EPI222:

Lecture 4 Biological Determinants, Mediators and Mechanisms

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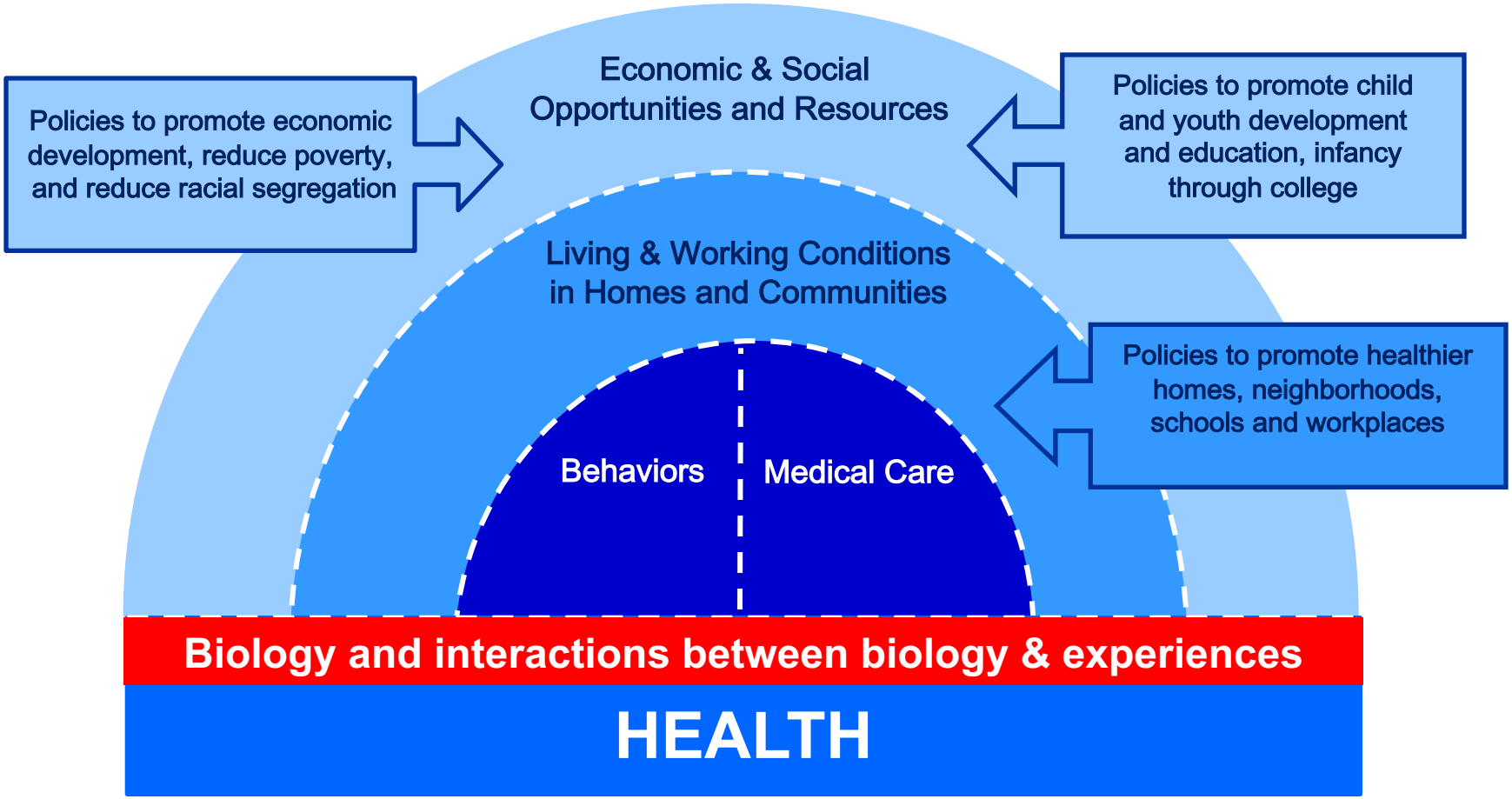
Where are we in the class?



Biological Mechanisms

- Frameworks
- (Behaviors, including use of medical care)
- Stress mediated pathways
- Epigenetics
- 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.

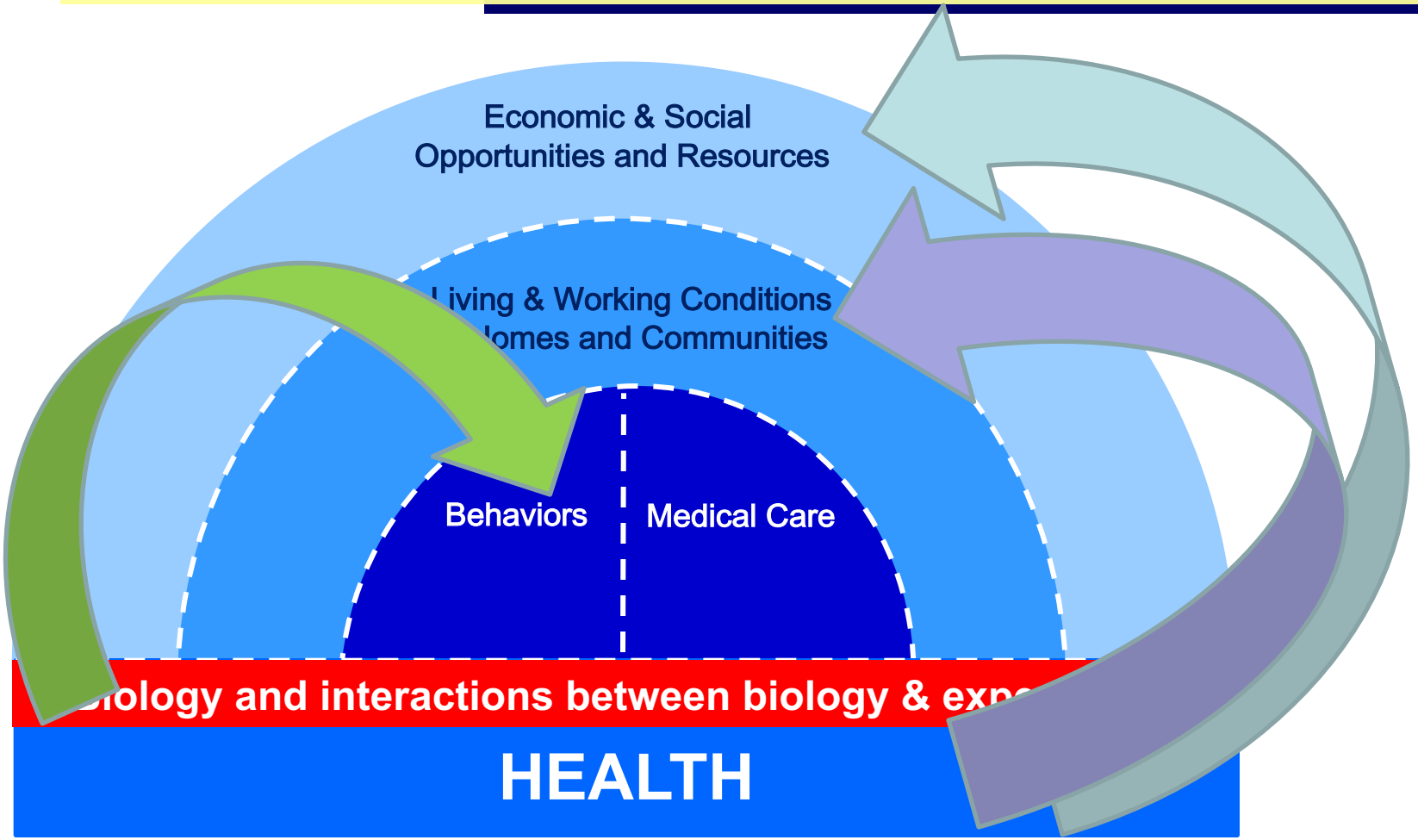
- Helpful in developmental sciences; fortunately, children have fewer measurable health outcomes so the hope is that understanding mechanisms can help us measure and predict risk

What do we mean by embodiment?

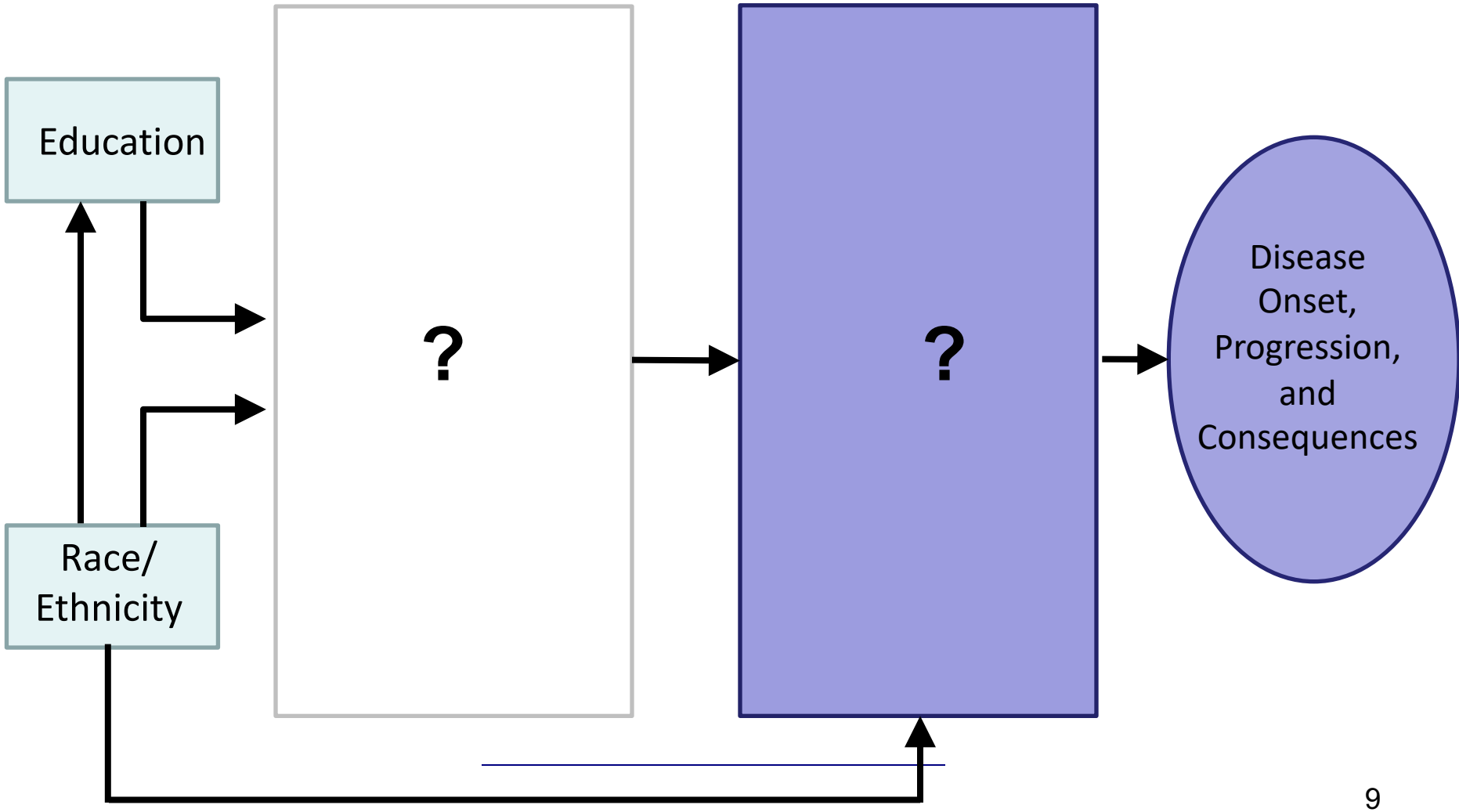
- "how we literally incorporate, biologically, the material and social world in which we live, from in utero to death…" Krieger 2005, JECH

- Many biological phenomena have social origins
- If you find biological correlates of a health disparity, it 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

