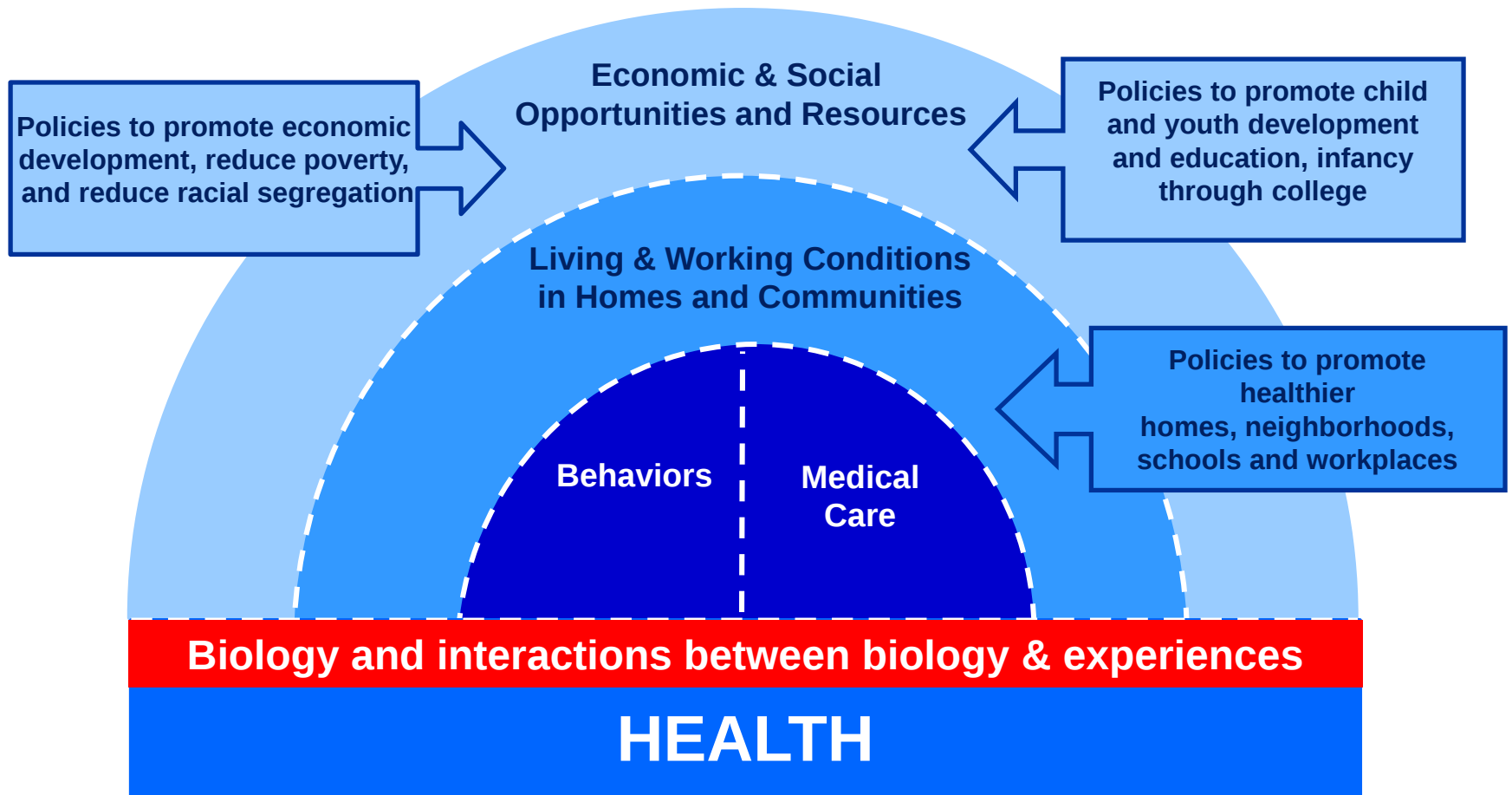


EPI222:

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?

- Designing 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 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](https://www.healthypeople.gov))



Comprehensive Center of Excellence for Health
and Risk in Minority Youth and Young Adults



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.”

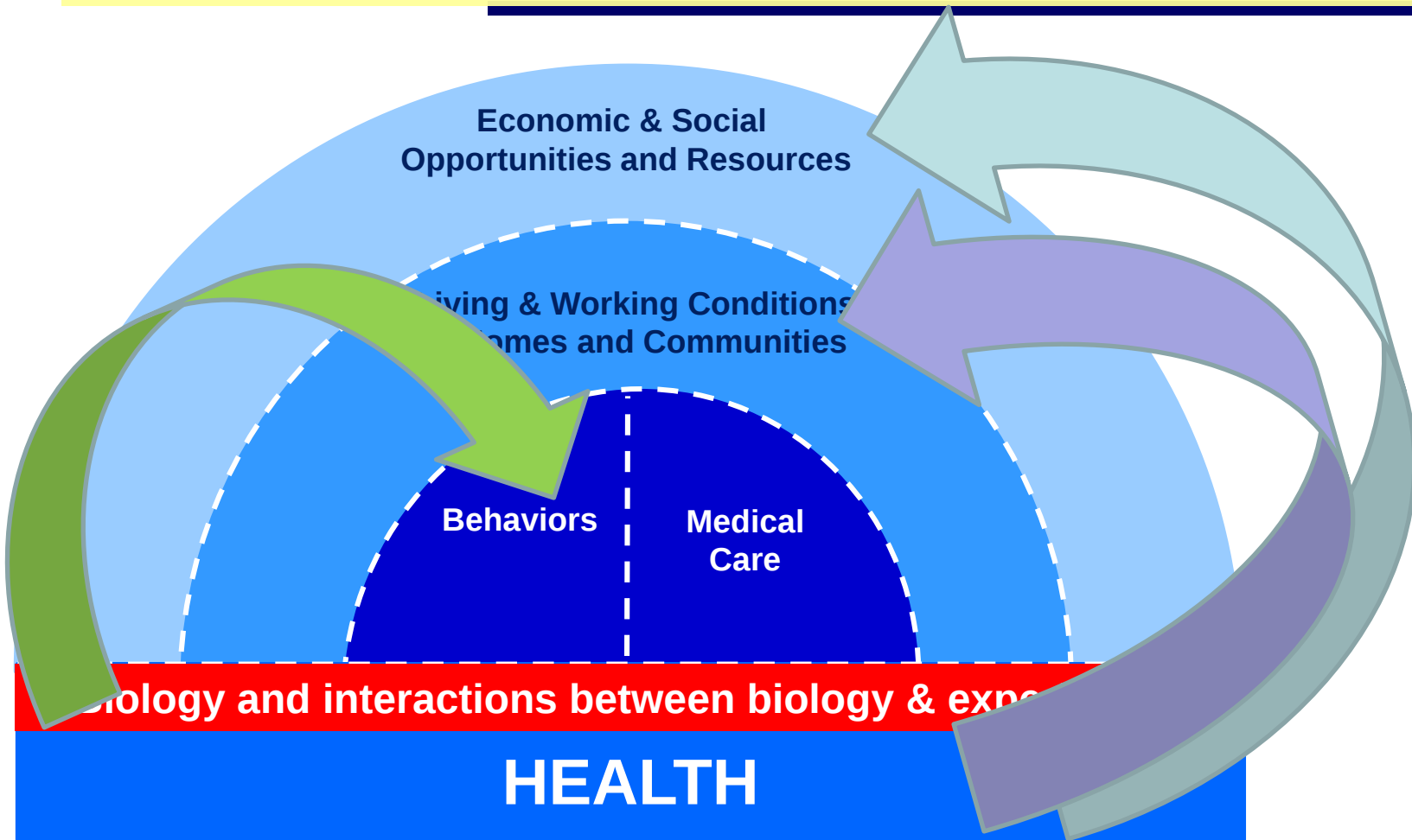
-Krieger, AJPH 2016



Embodiment

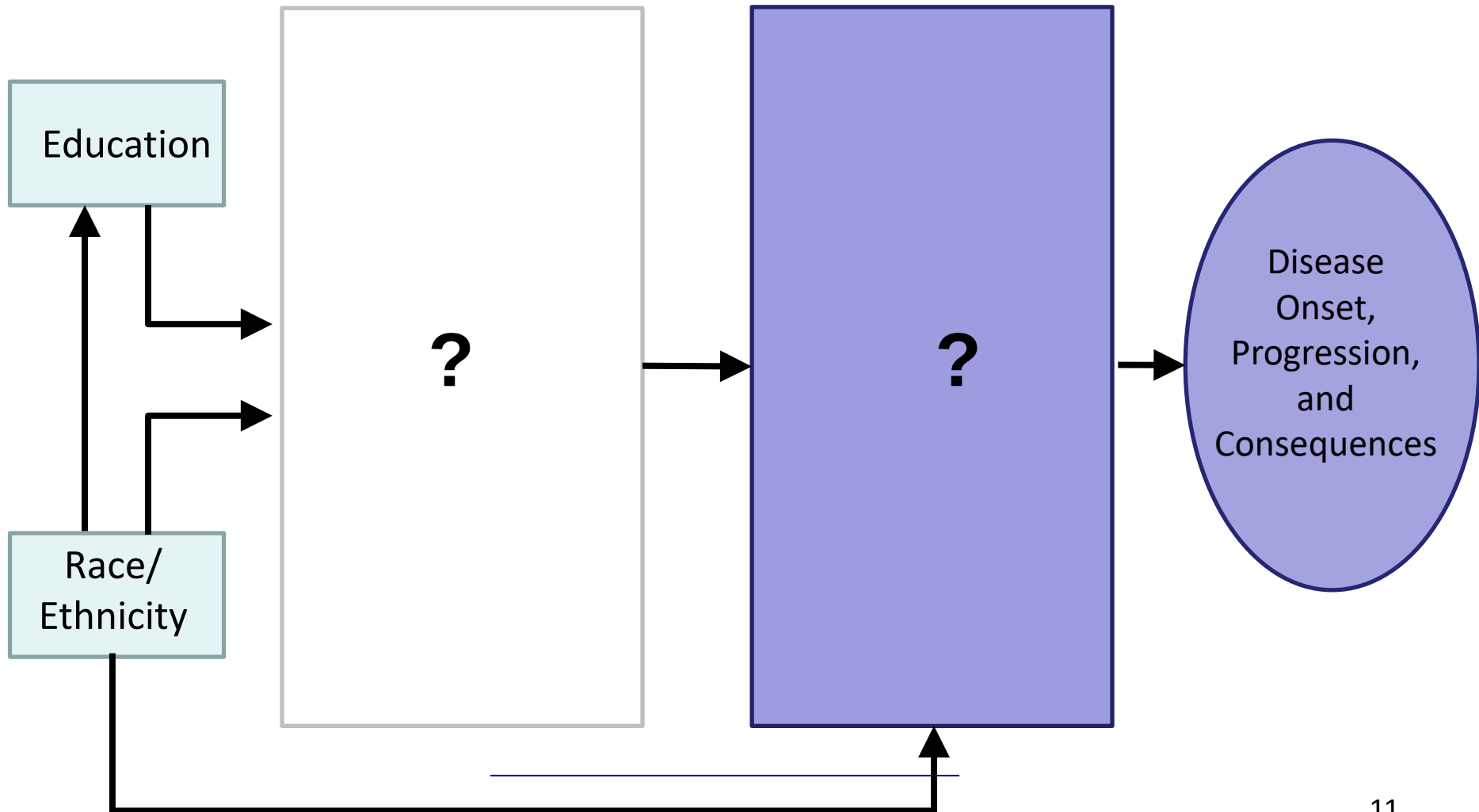
- “how we literally incorporate, biologically, the material and social world in which we live, from in utero to death...” Krieger 2005, JECH
- Many biological phenomena have social origins, so finding a biological basis for a health disparity does not imply that the root cause of that disparity is not 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→

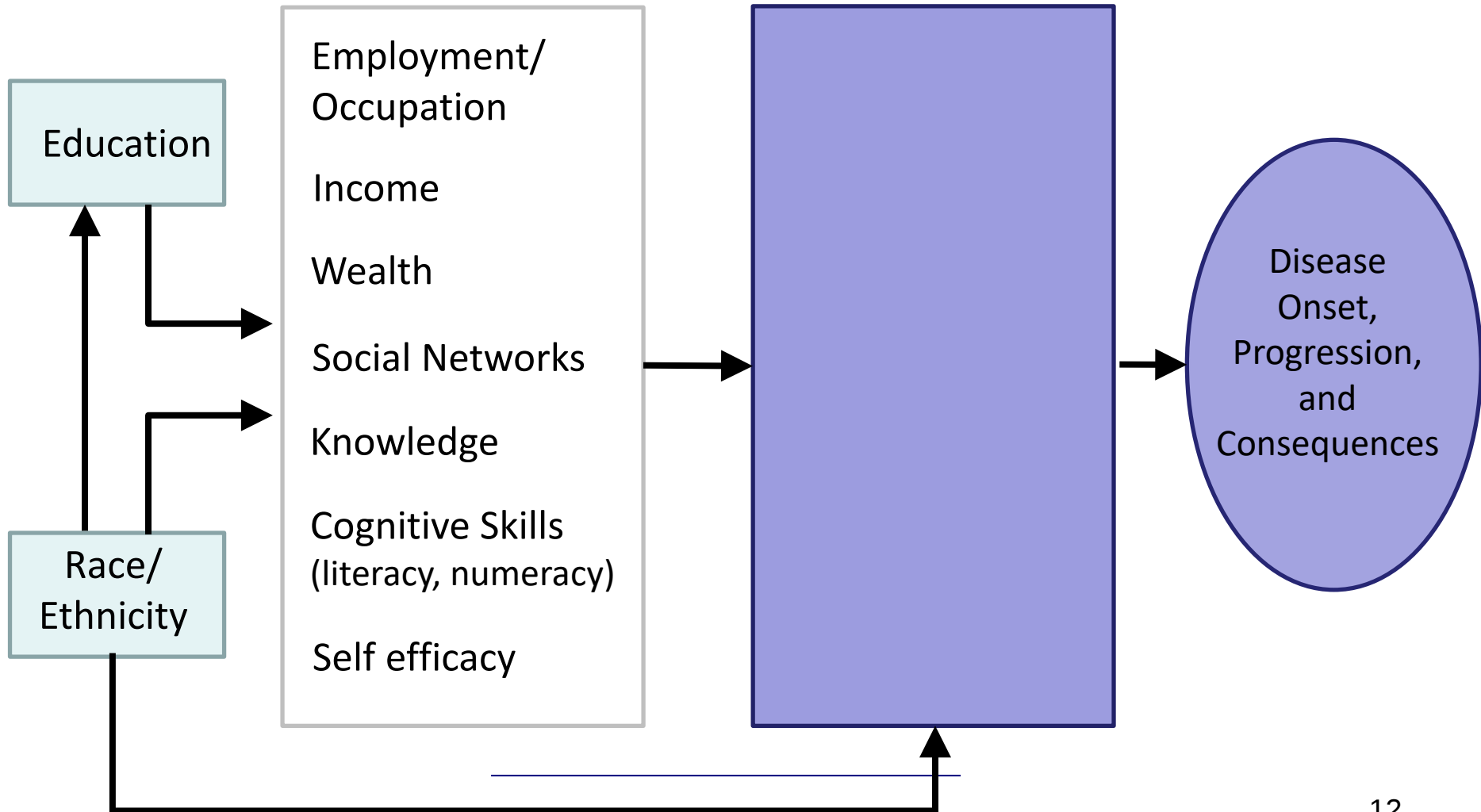


Social Factors and Health:

