Dr. Bada has no conflicts of interest and has nothing to disclose

Neonatal Abstinence Syndrome: Consequences of Prenatal Opiate and Other Drug Exposure

Influences from Teratology & Environment

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OBJECTIVES

Describe the early and long-term outcomes following prenatal drug exposure

List supporting data for behavior teratology as a basis for outcomes after prenatal drug exposure

List factors that may enhance child development

OUTLINE

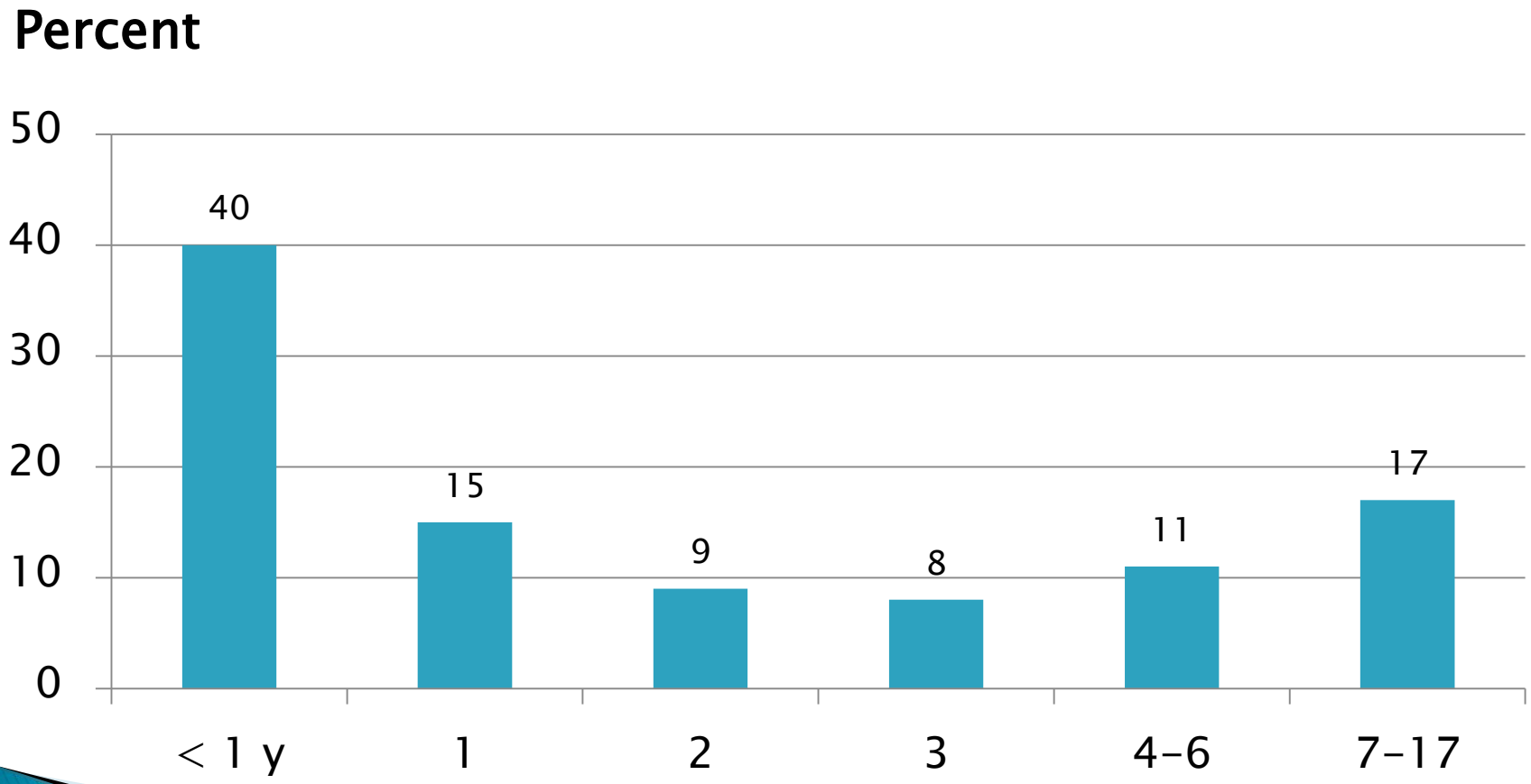
- Scope of the problem
- The newborn after prenatal exposure
- Recognizing abnormal neurobehavior
- Behavior intervention
- Maternal, family, environmental issues affecting outcome
- Underlying basis for early subtle outcomes
- Long-term outcomes of drug exposed newborns
- Role of risk and protective factors
- Long-term implications

Dr. Bada has no conflicts of interest and has nothing to disclose

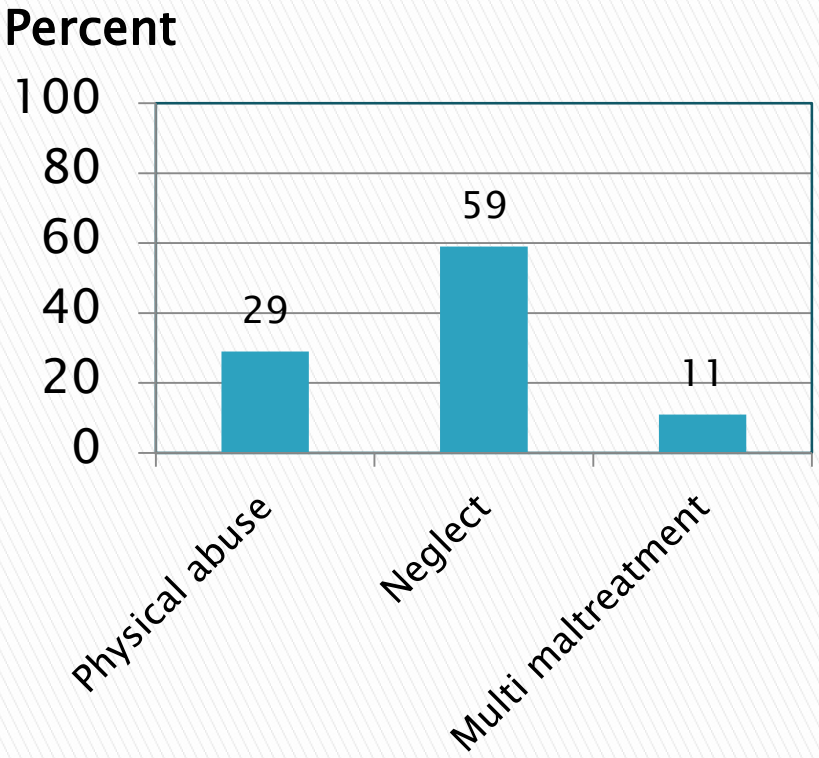
INFANT MORTALITY SUMMIT

- WHY NEONATAL ABSTINENCE SYNDROME?

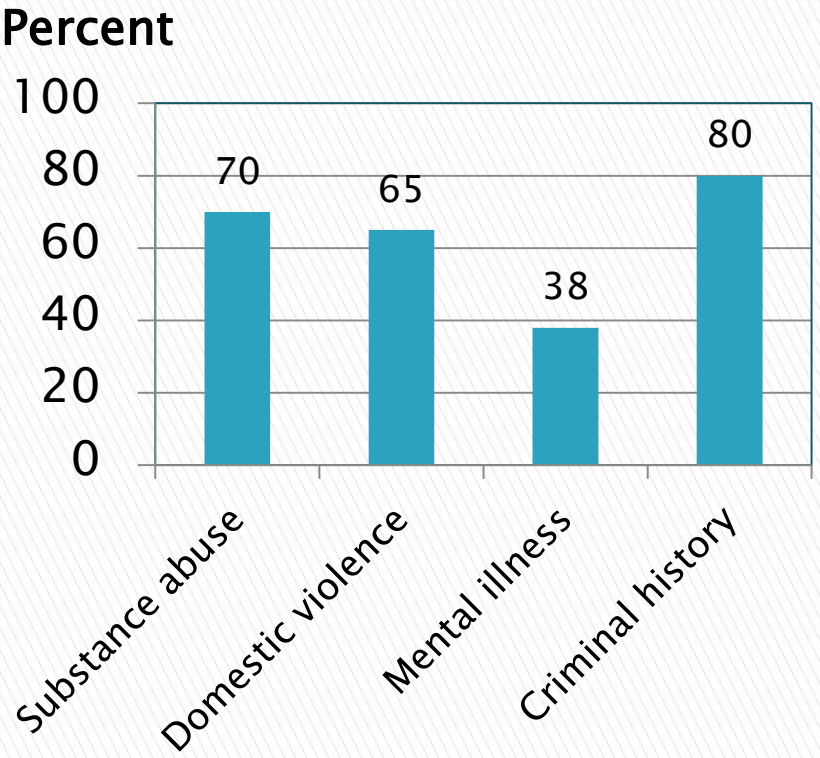
Age of Child (Fatalities/Near Fatalities (KY 2006 –2010)



Child Fatalities/Near Fatalities (KY 2006–2009)



Categories of maltreatment



Risk factors in fatalities/near fatalities

Drugs of Abuse During Pregnancy

- Illegal and Legal substances

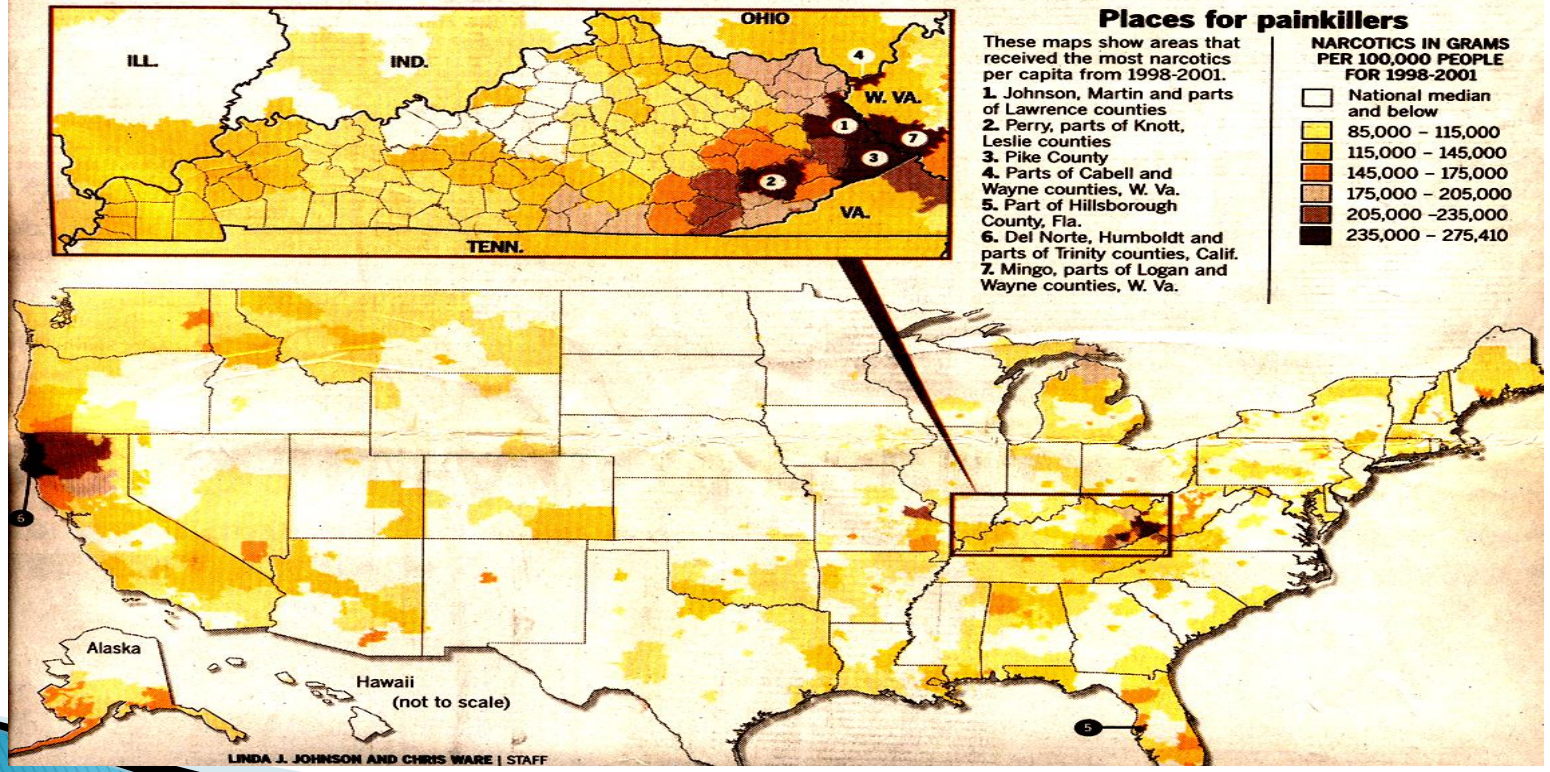
JANUARY 19, 2003 | SUNDAY | METRO FINAL EDITION

Lexington Herald-Leader

SPECIAL REPORT | PRESCRIPTION FOR PAIN

EASTERN KENTUCKY: PAINKILLER CAPITAL

INVESTIGATION REVEALS NARCOTICS FLOOD MOUNTAIN COUNTIES AT HIGHEST RATE IN NATION



Places for painkillers

These maps show areas that received the most narcotics per capita from 1998-2001.

