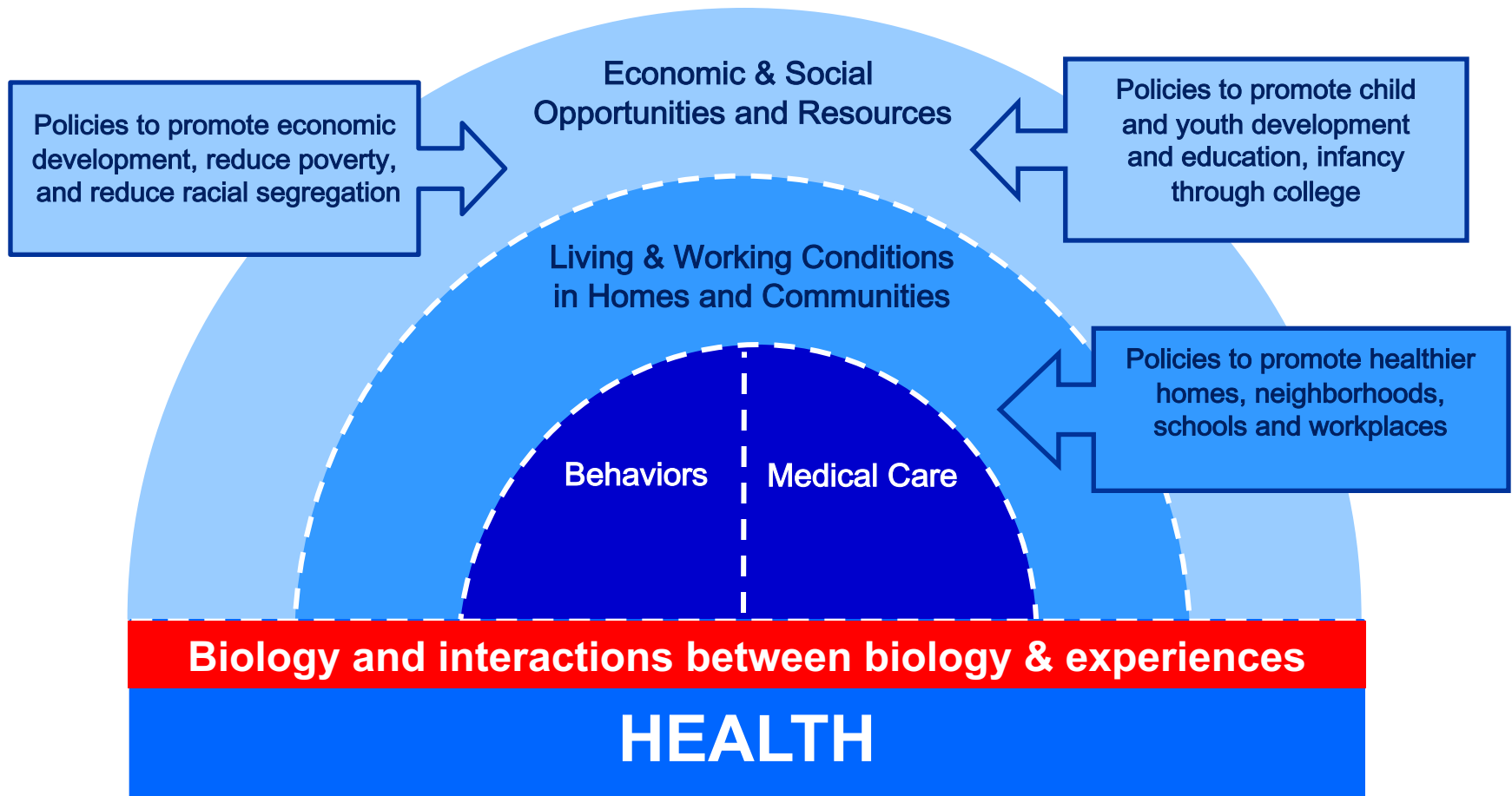


EPI222:

Lecture 4 Biological Determinants, Mediators and Mechanisms

Where are we in the class?



Biological Mechanisms

- Frameworks
- (Behaviors, including use of medical care)
- Epigenetics
- Stress mediated pathways
- Direct toxic exposures
- Major controversies or uncertainties
 - Lifecourse/sensitive periods
 - Qualitative interactions/dandelion vs orchid
 - Role of genetics

Biological Mechanisms

- **Frameworks**
 - Why care about the biology?
 - Embodiment
 - Pathways
 - Sensitive/critical periods
 - Where do genetics fit in?

Frameworks

- Many health disparities fall along lines that appear to be arbitrary social boundaries, e.g., high versus low education.
- Yet these lines correspond with huge differences in physical health.
- The mechanisms by which social experiences, things outside the body, get “under the skin” and become “embodied” is a controversial and rapidly developing field.
- This is not *just* about the biological correlates of differences in health and illness, but rather about the mechanisms via which something fundamentally social is transformed into something fundamentally physiologic.
- Similar mechanisms are assumed to apply to multiple dimensions of inequality: SES, race, sexual orientation, geography, but some mechanisms will be unique or especially relevant.

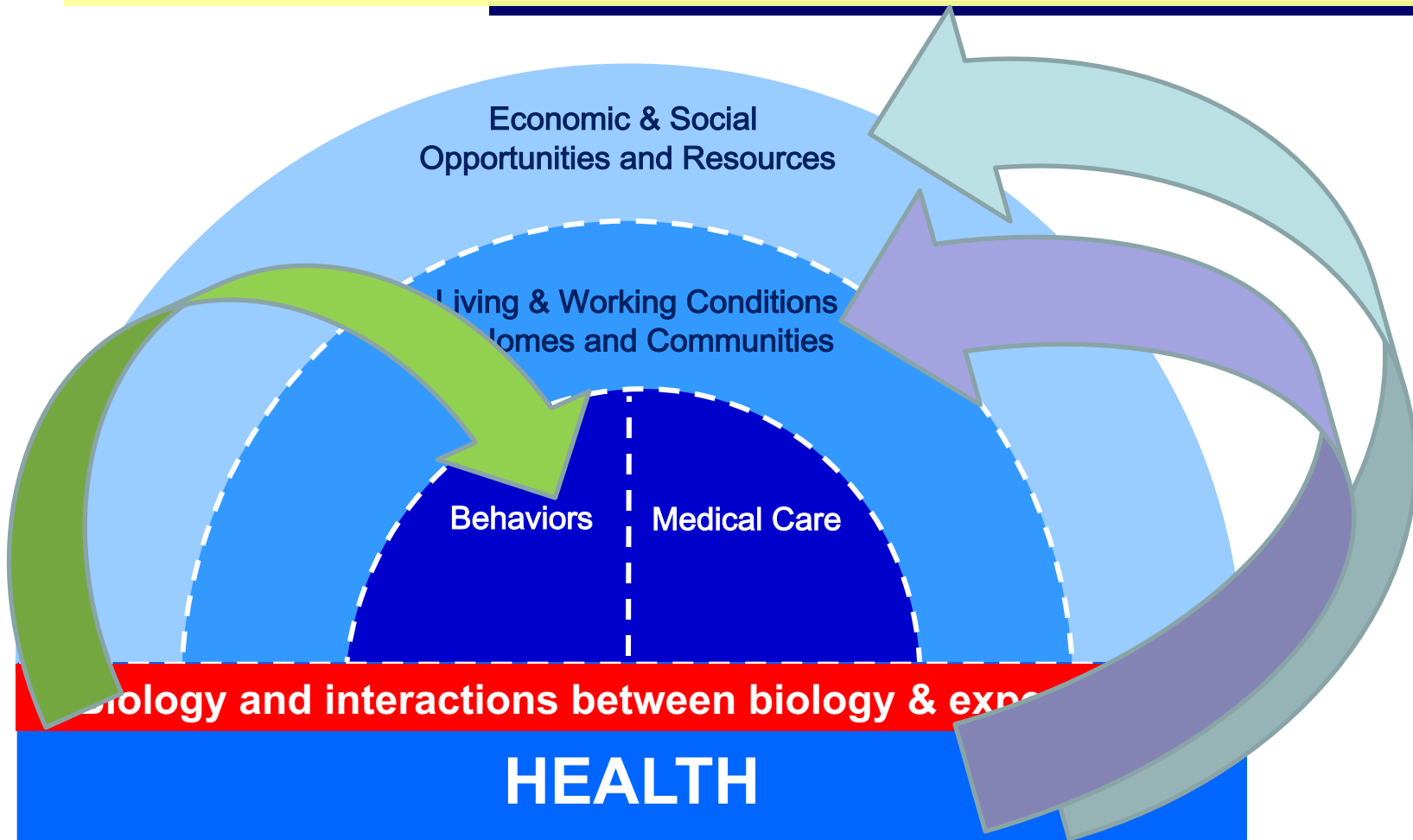
Why worry about the biological mechanism?

- Helps us design effective interventions to interrupt the pathway (not always necessary to understand biological mechanisms for this, but it's helpful)
- Evidence that associations are “causal” (because if not causal, there is no hope of effective interventions on this exposure)
- Motivating action: biologically grounded explanations often move decision makers more than statistical associations.

What do we mean by embodiment?

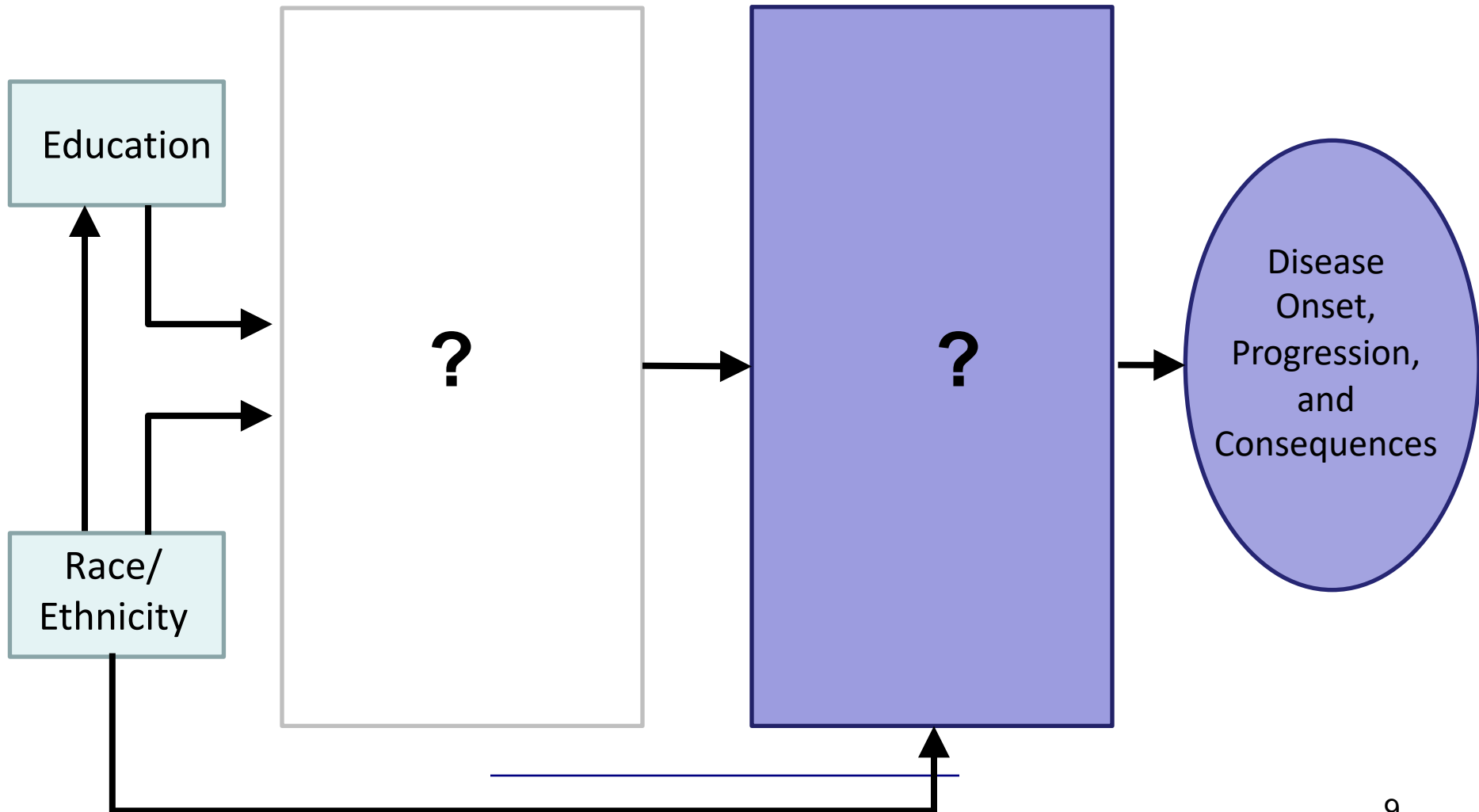
- “how we literally incorporate, biologically, the material and social world in which we live, from in utero to death...” Krieger 2005, JECH
- Many biological phenomena have social origins, so finding a biological basis for a health disparity does not imply that the root cause of that disparity is not social or could not be eliminated by a social or behavioral intervention.
 - Cultural norms regarding diet can lead to differences in average body fat, hypertension, and effectiveness of hypertension medications.
- Many social phenomena have biological origins, so a finding of a social pattern may have root causes in biological differences.
 - Birthweight → cognitive scores, educational attainment → earnings

Social → Biological → Social →

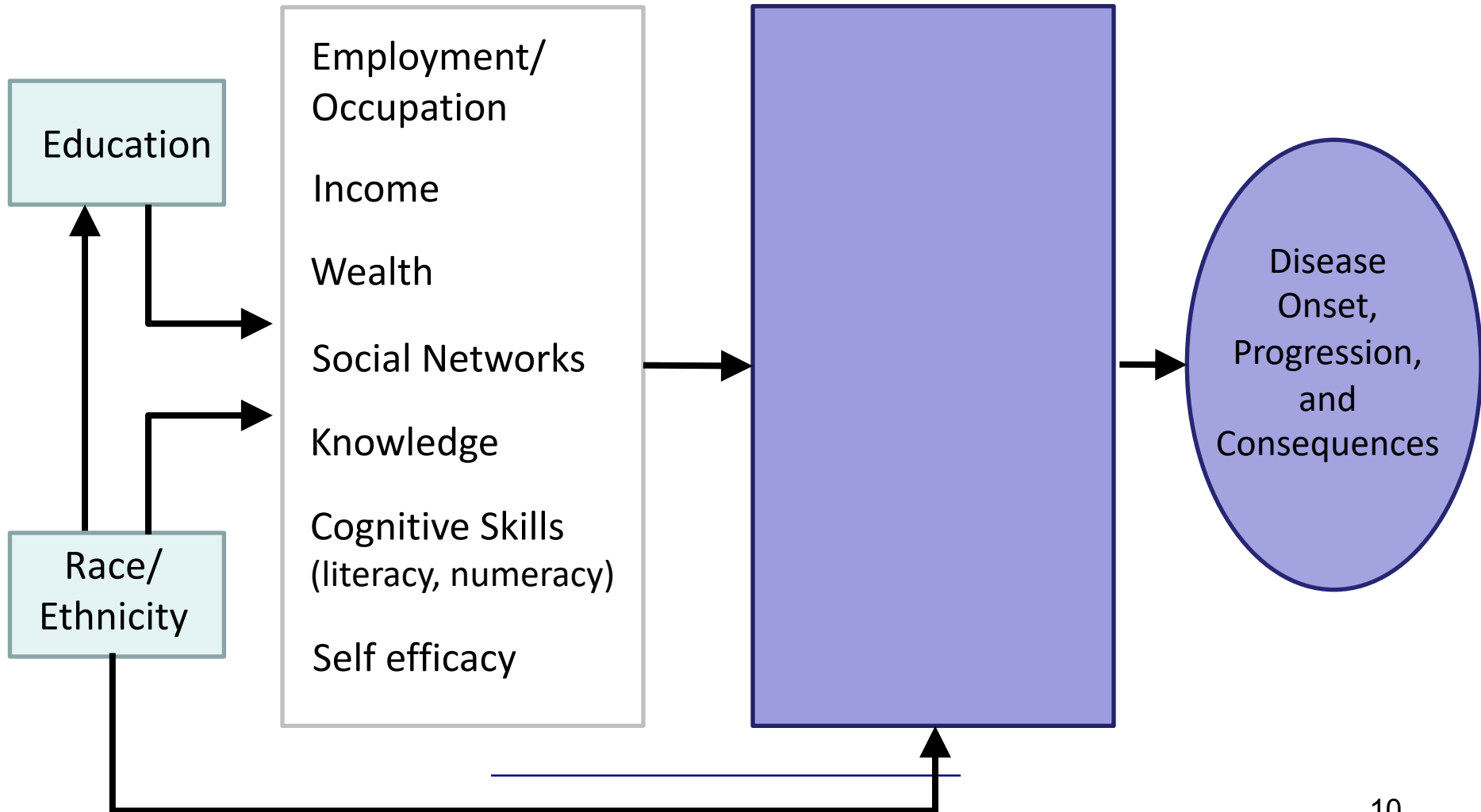


Social Factors and Health:

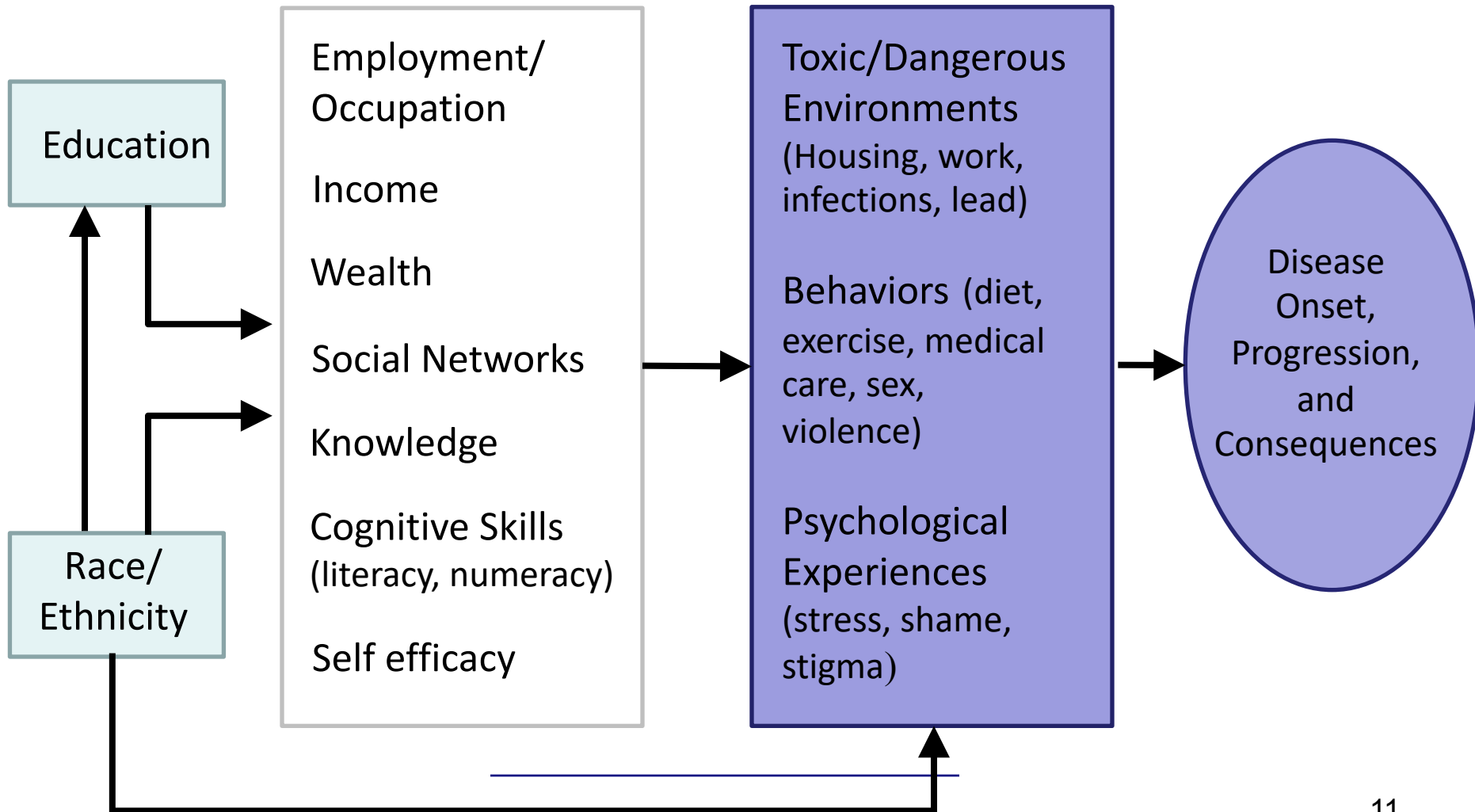
What pathways explain the link?



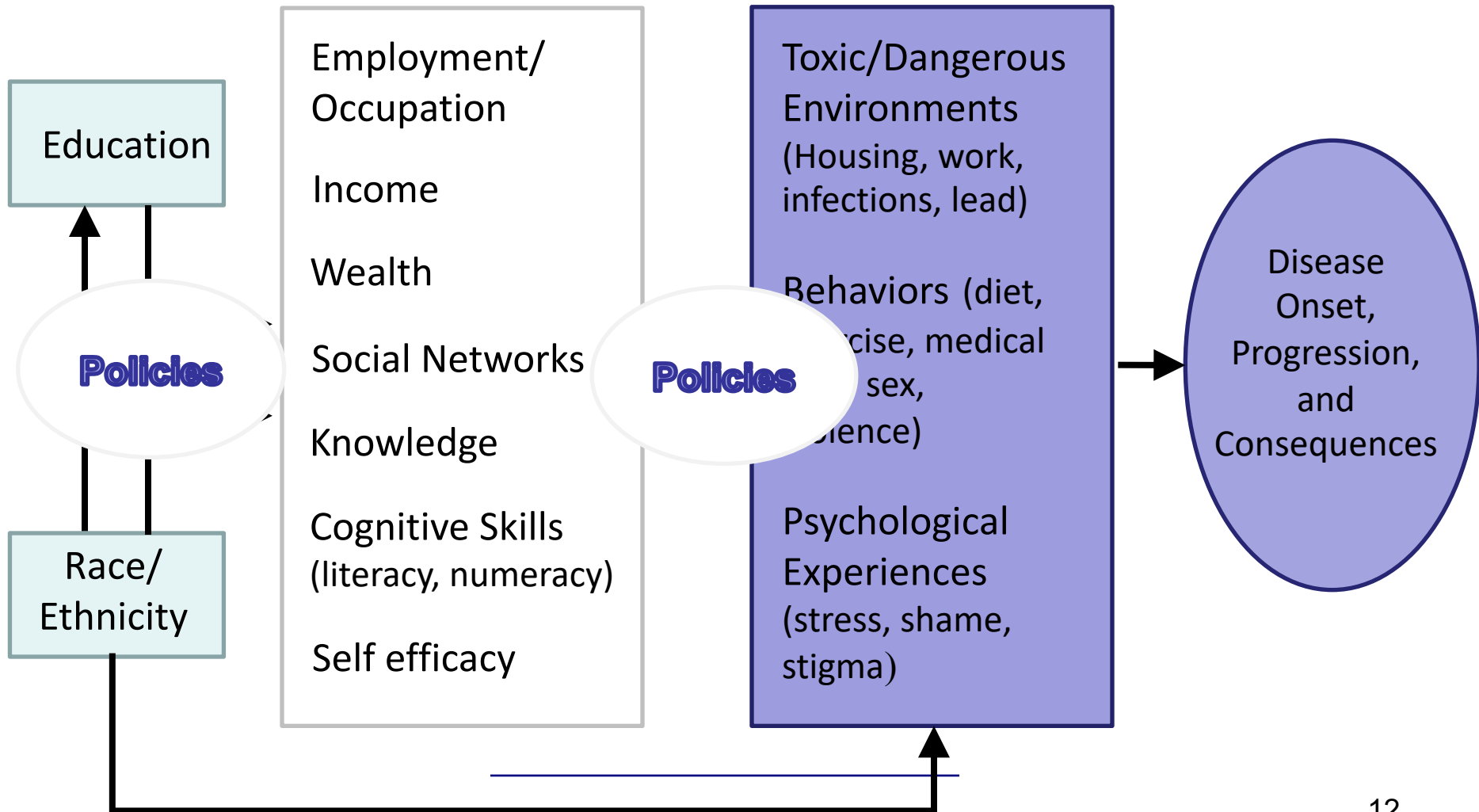
Social Factors and Health: Many socioeconomic, cognitive, and *network* resources



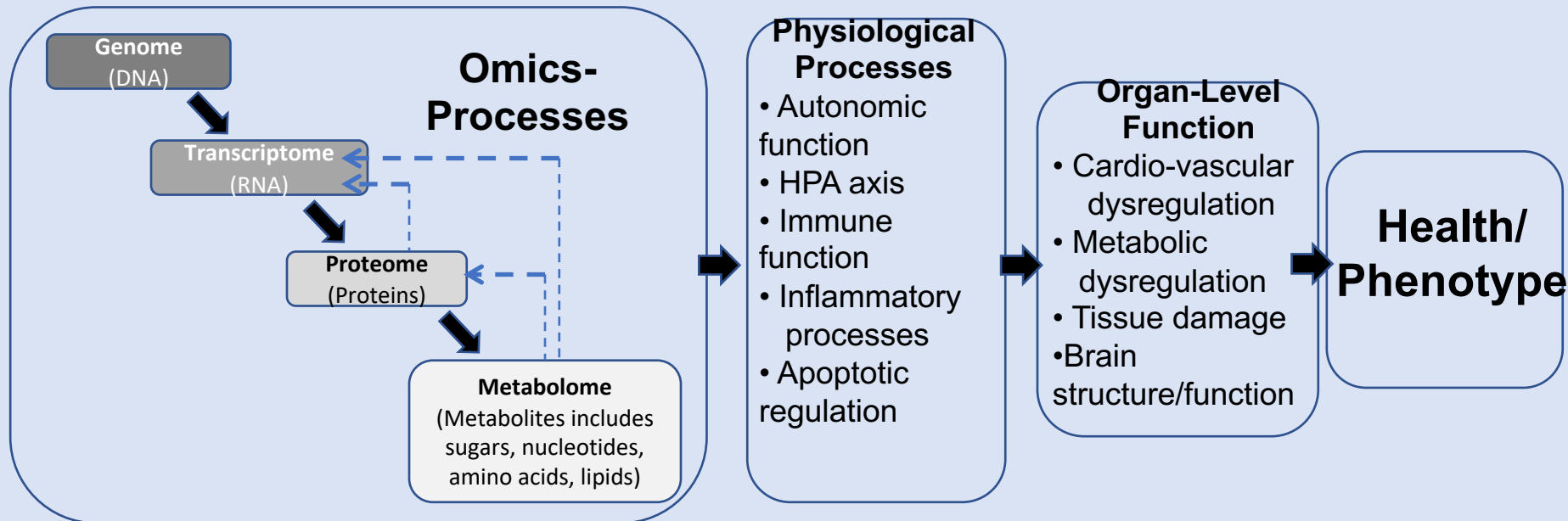
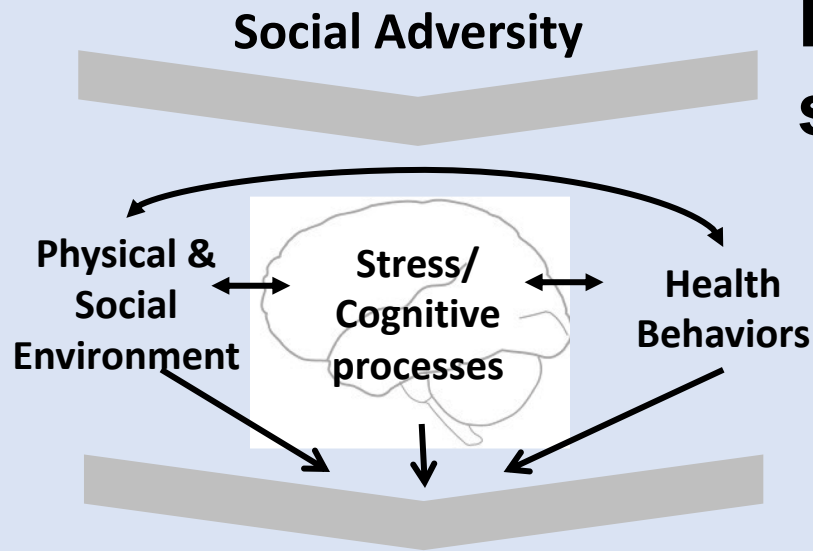
...which in turn influence material, behavioral, and psychological risk



Not a law of physics: These pathways can be weakened or broken.



Biological pathways linking social conditions & health

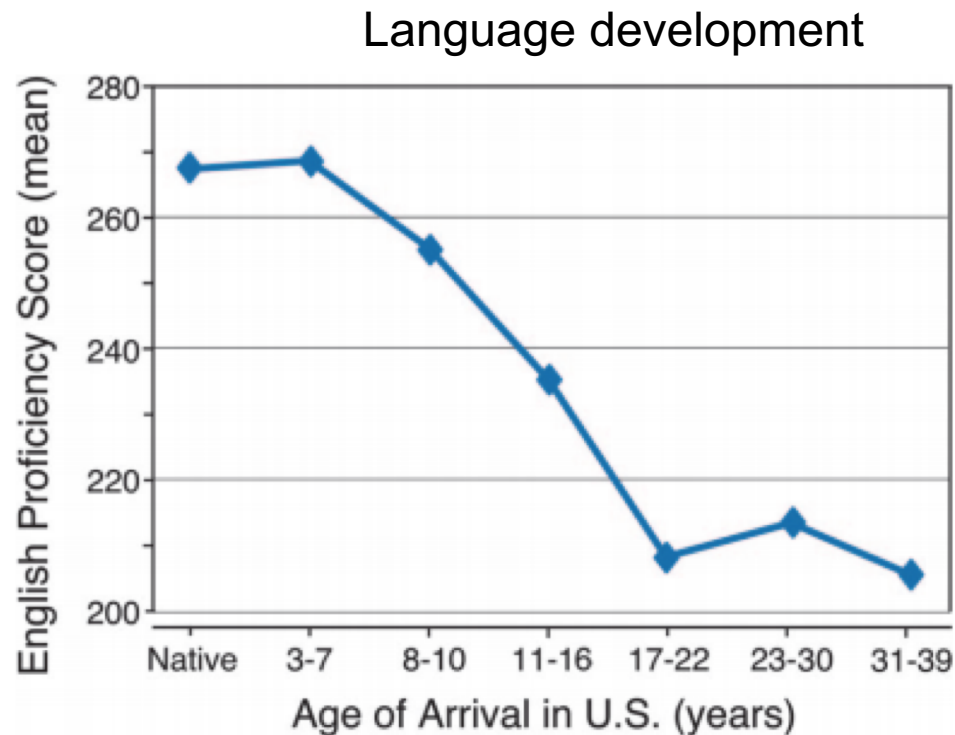


Key Idea in Biological Embedding: Sensitive Periods

- Arguments for special sensitivity during specific windows because of very rapid physical development or change
- Sensitive period: an age when the influence of the stimulus is disproportionate
- Critical period: an age when the influence of the stimulus is essential for normal development
- However, there is clearly a persistence of plasticity (capacity to change) throughout life and into old age
- Sensitive periods can be defined with respect to *physical* or *social* experiences.

Sensitive periods for language development

- There are windows during which the development of specific neural circuits and mediated behaviors are most plastic



Johnson and Newport, 1989

Periods and Physical Pathways for Special Sensitivity to Early Context

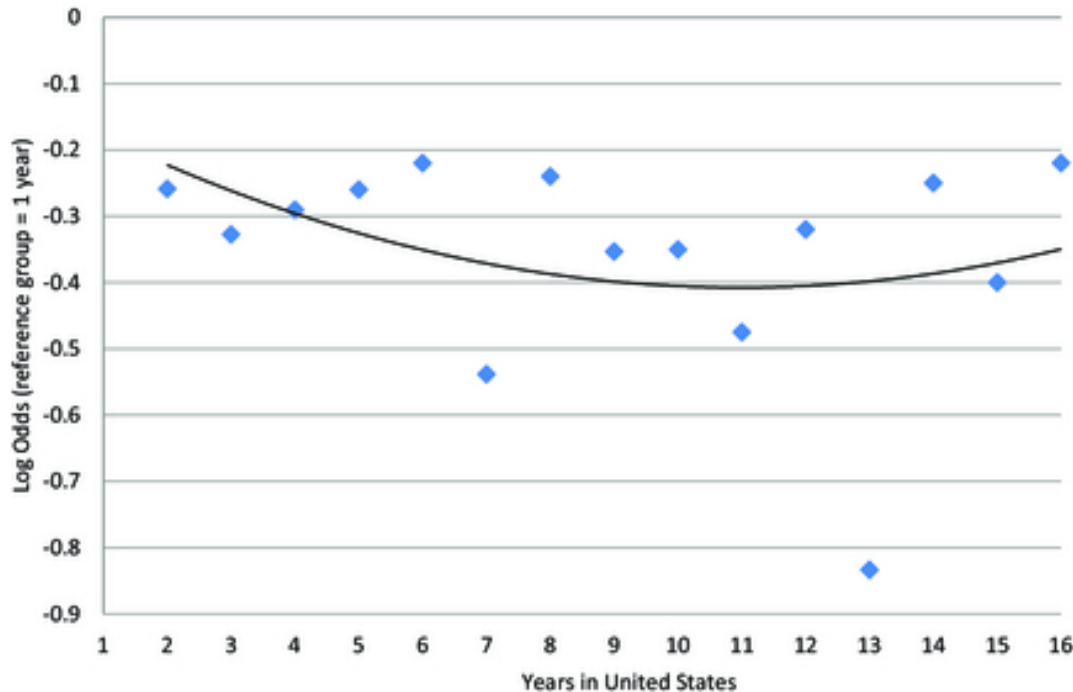
- Periods of rapid growth
- Periods of rapid brain development
- Periods of physiological changes (puberty)
- Enduring changes to gene expression patterns
- Exposures at specific developmental periods set in place behavioral patterns/addictions
- Hierarchy of skill development

Feedback Occurs Across the Lifecourse

- Social patterns create biological & physiological patterns.
- Physiological patterns create social patterns.
- Feedback occurs across the lifecourse, in ways that depend on both the biology and the social context.
 - Community norms influence whether an adolescent starts smoking.
 - Cigarette use is initiated in adolescence and is highly addictive,
 - Smoking reflects place of residence in adolescence
- Because smoking is such a powerful influence on health, this manifests in other outcomes, such as LBW

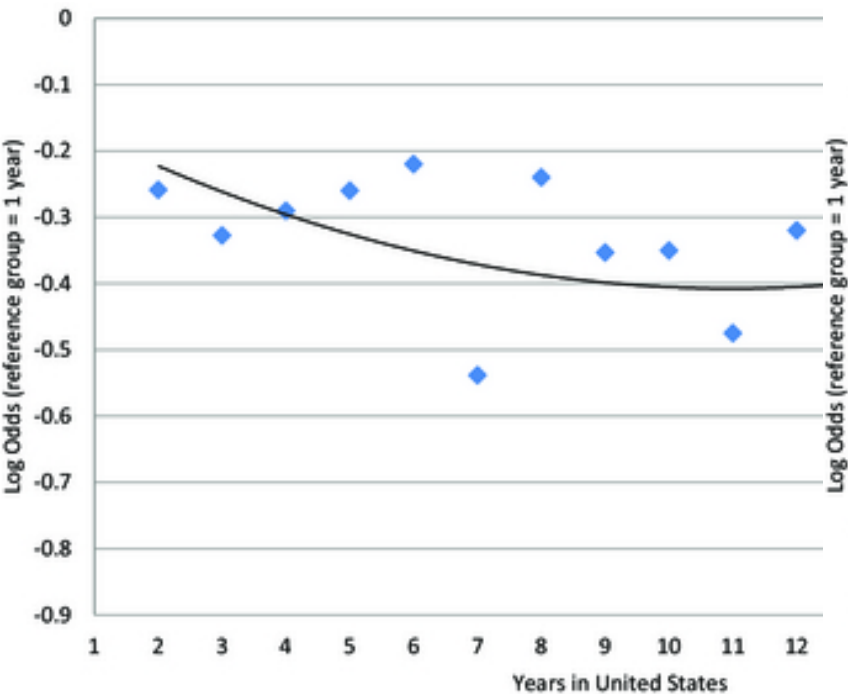
Feedback Occurs Across the Lifecourse

Duration of US Residence and Low Birthweight among Mothers Who Arrived at Ages 18+ Years