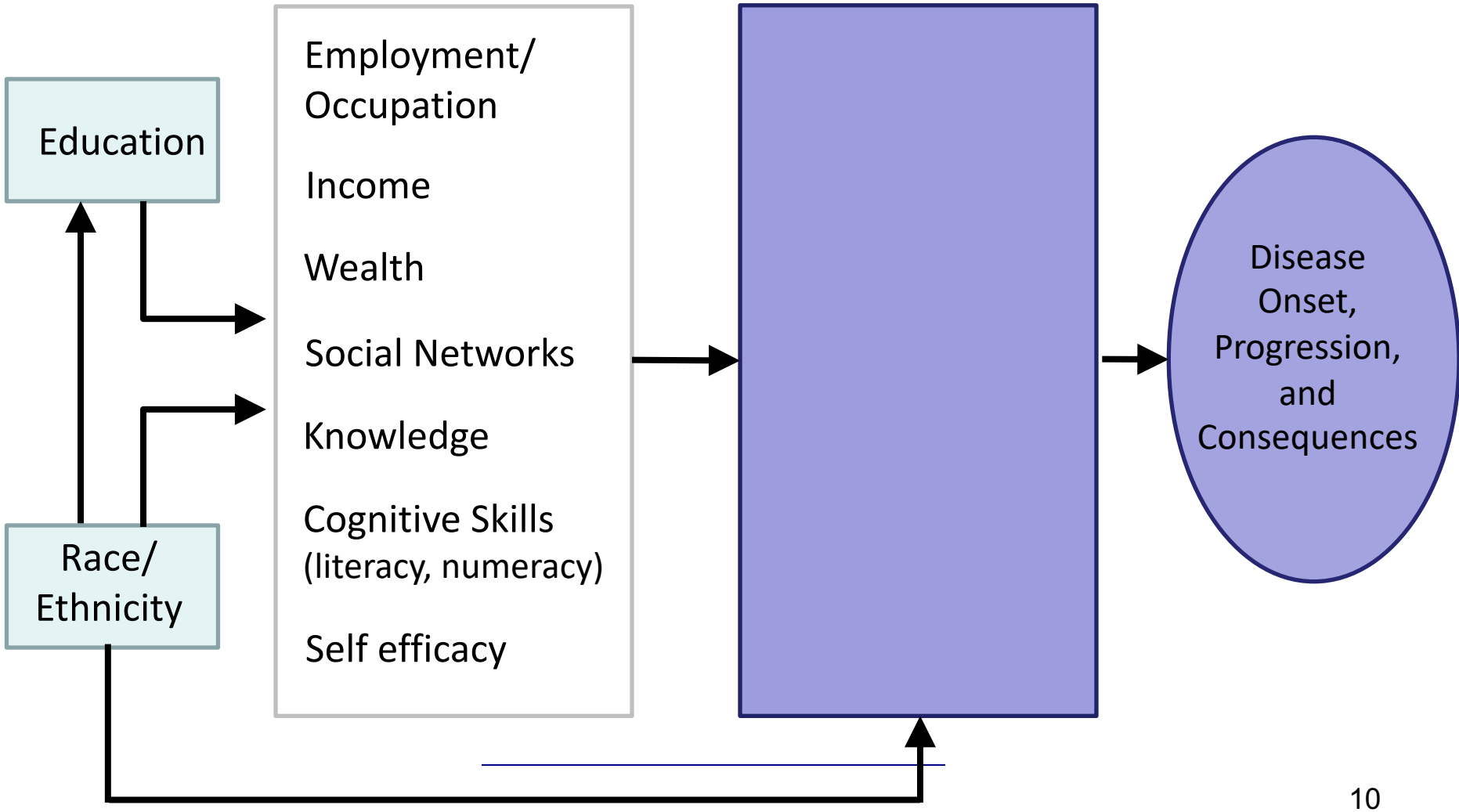
Social→Biological→Social→



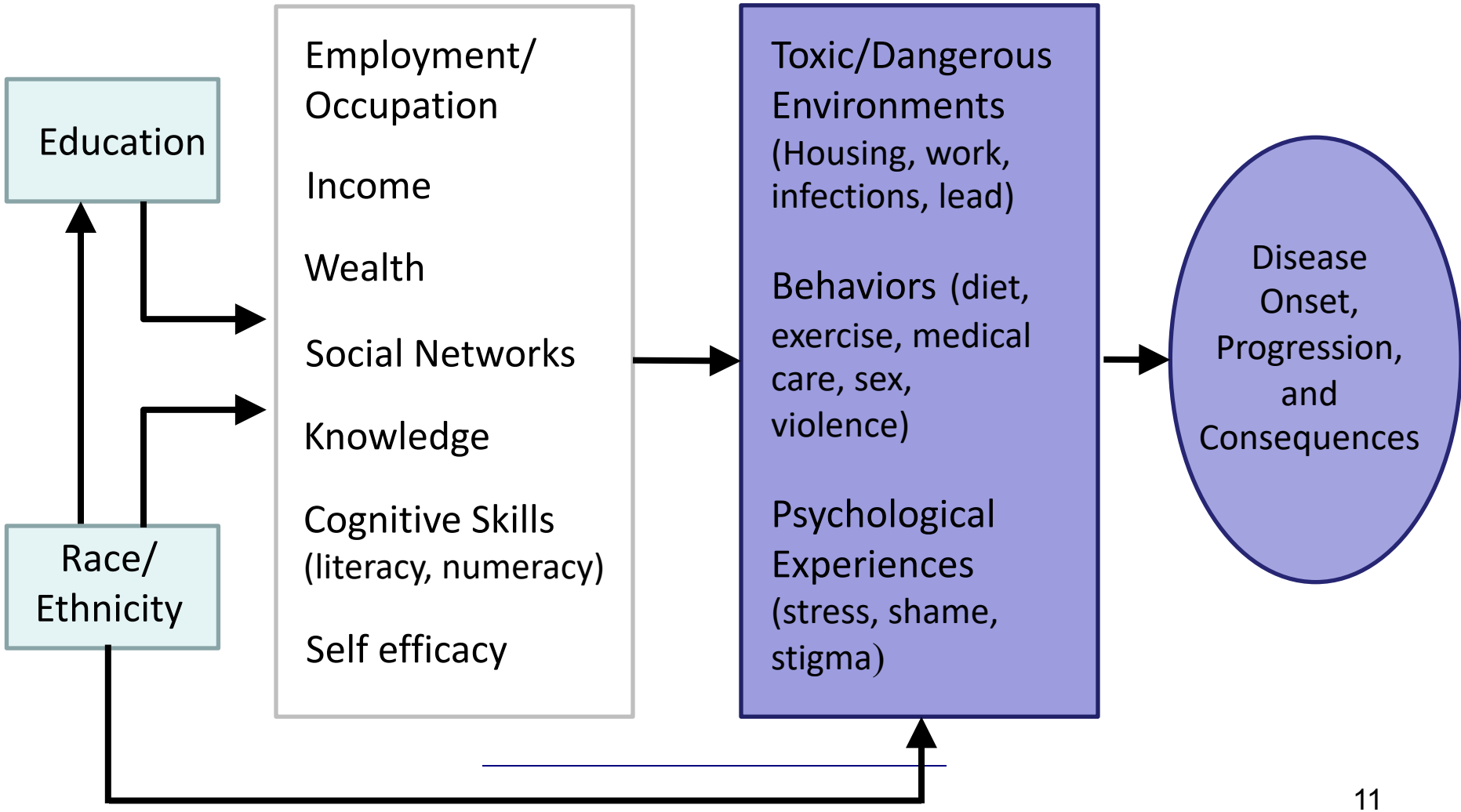
Social Factors and Health: What pathways explain the link?



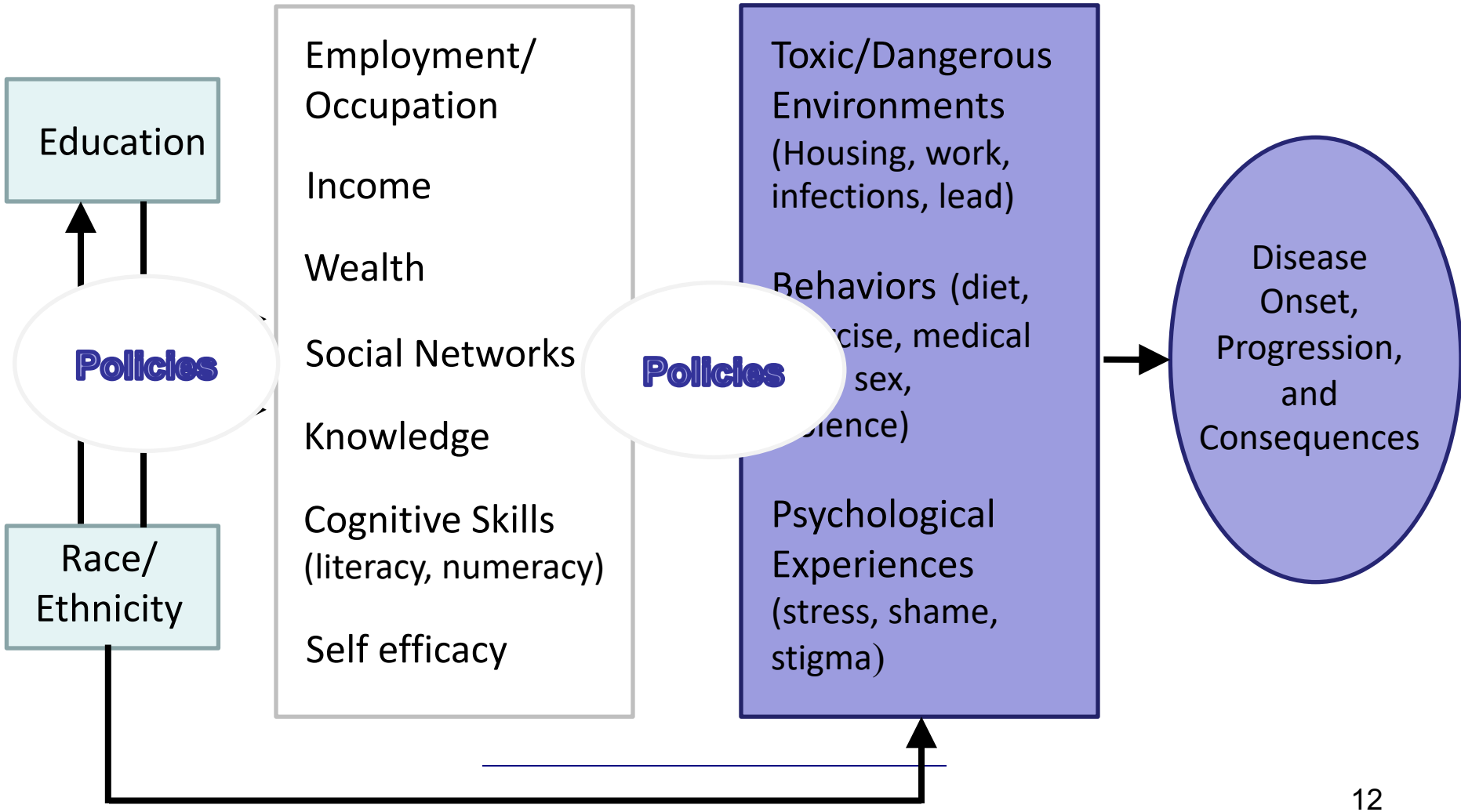
Social Factors and Health: Many socioeconomic, cognitive, and *network* resources



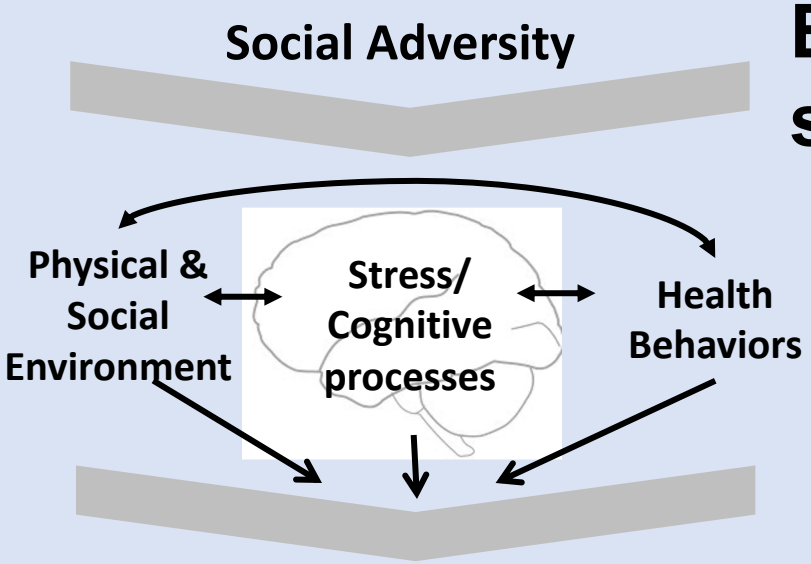
…which in turn influence material, behavioral, and psychological risk

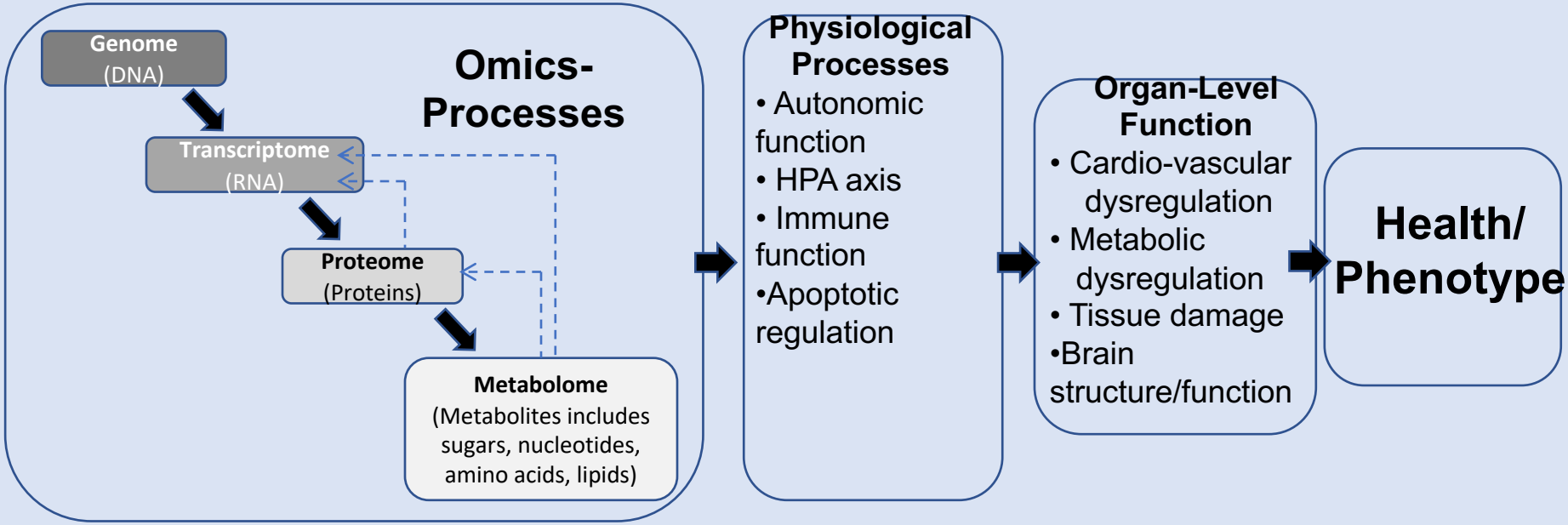


Not a law of physics: These pathways can be weakened or broken.



