

NATIONAL SCIENTIFIC COUNCIL ON THE DEVELOPING CHILD

# **Brain and Child Development: The Core Story, Foundational Mechanisms and Challenges**

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SIMMS/MANN CHAIR IN DEVELOPMENTAL NEUROGENETICS

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Florida State Summer Training Institute on Autism

June 14, 2022

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<http://www.developingchild.harvard.edu>

## Today's Workshop

- The challenge in the U.S. when it comes to healthy child development
- A primer of brain development (pre- and postnatal) and the requirement of early experience
- Why (and how) does 'early' have such lasting effects?
- Toxic Stress -what's it all about and can we measure it?
- Three key brain and health targets for success
  - Reward and Motivation
  - Executive Function
  - Resilience
- What comes next - measurement, screening and interventions

# Prevalence of Adverse Childhood Experiences From the 2011-2014 Behavioral Risk Factor Surveillance System in 23 States

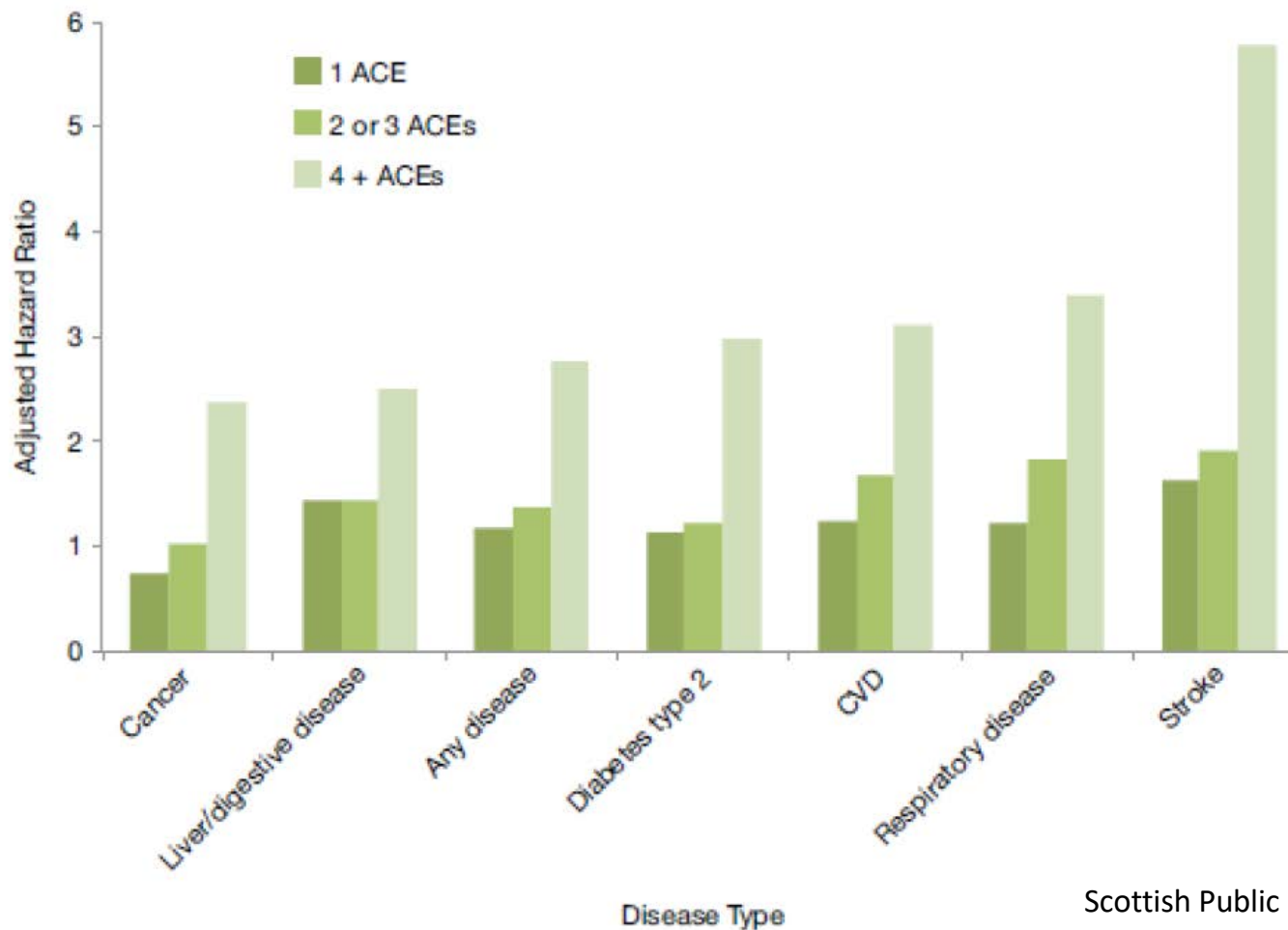
Melissa T. Merrick, PhD; Derek C. Ford, PhD; Katie A. Ports, PhD; Angie S. Guinn, MPH

## **215,000 respondents from 23 states using Behavioral Risk Factor Surveillance System (includes ACE**

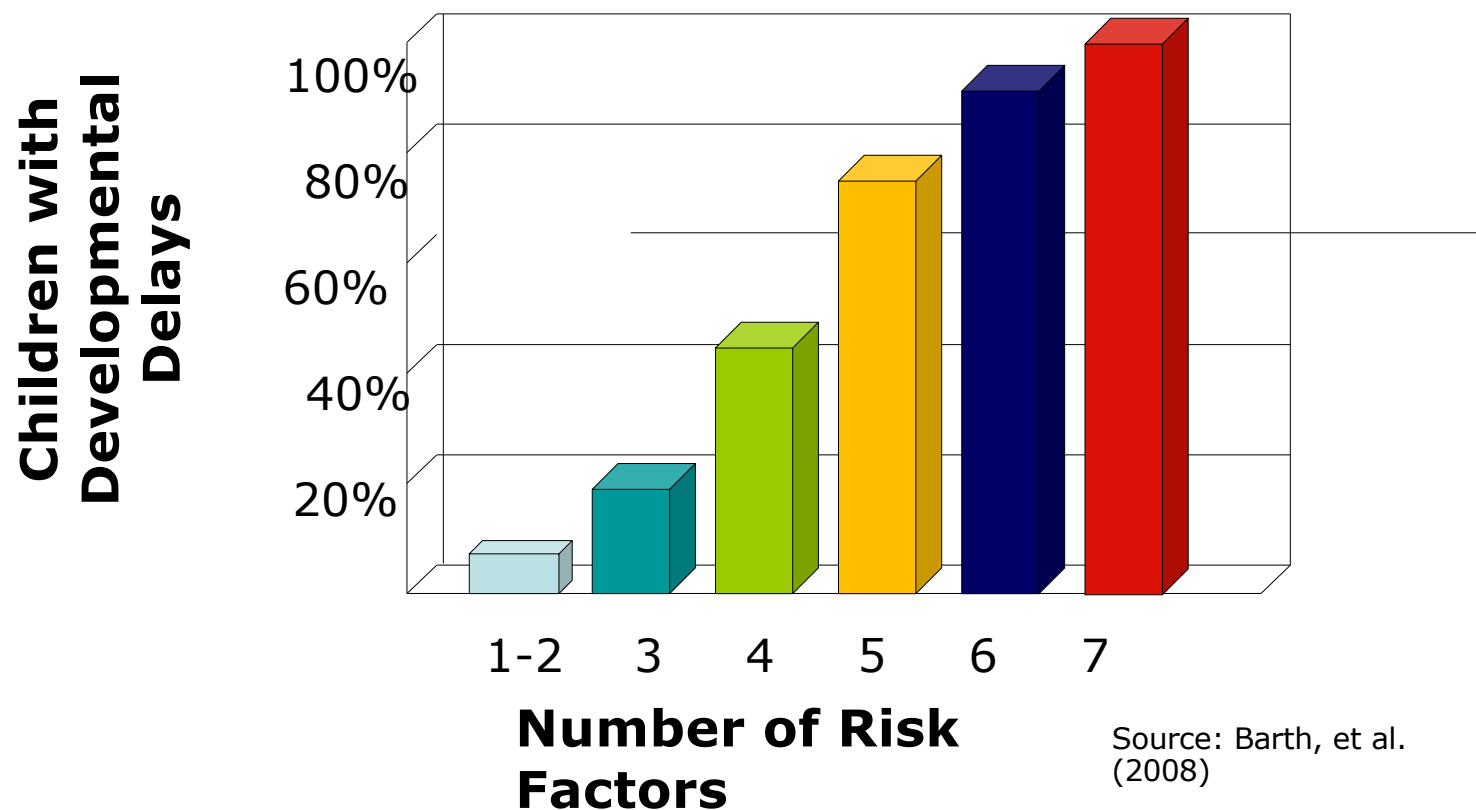
- 62% report at least 1 ACE
- 25% report 3 or more ACES
- 1.7-2.3X higher exposure in African Americans or Multi-Racial
- Other factors that increase exposure:
  - very low income
  - low education achievement
  - extended unemployment
  - gay/lesbian, bisexual
  - Developmental disabilities

**Figure 1** Changes in risk of disease with increase history of ACE 2013

*Changes in risk of disease development with increased history of ACE, English survey data, 2013*



# The Cumulative Pile Up of Adversity Impairs Development in the First Three Years





## Adverse childhood experiences in children with autism spectrum disorder

*Daniel W. Hoover<sup>a,b</sup> and Joan Kaufman<sup>a,b</sup>*

### KEY POINTS

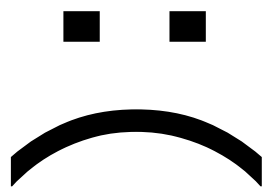
- Children with ASD are bullied at a rate three to four times that of nondisabled youth, with bullying associated with negative effects on children's academic functioning and mental health, including an increased risk for suicidality.
- Adverse childhood experiences (ACEs) are reported more frequently by families of children with autism, particularly experiences of parental divorce and income insufficiency.
- Extant studies do not show increased risk of child maltreatment in the ASD population.
- ACE exposure is associated with increased risk of comorbid mental health and medical problems, and later diagnosis and initiation of treatment in youth with ASD.

## Prevalence and Variation of Developmental Screening and Surveillance in Early Childhood

Ashley H. Hirai, PhD; Michael D. Kogan, PhD; Veni Kandasamy, MSPH; Colleen Reuland, MS; Christina Bethell, PhD

Screening or Surveillance (social/language), 9-35 mo, 5668 survey:

- 30% screening nationally (state range 17% - 59%)
- 37% verbal surveillance nationally - (state range 19% - 61%)
- Factors that reduce both - ethnicity, income, parental education







# We Are in BIG Trouble


**CONCLUSIONS AND RELEVANCE** Despite more than a decade of initiatives, rates of developmental screening and surveillance remain low. However, state-level variation indicates continued potential for improvement. Systems-level quality improvement efforts, building on the medical home, will be necessary to achieve recommended screening and surveillance goals.

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## A Decade of Science Informing Policy

The Story of the National Scientific Council on the Developing Child



Center on the Developing Child  HARVARD UNIVERSITY

• **Jack Shonkoff (Chair)**

• **Pat Levitt (co-SD)**

• **Nathan Fox (co-SD)**

• **Silvia Bunge**

• **Judy Cameron**

• **Greg Duncan**

• **Damien Fair**

Former members

**Tom Boyce \***

**Silvia Bunge\***

**William Greenough**

**James Heckman**

**Eric Knudsen**

**Betsy Lozoff**

**Linda Mayes\***

**Deborah Philips**

**Art Rolnick\***

• **Phil Fisher**

• **Megan Gunnar**

• **Takao Hensch**

• **Fernando Martinez**

• **Bruce McEwen**

• **Charles Nelson III**

• **Patricia Pelufo Silveira**

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NATIONAL FORUM ON EARLY CHILDHOOD POLICY

### The Foundations of Lifelong Health Are Built in Early Childhood



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### The Science of Neglect: The Persistent Absence of Responsive Interactions Disrupts the Developing Brain

WORKING PAPER 12

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### Mental Health Problems in Early Childhood

## A Science-Based Framework for Early Childhood Policy

Using Evidence to Improve Outcomes  
in Learning, Behavior, and Health for  
Vulnerable Children



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### Persistent Fear and Anxiety Can Affect Young Children's Learning and Development

WORKING PAPER 9

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### Early Childhood Development

Closing the Gap Between  
What We Know and  
What We Do



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## Understanding Motivation: Building the Brain Architecture That Supports Learning, Health, and Community Participation

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### Early Experiences Can Alter Gene Expression and Affect Long-Term Development

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YOUNG CHILDREN DEVELOP IN AN ENVIRONMENT OF RELATIONSHIPS



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### EXCESSIVE STRESS DISRUPTS THE ARCHITECTURE OF THE DEVELOPING BRAIN

SUMMER 2005

WORKING PAPER 11



<http://developingchild.harvard.edu>

The National Academies of  
SCIENCES • ENGINEERING • MEDICINE

July 2019

CONSENSUS STUDY REPORT

[nationalacademies.org/VibrantHealthyKids](https://nationalacademies.org/VibrantHealthyKids)

**The well-being  
of children  
starts with the  
well-being of  
caregivers.**

 **#VibrantHealthyKids**

The National  
Academies of  
SCIENCES  
ENGINEERING  
MEDICINE

## Vibrant and Healthy Kids

ALIGNING SCIENCE, PRACTICE, AND POLICY  
TO ADVANCE HEALTH EQUITY

## And It Is Intergenerational



The healthy development of young children provides a strong foundation for healthy and competent adulthood, responsible citizenship, economic productivity, strong communities, and a just and fair society.

## The Core Story

#1 - Child development is the foundation of prosperous communities

#2 - Brains are built over time, from the bottom up (*skill begets skill*)

#3 - Genes and experiences together build brains (*serve and return* relationships)

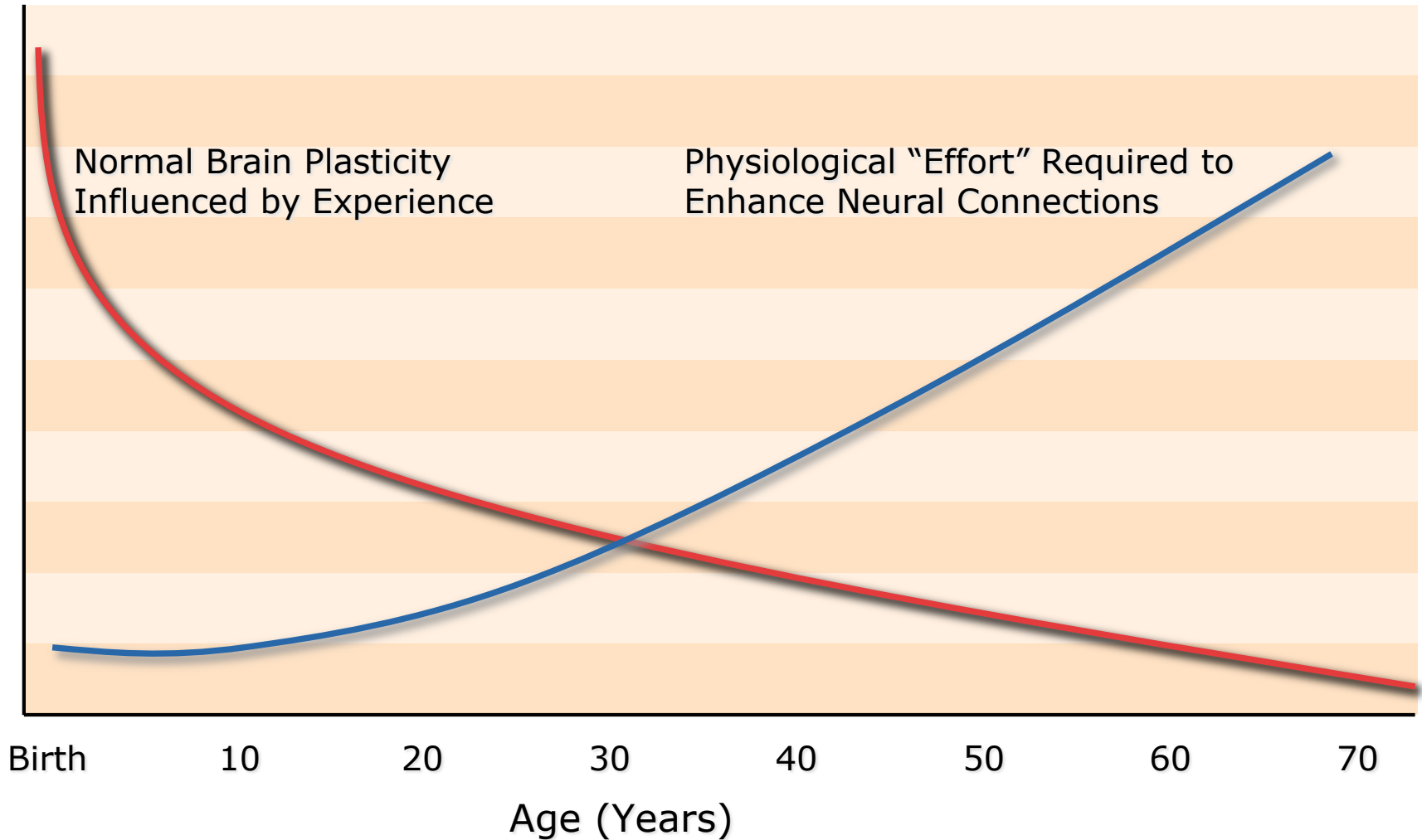
#4 - Cognitive, social and emotion development are inextricably intertwined

#5 - *Toxic stress* damages *brain architecture*

#6 - *Resilience* is not an internal character strength, but rather is built through combined impact of genes and experiences of a child

#7 - For many functions, the brain's capacity for change decreases over time (cost-effectiveness factor) - *but not all functions are*

- For many functions, the brain's capacity for change decreases over time (most-effective factor) - **but not all functions are impacted equally**



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Early Child Brain Development Video

<https://developingchild.harvard.edu/resources/experiences-build-brain-architecture/>





## GENES

- DNA sequence variation
- G-E correlation
- GxE contingent interactions
- Epigenetic processes



## ENVIRONMENTS

- Adverse childhood experiences
- Poverty/racism/violence
- Access to resources
- Responsive caregiving



## TIME



## BIOLOGICAL MEDIATORS AND MODERATORS

- DIFFERENTIAL SUSCEPTIBILITY/RESILIENCE
- GUT/AIRWAY MICROBIOME
- IMMUNE COMPETENCE/INFLAMMATION
- METABOLIC REGULATION

- Critical/sensitive periods
- Timed neural plasticity
- Excitatory/inhibitory neuronal balance
- Developmental pace



## PHYSICAL AND MENTAL HEALTH OUTCOMES

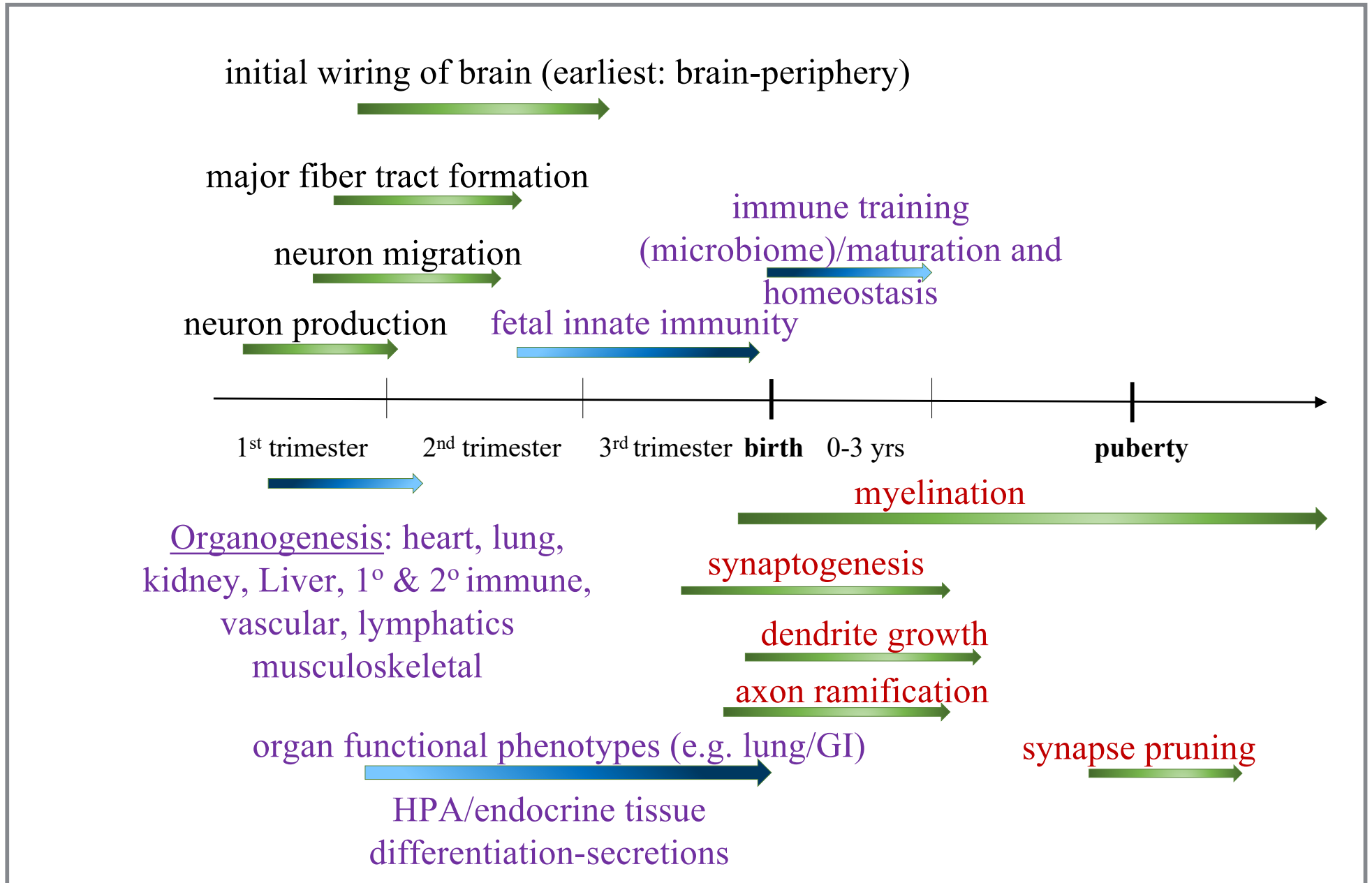
- Learning/behavior/adaptive skills
- Stress reactivity
- Inflammatory/immune balance
- Metabolic balance
- Organ architecture

# Frameworks Institute Research

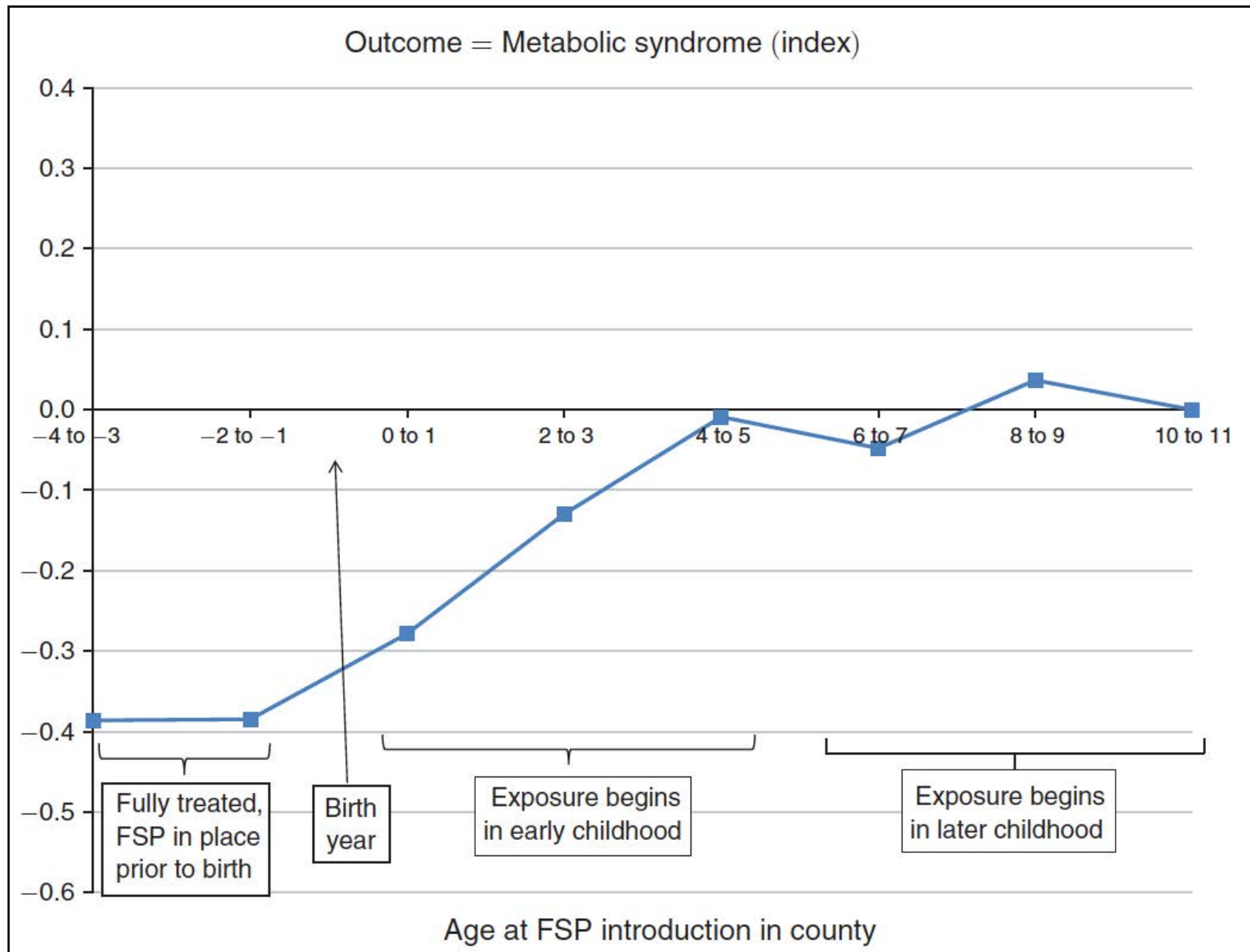
## “Tipping the Balance”

