"Social Modifiers in Environmental Neuroepidemiology: The Role of Context in Chemical Exposure"

Robert Wright MD MPH

Department of Pediatrics,

Children's Hospital, Boston,

Department of Environmental Health

HSPH

Biological Vulnerability

- Construction of the central nervous system (CNS) begins in utero,

- Continues throughout childhood and involves the production of 100 billion nerve cells and 1 trillion glial cells.

- Cell migrate, differentiate, and form synapses

Synapses

- Transmits signals between neurons
  - Environmental stimuli will cause neurons to fire
  - Neuronal/synaptic firing is a signaling process to mold the synaptic architecture of the brain

Strauer Associates, Inc.
Feldman
Fundamentals of
Neuropsychopharmacology
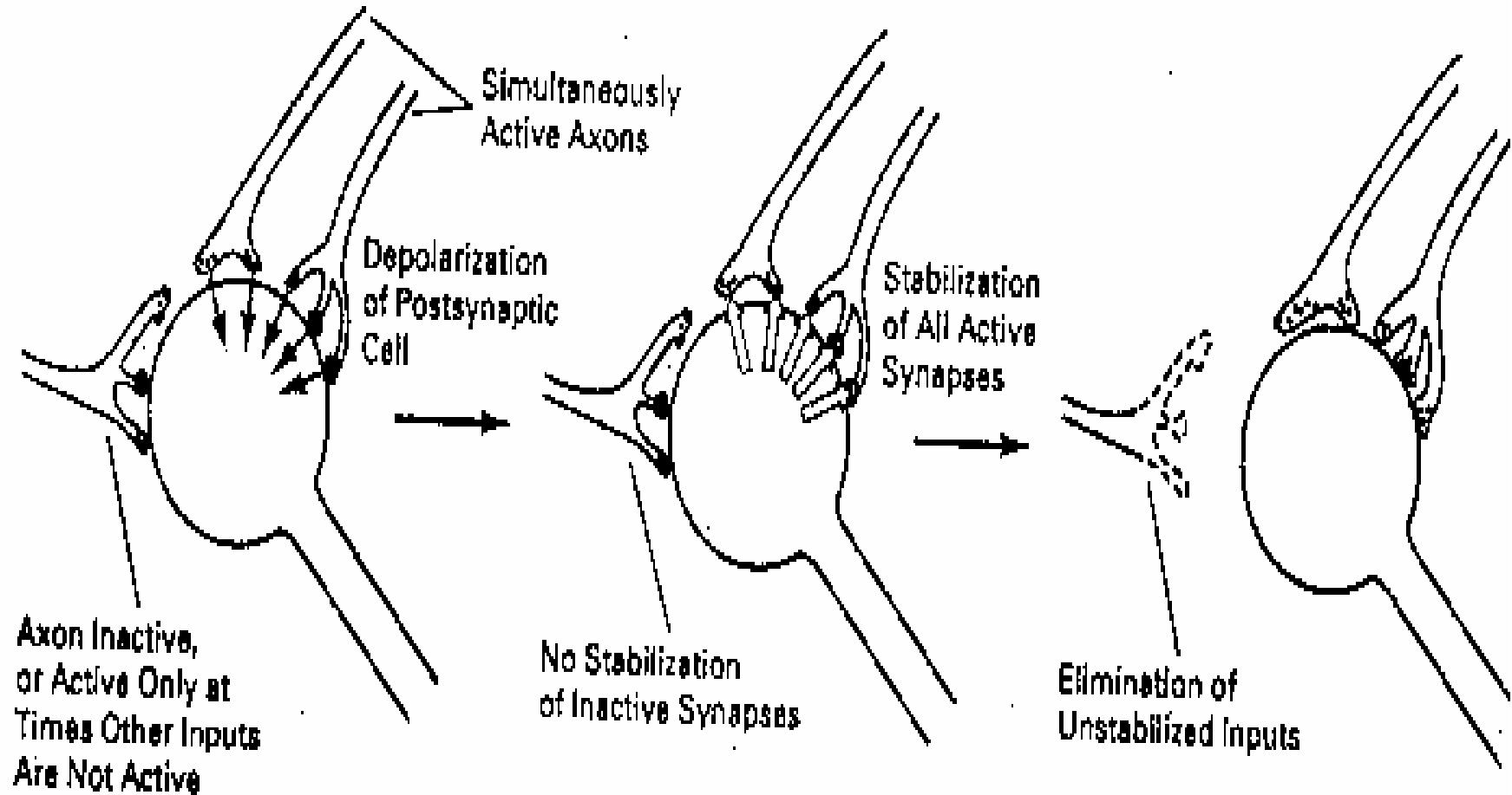Fig. 6-5
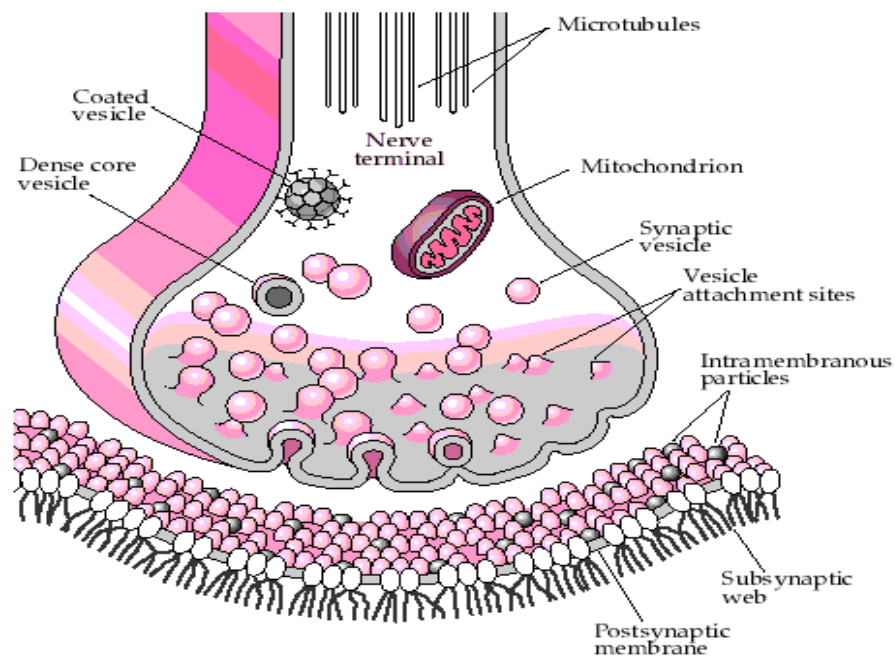
How does the Brain Build this Network?