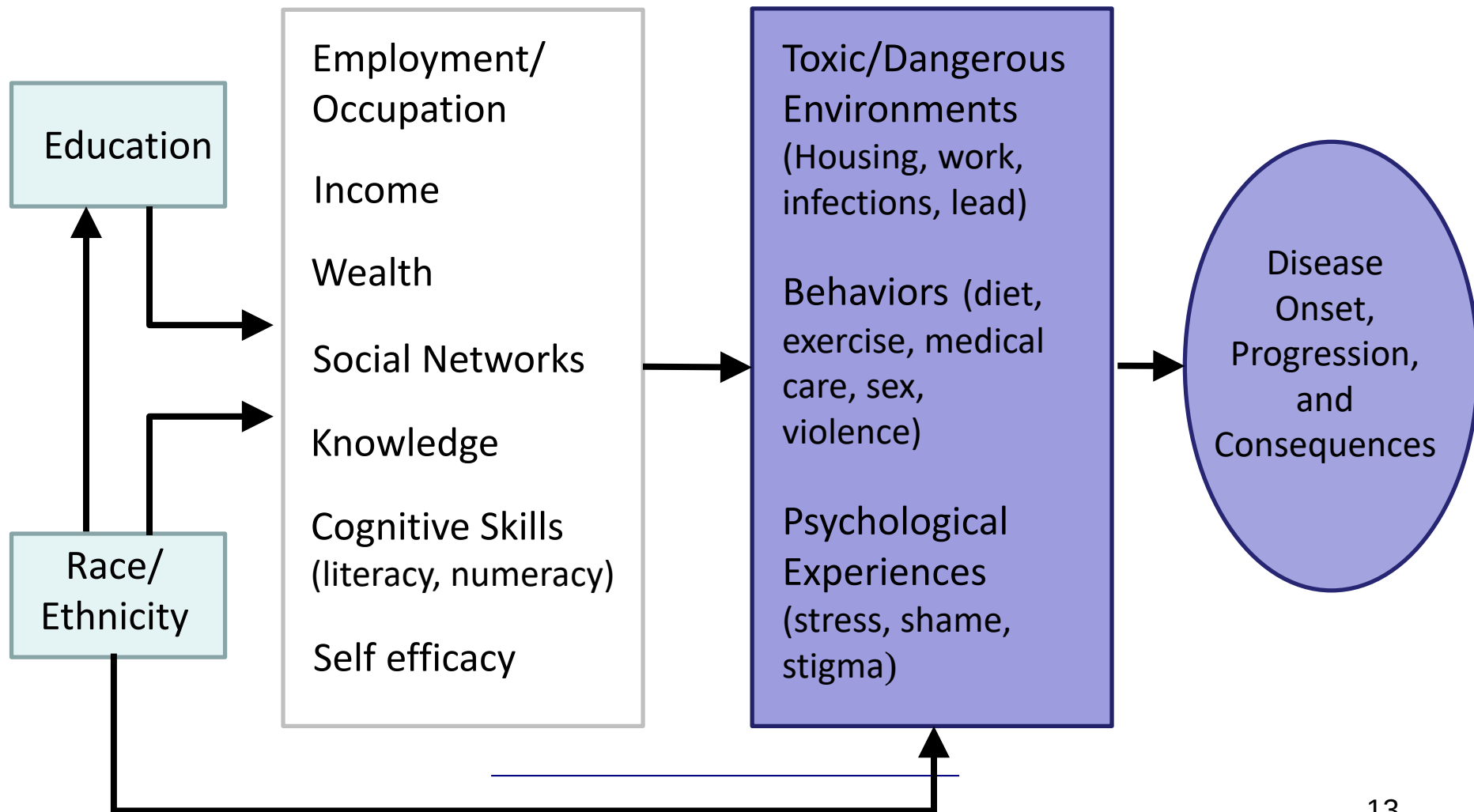
What pathways explain the link?



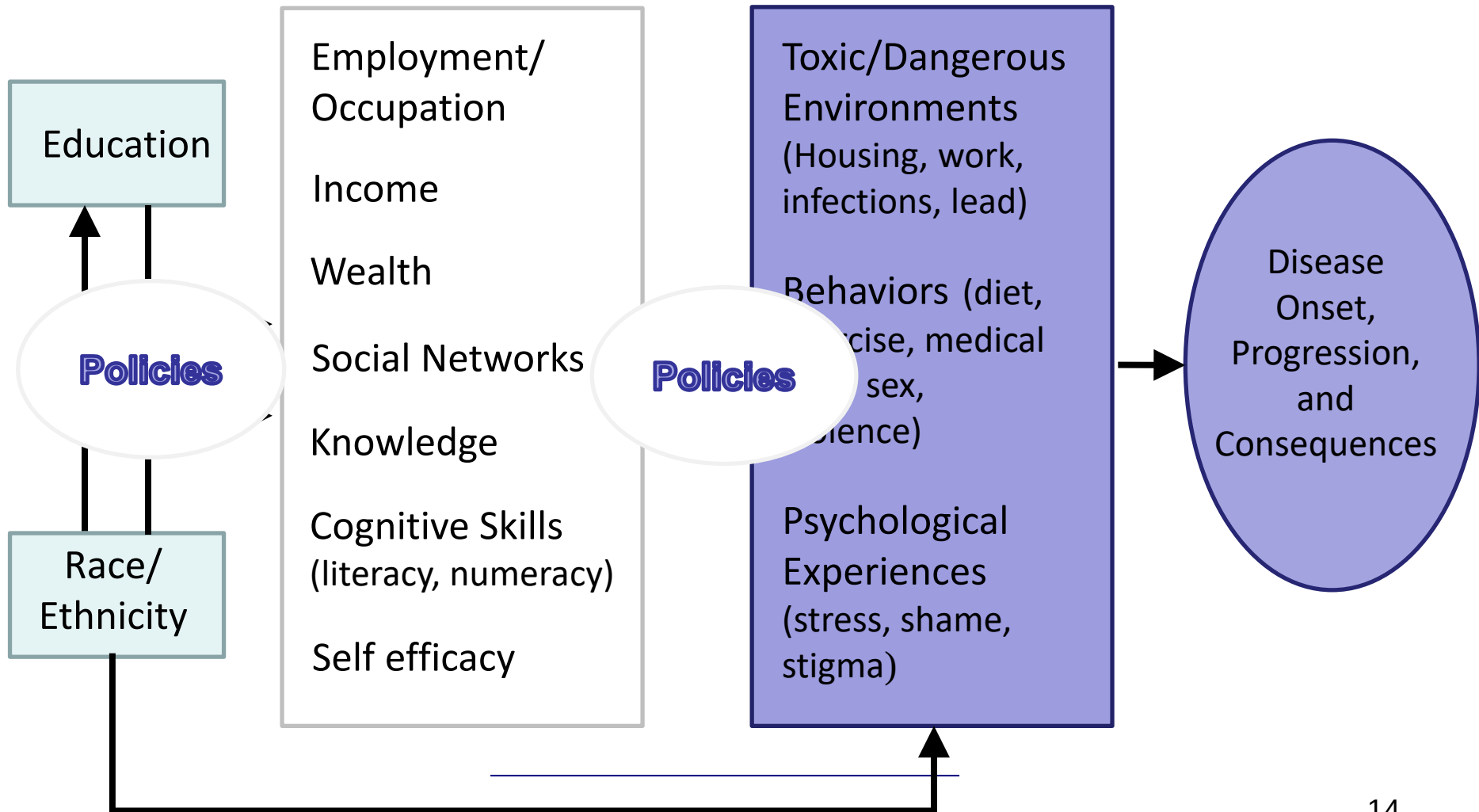
Social Factors and Health: Many socioeconomic, cognitive, and *network* resources



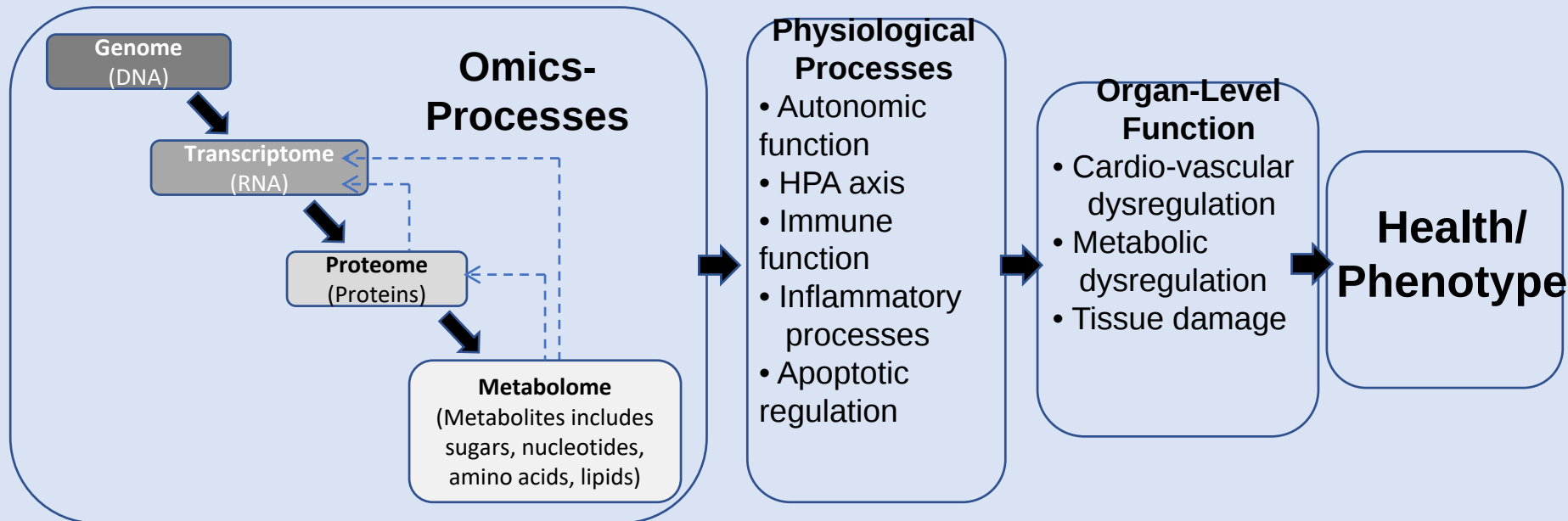
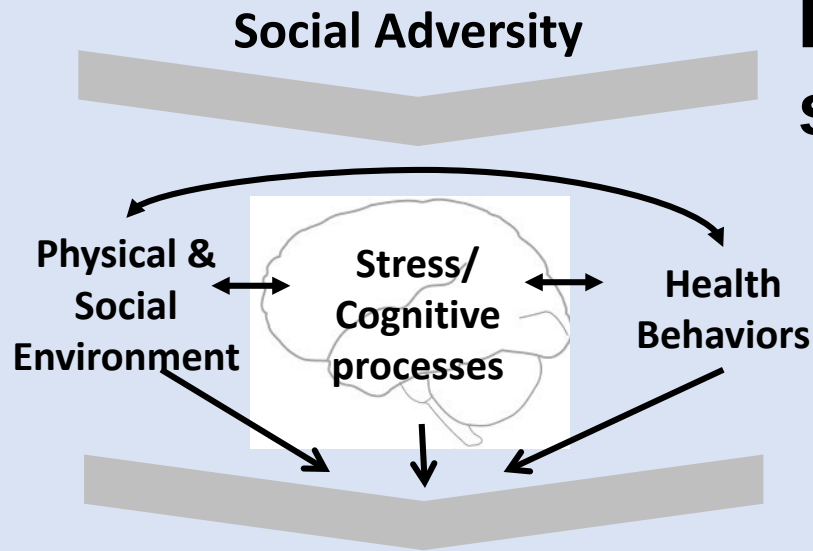
...which in turn influence material, behavioral, and psychological risk



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



Biological pathways linking social conditions & health



What I Want You to Leave Knowing

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

Biological Mechanisms

- **Frameworks**

- What this lecture is *not* about
- Why care about the biology?
- Embodiment
- Pathways
- Sensitive/critical periods
- Where do genetics fit in?

Key Idea in Biological Embedding: Sensitive Periods

- Arguments for special sensitivity in early life because this is a period of very rapid physical development
- 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.

Physical Pathways for Special Sensitivity to Early Context

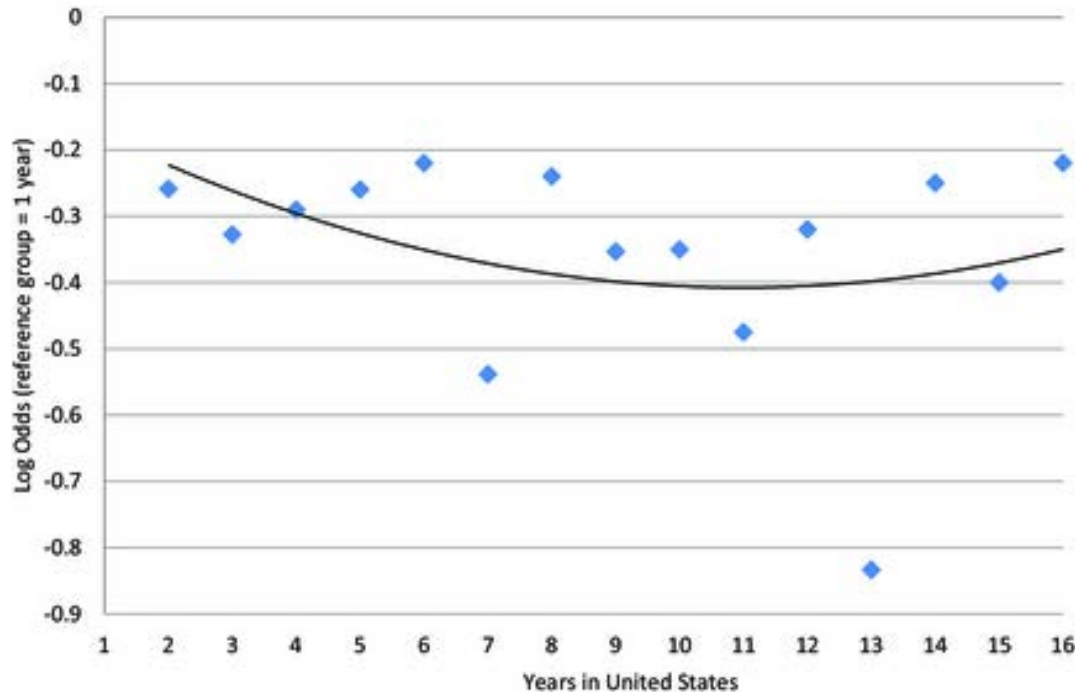
- Periods of rapid growth; “catch-up” is hard
- Critical periods for certain skills (e.g., language)
- Enduring changes to gene expression patterns
- Exposures at specific developmental periods set in place behavioral patterns/addictions (e.g. smoking, education → soft skills)
- Hierarchy of skill development

