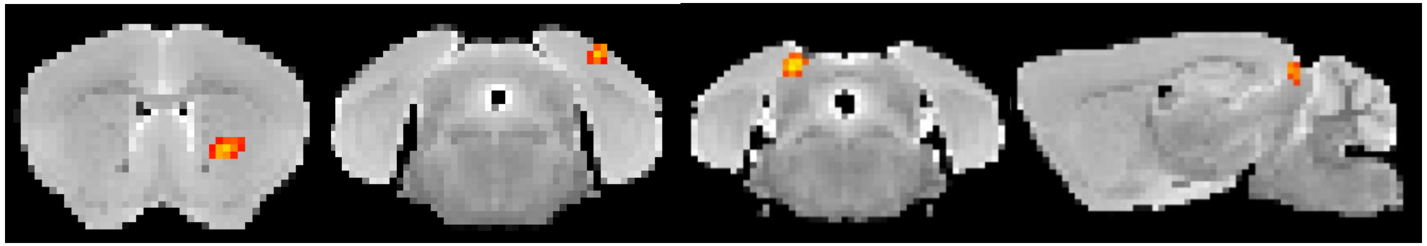
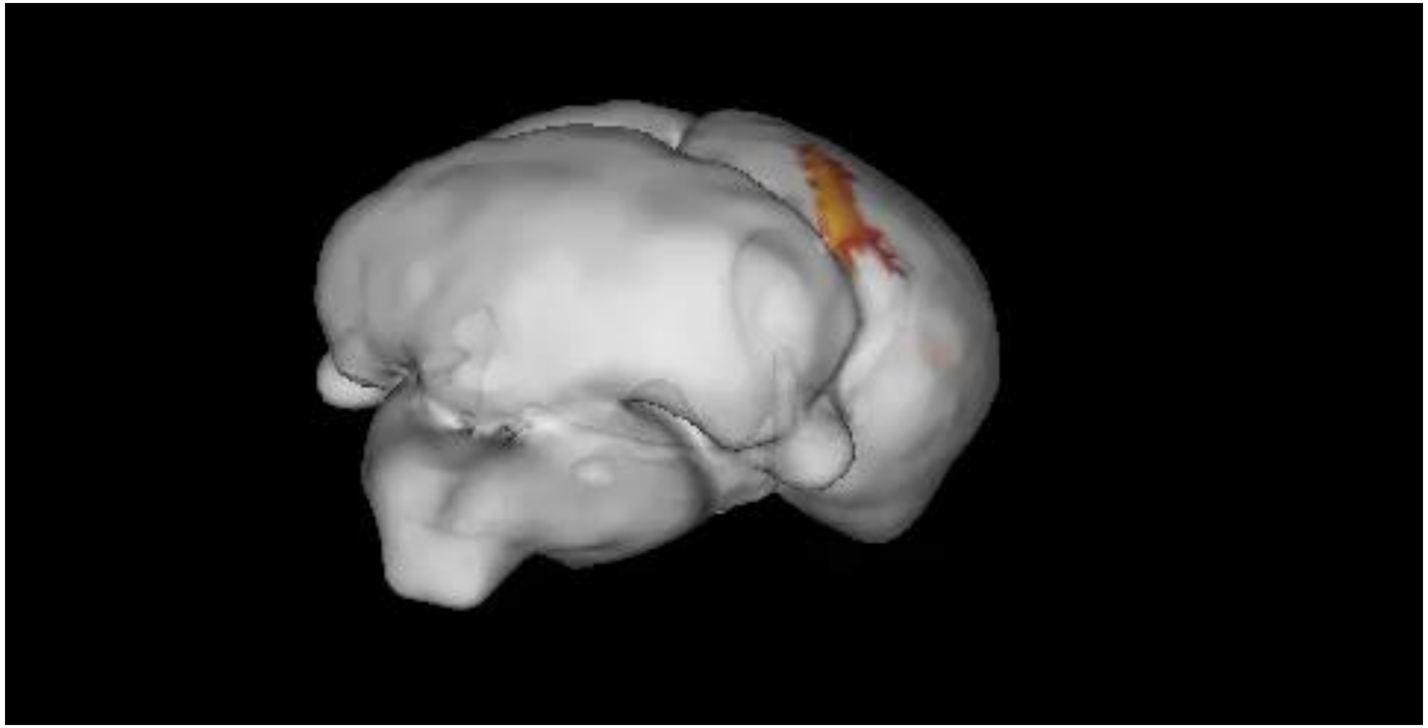
Results: Voxel-based resting-state functional MRI (rsfMRI)

(B) Interaction ($\Delta_{Nulli} > \Delta_{Primi}$) (C) Interaction ($\Delta_{Primi} > \Delta_{Nulli}$)





Midbrain Auditory & Orienting Circuit: Sensory-Motor Integration- Enhances auditory sensitivity and visceral/motor orienting responses specifically tuned to pup distress vocalizations.

Limbic, Hippocampal & Olfactory Plasticity: Strengthens pup olfactory sign-learning, maternal emotional bonding, and spatial memory for nest navigation.

Auditory-DMN Attenuation: Targeted post-delivery decoupling in Inferior Colliculus and Retrosplenial Cortex

Summary

- **Objective met:** Established a preclinical rodent model to investigate structural and functional brain changes associated with motherhood.

- **Species Divergence:** Unlike humans—who show pregnancy-related decreases in gray matter volume (likely due to hormone-driven synaptic pruning)—rodent exhibit an alternative mechanism where hormone surges drive **structural growth**.