<http://www.frameworksinstitute.org/>

# HUMAN DEVELOPMENT - STARTS EARLY & EXTENDS INTO ADULTS



# ACCESS TO RESOURCES MATTERS - and so does timing

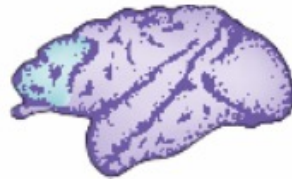


# Expansion of the Cerebral Cortex – What Makes All of Us Human

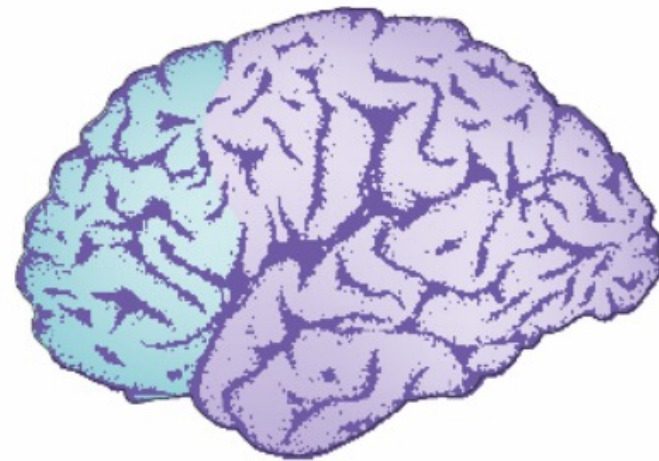
a Mouse



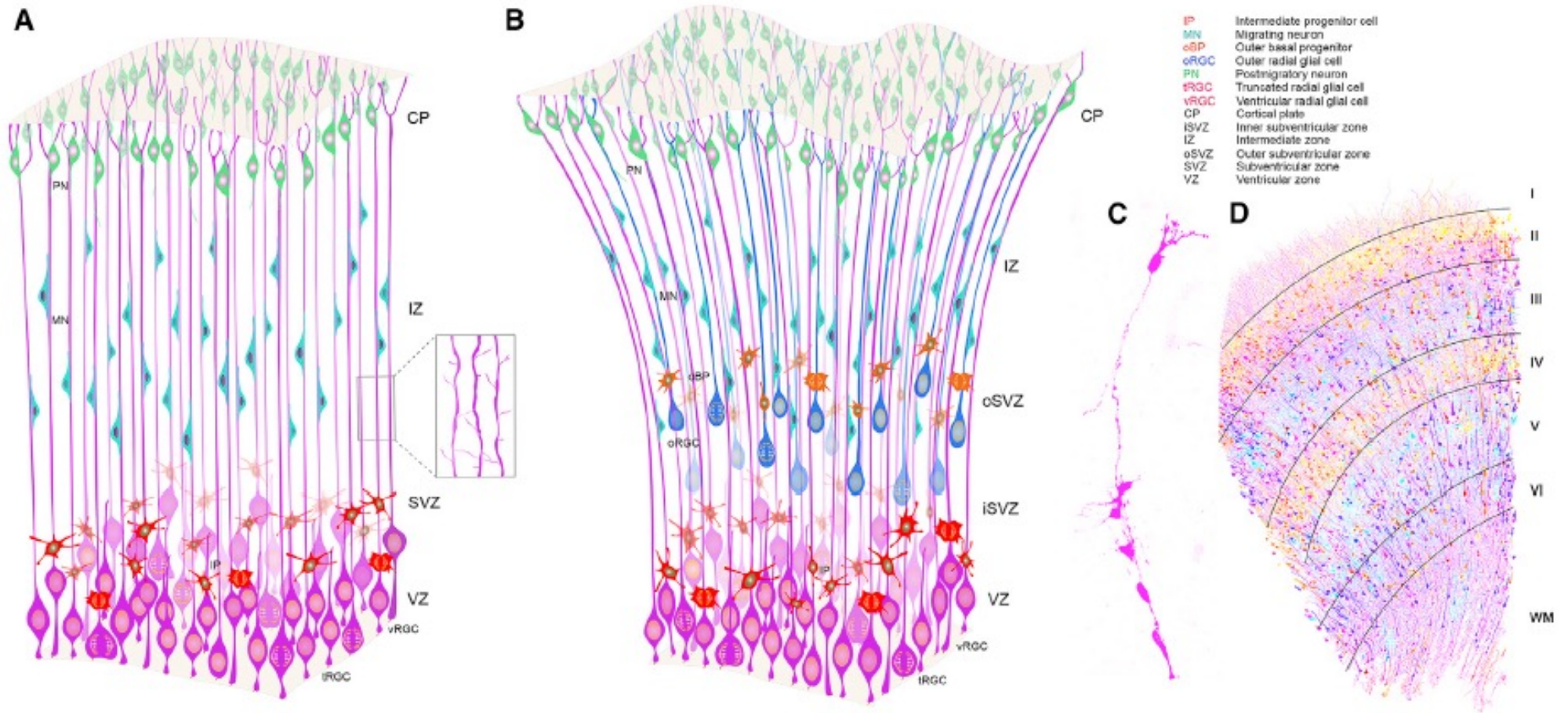
b Macaque



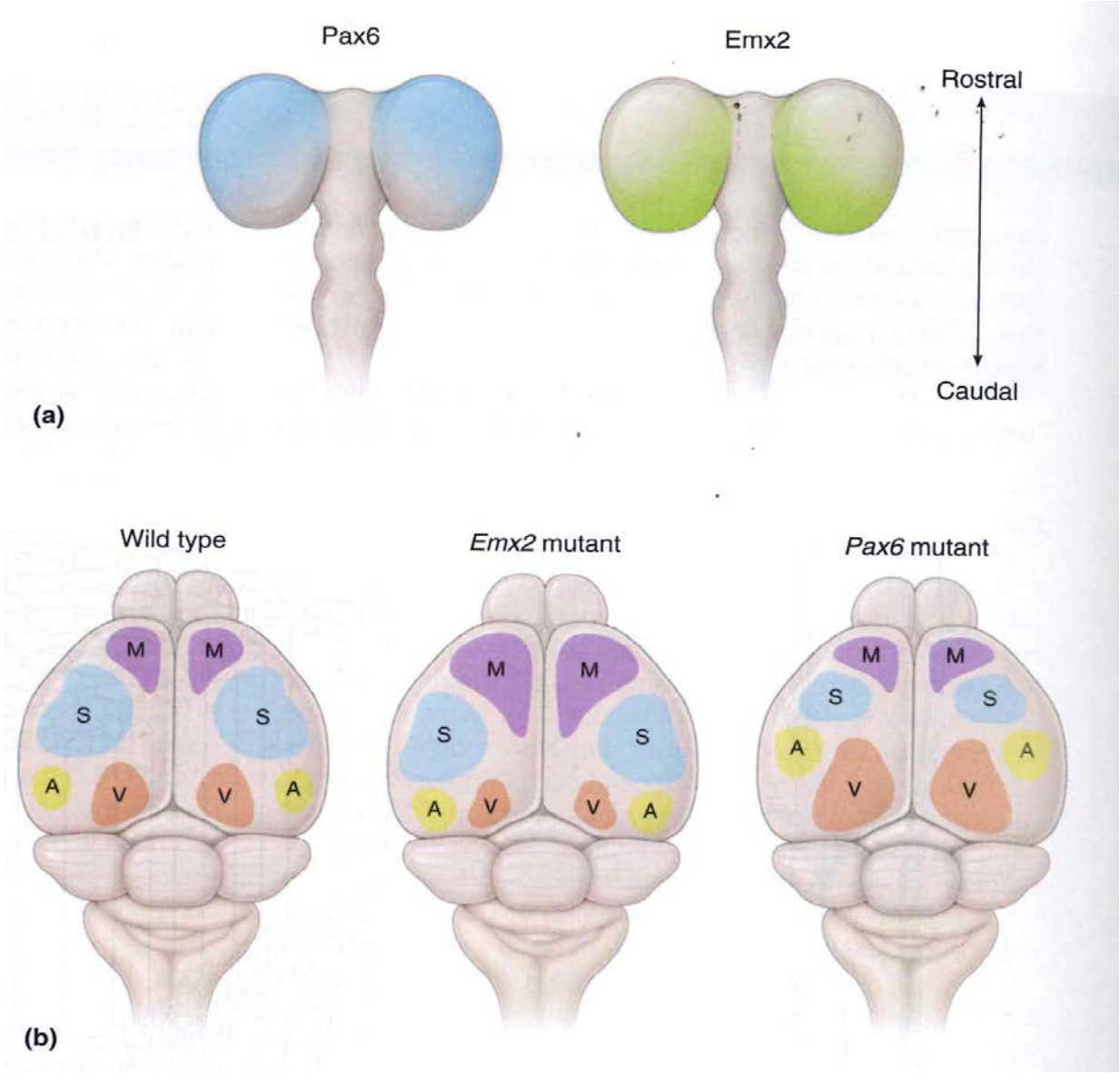
c Human



# An Orchestrated Assembly of the Brain

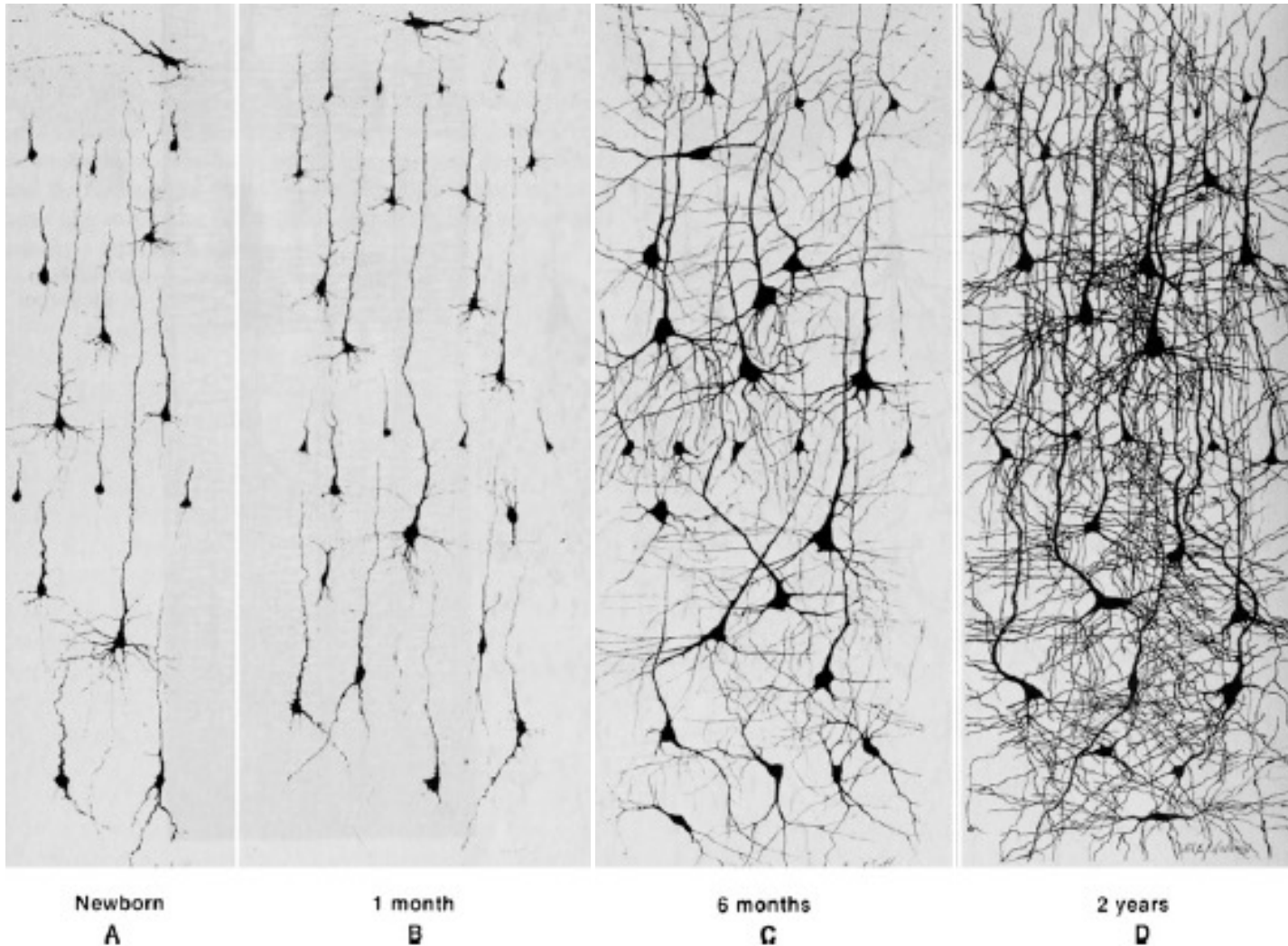


# Patterning 'Centers' Create Basic Organization of the CNS/Neocortex



## Dramatic Growth of Neuronal Architecture - Birth - 2 yrs

**(1-2 million synapses formed per second in the early years)**



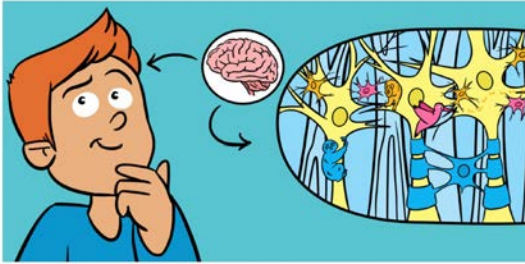


# Experience Shapes Brain Architecture by Over-Production Followed by Pruning Through Childhood



**birth**

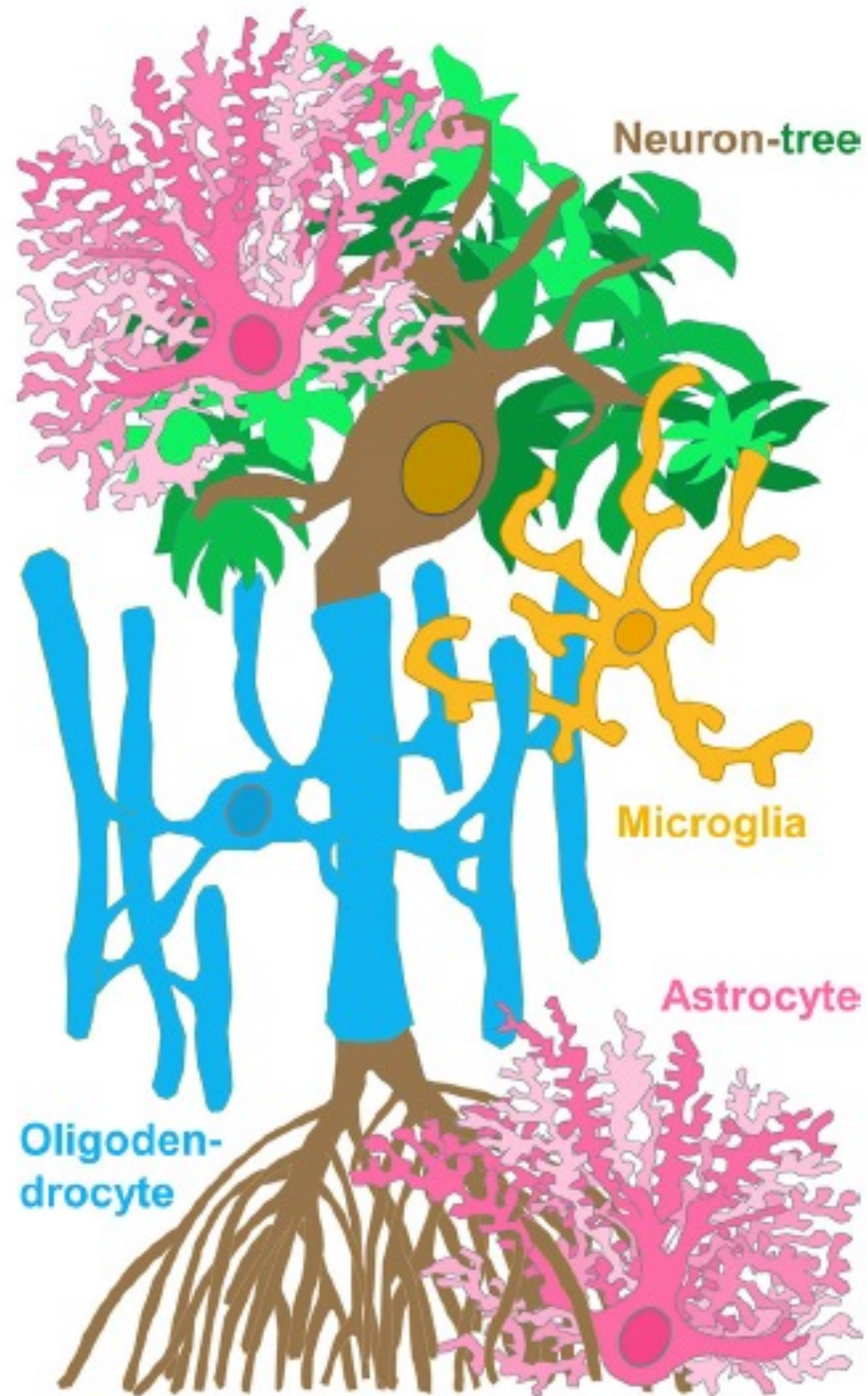




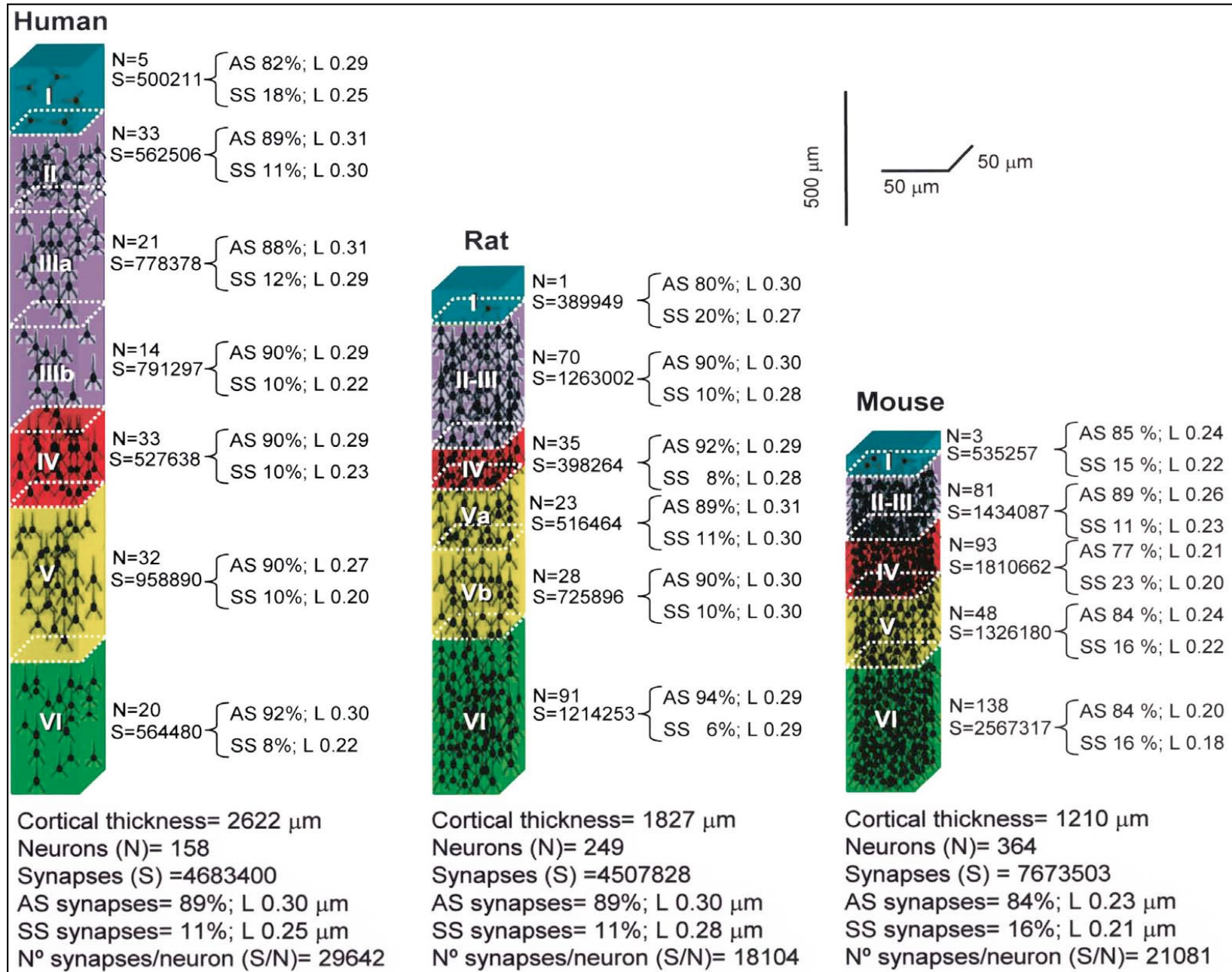
## THE "CREATURES" IN YOUR HEAD

Lasse Dissing-Olesen\*

Boston Children's Hospital, Harvard Medical School, Boston, MA, United States

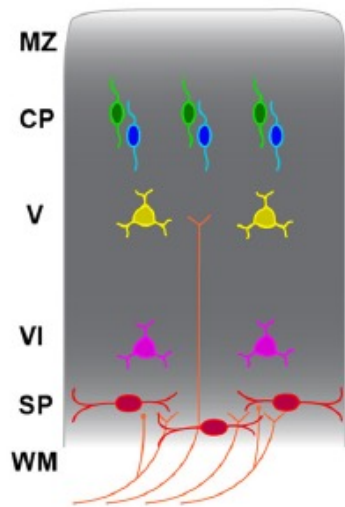


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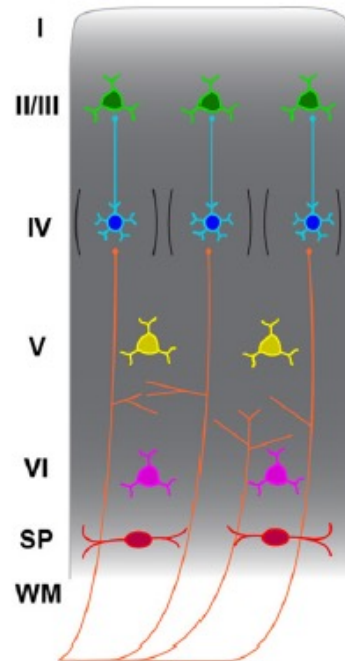


# Orderly Progression of Development is Conserved

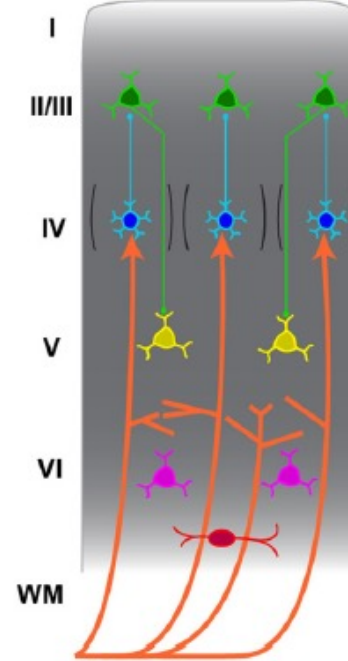
**Mouse  
(Human)** **P0  
(12-14GW)**



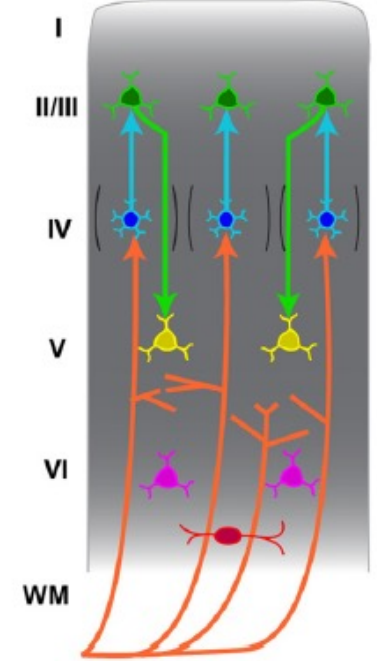
**P4  
(24-32GW)**



**P8  
(24-32GW)**

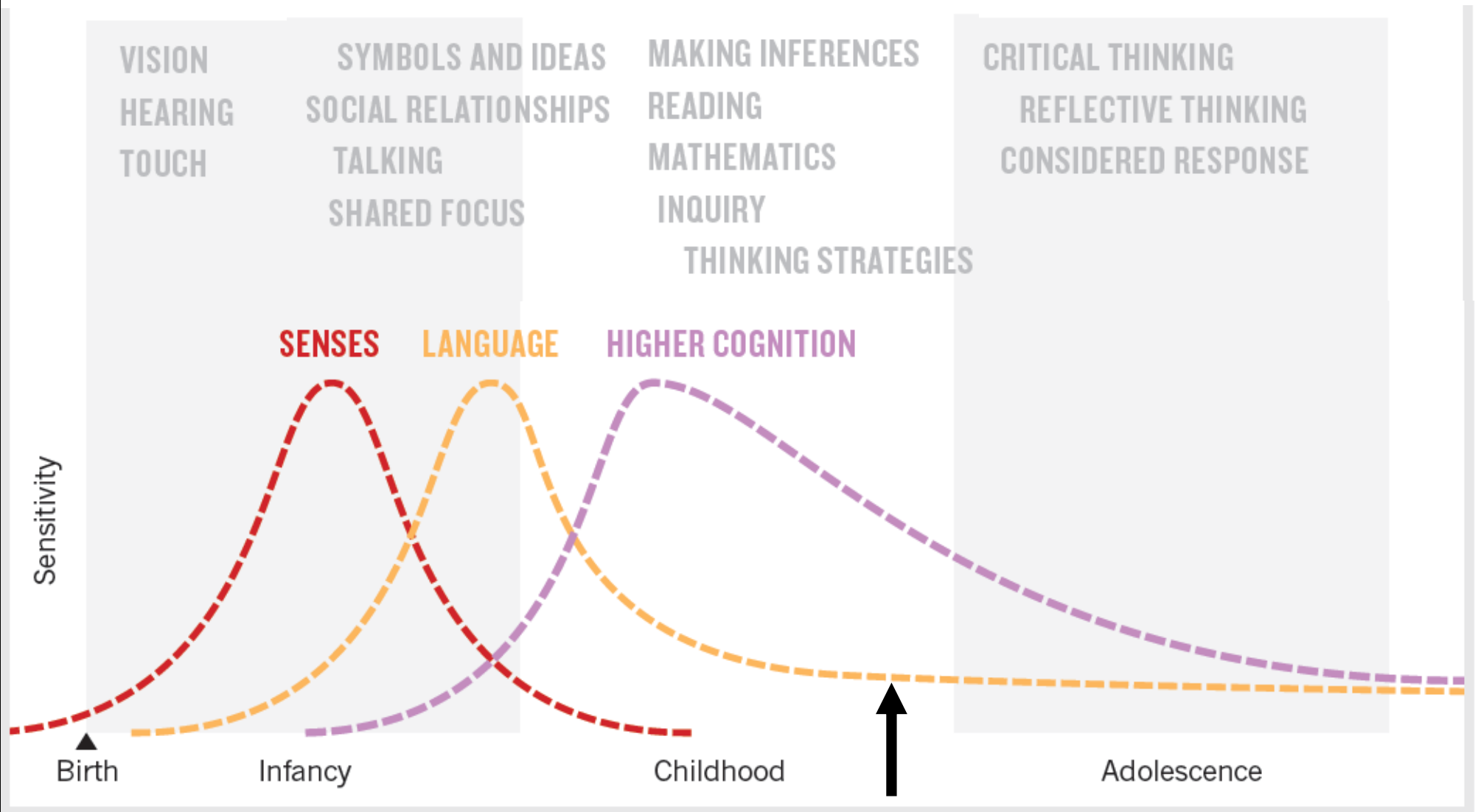


**P12  
(>32GW)**



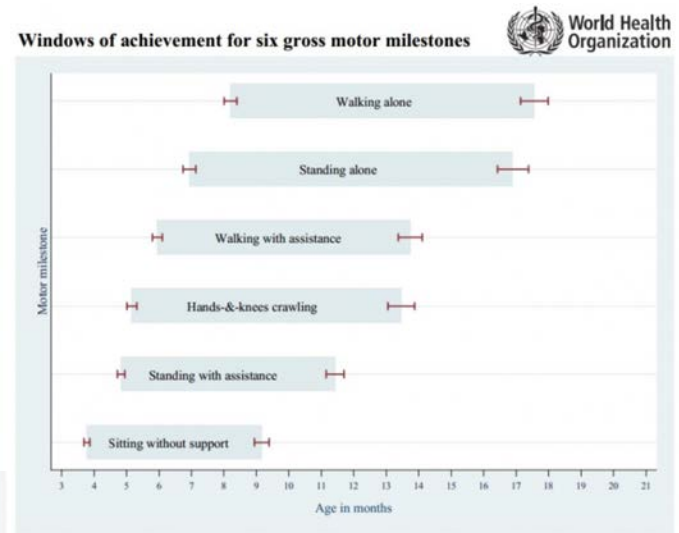
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## Open and Shut - Critical Periods of Brain and Child Development



*When do most U.S. school systems start to teach foreign language?*

# Heterogeneity of Development

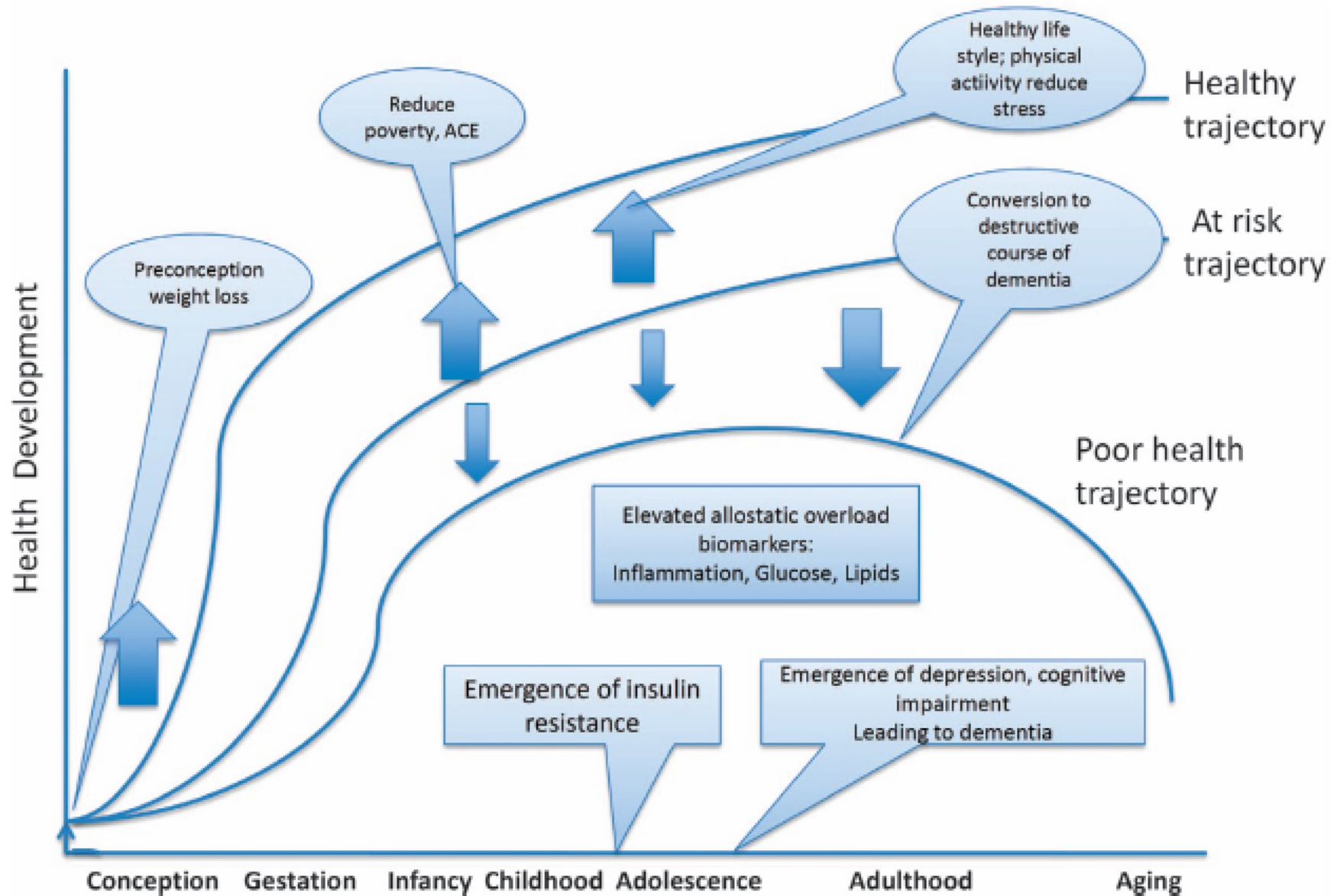


Reference: WHO Multicentre Growth Reference Study Group. WHO Motor Development Study: Windows of achievement for six gross motor development milestones. Acta Paediatrica Supplement 2006;450:86-95.

Experience as an Important Driver of Development



# Preconception and Prenatal Metabolic Status of Parents, Pre- and Early Postnatal Economic Resources, ELS Prevalence Contribute to Lifespan Health



# Preconception and Prenatal Origins of Health Disturbances – Generational Implications Due to Impact on Germ Cells

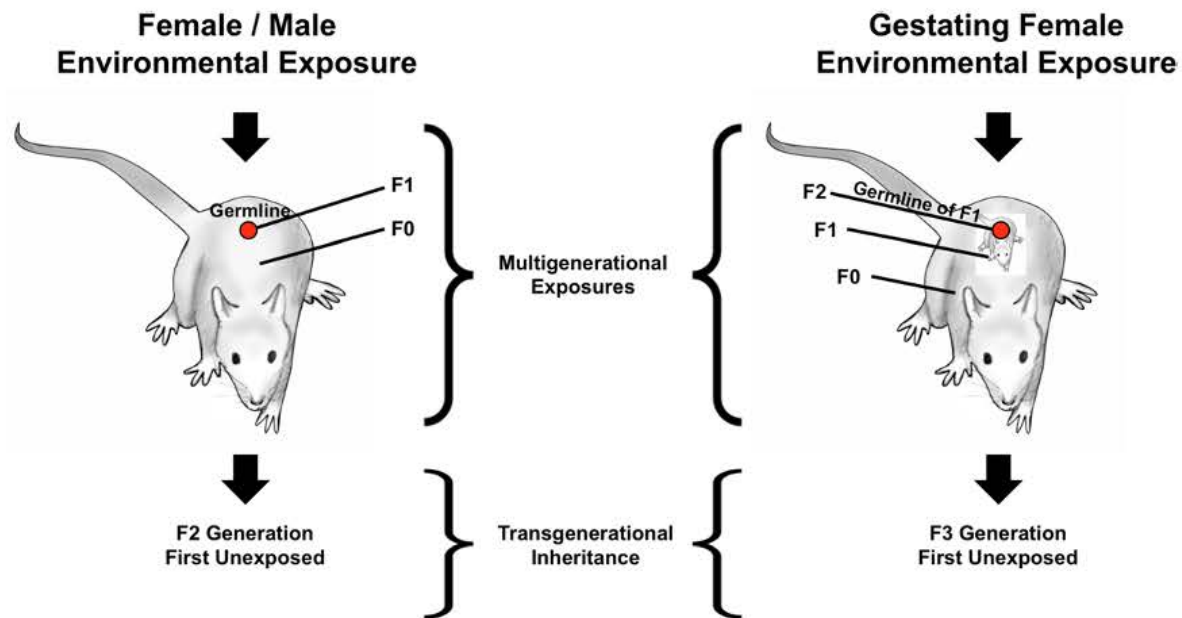
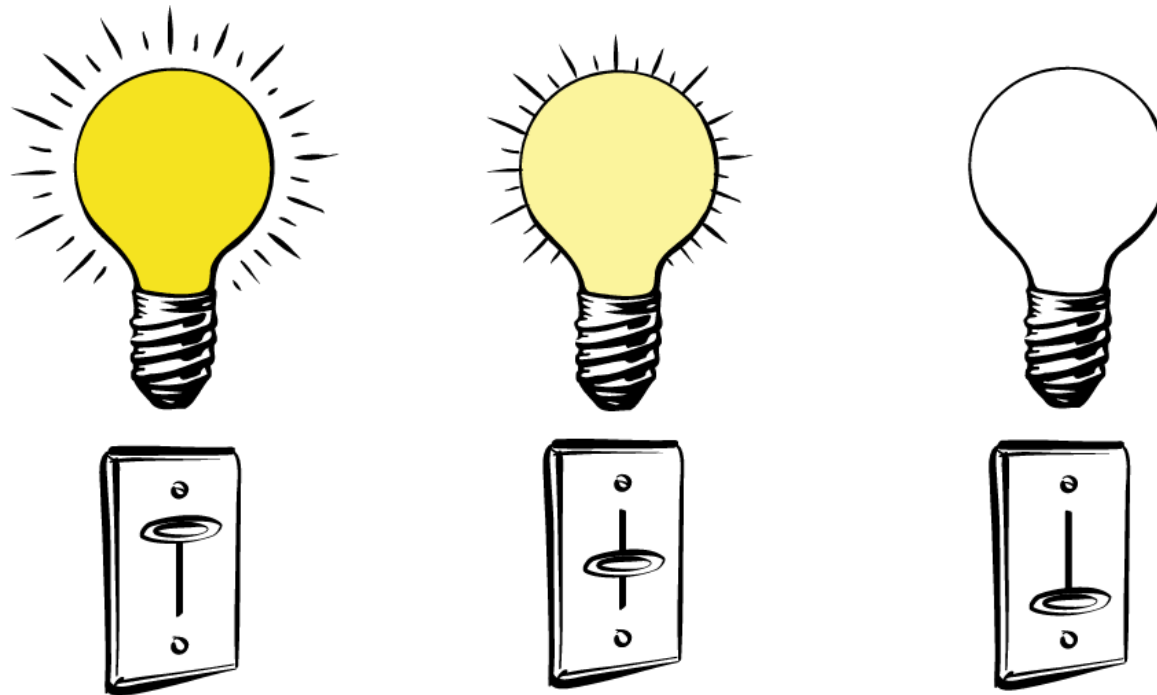


Figure 1 Schematic of multigenerational exposure and transgenerational inheritance.

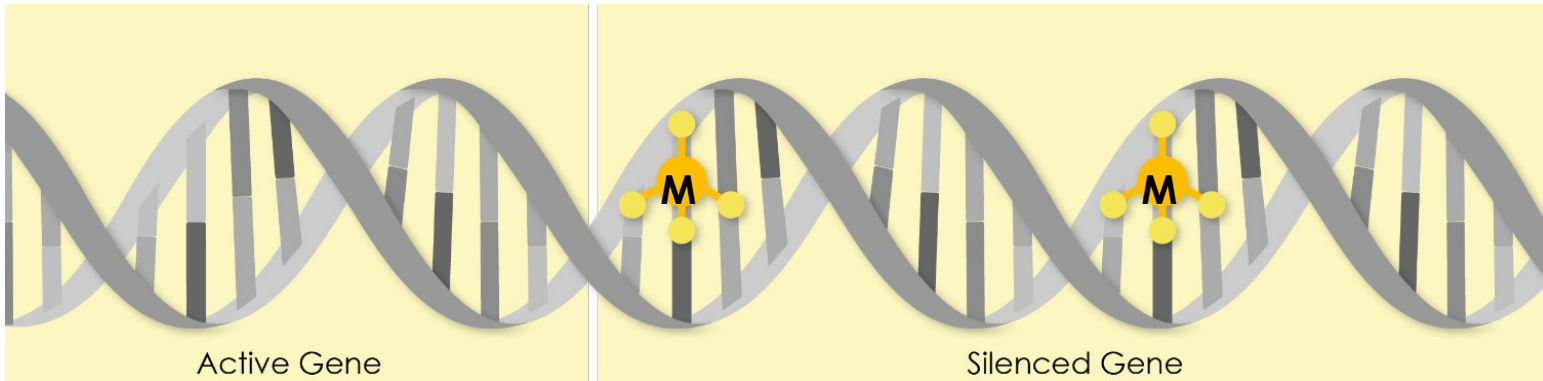
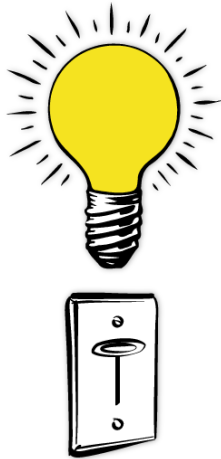
Powerful Recent Examples of Preconception Epigenetic Markings

Why does early development  
have long-lasting effects?

