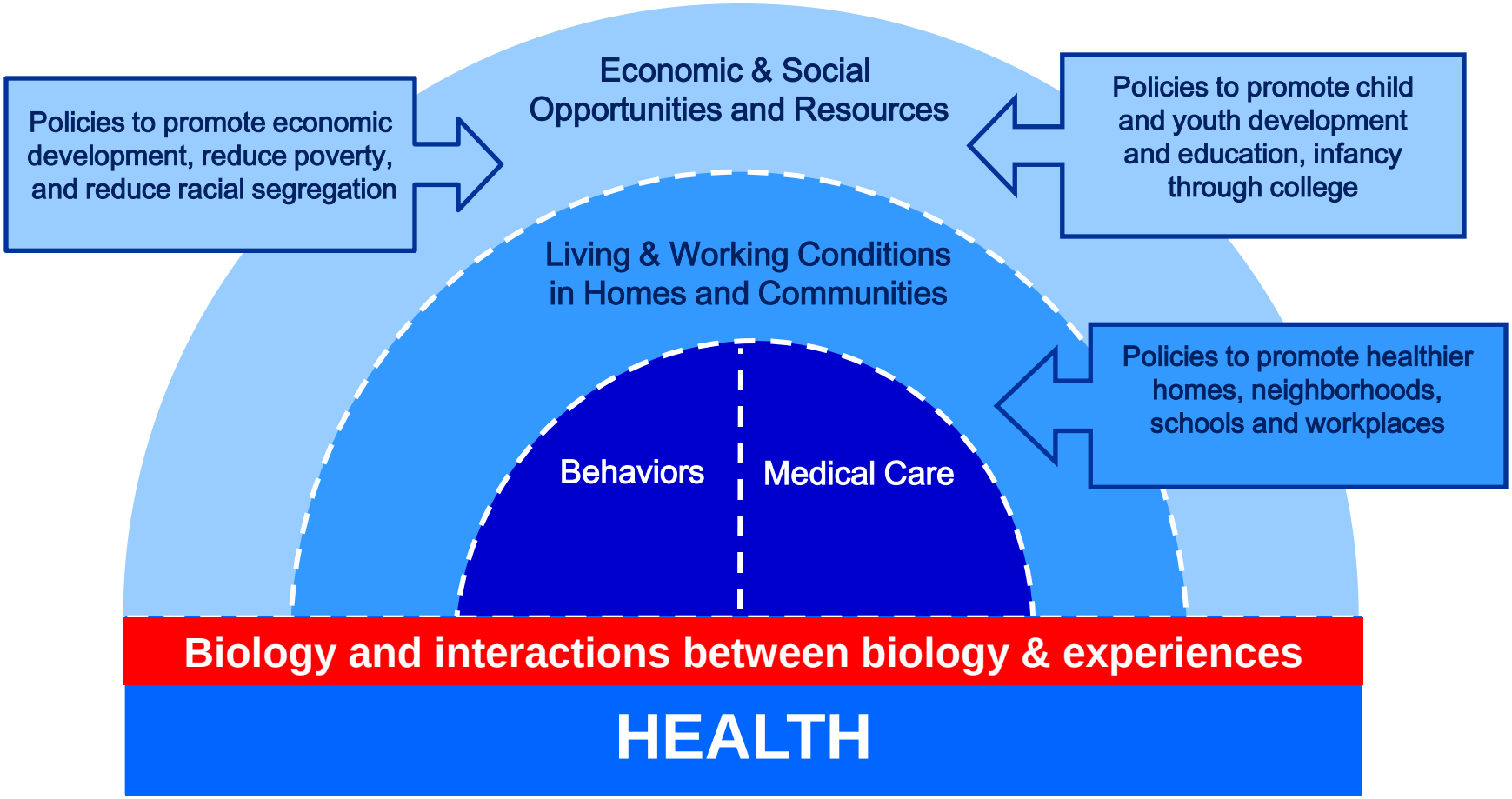
EPI222: Multi-Level and Longitudinal Conceptual Approaches for Health Disparities Research

Lecture 5 (numbered conceptually) or Lecture 4 (numbered consecutively):
Biological Mechanisms Mediating Health Disparities

Where are we in the class?



Biological Mechanisms

- Preliminaries
- Behaviors, including use of medical care
- Where do genetics fit in?
- Direct toxic exposures
- Stress mediated pathways
- Major controversies or uncertainties
  - Lifecourse/sensitive periods
  - Qualitative interactions/dandelion vs orchid
  - Role of genetics

Biological Mechanisms

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

Preliminaries

- 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.
- 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?

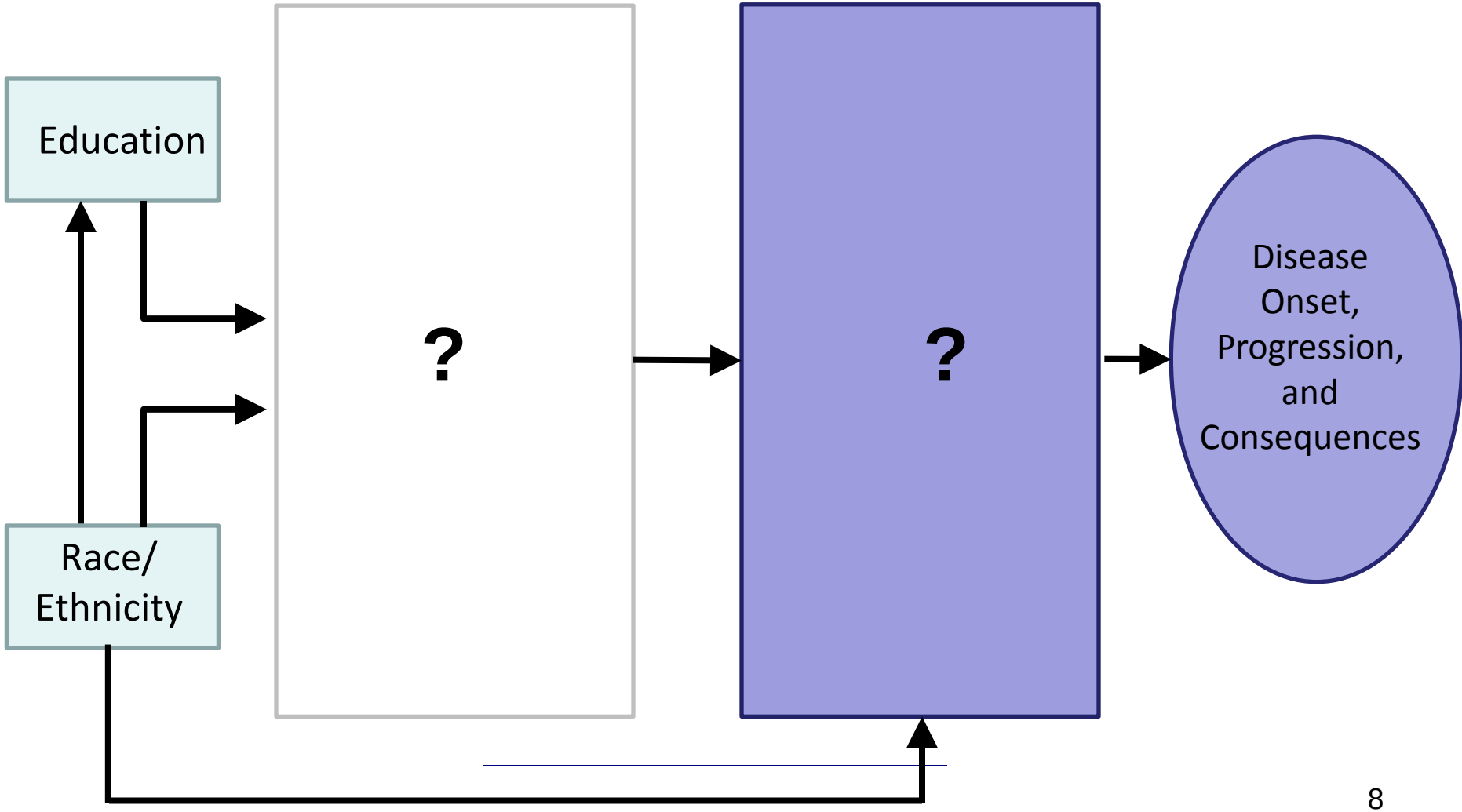
- Designing effective interventions to interrupt the pathway (not always necessary but it's helpful)
- Evidence that associations are "causal" (because if not causal, there is no hope of effective interventions on this exposure)
- Motivating action: biologically grounded explanations often move decision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

