

The Long and the Short of It: The Trajectory of the Effects of Developmental Exposures of Mice to Air Pollution



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Growing Evidence for Air Pollution Effects on Brain: Neurodevelopmental Disorders and Neurodegenerative Diseases and Disorders

- Neurodevelopmental Disorders

- Autism Spectrum Disorder
- Attention Deficit Hyperactivity Disorder
- Schizophrenia

- Neurodegenerative Diseases and Disorders

- Alzheimer's Disease
- Parkinson's Disease
- Amyotrophic Lateral Sclerosis
- Multiple Sclerosis

What Underlies the Breadth of Air Pollution Effects on Neurodevelopmental Disorders and Neurodegenerative Diseases and Disorders?

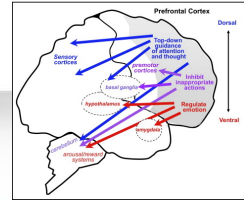
- Commonality of air pollution contaminants across geographical areas/studies
- Impacts features that are shared across neurodevelopmental disorders and neurodegenerative diseases and disorders

Breadth of AP Effects Likely Reflects Shared Features

Characteristic	Neurodevelopmental Disorders	Neurodegenerative Diseases
Ventriculomegaly	ASD, SCZ, ADHD	AD,PD,MS,ALS
Altered Myelination	ASD, SCZ, ADHD	AD,PD,MS,ALS
Interhemispheric Disconnection	ASD, SCZ, ADHD	AD,PD,MS,ALS
Glutamatergic Dysfunction	ASD, SCZ, ADHD	AD,PD,MS,ALS
Neuronal Cell Death	ASD, SCZ	AD,PD,MS,ALS
Inflammation/Microglial Activation	ASD, SCZ, ADHD	AD,PD,MS,ALS
Oxidative Stress	ASD, SCZ, ADHD	AD,PD,MS,ALS
Cognitive/Executive Deficits	ASD, SCZ, ADHD	AD,PD,MS,ALS
Mitochondrial Dysfunction	ASD, SCZ, ADHD	AD,PD,MS,ALS
Social Behavioral Deficits	ASD, SCZ, ADHD	AD,PD,MS,ALS
Impulsivity	ASD, SCZ, ADHD	AD,PD,MS

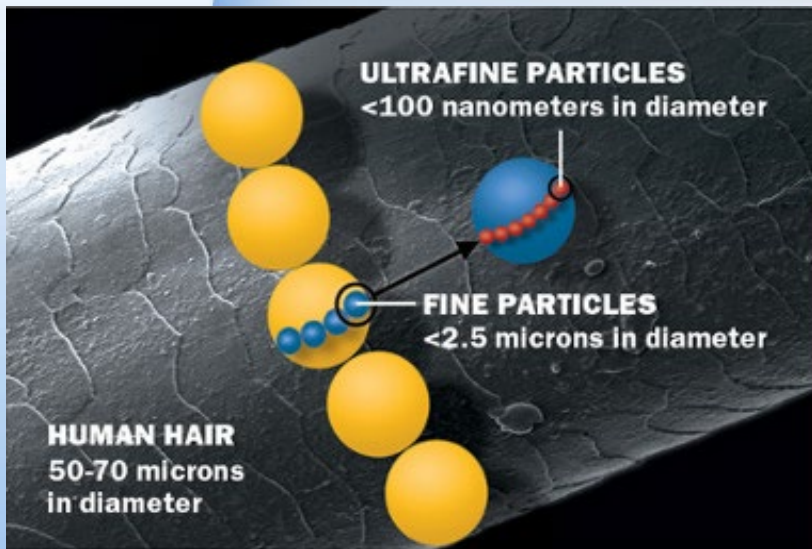
ASD=autism spectrum disorder, SCZ=schizophrenia, ADHD=attention deficit hyperactivity disorder
 AD=Alzheimer's Disease, PD=Parkinson's disease, MS=multiple sclerosis; ALS=amyotrophic lateral sclerosis

Dynamics of Developmental Air Pollution Exposures Impact on Brain?

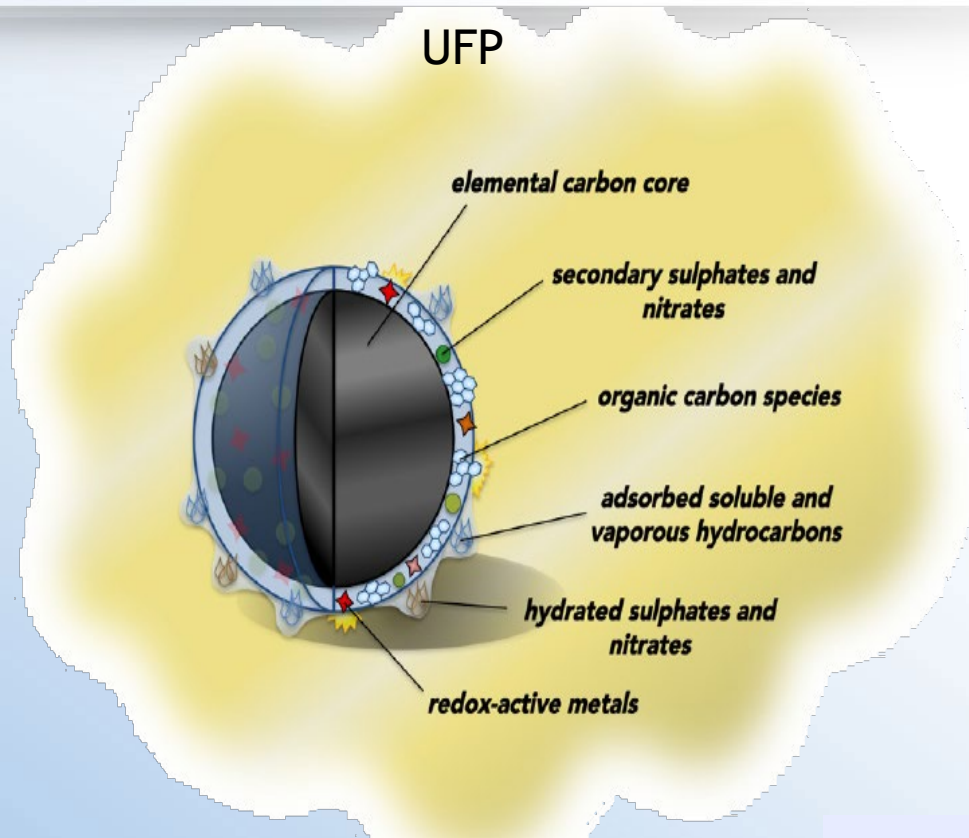


- What is the trajectory of air pollution impacts on brain frontostriatal neurotransmitter systems after developmental exposures?
- Does air pollution cause developmental reprogramming of these systems?
- Do alterations at different physiological stages (e.g., adolescence, aging) trigger recurring adverse effects?
- Does behavioral experience modify the consequences?

Ultrafine Particles (UFPs): Air Pollution's Most Reactive Component

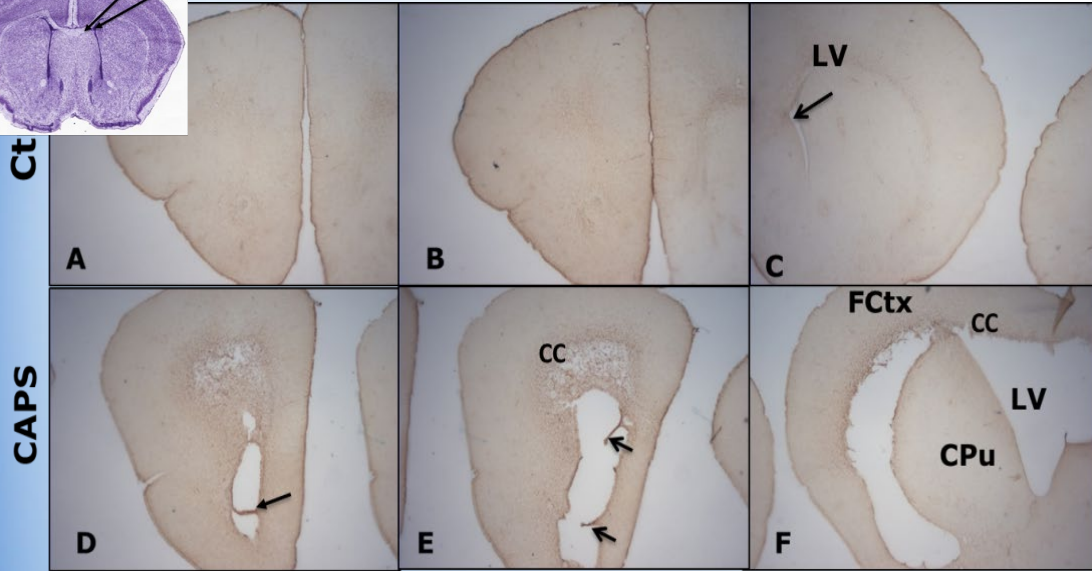
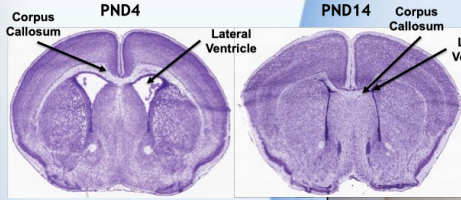


