EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Early Genetic and Environmental Factors Impacting the Reward and Motivation System

Pat Levitt, PhD.

Alberta family wellness initiative

Where science meets real life

Movie

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Our Default Thoughts

- **Sensory systems require experience (activity) to develop – 1960s**
- **Motor systems require experience (activity) to develop – 1970s**
- **Cognitive systems require experience (activity) to develop – 1980s**
- **Social-emotional systems require experience (activity) to develop – 1990s**
- **Reward/motivation systems require experience to develop - ????**

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Our Default Thoughts

The Divisions are Artificial

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Our Default Thoughts

Where we have been……

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Our Default Thoughts Regarding Reward Systems

0022-3565/98/2853-0931$03.00/0
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 1998 by The American Society for Pharmacology and Experimental Therapeutics
JPET 285:931–945, 1998

Vol. 285, No. 3
Printed in U.S.A.

The 1998 ASPET Otto Krayer Award Lecture

Fetal Nicotine or Cocaine Exposure: Which One is Worse?[1]

THEODORE A. SLOTKIN
Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, North Carolina

Accepted for publication March 24, 1998 This paper is available online at http://www.jpet.org

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Our Default Thoughts Regarding Reward Systems

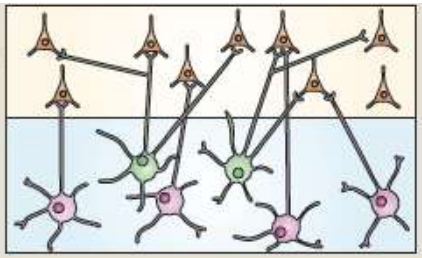
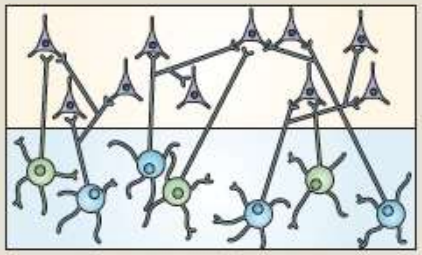
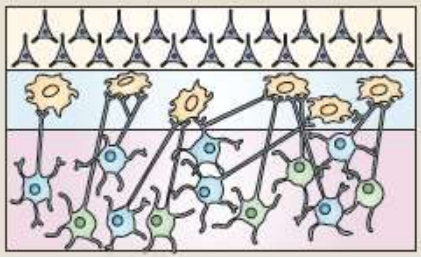
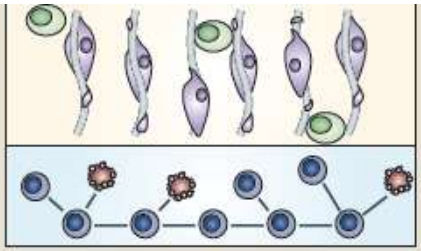
Table 1 | **Neurodevelopmental consequences of prenatal drug exposure**

Age of exposure	Drug	Neurochemistry involved	Neurodevelopmental consequences	Refs
Late early to mid gestation (primarily based on animal studies)	Cocaine	DA > NA and 5-HT. Blocks monoaminergic transporters and increases synaptic concentrations of monoamines	Altered neuroanatomical morphology, disrupted cognition and altered cellular signalling	18–37,42–47,54–59,63–65,203
Throughout gestation	Alcohol	GABA and NMDA. Blocks NMDA receptor activity and increases GABAergic activity	Craniofacial dysmorphologies, decreased birth weight, hyperactivity, cognitive deficits, cortical dysgenesis, cell death and reduced brain volume	113–115,118–120,126–132
Throughout gestation	Nicotine	Acetylcholine. Activates nAChRs	Decreased birth weight, hyperactivity, cognitive disabilities and emotional disruptions	82,86–94,96–98,100–105,107,108
Throughout gestation and early postnatal exposure	Amphetamine or methamphetamine	DA > NA and 5-HT. Reverses the action of monoaminergic transporters and increases synaptic concentrations of monoamines	Low birth weight, decreased arousal, deficits in learning and decreased volume of the hippocampus and striatum	66,67,70–73,76–81

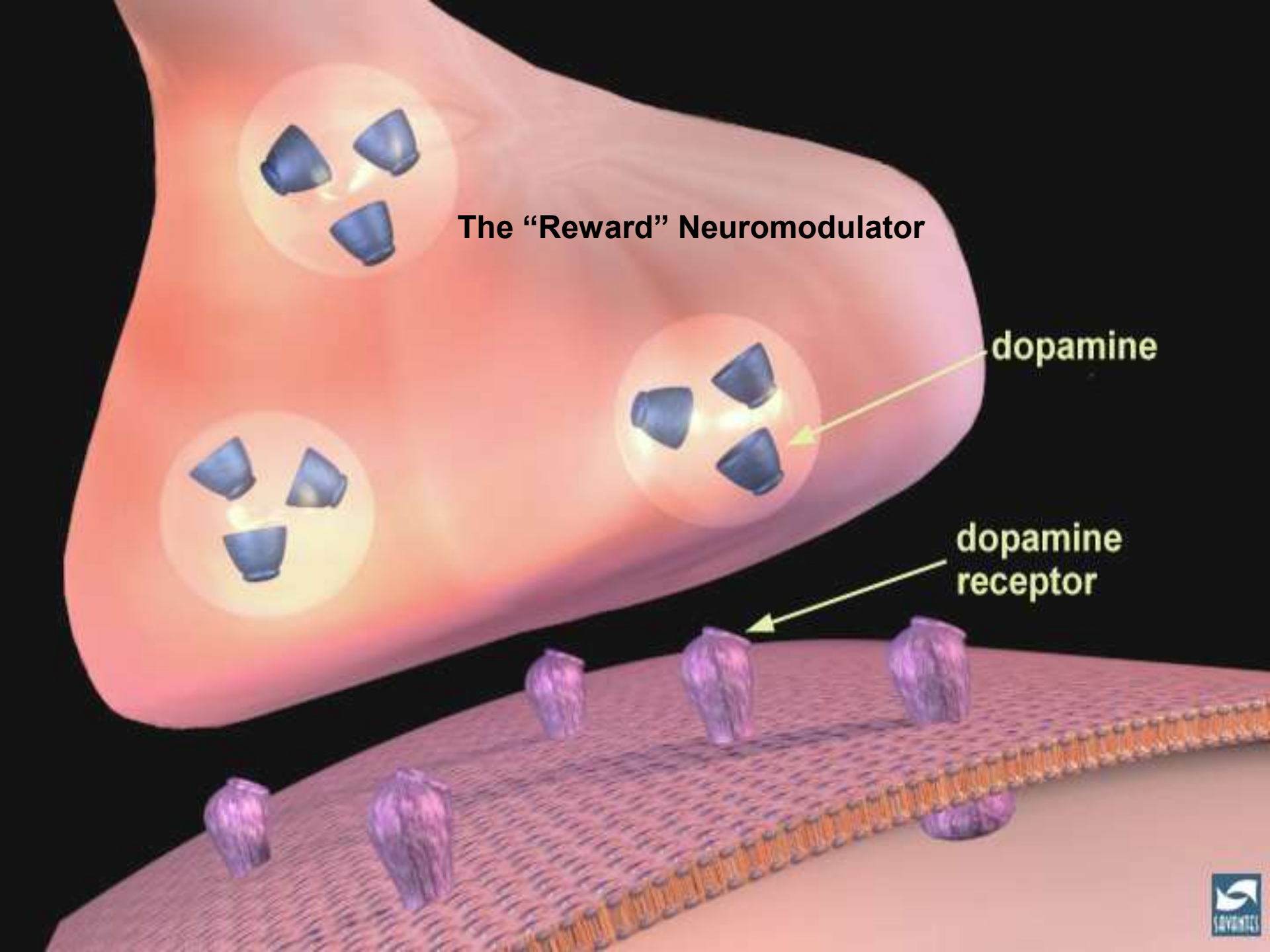
Thompson, Levitt and Stanwood, Nat Rev Neurosci 2009

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

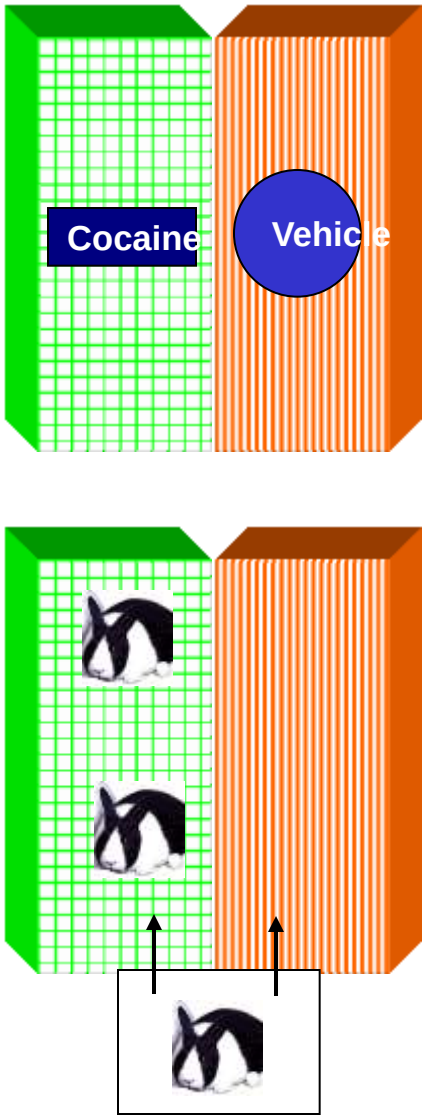
Orderly Assembly of Brain Architecture – Including Reward Systems