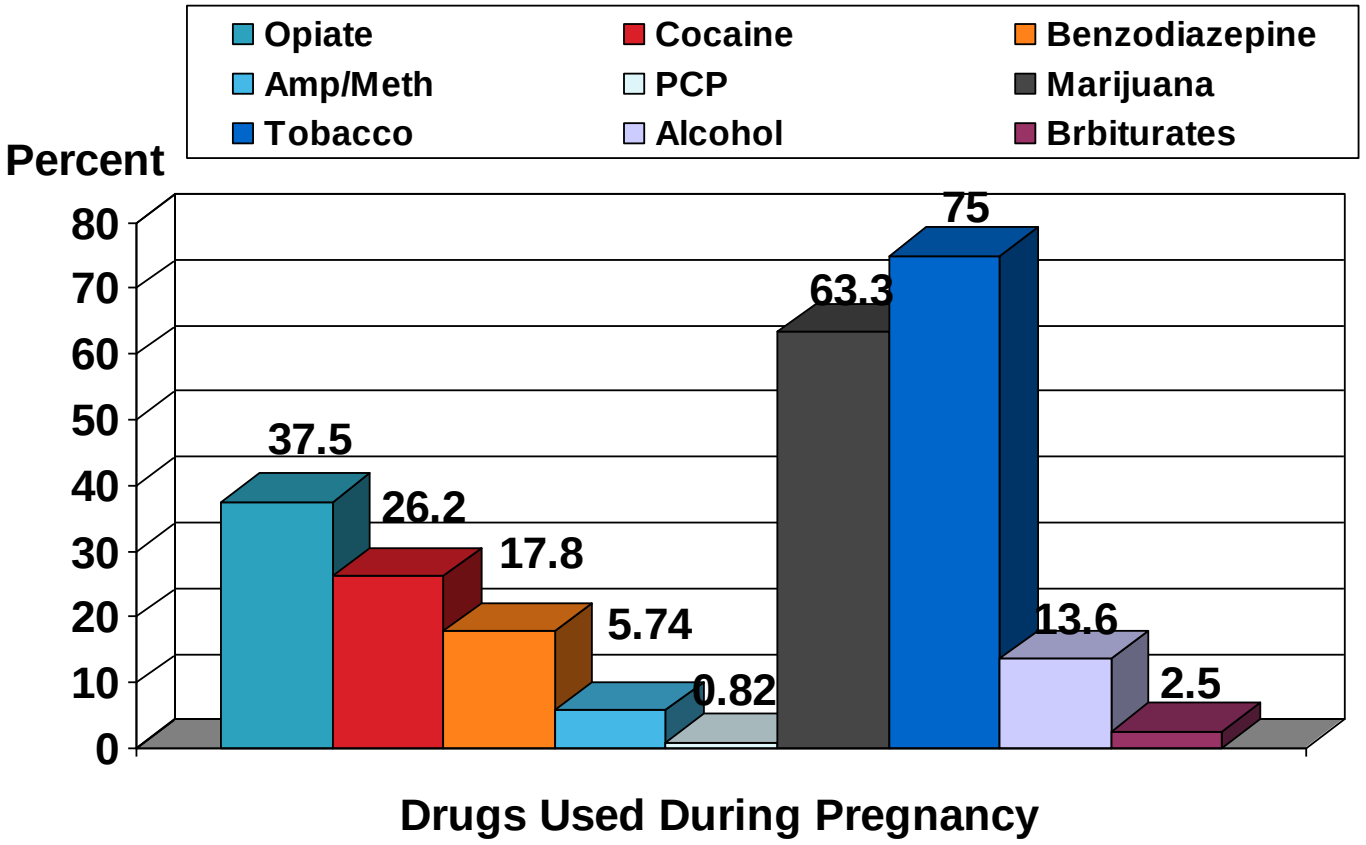
1. Johnson, Martin and parts of Lawrence counties
2. Perry, parts of Knott, Leslie counties
3. Pike County
4. Parts of Cabell and Wayne counties, W. Va.
5. Part of Hillsborough County, Fla.
6. Del Norte, Humboldt and parts of Trinity counties, Calif.
7. Mingo, parts of Logan and Wayne counties, W. Va.

NARCOTICS IN GRAMS PER 100,000 PEOPLE FOR 1998-2001

- National median and below
- 85,000 – 115,000
- 115,000 – 145,000
- 145,000 – 175,000
- 175,000 – 205,000
- 205,000 –235,000
- 235,000 – 275,410

Source: Drug Enforcement Administration

Prevalence of Use Among Drug Using Pregnant Women (%)



EASTERN KENTUCKY EXPERIENCE (%)

Zip Codes	Opiate N=183	Cocaine/ no opiate N=89	Benzo /no opiate or cocaine N=19	Meth /no opiate, cocaine or benzo N=7	All others with THC N=175	Smoke /no illegal drugs N=152
Lexington	24.59	80.90	21.05	28.57	76.0	39.47
Rural	75.41	19.10	78.95	72.43	24.0	60.53

Drugs of Abuse During Pregnancy

- OPIATES or OPIOIDS
  - Morphine
  - Heroin
  - Codeine
  - Semi-synthetic and synthetic opioids
    - Oxycodone
    - Hydrocodone
    - Methadone
    - Buprenorphine
    - Tramadol

DRUGS OF ABUSE DURING PREGNANCY

Even semi-synthetic and synthetic opioids for rehabilitation or treatment are being abused:

Methadone ("street methadone")
Buprenorphine

Prenatal Exposure & Brain Development

- Behavior Teratology Framework: Agents that are relatively harmless to the mother could still have a harmful effect or consequences to the fetus
  - Based on 2 principles (*Vorhees CV in Hutchins DE, Editor. Prenatal abuse of licit and illicit drugs NYAS 1989, p31-41*.)
    - Vulnerability of the CNS to injury extends beyond fetal, neonatal, and infancy stage
    - Most frequent manifestations of injury to the developing CNS do not result in nervous system malformation but in functional abnormalities that may not be detected at birth, but later in childhood, adolescence, or adulthood.

- Related to Barker hypothesis: Any perturbation during fetal development may have enduring effects on later behavior.

The Developing Brain

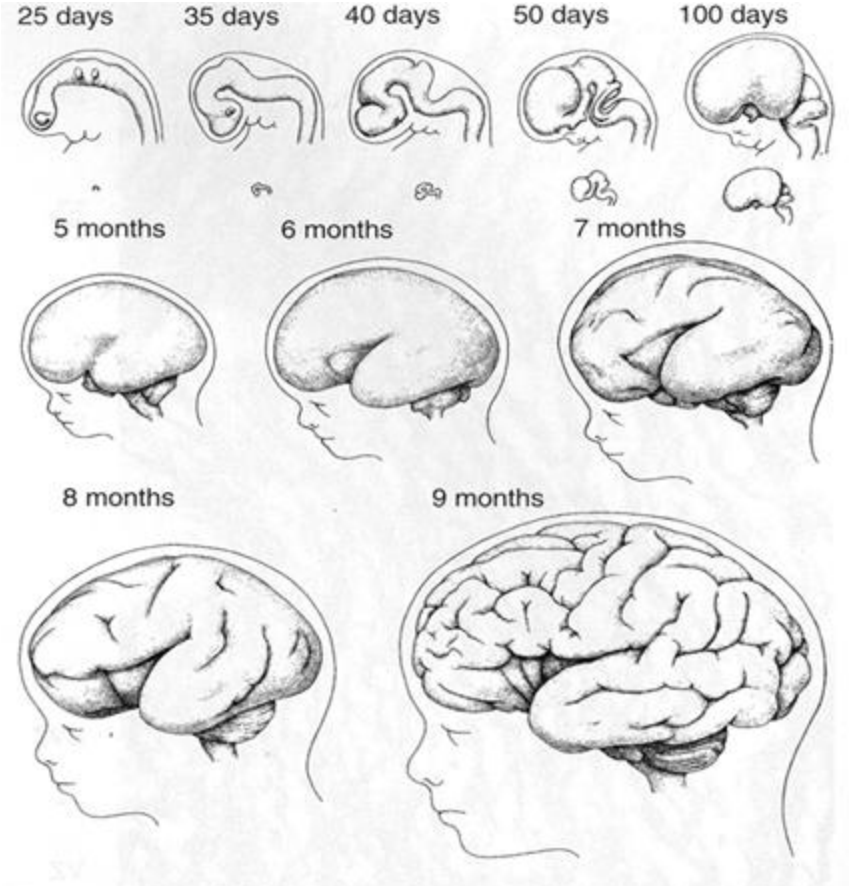
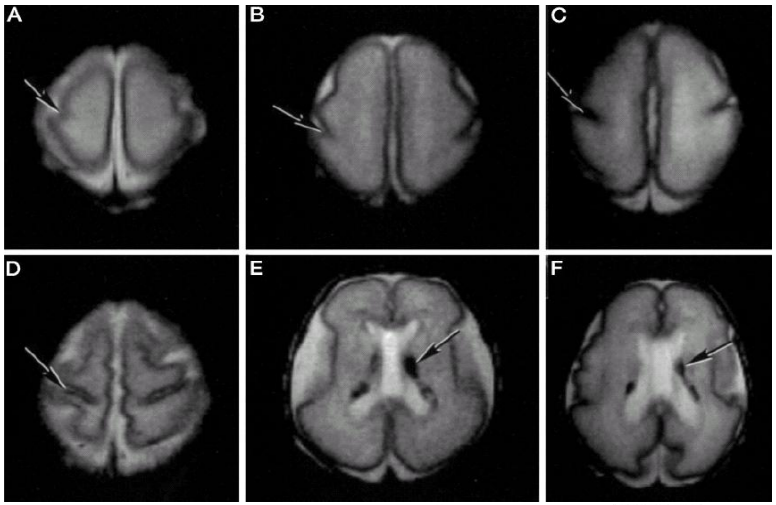


Figure 2-19 Schematic depiction of gyral development in human brain. Note the particularly prominent changes in the last 3 months of gestation. (From Cowan WM: *Sci Am* 241:113, 1979.)



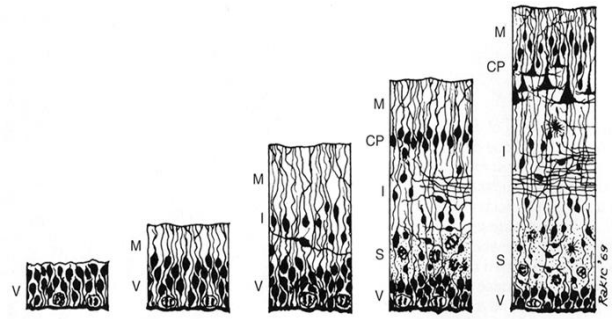


Figure 2-3 Schematic drawing of the cerebral wall during development of the mammalian cortical plate *(CP)* to demonstrate the major zones: ventricular *(V)*, subventricular *(S)*, intermediate *(I)*, and marginal *(M)*. (From Rakic P: Timing of major ontogenetic events in the visual cortex of the rhesus monkey. In Buchwald NA, Brazier MAB, editors: *Brain mechanisms in mental retardation,* New York, 1975, Academic Press.)

Prenatal Exposure & Brain Development

- All legal and illegal drugs will affect brain development; effects dependent on stage of gestation the fetus had drug exposure
- Various stages of brain development
  - Dorsal induction (3-4 weeks)
  - Ventral induction (5-6 weeks)
  - Neuronal proliferation (2-4 months)
  - Migration (3-5 months)
  - Organization (6 months – years postnatal)
  - Myelination (birth to years postnatal)

Prenatal Alcohol Exposure & Brain Development

- Severe alteration in brain development
  - Neuronal loss
  - Altered neuronal circuitry
  - Apoptotic neurodegeneration of the developing forebrain.
- Dose response relationship with morphology of the corpus callosum and the glutaminergic neurotransmitter function in the hippocampus.

Huizink AC, Reproductive Toxicology 2009

Prenatal Tobacco Exposure & Brain Development

- nAChRs (nicotine acetylcholine receptors) promote cell division and the subsequent switch from cell replication to cell differentiation during fetal brain development.
  - **Binding of nicotine to nAChRs may result in increase in receptor density of fetal nAChRs yielding an up-regulation of receptors and premature switch from cell replication to differentiation.**
  - **Switch in stages of brain development leads to cell death, structural changes in brain regions, and altered neurotransmitter system.**

Huizink AC, Reproductive Toxicology 2009

Prenatal Marijuana Exposure & Brain Development

- Influence on gene expression of neural adhesion molecule L1, key protein for brain development
  - Role in cell proliferation, migration, and synaptogenesis.
- Alterations in the development of the nigrostratial and mesolimbic dopaminergic neurons.