Embodiment

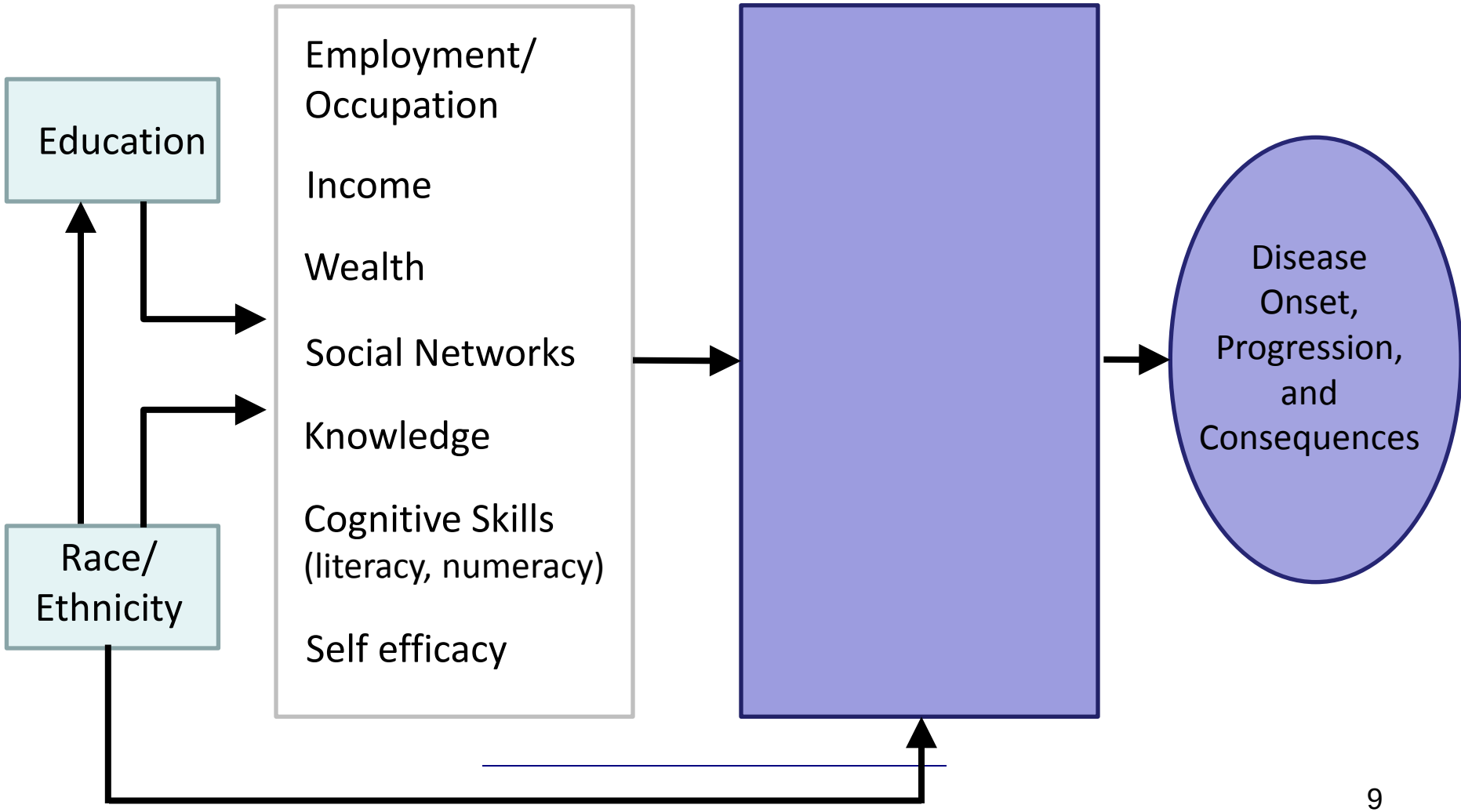
- “how we literally incorporate, biologically, the material and social world in which we live, from in utero to death…” Krieger 2005, JECH

- 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

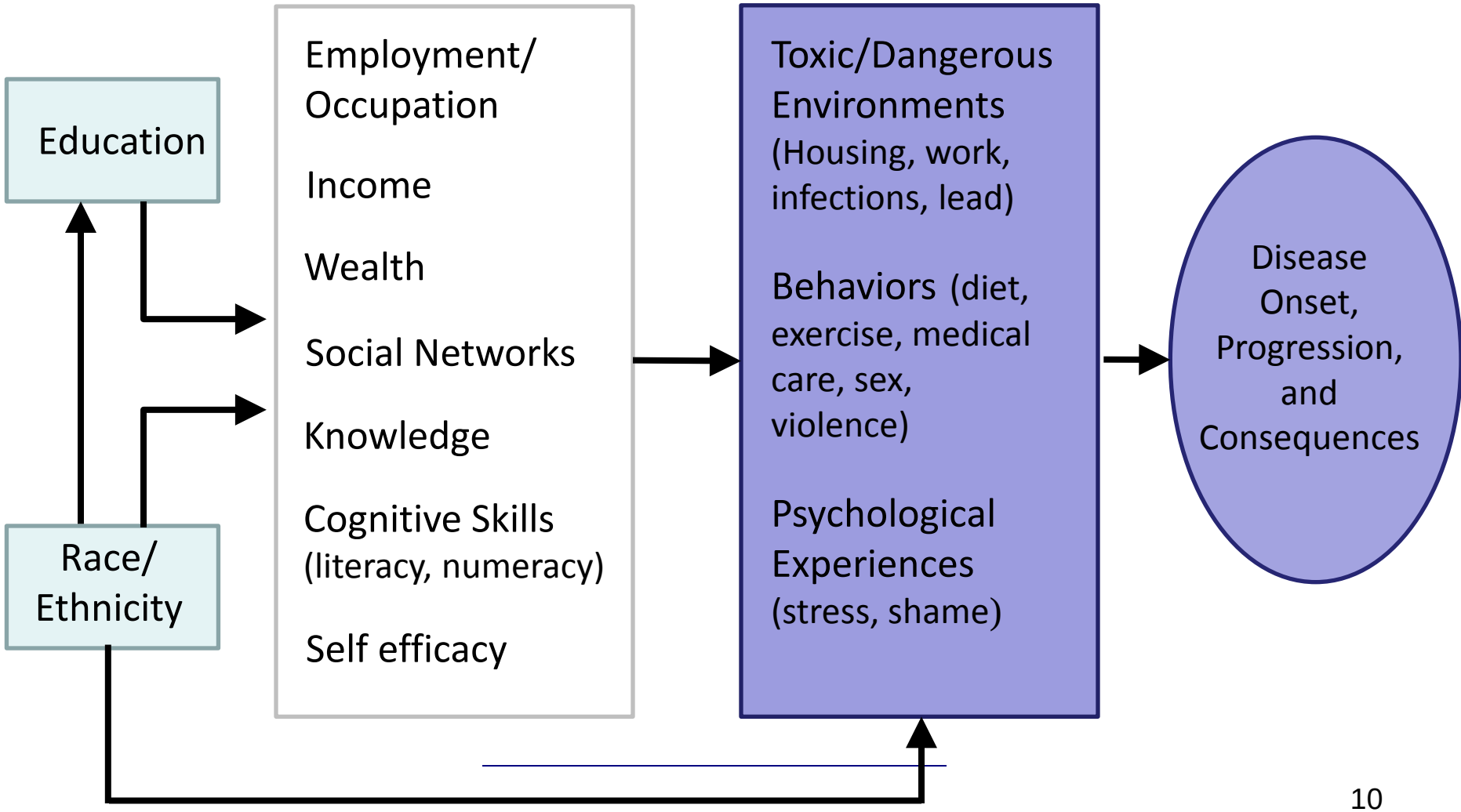
Social Factors and Health: Hypothesized Pathways



Social Factors and Health: Hypothesized Pathways



Social Factors and Health: Hypothesized Pathways



Take Home Messages

- Physiologic mechanisms for embodiment
- Examples of some promising areas of research
- Intersection of human development and social stratification→ lifecourse determinants
- Recognition of key research approaches and challenges
- Recognition of major points of controversy

Feedback Across the Lifecourse

- Social patterns create biological and physiological patterns.
- Physiologic patterns create social patterns.
- These paths feedback across the course of an individual's life, in ways that depend on both the biology and the social context.
  - Community norms are a strong influence on whether an adolescent takes up smoking.
  - Cigarette use is initiated in adolescence or early adulthood, so people often carry the norms (and therefore the cancer and CVD risk) of the place they lived in adolescence or early adulthood

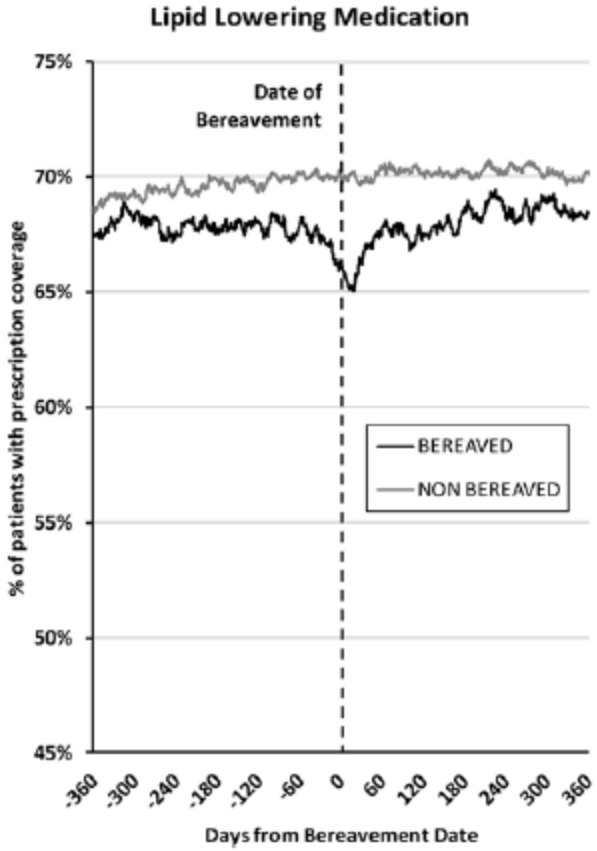
Key Idea in Biological Embedding: Sensitive Periods

