Effects of Lead on Brain Development and Function and Implications for Academic Achievement

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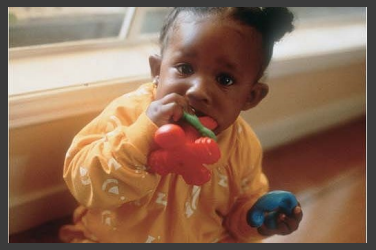
Lead Poisoning: A Global Problem
Sponsored by The Lead Poisoning Prevention Program and
Children's Hospital at Montefiore,
October 13, 2017

www.ocregister.com/investigation/lead/



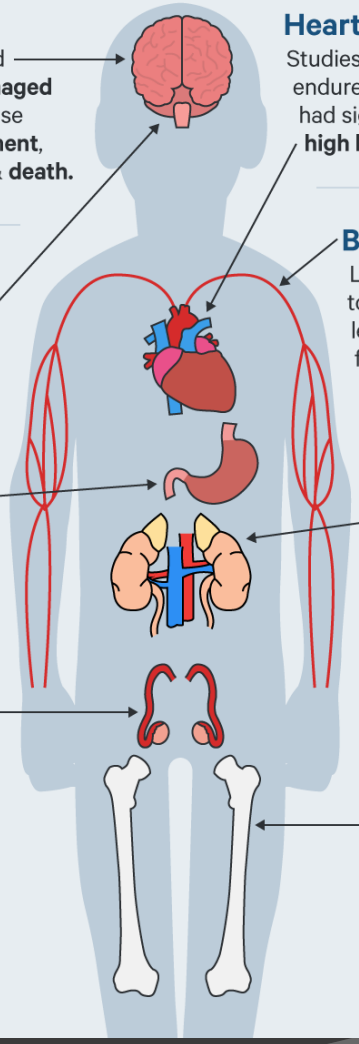
How **lead** affects childrens' health

Brain
Any exposure is linked to lowered **IQ**, **ADHD**, **hearing loss**, and **damaged nerves**. Acute exposures can cause convulsions, **loss of body movement**, **coma**, **stupor**, **hyperirritability,** & **death.**

Hormones
Lead disrupts levels of vitamin D, which can **impair cell growth**, maturation, and tooth and bone development.

Stomach
Severe lead exposure can create intense **abdominal pain** and **cramping**.

Reproductive System
A moderate exposure can not only **lower sperm count**, but also **damage them**. Chronic exposures can diminish the concentration, total count, and motility of sperm, though it's unclear how long these effects last after the exposure ends.



Heart
Studies suggest that adults who endured lead poisoning as children had significantly higher risks of **high blood pressure** 50 years later.

Blood
Lead inhibits the body's ability to make hemoglobin, which can lead to anemia. This reduces oxygen flow to organs, causing **fatigue**, **lightheadedness**, **rapid heartbeat**, **dizziness,** & **shortness of breath.**

Kidneys
Chronic exposures can cause chronic inflammation, which can lead to **kidney failure**, **bloody urine**, **fever**, **nausea**, **vomiting**, **drowsiness**, **coma**, **weight gain**, **confusion**, **rash**, and **urinary changes**.

Bones
Lead may impair development and the health of bones, which can **slow growth in children**.

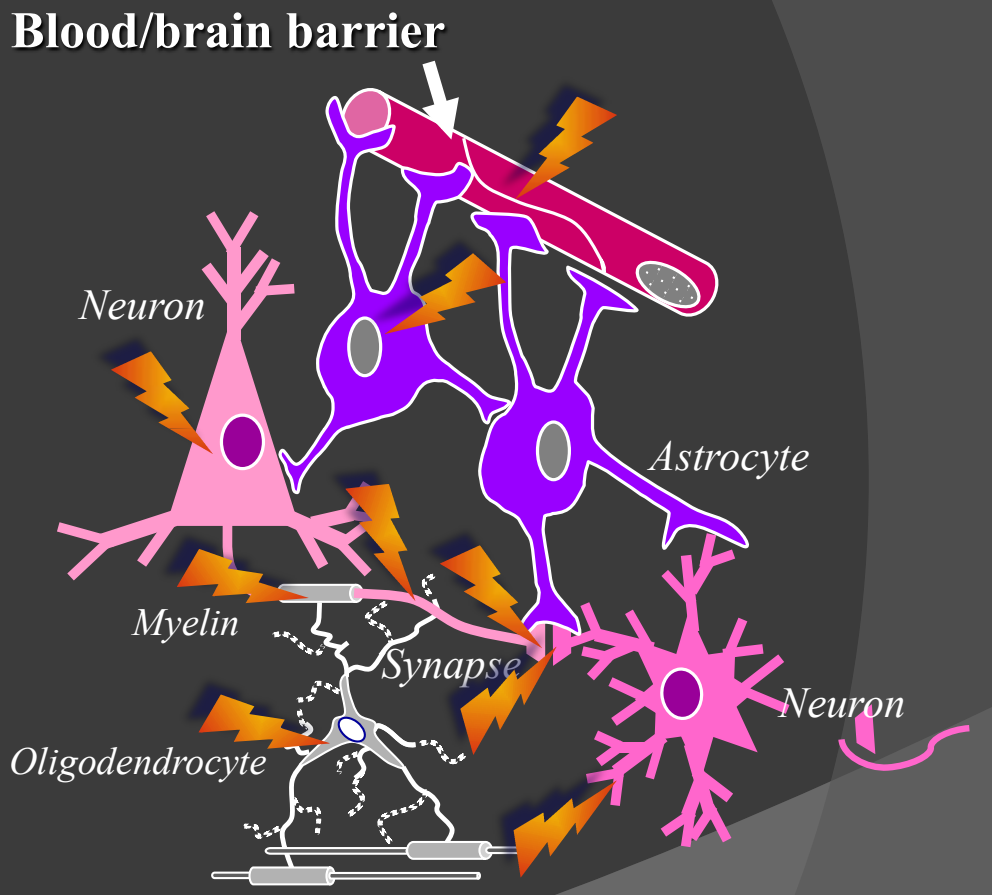
SOURCES: Centers for Disease Control; World Health Organization

TECH INSIDER

Developmental Exposure to Lead Has Far-Reaching Effects on the Nervous System

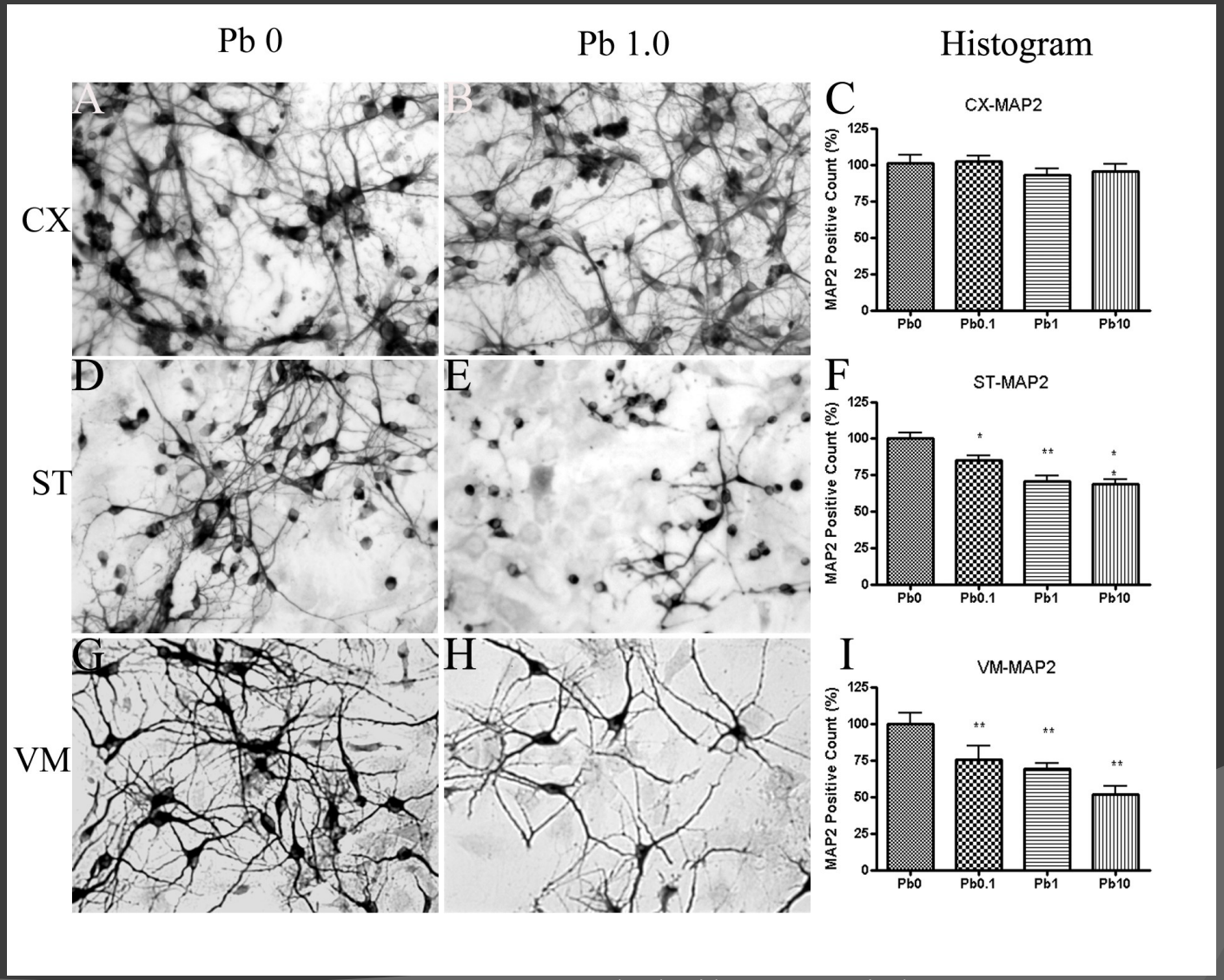
Developmental exposure to even low levels of lead adversely affects the structure and function of the brain.