Huizink AC, Reproductive Toxicology 2009

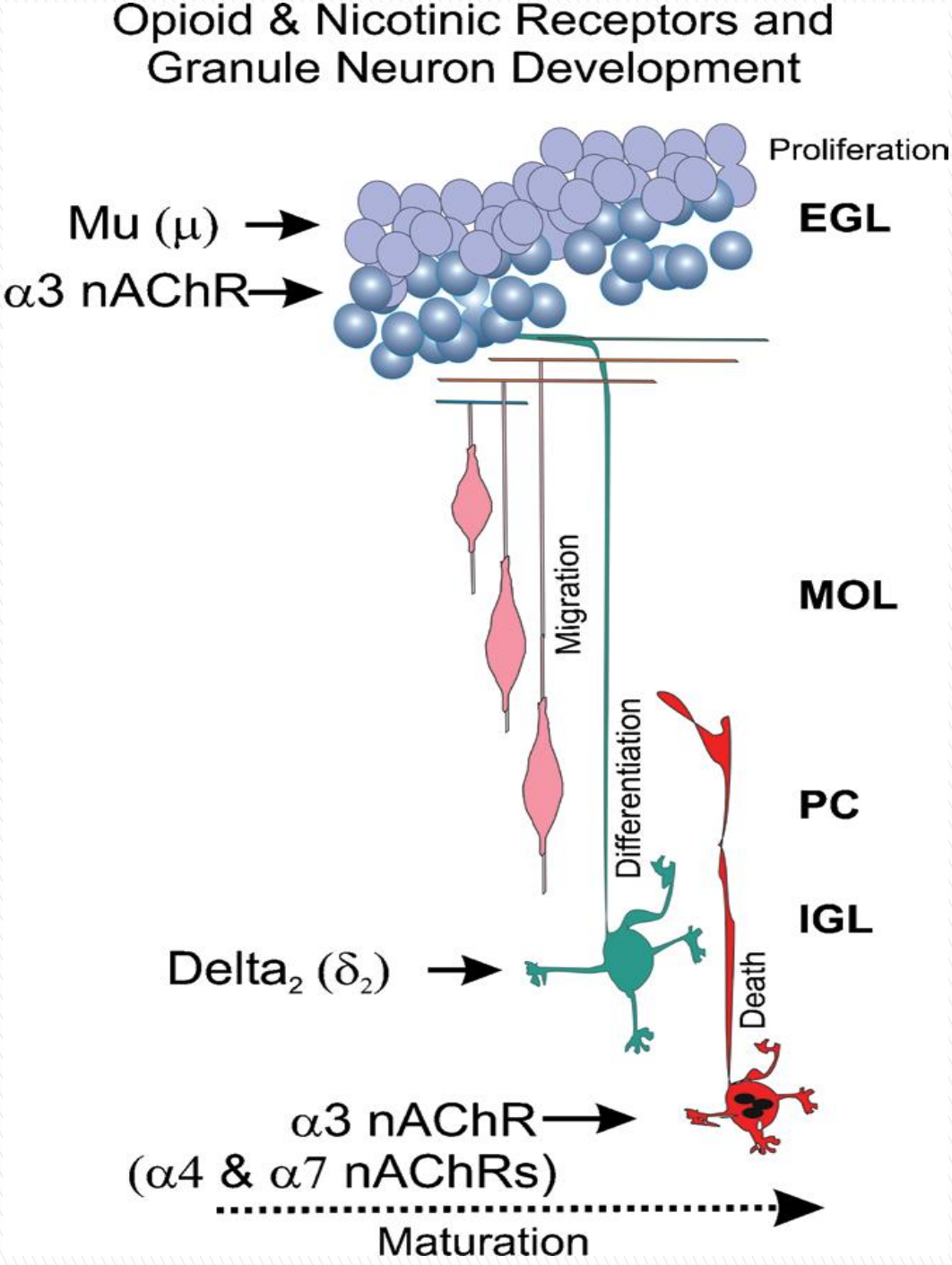
Prenatal Cocaine Exposure & Brain Development

- Direct effect on neuronal proliferation
  - Decrease number of neurons
  - Degeneration of connective processes through which communication with other neurons occur.
- Effects: on monoaminergic system regulating brain development:
  - Decrease in cortical glial connective elements
  - Disorganization of axon-dendritic bundle.
  - Migration: radial gliogenesis; Disrupts neuronal migration
  - Disruption of cortical laminar architecture
  - Increased number of cells in underlying white matter.
- Cocaine initiates apoptotic processes by yet undefined mechanism
- Adults with prenatal exposure: reduction in basal dopamine release and decreased activity of dopaminergic cells, which may lead to increased receptor sensitivity and proliferation.
- Effects on serotonin system (greater affinity for serotonin transporter responsible for the teratogenic effects)

Mayes L, Development and Psychopathology 1999

Prenatal Opiate Exposure & Brain Development

- Decrease in number of subpopulations of neurons, astrocytes, and oligodendrocytes in the subventricular zone
- Suppression of DNA synthesis in glia and glial precursors
- Retardation in cerebellar growth
- Inhibits proliferation of cerebellar neuroblasts and astroglia affecting cell differentiation and survival.



Opioid and nicotine actions during granule cell development

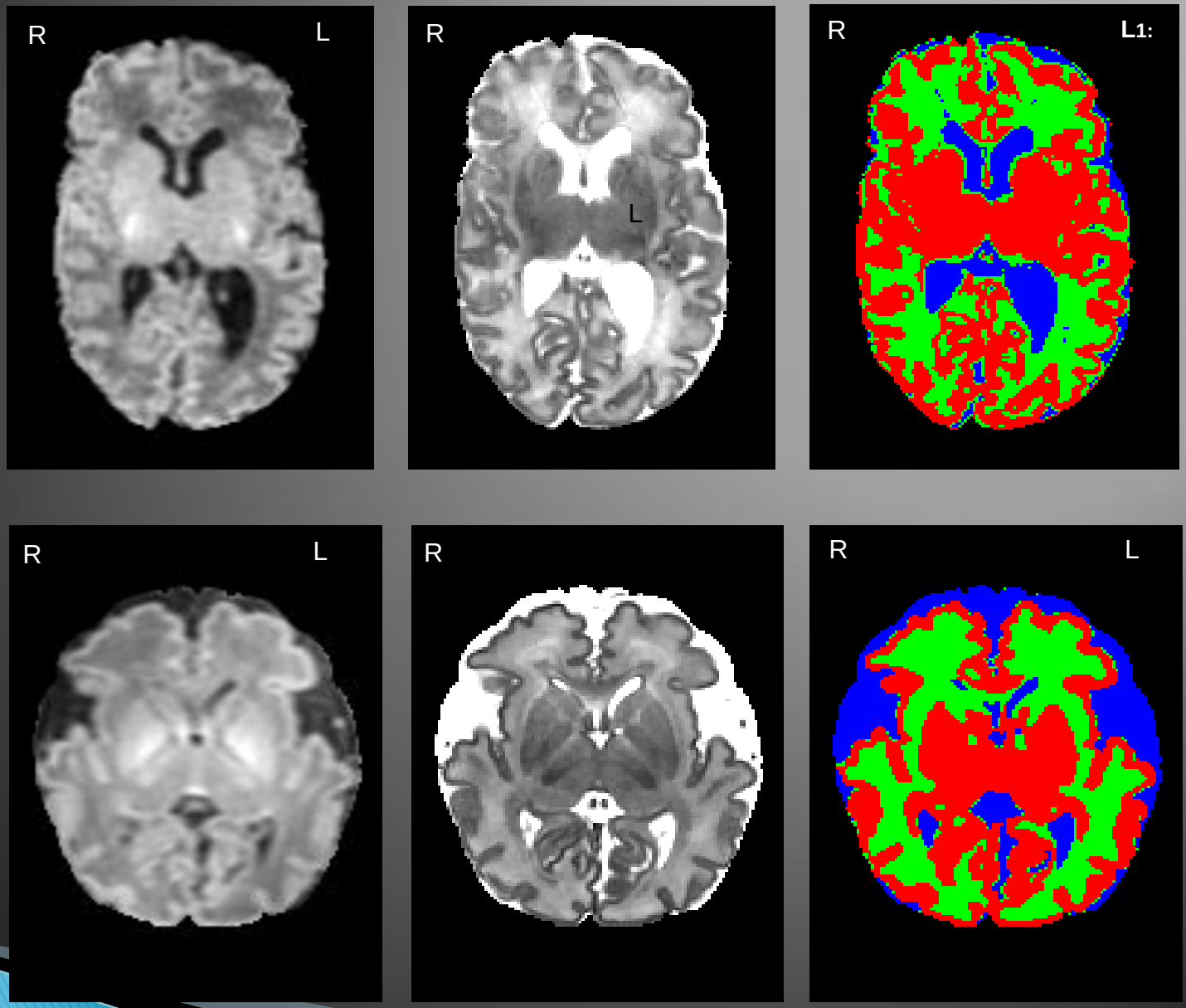
EGL – external granular layer

MOL– molecular cell

IGL – Internal granule layer

PG – purkinje cell

Hauser et al.
The Cerebellum 2003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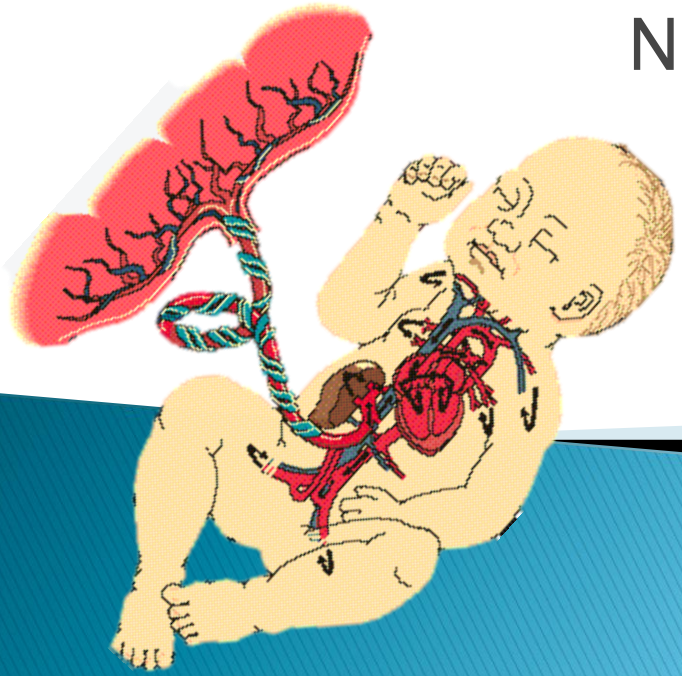
The Newborn With Prenatal drug Exposure

- Low birth weight
- Small head circumference
- Congenital malformations (over reported)
- Signs of drug effects
  - Abnormal tone may persist for months
- Seizures & abnormal EEG pattern
- Signs of **withdrawal** (drug dependency)

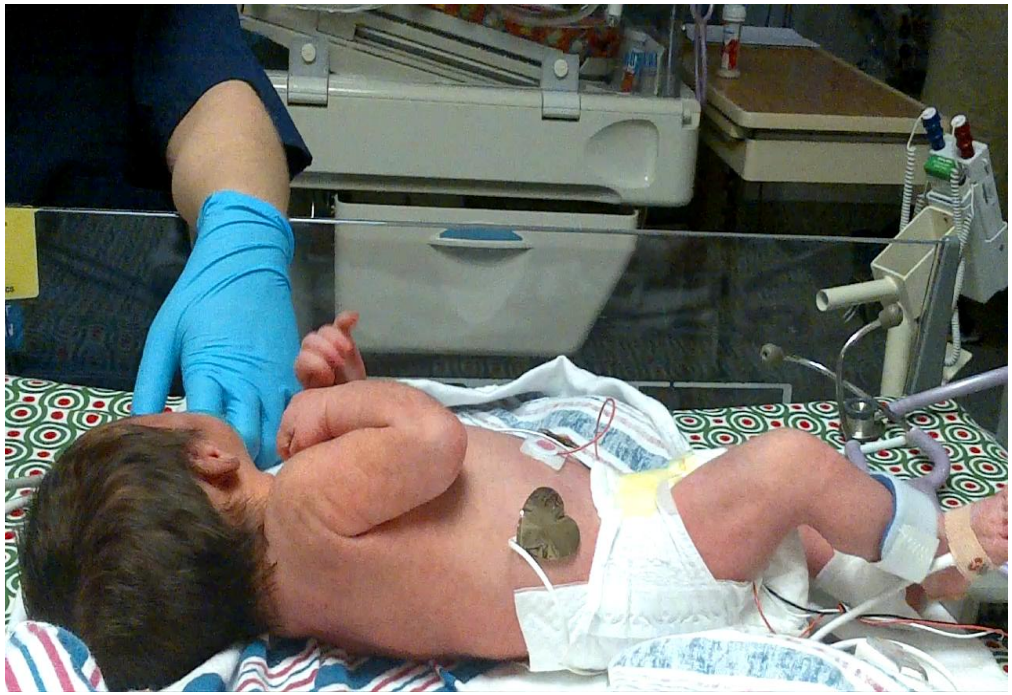
Opiate Exposure Effects

Neonatal Abstinence Syndrome



Signs of Neonatal Abstinence or Withdrawal

- Central Nervous System Signs
  - High-pitched cry
  - Decreased sleeping time
  - Hyperactivity
  - Hyper-reflexia
  - Tremors
  - Hypertonia
  - Myoclonic jerks
  - Convulsions
  - Irritability



Signs of Neonatal Abstinence

- Respiratory disturbances
  - Nasal stuffiness
  - Sneezing
  - Nasal flaring
  - Tachypnea
  - Retractions
- Other Manifestations
  - Abrasions or excoriations (knees, elbows, chin)
  - Fever

CNS/ANS Withdrawal Manifestations

Exposure	Incidence	Odds Ratio (95% CI)	P value
Cocaine	28.2%	1.7 (1.4–2.2)	0.0001
Opiate	44.8%	2.8 (2.1–3.7)	0.0001
Cocaine + opiate	62.0%	4.8 (2.9–7.9)	0.0001
Smoking<1/2 ppd	29%	1.27 (1.04–1.55)	0.02
Smoking ≥1/2 ppd	50%	1.40 (1.20–1.60)	0.003

Bada et al. Arch Dis Child 2002

Goals of Treatment and Management

- Minimize symptomatology (supportive & pharmacologic)
- Promote growth and weight gain
- Promote caretaker-child interaction
- Strategies directed to social issues
  - Improve short-term and long-term outcomes
  - Endangered children (child abuse/neglect)
  - Long-term behavioral problems