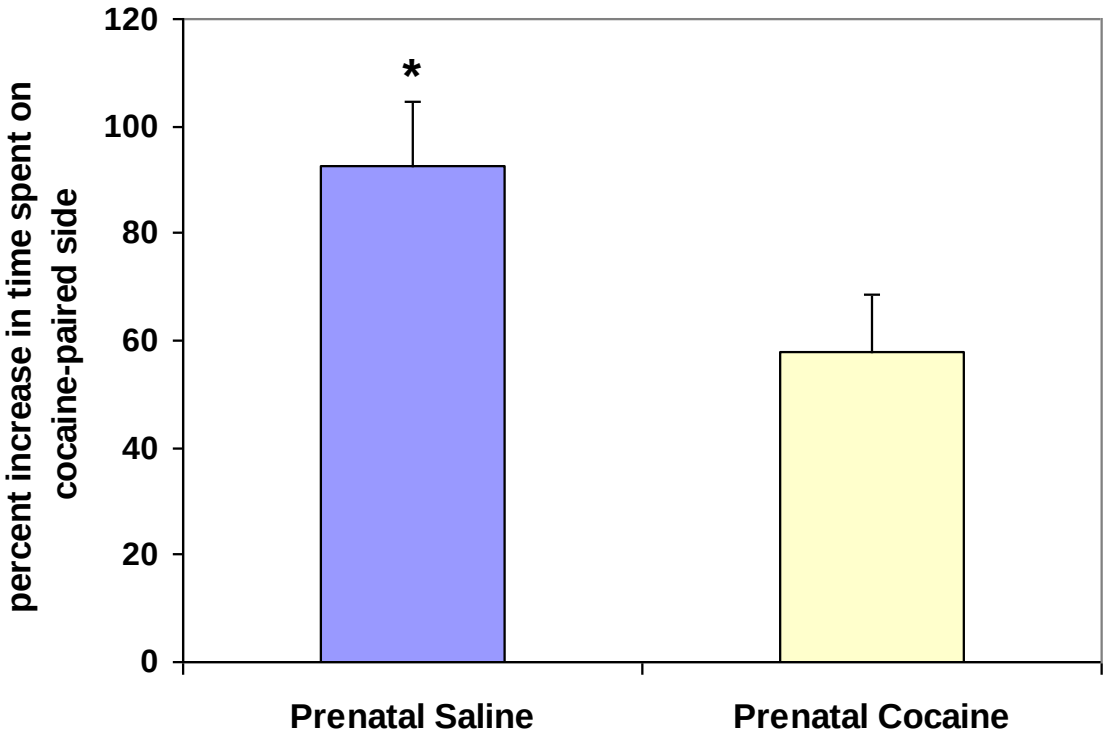
34W–36M	P2–P21	CTX		Synaptogenesis (local tuning)	Cortical pattern established for NA, 5-HT, DA, GABA and glutamate
		Aff		Biochemical differentiation	
24–28W	E18–P7	CP		Establishment of topography	
		Aff		Cell death	
22–34W	E16–P0	CP		Aggregation	Innervation by GABAergic interneurons and glutamatergic projection neurons
		SP		Appearance of transient projections	
8–15W	E16–P0	Aff		Aggregation	Innervation by VTA, LC and raphe neurons
5W	E11–17	MZ		Migration	Generation and migration of GE interneurons and pallium projection neurons
		PZ		Proliferation Cell death	Generation of LC, VTA and raphe neurons

Thompson, Levitt and Stanwood, Nat Rev Neurosci 2009


The “Reward” Neuromodulator
dopamine
dopamine receptor

Prenatal Exposure to Cocaine – Alters Effective Concentration to Obtain the Reinforcing Properties of Cocaine in Adult Offspring





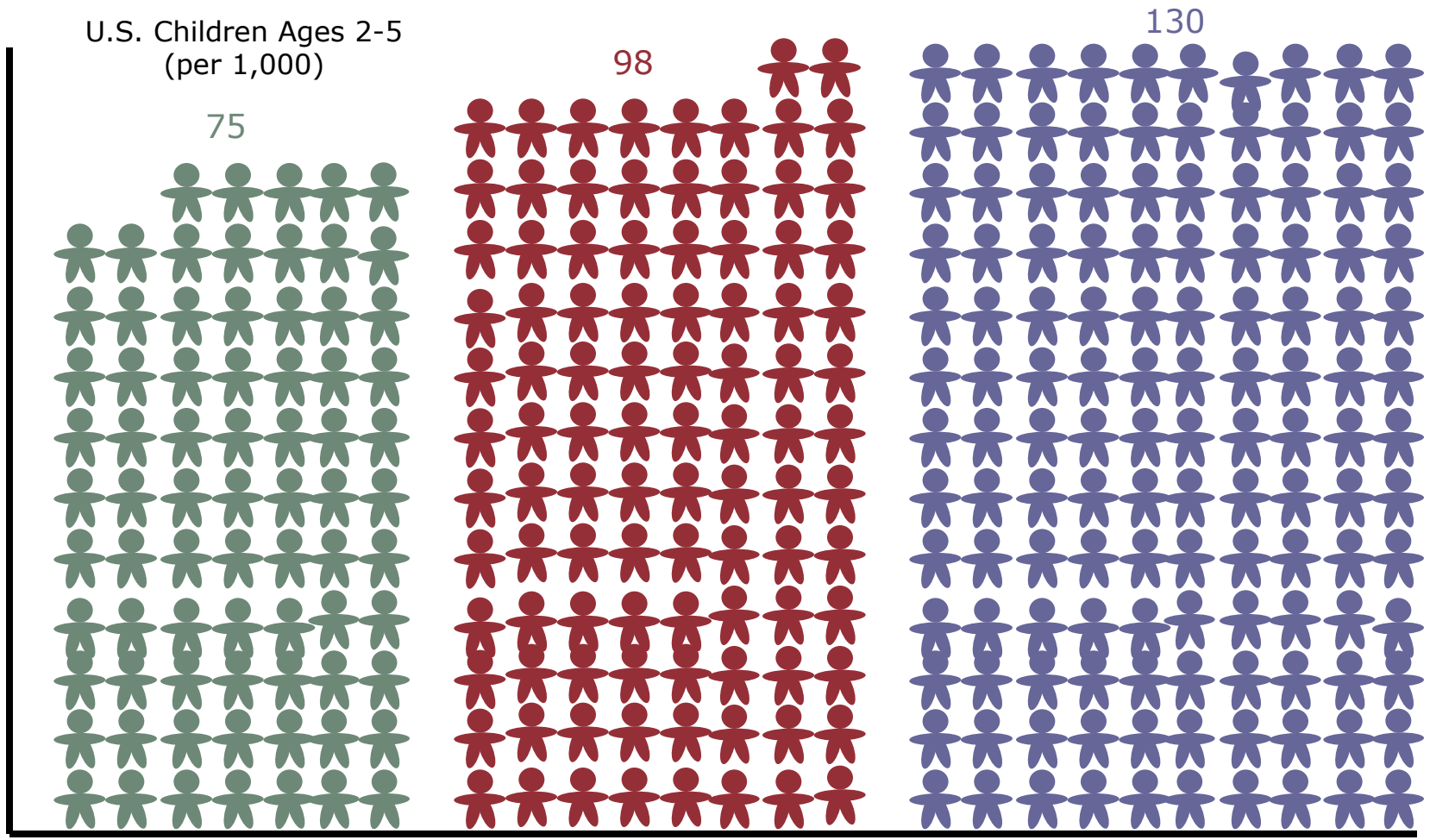
Thompson, Stanwood & Levitt, unpublished

Non-Drug Factors in Early Development Also Can Alter These Systems – And Create Vulnerability For A Lifetime

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Early Childhood Stress Influences Developmental Outcomes

Sources of Toxic Stress in Young Children



Source: Finkelhor et al. (2005)

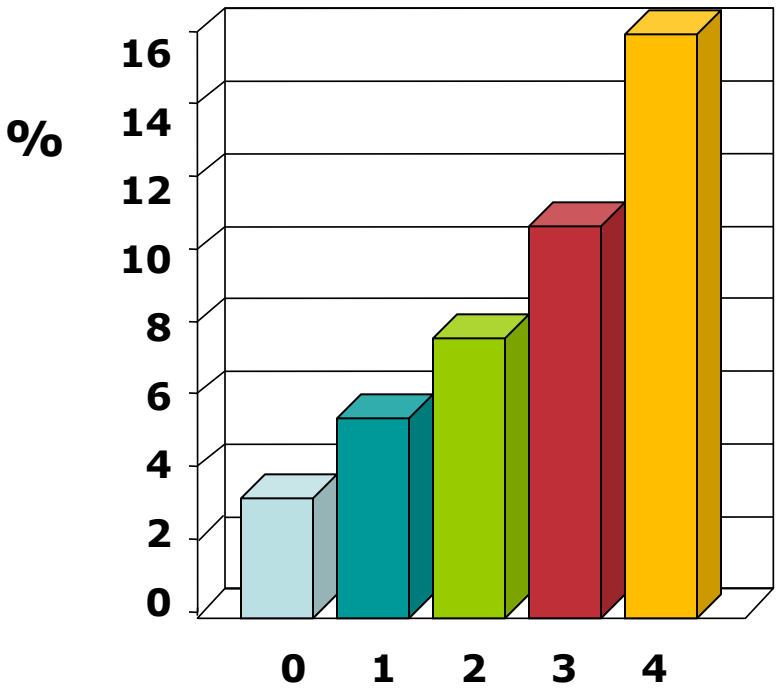
Source: SAMHSA (2002)

Source: O-Hara & Swain (1996)

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

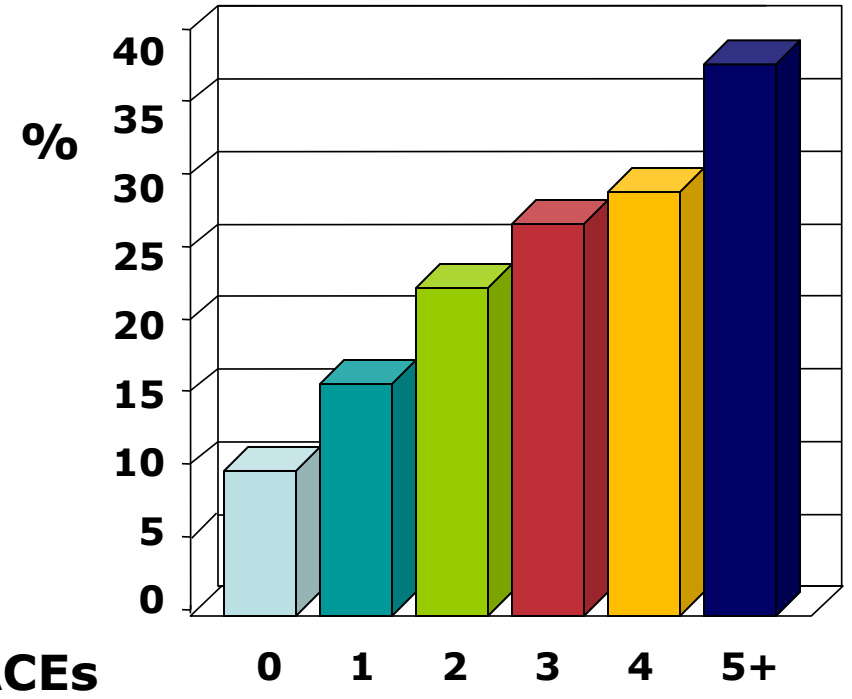
Risk Factors for Adult Substance Abuse are Embedded in Adverse Childhood Experiences (ACEs)

