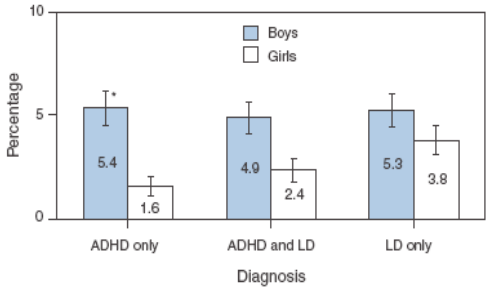
Putative Mechanisms in ADHD

Heterogeneity of ADHD

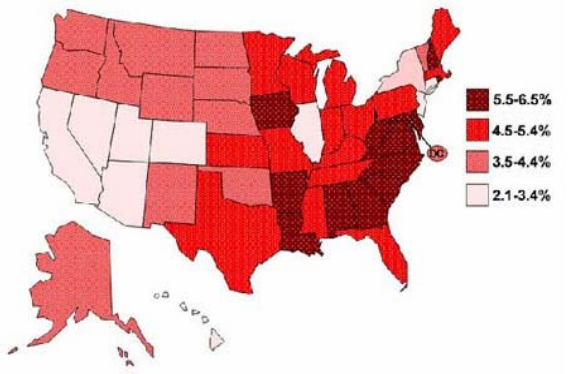
- ADHD is a Complex Spectrum Disorder
  - Variable Symptoms
  - Variable Response to Therapeutics
  - Numerous Co-Morbid Conditions

Percentage of Children Aged 5–17 Years Ever Having Diagnoses of Attention Deficit/Hyperactivity Disorder (ADHD) or Learning Disability (LD), by Sex and Diagnosis — United States, 2003