U.S. EPA regulates fine ($PM_{2.5}$, ≤ 2.5 μm) and coarse (PM_{10} , ≤ 10 μm) particles, but not UFPs

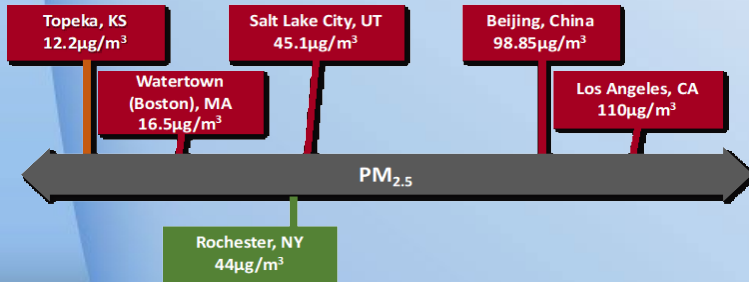
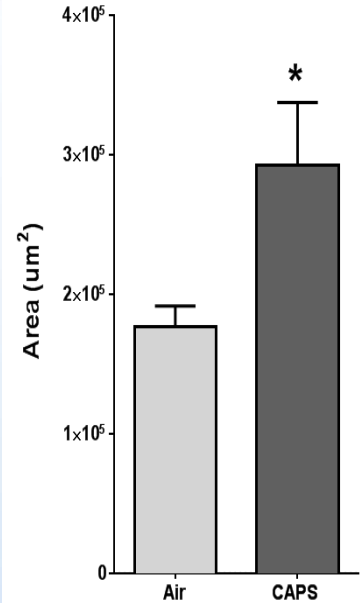


Biological Model of Third Trimester Brain Development: Postnatal Concentrated Ambient Ultrafine Particles (CAPs) Exposure in Mice

Persistent CAPS-Induced Male-Biased Ventriculomegaly



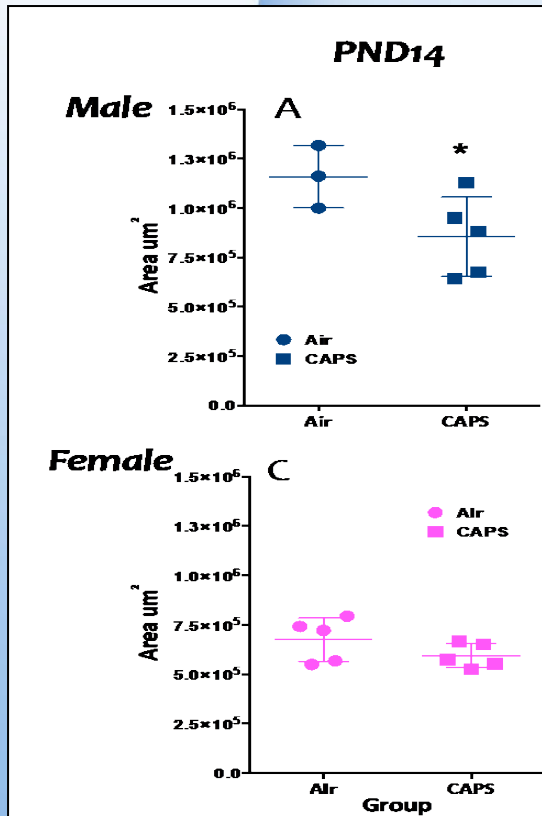
Males PND270



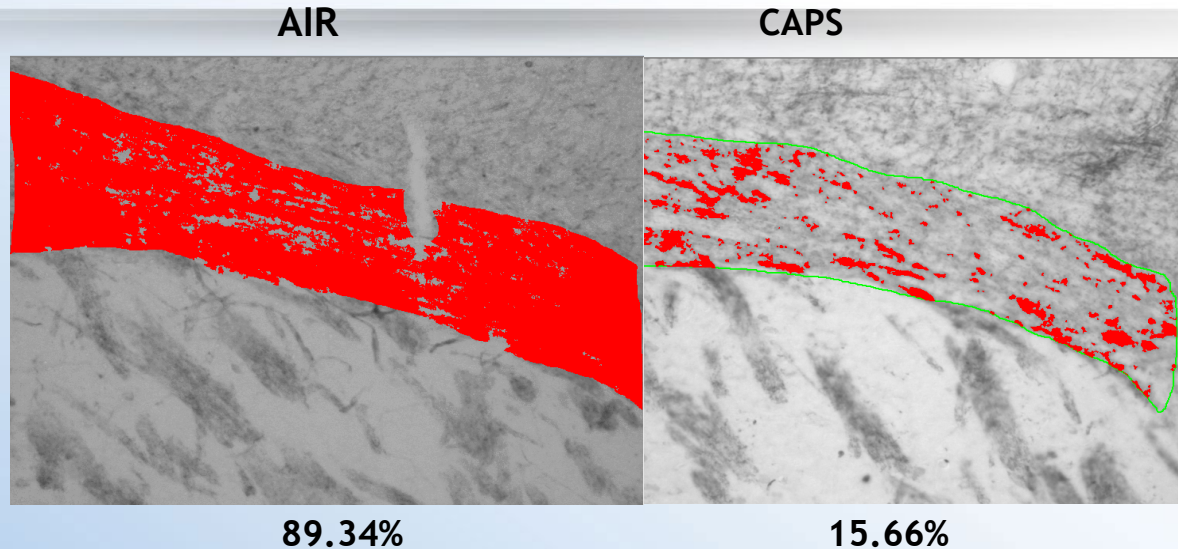
Seen even at 44 ug/m³

Male-Specific CAPS Reductions in Corpus Callosum Area and Myelination

Corpus callosum area

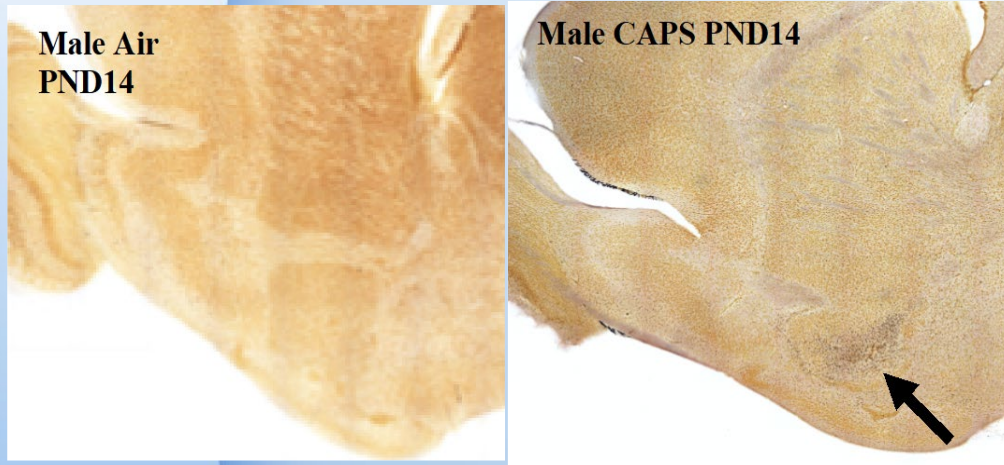


Corpus callosum Myelination

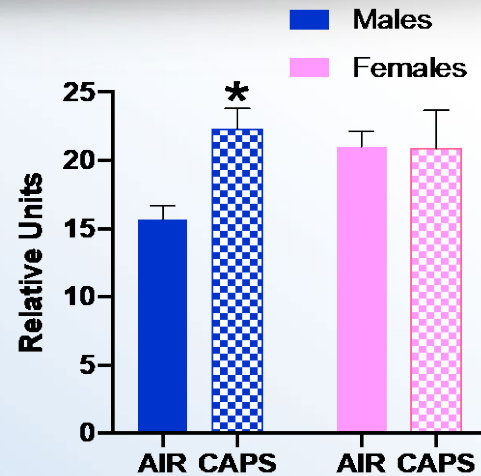


Percent of corpus callosum area myelin basic protein (MBP) staining in males at PND 14 quantified using Image Pro Plus programmed to contrast density of MBP staining via histogram segmentation.

