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

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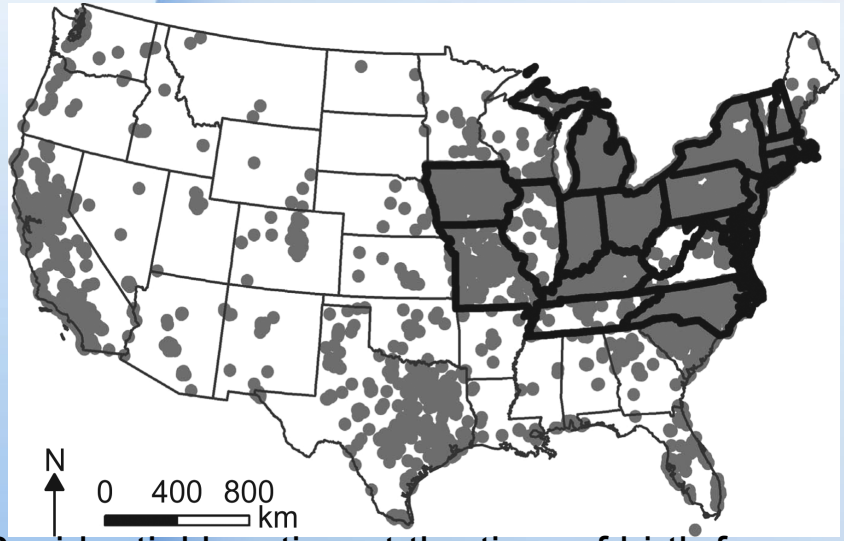
Evidence for Association of Air Pollution Effects With Neurodevelopmental Disorders:

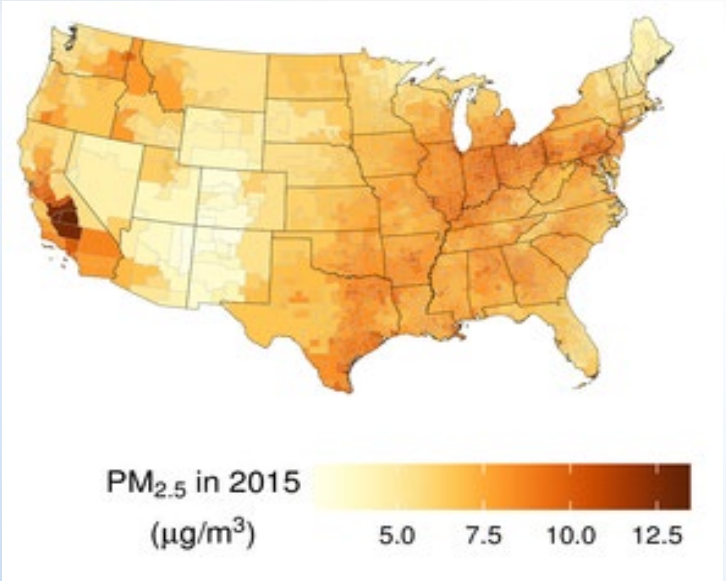
- Epidemiological Studies Have Associated Air Pollution with:
  - Autism (approximately 15 studies)
  - Schizophrenia
  - Attention deficit disorder
  - Decline in rate of cognitive growth
  - Interhemispheric disconnectivity

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

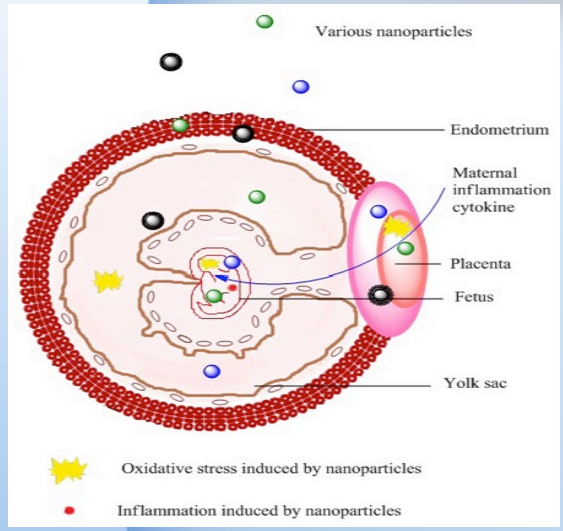
Hoffman et al., **2017**



Bennett et al., **2019**

Lifelong Exposure to Ultrafine Particles

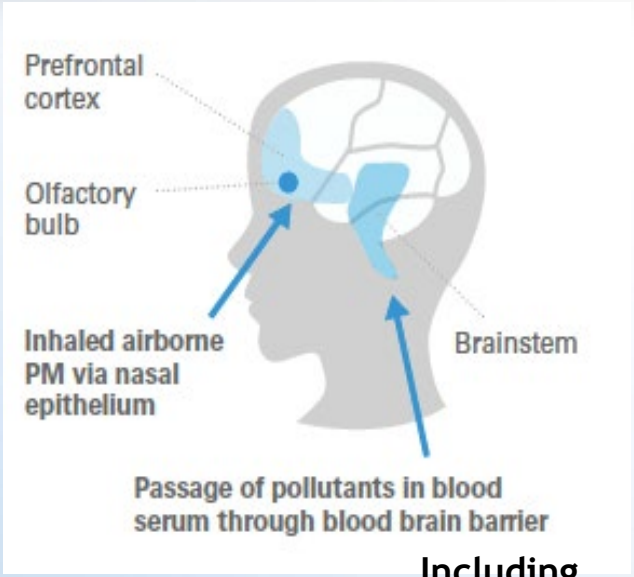
Prenatal



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

After Birth

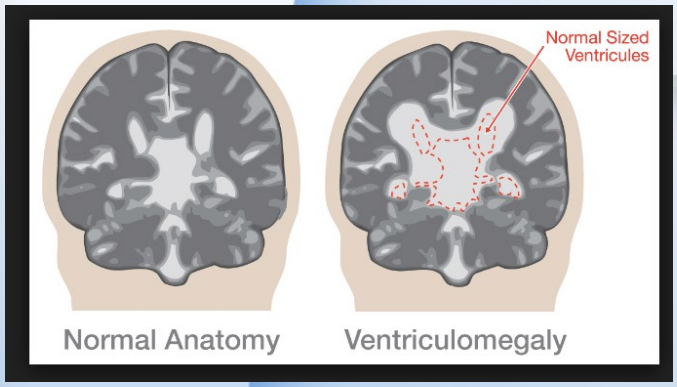


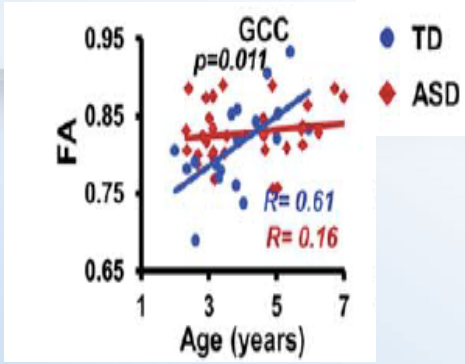
Including via vagal and trigeminal nerves

