Environmental Justice and the Early-Life Origins of Health Disparities: Why Mom Matters

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Bass Connections: Brain and Society, Summer 2013

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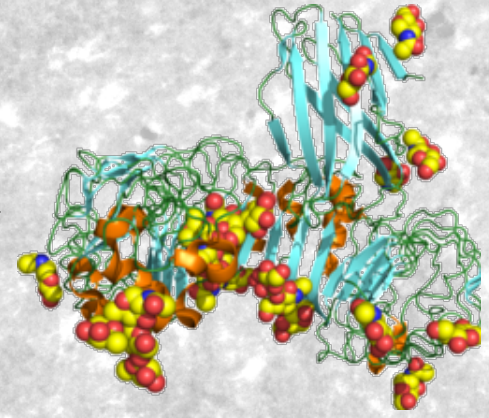
Background: Poor Living Conditions and Low Socioeconomic Status

- Problems in our society: air pollution, stress, poor nutrition
- Why should we care about perinatal programming?
- What is psychoneuroimmunology, and how does it fit into the picture?

Pathogen-Associated Molecular Patterns (PAMPs)

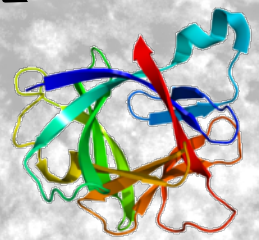
Danger-Associated Molecular Patterns (DAMPs)

bind



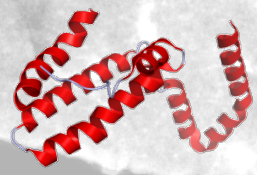
Toll Like Receptor 4 (TLR-4)

upregulates



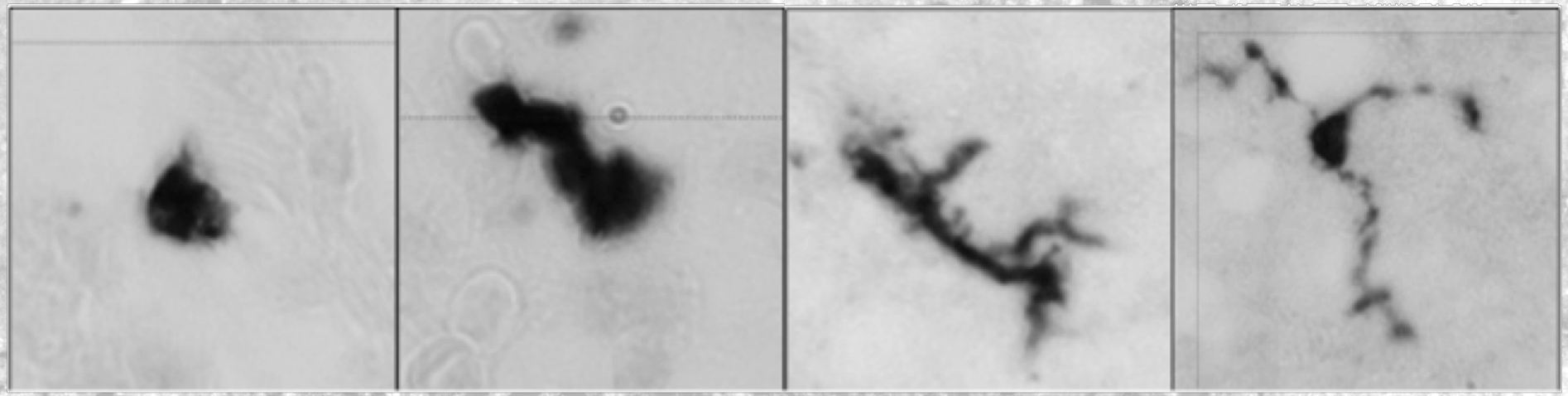
Interleukin-1β (IL-1β)

Inflammatory Response
Immune Cell Recruitment
Phagocytosis
Bidirectional neuroimmune communication



Interleukin-10 (IL-10)

Microglia

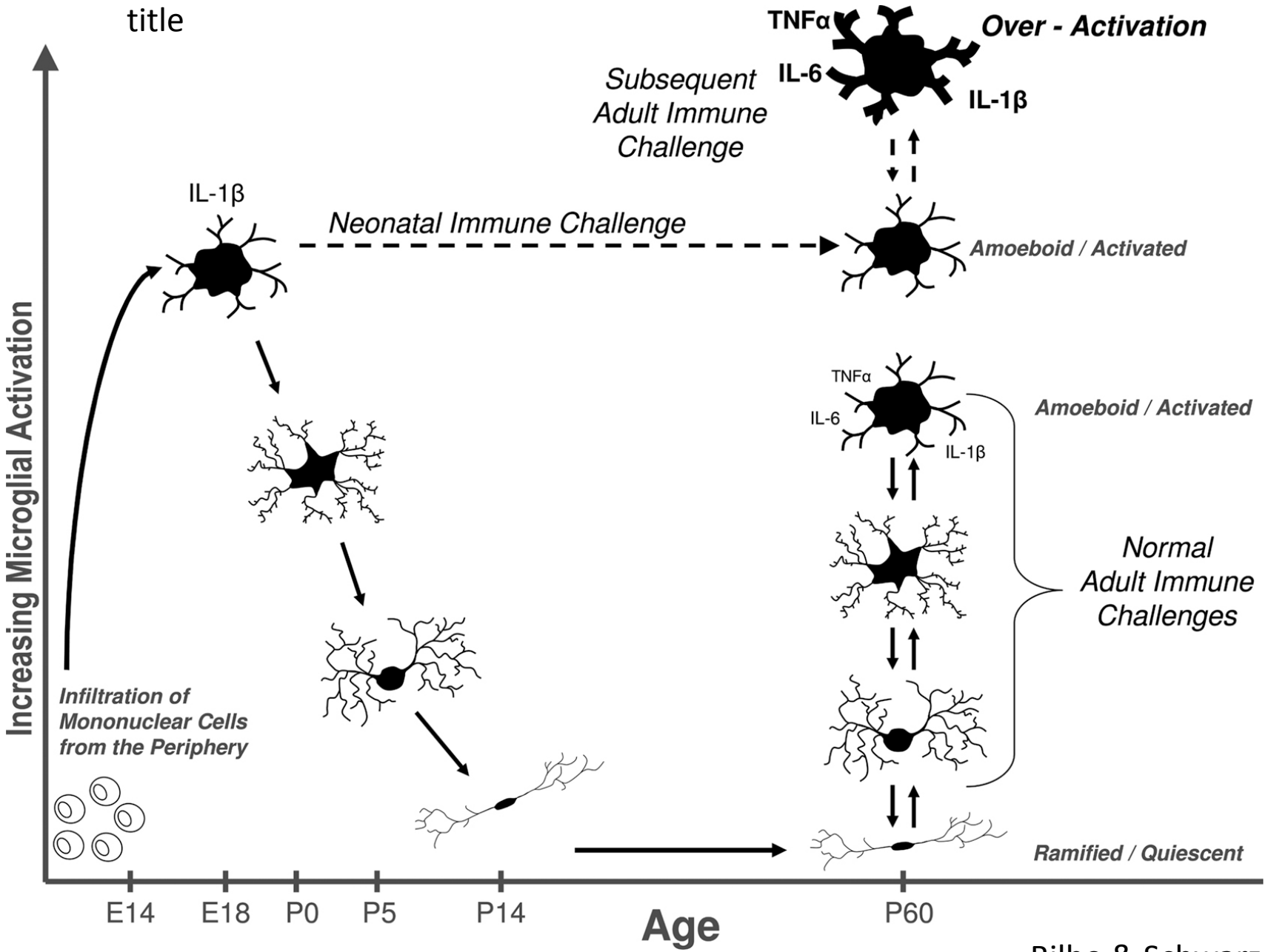


ROUND STOUT THICK THIN

Immune System in Brain Development

- Normal development depends on immune signaling
  - Synaptic pruning
  - Adult neurogenesis

- Perinatal “sensitive period” to immune effects on CNS development



Bilbo & Schwarz, 2009

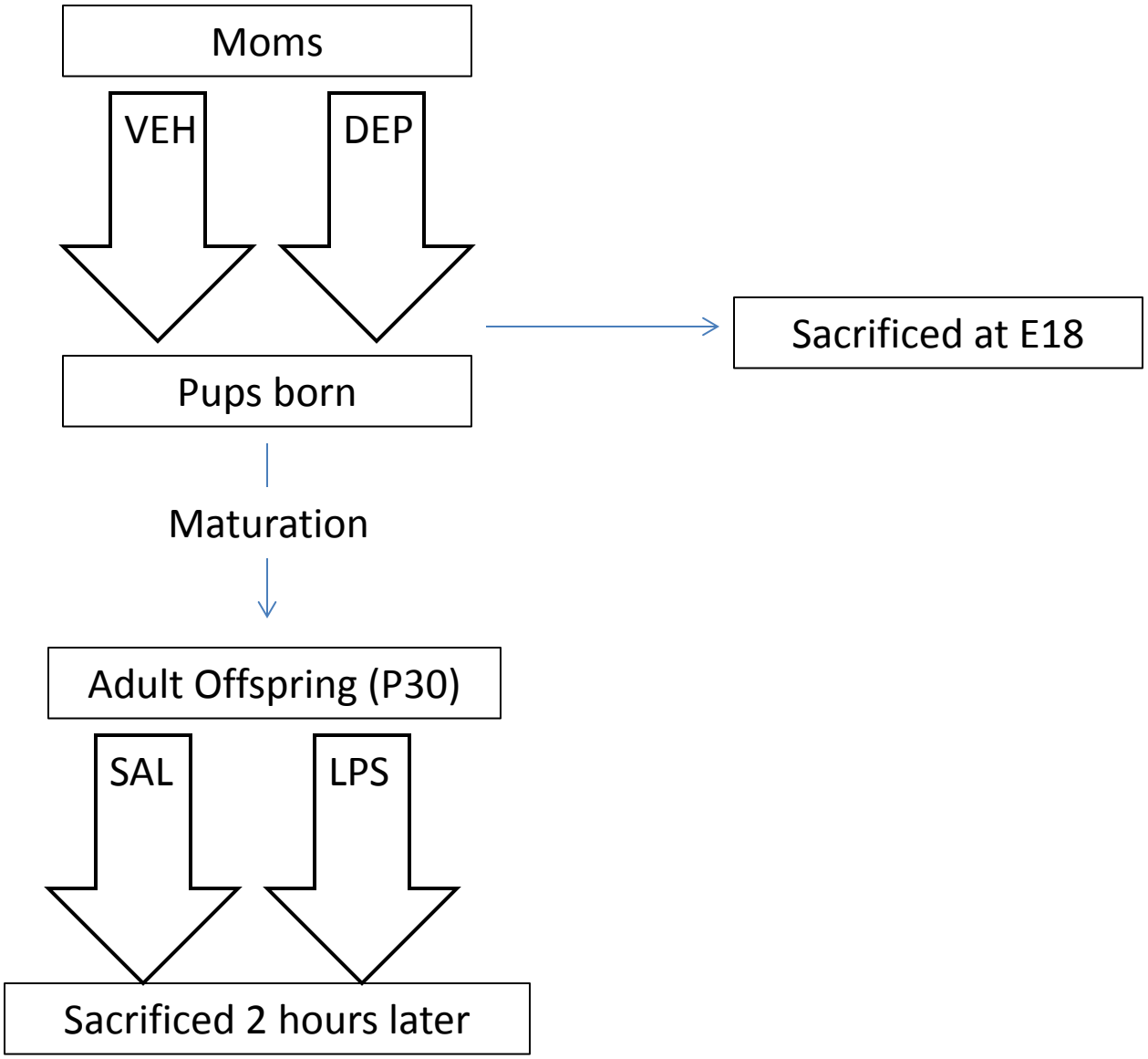
Prenatal Air Pollution Study: Design & Notable Findings