It interferes with gene transcription, protein expression, and numerous molecular and cellular processes affecting the growth and development of the brain as well as the transmission of information in the brain.



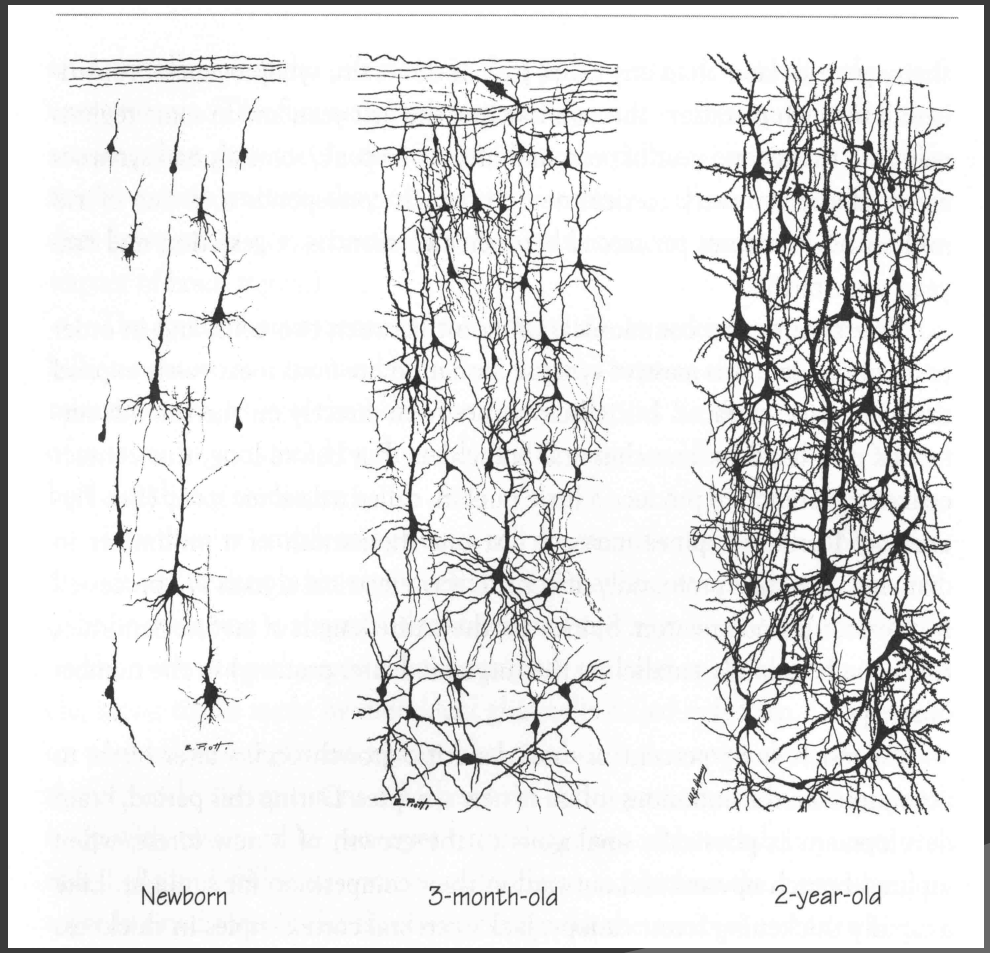
Adapted from E. Tiffany-Castiglioni

Lead Inhibits the Ability of Neural Precursor Cells to Turn into Neurons



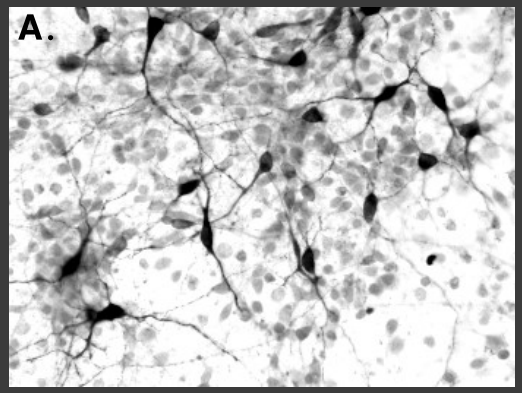
From: Huang and Schneider, NeuroToxicology, 2004, 25: 1001-1012

The Growth of Neurons and the Increase in Complexity of Neural Connections is Critical to the Normal Maturation of the Brain, Leading to Normal Cognitive Development

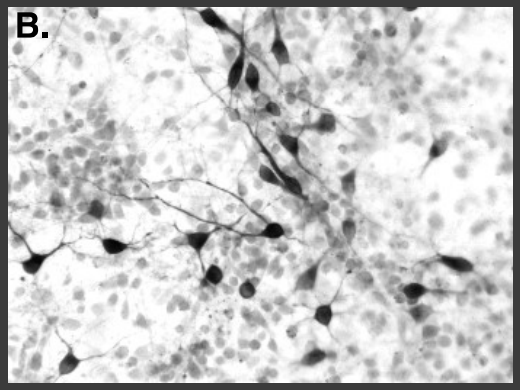


Developmental Lead Exposure Stunts the Growth and Maturation of Neuronal Processes

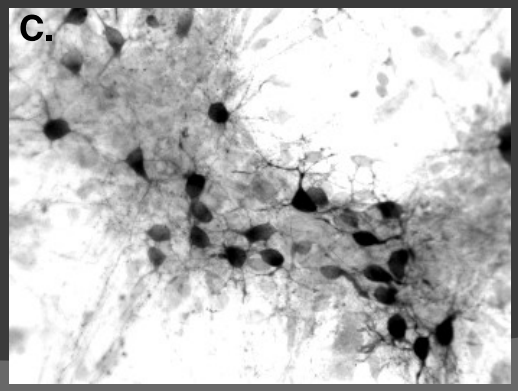
No Lead

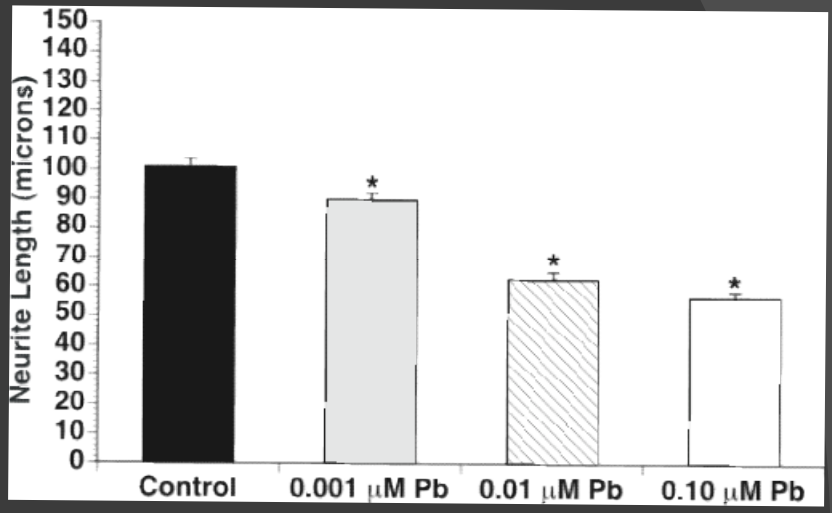


0.001 µM
0.024 µg/dl



0.01 µM
0.24 µg/dl





The lowest concentration of lead acetate used (0.001 µM) caused a significant decrease in neurite length (after 48 hrs of exposure), that was exacerbated by exposure to higher concentrations of lead (0.01 and 0.10 µM).

Result: Improperly wired brain: effects on transmission of information

From: Schneider et al., Neurotoxicology and Teratology, 2003, 25: 555 - 559.

Real Life Implications: Decreased Brain Volume with an Inverse Dose-Effect Relationship Between Childhood Blood Lead Concentration and Brain Volume