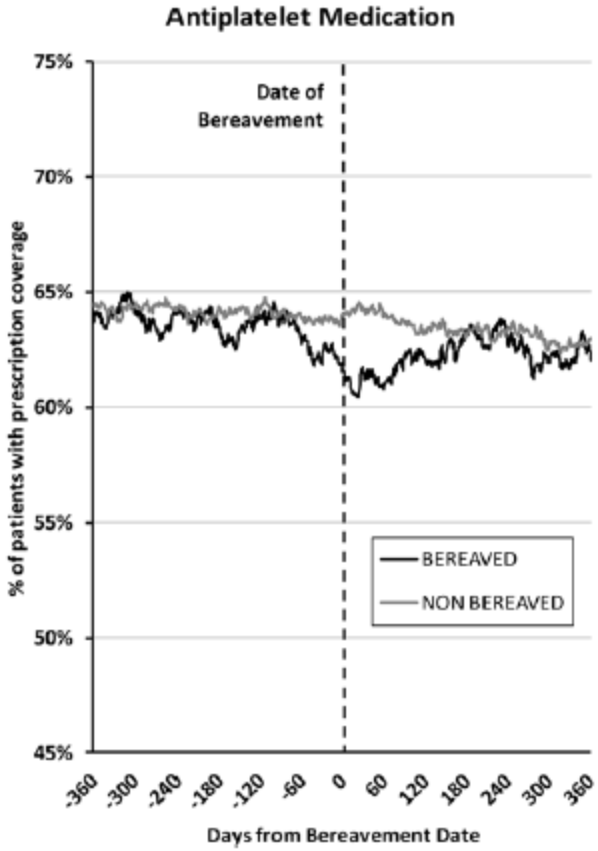
- Arguments for special sensitivity in early life because this is a period of very rapid physical development
- Sensitive period: an age when the influence of the stimulus is disproportionate
- Critical period: an age when the influence of the stimulus is essential for normal development
- However, there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

(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

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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

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.

Uylings, H.B.M. (2006) Development of the Human Cortex and the Concept of “Critical” or “Sensitive” Periods. Language Learning, 56, 59-90.

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

Uylings, H.B.M. (2006) Development of the Human Cortex and the Concept of “Critical” or “Sensitive” Periods. Language Learning, 56, 59-90.

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					
Comparison between Whites and Blacks					
White	1617	3.9 (62)	ref	ref	ref
Black no APOL1	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)
APOL1 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)

In Blacks, population attributable fraction for *APOL1* in Blacks was 9.4%
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 MAF difference
- 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

Biological Mechanisms

- Preliminaries
- **Behaviors**
- Direct toxic exposures
- Stress mediated pathways
- Major controversies or uncertainties
  - Lifecourse/sensitive periods
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Behaviors are shaped and constrained by social context

- Behaviors are the focus of another lecture. 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

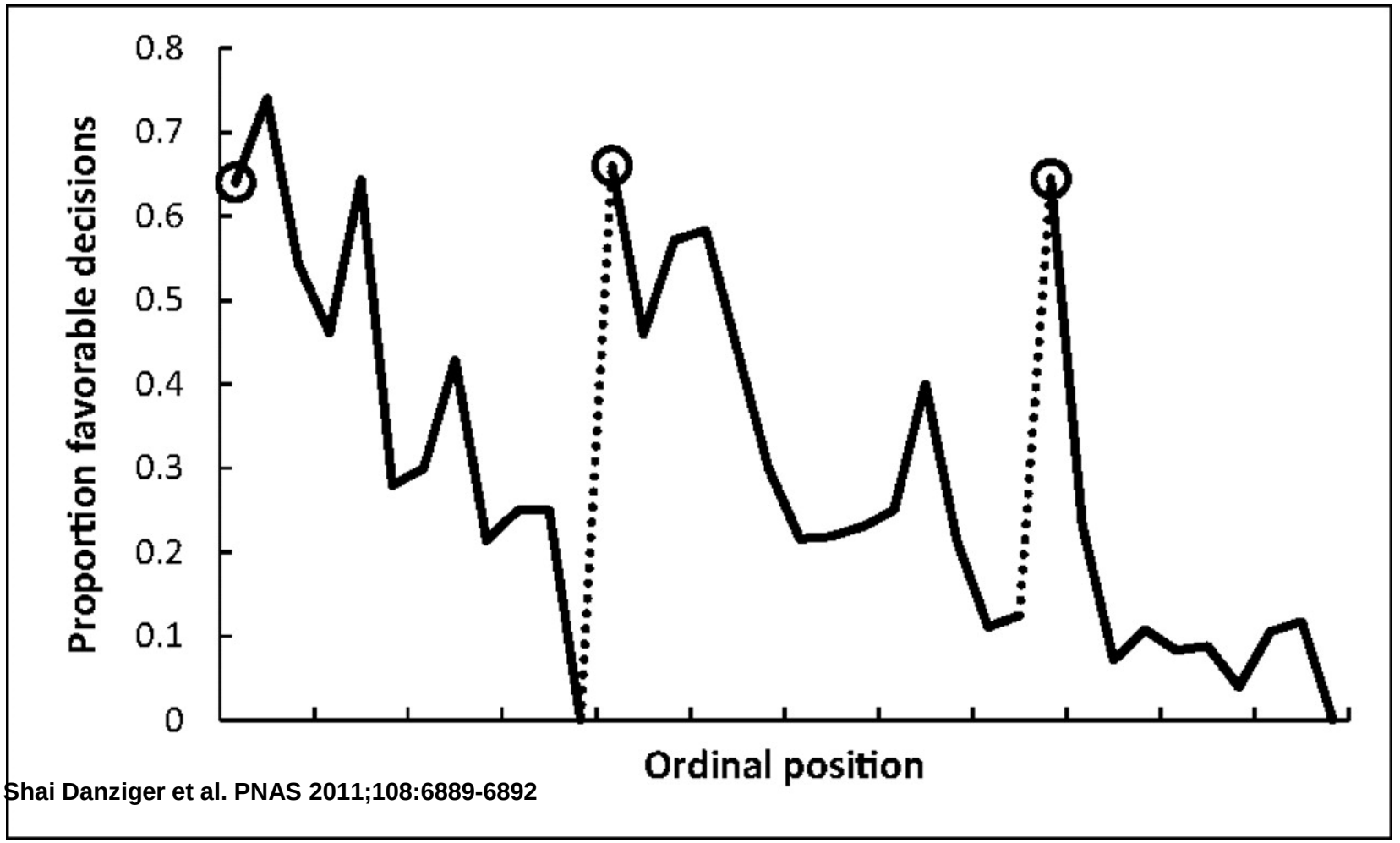
Example 1

- 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 (Gailliott)
  - Meta-analysis shows persistence across task demands and subsequent displays of self-control

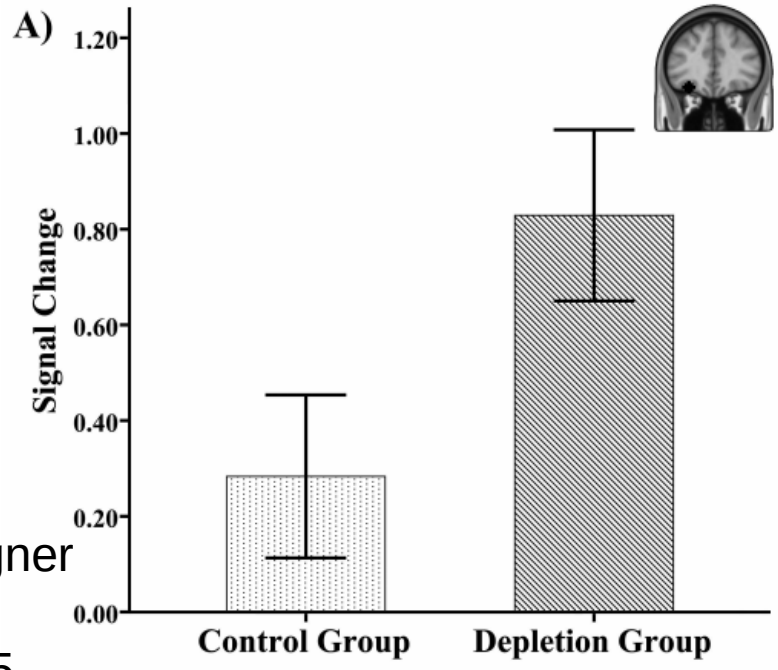
Proportion of rulings in favor of the prisoners by ordinal position

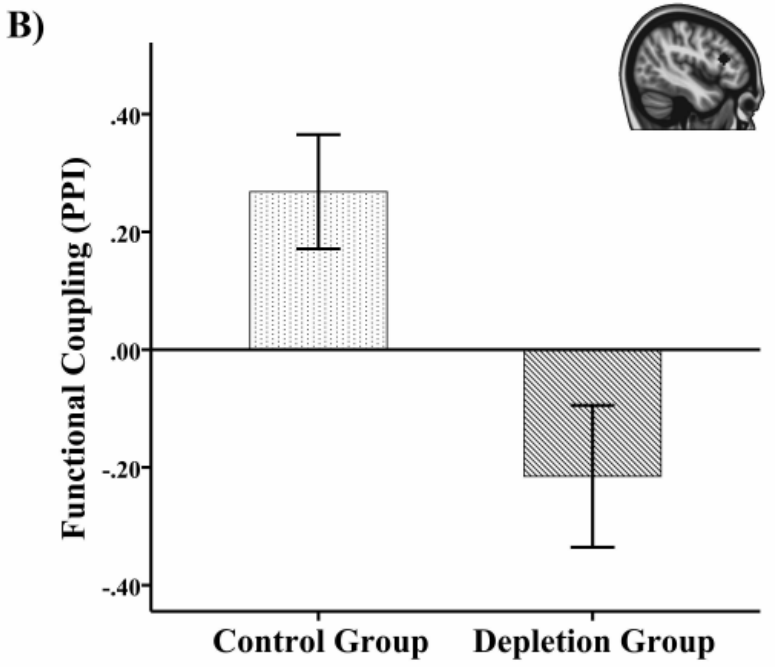


Shai Danziger et al. PNAS 2011;108:6889-6892

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.