Neonatal Abstinence Syndrome

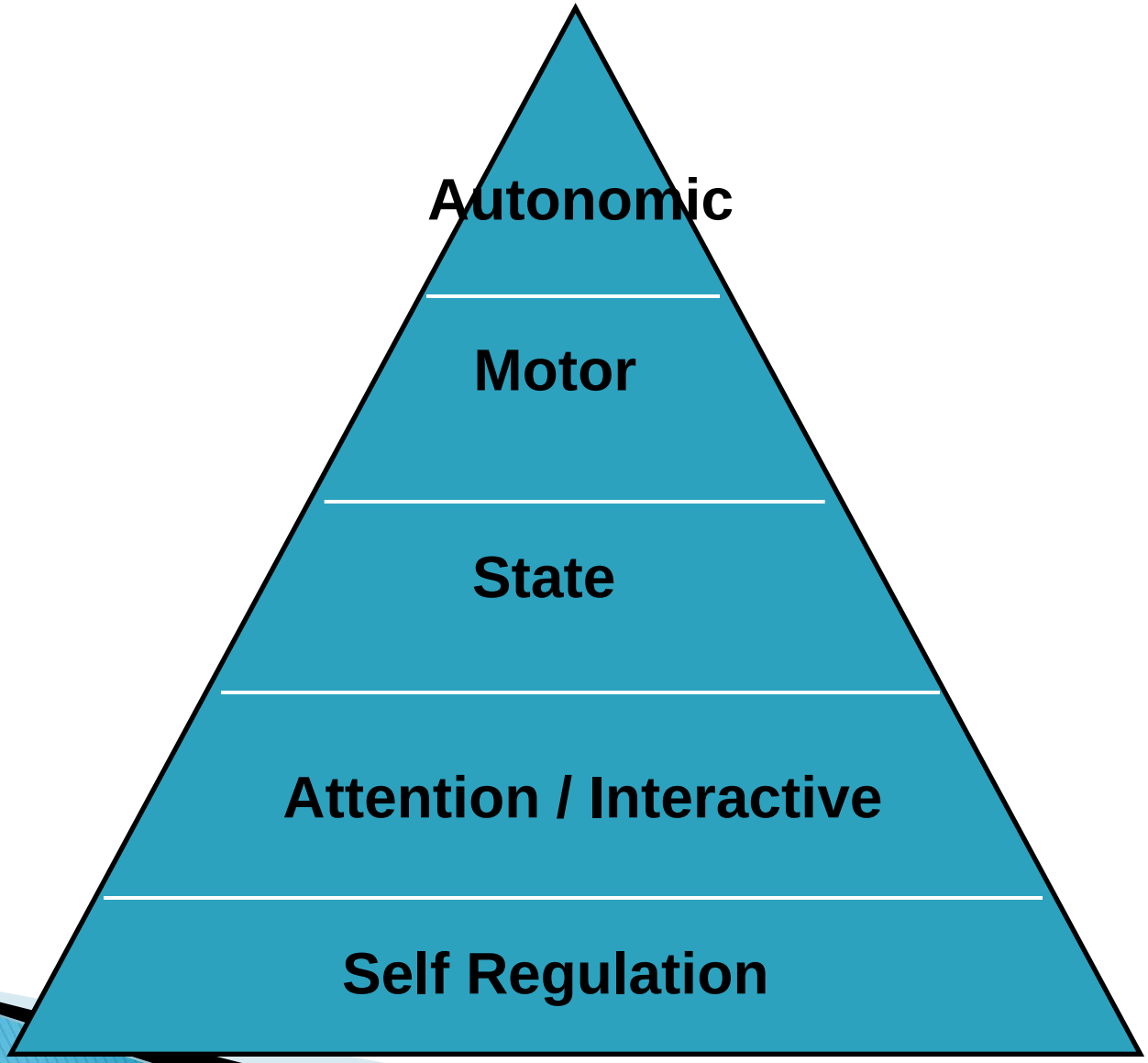
- Supportive Treatment (essential before pharmacological intervention)
  - Promote growth (IV fluids, small frequent feedings, high nutrient density formula) & monitor weight gain
  - Monitor closely for other disease status
  - Behavioral intervention such as
    - Decrease sensory stimulation
    - Swaddling
    - Vertical rocking
- Pharmacologic treatment

Behavioral Intervention

- Synactive Theory
  - Basis for developmental care in premature infants
  - Could be applied in those late preterm and term
  - Addresses the functioning and interactions of subsystems:
    - Autonomic
    - Motor
    - State
    - Attention/interactive
    - Self-regulation
  - Although most drug exposed infants are mature
    - Behavioral subsystems – over functioning

Als H et al. Infant Ment Health J 1982

Behavioral Intervention



Behavioral Manifestations

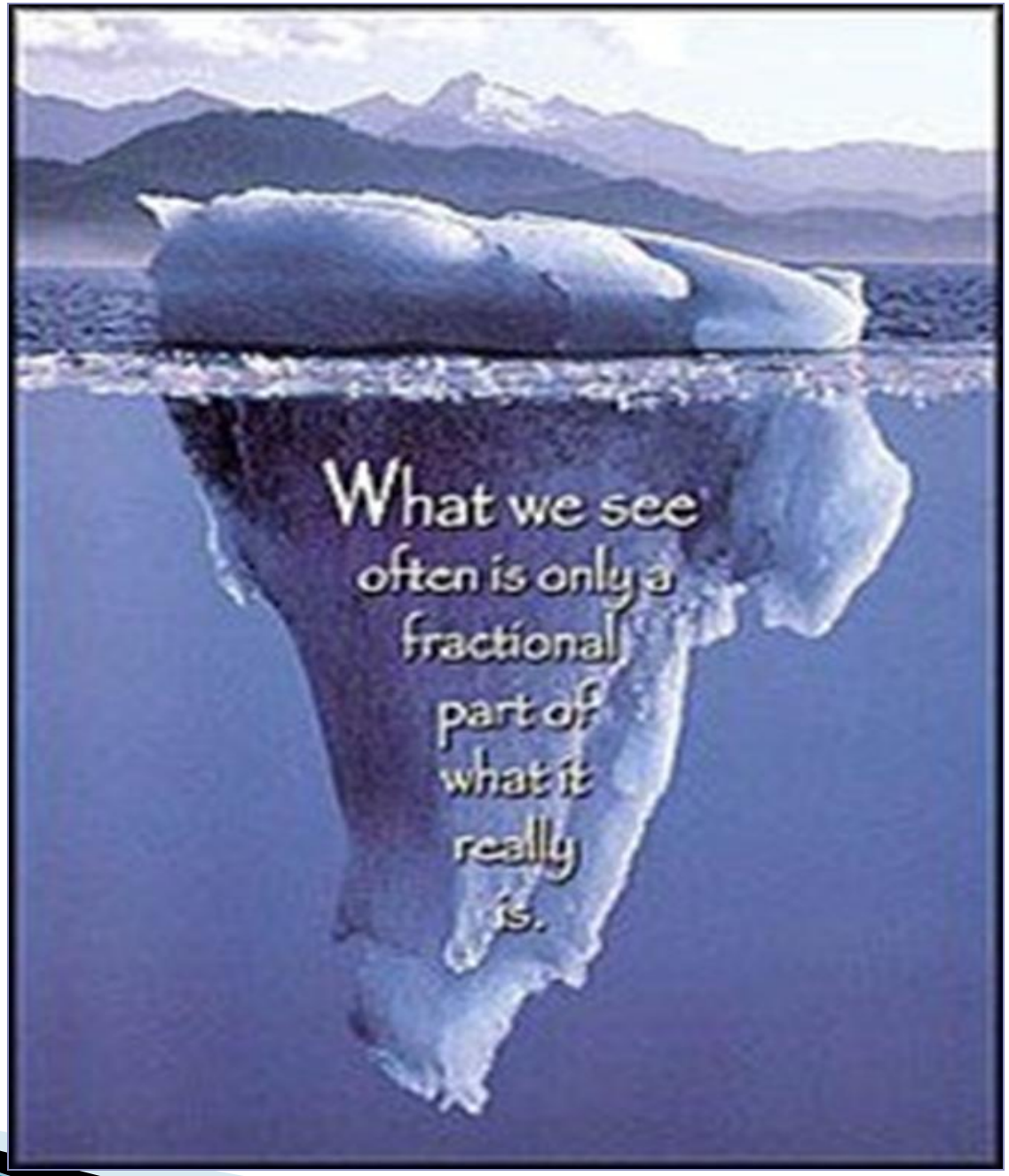
Behavioral Subsystems	Symptoms of Prenatal Drug Exposure	
Autonomic	Poor temperature control Respiratory distress Nasal stuffiness Mottling of the skin Sweating	Low or fast heart rate Vomiting Watery stools Sneezing Frequent yawning
Motor	Hyperactivity Tremors Arching	Increased muscle tone Irritability Excessive sucking
State	Less sleep	Cries a lot High-pitch cry
Attention/interactive	Irritability Difficult to handle	Poor feeding Very excitable
Self-regulation	Difficulty to self soothe	Less cuddly Difficult to regulate

Behavioral intervention

Intervention measures	Rationale	Subsystems
Environmental modification: **Decrease noise** **Light/dark cycle**	Decrease sensory stimulation leads to decease startle; Decrease excitability	Motor Self-regulation Autonomic
Non-nutritive sucking **Initiate feedings at the appropriate state** **Appropriate positioning** **Swaddling during feedings**	Limits motor activity Avoids fluctuation in temperature Promotes self-regulation	Self regulation Autonomic Attention/interactive Motor
Vertical rocking	Will calm infant without jarring motion Lessen excitability	Self-regulation

Neonatal Abstinence Syndrome

- <2 weeks of pharmacological treatment
- Finnegan Scores 1 -4, all less than 8
- Infant going home to foster care
- Complete Rx at home
- Caretaker appears to understand giving meds and other aspects of care
- Decreased length of stay.


What we see
often is only a
fractional
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Prenatal Exposure & Brain Development

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  - Based on 2 principles (*Vorhees CV in Hutchins DE, Editor. Prenatal abuse of licit and illicit drugs NYAS 1989, p31-41*.)
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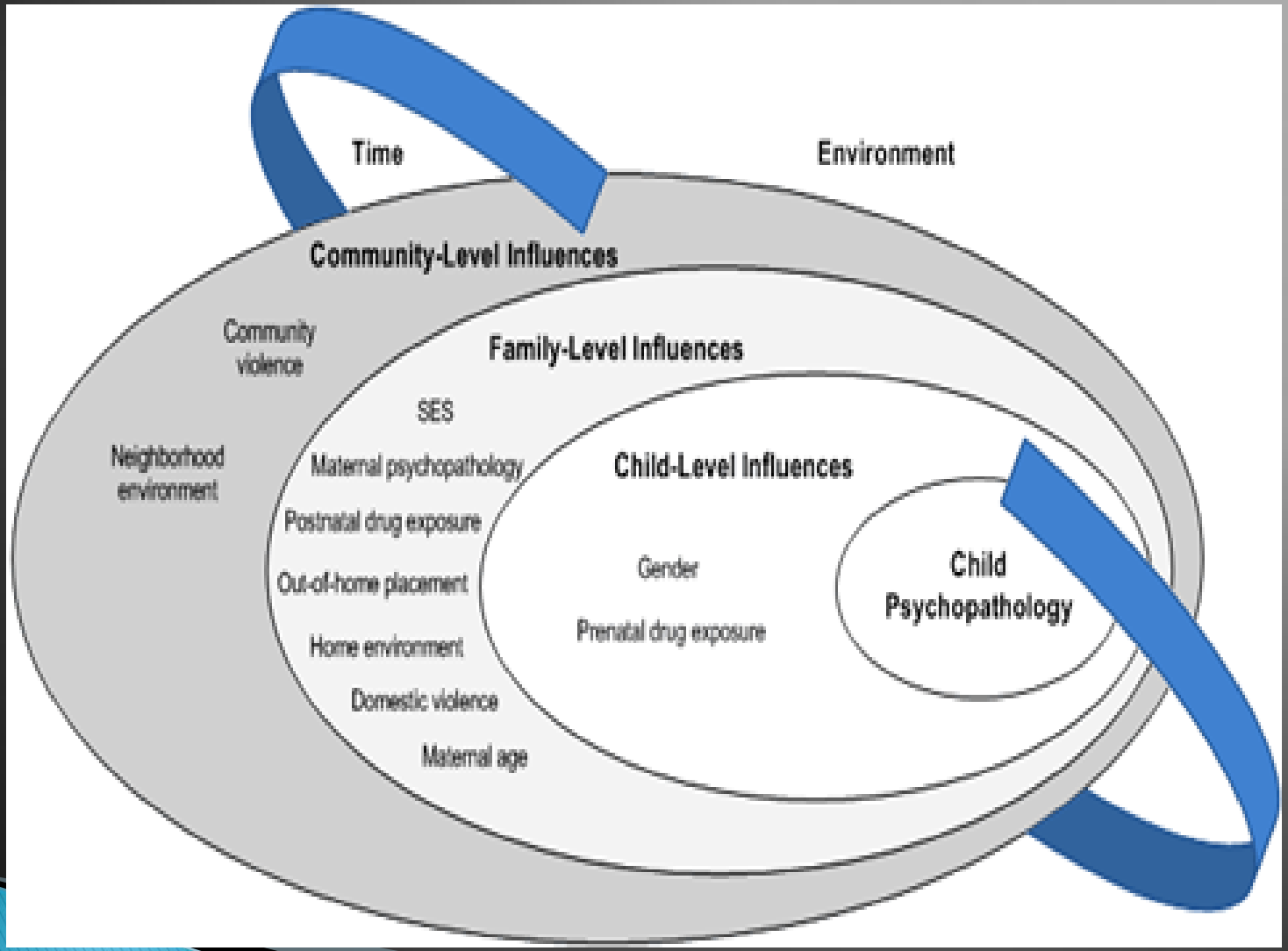
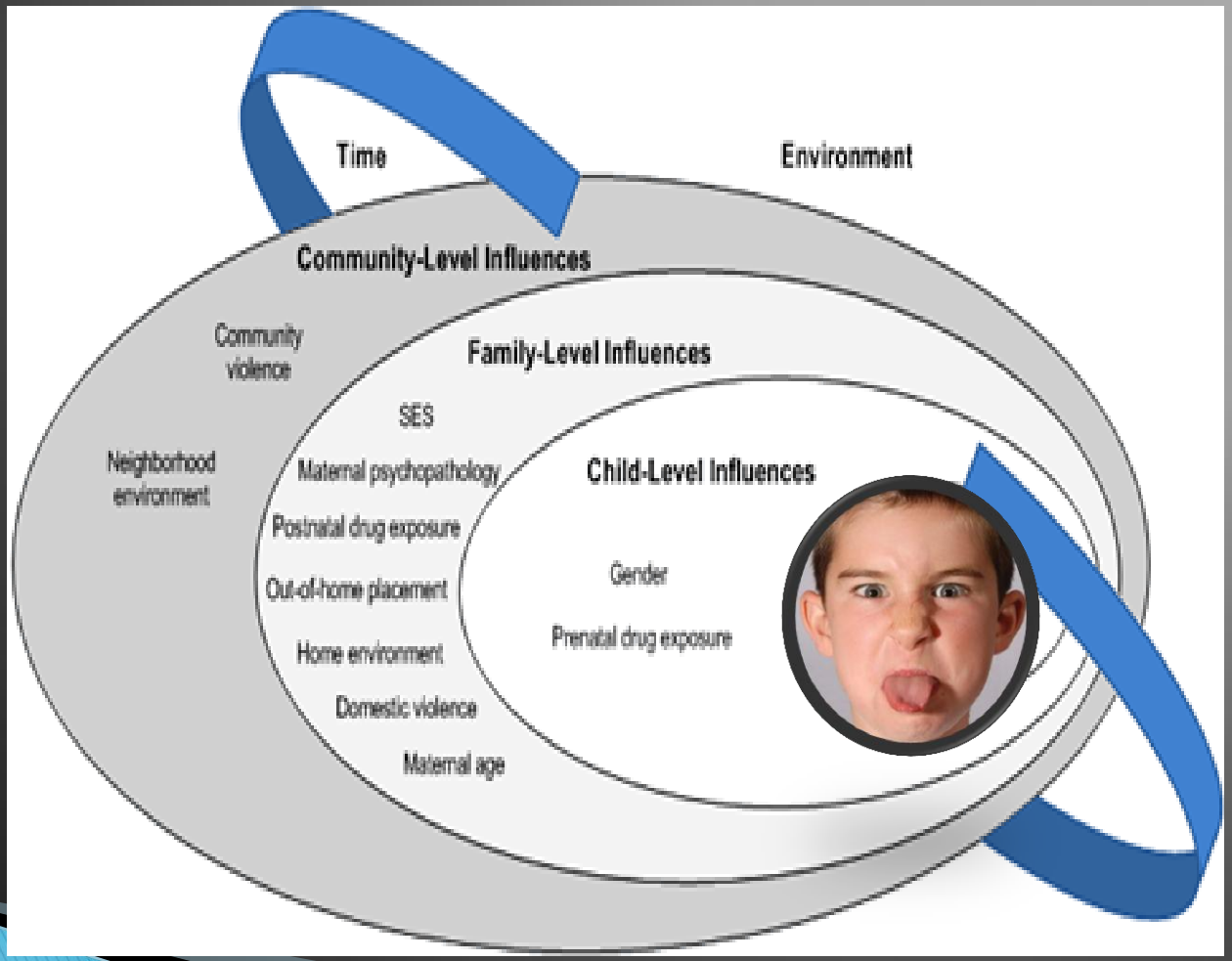
- Related to Barker hypothesis: Any perturbation during fetal development may have enduring effects on later behavior.