- Two-by-two design
- First level: treatment of pregnant moms with vehicle (control solution) or diesel exhaust particle during pregnancy
- Second level: maternal nest restriction (inducing stress) or postnatal dietary manipulation
- Prenatal diesel exposure + postnatal dietary manipulation
  - Low-fat vs. high-fat postnatal diet
- Prenatal diesel exposure + maternal stress during pregnancy
  - Nest restriction (NR) paradigm
  - *Male, DE/NR offspring upregulate TLR4 expression

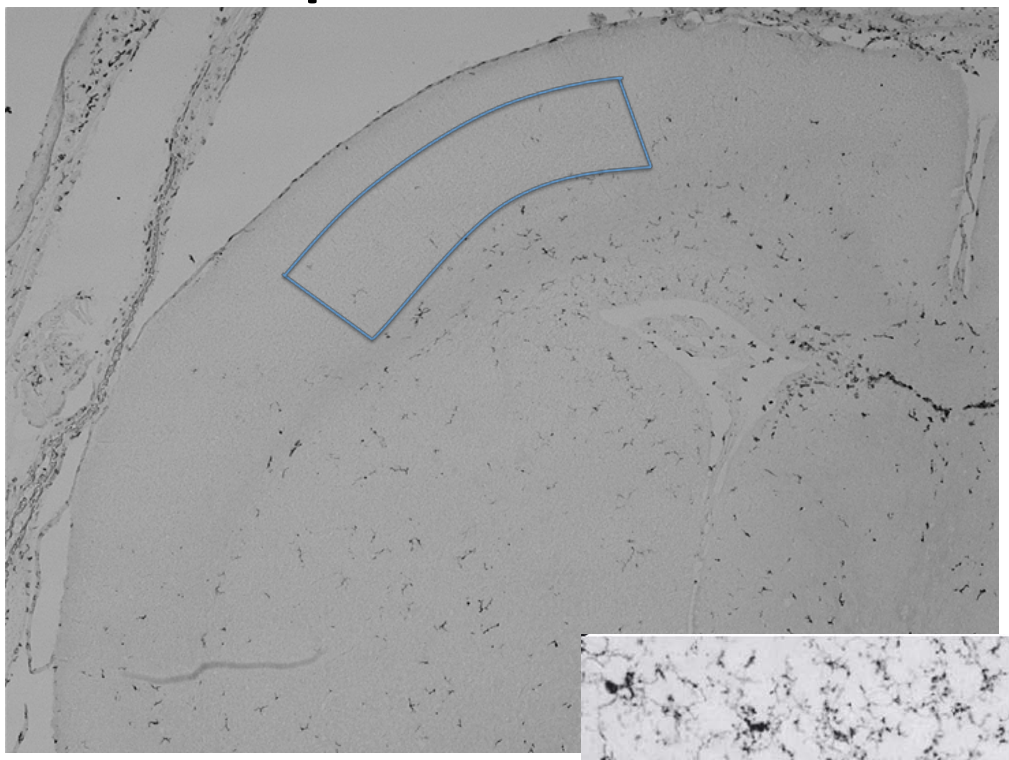
Prenatal Air Pollution Study: Current Project

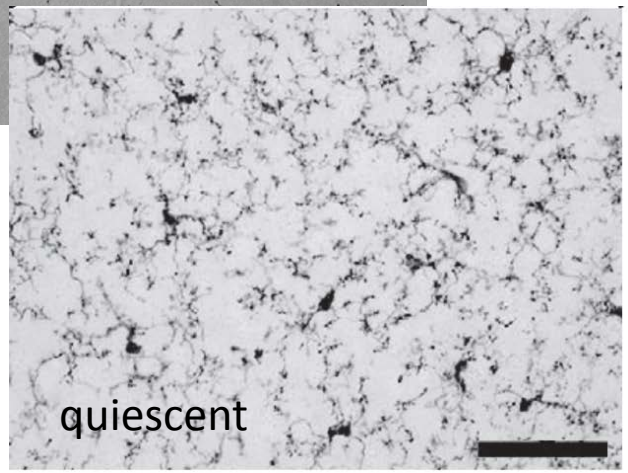
- **Purpose:**
- 1) To investigate whether microglial TLR4 expression is necessary for activation in response to prenatal diesel exposure
- 2) To explore the interaction between prenatal diesel treatment, adult infection, sex, and genotype (TLR4 +/- or -/-) with respect to microglial expression

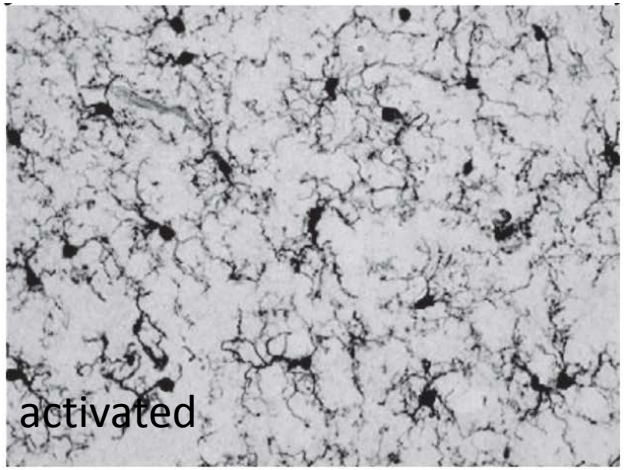
Experimental Paradigm



Cell counting and volumetric analysis: example contour in E18 parietal cortex

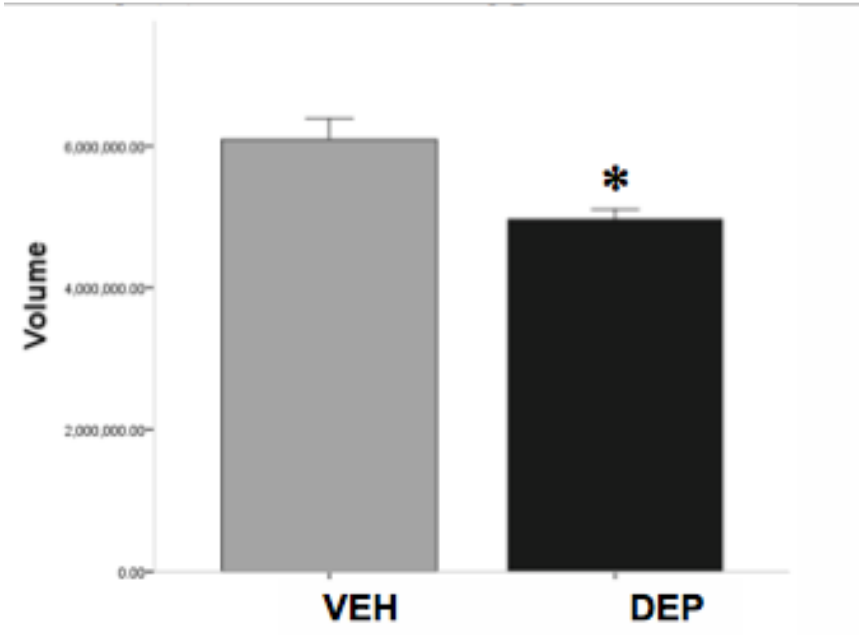






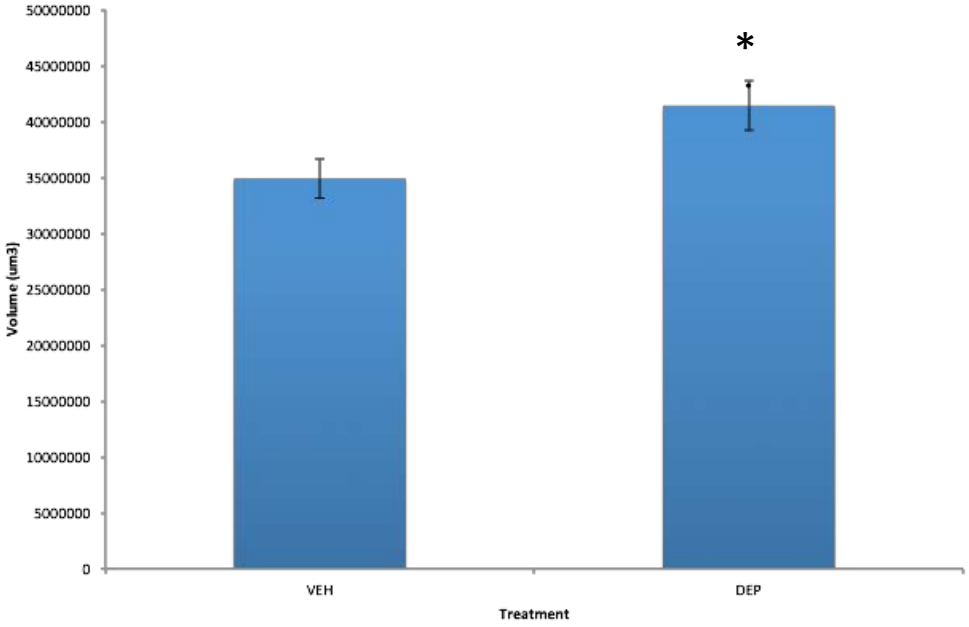
E18 Amygdala vs. Parietal Cortex:Regional Volume Differences