- **Some of it is stochastic**
  - Synapses are made by the billions, and in some respects randomly, between neurons.
  - We make a net gain in synapses from fetal life till about age 2 years
  - Then the number of synapses in our brain starts to decrease
    - Why?

Synaptic Networks

- Environmental Stimuli cause nerves to fire:
- When they fire neurotransmitters are released into synaptic junctions
  - This releases growth factors- signals that this is an important neuronal connection (i.e. it gets used)
- In other words there is a "natural selection" process
  - Functional synapses release growth factors
  - Nonfunctional synapses do not release the growth factors

Hebb Synapses

Simultaneously Active Axons

Depolarization of Postsynaptic Cell

Axon Inactive, or Active Only at Times Other Inputs Are Not Active

Stabilization of All Active Synapses

No Stabilization of Inactive Synapses

Elimination of Unstabilized Inputs

So how do Environmental Chemicals affect Development?

- At "low" doses (blood lead around 5-10 ug/dL)
  - Lead will interact with Protein Kinase C
    - Stimulate neurotransmitter release
    - Neurons fire in the absence of an appropriate environmental stimuli
  - Lead mimics calcium
    - Calcium is critical to nerve signal transmission
    - Calcium enters neurons during depolarization
    - Lead blocks calcium channels

Lead and the Brain

- Net effect
  - Lead stimulates nerves to fire in a more stochastic fashion
  - Lead also inhibits neurotransmission (both appropriate neurotransmission and inappropriate neurotransmission)
- Changes the underlying synaptic architecture, making it less efficient

Plasticity

- The brain's capacity to diminish the effects of toxic insults through structural/functional changes
    - This occurs through the same processes as synaptic selection
    - In other words plasticity allows for new connections to be made which improve function following an insult
- Maladaptive vs adaptive plasticity

Neurodevelopment and Social Environment

- Chronic Stress known to impair memory and learning capacity
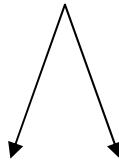
Example: Handling Paradigm

- Licking/grooming in mothers is stimulated by human handling of pups.