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

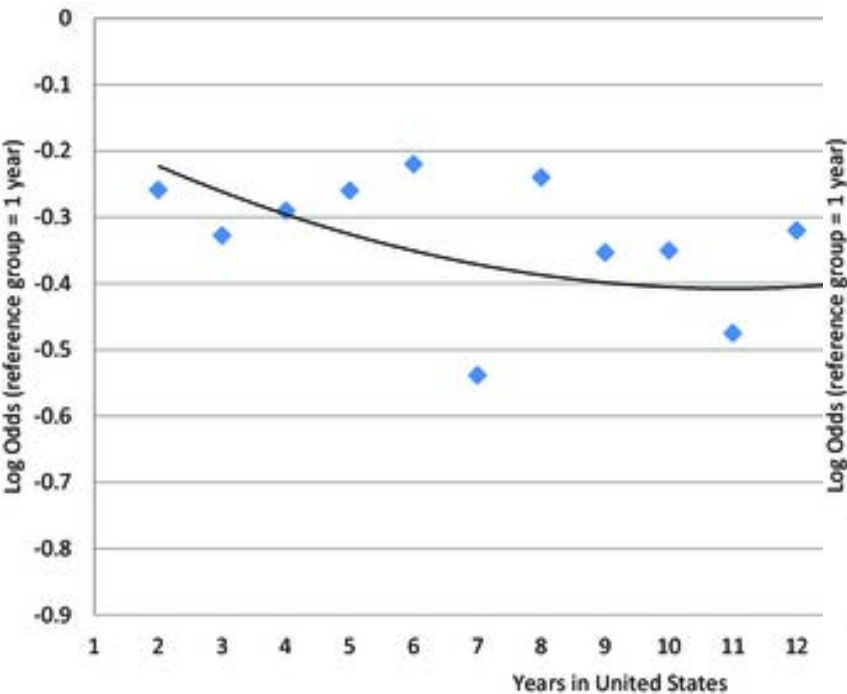
Feedback Occurs Across the Lifecourse

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

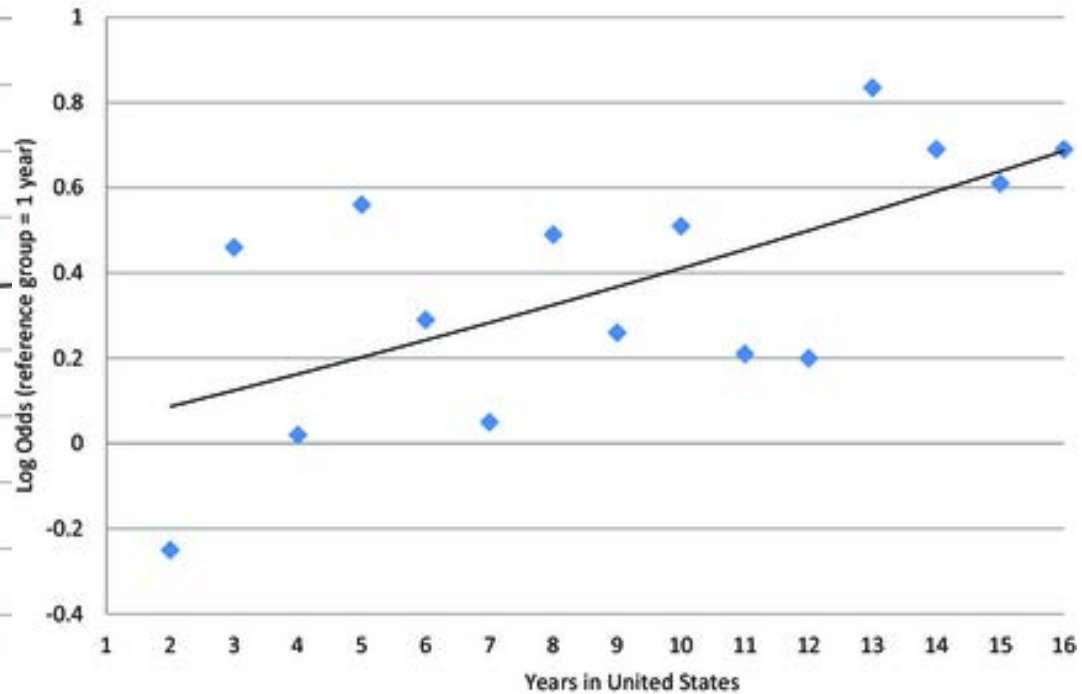


Feedback Occurs Across the Lifecourse

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



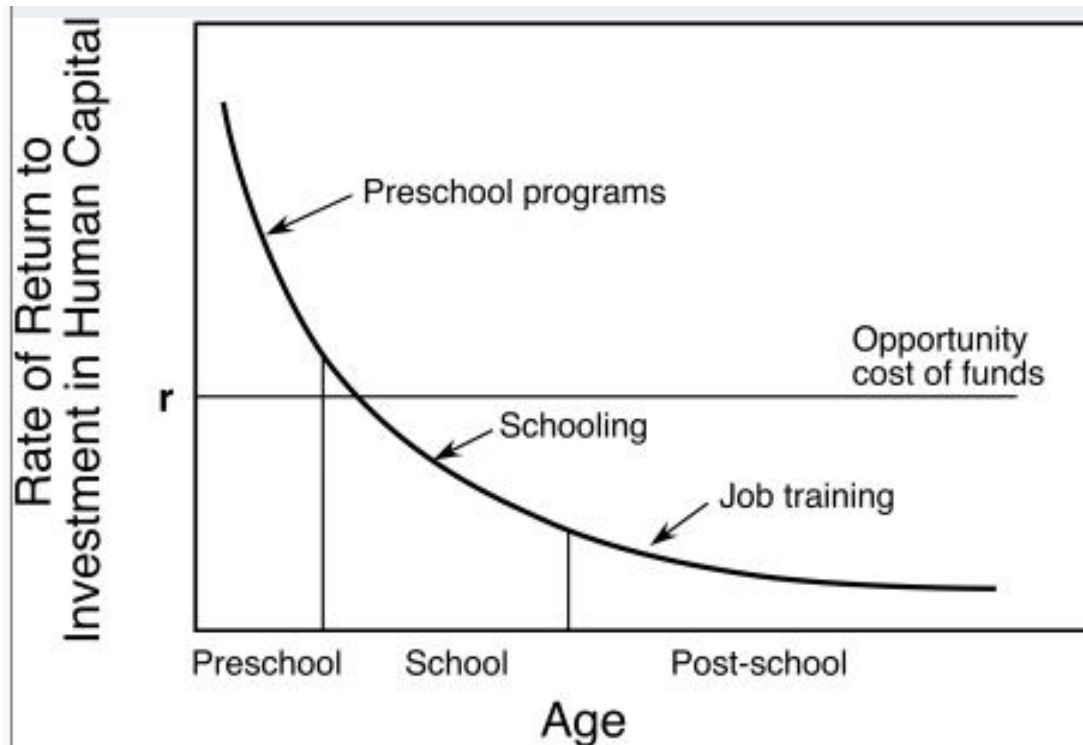
Dendritic growth

- The major outgrowth of dendrites starts after birth and continues during the first 2-3 years. This phase of the fastest dendritic outgrowth parallels the phase of fast cerebral cortex expansion, which also lasts until about 4 years of age.
- After 5 years of age, a large interindividual variation in dendritic tree size becomes apparent.

Human cortical development

- Critical periods...exist for those functions for which axonal rewiring across a long distance in the brain is necessary. This is virtually impossible after completion of the developmental competition between different axonal systems.
- Under dramatic circumstances, environmental factors during the first years of life can be quite decisive for the development of language social or other intellectual functions

Giving up on grown-ups: Is there any “return” to investing in adults?



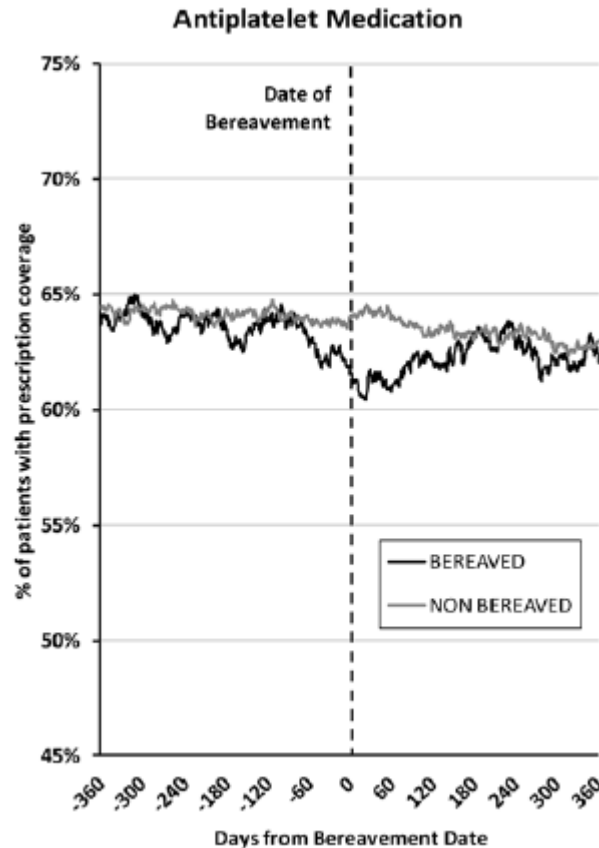
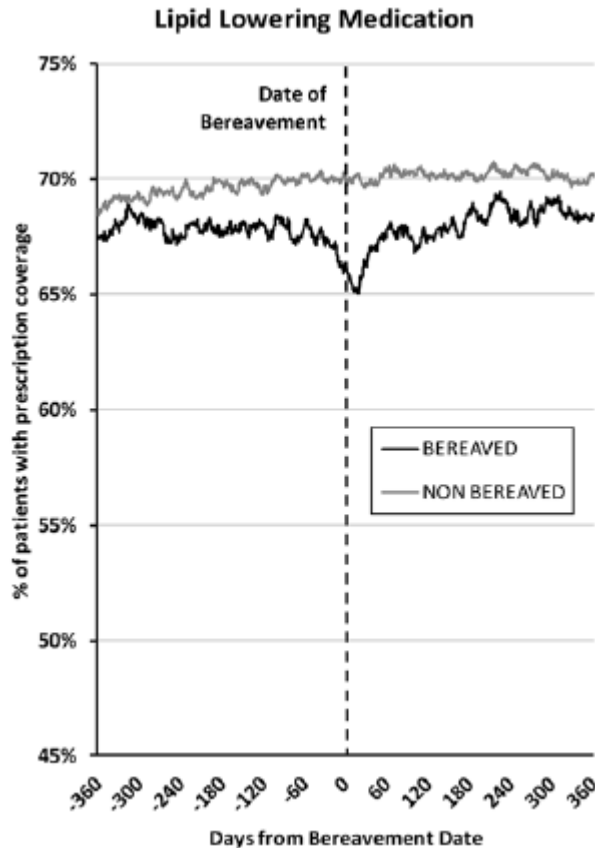
Rates of return to investment in human capital as function of age when the investment was initiated. Data from a life cycle model of dynamic human capital accumulation with multiple periods and credit constraints.

Investments were initially set to be equal across all ages. r represents the cost of the funds. 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
- Retirement
- Bereavement

Bereavement as a Sensitive Period



In a large UK cohort of older adults with preexisting CVD, there was lower uptake of cardiovascular care and reduced medication coverage in the year leading up to bereavement.

Shah et al Circulation 2013

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* health disparities, because this would imply that race/SES/place influences genetic code (draw the DAG to see what an unlikely claim this is).
- 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. Rarely major MAF differences that could account for disease differences.

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

Peralta, Bibbins-Domingo *et al.* under review

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)

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 $RR = 4$,
 $PAF = .5 * 3 / (.5 * 3 + 1) = 0.60$

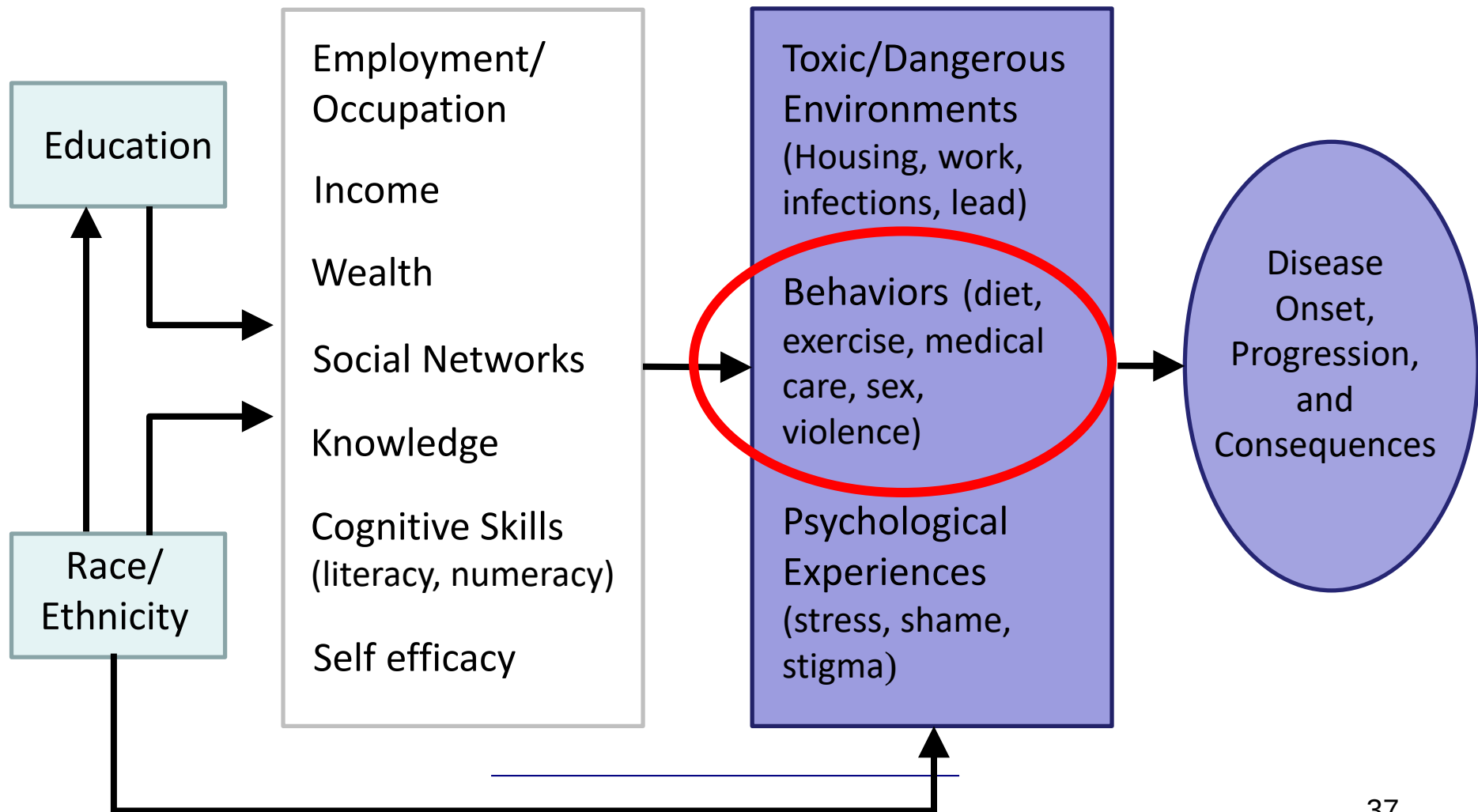
Role of genetics vs social experiences in health differences

- 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



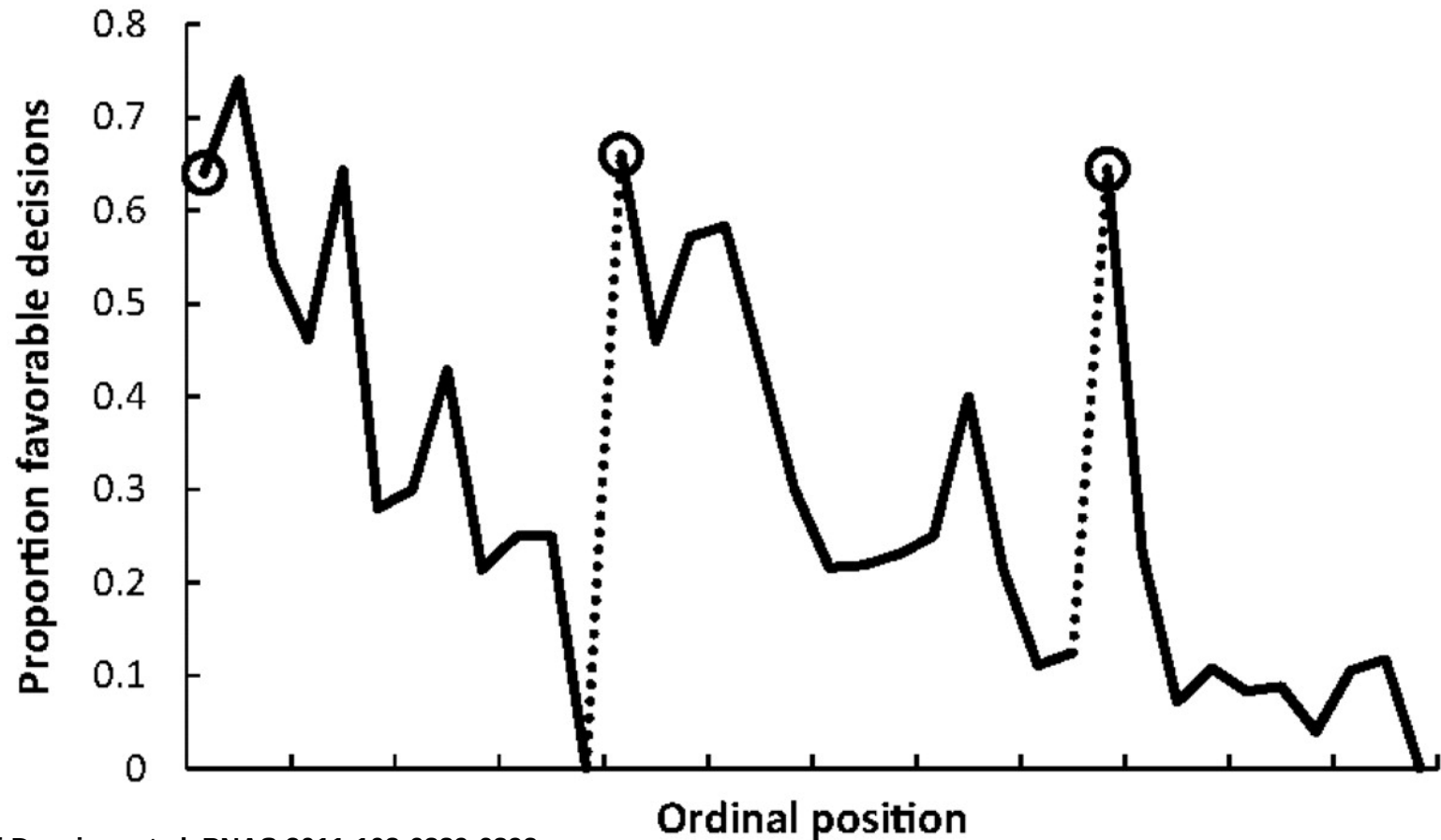
Behaviors are shaped and constrained by social context