Amygdala



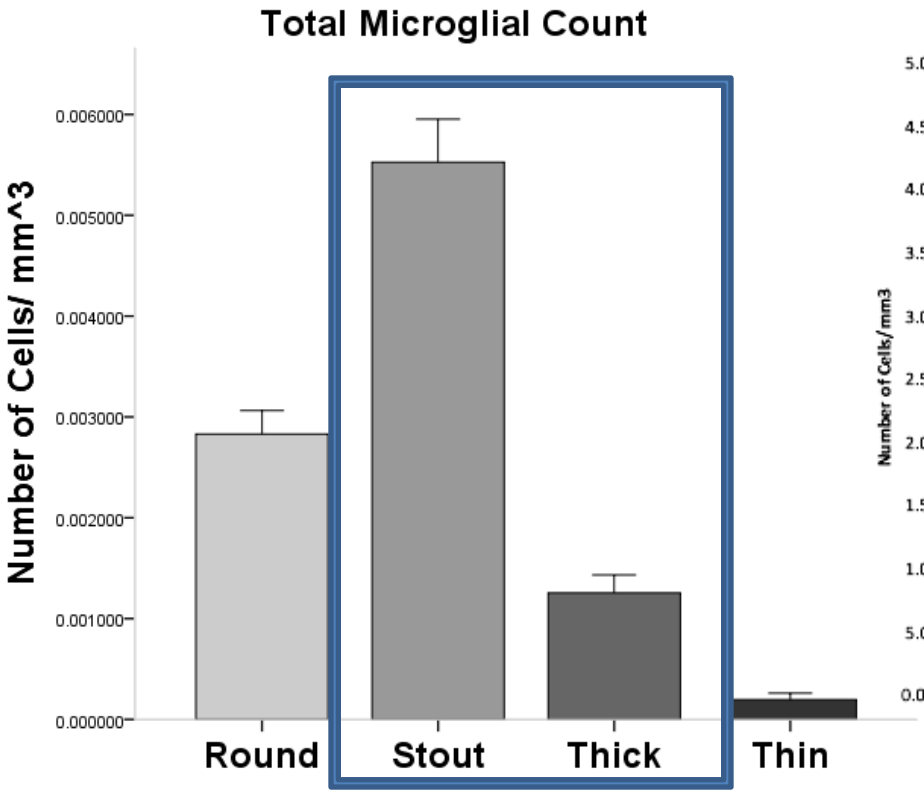
p<0.05

Parietal Cortex

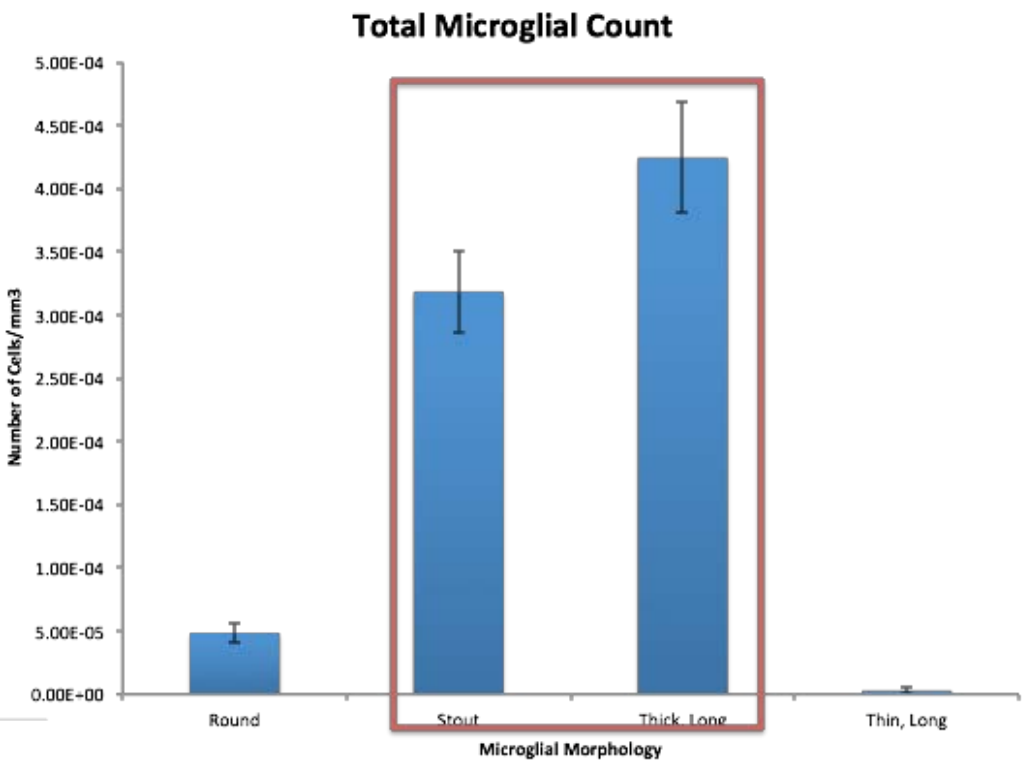


E18 Amygdala vs. Parietal Cortex: Microglial Morphology

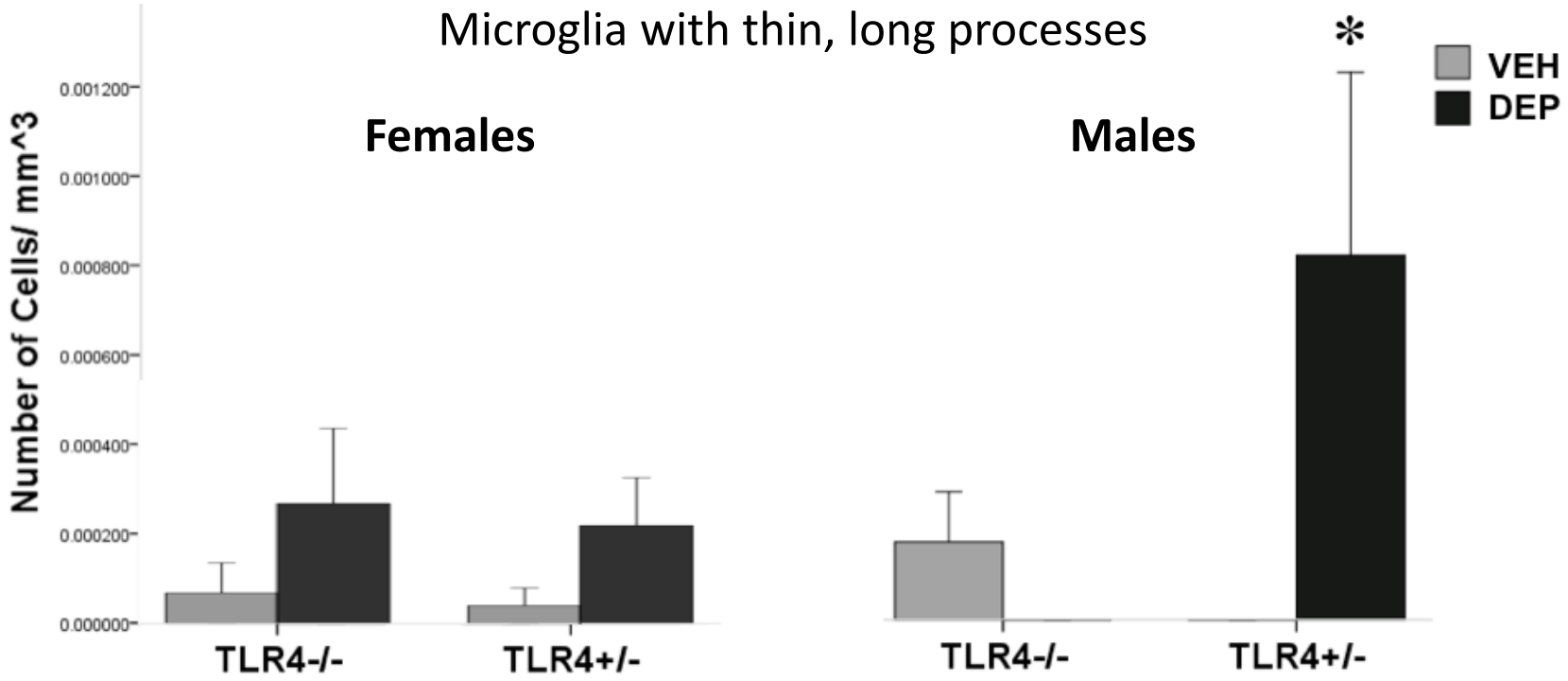
Amygdala



Parietal Cortex

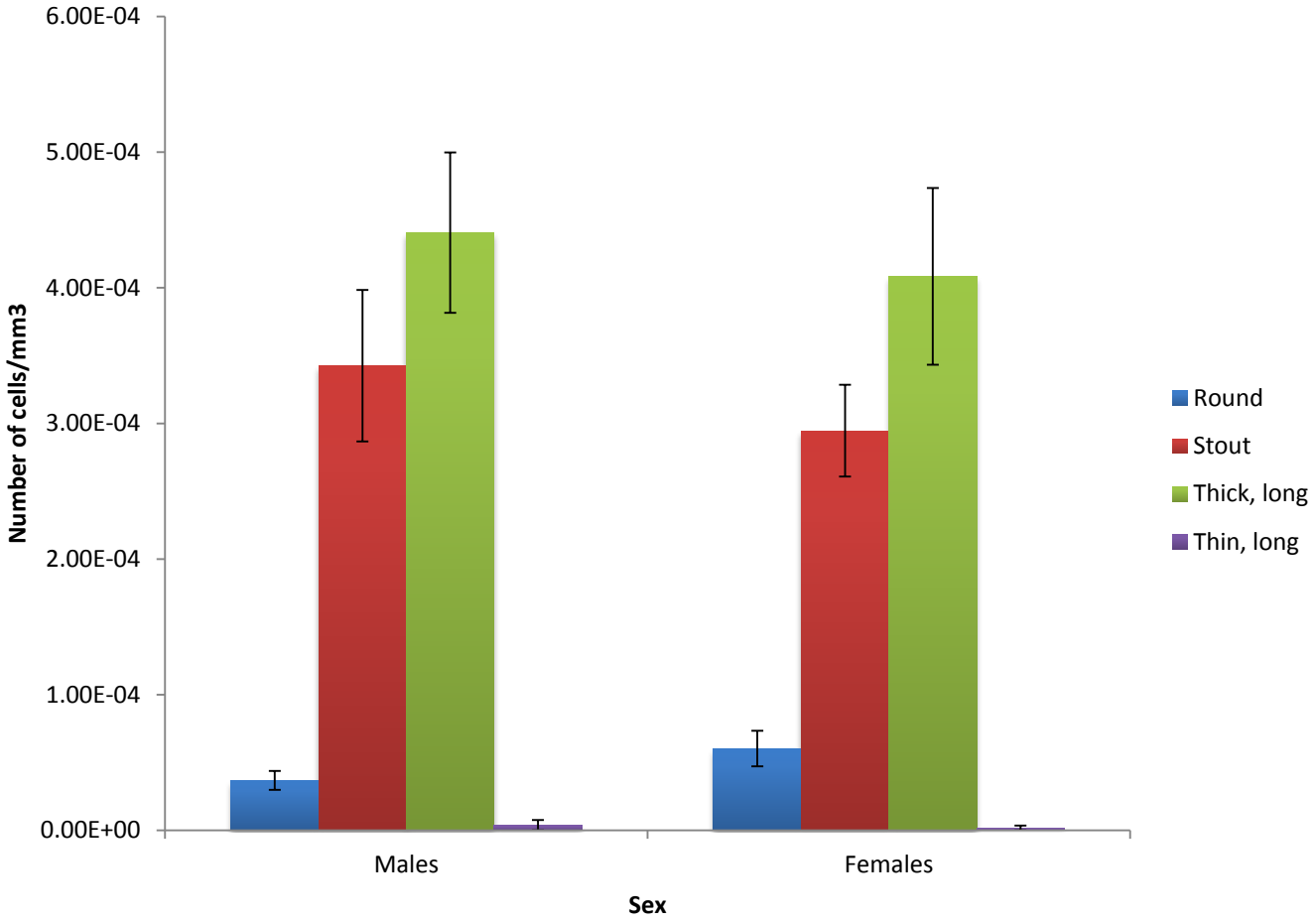


E18 Amygdala: DEP, TLR4 +/- males express significantly more quiescent microglia than DEP, TLR4 -/- males