Biological pathways linking social conditions & health



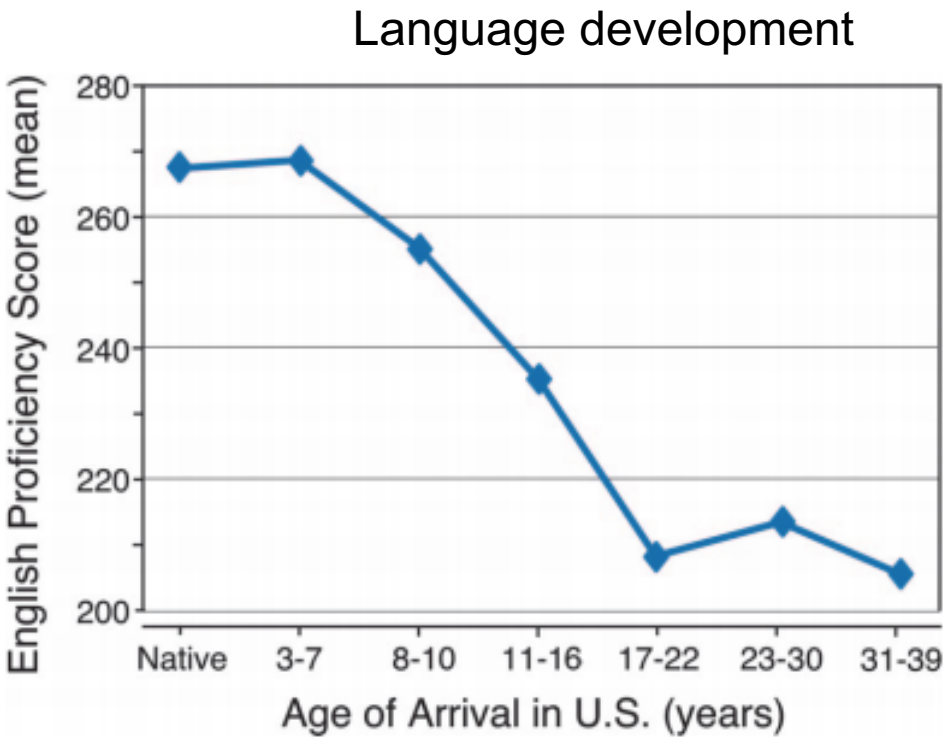


Key Idea in Biological Embedding: Sensitive Periods

- 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

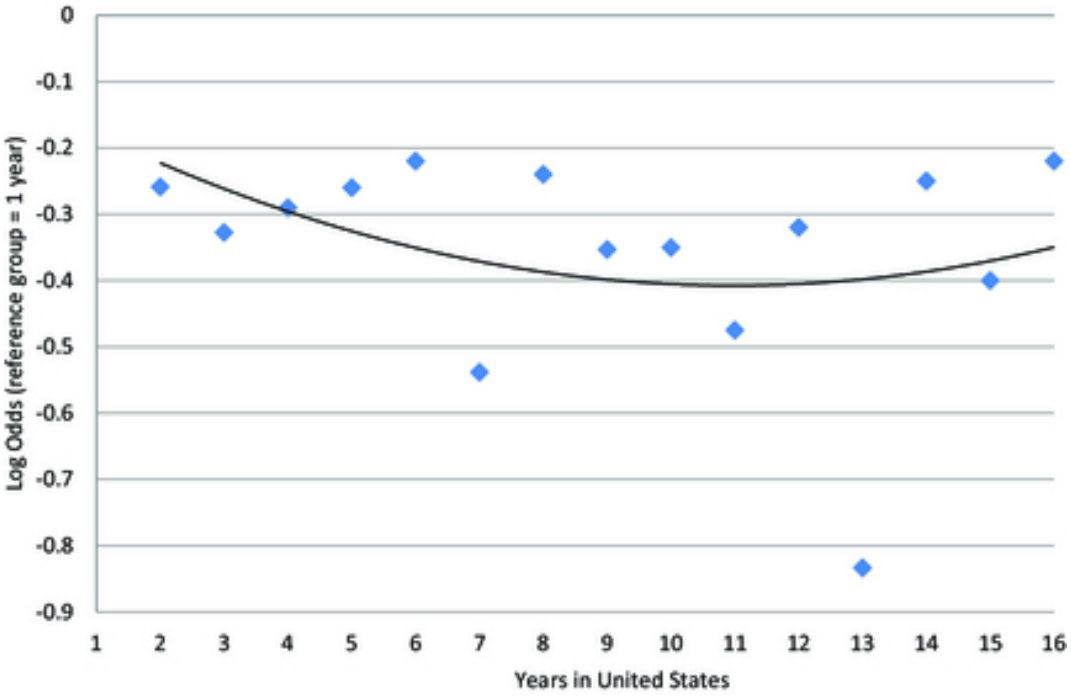
- Periods of rapid growth
- Periods of rapid brain development
- Periods of physiological changes (puberty)
- Enduring changes to gene expression patterns
- Exposures at specific developmental periods set in place behavioral patterns/addictions
- Hierarchy of skill development

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
- These patterns can manifest in outcomes for the next generation, such as LBW

Feedback Occurs Across the Lifecourse

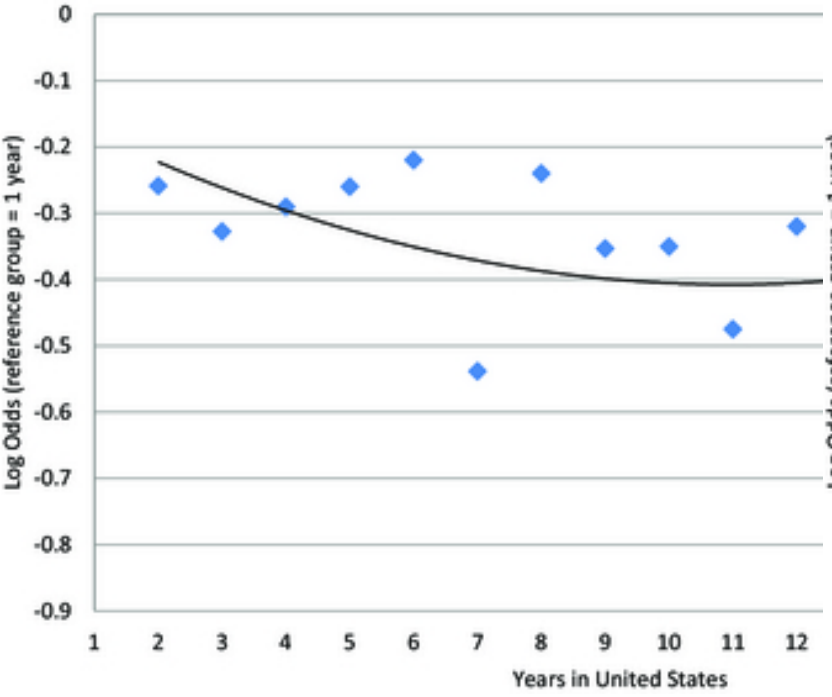
Duration of US Residence and Low Birthweight among Mothers Who Arrived at Ages 18+ Years



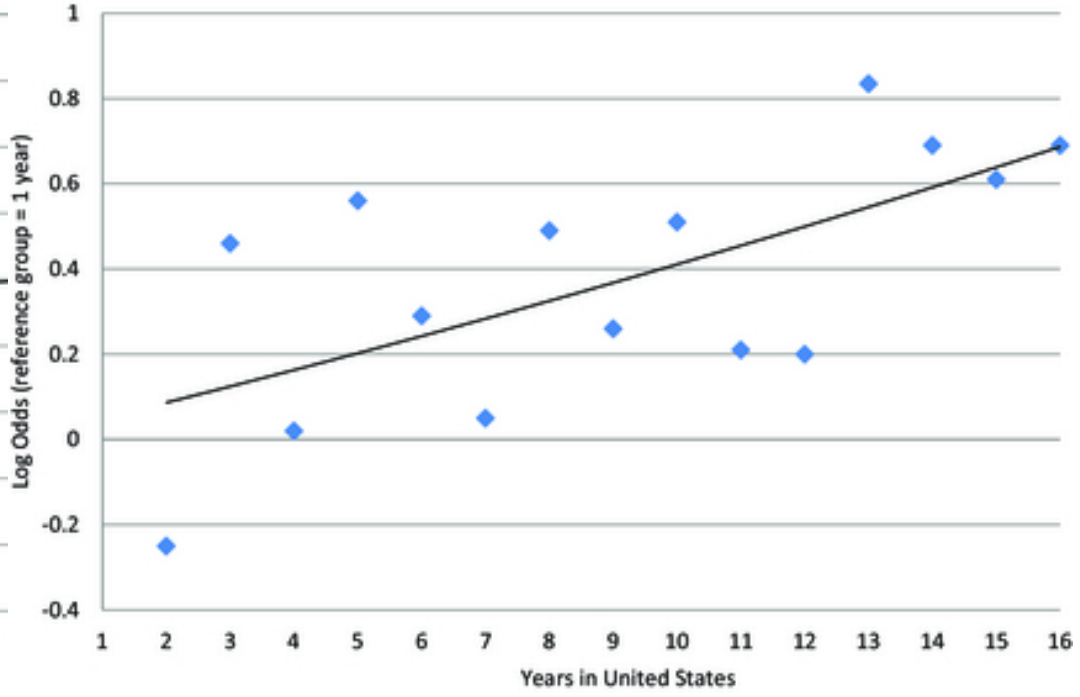
Teitler et al., International Migration Review
18 AUG 2015 DOI: 10.1111/imre.12207
http://onlinelibrary.wiley.com/doi/10.1111/imre.12207/full#imre12207-fig-0005

Feedback Occurs Across the Lifecourse

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



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



Teitler et al., International Migration Review
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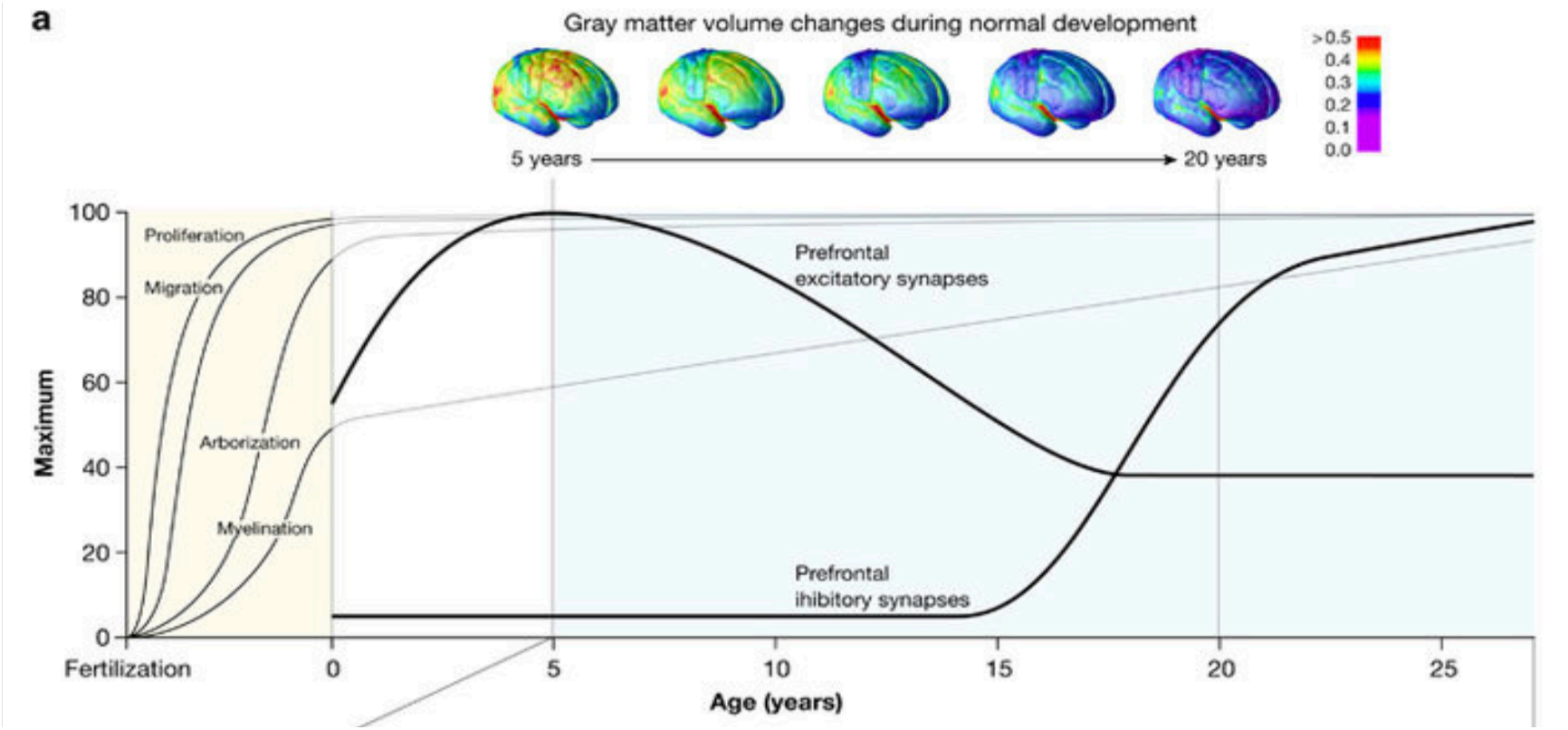
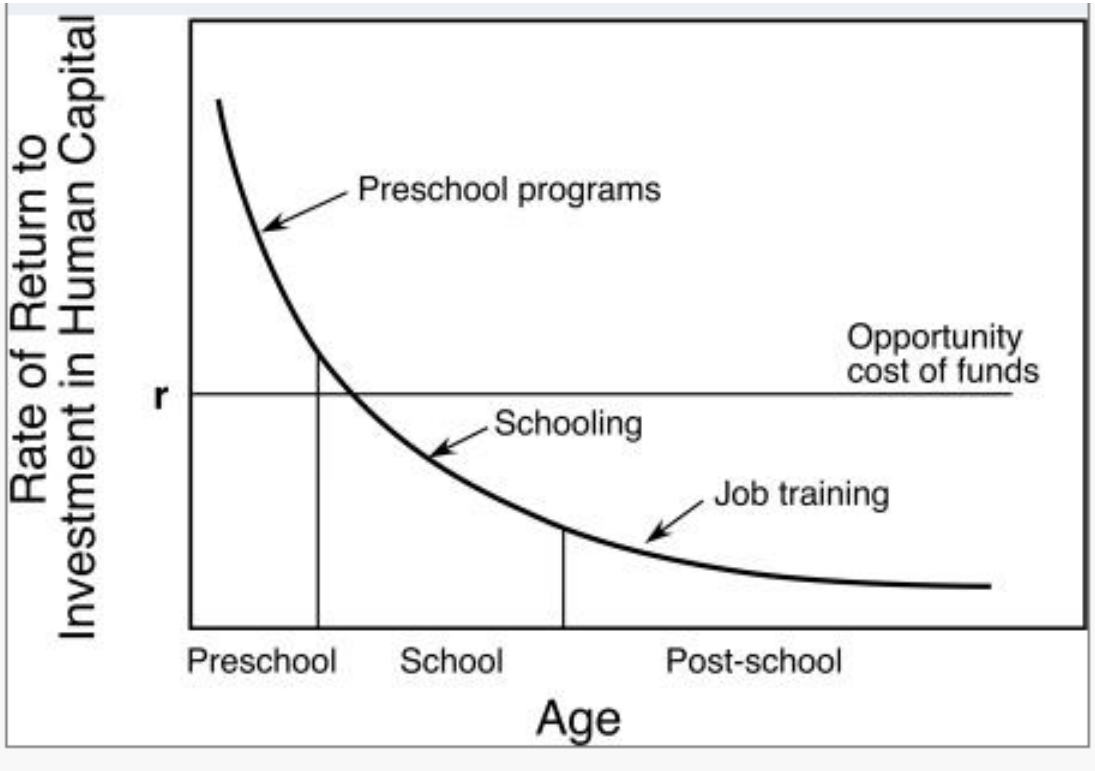
Brain development: Sensitive periods