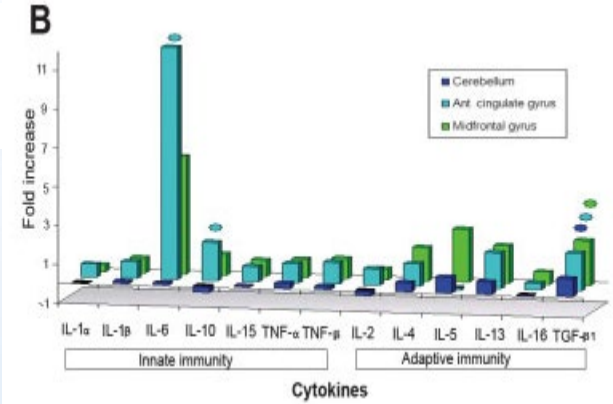
Autism Spectrum Disorder

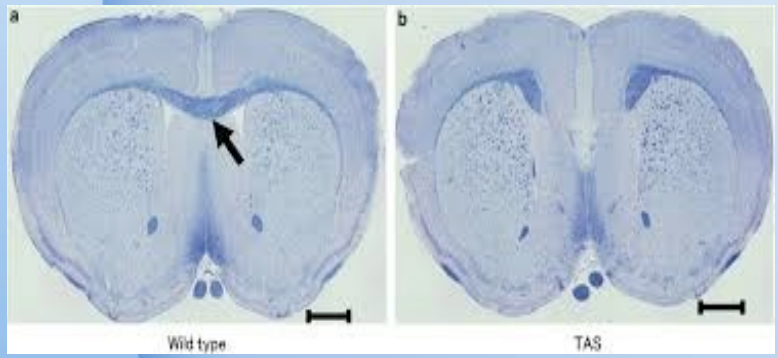
- ***Phenotype***
  - Social communication and interaction deficits
  - Repetitive behavior, inability to inhibit responding
  - Sensory/motor deficits
  - Cognitive deficits
  - Neuropathology: cortical overgrowth, reduction in white matter, ventriculomegaly, inflammation, excitatory/inhibitory imbalance
- ***Hypothesized Mechanisms***
  - ROS, redox metabolism
  - Excess glutamate (excitatory/inhibitory imbalance)
  - Inflammation (prenatal)/microglial activation
  - Mitochondrial dysfunction
  - Excess testosterone
  - Astrocyte dysfunction
  - Gut microbiome?

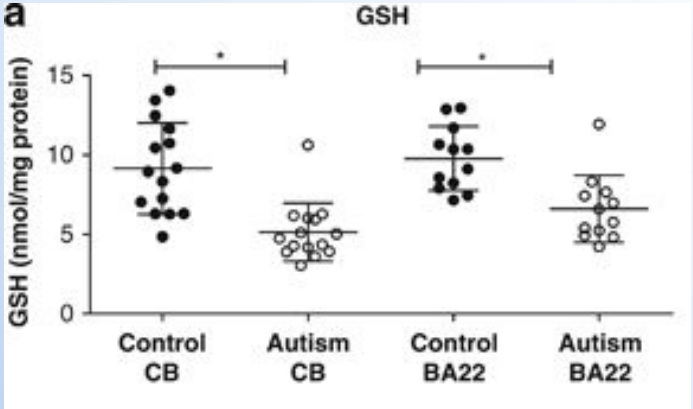
Autism Neuropathology: Dynamic Changes in Early Life



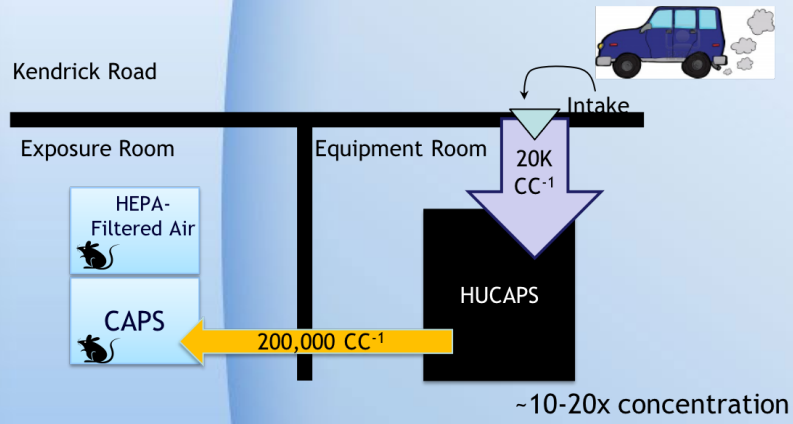


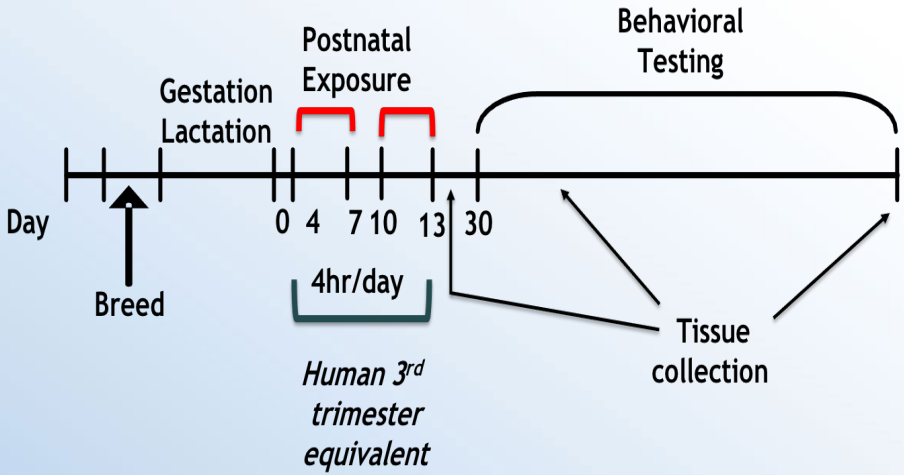






Biological Plausibility from Experimental Animal Models: Concentrated Ambient Ultrafine Particles (CAPs) Exposure in Mice