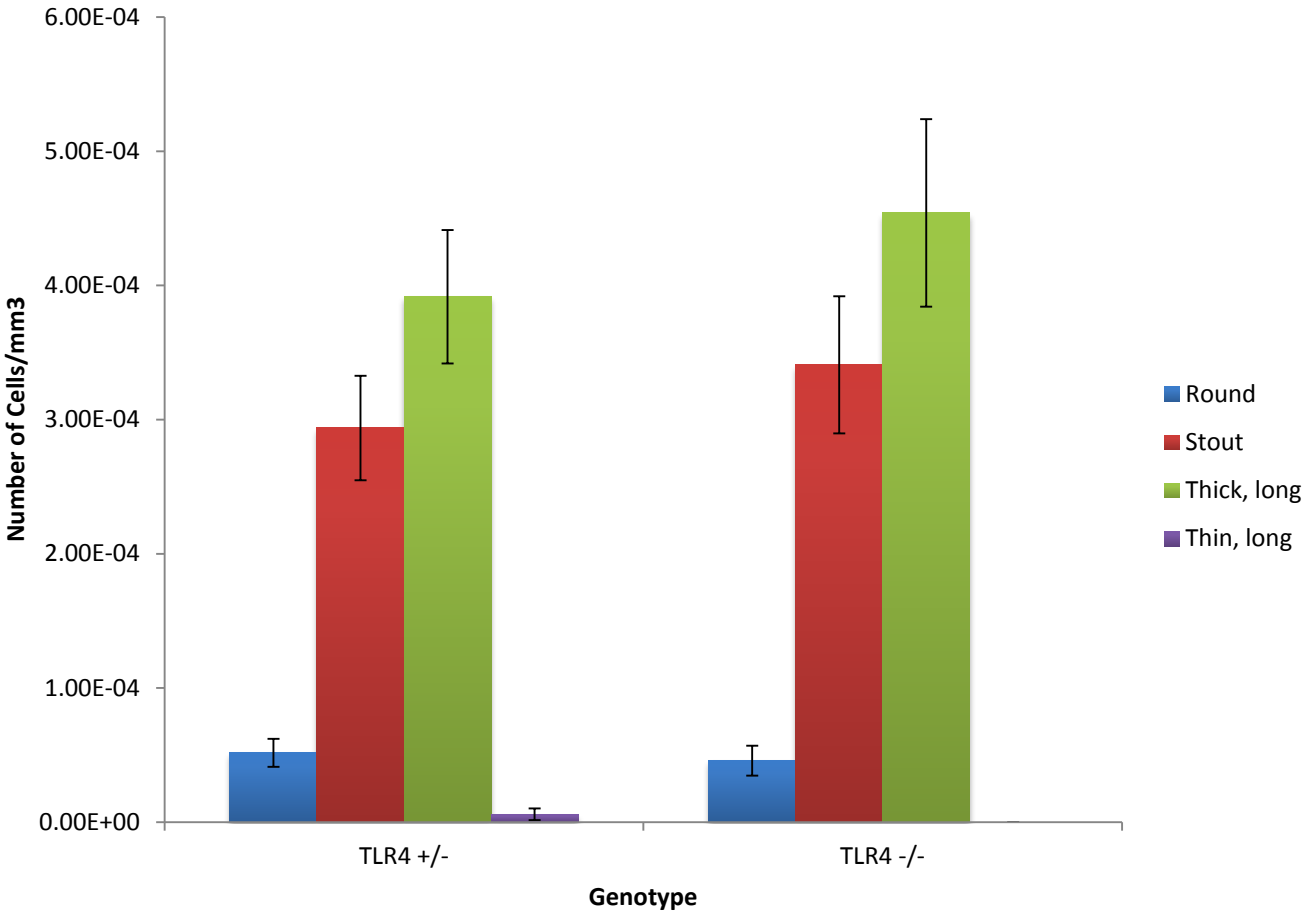


Significant DEP x genotype x sex interaction for males

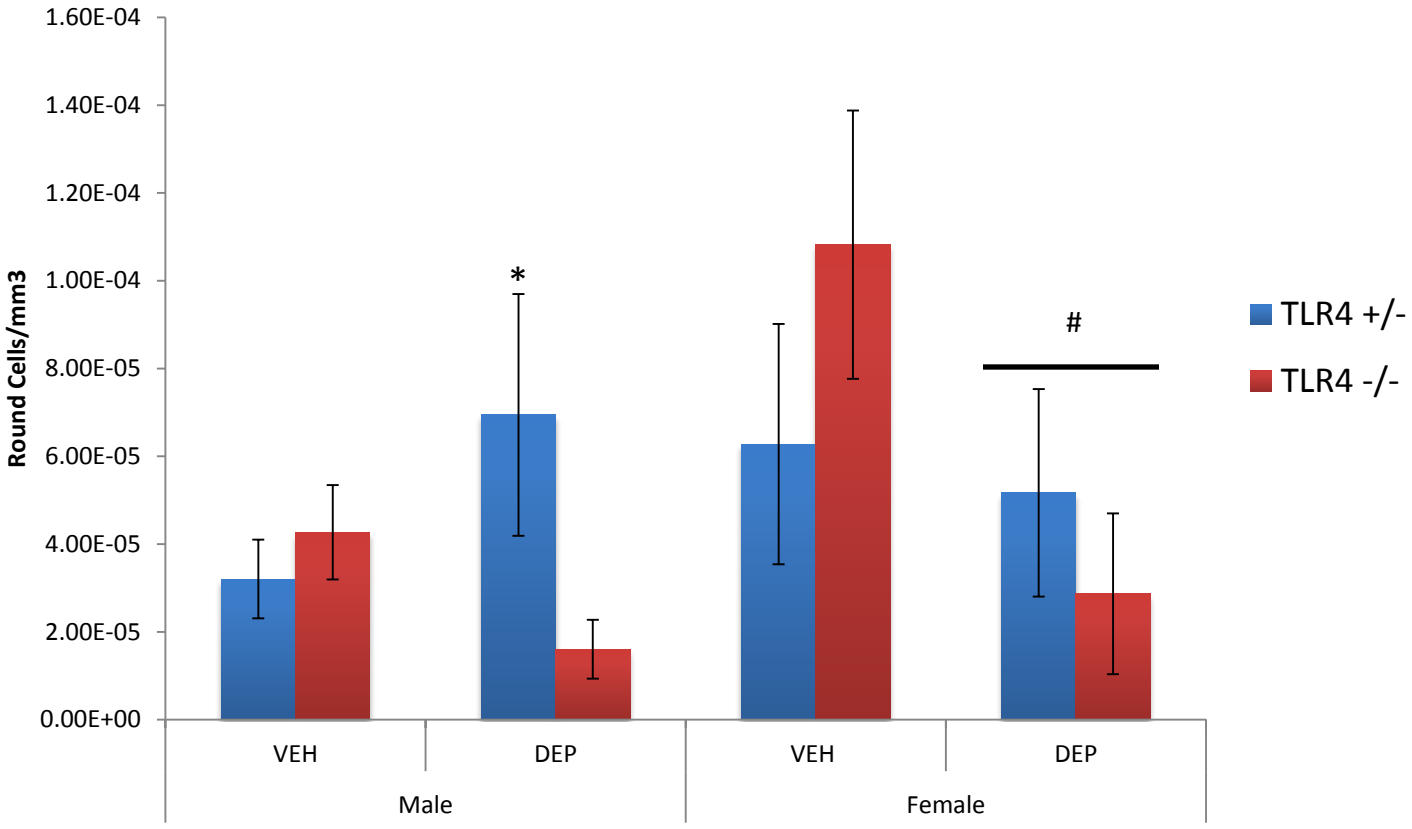
E18 Parietal Cortex: No significant difference in number of cells of any cell type due to sex



E18 Parietal Cortex: No significant difference in number of cells of any cell type due to genotype



E18 Parietal Cortex: DEP, TLR4 +/- males express significantly more round microglia than DEP, TLR4 -/- males



*p<0.05
#p=0.088

Significant DEP x genotype interaction for males
Females show trend for main effect of diesel

What does this all mean?

1. Differences in regional volume
   - This suggests variations in synaptic pruning due to the diesel treatment
   - Relation to autism?

2. Differences in morphology
   - This suggests either a difference in microglial maturation and/or activation by prenatal diesel exposure

3. TLR4 mediates diesel effect

4. Males are more vulnerable
   - Consistent with previous studies

Future Directions

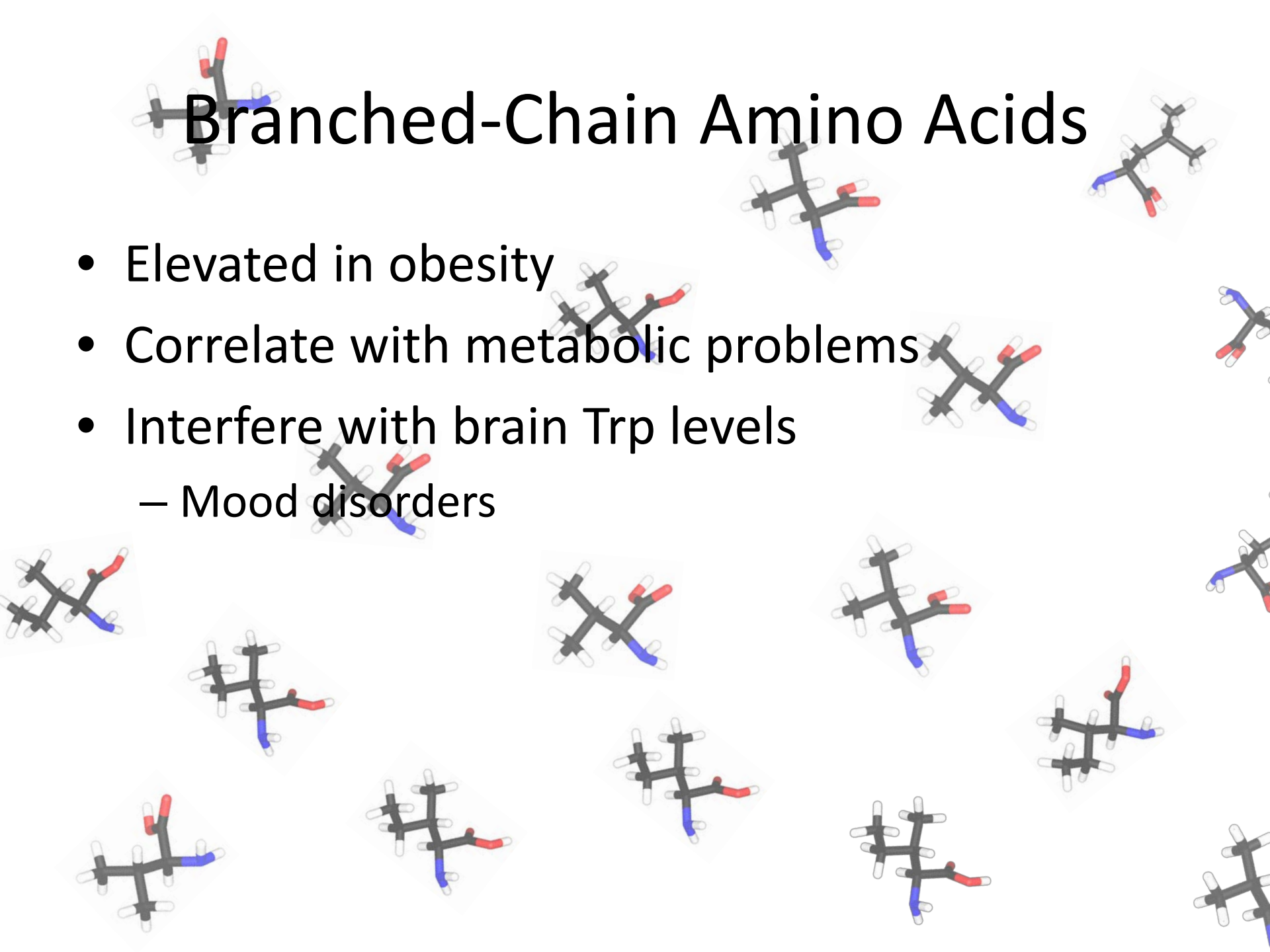
- Currently: quantifying microglial morphology in the E18 hippocampus
- Future: doing the same in parietal cortex and hippocampus of adult cohort
  - How does the immune challenge affect microglial morphology?
  - Will females be more vulnerable than males?
- Afterward: examine how maternal obesity in conjunction with an LPS challenge affects microglial expression and morphology in offspring parietal cortex and hippocampus