Complexity in Outcomes: Cumulative Risk Will Influence Outcomes



Cumulative Risk Will Influence Outcomes



Individual, Maternal, and Family Factors

- Polydrug or Other Drug Use (rarely single drug use) affecting fetal brain development
- Maternal, family/caretaker, and community have influences on child development.

Maternal and Family Factors

- Maternal age
- Co-morbidities (psychological/psychiatric disorders)
  - Depression, anxiety disorders, PTSD, etc.
- Pregnancy complications
- Sexually transmitted diseases (increasing prevalence of Hepatitis C)
- Hospitalizations (due to violence)
- Parenting
- High-risk lifestyle
- CPS reporting and involvement
- Discharge placement: biological parent, kinship care, non-kinship care

Significant Maternal Conditions

Conditions	Exposed % (n=1185)	Non-Exposed % (n=7442)	Adjusted Odds Ratios 95% CI
Hepatitis	2.9	0.6	4.8 (2.6-8.9)
HIV tested	31.4	27.7	1.1 (1.0-1.4)
Positive HIV	12.0	1.9	8.2 (4.3-15.4)
AIDS	0.9	0.1	19.5 (4.1-91.6)
Syphilis	11.3	1.5	6.7 (4.8-9.6)
Gonorrhea	4.5	1.8	1.9 (1.3-3.0)
Chr Hypertension	3.9	2.6	1.3 (0.9-2.1)
Psych/Nervous Dis	2.4	1.0	4.0 (2.2-7.4)

Bauer CR et al. Am J Obstet Gynecol 2002

Significant Pregnancy/labor Characteristics

Characteristics	Exposed % (n=1185)	Non-Exposed % (n=7442)	Adjusted Odds Ratios (95% CI)
Hospitalizations	11.5	10.8	1.08 (0.89-1.3)
Hospitalizations due to violence	0.7	0.0	16.9 (6.4-44.6)
Hospitalizations due to detox	1.2	1.3	29.6 (13.00-66.5)
Medications during pregnancy	59.9	71.0	0.6 (0.5-0.7)

Bauer CR et al. Am J Obstet Gynecol 2002

Living Situation At Discharge

	Cocaine (n=717)	No Cocaine (n=7442)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
CPS report/referral	275 (38.5%)	74 (1.0%)	62.18 (43.37-89.15)	42.98 (28.77-83.20)
Discharge with biological mother	570 (81.2%)	7350 (99%)	0.04 (0.03-0.06)	0.05 (0.03-0.10)
Home with bio father	6	15	0.17(0.05-0.63)	0.09 (0.01-0.88)
Home with other relative	38	14	1.57 (0.63-3.93)	n.s.
Foster or pre-adoptive family	61	36	0.78 (0.36-1.67)	n.s.
Congregate facility	28	2	8.93(1.30-61.41)	9.69 (1.37-68.65)
Mother wishes for child adoption	15	26	6.10 (2.63-14.16)	5.65 (1.72-18.53)

Bauer CR et al. Arch Pediatr Adolesc Med 2005

Table 2 Number of Children by Each Type of Living Arrangement for Each Visit from Discharge

Living Situation	Discharge	12 Months	24 Months	36 Months
Biological mother	1262	1195	1155	1118
Subsequently left this arrangement to others	94	59	55	
Entered from other arrangements		32	22	19
No. who died		5	3	1
Biological father, mother not in the home	5	22	37	38
Subsequently left this arrangement to others	3	5	13	
Entered from other arrangements		20	20	14
Grandparent(s)	35	46	54	72
Subsequently left this arrangement to others	21	9	13	
Entered from other arrangements		32	17	31
Other relatives	1	44	50	56
Subsequently left this arrangement to others	0	12	11	
Entered from other arrangements		43	18	17
Nonrelative foster care	67	71	80	87
Subsequently left this arrangement to others	26	8	7	
Entered from other arrangements		31	17	15
No. who died		1		1
Institution/group home	17	3	2	5
Subsequently left this arrangement to others	17	1	0	
Entered from other arrangements		3	0	3

For each living arrangement, the number of children who left and the number who entered that specific arrangement since previous visit are shown.

Bada H et al. J Dev Behav Pediatr 2005

Prenatal Drug Exposure

- The focus has turned to the long term developmental outcome of children with prenatal drug exposure, especially as they reach adolescence

Long term outcomes of Prenatal Drug Exposure

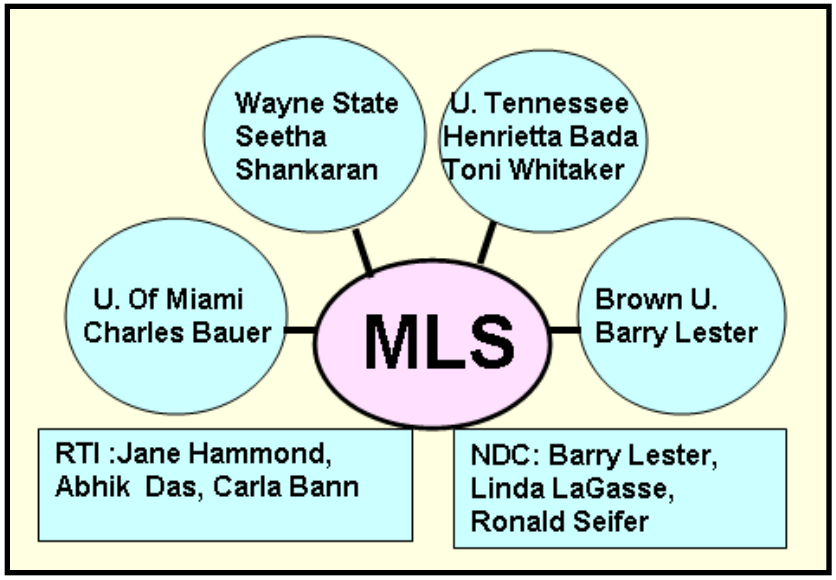
- No significant abnormalities in MRI in the newborn period but long term studies in older children and adolescents – decrease in brain volumes

Opiates and Long term Outcomes

- No studies on opiate exposure only; most addicts use multiple substances and difficult to isolate opiate
- Earlier studies showed equivocal results because of small number on follow-up
- Earlier studies have been on heroin and methadone
- Longitudinal studies up to 15 years in prenatal poly drug exposure (cocaine, opiate, marijuana, tobacco, alcohol)

Maternal Lifestyle Study (MLS)

MLS is conducted under the auspices of the following Institutes (Program Scientists):
- **NIDA (Nicolette Borek),**
- **NIMH (Julia Zehr)**
- **NICHD NICU Research Network (Rosemary Higgins).**



Phases 1 and 2: The NICHD Neonatal Research Network
NIDA, ACYF, CSAT
Phases 3, 4, 5: NICHD Neonatal Research Network, NIDA, NIMH

Patient Recruitment

- Enrollment period: May 1993-May 1995
- Screening for enrollment
  - Birth weight >500 grams
  - Gestational Age <43 weeks
  - Singletons
- Informed consent and maternal interview
- Meconium collection

Results

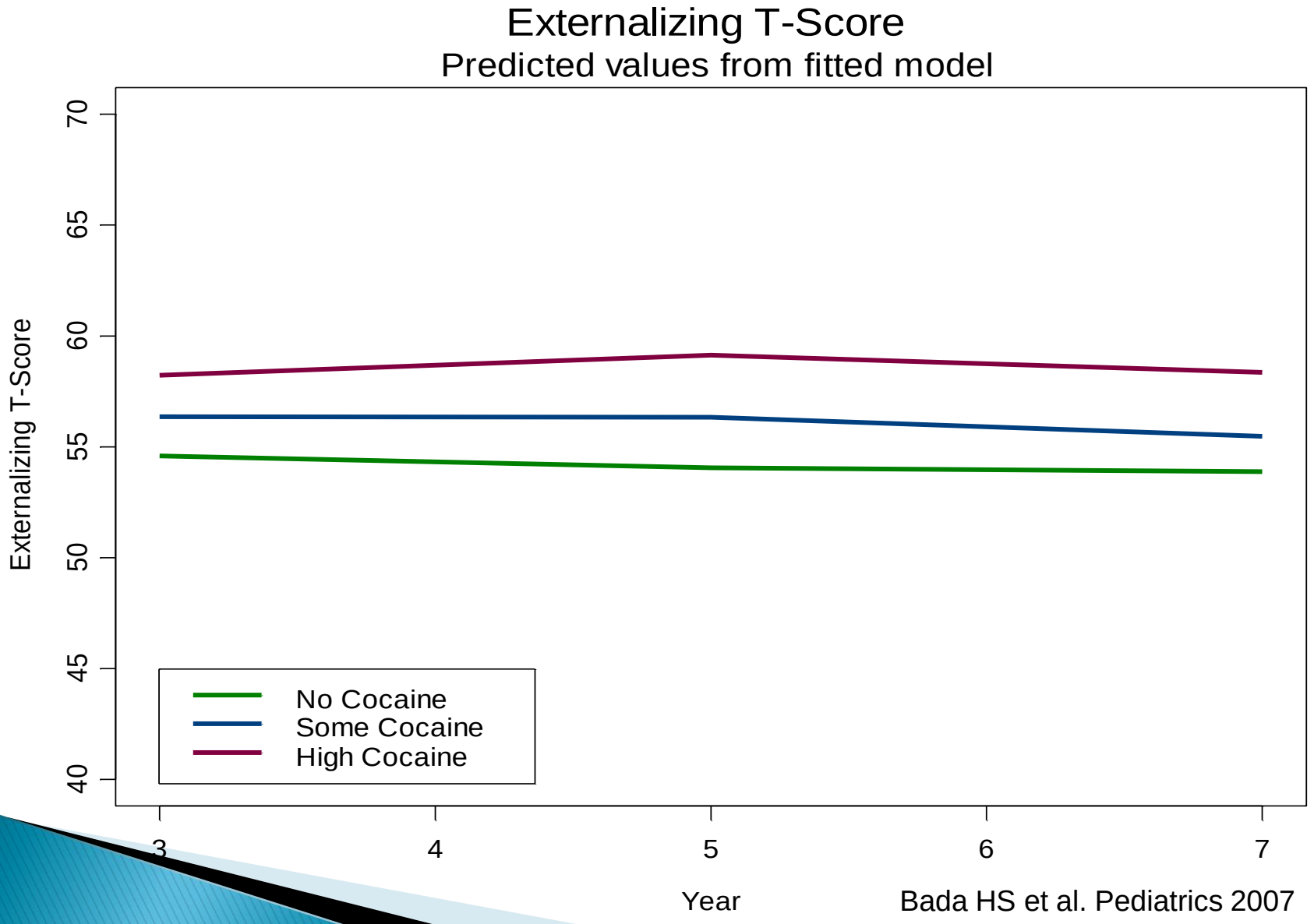
- Enrollment

19,079 – mother/infant dyads screened for recruitment
16,988 – eligible for enrollment
11,811 – consented to study participation
3,184 – no meconium or inadequate for confirmation
7,442 – confirmed non-exposed (NON)
1,185 – exposed (EXP)
977 – exposed to cocaine only (C)
113 – exposed to opiate only (O)
92 – exposed to opiate and cocaine (O+C)