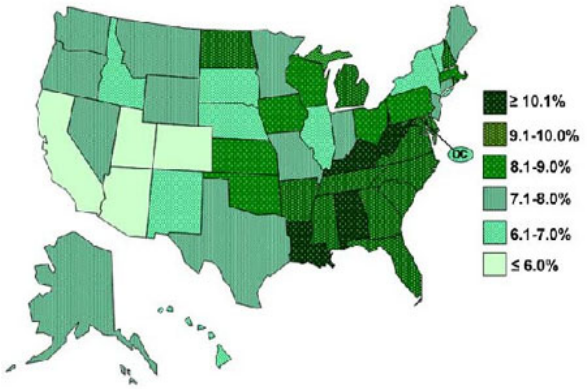


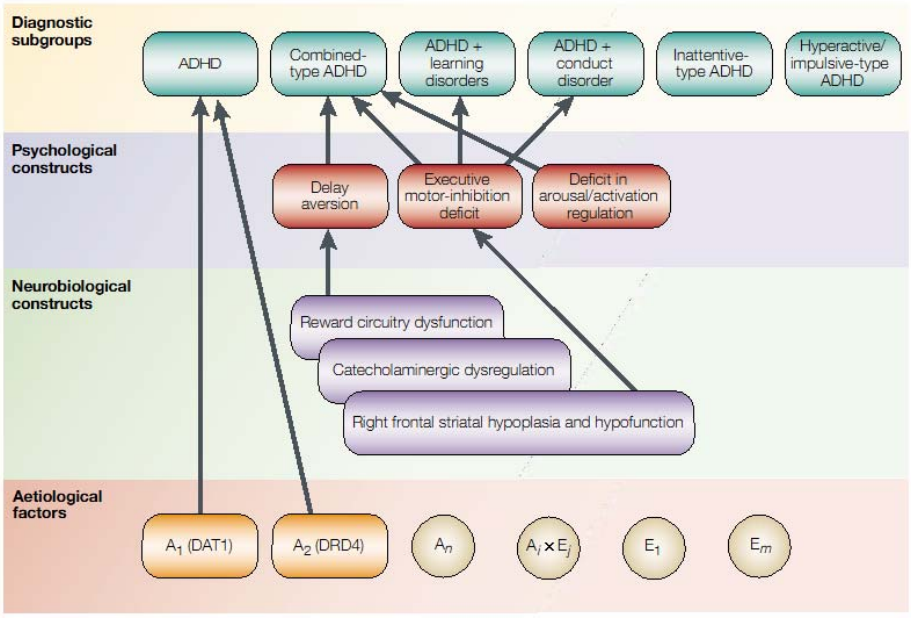
CDC, 2005

Parent Reported ADHD Medication



Parent Reported ADHD Diagnosis





Genetic Etiology of ADHD

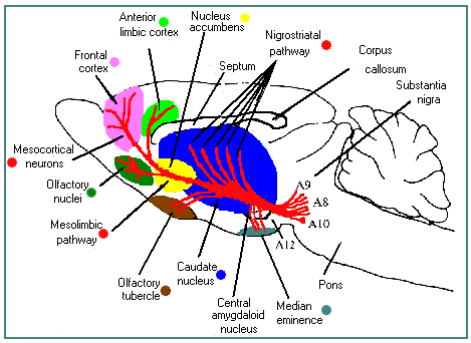
- 2-8 fold increase in siblings of ADHD patients
- Twin Studies Heritability 0.5-0.9
- Hudziak et al. Twin Cohort
  - 48% Genetic Dominance
  - 30% Additive Genetic Factors
  - 22% “Environmental Factors”

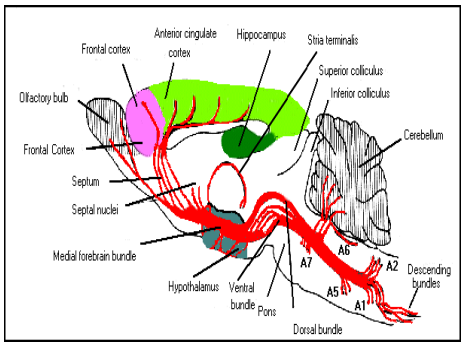
Genes and ADHD

Gene	Study Design	Pooled OR	95% CI
Dopamine D4 Receptor (exon III VNTR, 7-repeat)	Family	1.16	1.03–1.31
Dopamine D4 Receptor (exon III VNTR, 7-repeat)	Case–control	1.45	1.27–1.65
Dopamine D5 Receptor (CA repeat, 148 bp)	Family	1.24[a]	1.12–1.38
Dopamine Transporter (VNTR, 10-repeat)	Family	1.13	1.03–1.24
Dopamine β-Hydroxylase (TaqI A)	Case–control	1.33	1.11–1.59
SNAP-25 (T1065G)	Family	1.19	1.03–1.38
Serotonin Transporter (5-HTTLPR long)	Case–control	1.31	1.09–1.59
HTR1B (G861C)	Family	1.44	1.14–1.83