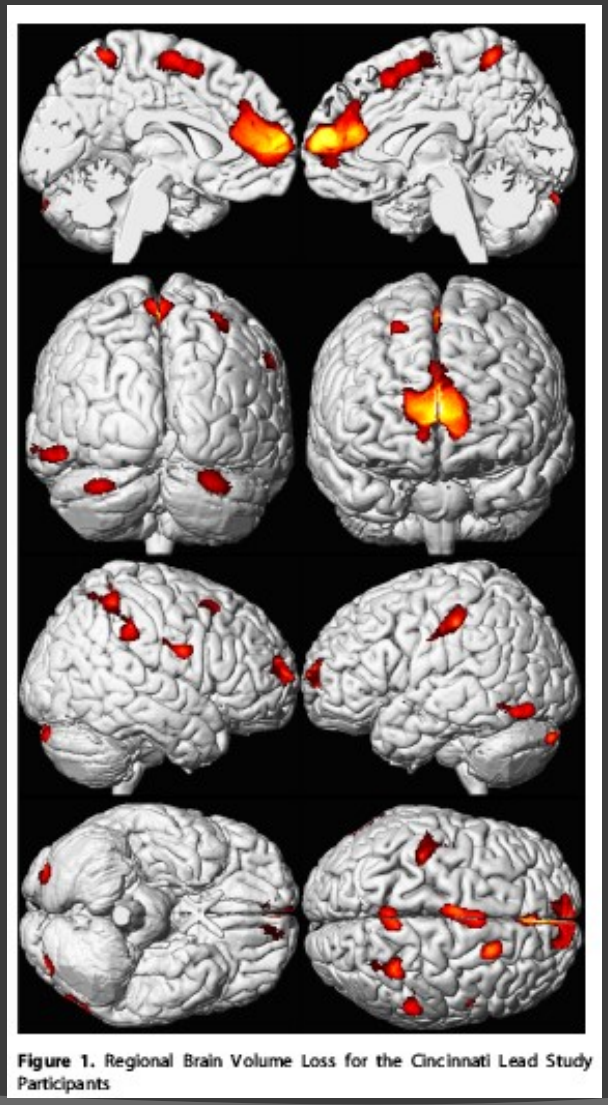


Figure 1. Regional Brain Volume Loss for the Cincinnati Lead Study Participants

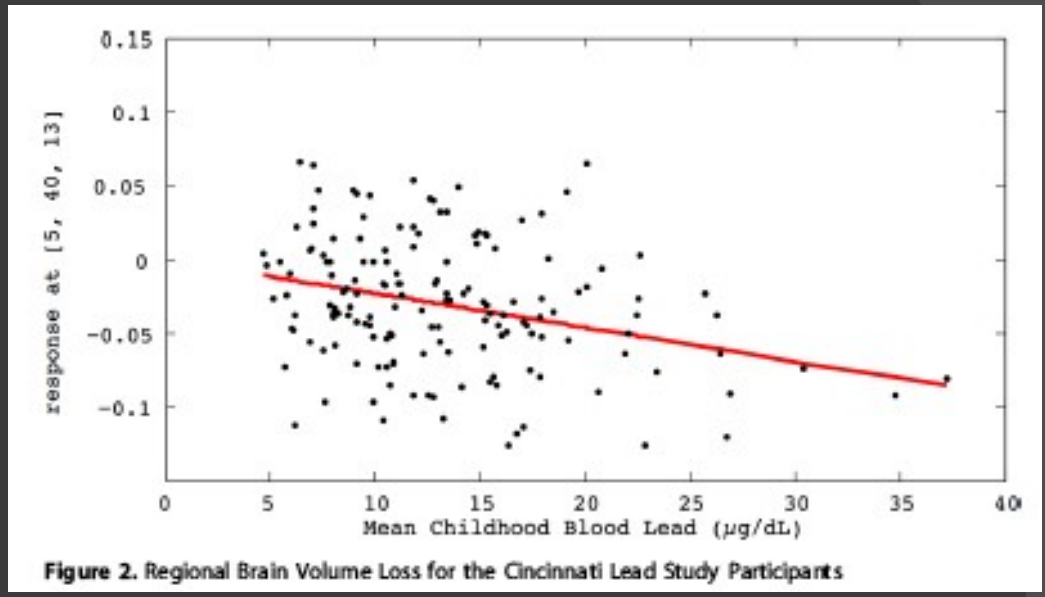


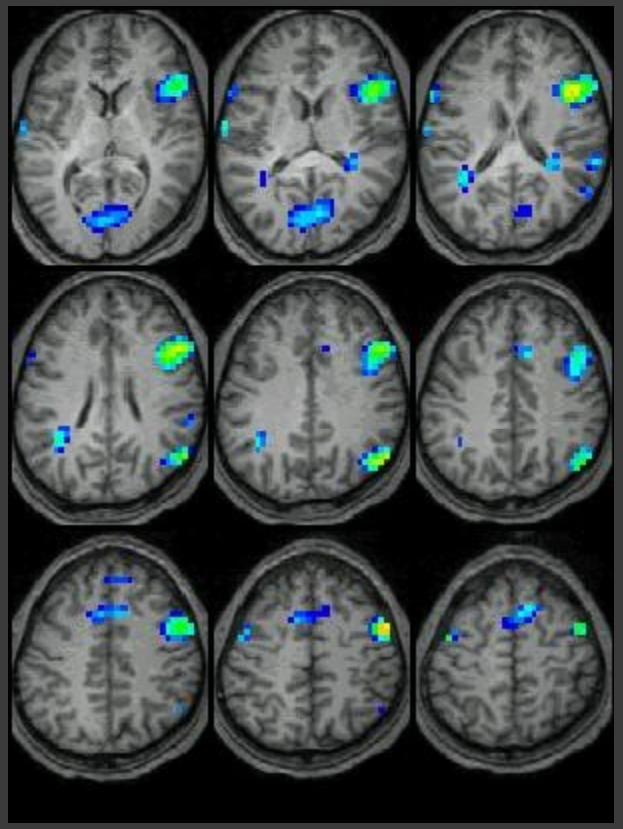
Figure 2. Regional Brain Volume Loss for the Cincinnati Lead Study Participants

Decreased brain volume can be due to cell loss but more likely, loss of neuropil (the complex network of axonal, dendritic, and glial branchings that forms the bulk of the CNS gray matter of the brain and in which the nerve cell bodies are embedded).

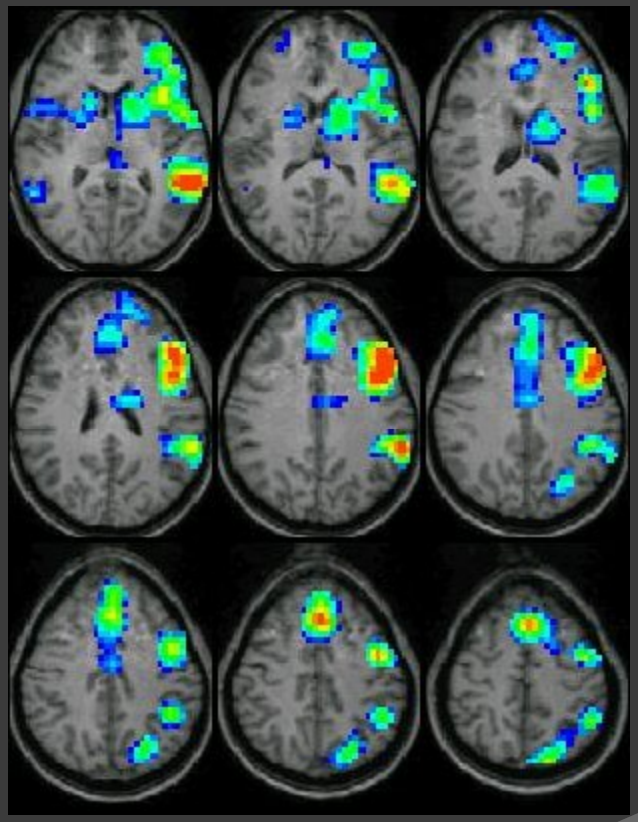
Effects greater in males than in females

KM Cecil et al., PLoS, 2008, 5: 741-750

Functional Implications: Childhood Lead Exposure Has a Significant and PERSISTENT Effect on Functional Brain Organization/Information Processing

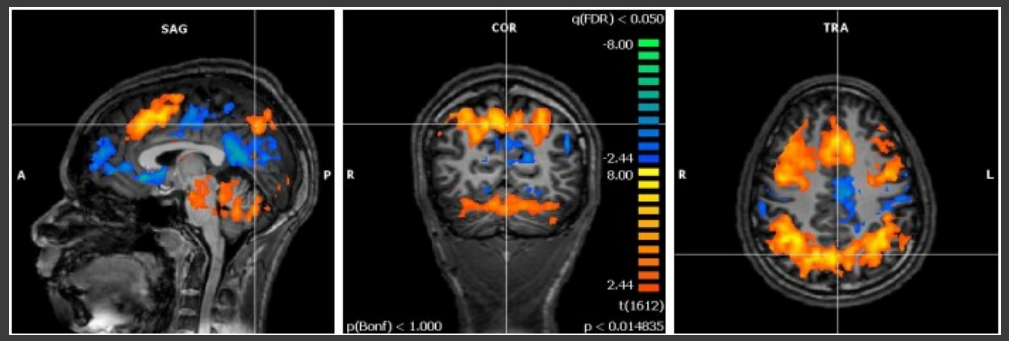


High Lifetime Mean Blood Lead (26 μg/dL)

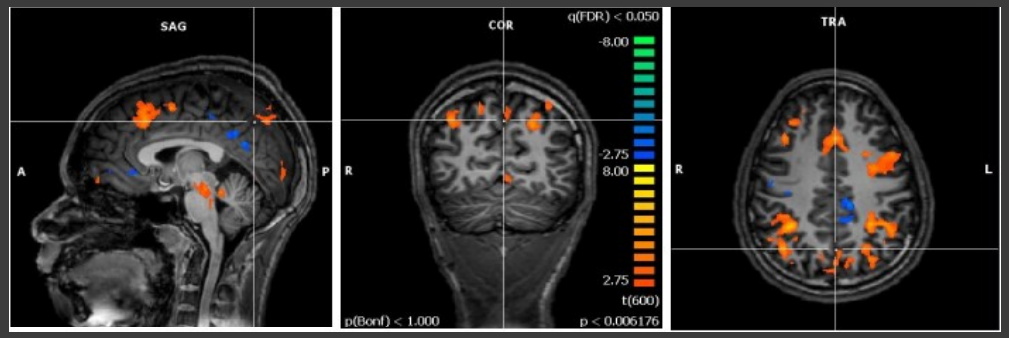


Low Lifetime Mean Blood Lead (7.6 μg/dL)

Yuan, et al. 2006



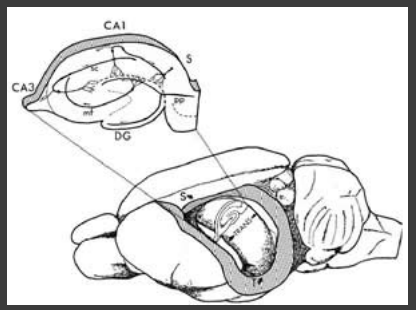
2-back-letter,
Group 1
8 subjects,
Peak Mean BLL 33 µg/dl