- 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

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

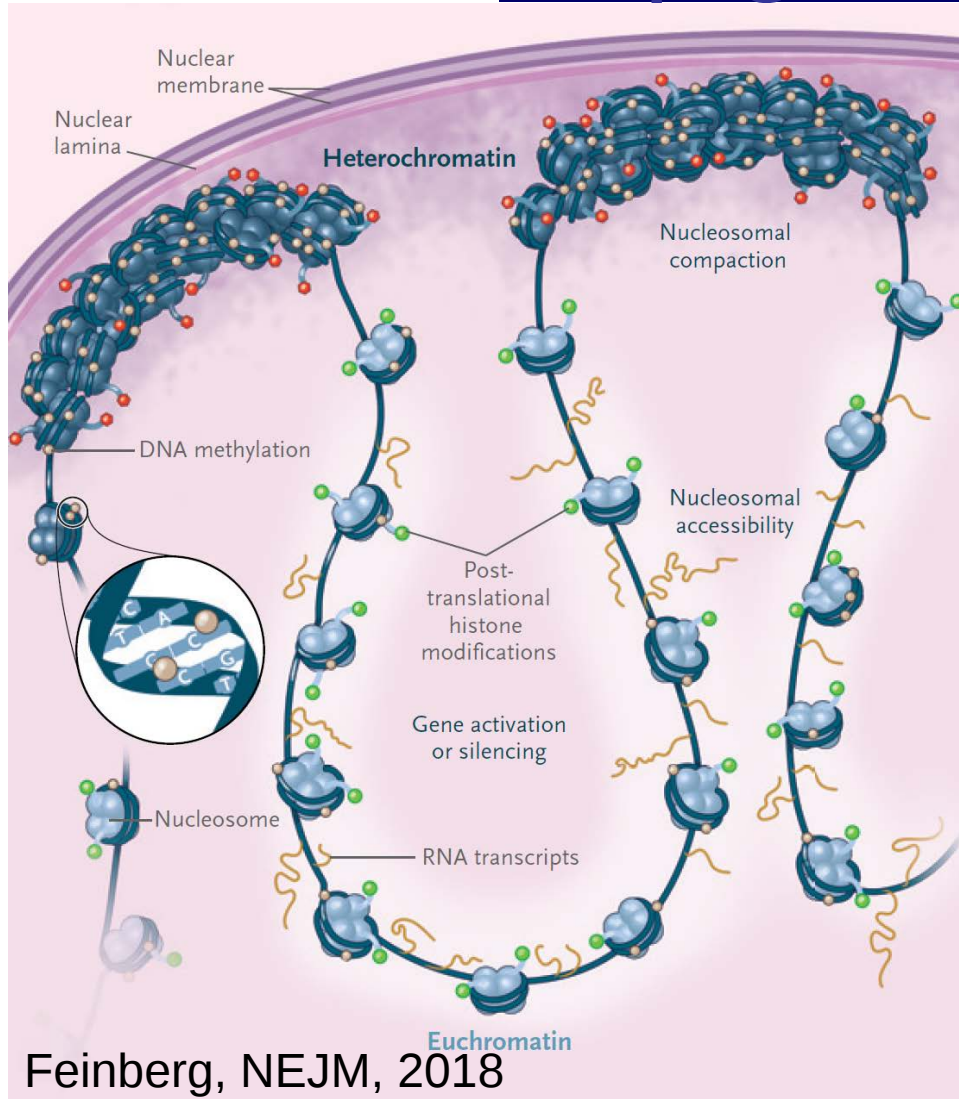
Biological Mechanisms

- Frameworks
- Behaviors, including use of medical care
- **Epigenetics**
- Direct toxic exposures
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Example Mechanism: Epigenetics

- Epigenetic modifications provide a possible physiologic mechanism linking parental behaviors to individual behaviors and health outcomes

Example Mechanism: Epigenetics



3 Categories of epigenetic regulation of gene expression

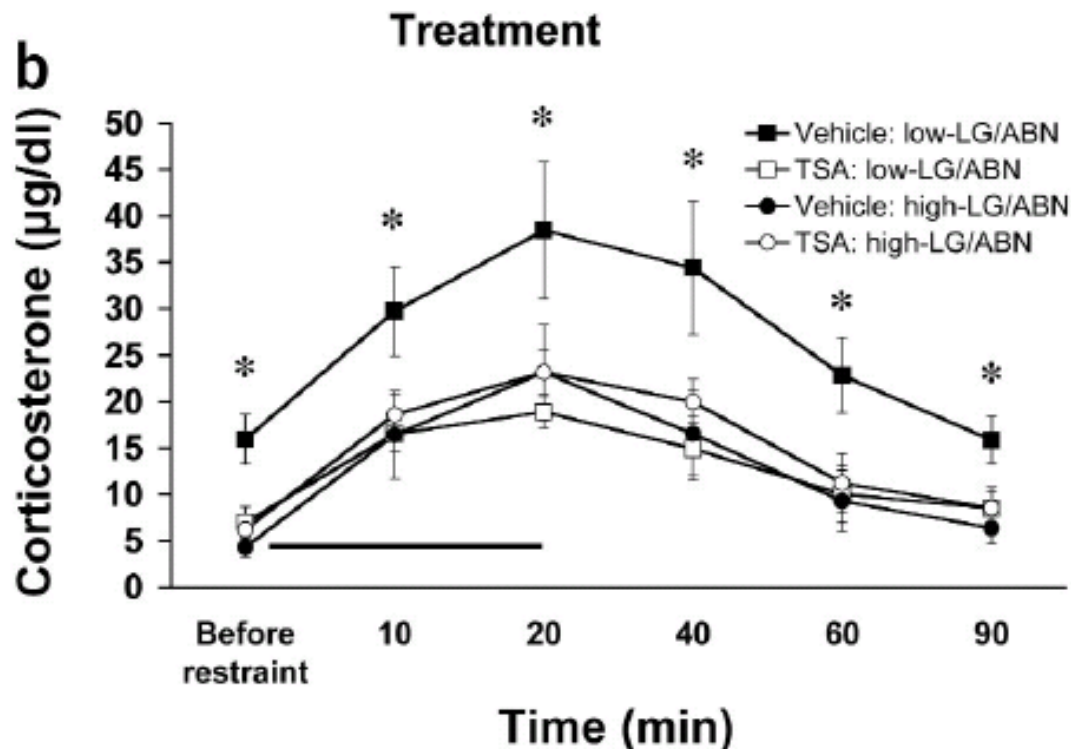
- 1) Methylation
- 2) Post-translational histone modifications (>200 known)
- 3) Chromatin structure, e.g., looping

Epigenetic Modifications: Regulate Gene Expression

- Methylation: Attach a methyl (CH₃) group to CpG dinucleotides in “islands”
 - Catalyzed by DNA methyltransferase, which connects the methyl to a cytosine
 - Changes the shape of the double helix, reducing binding or access of some proteins
 - Reduces access of polymerase and silences expression
 - Often on a “promoter” region that controls extent of expression or tissue specificity
- Epigenetic patterns change rapidly, often in a tissue-specific fashion, at a small number of developmentally specific ages
- Methylation patterns can be maintained if the DNA is copied, and potentially persist throughout life and across generations.

Meaney & Szyf: Parent-offspring interactions shape epigenetic patterns

Basic observation: rat pups handled postnatal days 1-5 have lower stress responses for the rest of their lives.



“Handled” rats – with more engaged maternal care - had better cognitive aging

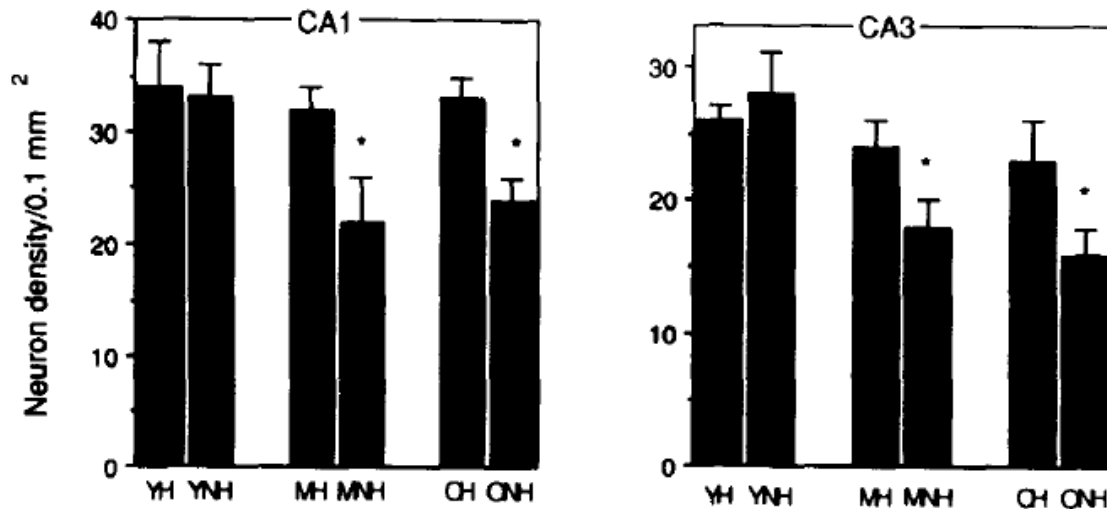


FIG. 2. Mean ($\pm$ SEM) neuron density in various hippocampal cell fields in young (Y; 6-month-old), midaged (M; 12-month-old), and old (O; 24-month-old) handled (H) and nonhandled (NH) females ($n=3-5$ animals/group; *indicates a significant treatment effect at $p<0.05$).

At 24 months, significant differences in neuron density in hippocampal regions.

-Meaney, Neurobio of Aging 1991

“Handled” rats – with more engaged maternal care - had better cognitive aging

PERCENTAGE OF ANIMALS SHOWING RECOVERY* TO BASAL CORTICOSTERONE CONCENTRATIONS 180 MINUTES FOLLOWING THE TERMINATION OF THE IMMOBILIZATION STRESSOR AS A FUNCTION OF AGE AND TREATMENT

Age	Handled	Nonhandled
6 Months	8/11 (73%)	8/14 (57%)
12 Months	9/11 (82%)	2/7 (28%)
24 Months	6/10 (60%)	1/9 (11%)

*Recovery is defined as a value that falls below the group prestress value + 2SD.

Better stress recovery (per cortisol) and better memory (faster swim to landing).

-Meaney, Neurobio of Aging 1991

“Handled” rats – with more engaged maternal care - had better cognitive aging

PERCENTAGE OF ANIMALS SHOWING RECOVERY* TO BASAL CORTICOSTERONE CONCENTRATIONS 180 MINUTES FOLLOWING THE TERMINATION OF THE IMMOBILIZATION STRESSOR AS A FUNCTION OF AGE AND TREATMENT

Age	Handled
6 Months	8/11 (73%)
12 Months	9/11 (82%)
24 Months	6/10 (60%)

*Recovery is defined as a value $\leq$ baseline value + 2SD.

MEAN ($\pm$ SEM) SWIMMING DISTANCE		
Age	Handled	Nonhandled
6-Month-old	4.3 $\pm$ 1.1	5.5 $\pm$ 2.9
12-Month-old	5.1 $\pm$ 1.0	9.0 $\pm$ 2.5*
24-Month-old	5.0 $\pm$ 1.3	11.2 $\pm$ 2.2*

*Significantly different from 6-month-old nonhandled animals and all H animals ($p < 0.05$).

Better stress recovery (per cortisol) and better memory (faster swim to landing).

-Meaney, Neurobio of Aging 1991

Epigenetic changes are a mechanism for enduring behavioral differences

- First finding: mediated by maternal behavior (arch-backed nursing, licking and grooming)
 - Directly observed changes in maternal behavior after handling
 - After handling, such changes in maternal behavior predict outcomes
 - Showed that natural variations in maternal behavior predicted same outcomes
 - Cross-fostering of pups to high or low LG mothers produced same patterns

Epigenetic changes are a mechanism for enduring behavioral differences

- Mediated by hippocampal glucocorticoid receptor expression and negative feedback
 - The adult offspring of high- compared with low-LG-ABN mothers show increased hippocampal GR expression and enhanced glucocorticoid feedback sensitivity
 - Eliminating the difference in hippocampal GR levels abolishes the effects of early experience on HPA responses to stress in adulthood

Epigenetic changes are a mechanism for enduring behavioral differences

- How does maternal care influence GR expression for offspring's whole life?
 - Maternal care → serotonin in pup
 - Serotonin → NGFI-A expression
 - NGFI-A binds to promoter for GR gene (I_7)
 - Post-natal day 1, methylated regardless of maternal care
 - Post-natal day 6, I_7 demethylated in licked/groomed pups
 - NGFI-A binding at critical period of demethylation creates access for the demethylase?

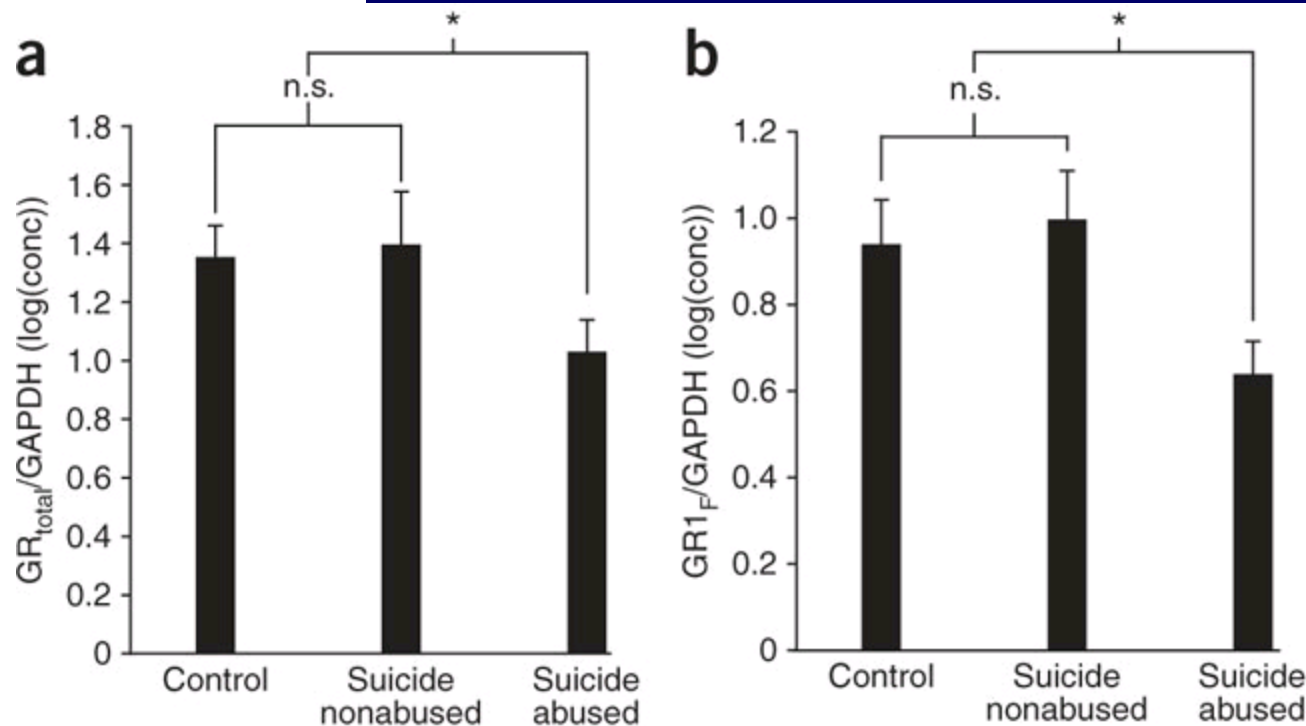
Why this is *extremely* powerful, if it's true

- Epigenetic patterns are quite stable across the lifecourse
- Formerly thought almost no changes in methylation patterns after birth; not *strictly* true (studies in twins show greater divergence in methylation patterns in older twins)
- Epigenetic changes are a mechanism by which an organism can respond to early life environment, and make changes to gene expression patterns that endure for a lifetime
- Changing fundamental feature of (rat-)behavior

Does it translate to humans?

- What is the human parallel for postnatal day 1-5 licking and grooming?
- Is this just a specific case of a general model, i.e. other exposures may induce epigenetic modifications of other genes and lead to fundamental behavioral changes?

Does it translate to humans?



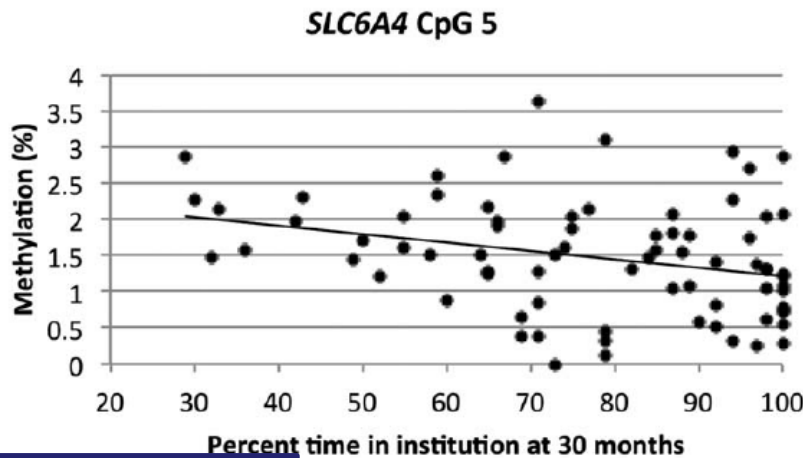
Mean /s.e.m. expression levels of glucocorticoid receptor (GR) mRNA (a) and glucocorticoid receptor 1_F (GR1_F) in 12 suicide victims with a history of childhood abuse, 12 nonabused suicide victims and 12 control subjects (b).