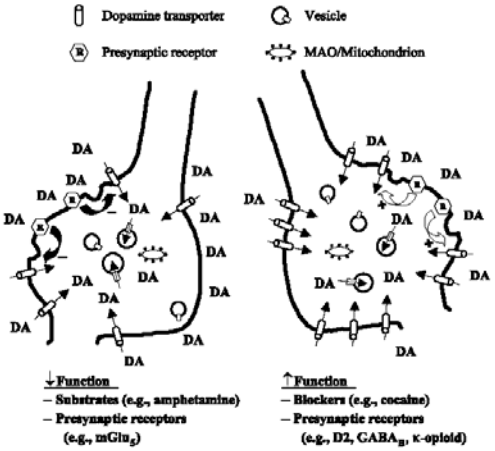
Faraone and Khan, 2006

Catecholamine Pathways



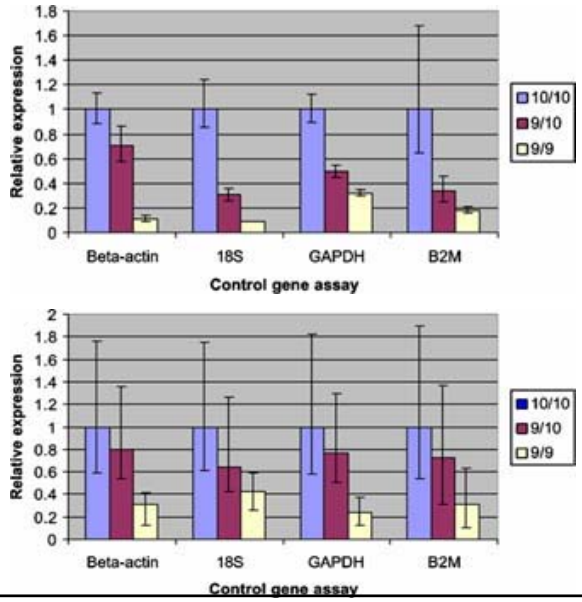


Dopamine Transporter Regulation

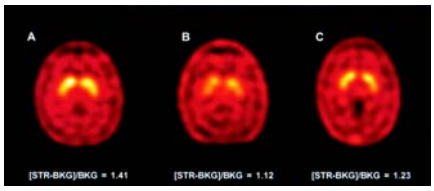


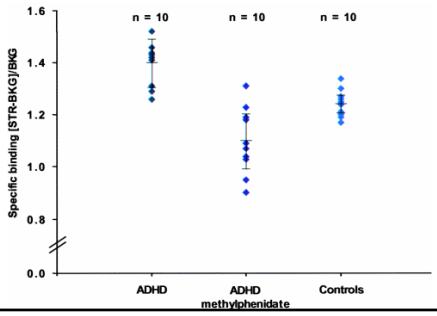
Gulley and Zahniser, 2003

VNTR Regulates DAT Levels



Elevated DAT Levels in ADHD





Ideal Qualities of Animal Models

- Face Validity
  - Mimic Behavioral Effects
- Construct Validity
  - Theoretical Rationale
  - Responds to Intervention
- Predictive Validity
  - Environmental Factors

Table 1
Comparison of animal models of ADHD

Model	Similarities to ADHD	Differences from ADHD	Comments
SHR	Hyperactivity in novel environment Motor impulsivity Attention deficit Some response to stimulants	Little association of hypertension with ADHD No sex differences in model Antihypertensives reduce model cognitive deficits and α_2 agonists benefit ADHD (direct central effect?)	Most thoroughly studied ADHD model Need more comparisons of pure hyperactive (WKHA) and hypertensive (WKHT) rats
DAT-KO mouse	Environment-dependent hyperactivity Stimulants reduce hyperactivity Cognitive impairment (radial maze)	Stimulant effects on cognition untested Methylphenidate requires high doses 5-HT agents beneficial in model, not in ADHD Evidence of DAT-*excess* in ADHD	No evidence of DA functional excess in ADHD
Coloboma neutron-irradiated mouse	Spontaneous hyperactivity Low-dose amphetamine reduces hyperactivity	Questionable relationship of ADHD to SNAP-25 gene Not improved by methylphenidate	Specific neural deficits not clear Cognition not well evaluated
NHE rat	Hyperactivity and attention deficits	Circadian motility normal	Requires neuropharmacological evaluation
Acallosal Mouse (I/LnJ)	Excessive arousal in novel environment Impulsive	Stimulants not tested No evidence of callosal dysfunction in ADHD	Needs further characterization
6-OHDA lesioned juvenile rat	Increased nonadaptive locomotor activity No sensory or motor deficits Stimulants attenuate hyperactivity and learning deficits	Lack of sex differences D_4 antagonists reduce hyperactivity	More assessment of attention and impulsivity needed D_4 antagonists need clinical testing
Neonatal anoxic rat	Some hyperactivity Deficits in learning and spatial memory Less active with amphetamine	Hyperactivity short-lived Cognitive effects of stimulants unknown Role of hypoxia in ADHD uncertain	Requires more pharmacological analysis
Cerebellar stunted rat	Hyperactive in novel environment Males more hyperactive	Attention and impulsivity not tested Stimulants untested Cerebellar dysfunction unproved in ADHD	Needs more behavioral comparisons to ADHD Role of cerebellum in ADHD requires assessment
Environmental toxins	Motor hyperactivity common in many species with varied toxins	Stimulant effects have limited testing Relationship of toxins to ADHD not proved	Mediating mechanisms not specified
Hippocampal X-irradiated rat	Hyperactivity present Deficits in memory-based learning Amphetamine improves learning	Stimulant effects on hyperactivity untested Radiation not implicated in ADHD	May model microneuronal hypoplasia or 'minimum brain dysfunction'
Spontaneously inattentive rats	Deficits in sustained attention	Ethylphenidate not beneficial	Pathophysiology undefined
Hyposexual male rat	Spontaneous hyperactivity Deficits in attention Amphetamine reduces hyperactivity	Stimulants untested in ADHD ADHD also in females	ADHD sex-linked in hyperactivity, not to attentional deficits