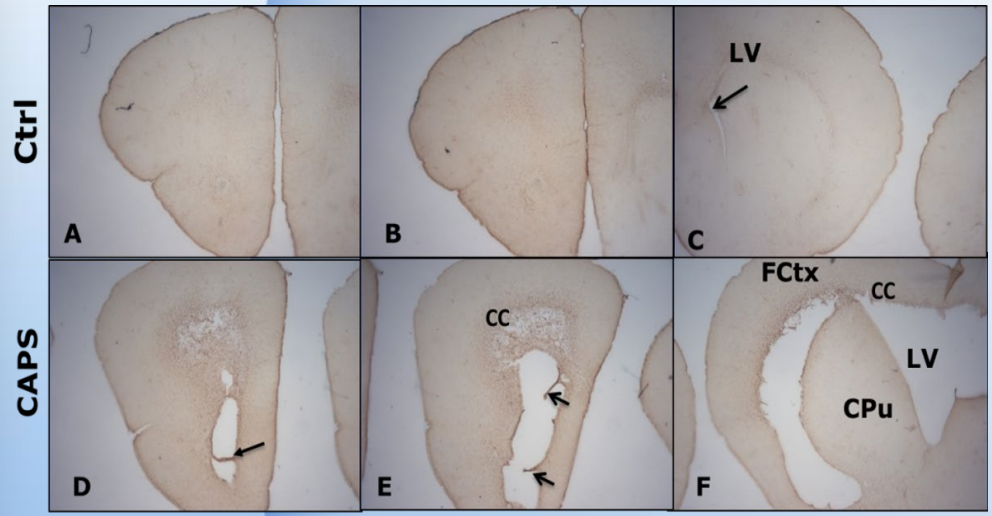


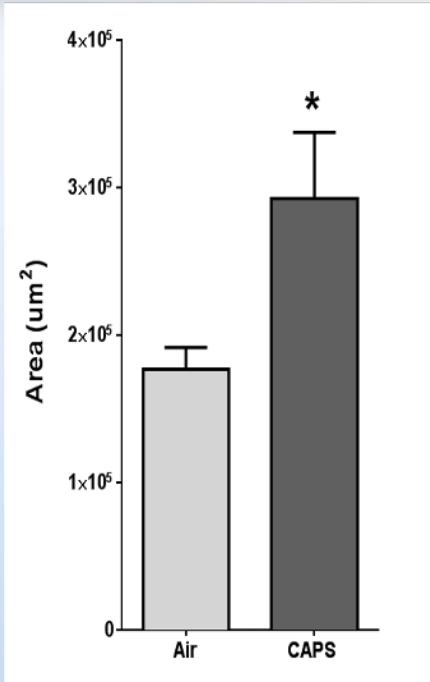


Postnatal UFP-Induced Changes in Mice are Consistent with Hypothesized Mechanisms of Autism

- 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

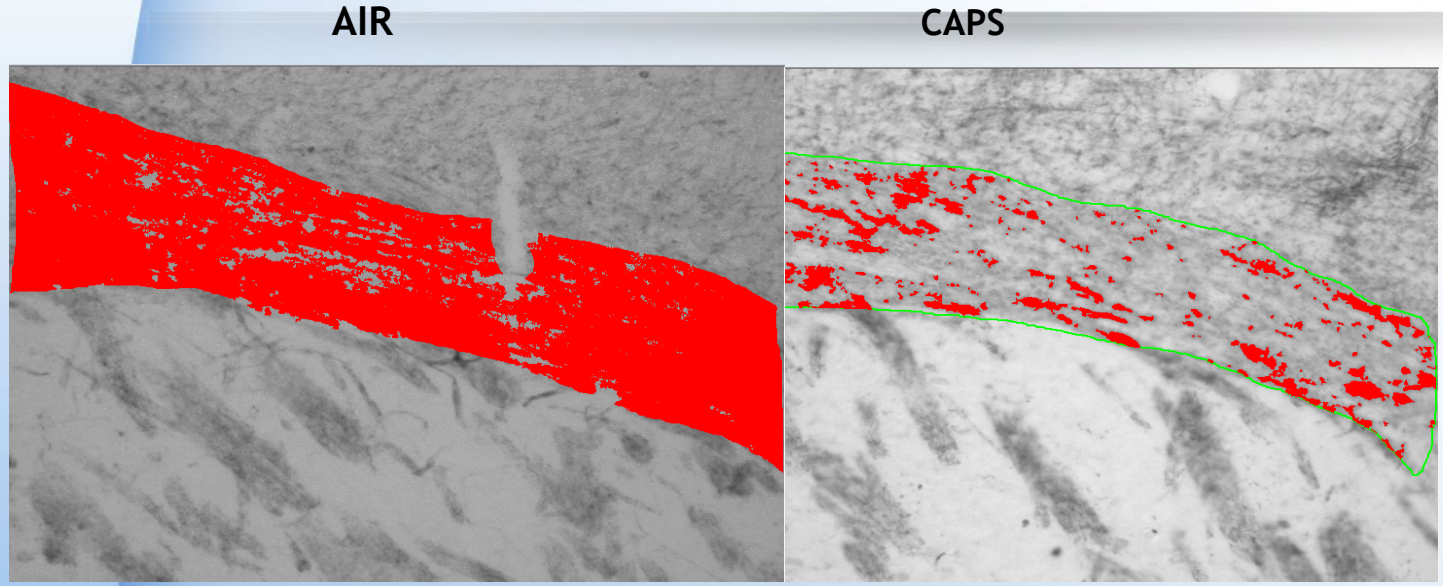
Male-Specific Ventriculomegaly





Modified from Allen et al., 2013; Allen et al., 2017

Disrupted CC White Matter Development

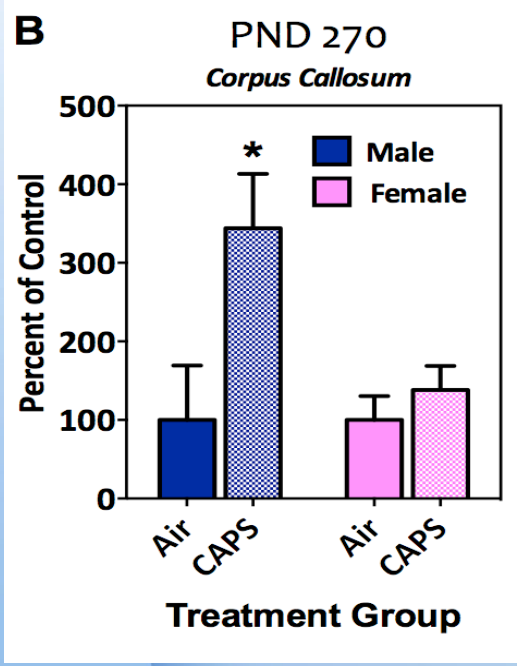


Percent of corpus callosum area myelin basic protein (MBP) staining in males at PND 14 quantified using Image Pro Plus programmed to contrast density of MBP staining via histogram segmentation.