Wagner et al 2015

Example 2

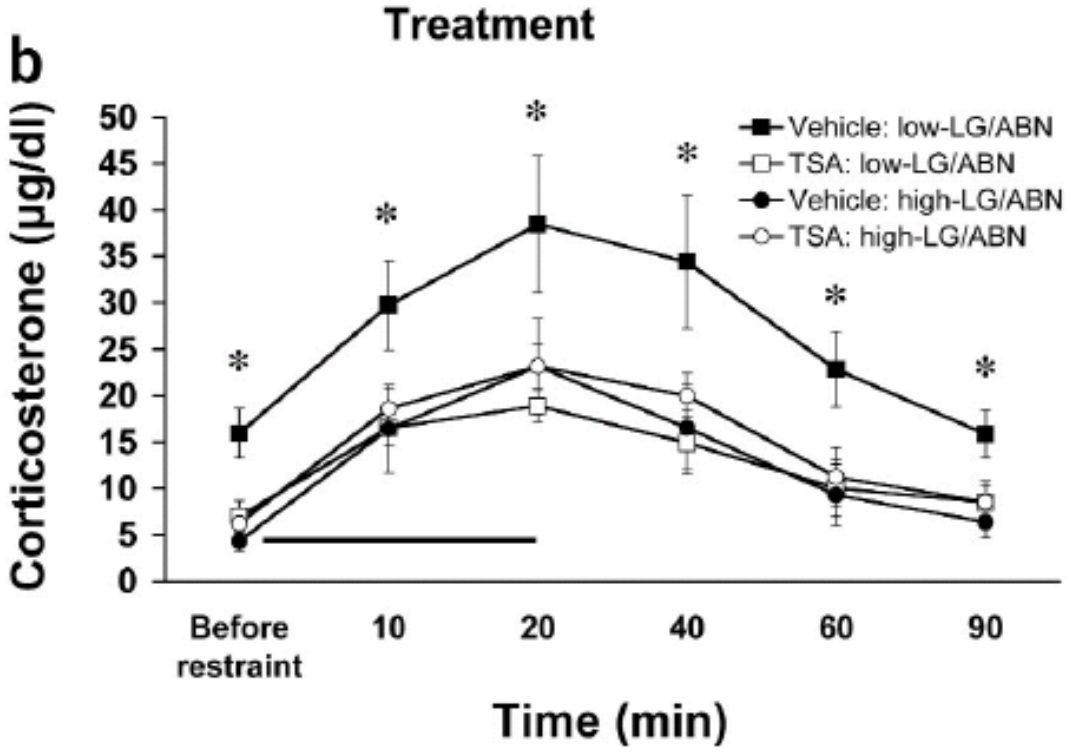
- Epigenetic modifications provide a possible physiologic mechanism linking parental behaviors to individual behaviors and health outcomes

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
- Histone acetylation enhances transcription while histone deacetylation represses transcription.
- Epigenetic patterns change rapidly 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

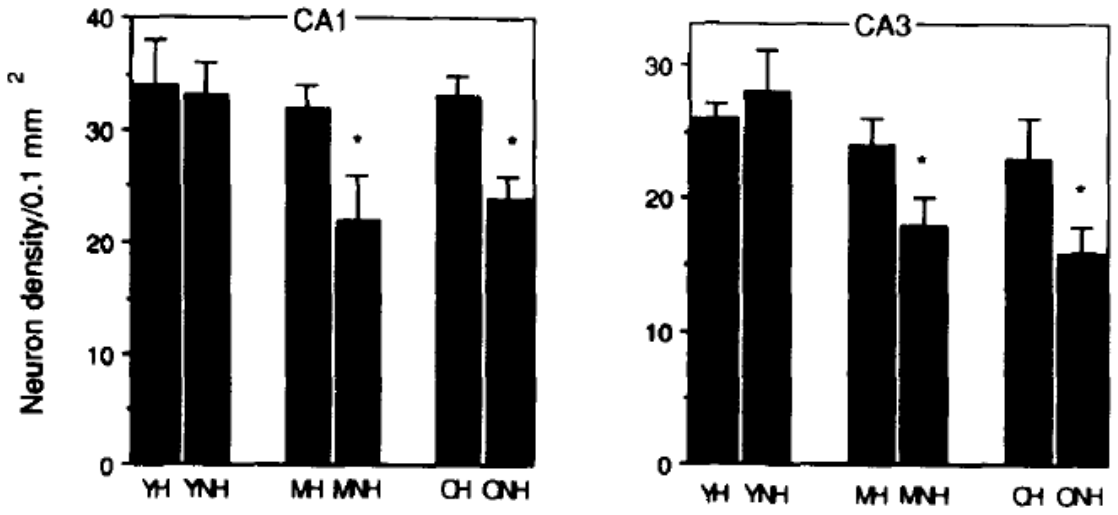


FIG. 2. Mean (±SEM) neuron density in various hippocampal cell fields in young (Y; 6-month-old), midaged (M; 12-month-old), and old (O; 24-month-old) handled (H) and nonhandled (NH) females (n = 3–5 animals/group; *indicates a significant treatment effect at $p<0.05$).

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

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Age	Handl
6 Months	8/11 (7
12 Months	9/11 (8
24 Months	6/10 (6

*Recovery is defined as a value t
value + 2SD.

MEAN (±SEM) SWIMMING DISTANCE

	Group	
Age	Handled	Nonhandled
6-Month-old	4.3 ± 1.1	5.5 ± 2.9
12-Month-old	5.1 ± 1.0	9.0 ± 2.5*
24-Month-old	5.0 ± 1.3	11.2 ± 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?

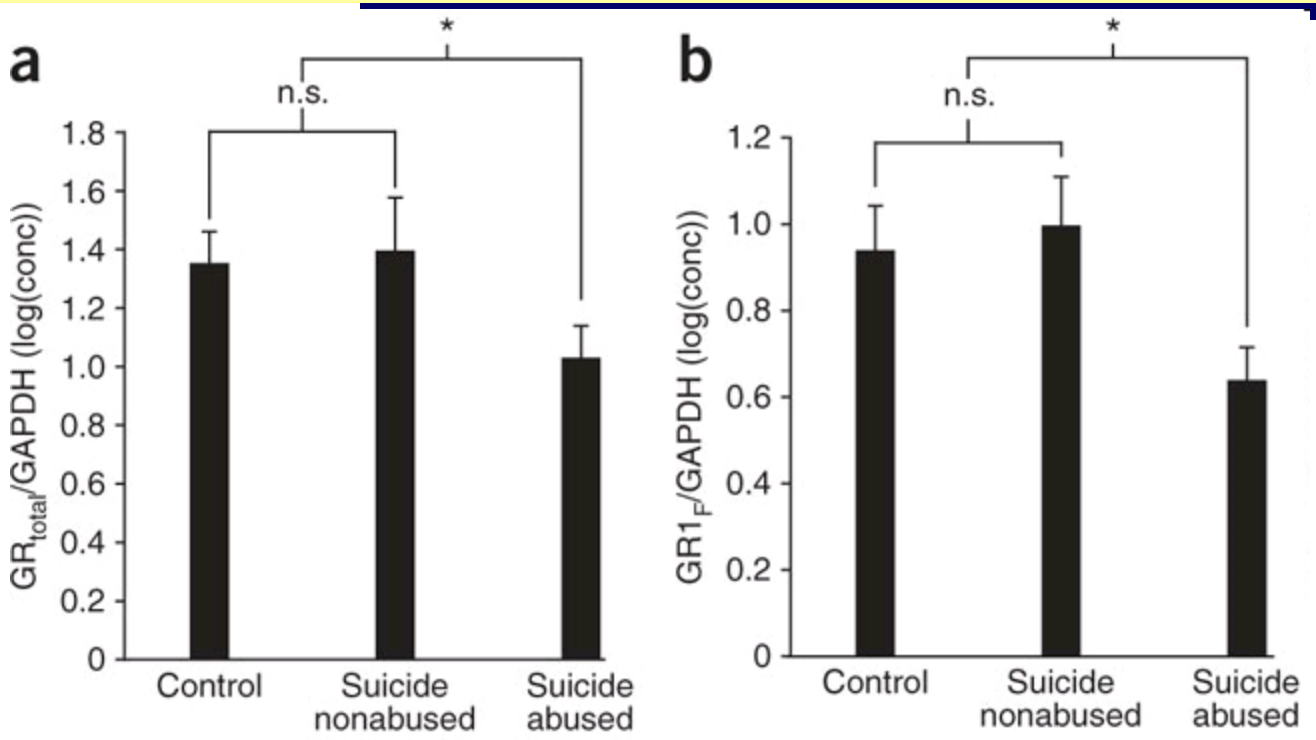
Why this is so powerful, if it's true

- Formerly thought almost no changes in methylation patterns after birth
- Increasingly recognized as not true (studies in twins show greater divergence in older twins), but epigenetic patterns are quite stable
- Thus, this is a mechanism by which 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.