Insel, 2010

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



Sensitive periods influence when interventions might be most effective

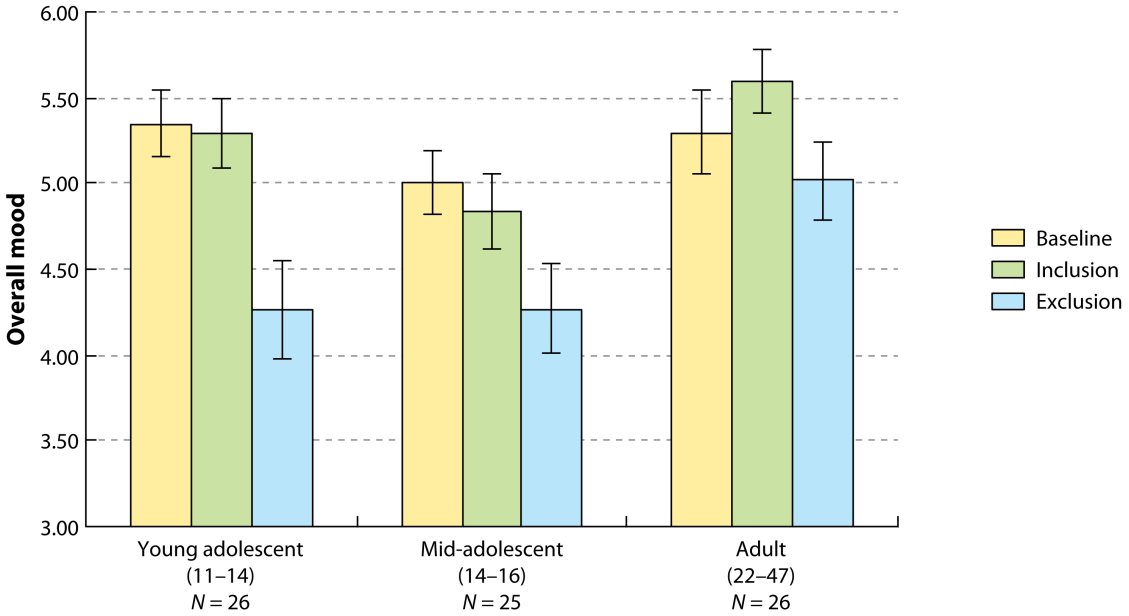
Rates of return to investment in human capital as function of age when the investment was initiated.

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

Annual Reviews

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
- Genetics are an unlikely major cause of health disparities. This would require common genes that cause poor health outcomes and low SEP, for example, or that there are dramatic differences across race/ethnic groups in genetic polymorphisms linked to disease.
- Evidence for genetics as a cause of disparities in most complex disorders is sparse. Few identified genes have large effects and generally don't account for large differences in disease.
- However, there are a few genes that do seem to explain some amount of racial disparities in outcomes, APOL-1 is an example

Apolipoprotein L1

- Apolipoprotein L1 (APOL1) is a minor apoprotein component of HDL cholesterol.
- People who have at least one copy of either the G1 or G2 variant are resistant to infection by trypanosomes
- Two coding sequence variants in APOL1 were identified by looking at variation in genetic ancestry in African Americans with kidney disease.
- 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*

Peralta CA , Bibbins-Domingo, K *et al.* J Am Soc Neph, 2

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
			2.46*	2.93*	2.88*
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)

In Blacks, population attributable fraction for *APOL1* was 10.3%
HTN and DM was 27.6%

Example of Genetics: APOL1

- Example of use of ancestry differences clearly useful for *insights into disease*
- Large beta effect estimate (RR~2), large difference in frequency of the alleles
- But 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 of exposure =.5 and RR=1.5, PAF=.5*.5/(.5*.5+1)=0.2
- If p=.5 and RR=4, PAF=.5*3/(.5*3+1)=0.60

Race in Clinical Decision Making

- Differences in clinical algorithm/guidelines by race exist across a range of contexts
  - Diagnosis: Kidney disease, PFTs
  - Treatment: HTN, ASCVD
- Often supported by data – but what data?
  - Why do we have this data in the first place?
- Reinforce biological definitions of race
- Can these contribute to inequities? Address inequities?

Events

Race-Conscious Medicine Event Series: Spring 2021

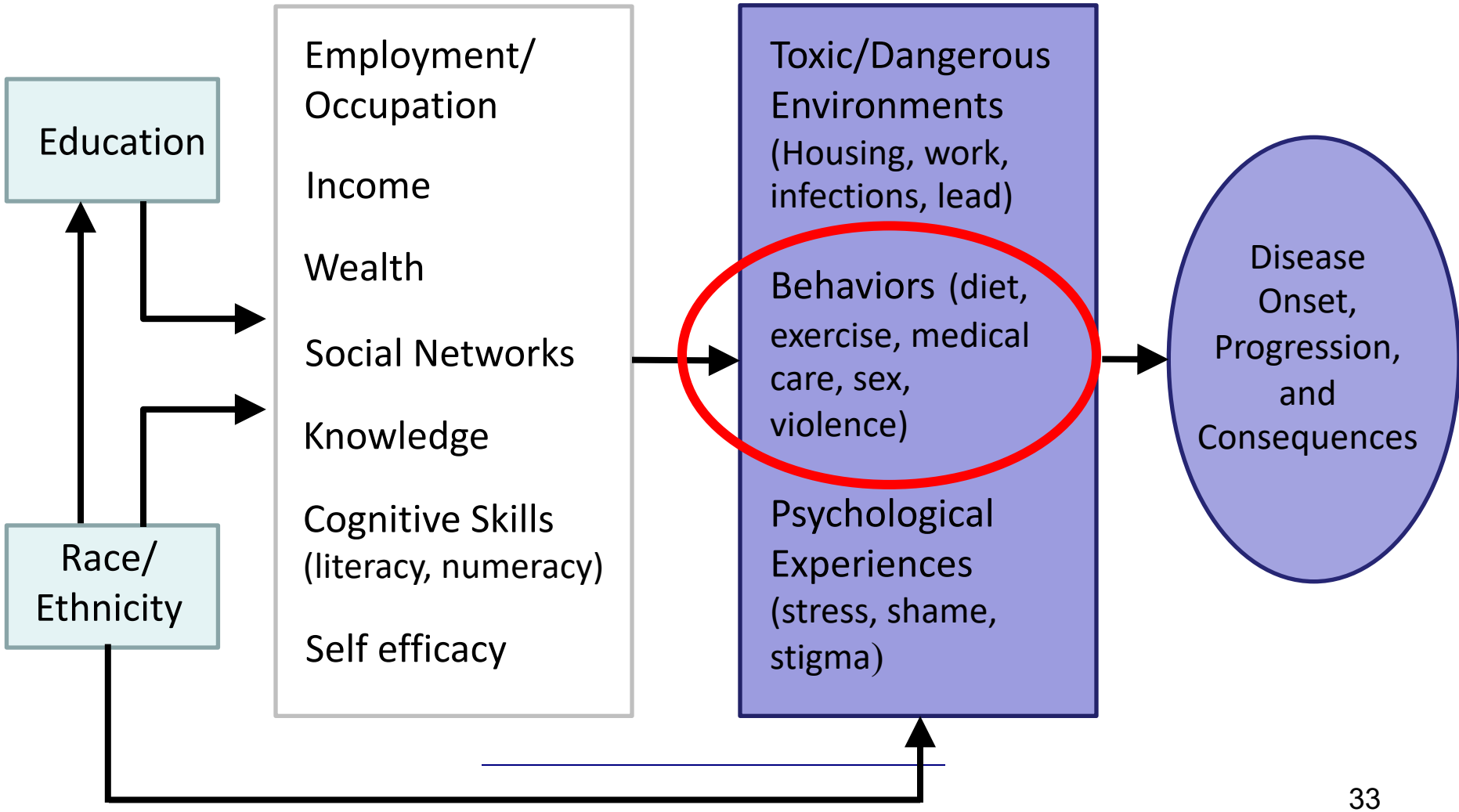
Background:
Over the past few years, there has been increasing attention and discourse focusing on social determinants of health, root causes of health inequities, and the role of structural racism in these inequities. In these conversations, how medicine considers and engages with the construct of race has surfaced as an area of controversy. Those in academic medicine have grappled with questions such as:

- What is the history of race in the health sciences, and how does that narrative operate in clinical practice, health research, and medical education today?
- How does inclusion of race in diagnostic and therapeutic algorithms reconcile with thinking about social determinants of health and how they produce and perpetuate health inequities?
- How does the current approach to considering race in medicine relate to and potentially contribute to ongoing societal narratives about racial differences and racial inequities?
- How does the conversation about the use of race in medicine relate to the growing attention to genetic ancestry and population-based variation in genetic polymorphisms?

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



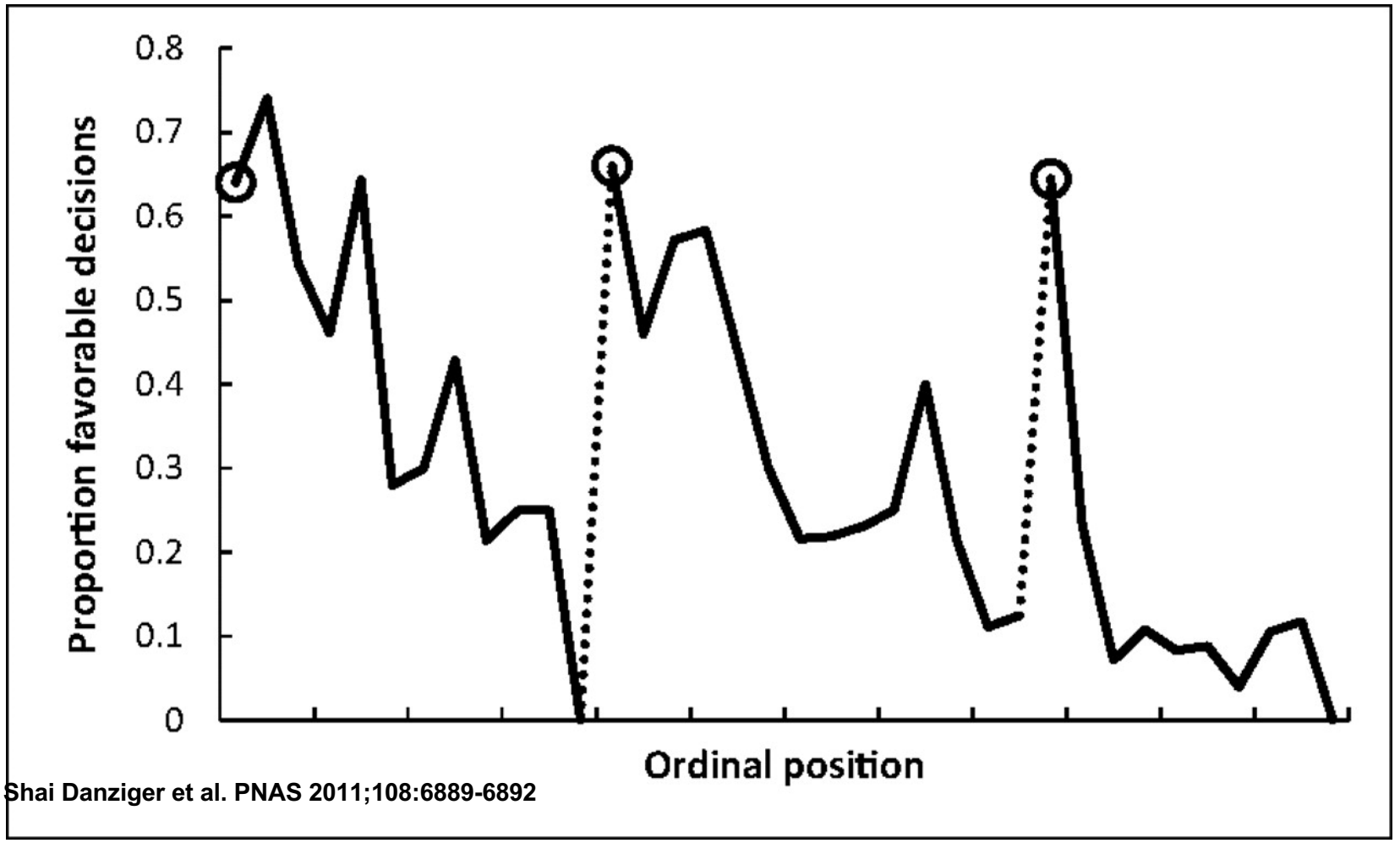
Behaviors are shaped and constrained by social context

- 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 (neurodevelopment and risk taking behavior)
  - Biological embedding and sensitive periods imply that environmental causes may be relevant at developmentally specific ages (e.g. cigarette example)

Physiology and behavior: Self-regulatory depletion

- Self-regulation conceptualized as a “resource” depleted by making difficult decisions or resisting temptation; influenced by blood glucose
  - 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 (Gailliott)
  - Meta-analysis shows persistence across task demands and subsequent displays of self-control
  - Famous example: Judges make more lenient parole decisions early in the morning and right after lunch (moral: bring your dissertation committee snacks)