- Maternal LG and Arch back nursing behaviors program more appropriate long term HPA axis response to stress.

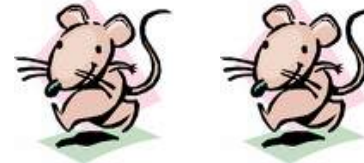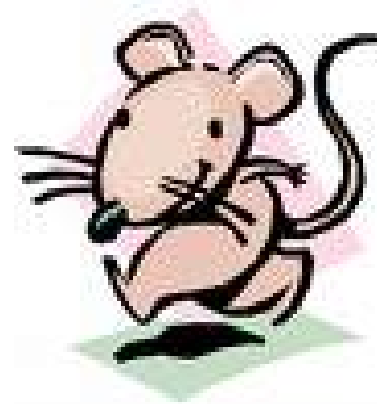- Maternal LG/ABN clusters in family lines
  - Is it genetic?

low LG and ABN mothers

high LG and ABN mothers

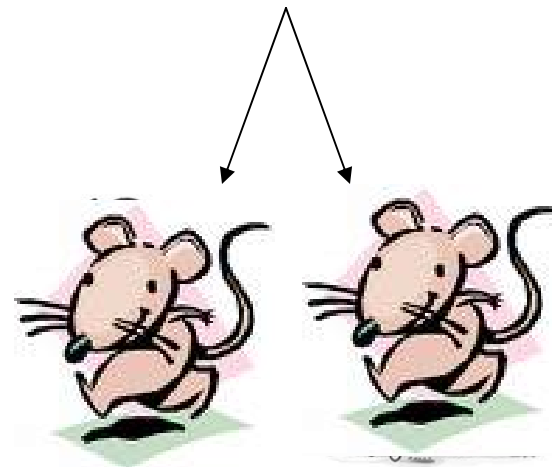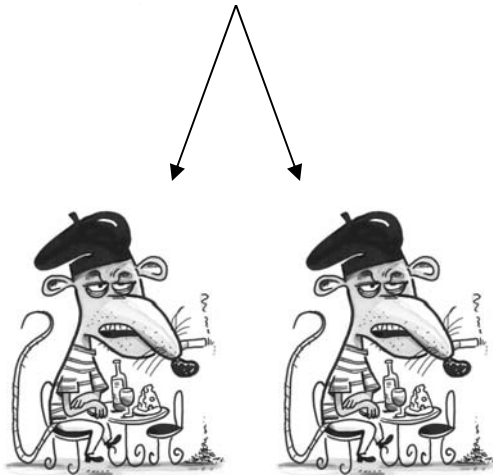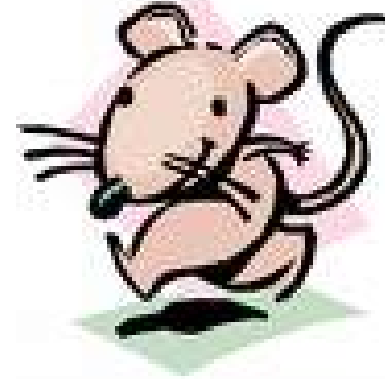Fearful offspring with brisk HPA stress response