Abbreviations: DA, dopamine; DAT-KO, dopamine transporter gene knock-out mouse; 5-HT, 5-hydroxytryptamine, serotonin; NHE rat, Naples high-excitability rat; 6-OHDA, 6-hydroxydopamine; SHR, spontaneously hypertensive rat; SNAP-25, synaptosomal associated protein of 25 kDa; WKY, Wistar-Kyoto rat; WKHA, Wistar-Kyoto rat, hyperactive not hypertensive; WKHT, Wistar-Kyoto rat, hypertensive not hyperactive.

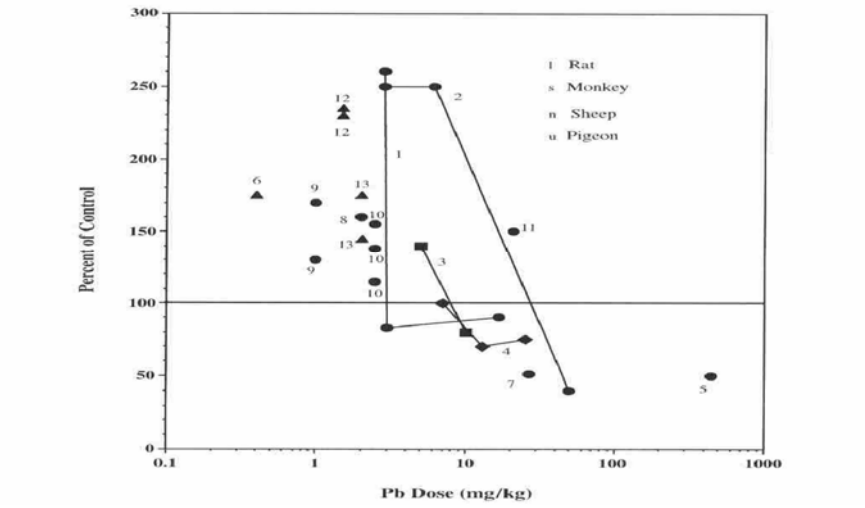
SHR Model of ADHD

- Hyperactive
- Impulsive-Like Behavior
- Attention-Deficits
- Elevated Dopamine Transporter Levels and Altered Dopamine Receptor Function
  - Response to Psychostimulants Not Well Characterized
  - Sex Differences Variable
  - Hypertension as a Confounder
  - Issues with “Control Strain”
  - Reproducibility

Environmental Factors in ADHD

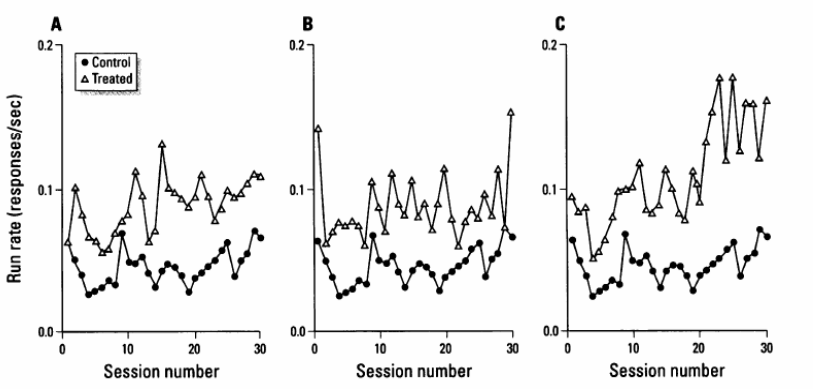
- Low Birth Weight
- Hypoxia
- Cigarette Smoking
- Lead?
- PCBs?
- Pesticides?
- Methyl Mercury?