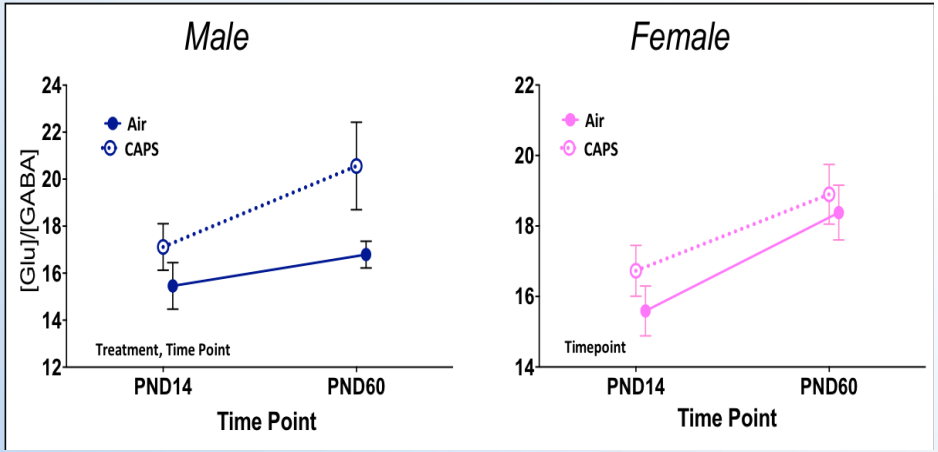
Allen et al., 2015

Male Specific CAPS-Induced Glial Activation and Increased Glutamate

Glial Activation

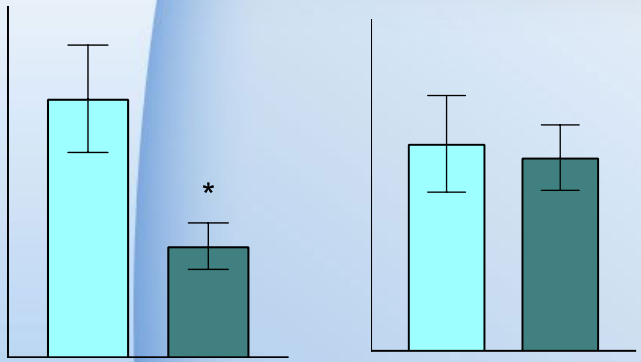


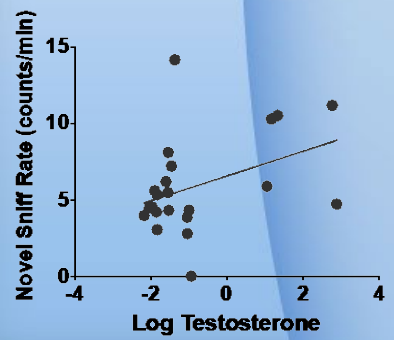
Increased Glutamate

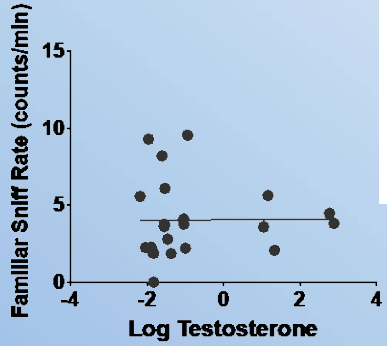


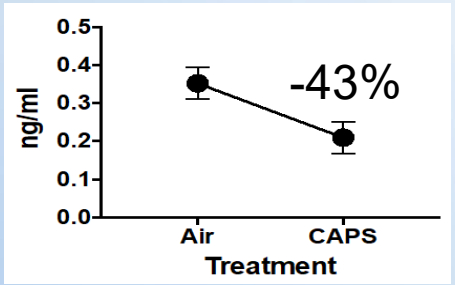
Allen et al., 2015

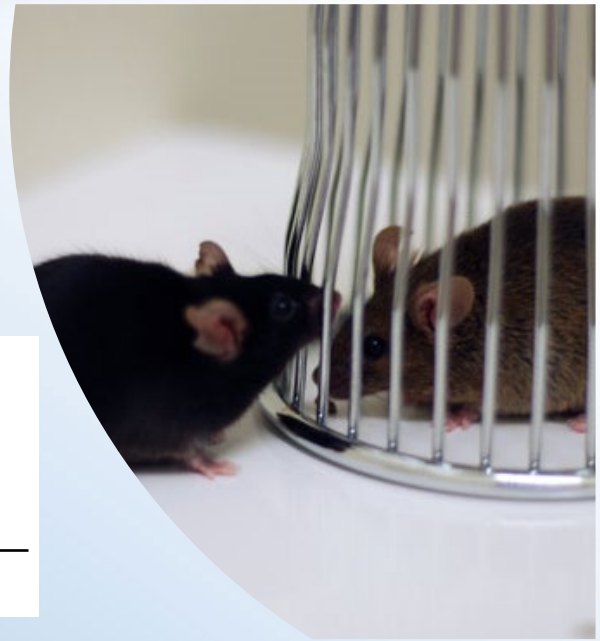
CAPS-Induced Reduced Preference for Novel Conspecific Correlates with Reduced Testosterone