Less fearful offspring with more modest HPA stress response

EFFECTS OF CROSS-FOSTERING

low LG and ABN mothers

high LG and ABN mothers

Fearful offspring with brisk HPA stress response

Less fearful offspring with more modest HPA stress response

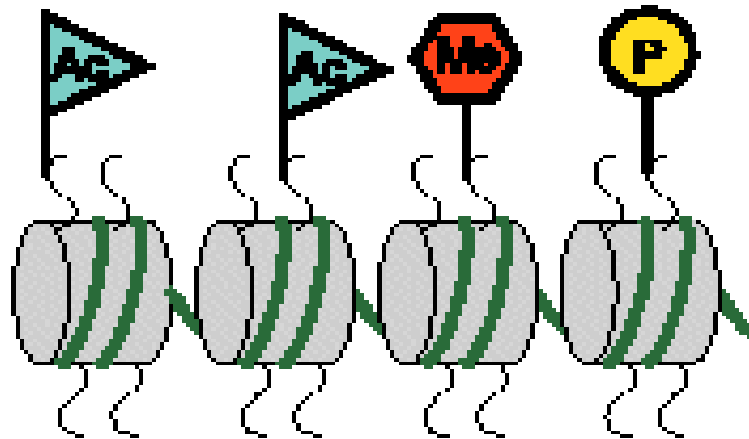# Programming And Epigenetics

- Fetal origins of Disease
  - Prenatal (and early life exposures), increase risk of late life disease
    - HTN,
    - Obesity
  - Handling paradigm is an example of neuro-programming

- Methylation of histone or of DNA usually turns a gene off.
- Acetylation of histone usually turns a gene on.
- Phosphorylation -- we're not sure what that does.

The Histone Code

Epigenetics and the Brain

- Epigenetics plays an important role in synaptic pruning via environmental stimuli.
  - Epigenetic marks within neurons change with synaptic activity
- This "epigenetic opening" of synaptogenesis to environment is maximal during childhood
- It is the source of the exceptional cognitive adaptability of humans, and possibly the source of its fragility

Handling Paradigm

- Weaver et al
  - Glucocorticoid receptor expression is more active in offspring of high-LG mothers compared with low- LG mothers,
  - Effect inversely correlated with methylation across Glucocortoid Receptor promoter sequence in the hippocampus