# The Epigenome - Regulating Gene Activity



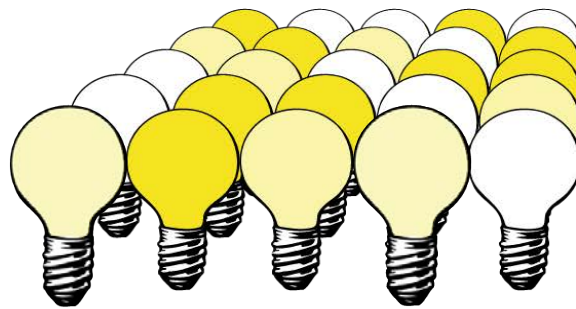
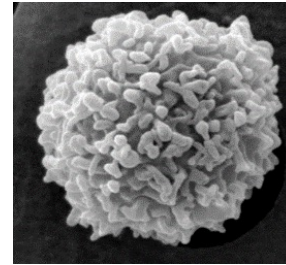
# DNA Methylation



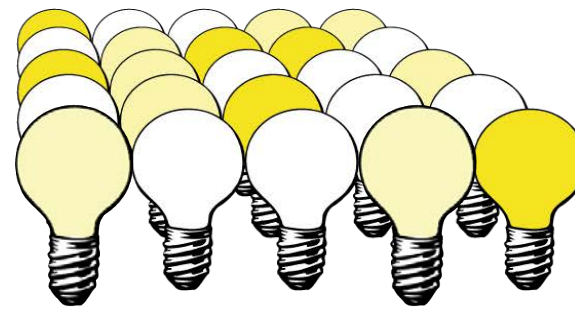
Brain Cell



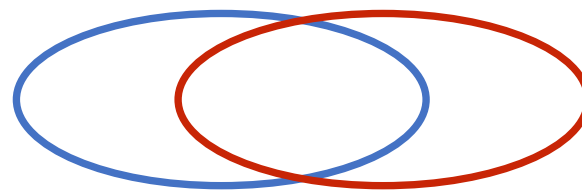
Blood



Brain Cell

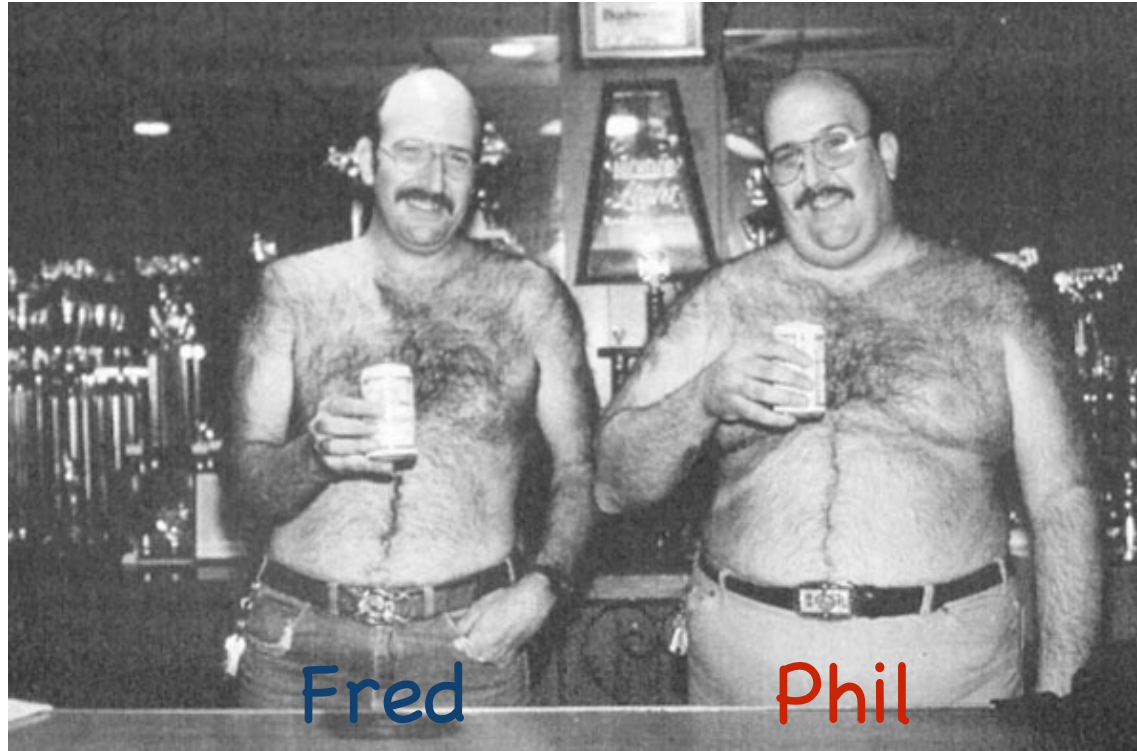


Blood Cell



Expressed Genes

# Multiple phenotypes from a common genotype



Fred

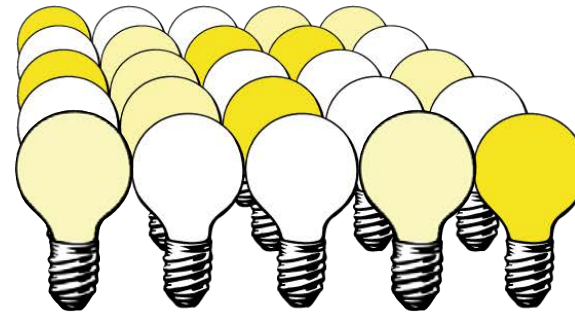
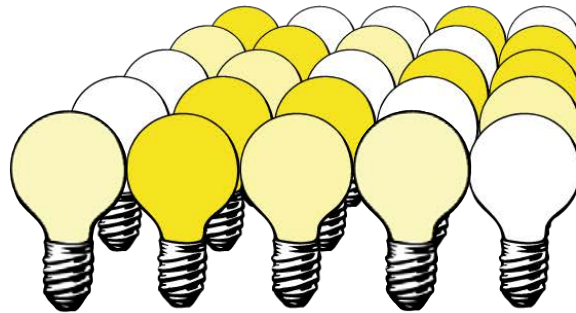
Phil

**Every cell in your body has the same nuclear genes, but...?**

Fred

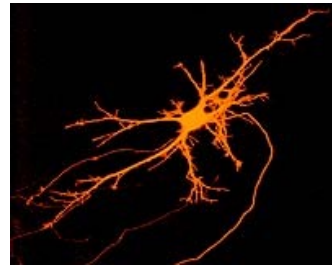


Phil

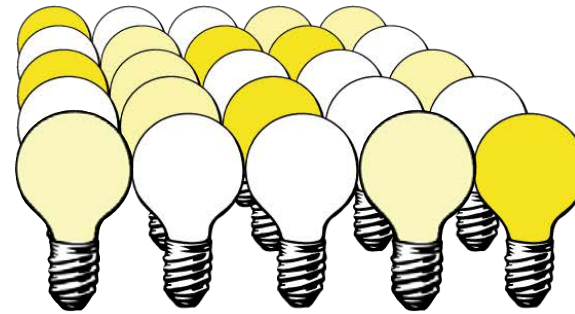
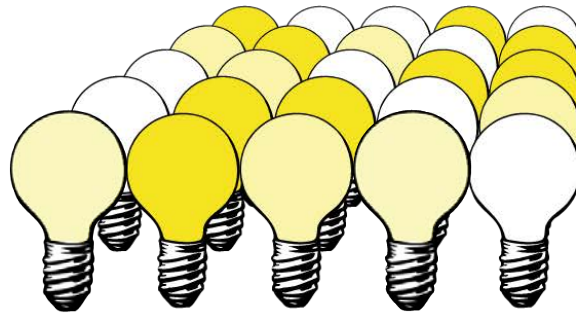




Adversity



Typical



Genes involved in activation of stress responses

## **Factors that alter DNA methylation signals in children**

- Resource access (e.g. maternal prenatal/child postnatal nutrition) - What else????
- Maternal emotional status (depression/anxiety)
- Paternal stress (experimental)
- Preconception paternal and maternal environmental exposures
- Metabolism, oxidative stress
- # of early life stress events (postnatal ACES)

# Many Risk Factors – Birth/Major Pregnancy Complications is the 'Big' One

## Box 1

### Clues from epidemiology that implicate the neurodevelopmental hypothesis

*Excess risk of schizophrenia associated with exposures and proxy markers that could impact on early brain development*

- Winter-spring birth (2)
- Born or raised in urban areas (2)
- Prenatal infection (2)
- Prenatal famine (2)
- Prenatal micronutrient deficiency (eg, vitamin D, iron, folate) (2-3)
- Pregnancy and birth complications (9)
- Early life motor and cognitive antecedents in cohort studies
- Increased prevalence of minor physical anomalies

Piper et al Psych Clin N. Amer. 2012

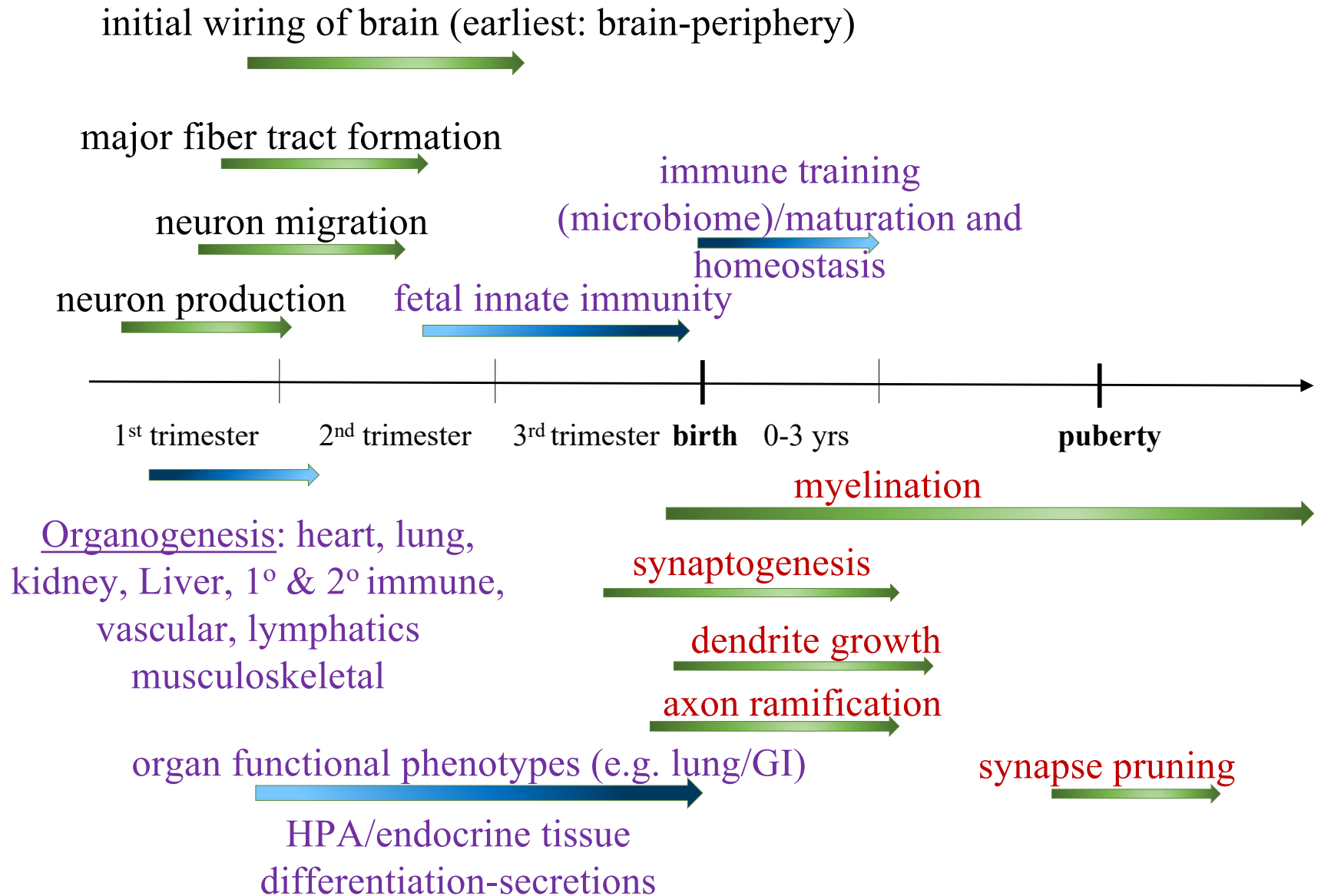
**Odds Ratios** Adapted from Jones and Cannon,  
Psychiatr Clin North Am, 1998

# Prematurity & Birth Complications – Broad Health and Policy Implications

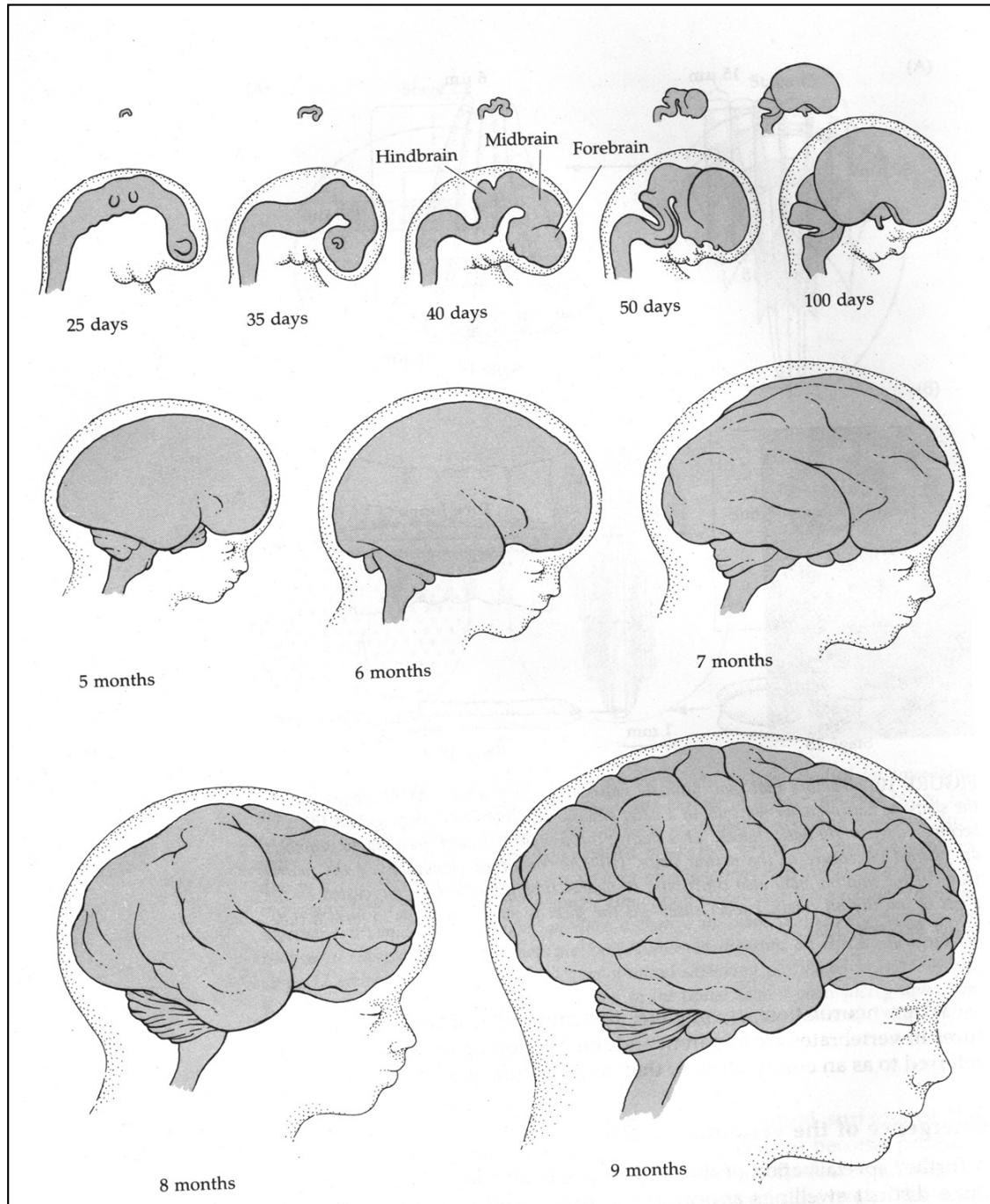
- **10% worldwide births (8.3% U.S.)**
  - Major disruptions – cerebral palsy, hydrocephalus, Intellectual Disability (ID), sensory and motor dysfunction
  - Other disruptions – IQ and cognitive performance, speech-language, balance/coordination, perception, ADHD, mood dysregulation, social communication
  - Health issues – pulmonary, infection/immune disturbances, GI, vascular/BBB integrity, obesity, metabolic syndromes

# Why Does Timing In Development Matter?

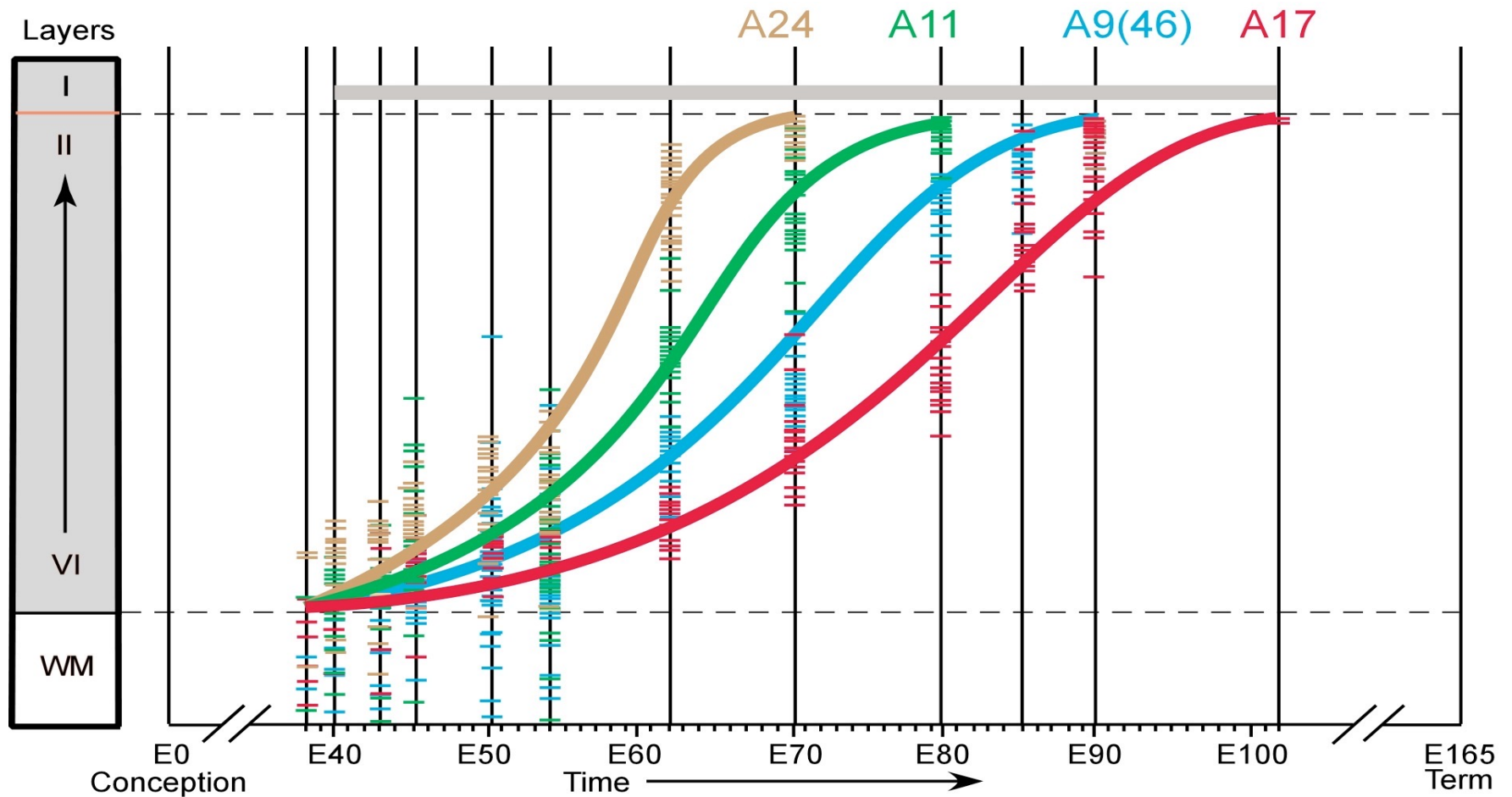
# Why Does Timing In Development Matter?



# Human Brain Development



# Timing of Insult Will Have Differential Effects





# Postnatal Refinement of Sensory Thalamus and Modulatory Circuits

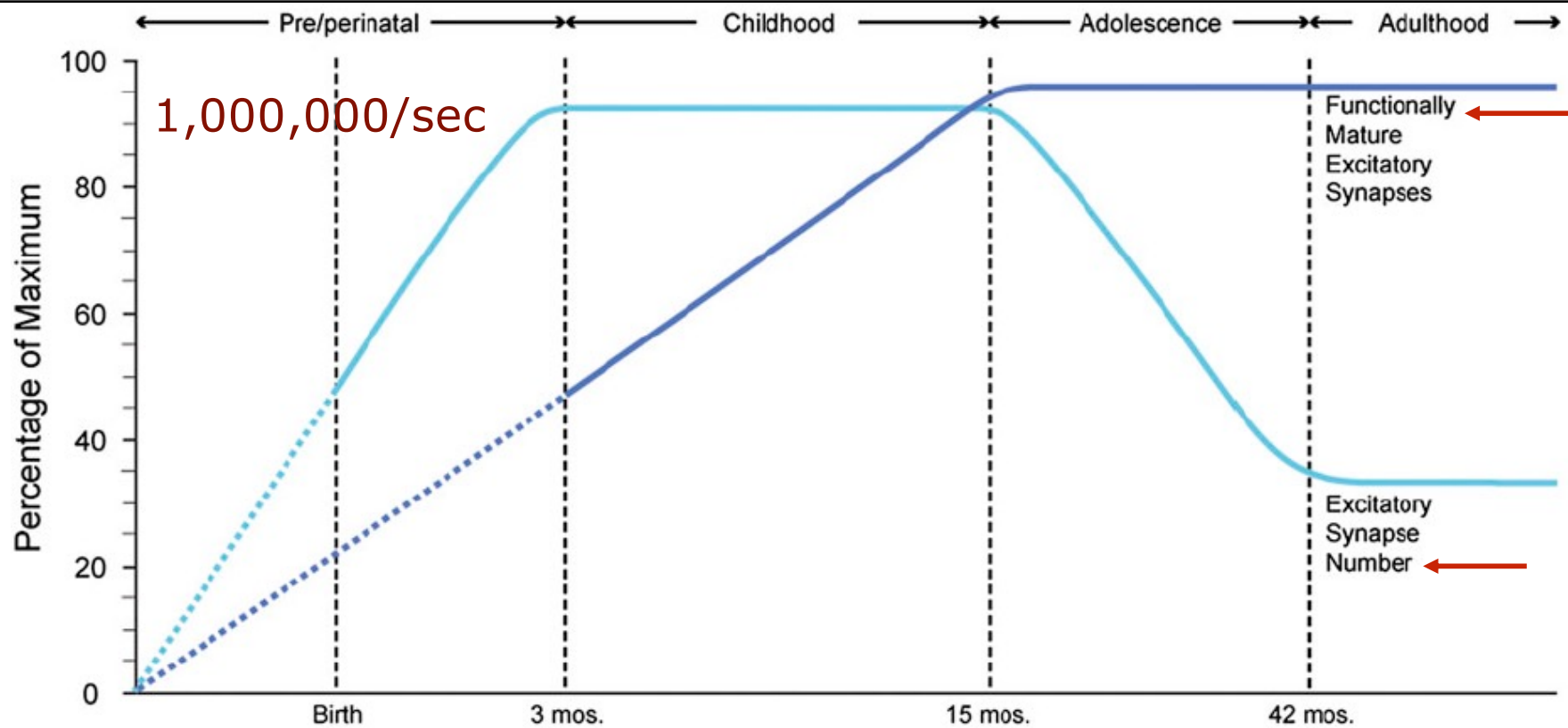


**28W**

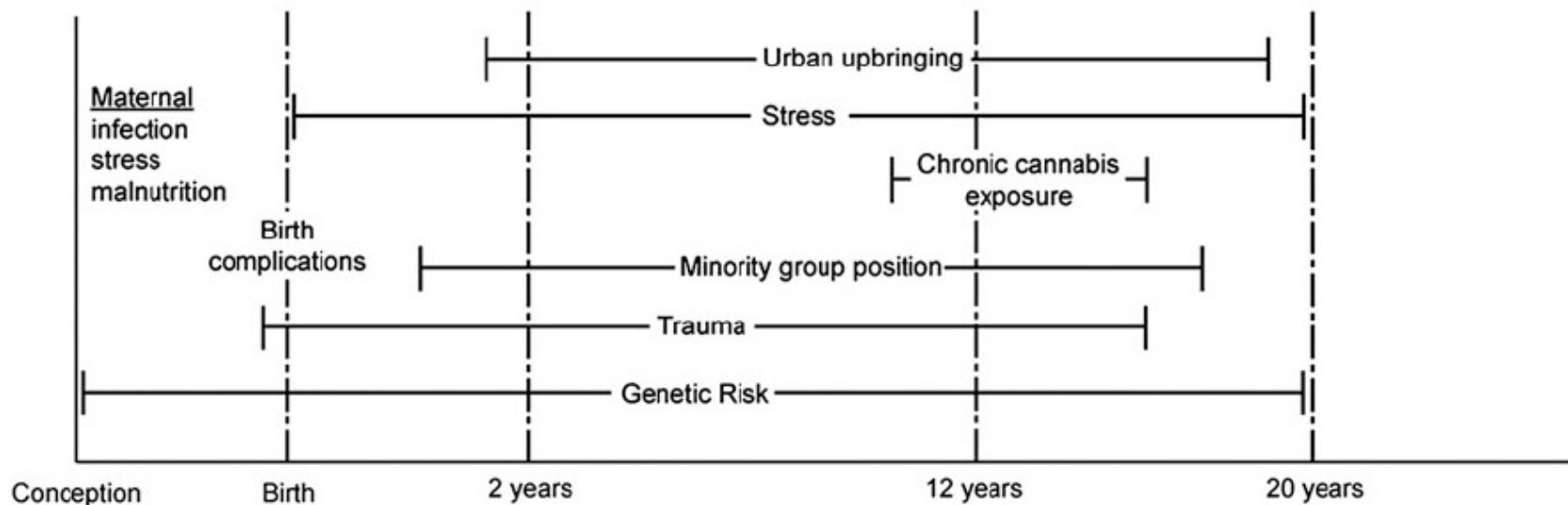
**NEWBORN**

**3 YRS**

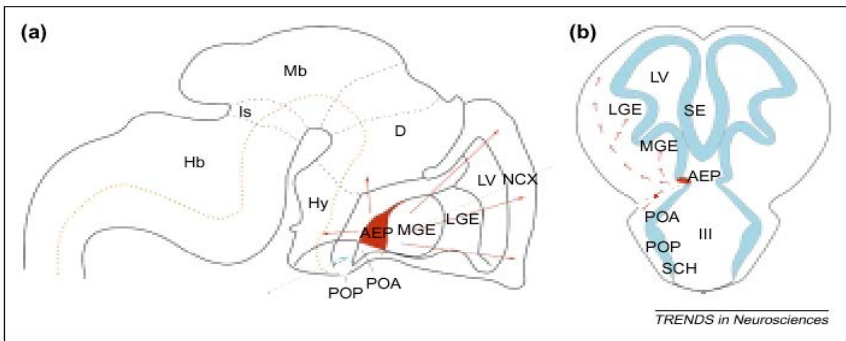
the exertion of a modifying or controlling influence on something



Timing of Risk Factors for Schizophrenia

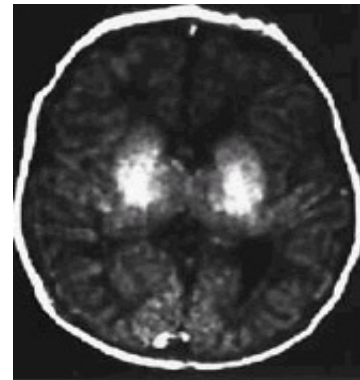


# Myelination: Cellular Origins and Temporal Development

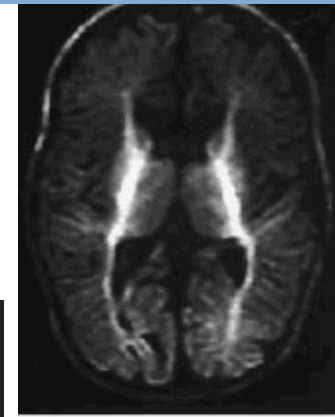
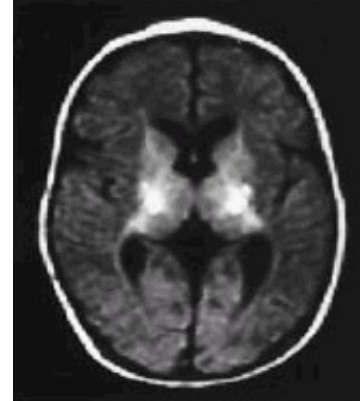


Qi et al, TINS 25:223, 2002

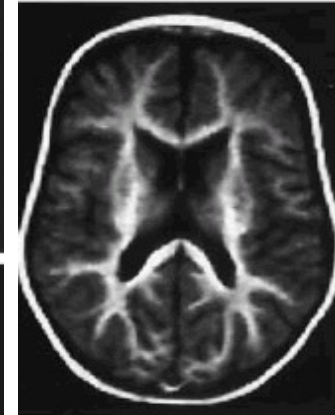
1M



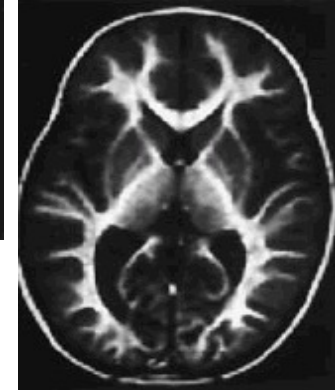
2M



3-6M



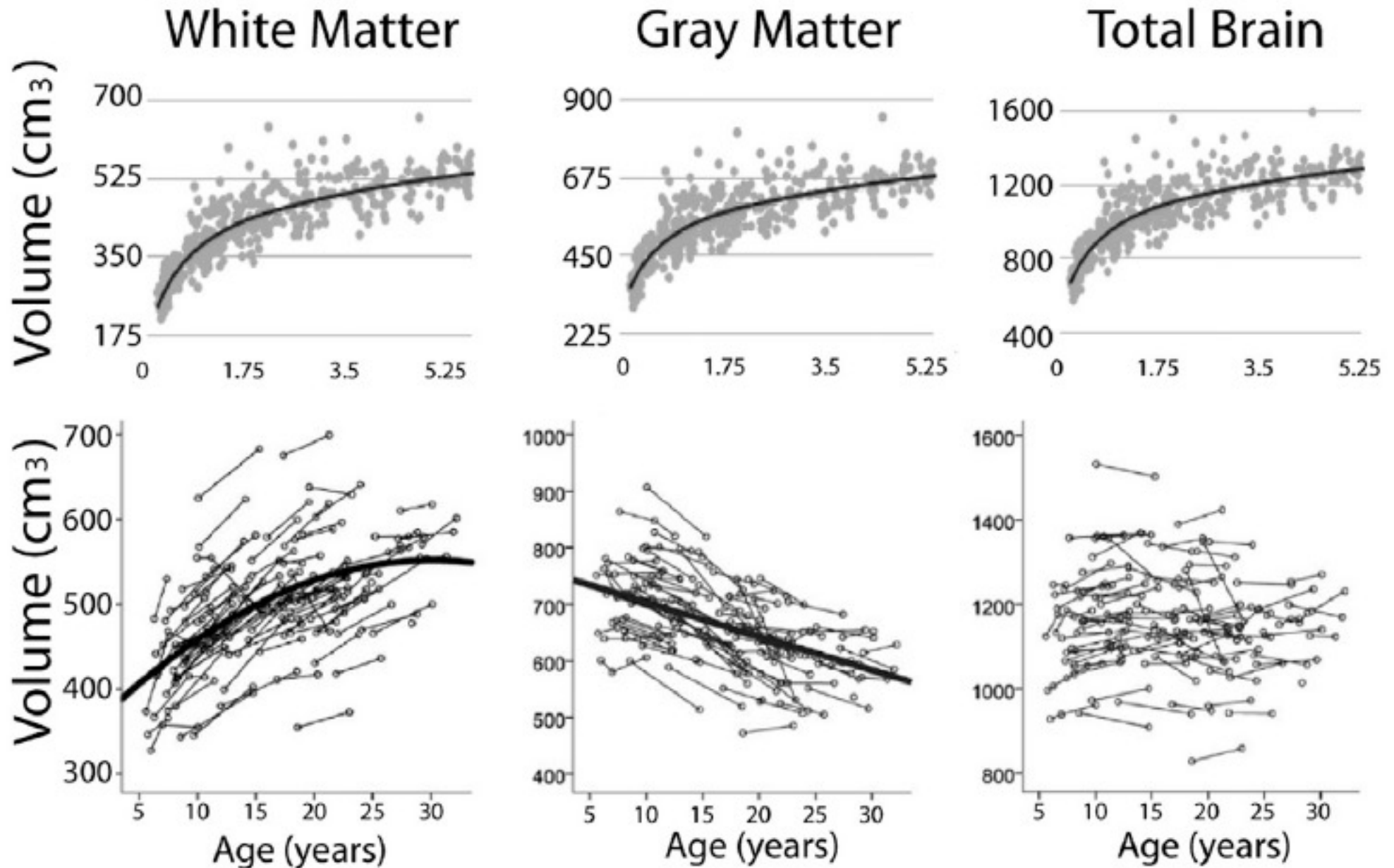
7-9M



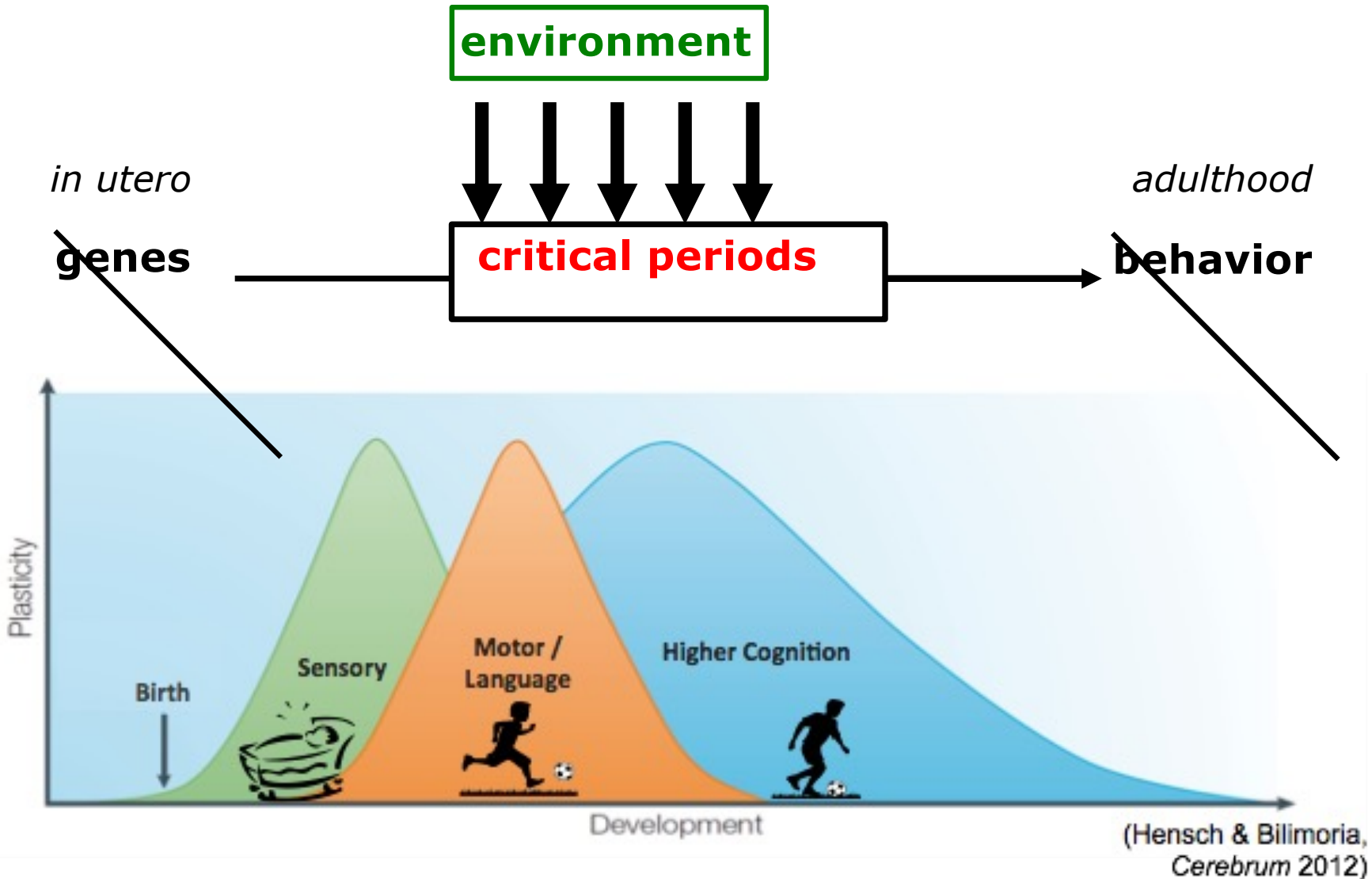
>9M

Through  
5<sup>th</sup> decade

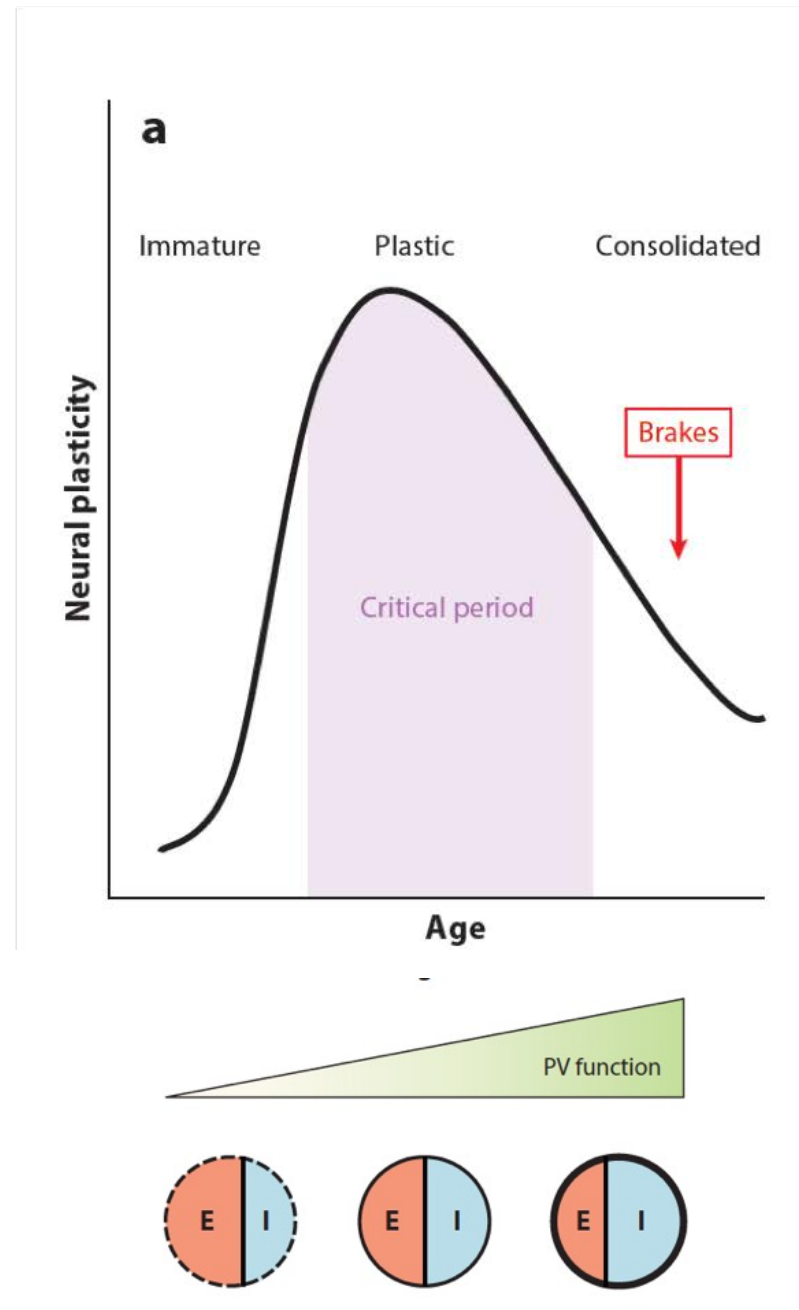
# Growth Trajectories of Different Elements - Heterogeneity