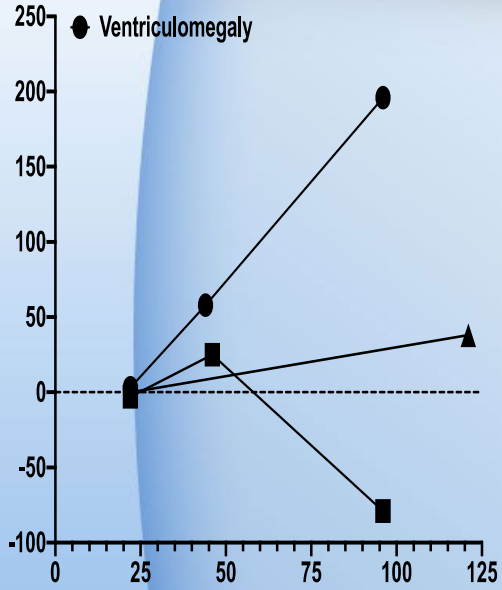


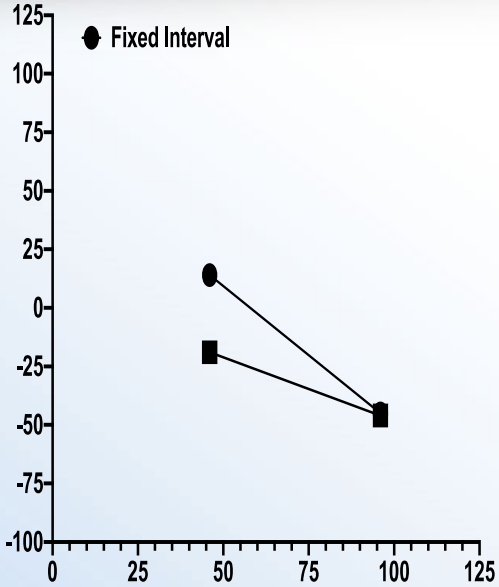




Sobolewski et al., 2018

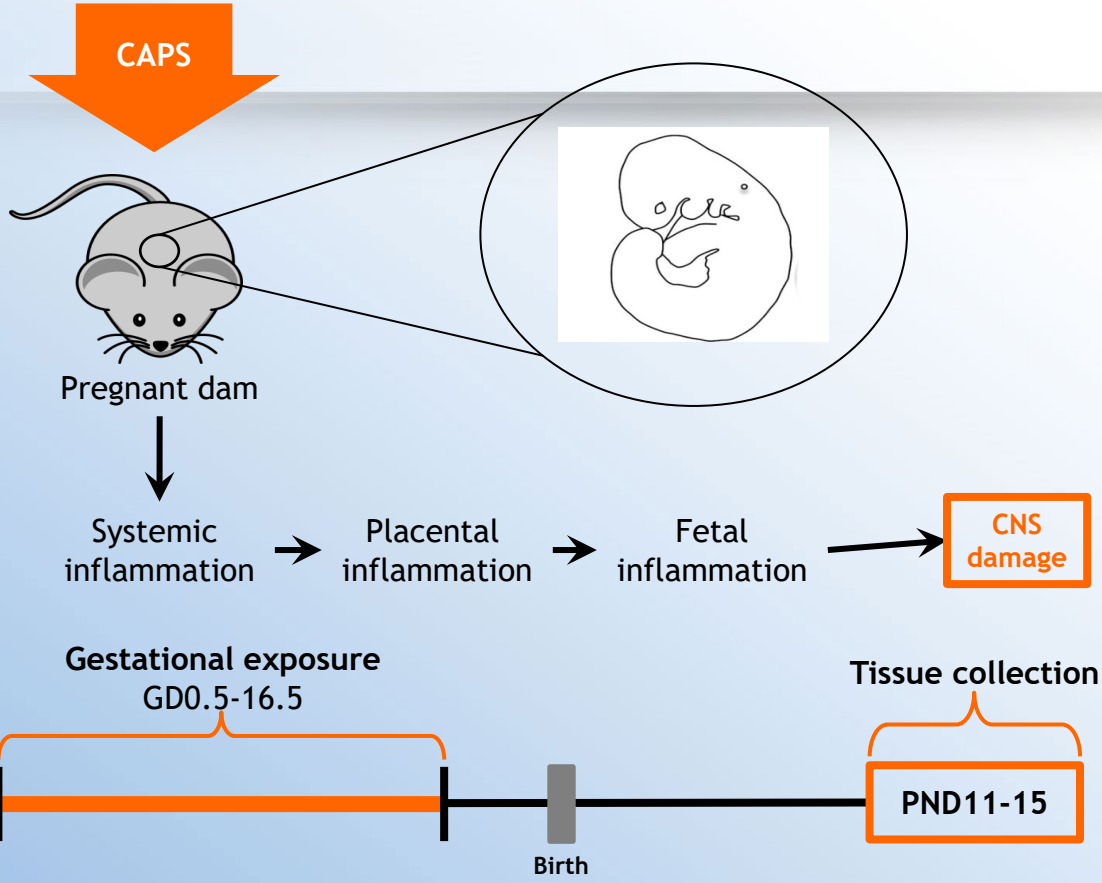
Concentration-Effect Data to Date





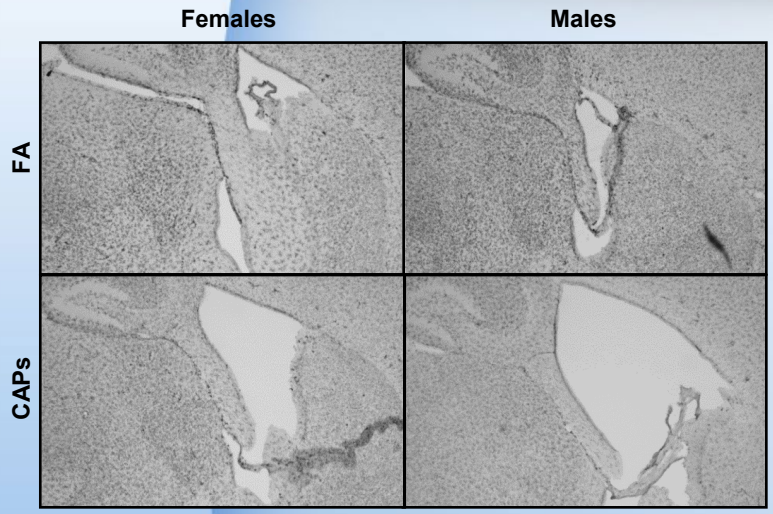
Cory-Slechta et al., in press

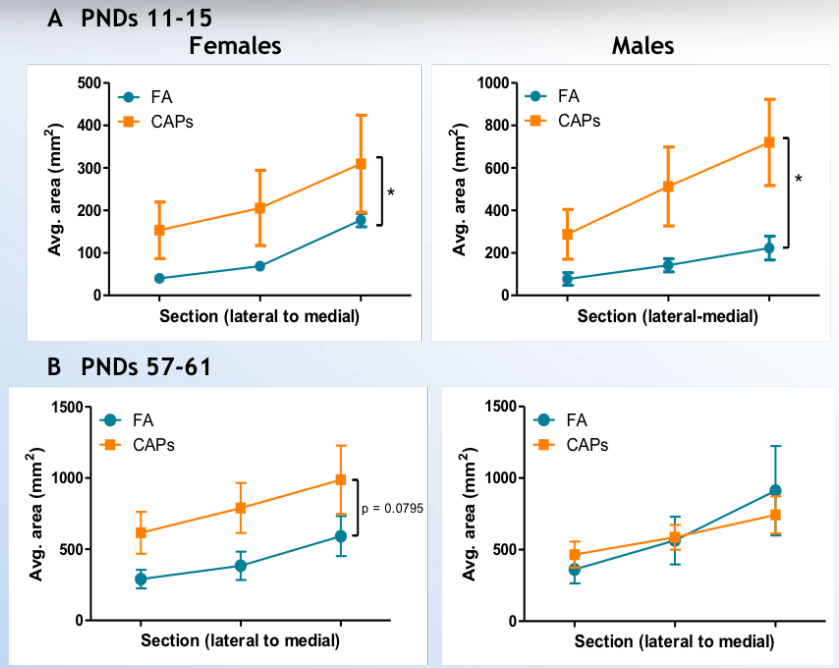
What About Gestational CAPS Exposures?



Klocke et al., 2017

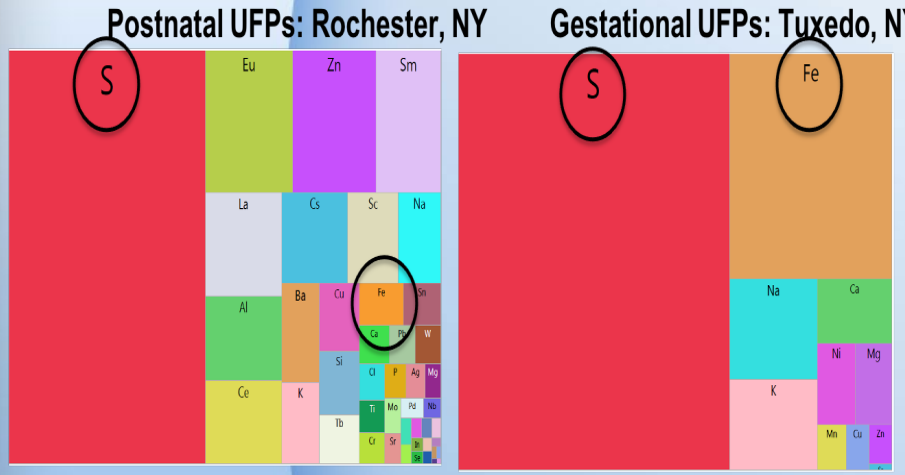