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

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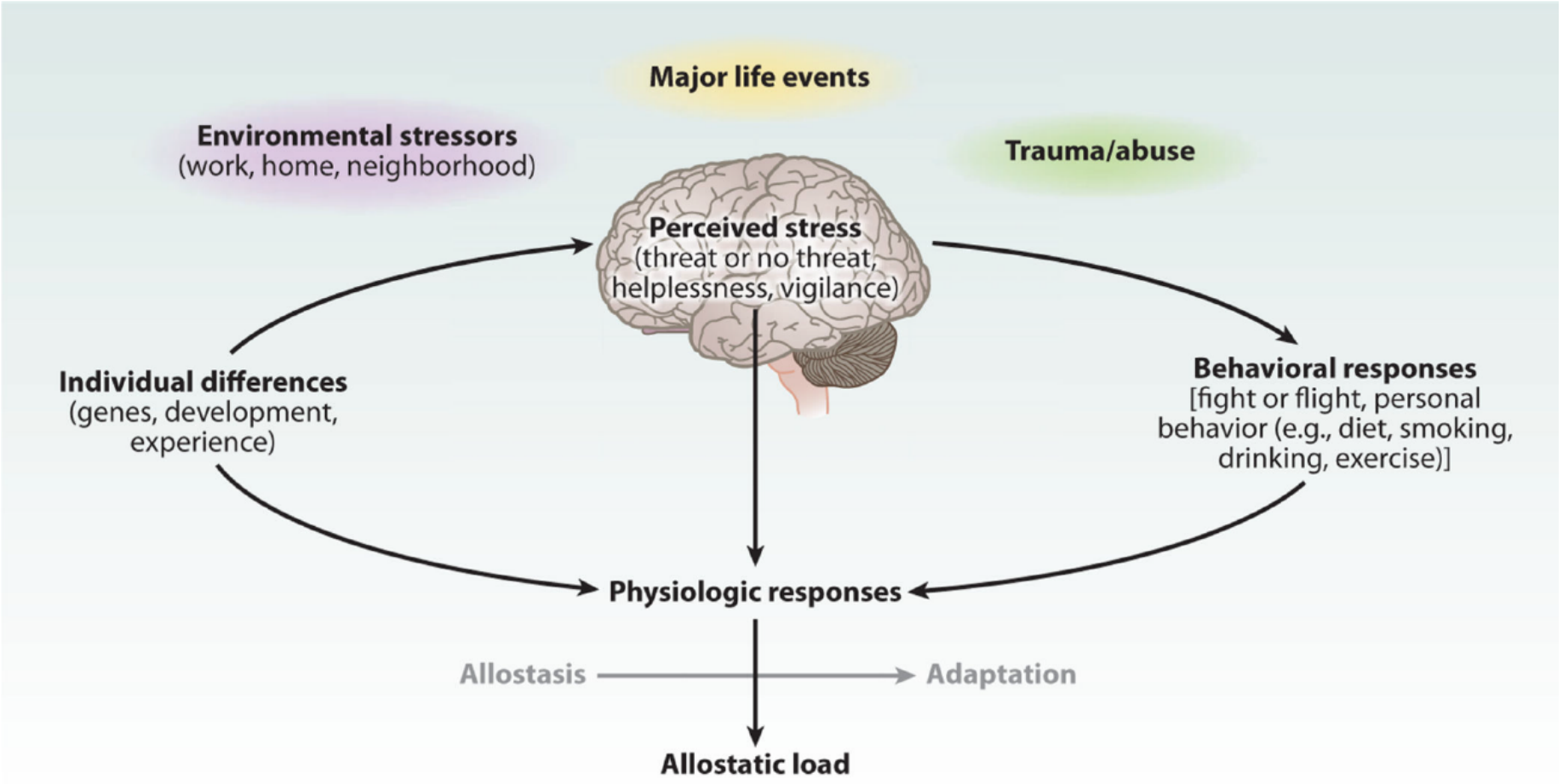
What are stress and stressors?

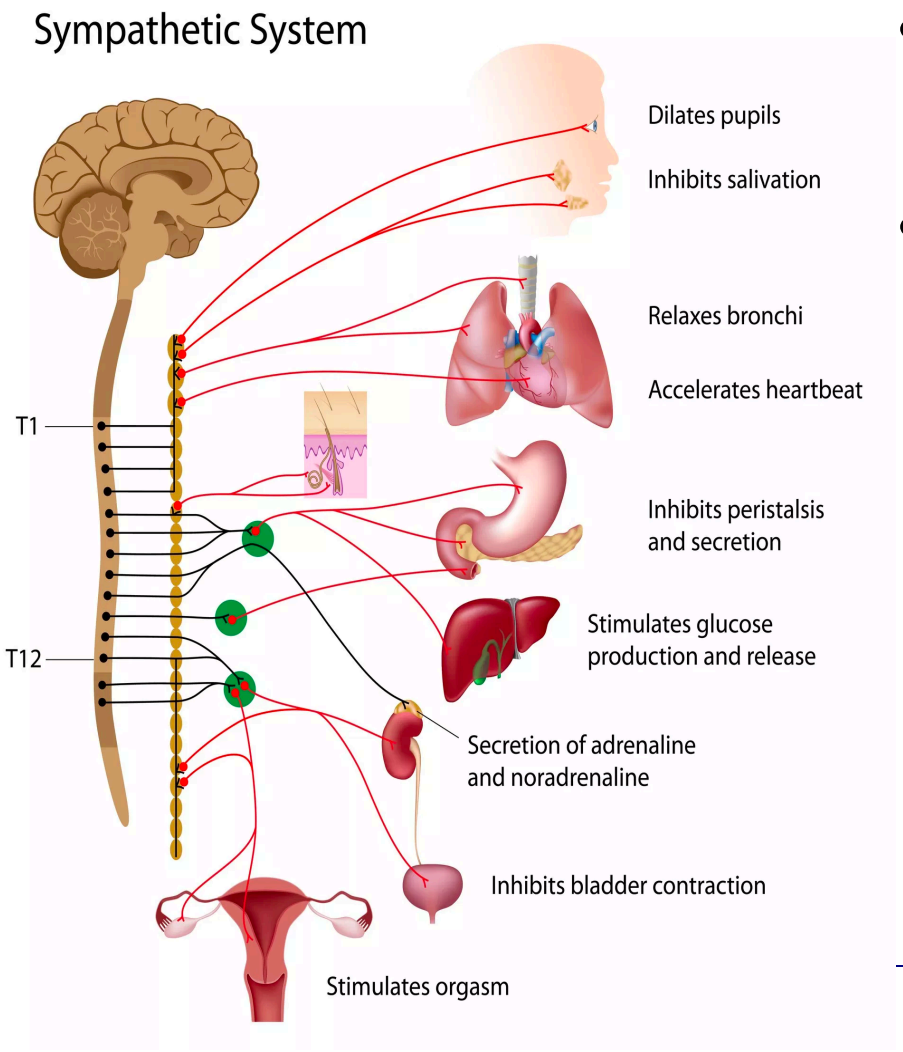
- Stressors: external demands encountered by the organism
  - Source:
    - Physical (cold, infection)
    - Psychological (fear, shame, anxiety)
  - Duration:
    - Acute (trauma)
    - Chronic (daily hassles)
- Stress occurs when demand is perceived to exceed capacity to respond
- Stressors induce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

Stress triggers many physiologic responses



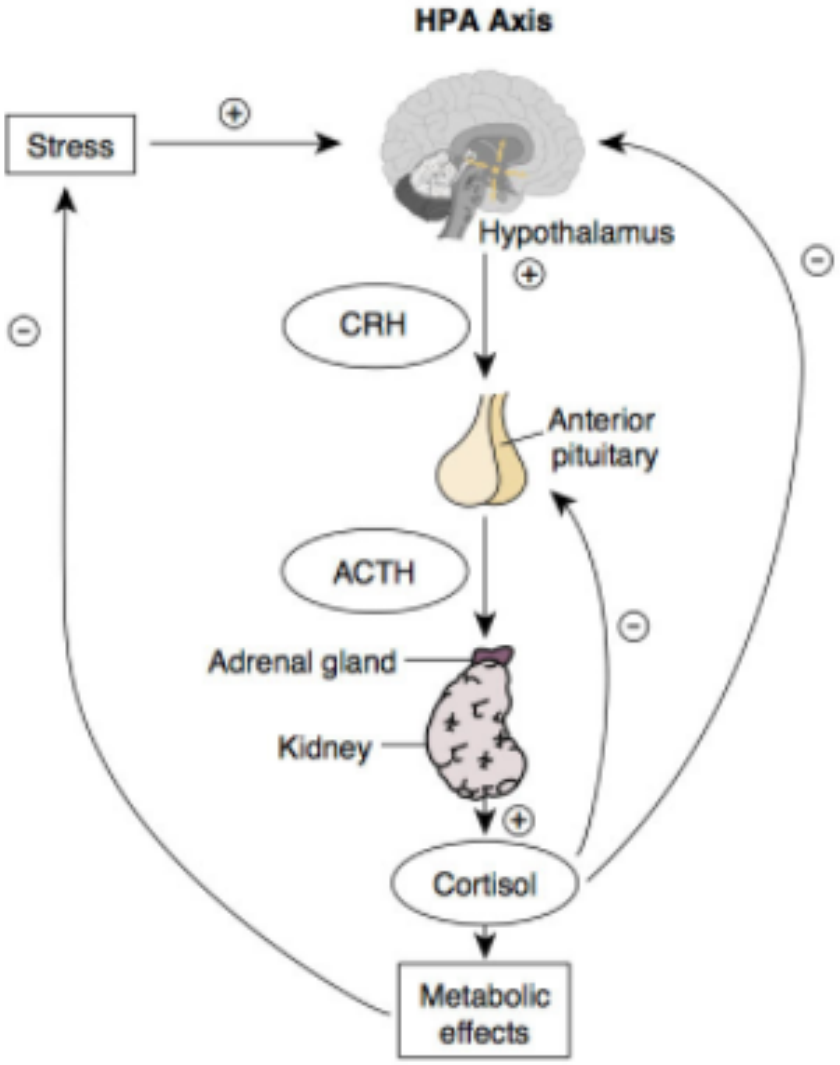
McEwen and Gianaros, annu rev med, 2011

Sympathetic NS response



- Immediate response- fight or flight
- Activation results in secretion of adrenaline and nor adrenaline from the adrenal cortex--> increase heart rate, dilation of pupils, etc.

HPA axis response



Hypothalamus-pituitary-adrenal axis: hypothalamus releases corticotropin releasing hormone triggering adrenocorticotropic 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

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

Allostatic Load and SES

- 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

Robinette, 2016

Predictors of Allostatic Load

Table 4
Multivariate models predicting overall allostatic load (regression estimates [SE]).

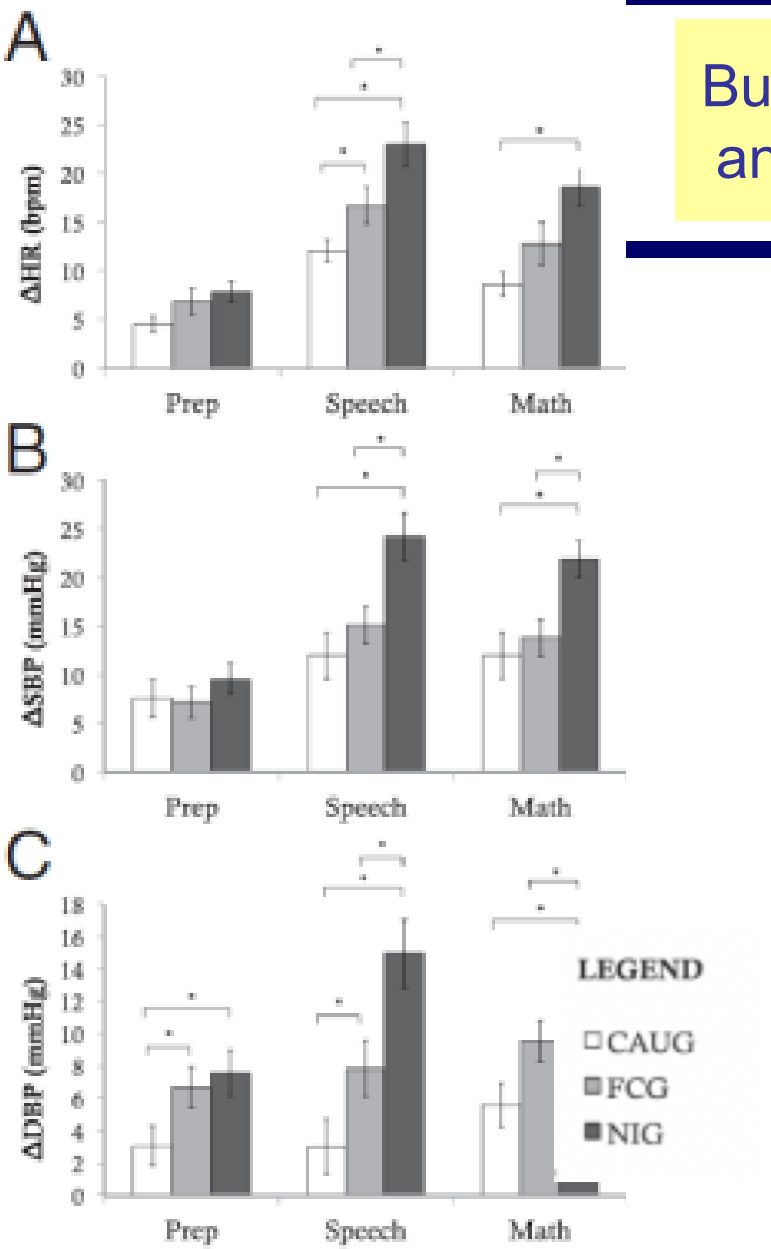
	Model 5
Intercept	−0.14 (0.31)
Neighborhood income	−0.04* (0.01)
Individual income	−0.01† (0.01)
Age	0.16*** (0.01)
Gender[a]	0.10 (0.07)
Safety[b]	−0.14† (0.07)
Cohesion	−0.02 (0.05)
Perceived stress	0.00 (0.01)
Anxious arousal	0.02* (0.01)
Exercise[c]	−0.19* (0.08)
Smoking	0.00† (0.00)
Fast food[d]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

† $p < 0.05$.
* $p < 0.01$.
** $p < 0.001$.
*** $p < 0.0001$.