Self-Report: Alcoholism



Source: Dube et al, 2002

Self-Report: Illicit Drugs

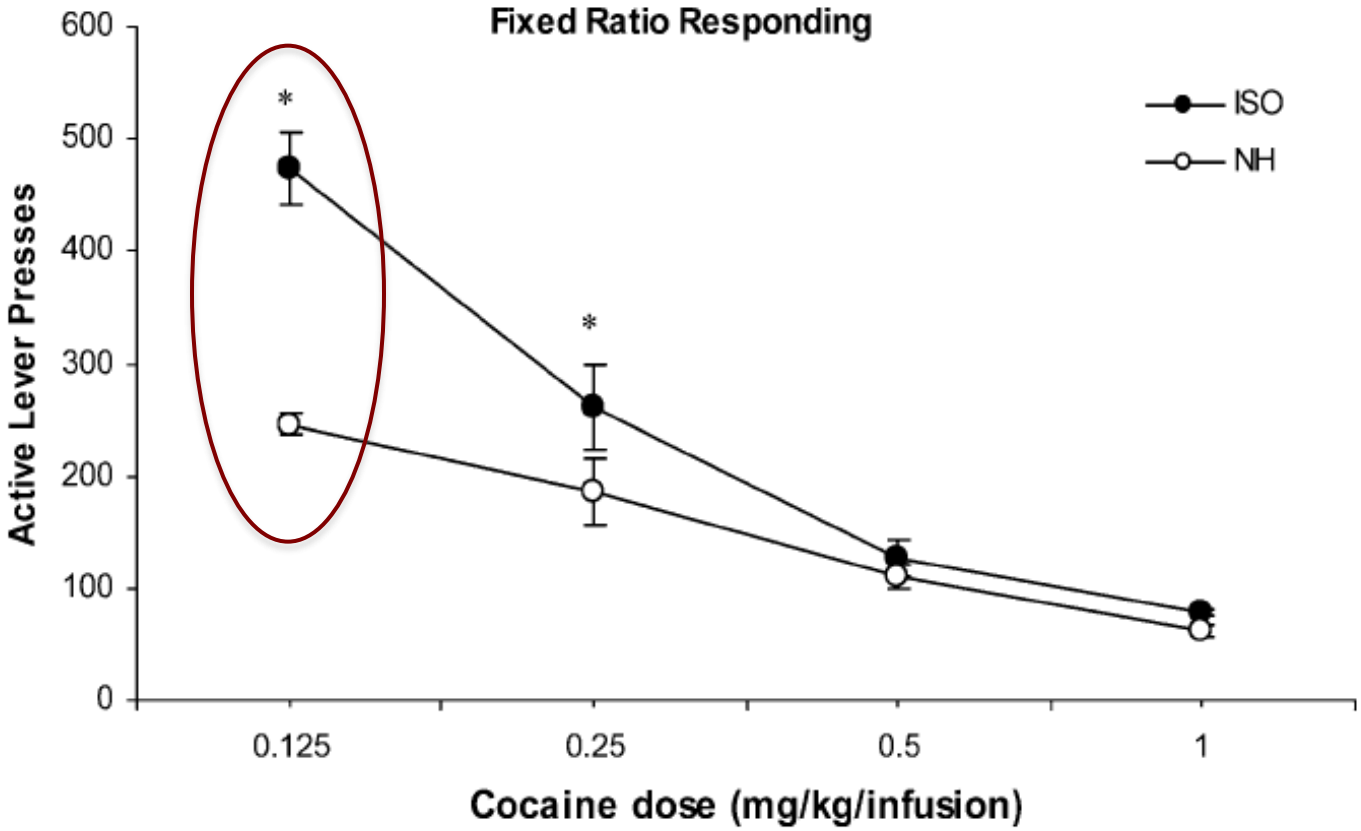


Source: Dube et al, 2005

Schilling et al, BMC Public Health 7 (2007)

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Early Neglect – Enhanced Drug-Seeking as Adults



Zhang et al Psychopharmacology, 2005

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Early Vulnerability

- **Brain chemicals – neurotransmitters – participate in the process of building brain architecture**

- **Genes and Environment tune these chemicals during development**

- **The neurotransmitters (i.e. DA), now tuned poorly, will have long-term impact on brain function – particularly related to the systems in which they serve important roles.**

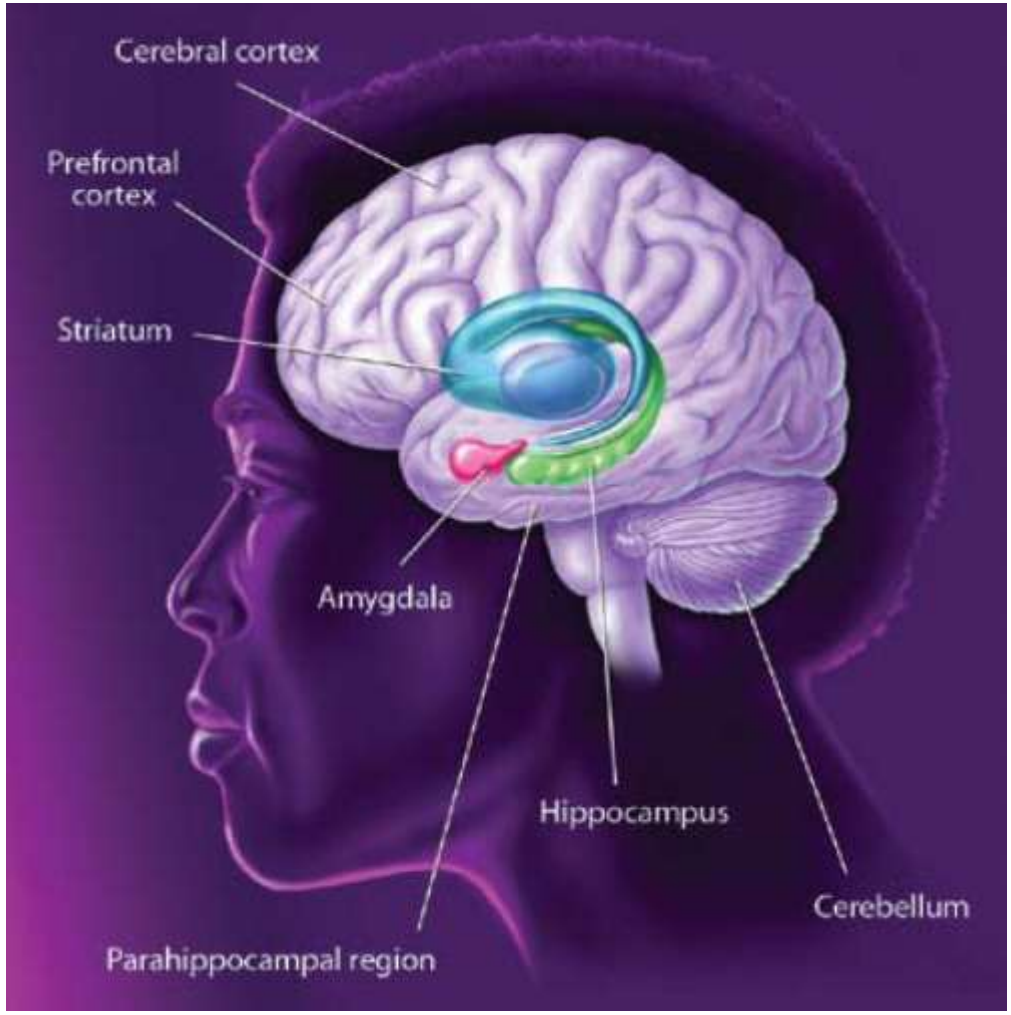
EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Concept

The cognitive, motivational (reward) and social-emotional links occur early in development, and the healthy development of these systems matter for long-term outcomes.

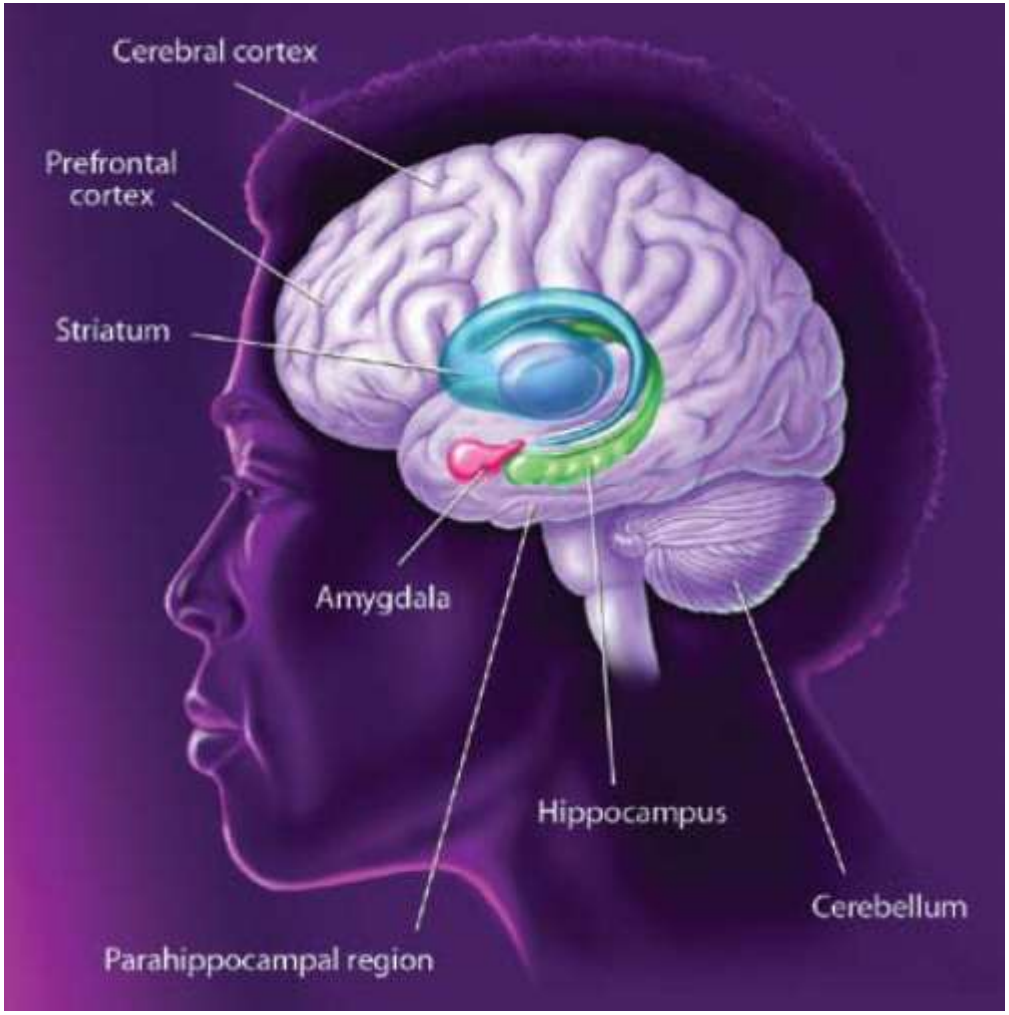
EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