Gestational CAPs Exposure Induces Ventriculomegaly



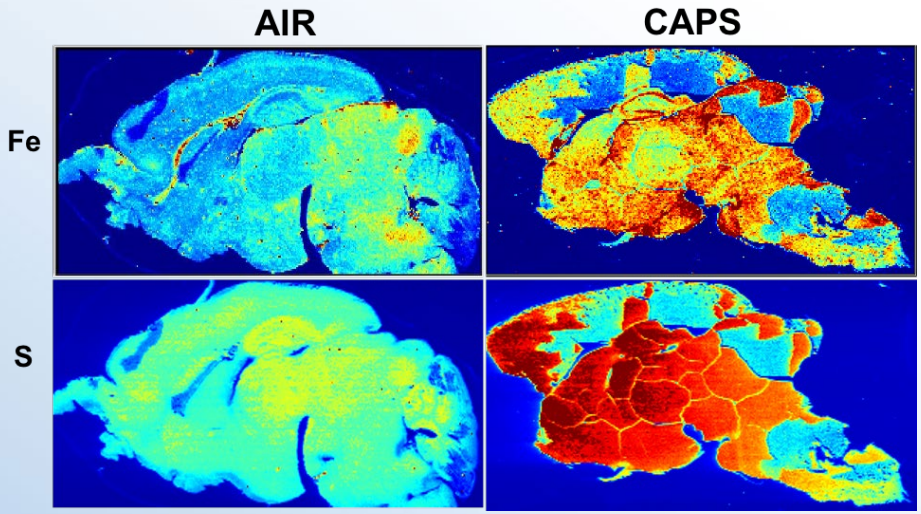


Klocke et al., 2017

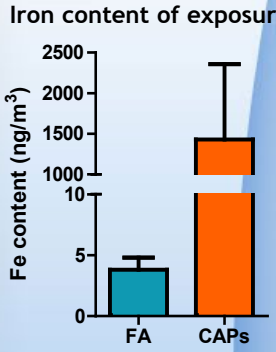
Brain Trace Element Accumulation as a Mechanism for Air PollutionNeurotoxicity

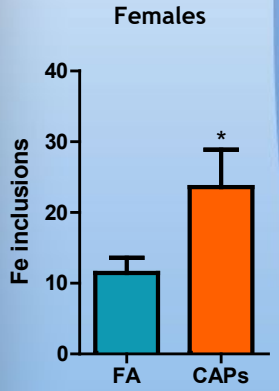


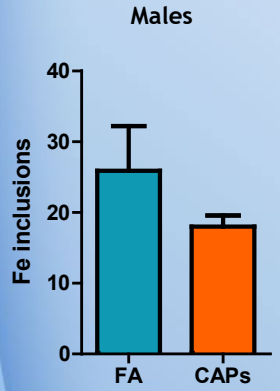
Both Fe and S are essential to brain development, but both are neurotoxic in excess