Robinette, 2016

Bucharest Early Intervention Study

Bucharest Early Intervention Study and Stress Response Differences



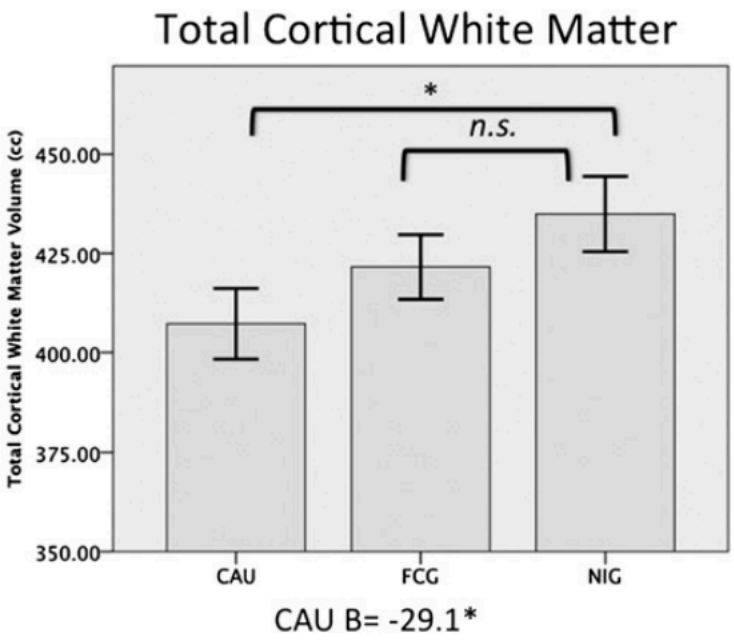
- Trier Social Stress Test at age 12
- Measure of SNS response during these tasks
- Blunting of SNS response is what is observed
- Seen across a variety of challenges- non social and social
- Chronic activation in early life→ blunted response

McLaughlin, 2015

Stress Mediated Pathways and Neurodevelopment

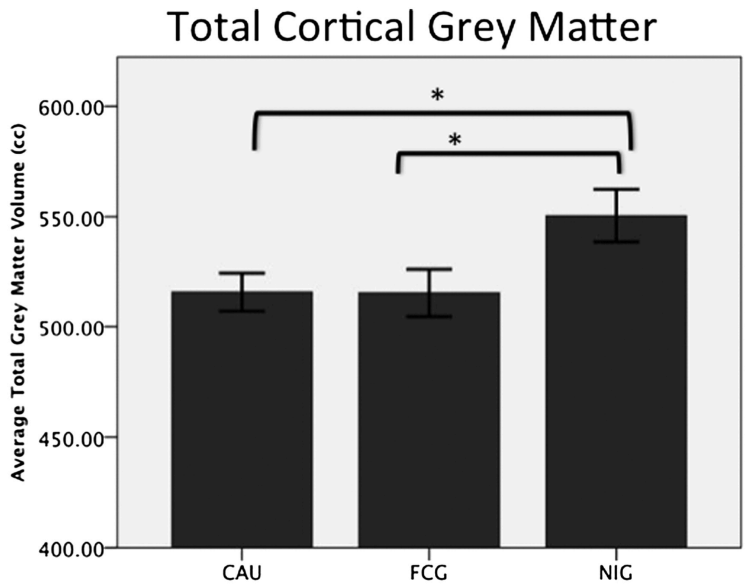
- Early life stress changes brain development and neurodevelopmental outcomes
- Not separate from the stress response pathways→ products of the stress response influence brain structure/function
  - There are cortisol receptors in many areas of the brain, including limbic system areas but also PFC. Animal 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



CAU B= -29.1*

Significant in Model 3 (controlling for gender and age)



CAU B= -31.4*

FCG B= -36.1*

Significant in Model 3 (controlling for gender and age)

Sheridan, 2012

Age at adoption predicts recovery from institutionalization: BEIP

Mean score in kids randomized younger than that age

Mean score in kids randomized older than that age

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

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

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

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

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

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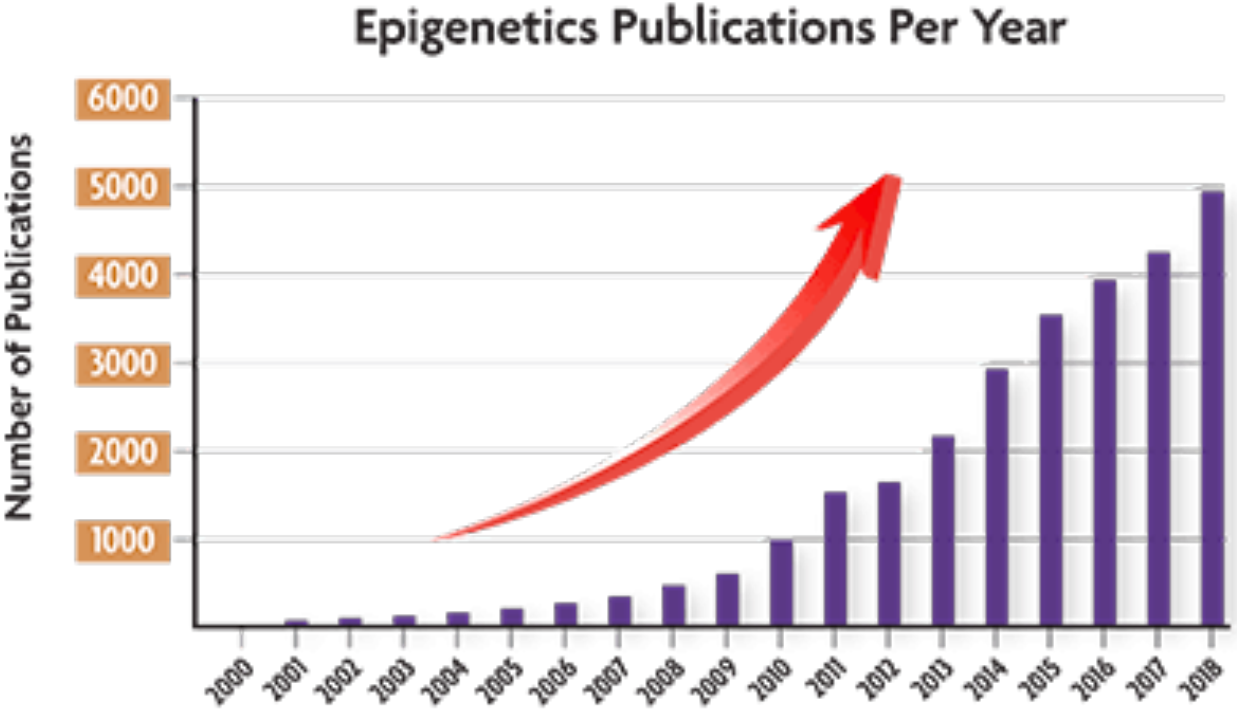
Epigenetics

- Epigenetics is the study of changes (some heritable) in gene expression 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
- May operate through multiple downstream physiologic pathways

Slide Credit: Meg Jones, PhD


Epigenetics Publications Per Year
Number of Publications
6000
5000
4000
3000
2000
1000
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

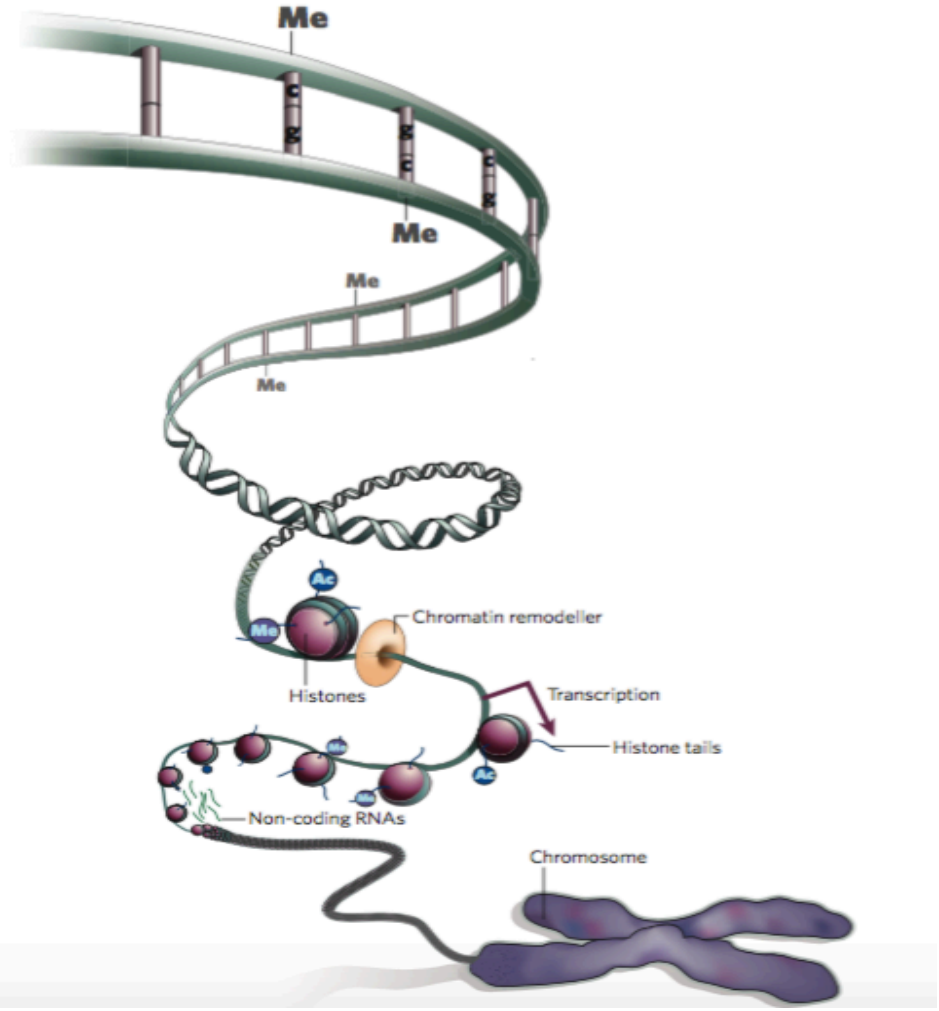

Joe Klein: The CIA's Afghan Disaster
Yemen: The New Center Of Terror
Why the Recession Hasn't Been Cool To Teens
TIME
WHY YOUR DNA ISN'T YOUR DESTINY
The new science of epigenetics reveals how the choices you make can change your genes —and those of your kids
BY JOHN CLOUD

What is Epigenetics?

Modifications to DNA that affect packaging without changing sequence

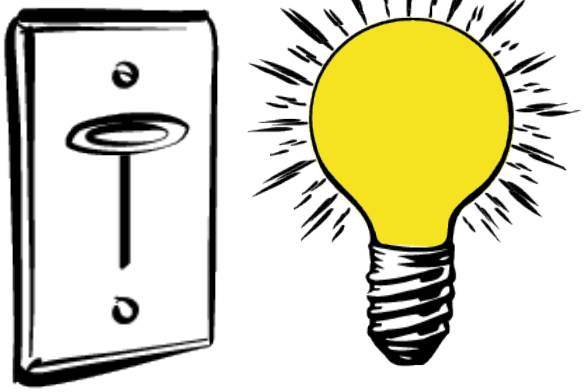
1. Histone variants and modifications
2. **DNA methylation**
3. ncRNAs

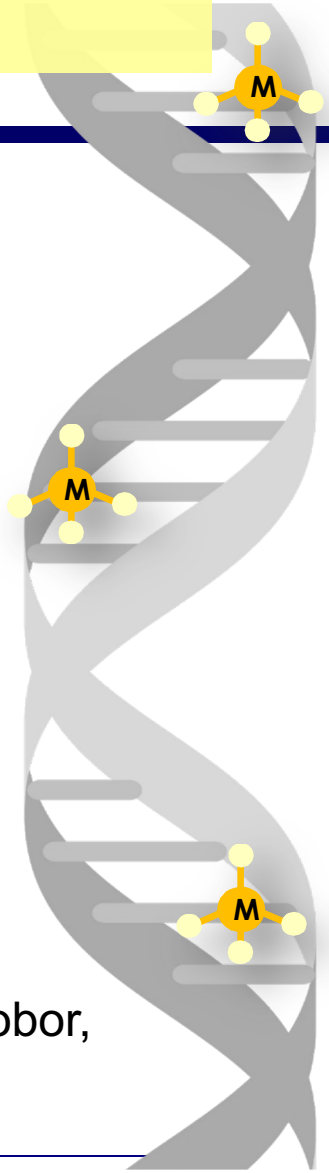
Important role in development and tissue specificity



