Developmental Exposures to Ambient Ultrafine Particulate Matter Produces Pathological and Behavioral Features Shared by Multiple Neurodevelopmental Disorders

D. A. Cory-Slechta
Department of Environmental Medicine
University of Rochester Medical School
Evidence for Association of Air Pollution Effects With Neurodevelopmental Disorders:

- Epidemiological Studies Have Associated Air Pollution with:
  - Autism (approximately 15 studies)
  - Schizophrenia
  - Attention deficit disorder
  - Decline in rate of cognitive growth
  - Interhemispheric disconnectivity
Geographical Distribution of Autism Diagnoses vs. PM2.5 Exposures in the U.S.

Residential location at the time of birth for 33,315 children born to women participating in Nurses’ Health Study

Hoffman et al., 2017

Bennett et al., 2019
Ultrafine particle contaminants can cross placenta and affect the fetus directly. Ultrafine particles can cause maternal inflammation that impacts the placenta and consequently the fetus.

Contaminants on UFPs are taken up into brain, bypassing the blood brain barrier and thus not reflected in serum markers including via vagal and trigeminal nerves.
Autism Spectrum Disorder

- **Phenotype**
  - Social communication and interaction deficits
  - Repetitive behavior, inability to inhibit responding
  - Sensory/motor deficits
  - Cognitive deficits
  - Neuropathology: cortical overgrowth, reduction in white matter, ventriculomegaly, inflammation, excitatory/inhibitory imbalance

- **Hypothesized Mechanisms**
  - ROS, redox metabolism
  - Excess glutamate
    (excitatory/inhibitory imbalance)
  - Inflammation
    (prenatal)/microglial activation
  - Mitochondrial dysfunction
  - Excess testosterone
  - Astrocyte dysfunction
  - Gut microbiome?
Autism Neuropathology: Dynamic Changes in Early Life
Biological Plausibility from Experimental Animal Models: Concentrated Ambient Ultrafine Particles (CAPs) Exposure in Mice

- 20K CC⁻¹
- 200,000 CC⁻¹

~10-20x concentration

Kendrick Road
Exposure Room
Equipment Room
HUCAPS

HEPA-Filtered Air
CAPS

Intake

Gestation
Lactation
Postnatal Exposure

Breed
4hr/day

Human 3rd trimester equivalent

Behavioral Testing

Tissue collection
Postnatal UFP-Induced Changes in Mice are Consistent with Hypothesized Mechanisms of Autism

- Ventriculomegaly
- Aberrant white matter tract development
- Interhemispheric disconnectivity
- Inflammation and persistent microglial activation
- Elevated levels of glutamate and excitatory/inhibitory imbalance
- Behavioral manifestations include perseverative and repetitive behavior
- Male biased
Male-Specific Ventriculomegaly

Modified from Allen et al., 2013; Allen et al., 2017
Disrupted CC White Matter Development

Percent of corpus callosum area myelin basic protein (MBP) staining in males at PND 14 quantified using Image Pro Plus programmed to contrast density of MBP staining via histogram segmentation.

Allen et al., 2015
Male Specific CAPS-Induced Glial Activation and Increased Glutamate

Glial Activation

Increased Glutamate

Allen et al., 2015
CAPS-Induced Reduced Preference for Novel Conspecific Correlates with Reduced Testosterone

Sobolewski et al., 2018
Concentration-Effect Data to Date

Cory-Slechta et al., in press
What About Gestational CAPS Exposures?

Pregnant dam

- Systemic inflammation
- Placental inflammation
- Fetal inflammation

Gestational exposure: GD0.5-16.5

CNS damage

Tissue collection: PND11-15

Birth

Klocke et al., 2017
Gestational CAPs Exposure Induces Ventriculomegaly

Klocke et al., 2017
Brain Trace Element Accumulation as a Mechanism for Air Pollution Neurotoxicity

Both Fe and S are essential to brain development, but both are neurotoxic in excess.
Gestational CAPs Increases Brain Iron Levels

Iron content of exposures

<table>
<thead>
<tr>
<th>Fe content (ng/m³)</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>FA</td>
<td>CAPs</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fe inclusions

<table>
<thead>
<tr>
<th>Fe inclusions</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>FA</td>
<td>CAPs</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Klocke et al., 2017
Particle Deposition in Corpus Callosum: What Happens During in vio Bioprocessing of UFPs

Klocke et al., unpublished data
Postnatal Iron and Sulfur Dioxide Inhalation In Mice Increases Ventricle Size

Cory-Slechta et al., unpublished data
And Increases Astroglial Activation
While Parallels to Autism are Evident, It is Critical to Recognize that Neurodevelopmental Disorders Have Multiple Overlapping Features

- Male Dominance: ASD, schizophrenia, ADHD
- Common behavioral deficits: ASD, schizophrenia
- Altered dopamine/glutamate function: ASD, schizophrenia, ADHD
- Inflammation: ASD, schizophrenia
- White matter reduction: ASD, ADHD, OCD
- Microglial Activation: ASD, schizophrenia
- Ventriculomegaly: ASD, schizophrenia
- Cognitive Deficits: ASD, schizophrenia, ADHD
- Interhemispheric Disconnectivity: ASD, ADHD, schizophrenia
- Shared Genetic Features: ASD, ADHD, schizophrenia
Can Air Pollution Heterogeneity Explain Heterogeneity of Phenotypic Expression and Geographical Distribution of Neurodevelopmental Disorders?

• The components of AP differ by geography, climate, season, and even on a day by day and hourly basis.

• This means that the specific components of AP exposures will differ for any individual across time, as well as across individuals at the same time.

• Further, these variations in components and levels of AP exposure will occur at different times during the trajectory of brain development, and thus impact different cell types and processes during development.