Synergistic Effects of Combined Lead and Stress: Implications for Disproportionate Environmental Health Impacts

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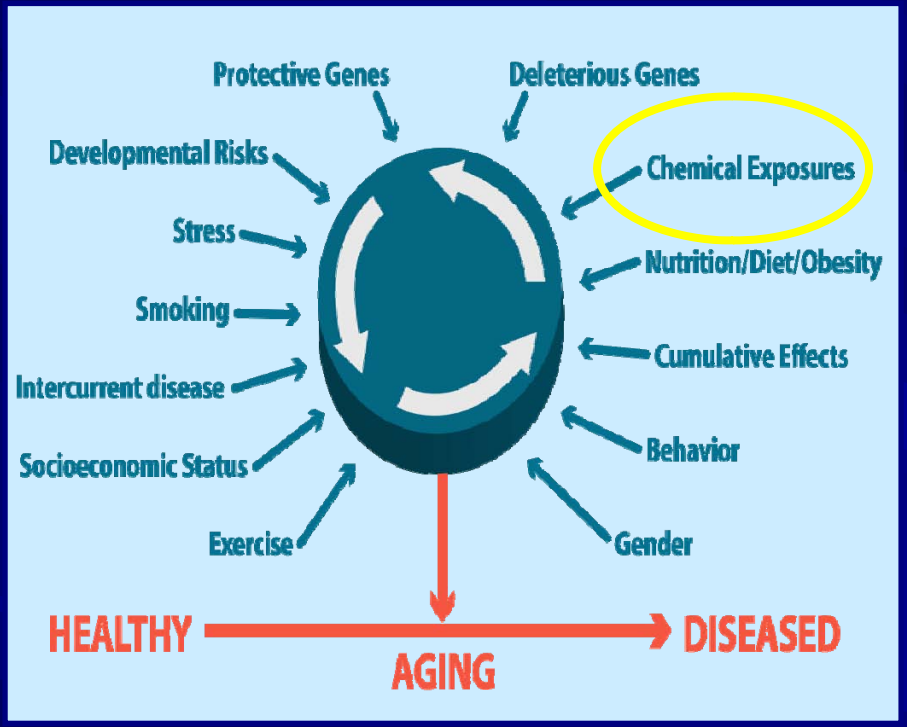
Current Toxicological Approaches do not Reflect Human Conditions

Complex Disease



Each individual experiences a unique set of risk factors

Animal and Epi Studies

Study of one chemical in isolation in a healthy young organism

Lead: An Enduring Public Health Problem

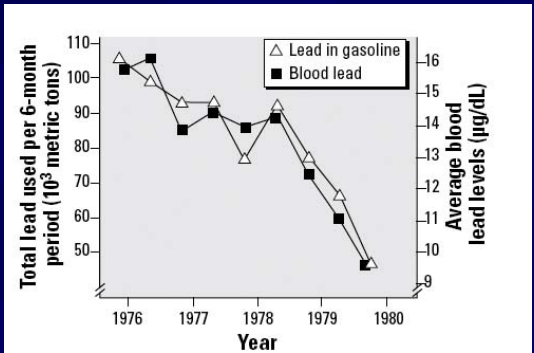
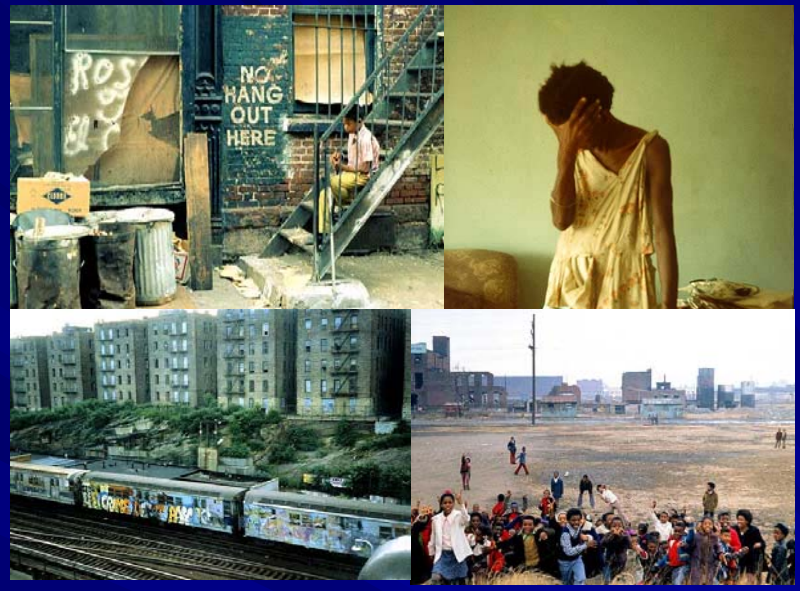


Figure 1. Parallel decreases in blood lead values and amounts of lead consumed in gasoline between 1976 and 1980 (U.S. EPA 1986).



Even Today:

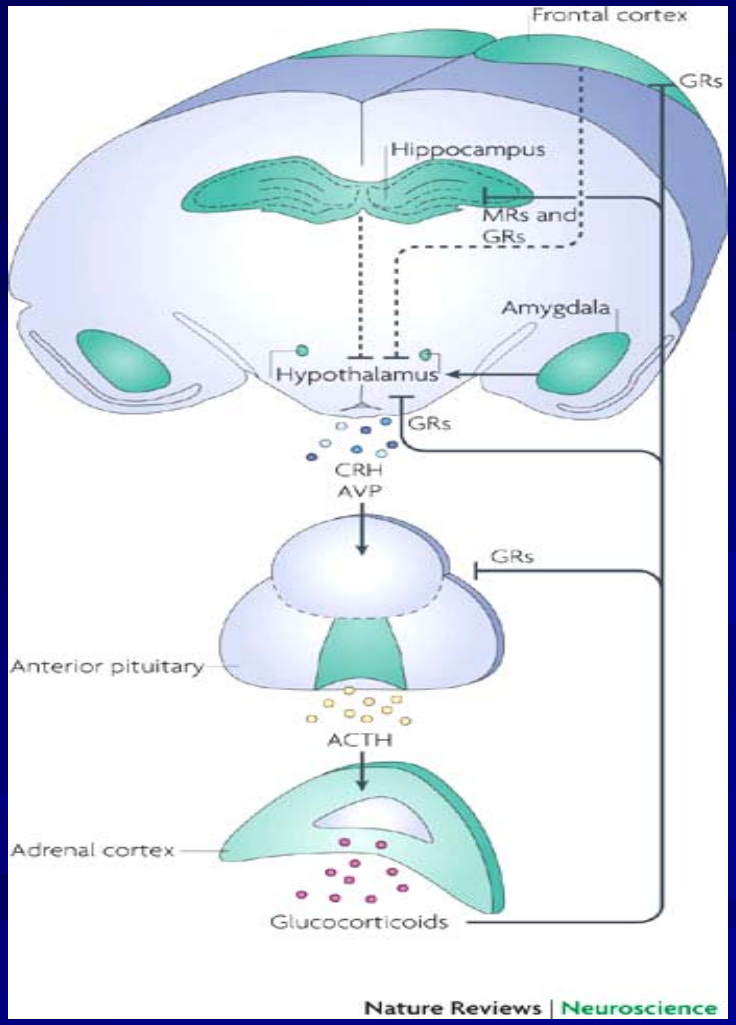
- Pb exposure has become demographially circumscribed:
- preferentially targets low socioeconomic status inner city minority communities, especially children
- transgenerational in these communities
- Cycle of Pb exposure has become coincident with the cycle of poverty in the U.S.

