What is the role of behavioral and social sciences in translating genetic research into population health benefits?

David B Abrams PhD.

Director

Office of Behavioral and Social Sciences Research (OBSSR)

National Institutes of Health

Office of the Director

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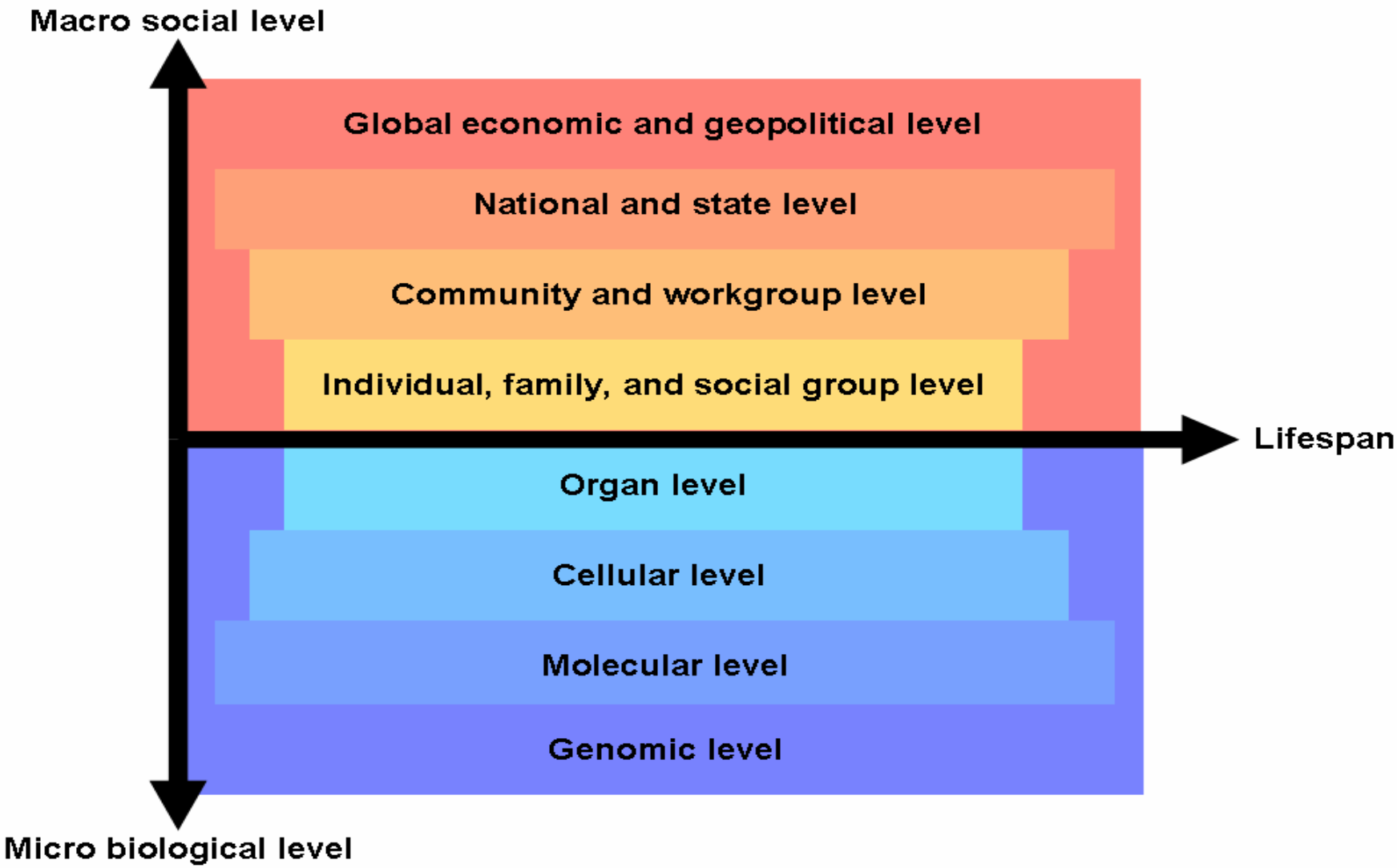
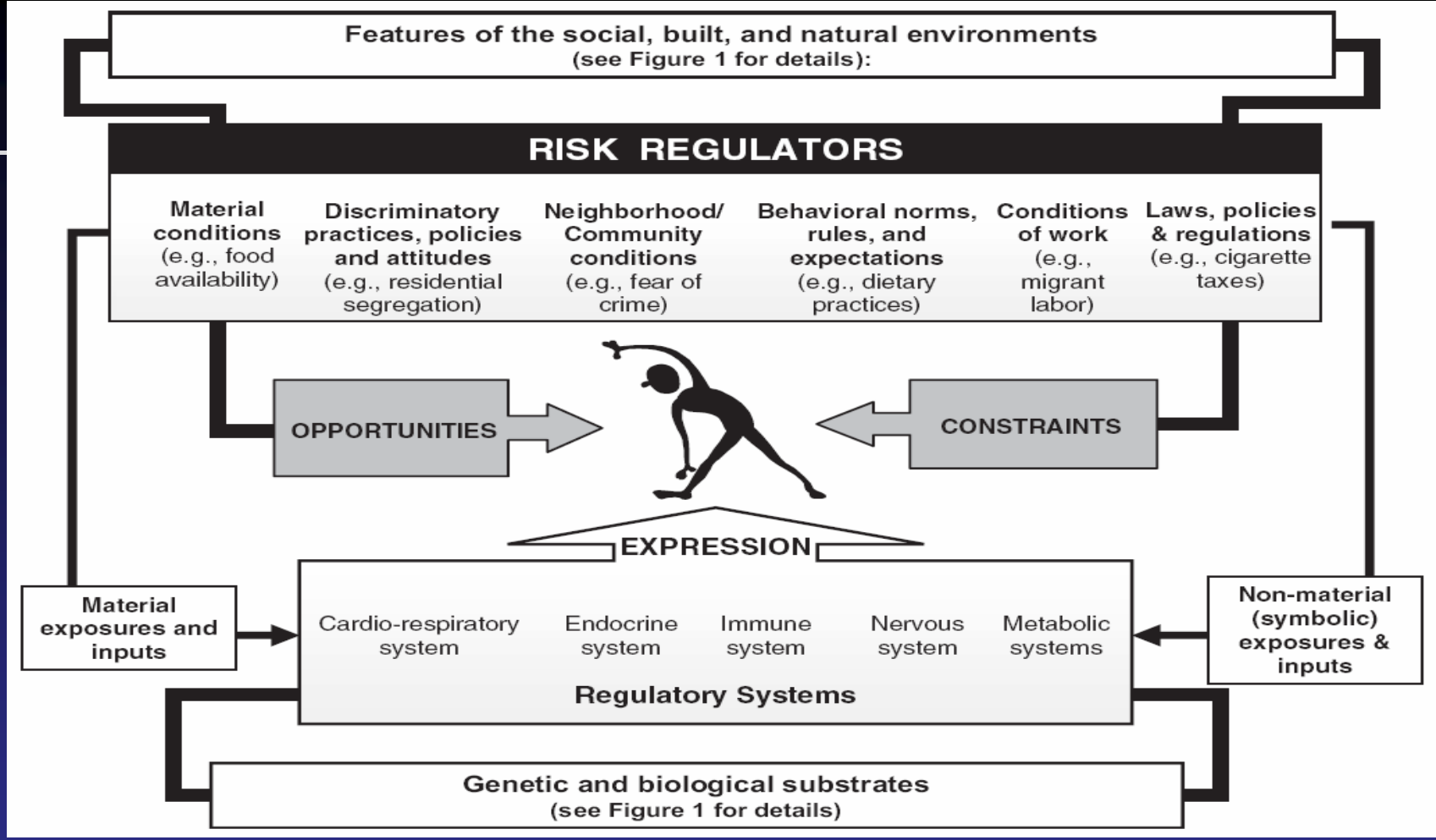
A very special thanks to Drs. Brad Wible, and Vivian Ota Wang for their invaluable assistance

12 March 2007

Health as a continuum between biological, behavioral and social factors across the lifespan with sensitive periods.



Adapted from Glass, McAtee (2006). *Soc. Sci. Medicine,* 62: 1650-1671



Risk regulators influence behavior

indirectly via structured contingencies (opportunities and constraints)

through effects on biological systems inside the body

material exposures, psychosocial experiences, and information to which regulatory systems must respond

Glass, McAtee (2006) *Soc Sci Medicine*, 62: 1650-1671

Experience and Brain Development

- Stimuli in early life switch on genetic pathways that differentiate neuron function
  – critical and sensitive periods.

- Stimuli affect the formation of the connections (synapses) among the billions of neurons (sensitive periods).

- The brain pathways that affect literacy, behavior, and health form early.

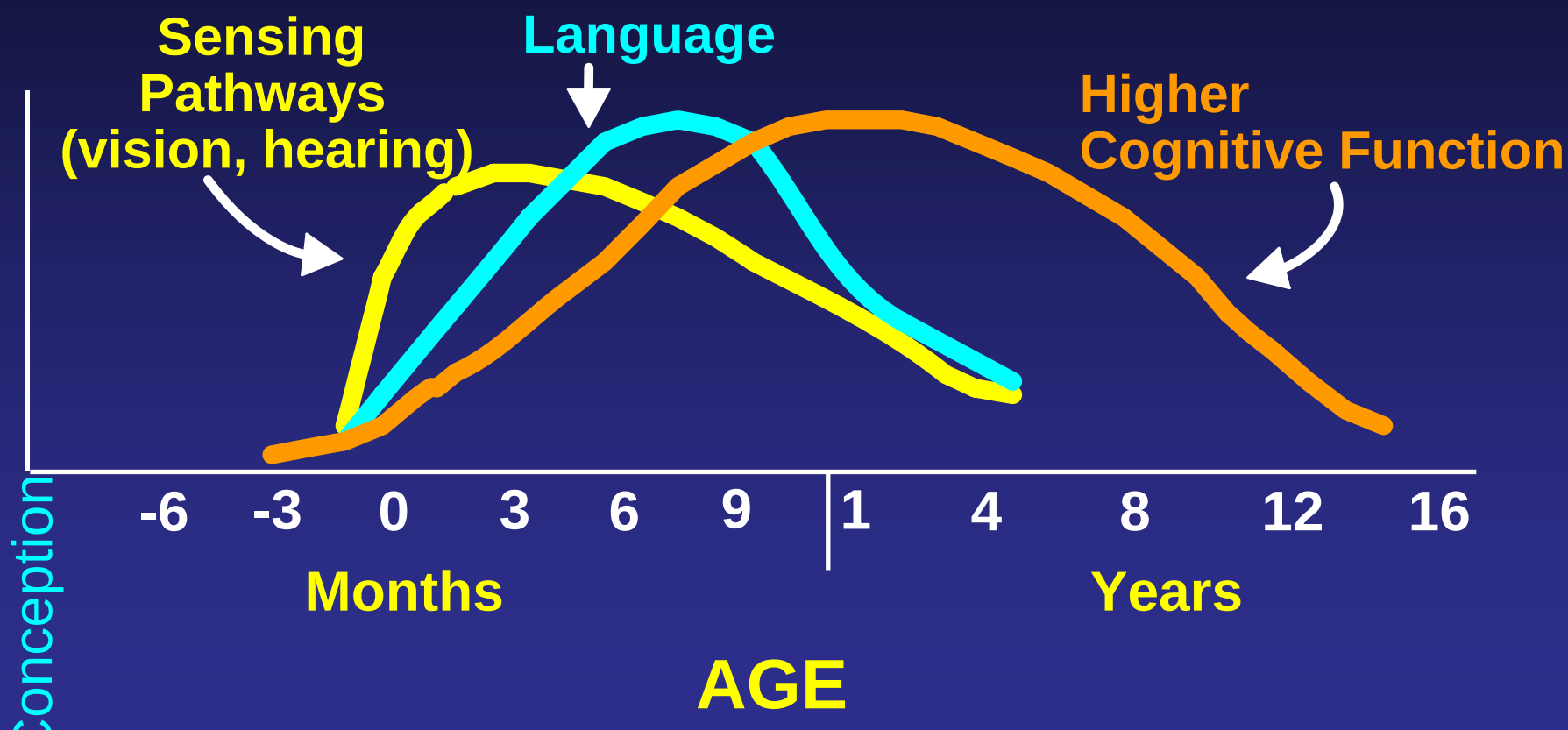
From studies in humans, monkeys and rats

Vision and Hearing Critical Period

Eye cataracts at birth prevent development of vision neurons in the occipital cortex (Hubel and Wiesel)

Cochlear defects at birth impair hearing development (Rauschecker and O'Donoghue)

Human Brain Development –Synapse Formation



C. Nelson, in From Neurons to Neighborhoods, 2000.

Protective and Damaging Effects of Stress Mediators

McEwen (1998) *NEJM*, 338: 171-179

Stress-activated physiology can protect and restore but also damage the body

- What links these roles?
- How does stress influence pathogenesis of disease?
- What accounts for the variation in vulnerability to stress-related diseases among people with similar life experiences?

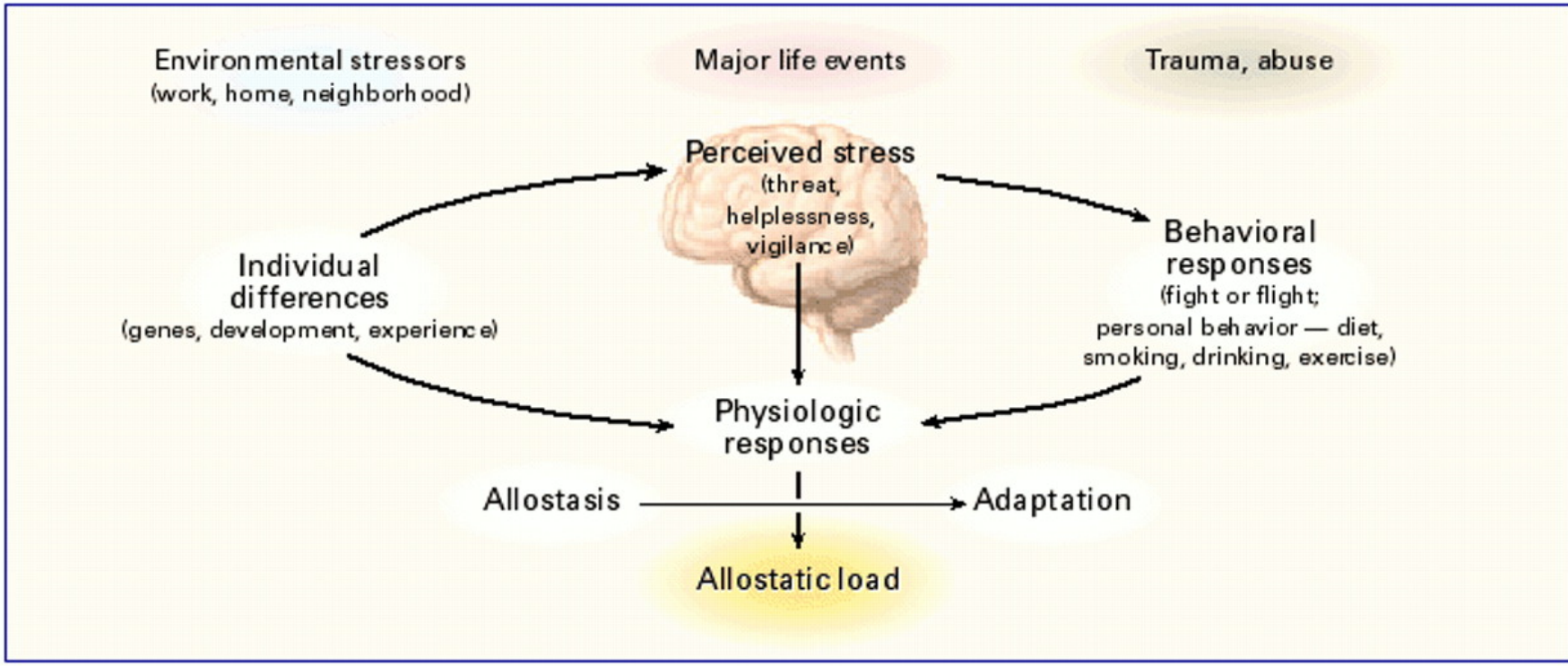
Allostasis - ability to achieve stability through change

- Autonomic nervous system, hypothalamic–pituitary–adrenal (HPA) axis, and cardiovascular, metabolic, and immune systems respond to internal and external stress

Allostatic Load - the price of this accommodation to stress

- Wear and tear from from chronic over- or under-activity of allostatic systems

The Stress Response and Development of Allostatic Load



Perceived stress

- influenced by experiences, genetics, and behavior
- initiates physiologic and behavioral responses leading to allostasis and adaptation

Allostatic load can accumulate over time

- overexposure to mediators of neural, endocrine, and immune stress can have adverse effects

McEwen (1998) *NEJM,* 338: 171-179

Types of Allostatic Load

Normal:

response initiated by stressor, sustained for appropriate interval, then turned off.

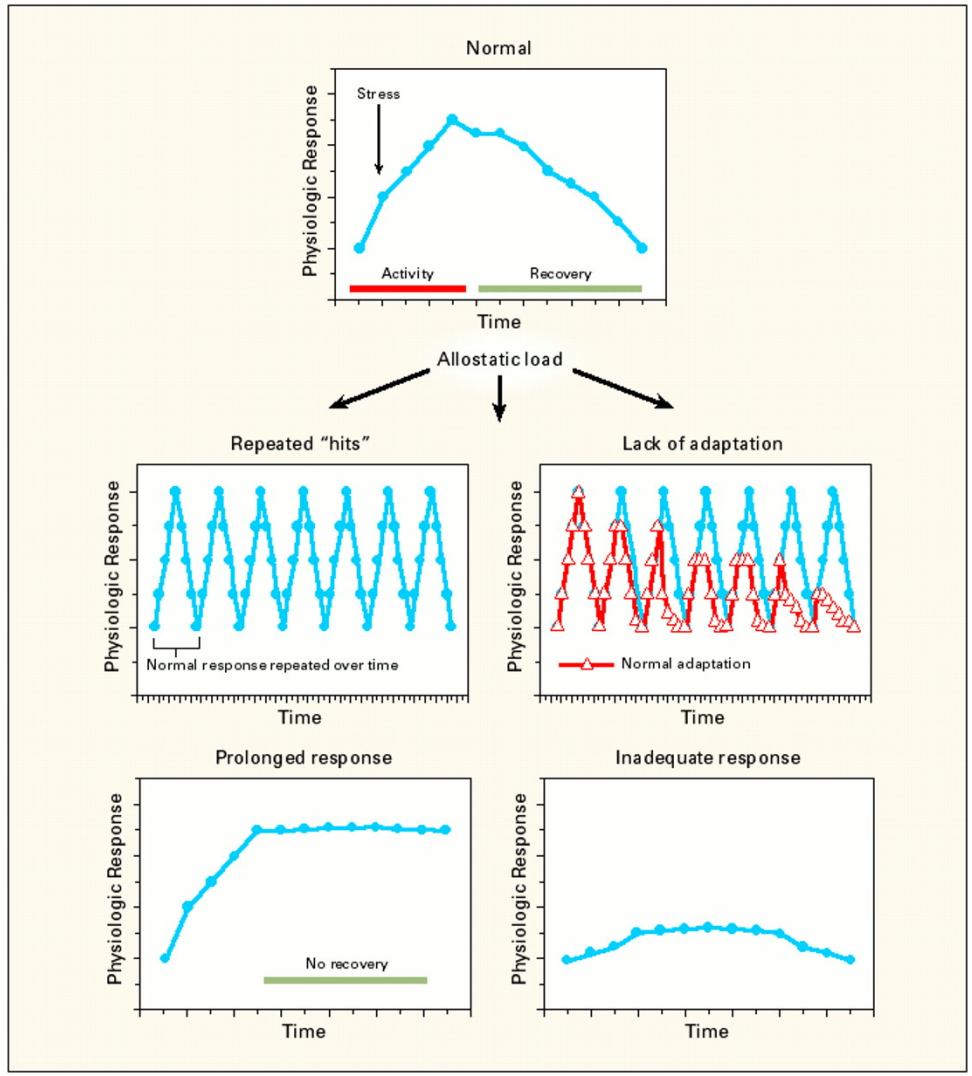
Abnormal:

repeated "hits" from multiple stressors

lack of adaptation

prolonged response due to delayed shutdown

inadequate response, which leads to compensatory hyperactivity of other mediators (e.g., inadequate secretion of glucocorticoids, resulting in increased concentrations of cytokines that are normally counterregulated by glucocorticoids).



McEwen (1998) *NEJM*, 338: 171-179

Limbic HPA Pathway - Stress

Cortisol – Over Production

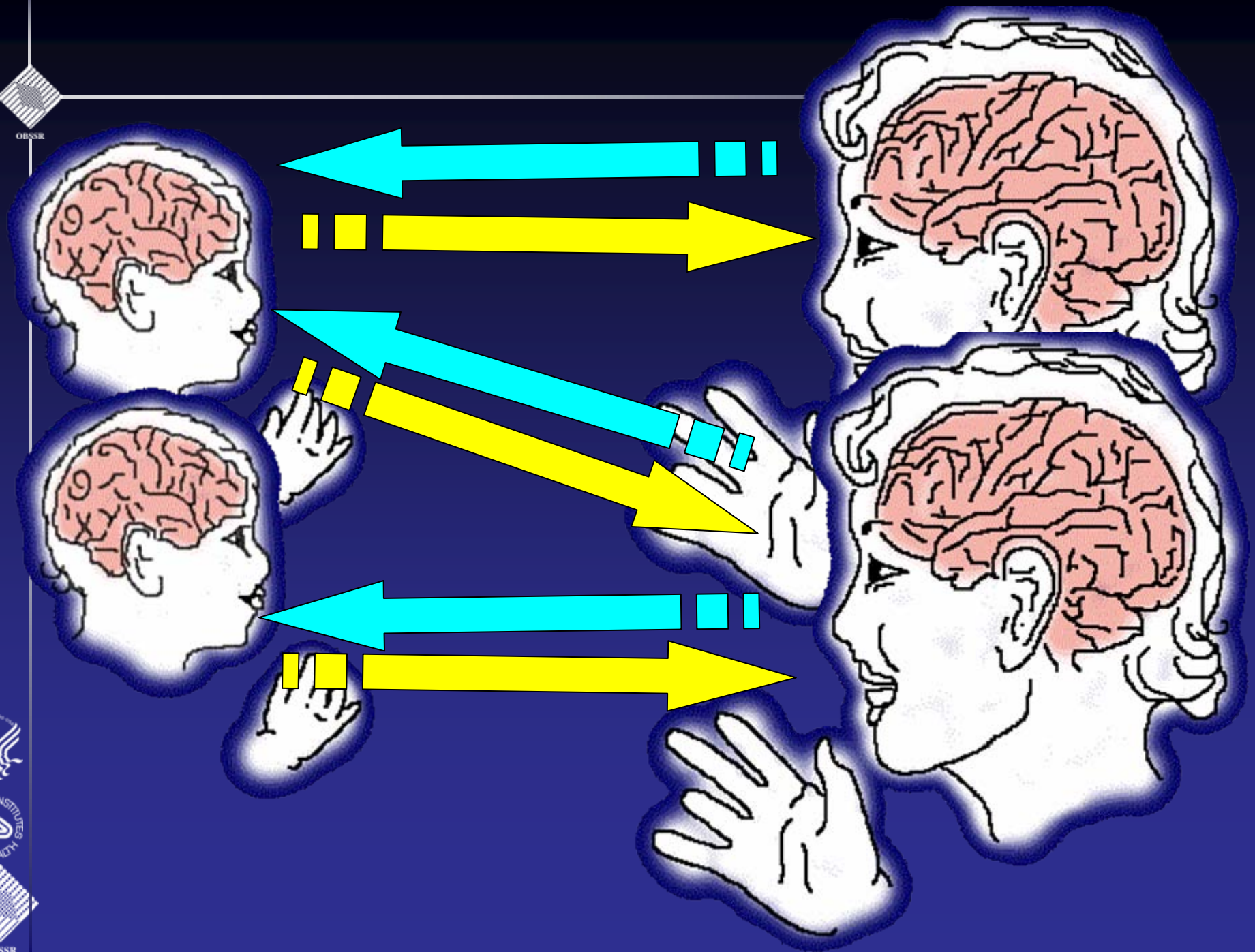
Behavior, depression, diabetes, malnutrition, cardiovascular disease, memory, immune system, drug and alcohol addiction