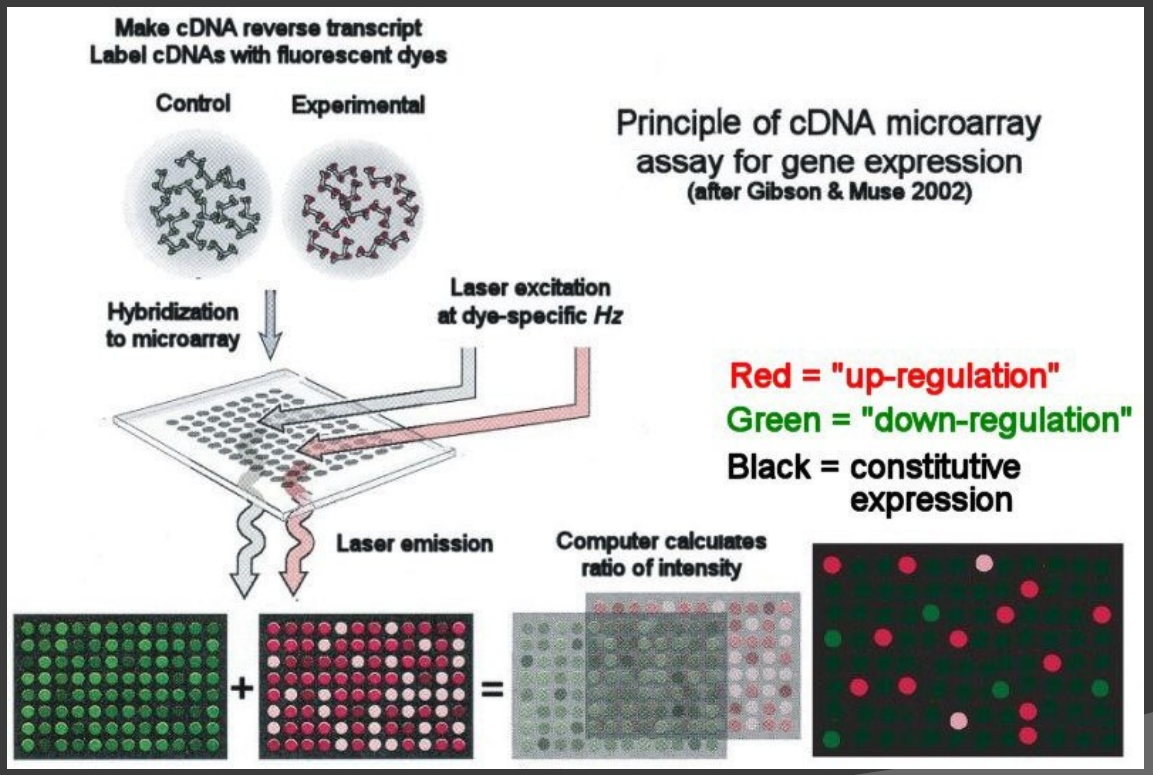


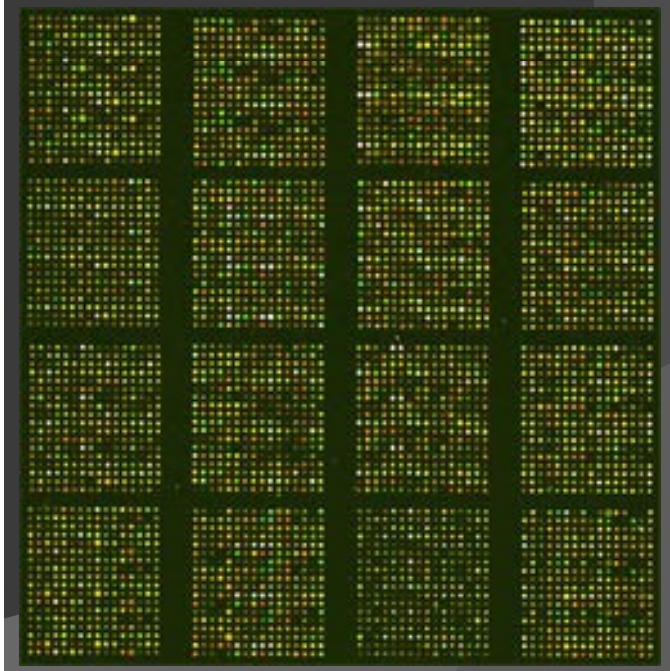
2-back-letter,
Group 2
3 subjects,
Peak Mean BLL < 5 µg/dl

- Greater resource utilization (recruitment of brain circuits involved in working memory) in individuals with higher prior BLLs.
- Need for injured memory circuits to recruit additional neural resources in order to meet task demands. Decreased activation may reflect more efficient processing
- Individuals with lead exposure may need to use different cognitive processing strategies to perform working memory tasks, than individuals with lower lead exposures.

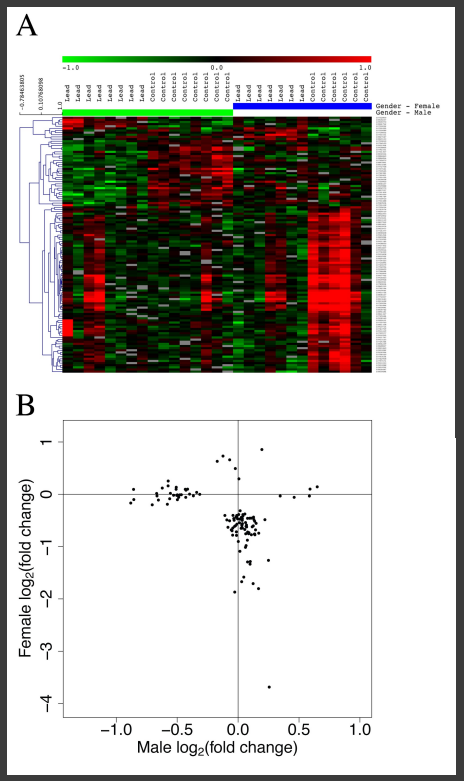
Studies of Lead Effects on Gene Expression Profiles in the Brain



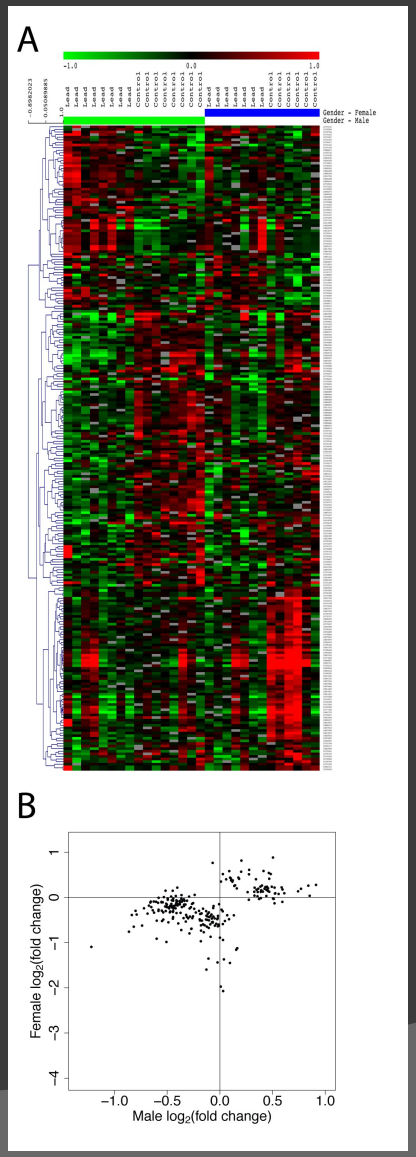




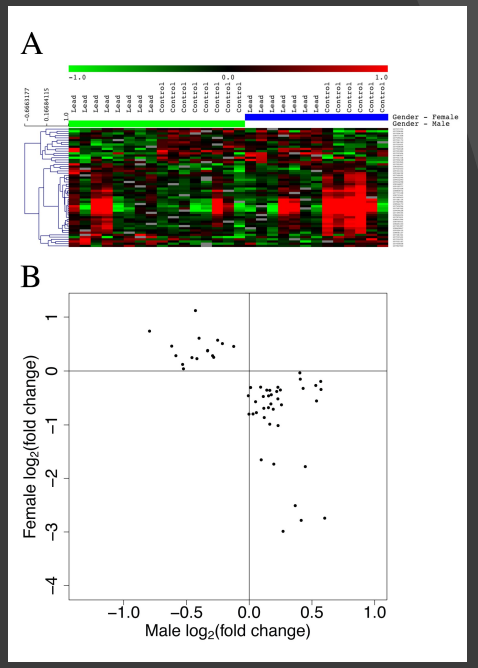
Developmental Lead Exposure Alters Gene Expression Patterns in Critical Brain Structures in a Sex Dependent Manner