McGowan, Nature Neuroscience, 2009

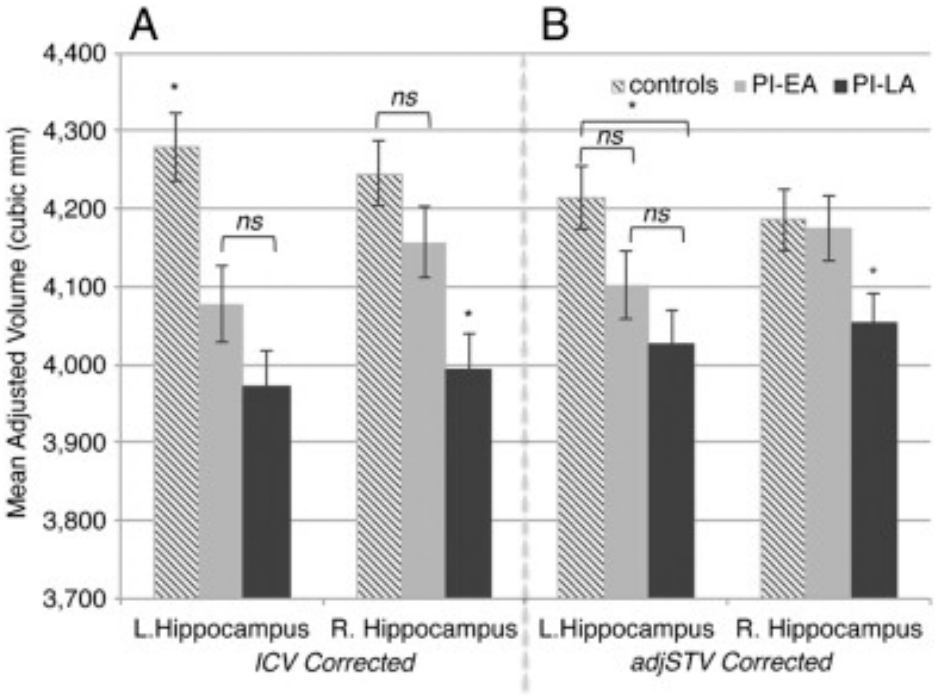
Example 3

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

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

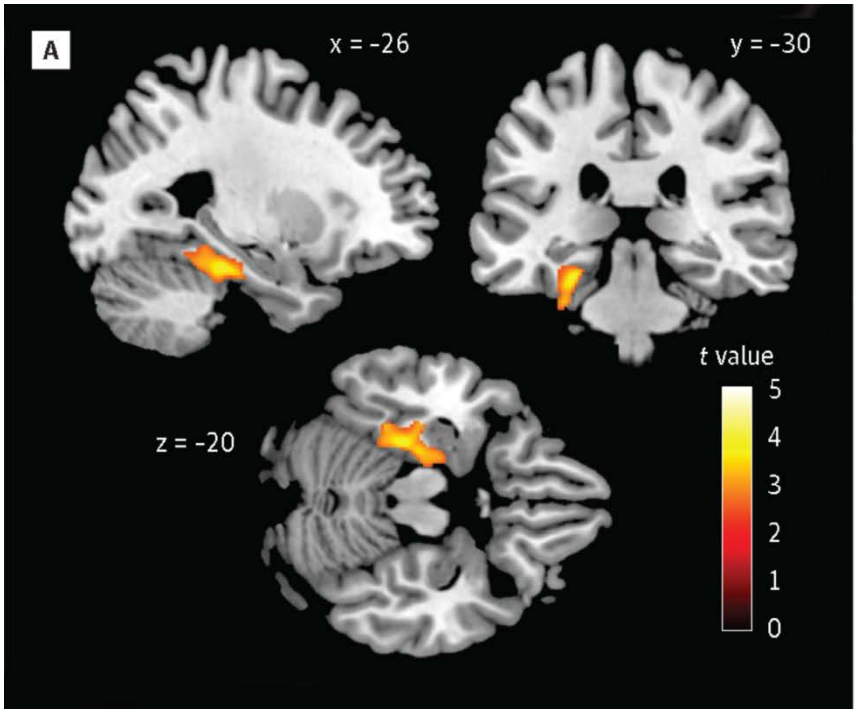
N=110 post-institutionalization children (internationally adopted: 3.5 to 60 months of institutional care, dichotomized at adoption before 12 months) compared to 62 children raised with biological families.

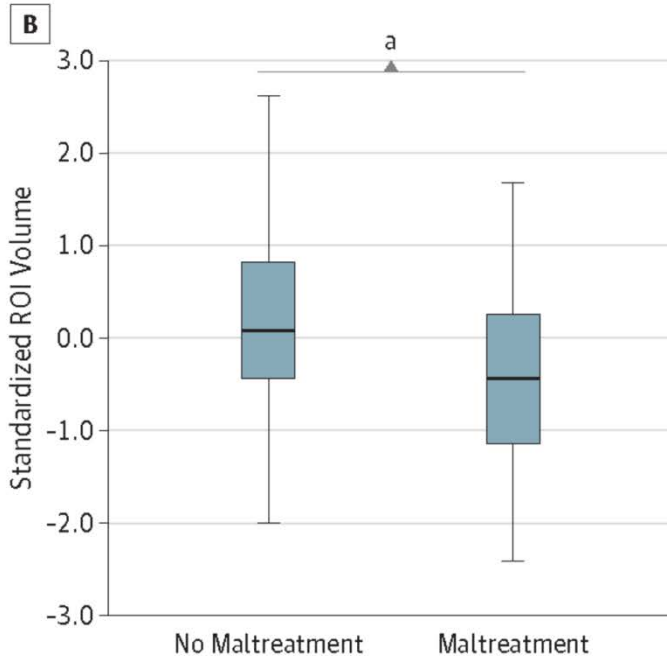
Duration of early adversity predicts hippocampal volume reduction (age and sex adjusted). Panel A: ICV corrected (± SEM). Panel B: adjSTV corrected (± SEM).



Amanda, NeuroImage 2015 **Duration of early adversity and structural brain development in post-institutionalized adolescents**

Child maltreatment influences GMV 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.[a]A 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
		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

Biological Mechanisms

- Preliminaries
- Behaviors
- **Direct toxic exposures**
- Stress mediated pathways
- Major controversies or uncertainties
  - Lifecourse/sensitive periods
  - Qualitative interactions/dandelion vs orchid

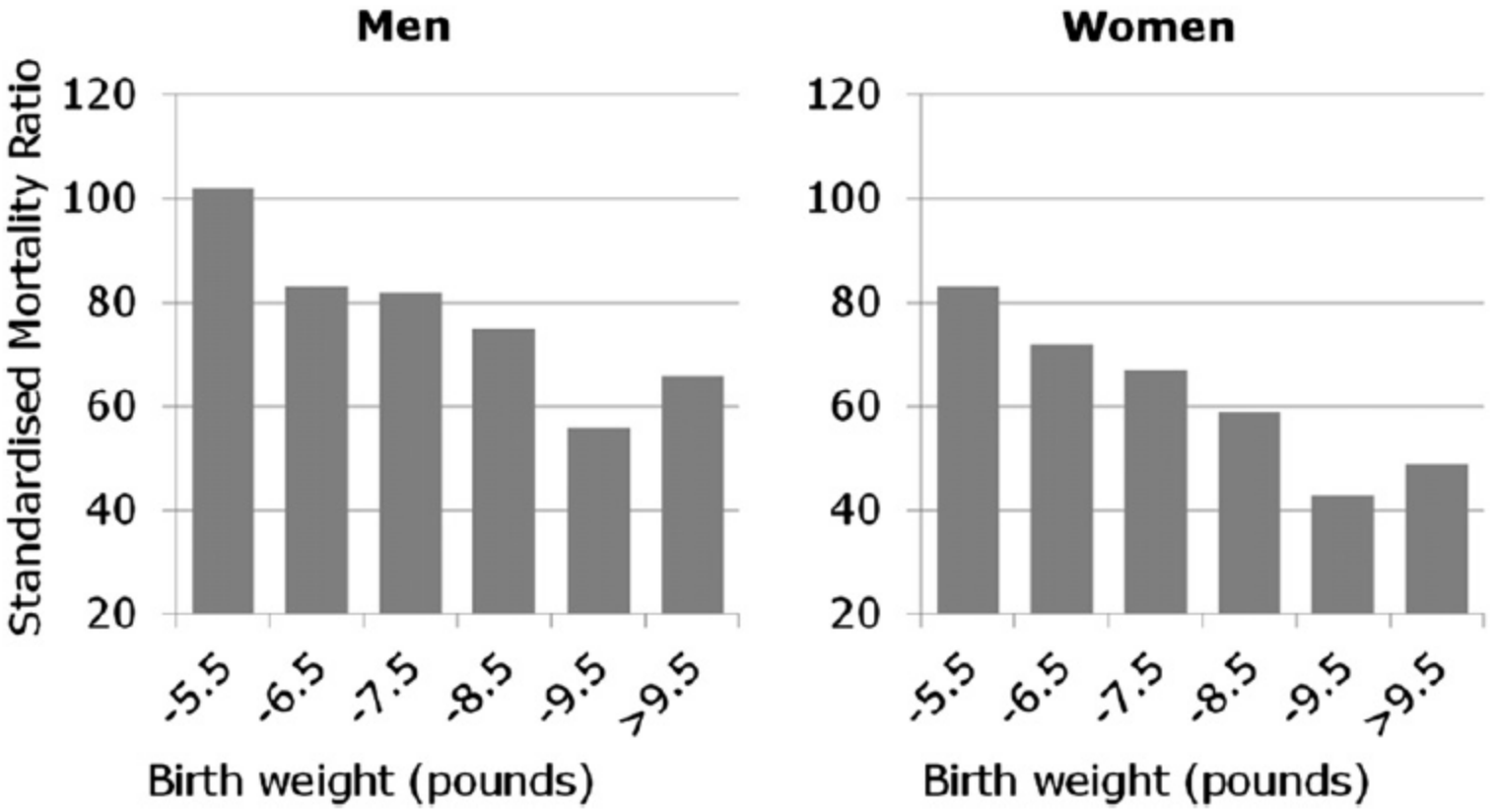
Direct Toxic Exposures

- Environmental toxins, e.g., lead, passive tobacco exposure, strongly socially patterned
- Affect both disease incidence and 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