Cortisol – Under Production

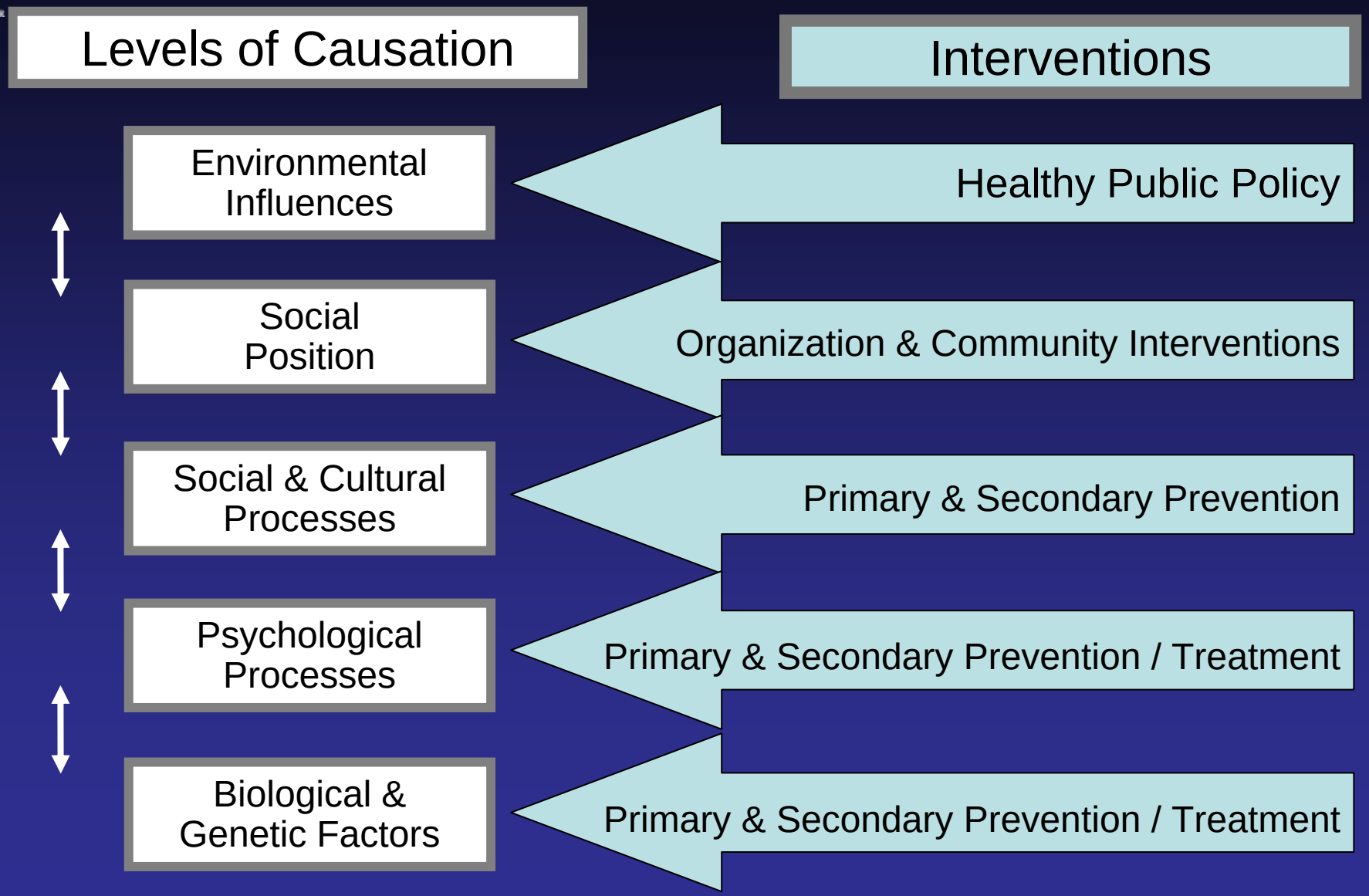
Chronic fatigue syndrome, fibromyalgia, immune system (autoimmune disorders) rheumatoid arthritis, allergies, asthma

But Is Stress Always Bad?

- During sympathetic arousal, you increase oxygen and glucose to your brain
- Acute stress can lead to heightened arousal and better task performance
- Mild elevation in glucocorticoid levels enhance memory by directly affecting the hippocampus

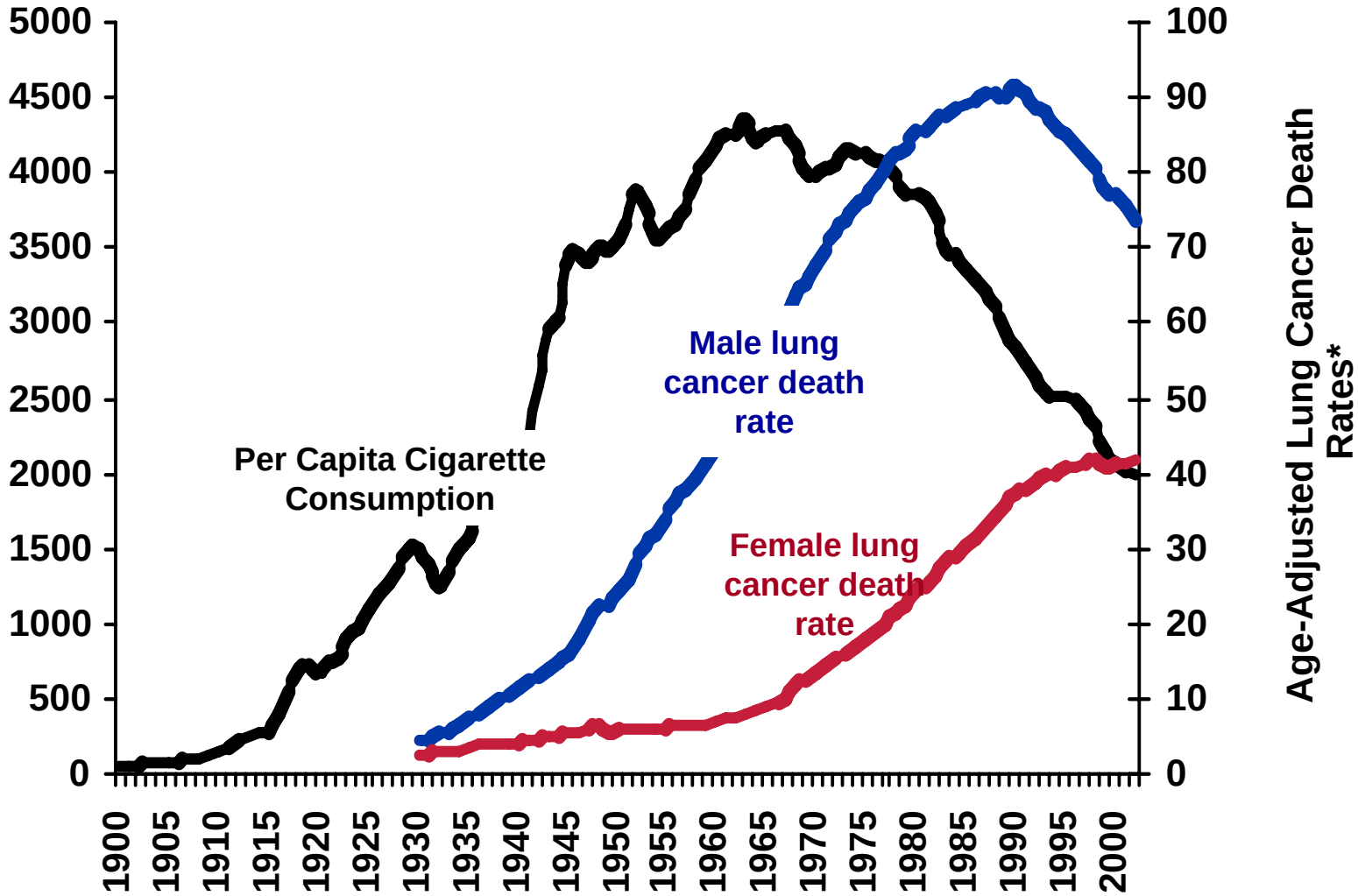


Levels of Causation for Health



from McKinlay & Marceau (2000). Public health matters. *Am J Pub Hlth, 90*, 25-33, p. 29.

Tobacco Use & Lung Cancer. USA



*Age-adjusted to 2000 US standard population. Source: Death rates: US Mortality Public Use Tapes, 1960-2002, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2005. Cigarette consumption: US Department of Agriculture, 1900-2002.

"My question is: Are we making an impact?"

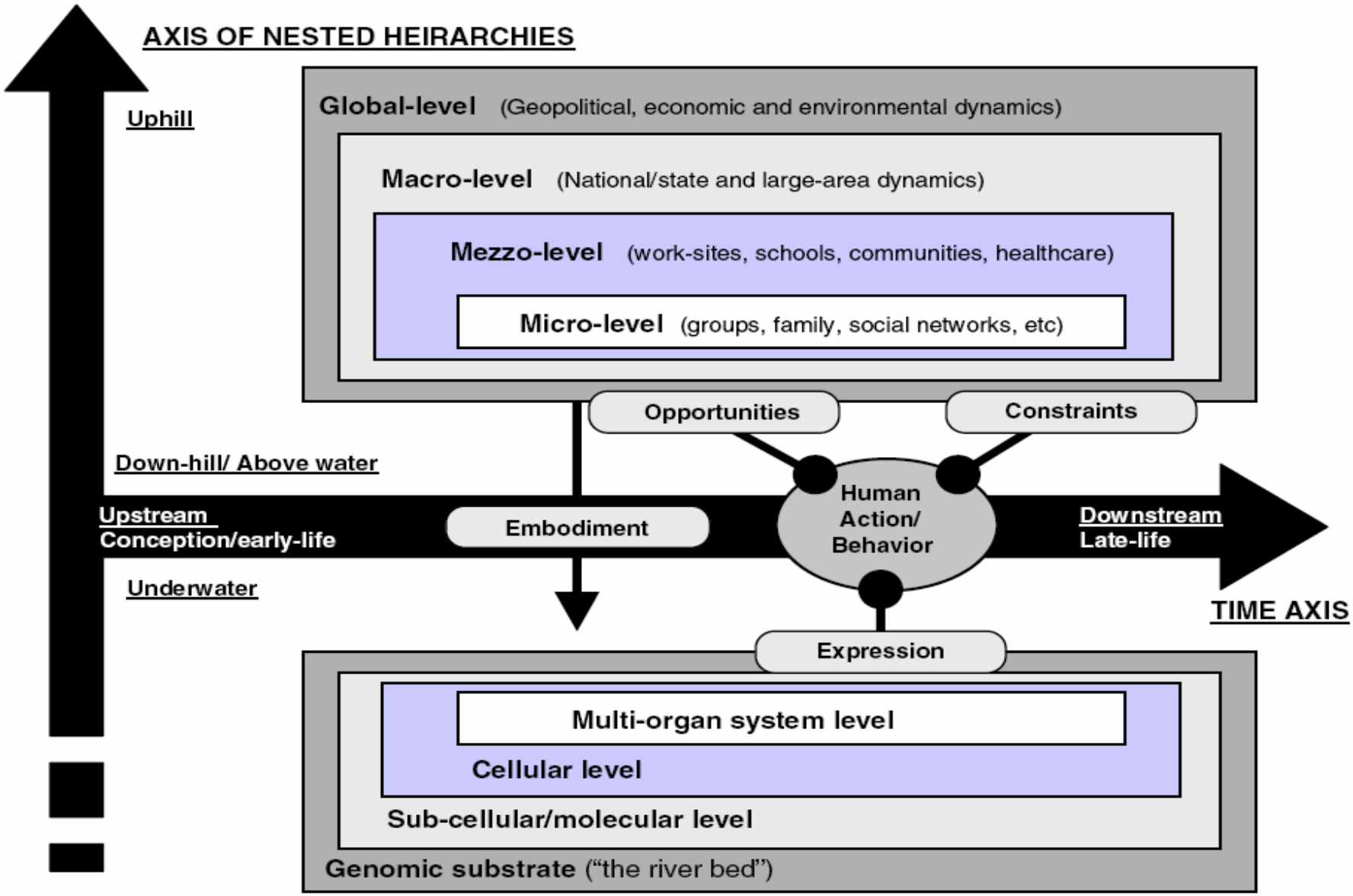


Fig. 1. The society-behavior-biology nexus as depicted in multidimensional space. The large arrows represent the axes of time and nested hierarchical structures. The sphere of health-related behavior and action moves through time from infancy to old age. Behavior is influenced by structured contingencies within the social and physical environment and by biological phenomena. Structural contingencies (opportunities and constraints) are shown by paths ending with nodes, while biological phenomena (embodiment and expression) are shown by paths ending with arrows or nodes.

A New Integrative Causal Model

The Biomedical Model:

Causes of disease lie in genes, molecules, proteins

The Ecological Model:

Causes of disease are behavioral and social factors

INTEGRATION OF BIOMEDICAL **CAUSES** & SOCIO-ECOLOGICAL **"CAUSES OF CAUSES"**

Measured Gene-Environment Interactions in Psychopathology

Concepts, Research Strategies, and Implications for Research, Intervention, and Public Understanding of Genetics

Terrie E. Moffitt,[1,2] Avshalom Caspi,[1,2] and Michael Rutter[2]

[1]Department of Psychology, University of Wisconsin, Madison, and [2]Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, United Kingdom

ABSTRACT—*There is much curiosity about interactions between genes and environmental risk factors for psychopathology, but this interest is accompanied by uncertainty. This article aims to address this uncertainty. First, we explain what is and is not meant by gene-environment interaction. Second, we discuss reasons why such interactions were thought to be rare in psychopathology, and argue instead that they ought to be common. Third, we summarize emerging evidence about gene-environment interactions in mental disorders. Fourth, we argue that research on gene-environment interactions should be hypothesis driven, and we put forward strategies to guide future studies. Fifth, we describe potential benefits of studying measured gene-environment interactions for basic neuroscience, gene hunting, intervention, and public understanding of genetics. We suggest that information about nurture might be harnessed to make new discoveries about the nature of psychopathology.*

A gene-environment interaction occurs when the effect of exposure to an environmental factor on health and behavior is conditional upon a person's genotype (or conversely, when the genotype's effect is moderated by the environment). In defining what gene-environment interaction is, it is useful to contrast gene-environment interaction against what it is not.

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GENE-ENVIRONMENT INTERPLAY VERSUS BIOLOGICAL INTERACTION

Increasingly, psychologists have come to appreciate that co-action between genetic risk and environmental risk influences behavior in many ways. Frequently, this co-action, or interplay, is referred to imprecisely as gene-environment interaction. However, interplay and interaction are not synonyms. In reality, gene-environment interplay comprises several different concepts and bodies of research findings, only one of which is the topic of this article: measured gene-environment interaction, which we refer to here as G × E. This section briefly defines four different forms of gene-environment interplay, to delimit what is particular about G × E. (We discuss the other three forms of interplay in greater depth in Rutter, Moffitt, & Caspi, in press.)

One type of gene-environment interplay, demonstrated in studies of twins, comprises quantitative models of *heritability-environment interaction*, in which the balance of heritable versus environmental influence on a phenotype's variation is shown to differ across subsegments of the population (Rowe, Jacobson, & van den Oord, 1999; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003). Findings from these twin models constitute a very important reminder that heritability estimates are population-specific. The models do involve statistical interaction. However, they do not address biological G × E because they focus on latent omnibus genetic effects in population variation, not on effects of a specific identified genotype in individuals. Moreover, these models do not indicate that sensitivity to the environment is moderated by variation in the DNA sequence. Heritability-environment interaction is clearly interesting, but it is not addressed in this article.

A second type of gene-environment interplay is *epigenetic programming*, in which environmental effects on an outcome

Moffitt, Caspi, Rutter (2006) *Perspectives on Psychological Science*, 1(1): 5-27

FOUR MAIN VARIETIES OF GENE-ENVIRONMENT INTERPLAY

1. Epigenetic effects of environments on gene expression
2. Variations in heritability according to environmental circumstances
3. Gene-environment correlation
4. Gene-environment interaction

Different types of gene-environment interplay

1. Epigenetic Effects

Environmental effects are mediated through altered gene expression (Levenson & Sweatt, 2005; Pray, 2004; Waterland & Jirtle, 2003)

Or through altered chromosomal structure (Epel et al., 2004; Sapolsky, 2004).

Early-life rearing can alter gene expression, and later behavior (Francis, Szegda, Campbell, Martin, & Insel, 2003; Meaney, 2001).

Effects are a biological process, and it involves specific measured genes, as well as specific environments.

RAT STUDIES OF MEANEY, SZYF, WEAVER, et. al.

1. Observation that lactating mother rats differed markedly in licking/grooming archback nursing of neonatal rat pups

2. These maternal differences associated with offspring differences in behavior, neuroendocrine response to stress, and neurotransmitters

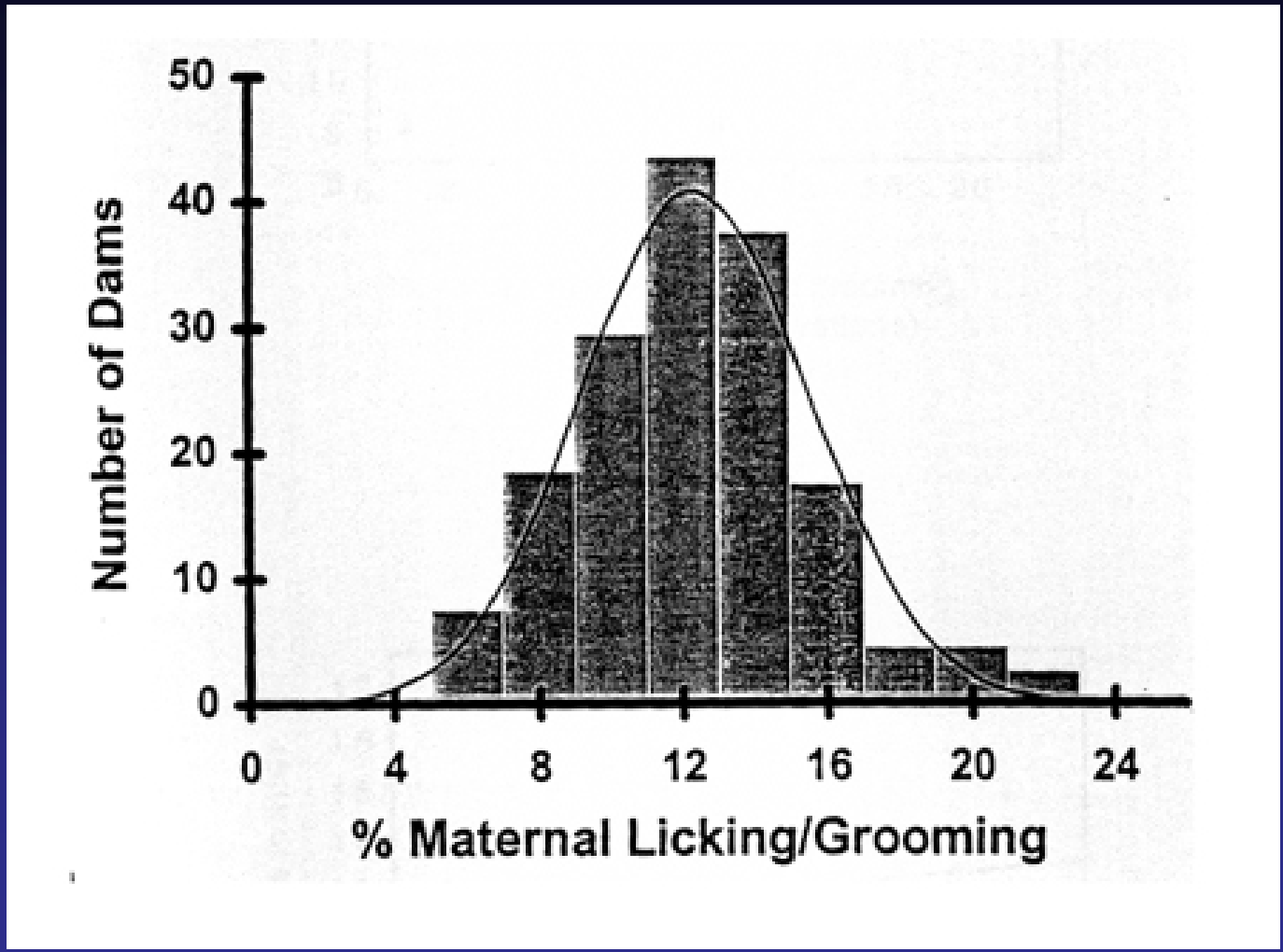
3. Cross-fostering design to determine if offspring differences are a function of nature or nurture

4. Determination of whether nursing differences effects associated with specific DNA methylation effects

5. Test of whether the rearing-mediated epigenetic marking could be chemically reversed

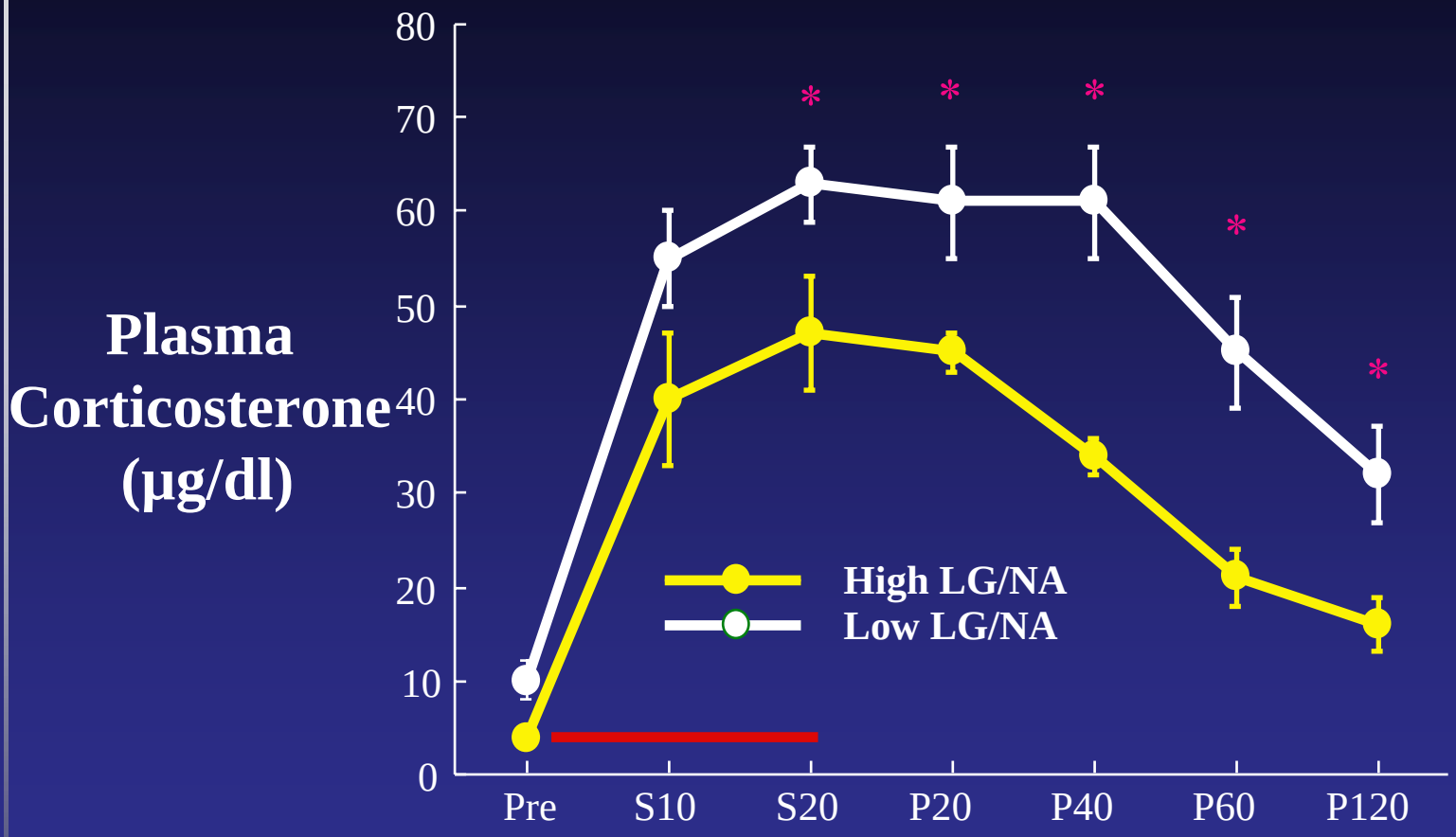
Maternal Behavior: Where Nurture Meets Nature