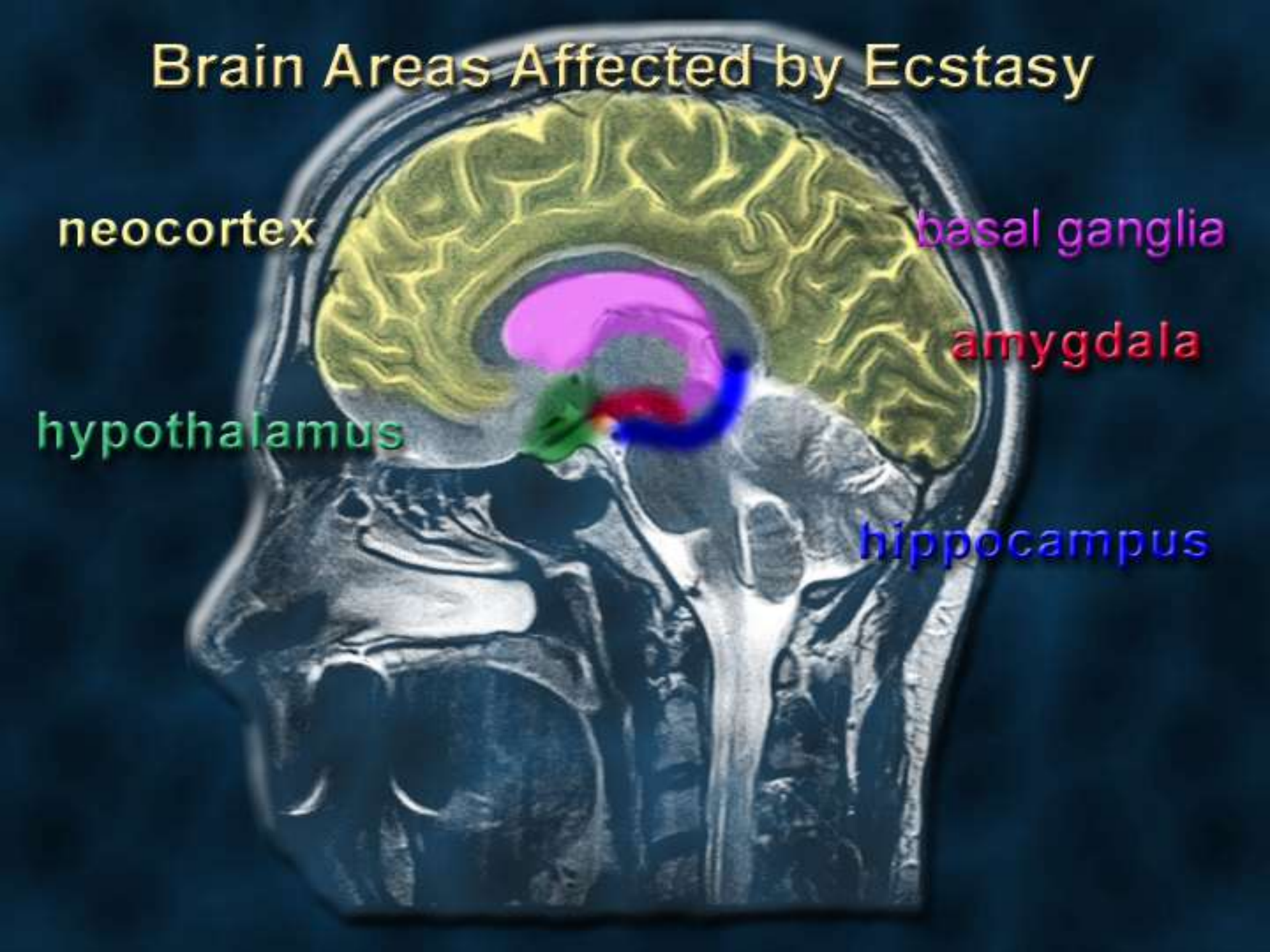
The Brain Architecture of Emotions



EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

The Brain Architecture of Memory and Learning




Brain Areas Affected by Ecstasy
neocortex
basal ganglia
amygdala
hypothalamus
hippocampus

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

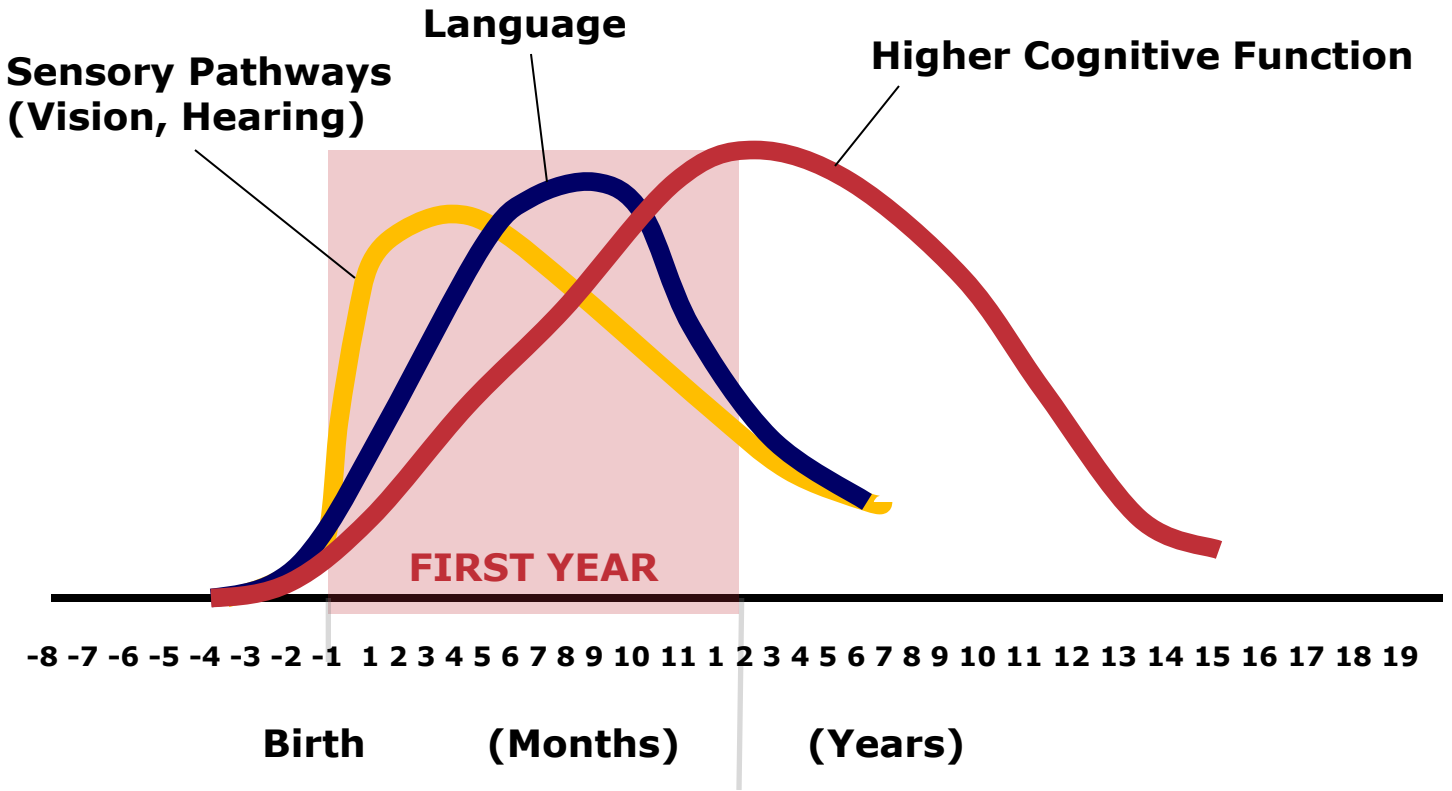
Concept

- **Building healthy architecture in these systems depends on a combination of factors – genes and environmental**

- **These systems are built over time**

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Neural Circuits are Wired in a Bottom-Up Sequence



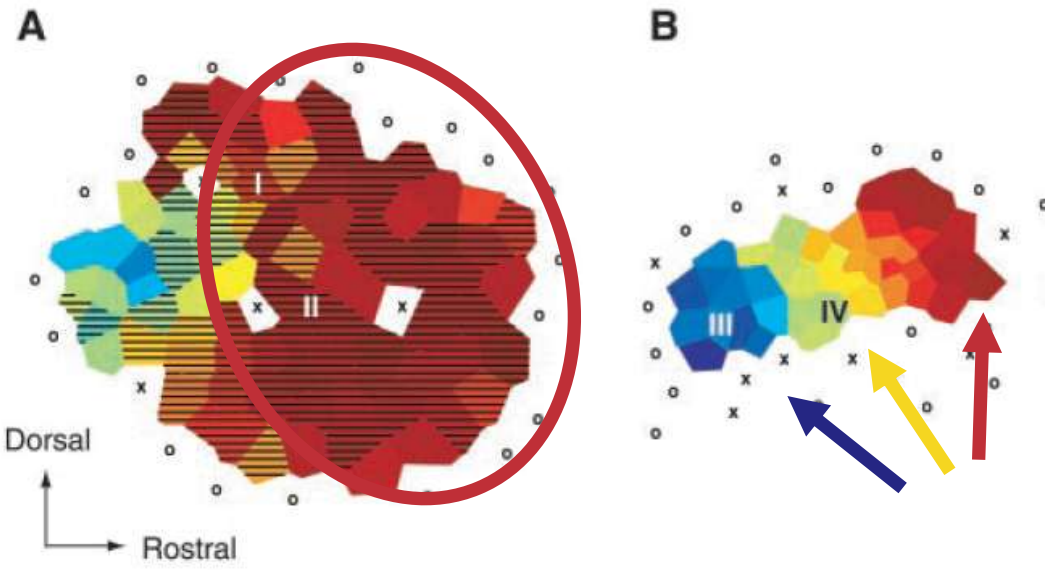
Source: C.A. Nelson (2000)

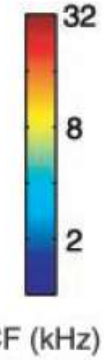
Extreme Early Experiences Can Dramatically Disrupt How Senses Form

16 days

50 days

50 days: exposed to early noise





Source: Chang & Merzenich (2003)