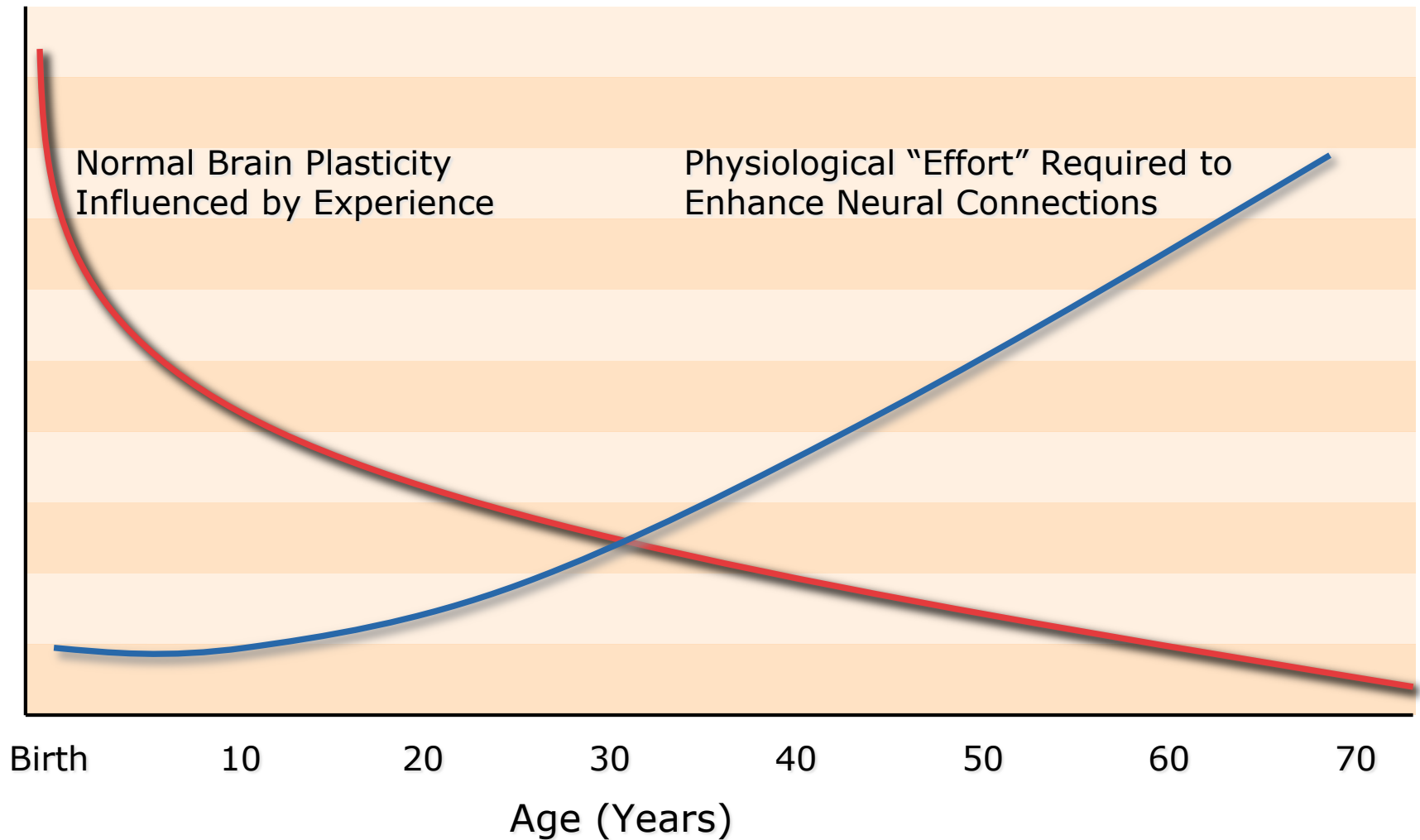
# Critical Periods Define Readiness for Experience to Impact Development of Function



# 'Critical Periods' Define Typical Optimal Timing of Change



# The Ability to Change Brains Decreases Over Time



**Powerful experiences,  
no matter what kind (+/-), matter**



# Extreme Early Experiences Can Dramatically Disrupt the Precision of Sensory Information Processing

16 days



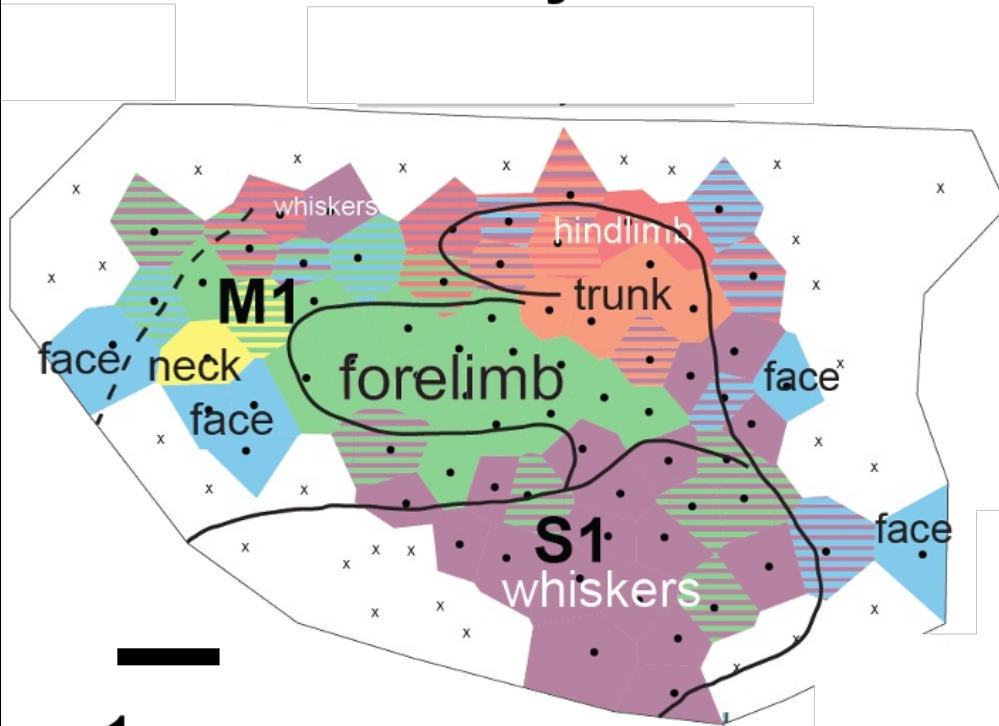
# Species-typical Behavior?



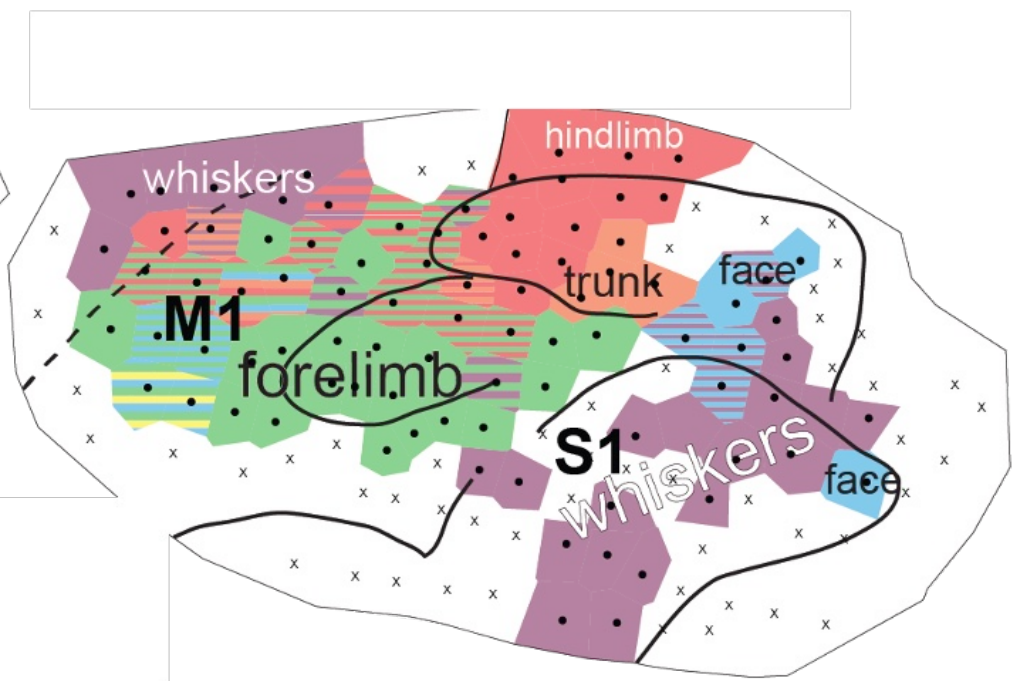
From Dylan Cooke, Danielle  
Stolzenberg, Leah Krubitzer,  
UC Davis

# Differences in maps of motor cortex

## Laboratory reared



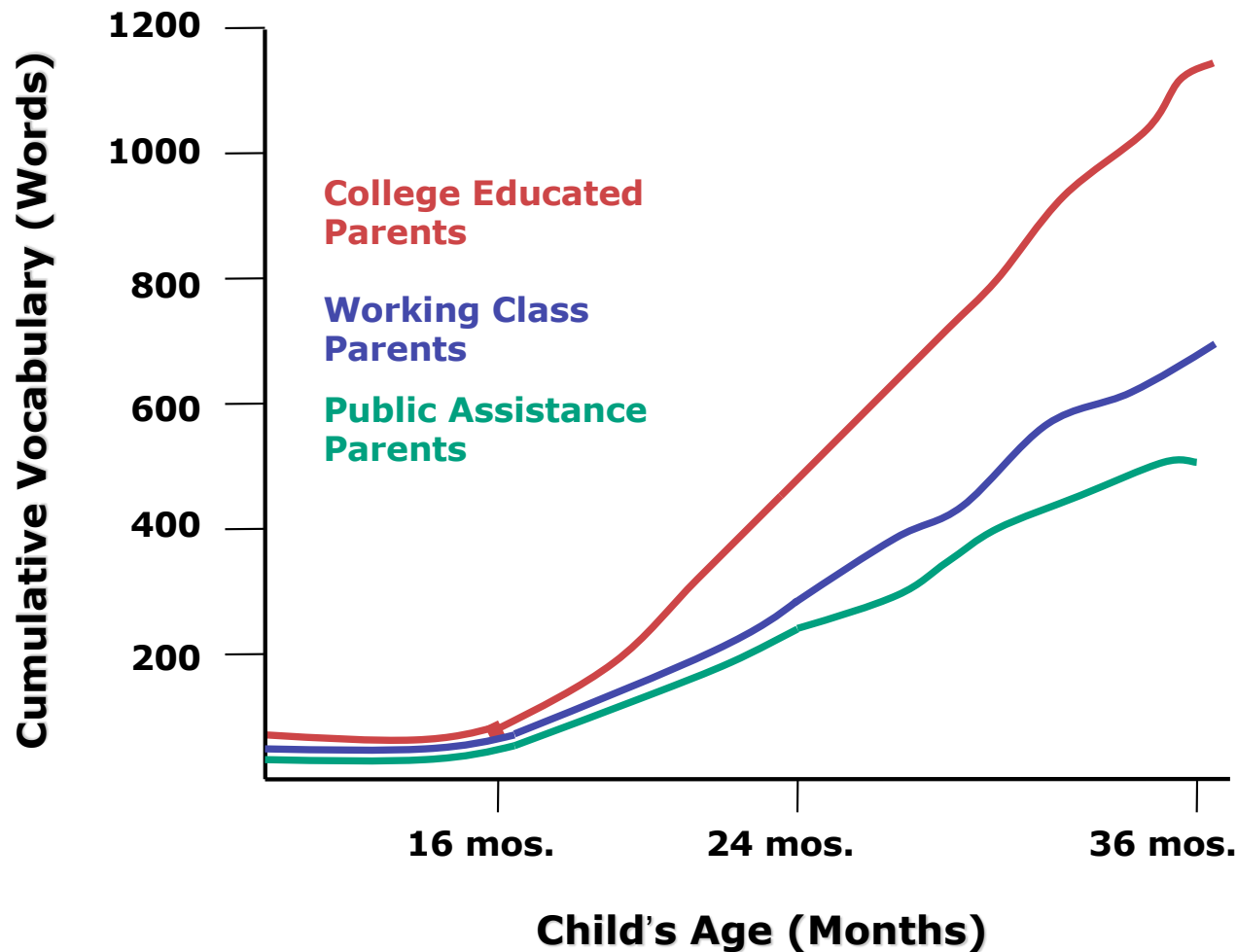
## Field pen reared



1mm



# Exposure to Complex Language Repertoire Begets Complex Language Repertoire



Source: Hart & Risley (1995)  
Fernald et al 2012

# Brains and Skills are Shaped by the "Serve and Return" Nature of Human Interaction



# 24-month-old children with larger vocabularies display greater academic and behavioral functioning at kindergarten entry

---

Paul L. Morgan<sup>a,d</sup> Carol Scheffner Hammer<sup>b</sup>

George Farkas<sup>c</sup> Marianne M. Hillemeier<sup>a,d</sup> Steve Maczuga<sup>a,d</sup>

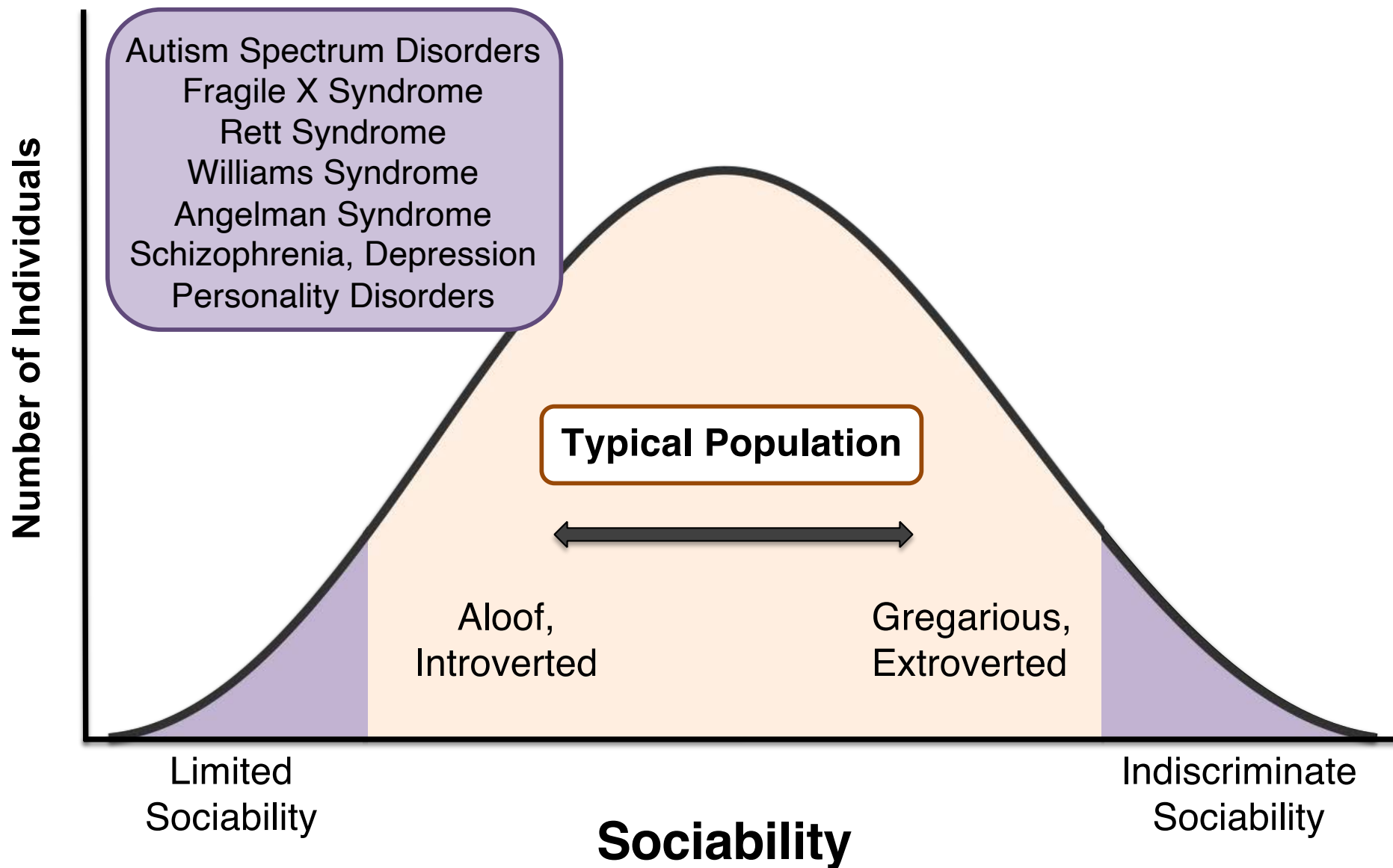
*<sup>a</sup>Penn State, <sup>b</sup>Temple, <sup>c</sup>University of California-Irvine, <sup>d</sup>Population Research Institute*

# Interaction as Serve and Return

Interaction as Serve and Return

<https://developingchild.harvard.edu/resources/serve-return-interaction-shapes-brain-circuitry/>

# Heterogeneity in Human Social Behavior





# **Social Behavior Dysfunction is Common**

- **Psychosis**

- **Psychopathy**

- **Depression**

- **PTSD**

- **Anxiety**

- **SAD**

- **Addiction**

- **OCD**

**Most Neurodevelopmental Disorders**

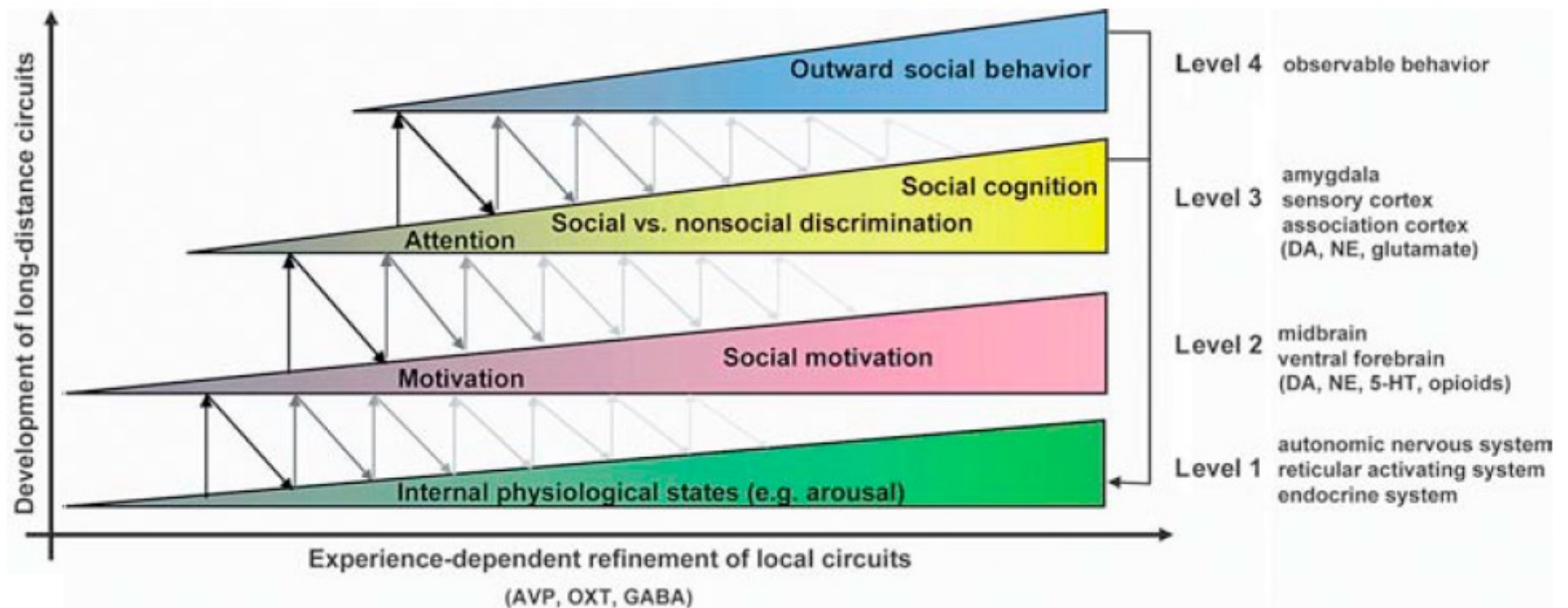
**ACE-generated psychopathologies (Reactive Attachment Disorder)**



**Based on the concept that simple skills beget more complex skills, and developmentally, simple circuits are built as foundations for more complex circuits.....**

# Hierarchical Development of Social Behavior - Basic Skills Beget More Complex Skills

(Hammock and Levitt, Human Development 49, 2006)



# Hierarchical Development of Social Behavior - Basic Skills Beget More Complex Skills

(Hammock and Levitt, Human Development 49, 2006)

## Multisensory Contingent Processing

- Olfaction (1° rodents)
- Vision (1° humans)
- Thermotactile (LiGr)
- Milk Transfer
- Auditory (USV)

↑ Approach ↓ Avoidance

## Cognitive Processing

- Attention
- Learning & Memory
- Social Recognition
- Motivation
- Emotional Processing

Recognize &  
Remember Partner

## Complex Motor Responses

- Proximity Seeking
- Nurturing Responses
- Defensive Responses
- Sexual Behavior
- Vocalization & USV

Engage Partner

# Is there a basic process that underlies social competence?



**Born with physiological & relational needs**



## Multisensory experience

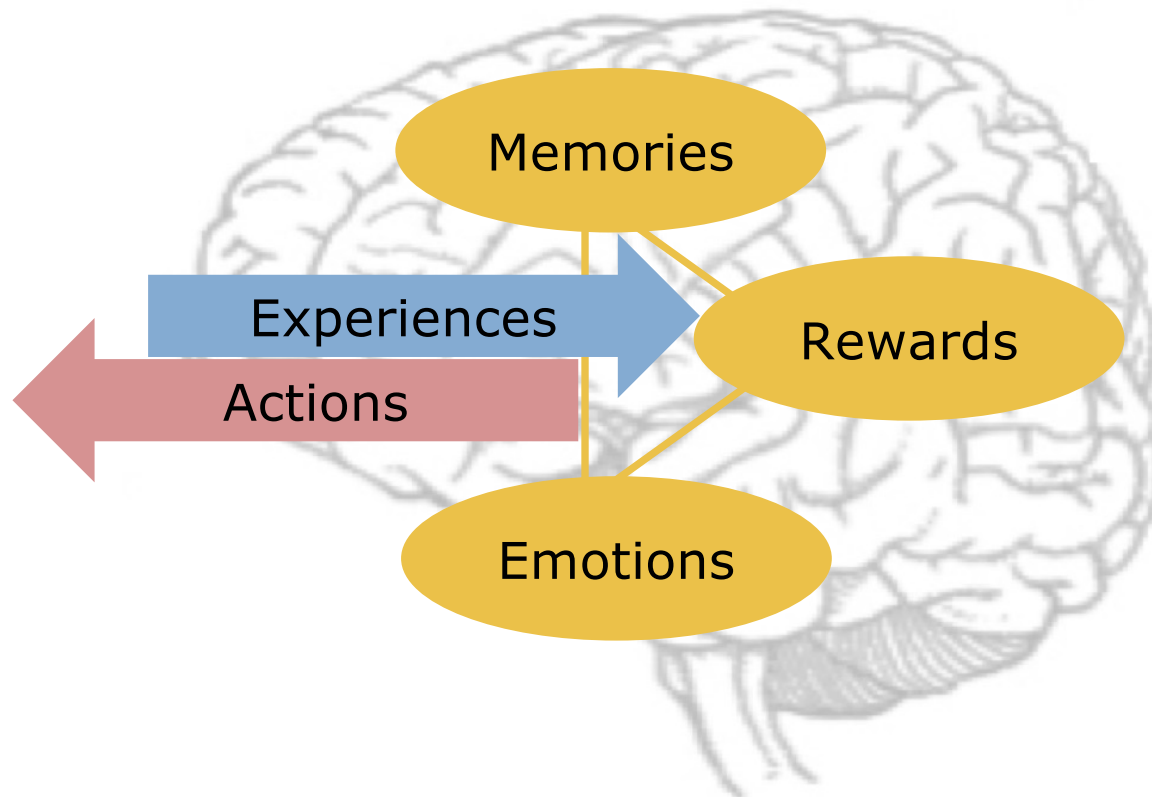
- Milk consumption (satiety)
- Thermotactile (warmth, Li-Gr)
- Olfactory
- Visual
- Auditory



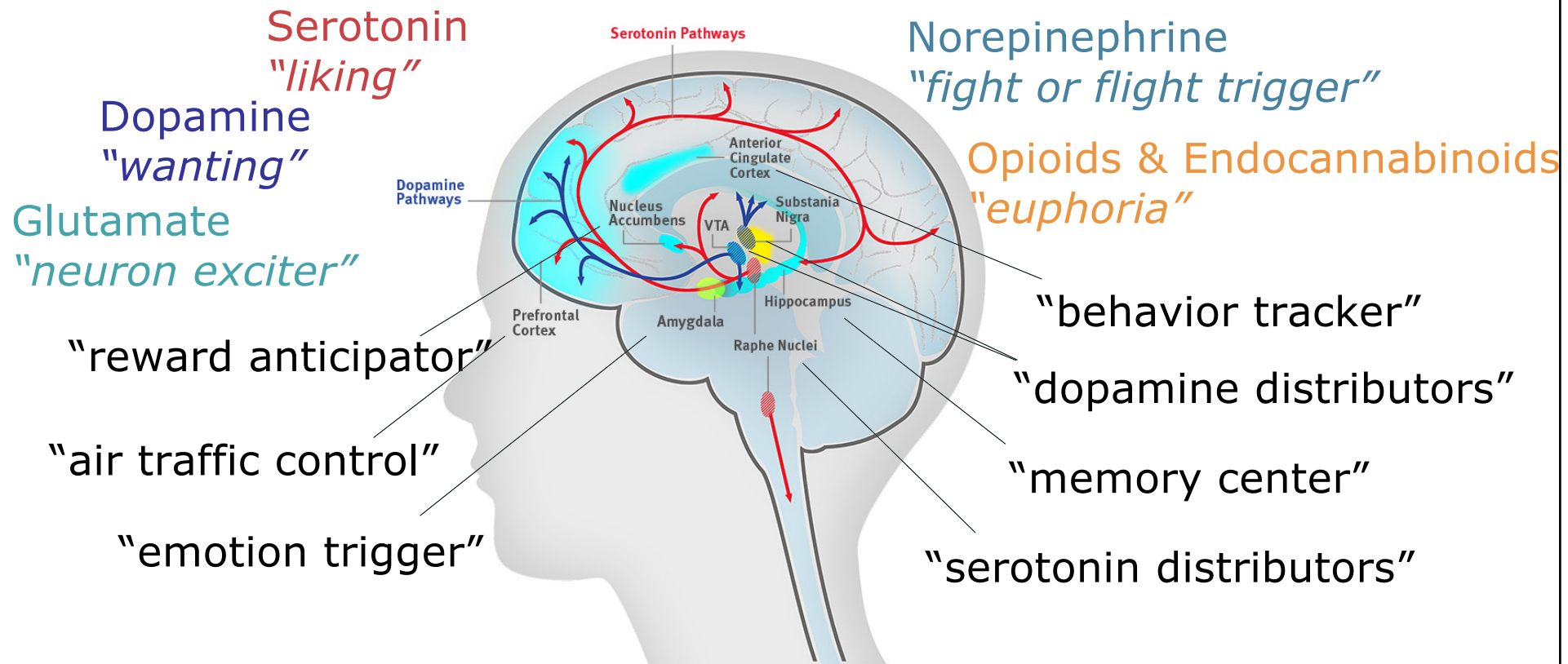
- 1) Needs are unmet
- 2) Non-social source of distress

- 1) Needs are met
- 2) Social source of satisfaction

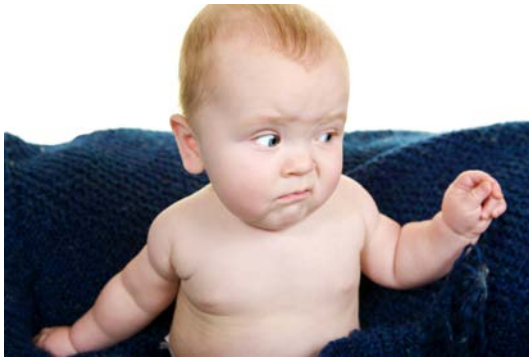
# Experiences Modify Pathways Between Brain Regions to Link Rewards, Memories, and Experiences



# There Are Different Kinds of Motivation, Each with its Own Neurobiological Network



# Motivation is Bidirectional: Away from Threat and Toward Reward



## Avoidance

- Associated with fear or disgust
- Hormones trigger fight or flight
- Learned through experience
- Focuses on immediate response at the expense of long-term goals