Male-Specific Cell Death and Oxidative Stress Follow Ambient UFP Exposure

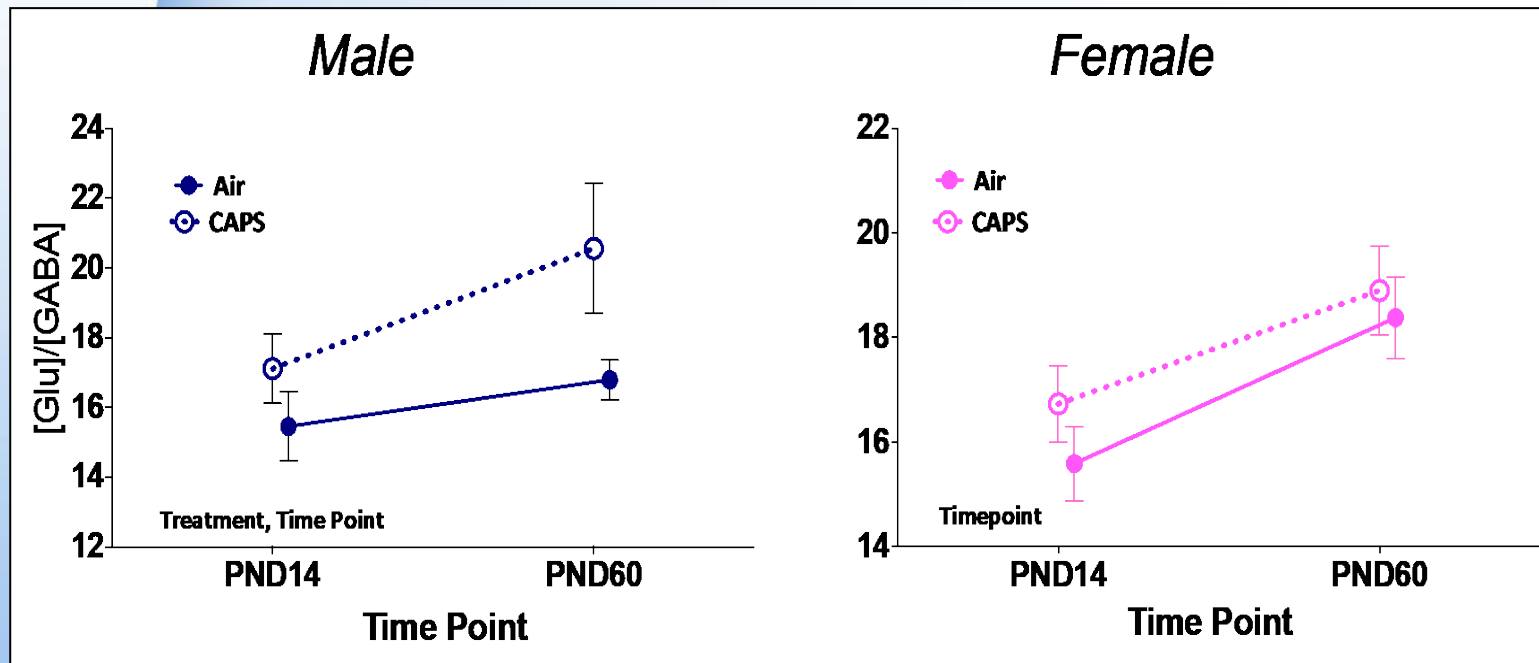


Male-specific degeneration of neurons in nucleus accumbens (arrow) at PND14 following postnatal exposure to UFPs; caspase staining was negative. Cory-Slechta et al., unpublished.



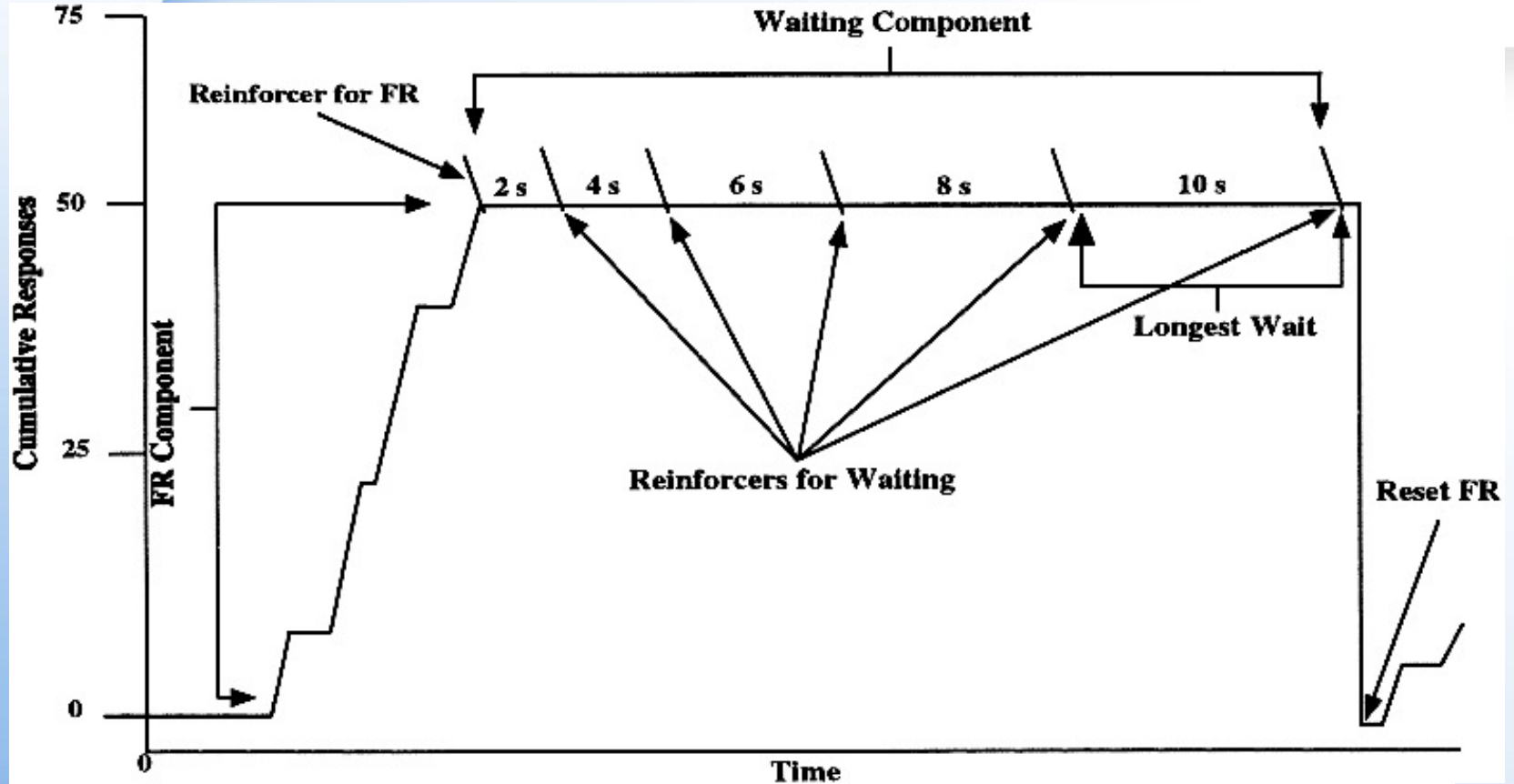
Serum oxidized glutathione levels following postnatal Air or CAPS; unpublished