- **Microstructural Remodeling:** Two weeks post-weaning, FA was reduced in the gray matter globally and TR (RD, AD not shown) were elevated at two weeks post-weaning. Indicates microstructural remodelling.

- **"Preserved Reward Circuits"+"Enhanced Salience Vigilance"+"Suppressed DMN Internal State"⟶"Optimized Maternal Caregiving":** Motherhood actively reverses time-dependent connectivity declines seen in nulliparous controls, selectively preserving reward circuits, boosting salience network vigilance, and pruning DMN/olfactory pathways for caregiving.

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Summary

- **Early-Onset Neuronal Decline:** The nulliparous group showed age-related decline - right after peak adolescence as reported (Morterá, P et al.).

- **Uncaptured Dynamic Changes:** Comparing only baseline to post-weaning misses critical, pregnancy-induced brain changes occurring during gestation and lactation.

- **Whole-Brain hormonal Expression:** Integrating peripheral hormonal tracking across gestation will enable predictive modeling of maternal cognitive resilience and stress susceptibility.

- This model provides an initial platform to characterize **maternal brain adaptations** and might guide targeted interventions, which can be utilized in military women's **mental health and mission readiness**.

Reference: Morterá, P., & Herculano-Houzel, S. (2012). *Frontiers in Neuroanatomy*, 6, 45.

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Thank you to the Team

USU SoM

- Alexandru Korotcov, PhD
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- T. John Wu, PhD

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- Nicholas Ieronimakis, PhD

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Animal Husbandry

Administrative Staff

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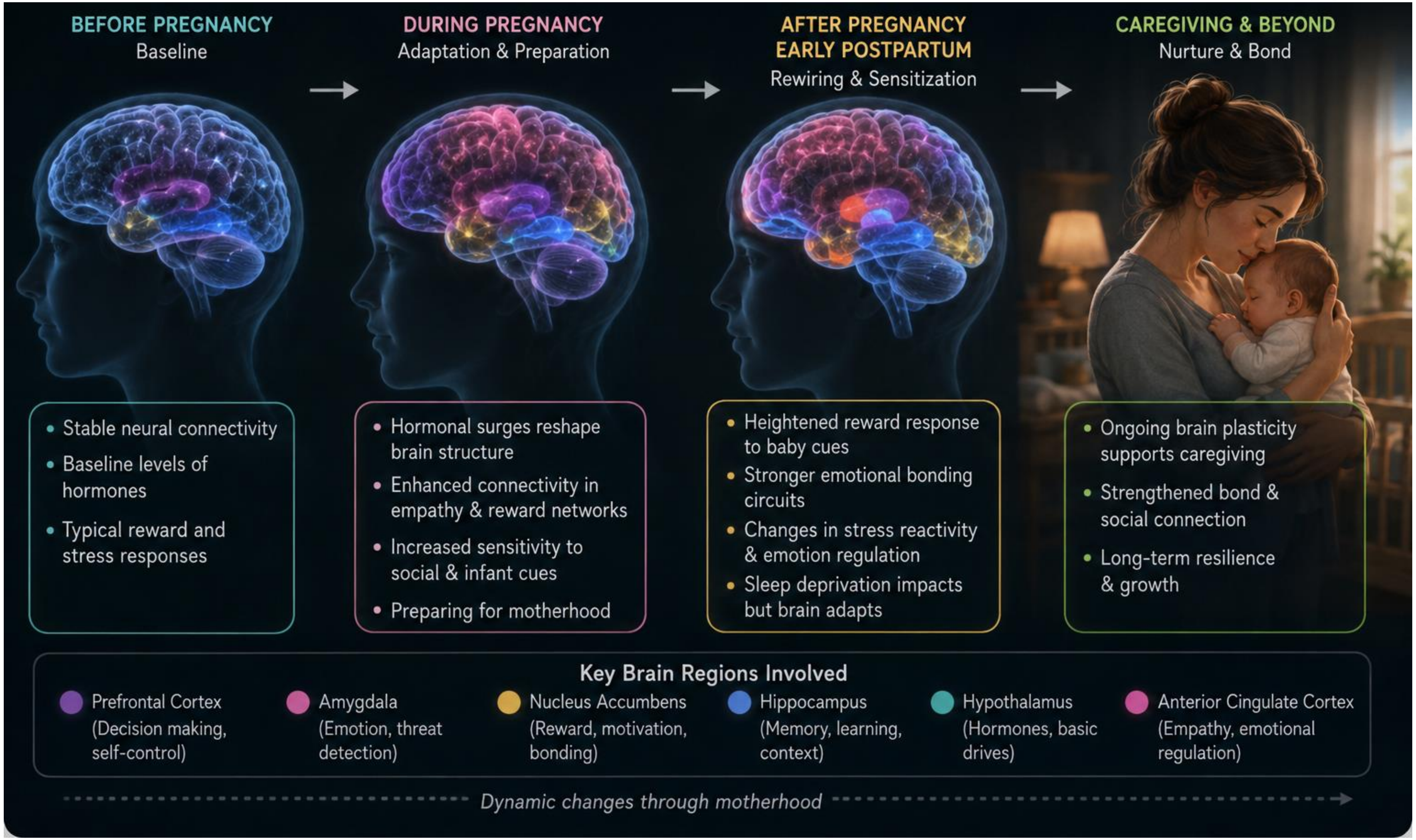
- Michael Junio
- Kasie Carriveau
- LaShawn Brown

Road ahead... Questions



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