  - REGARDLESS OF GENETIC BACKGROUND

Social Environment and Pb

- Guilarte et al
- Lead poisoned animals during lactation
- Randomized to 2 groups
  - Animals raised in social isolation
  - Animals raised in groups with social stimulation
    - Tested on memory in Water maze
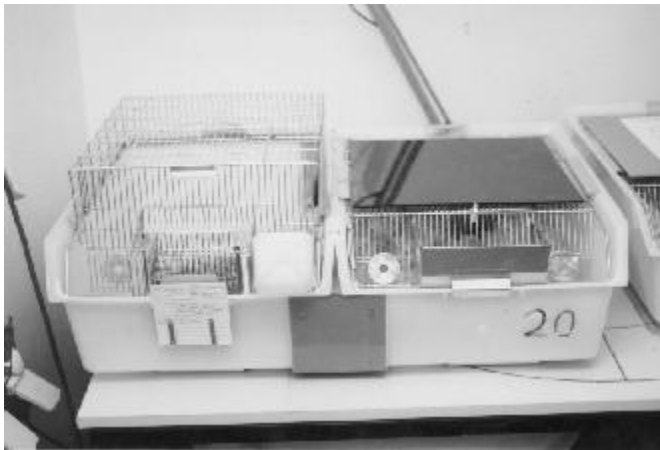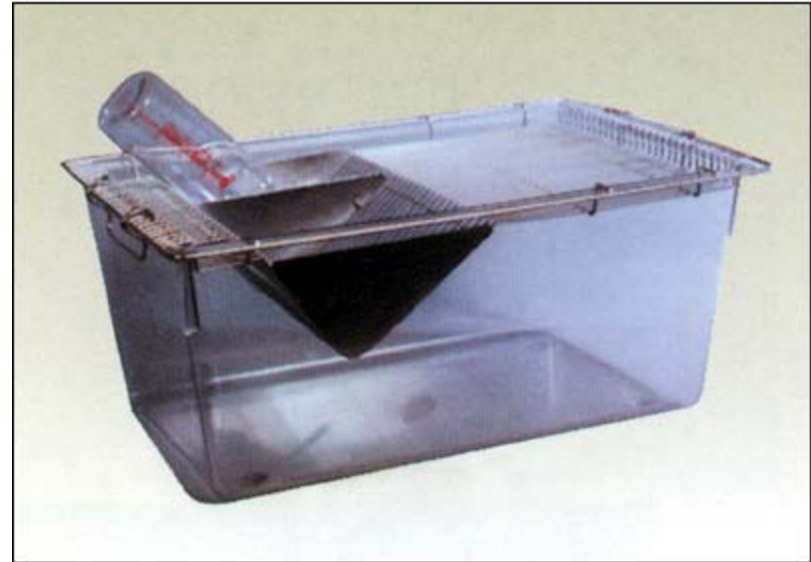
Acquisition Time
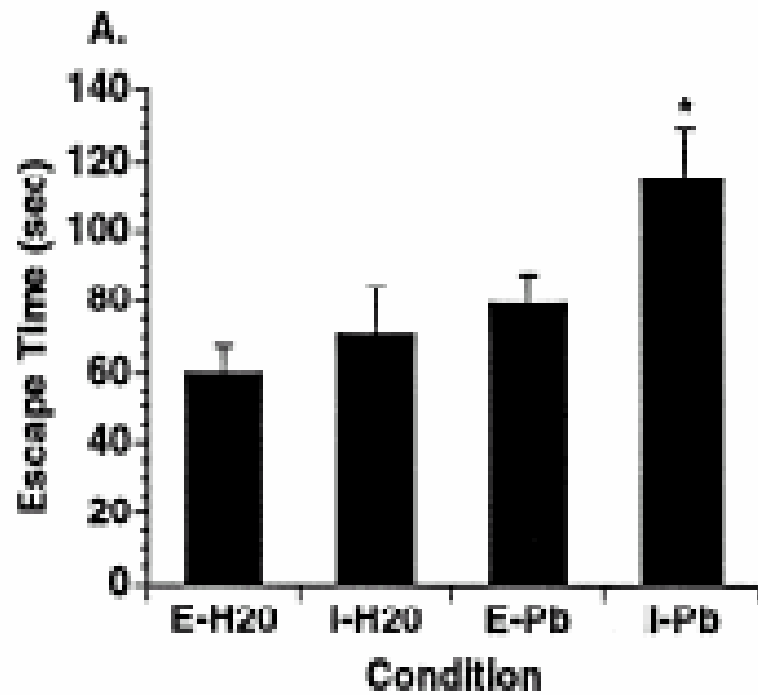
Probe Test
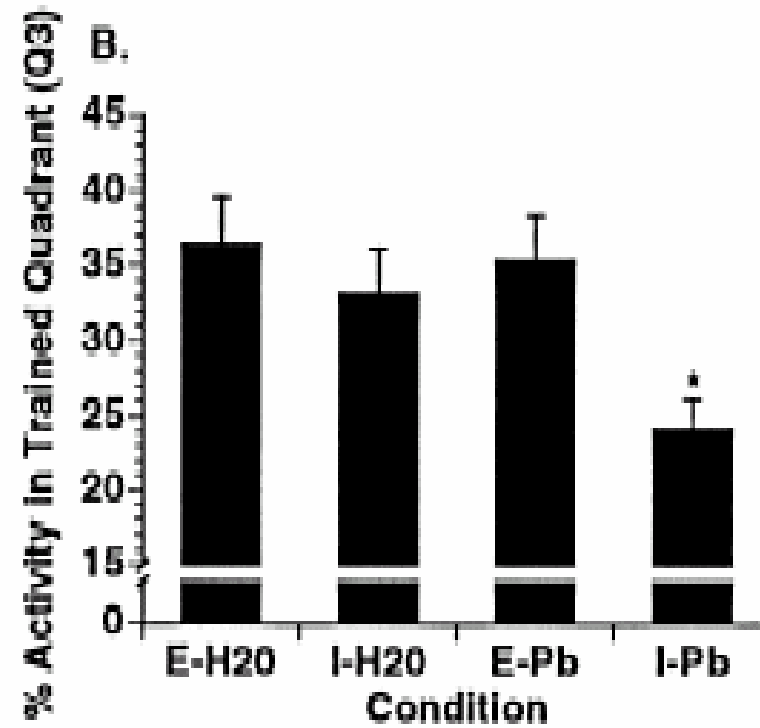
Can Reducing Stress be a Treatment?