Pb Effects on FI Performance



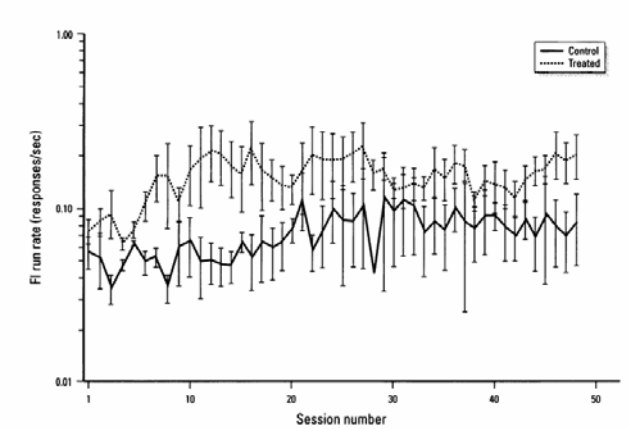
Cory-Slechta, 2003

Pb Effects on FI Performance in Monkeys



Rice, 2000

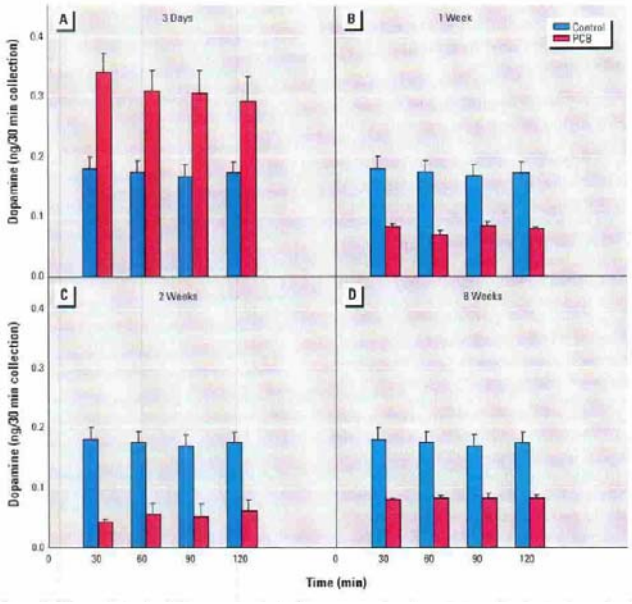
PCB Effects on FI Rates



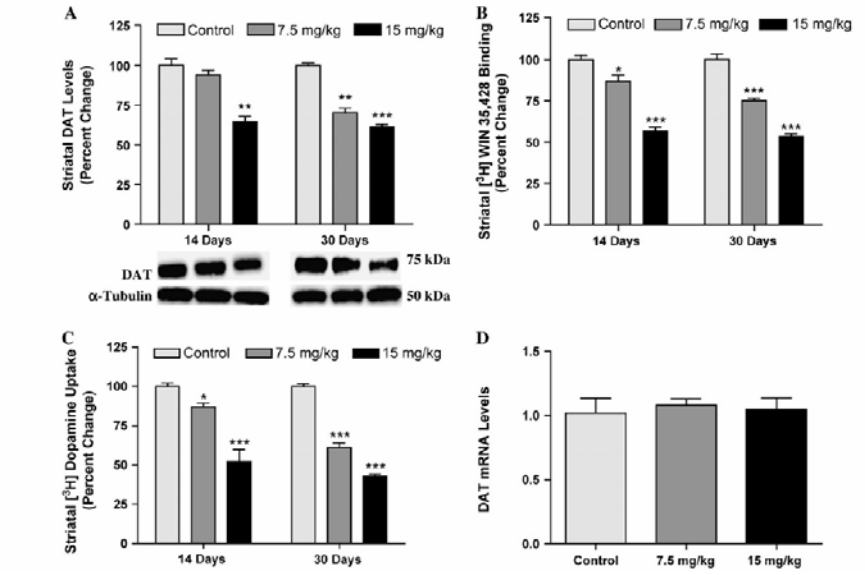
Rice, 2000

Are There Common Mechanisms?

- Impulsivity
  - Nucleus Accumbens
- Decreased DAT Levels
  - Activation of PKC