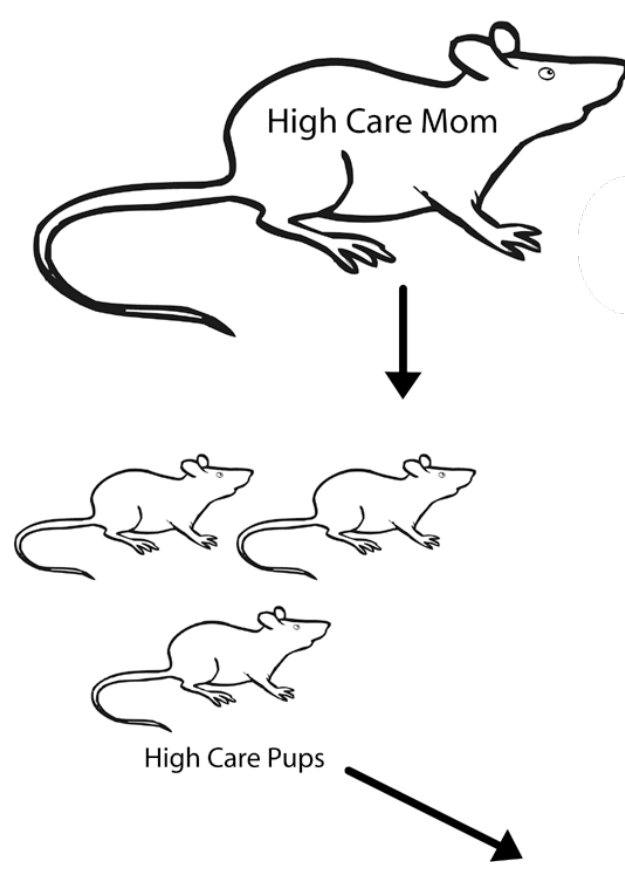


## Approach

- Key to most forms of learning
- Dopamine surge signals to expect new experiences of value
- Creates connections to emotions and memory of the reward

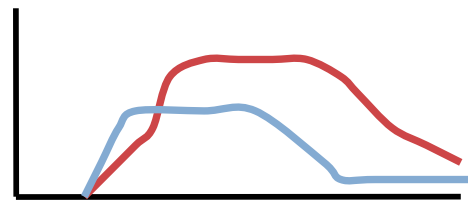


# Early Allostatic Load – Generation of Epigenetic Changes



Stress Response

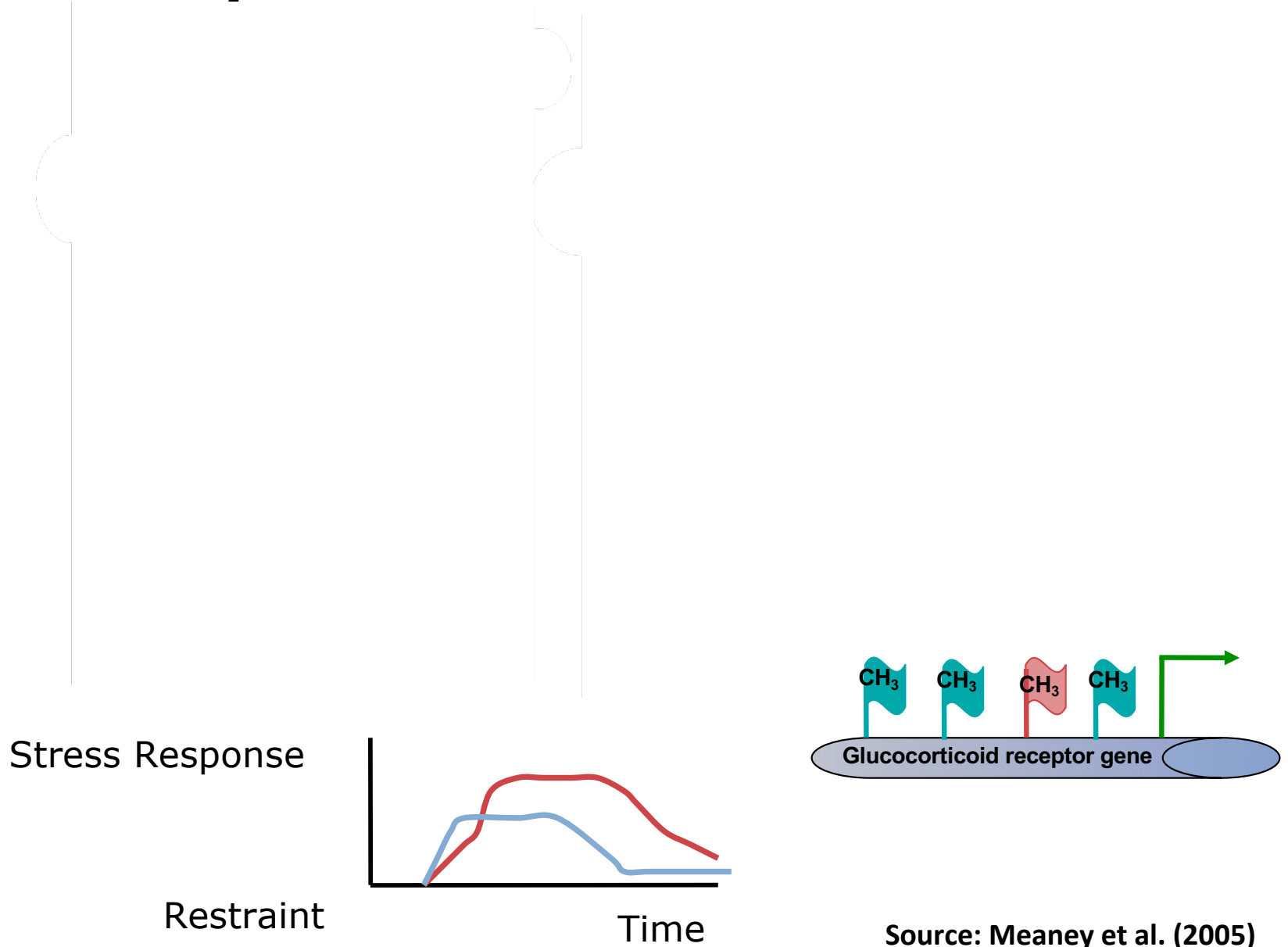
Restraint



Time

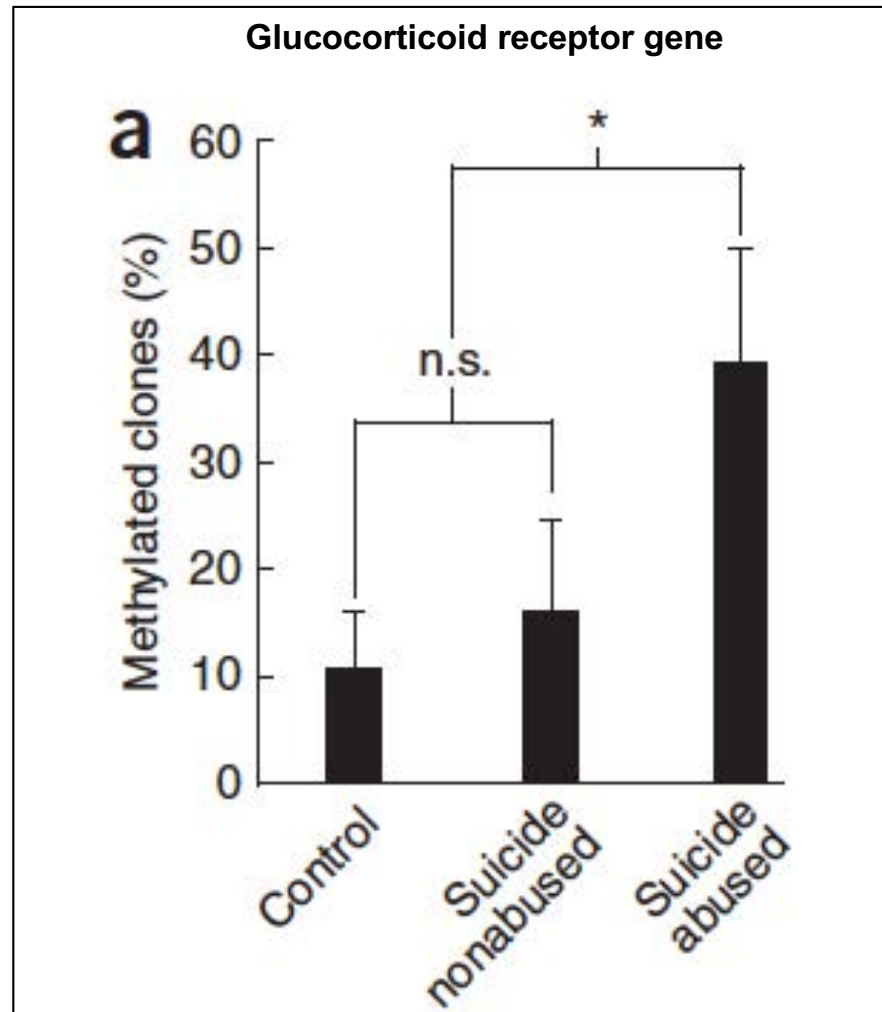
Source: Meaney et al. (2005)

# How Experience Influences Genes



Source: Meaney et al. (2005)

# Epigenetic '*Signatures*' Occur in Humans



**Powerful experiences,  
no matter what kind (+/-), matter**

## Three Levels of Stress

### Positive

Brief increases in heart rate,  
mild elevations in stress hormone levels.

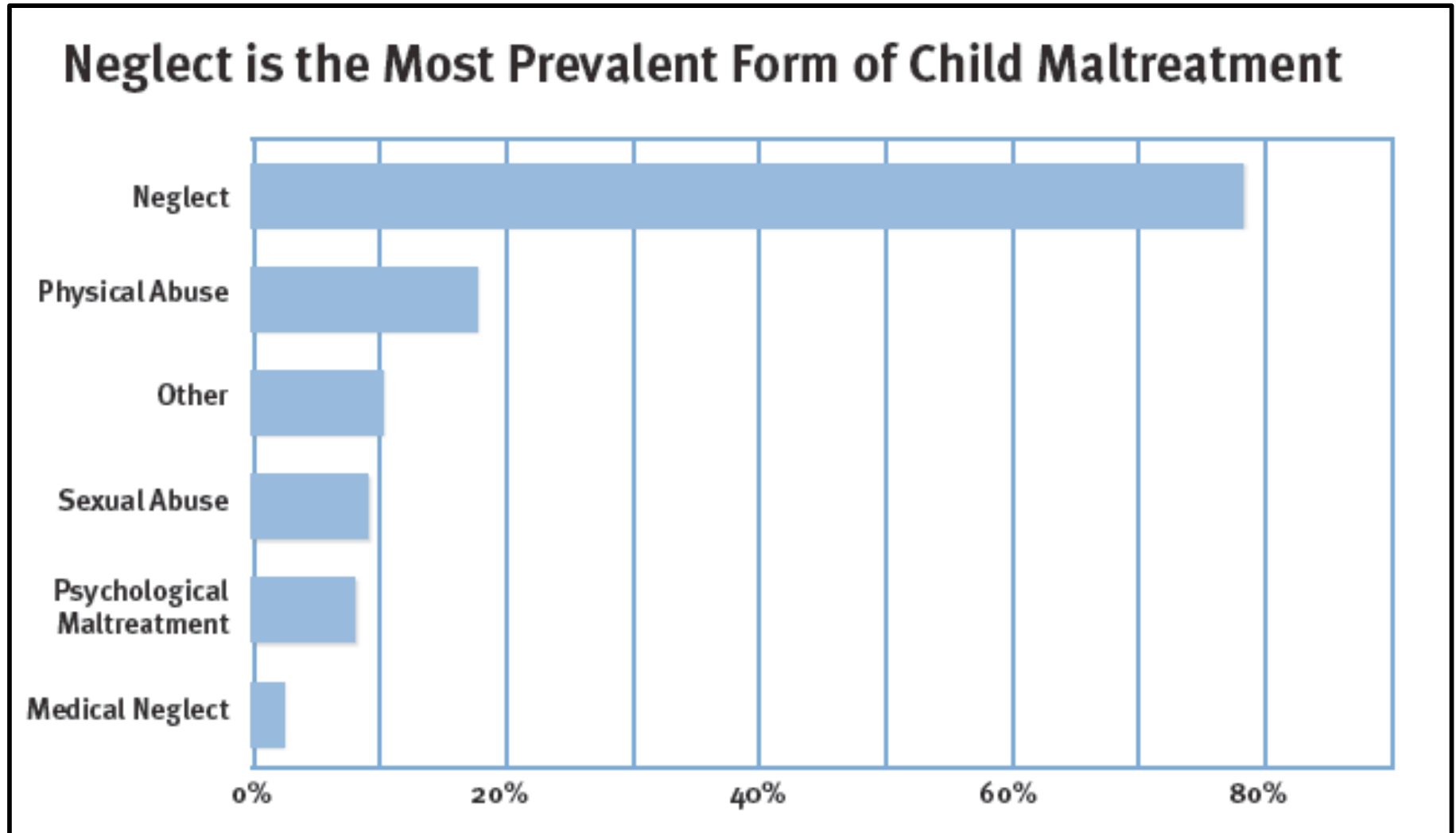
### Tolerable

Serious, temporary stress responses,  
buffered by supportive relationships.

### Toxic

Prolonged activation of stress response systems  
in the absence of protective relationships.

# We know that:



U.S. Dept. Health and Human Services, 2010

# NATIONAL SCIENTIFIC COUNCIL ON THE DEVELOPING CHILD

## Science Helps to Differentiate Four Types of Unresponsive Care

	OCCASIONAL INATTENTION	CHRONIC UNDER-STIMULATION	SEVERE NEGLECT IN A FAMILY CONTEXT	SEVERE NEGLECT IN AN INSTITUTIONAL SETTING
Features	Intermittent, diminished attention in an otherwise responsive environment	Ongoing, diminished level of child-focused responsiveness and developmental enrichment	Significant, ongoing absence of serve and return interaction, often associated with failure to provide for basic needs	“Warehouse-like” conditions with many children, few caregivers, and no individualized adult-child relationships that are reliably responsive
Effects	Can be growth-promoting under caring conditions	Often leads to developmental delays and may be caused by a variety of factors	Wide range of adverse impacts, from significant developmental impairments to immediate threat to health or survival	Basic survival needs may be met, but lack of individualized adult responsiveness can lead to severe impairments in cognitive, physical, and psychosocial development
Action	No intervention needed	Interventions that address the needs of caregivers combined with access to high-quality early care and education for children can be effective	Intervention to assure caregiver responsiveness and address the developmental needs of the child required as soon as possible	Intervention and removal to a stable, caring, and socially responsive environment required as soon as possible

# But Context Matters A lot

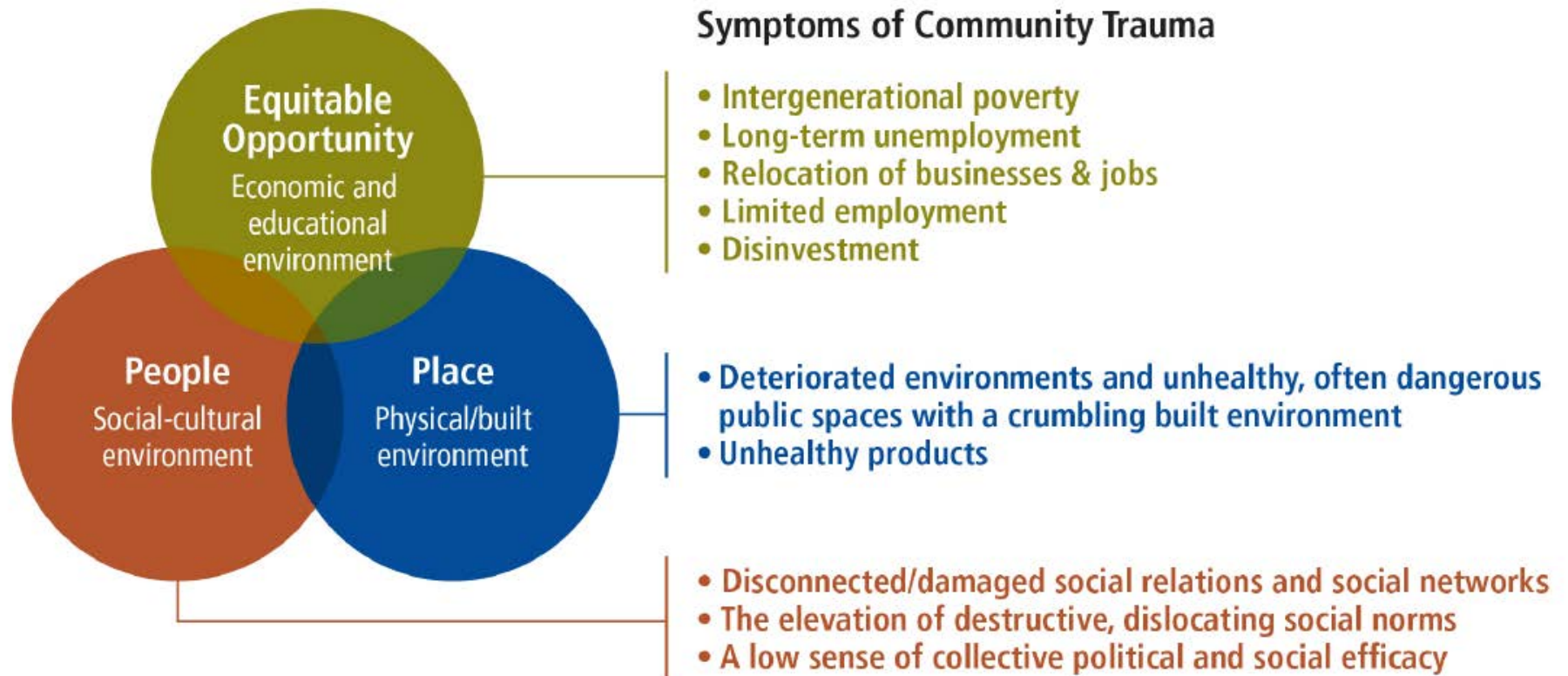
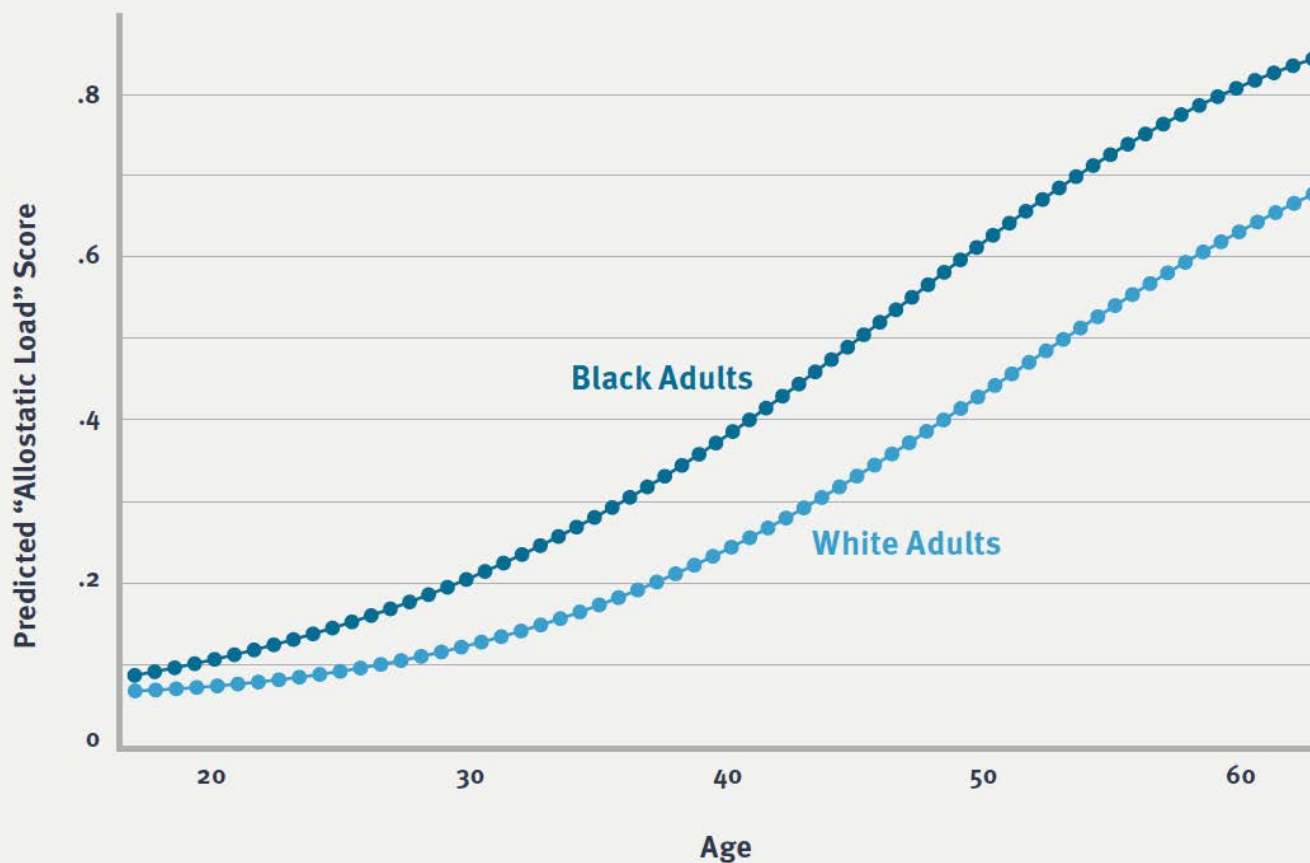


Figure 12. Community symptoms of trauma. Reproduced with permission from the Prevention Institute.<sup>1099</sup>



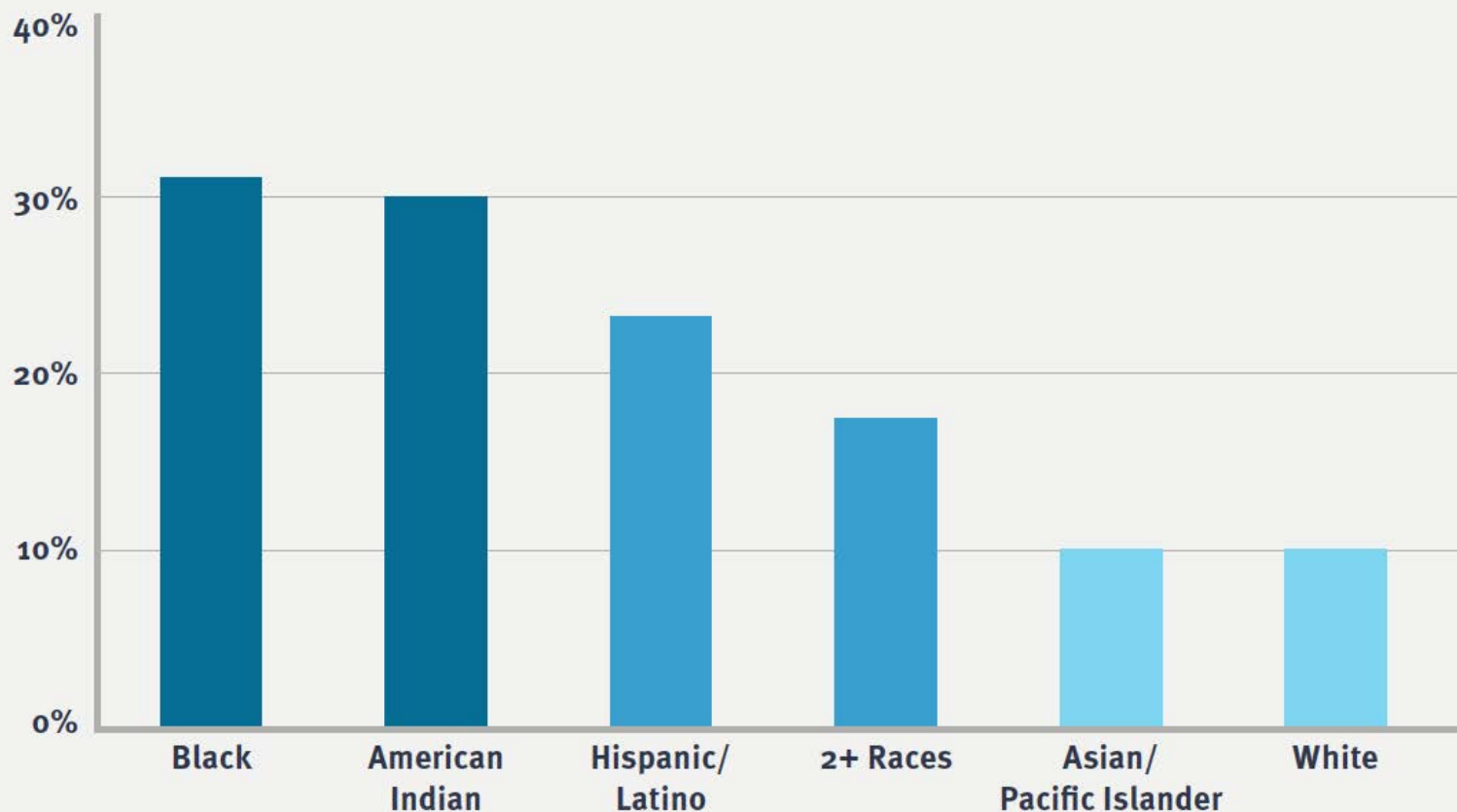
## A Higher Burden of Stress



Source: Geronimus, A.T., Hicken, M., Keene, D., & Bound, J. (2006). "Weathering" and age patterns of allostatic load scores among blacks and whites in the United States. *American Journal of Public Health*, 96(5), 826–833. <https://doi.org/10.2105/AJPH.2004.060749>

## US Children in Poverty by Racial Category

The 2019 share of children under age 18 who live in families with incomes below the federal poverty threshold (e.g., \$25,926 per year for a family of 4).



Source: KIDS COUNT Data Cent. 2020. Children in poverty by race and ethnicity in the United States. Data from U.S. Census Bureau, Am. Community Survey 2019, Annie E. Casey Found. KIDS COUNT Data Cent., Baltimore, MD.

# Environmental Factors AND Addressing Skill Building for the Care

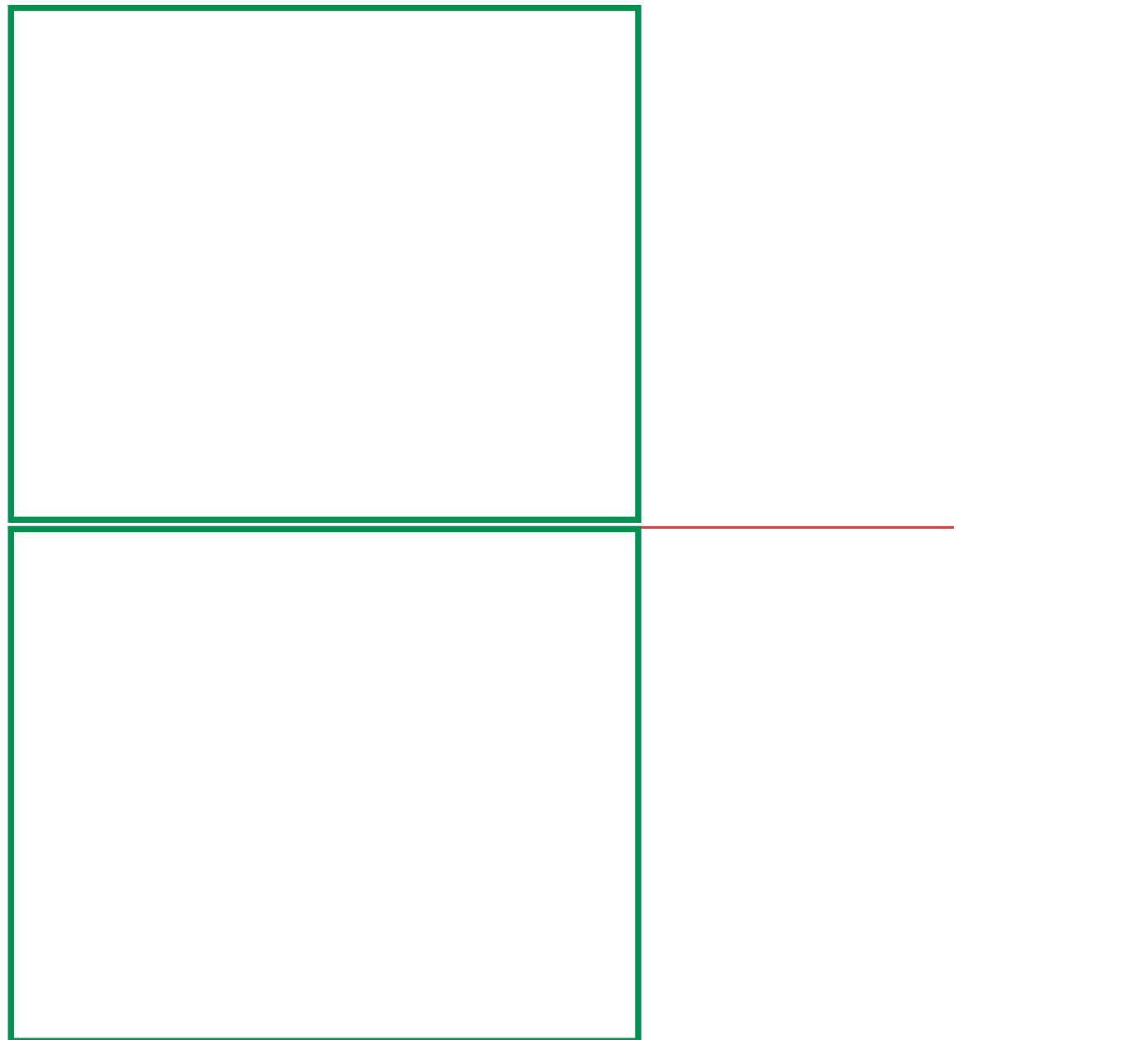


The Importance of Supporting Social Relationships

The science of Neglect

<https://developingchild.harvard.edu/resources/inbrief-the-science-of-neglect-video/>

Happy  
Happy  
Angry  
Angry



Fearful  
Sad  
Fearful  
Sad

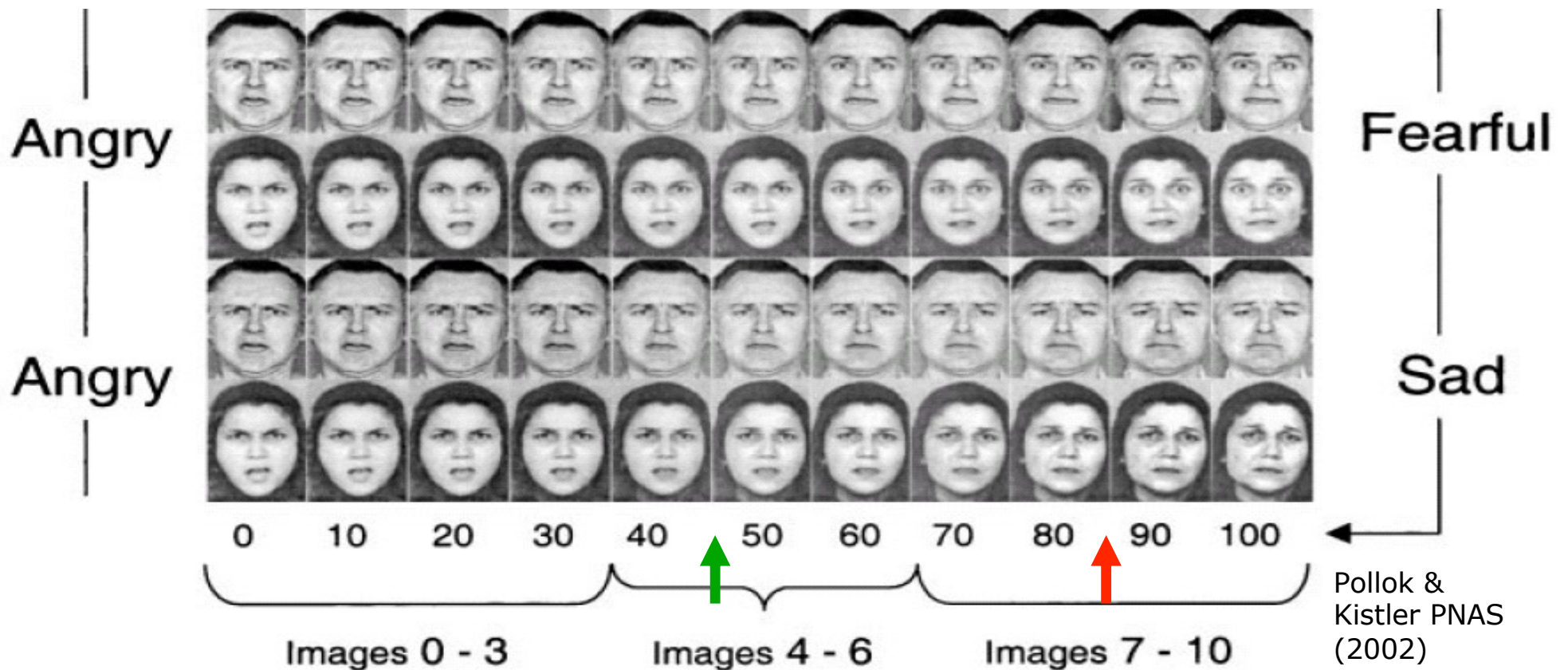
Images 0 - 3

Images 4 - 6

Images 7 - 10

Source: Pollok & Kistler (2002)

- **Abuse** - difficulty in distinguishing **anger** from other emotions, and difficulty disengaging
- **Neglect** - difficulty in distinguishing between **any** emotions, and poor face processing