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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

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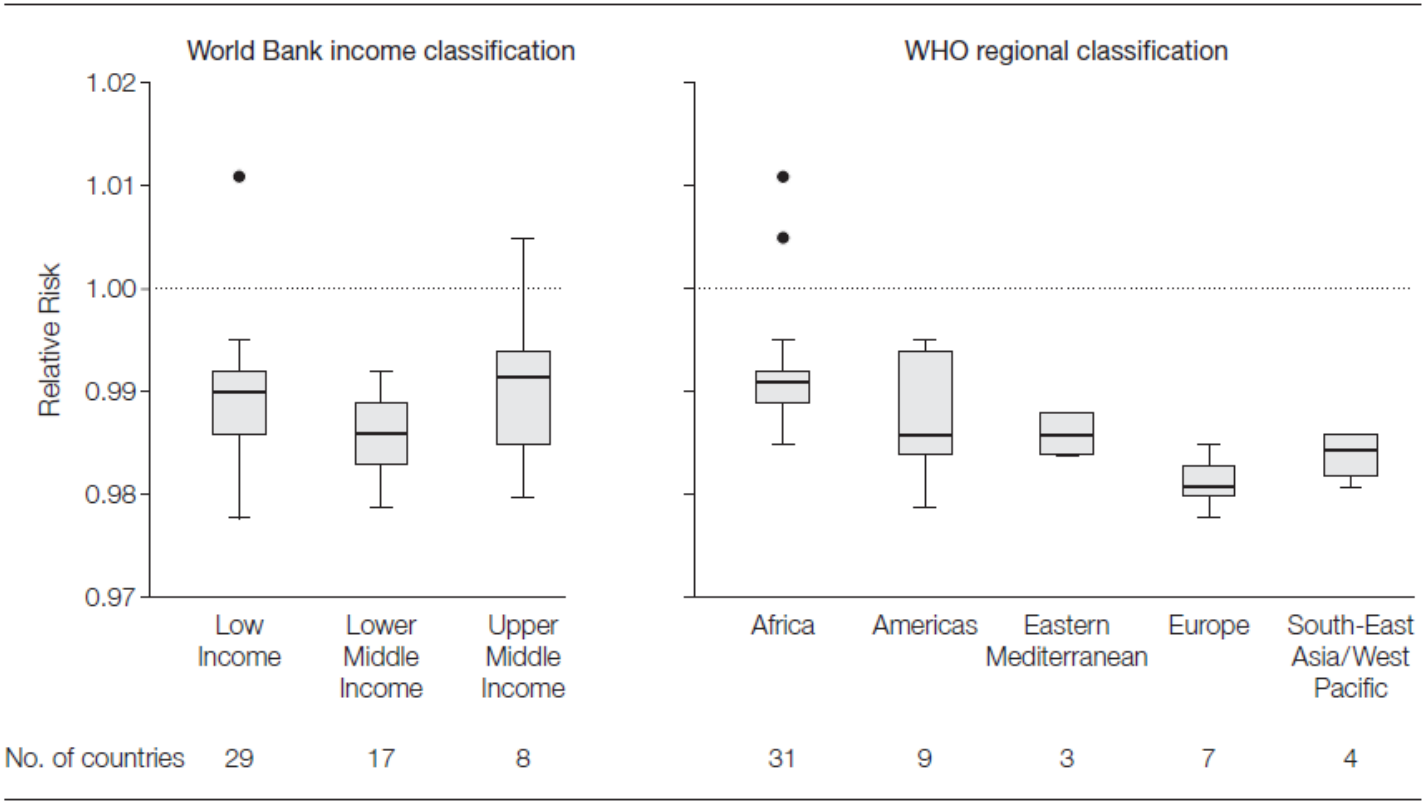
Maternal Height and Infant Mortality



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 × IQR and third quartile + 1.5 × IQR; all values outside the whiskers are shown as filled circles (outliers). An interactive information graphic is available at http://www.jama.com.

- Short stature indicates mother's nutritional status in childhood
- Each cm of mom's height associated with 1.4/1000 fewer deaths in children under 5.
- Ozaltin, JAMA, 2009

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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?