Genes with sex-based differences

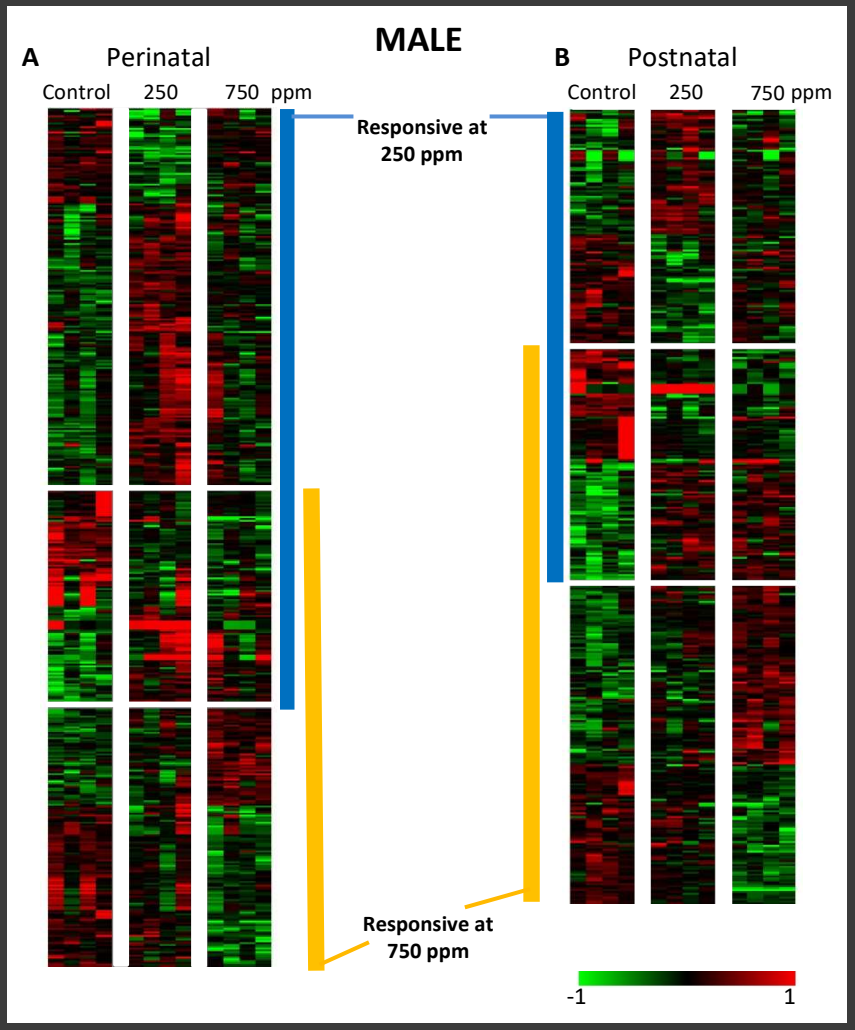


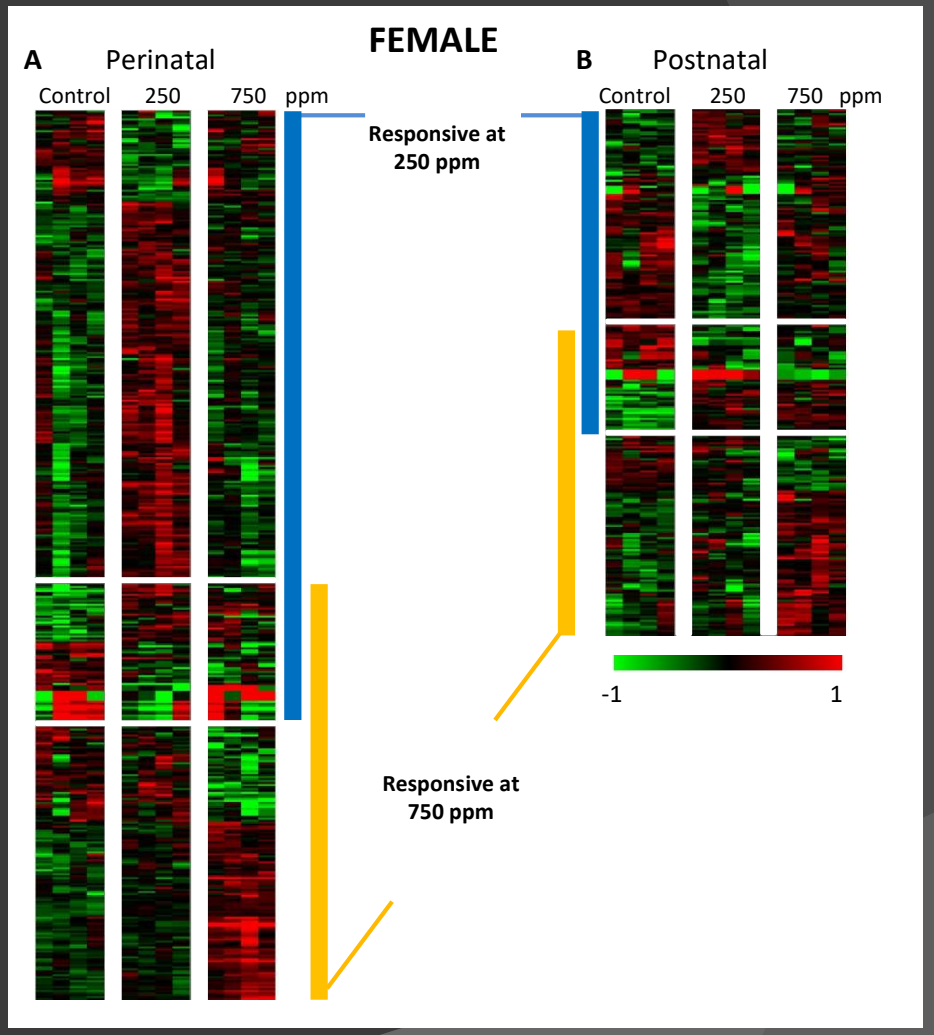
Genes similarly affected in both sexes



Genes differentially expressed in opposite directions in males and females

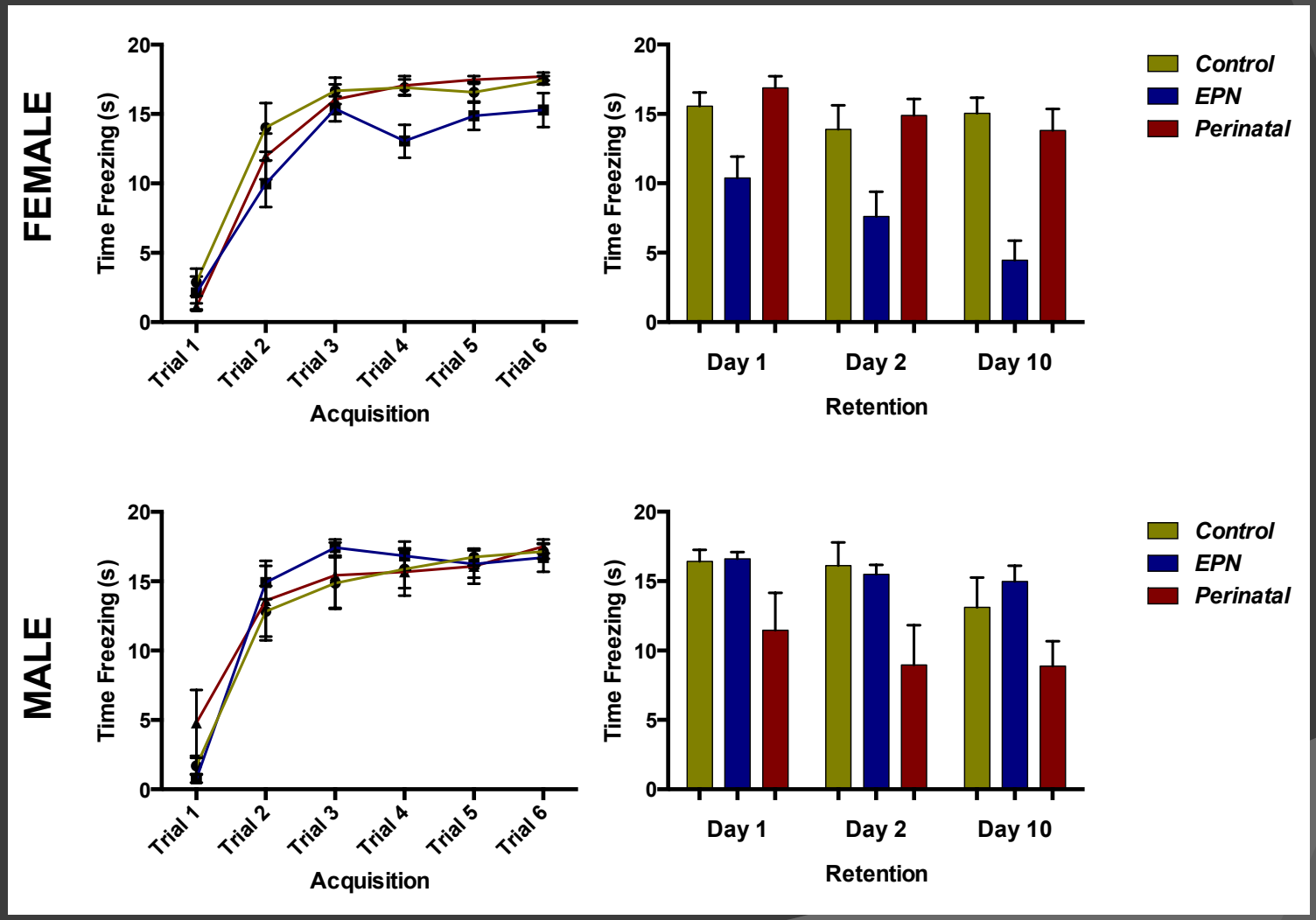
Male/Female Differences in the Effects of Lead on Gene Expression, Modified by Exposure Level and Developmental Window of Exposure





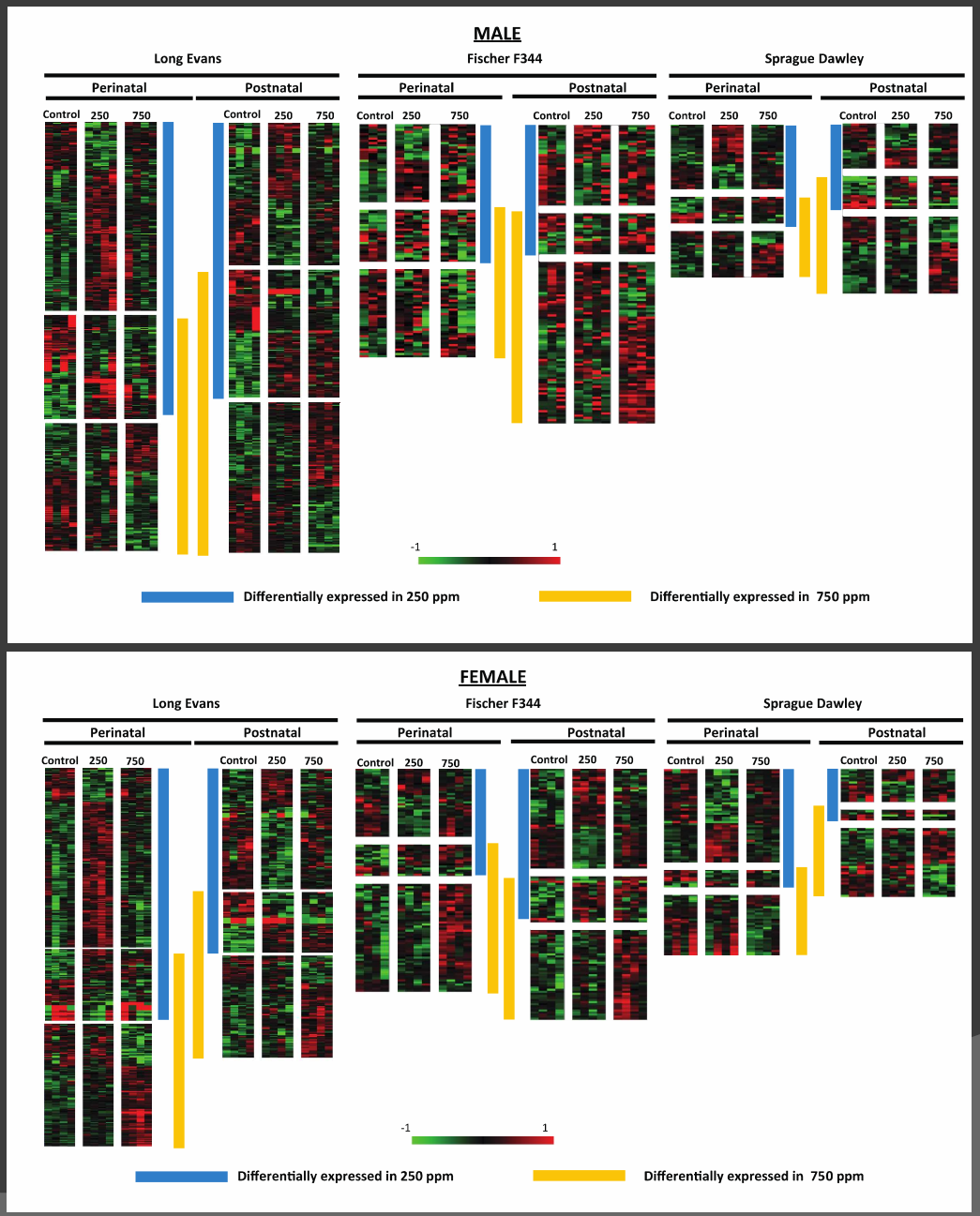
Expression of a number of genes controlling plasticity and synapse formation/function adversely affected by Pb