i.e, the same communities that experience the highest levels of stress:

- Maternal (prenatal) stress in particular has enduring negative consequences for children

Thus, Pb and Stress are Co-Occurring Risk Factors

Pb and Stress Act on Common Biological Targets

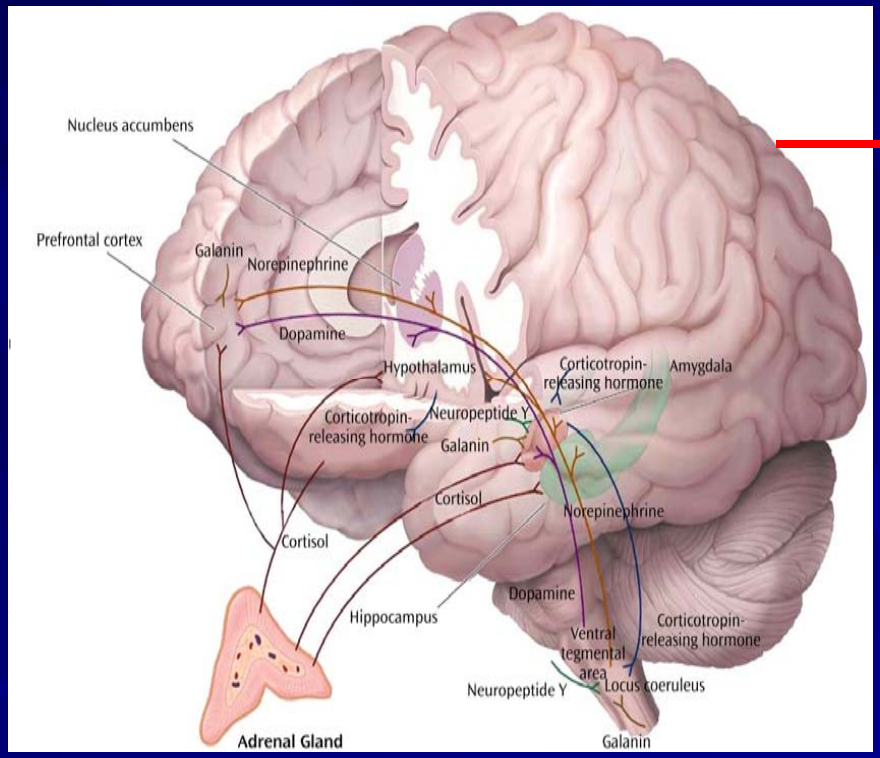


- Both Pb and stress can permanently alter function of the HPA axis, the physiological system that mediates the body's response to stress

The Broad Array of Consequences of HPA Axis Dysfunction

- Cushing Syndrome
- Diabetes
- Obesity/metabolic syndrome
- Hypertension
- Osteoporosis/Osteopenia
- Autoimmune disorders
- Depression
- Anorexia
- Obsessive-compulsive disorder
- Panic disorder
- Hyperthyroidism

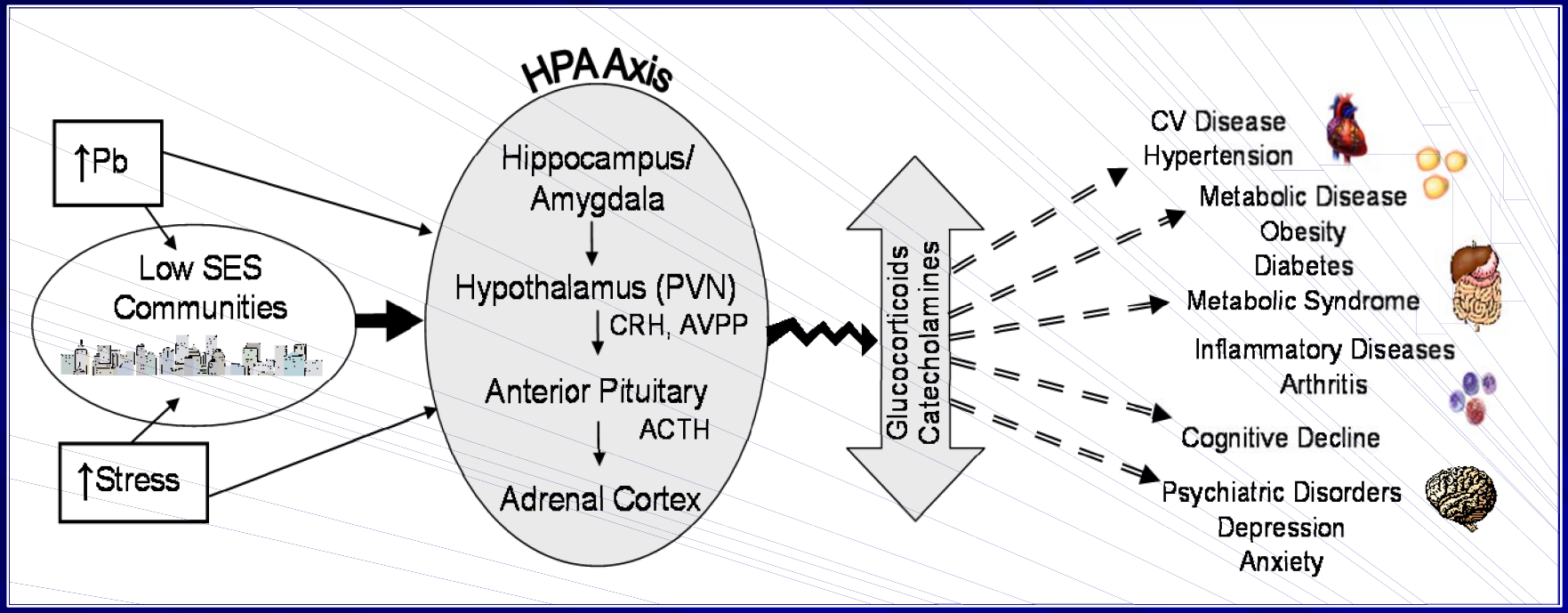
Pb and Stress Also Act on Brain Corticolimbic Systems and Cause Common Adverse Effects



Adverse Effects on Cognitive Function: Learning, Attention,

Thus, Pb and stress are co-occurring risk factors that have overlapping biological target and produce common adverse effects

Do Pb and Stress Act Synergistically?