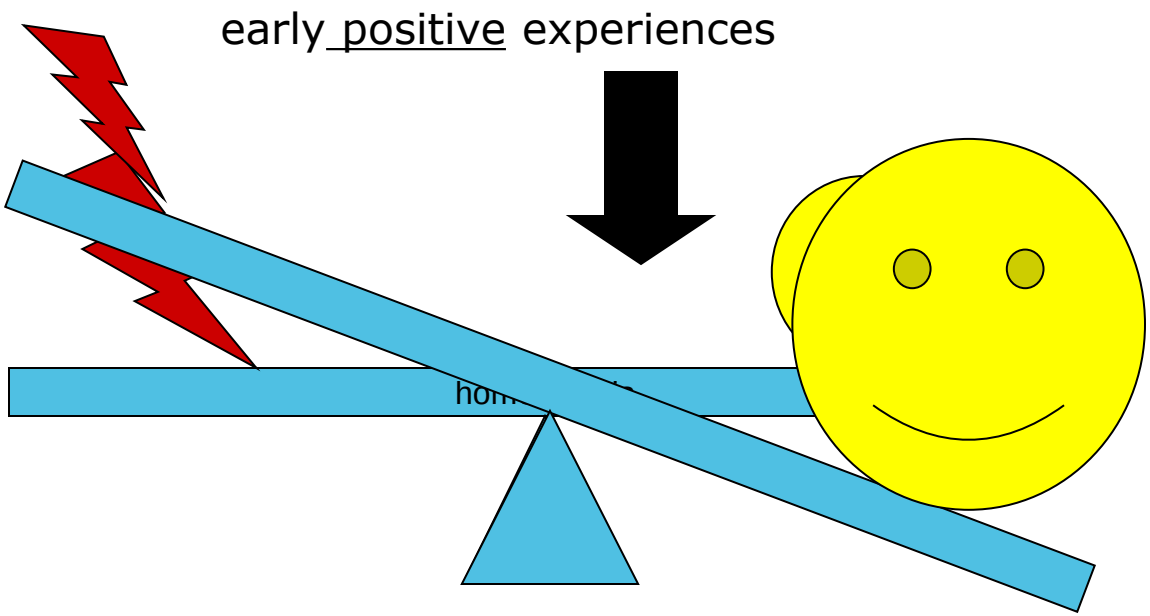
Interaction as Serve and Return

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Experiences in childhood have a lasting impact on how our brain systems work

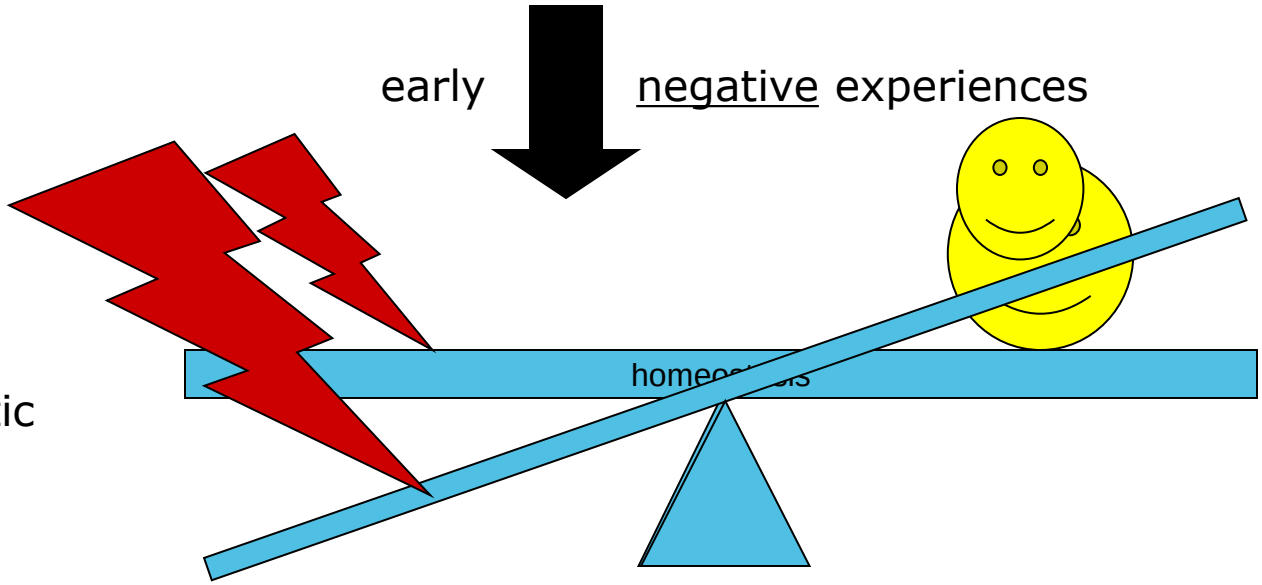
A balancing act

New homeostatic 'set point'



EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Experiences in childhood have a lasting impact on how our brain systems work



EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

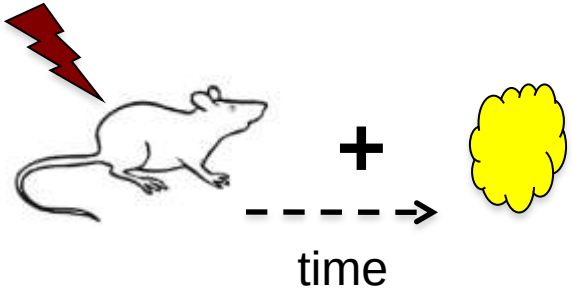
Early Childhood Adversity Can Influence a Range of Lifelong Outcomes

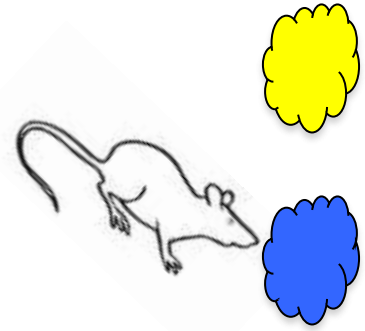
Research on the developmental biology of stress (developmental allostasis) helps explain some of the underlying reasons for differences in learning, behavior, and high risk for physical (cancer, cardio, diabetes), and mental health disorders.

Like Sensory and Stress-Response Systems, Our Reward Systems Are Tuned During Development