# **Social-Emotional and Cognitive Skill Building are Interconnected**

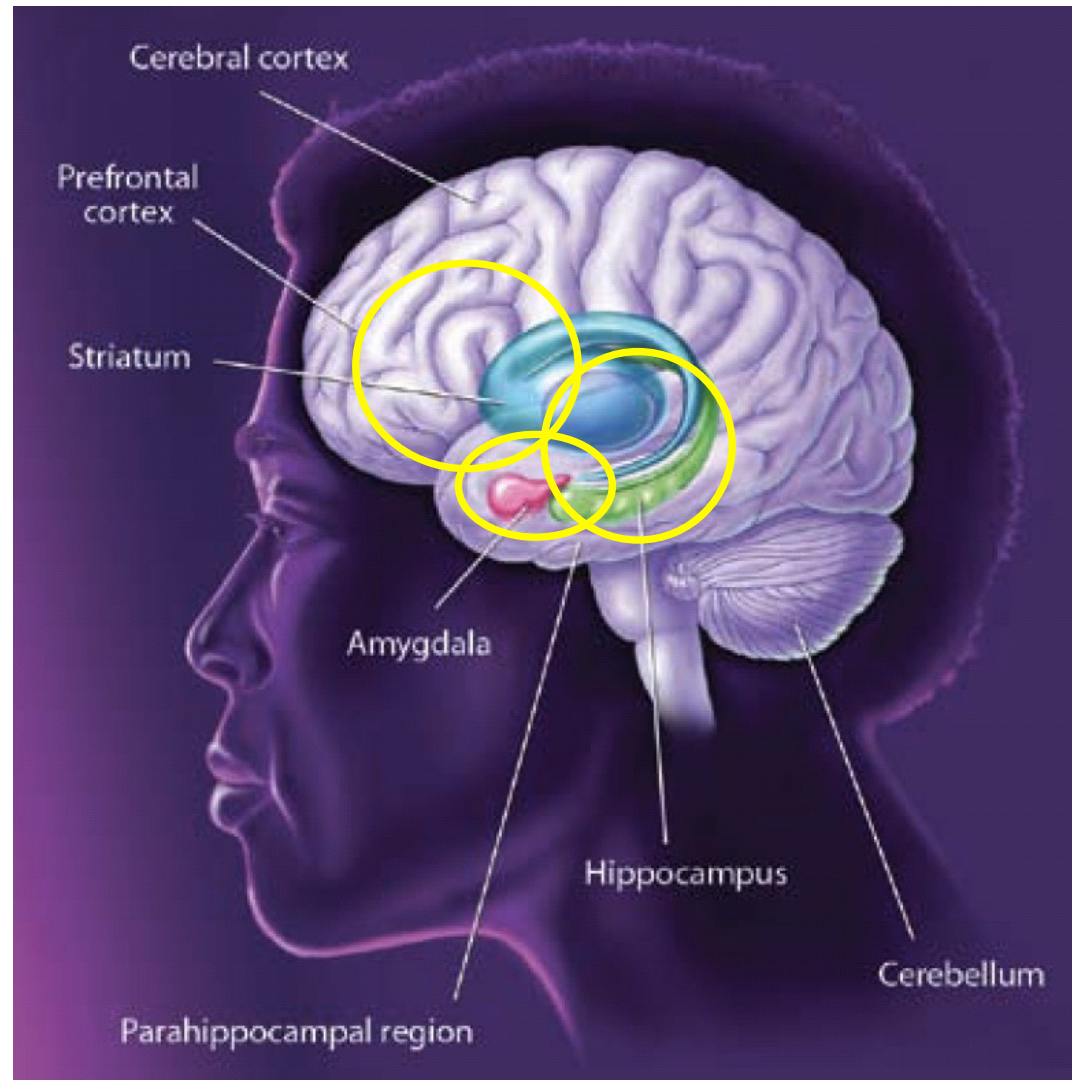
# FRAMEWORKS INSTITUTE

Skills Development Depends Upon Addressing the Whole Child

<http://www.frameworksinstitute.org/>



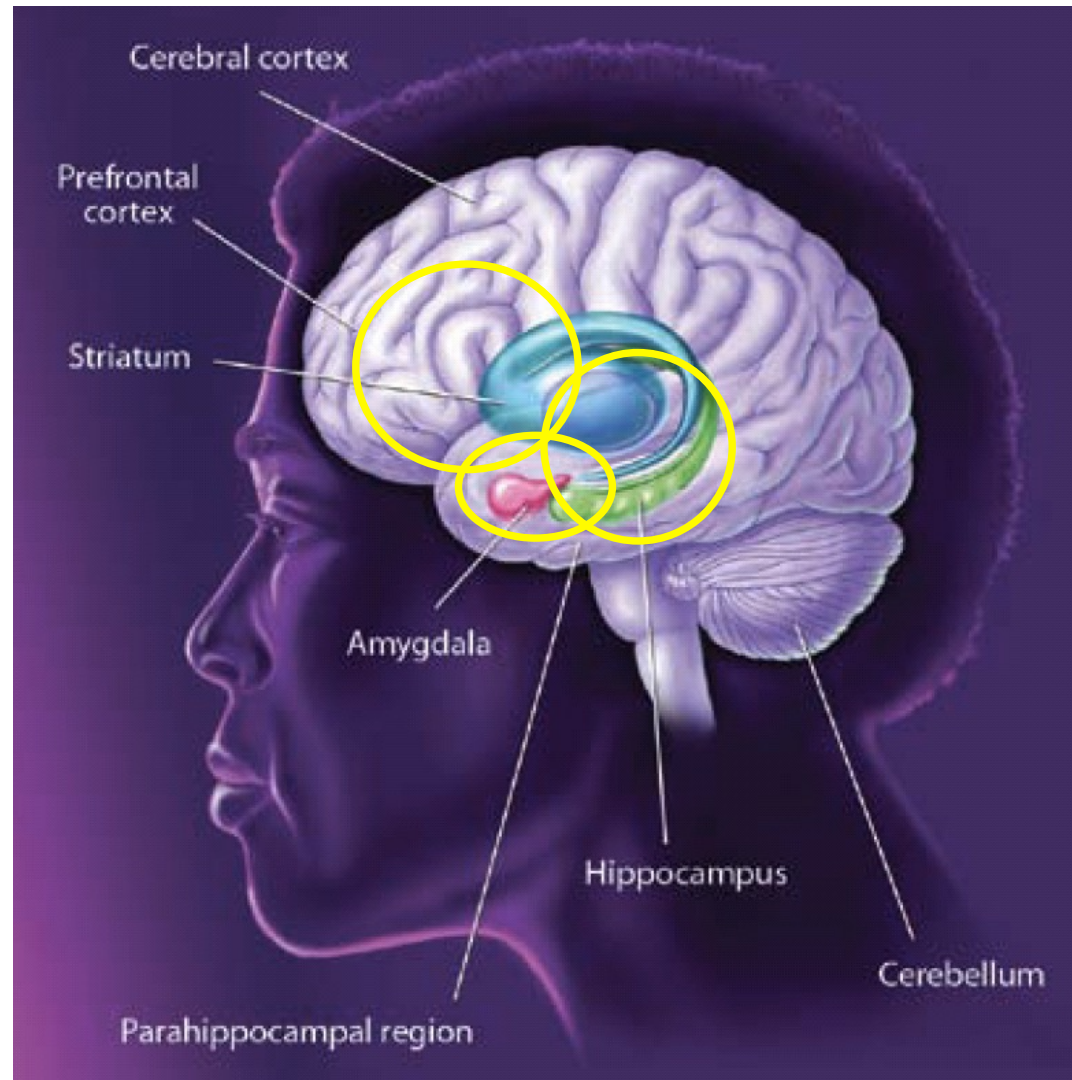
# The Brain Architecture of Anxiety and Fear



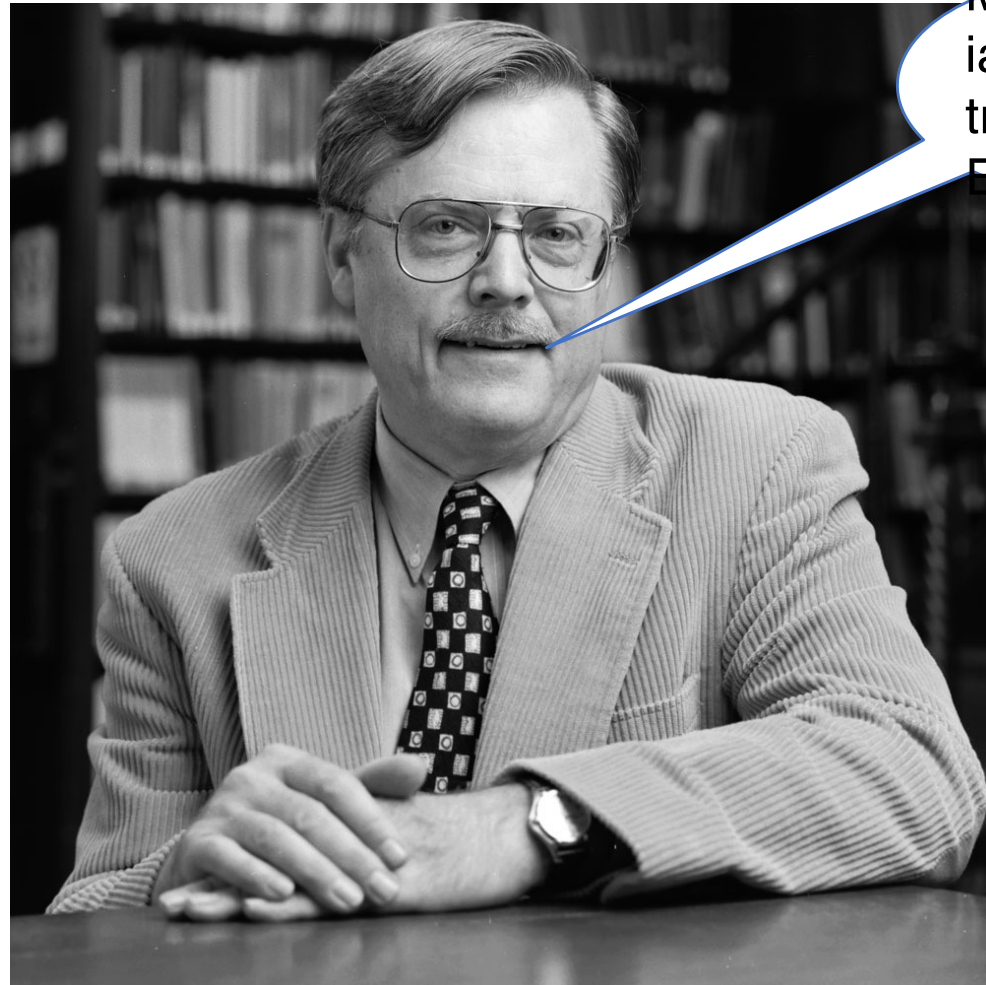
Toxic Stress Derails Healthy Development

<https://developingchild.harvard.edu/resources/toxic-stress-derails-healthy-development/>.

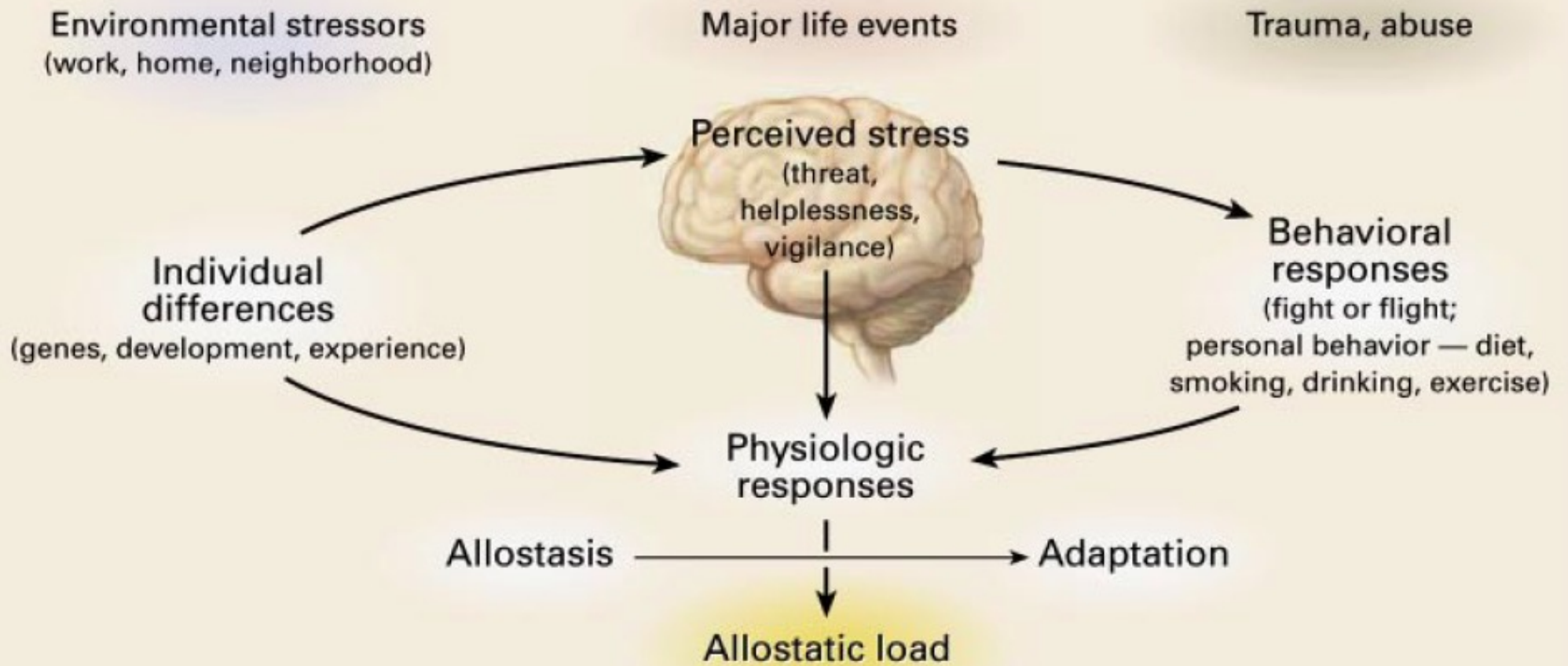
# The Brain Architecture of Memory and Learning



Bruce McEwen – stress, allostasis and adaptive processes

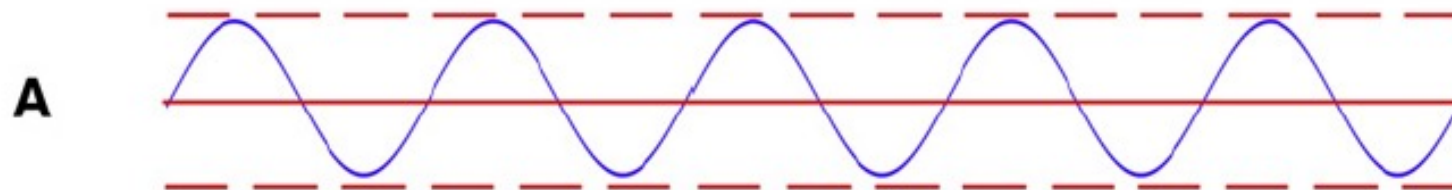


Mitochondr  
ia keep  
track of  
ELS

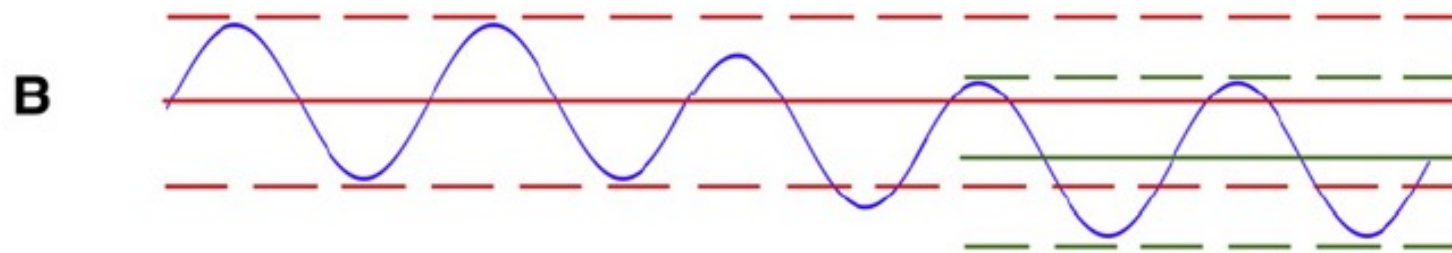


# Responses to Cellular and Physiological Challenges - Developmental Allostasis (chemo-physiological 'wear and tear')

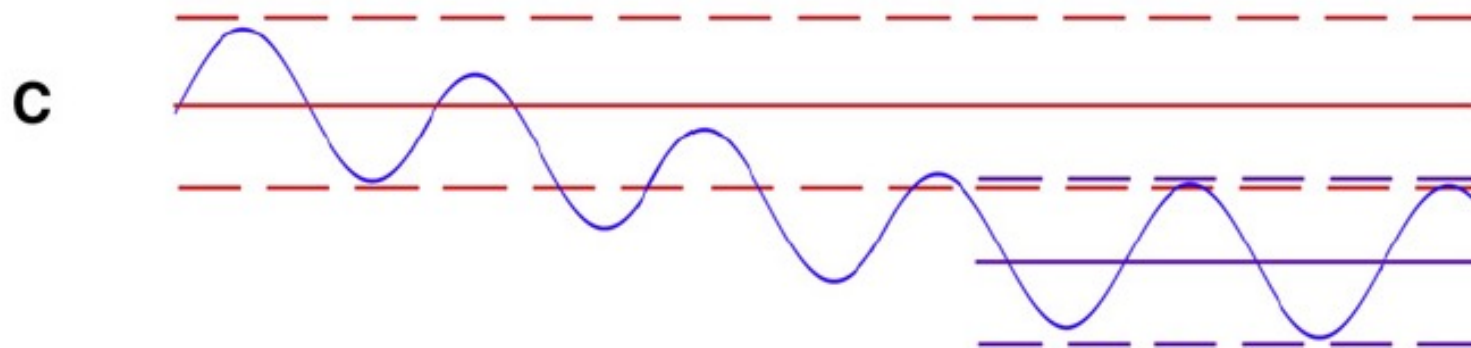
Homeostasis – narrow response range



Allostasis – broad response range for maintaining homeostasis



Allostatic Load – prolonged response shifts homeostatic range maladaptively



# **Acquired Biological Disruption**

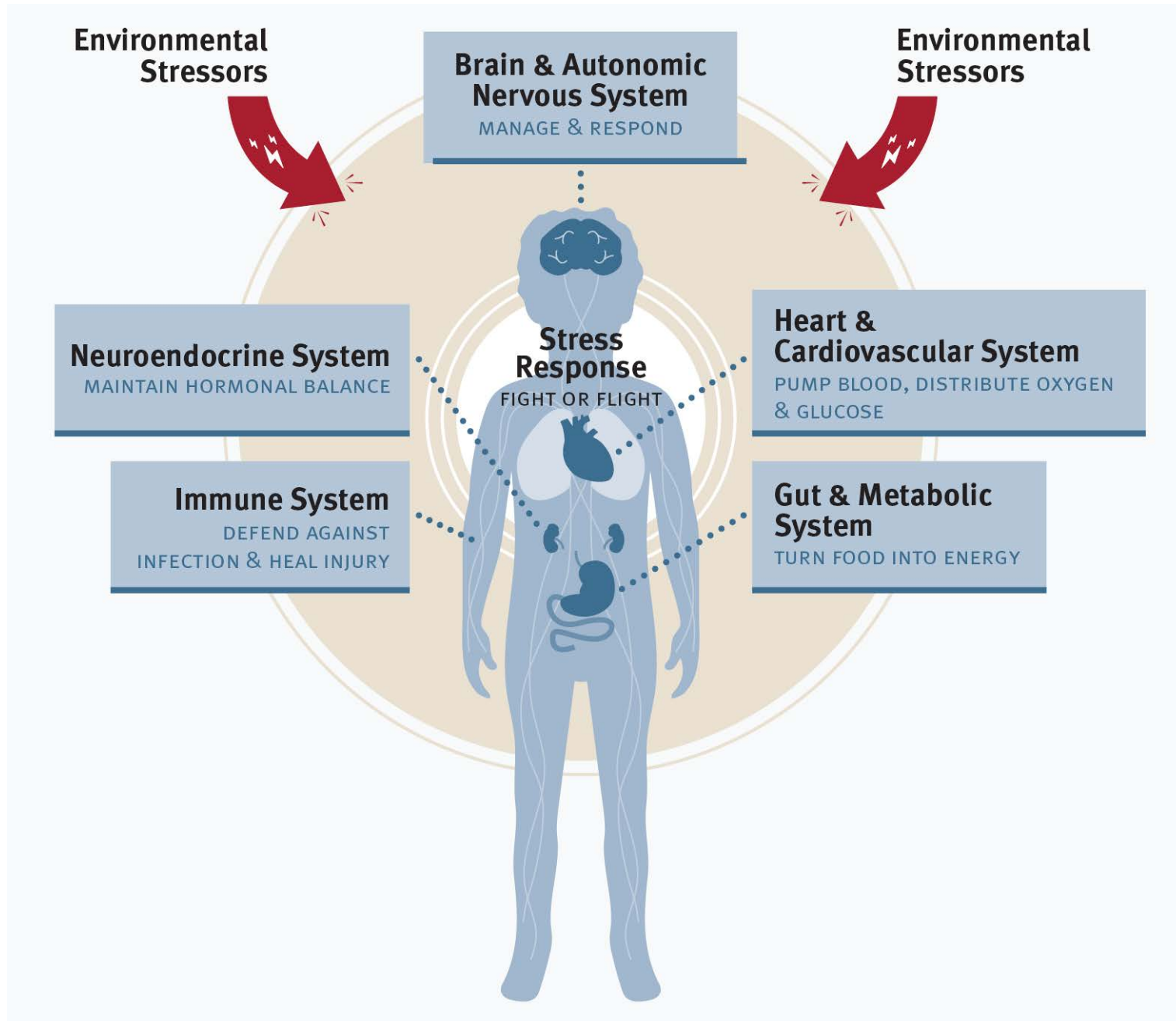
# Connecting the Brain to the Rest of the Body: Early Childhood Development and Lifelong Health Are Deeply Intertwined

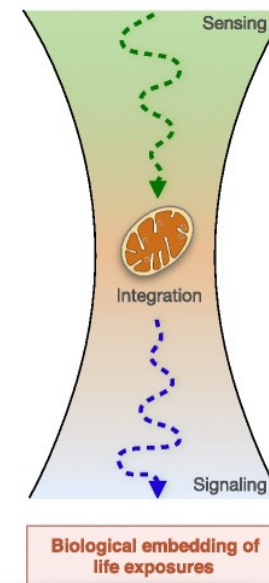
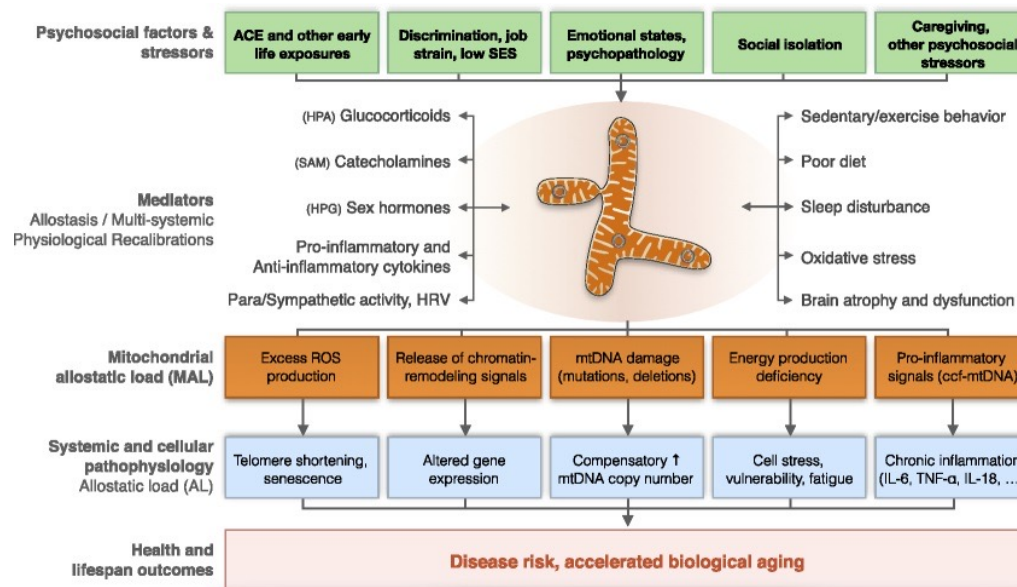
WORKING PAPER 15

15



# NATIONAL SCIENTIFIC COUNCIL ON THE DEVELOPING CHILD





Picard, M. & McEwen, B.S. Psychological stress and mitochondria: a conceptual framework. *Psychosom Med* 80, 126-140 (2018).

RESEARCH ARTICLE

# Identification of Biomarkers of Impaired Sensory Profiles among Autistic Patients

Afaf El-Ansary<sup>1,3</sup>, Wail M. Hassan<sup>4</sup>, Hanan Qasem<sup>2</sup>, Undurti N. Das<sup>5,6\*</sup>

Published in final edited form as:

*Schizophr Res.* 2016 October ; 176(2-3): 320–326. doi:10.1016/j.schres.2016.06.011.

## Elevated Plasma F2-isoprostane Levels in Schizophrenia

Ellen E. Lee, M.D.<sup>1</sup>, Lisa T. Eyler, Ph.D.<sup>1,2</sup>, Owen M. Wolkowitz, M.D.<sup>3</sup>, Averria Sirkin Martin, Ph.D.<sup>1,4</sup>, Chase Reuter, M.S.<sup>1,4</sup>, Helena Kraemer, Ph.D.<sup>5</sup>, and Dilip V. Jeste, M.D.<sup>1,4,6,7</sup>

Qasem et al. *Lipids in Health and Disease* (2016) 15:130  
DOI 10.1186/s12944-016-0298-0

Lipids in Health and Disease

RESEARCH

Open Access



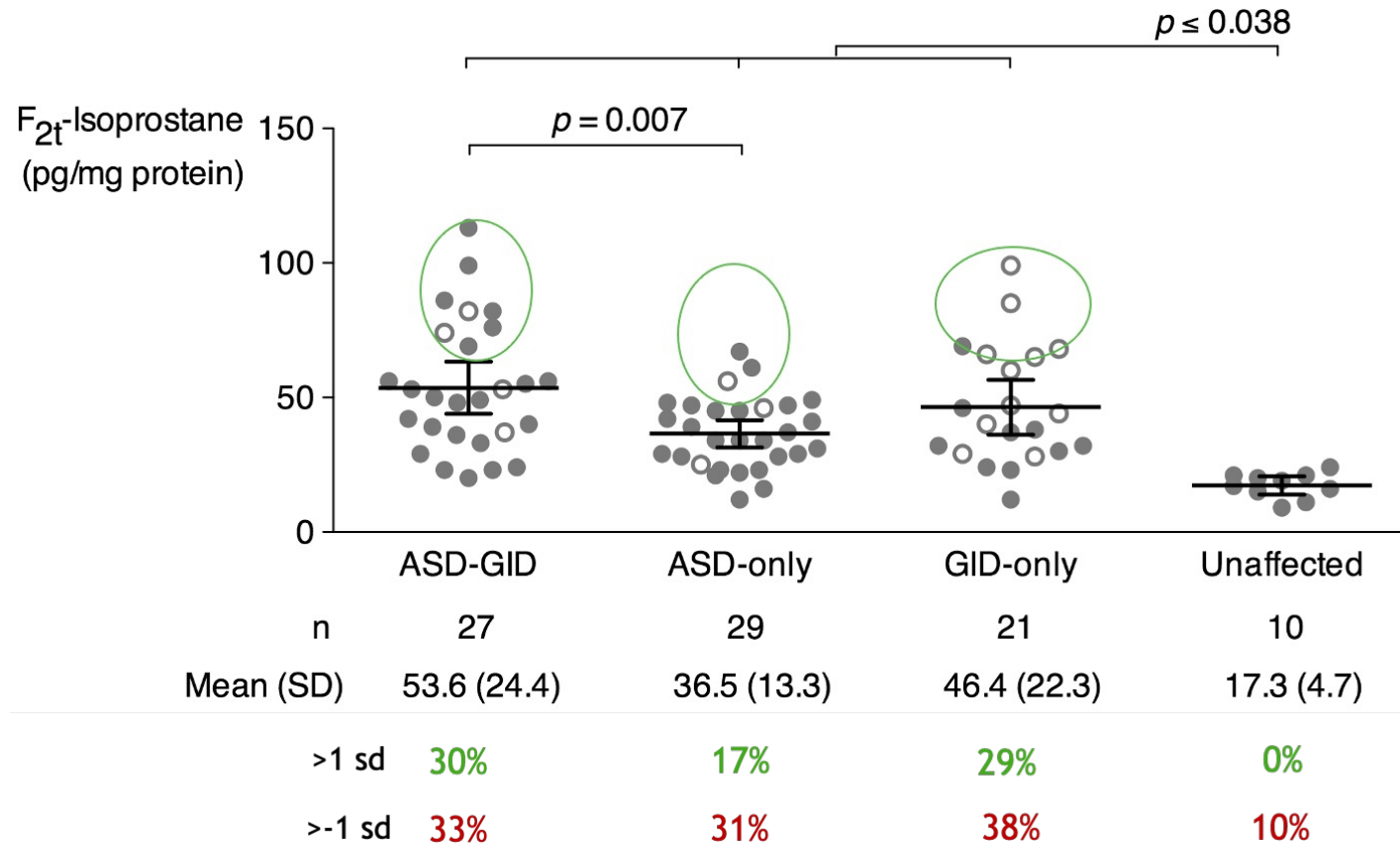
## Cysteinyl leukotriene correlated with 8-isoprostane levels as predictive biomarkers for sensory dysfunction in autism

Hanan Qasem<sup>2</sup>, Laila Al-Ayadhi<sup>3,4,5</sup> and Afaf El-Ansary<sup>1,3,4,6\*</sup>

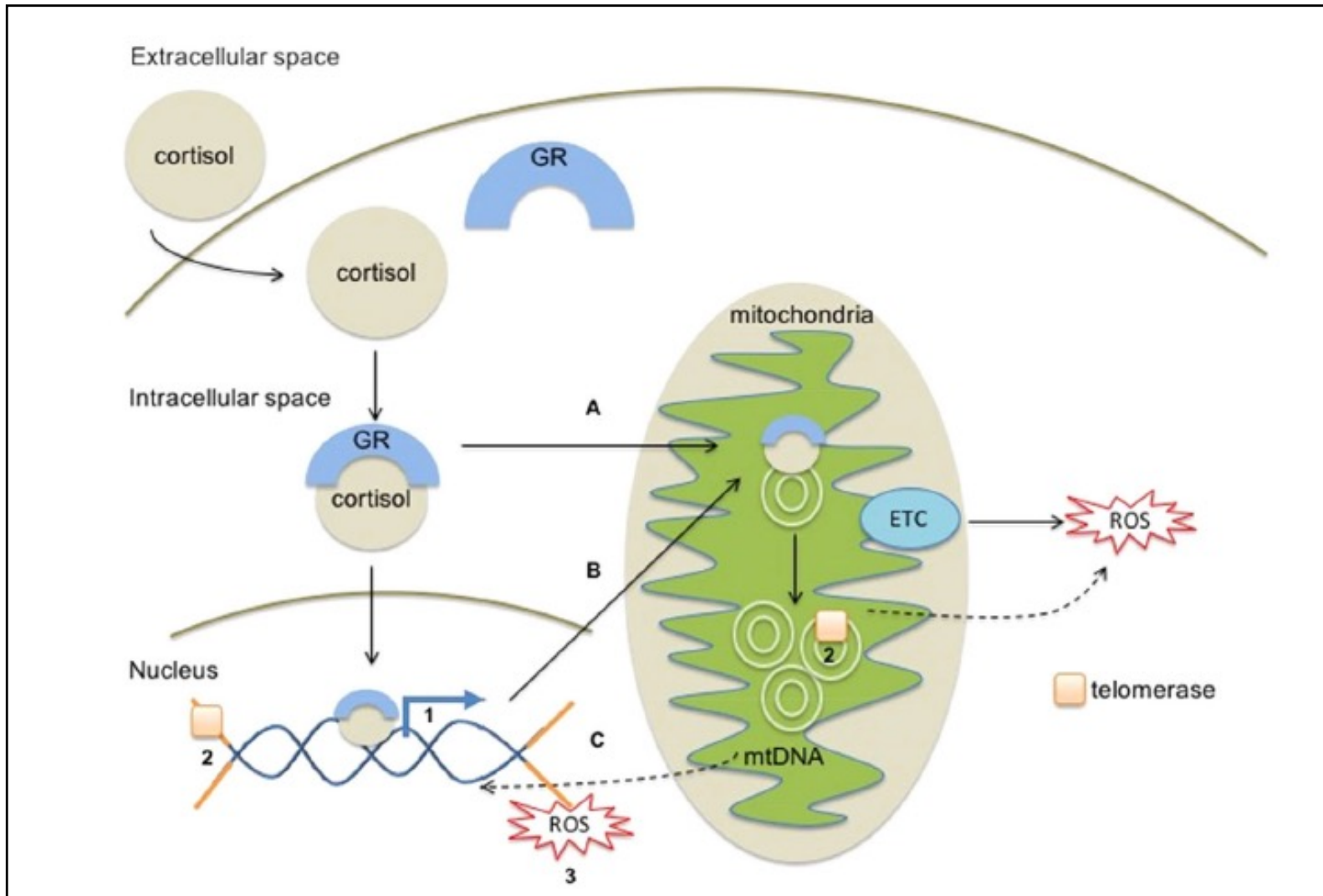
# Oxidative stress with an \* - \*heterogeneity

## Enrichment of Elevated Plasma F<sub>2t</sub>-Isoprostane Levels in Individuals with Autism Who Are Stratified by Presence of Gastrointestinal Dysfunction

Phillip Gorrindo<sup>1\*</sup>, Christianne Joy Lane<sup>2</sup>, Evon Batey Lee<sup>3,4,5,6</sup>, BethAnn McLaughlin<sup>3,7,8,9</sup>, Pat Levitt<sup>10,11</sup>



Chronic Stress = Mitochondrial Allostatic Load = Pathophysiology



# Early Life Stress Model



**Lower quality  
(maternal stress,  
'abusive')**



**Less predictable**

**Quality of  
Care**



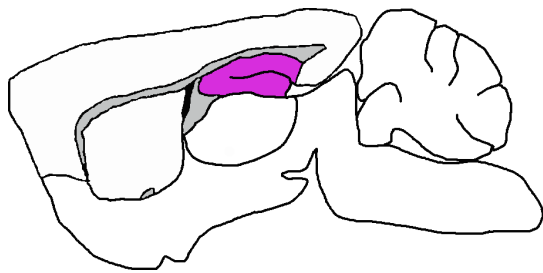
**Higher quality  
(low maternal  
stress, non-  
abusive)**