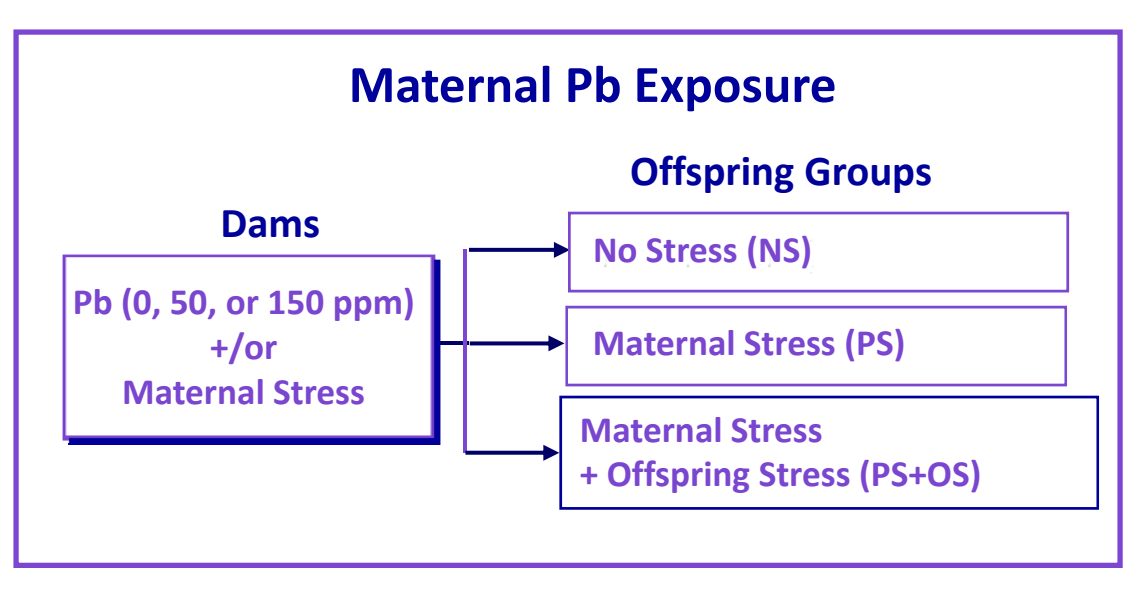


If Pb and stress act synergistically, then:

- actual exposure levels of concern for Pb may be lower than currently understood.
- elevated Pb exposure may contribute to the associated increase in incidence of diseases and disorders in low SES communities which have been postulated to arise from chronically elevated stress

Do Pb and Stress Act Synergistically? Maternal Pb Exposure

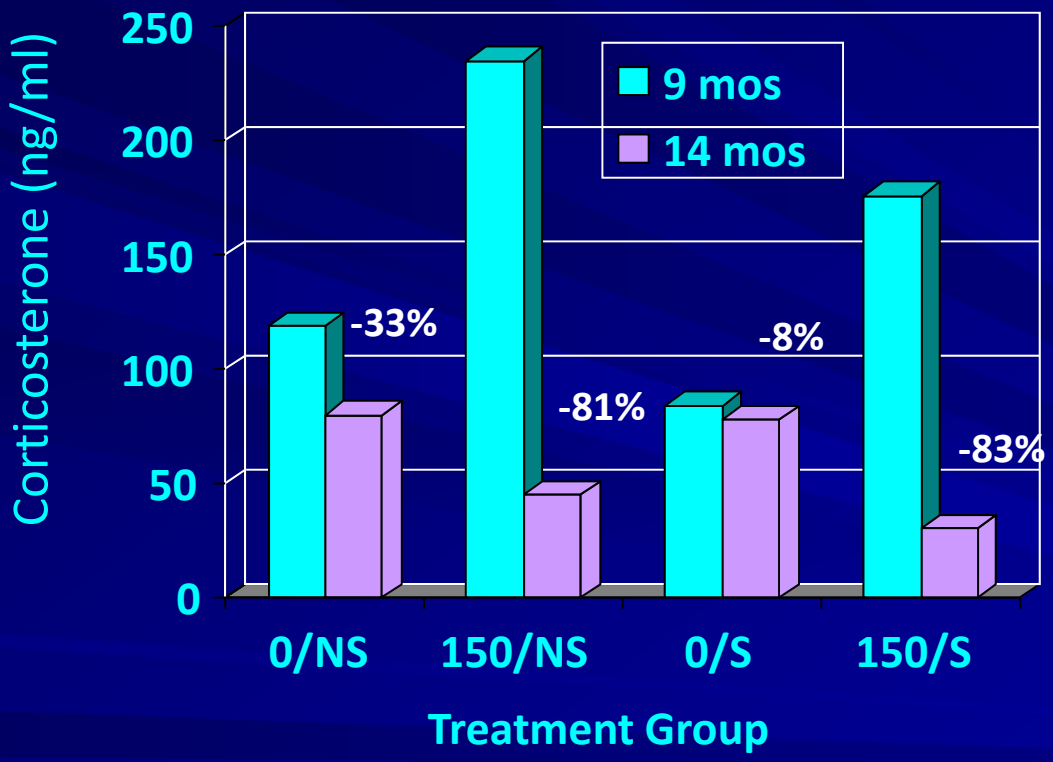
Maternal Pb*, +/-maternal stress,+/-offspring stress



- Pb exposure of rats beginning 2-3 months prior to breeding
- Blood lead levels of dams at weaning: <3, 11 and 32 ug/dl, respectively
- Blood lead of dams at weaning: <3, 19 and 32 ug/dl, respectively, declining to <3 by 40 days of age