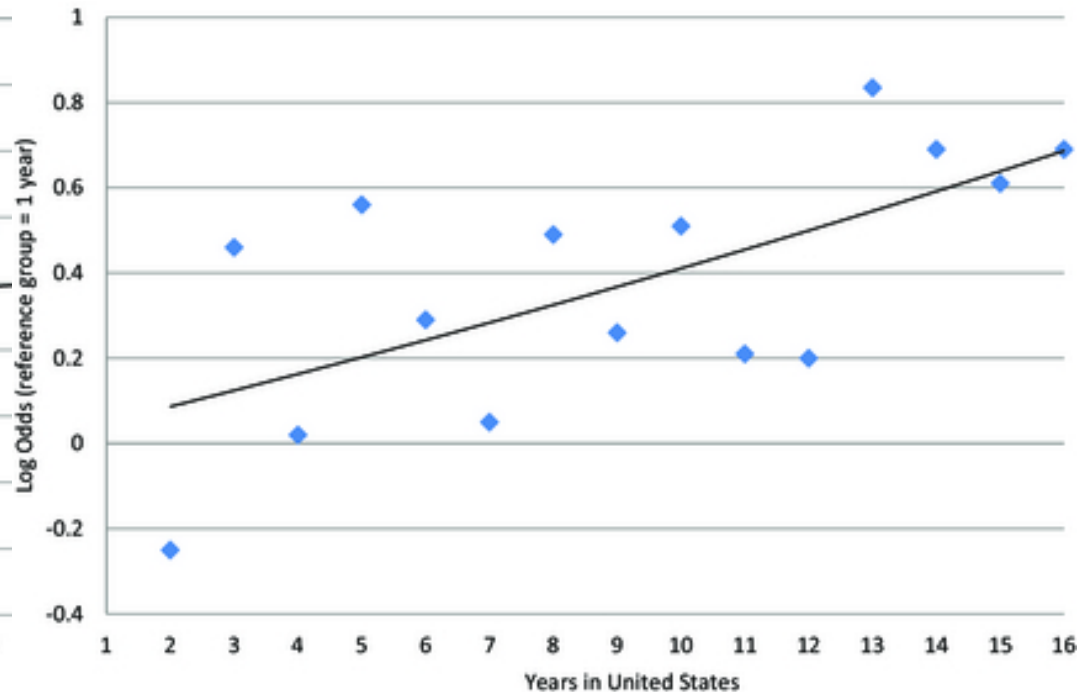


Feedback Occurs Across the Lifecourse

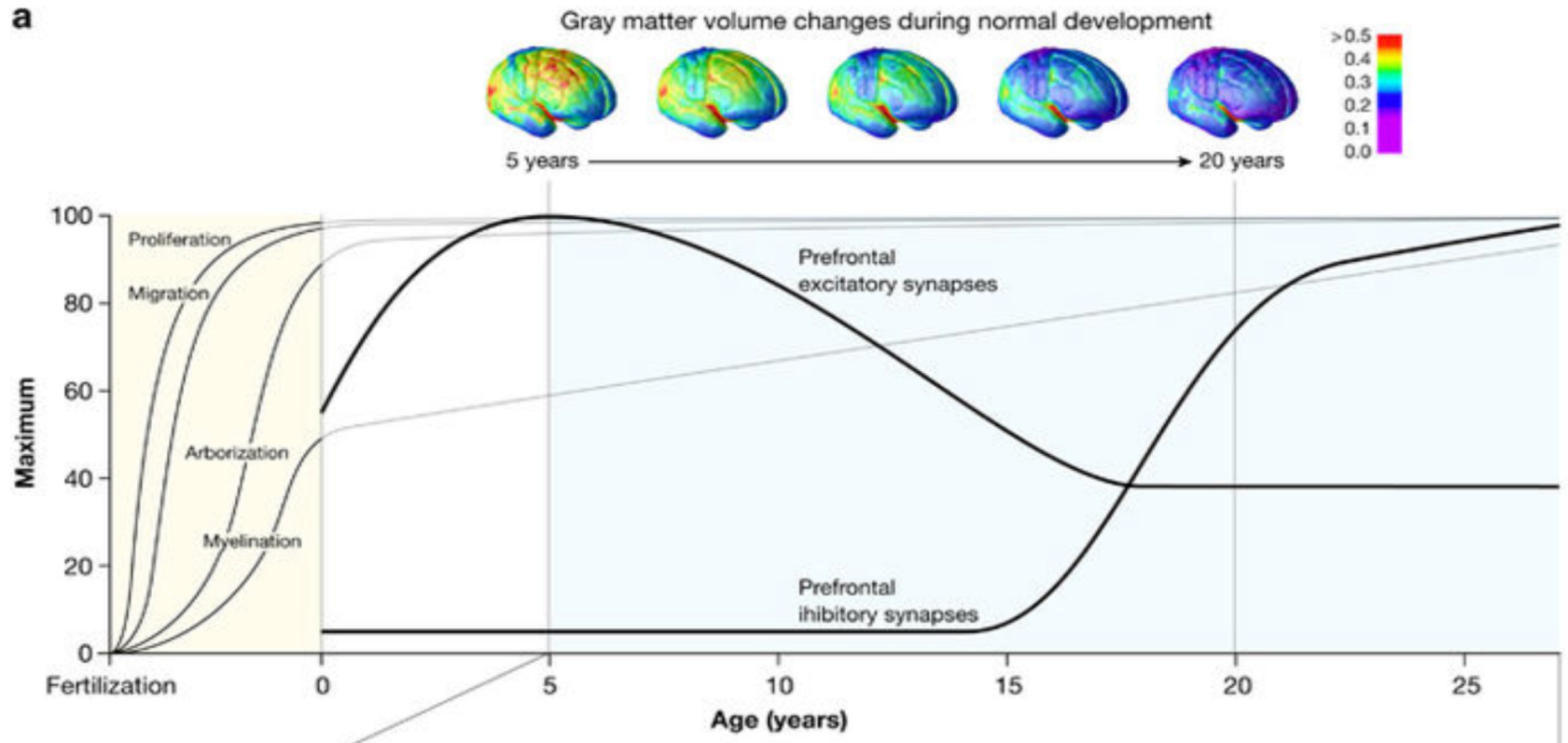
Duration of US Residence on Low Birthweight among Mothers Who Arrived at Ages 18+ Years



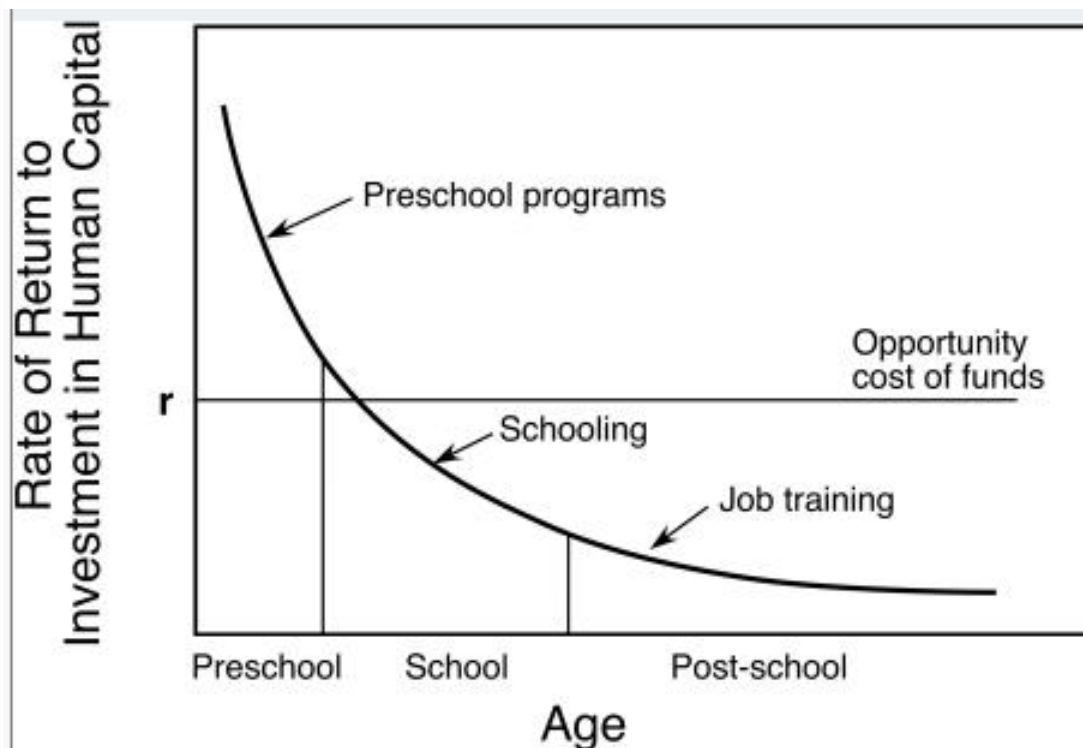
Duration of US Residence and Low Birthweight among Mothers Who Arrived at Ages <18 Years



Brain development: Sensitive periods



Sensitive periods: When do you get the biggest bang for your buck?



Sensitive periods influence when interventions might be most effective

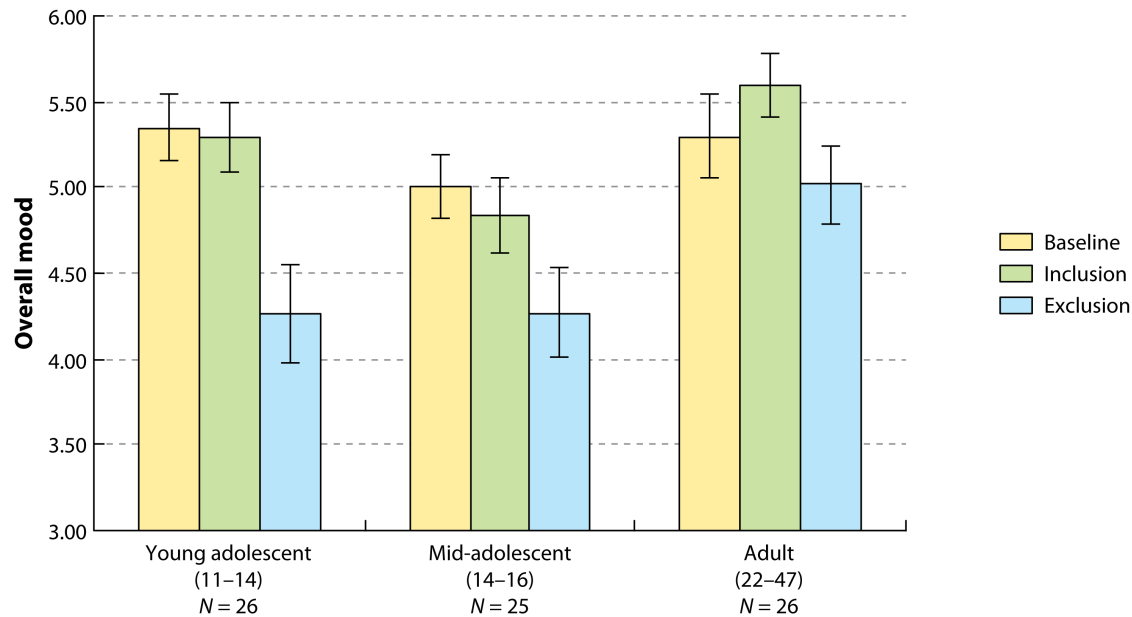
Rates of return to investment in human capital as function of age when the investment was initiated.

Reproduced from Knudson, data are from Cunha *et al.*

(Possible) Socially Defined Sensitive Periods

- Age when you meet and woo your spouse (who will influence your diet, behaviors, material conditions for decades to come)
- Departure from school/ Entry into the labor force.
- Departure of children from the household or from dependence
- Adolescence (social and biological)
- Retirement
- Bereavement

Adolescent mood in response to social exclusion



 Blakemore S-J, Mills KL. 2014.
Annu. Rev. Psychol. 65:187–207

Biological Mechanisms

- **Frameworks**
 - Why care about the biology?
 - Embodiment
 - Pathways
 - Sensitive/critical periods
 - Where do genetics fit in?

Where do genetics fit in?

- Gene *expression* probably central to explanations of disparities
- Genetic code cannot *mediate* all health disparities, because this would imply that race/SES/place influences genetic code
- Usually when people say genetics “mediate” health disparities, they mean “confound”: they hypothesize genes that cause people to be low SES also cause worse health, or that racial/ethnic groups have different frequencies of genetic polymorphisms linked to disease.
- Evidence for this is, for most complex disorders, largely speculative. Few identified genes have large effects and generally don’t account for large differences in disease.

Original Investigation

Association of Sickle Cell Trait With Chronic Kidney Disease and Albuminuria in African Americans

Rakhi P. Naik, MD, MHS; Vimal K. Derebail, MD; Morgan E. Grams, MD; Nora Franceschini, MD; Paul L. Auer, PhD; Gina M. Peloso, PhD; Bessie A. Young, MD; Guillaume Lettre, PhD; Carmen A. Peralta, MD; Ronit Katz, DPhil; Hyacinth I. Hyacinth, MD; Rakale C. Quarells, PhD; Megan L. Grove, MS; Alexander G. Bick; Pierre Fontanillas, PhD; Stephen S. Rich, PhD; Joshua D. Smith; Eric Boerwinkle, PhD; Wayne D. Rosamond, PhD; Kaoru Ito, MD; Sophie Lanzkron, MD; Josef Coresh, MD; Adolfo Correa, MD; Gloria E. Sarto, MD; Nigel S. Key, MBChB; David R. Jacobs, PhD; Sekar Kathiresan, MD; Kirsten Bibbins-Domingo, MD; Abhijit V. Kshirsagar, MD; James G. Wilson, MD; Alexander P. Reiner, MD

APOL-1 and risk of albuminuria in African Americans

Apolipoprotein L1

- Apolipoprotein L1 (APOL1) is a minor apoprotein component of HDL cholesterol, found in vascular endothelium, liver, heart, lung, placenta, podocytes, proximal tubules, and arterial cells.
 - Although its intracellular function has not been elucidated, APOL1 circulating in plasma has the ability to kill the trypanosome that causes sleeping sickness.
 - Two coding sequence variants in APOL1 were identified by looking at variation in genetic ancestry in African Americans with kidney disease.
 - People who have at least one copy of either the G1 or G2 variant are resistant to infection by trypanosomes, but people who have two copies of either variant are at an increased risk of developing a non-diabetic kidney disease.
-

Research question

To investigate the role of genetic variants in *APOL1*, traditional risk factors and socioeconomic position (SEP) in explaining race differences in albuminuria and kidney function decline in young adults.

PAF=Fraction of cases in the population that *would not have occurred if the exposure had been eliminated*

USRDS - 2007

Results- Incident albuminuria

Peralta CA , Bibbins-Domingo, K *et al.* J Am Soc Neph, 2016

	N	Incidence Rate per 1000 PY	Age Adjusted	Risk Factor Adjusted	SEP Adjusted
Comparison Within Blacks					
Black no APOL1	1090	7.8	ref	ref	ref
In Blacks, population attributable fraction for <i>APOL1</i> was 10.3% HTN and DM was 27.6%					
White	1651	3.9	ref	ref	ref
Black no APOL1	1090	7.8	2.32* (1.73-3.13)	1.33 (0.96-1.84)	1.21 (0.86 to 1.71)
APOL1 Black	152	15.6	5.71* (3.64-8.94)	3.89* (2.43-6.22)	3.50* (2.14 to 5.71)

Example of Genetics: APOL1

- Example of use of ancestry differences clearly useful for *insights into disease*
- Large beta effect estimate ($RR \sim 2$), large MAF difference, but still does not explain that much of the disparity
- Here's the math to keep in mind (it's friendly math!):
PAF = Fraction of cases in the population that *would not have occurred if the exposure had been eliminated*
- $PAF = p * (RR - 1) / (p * (RR - 1) + 1)$
- If p (prevalence of exposure) = .5 and $RR = 1.5$,
 $PAF = .5 * .5 / (.5 * .5 + 1) = 0.2$
- If prevalence of exposure = .5 and $RR = 4$,
 $PAF = .5 * 3 / (.5 * 3 + 1) = 0.60$