* indicates $P < 0.05$; n.s. indicates not statistically significant.

Does it translate to humans?

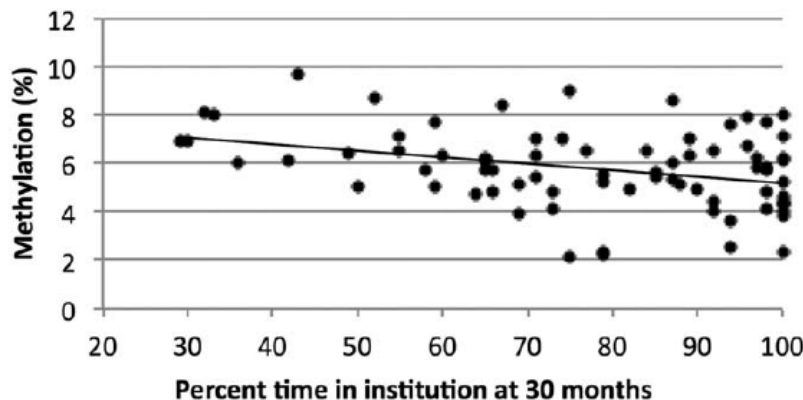
Bucharest Early Intervention Study

DNA METHYLATION AND EARLY ADVERSITY



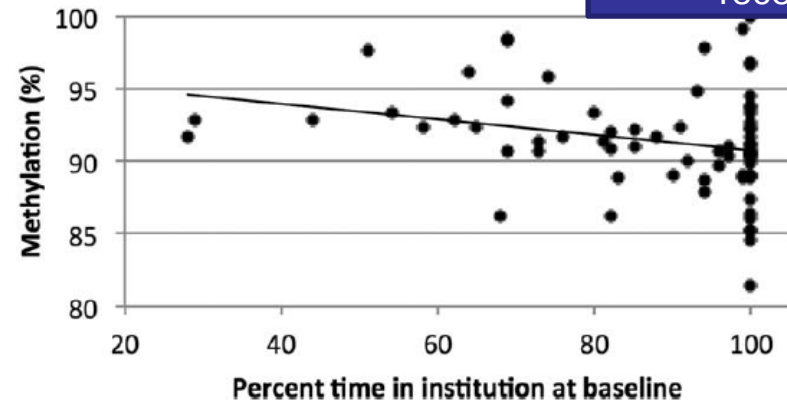
Serotonin
transporter gene

SLC6A4 CpG 6



FKBP5 CpG 1

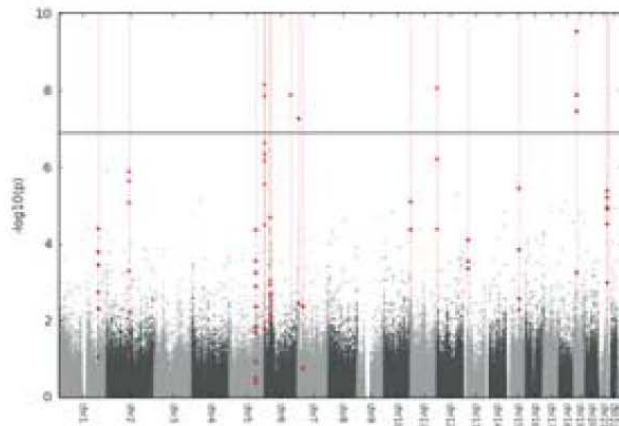
In the glucocorticoid
receptor



Relationship between proportion of time in institutional care and methylation level -- among children who had ever spent time in the institution -- for CpG sites with significant associations in SLC6A4 and FKBP5. Longer institutionalization, less methylation.

Does it translate to humans? PTSD in Combat Exposed Soldiers

a Discovery of longitudinal DNA methylation changes



Discovery analysis:

Regression analyses on longitudinal changes
in PTSD scores and DNA methylation levels

Statistical mediation analyses

Bioinformatics

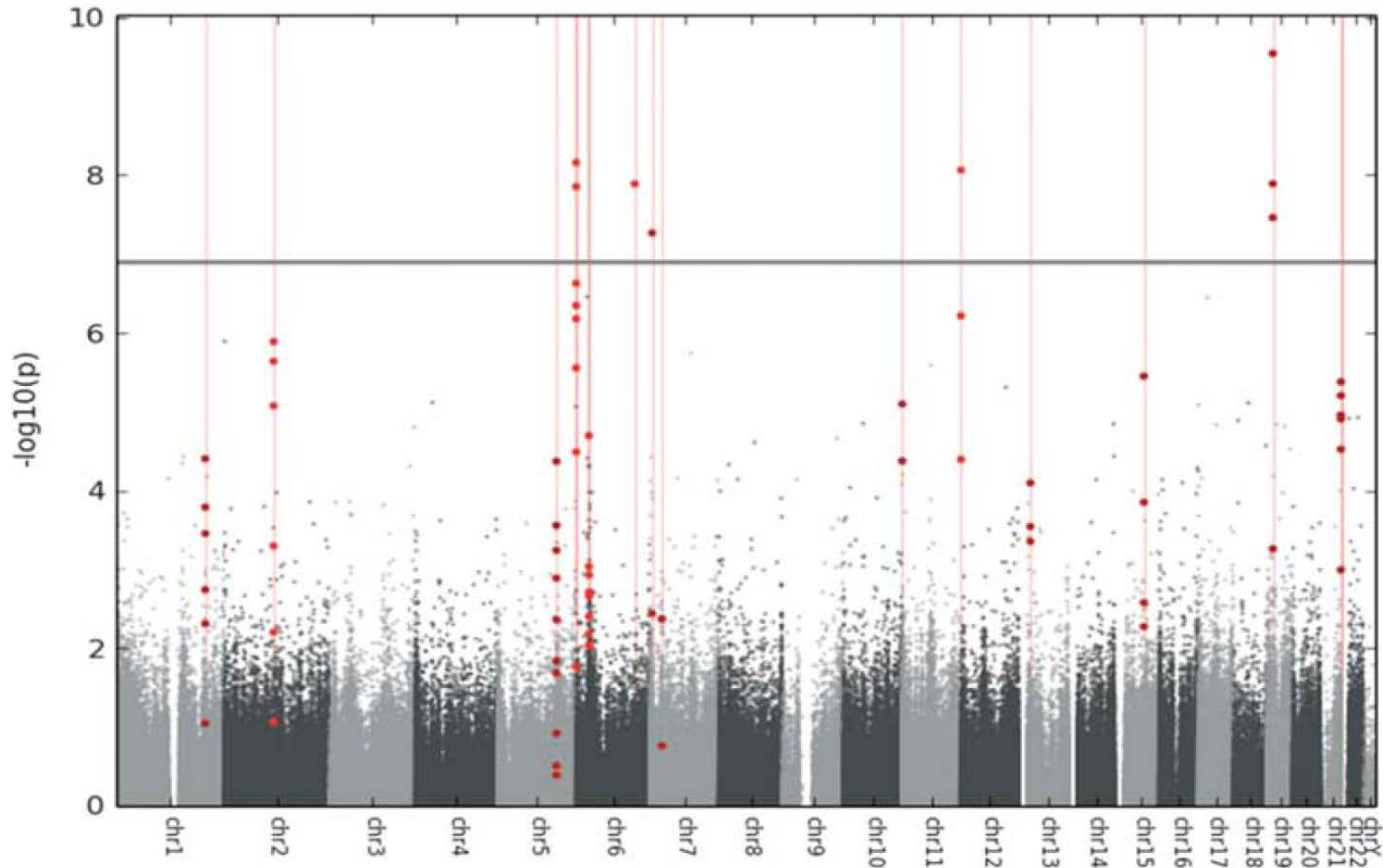
Targeted replication in
independent cohort



Does it translate to humans? PTSD in Combat Exposed Soldiers

b

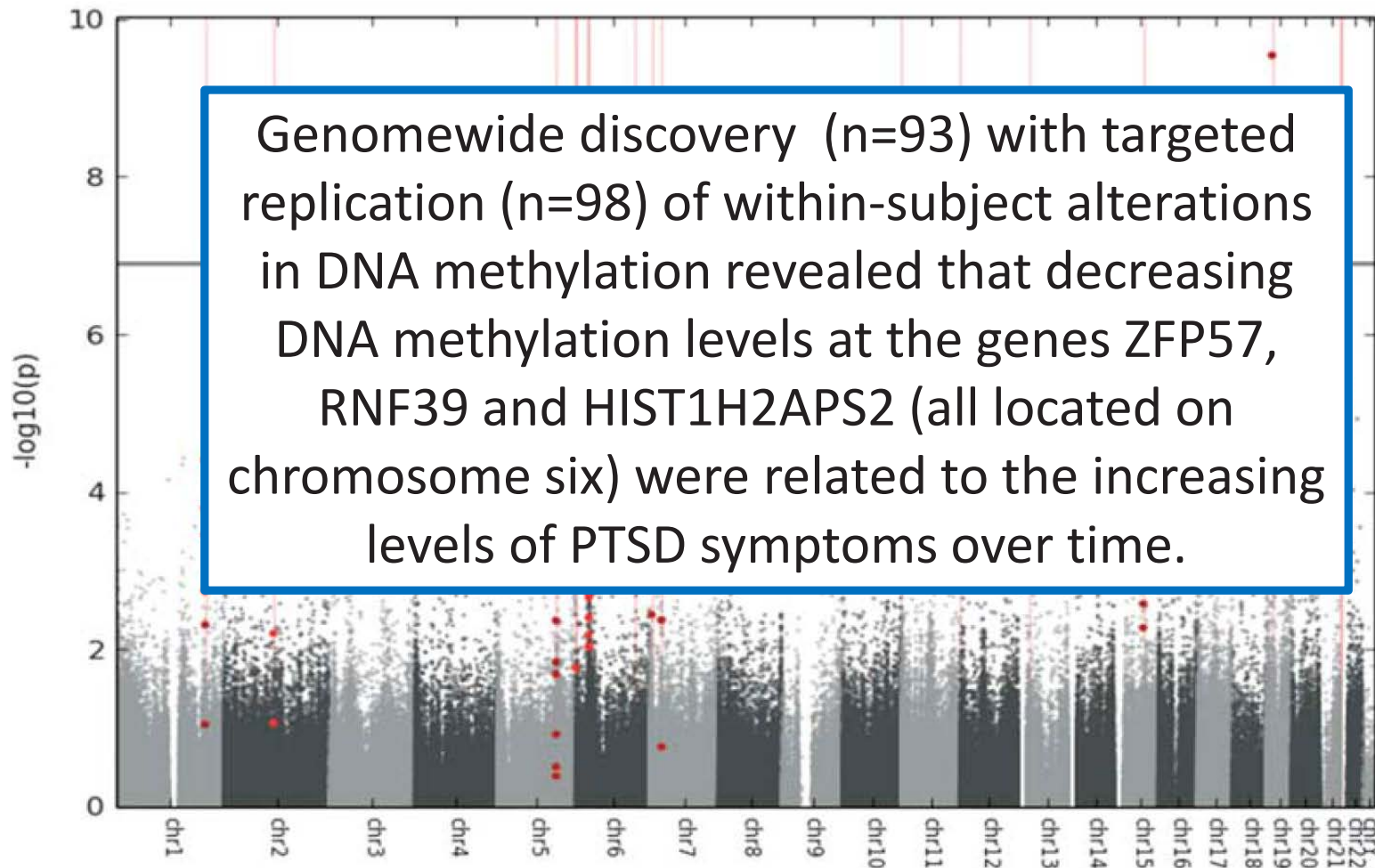
Manhattan plot of results of PTSD-related differential methylation



Does it translate to humans? PTSD in Combat Exposed Soldiers

b

Manhattan plot of results of PTSD-related differential methylation



Major Challenges with Epigenetics as Mechanism for Social Inequalities

- Multiple possible loci to evaluate
- Mostly hypothesis free
- Replication challenges
- Tissue specificity of epigenetic changes
- Disentangling cause from consequence

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

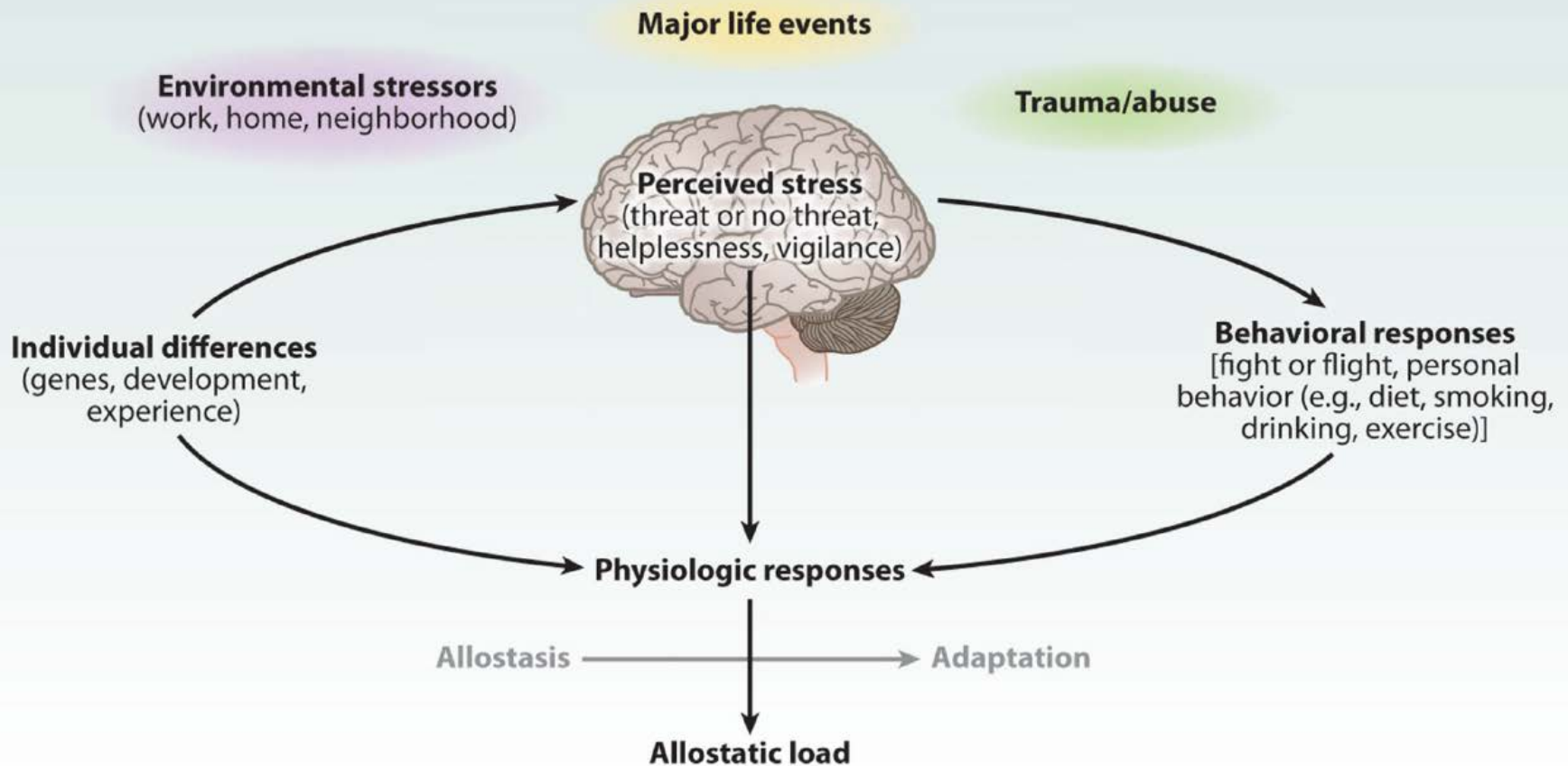
Stress Response

- 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

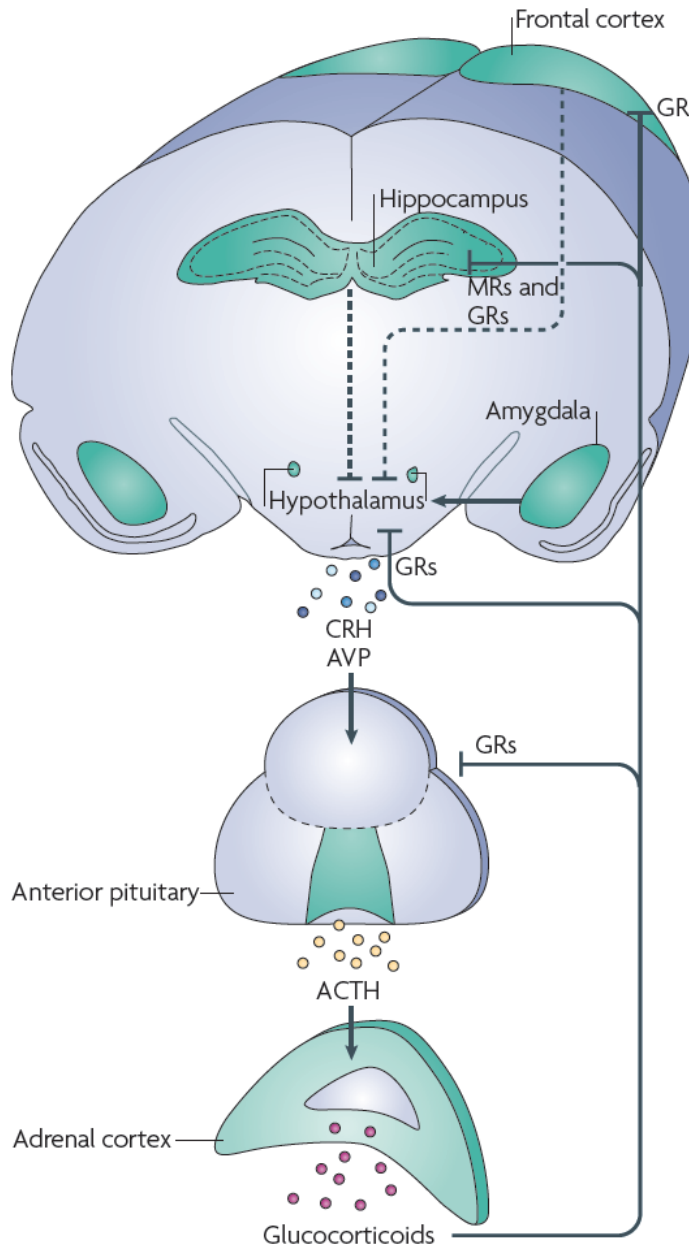
Allostatic Load

- 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 to improve behavioral response