Male-Specific Hyperglutamate and Excitatory/Inhibitory Imbalance

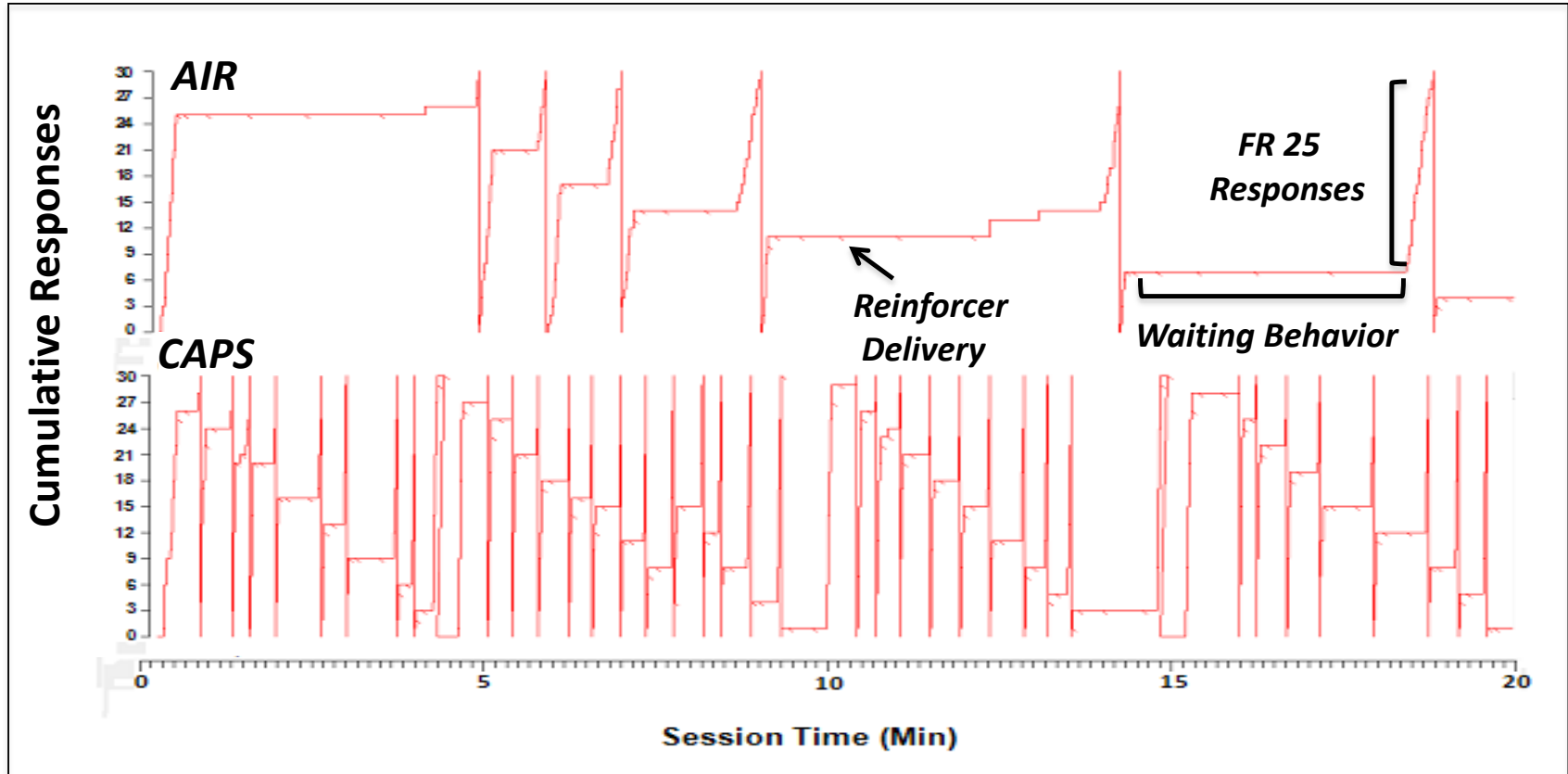


Glutamate/GABA ratios based on levels of frontal cortex extracellular glutamate, glutamine and GABA were significantly elevated by postnatal CAPS in males, but not females, n=9-12/group.

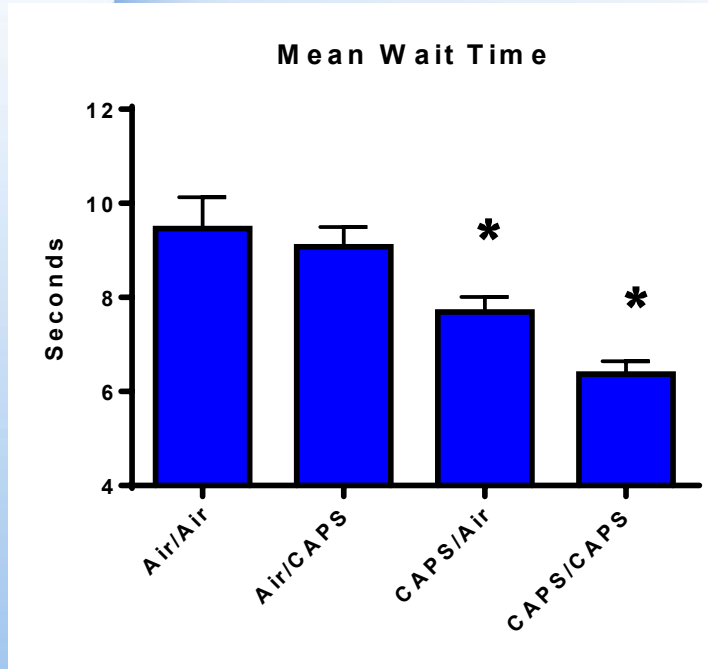
Fixed-Ratio Waiting-for-Reward Paradigm and Impulsive-Like Behavior