- Hypertension?

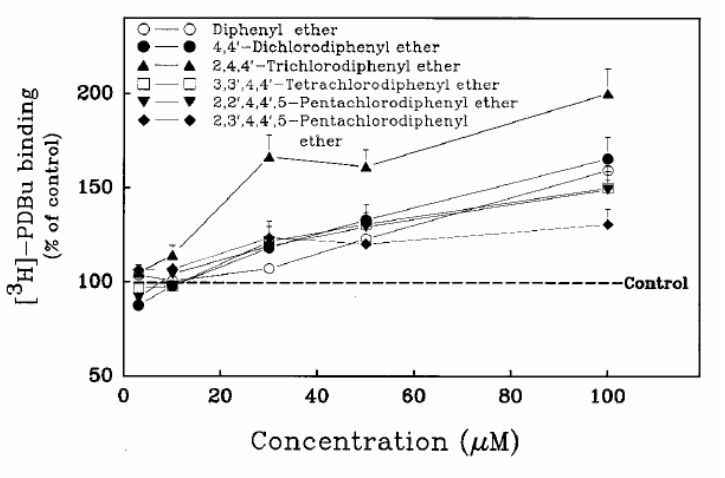


Seegal et al., 2002



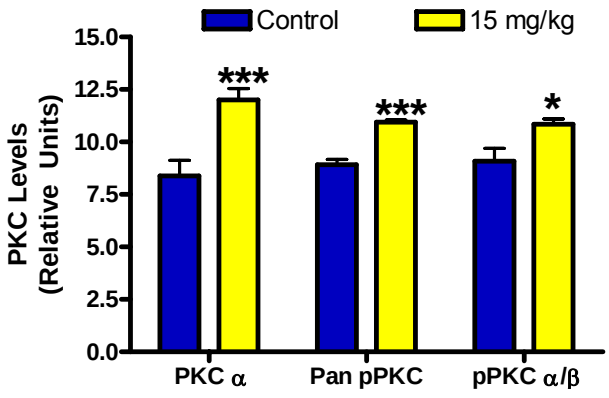
Caudle et al., 2006

PCB Effects on PKC



Kodavanti et al., 1996

Alteration of PKC by PCBs



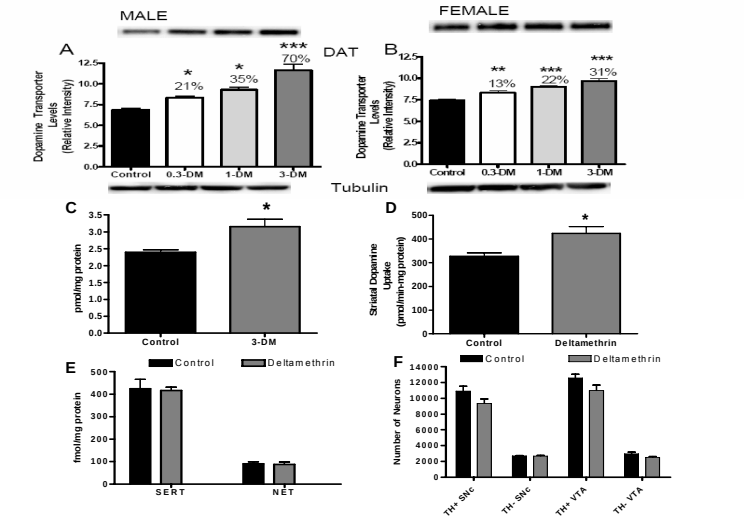
Oswego Cohort

Table 3. Relationship of PCBs, MeHg, DDE, HCB, and Pb exposure to money earned during the DRL task.