HPA axis response

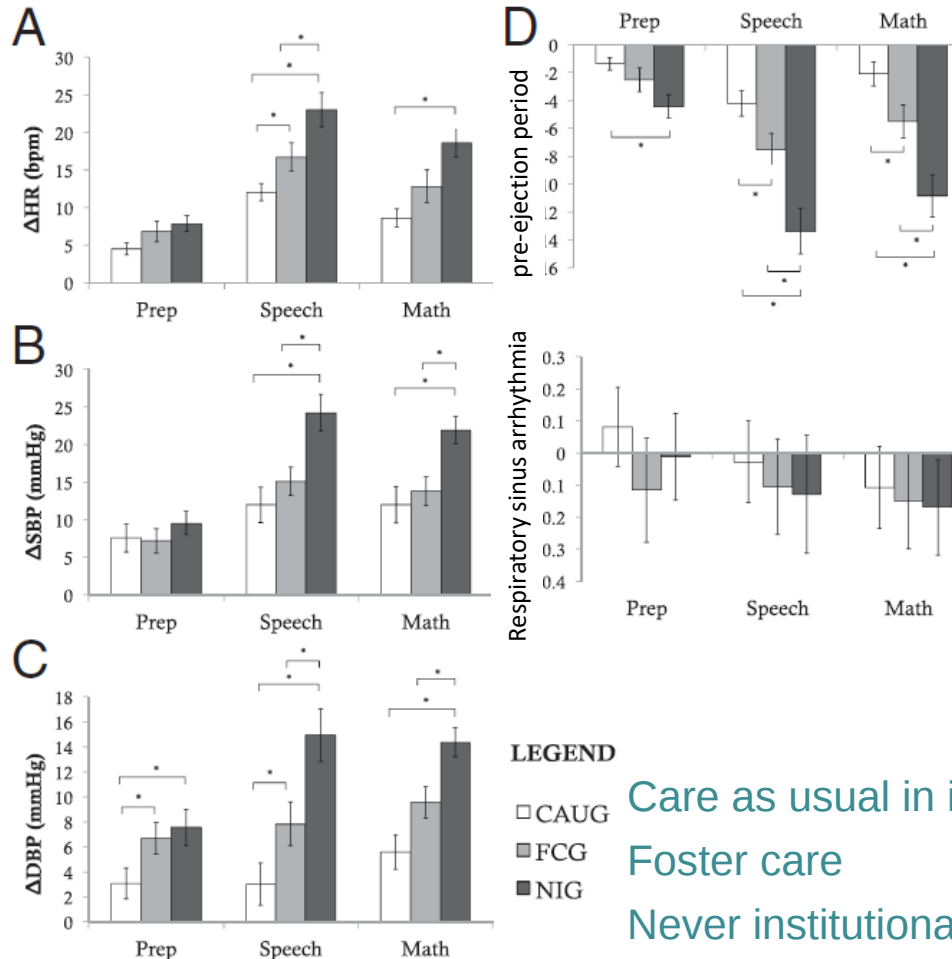


Threat/stress triggers autonomic, neuroendocrine, metabolic and immune responses.

Hypothalamus-pituitary-adrenal axis: hypothalamus releases corticotropin releasing hormone triggering adrenocorticotrophic hormone from pituitary → glucocorticoid production by adrenal → adrenaline and noradrenaline.

Glucocorticoids feed back and bind corticosteroid receptors to return to base state.

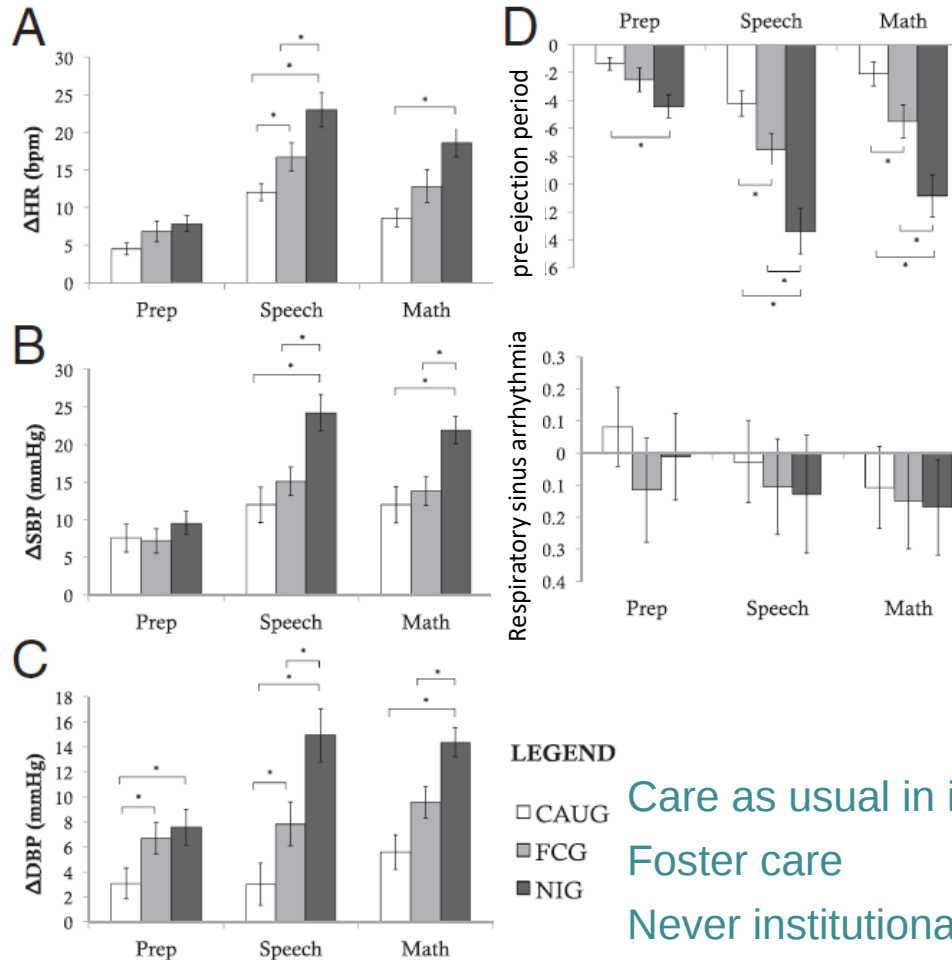
Bucharest Early Intervention Study and Stress Response Differences



Significant changes in all ANS measures were observed during the social tasks: HR, SBP, and DBP increased, and RSA and PEP decreased (indicating significant PNS withdrawal and SNS activation, respectively). ..evidence for causal effects of the caregiving environment on ANS reactivity to social stress. ... CAUG exhibited significantly **blunted** ANS responses compared with children randomized to FCG during the prep, speech, and math portions of the TSST

McLaughlin, PNAS 2015

Bucharest Early Intervention Study and Stress Response Differences



Intervention effects on both the PNS and HPA axis were evident for children placed before 24 months of age, suggesting the possible presence of a sensitive period during which stress response systems are most strongly influenced by environmental inputs.

McLaughlin, PNAS 2015

Stress Response

- Chronic stress predicts dysregulation of cortisol levels, but can be either up or down (diurnal fluctuation of cortisol is normal)
- Science on when upregulated versus downregulated not established
 - Serious methodological challenges because “healthy”=fluctuating

Stress Response: Active Research Areas

- Cell structure and tissue remodeling (e.g., apoptosis, dendritic shape and synapse formation, cellular developmental trajectories)
- SNS 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
- Dynamic relationships between physical dysregulation and stress, e.g., PTSD
- Other mechanisms to regulate gene expression, based on mRNA profiles: “conserved transcriptional response to adversity” → inflammation

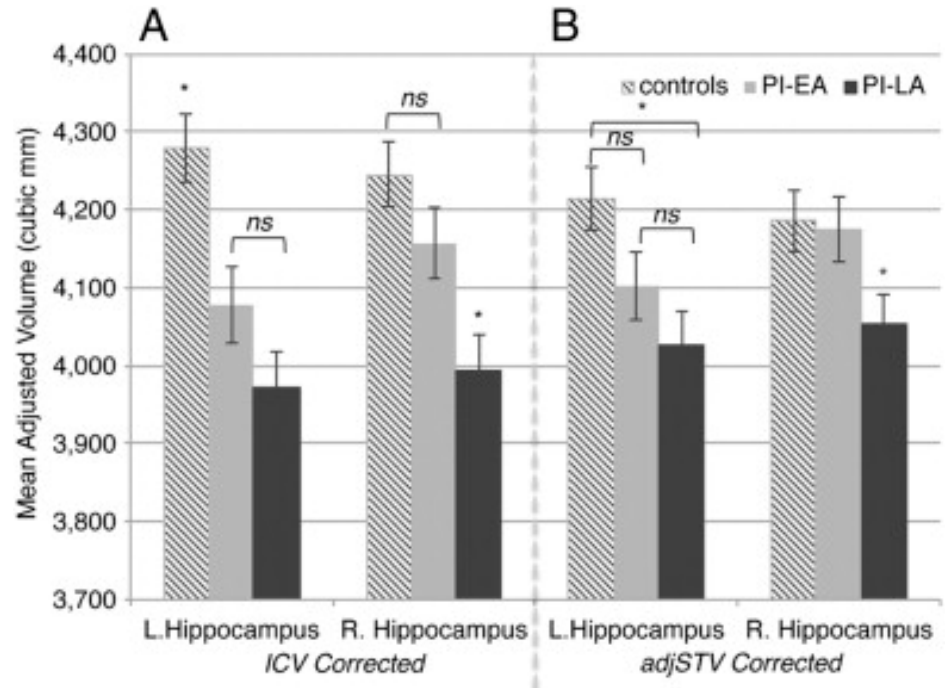
Example Mechanism: Neural development

- Early deprivation or trauma changes brain development and subsequent behavioral and health trajectories

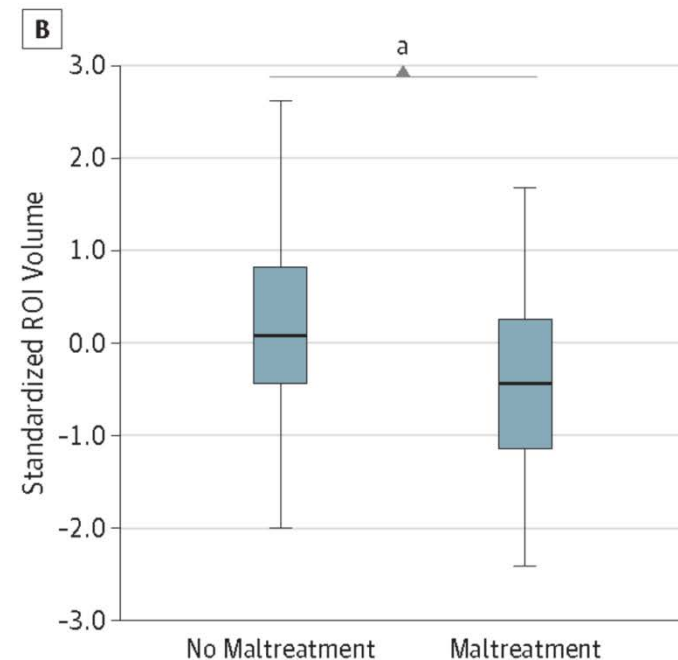
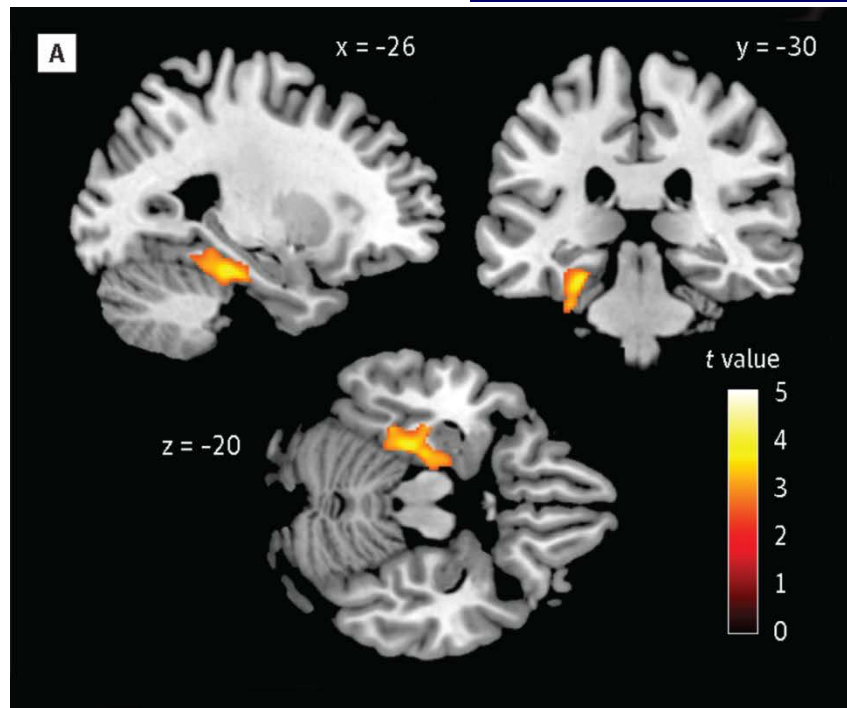
Early adversity changes brain development (volume, WMV, GMV)

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).



Child maltreatment influences Gray Matter Volume and substance use disorder



From: **Childhood Maltreatment, Altered Limbic Neurobiology, and Substance Use Relapse Severity via Trauma-Specific Reductions in Limbic Gray Matter Volume** JAMA Psychiatry. 2014.

GMV Differences Related to Childhood Maltreatment: Using whole-brain voxel-based morphometry, CM was associated with lower mean GMV, controlling for substance use disorder, psychiatric history, age, sex, total intracranial volume, and substance dependence by age, in the left medial temporal lobe. A, The GMV cluster predominantly includes regions of the hippocampus and parahippocampal and fusiform gyri. B, Box-and-whisker plot of estimated, standardized region-of-interest (ROI) cluster volumes by group (no trauma vs trauma). The shaded boxes indicate the 75th (top) and 25th (bottom) percentiles; horizontal lines in the middle of the boxes, the median (50th percentile); and whiskers, the minimum and maximum volumes.^aA t test revealed significant differences in the estimated volumes for the ROI between the 2 groups at $P < .001$.