Opiates and Long term Outcomes

- Longitudinal studies up to 15 years in prenatal poly drug exposure (cocaine, opiate, marijuana, tobacco, alcohol)
  - Worsening behavior problems at older ages (internalizing and total behavior problems and consistent with both parent and teacher report: attention problems)
  - Behavior problems may not be evident at 3 to 5 years but noted at preadolescence and adolescence.
  - Adult outcomes still unknown

Longitudinal Analysis: CBCL



Bada HS et al. Pediatrics 2007

Externalizing Behavior Problem: Results From Longitudinal Modeling[1]

Variables	Regn. Coefficient[2]	*p* value
Maternal age	-0.220	<0.001
Prenatal tobacco	0.072	0.044
Prenatal alcohol	0.870	0.015
Prenatal marijuana	-0.014	0.987
Prenatal opiate (year 5)	3.09	0.041
Prenatal cocaine (high use)	3.089	0.003
Caretaker SES	-0.045	0.048
Ongoing tobacco use	1.980	<0.001
Ongoing alcohol use	1.252	0.006

[1] Only effects for prenatal drug exposures and statistically significant ($p < 0.1$) covariates are presented
[2] Adjusted for time trends, site and other covariates listed previously

Bada HS et al. Pediatrics 2007

Effects of Prenatal Opiate at 13 years From Caretaker and Teacher Report

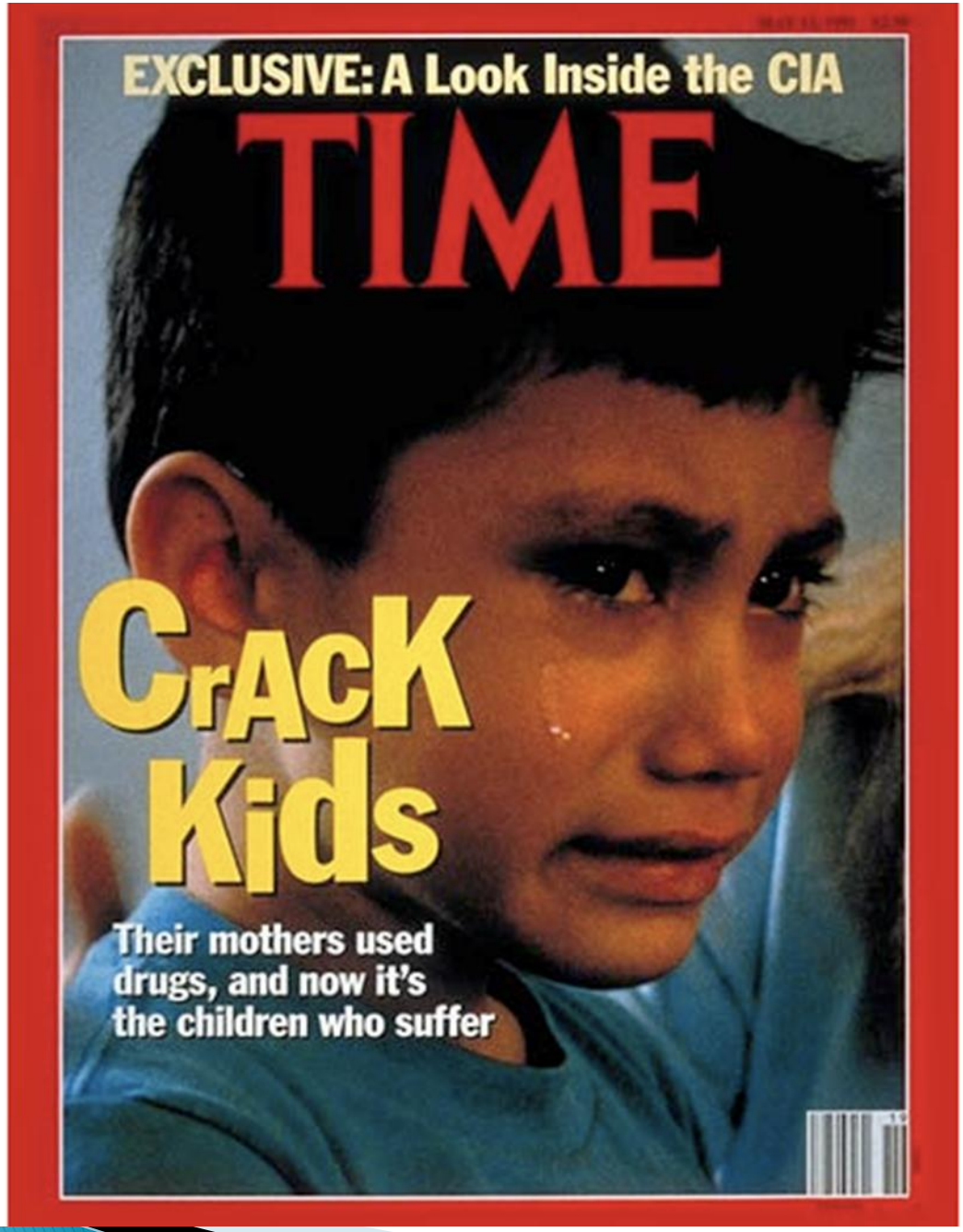
- Children with prenatal opiate exposure did not start out with high problem scores at early ages.
- From caretaker report: behavior problem scores: worse with time
  - Internalizing Behavior Problems
  - Total problems
  - Attention problems
- From teacher report
  - Attention Problem Scores worse with time

Bada HS et al. Neurotoxicology Teratology 2011

Summary: Prenatal Drug Exposure and Behavior outcomes at Late childhood

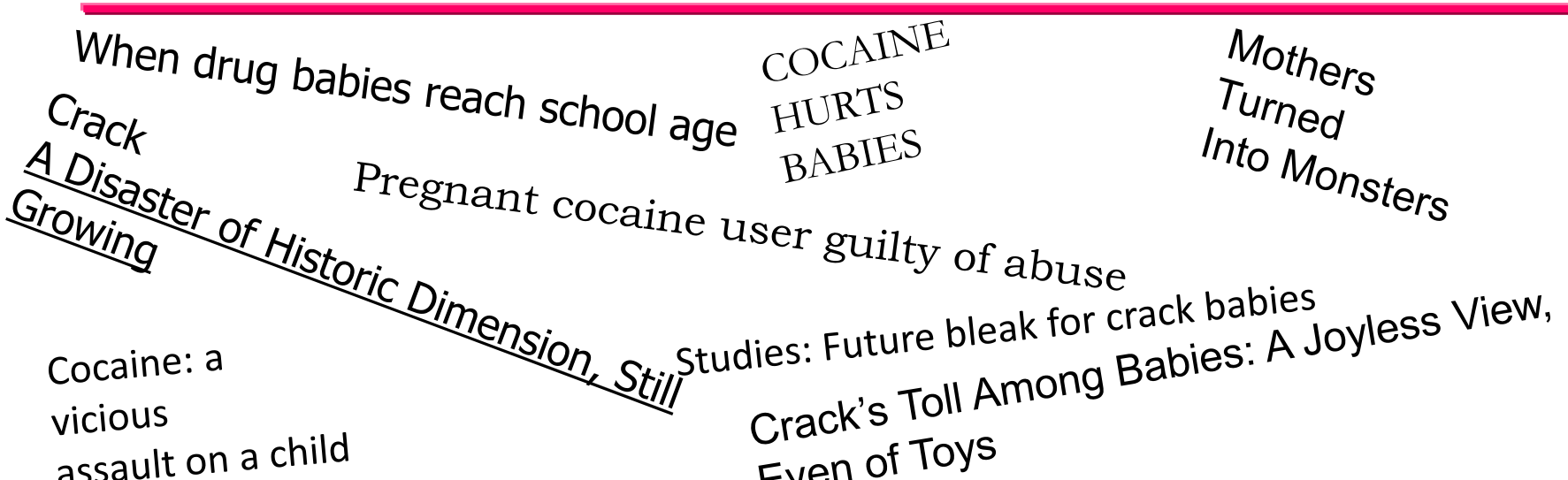
- Prenatal cocaine exposure has a significant long term effect on childhood behavior problems, independent of the effects of prenatal tobacco and alcohol exposure.
- Maternal age and caretaker SES have significant effects on the trajectory of childhood behavior problems.
- Significant separate influences of caretaker ongoing tobacco and alcohol use on childhood behavior outcomes.

- The effects of prenatal cocaine exposure on childhood behavior problems can be augmented by effects of postnatal drug exposure, specifically tobacco and alcohol.
- Prenatal opiate effects on behavior problems not noted in early childhood; but increase in problem scores over time.
- These prenatal and post natal drug exposure effects could have implications for antisocial behavior, child mental health, and school functioning.



TIME
May 13, 1991

Prenatal Drug Exposure



Early reports on prenatal cocaine effects created a public frenzy and the myth about "unfit to parent" women and their damaged "crack babies."

This impacted legal activities by states on policy decisions affecting women who use illegal drugs during pregnancy –

This is not the answer…

Prenatal Drug Use And Outcomes

Prenatal cocaine exposure has subtle effects on children's ability to focus their attention

"Crack Kids": Not Broken

Major Trial Finds Only Subtle Fetal Injury From Cocaine

A mother's cocaine use may not doom her child after all

Hope for 'Snow Babies'

A Rush to Judgment

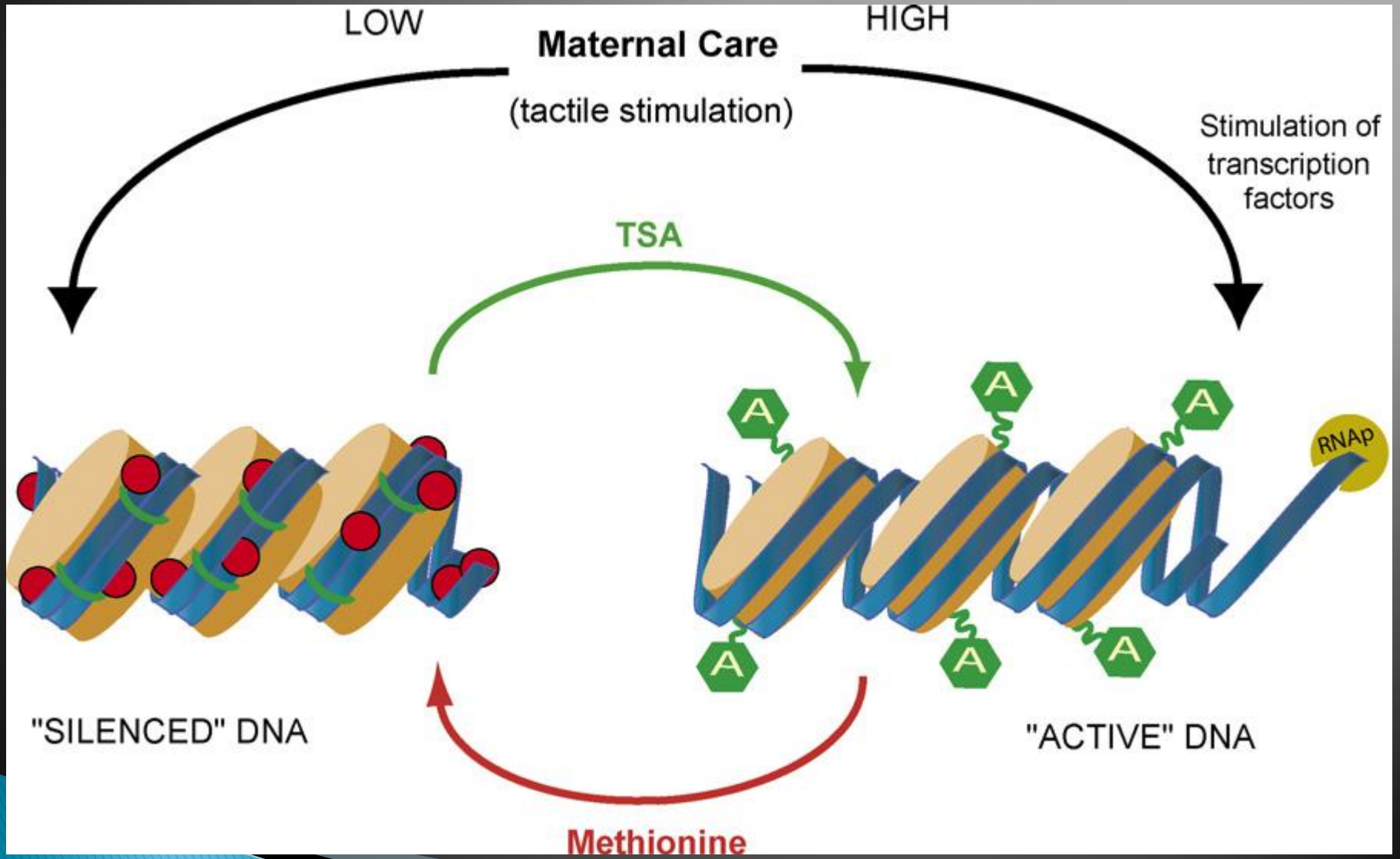
Researchers debunk myth of the 'crack baby'