- Mexico City
- Coopersmith self-esteem administered to mothers when child 24 months of age
- Cross-sectional analysis
- Covariates
  - Blood Pb, mom's IQ, mom's education, child's sex,

Main Effect of Maternal Self-Esteem

```
--------------------------------------------------------
    mdi24 |      Coef.  P>|t|        [95% CI]
--------------------------------------------------------
 Blood Pb |    -.11    0.569     -.50        .276
```
autoes | .46   0.006   .12   .78

Adjusted for Maternal IQ, education, Infant Sex,

Blood Pb and MDI

**Self esteem
Quartile 1,2,3**
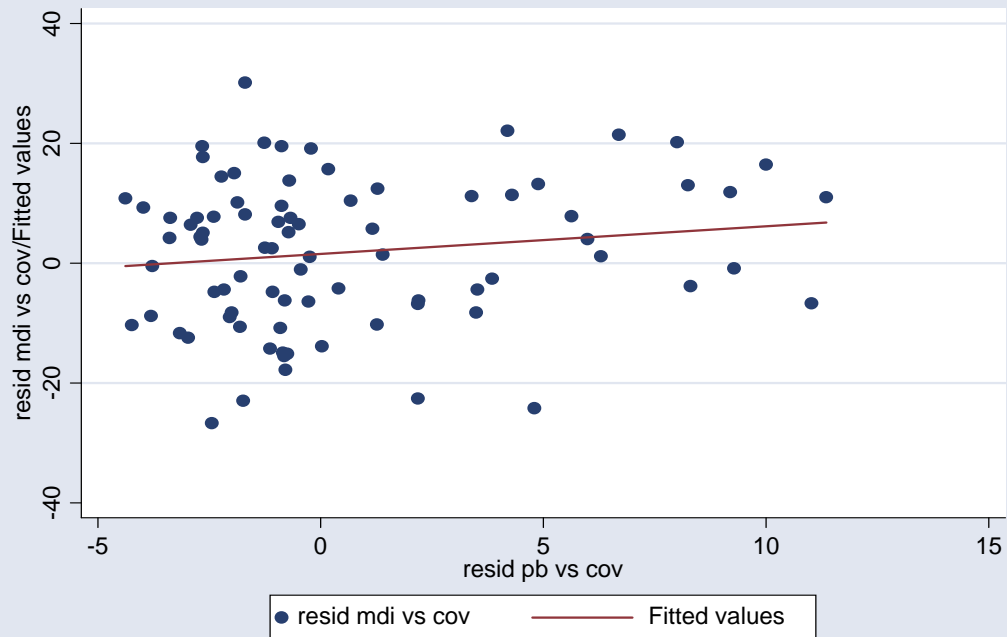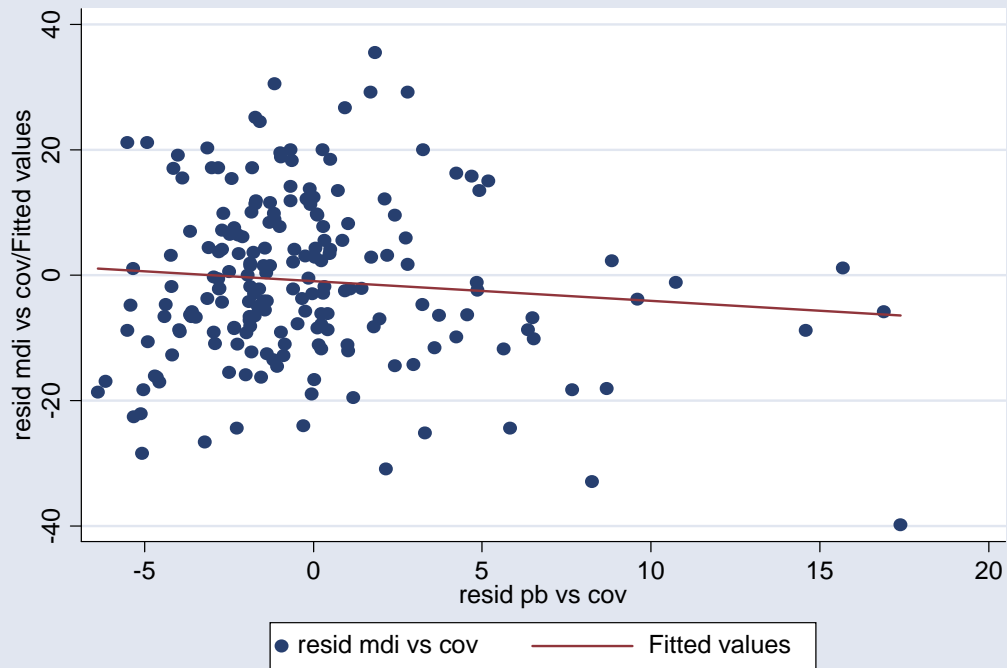
**Self esteem
Quartile 4**