Bucharest Early Intervention Project: High Quality Foster Care Offsets Cognitive Harm

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

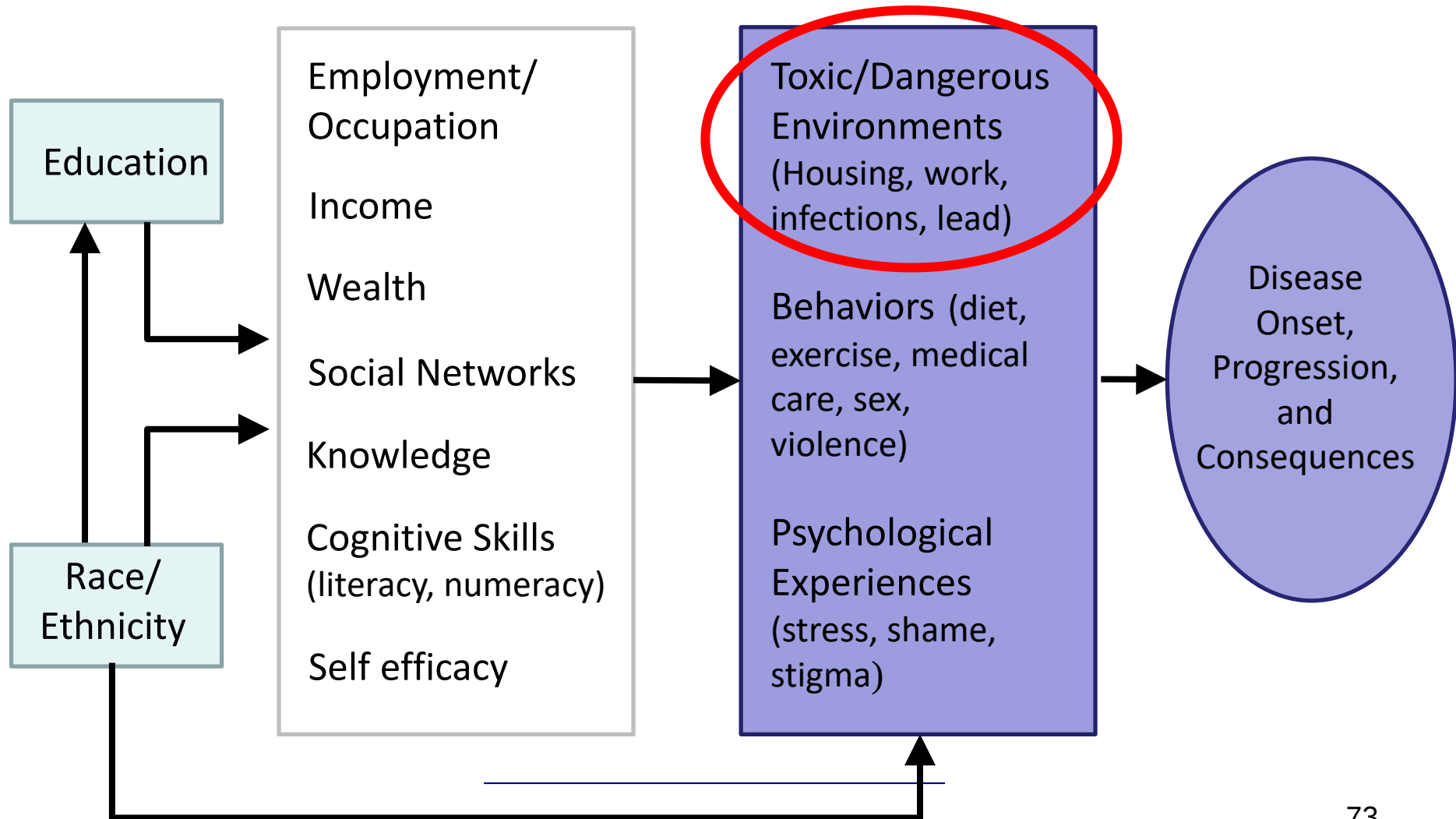
Mean score in kids randomized older than that age

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

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

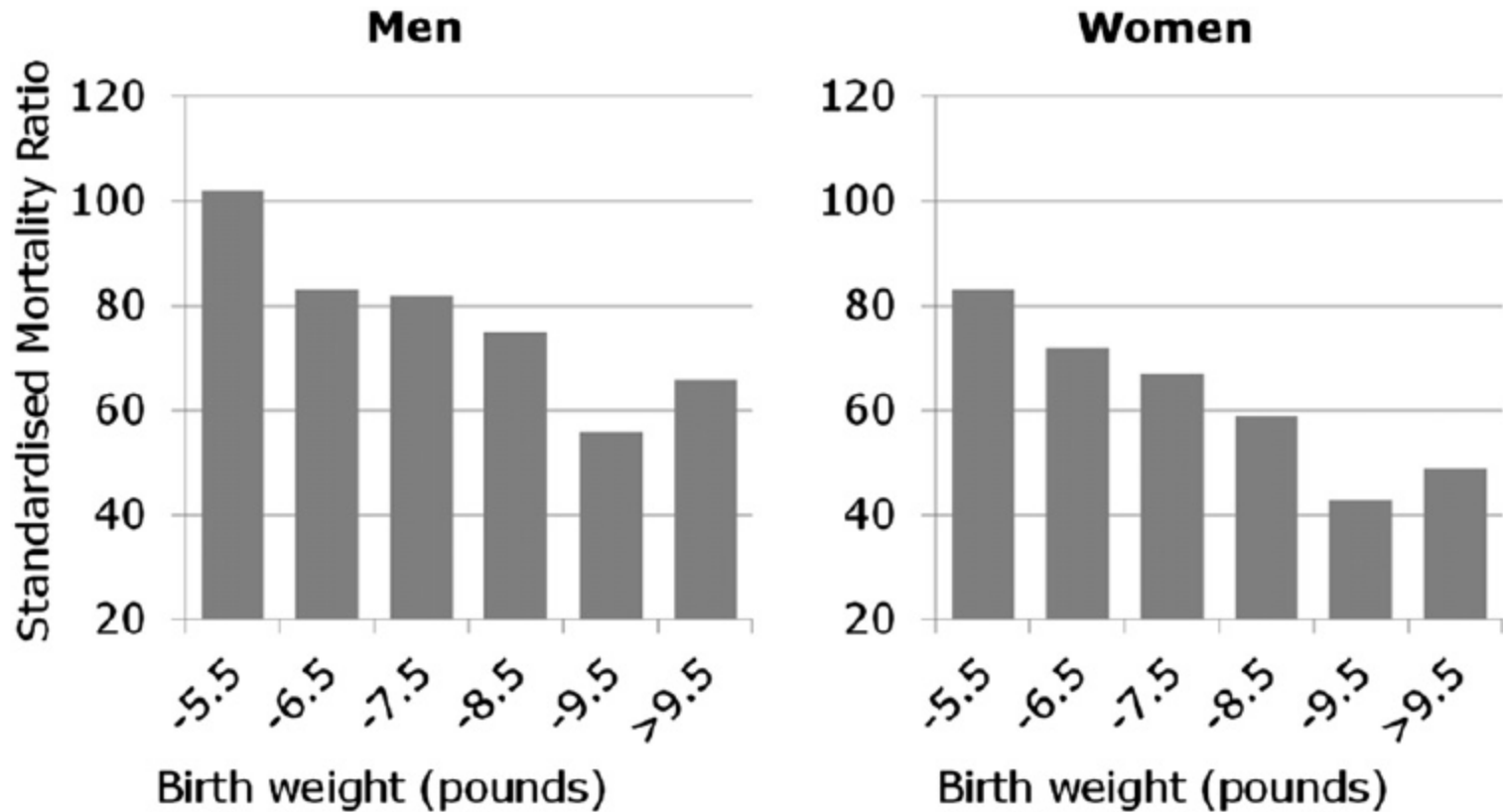
Direct Toxic Exposures

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

Nutritional Deprivation

- How to research long term effects of nutritional deprivation?
 - Use anthropometric measures because growth sensitive to both genetic and environmental conditions (distinguish from phrenology deterministic perspective)
 - Use administrative records, e.g., birthweight, as a proxy for a set of more diverse exposures
 - Use natural experiments (Dutch Famine study)
- Research in this area is extremely constrained by data availability

Barker Hypothesis: Birthweight and later CVD risk



Mortality from CHD in n=15,726 Hertfordshire
Barker, annual review of public health, 2012

Birthweight and later CVD risk

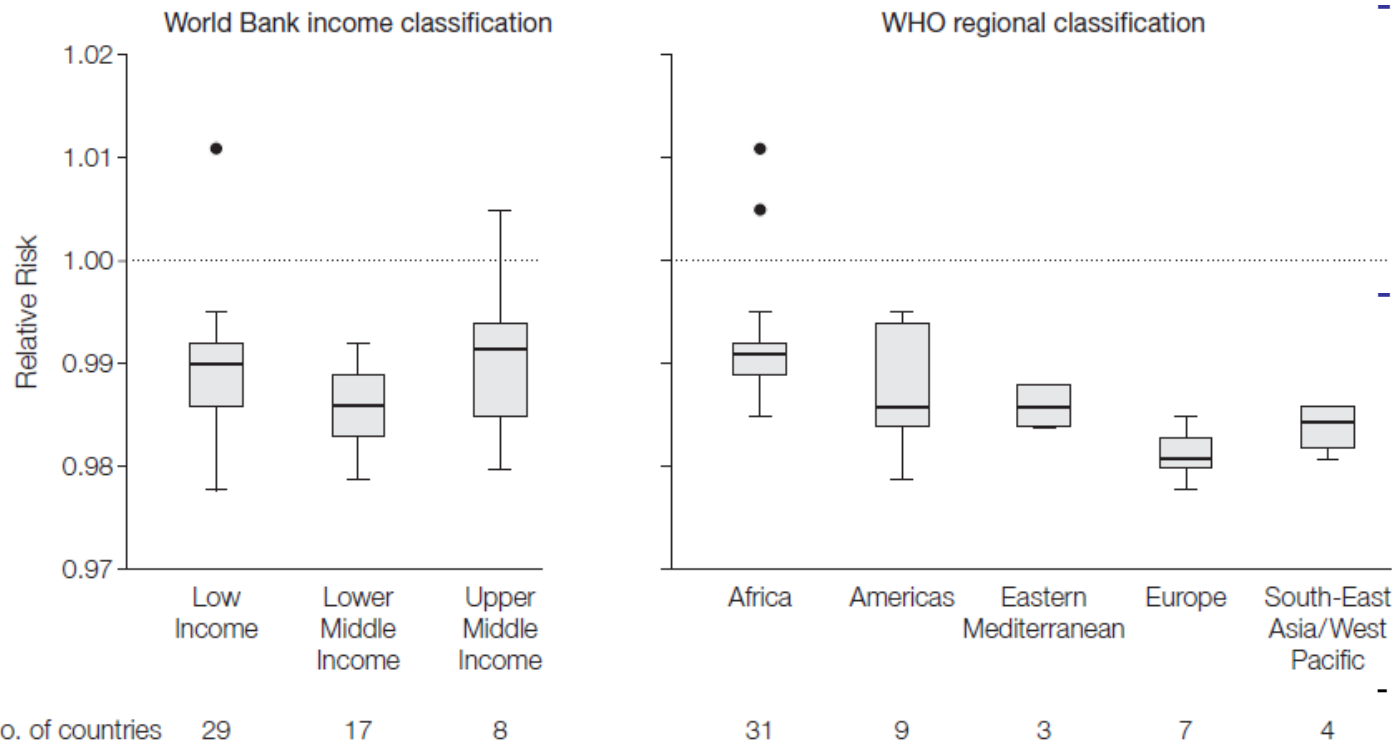
- Birthweight is an indicator of adverse exposure in utero (first 1000 days)
- Reduced function in organs such as kidney
- Modified “settings” in metabolism and hormonal feedback
- More vulnerable to adverse later environmental conditions
- Developing organism prioritizes resources for brain growth, low priority for kidney and lungs
- Compensatory growth costs other developmental activities.

Nutritional Deprivation

Several studies report associations between brain or head size and late life cognitive function.

- Women with neuropathological changes characteristic of AD but no clinical impairment had larger brain volume than women with similar neuropathological changes exhibiting clinical impairments. – Katzman, Ann Neurol 1988
- Larger head circumference predicts higher cognitive function scores in Japanese Americans in Washington State - Graves, 1996
- Women with head circumference in the lowest quintile were 2.9 times more likely to have AD (adjusting for age, education, and ethnicity); men were 2.3 times more likely to have AD – sample from Northern Manhattan- Schofield, 1997

Maternal Height (in cm) and Infant Mortality



- Short stature indicates mother's nutritional status in childhood

- Each taller cm of mom's height associated with 1.4/1000 fewer deaths in children under 5.

- Ozaltin, JAMA, 2009

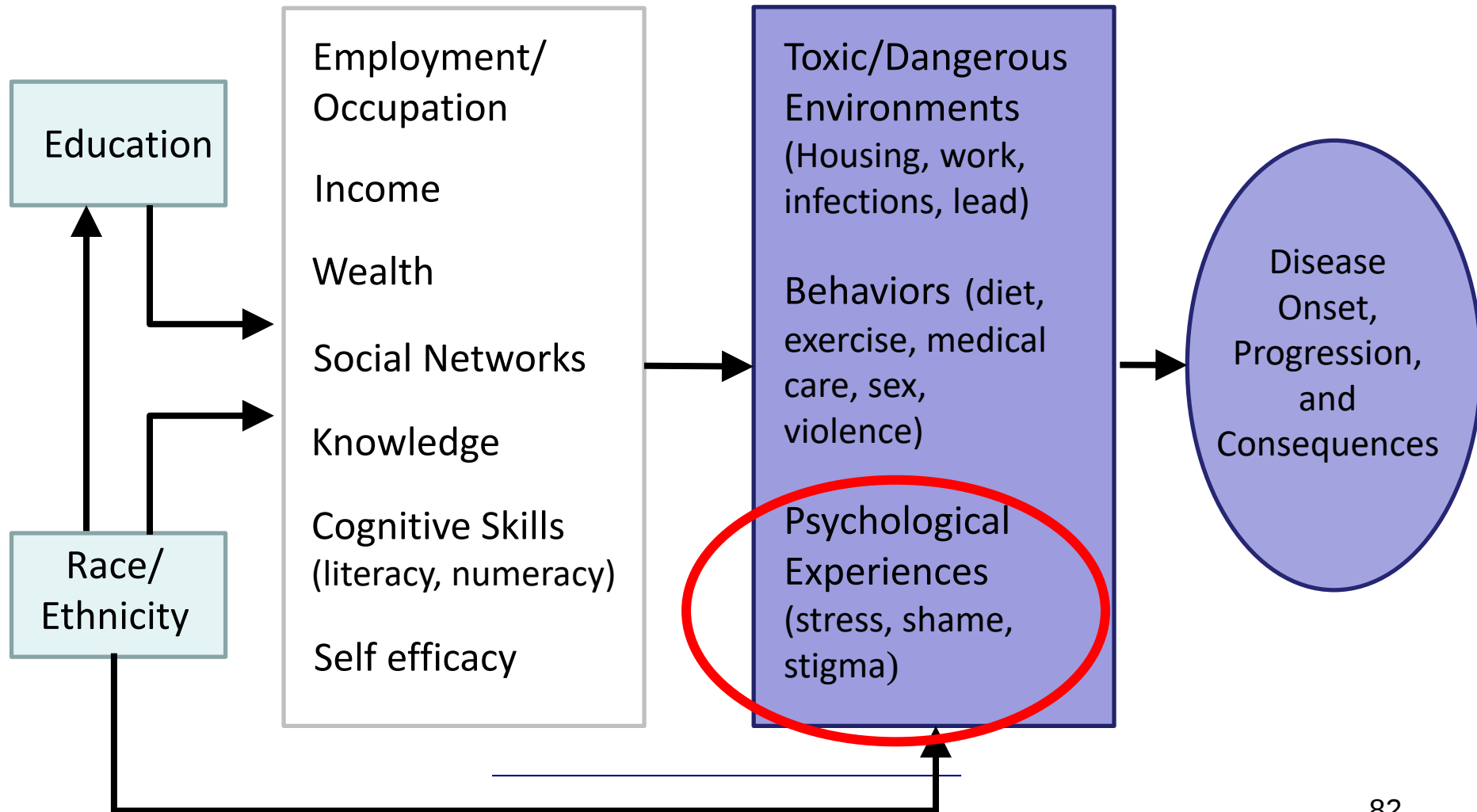
WHO, World Health Organization; IQR, interquartile range. Plotted on log scale. For World Bank income classification, low income indicates \$975 or less; lower middle income, \$976-\$3855; upper middle income, \$3856-\$11 905 (2008) gross national income per capita. Boxes indicate first and third quartiles with median lines; whiskers indicate first quartile minus $1.5 \times \text{IQR}$ and third quartile + $1.5 \times \text{IQR}$; all values outside the whiskers are shown as filled circles (outliers). An interactive information graphic is available at <http://www.jama.com>.