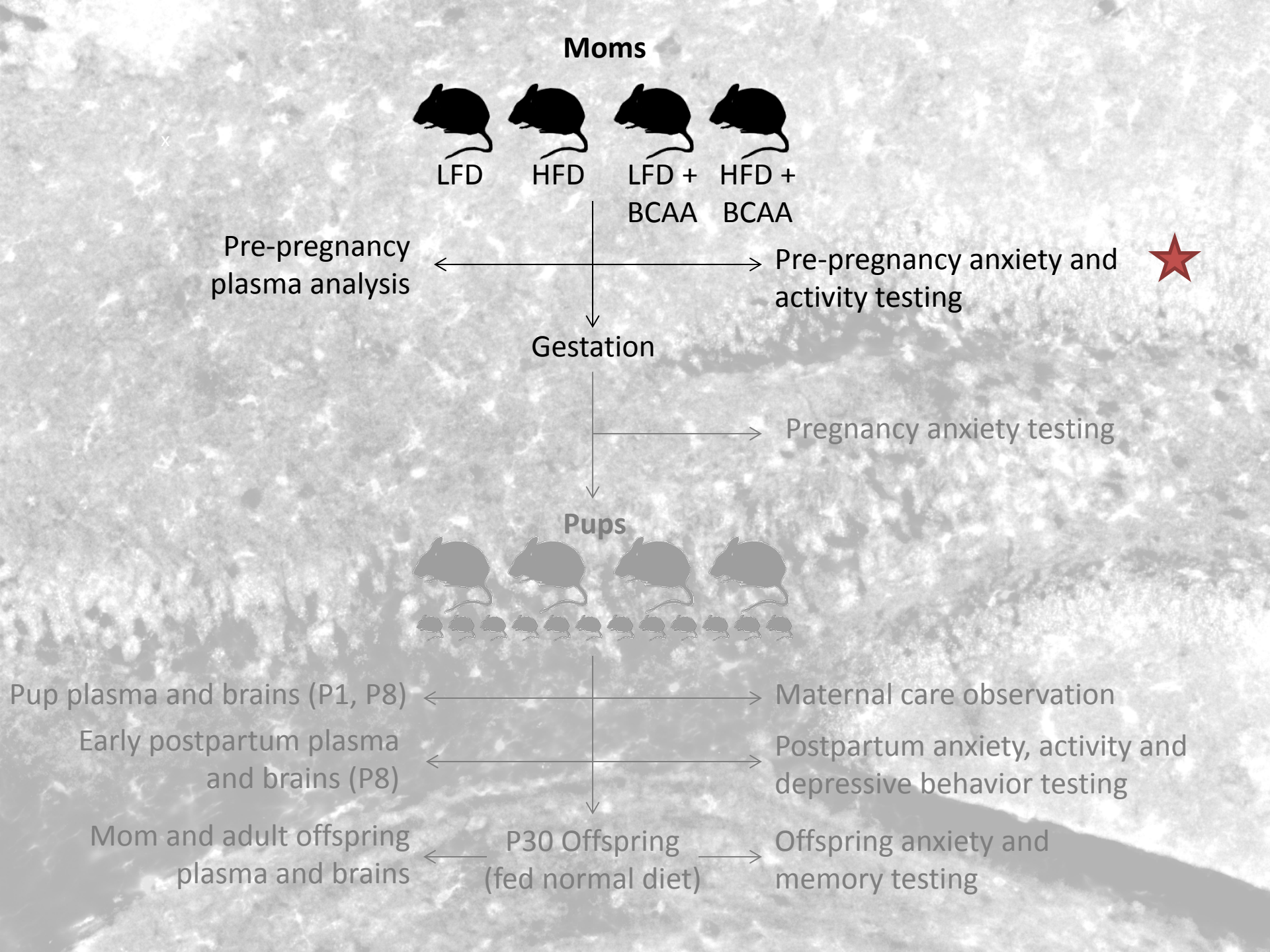
Maternal Obesity

- Causes
  - Genetics
  - Metabolic
  - Lifestyle
- Effects
  - Mother
  - Child

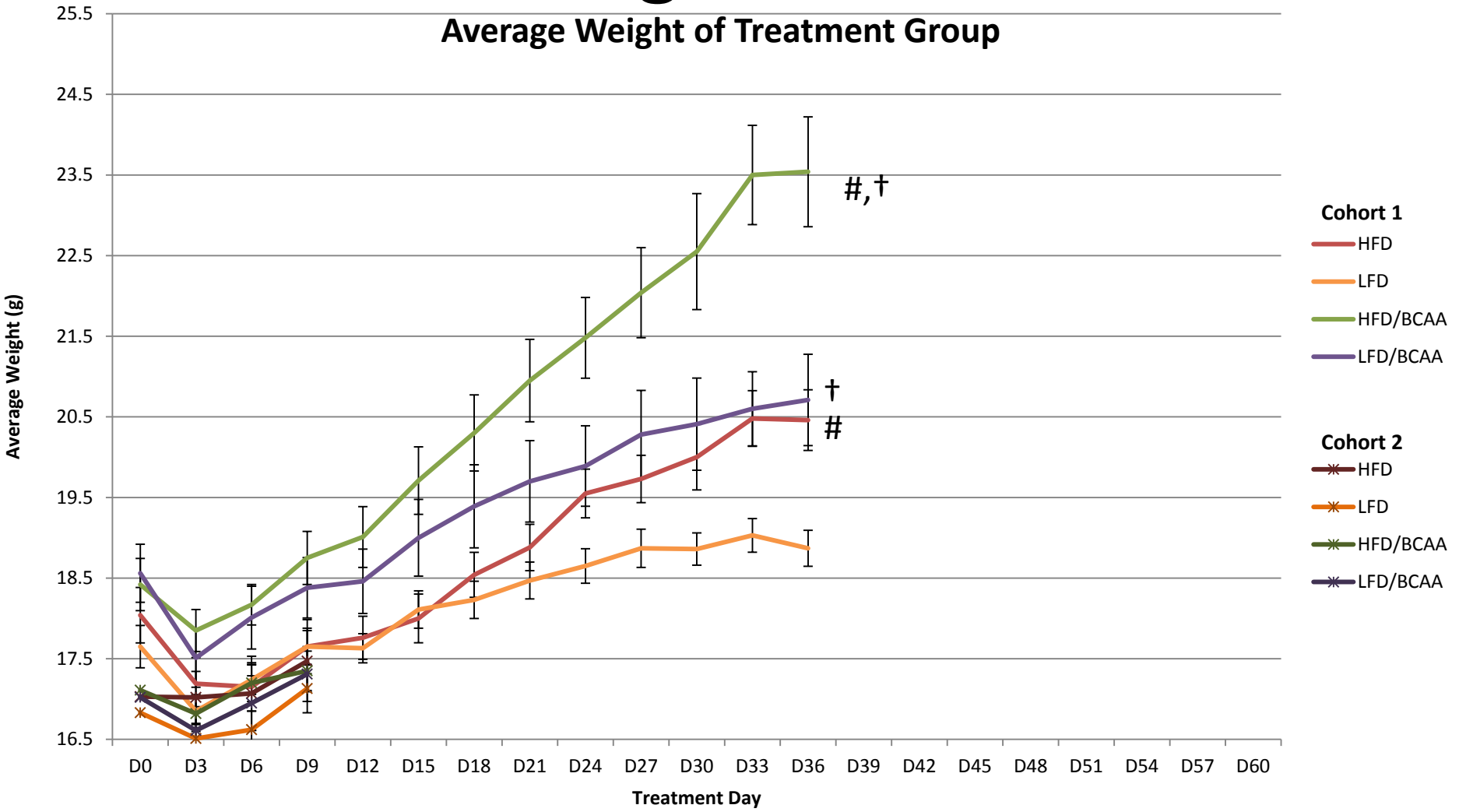
Branched-Chain Amino Acids

- Elevated in obesity
- Correlate with metabolic problems
- Interfere with brain Trp levels
  - Mood disorders



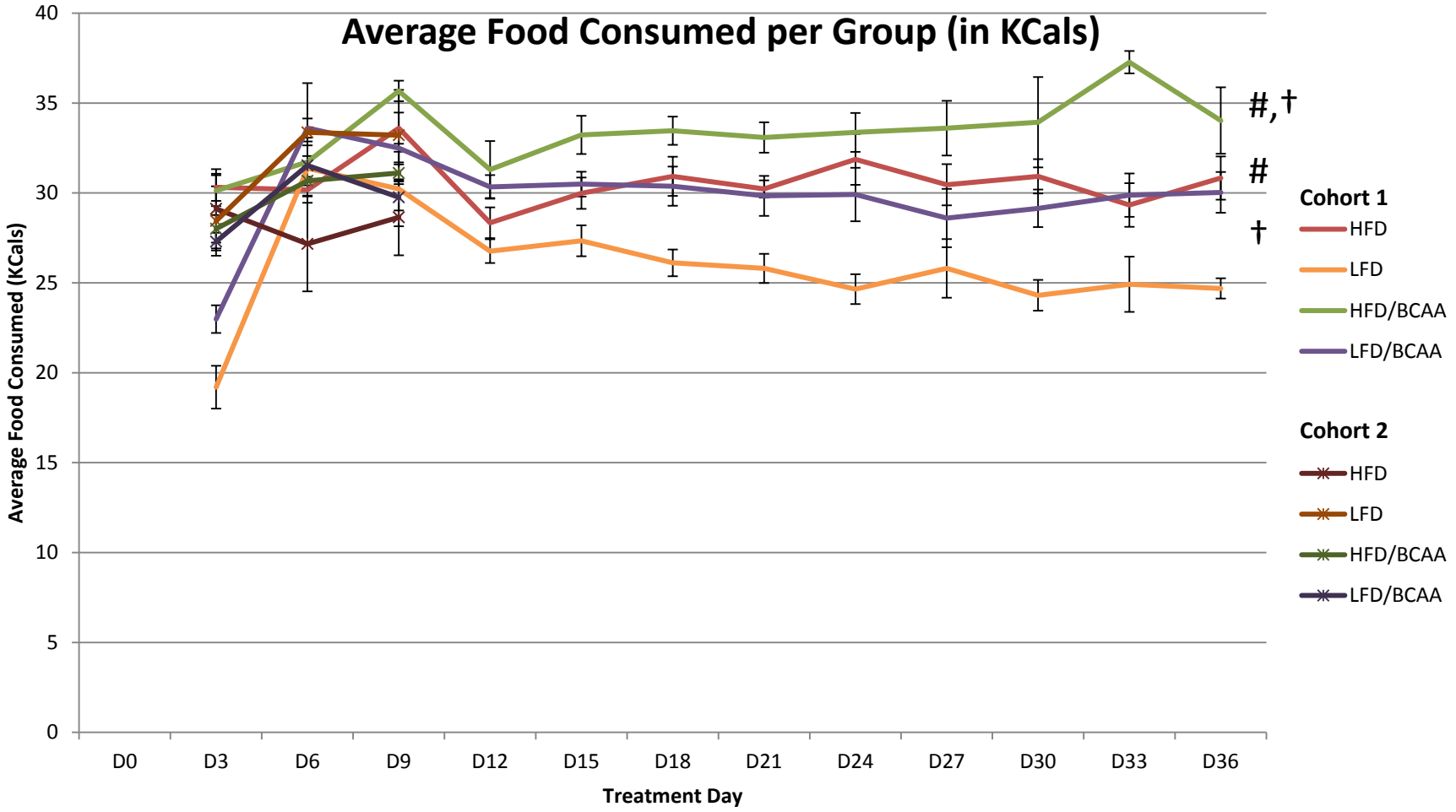

Moms
LFD
HFD
LFD + BCAA
HFD + BCAA
Pre-pregnancy plasma analysis
Pre-pregnancy anxiety and activity testing
Gestation
Pregnancy anxiety testing
Pups
Pup plasma and brains (P1, P8)
Maternal care observation
Early postpartum plasma and brains (P8)
Postpartum anxiety, activity and depressive behavior testing
Mom and adult offspring plasma and brains
P30 Offspring (fed normal diet)
Offspring anxiety and memory testing