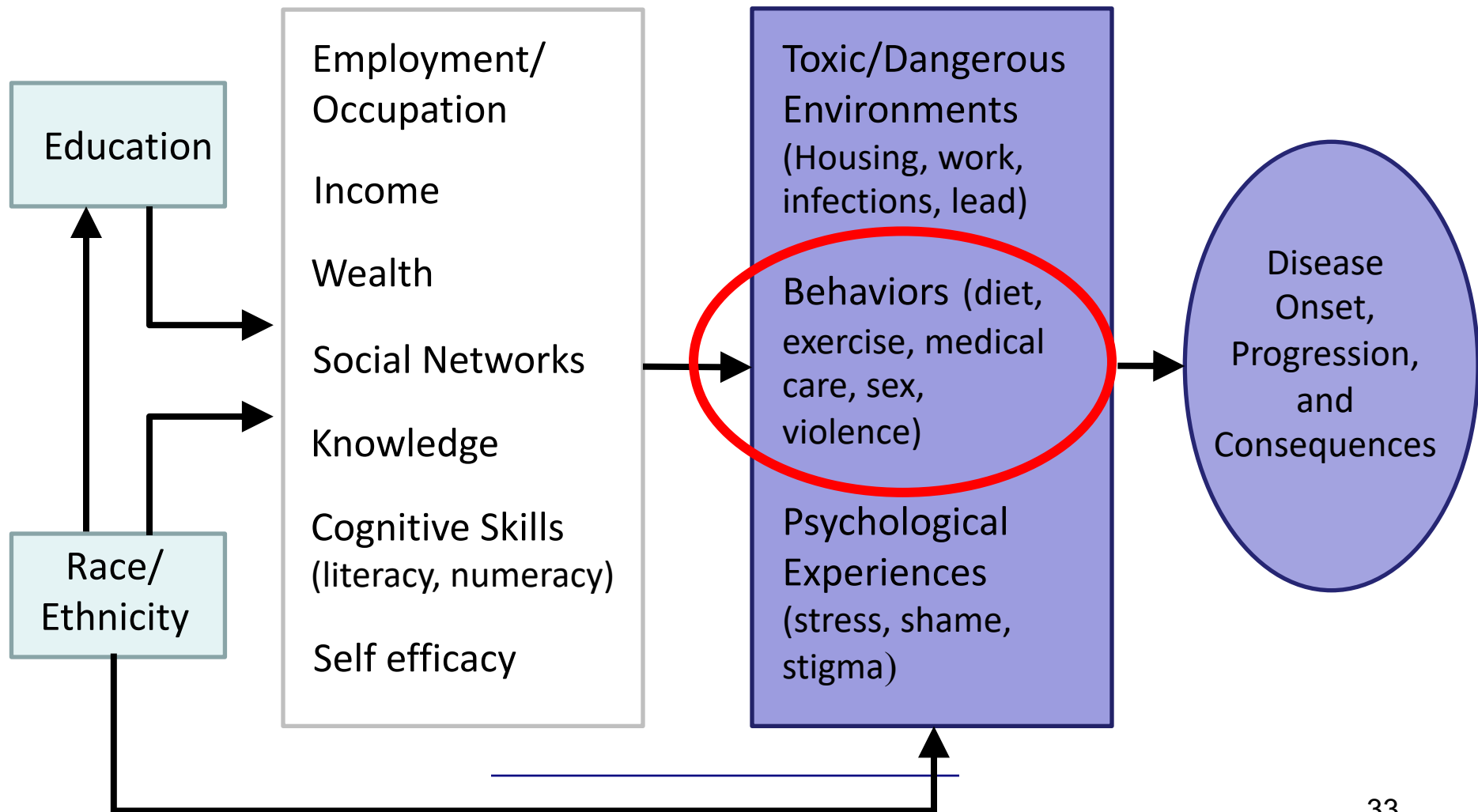
Role of genetics vs social experiences in health differences

- PAF=Fraction of cases in the population that *would not have occurred if the exposure had been eliminated*
- $PAF = p \cdot (RR - 1) / (p \cdot (RR - 1) + 1)$
- If prevalence of exposure=50% and $RR=4$,
 $PAF = .5 \cdot 3 / (.5 \cdot 3 + 1) = 0.60$
- How many risk factors have an RR of 4?
- How many risk factors have a difference in prevalence across social groups of 50%?

Biological Mechanisms

- ~~Frameworks~~
- Behaviors, including use of medical care
- Epigenetics
- Direct toxic exposures
- Stress mediated pathways
- Major controversies or uncertainties
 - Lifecourse/sensitive periods
 - Qualitative interactions/dandelion vs orchid
 - Role of genetics

Biological mechanisms for categories of mechanisms



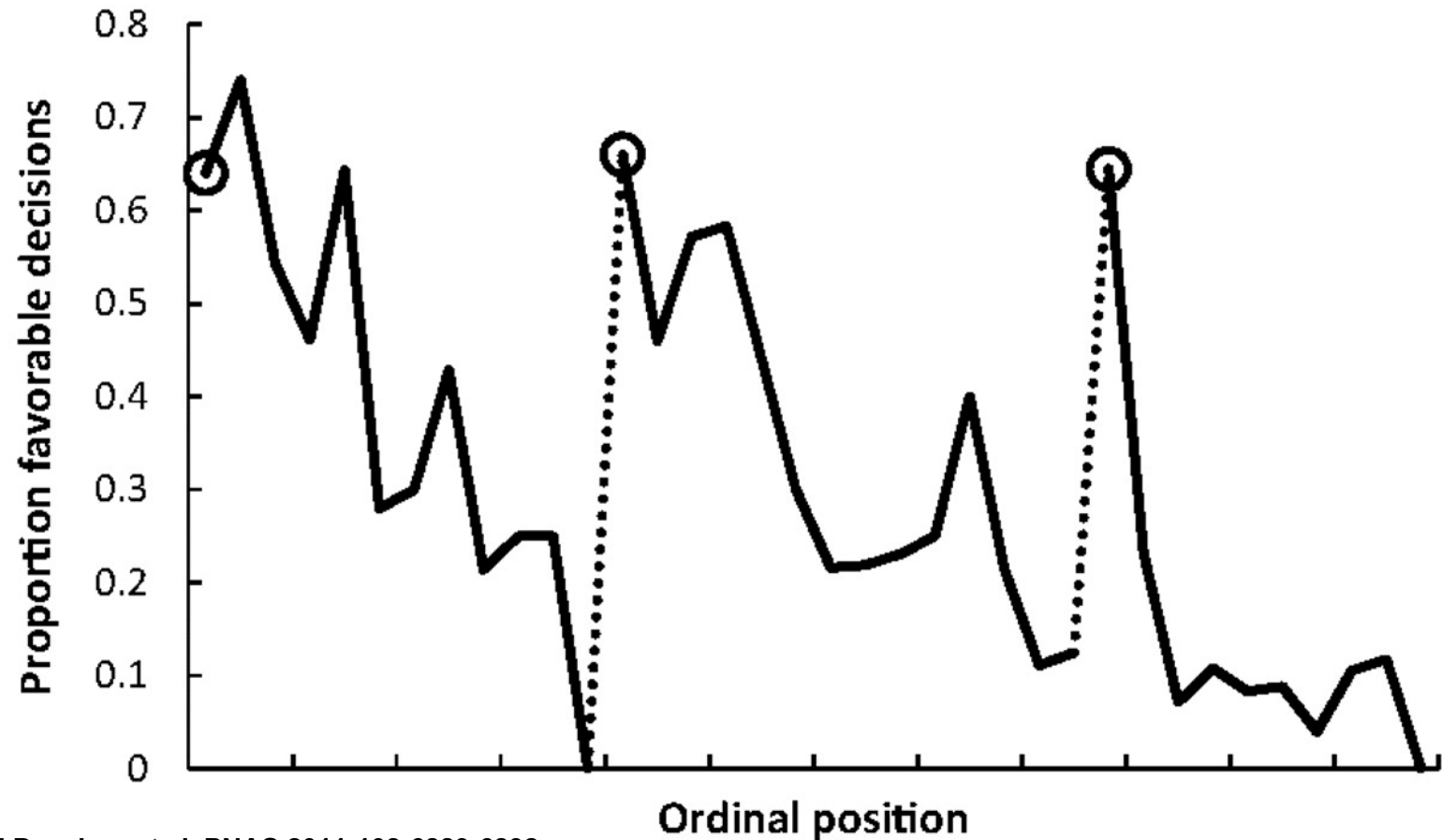
Behaviors are shaped and constrained by social context

- Behaviors addressed previously. Key messages in this lecture:
 - Behavioral patterns are shaped by social context
 - Influence of social context on behavior can be mediated by physiologic changes that occur in response to environmental stimuli (epigenetic regulation, neurological development)
 - The biological embedding implies that environmental causes may be relevant at developmentally specific ages

Physiology and behavior: Self-regulatory depletion

- Self-regulation conceptualized as a “resource” depleted by making difficult decisions or resisting temptation; influenced by blood glucose
 - Famous examples: Judges make more lenient parole decisions early in the morning and right after lunch (moral: bring your dissertation committee snacks)
 - Exposing people to radishes and cookies and asking them to only eat the radishes led to reductions in amount of time spent in a subsequent problem solving task
 - Giving people food (glucose) restores self-control (Gailliot)
 - Meta-analysis shows persistence across task demands and subsequent displays of self-control

Proportion of rulings in favour of the prisoners by order of decisions faced by the judge that day



Shai Danziger et al. PNAS 2011;108:6889-6892

Biological Mechanisms

- Frameworks
- Behaviors, including use of medical care
- **Epigenetics**
- Direct toxic exposures
- Stress mediated pathways
- Major controversies or uncertainties
 - Lifecourse/sensitive periods
 - Qualitative interactions/dandelion vs orchid
 - Role of genetics

Example Mechanism: Epigenetics

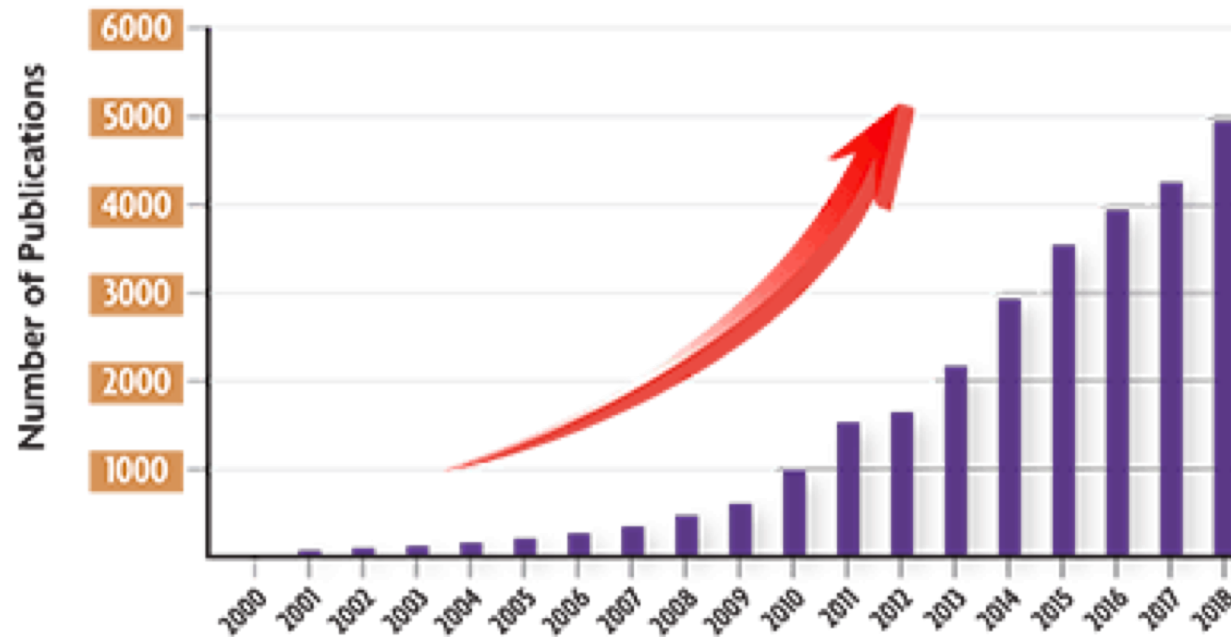
- Epigenetics is the study of heritable changes in gene expression (active versus inactive genes) that do not involve changes to the underlying DNA sequence which in turn affects how genes are expressed
 - → a change in phenotype without a change in genotype
- Epigenetic modifications provide a possible physiologic mechanism linking experiences (nutrition exposures, parenting, etc.) to individual behaviors and health outcomes



**If they ask you anything you don't know, just
say it's due to epigenetics.**

Slide Credit: Meg Jones,
PhD

Epigenetics Publications Per Year

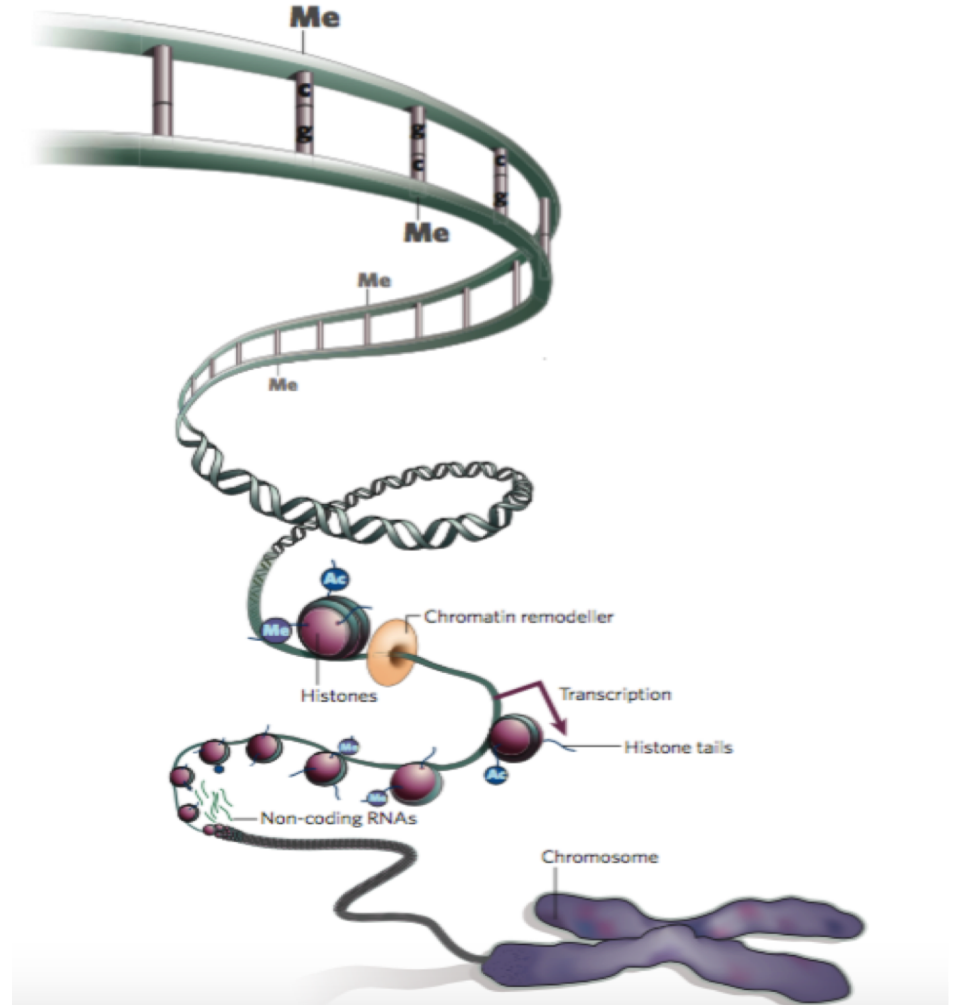


What is Epigenetics?

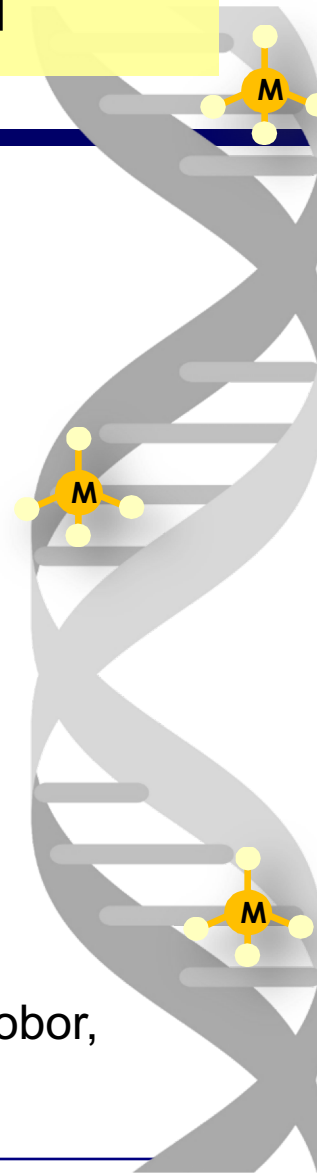
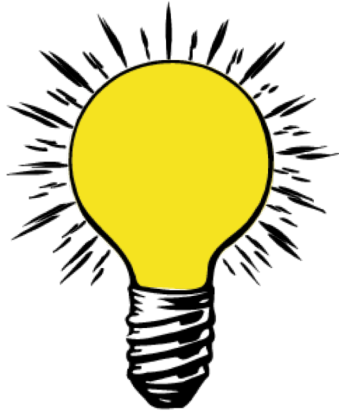
Modifications to DNA that affect packaging without changing sequence

1. Histone variants and modifications
- 2. DNA methylation**
3. ncRNAs

Important role in development and tissue specificity



DNA Methylation



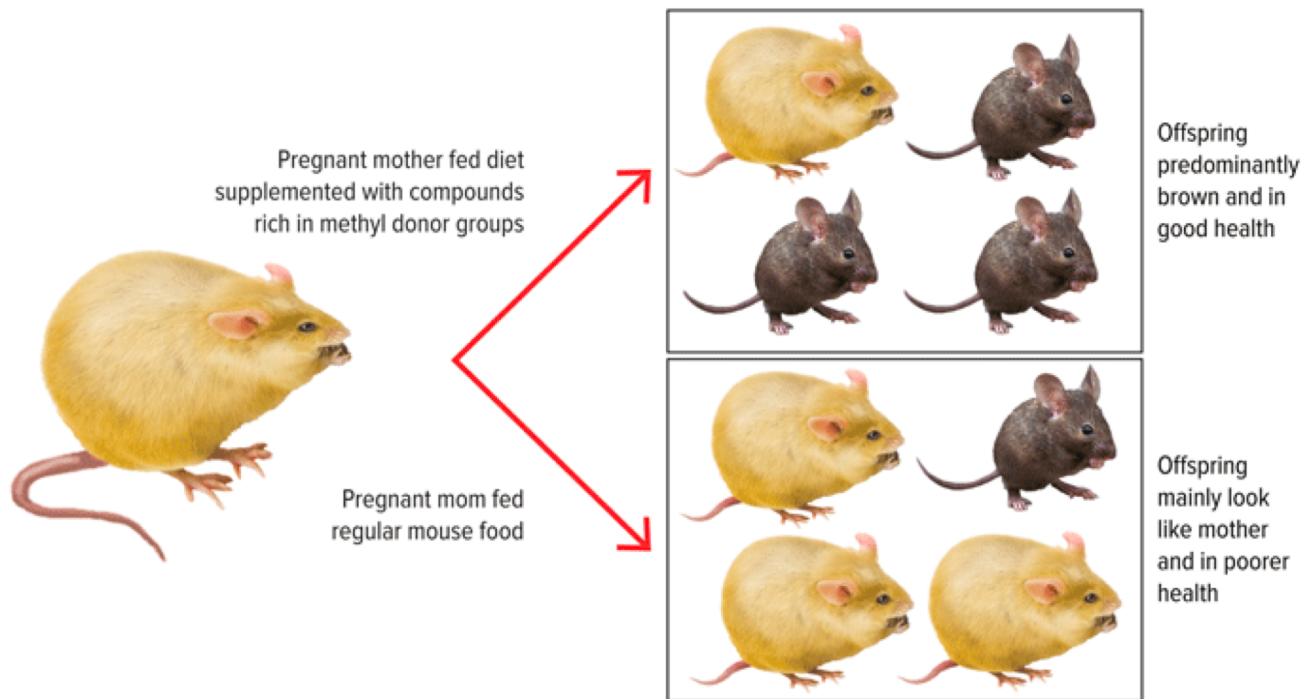
Slide Credit: Mike Kobor,
PhD

What do epigenetic alterations look like?