**Predictable,  
consistent**

**Patterns of  
Care**

**modeled after Walker et al.,  
*Stress*, 2017**



Male control



Male ELS



Female control



Female ELS

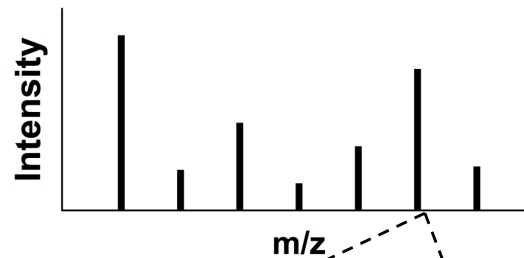


1

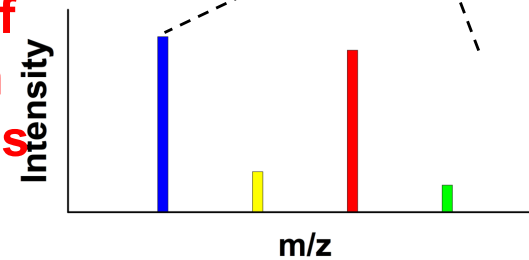
iTRAQ label tryptic peptides

2

Identify peptides



Quantify ratio of each peptide in different samples



3

Tandem MS/MS

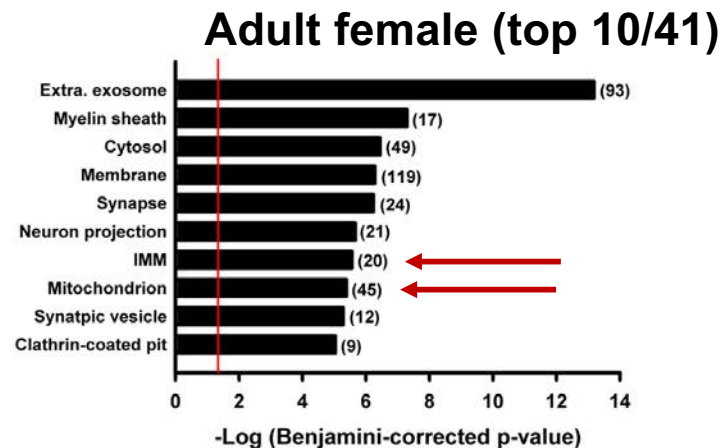
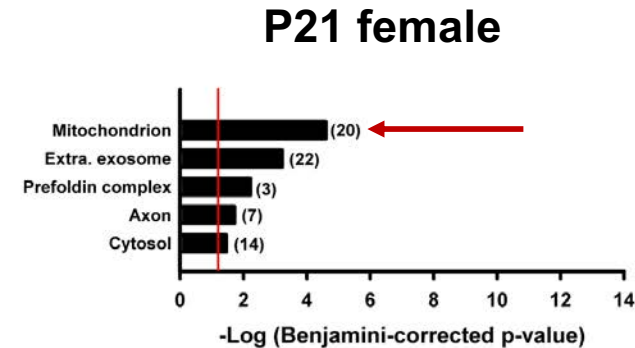
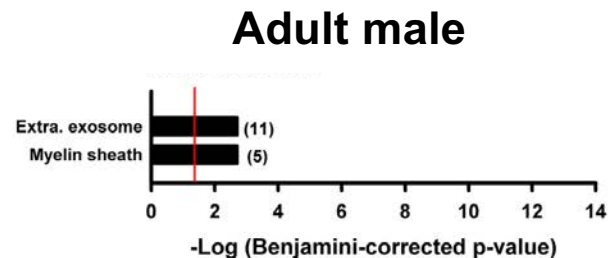


Mix equal amounts of labeled samples



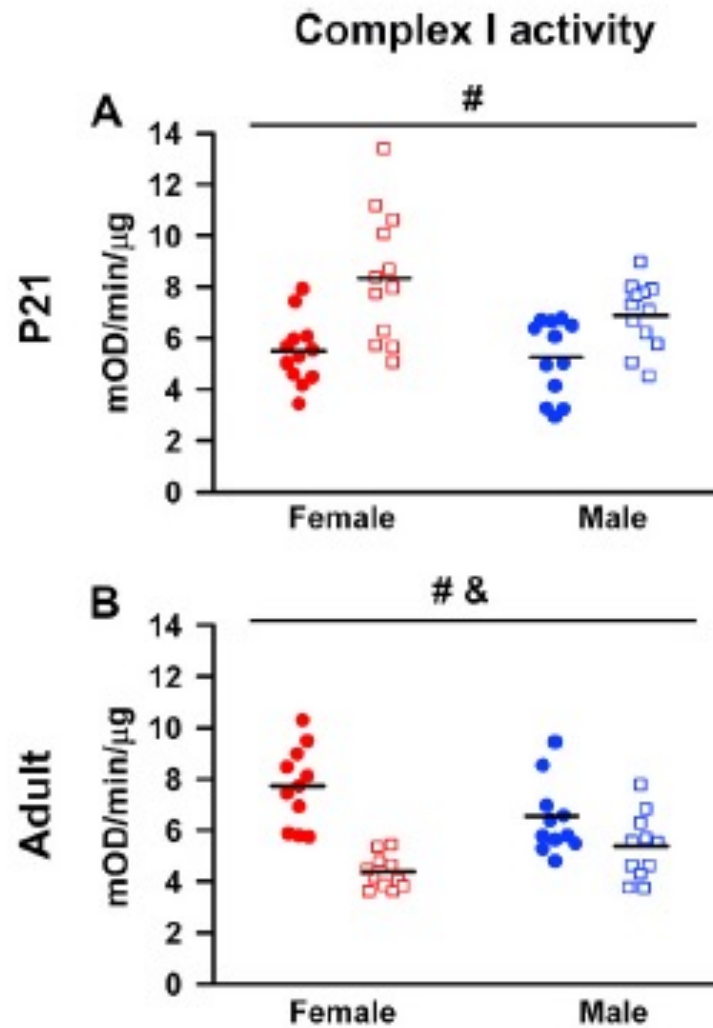
# Mitochondrial proteins are enriched in females only

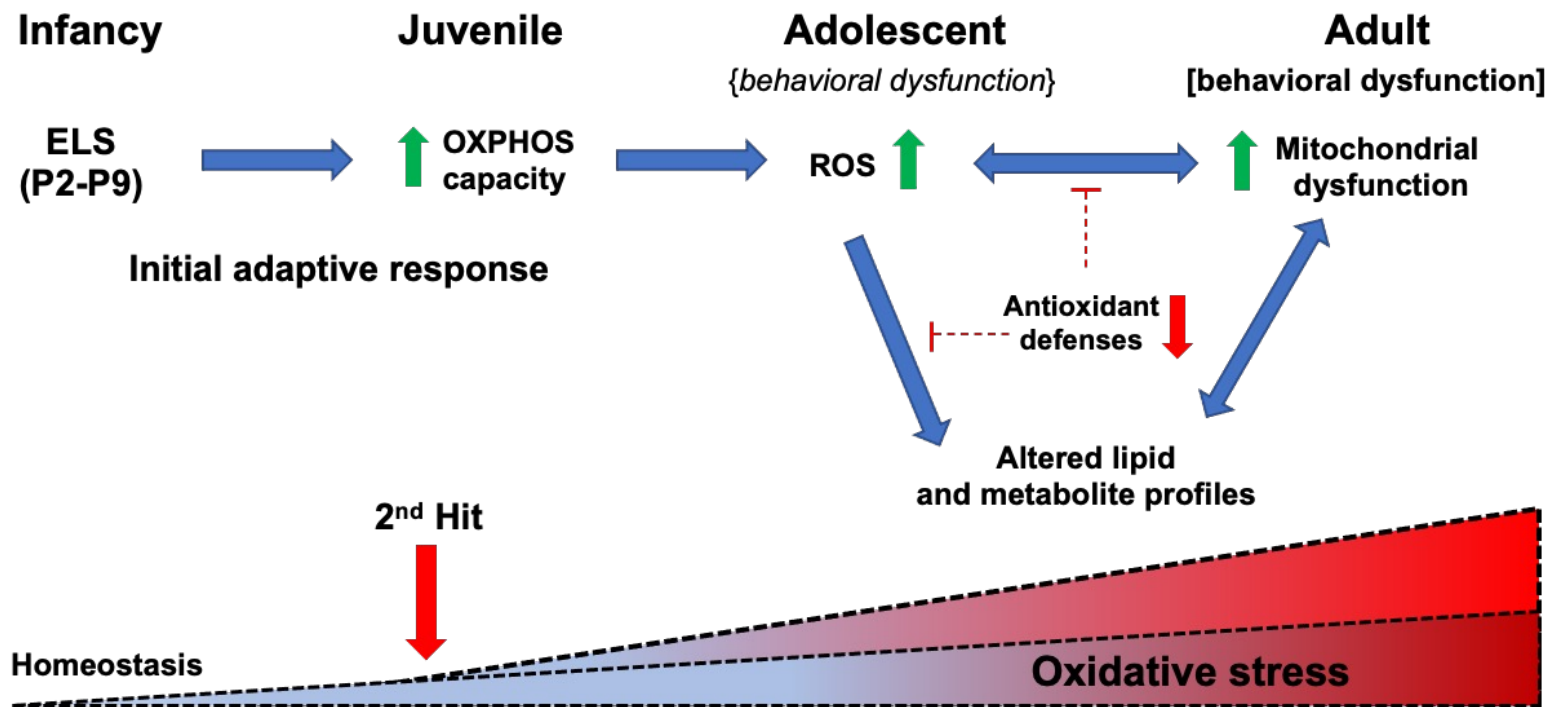
- Changes in expression for individual proteins typically in 20-30% range
- GO enrichment analyses





Mitochondrial Allostatic Load Demonstrated Experimentally



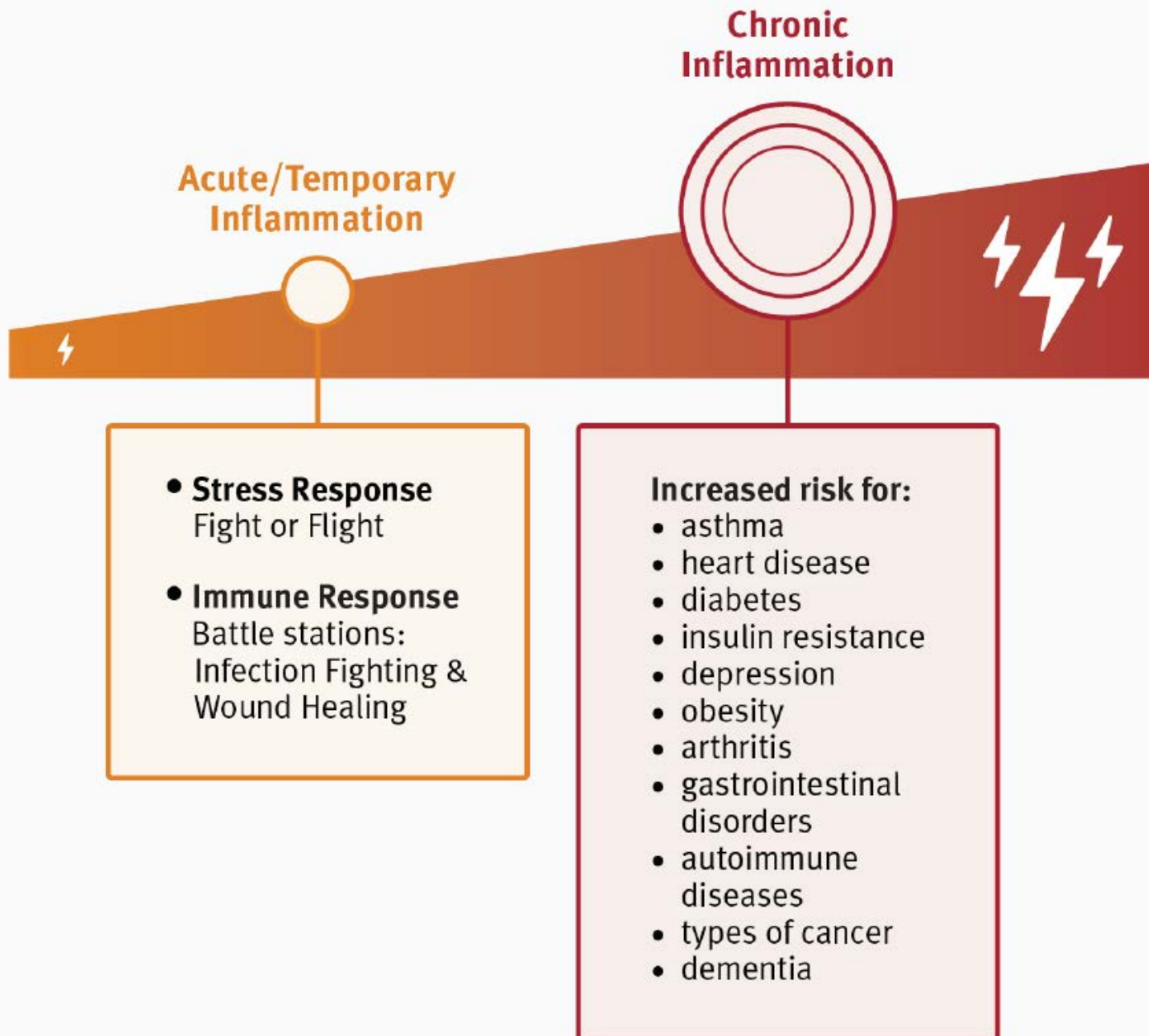


# Connecting the Brain to the Rest of the Body: Early Childhood Development and Lifelong Health Are Deeply Intertwined

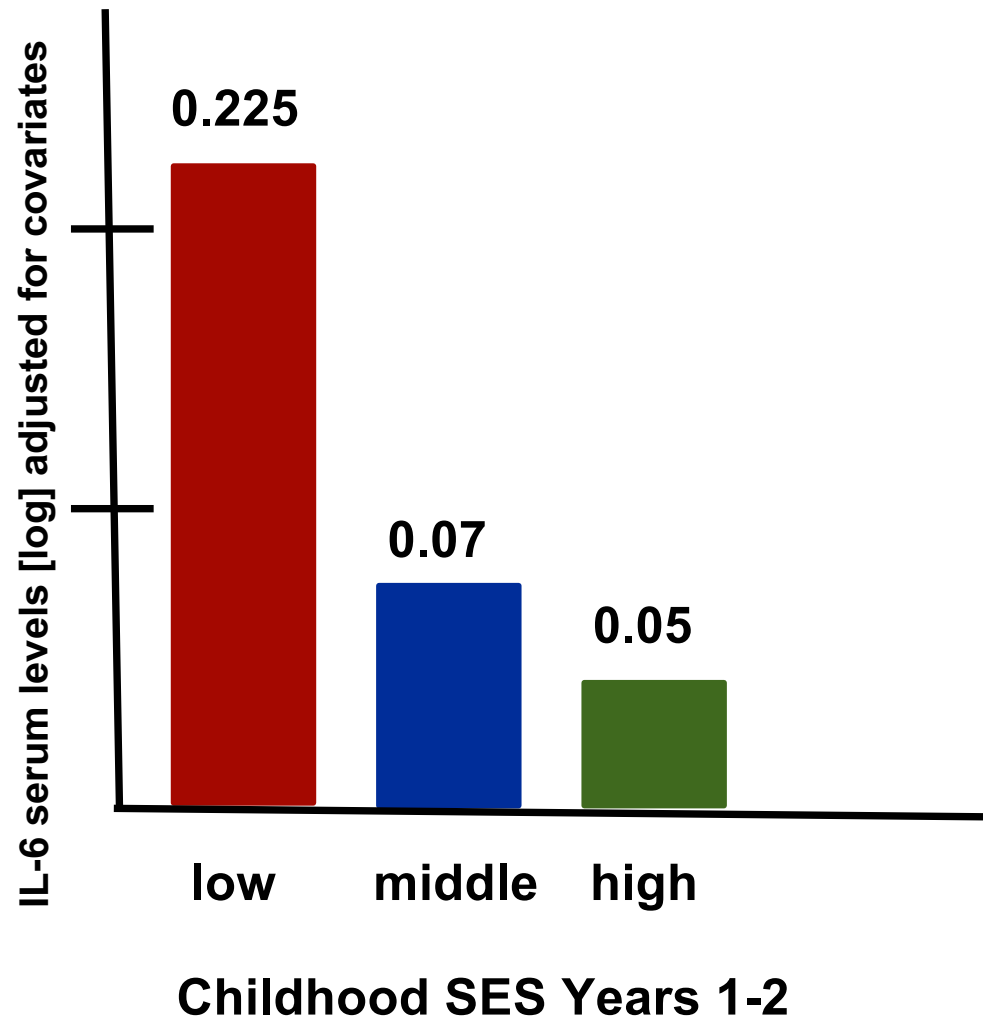
WORKING PAPER 15

15

# Acute to Chronic Inflammation



## Inverse Correlation Of Adult Inflammatory Protein IL-6 With Very Early SES



# Addressing Toxic Stress/Early Adversity - The Importance of Connecting the Brain and Body

Connecting the brain to the body

<https://developingchild.harvard.edu/resources/connecting-the-brain-to-the-rest-of-the-body-early-childhood-development-and-lifelong-health-are-deeply-intertwined/>

Thanks for the  
break! That  
was a lot of  
stuff\*%!

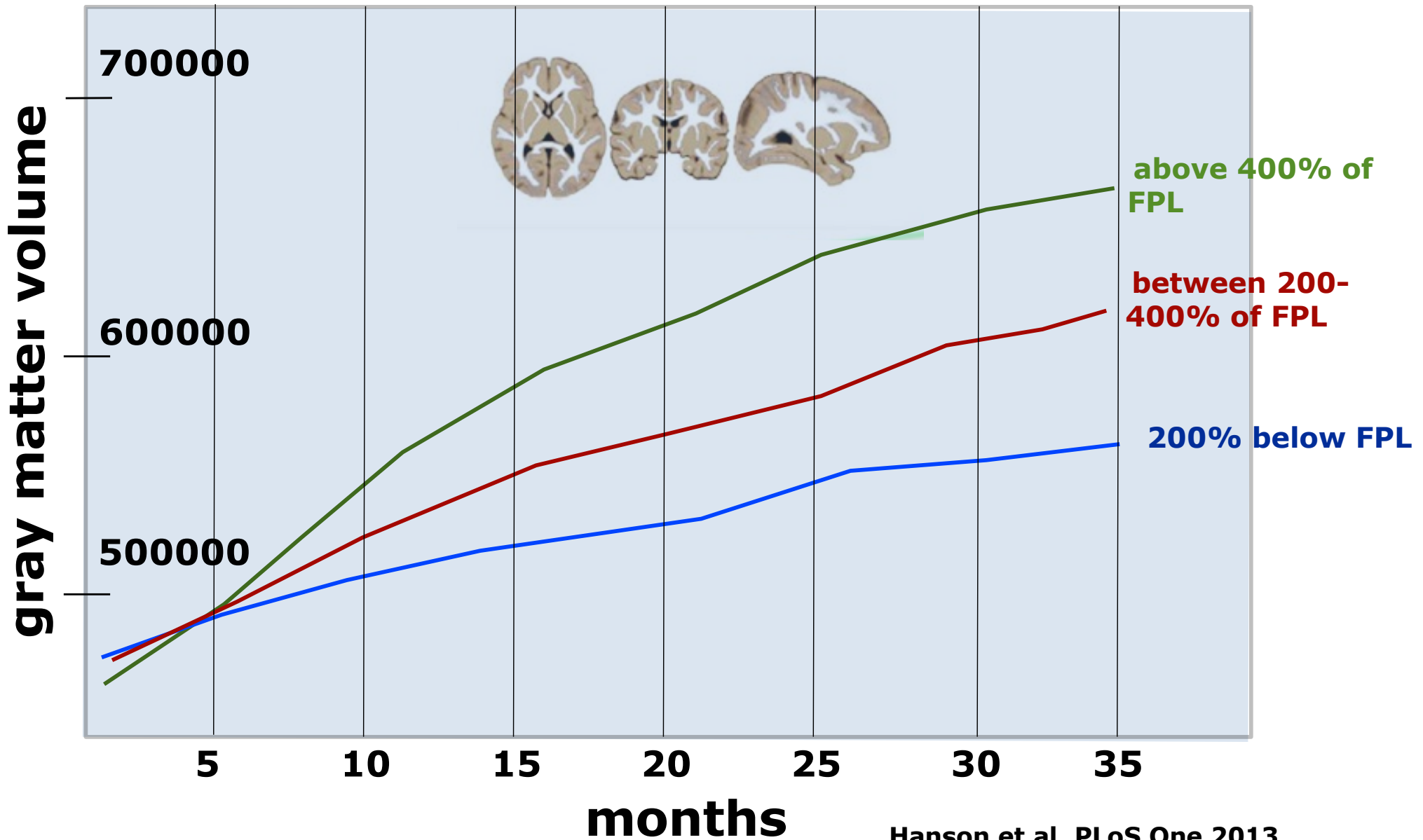


Pixar/Disney-Pixar, via Associated Press

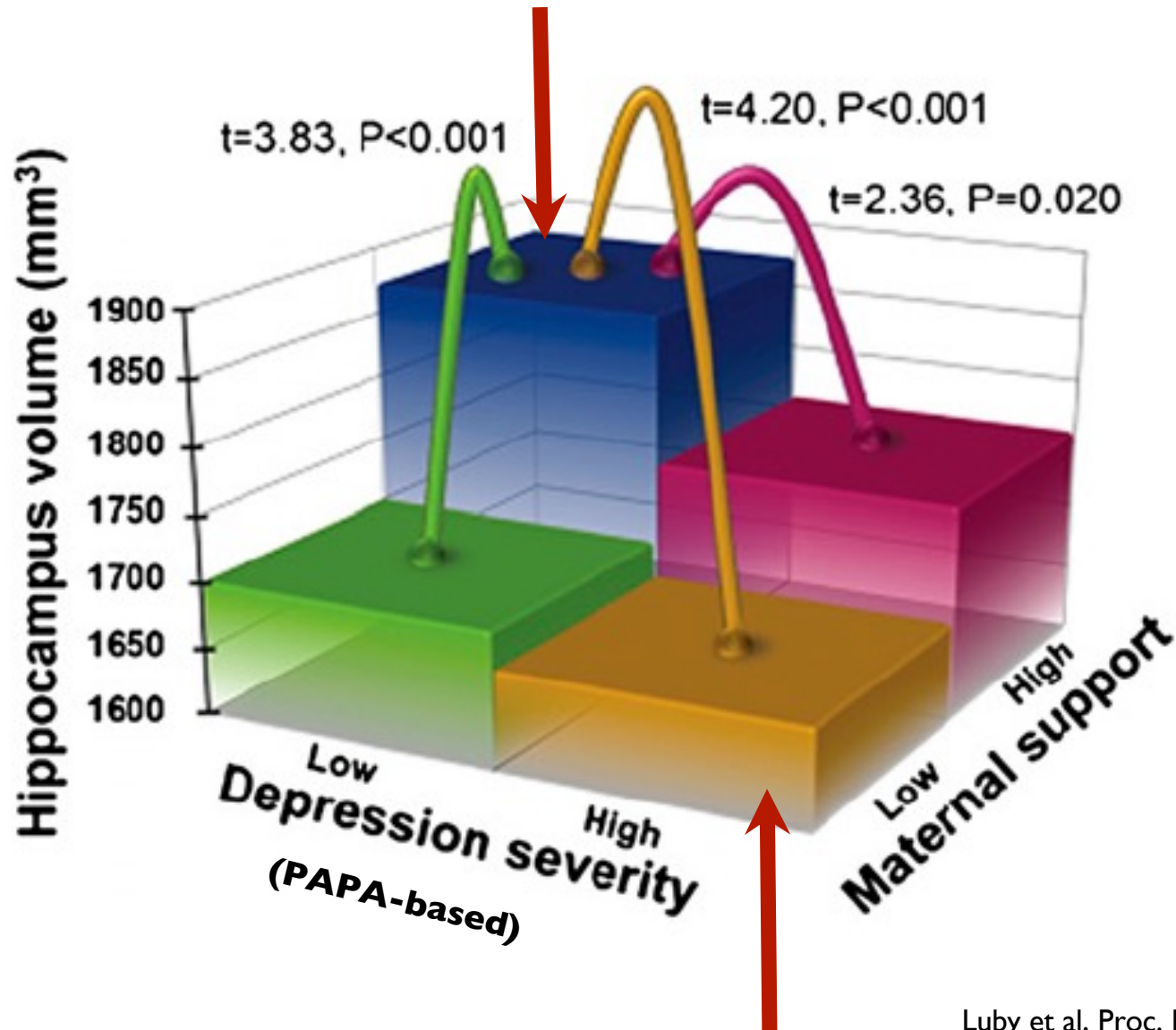
**Acquired Resources Influence  
Vulnerability to Social Origins of Disease**



### Brain Growth and Poverty



## Positive or Adverse Childhood Experiences - Impact on Brain Architecture



**13%!**

# Long-Term Health Outcomes

28 MARCH 2014 VOL 343 SCIENCE

## Early Childhood Investments Substantially Boost Adult Health

Frances Campbell,<sup>1</sup> Gabriella Conti,<sup>2</sup> James J. Heckman,<sup>3,4,5\*</sup> Seong Hyeok Moon,<sup>3</sup>  
Rodrigo Pinto,<sup>3</sup> Elizabeth Pungello,<sup>1</sup> Yi Pan<sup>1</sup>

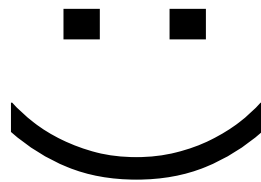
**(Carolina Abecedarian Project)**

# NATIONAL SCIENTIFIC COUNCIL ON THE DEVELOPING CHILD

## Long-Term Health Outcomes

Variable	Control mean	Treatment mean	Difference in means	Conditional treatment effect	Block P value	Stepdown P value
<i>Blood pressure</i>						
Diastolic blood pressure (mm Hg)	92.000	78.526	13.474	19.220	<b>0.024</b>	<b>0.024</b>
Systolic blood pressure (mm Hg)	143.333	125.789	17.544	24.828	<b>0.018</b>	<b>0.029</b>
Prehypertension (systolic bp $\geq$ 120 and diastolic bp $\geq$ 80)	0.667	0.421	0.246	0.321	0.119	0.172
Prehypertension (systolic bp $\geq$ 120 or diastolic bp $\geq$ 80)	0.778	0.684	0.094	0.096	0.235	0.235
Hypertension (systolic bp $\geq$ 140 and diastolic bp $\geq$ 90)	0.444	0.105	0.339	0.537	<b>0.010</b>	<b>0.018</b>
Hypertension (systolic bp $\geq$ 140 or diastolic bp $\geq$ 90)	0.556	0.211	0.345	0.404	<b>0.038</b>	<b>0.038</b>
<i>Laboratory tests</i>						
High-density lipoprotein (HDL) cholesterol (mg/dL)	42.000	53.211	11.211	11.720	<b>0.066</b>	0.110
Dyslipidemia (HDL < 40 mg/dL)	0.417	0.106	0.311	0.255	0.179	0.179
Prediabetes (HbA1C $\geq$ 5.7%)	0.583	0.473	0.110	0.043	0.426	0.426
Vitamin D deficiency (<20 ng/mL)	0.750	0.368	0.382	0.435	<b>0.021</b>	<b>0.021</b>
<i>Obesity</i>						
Overweight (BMI $\geq$ 25)	0.750	0.722	0.028	0.190	0.239	0.239
Obese (BMI $\geq$ 30)	0.625	0.556	0.069	0.211	0.233	0.345
Severely obese (BMI $\geq$ 35)	0.375	0.111	0.264	0.404	0.115	0.232
Waist-hip ratio (WHR)	0.962	0.937	0.025	0.045	0.293	0.293
Abdominal obesity (WHR > 0.9)	0.875	0.647	0.228	0.294	0.137	0.218
<i>Multiple risk factors</i>						
Obesity and hypertension	0.500	0.111	0.389	0.529	<b>0.016</b>	<b>0.016</b>
Severe obesity and hypertension	0.375	0.000	0.375	0.502	<b>0.005</b>	<b>0.012</b>
Hypertension and dyslipidemia	0.333	0.000	0.333	0.435	<b>0.006</b>	<b>0.012</b>
Metabolic syndrome (NCEP definition)	0.250	0.000	0.250	0.465	<b>0.007</b>	<b>0.014</b>
Framingham risk score (34)	7.043	4.889	2.154	3.253	<b>0.038</b>	<b>0.038</b>

**Social-Emotional and Cognitive  
Adaptation.....for a lifetime!**



# Executive Function: What is it?

Executive Function

<https://developingchild.harvard.edu/resources/inbrief-executive-function-skills-for-life-and-learning/>

**A remarkable example of developing EF**





## **EF Develops Over Decades**

**Early Positive = Adaptive Skills**

**Early Negative = Later problems**

# Early Executive Function Disruption - Predictor of At-Risk Adolescents and Adults

## The Dunedin Study

### CHILDHOOD RISK FACTORS



SELF-CONTROL

IQ

SOCIOECONOMIC STATUS

### ADOLESCENT SNARES



EARLY SMOKING

SCHOOL DROP-OUT

TEEN PARENTHOOD

### ADULT HEALTH

METABOLIC SYNDROME  
RESPIRATORY DISEASE  
PERIODONTAL DISEASE  
SEXUALLY TRANSMITTED INFECTIONS  
INFLAMMATION  
SUBSTANCE DEPENDENCE

### ADULT WEALTH

SOCIOECONOMIC STATUS  
SINGLE PARENT, SAVING  
INCOME, CREDIT PROBLEMS

### ADULT CRIME

AGE: BIRTH	3	5	7	9	11	13	15	18	21	26	32	
Year:	1972-73	1975-76	1977-78	1979-80	1981-82	1983-84	1985-86	1987-89	1990-91	1993-94	1998-99	2004-05
N =	1037	991	954	955	925	850	976	993	992	980	972	

# Signs of Early EF Disruption

Undercontrolled behavior

Low persistence

Aggressive

Impulsive

inattention

Liability to behavioral disinhibition

Childhood Disruptive Disorders

Externalizing Behaviors

Nicotine dependence  
Mental Illness

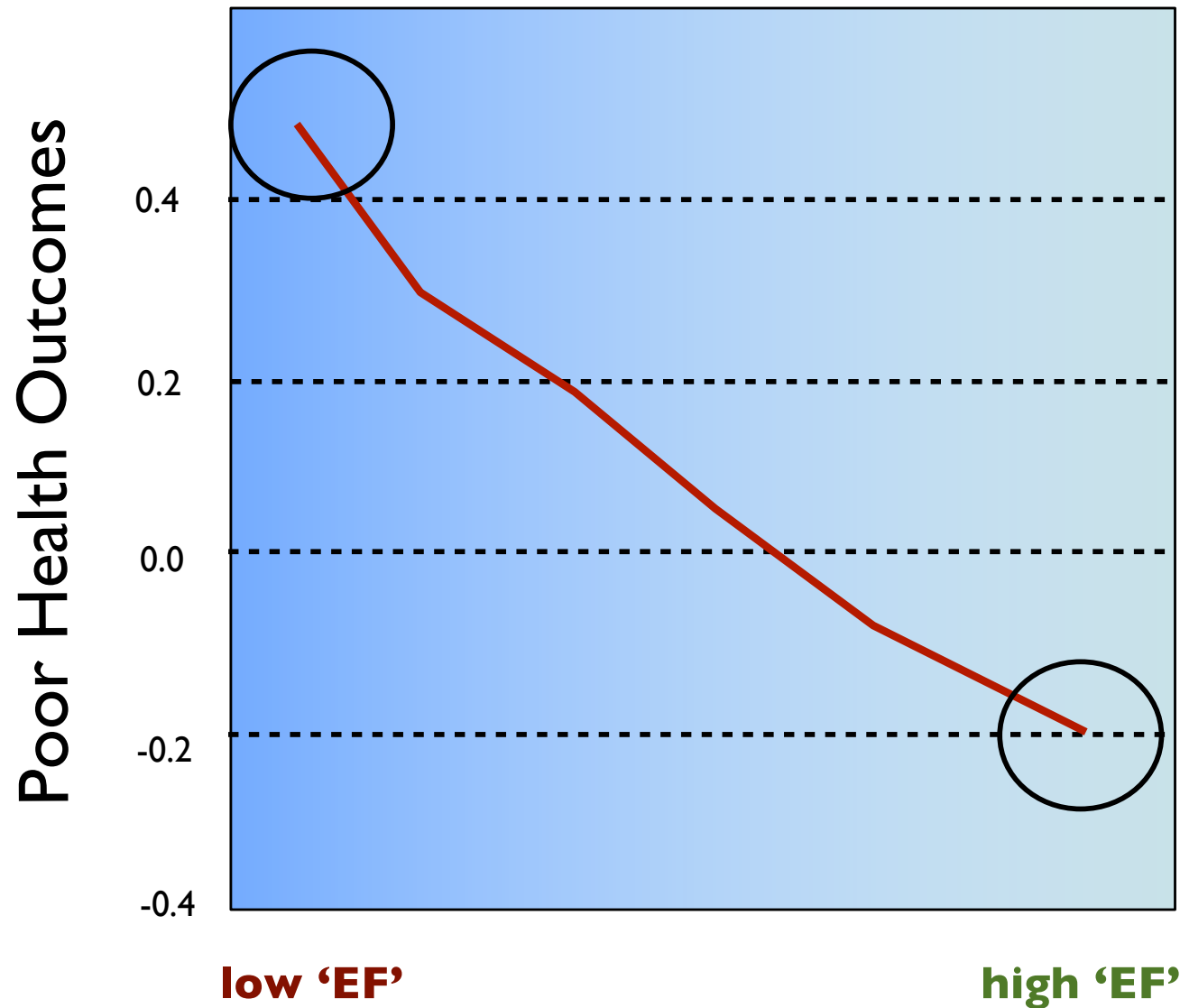
Low education achievement  
Alcohol dependence