‘Toxic’ Stress Is Interpreted As Aversive

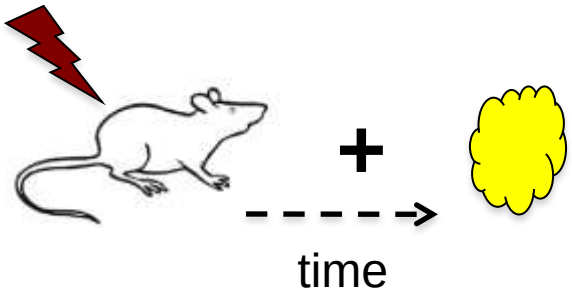
> P10

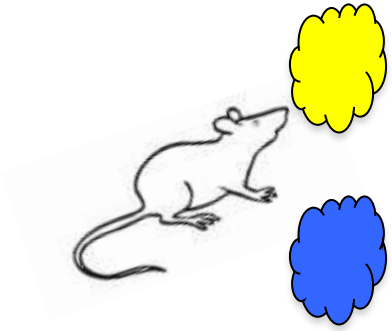




Early 'Toxic' Stress Can Be Interpreted As Rewarding

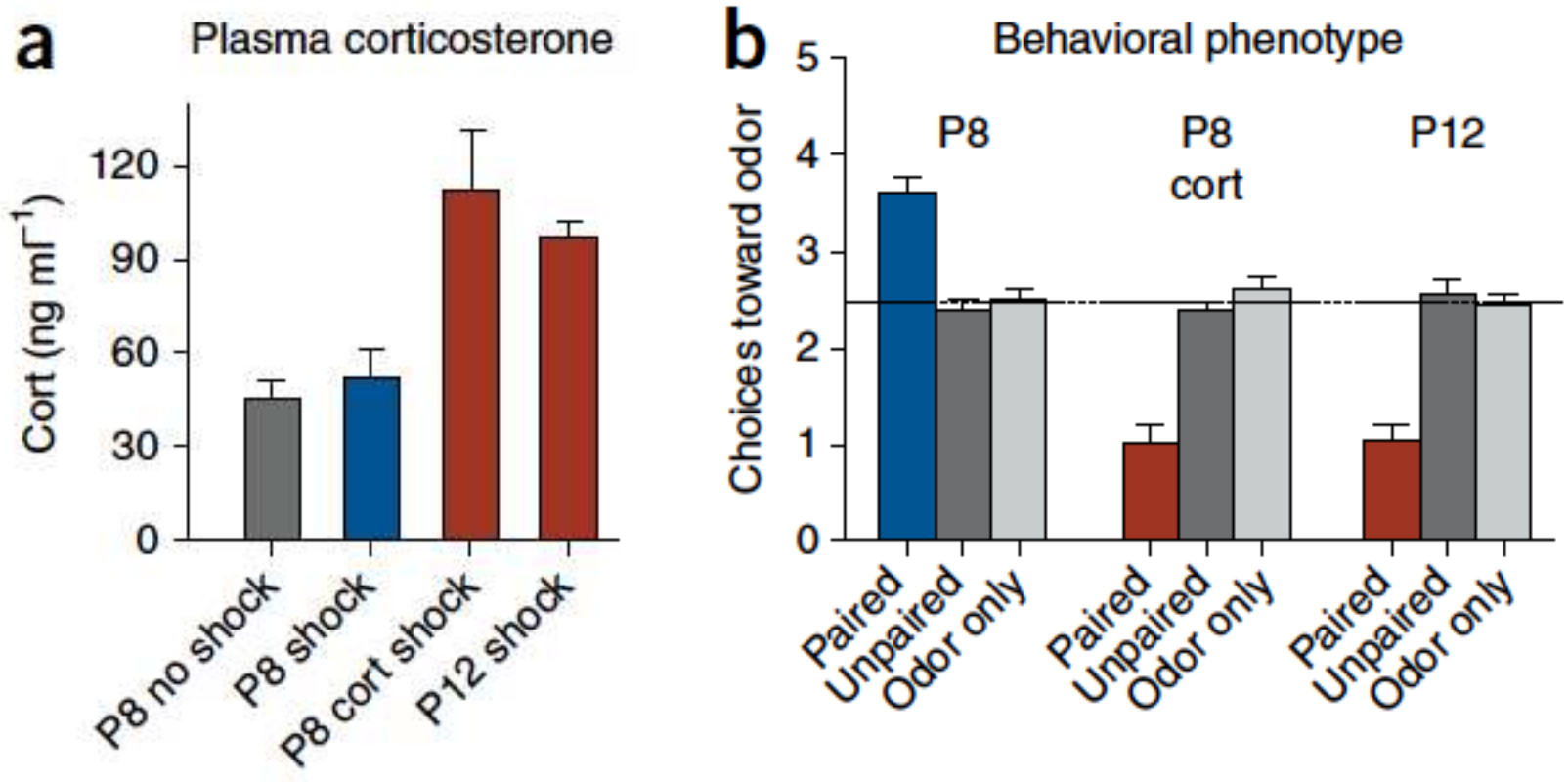
Birth – P10





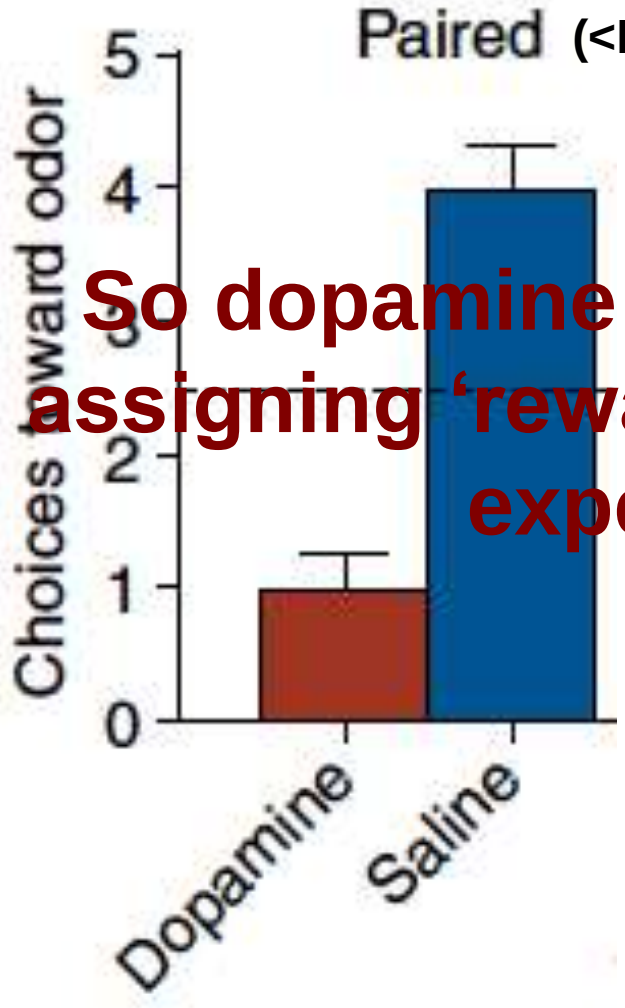
EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Early Stress Response – Reveals Hyporesponsive Period



Barr et al, Nat Neurosci, 2009

At Early Ages, Dopamine Controls Aversive or Rewarding Properties of Stressors



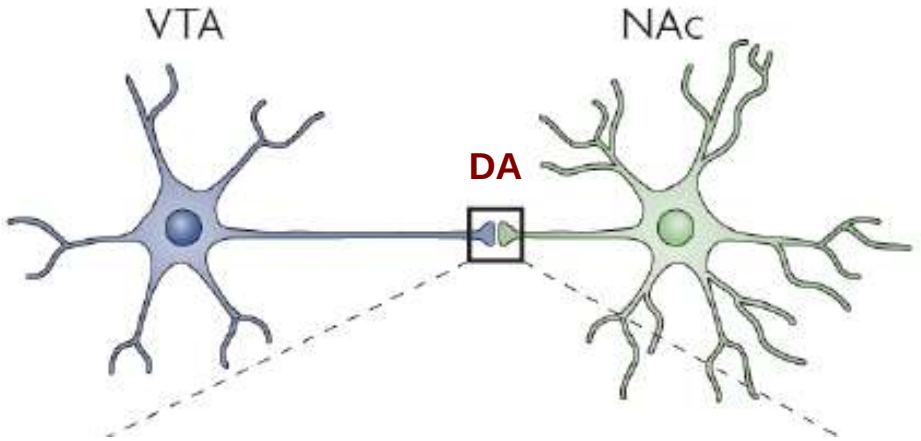
So dopamine sets the timing of assigning 'reward' or 'aversion' to experiences

Barr et al, Nat Neurosci, 2009

“Social Defeat”, Dopamine and Reward Systems

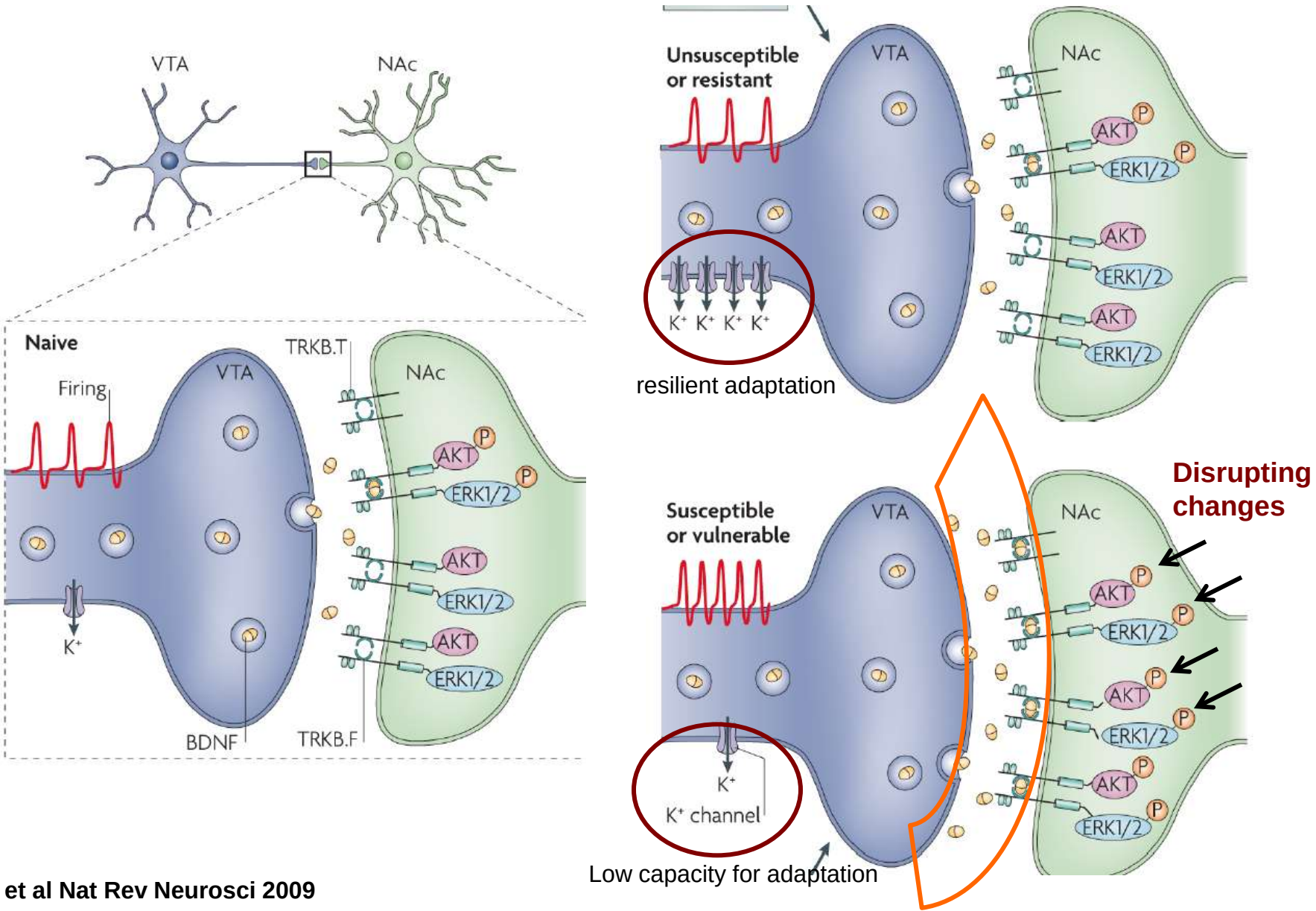
(5 min bouts of aggression w/o physical injury)