Individual Variation in Maternal Licking and Grooming



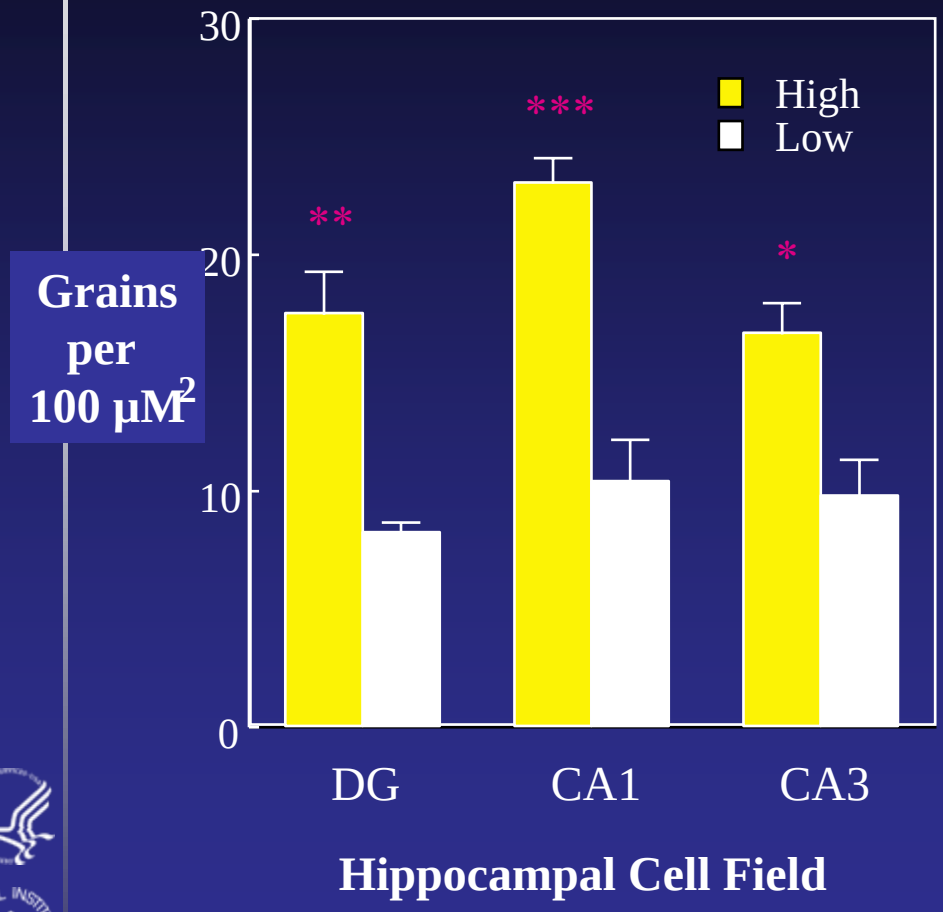
Meaney, Ann Rev. Neurosci. 2001

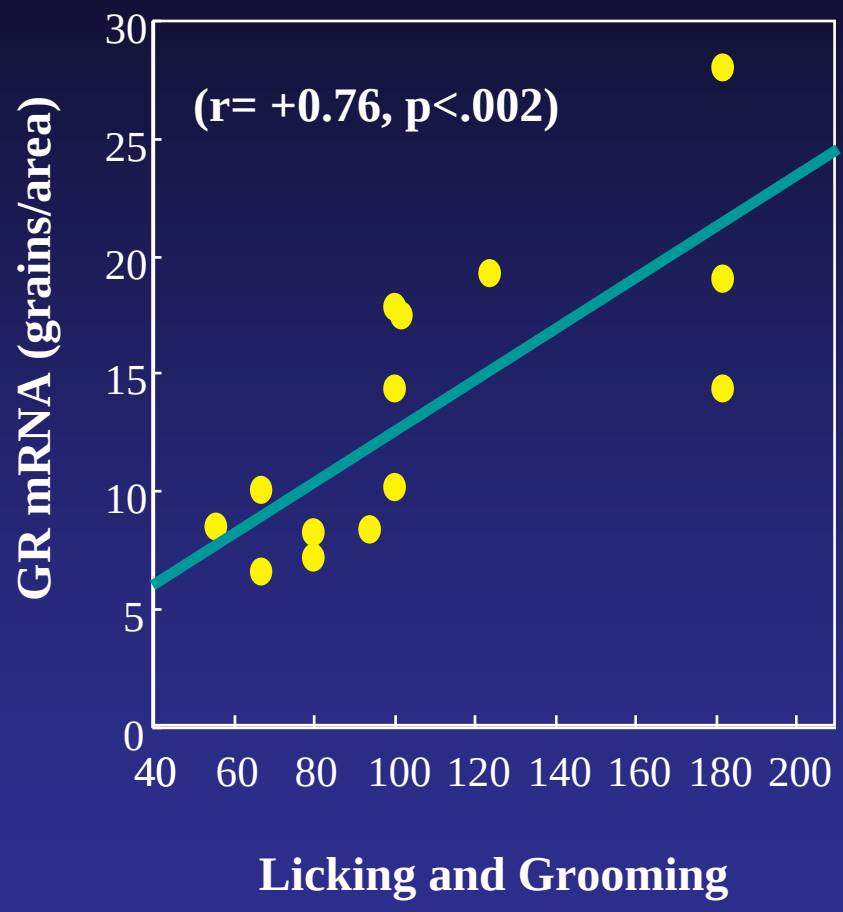
Offspring of high licking-grooming mothers - response to stress is reduced



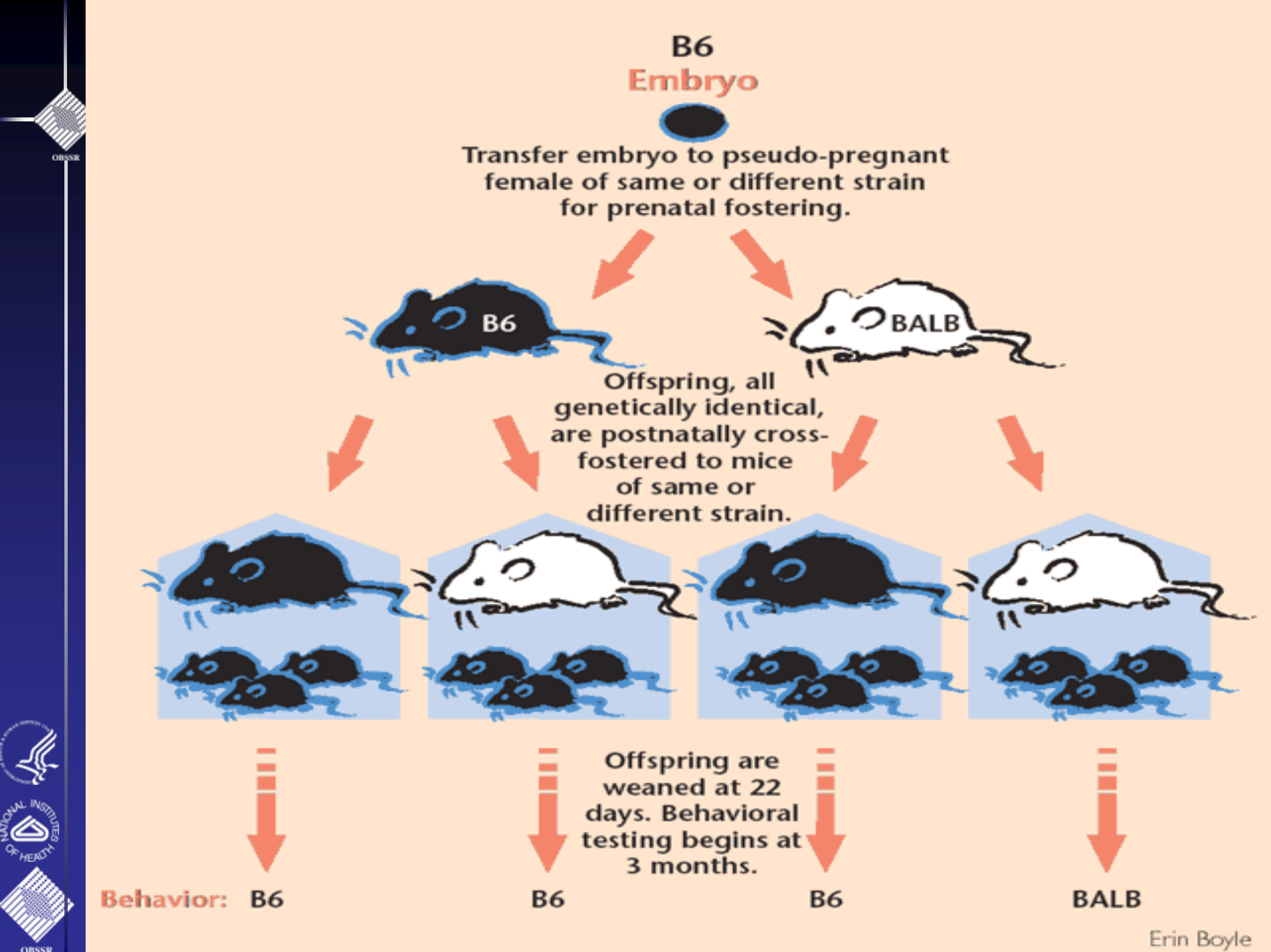
Meaney, Ann Rev. Neurosci. 2001

Offspring of high licking-grooming mothers - increased glucocorticoid receptors in the hippocampus





Meaney, Ann Rev Neurosci. 2001

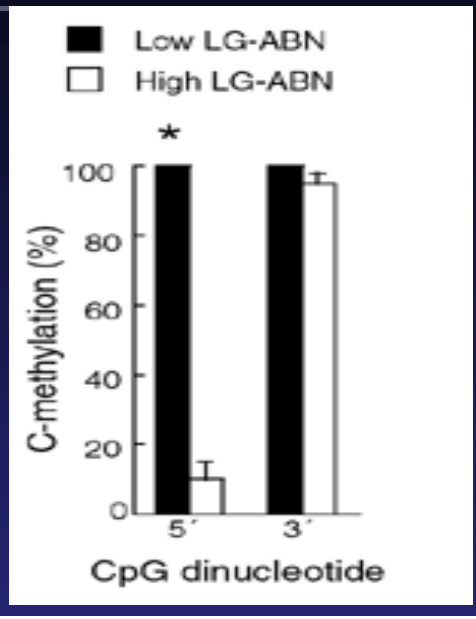

B6
Embryo
Transfer embryo to pseudo-pregnant female of same or different strain for prenatal fostering.
B6
BALB
Offspring, all genetically identical, are postnatally cross-fostered to mice of same or different strain.
Offspring are weaned at 22 days. Behavioral testing begins at 3 months.
Behavior: B6
B6
B6
BALB
Erin Boyle

Different types of gene-environment interplay

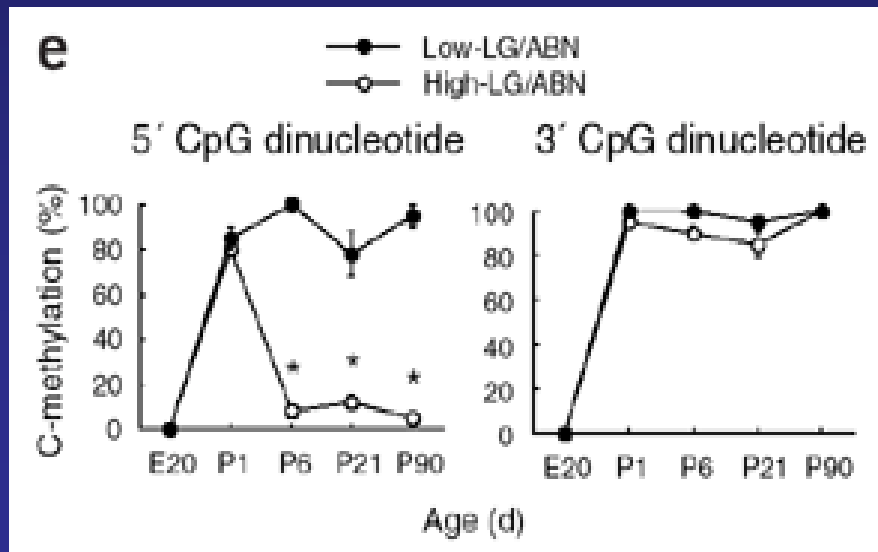
Epigenetic programming

Epigenetic programming by maternal behavior

Maternal licking and grooming (LG) and arched-back nursing (ABN) of rat pups altered offspring epigenome at a glucocorticoid receptor (GR) gene promoter in hippocampus.



Offspring of mothers that showed high levels of LG and ABN were found to have differences in DNA methylation, as compared to offspring of 'low-LG-ABN' mothers.



Differences were associated with altered histone acetylation and transcription factor (NGFI-A) binding to the GR promoter.

Weaver et al. (2004) *Nature Neuroscience*, 7(8): 847-854

Basic behavioral mechanisms underlying genetically-mediated alterations in the development of stress responsivity

Meaney, Szyf et al.

- Low maternal rat pup licking & arched back nursing during 1st wk
- Leads to permanently reduced glucocorticoid receptor gene expression in the hippocampus of pups.
- Increased & prolonged reactivity of the HPA axis.

- Mediated by ↑DNA methylation, preventing NGFI-A binding to the promoter for the glucocorticoid receptor gene – inhibiting transcription and ↓ Gc expression

Different types of gene-environment interplay

2. Quantitative models of heritability-environment interaction

Demonstrated in studies of twins

Balance of heritable versus environmental influence on phenotype's variation differs across subsegments of the population (Rowe, Jacobson, & van den Oord, 1999; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003)

Why not GxE?

Focus on latent omnibus genetic effects in population variation, not on effects of a specific identified genotype in individuals

Do not indicate that sensitivity to the environment is moderated by variation in the DNA sequence

Moffitt, Caspi, Rutter (2006) *Perspectives on Psychological Science,* 1(1): 5-27

Different types of gene-environment interplay

3. Gene-environment correlation

Person's genotype influences his or her probability of exposure to environmental risks (Plomin, DeFries, & Loehlin, 1977; Rutter & Silberg, 2002).

Gene-environment correlations are often discussed as if the genes have direct biological effects on an environmental risk factor (e.g., the tendency to experience stressful life events is partly heritable).

Why not GxE?

Inevitably the genetic effect is mediated through some behaviors (in the case of life events, personality traits) that in turn bring about the environmental risk.

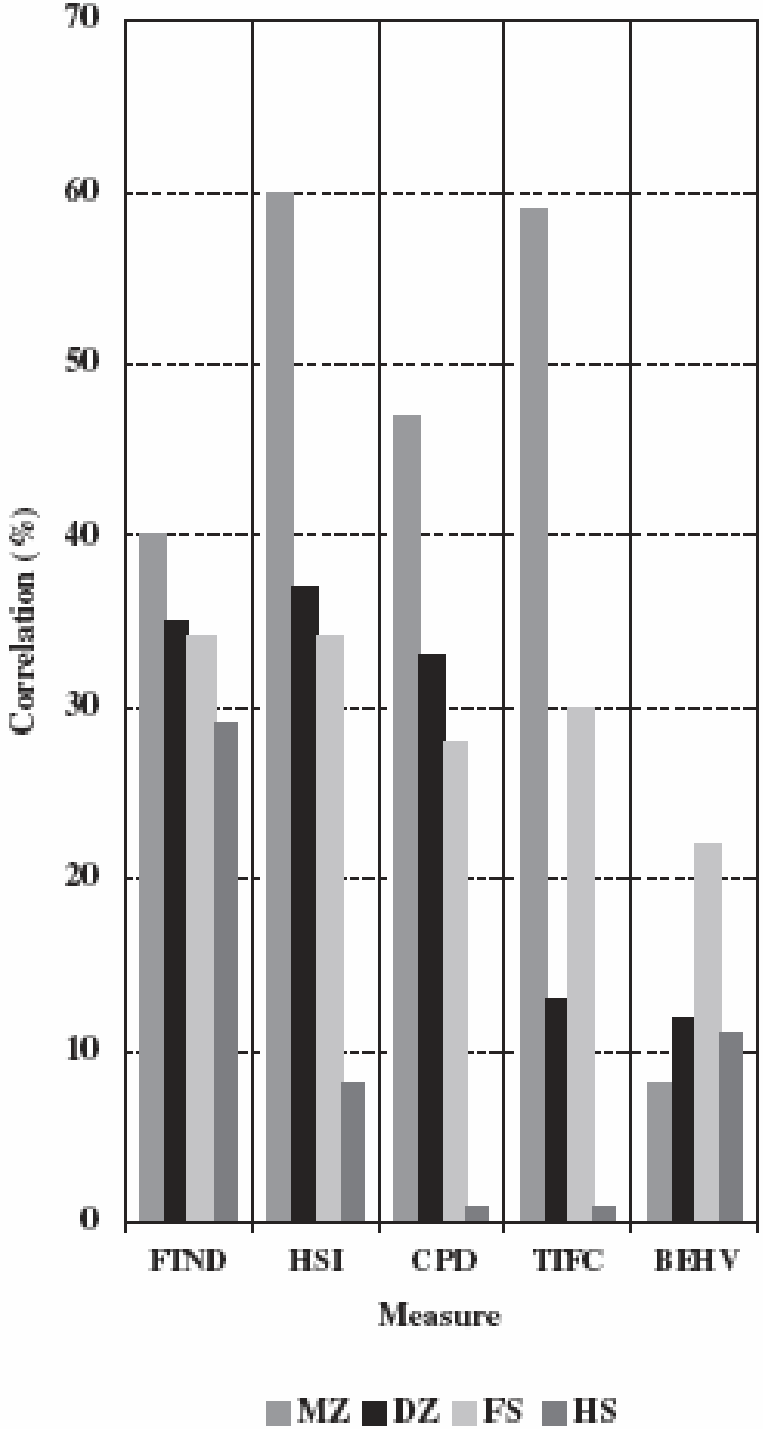
Moffitt, Caspi, Rutter (2006) *Perspectives on Psychological Science,* 1(1): 5-27

Genes, Individual Specific environment and Nicotine Dependence.

Ad Health longitudinal cohort study

Figure 1 Sibling correlations. MZ, monozygotic twins; DZ, dizygotic twins; FS, full-siblings; HS, half-siblings; FTND, Fagerström Test for Nicotine Dependence; HSI, Heaviness of Smoking Index; CPD, cigarettes per day; TTFC, time to first cigarette; BEHV, summary scale of the FTND behavioral items

Haberstick, et.al., 2007 Addiction.in press.



Genes, Individual Specific environment and Nicotine Dependence.

Haberstick, et.al., 2007. Addiction.

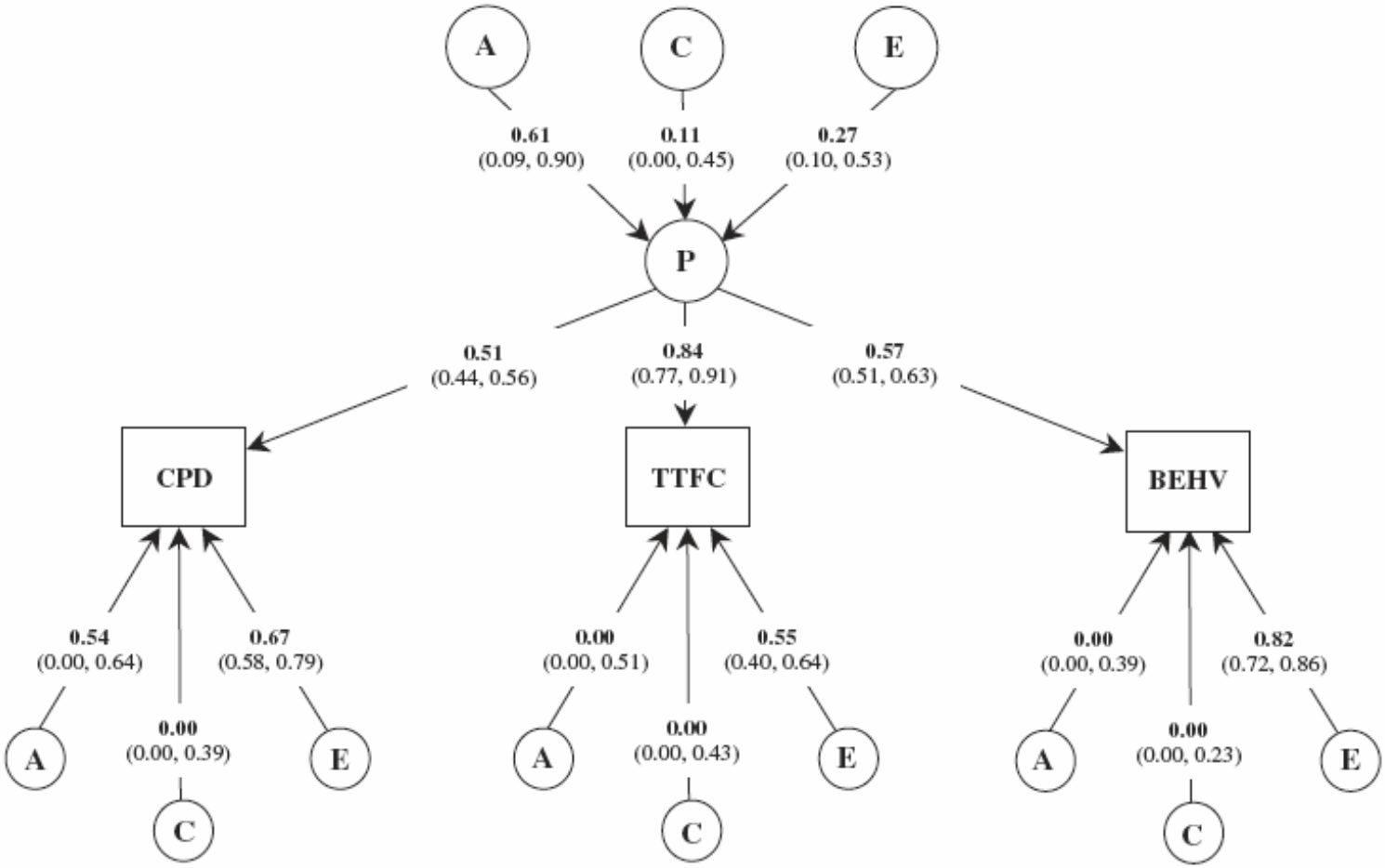


Figure 3 Common pathway model. Variance component estimates (95% confidence intervals) are shown for the latent common factor and standardized path coefficients for each observed variable. The χ^2 goodness-of-fit for the overall ACE model is: $\Delta\chi^2 = 83.82$, Δ df = 70, $P = 0.12$, AIC = −56.18. Latent variables are depicted in circles, observed variables in rectangles. Single headed arrows represent the partial regression of an observed variable on the latent factor. Variances for each observed variable was standardized to 1.0. A: additive genetic influences; C: shared environmental influences; E: non-additive genetic influences and includes measurement error; P: common underlying pathway or phentotype; CPD, cigarettes per day; TTFC, time to first cigarette; BEHV, behavioral FTND items

Different types of gene-environment interplay

4. Gene-environment interaction, G x E:

Behavioral effects due to interdependence between a specific identified variation in the DNA sequence and a specific measured environment.

G × E has a long scientific history (Haldane, 1946)

e.g., Agricultural research

animals' and crops' genotypes moderate resistance to pests and disease

e.g., Infectious-disease research

hosts' genotypes moderate susceptibility to diseases such as malaria and tuberculosis

e.g., Behavioral sciences

developmental psychology's resilience theories about children who have good mental health despite adversity, and in psychopathology's diathesis-stress theories of mental illness

Moffitt, Caspi, Rutter (2006) *Perspectives on Psychological Science,* 1(1): 5-27

Measured Gene-Environment Interactions in Psychopathology: Concepts, Research Strategies, and Implications for Research, Intervention, and Public Understanding of Genetics

Moffitt, Caspi, Rutter (2006) *Perspectives on Psychological Science,* 1(1): 5-27

A gene-environment interaction occurs

When the effect of exposure to an environmental factor on health and behavior is conditional upon a person's genotype

Or conversely, when the genotype's effect is moderated by the environment.

Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

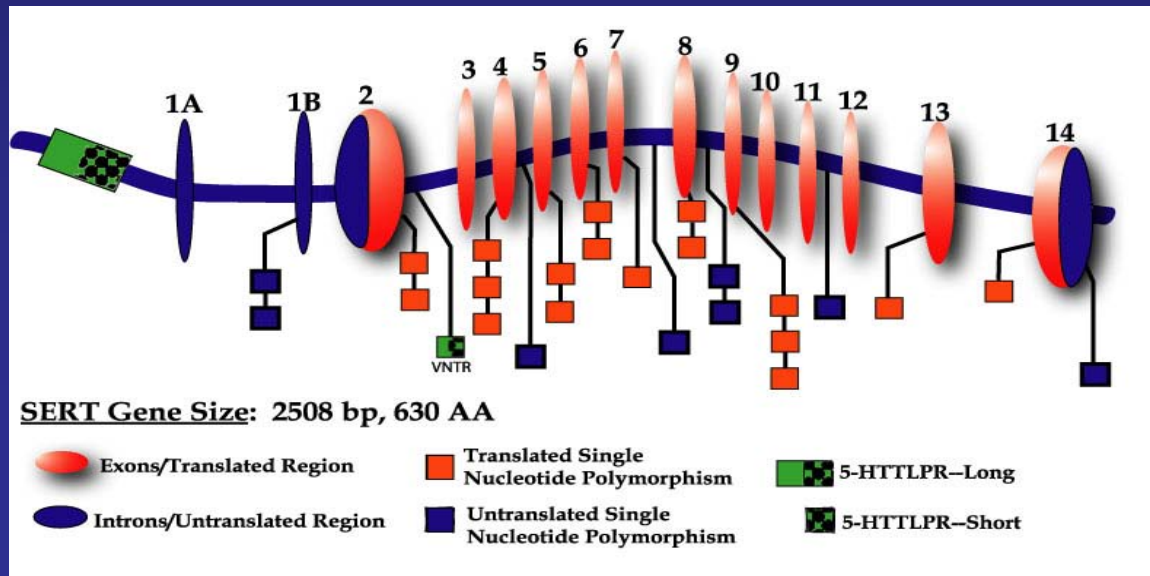
Avshalom Caspi,[1,2] Karen Sugden,[1] Terrie E. Moffitt,[1,2*]
Alan Taylor,[1] Ian W. Craig,[1] HonaLee Harrington,[2]
Joseph McClay,[1] Jonathan Mill,[1] Judy Martin,[3]
Antony Braithwaite,[4] Richie Poulton[3]

Science, 302: 386-388. 2003

1057 consecutive births in Dunedin, New Zealand followed for 26 years with evaluation every 2-3 years beginning in first year.

At age 26, 17% met criteria for major depressive disorder.

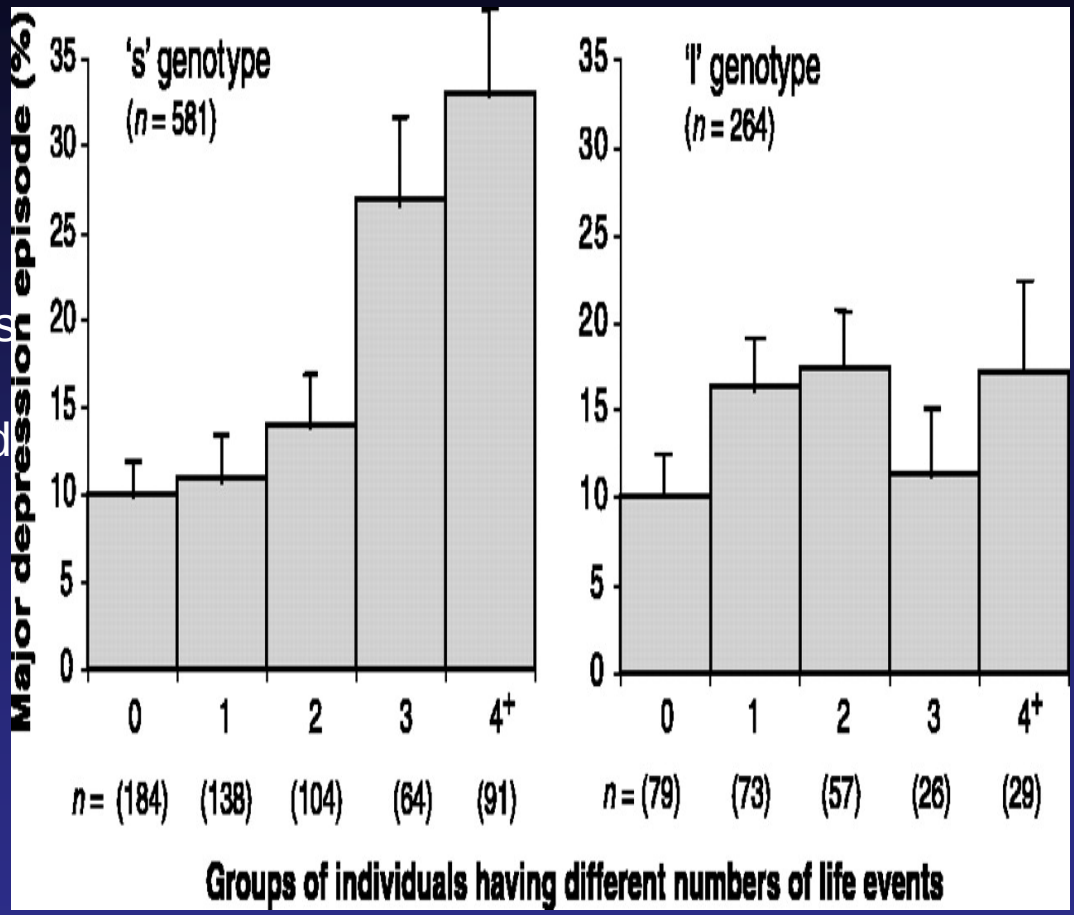
Neither life stress alone nor serotonin transporter genotype predicted depression.



Results of regression estimating the association between childhood maltreatment and adult depression, as a function of 5-HTT genotype.

Influence of Life Stress on Depression:

Individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele

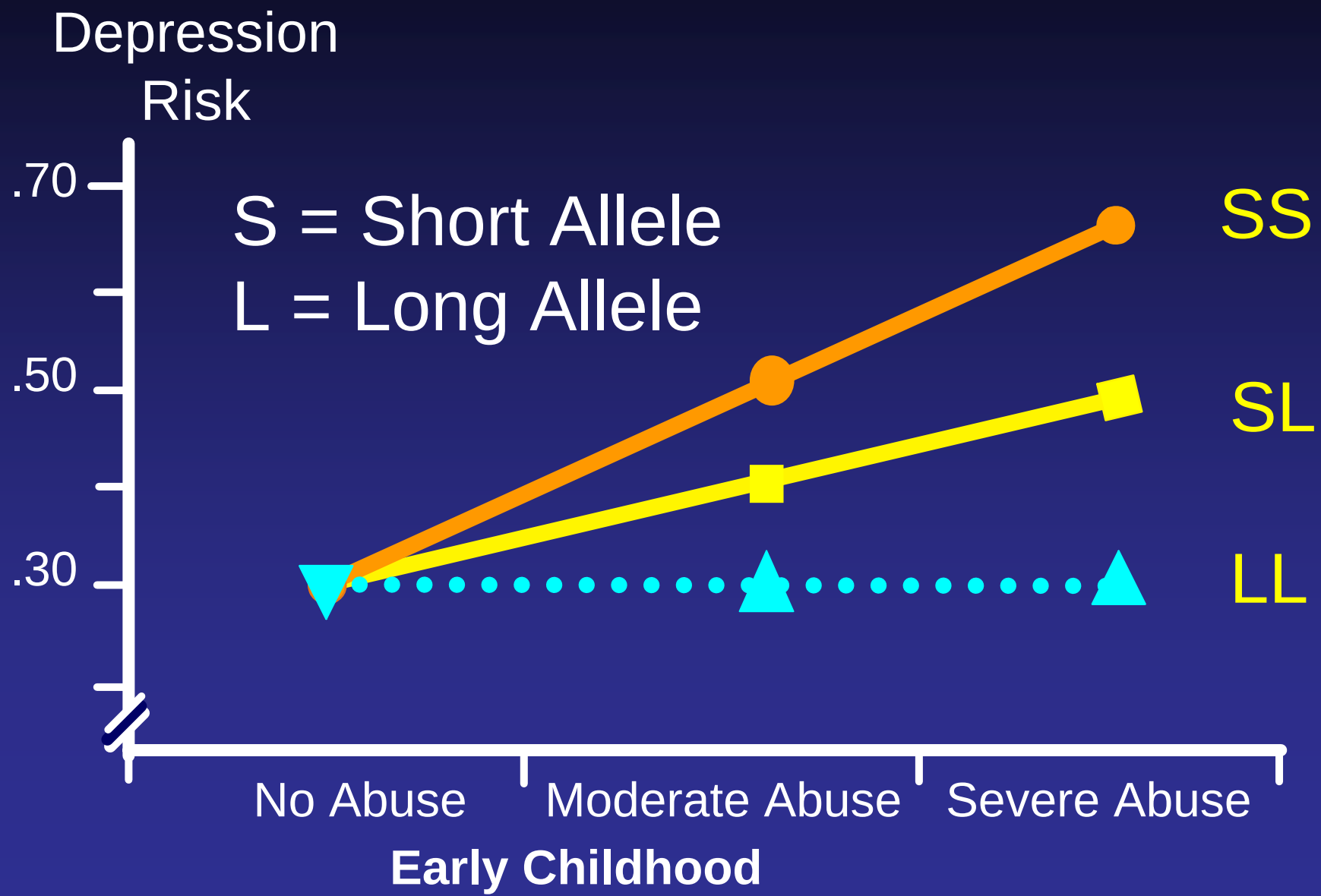


This epidemiological longitudinal cohort study thus provides evidence of a gene-by-environment interaction, in which an individual's response to environmental insults is moderated by his or her genetic makeup.

Caspi et al. (2003) *Science*, 301: 386-389

Serotonin Gene, Experience, & Depression Age 26

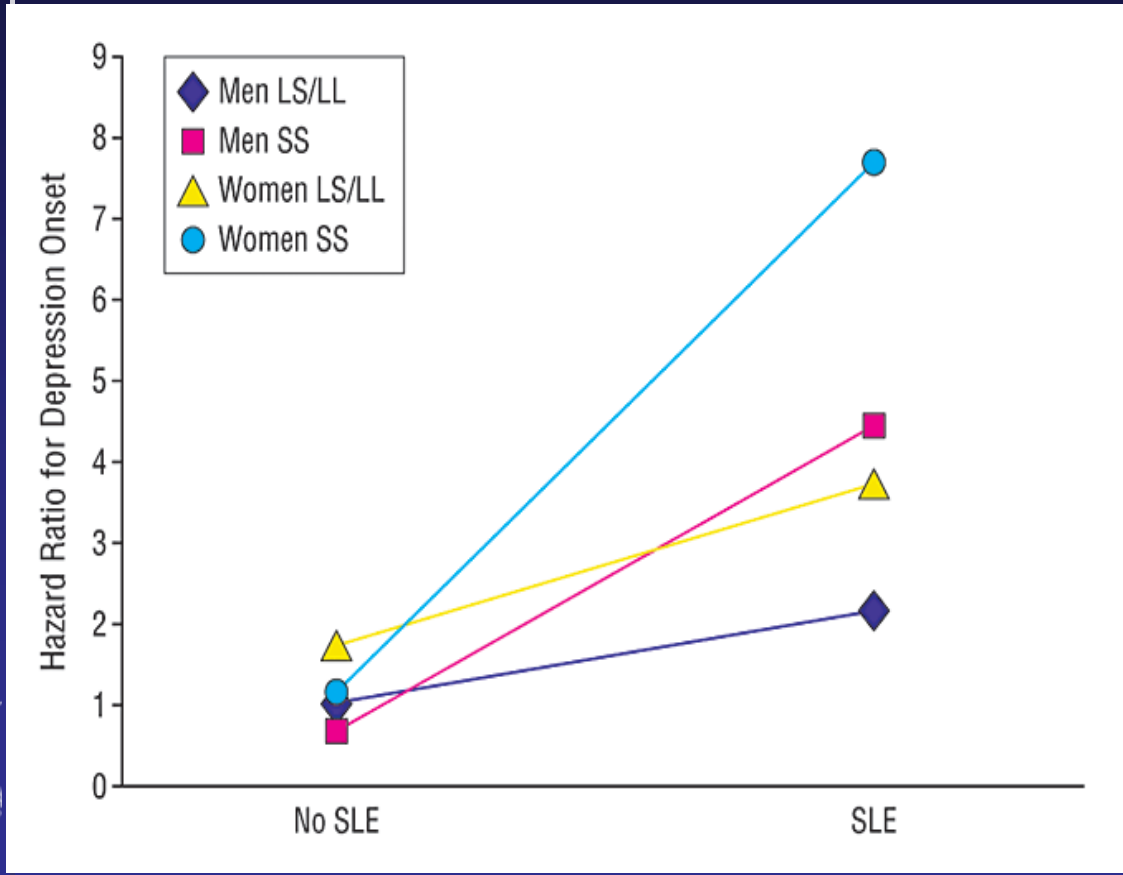
A. Caspi, Science, July 2003, Vol 301.



Individuals with 2 short (S) alleles at the 5-HTT locus were more sensitive to the depressogenic effects of all SLEs than were those with 1 or 2 long (L) alleles.

The hazard ratio of onset of major depression within a 2-month period

hazard rate = 1: defined as risk level for SS male with no SLE



For prediction of episodes of major depression:

Significant main effects for sex and SLE occurrence, but not for genotype

Significant genotype x SLE interaction

Kendler et al. (2005) *Arch Gen Psych*, 62(5): 529-535

STRATEGIES FOR PROGRAMMATIC RESEARCH INTO MEASURED G × E

Testing for an Interaction

Study Sampling Designs

Most informative design for testing G × E begins with cohort sample

- Represents population variation in genotype, exposure to environmental pathogens, and variety of health outcomes

Ideal if cohort enlisted prospectively in early life and followed longitudinally

- Repeated assessments obtain unbiased measures of cumulative exposure to environmental pathogens, and ascertain history relative to timing of exposure (Collins, 2004; Hunter, 2005)

In simple case of dichotomous genotype and environment variables, four cells of participants can be compared:

Genetic Risk \ Environmental Risk	Low	High
Low	Baseline outcomes associated with factors apart from G x E	Effect of environment
High	Effect of gene	Is joint association of risk factors with outcomes additive of multiplicative?

Moffitt, Caspi, Rutter (2006) ***Perspectives on Psychological Science,*** **1(1): 5-27**

Modeling the Epigenetic Pathway

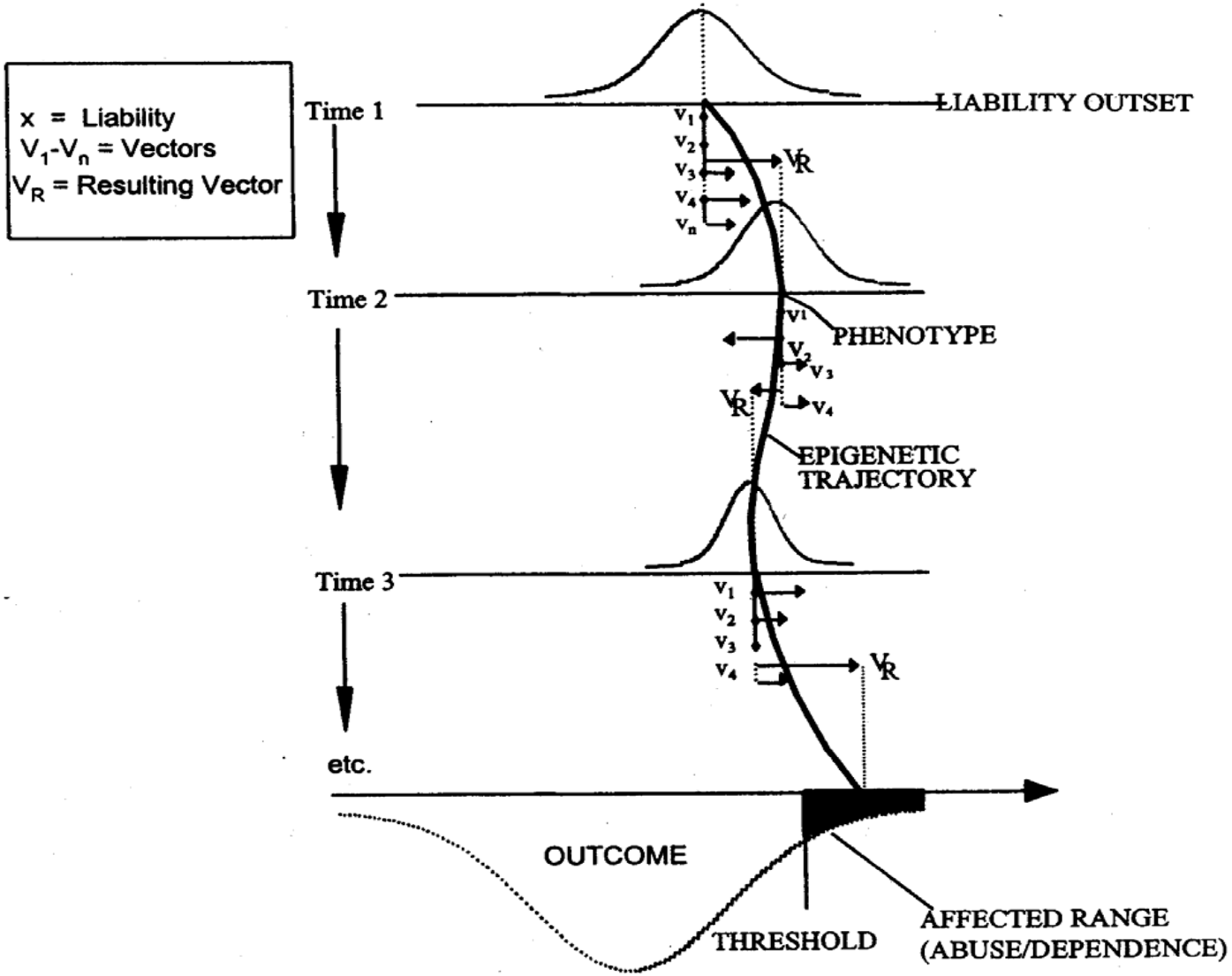
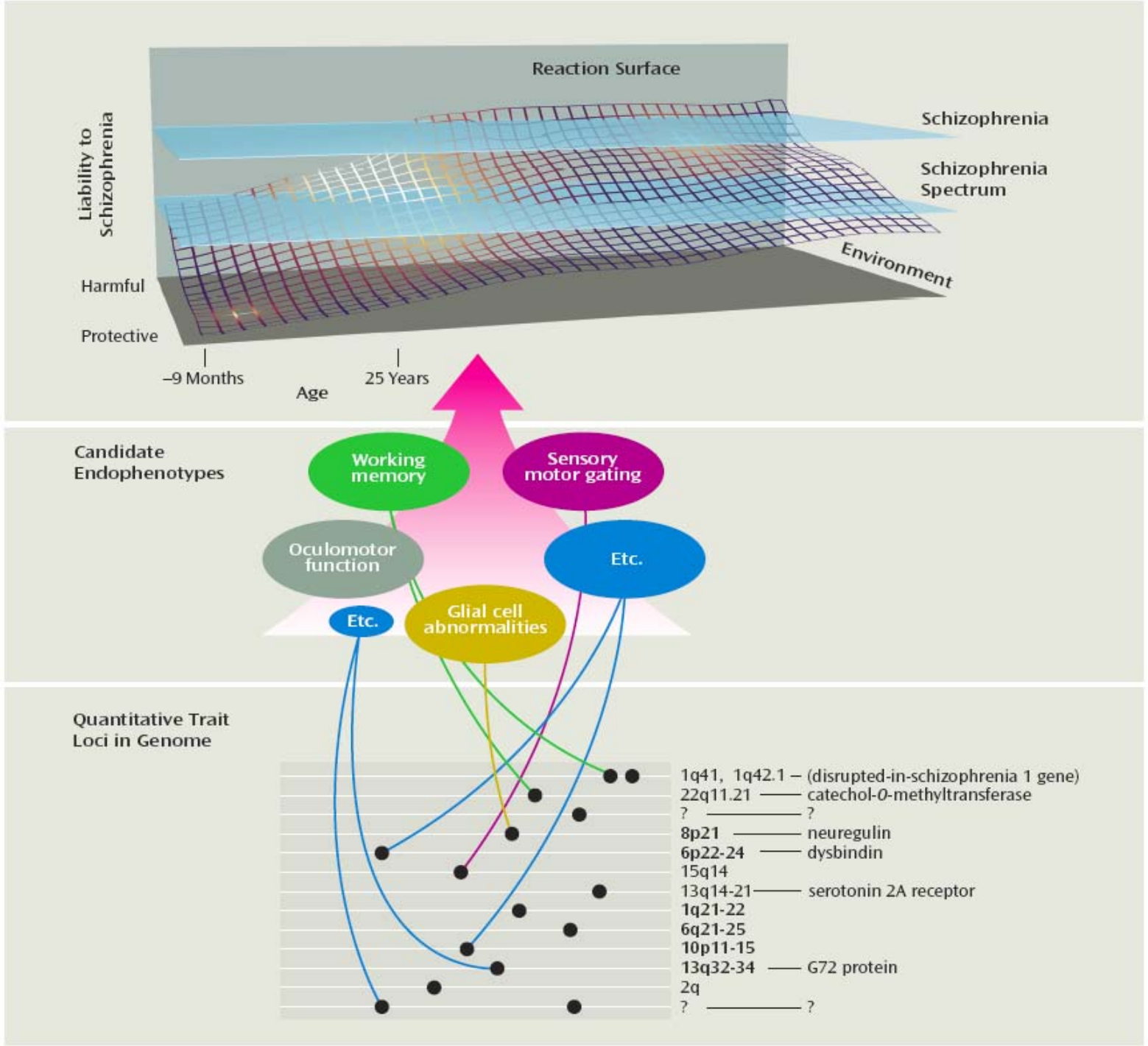


Figure 2. Modeling the epigenetic pathway.

Source: Tarter, R., et. al. *Psychology of Addictive Behaviors, 16,* (4S), S5.


Reaction Surface
Liability to Schizophrenia
Schizophrenia
Schizophrenia Spectrum
Environment
Harmful
Protective
–9 Months
Age
25 Years
Candidate Endophenotypes
Working memory
Sensory motor gating
Oculomotor function
Etc.
Etc.
Glial cell abnormalities
Quantitative Trait Loci in Genome
1q41, 1q42.1 — (disrupted-in-schizophrenia 1 gene)
22q11.21 — catechol-O-methyltransferase
? — ?
8p21 — neuregulin
6p22-24 — dysbindin
15q14
13q14-21 — serotonin 2A receptor
1q21-22
6q21-25
10p11-15
13q32-34 — G72 protein
2q
? — ?

The Promise of **Personalized** Medicine

NIH Director **Elias A. Zerhouni**, M.D., leads the NIH's 27 Institutes and Centers, with more than 18,000 employees and a 2006 budget of $28.6 billion. A well-respected leader in the field of radiology and medicine, he has spent his career providing clinical, scientific, and administrative leadership. Recently, Dr. Zerhouni sat down with magazine coordinator Christopher Klose to discuss some of Dr. Zerhouni's own experiences and hopes for the future of medicine.

Klose: *What motivated you to become a doctor?*

Dr. Zerhouni: I just like people; the interaction and sense of being relevant. At first, I wanted to be a mathematician or a physicist. I was more interested in rocketry and some of the careers typical of the 1950s. Years later when I was in university, I volunteered in the poor areas. I saw what was going on with the poor and that touched me. That was when I realized that it's great to send rockets to the moon, but perhaps the most important thing is people. That's why I went into medicine.