Physical Illness  
CVD, Cancer, Obesity, Diabetes

Drug Use  
Incarceration

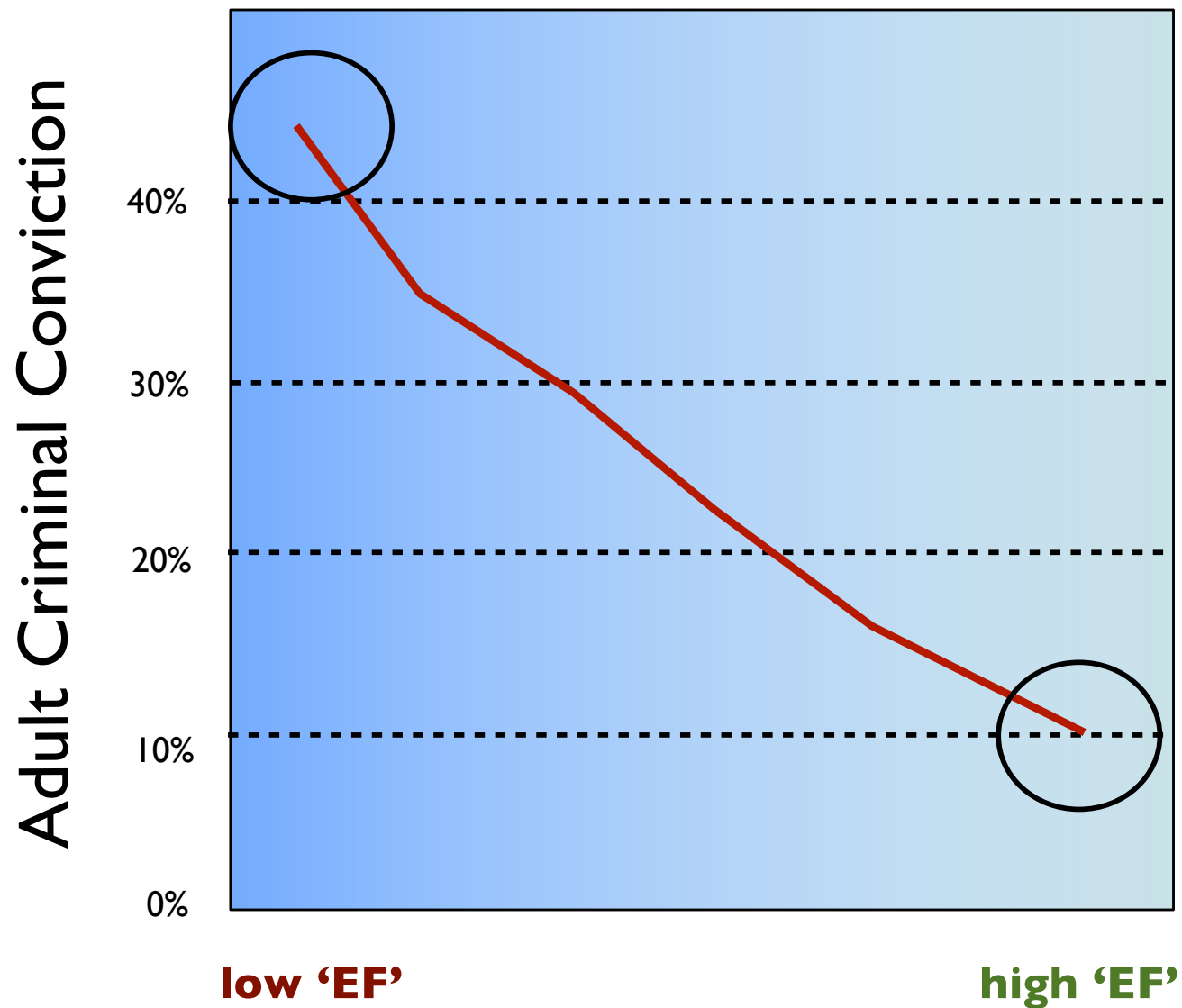
# Early Executive Function Disruption - Long Term Impact

## The Dunedin Study



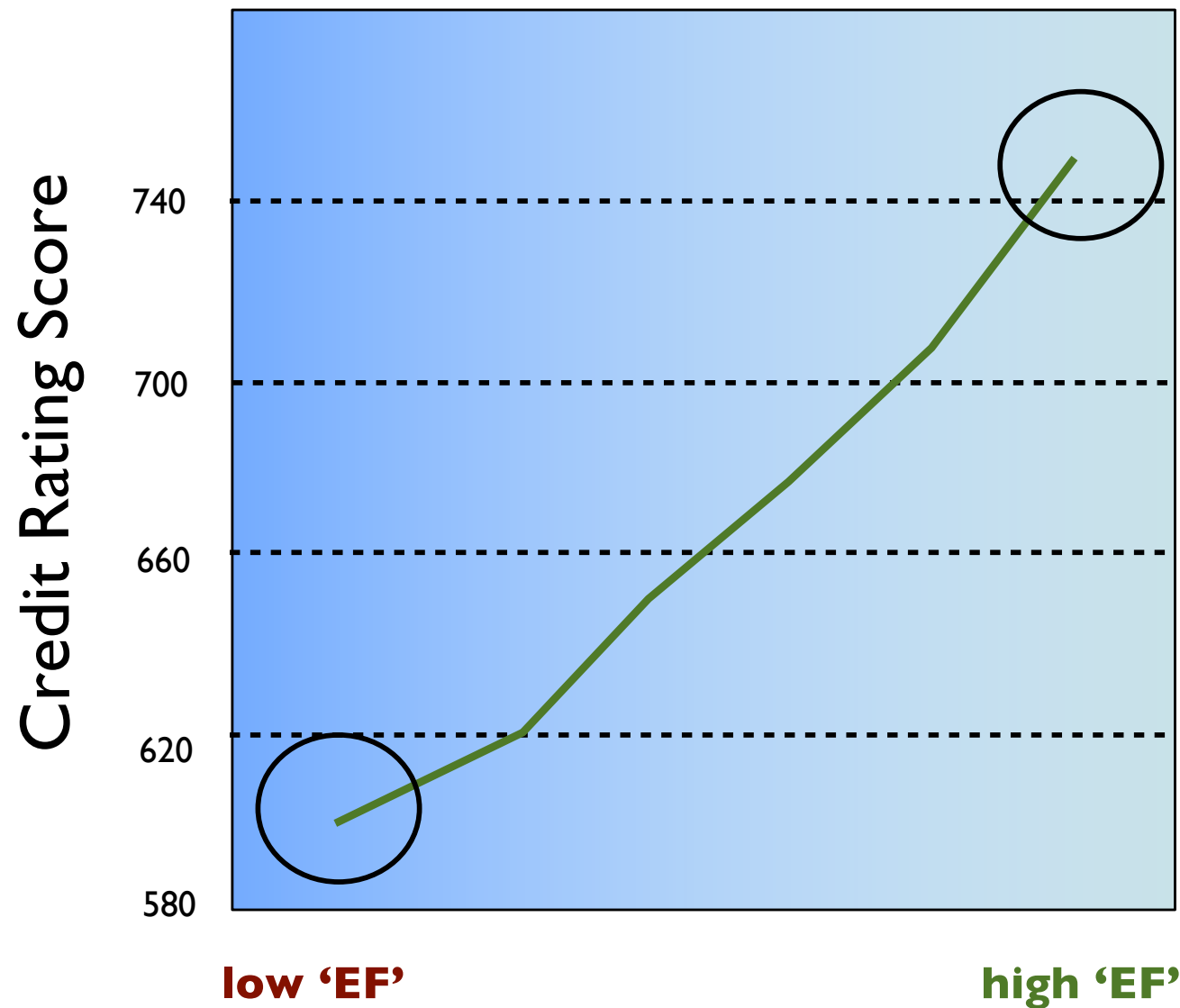
# Early Executive Function Disruption - Long Term Impact

## The Dunedin Study



# Early Executive Function Disruption - Long Term Impact

## The Dunedin Study



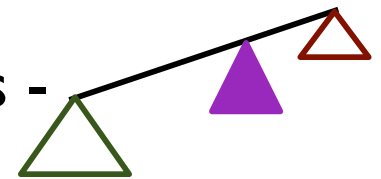
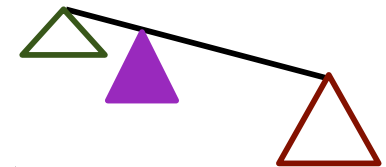
## The Dandelion and the Orchid Child



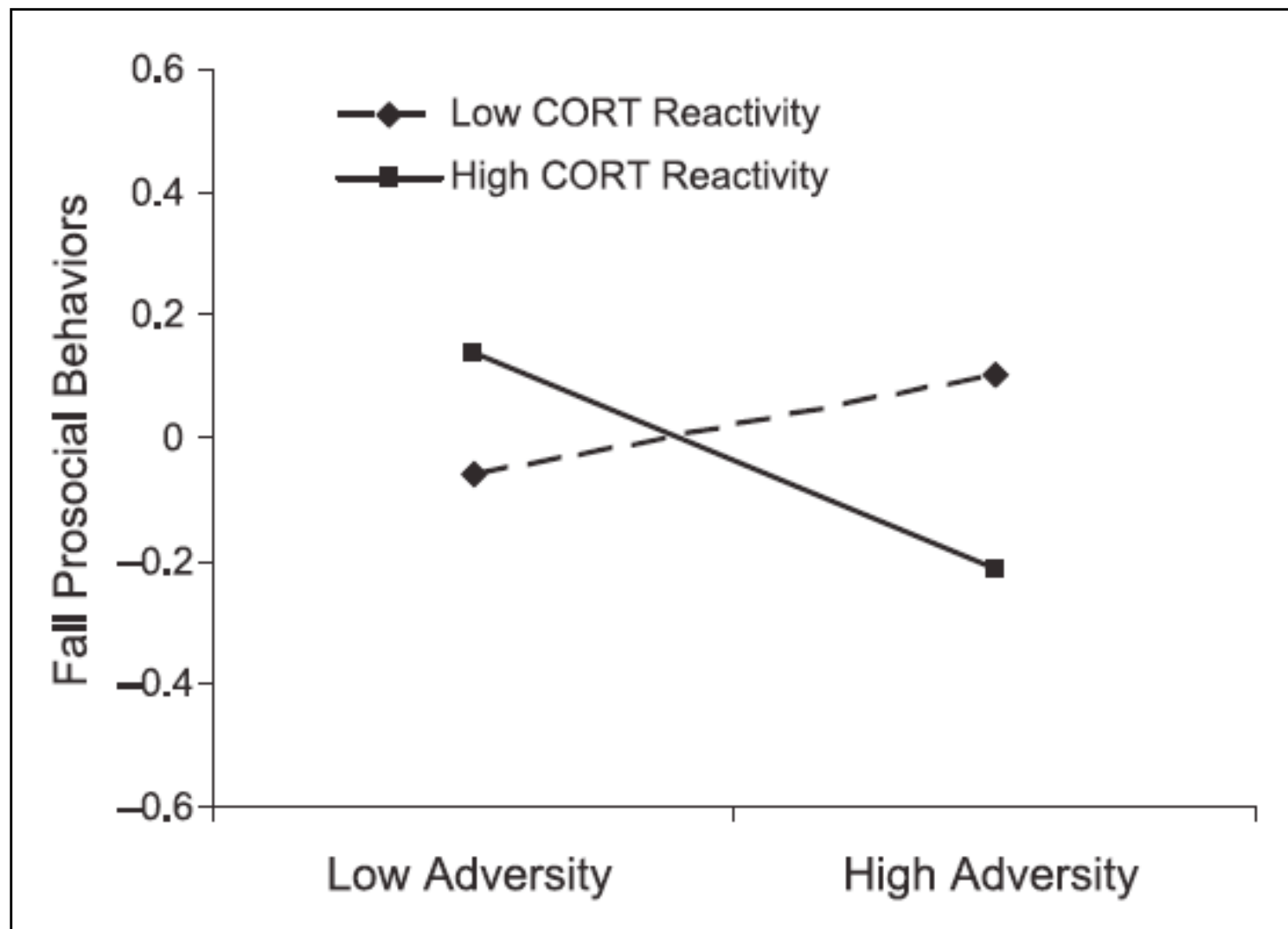
### The Orchid Child



- Context-dependent
  - e.g. high stress-reactive in highly adversity environments - poorer outcomes
  - e.g. high stress-reactive in low adversity environments - better outcomes



## Context Drives Behavior Differently in Children with Different Physiology





***"But I know someone who  
was ok after a traumatic  
childhood....."***

**Resilience – It is not about  
rugged individualism**

# Building Resilience is a Team Sport

What is Resilience

<https://developingchild.harvard.edu/resources/inbrief-what-is-resilience/>

**REMINDER:** Part of Executive  
Function Skill Development Is  
Building Capacity for Emotional  
Regulation and Sound Early Mental  
Health.....

# Executive Function Interventions

## The Recipe of Programs that Work (4-12 yr old in clinical studies)

- **Computerized training (CogMed) for working memory**
- **Reasoning and speed training - domain-specific**
- **Aerobic exercise (high dose - 40-70 min daily)**
- **Martial arts (inhibitory control, mindfulness)**
- **Curricula (*Tools of the Mind* - planning, inhibitory control)**

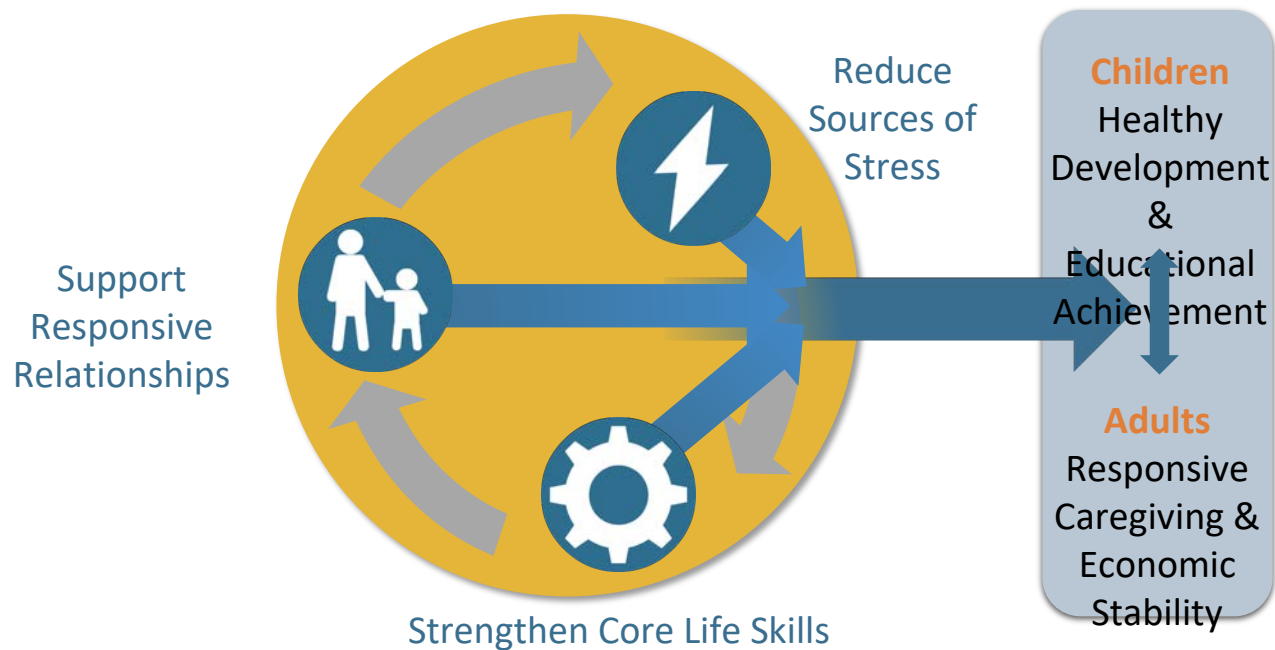
## **What early elements are most critical for building resilience?**

### **Executive Function:**

- **Mental Flexibility**
- **Working memory**
- **Response inhibition & response selection**
- **Emotions (emotional suppression; reappraisal of the situation)**

When '*at risk*' is identified - What are the options?

# Building Resilience - Three Core Principles of Effective Early Childhood Programs





DECEMBER 09, 2020

# Roadmap for Resilience

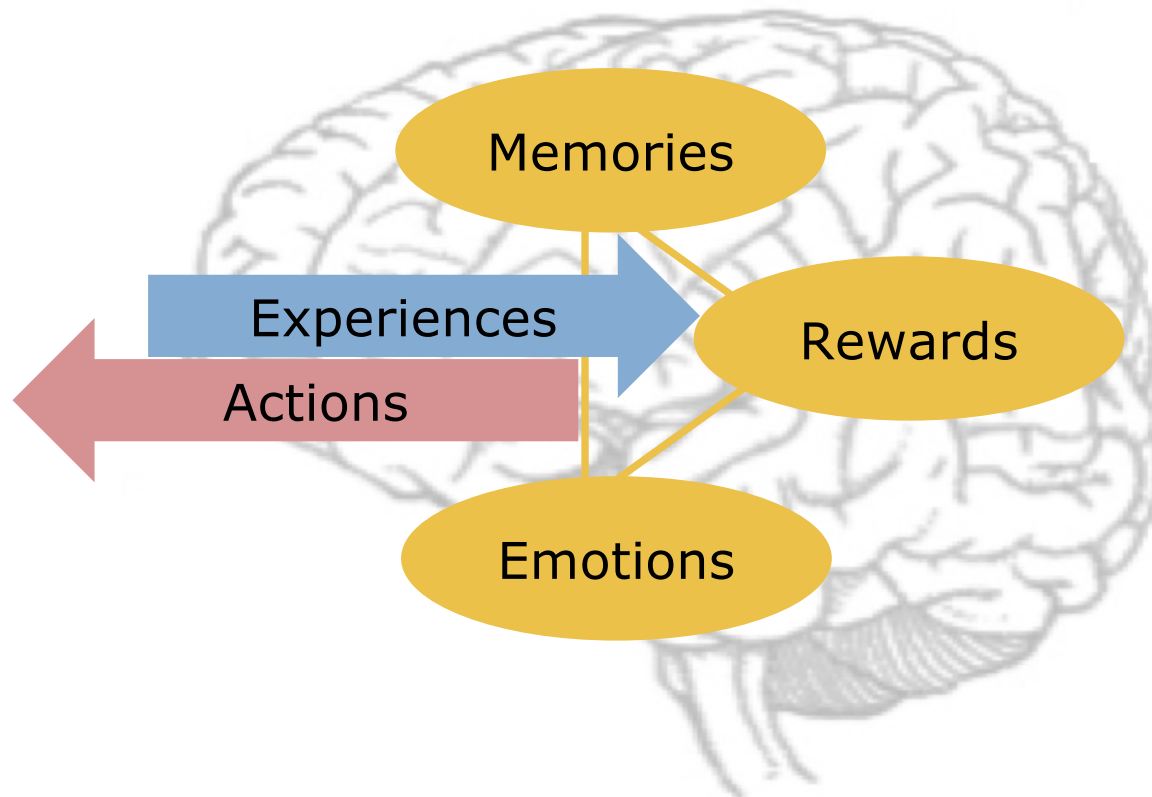
The California Surgeon General's Report on Adverse Childhood Experiences, Toxic Stress, and Health



## Routines and Predictability



# Predictable Experiences Link Rewards, Memories, and Experiences





# HealthySteps Evidence Summary

HealthySteps is supported by a strong evidence base, including a 15-site national evaluation and several more recent site-level evaluations. For more information on key outcomes, please visit our website: <https://www.healthysteps.org/the-evidence>

## Child Health & Development

- Children were more likely to receive a well-child visit on time<sup>1, 2, 3, 4</sup>
- Children were more likely to receive vaccinations on time<sup>1, 3, 4</sup> and 1.4x more likely to be up-to-date on vaccinations by age 2<sup>1, 2</sup>
- Children were 8x more likely to receive a developmental assessment at 30–33 months<sup>1</sup>
- Continuity of care was better for both total visits and well-child visits<sup>4, 5</sup>
- Children whose mothers reported childhood trauma scored better on a social-emotional screening after receiving HealthySteps than comparable children who did not receive the program<sup>6</sup>
- One longitudinal analysis indicated that HealthySteps participation was associated with greater security of attachment and fewer child behavior problems<sup>7</sup>

## Connections to Resources

- Children were 1.4x more likely to have nonmedical referrals, including for behavior, speech, hearing, child abuse or neglect, and early intervention<sup>1</sup>
- Families were 4x more likely to receive information on community resources<sup>1</sup>
- Parents received more services<sup>3, 4, 8</sup> and had longer clinic visits<sup>4</sup>

## Breastfeeding & Early Nutrition

- Mothers reported feeling more supported to breastfeed<sup>9</sup> and breastfed longer than the minimum 6 months recommended by the American Academy of Pediatrics<sup>2</sup>
- Mothers were 22% less likely to give newborns water and 16% less likely to introduce cereal by 2–4 months old (too young for solid foods)<sup>1</sup>
- Children identified as being “at risk” of social-emotional challenges demonstrated lower rates of obesity at age 5 than comparable children who did not receive HealthySteps<sup>10</sup>

## Child Safety

- Children were 23% less likely to visit the emergency room for injuries in a 1-year period<sup>1</sup>
- Mothers were 24% less likely to place newborns on their stomachs to sleep, reducing SIDS risk<sup>1</sup>
- Parents scored higher on an injury control index, and families were more likely to use stair gates and have access to the local poison control center’s telephone number<sup>2, 9</sup>



# Executive Function Interventions

## Some Programs that Work

Diamond and Lee, *Science* 2011; Hillman et al *Pediatrics* 2014; Krafft et al *Obesity* 2014; Ishihara et al *Neuroscience and Biobehavioral Reviews* 2021)

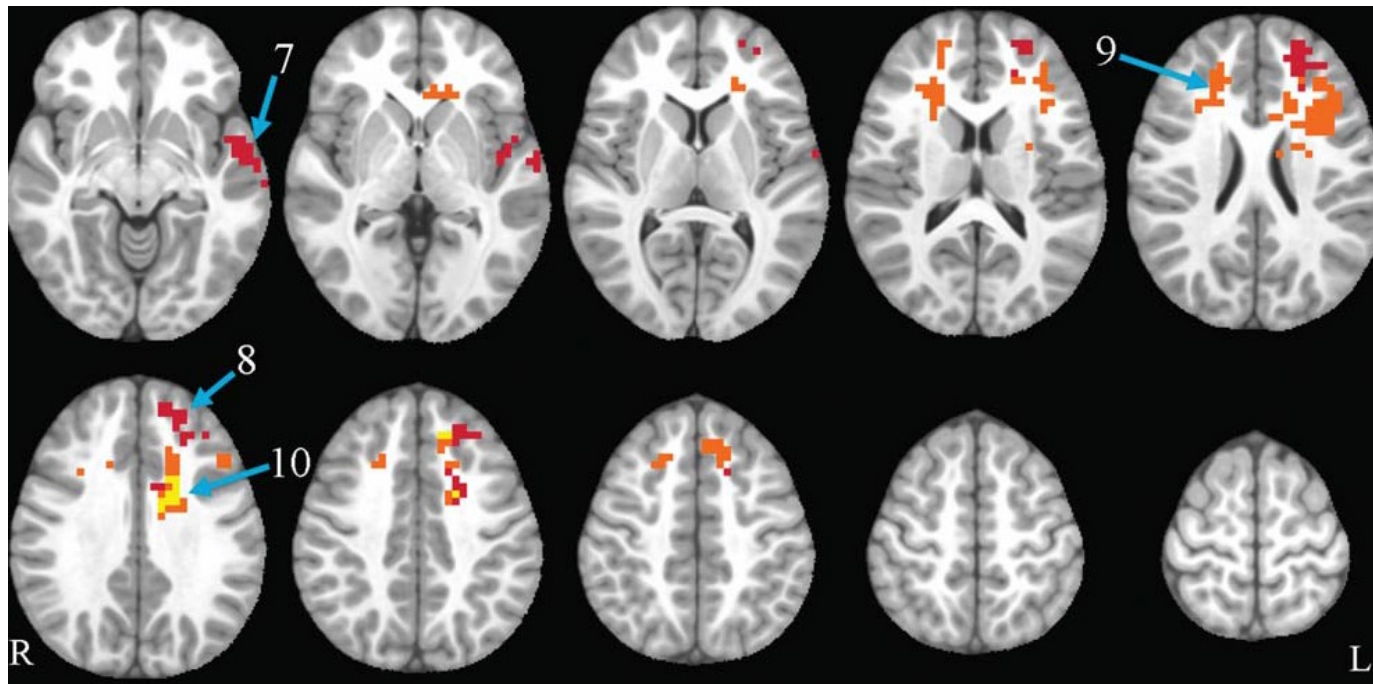
- Reasoning and speed training - domain-specific
- Aerobic exercise (FITKids)
- Curricula (*Tools of the Mind* - planning, inhibitory control)



## Brain Activation Changes - 8-Month Exercise Program

### 8-month Exercise Program Targeting At-Risk Children (8-11yrs)

40 min after-school aerobic exercise vs. sedentary activities



Krafft et al 2014

- Changes in brain activation patterns in fMRI
- Improved Attention & Working Memory
- Improved Inhibitory Control

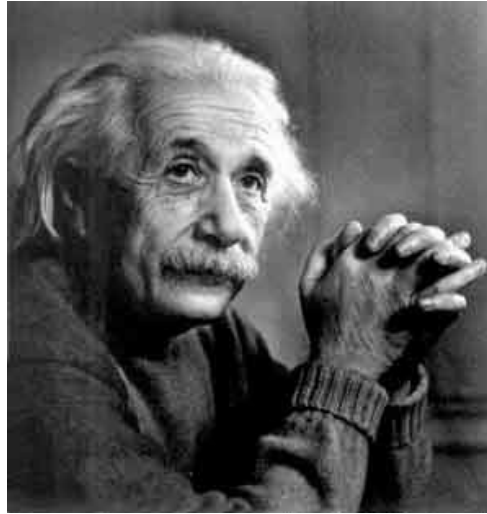
# How do we scale early identification of risk or resilience?

JAMA Pediatrics | [Original Investigation](#) Published online January 25, 2021.

## Population vs Individual Prediction of Poor Health From Results of Adverse Childhood Experiences Screening

Jessie R. Baldwin, PhD; Avshalom Caspi, PhD; Alan J. Meehan, PhD; Antony Ambler, MSc; Louise Arseneault, PhD; Helen L. Fisher, PhD; HonaLee Harrington, BA; Timothy Matthews, PhD; Candice L. Odgers, PhD; Richie Poulton, PhD; Sandhya Ramrakha, PhD; Terrie E. Moffitt, PhD; Andrea Danese, MD, PhD

**CONCLUSIONS AND RELEVANCE** This study suggests that, although ACE scores can forecast mean group differences in health, they have poor accuracy in predicting an individual's risk of later health problems. Therefore, targeting interventions based on ACE screening is likely to be ineffective in preventing poor health outcomes.



*"If you always do what you always did, you will always get what you always got."*

- Discovery of scalable measures
- Educating students and health professionals about why E
- Training a new generation of practitioners



# California Institute for Advancement of Precision Medicine -ACES Project



## Family First Research Study

Study Information for Clinical Practice Recruitment Partners

### Goals of study:

- 1) Improve screening for infants at greatest risk for ACEs (Adverse Childhood Experiences) and early life stress (ELS) by combining precision medicine, measures of infant development, and questionnaires
- 2) Better understand infant-mother well-being and stress-related health risk
- 3) Develop novel scalable measures to assess disruptions in metabolic health, including mitochondrial allostatic load (MAL)

**Target population:** We are recruiting healthy biological mother-infant dyads. Infants must be born between 32-42 weeks gestation, and under 150 days at the time of recruitment. Mothers must be 18 years or older, and English or Spanish speaking. Basic exclusionary criteria: Major metabolic, syndromic, or neurological disorders or a NICU stay > 7 days.

**Where the research visit takes place:** At Children's Hospital Los Angeles (CHLA), in the Levitt Neurodevelopment Laboratory at The Saban Research Institute



### Study Visit Activities

There are 2 compensated visits to CHLA when the infant is 6 and 12 months old. Each study visit takes 1.5 - 2 hours, and consists of:

#### Questionnaires

- Demographics and Medical History
- Family Routines
- Social Support
- Recent Life Events (RLEQ)
- Pediatric ACEs screener (PEARLS)
- Depression (PHQ-9)
- Resiliency (CD-RISC)

#### Biosamples

- Buccal swab from mother and infant
- Optional blood sample from mother
- Optional urine sample from infant



If you have any questions, please contact us at: [FamilyFirst@chla.usc.edu](mailto:FamilyFirst@chla.usc.edu) or (323)364-2536

To refer interested families, please go to: <https://redcap.link/FamilyFirstReferrals>



## Estudio de Familia Primero

Este estudio es diseñado para entender mejor las experiencias de nuevas madres y sus bebés durante el primer año de vida.

### ¿Quién es elegible?

Mujeres postpartos quien:

- Tienen un bebé menor de 5 meses de edad
- Son mayores de 18 años
- Hablan inglés o español



### ¿Qué implica la participación?

El estudio de CIAPM (la Iniciativa de California en el avance de la medicina de precisión) Familia Primero consiste en 2 visitas compensadas (60-90 minutos) en Children's Hospital, Los Angeles (CHLA) cuando su bebé tiene:

- 6 meses
- 12 meses



Madres contestarán cuestionarios, jugarán con sus bebés brevemente, y serán pedidas a darnos una muestra de sangre opcional y una muestra de mejilla en cada visita. Las muestras podrían ser guardadas en un banco de muestras.



Bebés participarán en una breve evaluación del desarrollo basada en el juego, y mirarán una serie de videos cortos mientras nuestro equipo de investigación rastrea donde están mirando sus ojos (rastreo de ojo).



Se colocará una bolsa pequeña adentro del pañal de su bebe para recolectar una muestra de orina opcional. También se pasará un pequeño hisopo de algodón por la mejilla del bebé para recolectar una muestra de mejilla. Las muestras podrían ser guardadas en un banco de muestras.

### ¿Por qué participar?

Nos gustaría usar la información de este estudio para mejorar visitas de bienestar del bebé y los programas de desarrollo para la primera infancia que mejor satisfagan las necesidades únicas de estas madres y bebés. Usted será compensada por su tiempo. Nosotros cubriremos los costos de estacionamiento o los costos de transportación de viaje compartido desde y hacia la clinica de investigación. Usted no debería anticipar beneficios directos a usted o a su hijo/a como resultado de su participación en esta investigación.

¡Escanee el código QR



para aprender más!

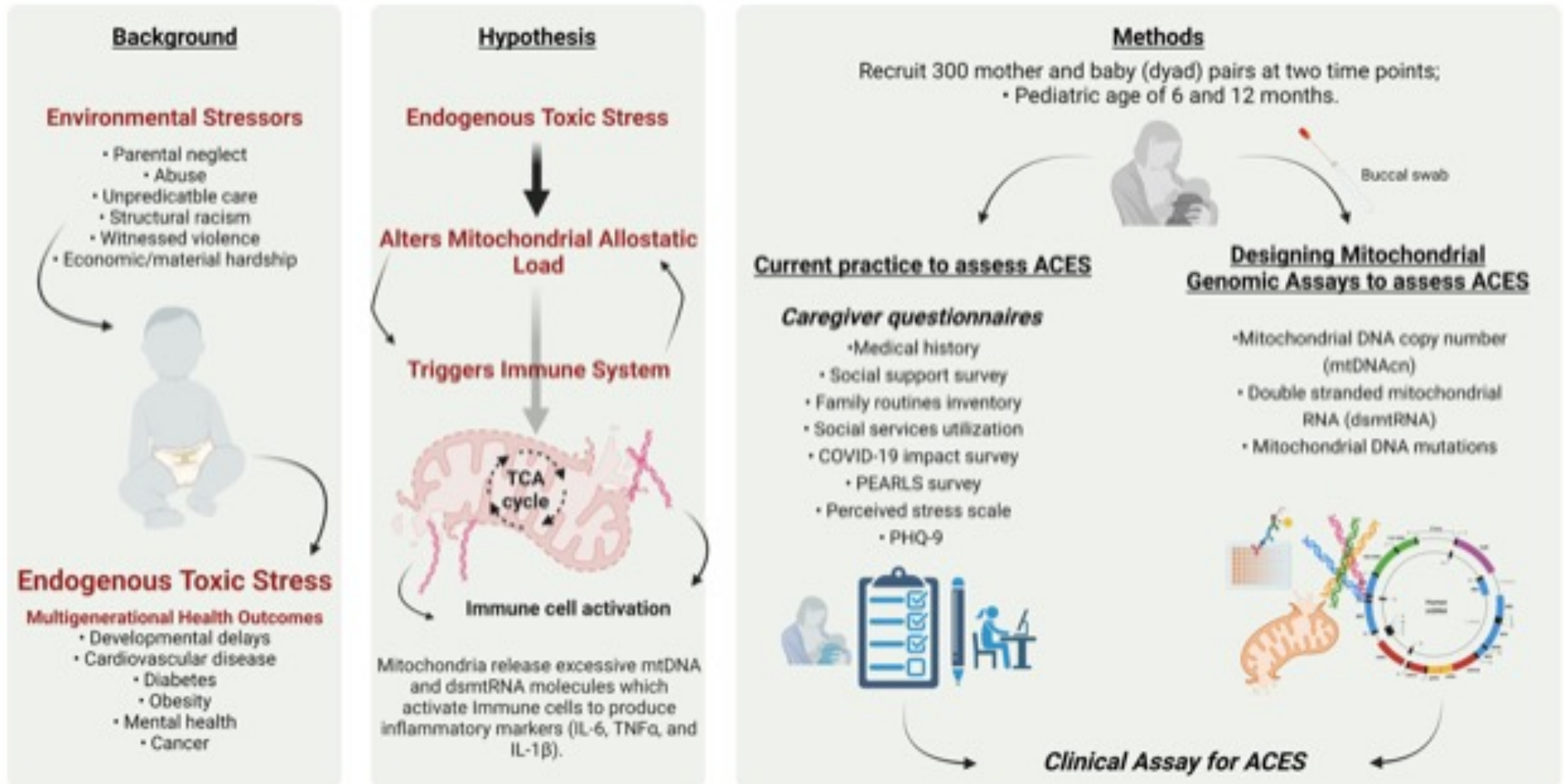
Para más información, contáctenos:

323-364-2536 | [familyfirst@chla.usc.edu](mailto:familyfirst@chla.usc.edu)

Este proyecto está siendo llevado a cabo por el Dr. Pat Levitt y es apoyado por la iniciativa de California en el avance de la medicina de precisión.

## Adverse Childhood Experiences Study (ACES)

*Developing a scalable clinical assay for mitochondrial biomarkers of toxic stress*



# Team, Recruitment & Community Partnerships



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**Liam North**  
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**Dianna Guerrero Jimenez**  
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**Alex Judkins, MD**  
Co-Investigator



**Xiaowu Gai, PhD**  
Co-Investigator



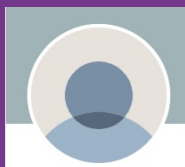
**Suzanne Roberts, MD**  
Co-Investigator



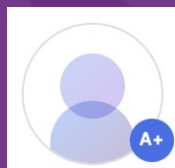
**Alma Gharib, PhD**  
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**Sahana Kalburgi, PhD**  
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Senior Bioinformatic  
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**Suchi Patel**  
Clinical Lab Tech II



**Gigi Ostrow**  
Translational  
Genomics Manager



**Jenny Kingsley, MD**  
Co-Investigator



**Marian Williams, PhD**  
Co-Investigator



**Hannah Perez, PsyD**  
Infant MH Staff

## Community Partners

## Recruitment Partners

**KARSH CENTER**  
at WILSHIRE BOULEVARD TEMPLE



Para los niños



for the childRen



**St Anne's**  
FAMILY SERVICES  
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PERMANENTE®**



# Thank You!

[plevitt@chla.usc.edu](mailto:plevitt@chla.usc.edu)

<https://www.chla.org/research/levitt-laboratory>

<http://www.developingchild.harvard.edu>