Cory-Slechta et al., 2004; Virgolini et al., 2008

Dynamic Nature of Corticosterone Changes Across the Lifespan: Male Offspring



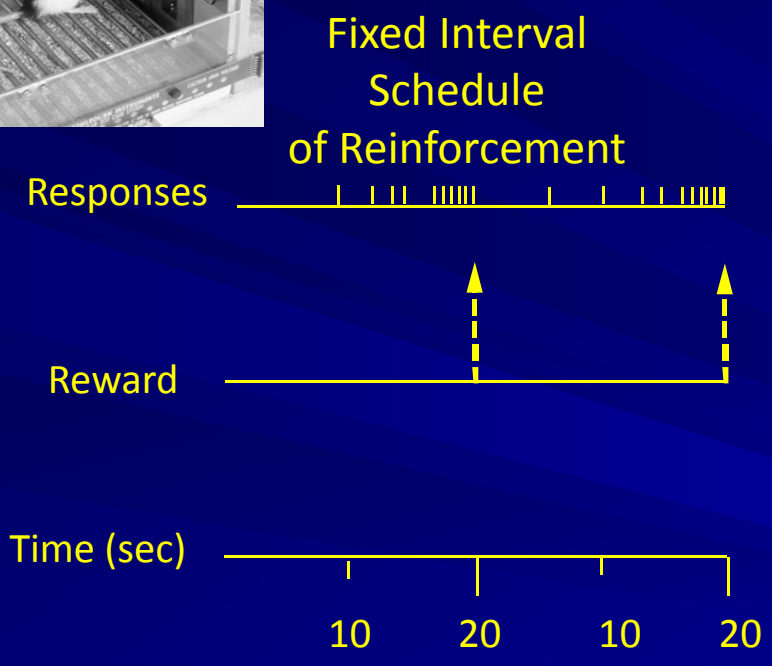
0/NS
no Pb, no stress

150/NS
maternal Pb

0/S
maternal stress

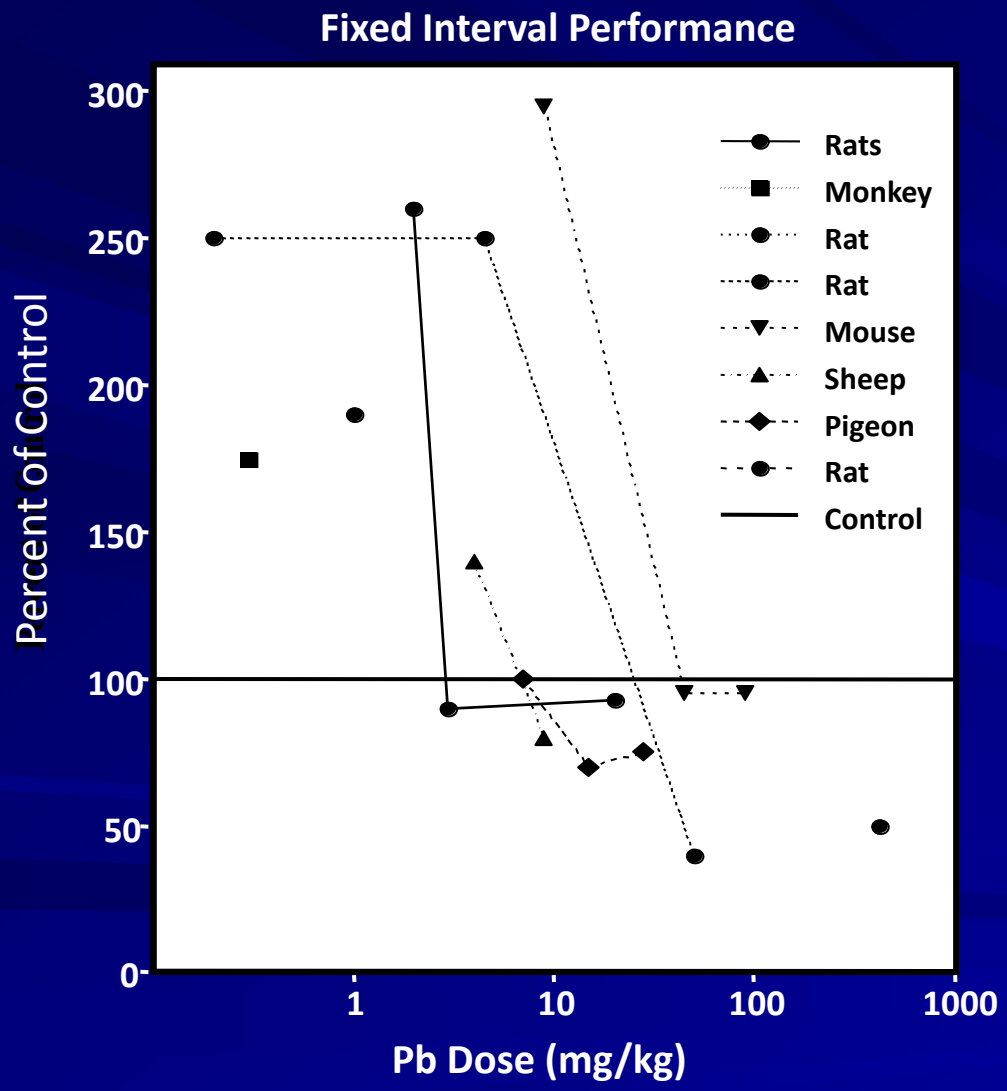
150/S
maternal Pb + stress

Fixed-Interval Schedule-Controlled Behavior



The first response occurring after a fixed interval of time has elapsed (20 sec in this example) results in reward delivery and the initiation of the next fixed interval of time. The schedule produces a pattern of responding that is very low early in the interval But increases as the time to reward approaches. Human example: studying for an exam

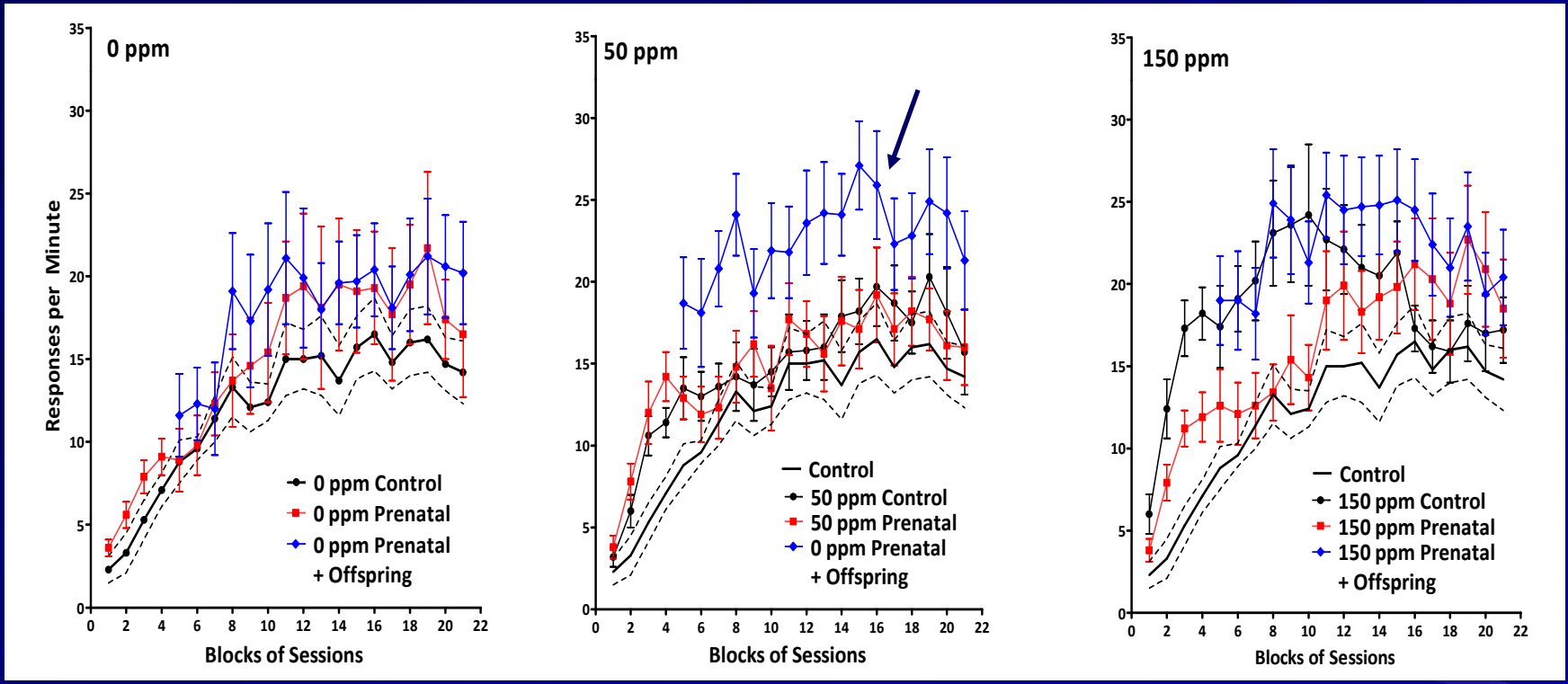
Behavioral Effects of Pb on FI Performance