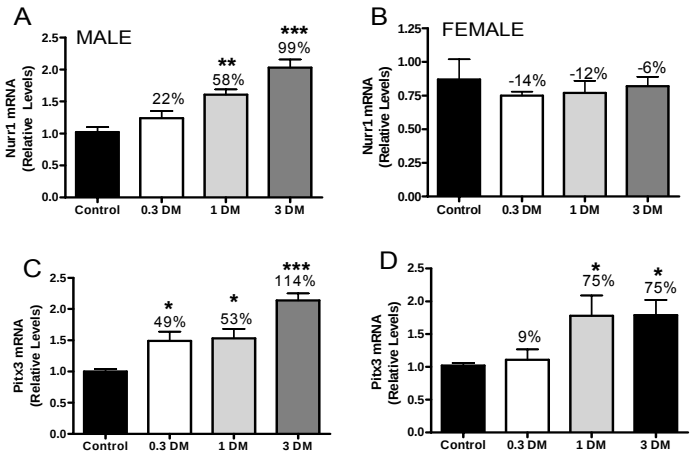
Contaminant	β	*p*-Value
Total PCB	–0.208	< 0.010
HighCl PCB	–0.076	0.338
MeHg 1st	–0.194	< 0.026
MeHg 2nd	–0.203	< 0.027
DDE	0.049	0.521
HCB	0.096	0.212
Postnatal Pb	–0.195	< 0.047
Prenatal Pb	0.035	0.641

Stewart et al., 2006

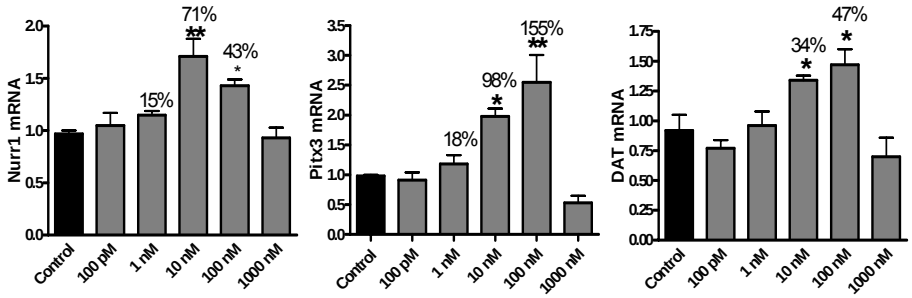
Developmental Deltamethrin Exposure Increases DAT Levels



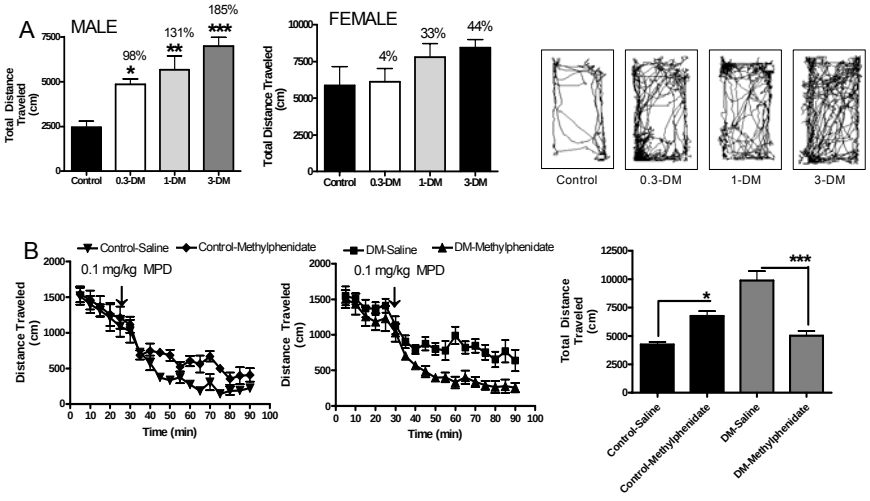
Gene Expression Changes Associated with DAT Increase