Fraga et al.
(2007)

Slide Credit: Nicki Bush, PhD

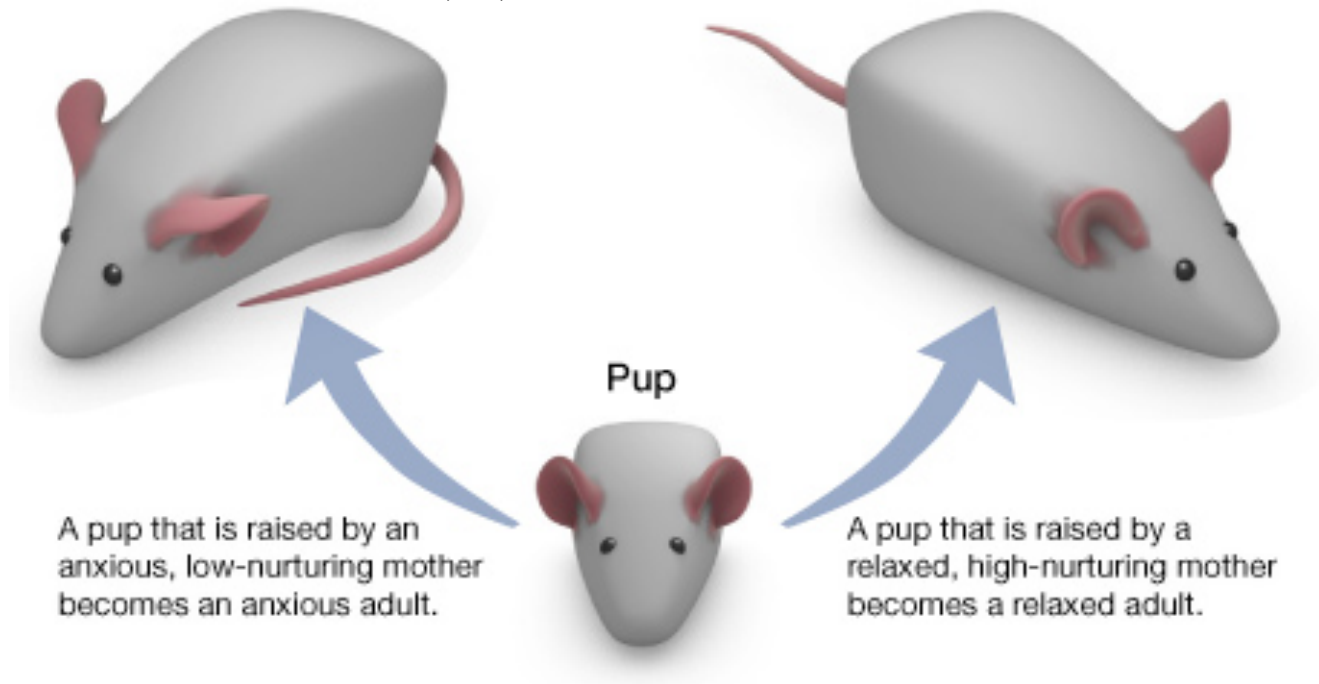


Jirtle (2006)

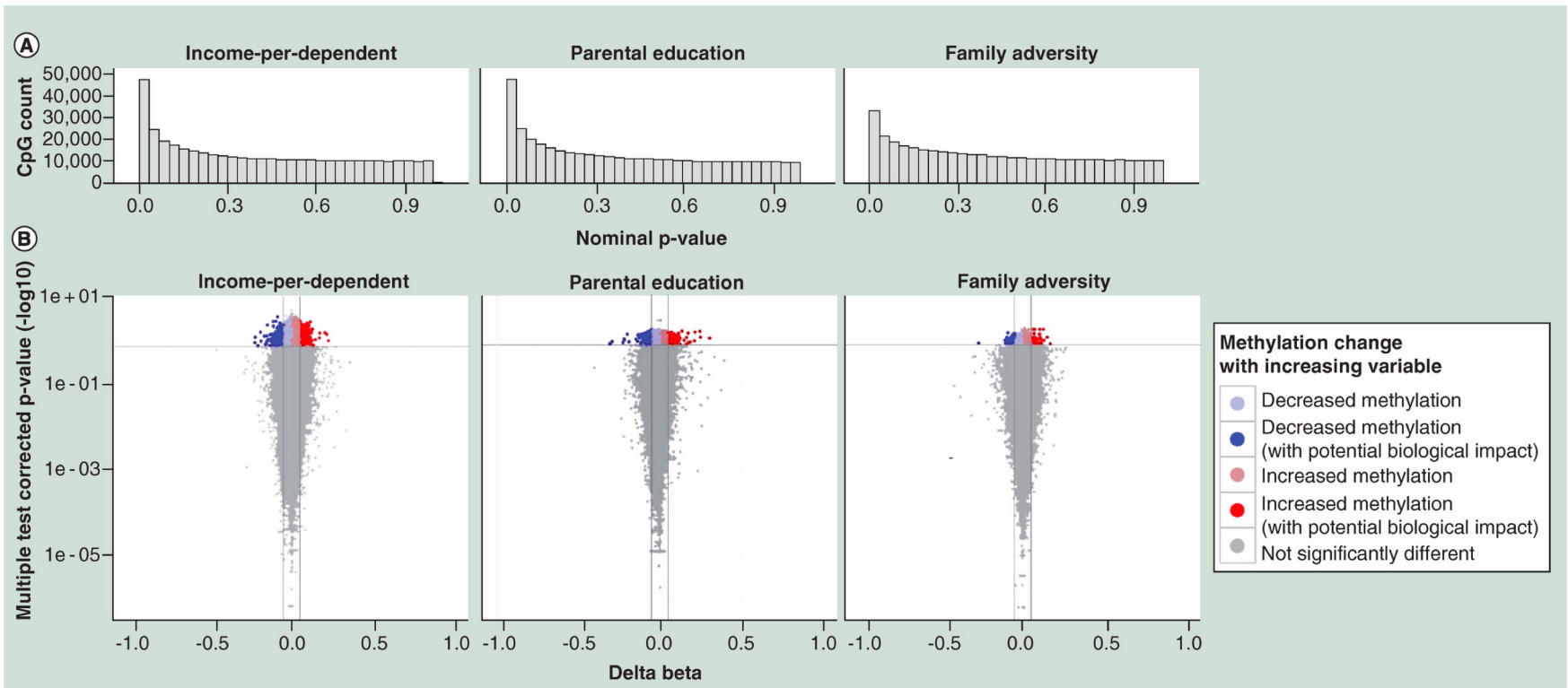


Maternal behavior in rodents

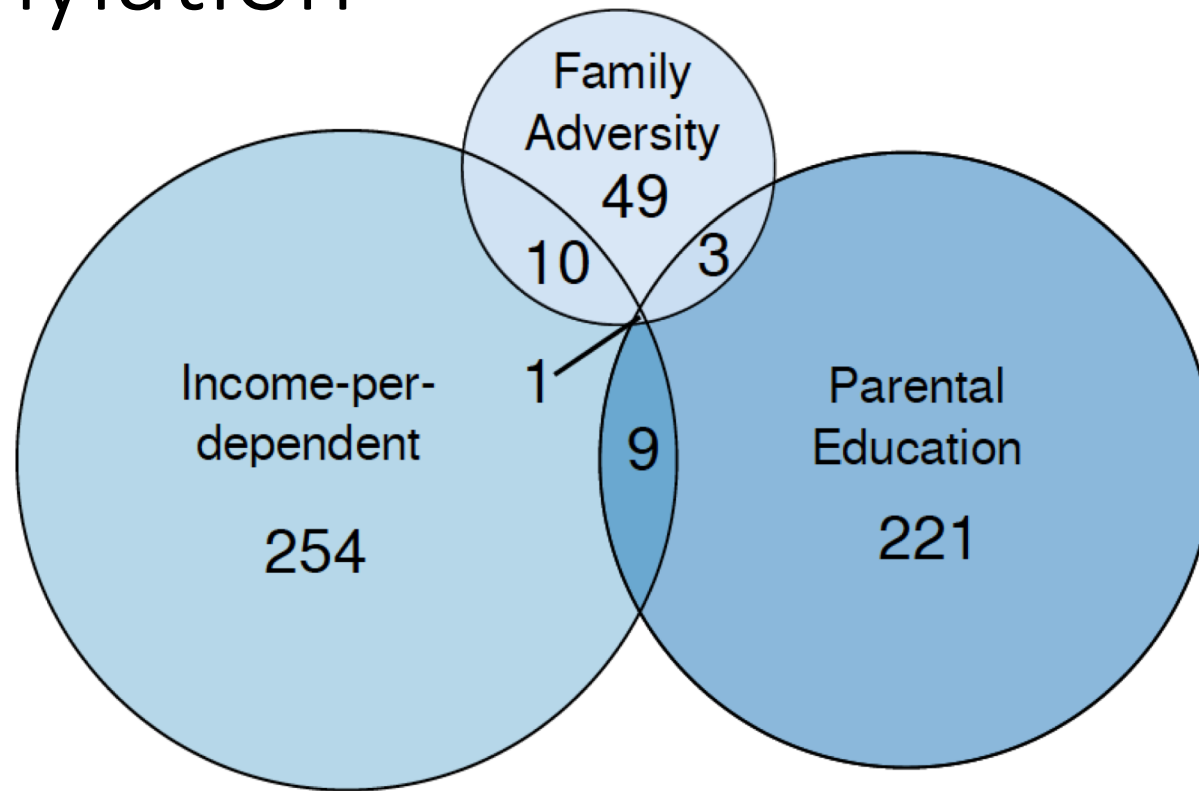
- Weaver, Cervoni, Champagne, D'Alessio, Sharma, Seckl, Dymov, Szyf, & Meaney, (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience*, 7, 847-854



Childhood Experience and DNA methylation



Childhood Experience and DNA methylation



Epigenetic clock: Horvath and Raj

- Biological aging results as an unintended consequence of both developmental programs and maintenance program, the molecular footprints of which give rise to DNA methylation age estimators.
- The precise mechanisms linking the innate molecular processes (underlying DNAm age) to the decline in tissue function probably relate to both intracellular changes (leading to a loss of cellular identity) and subtle changes in cell composition, for example, fully functioning somatic stem cells.
- At the molecular level, DNAm age is a proximal readout of a collection of innate aging processes that conspire with other, independent root causes of ageing to the detriment of tissue function.
- → weighted average of the 353 clock CpGs, which is then transformed to DNAm age using a calibration function (r with age is 0.96)
- → Comparisons between biological age and DNAm age yield insights into potential risk for disease or accelerated aging

Social experience and DNAm age

	ALSPAC age 29y	ALSPAC age 47y	NSHD age 53y
	(n = 989)	(n = 989)	(n = 773)
Emotional cruelty	-0.28 (-1.52, 0.95)	-0.32 (-1.61, 0.96)	n/a
Physical neglect	-0.83 (-3.60, 1.95)	-2.06 (-5.40, 1.27)	n/a
Emotional neglect	0.28 (-0.57, 1.13)	-0.12 (-1.01, 0.77)	n/a
Spent time in care	-0.35 (-3.44, 2.75)	-1.43 (-4.72, 1.86)	n/a
Poor family function	0.91 (-0.13, 1.95)	-0.48 (-1.71, 0.74)	n/a
Sexual abuse	2.74 (0.93, 4.56)	3.34 (1.47, 5.22)	n/a

DNA methylation

- Some takeaways
 - # of methyl groups influences gene activity (generally more methyl groups – less active)
 - These changes in gene expression can change physiology, behavior, etc.
 - Multiple exposures (diet, stress, toxins, etc.) can lead to changes in DNA methylation
 - These changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations
 - Mechanism of within generation and intergenerational embedding of environmental factors
 - DNAm age as an indicator of biological aging

Major Challenges with Epigenetics as Mechanism for Social Inequalities

- Multiple possible loci to evaluate; need large samples
- Mostly hypothesis free
- Replication challenges
- Tissue specificity of epigenetic changes
- Do epigenetic changes yield meaningful changes in gene expression?
- Disentangling cause from consequence

Biological Mechanisms

- Frameworks
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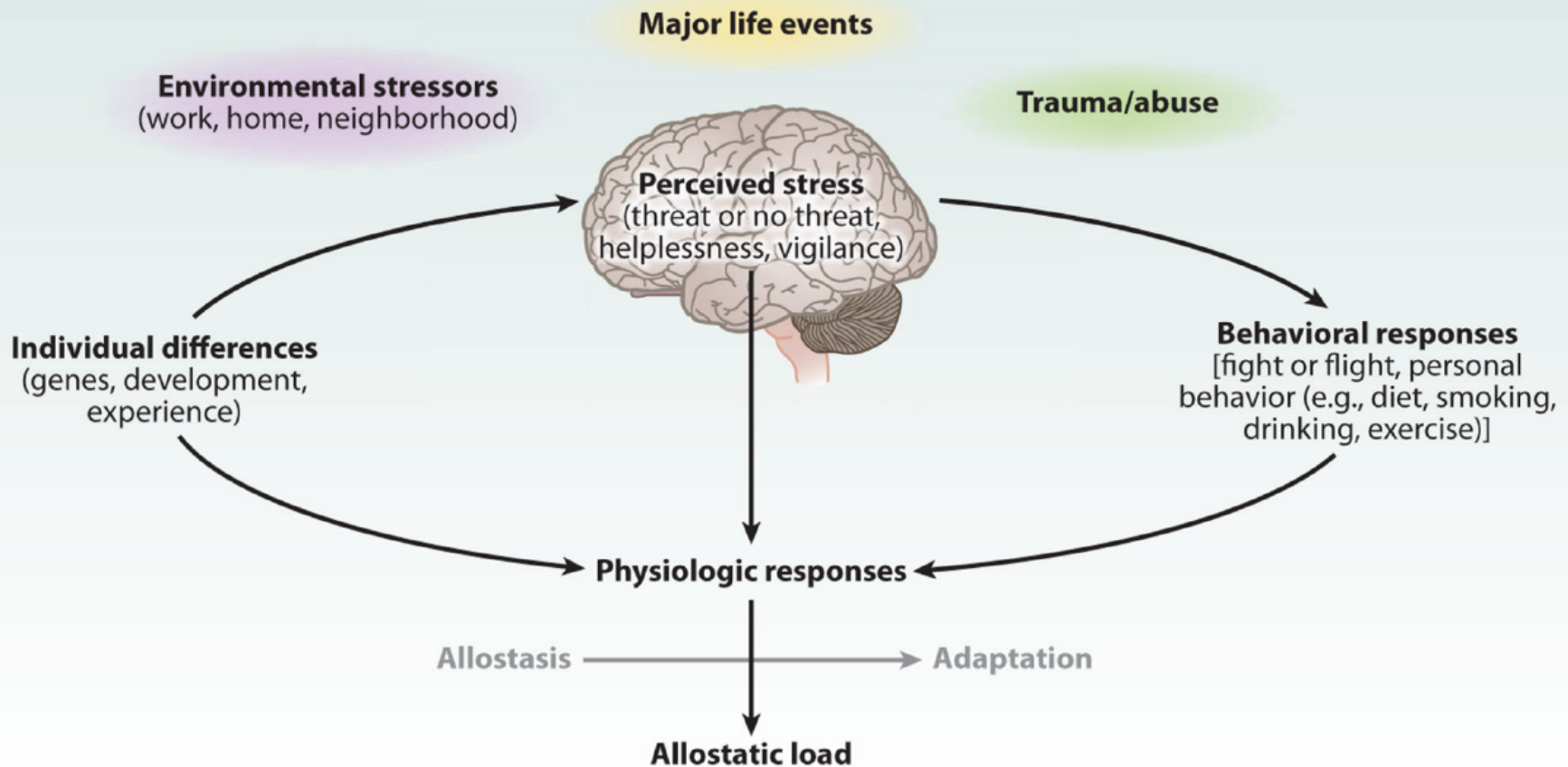
What are stress and stressors?