AACR Human Epigenome Task Force et al. Nature, 2008
Slide credit: Meg Jones, PhD

DNA Methylation



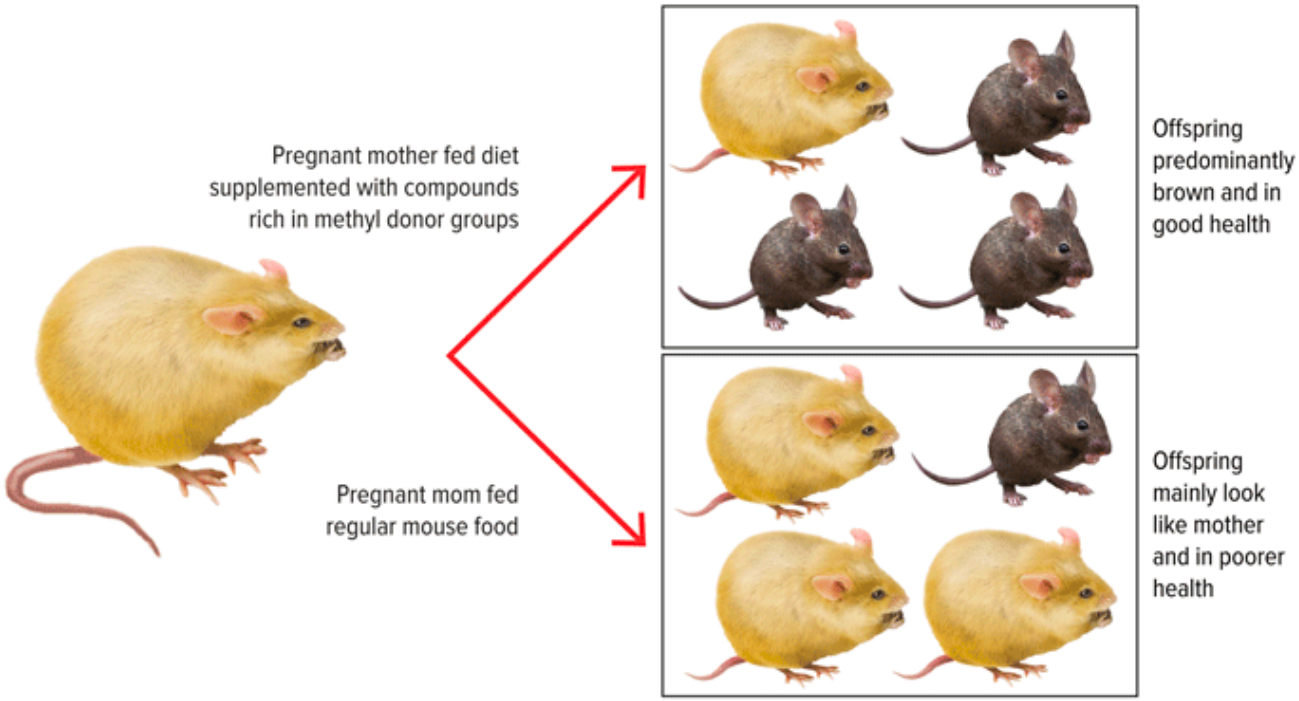


Slide Credit: Mike Kobor, PhD

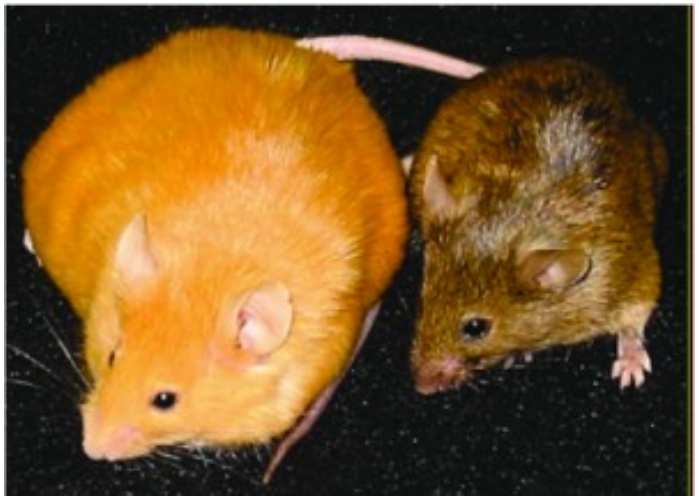
What do epigenetic alterations look like?

Fraga et al. (2007)

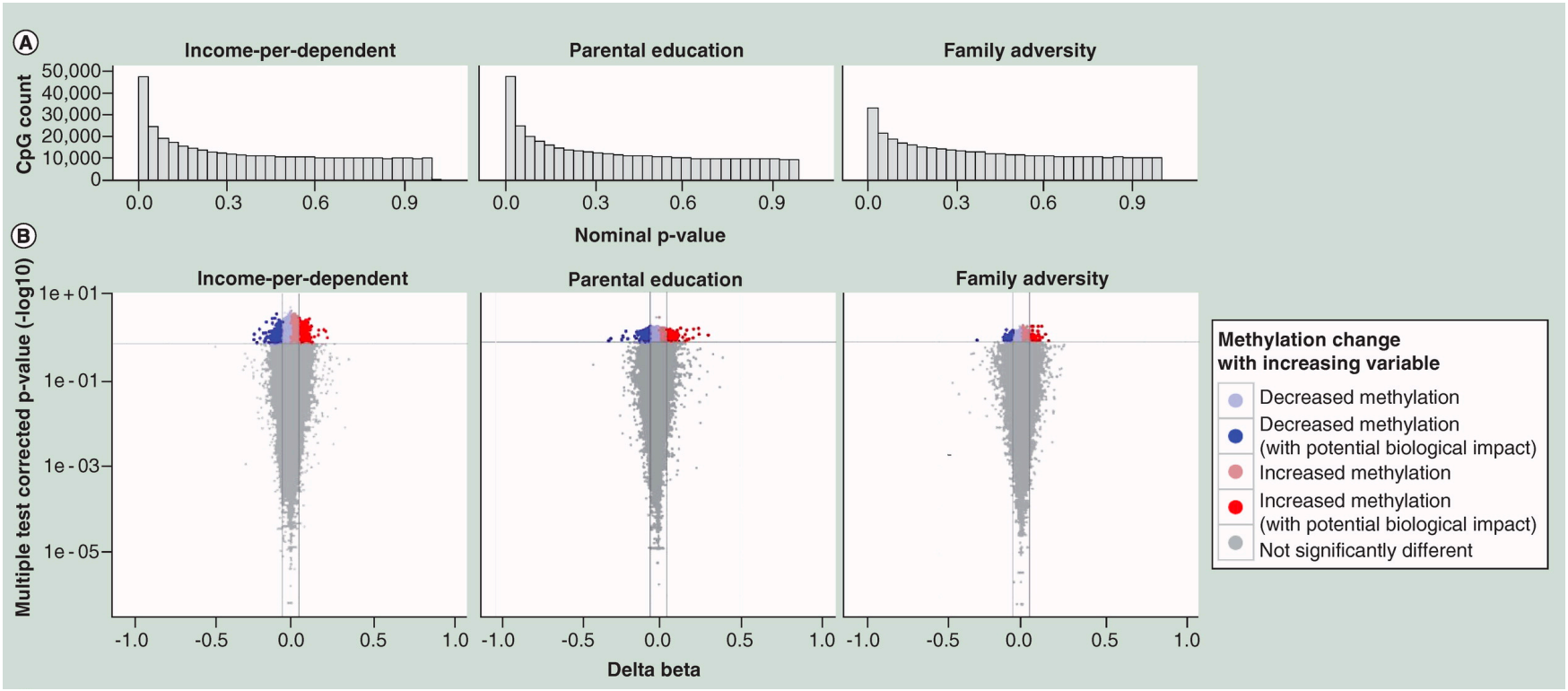
Slide Credit: Nicki Bush, PhD


Pregnant mother fed diet supplemented with compounds rich in methyl donor groups
Pregnant mom fed regular mouse food
Offspring predominantly brown and in good health
Offspring mainly look like mother and in poorer health

Jirtle (2006)

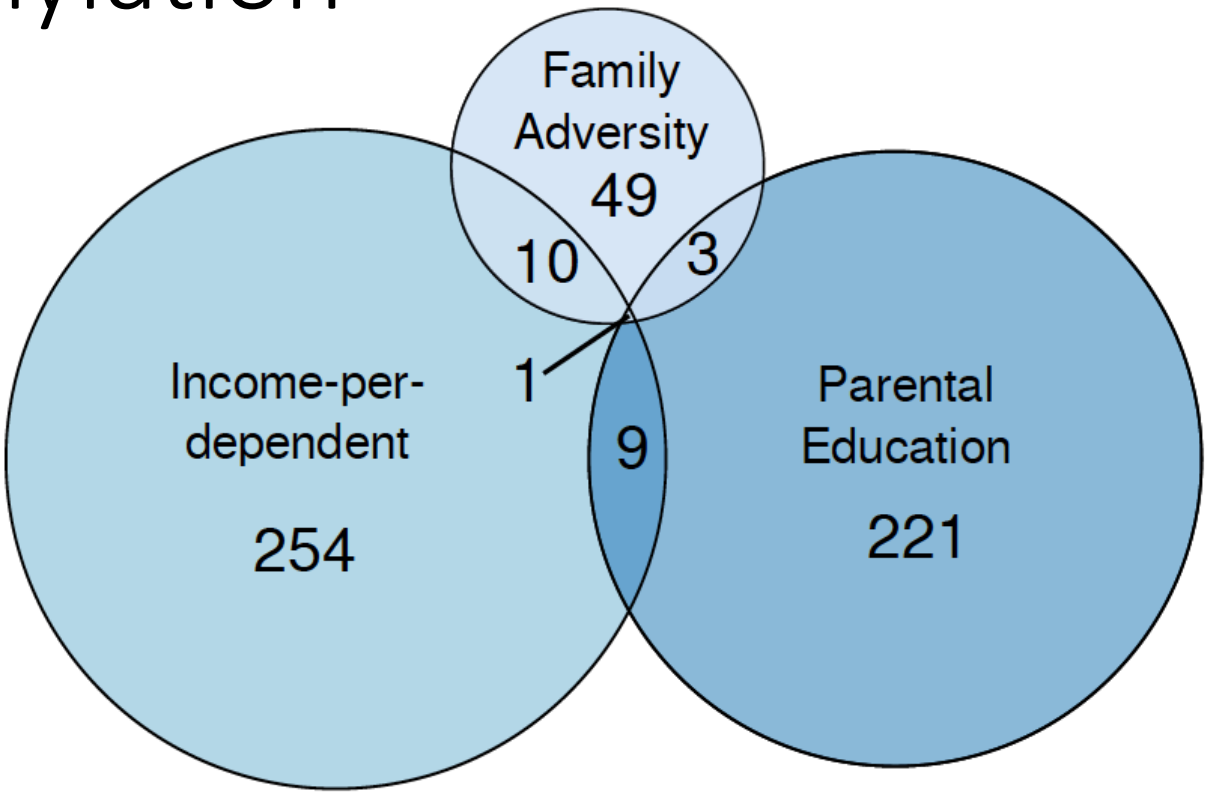


Childhood Experience and DNA methylation



Bush, Edgar. . . Adler, Kobor & Boyce (2018)

Childhood Experience and DNA methylation



Bush, Edgar. . . Adler, Kobor & Boyce (2018)

Epigenetic clock: Horvath and Raj

- Biological aging results in consistent changes in patterns of DNA methylation which has given rise to DNA methylation age estimators (i.e. the epigenetic clock).

- 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.

- → first clock was a weighted average of the 353 clock CpGs, which is then transformed to DNAm age (now there is more than just one clock)

- → Comparisons between biological age and DNAm age yield insights into potential risk for disease or accelerated aging

- Better suited to smaller data sets

More novel may not be more helpful

Table 4
Association of Socio-Economic Position (SEP) with unstandardized measures of Allostatic Load and Epigenetic Age Acceleration.

	Allostatic Load excluding meds	Allostatic Load including meds	Horvath EAA	Hannum EAA
	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)
Childhood social class				
Professional/Managerial	REF	REF	REF	REF
Non-manual/skilled manual	0.32(-0.43, 1.07)	0.33(-0.50, 1.17)	−1.34(-3.84, 1.17)	−0.63(-3.10, 1.85)
Semi-skilled/unskilled	0.24 (-0.17, 0.65)	0.23(-0.23, 0.68)	0.80(-0.56, 2.17)	0.93(-0.42, 2.28)
Adulthood social class				
Professional/Managerial	REF	REF	REF	REF
Non-manual/skilled manual	0.37(-0.43, 1.17)	0.46(-0.43, 1.35)	0.58(-2.14, 3.30)	0.77(-1.92, 3.45)
Semi-skilled/unskilled	0.76***(0.36, 1.16)	0.84***(0.40, 1.29)	0.06 (-1.30, 1.42)	0.24(-1.10, 1.58)
Social Class Trajectory				
Stable High	REF	REF	REF	REF
Upwardly mobile	−0.02(-0.56, 0.52)	−0.08(-0.68, 0.52)	0.11(-1.73, 1.94)	0.56(-1.26, 2.37)
Downwardly mobile	0.49(-0.05, 1.04)	0.53(-0.08, 1.14)	−0.80(-2.64, 1.05)	−0.17(-2.00, 1.66)
Stable low	0.90***(0.35, 1.44)	0.97**(0.37, 1.58)	1.16(-0.69, 3.01)	1.35(-0.48, 3.17)
Educational attainment				
Tertiary	REF	REF	REF	REF
Secondary	0.12(-0.33, 0.56)	0.15(-0.35, 0.64)	−0.57(-2.07, 0.93)	−1.18(-2.66, 0.30)
Primary	0.74**(0.23, 1.25)	0.88**(0.32, 1.45)	−0.03(-1.75, 1.69)	−0.40(-2.10, 1.30)
Household Income Tertile				
Highest	REF	REF	REF	REF
Intermediate	0.44(-0.05, 0.92)	0.59* (0.05, 1.13)	−0.50(-2.13, 1.13)	−1.08(-2.69, 0.53)
Lowest	0.71**(0.22, 1.20)	0.96***(0.41, 1.50)	0.56(-1.10, 2.22)	0.00(-1.65, 1.63)

Age and sex adjusted independent association of measures of SEP with AL and the epigenetic clocks.
***significant at the 0.001 level; ** significant at the 0.01 level; * significant at the 0.05 level.