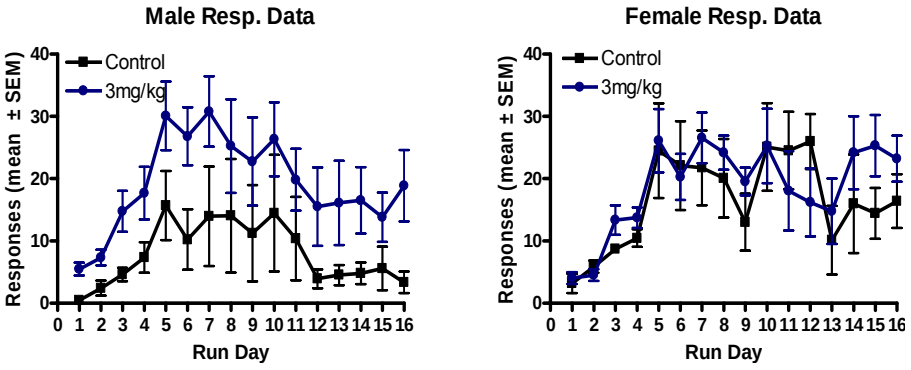
Use of In Vitro Systems to Test Mechanisms



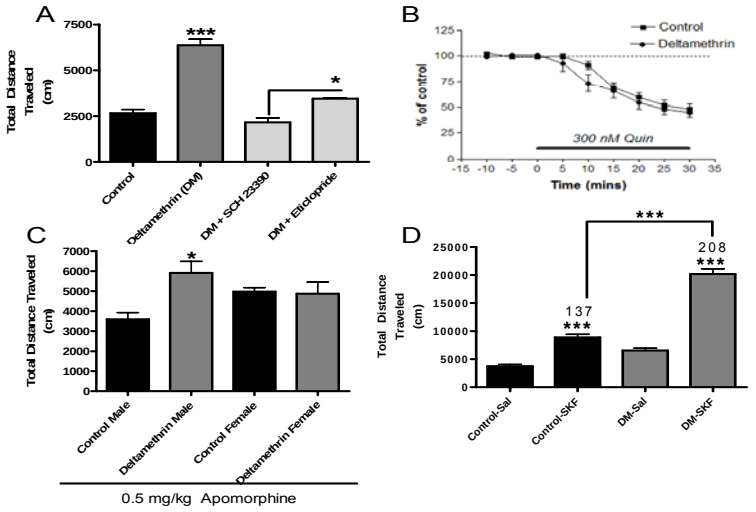
Developmental Deltamethrin Causes Hyperactivity Which is Abolished by Ritalin



"Impulsive-Like" Behavior Following Developmental Deltamethrin Exposure



Alteration of Dopamine Receptors May Contribute to Behavioral Effects



Can We Define Common Mechanisms?

- Catecholaminergic Dysfunction
- Interaction of Neurotransmitter Systems
- Anatomical Specificity
- Thyroid Hormones? (RTH, TRβ1)
- Hypertension?
- Hypoxia?
- Critical Periods of Exposure

Multiple Toxicants-Multiple Effects

- Common Pathways
- Genetic Susceptibility
- Other Environmental Factors
- Gene-Gene, Gene-Environment, Gene-Gene-Environment, etc.

Charges to Panel

- Recognition of Environmental Factors as Contributors to ADHD
  - Environmental Factors and Endophenotypes
- Utilize Cohorts Already Present and Prospective Cohorts in the Future
  - Identify Uniquely Susceptible Populations
- Integration of Basic, Epi, Clinical
  - Biomarkers to Aid Diagnosis
  - Better Design of Therapeutic Agents
  - Novel Therapeutic Strategies
  - Prevention