- Stressors: external demands encountered by the organism
 - Source:
 - Physical (cold, infection)
 - Psychological (fear, shame, anxiety)
 - Duration:
 - Acute (trauma)
 - Chronic (daily hassles)
- Stress occurs when demand is perceived to exceed capacity to respond
- Stressors induce a host of immediate physiologic changes

Allostatic Load

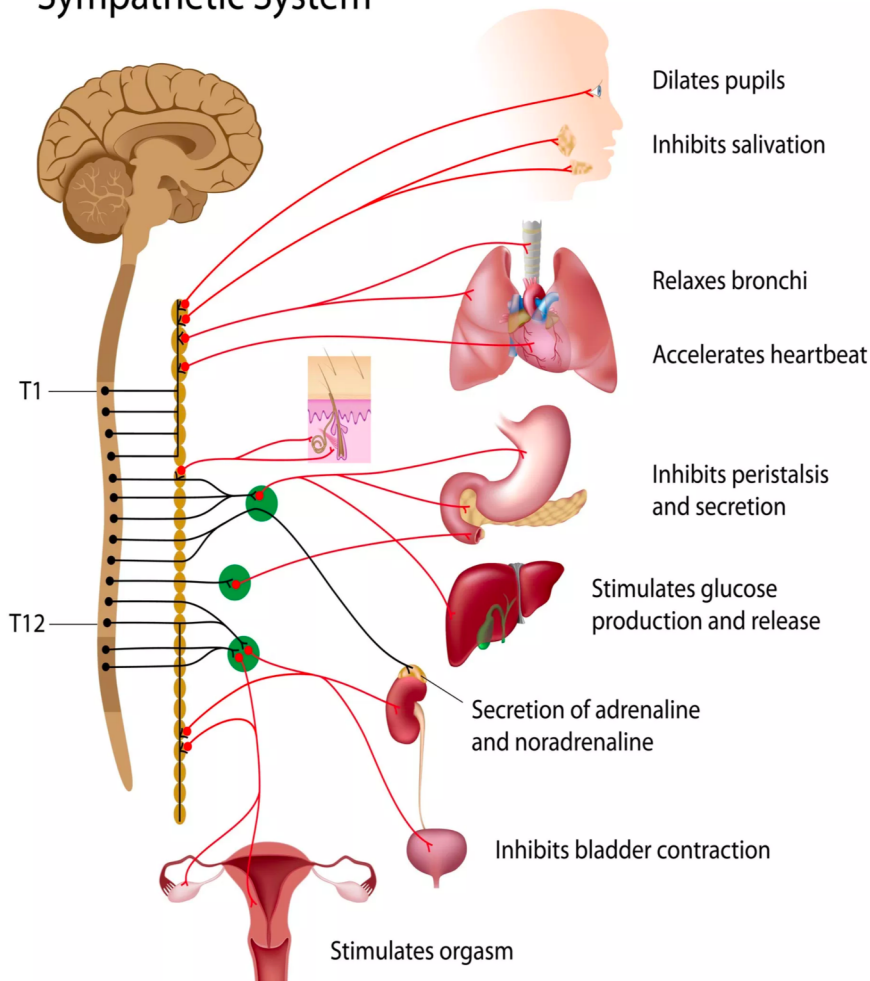
- Homeostasis: capacity of a biological system to maintain state through marked environmental changes
- Allostasis (robustness): capacity of a biological system to maintain functioning through marked environmental changes
 - Allostasis may require changes in state in order to maintain function
 - Biological regulatory systems alter functioning in order to *adapt* to changing conditions/demands
- Allostatic load: “wear and tear” accumulating as a result of chronic need to adapt to adverse environmental conditions, especially stress
- Although effects may have thresholds, concept emphasizes accumulation of harm.
- Measurements of allostatic load emphasize multi-system breakdown

Stress triggers HPA and SNS Response



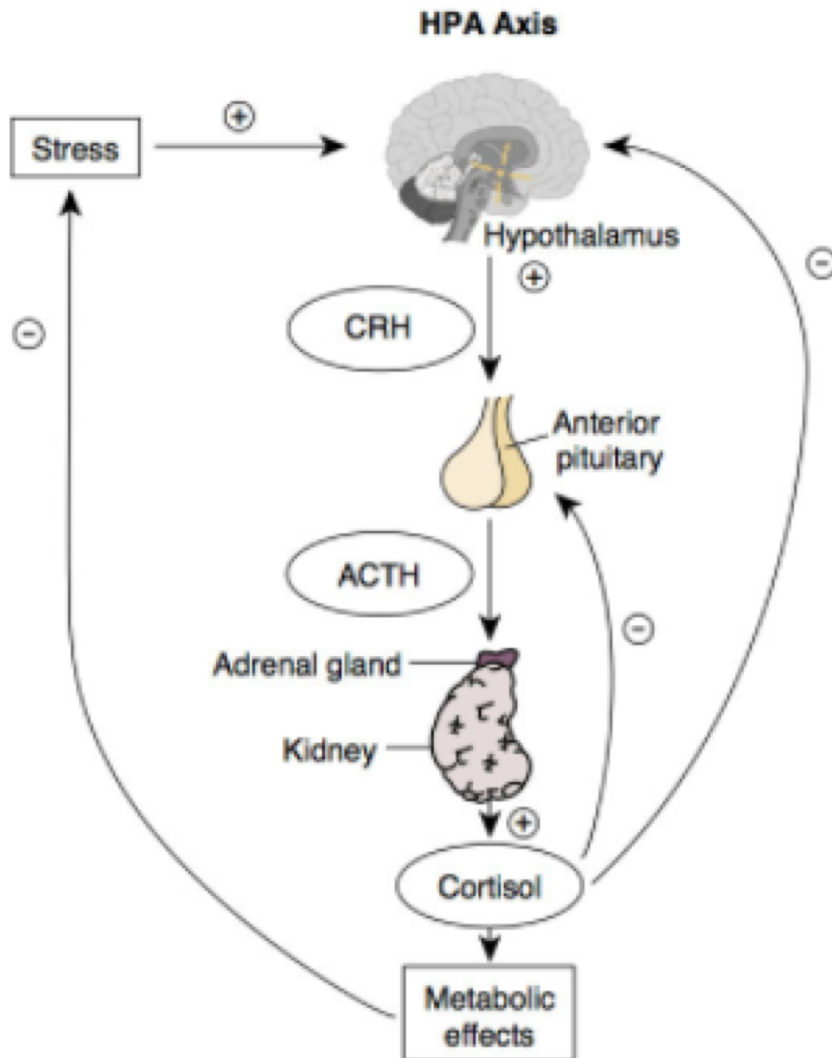
Sympathetic NS response

Sympathetic System



- Immediate response—fight or flight
- Activation results in secretion of adrenaline and noradrenaline from the adrenal cortex--> increase heart rate, dilation of pupils, etc.

HPA axis response

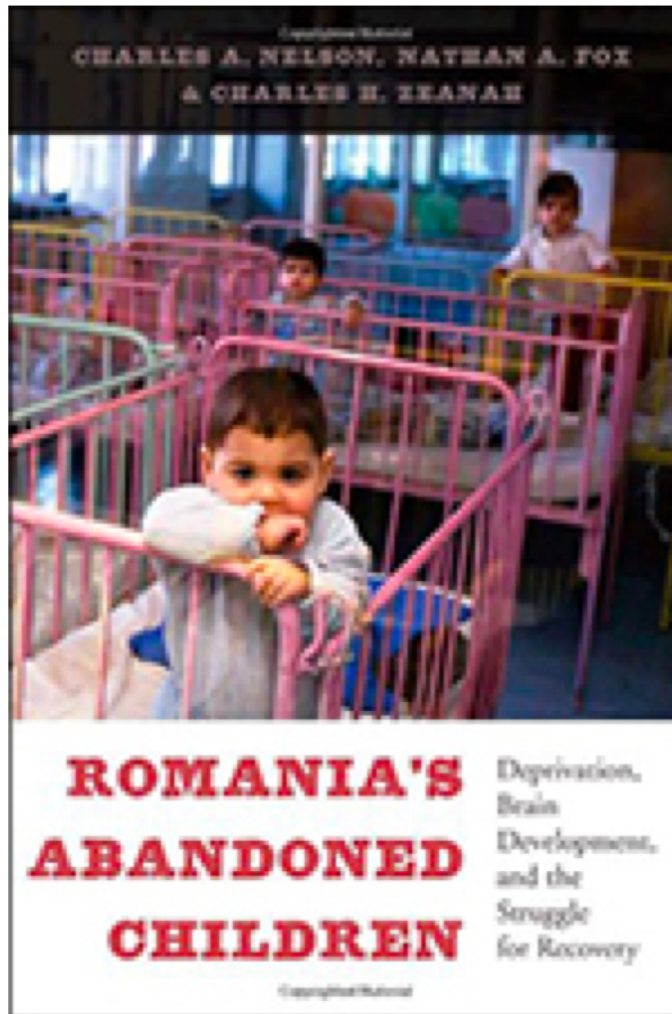


Hypothalamus-pituitary-adrenal axis: hypothalamus releases corticotropin releasing hormone triggering adrenocorticotrophic hormone from pituitary → glucocorticoid production by adrenal cortex

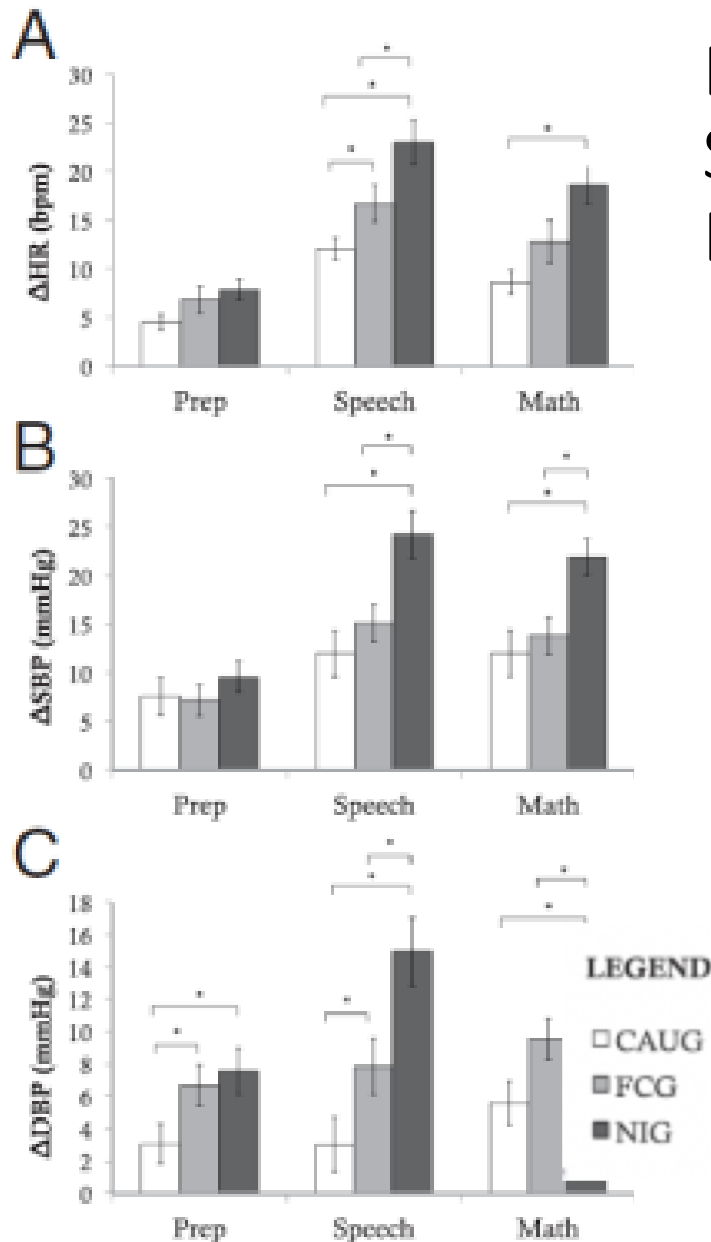
Glucocorticoids have actions throughout the body (influence immune functions, metabolism); feed back and bind corticosteroid receptors to return to base state.

But high levels of cortisol also change brain structure and response to future stressors

Bucharest Early Intervention Study



Bucharest Early Intervention Study and Stress Response Differences



- Trier Social Stress Test at age 12
- Measure of SNS response during these tasks
- Blunting of SNS response is what is observed
- Seen across a variety of challenges- non social and social
- Chronic activation in early life → blunted response

Allostatic Load (Robinette, 2016)

- Examined mediators of link between neighborhood SES and allostatic load
- A total of 24 physiological indices were assessed to calculate seven separate scales comprising the cardiovascular, sympathetic nervous, parasympathetic nervous, hypothalamic pituitary adrenal axis, inflammatory, lipid metabolism, and glucose metabolism systems.
- Used these subsystem scale scores to generate one overall "allostatic load" score
- Predictors: Perceptions of neighborhood, health behaviors, and affective pathways

Predictors of Allostatic Load

Table 4

Multivariate models predicting overall allostatic load (regression estimates [SE]).

	Model 5
Intercept	− 0.14 (0.31)
Neighborhood income	− 0.04* (0.01)
Individual income	− 0.01 [†] (0.01)
Age	0.16*** (0.01)
Gender ^a	0.10 (0.07)
Safety ^b	− 0.14 [†] (0.07)
Cohesion	− 0.02 (0.05)
Perceived stress	0.00 (0.01)
Anxious arousal	0.02* (0.01)
Exercise ^c	− 0.19* (0.08)
Smoking	0.00 [†] (0.00)
Fast food ^d	0.15*** (0.03)

[†] $p < 0.05$.

* $p < 0.01$.

** $p < 0.001$.

*** $p < 0.0001$.

Robinette, 2016

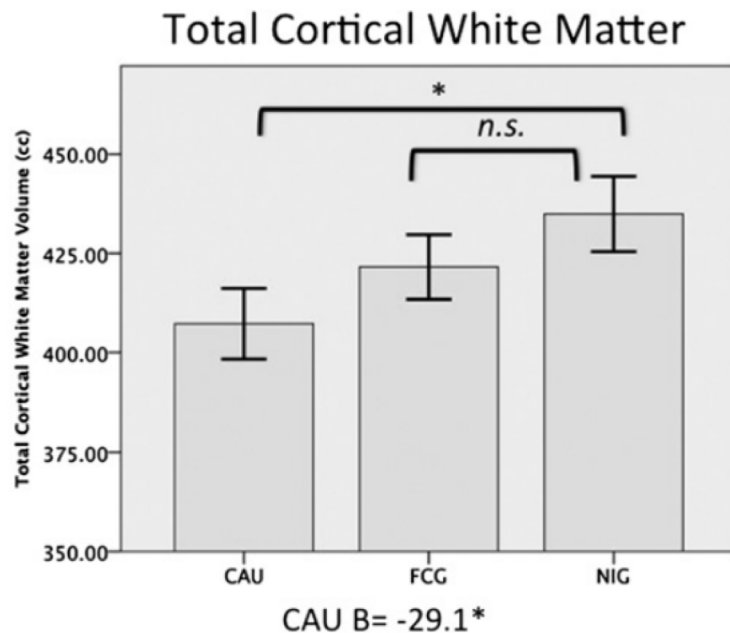
Stress Response: Active Research Areas

- Cell structure and tissue remodeling (e.g., apoptosis, dendritic shape and synapse formation, cellular developmental trajectories)
- SNS/HPA axis stimulation → increased pro-inflammatory profile of immune cells
- Telomere length and telomerase activity (chronic stress predicts shorter telomeres; racial patterns inconsistent)
- Metabolome: stress → HPA → gut microbiota

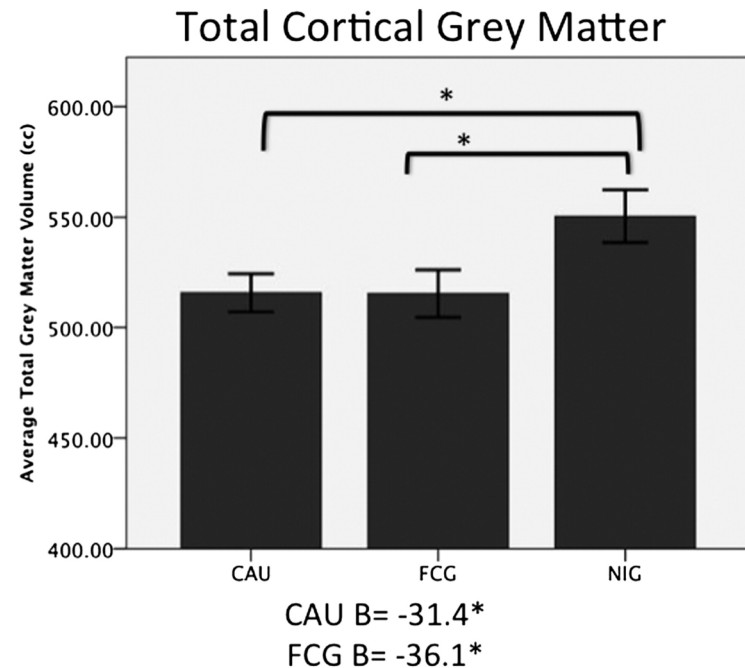
Stress Mediated Pathways and Neurodevelopment

- Early life stress changes brain development and neurodevelopmental outcomes
- Not separate from the stress response pathways → products of the stress response influence brain structure/function
 - E.g. there are cortisol receptors in many areas of the brain, including limbic system areas but also PFC. Animal model studies indicate direct links between exposure to GC and brain structure
 - But there are additional pathways at play: growing up in an environment with low exposure to language isn't necessarily a stressor but it does shape brain development (deprivation versus threat)
- Going to the source- just moving the measurement from peripheral indicators (like blood pressure) to CNS indicators like brain structure or function.

Brain structure differences in BEIP



Significant in Model 3 (controlling for gender and age)



Significant in Model 3 (controlling for gender and age)

Sheridan, 2012

Age at adoption predicts recovery from institutionalization: BEIP

Table 1. DQ and IQ at 42 and 54 months of age.