Another Pilot Study: Maternal Child Lung Study

- Pregnancy cohort recruited from 1986-1992
- Study of in utero/environmental tobacco smoke exposure and respiratory outcomes
- Women enrolled before 20th EGA week
- Children followed after birth
- Measured ETV (violence) and WCST as pilot

Effect of Cotinine in Predicting Errors on WCST: Stratified by Median Violence Exposure

	Cotinine Beta (Low violence)	Cotinine Beta (High violence)
% Errors	2.9 (p=0.6)	9.8 (p=0.07)
# Perseverative Responses	1.7 (p=0.7)	11.1 (p=0.007)
%Perseverative Responses	2.0(p=0.7)	10.7 (p=0.007)
# Perseverative Errors	0.8 (p=0.9)	10.7 (p=0.01)
% Perseverative Errors	1.4 (p=0.8)	9.9 (p=0.02)

Mexico Birth cohort

- The work just reviewed led to the establishment of a new birth cohort in Mexico City.

- R01 ES013744 Stress, Lead, Iron Deficiency and Neurodevelopment.

ELEMENT
Early Life Exposure in Mexico to
Environmental Toxicants Project

Mexico City Cohort

- Long term goals
  - Identify factors that increase/decrease metal toxicity
  - Understand the biology of metal neurotoxicity
  - Prevent toxicity
  - Treat toxicity after it has occurred

Cohort 4 — Metal mixture and stress (IMSS - Casita - Perinato)

Mothers

Mothers	Topics	Recruit	Pregnancy (Trimester)		partum	Post Partum (months)								
		OR	2T	3T	00	01	03	06	09	12	15	18	21	24
Questionnaire	Screening questionnaire (Inclusion criteria)	X												
	GPS coordinates (Home address)		X	X										
	Sociodemographic	X	X											
	Lead exposure questionnaire		X	X	X	X		X		X		X		X
	FFQ (baseline=1 yr recall; postpartum = 1 month recall)			X		X		X		X				
Samples	Blood (CBC) →ABC		X		X									
	Venous blood (Pb) →ABC		X		X									
	Venous blood (Pb Mn Cd) →Boston (royal blue top)		X		X									
	Serum (Ferritin & C- reactive protein)→ Perinato		X		X									
	PAXgene tube w/ Blood (Genotype) → Boston					X								
	Hair (As & Se) → Boston		X			X								
	Nail (As & Se) → Boston		X			X								
	Salivary Cortisol → Dresden Germany		X			X		X						
	Serum (2 Tubes) → storage Boston		X			X								
	Urine (1 tube)→ Michigan for phthalates		X			X								
	Urine (1 tube)→ storage Boston		X			X								
	Whole Blood (tube) → storage Boston		X			X								
Measures	Anthropometry (calf, skin-fold, weight, height*)		X*			X		X		X		X		X
	Bod Pod					X		X		X		X		X
	Blood Pressure		X			X		X		X				
	Bone Mineral Density		X	X		X		X		X				
	Bone lead (KXRF)					X		X						
Psychometric tests	1.- Self-esteem (Coopersmith)		X							X				
	2.- IQ (WASI)					X								
	3.- Exposure to violence		X									X	X	X
	4.- Crisis in Family Systems (CRISYS)		X							X	X	X	X	X
	5.- Perceived Stress Scale (PSS-4)*		X	X					X	X	X	X	X	X
	6.- Pregnancy Anxiety Scale		X	X										
	7.- Trait Anxiety Scale STI (SPIELBERGER)		X											
	8.- Life Orientation Test (LOT)		X											
	9.- Social Support Network (SSN)		X							X				X
	10.- COPE		X											
	11.- Center for Epidemiological Studies Depression Scale (CES-D) (EDINBURG)		X			X		X		X				X
	12.- Gender Role Conflict Scales		X											
	13.- Intrinsic Religious Motivation Scale		X											
	14.- Parenting Stress and self efficacy (BRAZELTON)(NBAS)					X								

* maternal height only measured once

▨ = indicates that information will be collected at this visit if not done previously at another visit

Tar Creek Superfund Site

Thanks

Element
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