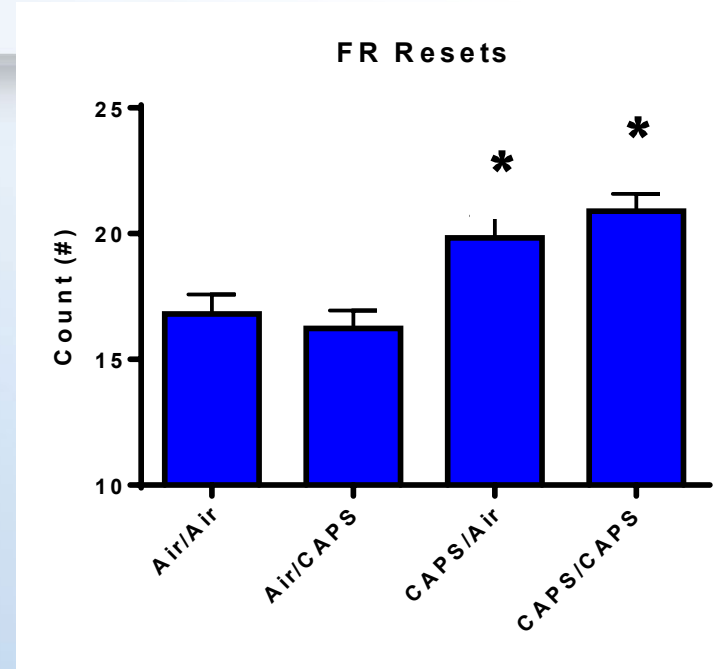
Postnatal CAPS Males Are Impulsive



Postnatal CAPS Males Are Impulsive



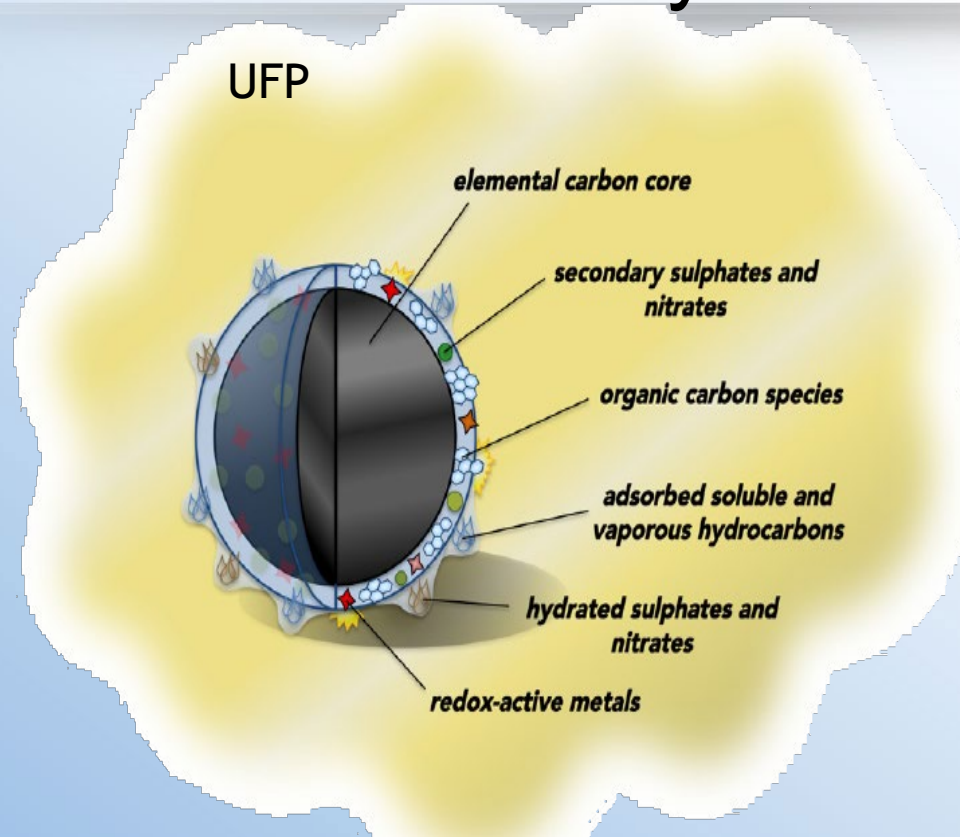
Less Waiting



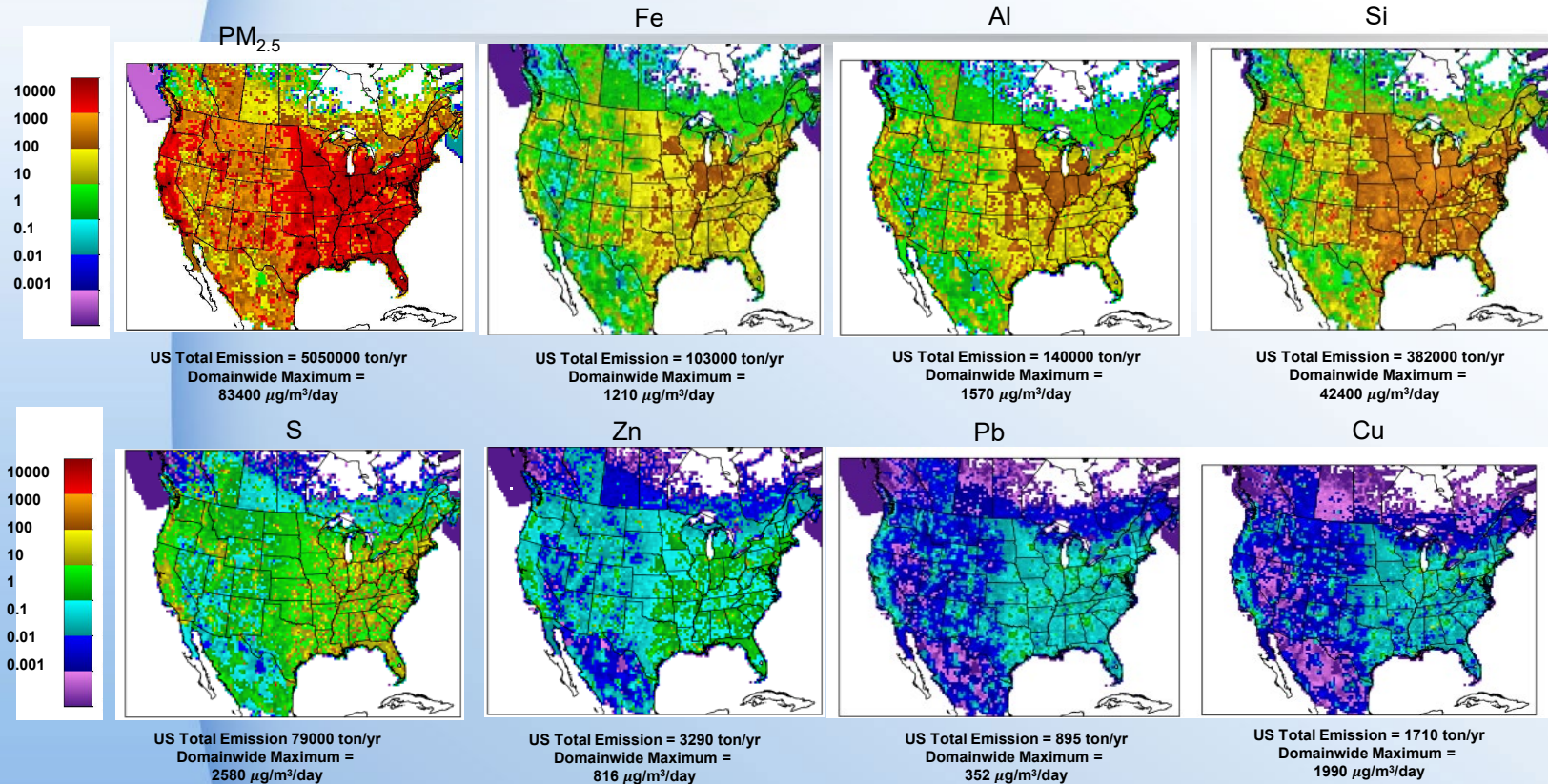
More Starting Over

Not yet measured in females

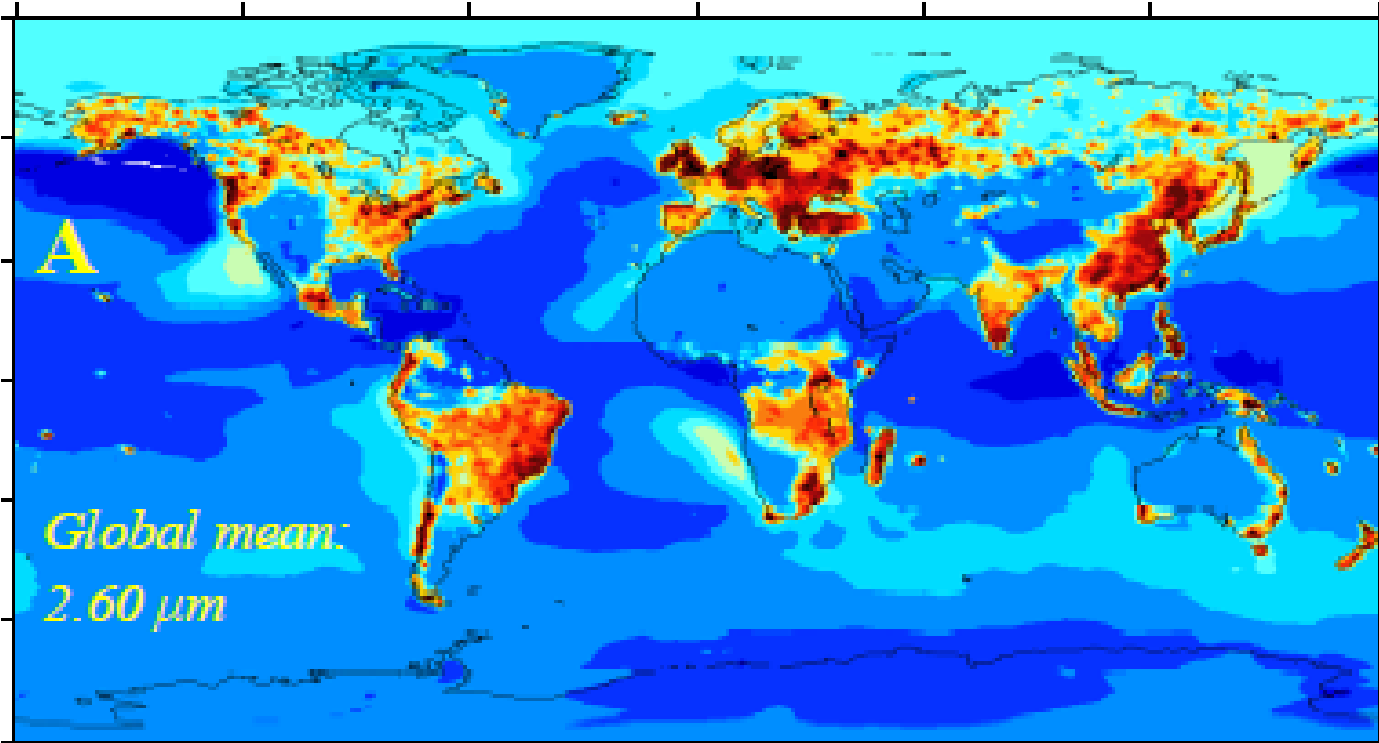
What Components of Air Pollution Cause Neurotoxicity?