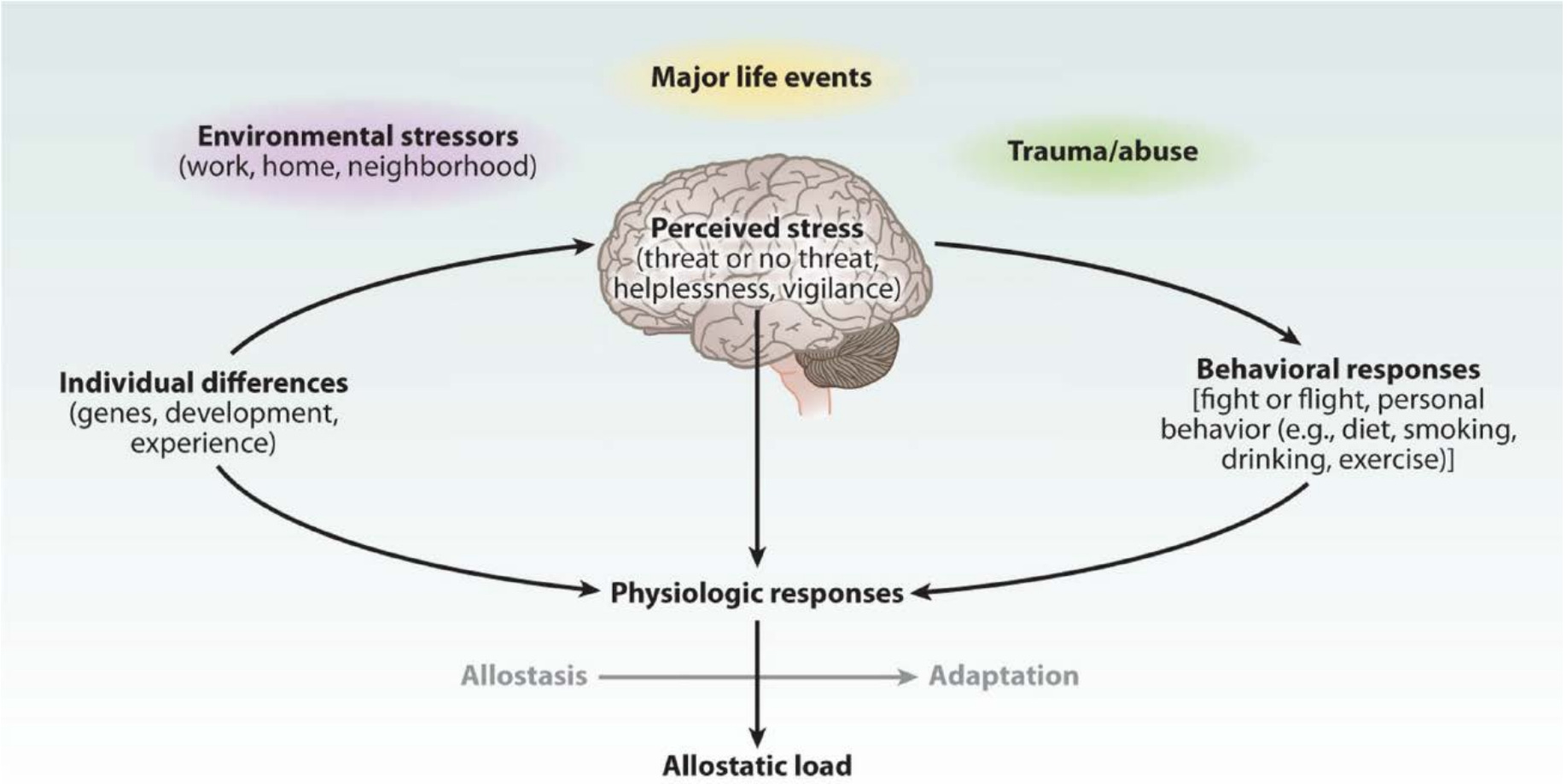
Biological Mechanisms

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

Stress Response

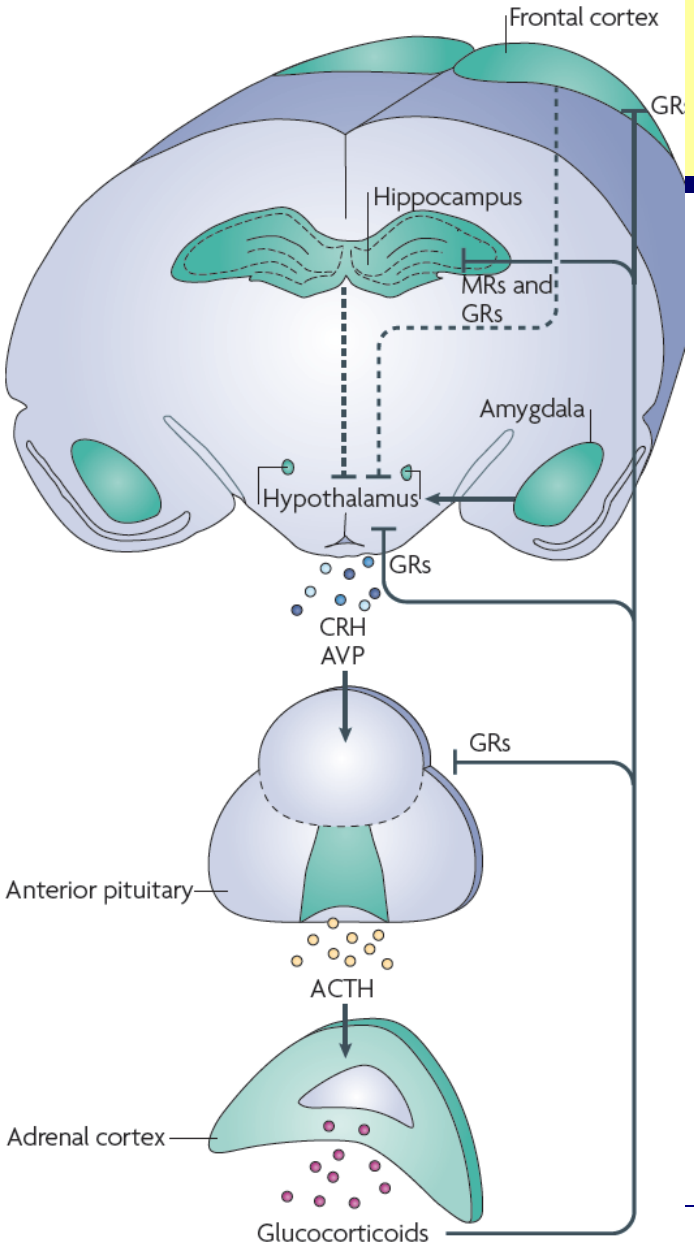
- Stressors: external demands encountered by the organism
  - Source:
    - Physical (cold, infection)
    - Psychological (fear, shame, anxiety)
  - Duration:
    - Acute (trauma)
    - Chronic (daily hassles)
- Stress occurs when demand is perceived to exceed capacity to respond

Stress triggers HPA and SNS Response to improve behavioral response



McEwen and Gianaros, annu rev med, 2011

HPA axis response



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

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

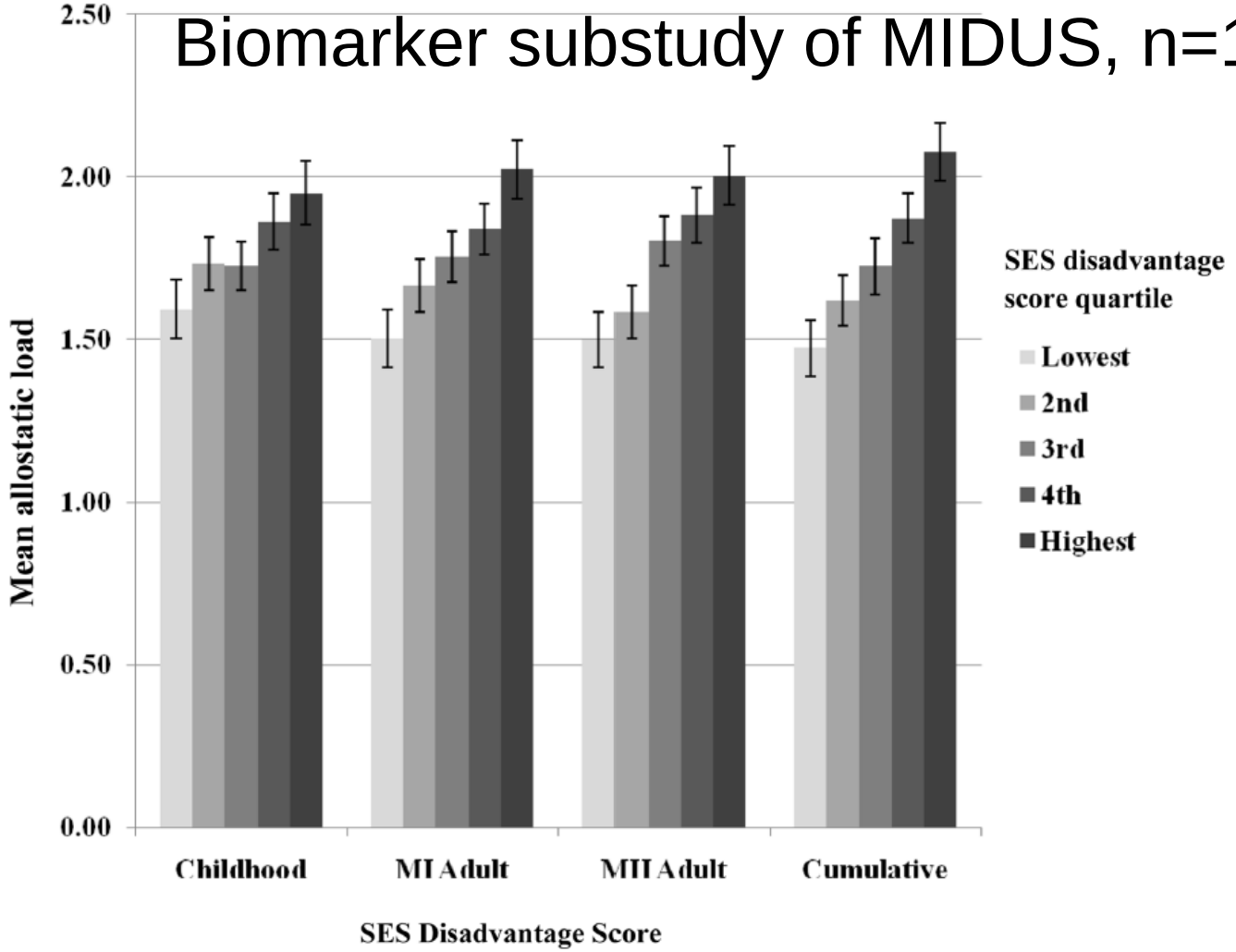
Glucocorticoids feed back and bind corticosteroid receptors to return to base state.

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 emphasize multi-system breakdown

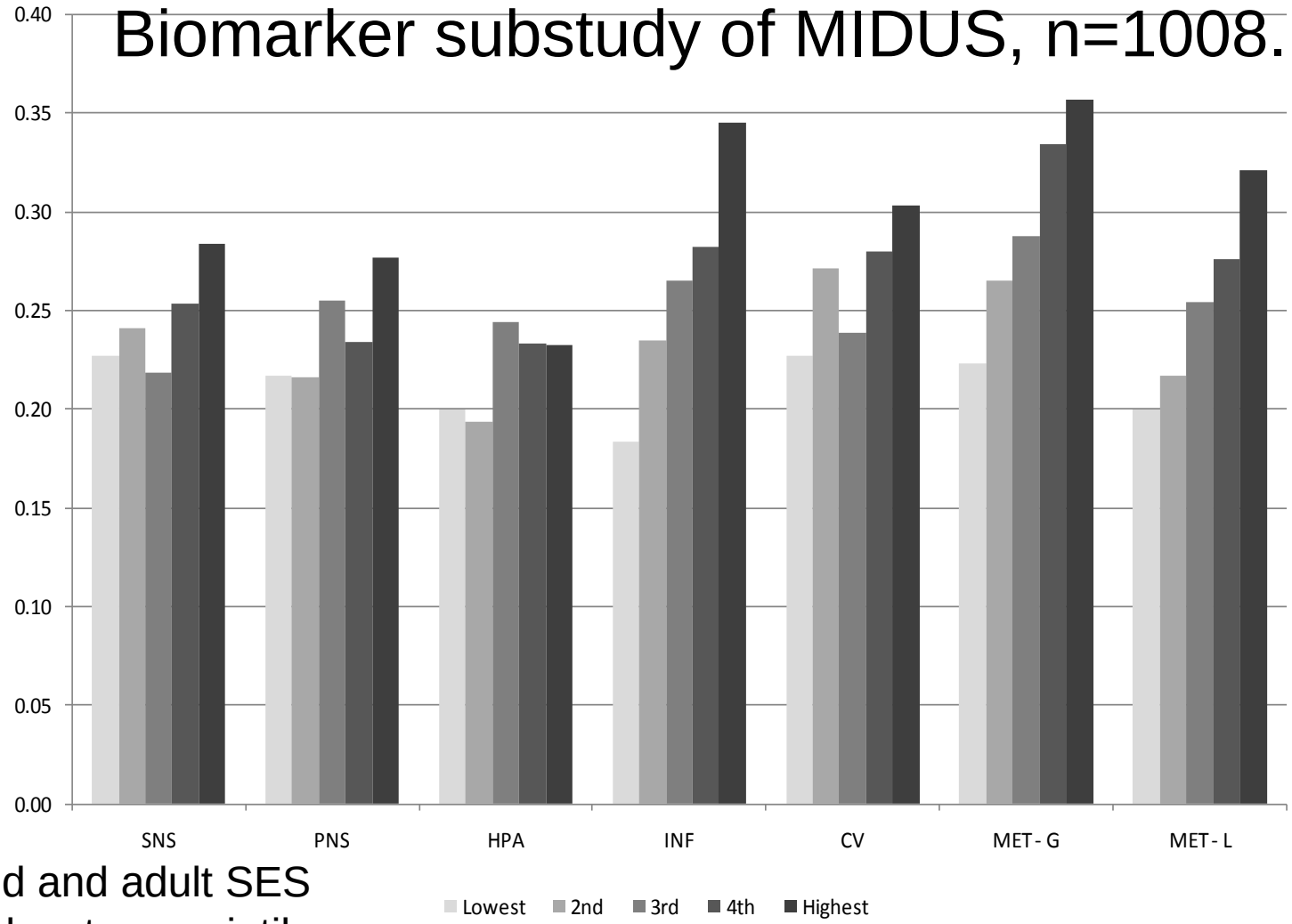
Allostatic Load: Multi-system dysregulation by cumulative lifetime SES

Biomarker substudy of MIDUS, n=1008.



Gruenewald, 2012 Soc Sci Med

Allostatic Load: Multi-system dysregulation by cumulative lifetime SES



Gruenewald, 2012 Soc Sci Med

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 proinflammatory profile of immune cells
- Telomere length and telomerase activity (chronic stress predicts shorter telomeres; racial patterns inconsistent)
- Metabolome: stress→ HPA → gut microbiota
- Other mechanisms to regulate gene expression, based on mRNA profiles: “conserved transcriptional response to adversity” → inflammation

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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

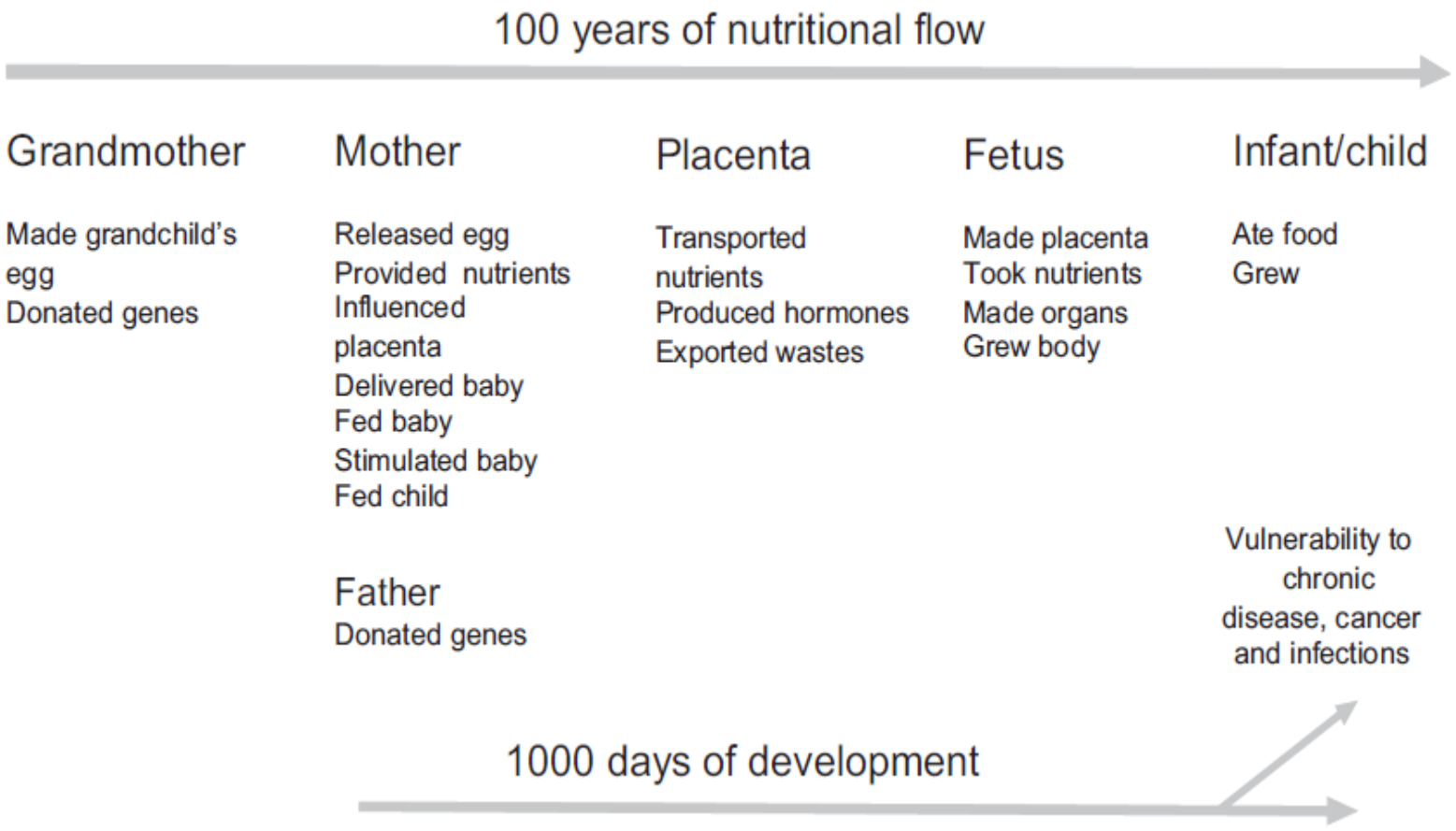
"Cortisol has received extensive attention as a potential mediator in the SES–health relationship. This review documented that more studies to date have found no association of cortisol with SES than have found the hypothesized association between lower SES and higher levels of cortisol, with several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



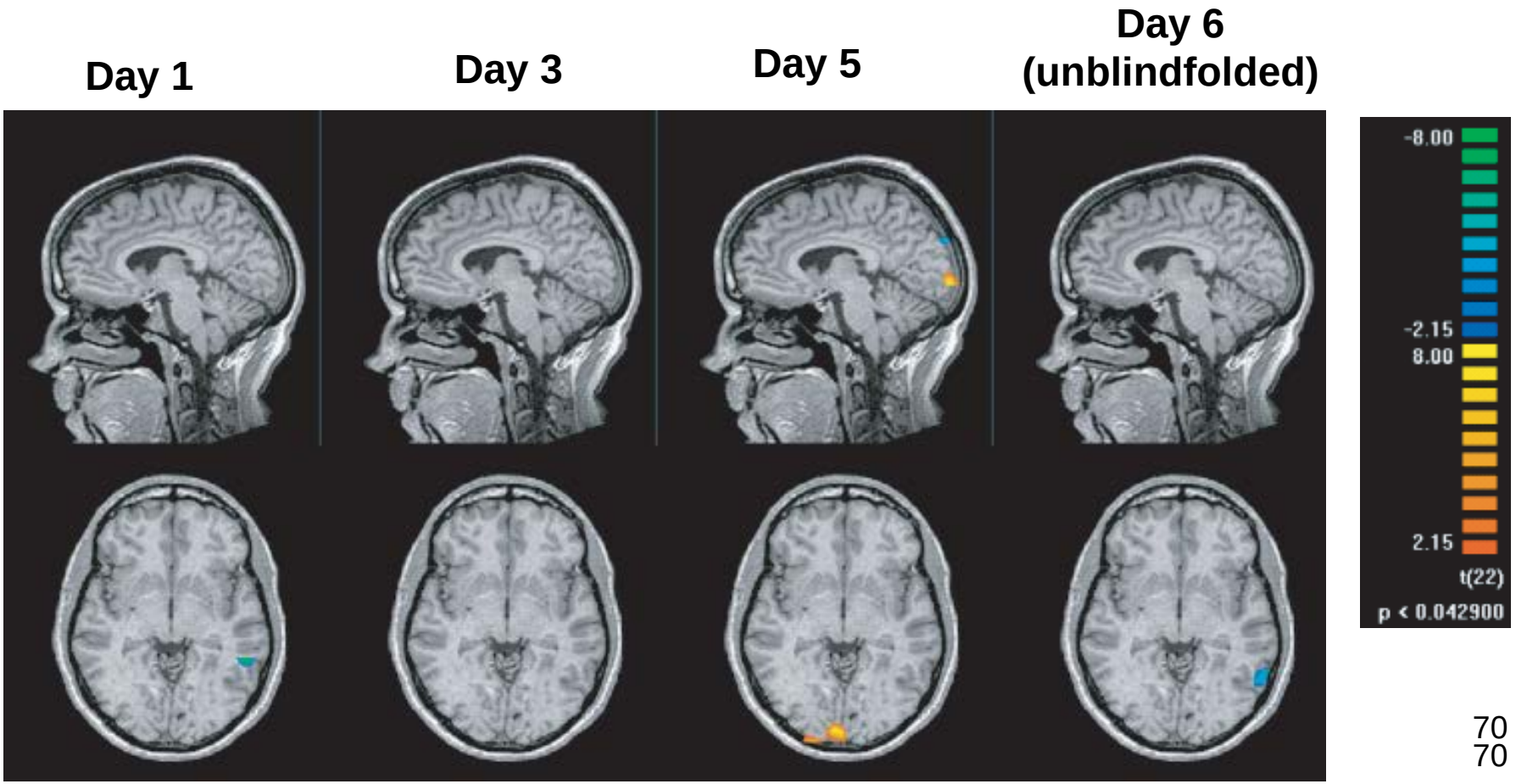
Barker, Public Health, 2012 Sir Richard Doll Lecture

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."

How much of *racial* disparities can be explained by genetic factors?

- So far, rarely major MAF differences that could account for disease differences: "Despite the rapid increase in the number of genomic studies over the past decade that covered many outcomes, the accumulated evidence for a genetic contribution to CVD disparities in blacks versus whites has been essentially nil." – Kaufman et al AJE 2015
- Genetic ancestry strongly tied to SES
  - highest to lowest quartile of African ancestry (among blacks)
  - OR for mother completed 8th grade=0.44
  - $12,000 less household wealth (Marden)
- Adjustment for measured social factors leaves much residual – interpret at "unobserved genetics" or "unobserved social"?
- Small samples of non-Europeans → more frequent fluke findings and non-significant results

In groups/ Homework

- Choose an aspect of environmental context that could have a profound effect on lifelong health
- Hypothesize a mediating pathway
- Outline studies you would like to conduct to test this pathway.
  - Outline one observational epi study and the major assumptions you would need to make to draw causal inferences about your exposure from that study
  - Outline how a lab or animal study might help address those assumptions