- Pb routinely impacts FI performance
  - Occurs across species and across developmental periods of exposure
  - Inverse U-shaped dose-effect curve

Cory-Slechta, 1995

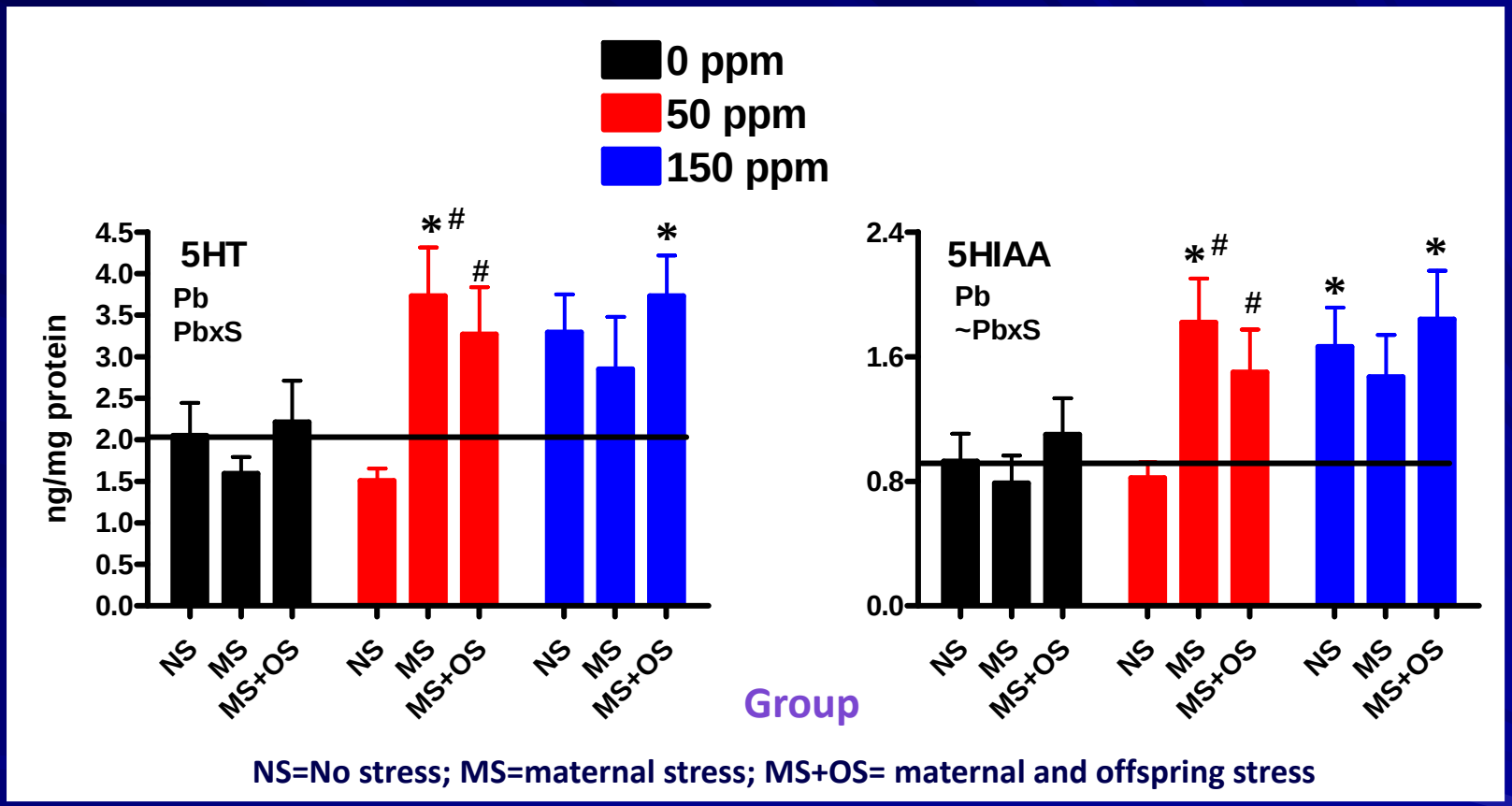
Maternal Pb + Stress Additive Effects on FI Performance in Females



Females exhibit 'Pb + additive increases in FI response rates; potentiated effects of 50 ppm and prenatal and offspring stress' FI performance has been shown to be a surrogate for 'impulsivity' in studies of children.