Metals as Toxic Components of Air Pollution

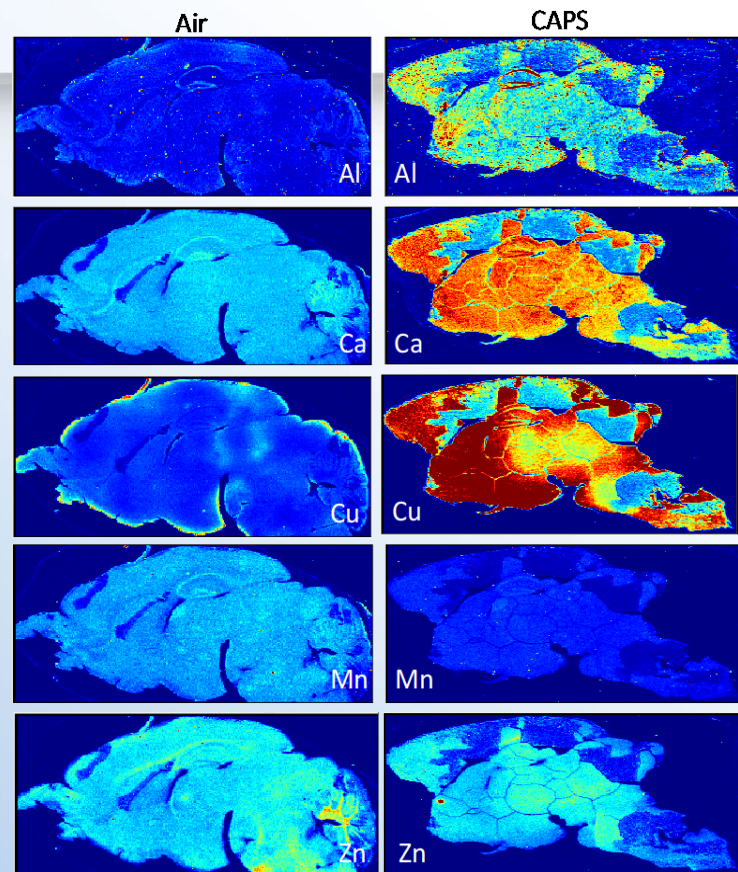
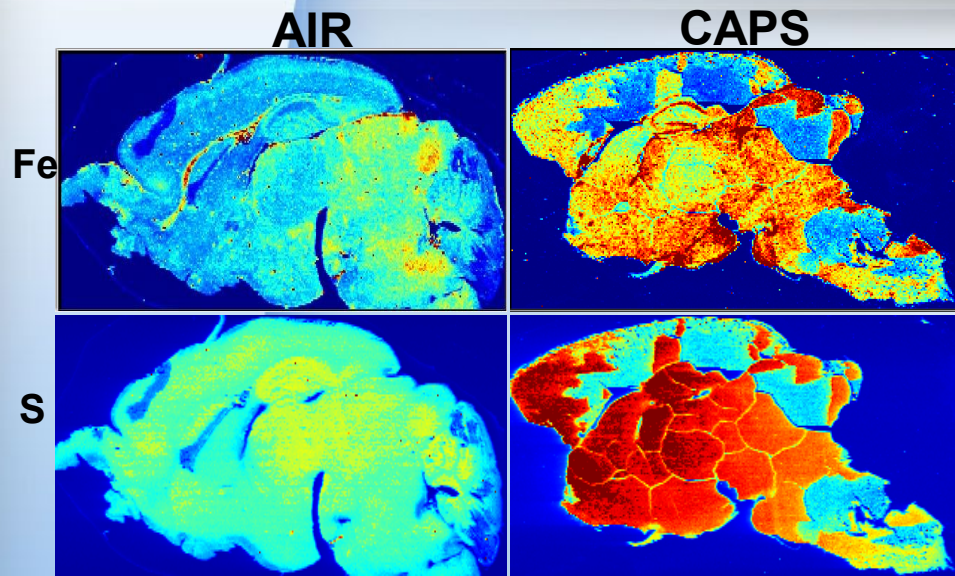


Fe: Not Just in the United States

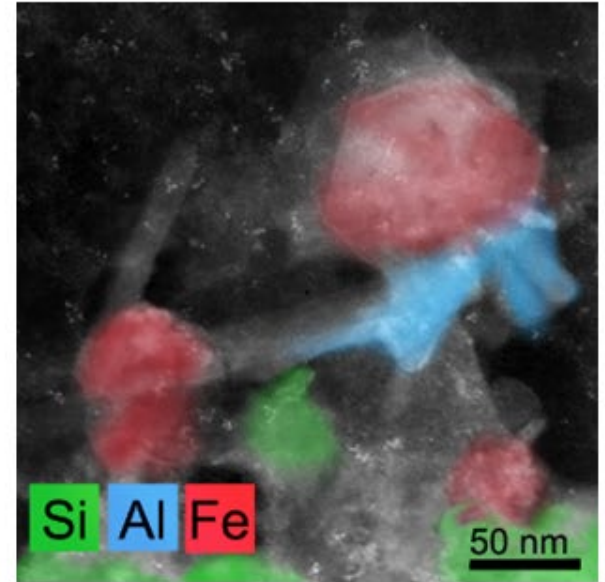
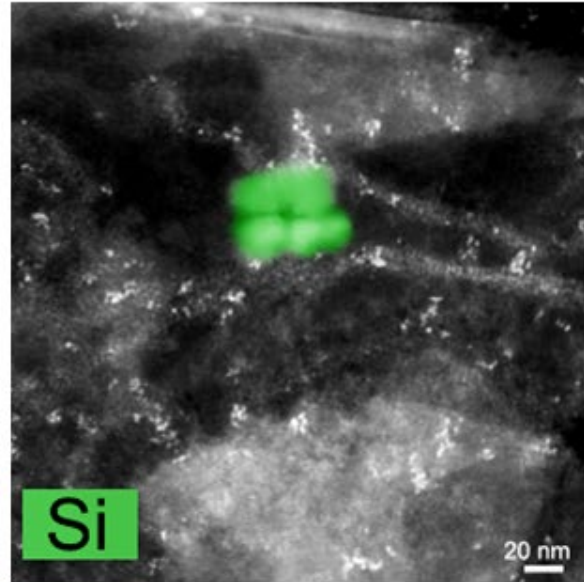
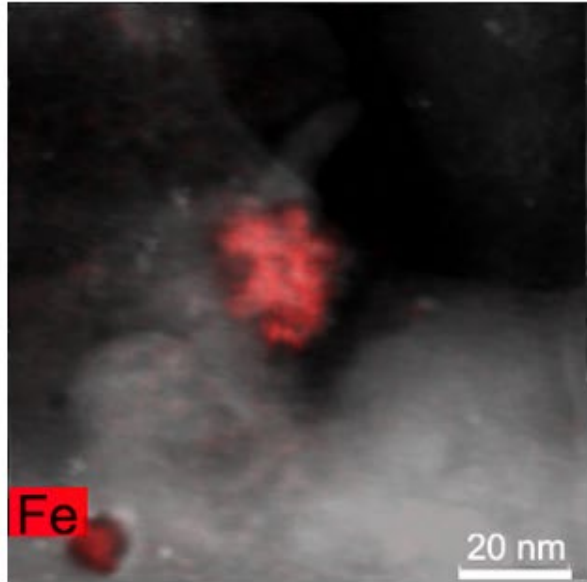


Excessive Fe and S Following Postnatal CAPS Exposures

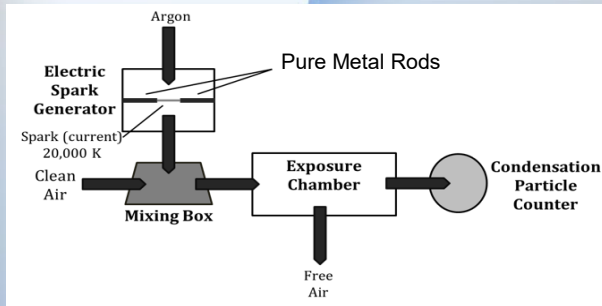
Evidence of Brain Metal Dyshomeostasis



Particle Deposition in Corpus Callosum: Trace Metal Contaminants



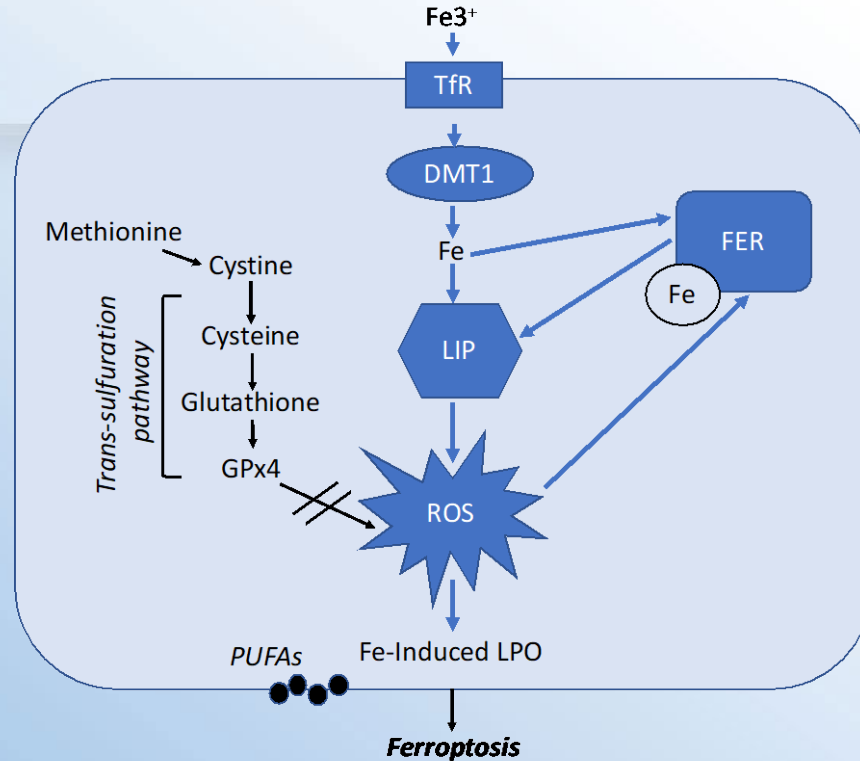
Developmental Exposures to Fe Ultrafine Particles Alone or with SO₂



Why Sulfur dioxide? SO₂ increased the uptake of iron and affected the distribution of intracellular iron among different cell types. It is possible that increased iron uptake is due to either injury or to changes in particle solubility produced by the SO₂. Watson and Brain, 1980.