Klose: *Why did you decide to specialize in radiology?*

Dr. Zerhouni: Sometimes, life is just a matter of encountering people who show you something interesting. I had a radiologist who showed me my first CAT [computed axial tomography] scan.

Right away, I realized this was important; this was something I could do.

Radiology has a direct impact on understanding the biology of disease. Here is the crux of my research. I'm not a biologist but I work in biology, I'm not a mathematician, yet I use mathematics. Every piece of work I've done has been to increase our abilit to quantify – to use quantitative methods – to extract biological information. For example, I first discovered CAT scans could b used to measure calcium density within tissues, which led to m getting a patent. This paved the way for doing the same with lu cancer and then osteoporosis. And I discovered a technique in MRI [magnetic resonance imaging] that allows you to measure cardiac function very precisely.

For me, it has been this constant intermarriage of the physica and biological sciences in which the whole is greater than the su of the parts.

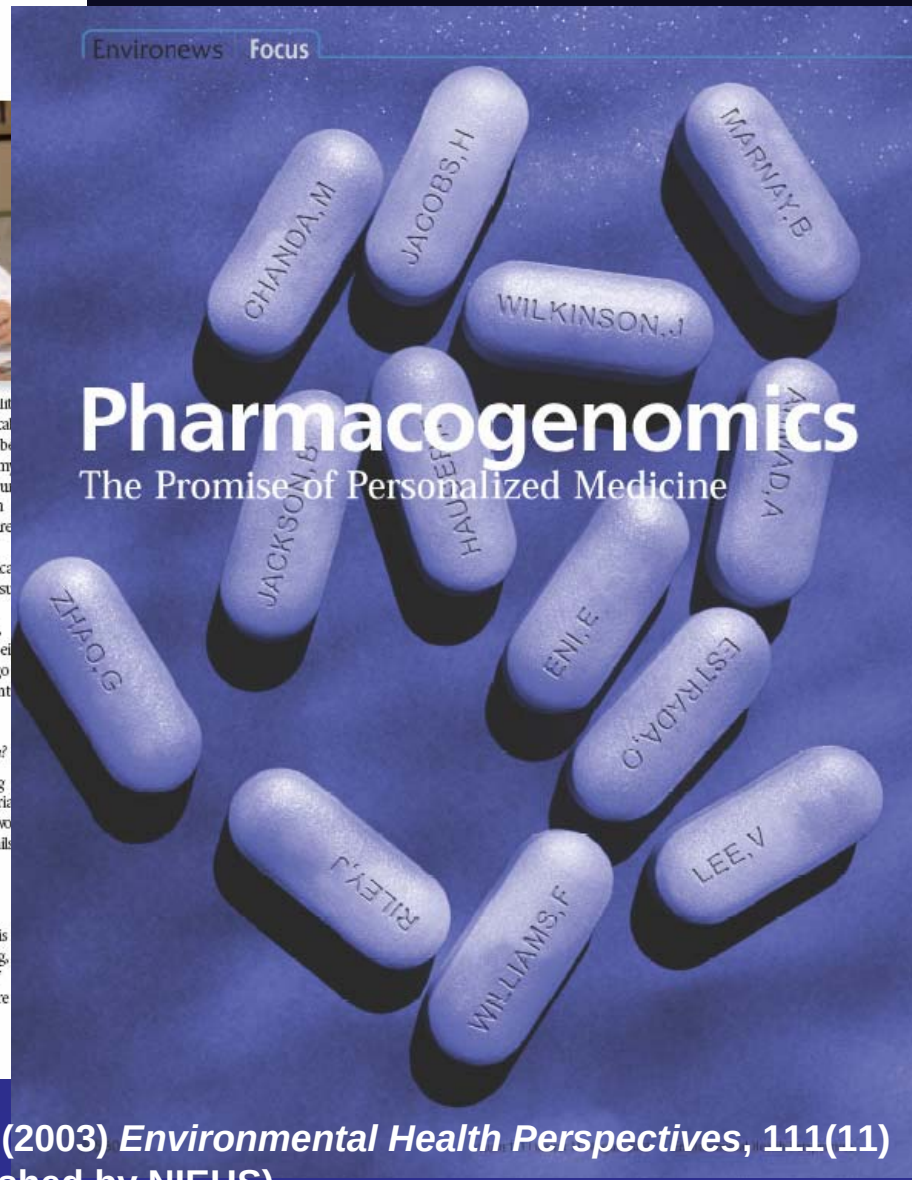
If you look at the history of medicine, of science in general, we've always gone from being able to empirically observe to bei able to measure accurately. The direction has always been to go from less precise to more precise tools, from less to more quant tive data, to inform yourself and increase your knowledge.

Klose: *How would you describe your own approach to research?*

Dr. Zerhouni: I'm sort of a hybrid because I believe that seeing trends is key. I don't like to just analyze things. I'm entrepreneuria and want to make a difference. And that really requires what I wo call operational attention. So I'm not really a detail person; details are a tool for reaching endpoints, to drive a particular vision.

Klose: *How do you see medicine today changing?*

Dr. Zerhouni: The relationship between patient and doctor is changing quickly. Before, the patient was passive and receiving, the doctor all-knowing and giving. We tried to cure people of whatever had evolved in them. Now we need to be much more

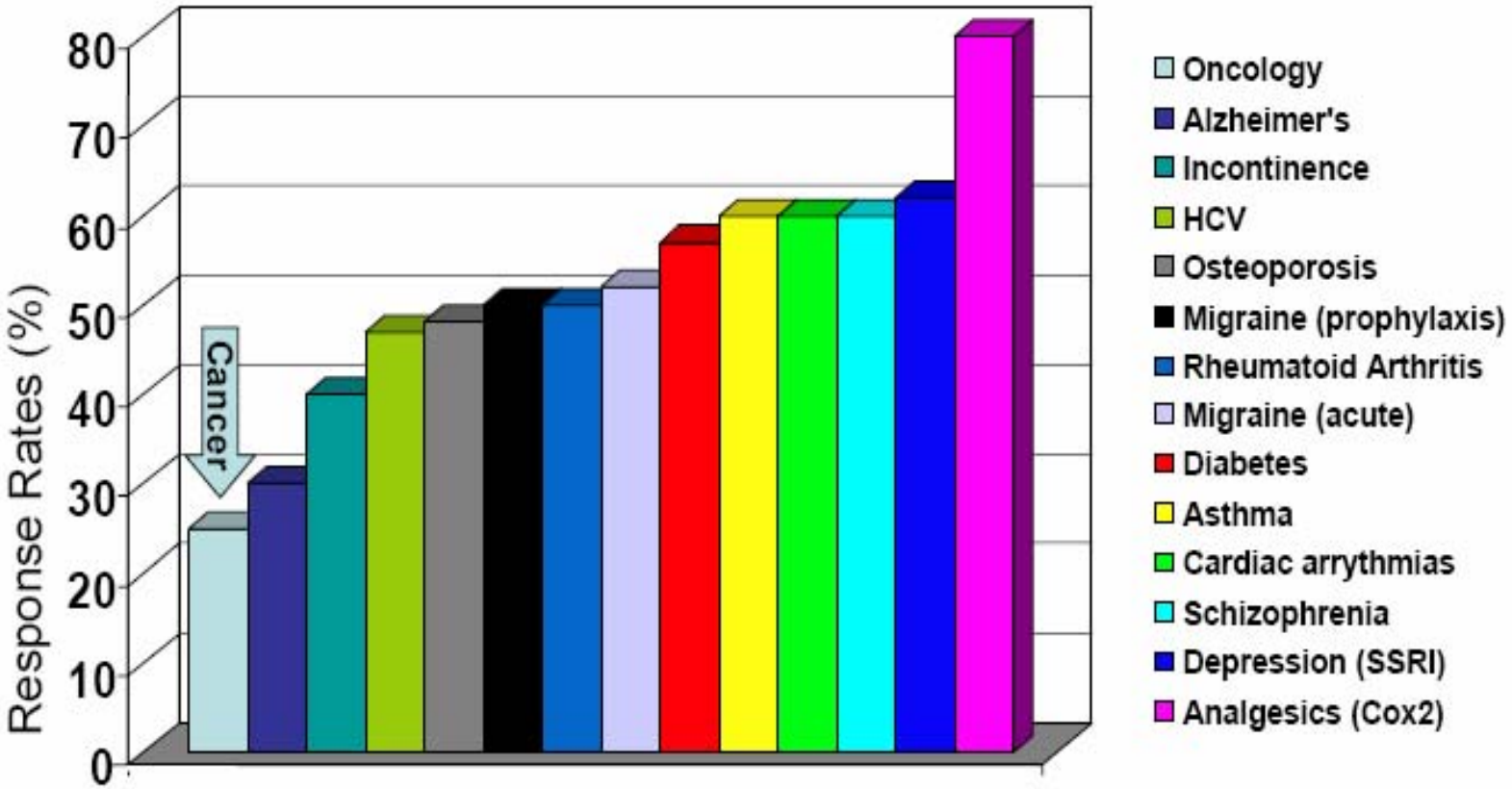


NIH MedlinePlus Magazine, Winter 2007

Hood (2003) *Environmental Health Perspectives*, 111(11) (published by NIEHS)

Mental Health Care in the Pre-Genomic Era??

The FDA acknowledges a large variation in response rates to treatments for a variety of conditions



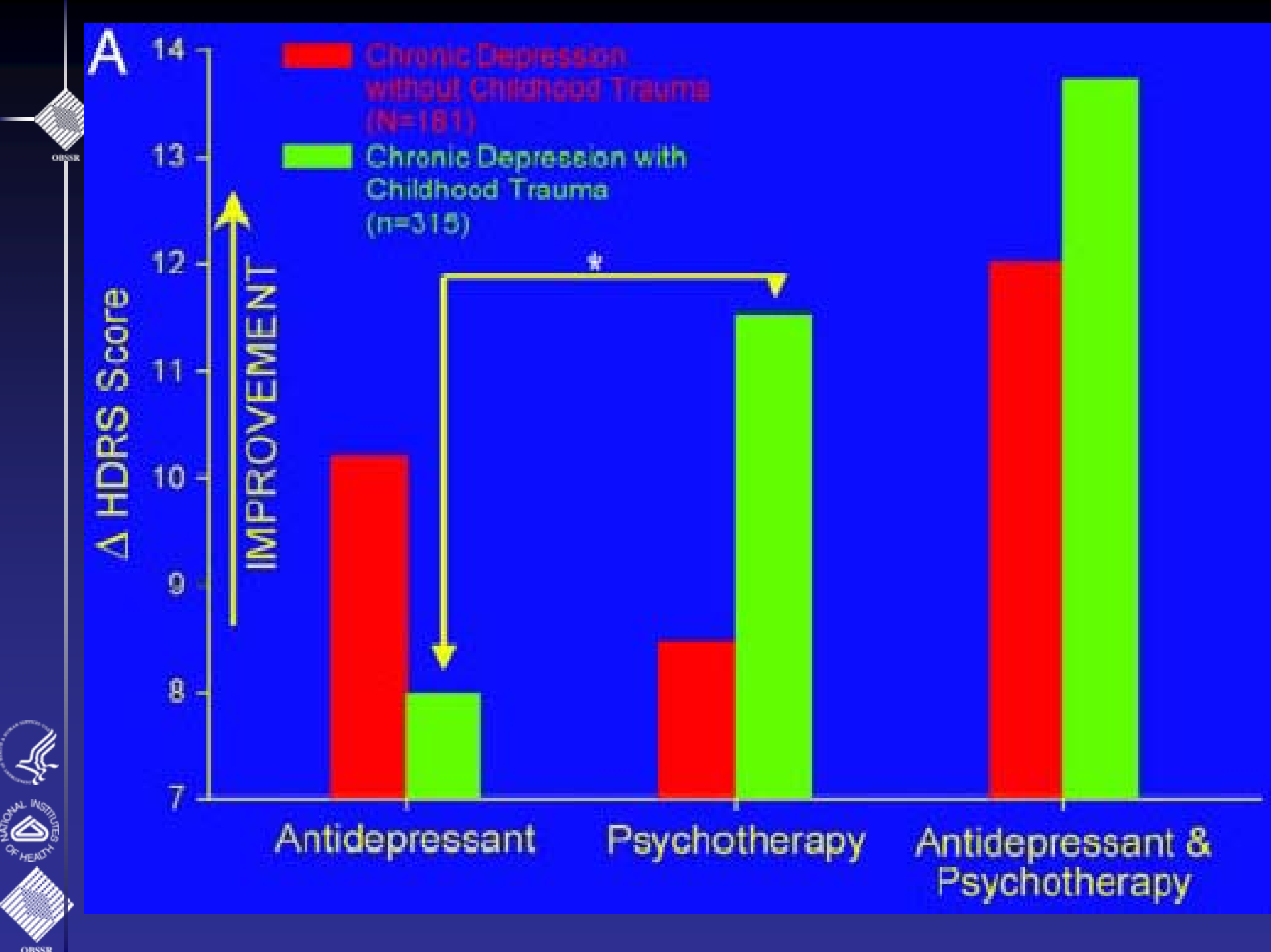
Frueh FW. (2006). Pharmacogenomics: Patient selection for clinical trial participation and enrichment strategies. Available at www.fda.gov/cder/genomics

Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma

Charles B. Nemeroff*†‡, Christine M. Heim*†, Michael E. Thase†‡, Daniel N. Klein§, A. John Rush†¶, Alan F. Schatzberg†‖, Philip T. Ninan*†, James P. McCullough, Jr.**, Paul M. Weiss††, David L. Dunner†‡‡, Barbara O. Rothbaum*†, Susan Kornstein†§§, Gabor Keitner†¶¶, and Martin B. Keller†¶¶

*Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30322; ††Department of Biostatistics, School of Public Health, Emory University, Atlanta, GA 30322; ‡Western Psychiatric Institute and Clinic, Pittsburg, PA 15213; §Department of Psychology, State University of New York, Stony Brook, NY 11794; ¶Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX 75390; ‖Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305; **Department of Psychology, Virginia Commonwealth University, Richmond, VA 23284; §§Department of Psychiatry/Ambulatory Care, Virginia Commonwealth University Health System, Richmond, VA 23284; ‡‡Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA 98105; and ¶¶Department of Psychiatry, Brown University, Providence, RI 02906

Nemeroff et al. 2003. PNAS November 100(24):14293-14296


A
Chronic Depression without Childhood Trauma (N=181)
Chronic Depression with Childhood Trauma (n=315)
Δ HDRS Score
IMPROVEMENT
14
13
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9
8
7
*
Antidepressant
Psychotherapy
Antidepressant & Psychotherapy

The DRD4 VNTR Polymorphism Influences Reactivity to Smoking Cues

Hutchinson et al. (2002) *J Abnormal Psychology*, 111(1): 134-143

Craving for tobacco can be reliably elicited by exposure to smoking cues

- Cue-elicited craving for tobacco may be a useful phenotype for research on genetic factors related to nicotine dependence

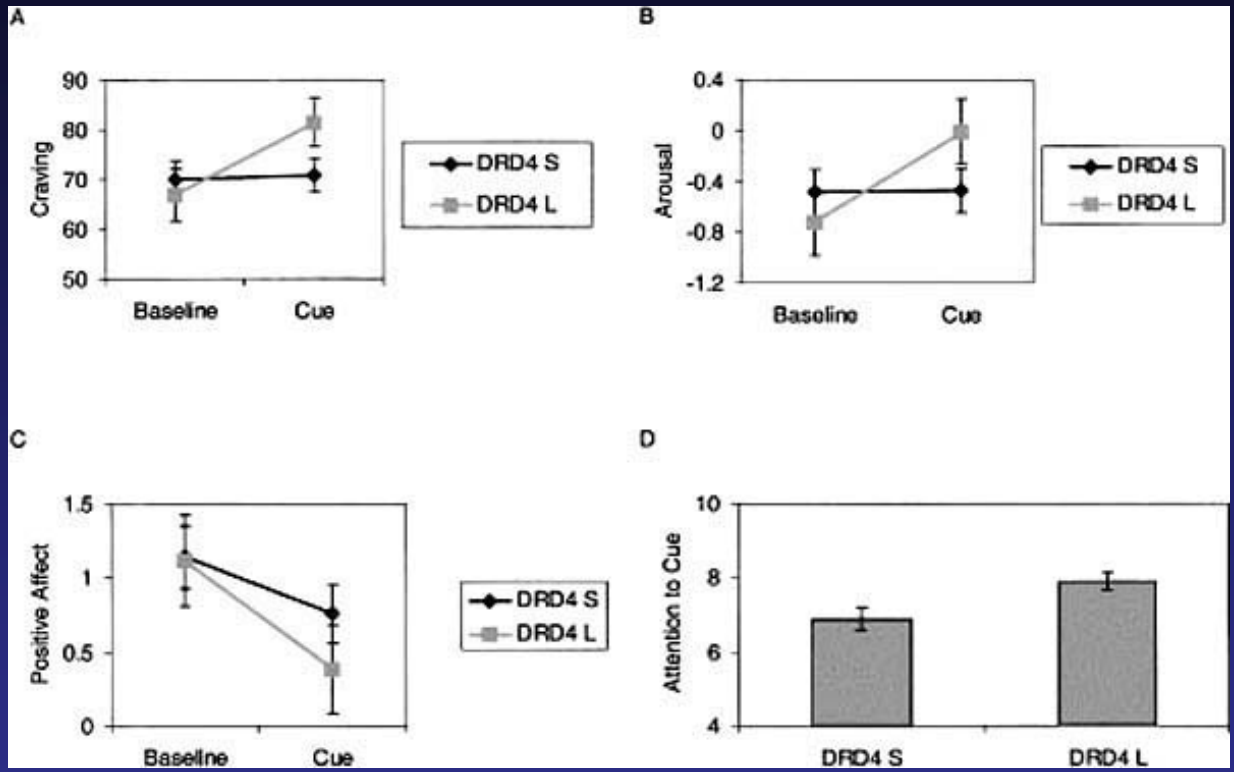
Given potential role of dopamine in cue-elicited craving, examine whether DRD4 VNTR polymorphism is associated with cue-elicited craving for tobacco

Participants who were homozygous or heterozygous for 7 repeat (or longer) allele classified as DRD4 L

All other participants classified as DRD4 S.

Participants exposed to smoking cues before smoking cigarettes (nicotine challenge - 3 cigarettes using dose delivery device.

L group demonstrated significantly greater craving, more arousal, less positive affect, and more attention to the smoking cues than did S group



(A) Only DRD4 L group reported increase in craving for tobacco after exposure to cues
(B) Only DRD4 L group reported increase in arousal after exposure to cues
(C) Only DRD4 L group reported decrease in positive affect after exposure to cues
(D) DRD4 L group reported more attention to cues during exposure than did S group

Hutchinson et al. (2002) *J Abnormal Psychology*, 111(1): 134-143

Genetic Variation in Nicotine Metabolizing Enzymes and Response to NRT

Caryn Lerman, Ph.D. (Penn TTURC)
Rachel Tyndale, Ph.D. (U. Toronto)
Neal Benowitz M.D. (UCSF, PNAT)

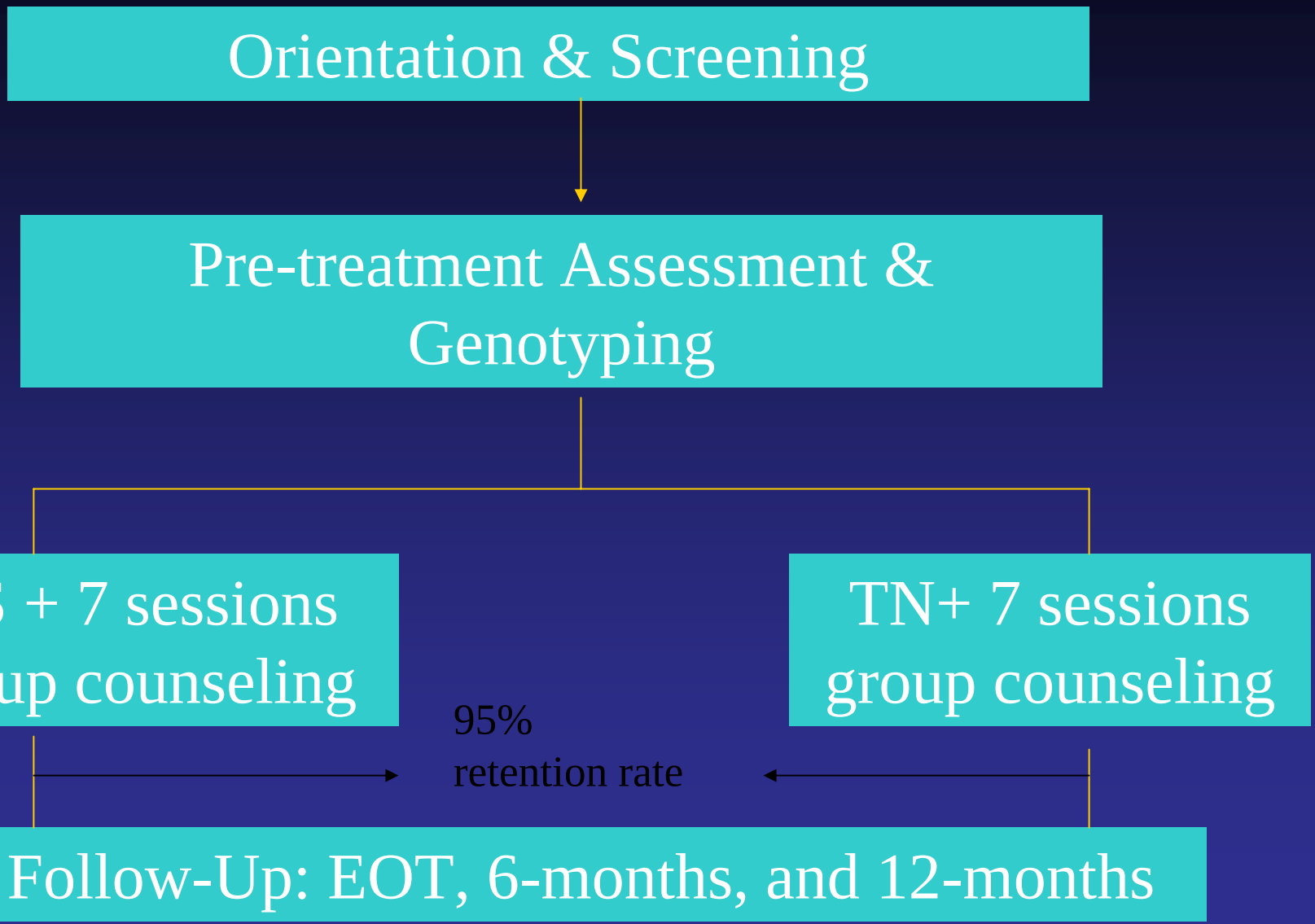
Research Objective

To examine the association of functional variation in *CYP2A6* with treatment-related variables in an NRT trial for smoking cessation.