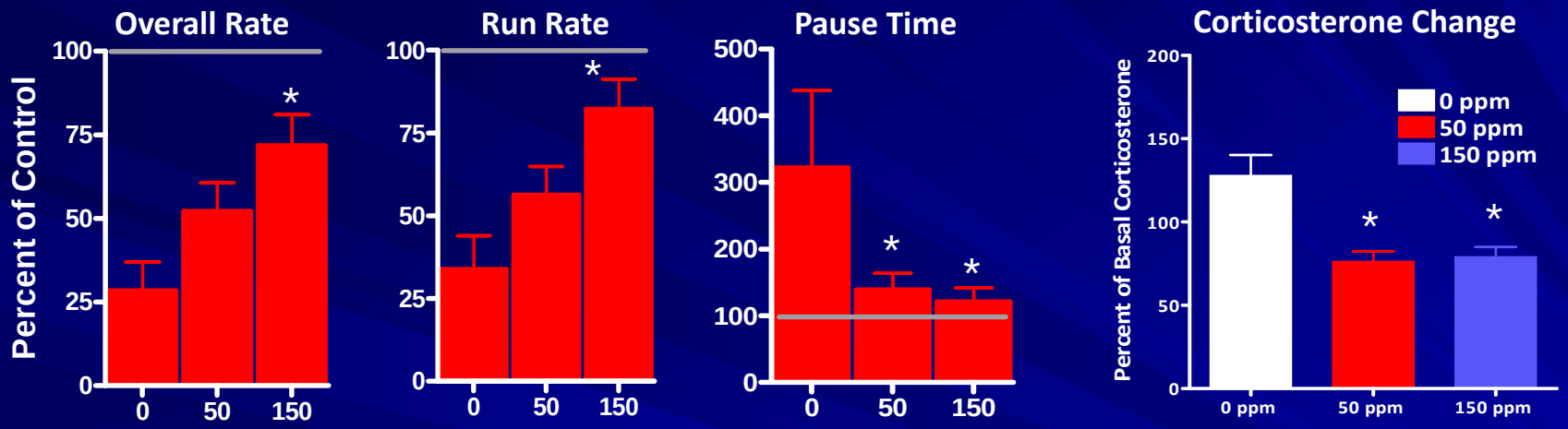
Virgolini et al., 2008

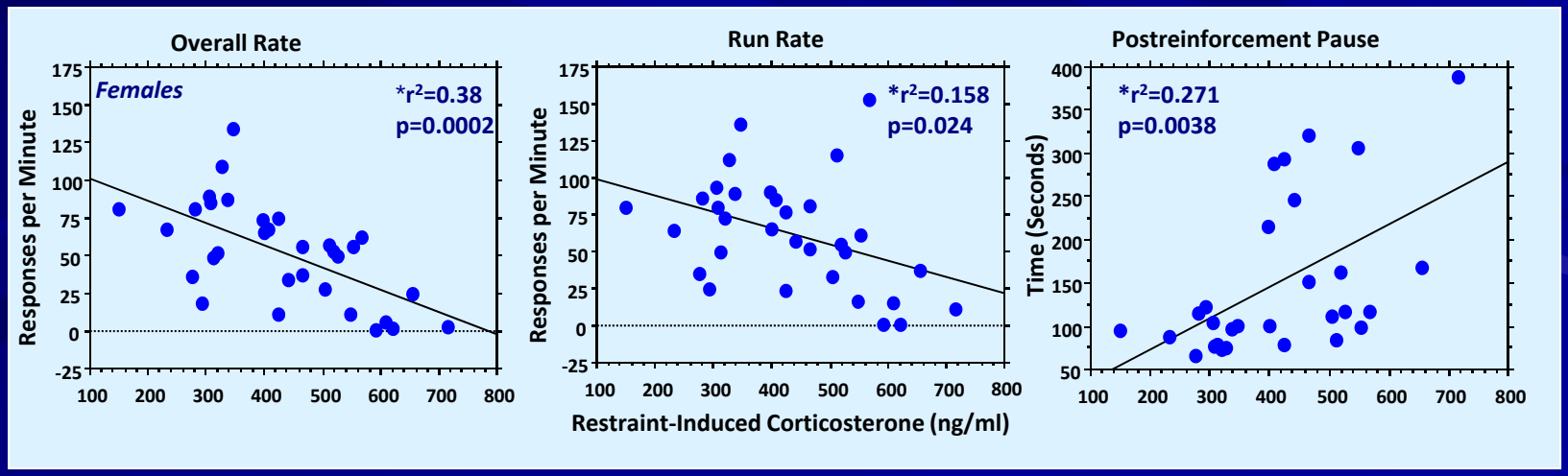
Pb + Stress Additive Changes in Brain Neurotransmitters: Frontal Cortex



Potentiated neurochemical changes occur in female offspring, and, importantly, in some cases changes reflect combined Pb + stress additive effects.

Altered Stress Response in Females and its Correlation with Corticosterone Changes

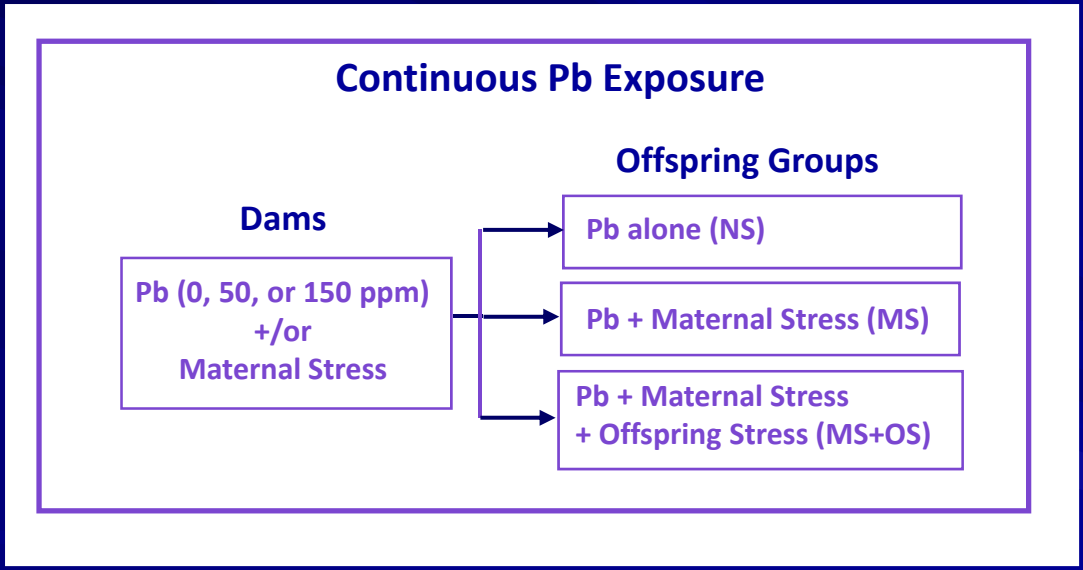




Virgolini et al., 2008

Do Pb and Stress Act Synergistically? Lifetime Pb Exposure

Lifetime Pb*, +/-maternal stress,
+/-offspring stress



- Pb exposure beginning 2-3 months prior to breeding
- PbBs of dams at prior to breeding: 5-7 µg/dl; at weaning: 13 µg/dl
- PbBs of offspring at PND 5-6: 11-13µg/dl; at 2.5 mos: 6-7 µg/dl