Key ‘reward’ pathway



Feder et al Nat Rev Neurosci 2009

“Social Defeat”, Dopamine and Reward Systems



Feder et al Nat Rev Neurosci 2009

"Social Defeat" – Low Capacity for Adaptation = Mental Health Issues

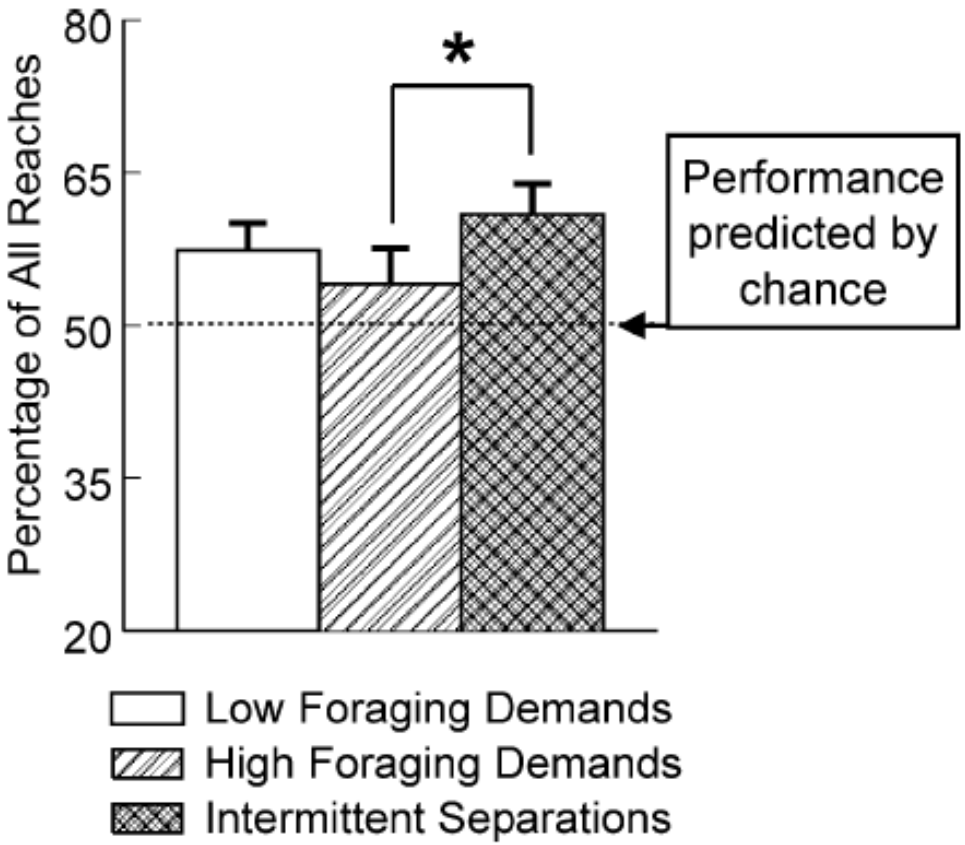
Low capacity for adaptation

- **Social aversion**
- **Depression**
- **Anxiety Disorders**

Feder et al Nat Rev Neurosci 2009

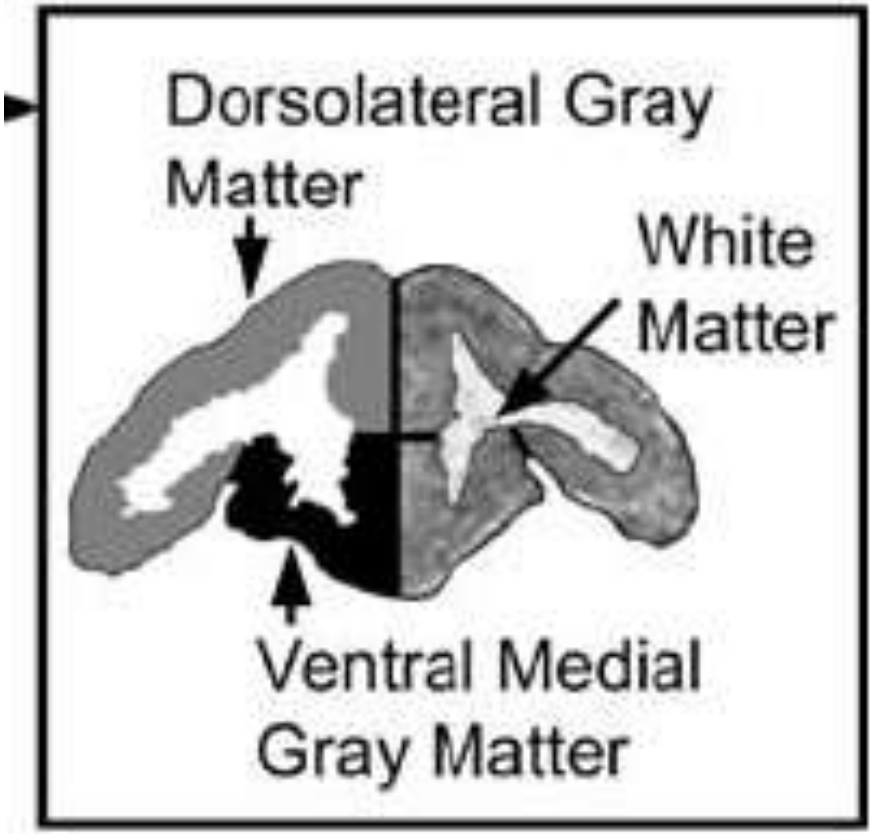
EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Toxic Stress (high foraging) Reduces Brain Size and Abilities to Connect Motivation, Reward and Cognition



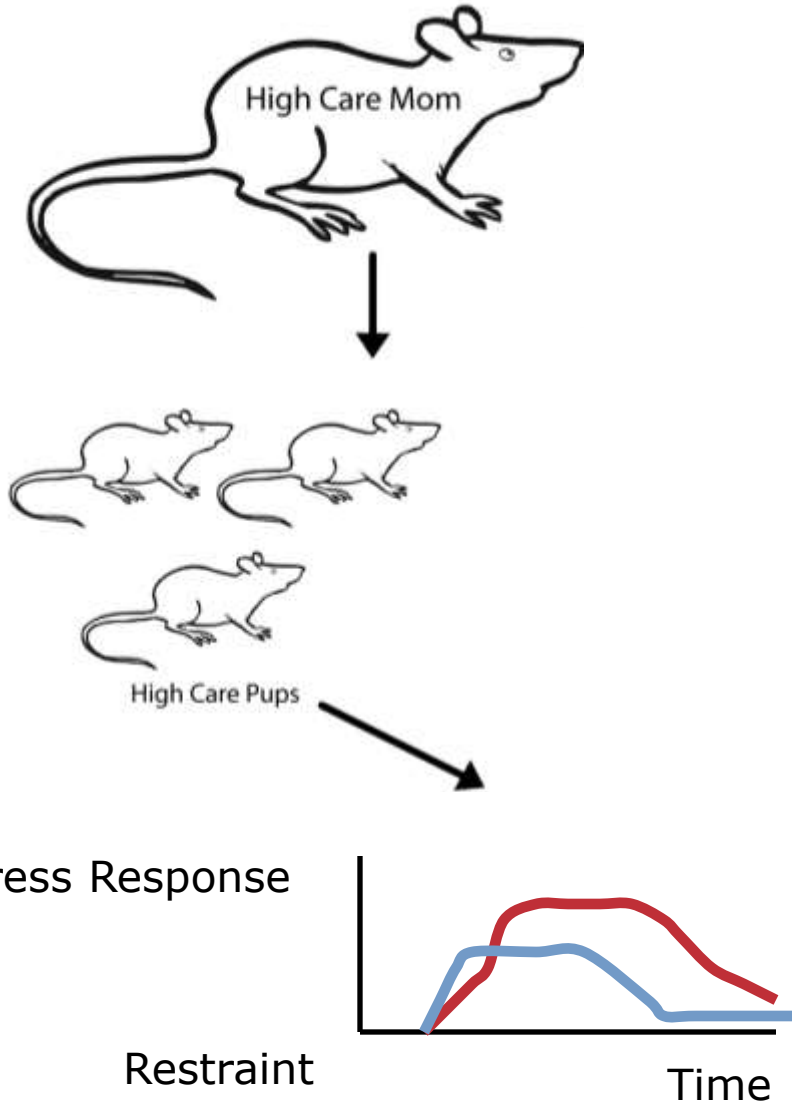
Lyons and Schatzberg, Neurobiol Learning Mem, 2003

Greater Abilities to Connect Motivation, Reward and Cognition – Larger Frontal Area of Intermittent Group



Lyons and Schatzberg, Neurobiol Learning Mem, 2003

Experience Affects Stress Response for a Lifetime!



Source: Meaney et al. (200?)

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Concept

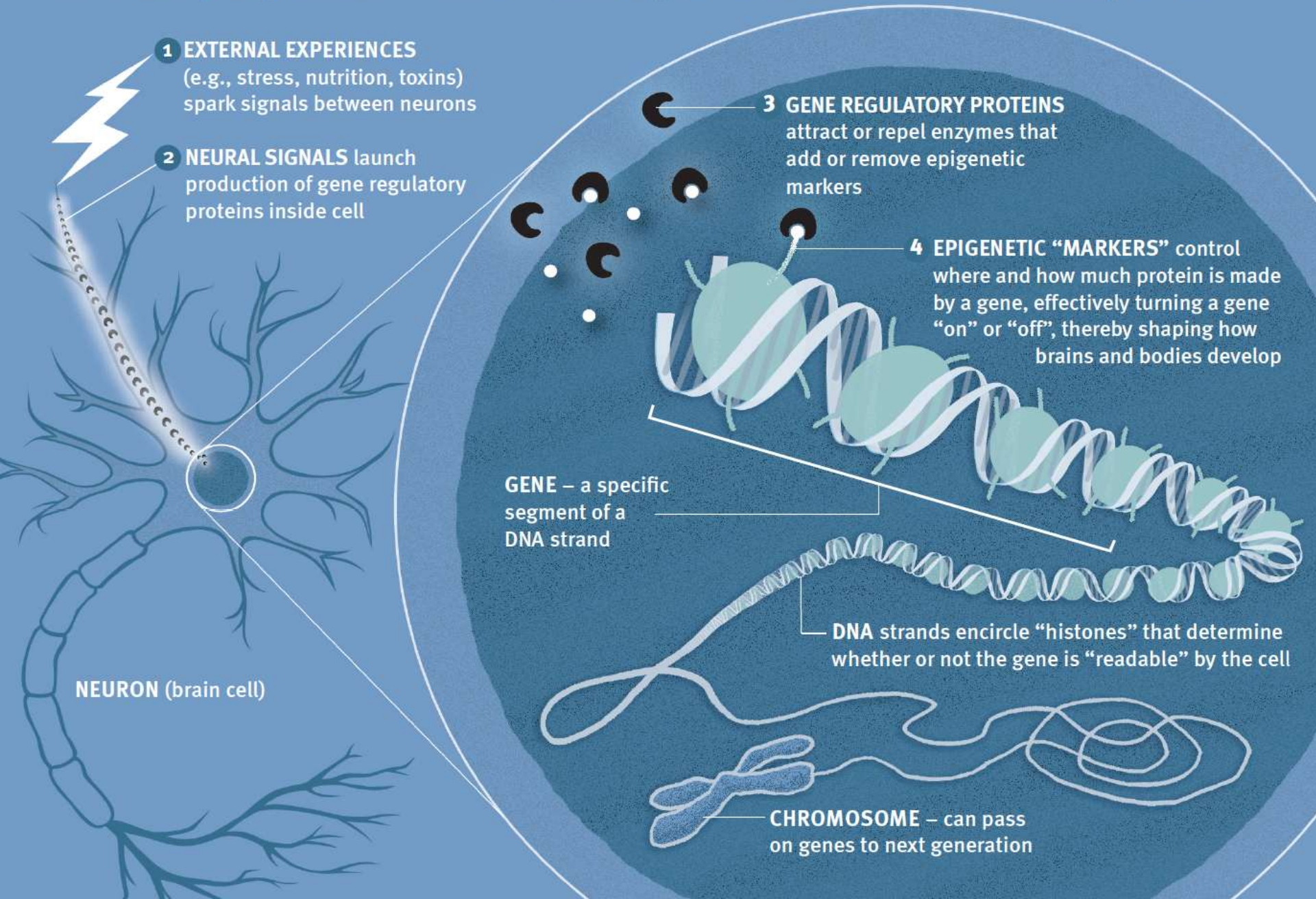
The links between cognitive, social-emotional and reward systems occur early in development, and the healthy development of these systems matter for long-term outcomes.

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN

How is the influence of early experience maintained for a lifetime?