Data indicate subtle effects

Consistent With Behavior Teratology: effects noted at later ages

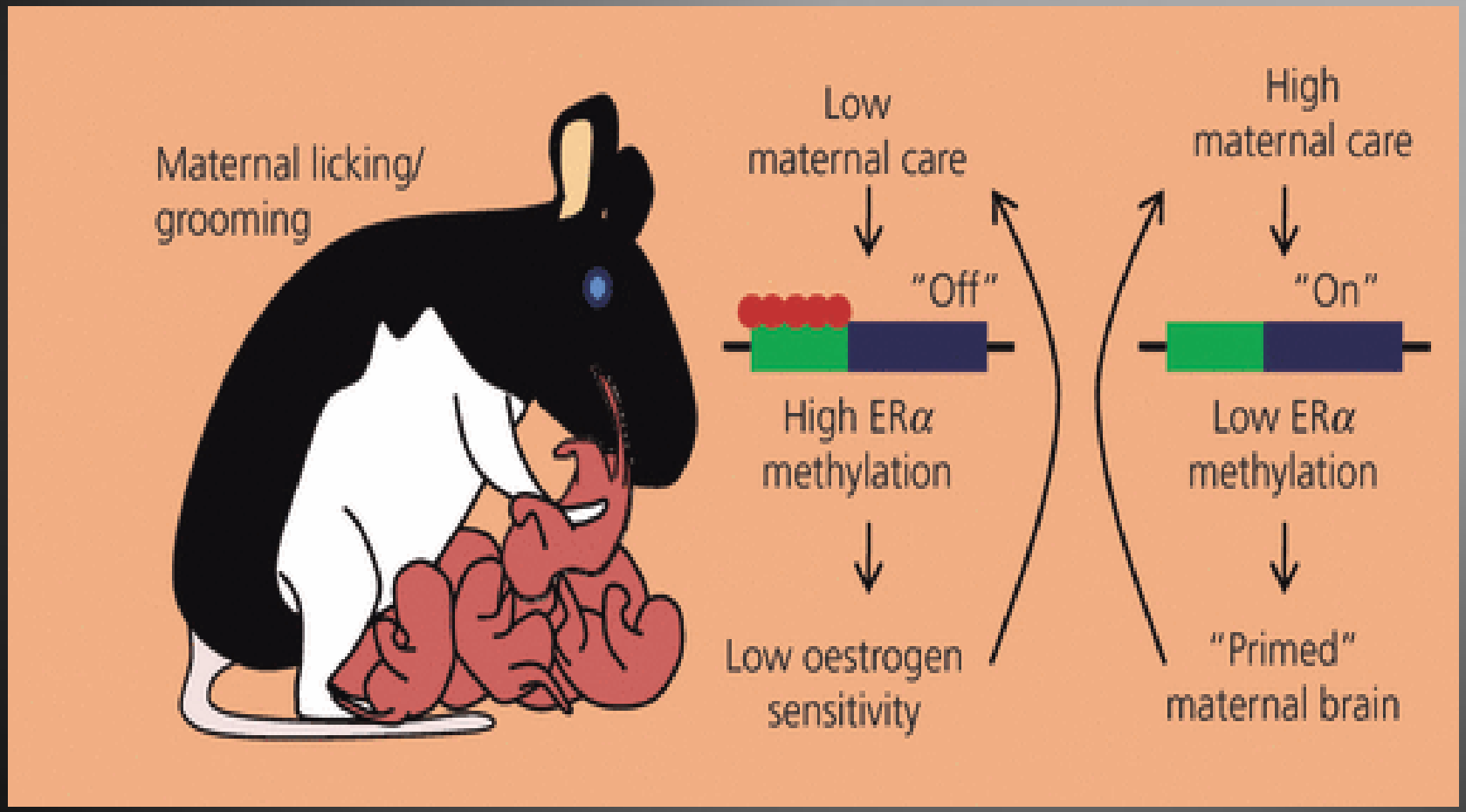
Increasing awareness of prescription opiate epidemic, increase in incidence of NAS but need to avoid the rush to judgment on these children and their families.

Influence of epigenetics



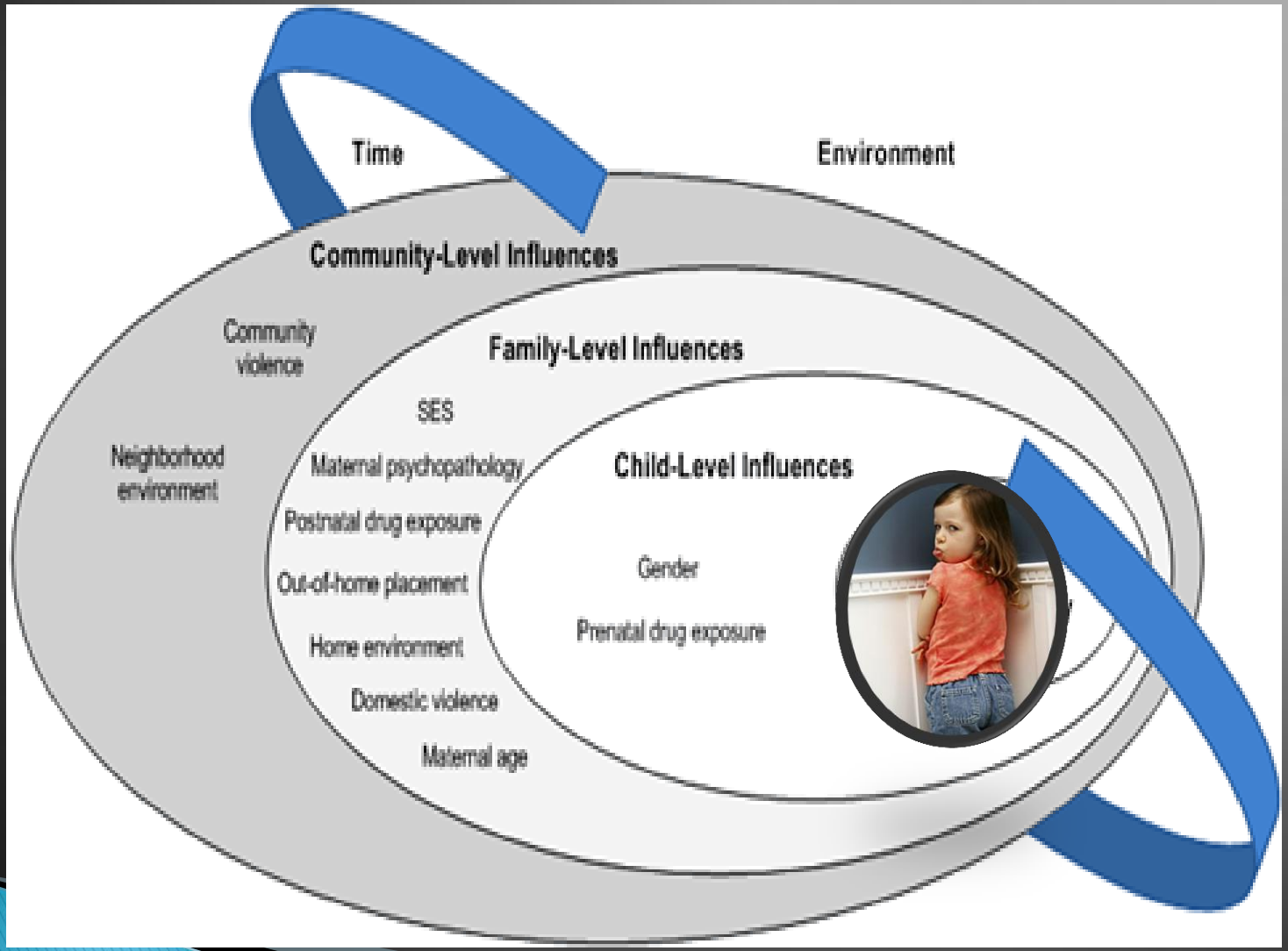
Champagne, 2009

Epigenetic: Transmission of Mothering Behavior

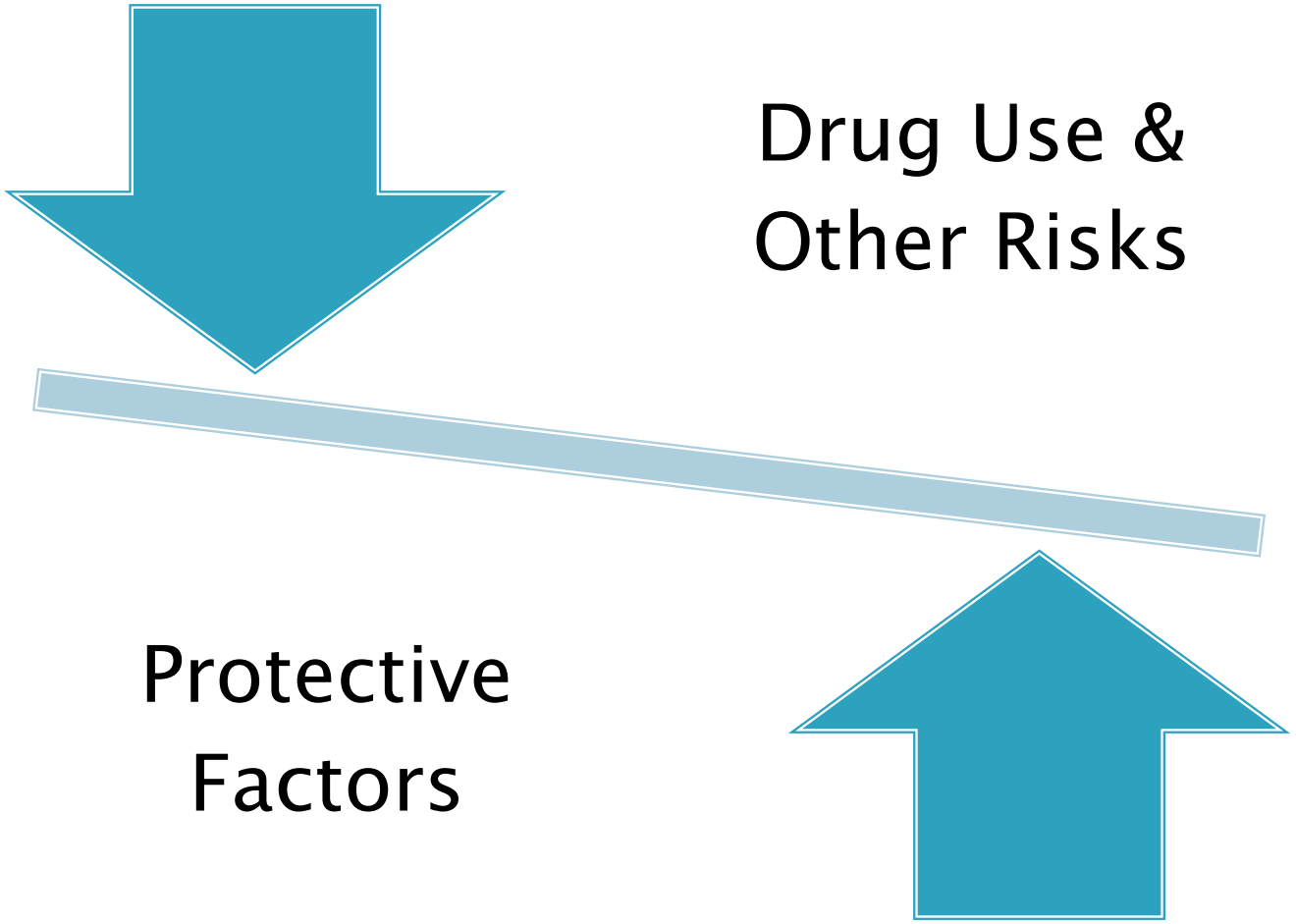


Mothering is transmitted epigenetically from mother to daughter through levels of the ERα gene promoter

Complexity in Outcomes: Cumulative Risk Will Influence Outcomes



CAN WE CHANGE CHILD OUTCOMES?



Categories of Prenatal Drug Exposure

- High Cocaine/Other Drug Exposure (High PCE/OD)
- Some Cocaine/Other Drug Exposure (Some PCE/OD)
- Other Drugs/No Cocaine (PCE-/OD+)
- No Cocaine/No other drugs (PCE-/OD-)

Problem Behaviors

- Externalizing Behavior Problems
  - Delinquent behavior
  - Aggressive behavior
- Internalizing Behavior Problems
  - Withdrawn
  - Somatic complaints
  - Anxious/depressed
- Total Behavior Problems
  - Externalizing, internalizing, social problems, thought problems, attention problems, sex problems

Risks and Protective Factors

	Risk	Protective Factors
Individual	Male	Resilience
	Small head	Temperament
	Low verbal or full IQ	
	Overweight (medical problems)	
Family	Depression, psychological functioning	Secure attachment
	Domestic violence	Home
	Illegal and legal drug Use	Caretaker involvement
		Caretaker supervision
		Family support/resources
Community	Violence	Neighborhood
	Gangs, Crimes	Friends, extracurricular activities

Risk and Protective Factors

- Determine outcomes with each risk factor and protective factor
- Determine outcomes with Cumulative Risk Index independent from Protective Factor Index
- Determine outcomes considering the balance between cumulative risk and protective index
  - High risk index – low protective index
  - High risk index – high protective index
  - Low risk index – low protective index
  - Low risk index – high protective index

Externalizing Behavior

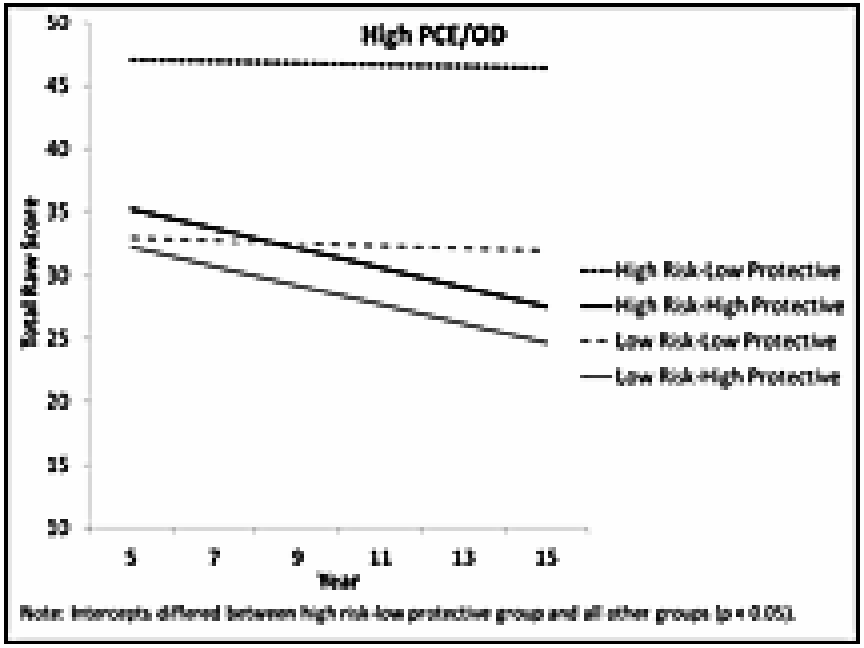
Risks	Protective Factors
High PCE/OD	Resilience
Male**	Caretaker involvement*
Low verbal IQ	
Caretaker BSI	
Child Abuse*	
Postnatal tobacco	
Postnatal Alcohol	** P<0.05 intercept and Slope * p<0.05 - slope

Internalizing Behavior

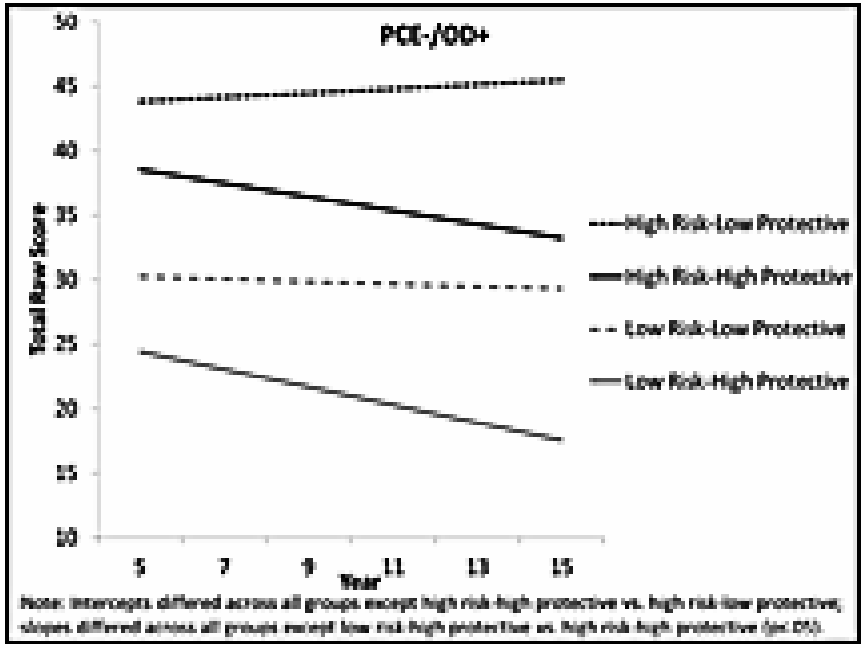
Risks	Protective Factors
Drug groups – n.s.	Resilience
Male*	Caretaker involvement*
Caretaker depression	Family resources
Caretaker BSI	Number of Friends**
	** P<0.05 intercept and Slope * p<0.05 - slope

Total Problems

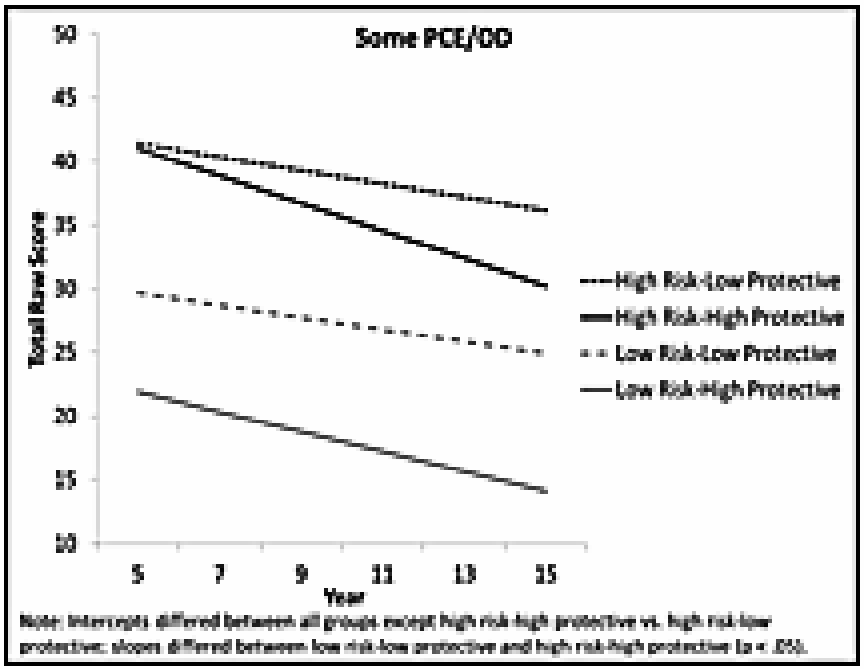
Risks	Protective Factors
High PCE	Resilience
Male*	Caretaker involvement*
Low verbal IQ	Family resources
Caretaker depression	
Caretaker BSI	
Child abuse**	
Postnatal tobacco/alcohol	** P<0.05 intercept and Slope * p<0.05 - slope



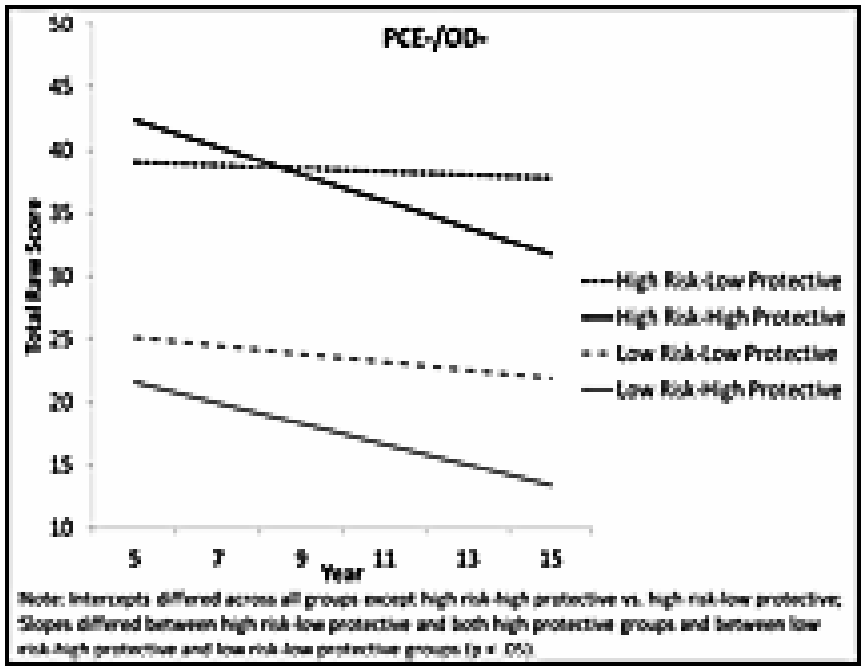
Note: Intercepts differed between high risk-low protective group and all other groups ($p < 0.05$).



Note: Intercepts differed across all groups except high risk-high protective vs. high risk-low protective; slopes differed across all groups except low risk-high protective vs. high risk-high protective ($p < .05$).

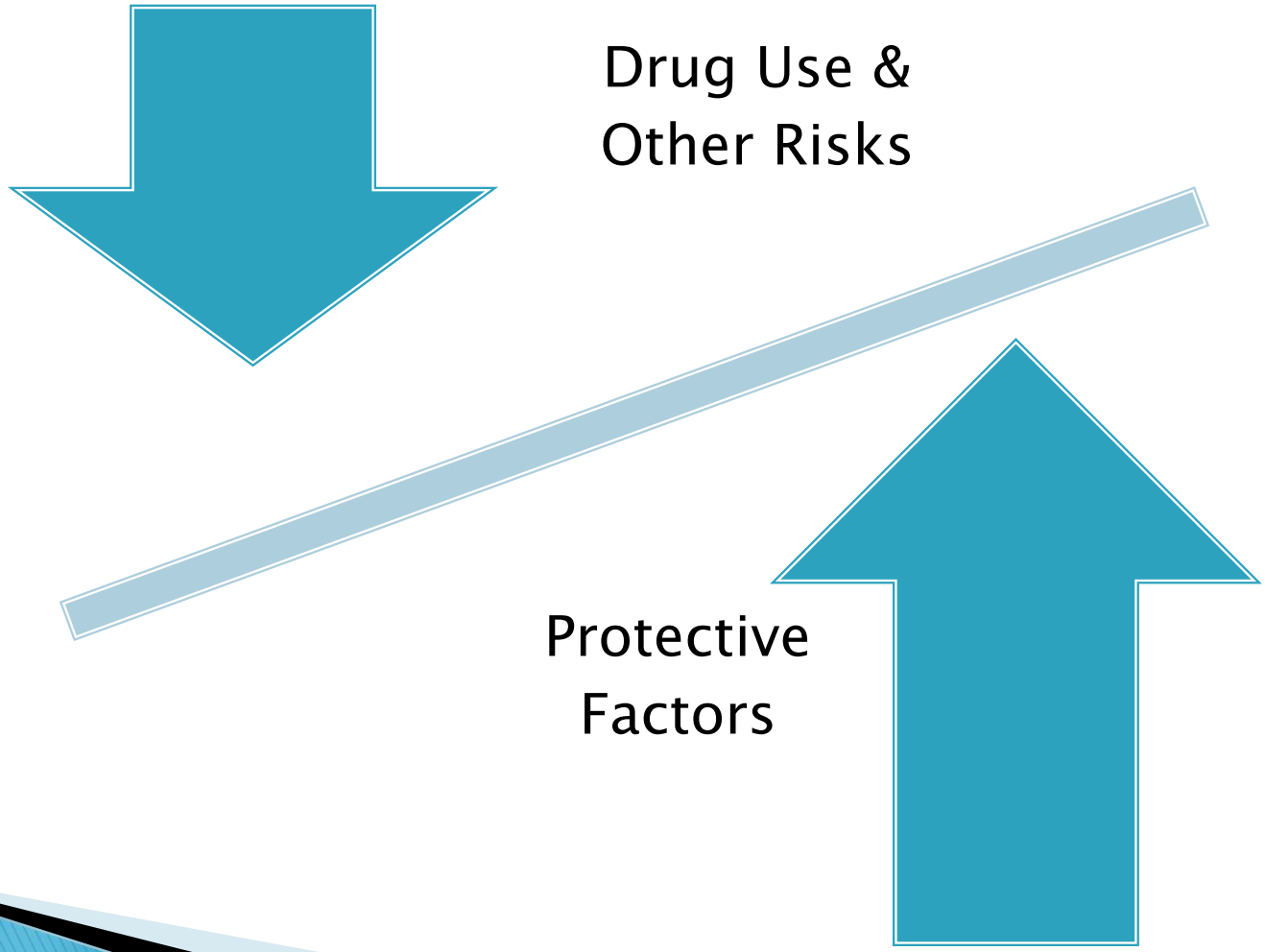


Note: Intercepts differed between all groups except high risk-high protective vs. high risk-low protective; slopes differed between low risk-low protective and high risk-high protective ($p < .05$).



Note: Intercepts differed across all groups except high risk-high protective vs. high risk-low protective; Slopes differed between high risk-low protective and both high protective groups and between low risk-high protective and low risk-low protective groups ($p < .05$).

YES, WE CHANGE CHILD OUTCOMES!



Maternal Drug Use And Child Outcome

GENETIC AND PRENATAL ENVIRONMENT

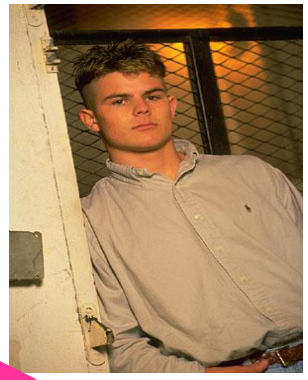
PRENATAL **POSTNATAL**

TERATOGENIC **CAREGIVING ENVIRONMENT**

IMMEDIATE **LATENT** **SPECIFIC** **GENERAL**

TRANSIENT **LONG LASTING** **COA** **RISK**

PROTECTIVE



BRAIN AND BEHAVIORAL DEVELOPMENT

Clinical Implications

- Prenatal drug exposure often occurs in the context of polydrug exposure
- No significant association with immediate newborn complications
- Effects are subtle initially but adverse effects noted at later childhood or adolescence
- Behavior problems are emerging long-term sequelae of prenatal drug exposure
- Prenatal exposure effects can be aggravated by environmental risks but can also be mitigated by protective factors (at individual, family, and community levels)
- Because of the effects of risks and protective factors, need to explore interventions to minimize the adverse effects of prenatal drug exposure.

The entangled web

A village is needed to disentangle the world of the drug-exposed child

THE END
Thank you