McCrory et. al., 2019

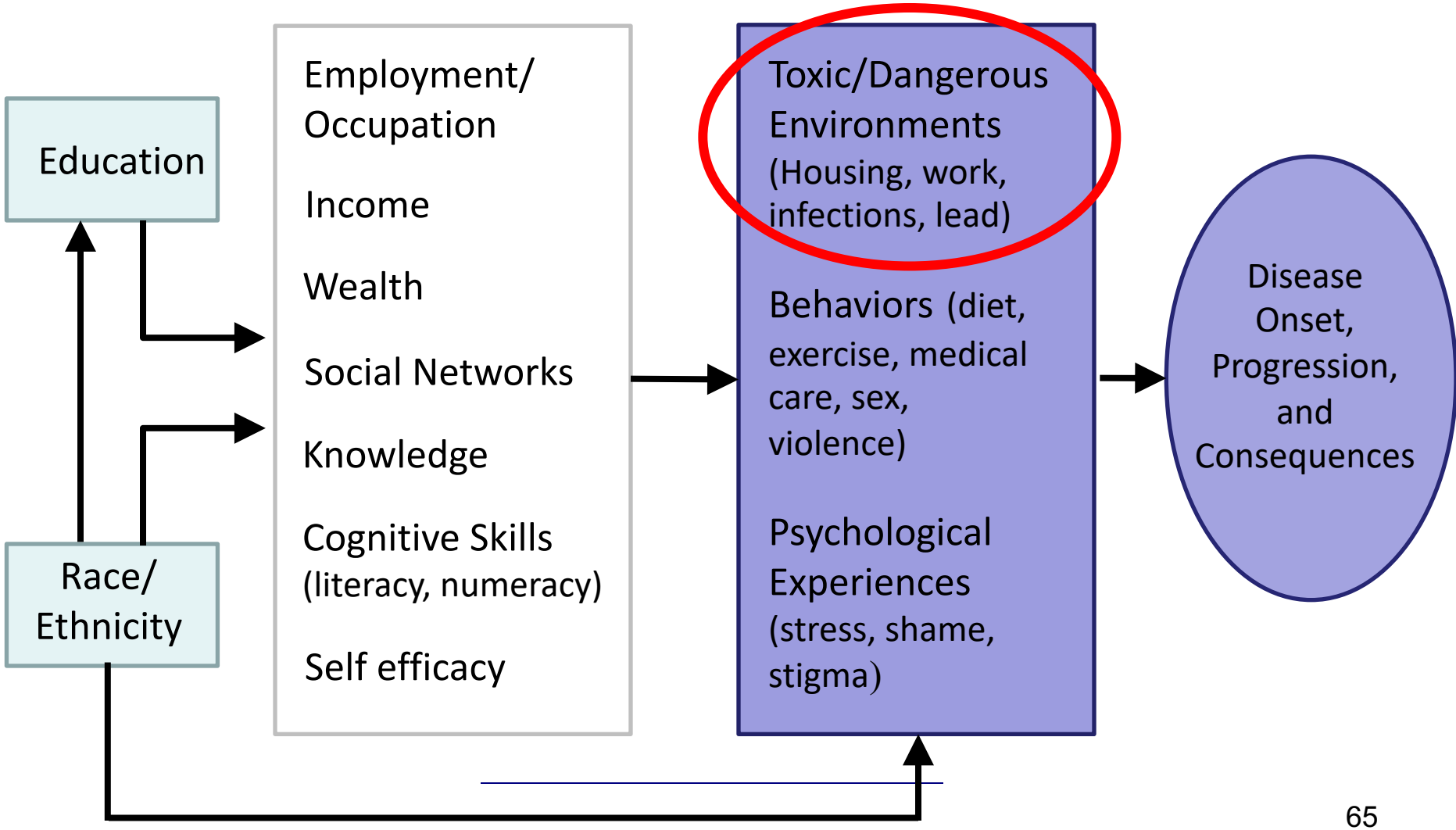
DNA methylation

- 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 (but not always the strongest correlate of experience!)

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 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 & severity
- Categories may interact (e.g. a toxic exposure may lead to worse outcomes in high stress environments)

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

IRISE

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

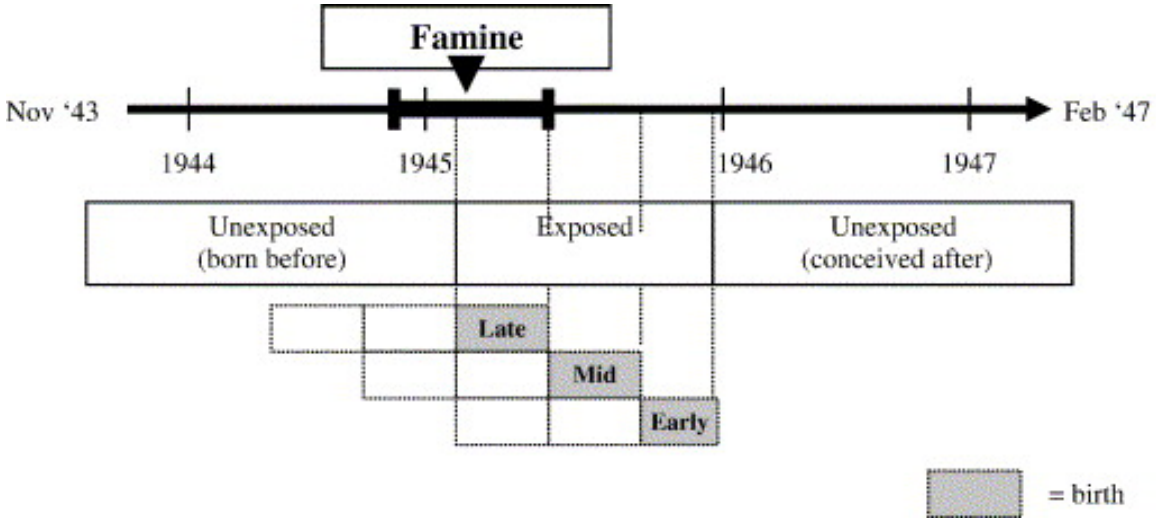
Sadler, LaChance, Hanna Attisha, 2017

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 unapparelled and includes how many calories each individual had over this period
- Nutritional deprivation during different trimesters of pregnancy established



Roseboom, 2006

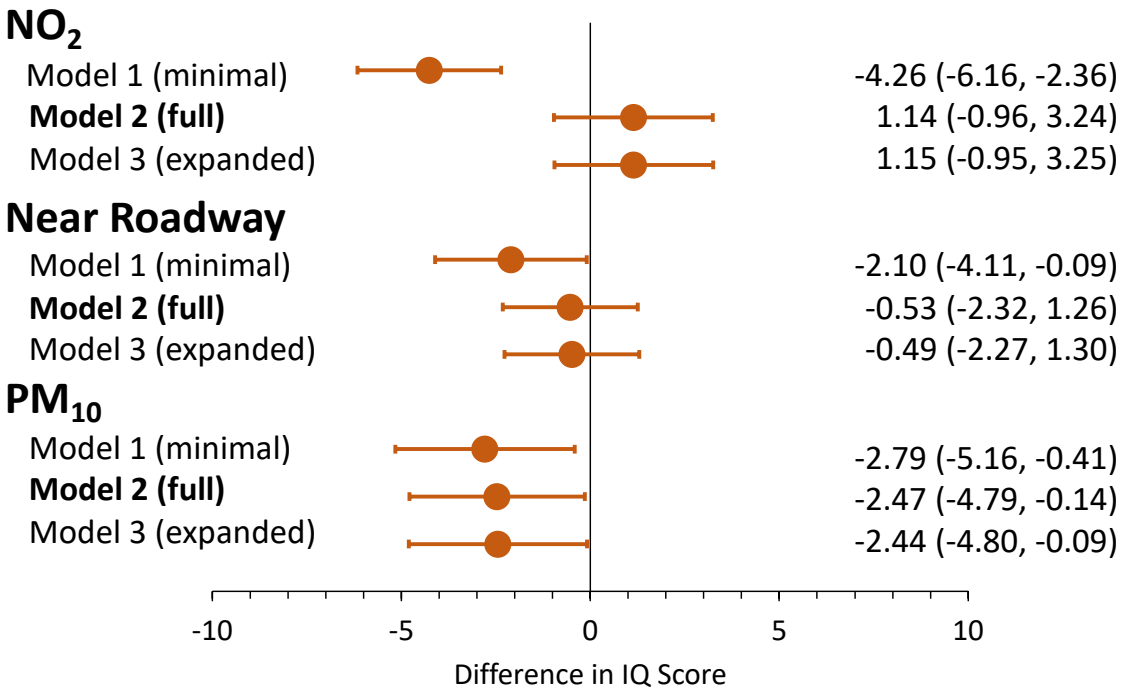
Trimester of exposure matters for adult outcomes

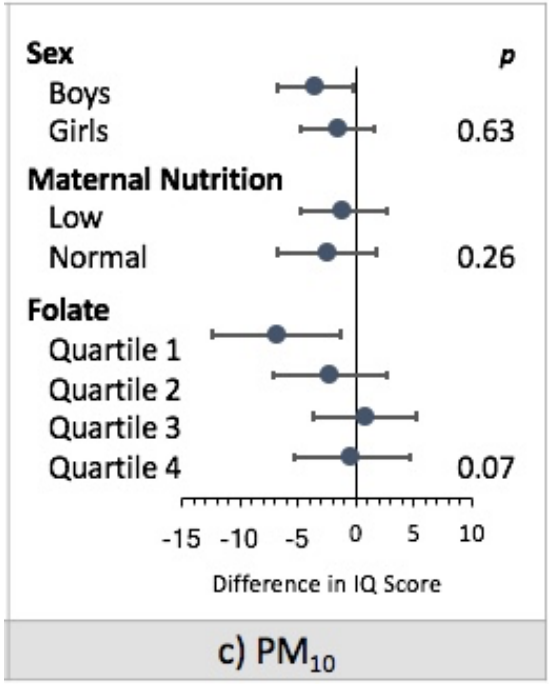
Exposure to famine		
In **late** gestation	In **mid** gestation	In **early** gestation
Glucose intolerance	Glucose intolerance	Glucose intolerance
	Microalbuminuria	Atherogenic lipid profile
	Obstructive airways disease	Altered blood coagulation
		Obesity (women only)
		Stress sensitivity
		Coronary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

A test of the Barker Hypothesis: Exposures in pregnancy can have a lasting impact on health

Roseboom, 2006

Air Pollution Exposure in Pregnancy and Child IQ in CANDLE





Notable disparities in levels of plasma folate by SES and race in CANDLE

Loftus et al.. . . , LeWinn, 2019; Loftus et al., . . , LeWinn, 2020

Nutritional Exposures: challenges

Key questions in nutrition studies generally:

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

75

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

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 and part of the pathway is evaluated
3. How common are qualitative differences in 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

Inconsistency across findings

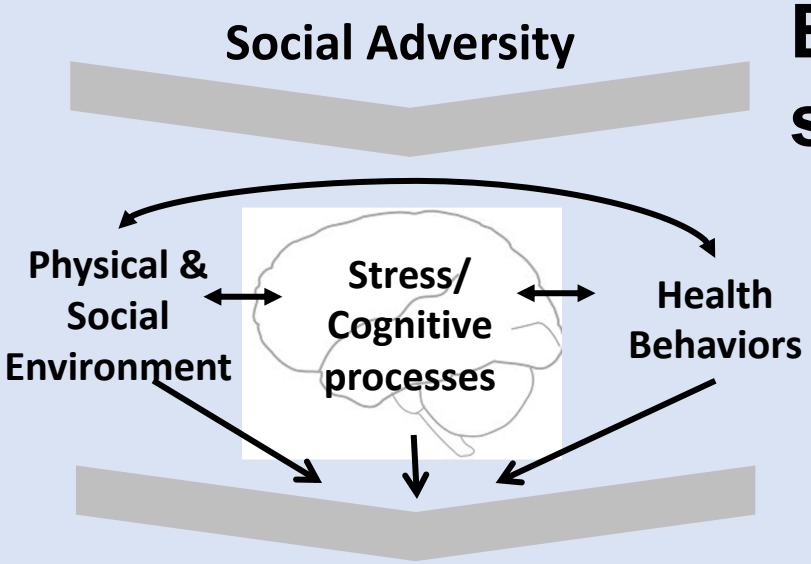
"Cortisol has received extensive attention as a potential mediator in the SES–health relationship. This review documented that more studies to date have found no association of cortisol with SES than have found the hypothesized association between lower SES and higher levels of cortisol, with several 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"

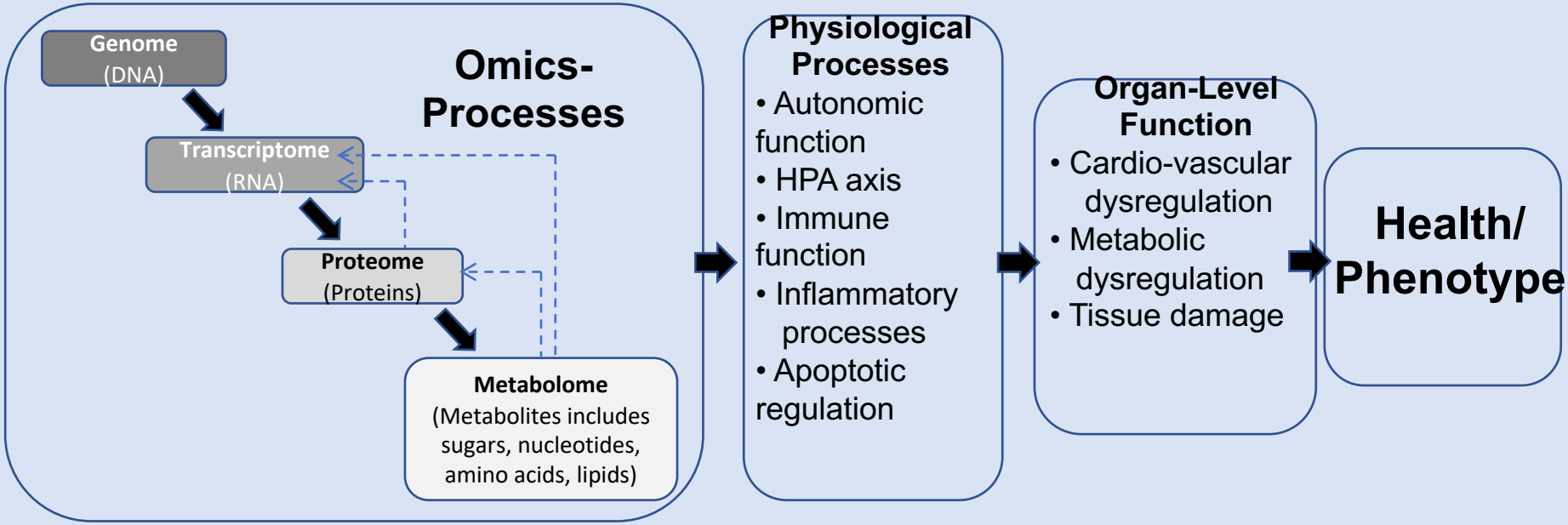
Dowd, IJE 2009

(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





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