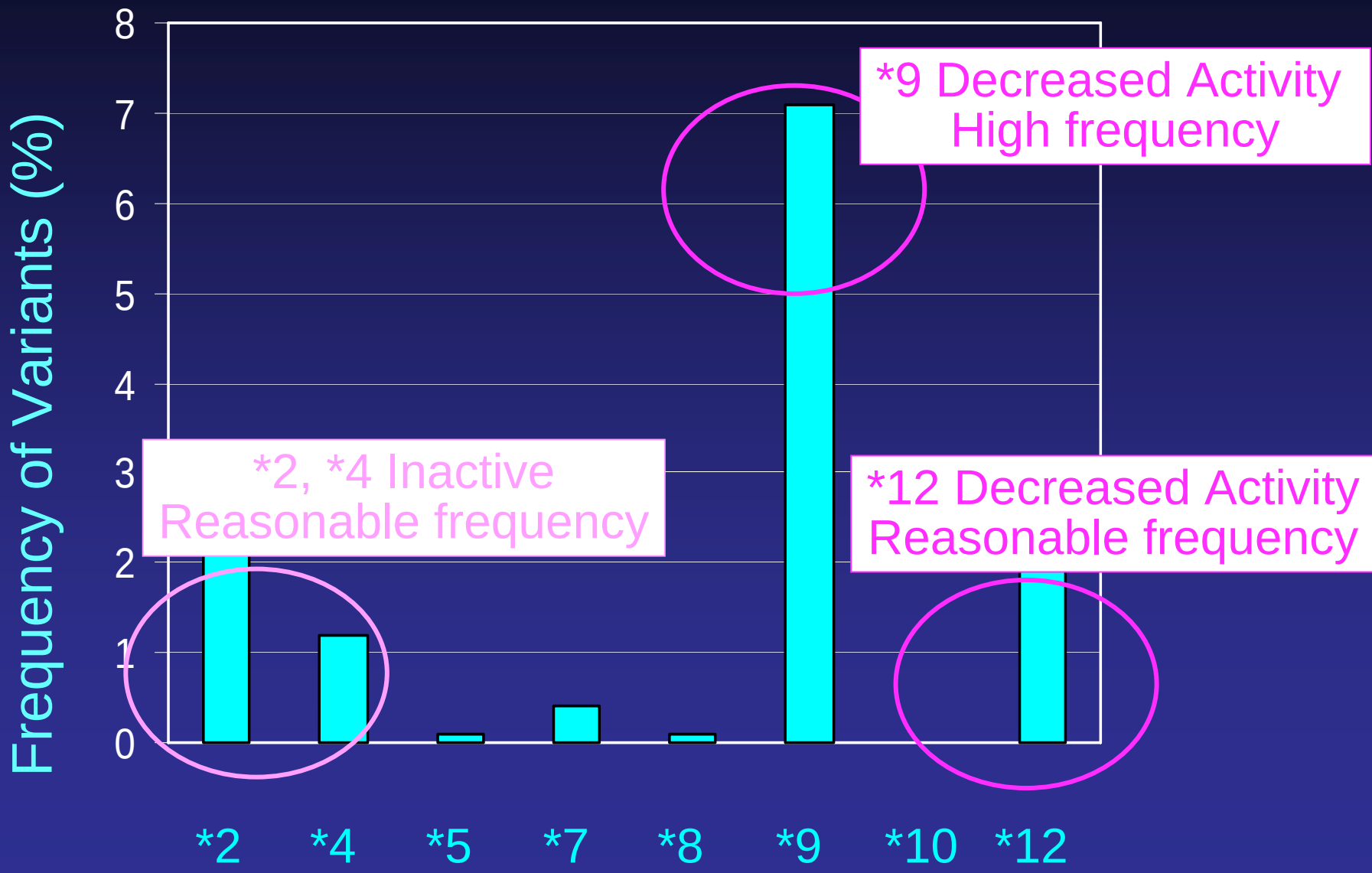
394 treatment seeking smokers

- **Genotype-phenotype correlation**
- **NRT usage**
- **Nicotine levels 1-week post-treatment**

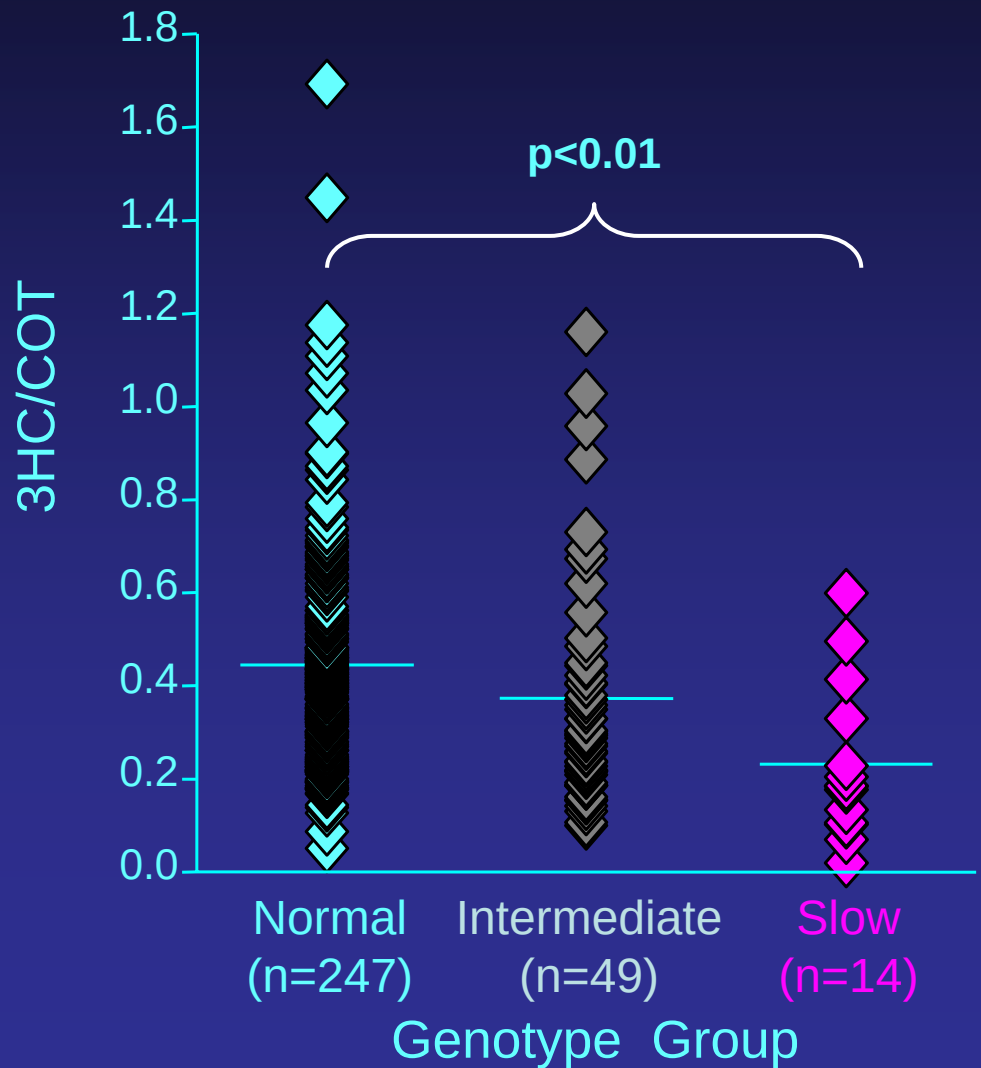
Open Label Trial of TN vs. NasalSp (n=599)



CYP2A6 Alleles (Caucasians >1600 tested by Tyndale et al)

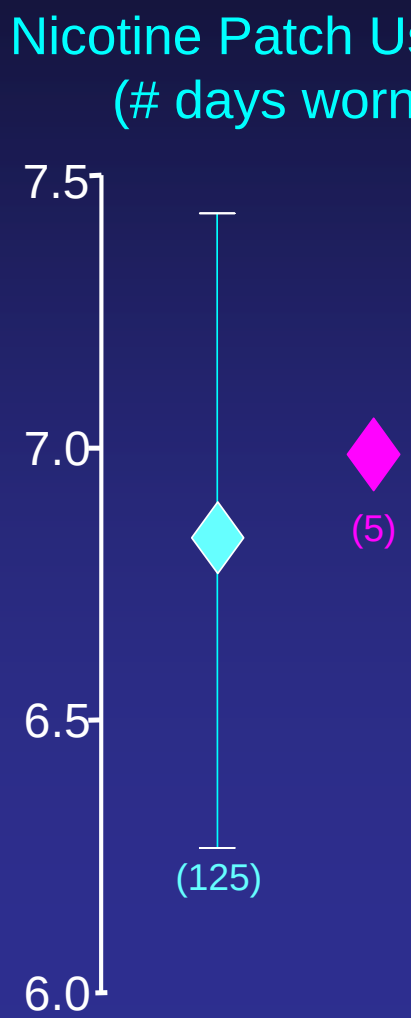


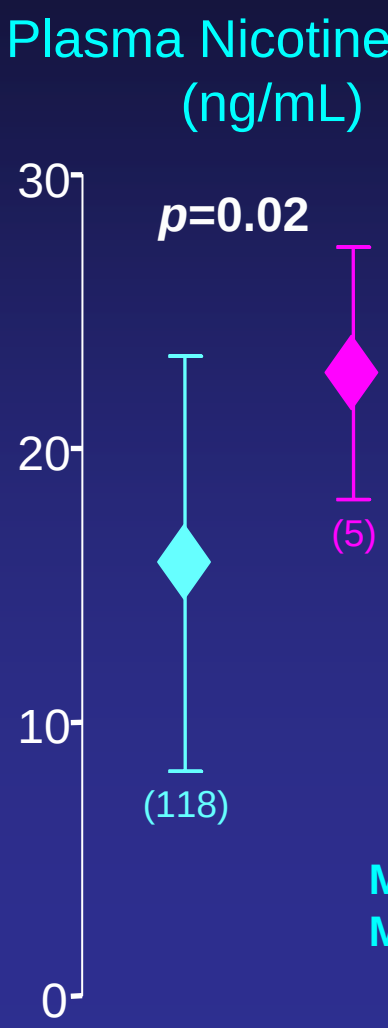
Genetically Slow Metabolizers have lower 3HC/COT ratios



Malaiyandi et al, Mol Psychiatry. 2006

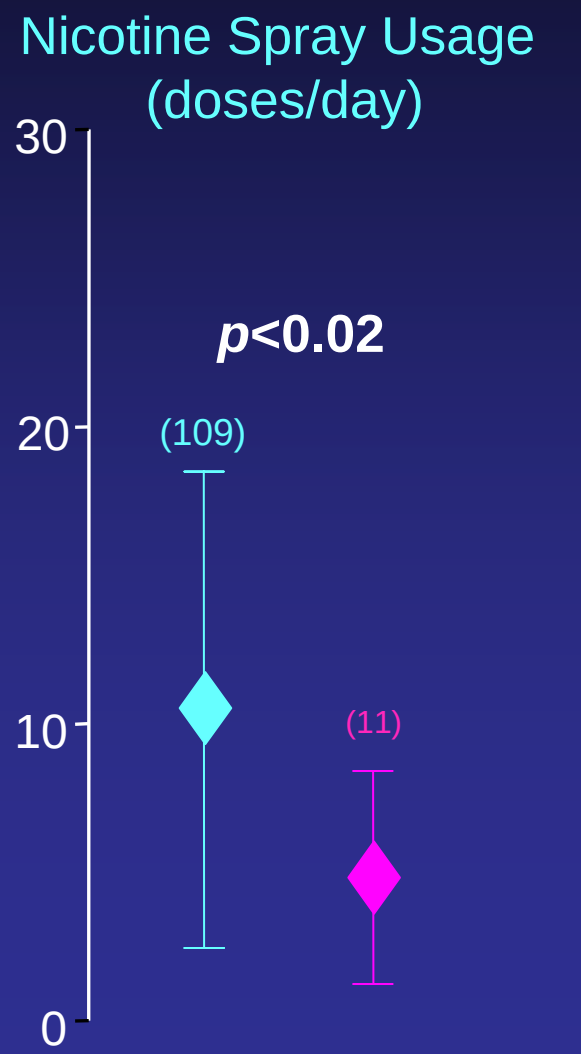
Genetically Slow Metabolizers have higher nicotine on the patch

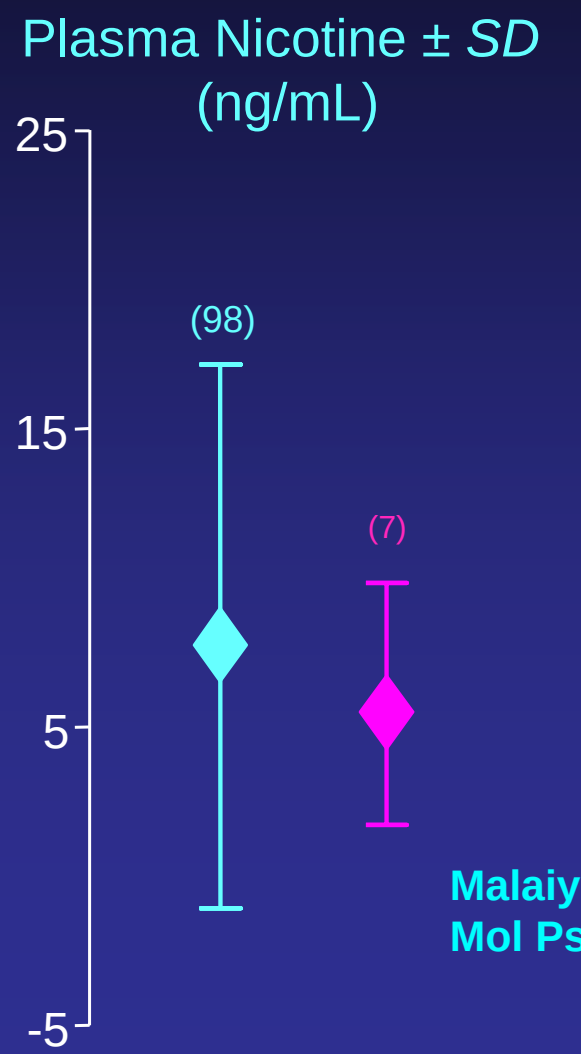




Malaiyandi et al,
Mol Psychiatry 2006

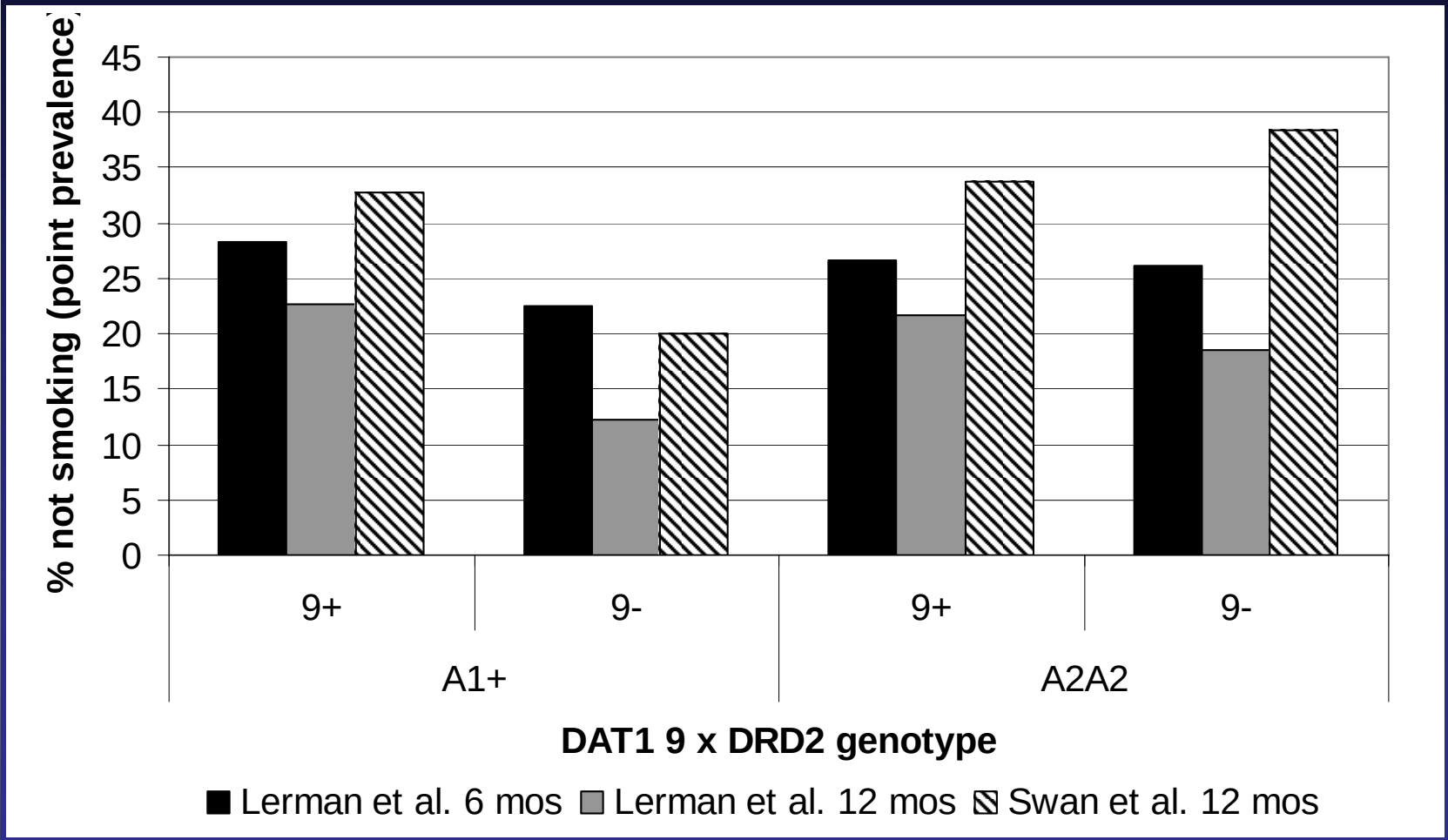
Genetically Slow Metabolizers have lower usage & equal nicotine on spray





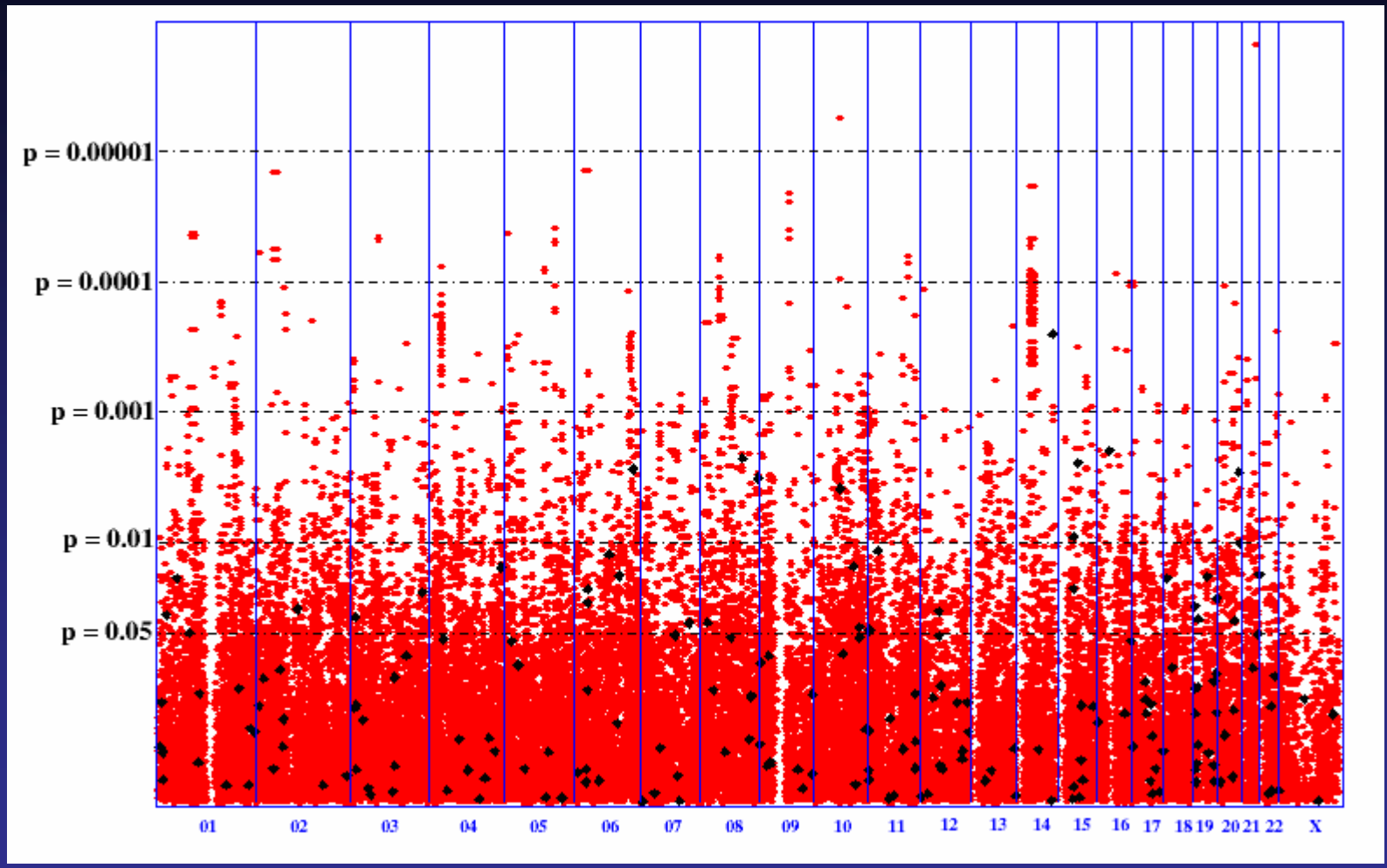
Malaiyandi et al, Mol Psychiatry 2006

Point prevalence nonsmoking rates in Lerman et al. (2003) with those of Swan et al. (2007)



From Swan et al. (2007). Health Psychology.

Graphical results of GWAS of nicotine dependence, FTND-defined



From: Bierut, Madden, Breslau, Johnson, Hatsukami, Pomerleau, Swan, Rutter, Bertelsen, Fox, Fugman, Goate, Hinrichs, Konvicka, Martin, Montgomery, Saccone, Saccone, Wang, Chase, Rice, Ballinger. (2006). Hum Mol Genet, Dec. 7.