Evaluation	N	Mean DQ and IQ	SD	SE
<i>IG</i>				
42 months	57	77.1	13.3	1.8
54 months	51	73.3	13.1	1.8
<i>FCG</i>				
42 months	61	85.7	14.2	1.8
54 months	59	81.0	18.5	2.4
<i>NIG</i>				
42 months	52	103.4	11.8	1.6
54 months	45	109.3	21.2	3.2

Mean score in kids randomized younger than that age

Mean score in kids randomized older than that age

Table 2. DQ and IQ of FCG by entry age group. η indicates standard deviation, and Y is younger than and O is older than

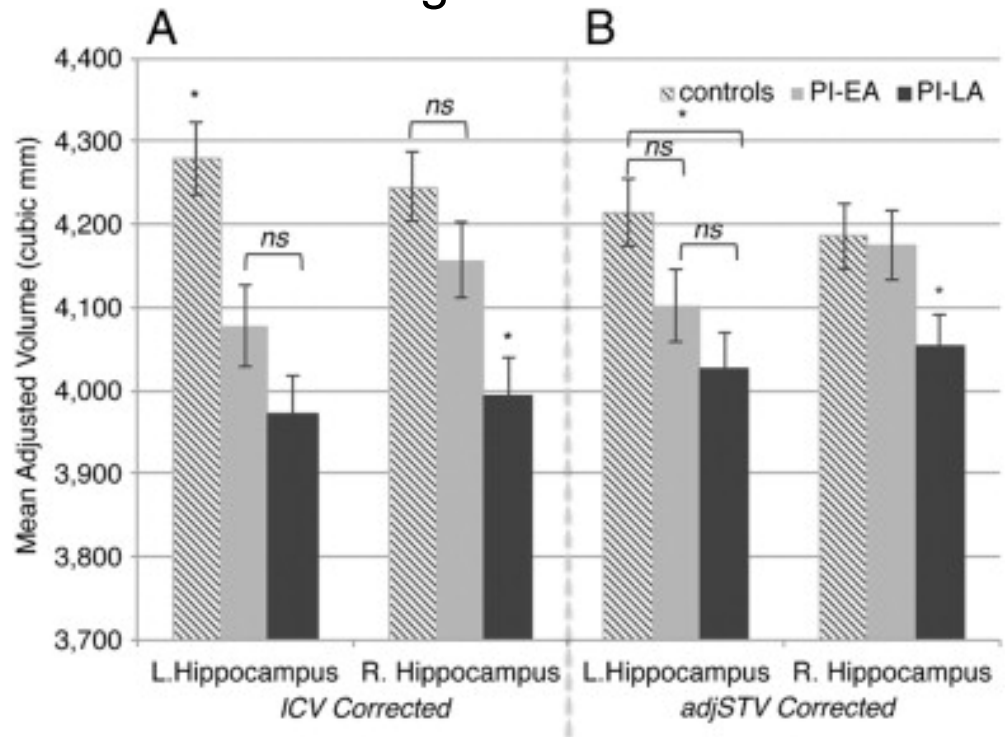
Age cutoff	42 months (BSID-II)				
	Y	O	t(59)	η	P
20 months	93.5	82.6	2.82	0.81	0.007
22 months	90.4	83.0	2.01	0.54	0.051
24 months	91.5	80.0	3.46	0.89	0.001
26 months	90.9	79.1	3.53	0.91	0.001
28 months	89.8	78.8	3.14	0.83	0.003

- Children in the institutional group had significantly worse IQ than children randomized to high quality foster care or a never-institutionalized group.
- Earlier age at randomization associated with better outcomes
- Thresholds for some cognitive and behavioral outcomes, age-thresholds differed across outcomes.
- -Nelson Science 2007

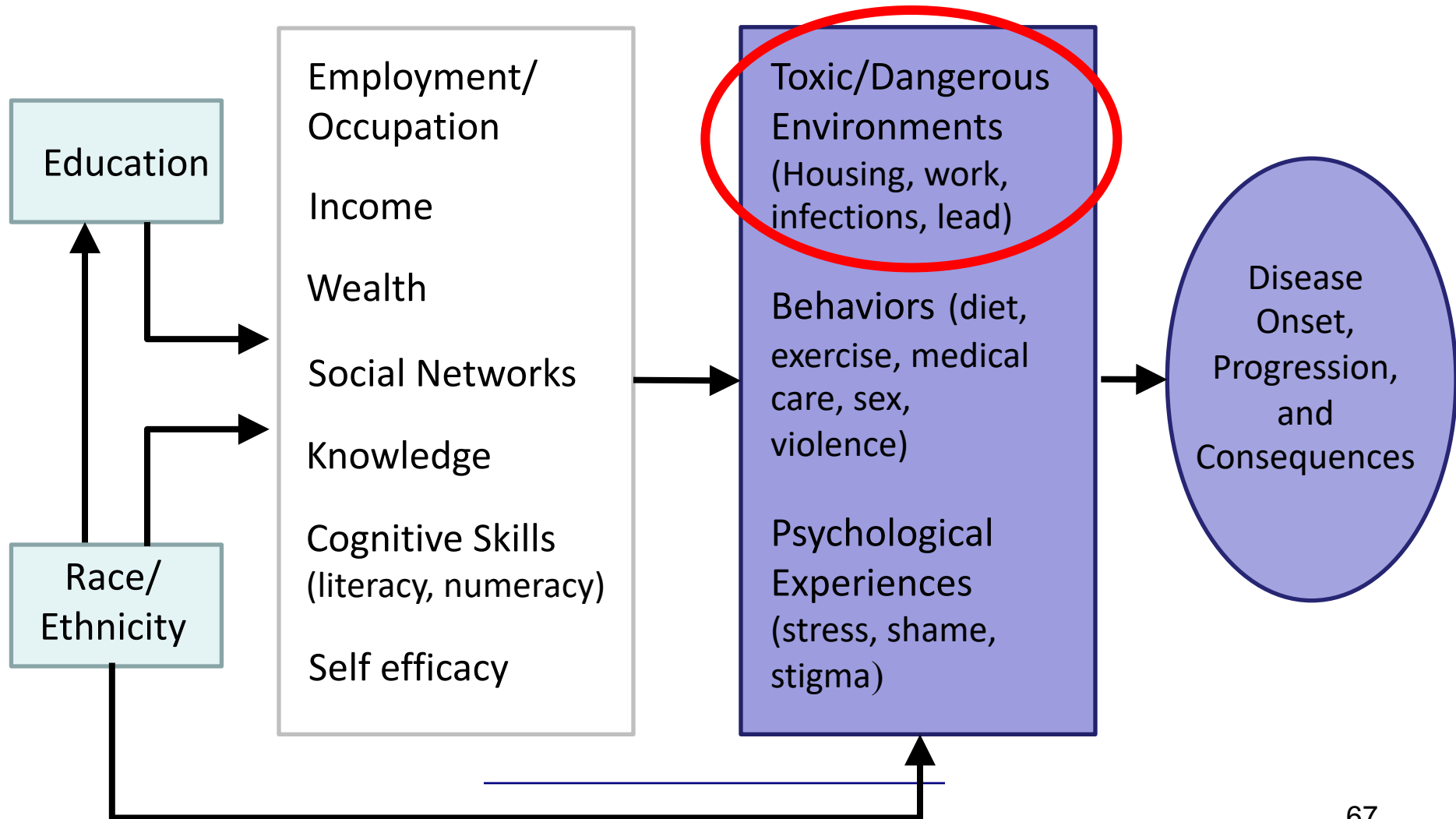
Age at adoption predicts recovery from institutionalization

N=110 post-institutionalization children (internationally adopted: 3.5 to 60 months of institutional care, dichotomized at adoption before 12 months) compared to 62 children raised with biological families.

Duration of early adversity predicts hippocampal volume reduction (age and sex adjusted). Panel A: ICV corrected ($\pm$ SEM). Panel B: adjSTV corrected ($\pm$ SEM).



Biological mechanisms for categories of mechanisms



Biological Mechanisms

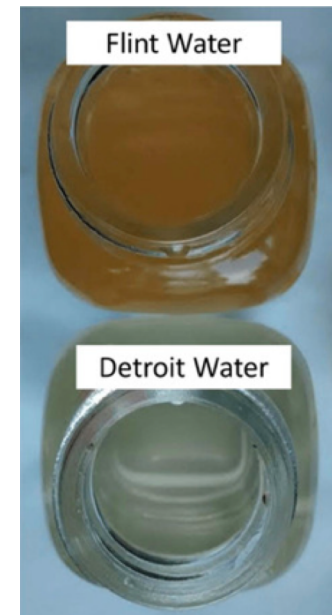
- Frameworks
- Behaviors, including use of medical care
- Epigenetics
- Stress mediated pathways
- **Direct toxic exposures**
- Major controversies or uncertainties
 - Lifecourse/sensitive periods
 - Qualitative interactions/dandelion vs orchid
 - Role of genetics

Direct Toxic Exposures

- Environmental toxins, e.g., lead, passive tobacco exposure, air pollution strongly socially patterned
- Food environments and nutritional deprivation
- Affect both disease incidence & outcomes/severity
- Categories may interact so lead exposure has worse consequences if combined with social stressors

Flint Water Crisis 2014

- In April 2014, Flint changed it's water sources from Lake Huron/Detroit River to the Flint River
- This was primary a cost cutting measure and a choice
- Flint officials did not include the appropriate corrosion inhibitors in the water leading to degradation of the water pipes and lead being leached into the water.
- For 18 months, water quality was poor with no official warnings or statements
- Outbreaks of legionnaires disease
- 6,000- 12,000 children exposed to lead



Drs. Mona
Hanna-Attisha
and Somer
Bishop

Flint Kids Sociodemographics

Indicators	Flint	MI	US
Children living in poverty	58%	22%	21%
Median household income	\$25,342	\$51,063	\$55,775
Children living in high poverty areas	82%	17%	14%
Children in one parent households	74%	35%	35%

The Annie E. Casey Foundation, KIDS
COUNT Data
Center, <http://datacenter.kidscount.org>.

Extent of lead exposure socially patterned

TABLE 3—Associations With Change in Blood Lead Levels: Flint, MI, 2013–2015

Model	b (SE)	B	P
(Constant)	12.32 (0.17)		<.001
Neighborhood housing condition	0.20 (0.00)	0.26	<.001
Residence time in pipes	0.13 (0.00)	0.32	<.001
House age	−0.01 (0.00)	−0.29	<.001
Socioeconomic distress	0.02 (0.00)	0.14	<.001
Land use mix	−0.17 (0.01)	−0.10	<.001

- Within Flint, impact of the water crisis on change in BLL is patterned by social factors

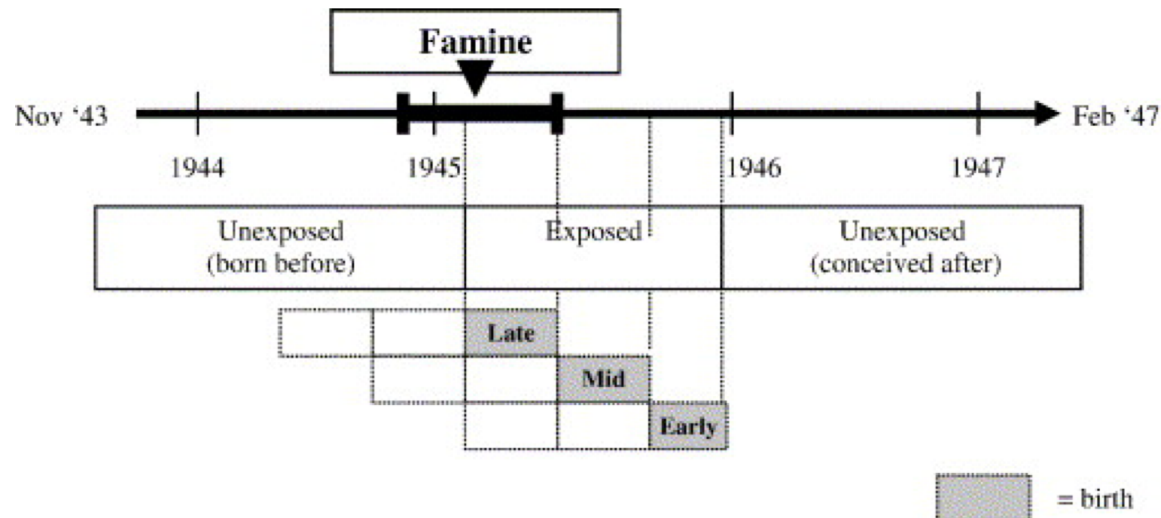
Sadler, LaChance, Hanna Attisha, 2017

Impact on neurodevelopmental outcomes

- Negative impacts of lead exposure on multiple neurodevelopmental outcomes (e.g., Al-Saleh et al., 2009; Chandramouli et al., 2009; Liu, J.A. et al., 2014; Liu, J.H., et al., 2014; Lanphear et al. 2005; Surkan, 2007)
 - Verbal/performance IQ, academic skills (reading and math), visual/spatial skills, problem solving skills, executive functions, fine and gross motor skills, problem-solving skills, memory and language skills, problem behaviors
 - Neurodevelopmental deficits found at low levels (<5ug/dl) of exposure in children (Lanphear, et al. 2005; Chiodo et al., 2004; Nigg et al., 2008; Chandramouli et al., 2009; Evens et al., 2015)
 - Deficits of 6.5-7.5 IQ point associated with an increase from 1 to 10ug/dl lead exposure (Lanphear, 2005; Canfield, 2003)
 - Known social patterning of lead exposure by race and SES across the US
-

Nutritional Deprivation and the Dutch Famine study

- End of WWII, Holland's food supply is cut off by the Nazis
- A hard winter follows and extreme famine issues
- Dutch record keeping is unparalleled and includes how many calories each individual had over this period
- Nutritional deprivation during different trimesters of pregnancy established
- A test of the Barker Hypothesis: Exposures in pregnancy can have a lasting impact on health

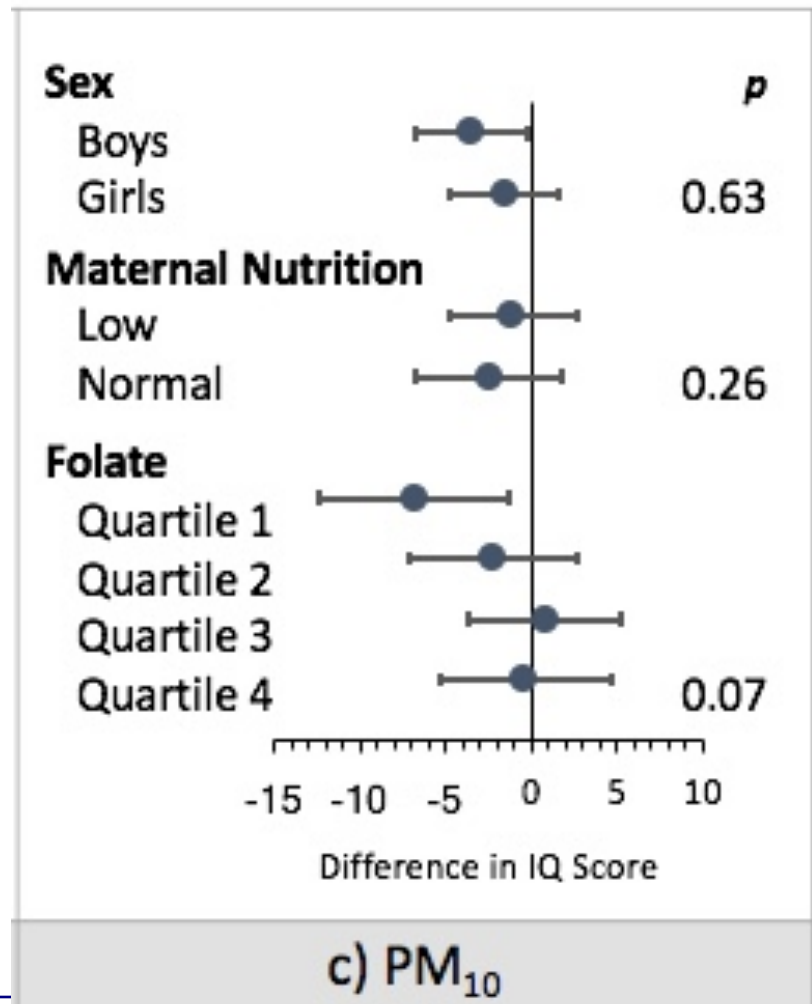


Trimester of exposure matters for adult outcomes

Exposure to famine		
In late gestation	In mid gestation	In early gestation
Glucose intolerance	Glucose intolerance	Glucose intolerance
	Microalbuminuria	Atherogenic lipid profile
	Obstructive airways disease	Altered blood coagulation
		Obesity (women only)
		Stress sensitivity
		Coronary heart disease
		Breast cancer

Nutrition during pregnancy as buffer

- CANDLE Study in Memphis, TN
- Examined association between air pollution exposures during pregnancy and child IQ at age 4-6
- Significant association with PM₁₀ (~2.5 points per IQR increase)
- Preliminary evidence of EM by prenatal maternal plasma folate
- Only those in lowest quartile demonstrate lower IQs (~6points)
- Lowest quartile is borderline deficient
- Higher proportion of African Americans than Caucasians in this category



Nutritional Deprivation: challenges

Key questions in nutrition studies generally:

- Other SES measures or entirely confounding?
- Timing of exposures that matter?
- Which outcomes are affected?