Weight Gain



Significant main effect of HFD, $p<0.05$

† Significant main effect of BCAA, $p<0.05$



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Pre-Pregnancy Behavioral Testing

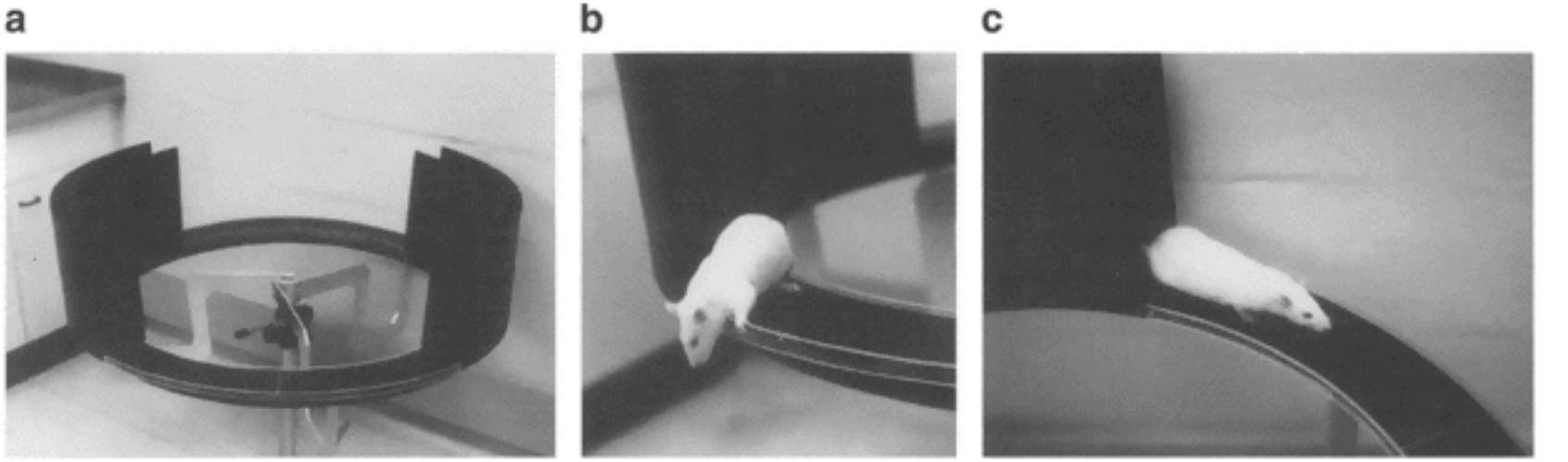
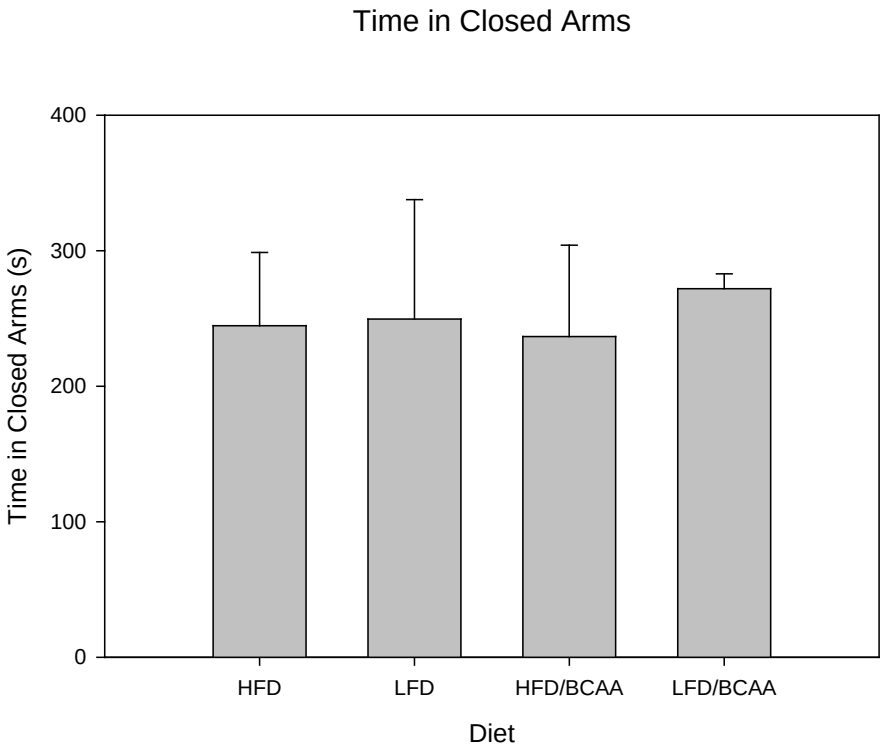
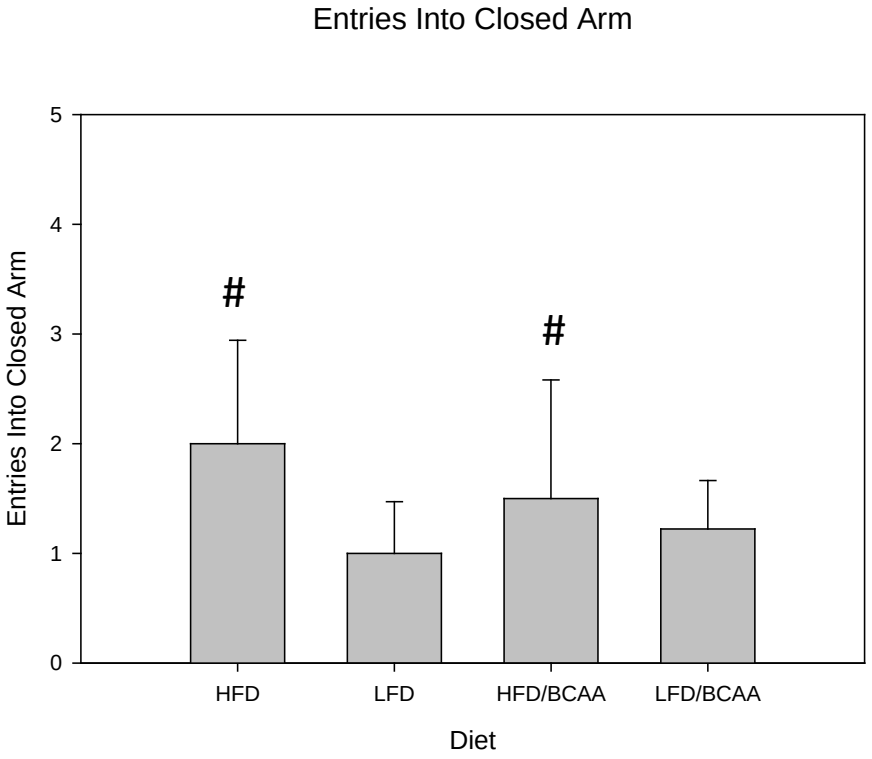


Fig. 2a–c. Photographs of **a** the zero-maze apparatus, **b** a rat head-dipping over the edge of the zero-maze platform, **c** a rat exhibiting the stretched attend posture

Shepherd et al., 1994

Zero Maze





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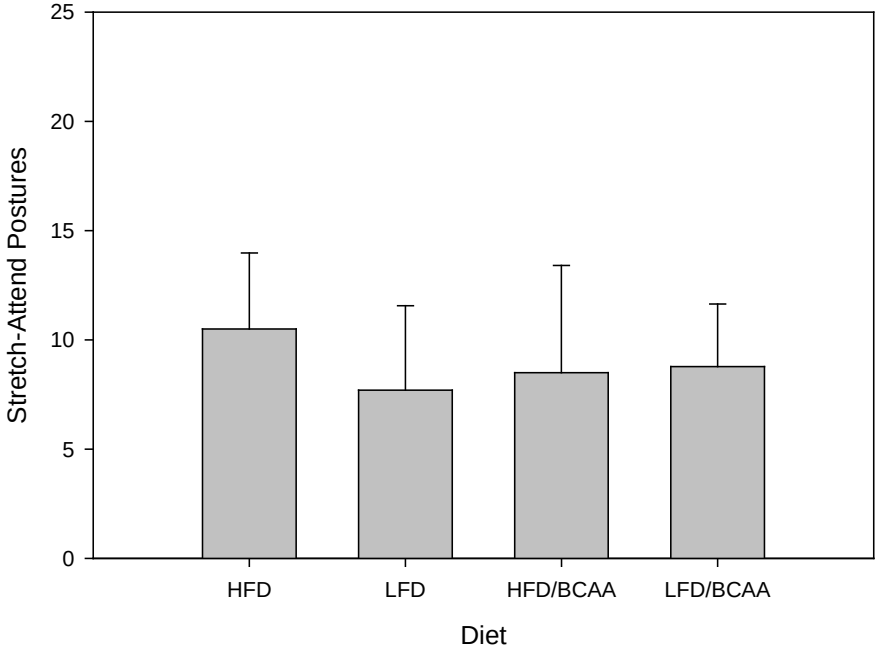
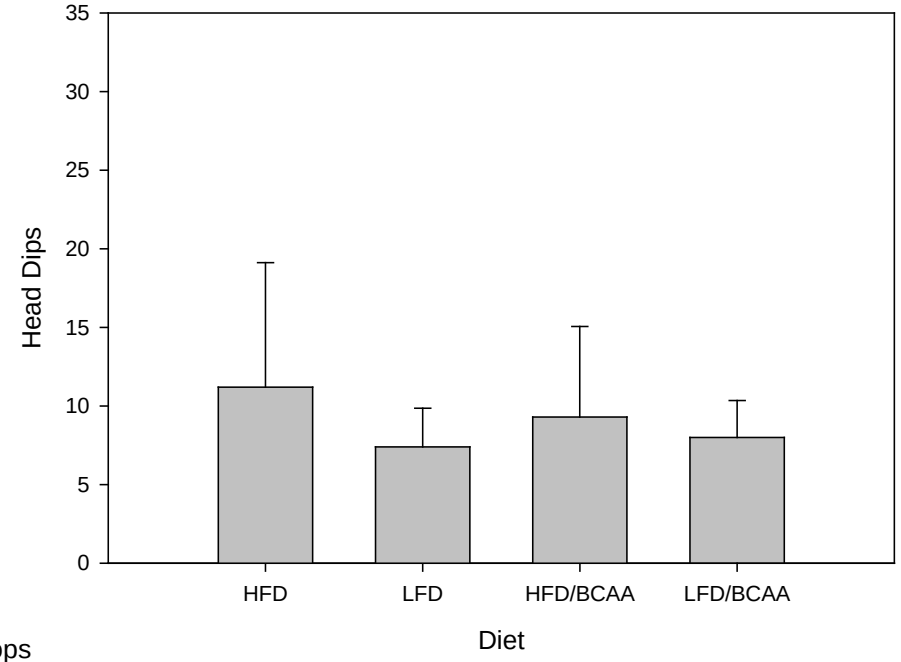
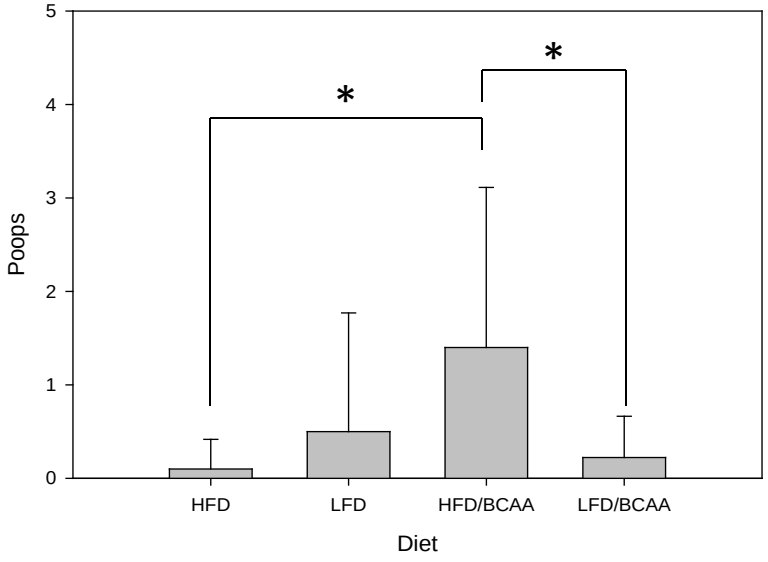
Stretch-Attend Postures