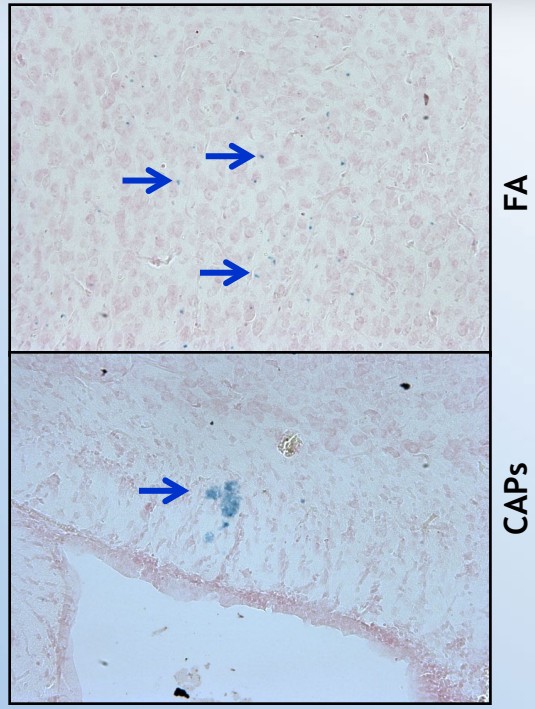


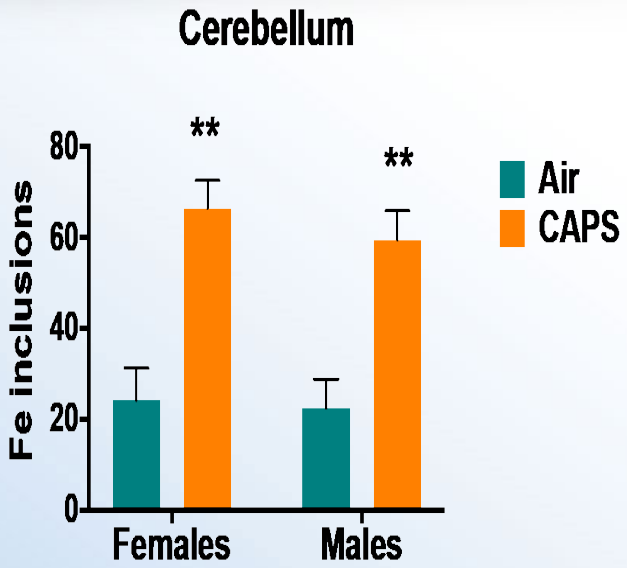
Gestational CAPs Increases Brain Iron Levels





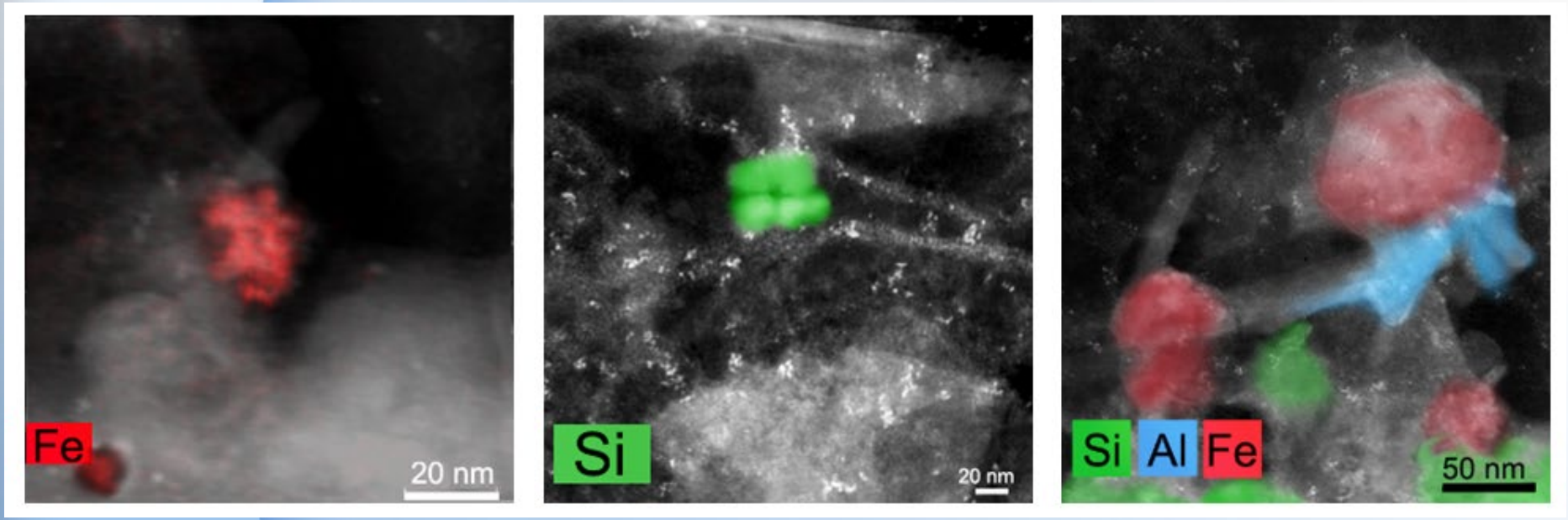






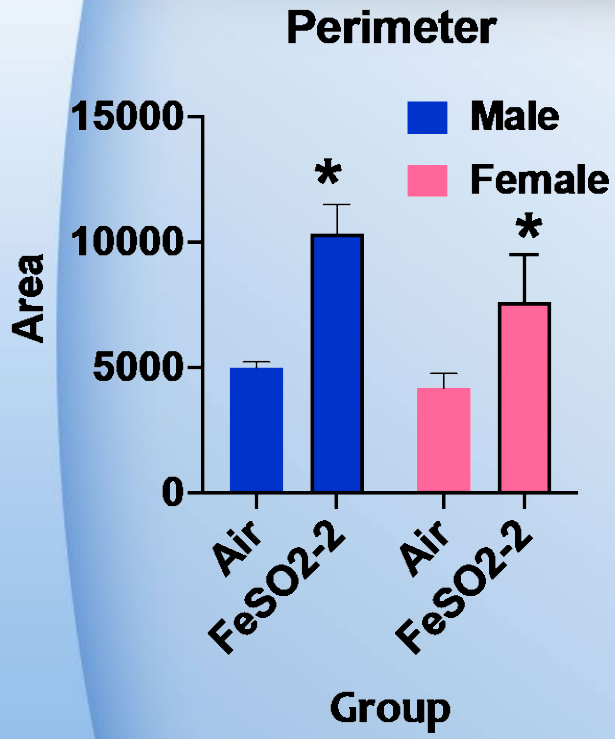
Klocke et al., 2017

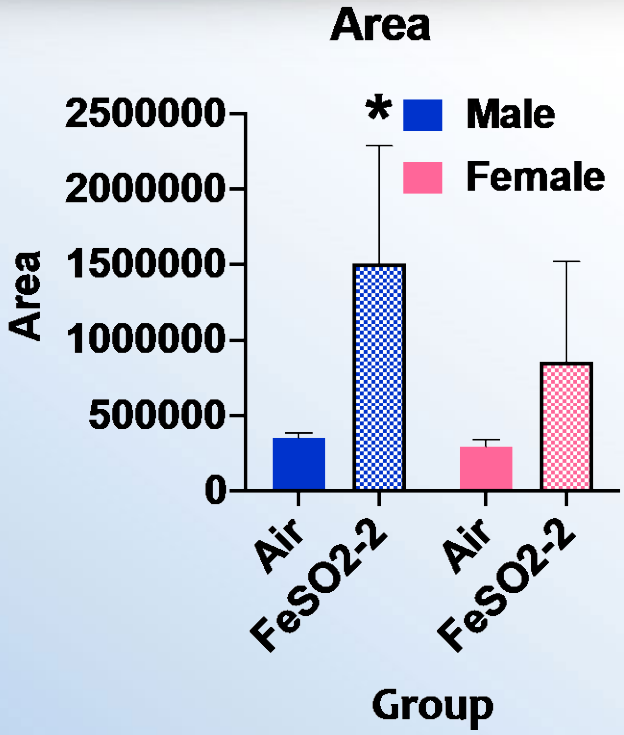
Particle Deposition in Corpus Callosum: What Happens During in vio Bioprocessing of UFPs