Biological Mechanisms

- Frameworks
- Behaviors, including use of medical care
- Epigenetics
- Stress mediated pathways
- Direct toxic exposures
- **Major controversies or uncertainties**
 - Lifecourse/sensitive periods
 - Qualitative interactions/dandelion vs orchid
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Uncertainties and Controversies

1. Physiologic mechanisms still controversial, many hypothesized mechanisms have limited empirical evidence – piecing together evidence from animals, experimental human studies in labs, and observational epidemiologic evidence. Research limited by the tools.
2. Generally a single mechanism is evaluated at a time
3. How common are qualitative reversals of effects (i.e., the same exposure that is *good* for some people is *bad* for others)?
 - Boyce: dandelion children versus orchid children
 - Air pollution example- bad for some not for others
 - GxE? (Candidate gene approach no longer viable)
4. Adaptive plasticity: adaptations optimize to environment that prevailed during critical developmental period, and illness is due to a mismatch with new environments?
5. Reversibility: can advantageous environments undo harm?
6. The role of genetics- hotly debated

Controversy regarding stress mechanisms

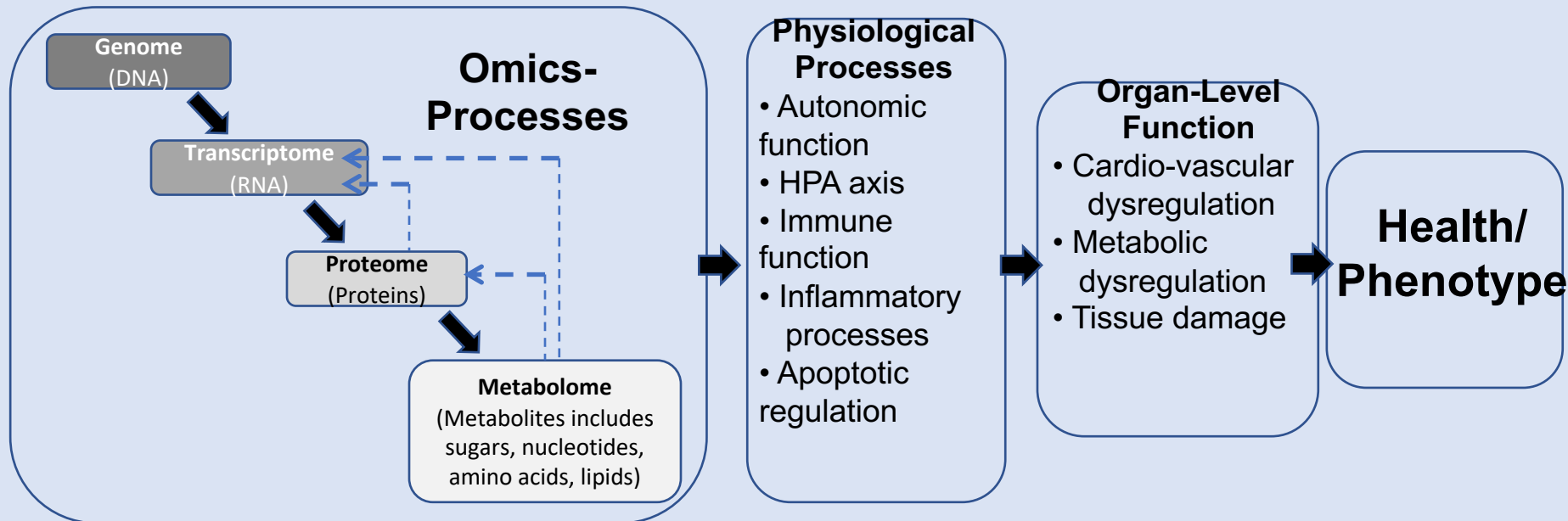
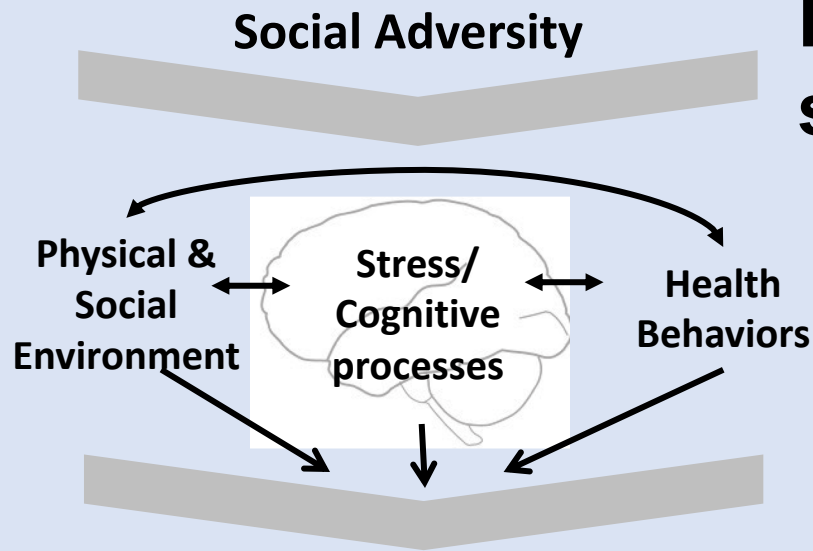
“Cortisol has received extensive attention as a potential mediator in the SES–health relationship. This review documented that more studies to date have found no association of cortisol with SES than have found the hypothesized association between lower SES and higher levels of cortisol, with several studies identifying ‘reverse’ associations for the whole sample or subgroups. These results may point to genuine inconsistencies in the nature of these relationships, or current inconsistencies in the measurement and analysis cortisol and SES”

Dowd, IJE 2009

(Semi-)Competing Theoretical Perspectives

- Developmental origins and health and disease (DOHAD): insults in early development periods have enduring consequences, possibly because the organism makes developmental choices optimized for a different environment (“fetal programming”).
- Weathering/cumulative allostatic load: Large and small insults each have small physiologic consequences which accumulate and accelerate aging. Eventually the body’s ability to compensate for these accumulating injuries is overwhelmed.
- Although these seem very distinct theoretically, many people believe both or believe it depends on the outcome. Open empirical question.

Biological pathways linking social conditions & health



end

Goals of Today

- There are physiologic mechanisms for embodiment of social experiences and adversity
- Examples of some promising areas of research on mechanisms: epigenetic modifications, stress related pathways/ allostatic load, biological regulation of behavior
- Know (some) key research approaches & challenges
- Know (some) major points of controversy

What are Health Disparities?

“A particular type of health difference that is closely linked with economic, social, or environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater social or economic obstacles to health based on their racial or ethnic group, religion, socioeconomic status, gender, age, or mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion.”

Healthy People 2020
(HealthyPeople.gov)

Mechanism is essential to disparities research

“The most fervid debates in public health...are rarely about “the facts” but rather their explanation. For example, none would dispute, 100 years ago ...the on-average life expectancy is shorter among people in the United States classified as Black versus White ...; by contrast, controversies have raged, then and now, over whether this pattern reflects biological or cultural inferiority versus social injustice.”

-Krieger, AJPH 2016



Example 3

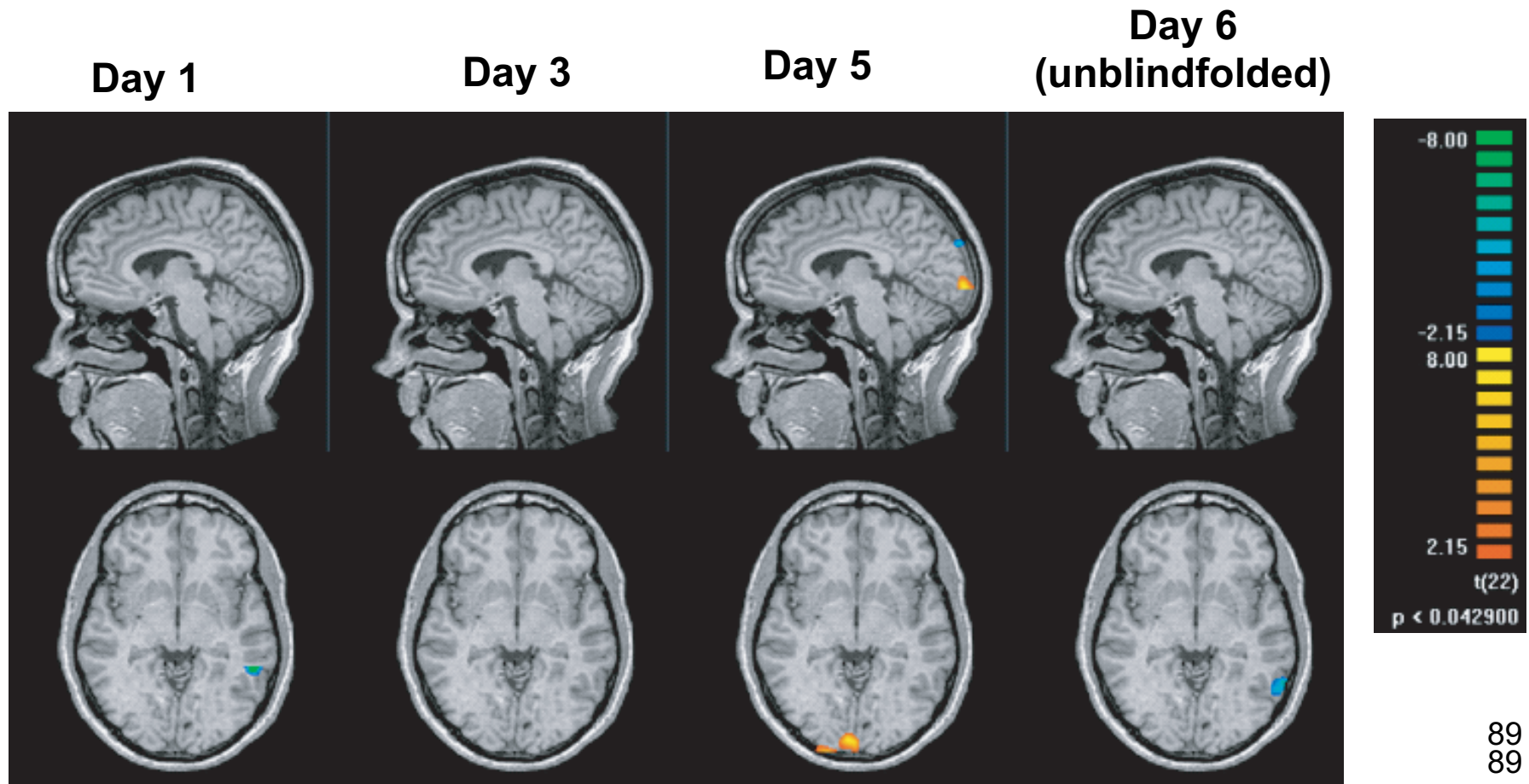
- Depletion of self-regulation by repeated exertions of self-control

How special are early developmental periods?

- Example of Extreme Induced Neuroplasticity in Adults:
 - 18-30 year olds randomized to 5 days of complete visual deprivation
 - All receive intensive Braille training, plus two hours of other tactile games.
 - Both improved Braille skills
 - Blindfolded group performed better on Braille discrimination.

Quick, reversible plasticity

- Sighted recruited occipital cortex for Braille



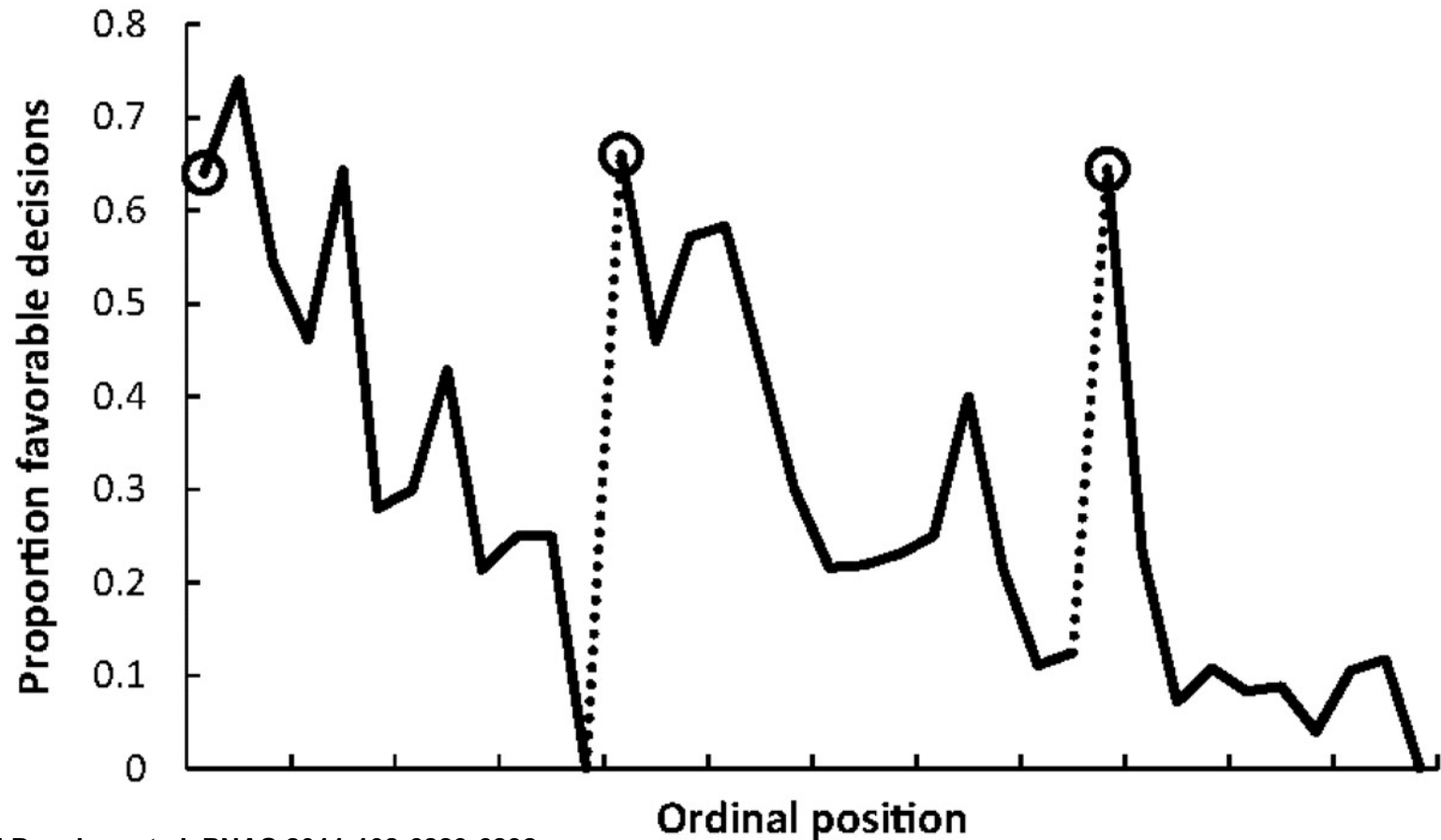
Merabet et al., 2008

“...sudden and complete visual deprivation in normally sighted individuals can lead to profound, but rapidly reversible, neuroplastic changes by which the occipital cortex becomes engaged in processing of non-visual information. The speed and dynamic nature of the observed changes suggests that normally inhibited or masked functions in the sighted are revealed by visual loss.”

Self-regulatory depletion- blood glucose influences self-regulation

- Self-regulation conceptualized as a “resource” depleted by making difficult decisions or resisting temptation
 - Famous examples: Judges make more lenient parole decisions early in the morning and right after lunch (moral: bring your dissertation committee snacks)
 - Exposing people to radishes and cookies and asking them to only eat the radishes led to reductions in amount of time spent in a subsequent problem solving task
 - Giving people food (glucose) restores self-control (Gailliot)
 - Meta-analysis shows persistence across task demands and subsequent displays of self-control

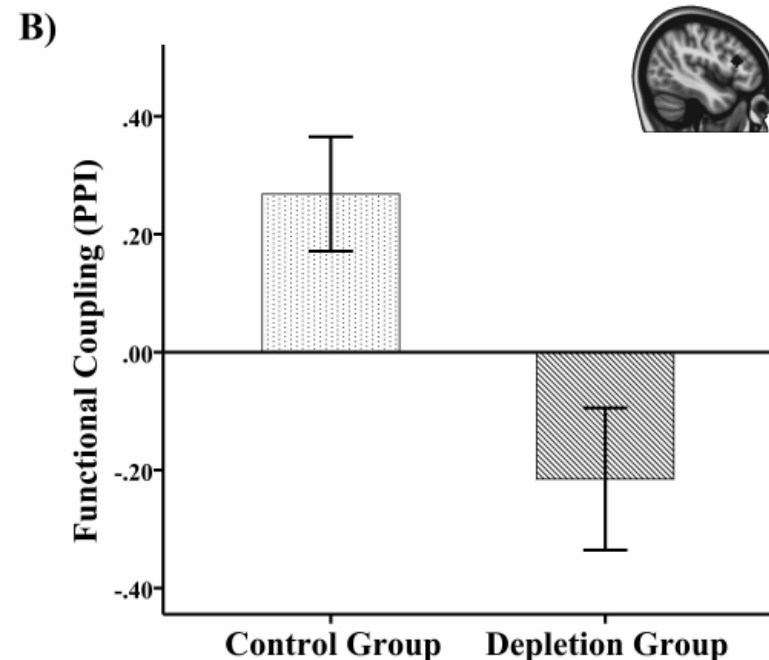
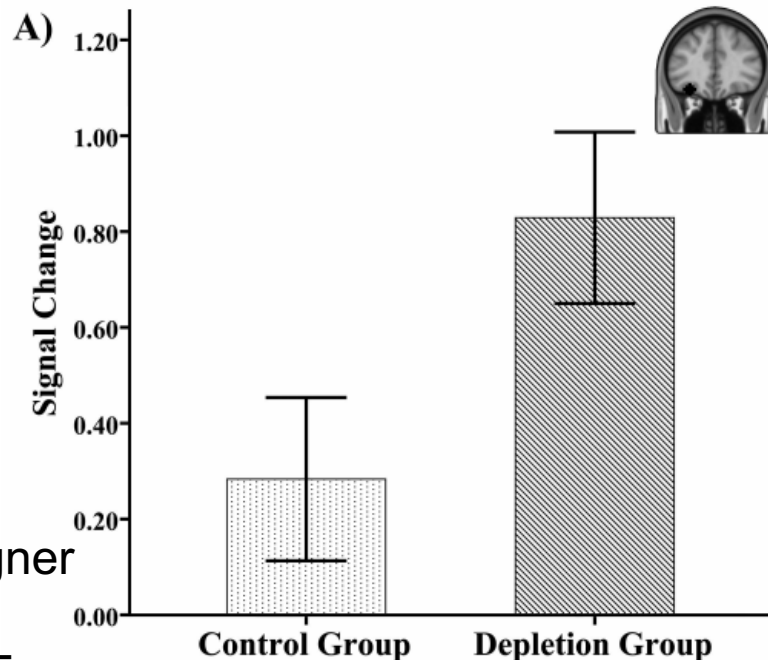
Proportion of rulings in favor of the prisoners by order of decisions faced by the judge that day



Shai Danziger et al. PNAS 2011;108:6889-6892

Recent efforts seek to identify differential neural activity after depletion of self-regulation

Increased reactivity in ventral striatum and differential functional connectivity between orbitofrontal cortex, inferior frontal gyrus. Research preliminary.



Results- Incident albuminuria

Peralta CA , Bibbins-Domingo, K *et al.* Under review

	N	Incidence Rate per 1000 PY	Age Adjusted	Risk Factor Adjusted	SEP Adjusted
Comparison Within Blacks					
In Blacks, population attributable fraction for <i>APOL1</i> was 9.4% HTN and DM was 27.6%					
Comparison between Whites and Blacks					
White	1617	3.9 (62)	ref	ref	ref
Black no <i>APOL1</i>	1058	7.3 (72)	2.06* (1.45 to 2.93)	1.11 (0.75 to 1.65)	1.09 (0.73 to 1.65)
<i>APOL1</i> Black	143	14.8 (20)	4.83* (2.81 to 8.31)	3.12* (1.76 to 5.51)	3.07* (1.69 to 5.60)