Nutritional Deprivation: other measures

Key questions:

- Other SES measures or entirely confounding?
- Timing of exposures that matter?
- Does the sources of stress matter?
 - (Nutrition? Infection? Emotional?)
- Which outcomes are affected?

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
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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 is very limited by the tools.
2. 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
 - GxE?
3. Adaptive plasticity: adaptations optimize to environment that prevailed during critical developmental period, and illness is due to a mismatch with new environments?
4. Mechanisms of intergenerational transmission
5. Reversibility: can advantageous environments undo harm?
6. The role of genetics

Controversy regarding stress mechanisms

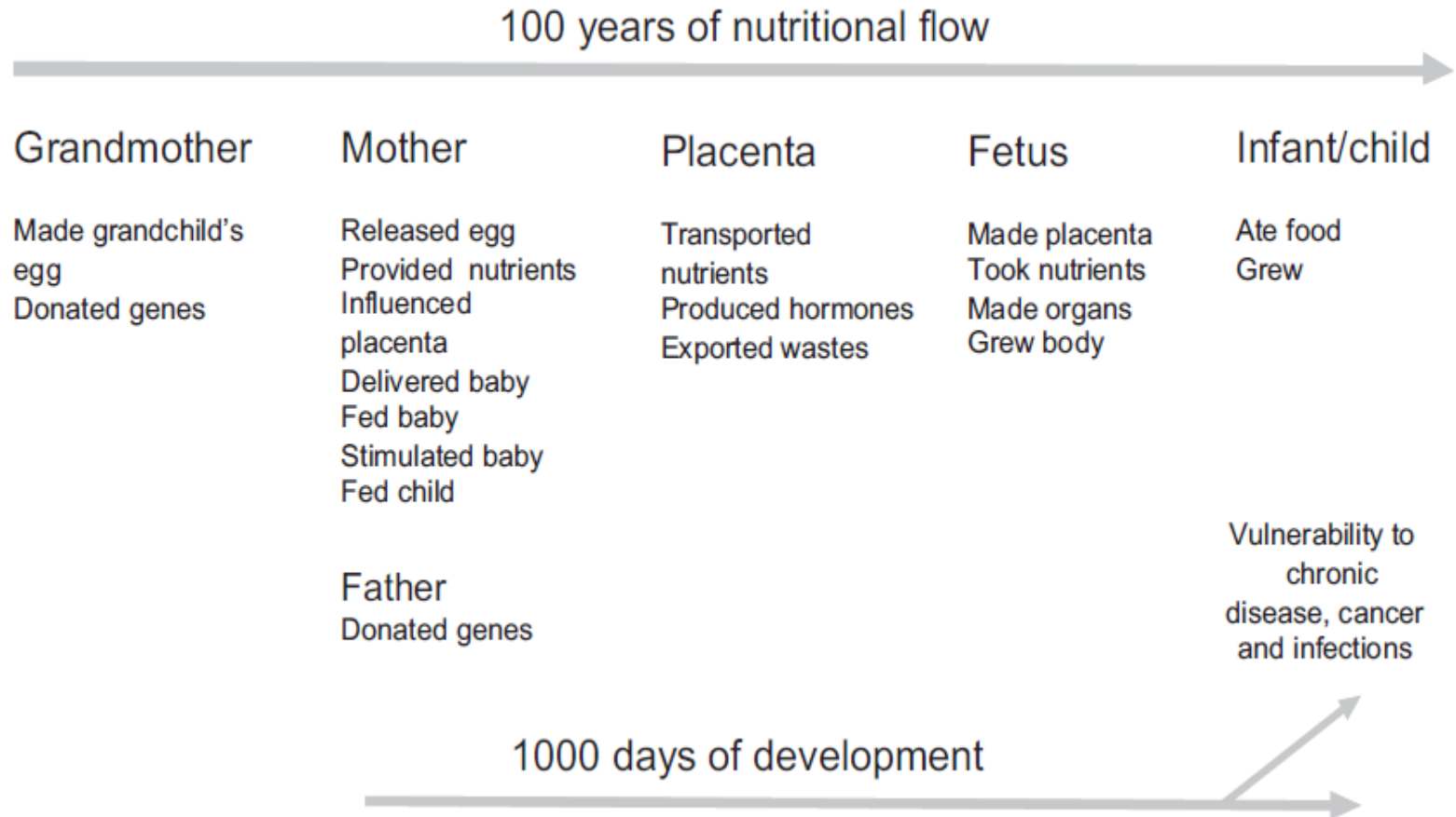
“Cortisol has received extensive attention as a potential mediator in the SES–health relationship. This review documented that more studies to date have found no association of cortisol with SES than have found the hypothesized association between lower SES and higher levels of cortisol, with several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

Hypothesized transgenerational flow of risk for chronic disease

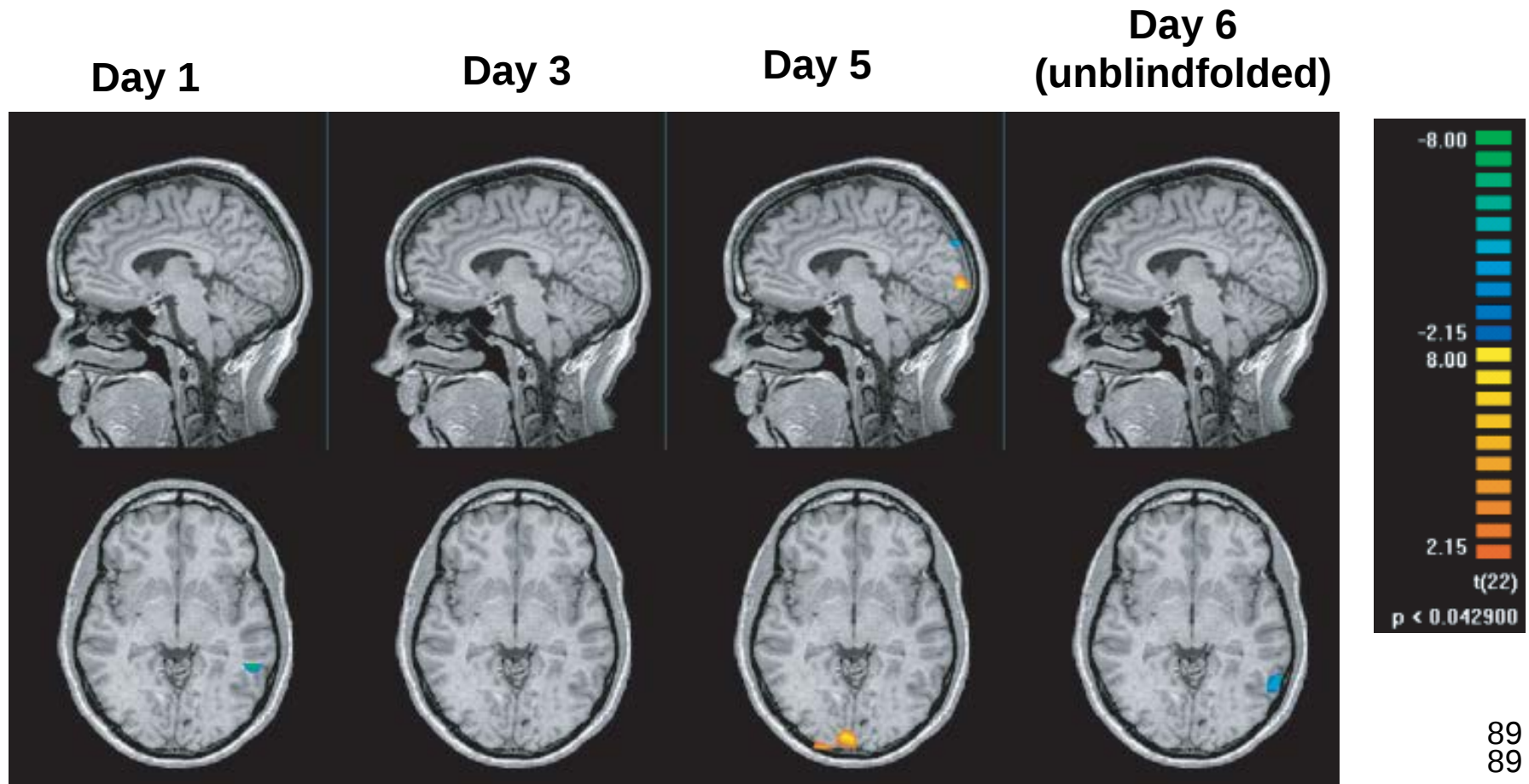


How special are early developmental periods?

- 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

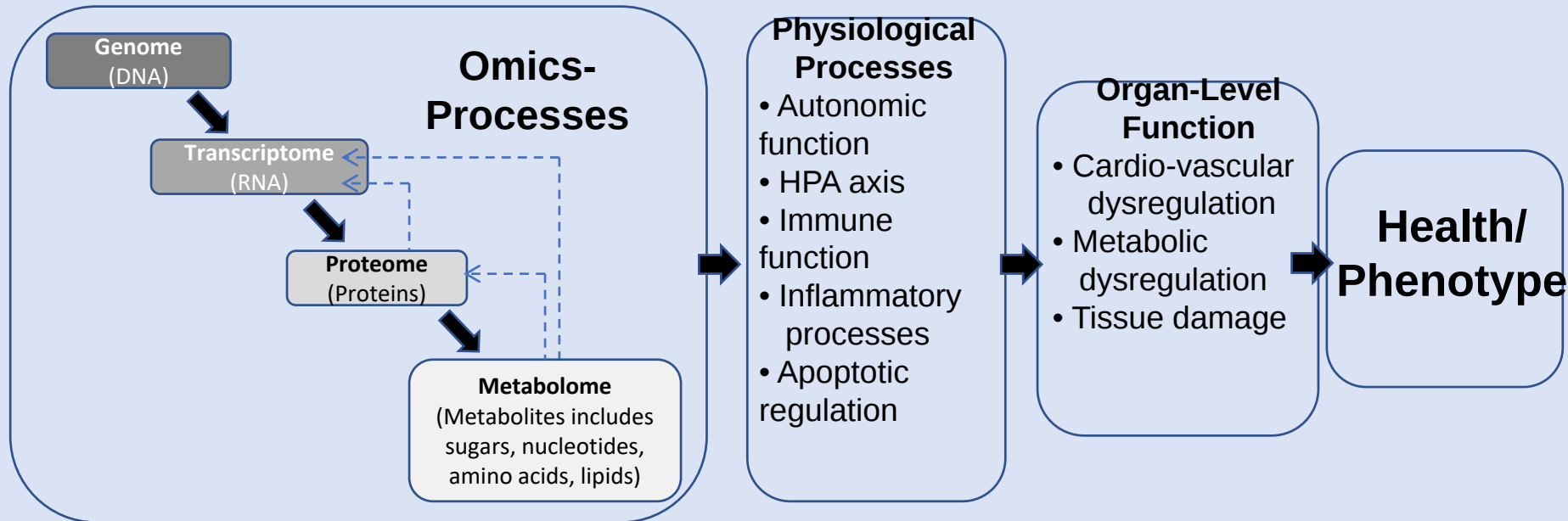
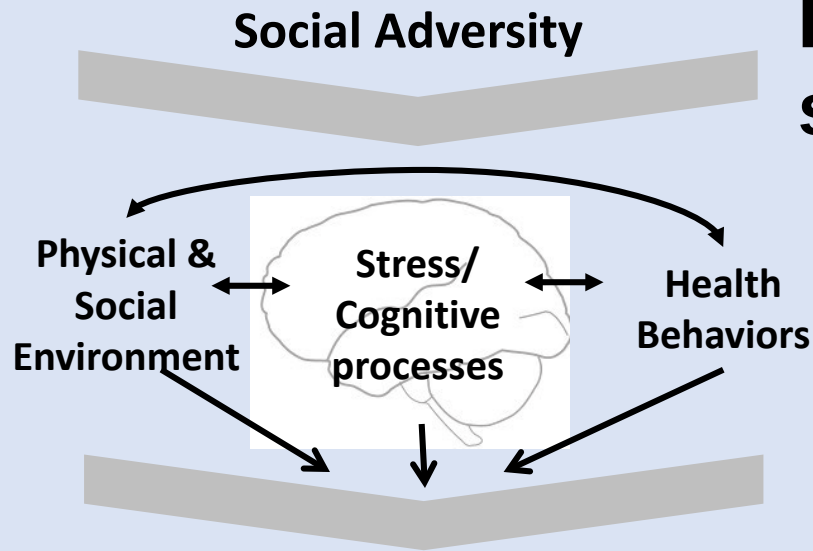
- Sighted recruited occipital cortex for Braille



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.”

Biological pathways linking social conditions & health



end

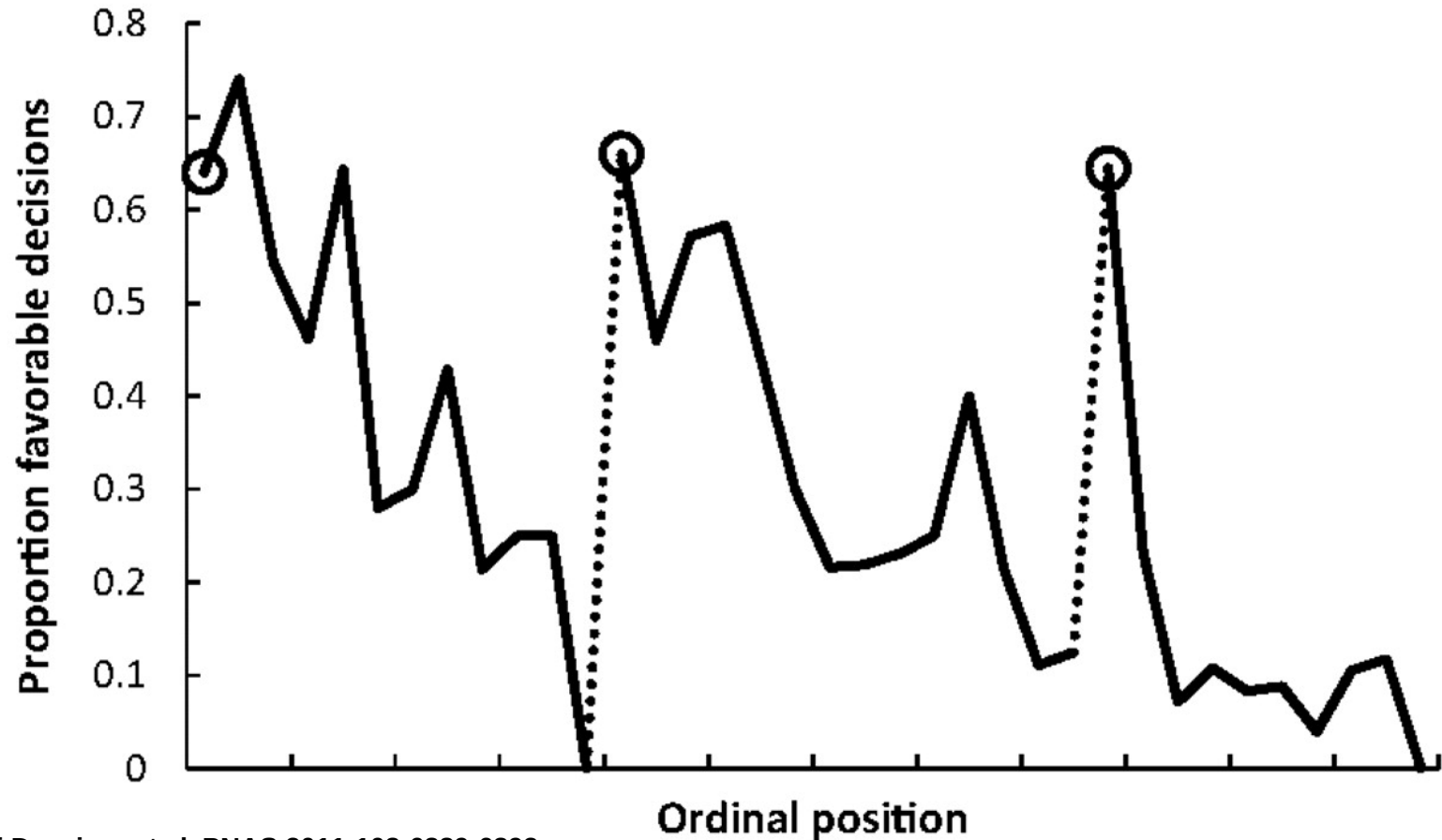
Example 3

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

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.