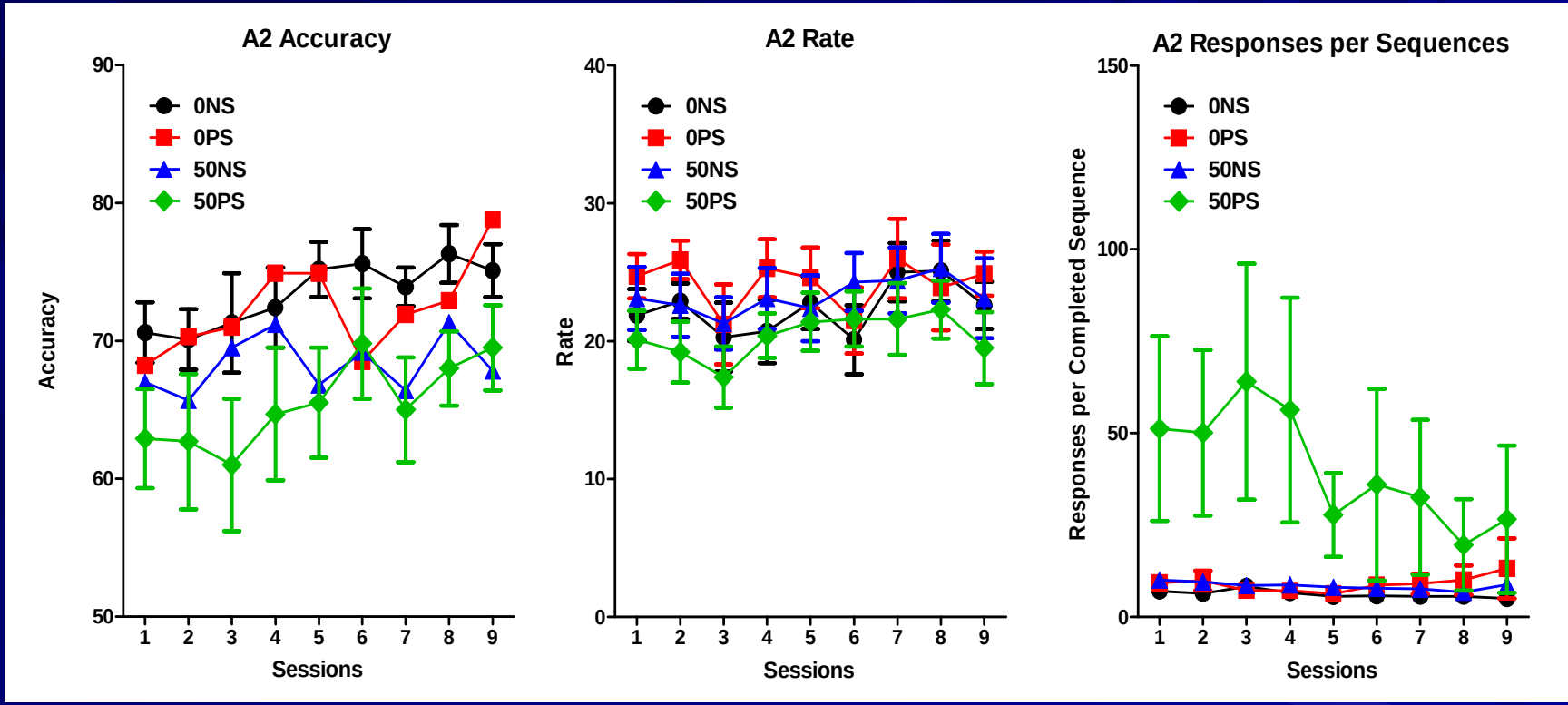
Can Stress Enhance Pb-Associated Impairments in Learning?

Multiple Schedule of Repeated Learning and Performance

Rat pressing one of 3 levers in an operant chamber to produce food reward.
Each day the rat was required to learn a new sequence of 3 responses.

Cohn, Cox and Cory-Slechta, 1993

Synergistic Effects of Combined Lifetime Pb & Stress on Learning in Female Offspring

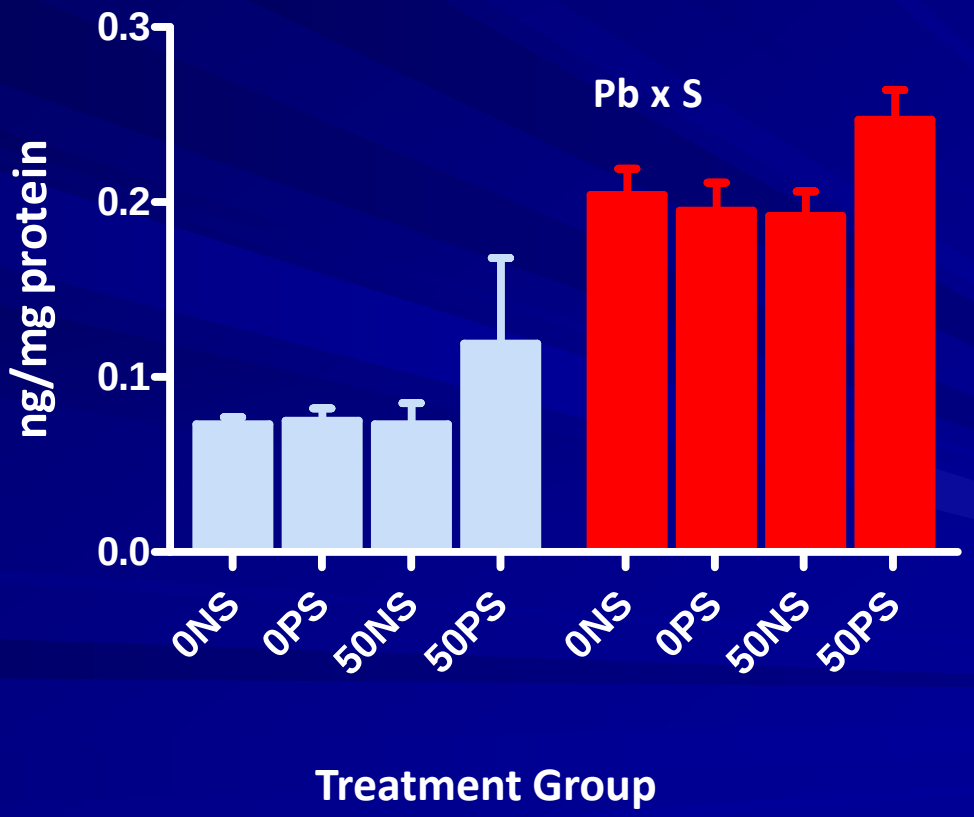


Preferential impairments in learning in females: Lower accuracy and delayed improvement over time, requiring more responses to achieve a completed sequence, an effect that does not reflect lowered response rates.