In part, through '*epigenetics*'.....
and it's is really powerful

How Early Experiences Alter Gene Expression and Shape Development



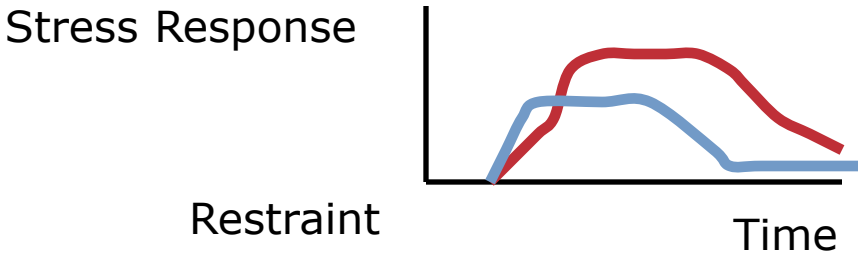
Early Experiences Can Transmit Across Generations

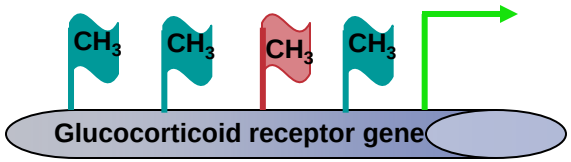
Maternal diet supplements during pregnancy causes shift in offspring's **fur color**, reduced **obesity** and **cancer risk** in genetically identical mice.

choline/folate →

Source: Jirtle & Skinner (2007)

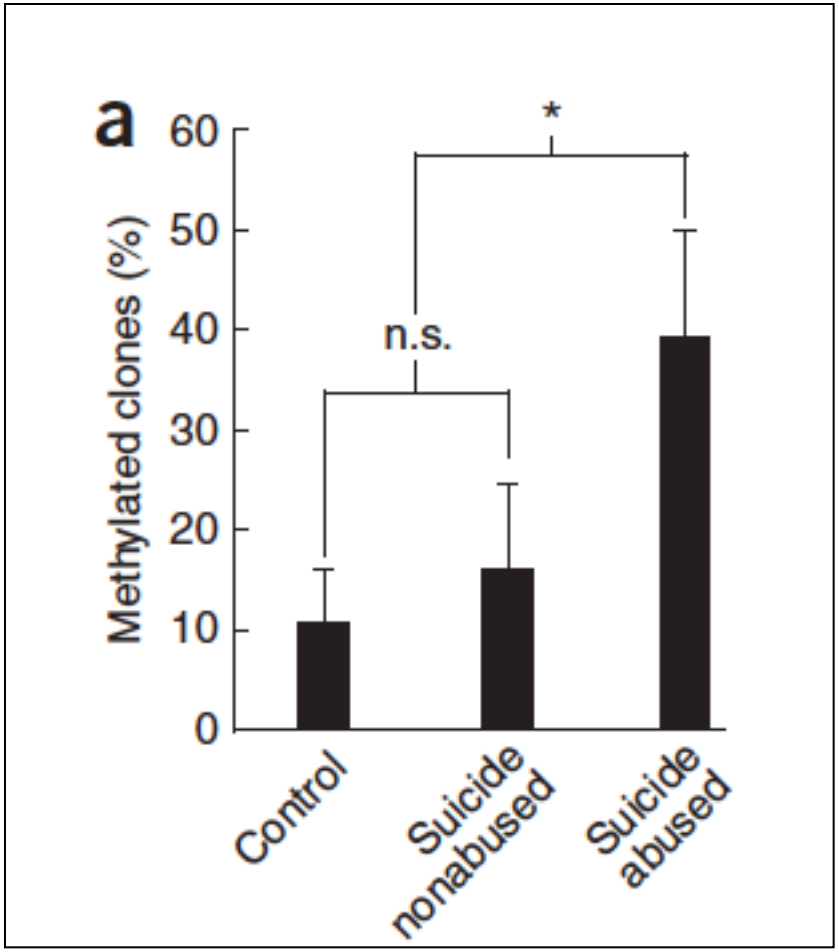
How Experience Influences Genes





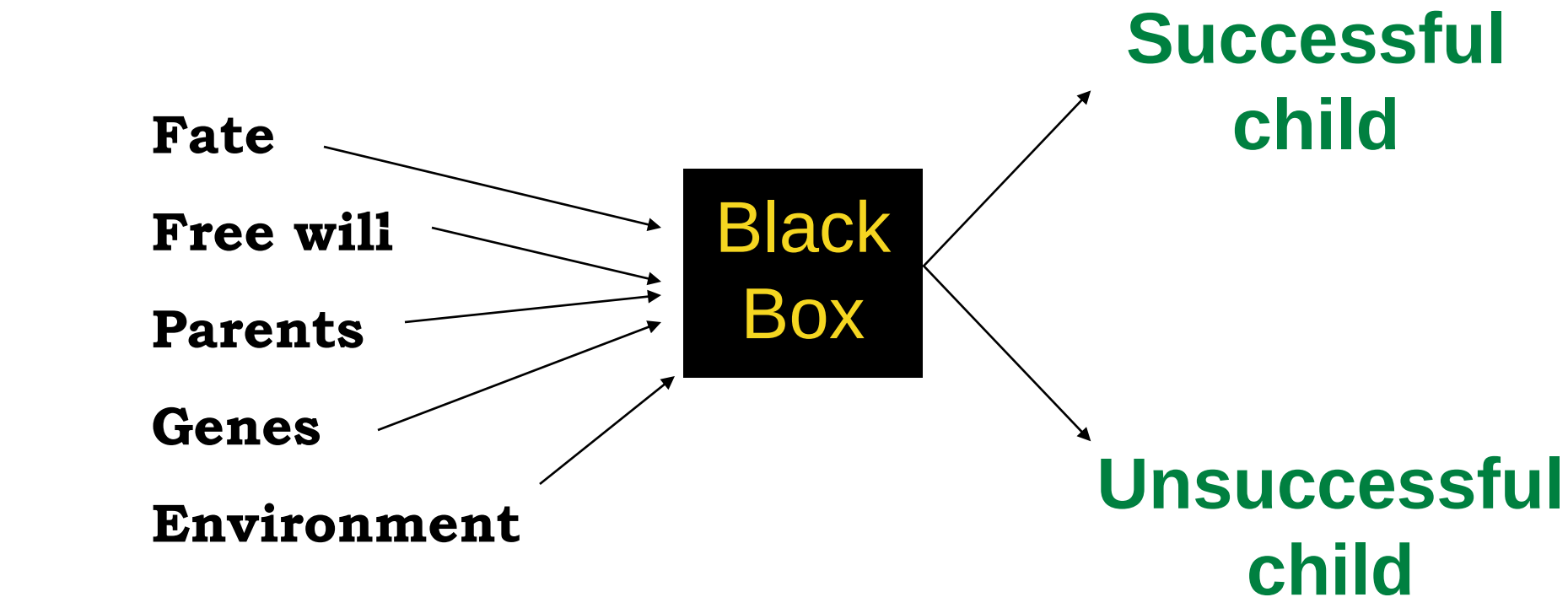
Source: Meaney et al. (2005)

The Epigenetic Changes also Occur in Humans



McGowan et al, Nature Neurosci 2009

Policy Implications: Child Development is not a Black Box



EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

A Central Message for Policy Makers

Interactions (+/-) ⟷ **Brain Architecture**

(serve & return)

Reward/Motivation Development

Emotional Development

Social Development

Cognitive Development

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Early Childhood Stress Influences Developmental Outcomes

Positive

- Important to development & in the context of stable and supportive relationships

Tolerable

- Potentially disruptive, but buffered by supportive relationships & safe environments

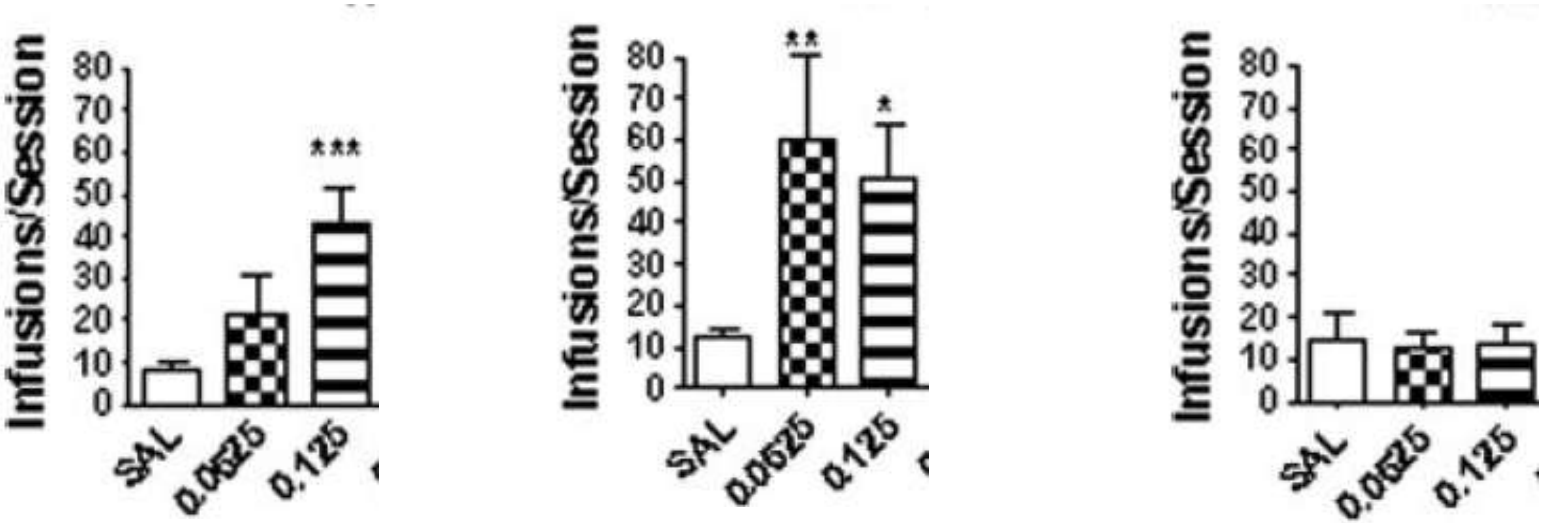
Toxic

- Disrupts brain architecture, increases the risk of stress-related physical and mental illness

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Not All Early Stress Is The Same – Toxic vs Positive Stress and the Reward System

Controls | **Toxic Stress** | **Positive "Innoculating" Stress**



Cocaine Dose

Moffett et al J. Pharm Exp Ther 2006

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Some Final Thoughts

- All systems require experience to develop
- Patterns of activity (experience), good or bad, will impact brain architecture and chemistry
- Cognitive, social-emotional and reward systems are interconnected
- There are sensitive periods during which time the architecture and chemistry of systems can be changed
- The early impact on brain architecture and chemistry will have long-lasting consequences

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Some Final Thoughts

In the context of the reward systems, distinguishing between a brain architecture and chemistry that reflects *motivated, non-motivated or aversive behavior* will be critical in designing interventions that work……

So remember……..

EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

Research Informs The Way That We Intervene

Thank You!