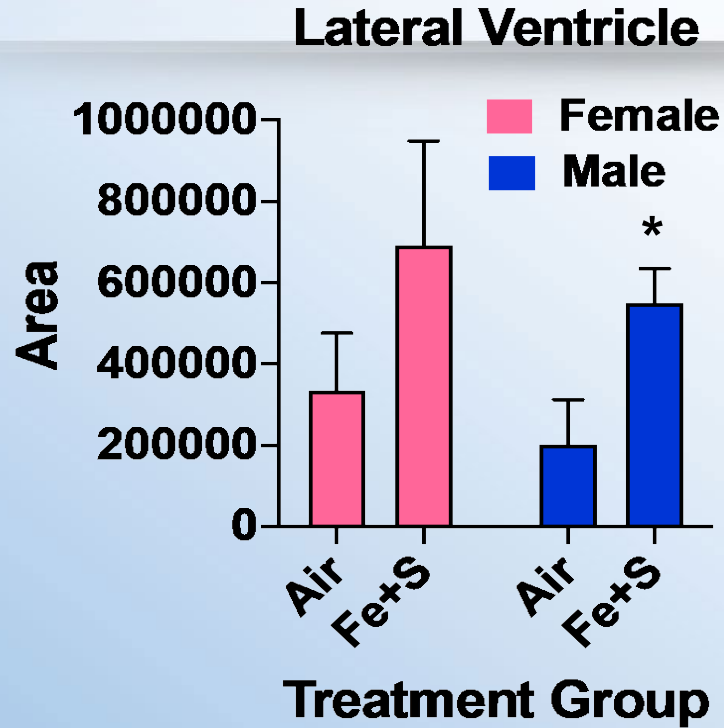
Eckard et al., 2023
Sobolewski et al., 2022

Potential Ferroptotic Mechanism of UFP?

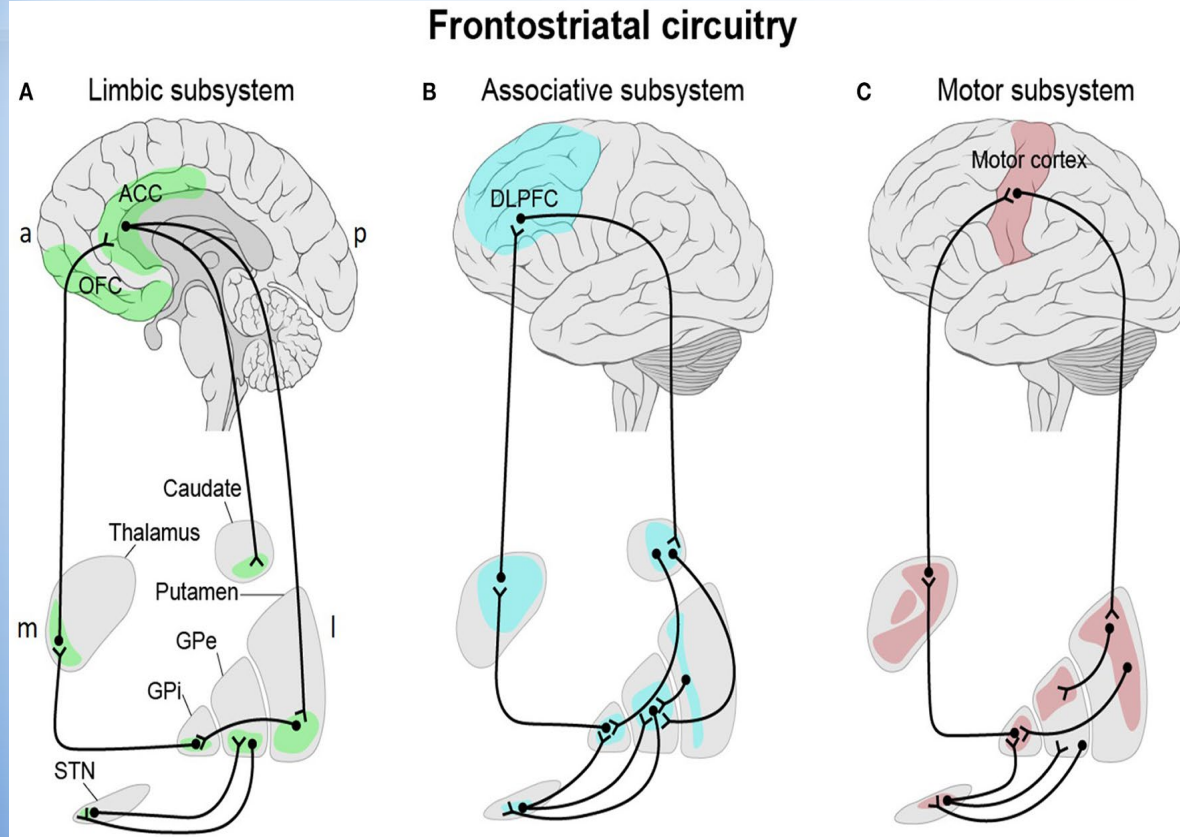


An Fe-dependent form of cell death, characterized by the accumulation of iron and lipid peroxidation of plasma membranes as well as altered iron homeostasis. The importance of sulfur to this mechanism is through the fact that glutathione levels, a product of the trans-sulfuration pathway, negatively regulate ferroptosis. Thus, low levels of glutathione would likewise contribute to ferroptosis

FeSO₂ Results in Ventriculomegaly



Postnatal Fe Males Also Showed Impulsivity: Behavior Mediated by Fronto-Striatal Neurotransmitter Circuits



FeSO₂ Exposure Blocks Increases in Brain Frontostriatal Neurotransmitters Required for Behavioral Function in Males

Frontal Cortex

Striatum

Females

Males

Behavioral Experience Leads to Serotonergic and Dopaminergic Overshoot after Fe Exposure in Both Sexes

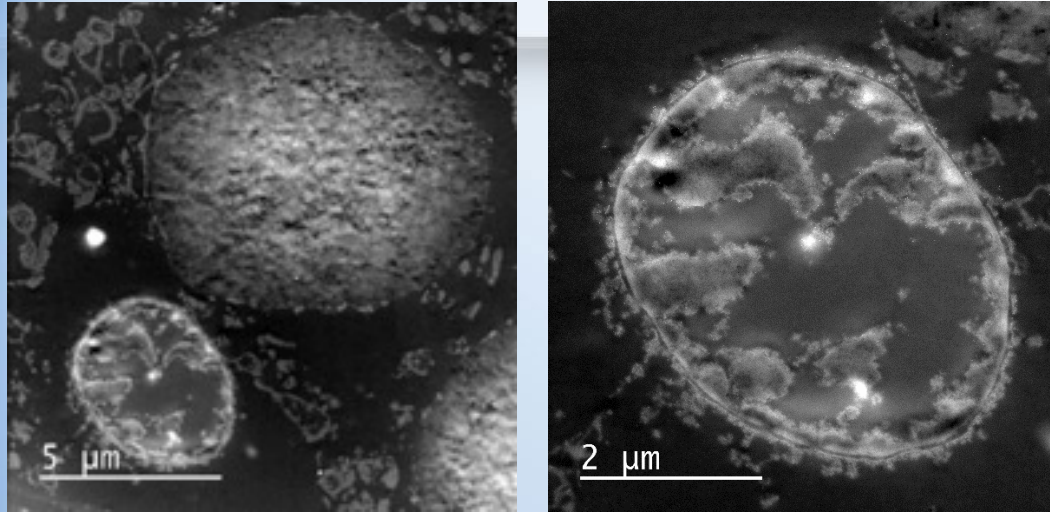
Frontal Cortex

Striatum

Females

Males

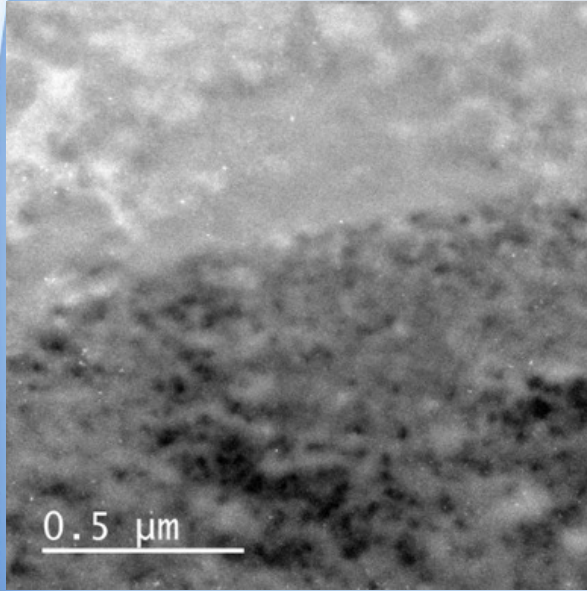
Corpora Amylacea (CA) and Brain Iron Dyshomeostasis