Cory-Slechta et al., in preparation

Synergistic Effects of Combined Lifetime Pb & Stress on Learning in Female Offspring

Nucleus Accumbens Dopamine Turnover



Cory-Slechta et al., in preparation

Higher Pb Enhances the Cortisol Response to Acute Stress in Children

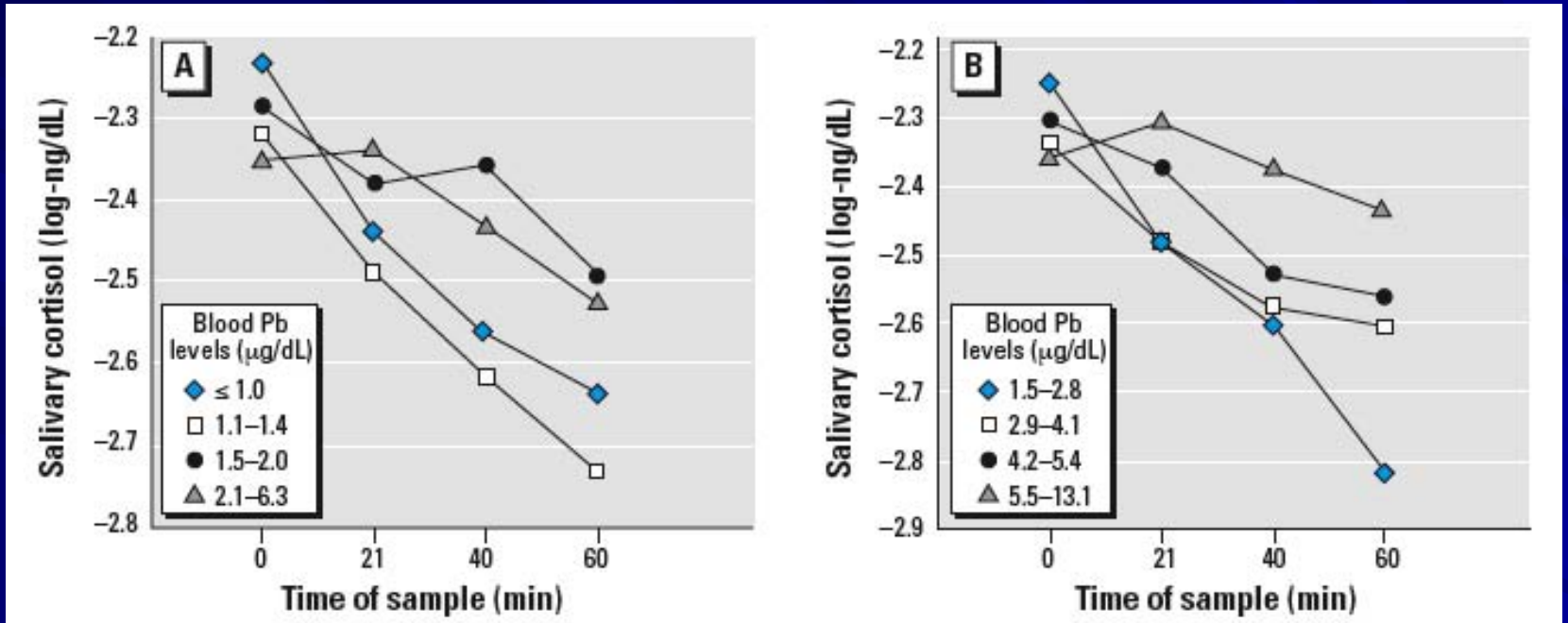
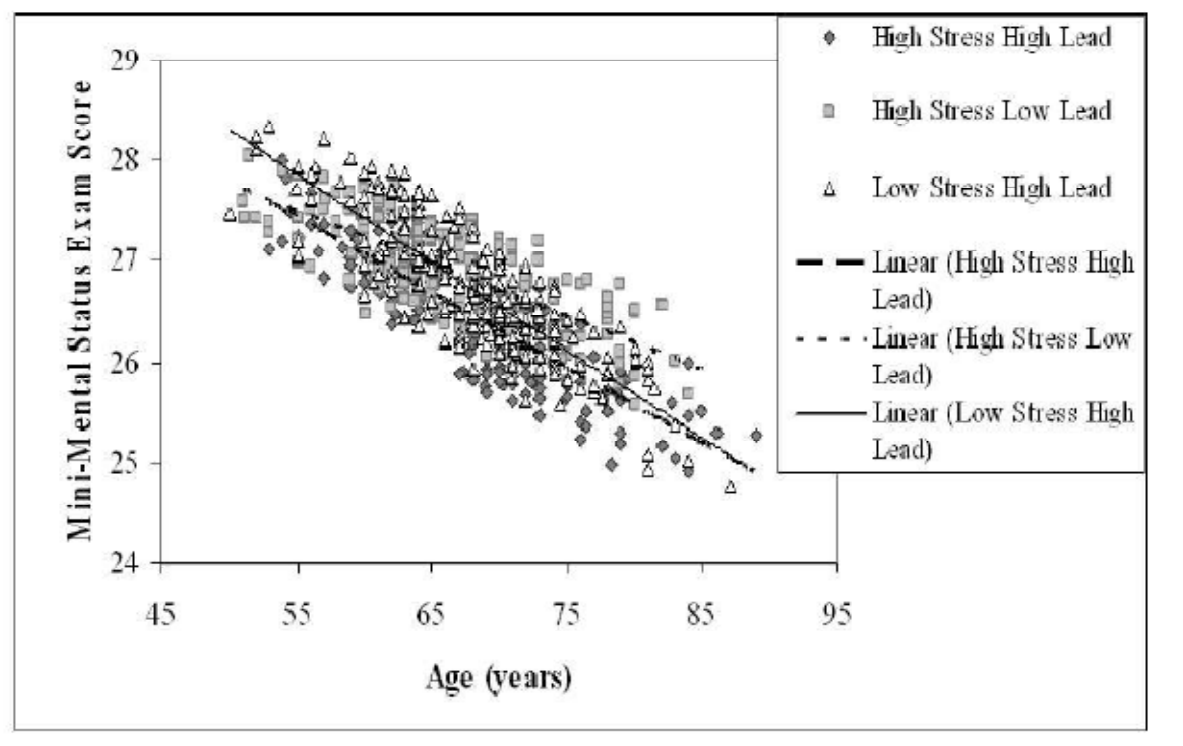


Figure 1. Children's unadjusted initial salivary cortisol levels (log-ng/dL) and after an acute stress task as a function of quartiles of prenatal (*A*) and postnatal (*B*) Pb exposure.

Gump et al., 2007

Interactions of Stress, Lead Burden and Age on Cognition in Older Men: the VA Normative Aging Study



Men with high perceived stress scores had a lower Mini Mental State Exam (MMSE) score for a two-fold increase in blood lead compared to those with lower stress. In addition, combinations of high perceived stress scores and high blood lead categories were associated with greater reduction on the MMSE score for each year of age. Thus, psychological stress had both an independent inverse association and modified the relationship between lead exposure and cognitive performance among older men. Furthermore, high stress and lead together modified the association between age and cognition.

Peters et al., 2009

Conclusions

- Even maternal only Pb exposure can permanently change HPA axis function
- Based on its ability to permanently impair HPA axis function, elevated Pb exposure could serve as a risk factor for the increased incidence of diseases and disorders in low SES communities
- Screening programs for elevated Pb exposure focus on young children; such programs need to be expanded to include pregnant women, particularly those in high stress environments

Conclusions

- A critical need to evaluate effects of toxicants in the context of other extant risk factors with which they share common biological substrates and/or common adverse outcomes
  - Studying chemicals in isolation does not reflect the human environment
  - May result in lower effect levels
  - Current approaches leave us picking the low-hanging fruit

- Using criteria including co-occurrence and shared biological substrates and/or adverse outcomes is a strategy to prioritize and address the 'mixtures' problem.