Early Warning Sign

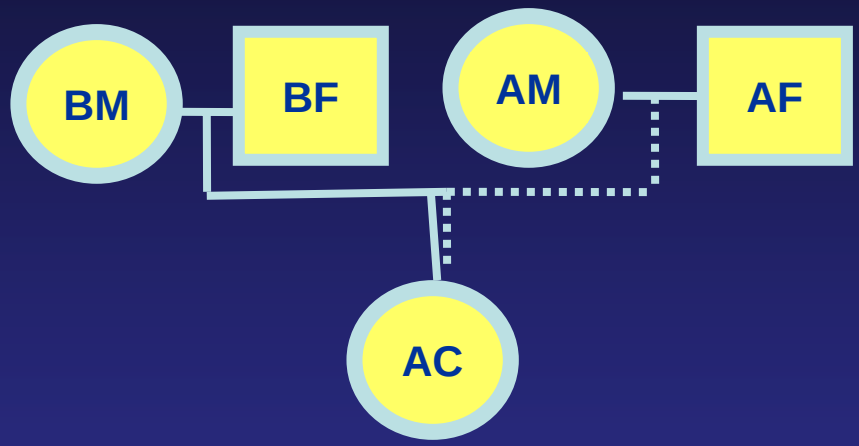
Early Growth and Development Study (EGDS)

Presentation to
Office of Behavioral and Social Sciences Research
Office of the Director, NIH

November 21, 2006

Leslie Leve, Ph.D.
Oregon Social Learning Center
Jenae Neiderhiser, Ph.D.
David Reiss, MD
George Washington University Medical Center

Prospective adoption study



Yoked Adoption Unit

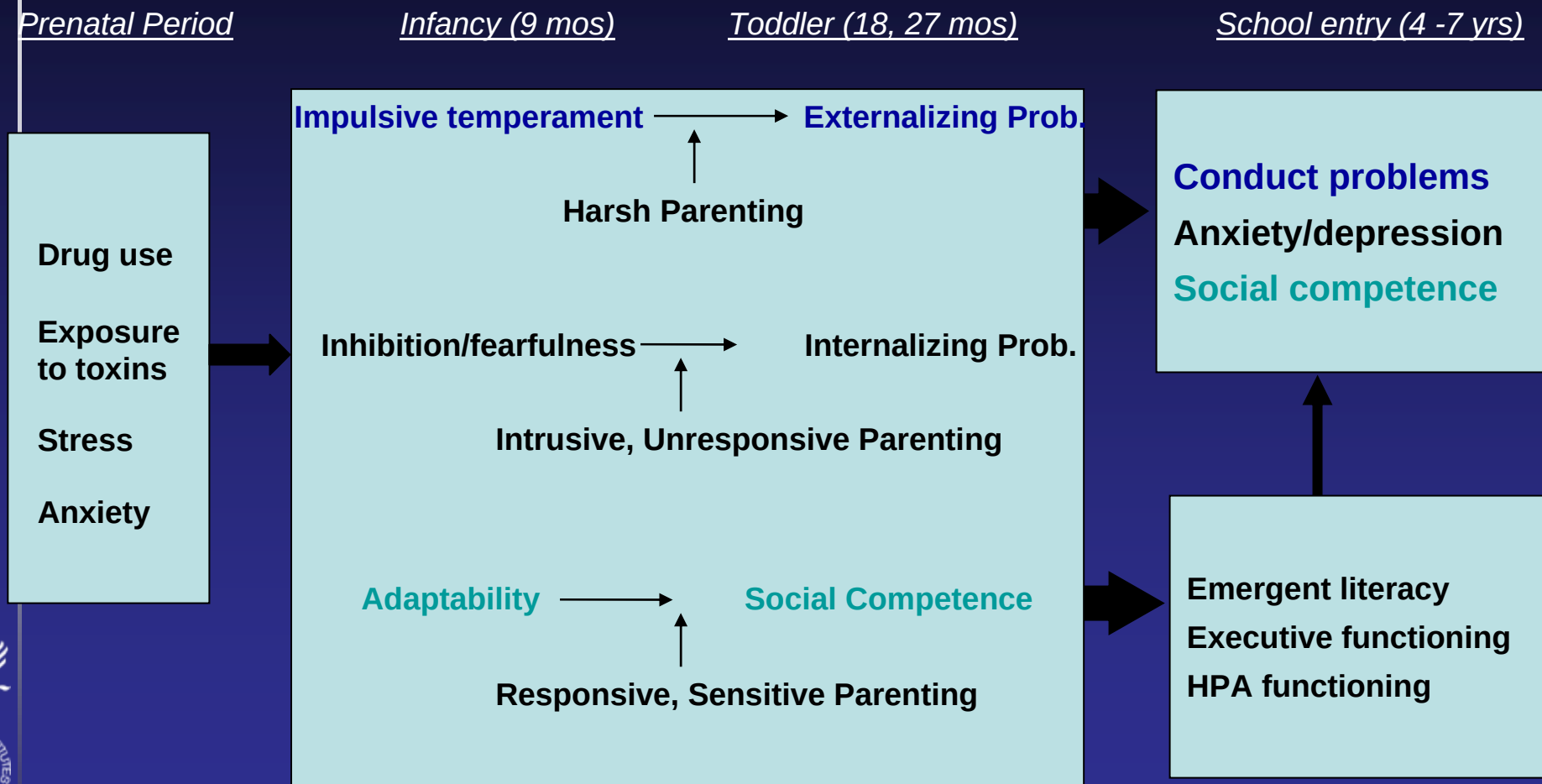
EGDS study design

- 559 domestic adoption placements to non-relative families (359 in EGDS-Toddler and *200 in EGDS-Prenatal*)
- Yoked Adoption Unit: Birth mother/birth father, adoptive mother/father, & adoptive child
- Adoption occurred within 3 mo. post-partum
- Infant free of major medical problems
- *3 major assessments* for birth parents and *6 major assessments* for adoptive families spanning infancy *through 1st grade (EGDS-School)*
- Multimethod, multiagent approach

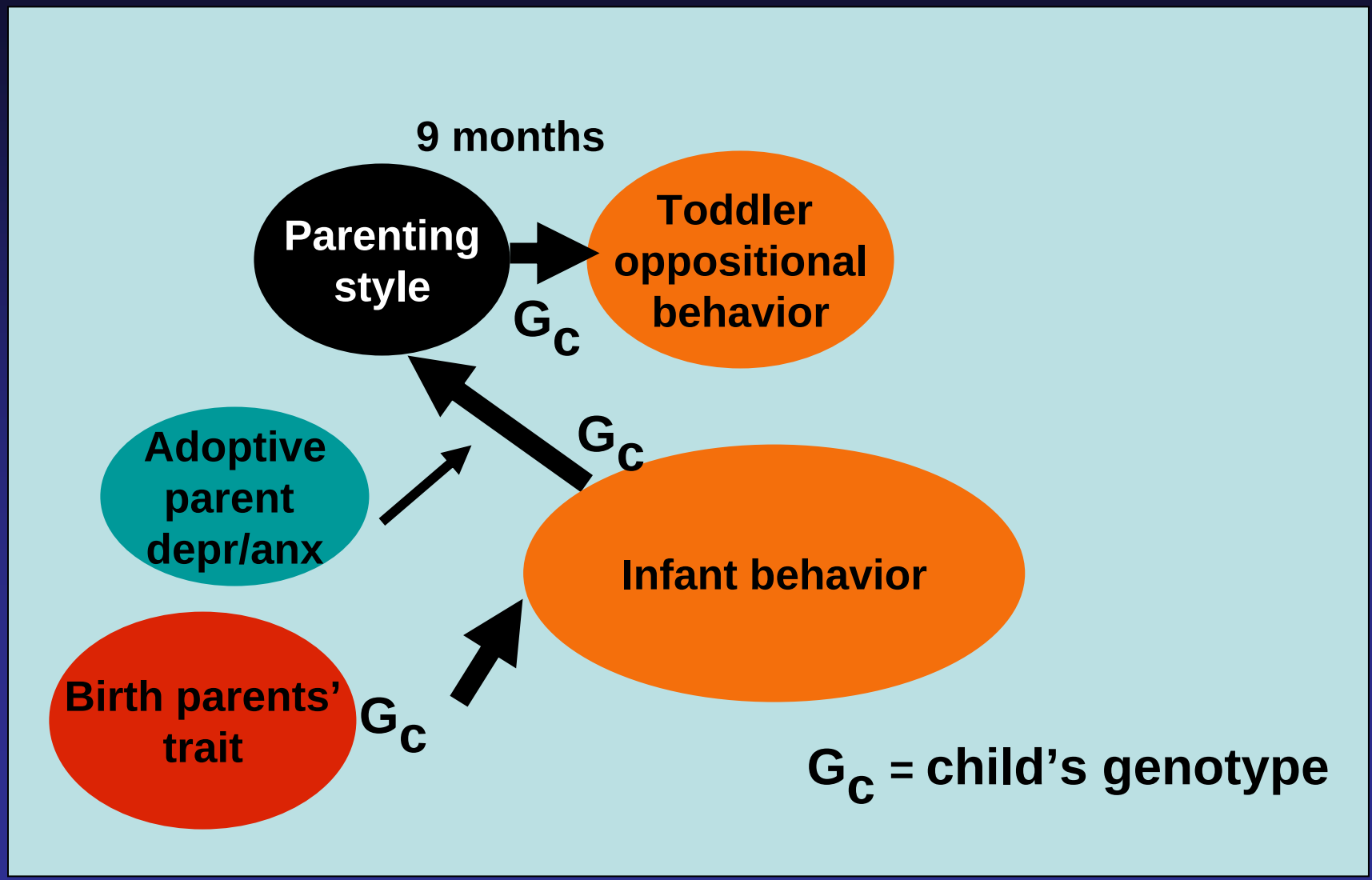
EGDS constructs

- Birth parents, adoptive parents, and children
  - Externalizing, internalizing, social competence
  - Alcohol & drug use and problems
  - Temperament
  - Social context (stress, social support, economic circumstances, partner/marital relations)
  - *Executive functioning and literacy*
  - *DNA and salivary cortisol samples*
- Adoptive parents only
  - Parenting
- Birth parents only
  - Prenatal exposure to drugs, toxins, stress

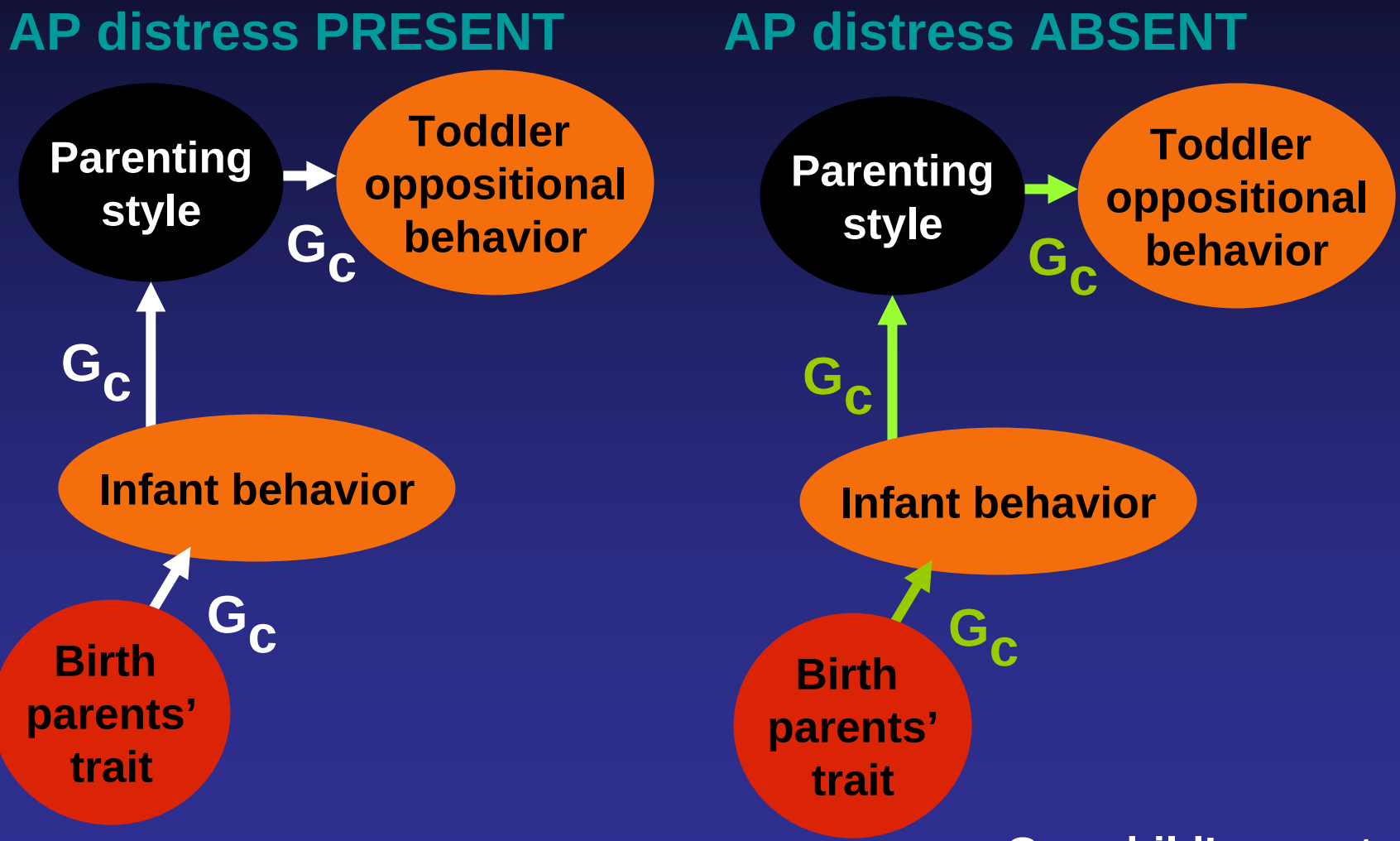
Environmental influences on three developmental pathways



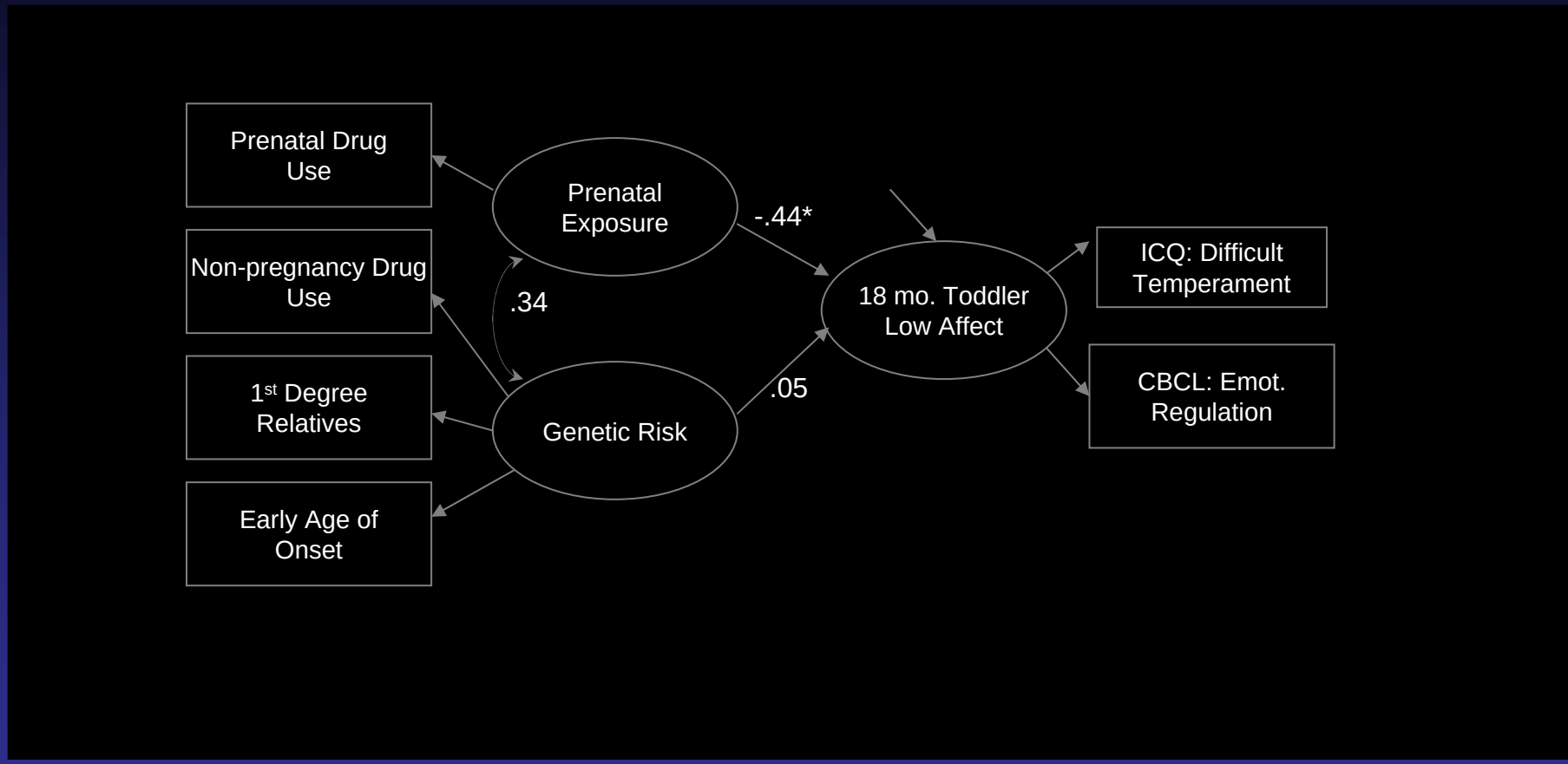
A hypothetical evocative mechanism of G x E interaction



A hypothetical evocative mechanism of G x E interaction



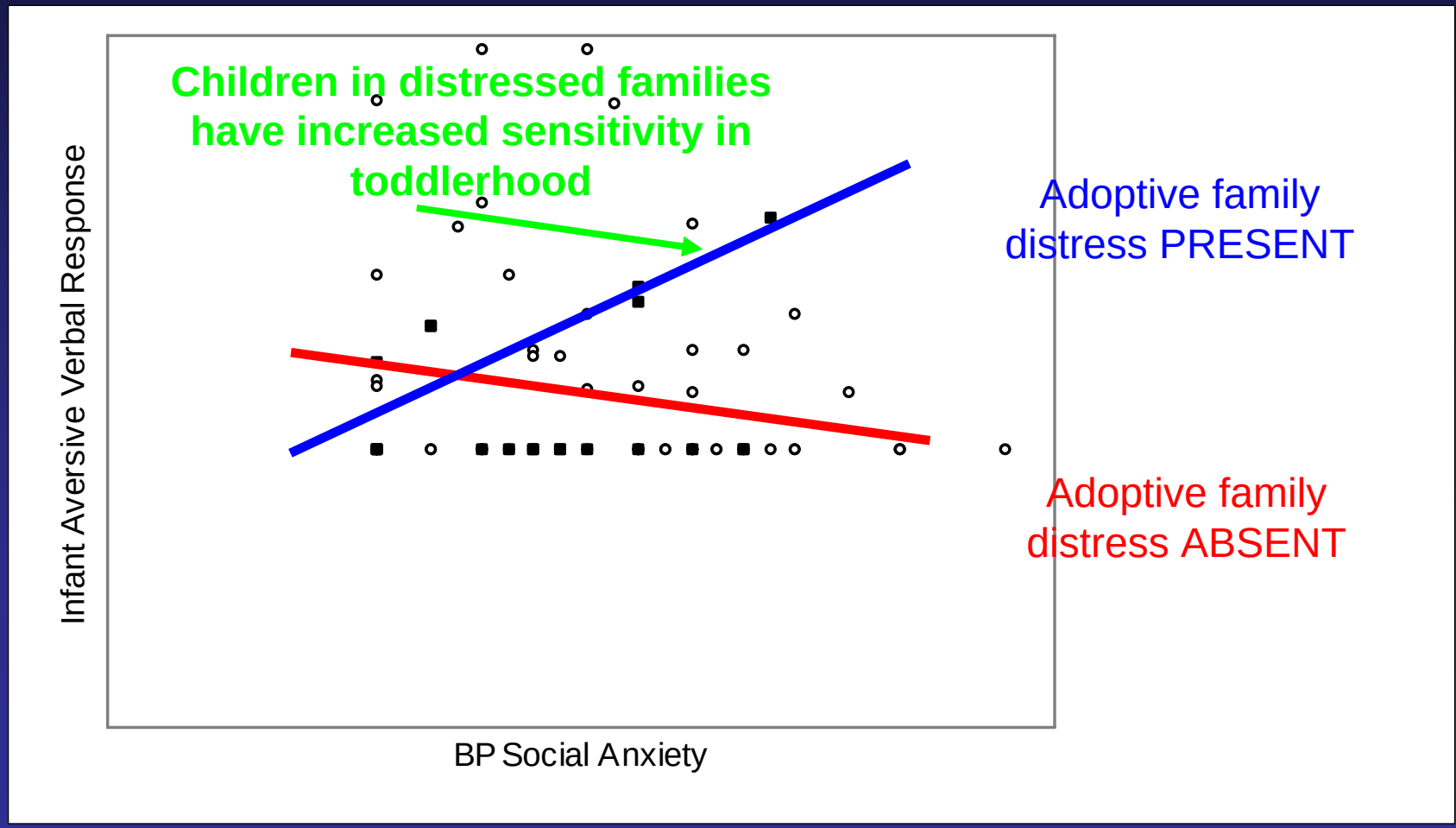
Combining genetic risk & prenatal exposure to drugs



n=127 yoked families who completed the 18-month assessment by May 1 2006. High levels of prenatal drug use significantly contributed to suppressed toddler affect and the effects of genetic risk influenced toddler suppressed affect only via prenatal drug exposure ($\chi^2_{(6)}$ =6.5; GFI=.98).

****Note: Confidence intervals decrease 50% when *n* increases to 550.**

Comparing genetic influence on *infants' response to parenting* in the presence and absence of adoptive family distress in EGDS-Toddler



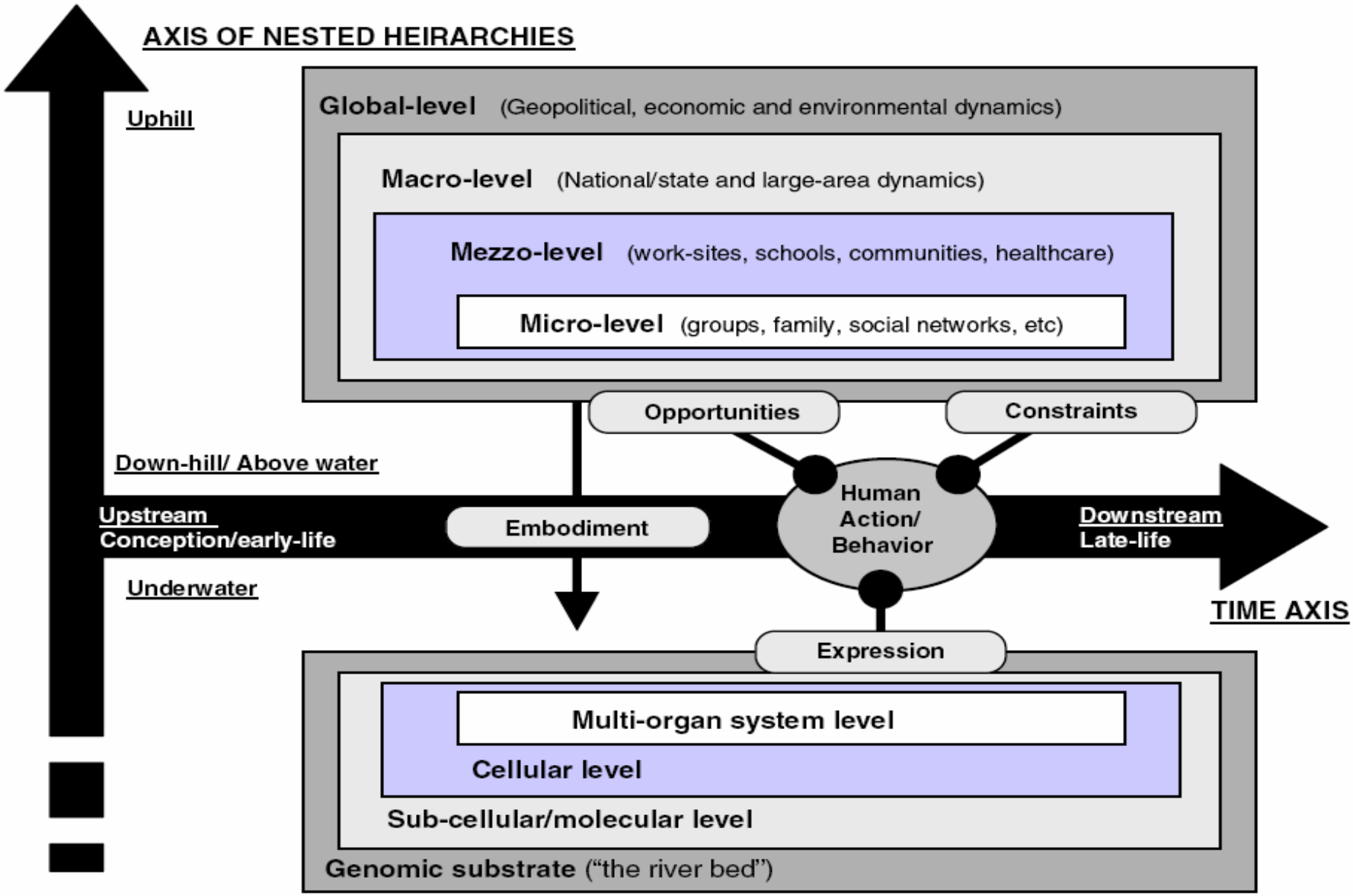
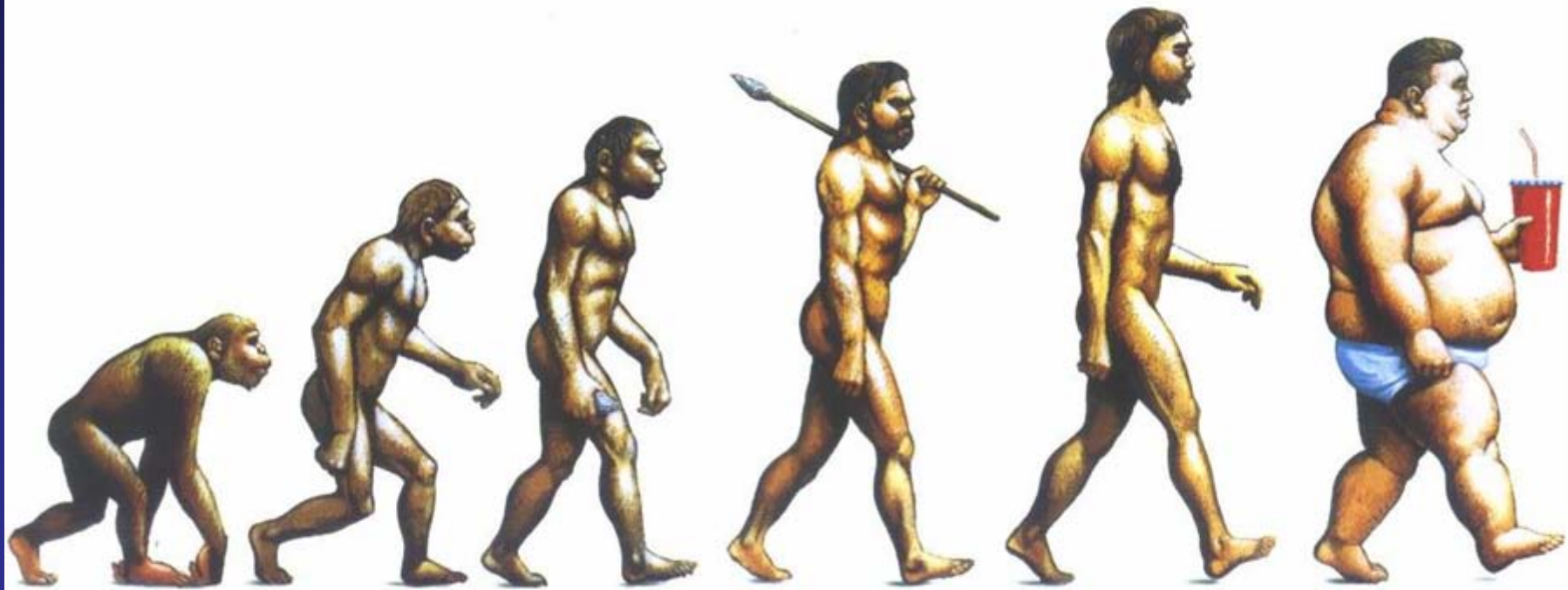
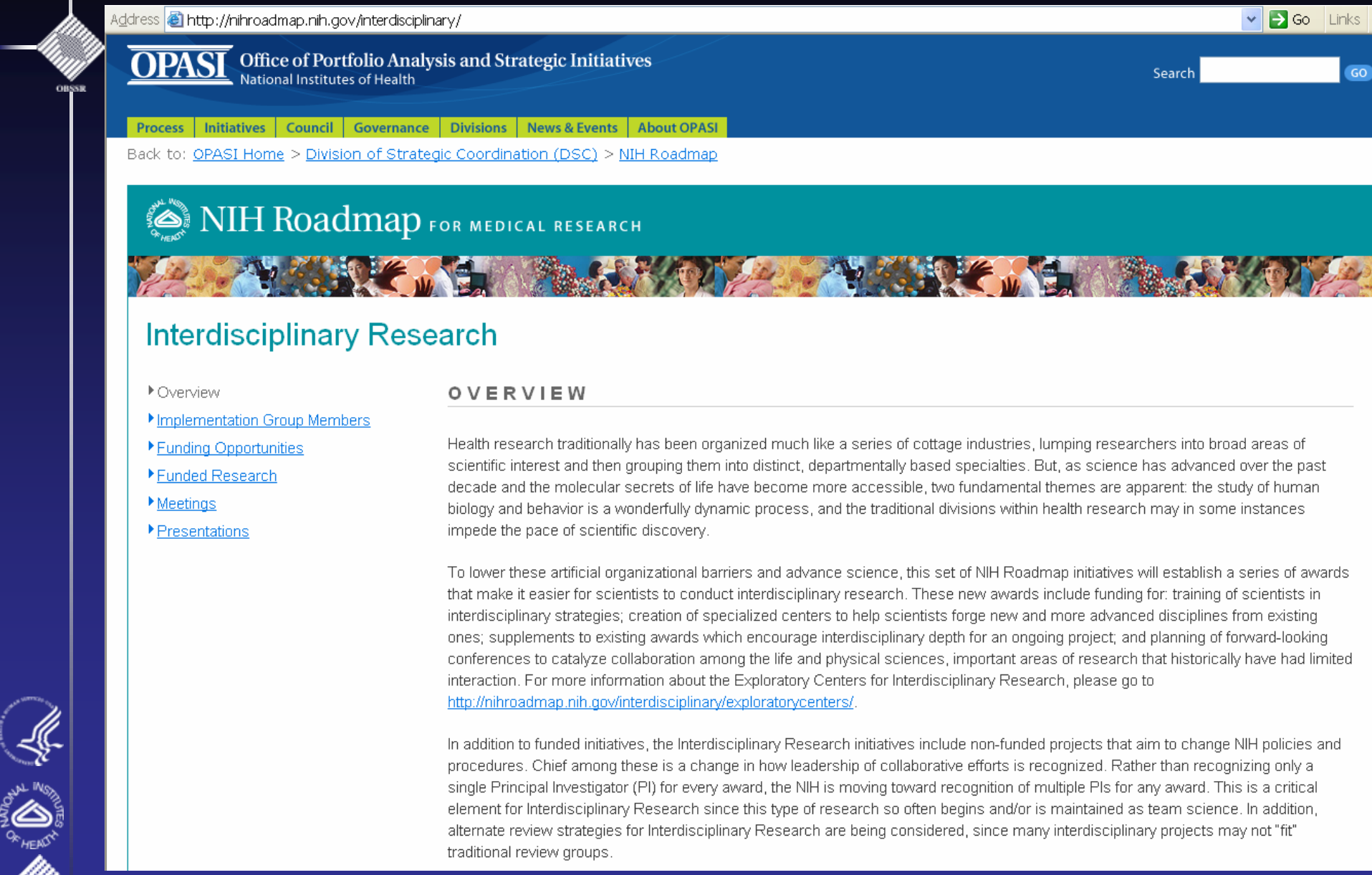