Klocke et al., unpublished data

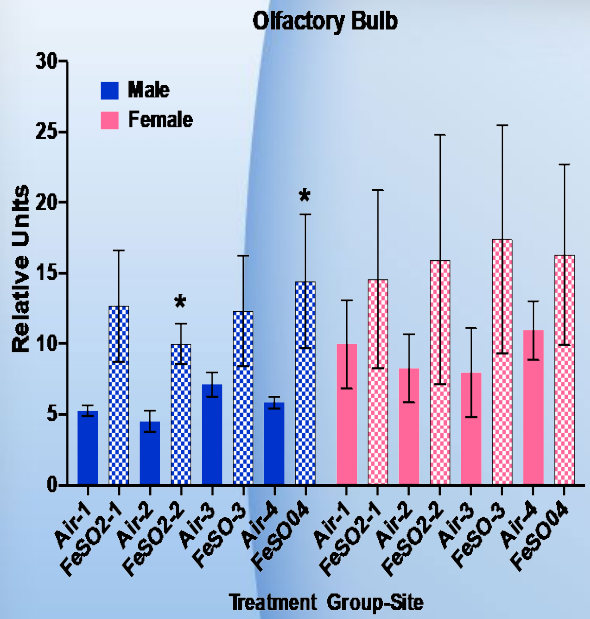
Postnatal Iron and Sulfur Dioxide Inhalation In Mice Increases Ventricle Size

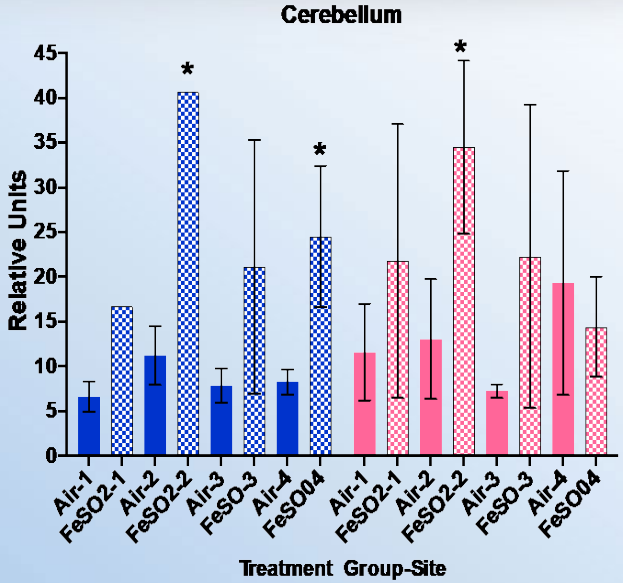


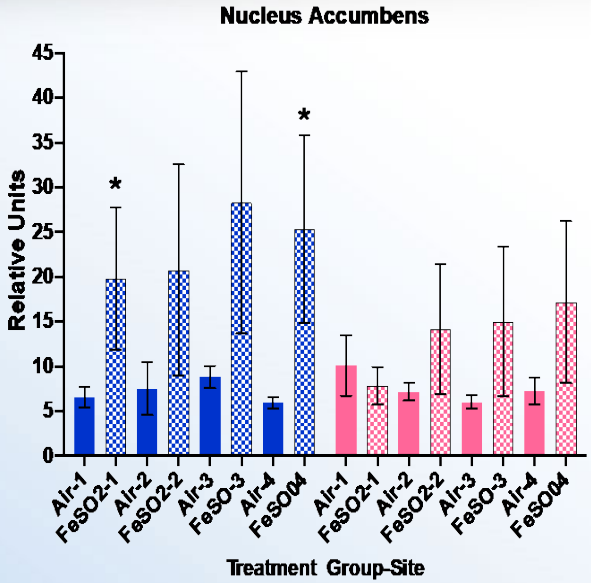


Cory-Slechta et al., unpublished data

And Increases Astroglial Activation







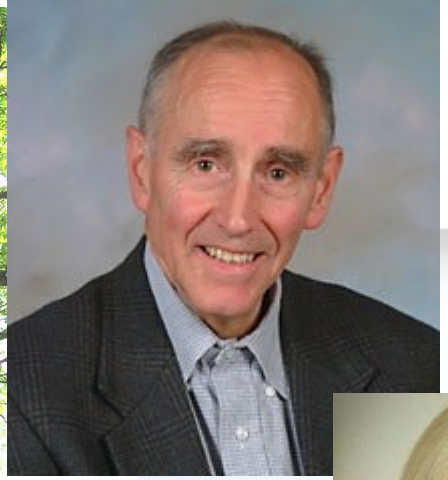
Cory-Slechta et al., unpublished data

While Parallels to Autism are Evident, It is Critical to Recognize that Neurodevelopmental Disorders Have Multiple Overlapping Features

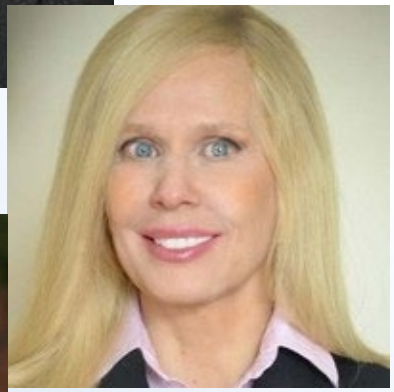
- Male Dominance: ASD, schizophrenia, ADHD
- Common behavioral deficits: ASD, schizophrenia
- Altered dopamine/glutamate function: ASD, schizophrenia, ADHD
- Inflammation: ASD, schizophrenia
- White matter reduction: ASD, ADHD, OCD
- Microglial Activation: ASD, schizophrenia,
- Ventriculomegaly: ASD, 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.



Gunter Oberdorster



Uschi Graham, Univ Kentucky

Brian Jackson, Dartmouth

Funding: NIEHS