Head Dips

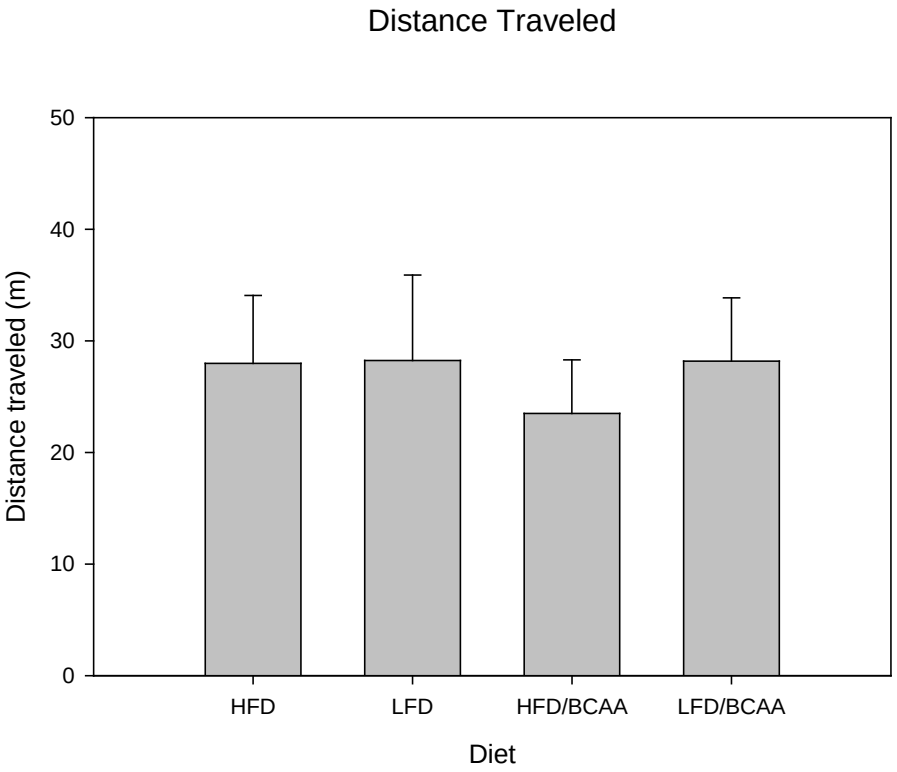


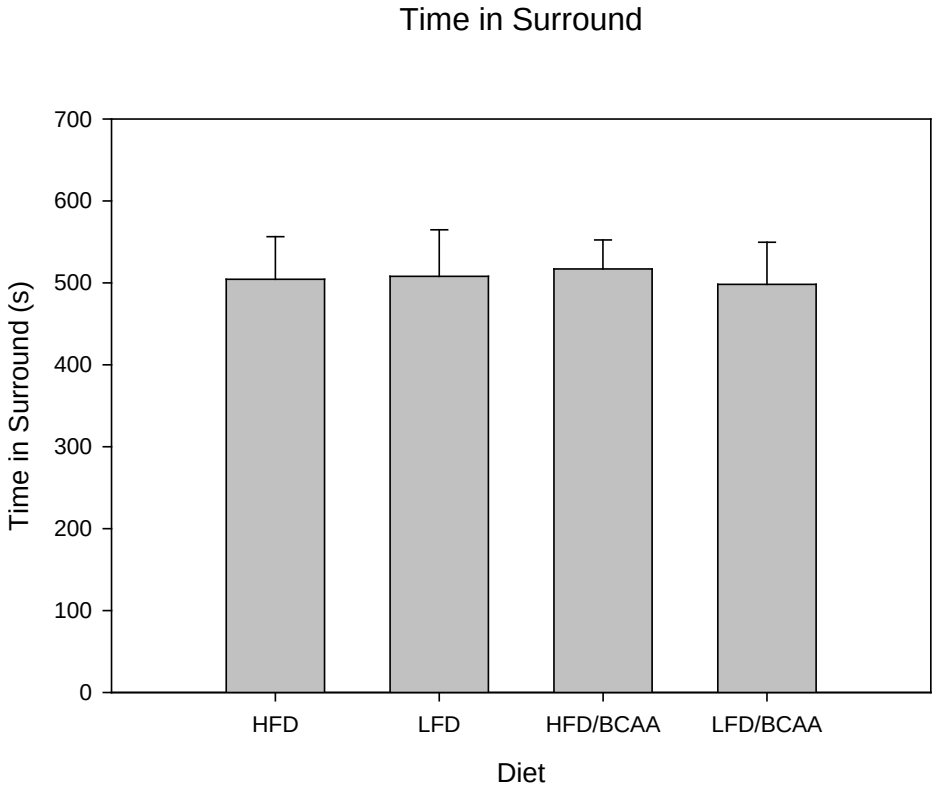
Poops



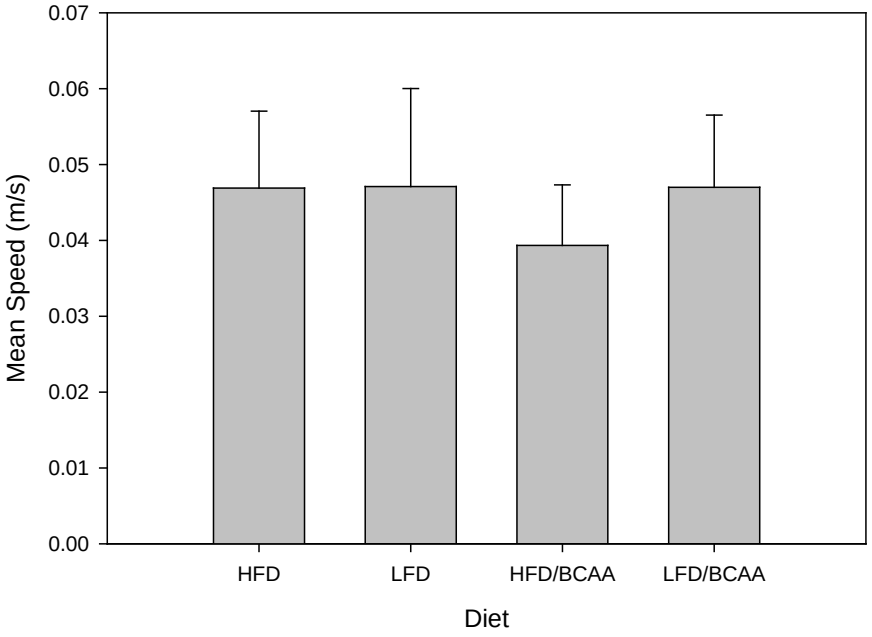
* Significant HFD x BCAA interaction, $p<0.05$

Open Field

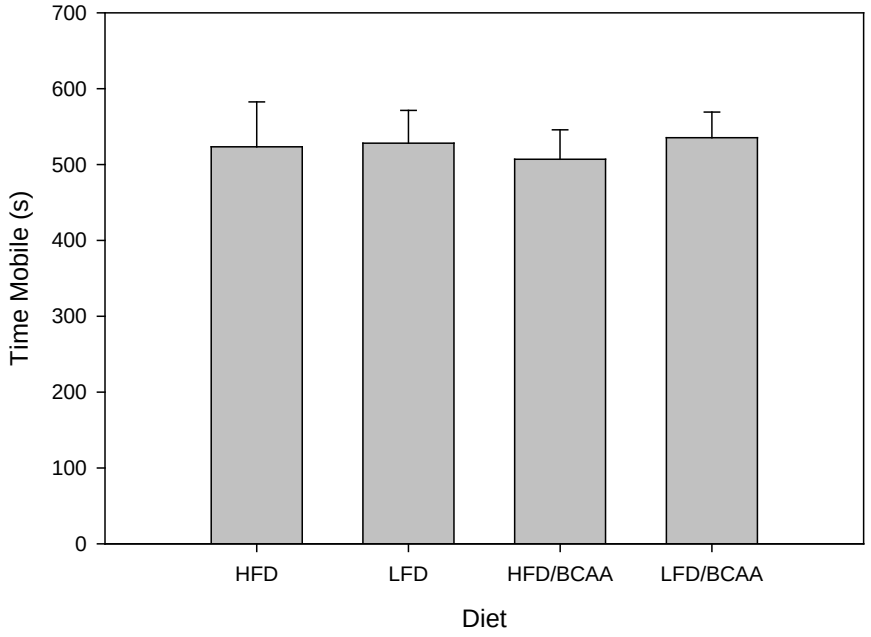

Distance Traveled
Distance traveled (m)
50
40
30
20
10
0
HFD
LFD
HFD/BCAA
LFD/BCAA
Diet


Time in Surround
Time in Surround (s)
700
600
500
400
300
200
100
0
HFD
LFD
HFD/BCAA
LFD/BCAA
Diet