Sex and Developmental Window of Pb Exposure Affect Behavioral Outcome

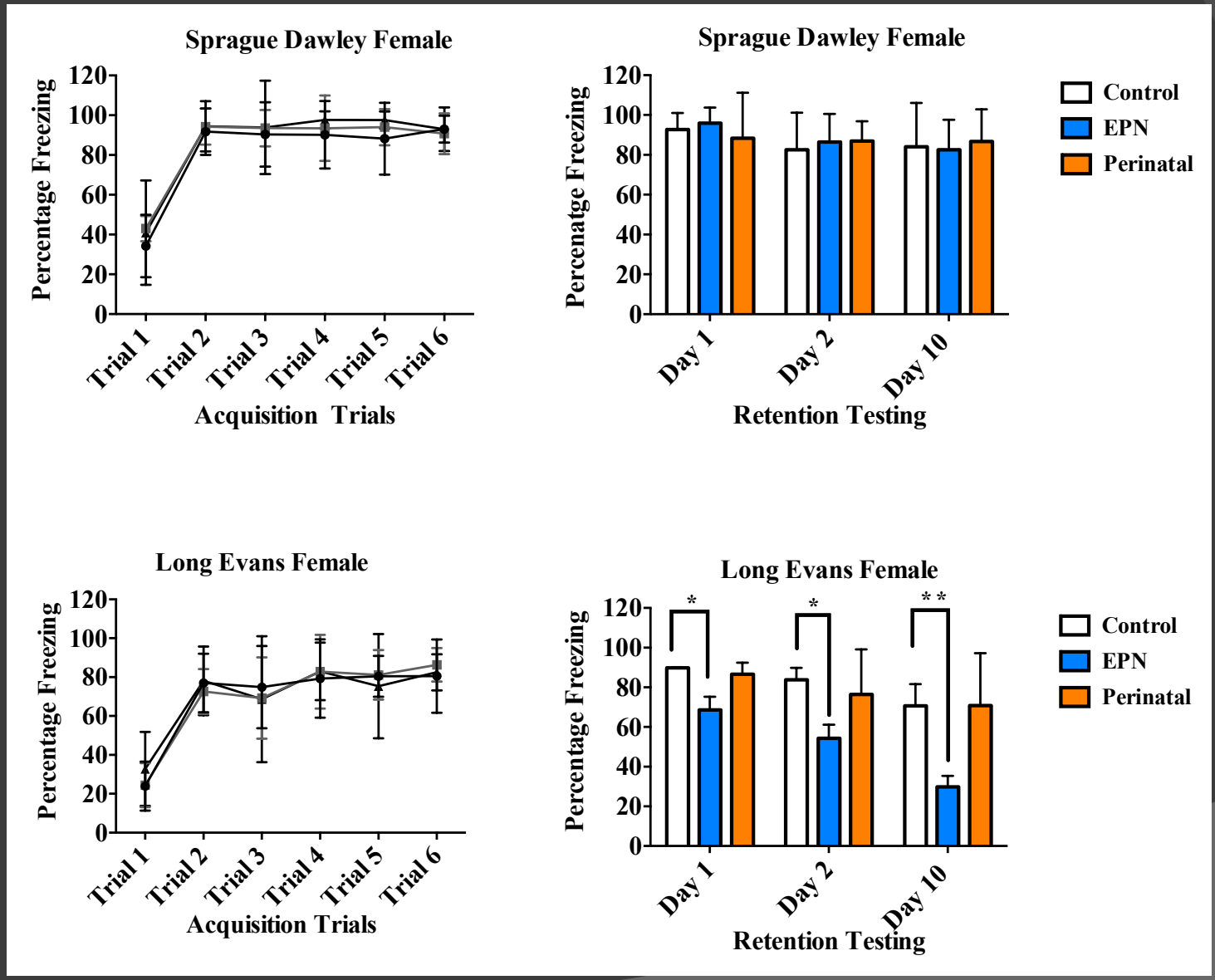


< 5 μg/dl

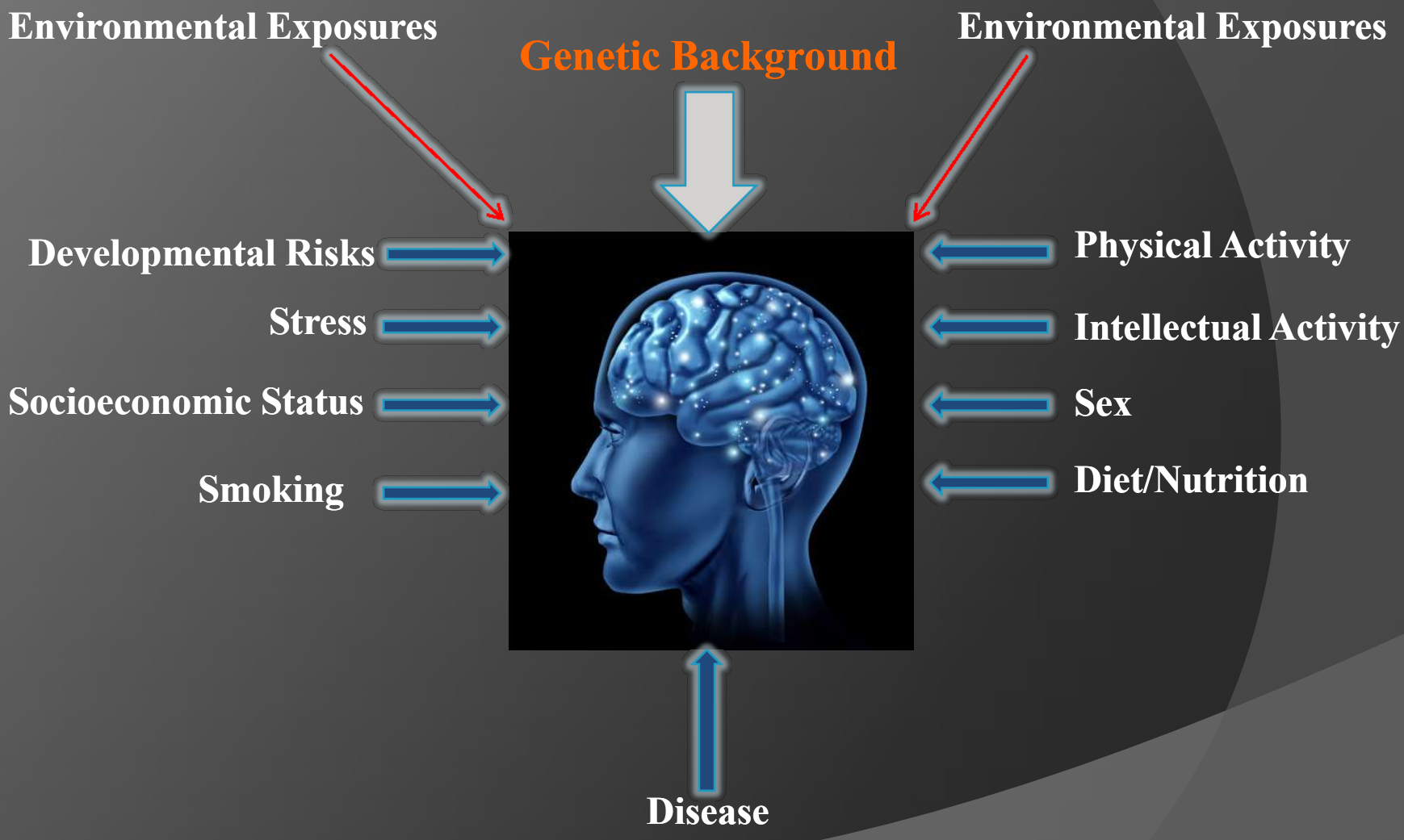
Genetic Background Modifies Effects of Lead on Gene Expression the Brain