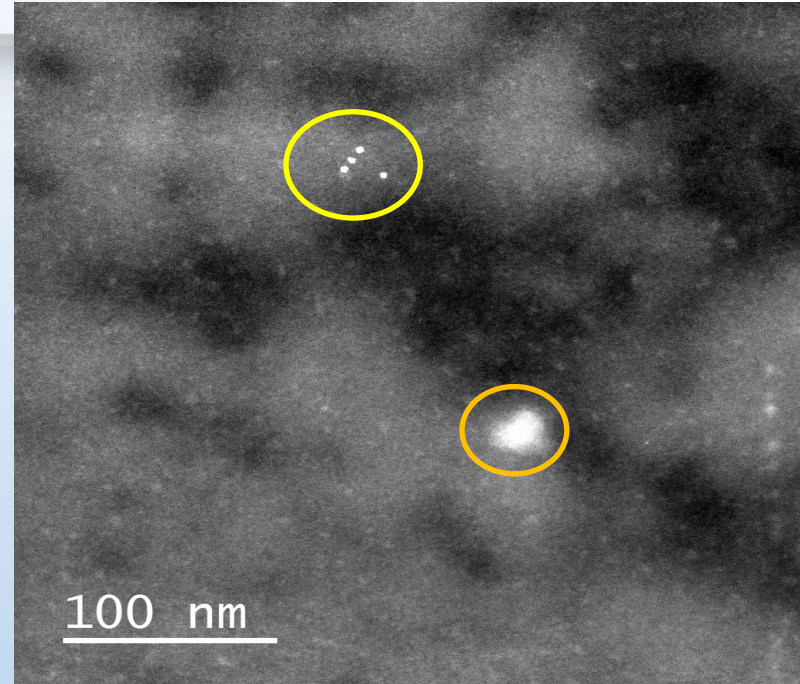
Side-by-side: Intact and Disintegrating Wasteosomes in
Olfactory Bulb with Iron Load

Corpora amylacea are hyaline glycoprotein rich aggregates observed with increasing frequency in aging human brain, particularly in ventricular and subventricular regions. Initially discovered by Purkinje in 1837, these bodies lack enclosing membranes and thought to be of neuronal or astrocytic debris.

Exogenous and Endogeneous Fe Accumulate in CA in Olfactory Bulb Following Fe Inhalation

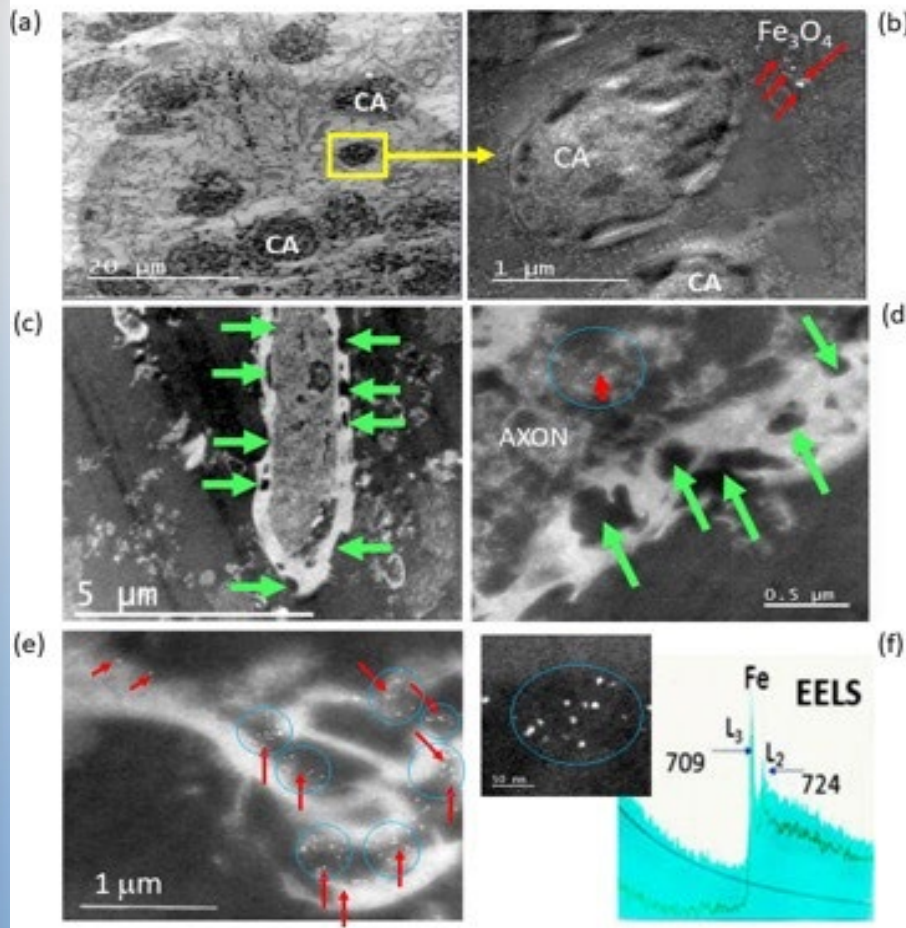


STEM image showing interface of wasteosome and OB tissue



Magnification with ferritin (yellow circle) and Fe-NPs (orange circle) inside the wasteosome.

Corpora Amylacea in Human Post-Mortem Brain



Corpora amylacea in human olfactory bulb with colocalization of magnetite (exogenous Fe) and ferritin (endogenous Fe) and presence near neurons with demyelination

Do CAs Play A Role in Ionic Balance in Brain?

CA Accumulation as a Mechanism of Demyelination?

In Summary

- ◆ Exposures to real-time, real world, human relevant levels of ultrafine particulate matter during periods of brain development can produce lasting adverse effects shared by neurodevelopmental disorders and neurodegenerative diseases and disorders
 - ◆ Among these are demyelination, ventriculomegaly, excitotoxicity, altered neurotransmitter connections, brain metal imbalance
- ◆ Corpora amylacea, first described in 1837, may play a role in brain metal (ionic) balance, and accumulation of CAs play a role in the vacuolation form of demyelination
- ◆ Studies of the components of air pollution that may be responsible for these effects are critical to refining animal models, more focused mechanistic assessments and potential intervention strategies, as well as to public health protection and regulations
 - ◆ The role of metals and trace elements, e.g., Fe and Cu, both frequent in AP and often in high concentrations, are of particular interest, especially as reduced glutathione and altered redox metabolism are increasingly considered biomarkers of ASD. Studies of combinations of inhaled metals are also needed

It Really Does Take a Village



Jithin
George

Margaux
Maston

Kate
Morton

Deborah
Cory-Slechts

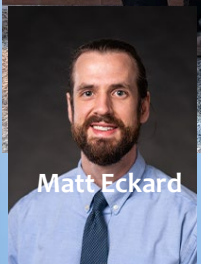
Marissa
Sobolewski

David
Ndambuki

Travis
Covitz

Erin
Murray

Elena
Marvin



Matt Eckard

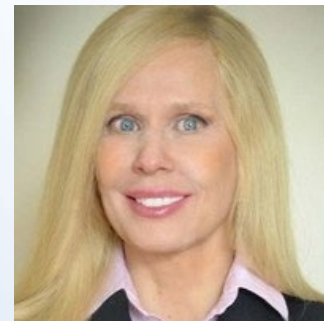


Dave Chalupa

Funding: NIEHS



Gunter
Oberdorster



Uschi Graham, Univ Kentucky



Brian Jackson, Dartmouth