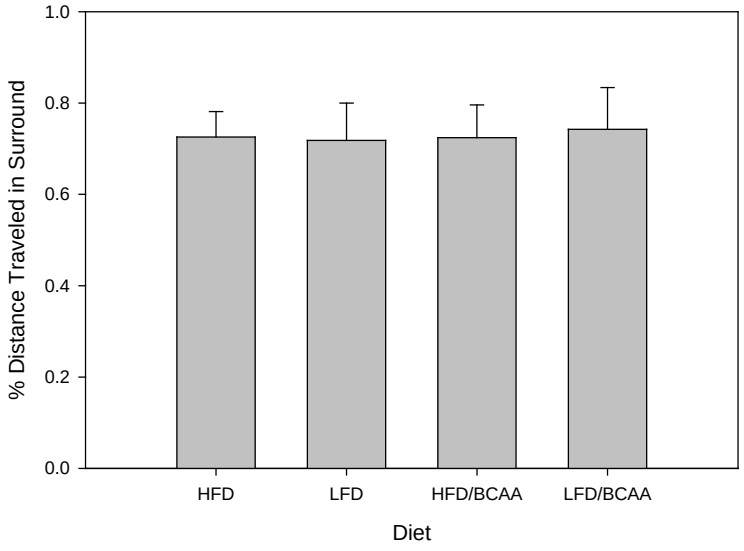
Mean Speed



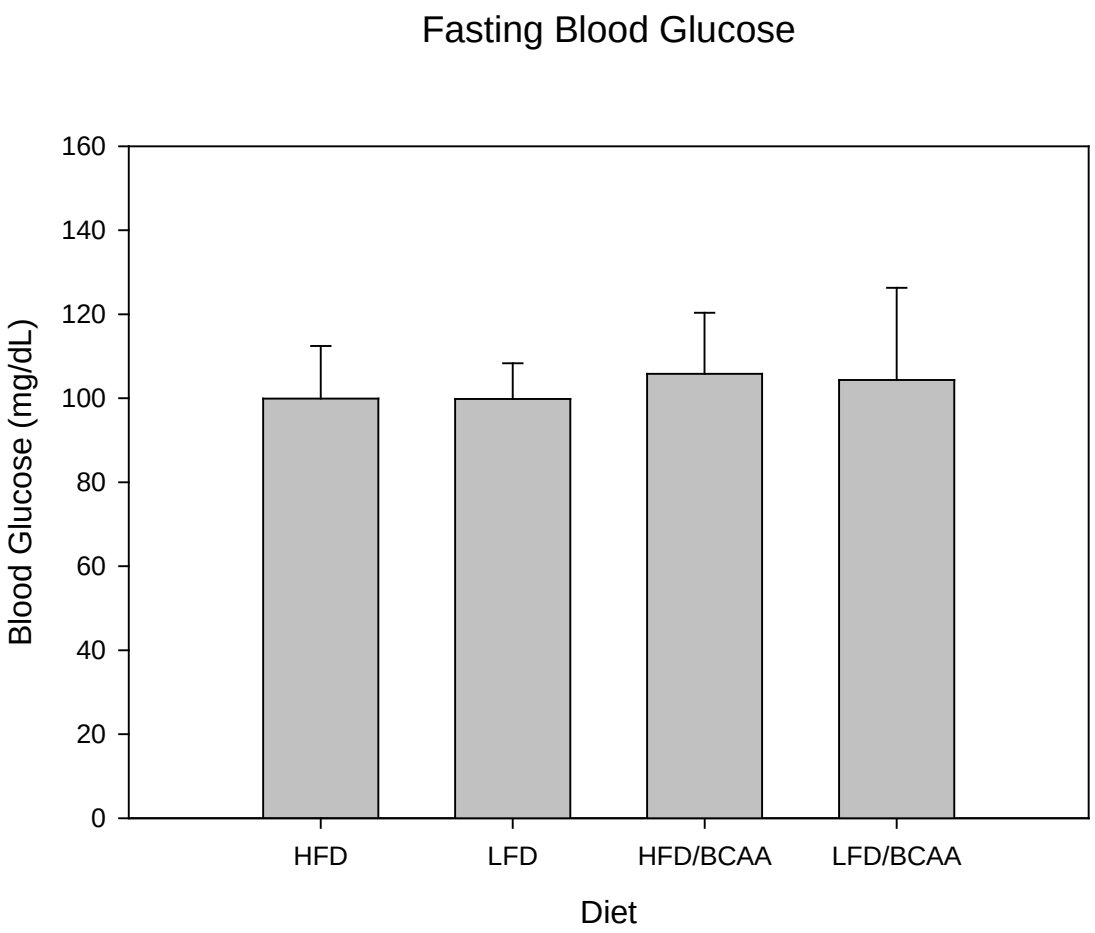
Time Mobile



Percent of Distance



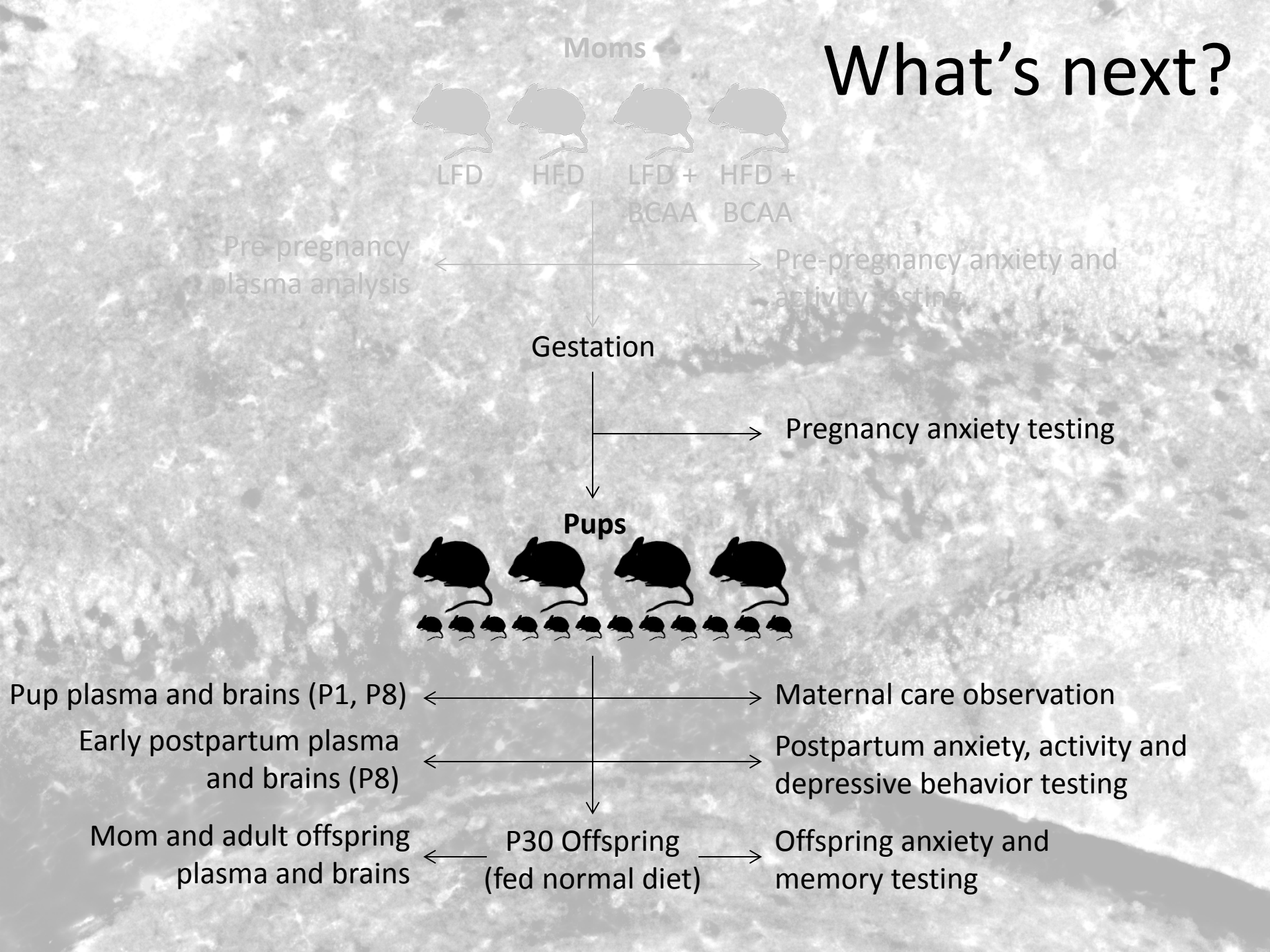
Metabolic Markers



Discussion

- No strong effect of pre-pregnancy diet alone
- Behavioral, metabolic, endocrine changes during pregnancy may interact with diet
  - Post-partum depression
  - Gestational diabetes

What's next?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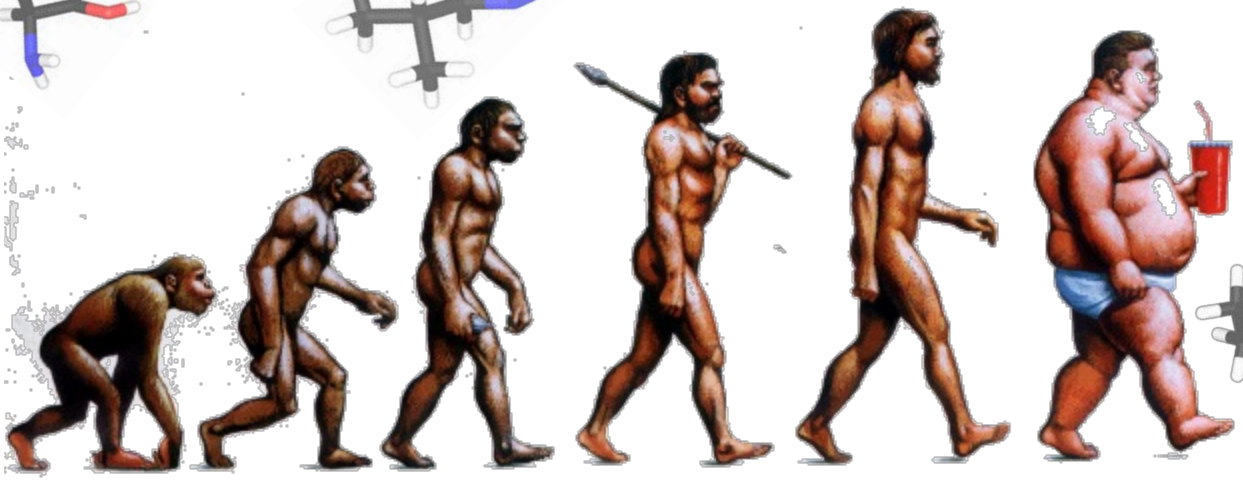
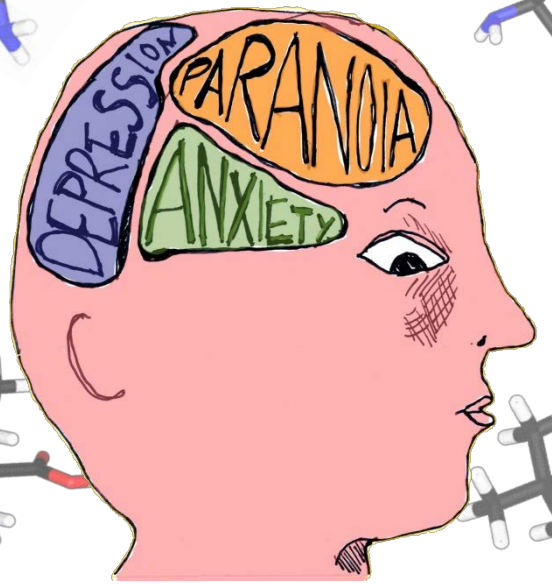
Maternal obesity study: from a clinical perspective

- **Purpose:** to investigate the effect of weight gain and nutrition during pregnancy on the incidence of post-partum depression
- **Methods:**
  - We will pre-screen potential candidates, who are women who have just given birth
  - Recruited moms' blood will be drawn a couple of days after child's birth and several months later
    - Will be analyzed for 5-HT and BCAA levels
  - Behavioral assessment of post-partum depression
  - Moms can elect to receive (long-term) health counseling

Conclusion





Acknowledgements

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- Dr. Staci Bilbo, Dr. Richard Auten, and Dr. Leigh Anne Simmons