Genetic Background Modifies Effects of Lead on Cognitive Performance

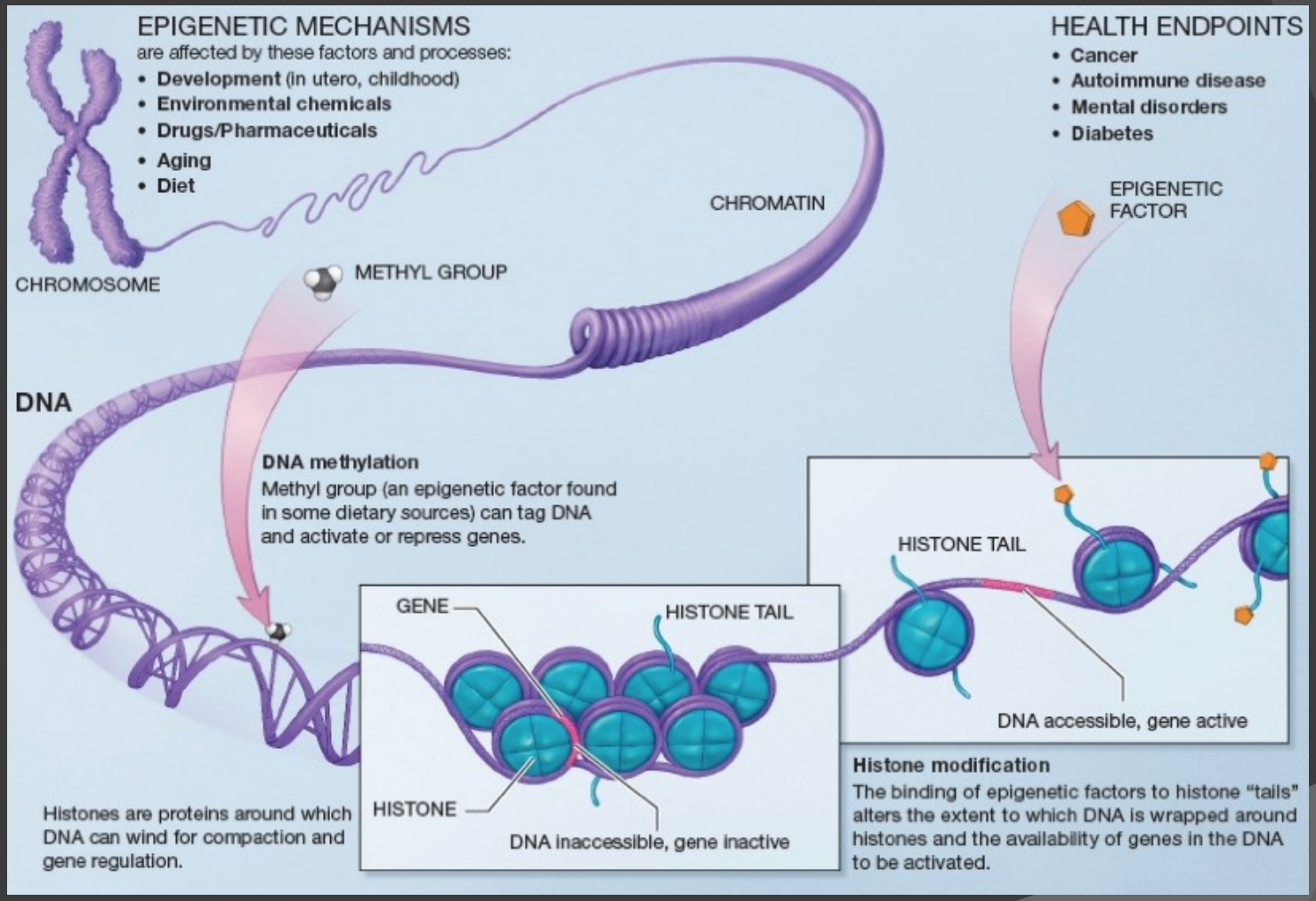


Various Factors Can Significantly Modify the Influence of Environmental Exposures



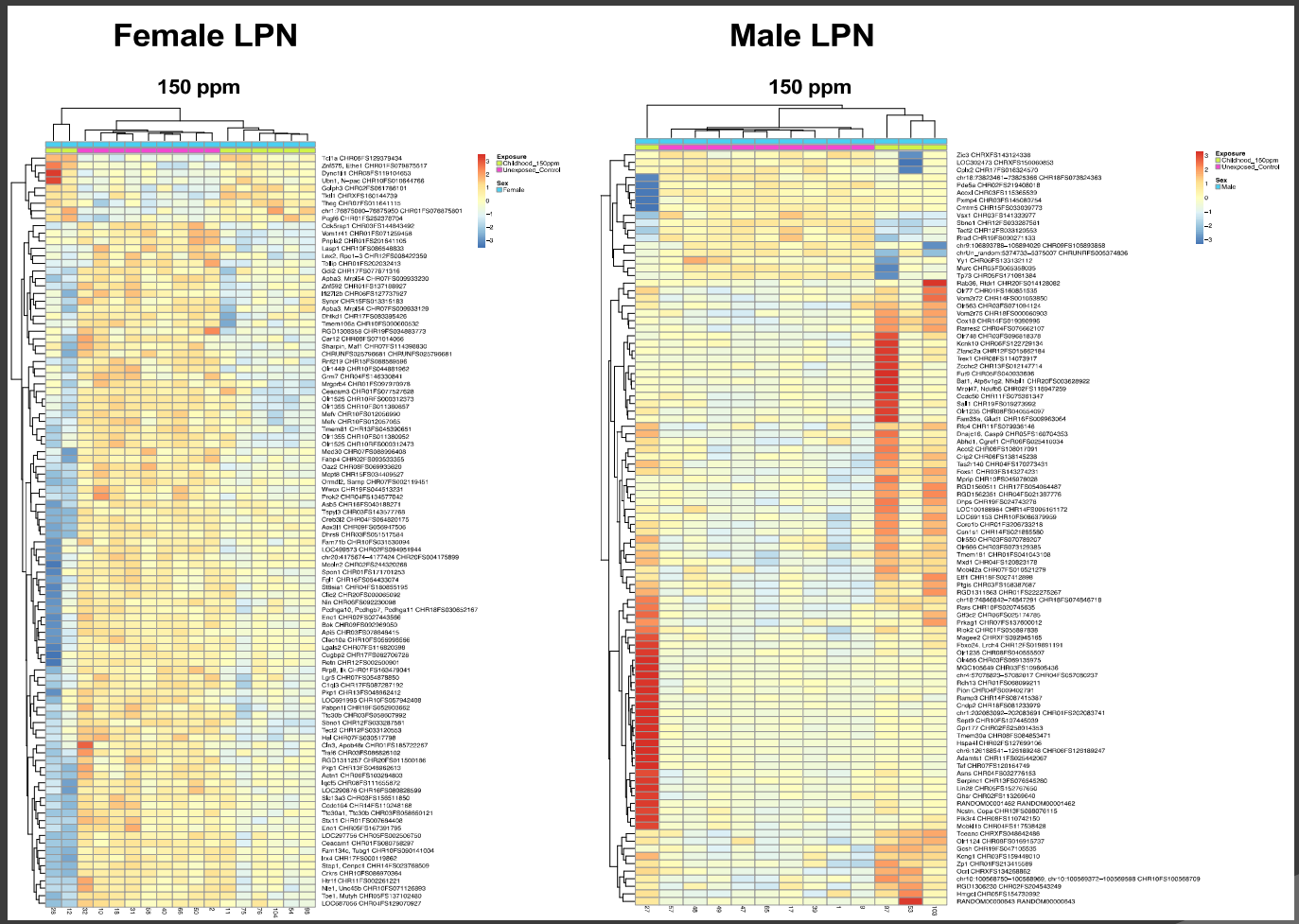
Risk Factors Are Unique to Each Individual

Epigenetics: chemical modifications of DNA that can switch genes on and off without a change in the DNA sequence.



DNA methylation is what occurs when methyl groups tag DNA and activate or repress genes. Histone modification occurs when epigenetic factors bind to histone "tails" altering the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

Differential Methylation Patterns Across the Genome by Sex and Pb Exposure



Effects in males and females are for the most part in opposite directions. Among the 100 probes shown, 9 are hypermethylated and 91 are hypomethylated in females while in the males 83 are hypermethylated and 17 are hypomethylated.

Epigenetic Component to Developmental Lead Exposure: Much To Be Learned

- Although methylation array data show aberrant DNA methylation profiles in the hippocampus of Pb-exposed animals, it is not clear *how* this Pb-induced aberration in DNA methylation contributes to specific learning and memory problems that are common sequelae of developmental Pb exposure.

- However, DNA methylation in the brain is *highly dynamic* and driven by experience. Dynamic regulation of methylation in the pre-frontal cortex (PFC) and hippocampus play integral (although different) roles in memory formation and consolidation.

- Prenatal exposure to Pb affects levels of a variety of PTHMs (activating and repressive) in hippocampus and PFC in a sex dependent manner that could have far-reaching effects on gene expression profiles. Effects persist into adulthood. PTHMs are also dynamically regulated in response to experience.

- The epigenetic effects of Pb on the hippocampus and PFC may alter the potential for these systems to be dynamically regulated correctly during learning and memory formation/consolidation, as well as during other behaviors, leading to deficits in cognitive performance and abnormal behavior.

What Does All This Mean for a Pb-Poisoned Child and His/Her Ability to Learn and Achieve?