Fig. 1. The society-behavior-biology nexus as depicted in multidimensional space. The large arrows represent the axes of time and nested hierarchical structures. The sphere of health-related behavior and action moves through time from infancy to old age. Behavior is influenced by structured contingencies within the social and physical environment and by biological phenomena. Structural contingencies (opportunities and constraints) are shown by paths ending with nodes, while biological phenomena (embodiment and expression) are shown by paths ending with arrows or nodes.

The shape of things to come



Cover of "The Economist", Dec. 13-19, 2003.


Address http://nihroadmap.nih.gov/interdisciplinary/
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Links
OPASI
Office of Portfolio Analysis and Strategic Initiatives
National Institutes of Health
Search
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Process
Initiatives
Council
Governance
Divisions
News & Events
About OPASI
Back to: OPASI Home > Division of Strategic Coordination (DSC) > NIH Roadmap
NIH Roadmap FOR MEDICAL RESEARCH
Interdisciplinary Research
Overview
Implementation Group Members
Funding Opportunities
Funded Research
Meetings
Presentations
OVERVIEW
Health research traditionally has been organized much like a series of cottage industries, lumping researchers into broad areas of scientific interest and then grouping them into distinct, departmentally based specialties. But, as science has advanced over the past decade and the molecular secrets of life have become more accessible, two fundamental themes are apparent: the study of human biology and behavior is a wonderfully dynamic process, and the traditional divisions within health research may in some instances impede the pace of scientific discovery.
To lower these artificial organizational barriers and advance science, this set of NIH Roadmap initiatives will establish a series of awards that make it easier for scientists to conduct interdisciplinary research. These new awards include funding for: training of scientists in interdisciplinary strategies; creation of specialized centers to help scientists forge new and more advanced disciplines from existing ones; supplements to existing awards which encourage interdisciplinary depth for an ongoing project; and planning of forward-looking conferences to catalyze collaboration among the life and physical sciences, important areas of research that historically have had limited interaction. For more information about the Exploratory Centers for Interdisciplinary Research, please go to http://nihroadmap.nih.gov/interdisciplinary/exploratorycenters/.
In addition to funded initiatives, the Interdisciplinary Research initiatives include non-funded projects that aim to change NIH policies and procedures. Chief among these is a change in how leadership of collaborative efforts is recognized. Rather than recognizing only a single Principal Investigator (PI) for every award, the NIH is moving toward recognition of multiple PIs for any award. This is a critical element for Interdisciplinary Research since this type of research so often begins and/or is maintained as team science. In addition, alternate review strategies for Interdisciplinary Research are being considered, since many interdisciplinary projects may not "fit" traditional review groups.

NATIONAL INSTITUTES OF HEALTH

Genes and Environment Initiative (GEI)

Determining Genetic and Environmental Roots of Common Diseases

Back to: GEI Home Page > Exposure Biology Program

GEI Home Page

Exposure Biology Program

Funding Opportunities

Funding Opportunity Contacts

Exposure Biology Program Coordination

Meetings and Workshops

Funding Opportunities

RFA-ES-06-011 – Environmental Sensors for Personal Exposure Assessment (U01)

Development of new technologies for measuring human contact exposure and internal dose to priority environmental chemical/biological agents (e.g., airborne particulates, reactive gases, microbial toxins, solvents, pesticides, and mold/microbi toxins) with temporal and spatial resolution.

RFA-ES-06-012 – Biological Response Indicators of Environmental Stress Centers (U54)

Development of Centers that integrate biological response indicators with the development of field deployable biosensors to tra exposures from point of contact to biological response.

RFA-ES-06-013 – Biological Response Indicators of Environmental Stress (U01)

Development of biological response indicators reflecting components of key physiologic and pathogenic processes, such as oxidative stress, immune response and inflammation, epigenetics, DNA damage and apoptosis, endocrine disruption, and defects in drug metabolizing enzymes.

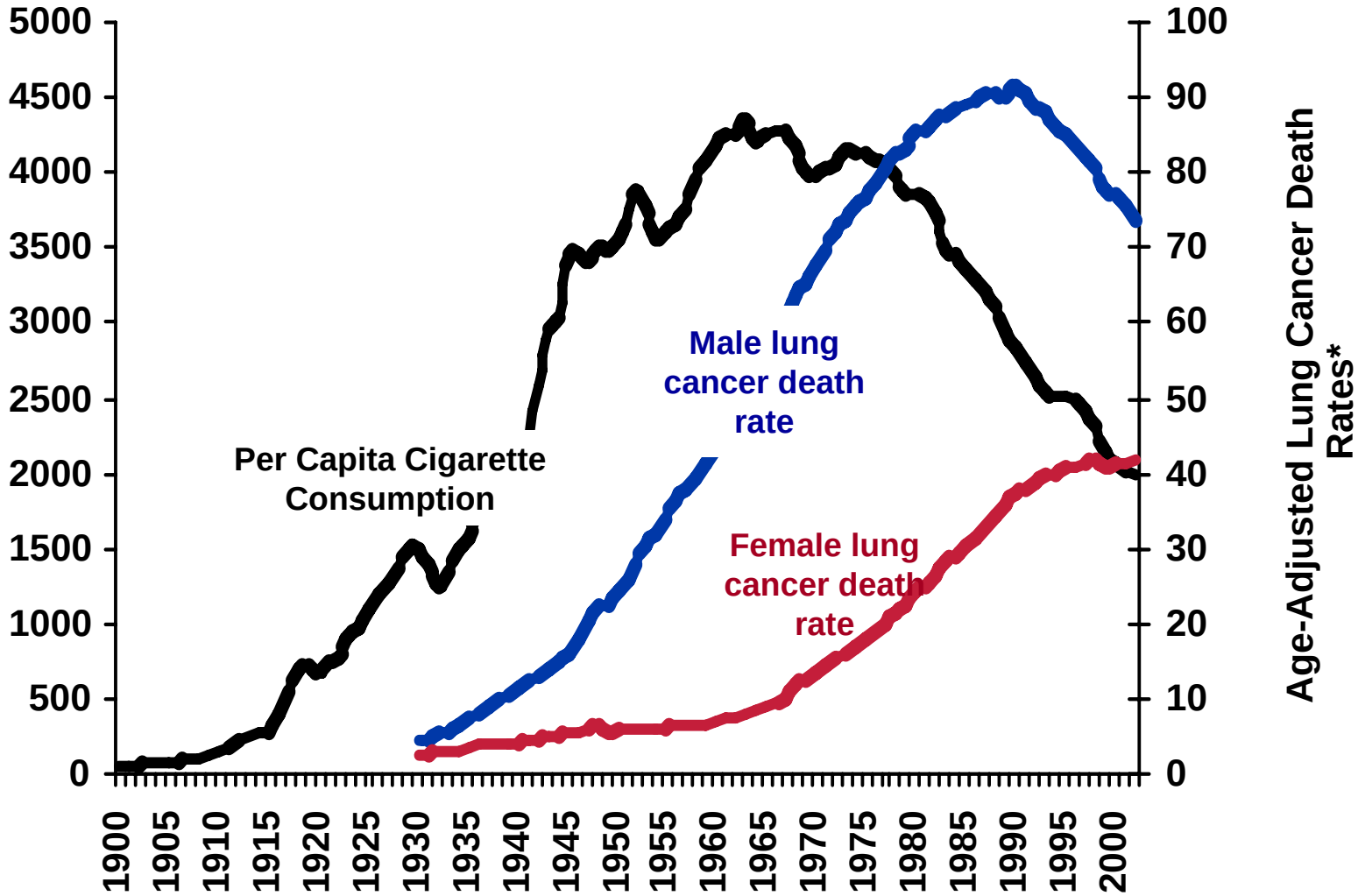
RFA-CA-07-032 – Improved Measures of Diet and Physical Activity for the Genes and Environment Initiative (GEI) (U01)

Development of new technologies for measuring dietary/supplement intake and measures of physical activity using hand-held sensors, scanners or other devices, personal digital assistants (PDAs), imaging detection software, or wireless technology, ar new technologies for measuring motion simultaneously with physiologic indicators of response (heart rate, respiration) with temporal and spatial resolution.

RFA-DA-07-005 – Field-Deployable Tools for Quantifying Exposures to Psychosocial Stress and to Addictive Substances for Studies of Health and Disease (U01)

Development of new technologies for measuring exposure to psychosocial stress and addictive substances usage including th use of hand-held devices for automated self-report and recall, innovative software, wireless technology, or other technology.

Tobacco Use & Lung Cancer. USA



*Age-adjusted to 2000 US standard population. Source: Death rates: US Mortality Public Use Tapes, 1960-2002, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2005. Cigarette consumption: US Department of Agriculture, 1900-2002.

Eight Americas: Investigating Mortality Disparities across Races, Counties, and Race-Counties in the United States.

C. J. L. Murray, et al., 2006. Eight Americas: Investigating Mortality Disparities across Races, Counties, and Race-Counties in the United States. PLoS Medicine: Sept. 2006. Volume 3, Issue 1513 9, e260 www.plosmedicine.org

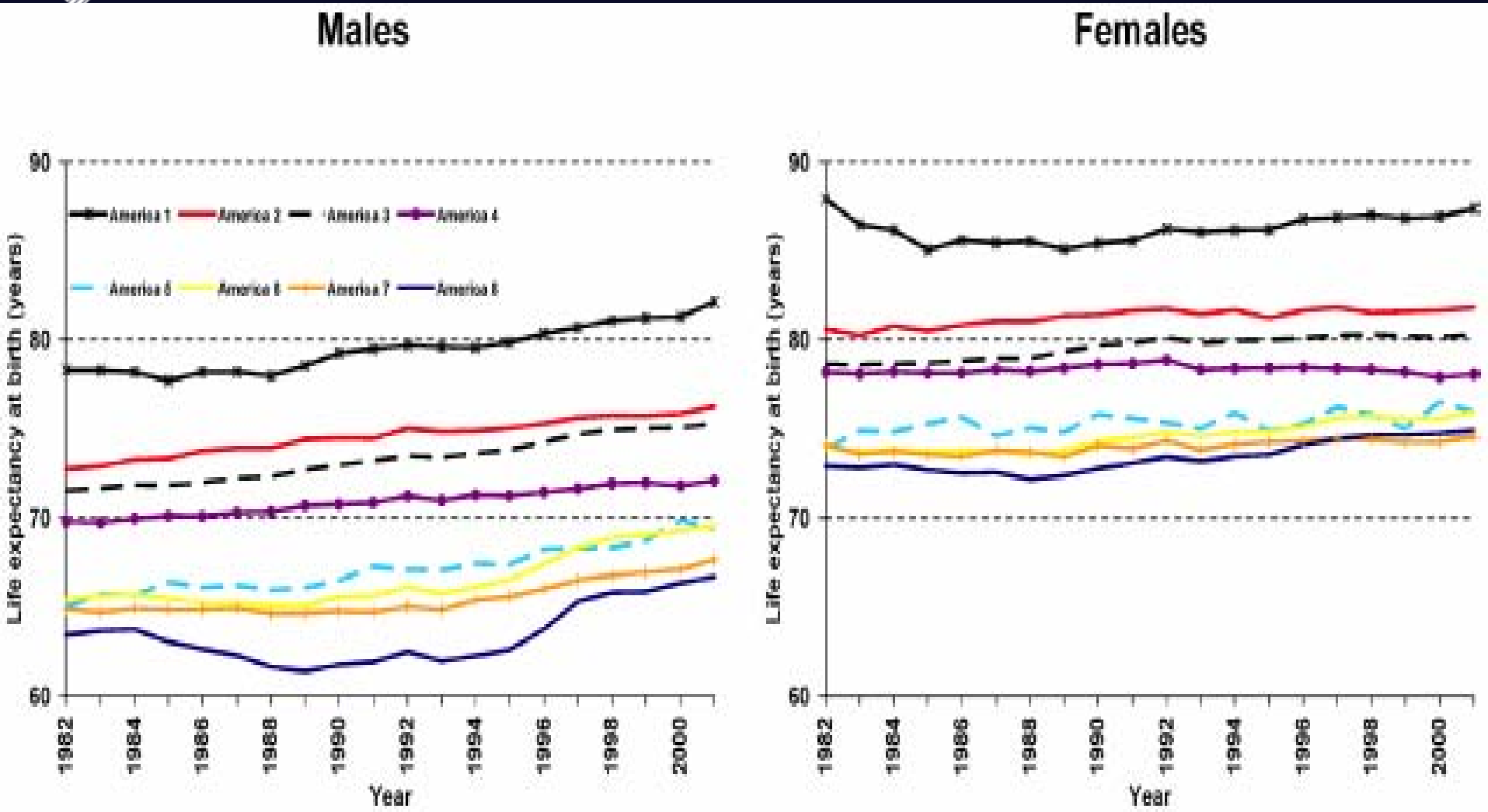


Figure 3. Life Expectancy at Birth in the Eight Americas (1982–2001)

Estimates for Americas 1 and 3 have been adjusted for differential underestimation of population and mortality among Asians (see Methods).

DOI: 10.1371/journal.pmed.0030260.g003

B

Males

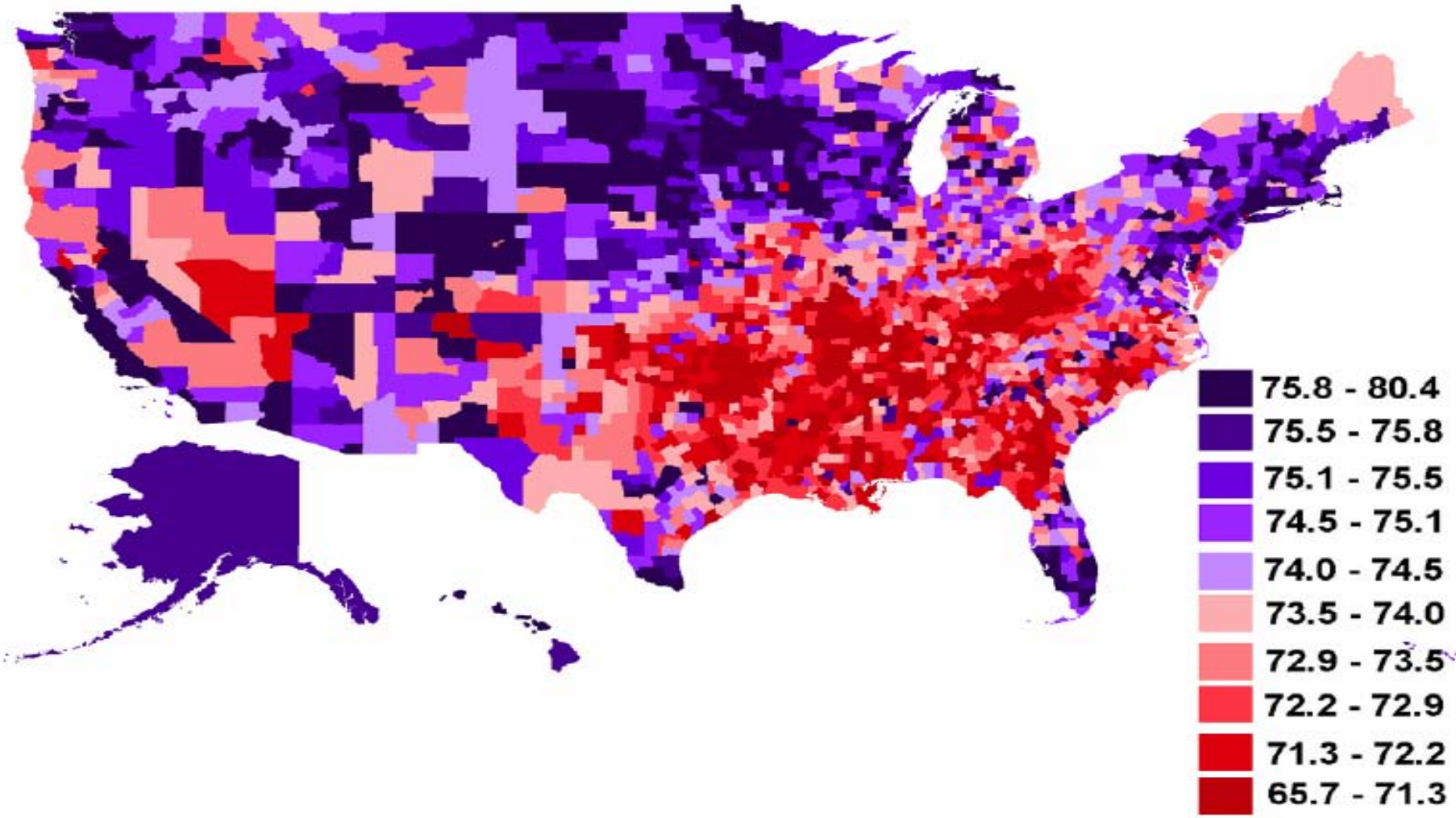


Figure 1. County Life Expectancies by Race

RESEARCH NEEDS

Identify candidate genes for G × E hypotheses

- Find genes associated with variation in biological or psychological reactivity to environmental pathogens

Identify candidate environmental risk factors for G × E hypotheses

- Uncover new risk factors and better characterize known risk factors
- New, better, and cheaper normed and standardized methods for precise, accurate measurement of environmental exposure
- Evaluate whether risk factor is a true pathogen having environmentally mediated causal effects on disorder
- Uncover which brain systems influenced by environment, and how

Frame and test biologically plausible G × E hypotheses

- Longitudinal cohort studies when possible
- Collect DNA from individuals in existing longitudinal cohort studies with well-characterized environmental histories

Moffitt, Caspi, Rutter (2006) *Perspectives on Psychological Science,* 1(1): 5-27

RESEARCH NEEDS

Attempt linkage pedigree studies, association studies, and genomic scans

Unrecognized G × E may undermine efficiency of conventional measured-gene designs, and could account for nonrobust status of many findings

Above mentioned studies could enhance performance by importing environmental data, perhaps to reveal larger-than-expected effects of genes or even to uncover new genes conveying susceptibility to disorders

Integrate G × E processes with other forms of gene-environment interplay

Research must integrate gene-environment correlation, heritability-environment interaction, and epigenetic programming to achieve a fuller understanding

Moffitt, Caspi, Rutter (2006) *Perspectives on Psychological Science,* 1(1): 5-27

POTENTIAL IMPLICATIONS OF MEASURED G × E EFFECTS

Environmental Researchers and Interventionists

Because it is difficult to alter genes in humans, the outcome of G × E research that is most likely to be relevant for application is new information about which environmental risks to modify (Guttmacher & Collins, 2003)

Refine understanding of heterogeneity in responses to environmental pathogens

Allow greater precision, less error in studies of environmental risk processes

Categorize genetic heterogeneity in response to environmental interventions, to facilitate individualized treatments for disorders

Scarce public-health resources could be directed toward population segments most vulnerable to environmental pathogens

Moffitt, Caspi, Rutter (2006) *Perspectives on Psychological Science,* 1(1): 5-27

Conclusions

- Behavior is the bridge between biology and society
- The vision of OBSSR is to mobilize the biomedical, behavioral, social science, and population science research communities as partners to solve the most pressing health challenges faced by our society.