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

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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) bind to Toll Like Receptor 4 (TLR-4) and upregulate Interleukin-1β (IL-1β) and Interleukin-10 (IL-10). This leads to an inflammatory response, immune cell recruitment, phagocytosis, and bidirectional neuroimmune communication.
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
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

Moms

VEH  DEP

Pups born

Maturation

Adult Offspring (P30)

SAL  LPS

Sacrificed 2 hours later

Sacrificed at E18
Cell counting and volumetric analysis: example contour in E18 parietal cortex
E18 Amygdala vs. Parietal Cortex: Regional Volume Differences

Amygdala

VEH

DEP

p<0.05

Parietal Cortex

VEH

DEP

*
E18 Amygdala vs. Parietal Cortex: Microglial Morphology
E18 Amygdala: DEP, TLR4 +/- males express significantly more quiescent microglia than DEP, TLR4 -/- males

Microglia with thin, long processes

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

![Graph showing the number of cells/mm³ for Males and Females, categorized by cell type (Round, Stout, Thick, long, Thin, long).](image-url)
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
Maternal care observation

LFD  HFD  LFD + BCAA  HFD + BCAA

Pre-pregnancy plasma analysis

Pre-pregnancy anxiety and activity testing

Gestation

Pregnancy anxiety testing

Pups

Maternal care observation

Pup plasma and brains (P1, P8)

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
# Significant main effect of HFD, $p<0.05$
† Significant main effect of BCAA, $p<0.05$
Average Food Consumed per Group (in KCals)

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

Time in Closed Arms

Entries Into Closed Arm

# Significant main effect of HFD, \( p < 0.05 \)
Stretch-Attend Postures

Diet

HFD LFD HFD/BCAA LFD/BCAA

Poops

Plot 1

* Significant HFD x BCAA interaction, \( p<0.05 \)
Open Field

Distance Traveled

Time in Surround

Diet

Distance traveled (m)

Time in Surround (s)

HFD  LFD  HFD/BCAA  LFD/BCAA

HFD  LFD  HFD/BCAA  LFD/BCAA
### Mean Speed

<table>
<thead>
<tr>
<th>Diet</th>
<th>HFD</th>
<th>LFD</th>
<th>HFD/BCAA</th>
<th>LFD/BCAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Speed (m/s)</td>
<td>0.00</td>
<td>0.01</td>
<td>0.02</td>
<td>0.03</td>
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</table>

### Percent of Distance Traveled in Surround

<table>
<thead>
<tr>
<th>Diet</th>
<th>HFD</th>
<th>LFD</th>
<th>HFD/BCAA</th>
<th>LFD/BCAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of Distance Traveled in Surround</td>
<td>0.0</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
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</table>

### Time Mobile

<table>
<thead>
<tr>
<th>Diet</th>
<th>HFD</th>
<th>LFD</th>
<th>HFD/BCAA</th>
<th>LFD/BCAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Mobile (s)</td>
<td>0</td>
<td>100</td>
<td>200</td>
<td>300</td>
</tr>
</tbody>
</table>

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**Plot 1** shows the mean speed, percent of distance traveled in the surround, and time mobile for different diets (HFD, LFD, HFD/BCAA, LFD/BCAA). Each diet group is represented by bars with error bars indicating variability.
Metabolic Markers

Fasting Blood Glucose

Plot 1
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?

**Moms**

- LFD
- HFD
- LFD + BCAA
- HFD + BCAA

**Pre-pregnancy plasma analysis**

**Gestation**

- Pre-pregnancy anxiety and activity testing
- Pregnancy anxiety testing

**Pups**

- Pup plasma and brains (P1, P8)
- Early postpartum plasma and brains (P8)
- Mom and adult offspring plasma and brains
- P30 Offspring (fed normal diet)

**Maternal care observation**

- Offspring anxiety and memory testing
- Postpartum anxiety, activity and depressive behavior testing
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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