Lead Poisoning Results In An Acquired Brain Injury

- Each child is different, but there is typically a cluster of cognitive/behavioral problems that exists.
- Problems determined by how Pb has affected different parts of the brain and that can be different in different children.
- Frontal lobes are particularly vulnerable (attention/executive functioning): clinical features of frontal lobe dysfunction: lack of motivation, inability to plan ahead, poor judgment, difficulty moving from one task or idea to another, difficulty staying on task, pulled by internal and external distractions, irritability, problem with impulse control, aggression, frustration

Cognitive Functions Often Affected by Childhood Pb Poisoning

- Language skills
- Attention (sustained/selective)
- Memory & Learning
- Executive Functions
  - Concept Formation
  - Planning
  - Cognitive Flexibility
- Fine motor skills

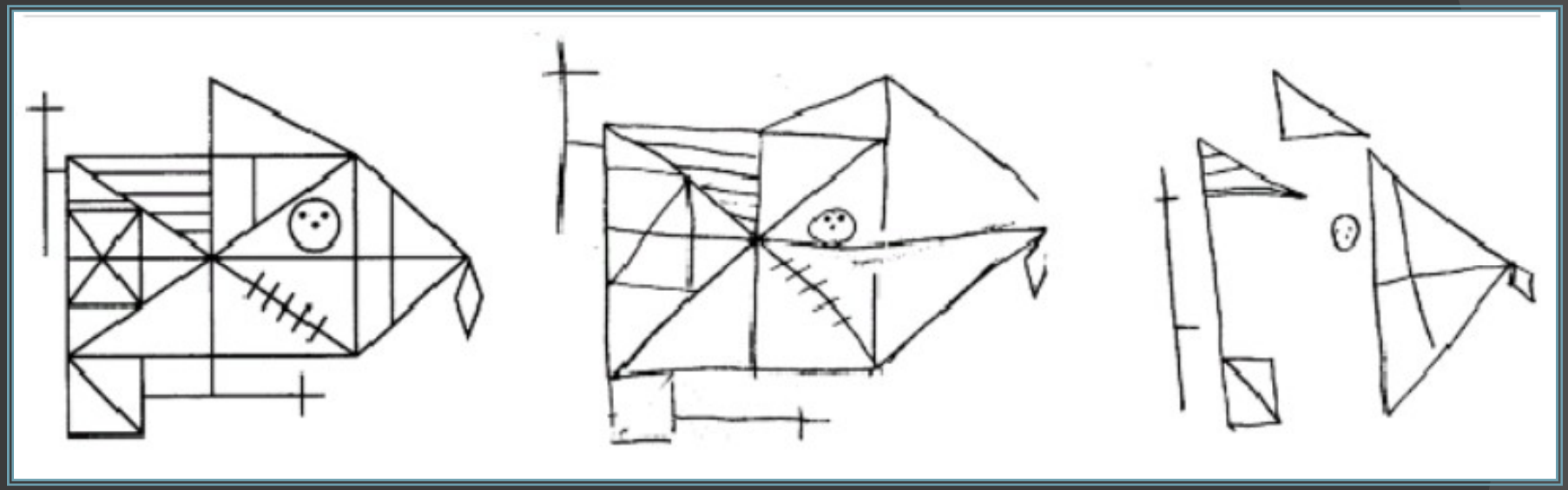
Behavioral problems: socialization; aggression; impulsivity

Neuropsychological Testing: Best Way to Assess Cognitive Abilities in Pb-Poisoned Children

- **Very tightly focused tests that target behavioral functions of specific brain systems (i.e. neuropsychological functions)**
- **Objective**
- **Valid**
- **Reliable**
- **Reference Baseline**

Many aspects of cognitive functions (language, memory, attention, executive function are unmeasured or poorly measured by IQ tests and IQ tests are not sensitive for detecting brain injury.

Effect of Lead on Visual Memory



Complex Figure | Normal Child | Lead Poisoned Child

All functions are at risk (e.g. attention, memory, executive functioning)

Effects of Pb on the Brain Lead to Poor Academic Performance

- Numerous reports documenting academic difficulties in Pb poisoned children
- BLLs well below 10 µg/dL were associated with lower reading readiness at kindergarten entry (Providence , RI (Pediatrics 2013;131:1081–1089).
- Studies of children in North Carolina found a dose-response relationship between 4th grade end-of-grade reading and math scores and BLLs, with levels of 3 µg/dL and above associated with decreases in reading and math test scores (Environ. Health Perspect 2007; 115: 1242-1247).
- Adverse educational outcomes reported for children in Connecticut, where associations between increasing blood Pb levels (between 2 and ->10 µg/dL) and decreased achievement on 4th grade reading and math test scores have been described.
- Similar report from Wisconsin, Chicago, Detroit.
- Exposure to Pb negatively potentially impacts a child's life trajectory: Childhood BLLs associated with lower adult IQs 3 decades later; childhood BLLS associated with lower adult SES, reflecting downward social mobility through midlife following childhood Pb exposure (JAMA 2017; 317: 1244-1251).

Why Schools Frequently Fail Lead Poisoned Children

- Unaware that child had been poisoned
- Unaware that lead poisoning causes brain damage
- Services not provided because child's IQ is "normal"
- No access to neuropsychologists or neuropsychological testing

Issues Regarding Effectively Educating the Lead-Poisoned Child

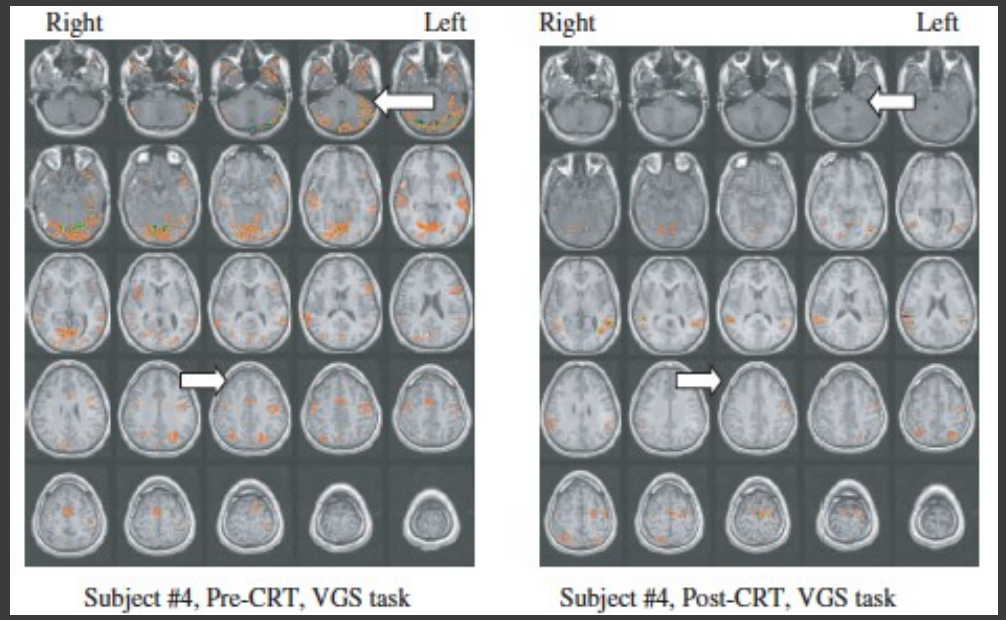
- Understand what their deficits are
- Educate staff as to how Pb poisoning may affect the young student and how to identify cognitive issues affecting classroom performance
- Develop guidance and **evidence-based recommendations** for helping Pb-poisoned children in the academic environment
- **Need rigorous, scientifically valid clinical research to understand what strategies may or may not work**
- Understand that effective management will require an **individualized approach** for each Pb-poisoned student

Improving Educational Outcomes For Lead Poisoned Children

- **Identify the cognitive problems in each child: Neuropsychological evaluation**
- **Design programs to enhance Pb-poisoned child's capacity to process information more effectively and improve adaptive functioning: How does a particular Pb-poisoned child learn most effectively?**
- ***Stimulate plasticity: To what extent is that possible? No clinical research to date to address the extent to which plasticity-enhancing approaches will be effective***

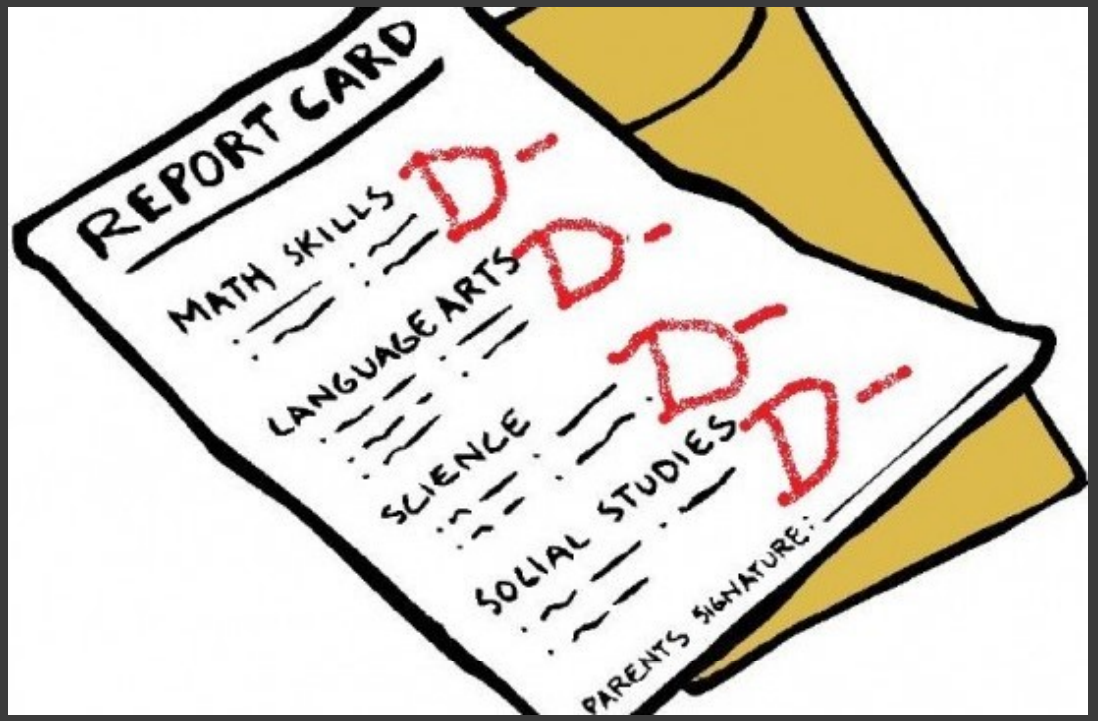
Need to Perform Controlled, Scientifically Valid Clinical Studies In Order Make Rational, Effective Recommendations

- **Can specific cognitive training exercises/learning strategies based on cognitive rehabilitation principles be effective?**



Laatsch, et al., 2004

- ***Services should be matched to the needs, strengths, and capacities of each individual***


REPORT CARD
MATH SKILLS D-
LANGUAGE ARTS D-
SCIENCE D-
SOCIAL STUDIES D-
PARENTS SIGNATURE: