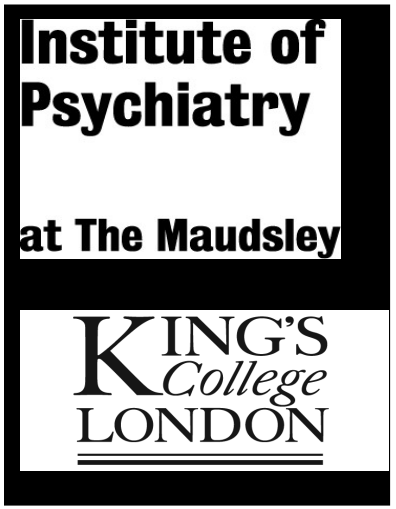
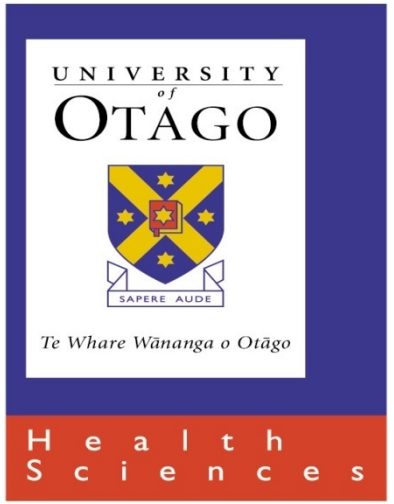
In honour of Prof. Dr. Klaus Grawe
(1943 – 2005)

Gene x Environment Interactions in Mental Health

Terrie Moffitt
Universitat Zurich, May 2009



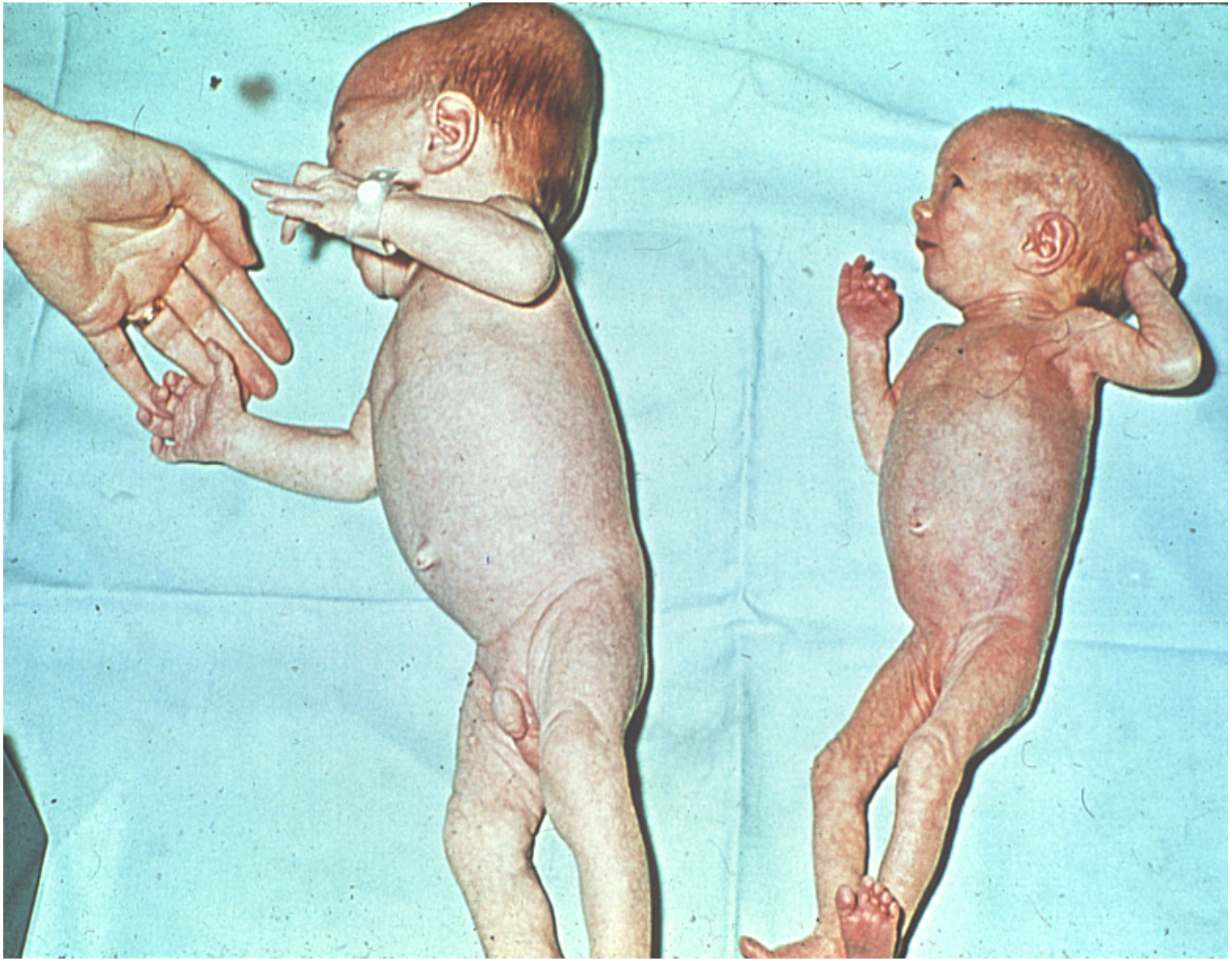


Definition

- A gene-environment interaction (*denoted as GxE*) occurs when the effect of exposure to an environmental pathogen on health is conditional upon a person's genotype (or conversely, when environmental experience moderates genes' effects on health)

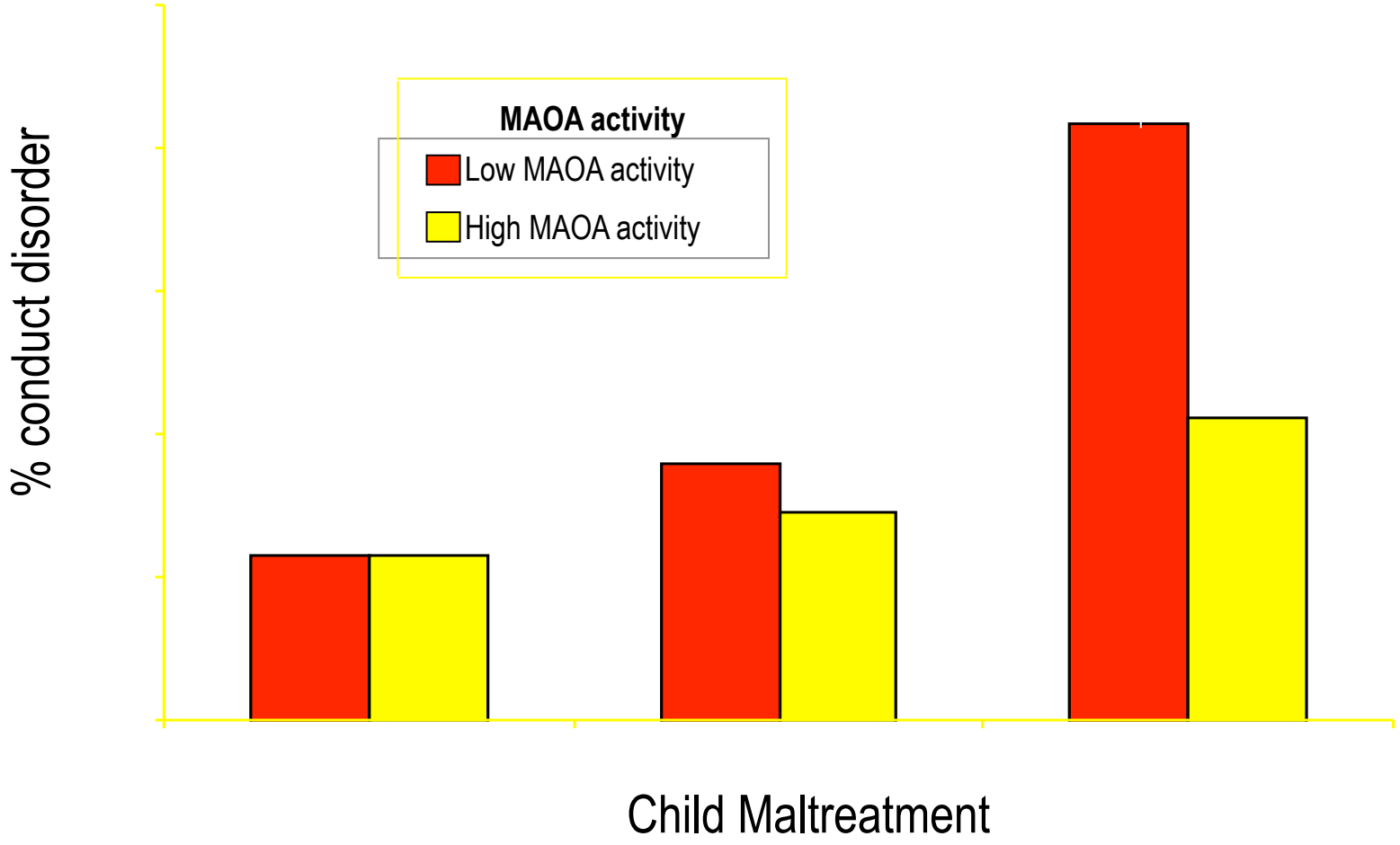
Outline

- Emerging evidence of GxE in psychiatric conditions and psychological phenotypes
- A program of research into GxE: Strategic steps
- Implications and future directions for research about GxE



Age 32 years
2005
96% participation

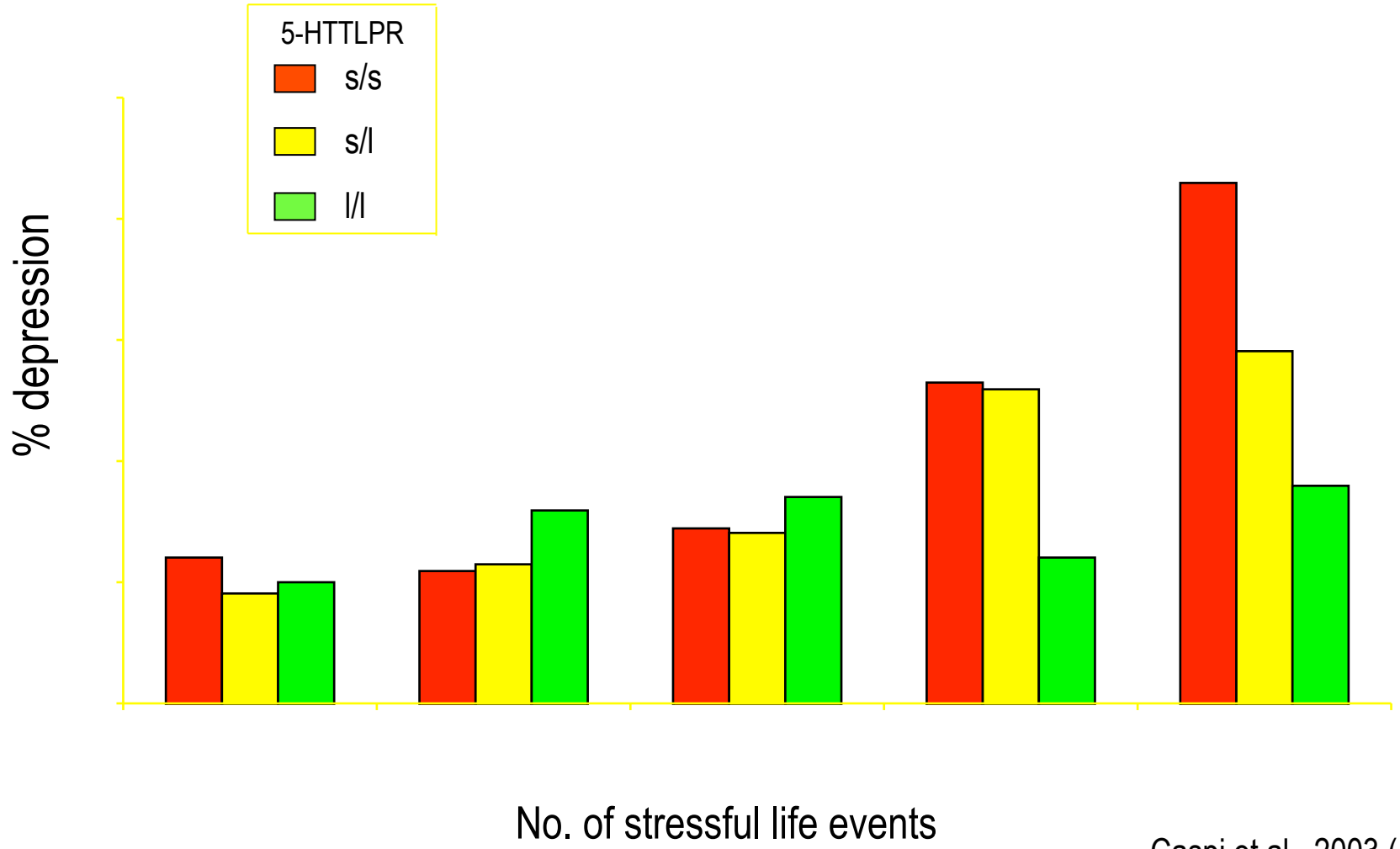
Male conduct disorder:
Child maltreatment interacts with genotype (*MAOA*)



Caspi et al., 2002 (*Science*)

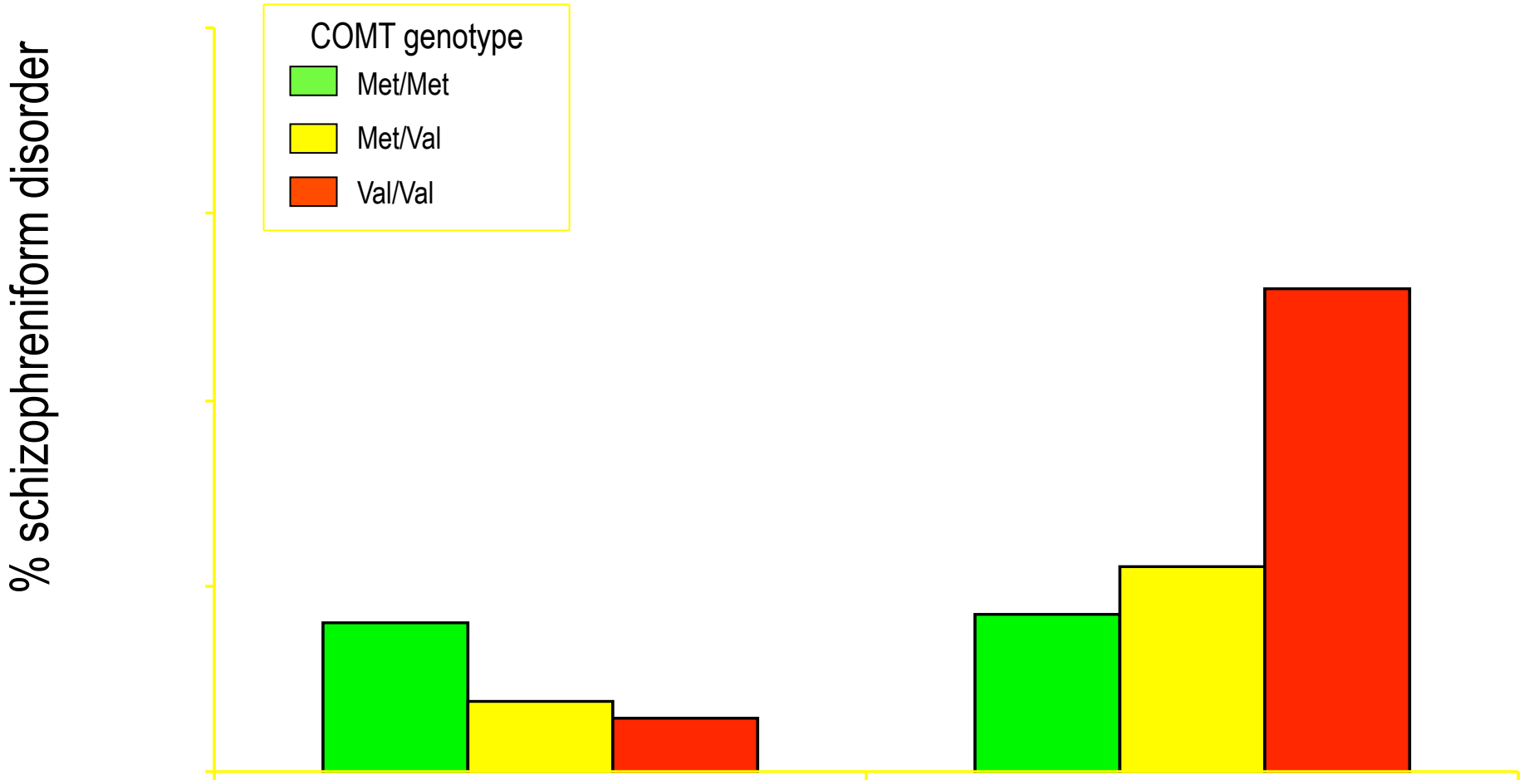
Adult depression:

Life stress interacts with genotype (*5-HTT*)



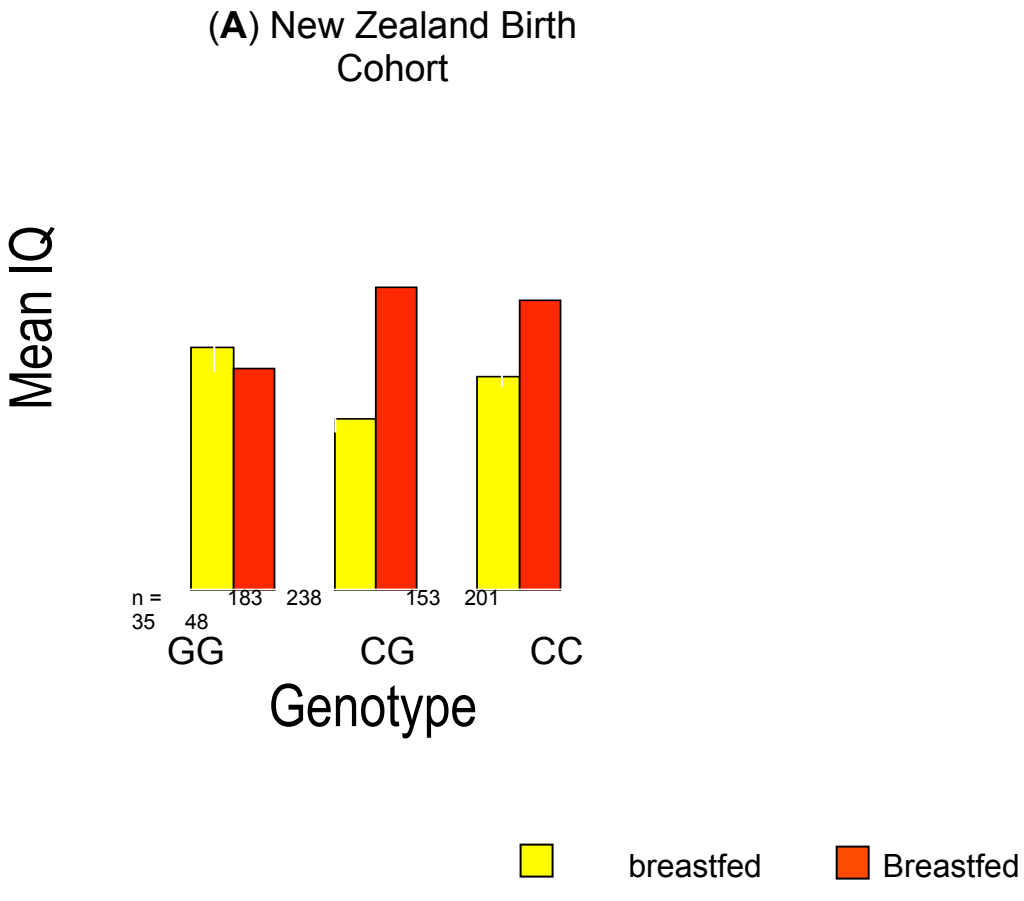
Caspi et al., 2003 (*Science*)

Schizophrenia spectrum disorder: Cannabis use interacts with genotype (*COMT*)



Caspi et al. 2005 (*Biol. Psychiatry*)

The IQ:
Breastfeeding interacts with genotype (*FADS2* rs174575)



Caspi et al., 2007 (PNAS)

The IQ:
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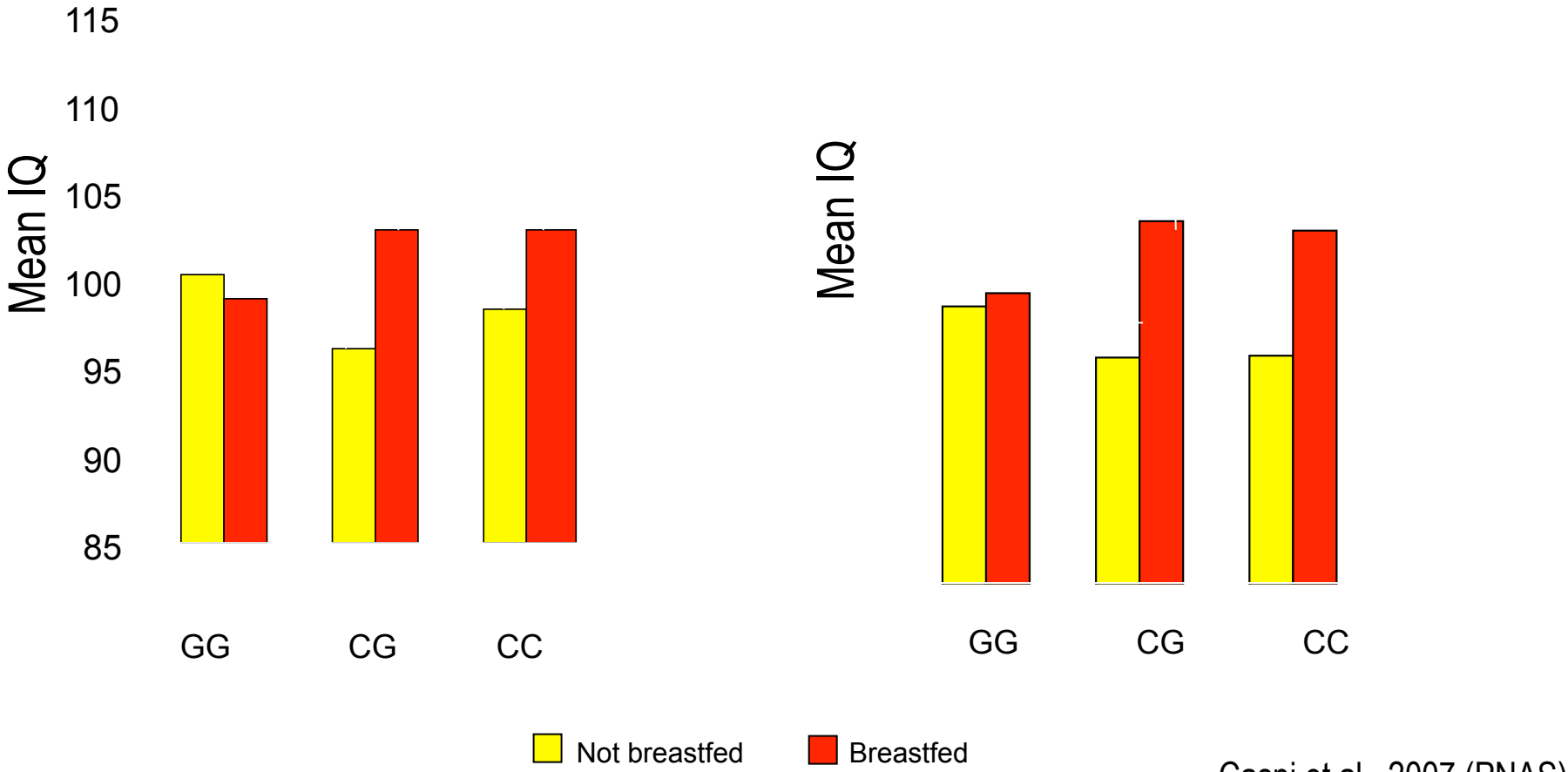
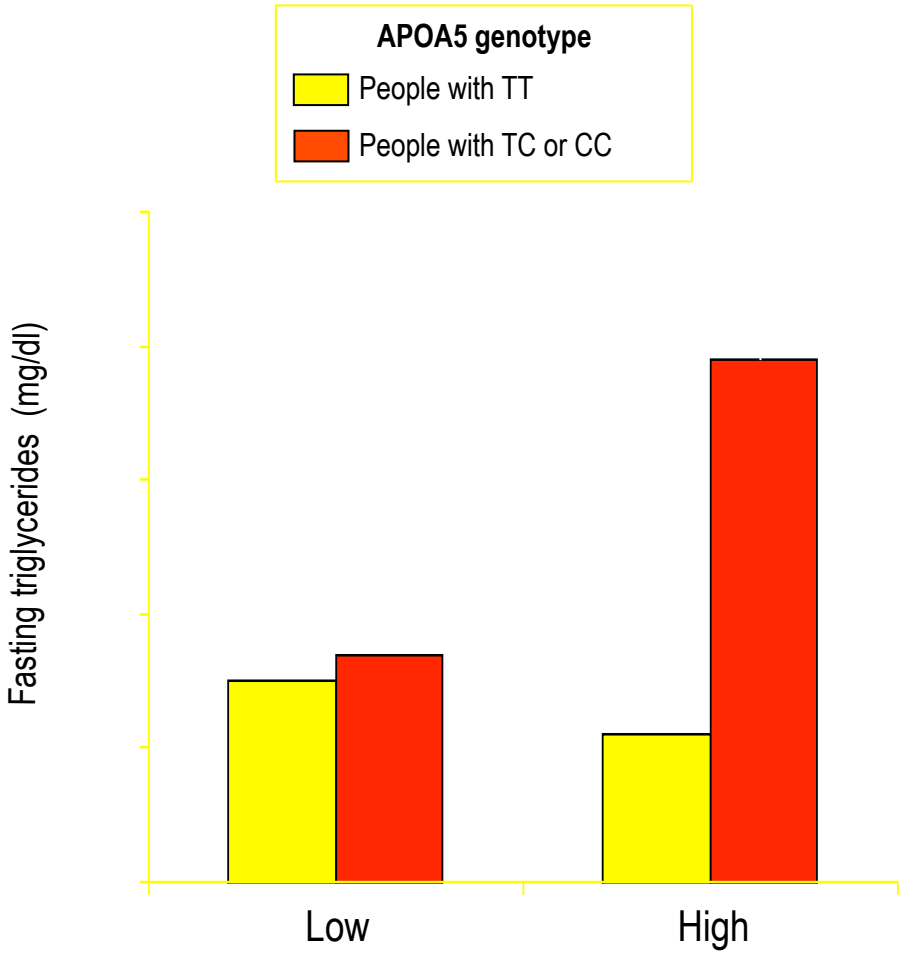
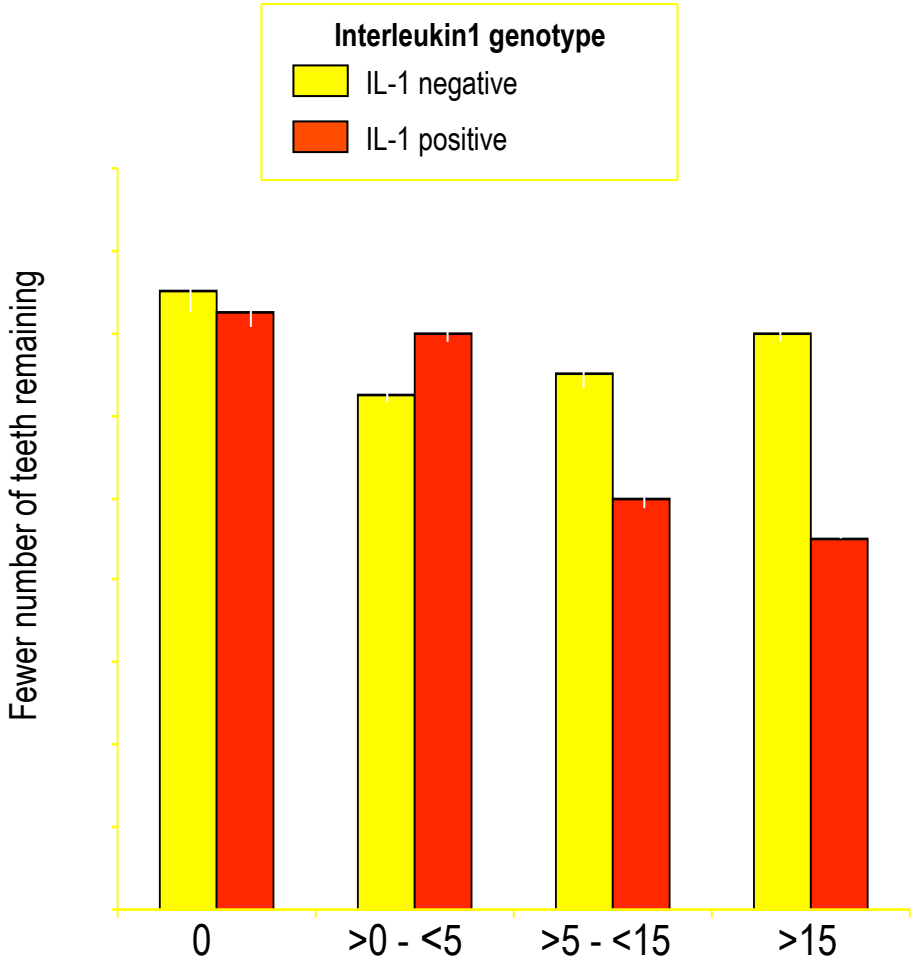


Caspi et al., 2007 (PNAS)

GxE in other branches of medicine: Heart disease to dentistry



Ordovas et al., 2006 (*Circulation*)



Meisel et al., 2004 (*J. Periodontol.*)

The future?

"The identification of GxE interactions will be one of the most important future goals of genetic epidemiology"

Merikangas & Risch, 2003 (*Am. J. Psychiatry*)

"GxE interactions are likely to remain a conceptual framework for health research rather than a practical goal for the foreseeable future"

Cooper, 2003 (*Ann. Med*.)

Outline

- Emerging evidence of GxE in psychiatric conditions and psychological phenotypes
- A program of research into GxE: Strategic steps
- Implications and future directions for research about GxE

Strategic steps for research into measured GxE

Step 1: Identifying and measuring the candidate environmental pathogen

Step 2: Identifying the candidate gene

Step 3: Testing for an interaction

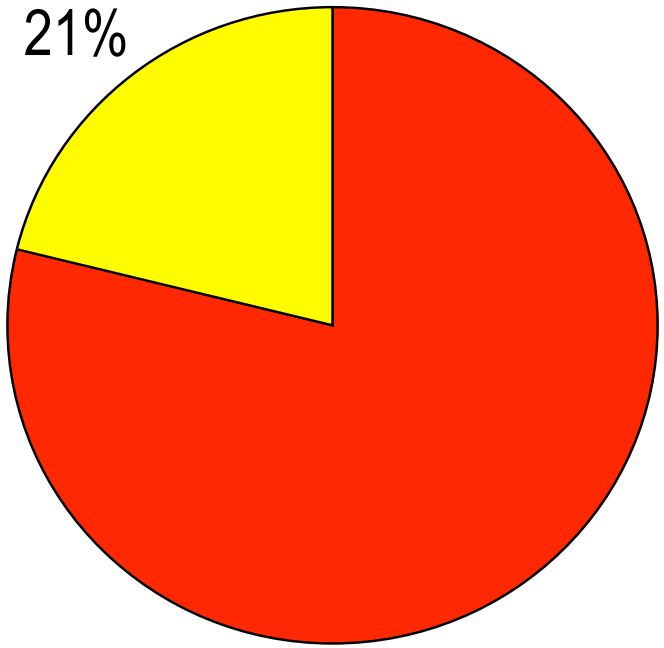
Step 4: Replication and beyond

Moffitt et al. 2005 (*Arch Gen Psychiatry*);
Moffitt et al. 2006 (*Perspectives on Psych Science*)

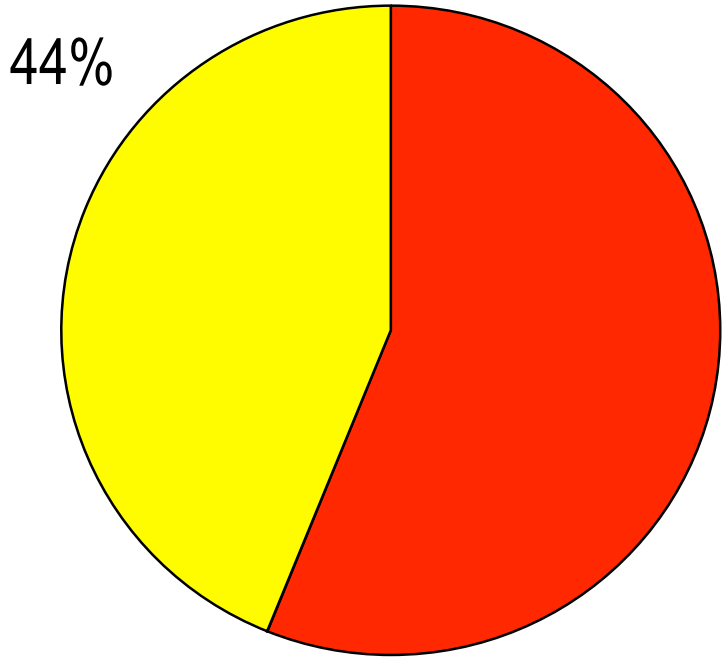
Selecting & measuring candidate environmental risks for GxE hypotheses

- Marked variability in response among people exposed to the environmental risk
- Evidence that the putative risk is environmental
- Developmental focus
- Optimizing reliable measurement

Variability in response to an e-risk



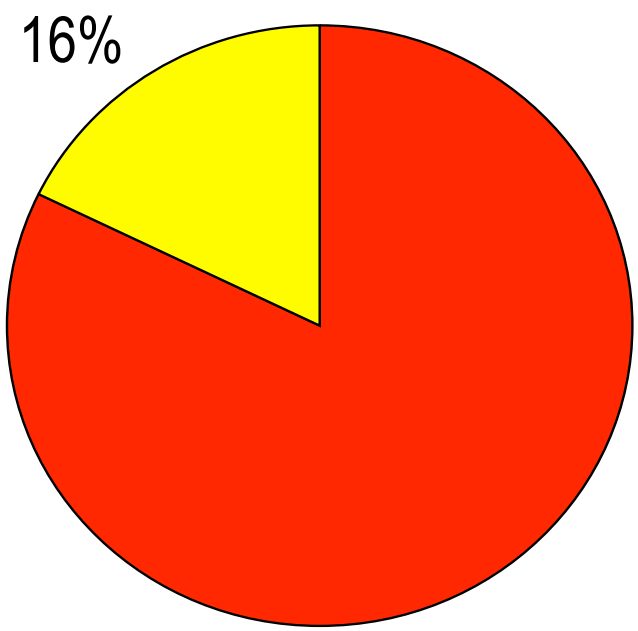
Cohort rate of
Conduct Disorder



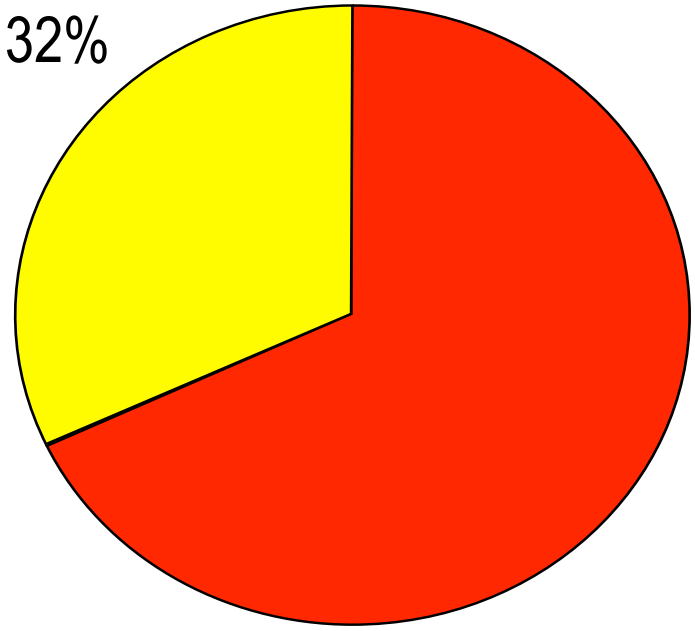
CD in maltreated cohort
members

Source: Dunedin Longitudinal Study

Variability in response to an e-risk



Cohort rate of depression



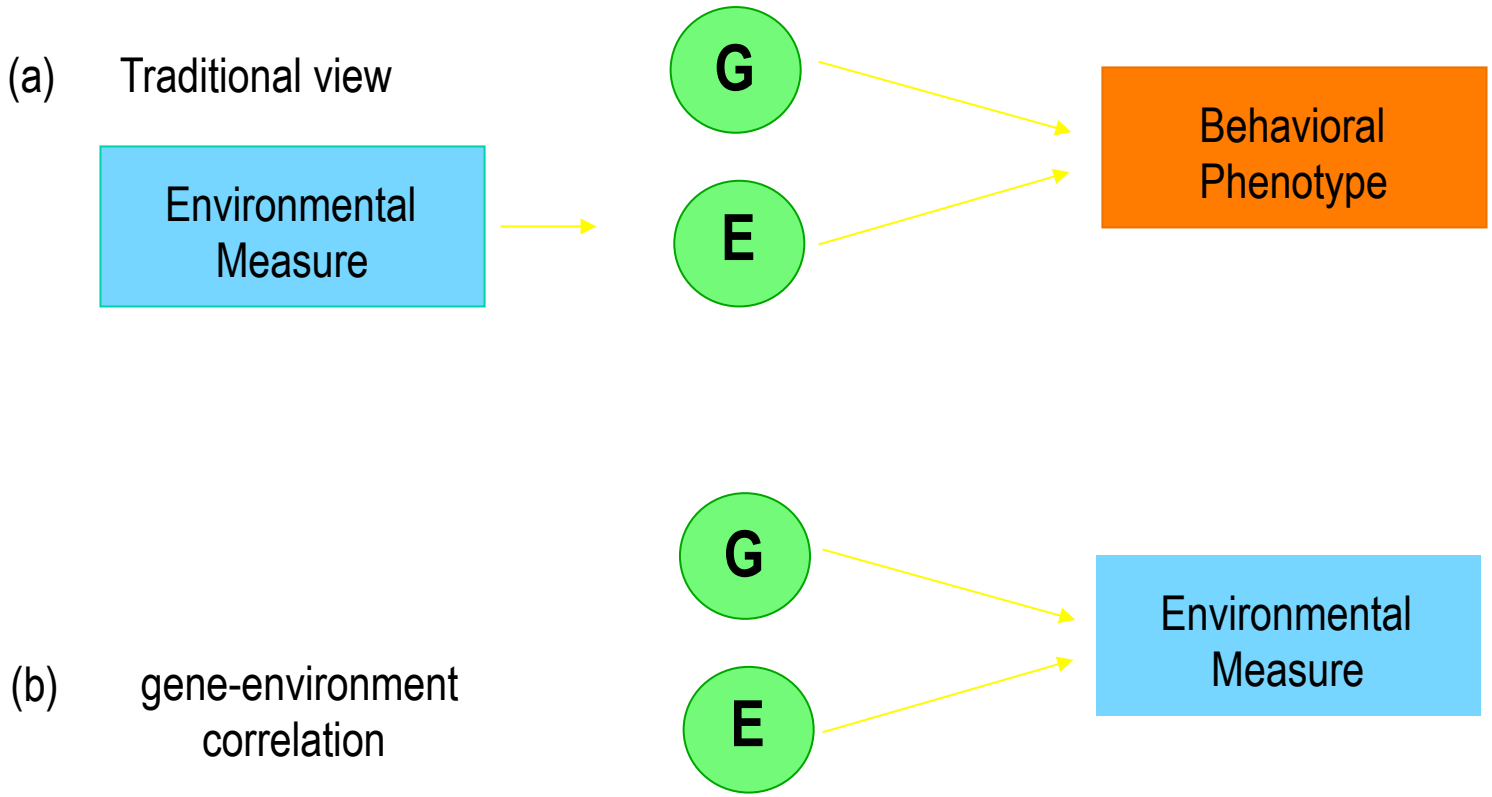
Depression in cohort members with stressful life events

Source: Dunedin Longitudinal Study

Selecting & measuring candidate environmental risks for GxE hypotheses

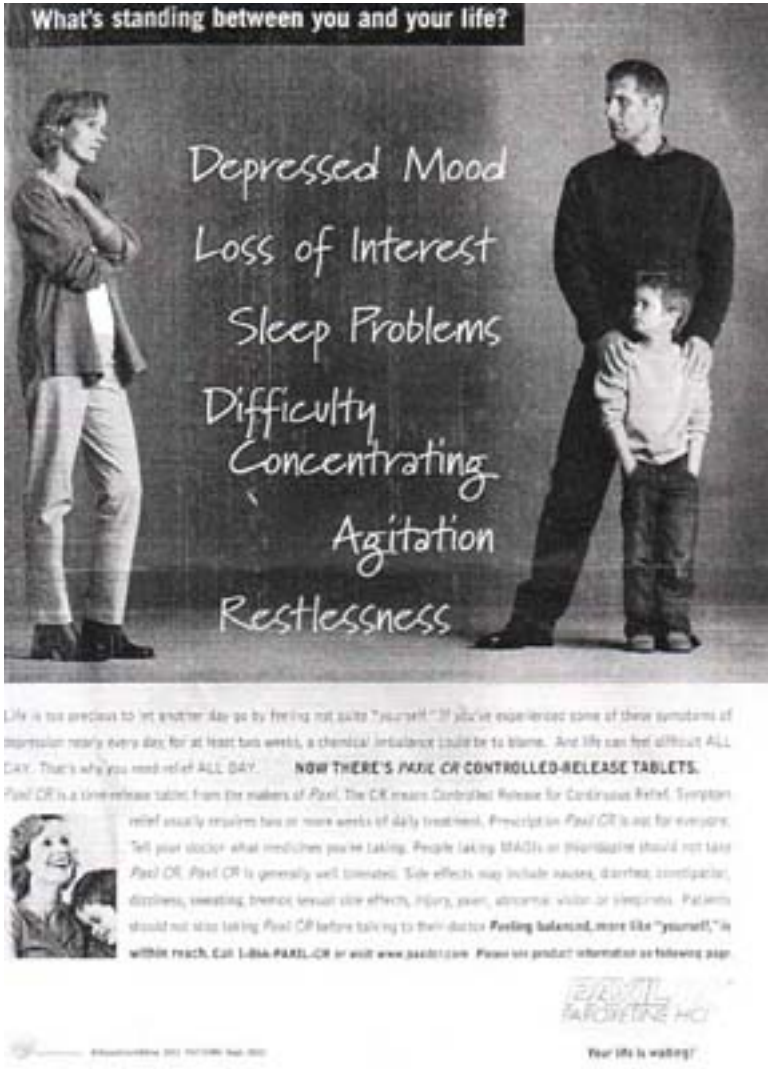
- Marked variability in response
- Evidence that the putative risk is a true environmental pathogen having non-genetic causal effects
- Developmental focus on age-specific risks
- Optimizing reliable measurement

Is the risk factor a true environmental cause?

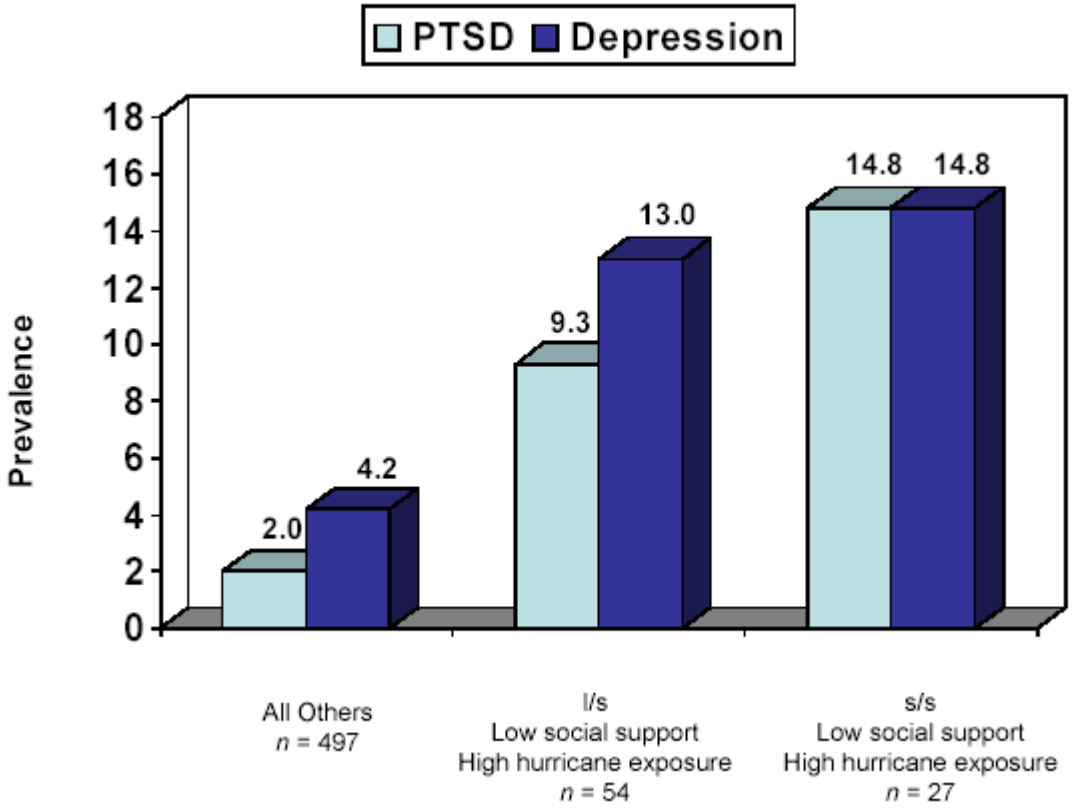


Plomin, 1994

A depressed patient's illness harms relationships and causes stressful life events



Exploiting Hurricane Exposure as Life Stress



Genotype Groups

Kilpatrick et al., 2007 (*Am J Psychiatry*)

Methodologies to establish that the putative risk is a true environmental pathogen having causal effects

- Experiments of nature
  - *Rule out gene-environment correlations because people are randomly exposed to an environmental risk*
- Within-individual change
  - *Rule out gene-environment correlation by using subjects as own control*
- Randomized treatment trials
  - *Rule out gene-environment correlations by random assignment*
- Twin & adoption designs
  - *Rule out gene-environment correlations with genetic controls*

Rutter et al., 2001 (*Psychol. Bull.*)

The environmental Cycle of Violence

Abused Child

Violent and Antisocial Adult

Violent and Antisocial Parent

Abusive Parent

Cycle of Violence, considering gene-environment correlation

Abused Child
With antisocial-prone genotype

Violent and Antisocial Adult with antisocial-prone genotype

Violent and Antisocial Parent
With antisocial-prone genotype

Abusive Parent
With antisocial-prone genotype

The Environmental Risk (E-Risk) Longitudinal Twin Study

- 1,116 families with twins
- Nationally representative UK cohort born in 1994-95
- Studied at ages 5, 7, 10, 12 years
- Assessed maltreatment separately for each twin

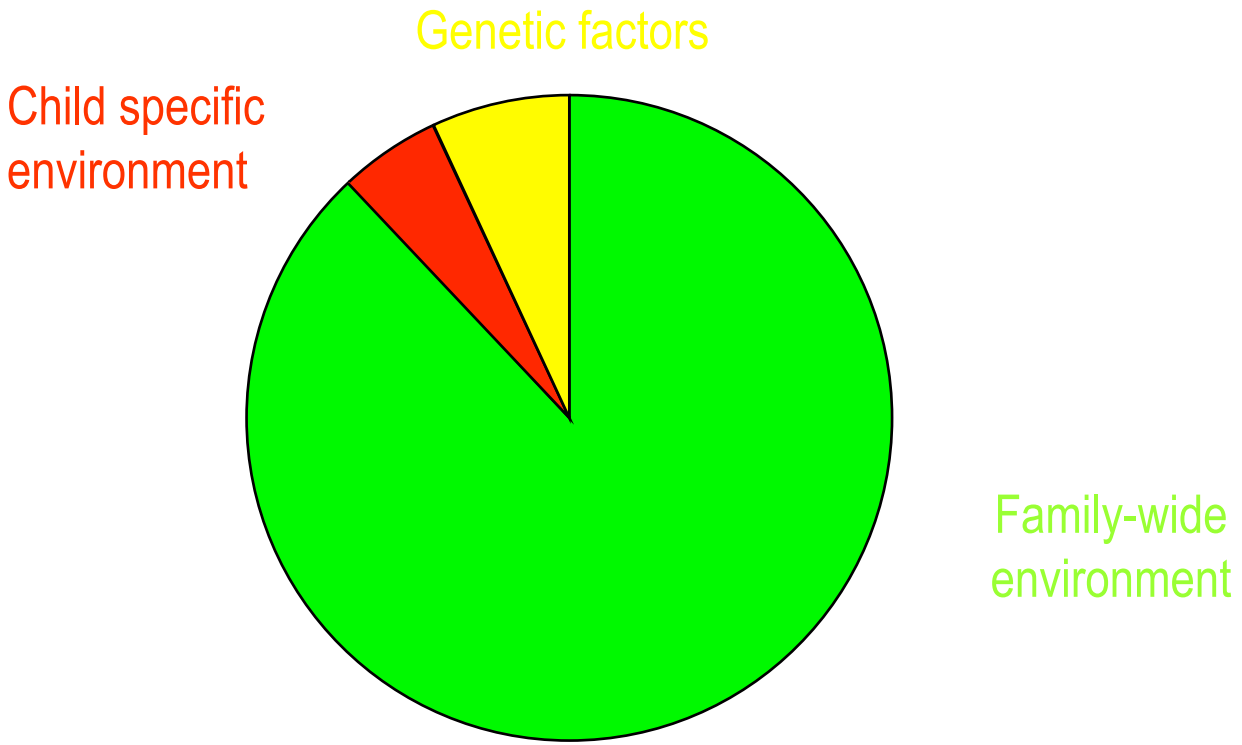
Moffitt et al., 2002 (*J Child Psychol Psychiatry*)

Evidence for environmental mediation of maltreatment from the UK E-risk Study

- Controlling for the child's prior level of conduct problems, a maltreatment experience was followed by an increase in new conduct problems
- Maltreatment predicted conduct problems significantly, after controlling for both parents' antisocial behaviour
- A child's risk of maltreatment was not influenced by the child's genetic characteristics

Jaffee et al., 2004 (*J. Abnorm. Psychol*.)

Children's genetic characteristics did not influence their exposure to maltreatment

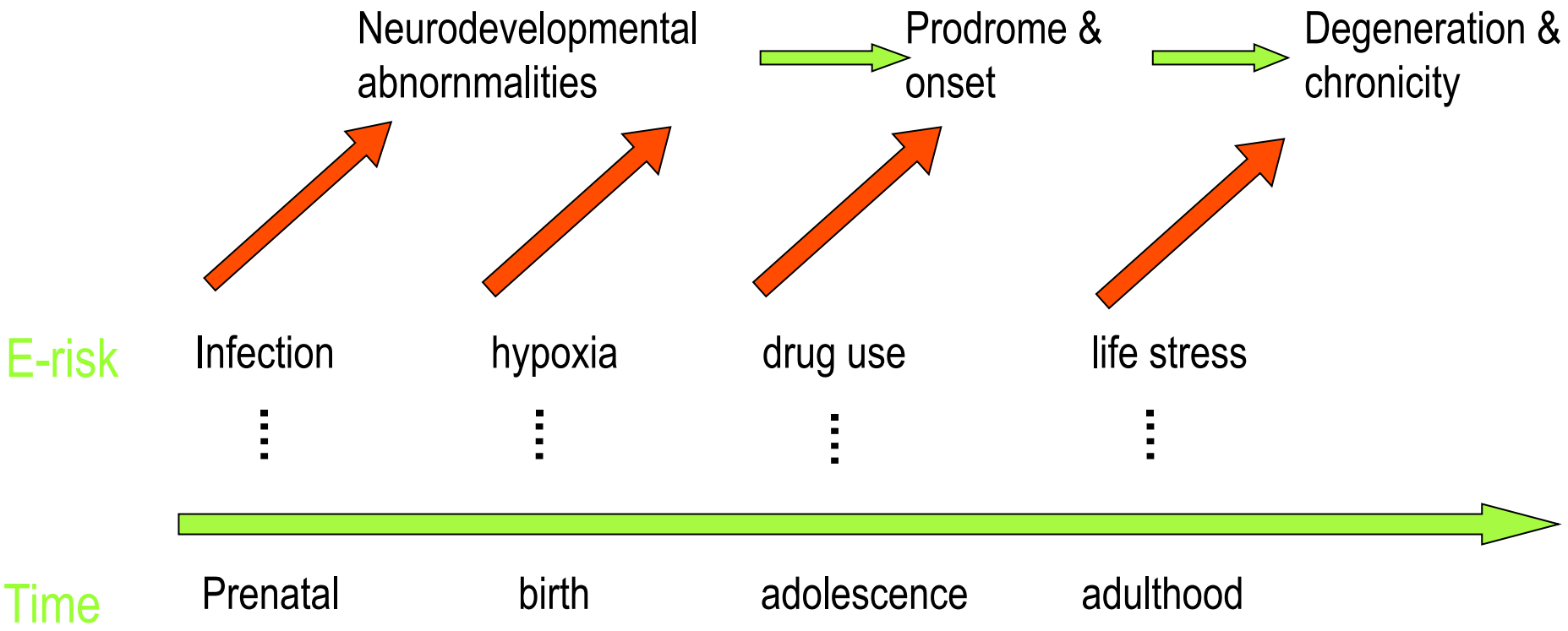


Jaffee et al., 2004 (*J. Abnorm. Psychol.*)

Selecting & measuring candidate environmental risks for GxE hypotheses

- Marked variability in response
- Evidence that the putative risk is environmental
- Developmental focus on age-specific environmental risks
- Optimizing reliable measurement

Environmental contributions in schizophrenia

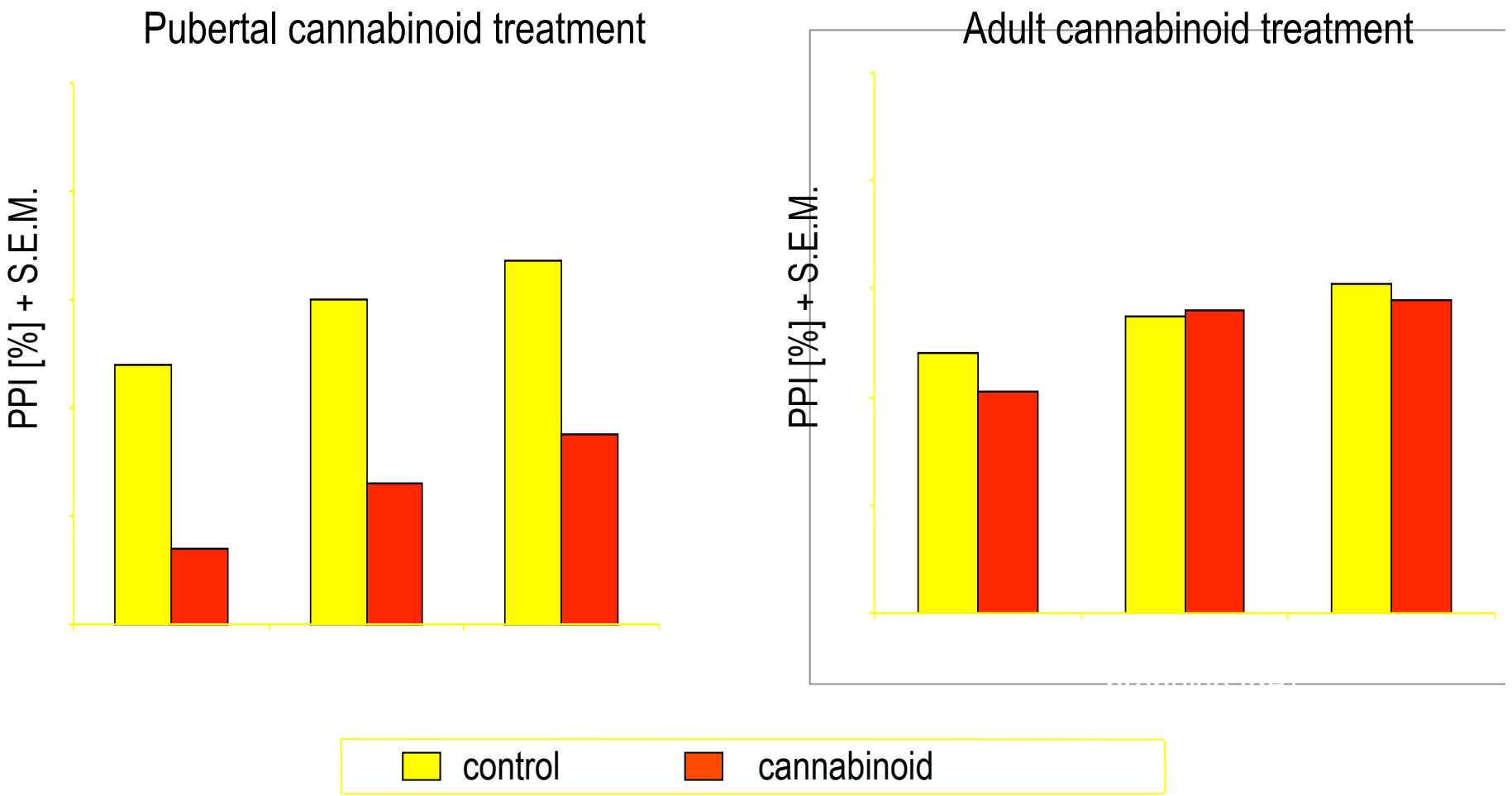


Adapted from Tsuang et al., 2001 (*Br. J.Psychiatry*)

Pubertal, but not adult, cannabis treatment

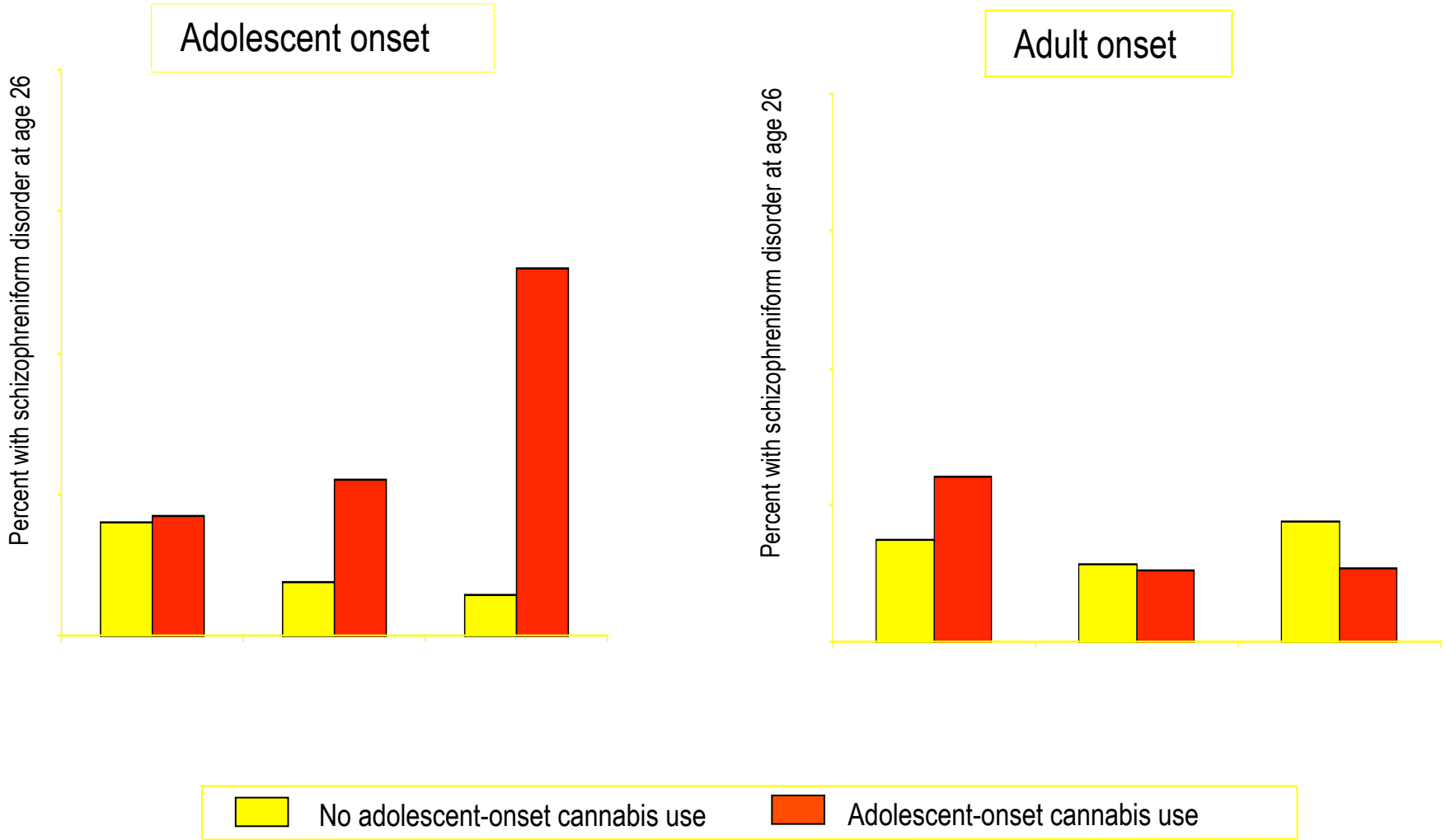
impairs cognition (e.g., startle, memory)

in rats



Schneider & Koch, 2003 (*Neuropsychopharmacology*)

Adolescent-, but not adult-onset, cannabis use is associated with adult psychosis in humans



Selecting & measuring candidate environmental risks for GxE hypotheses

- Marked variability in response
- Evidence that the putative risk is environmental
- Developmental focus on age-specific risks
- Optimizing reliable measurement of environmental risk

Sample size required to detect small GxE as a function of measurement reliability

		reliability of exposure		
		.4	.6	.8
reliability of outcome	.4	85,000	37,000	21,000
	.6	30,000	13,000	7,000
	.8	11,000	4,500	2,000

Wong et al., 2003 (*Int. J. Epid.*)

Strategic steps for research into measured GxE

Step 1: Identifying and measuring the candidate environmental pathogen

Step 2: Identifying candidate susceptibility genes

Step 3: Testing for an interaction

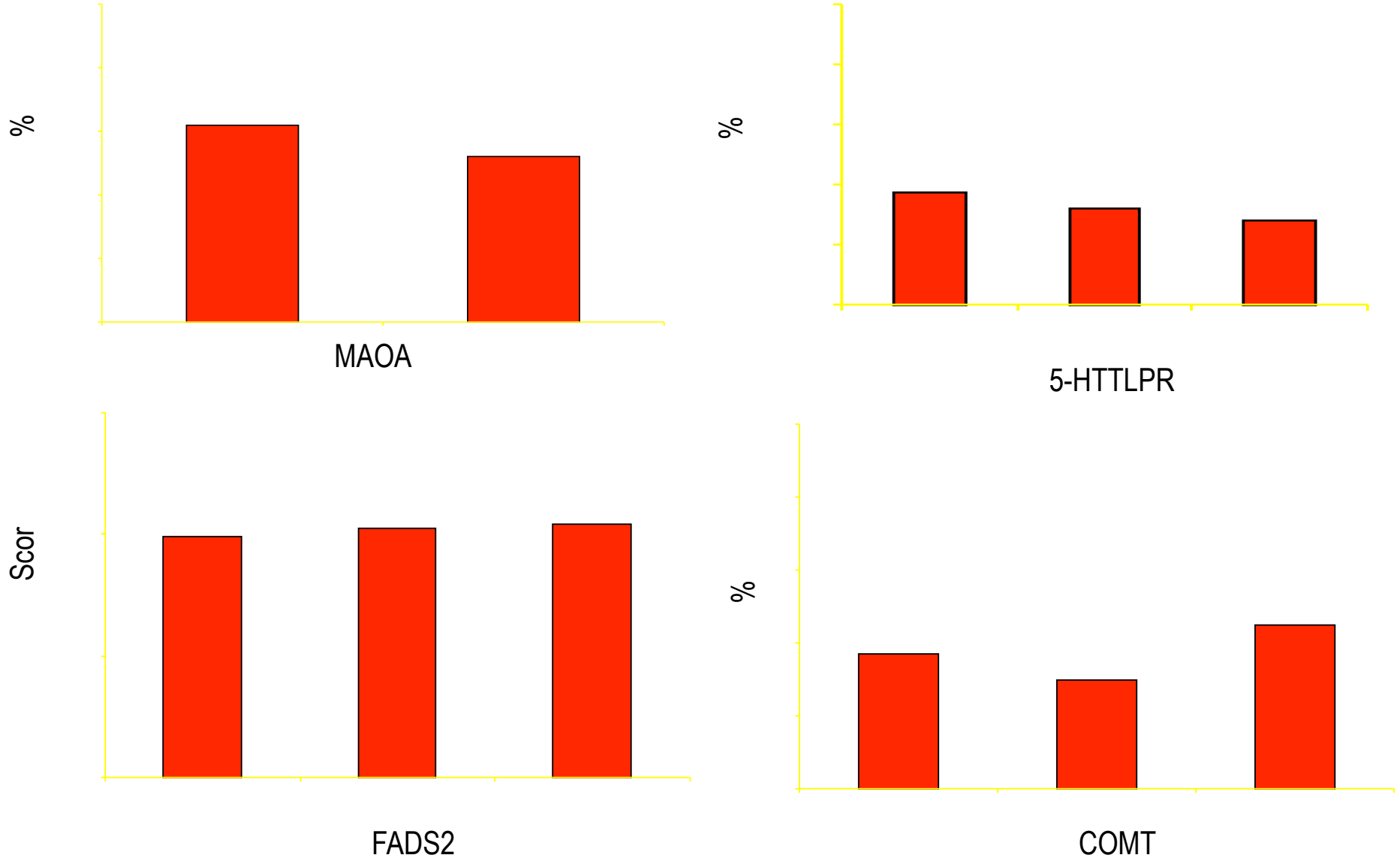
Step 4: Replication and beyond

Moffitt et al. 2005 (*Arch Gen Psychiatry*);
Moffitt et al. 2006 (*Perspectives on Psych Science*)

Choosing candidate genes for GxE hypotheses

- Evidence of direct gene-to-disorder association, from candidate-gene association studies or GWAS searches
- Use the plausible effect of the environmental risk pathogen on biological systems involved in the disorder to identify novel candidate genes

Nil gene-to-disorder associations concealing GxE



Choosing candidate genes for GxE hypotheses

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- Use the plausible effect of the environmental risk pathogen on biological systems involved in the disorder to identify novel candidate genes

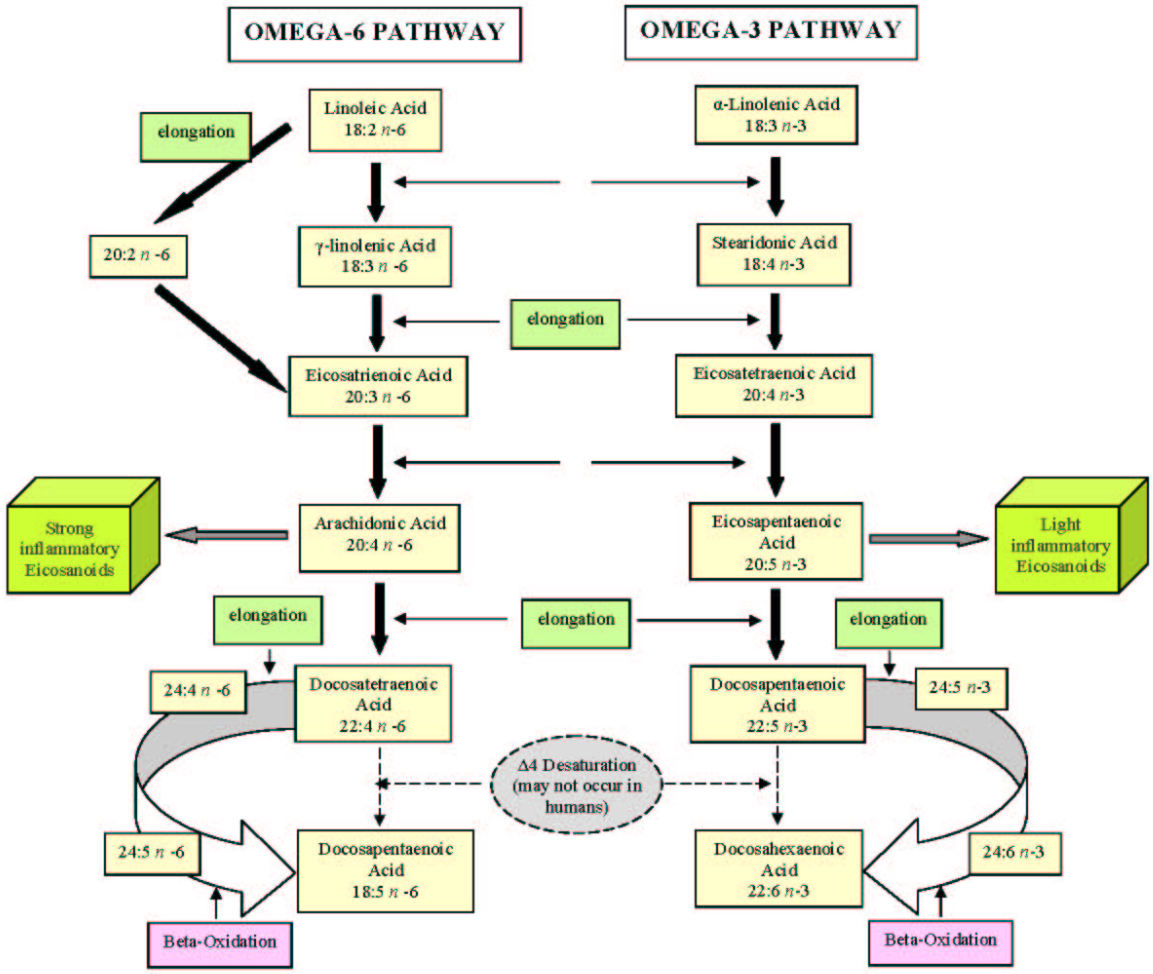
Normal healthy artery

Partially blocked artery

Blocked artery

Why select breastfeeding as an environmental exposure?
To help us identify novel candidate genes associated with IQ

Breastfeeding, fatty acids, and brain development



Choosing a candidate gene

Breast feeding Fatty Acid Ingestion **IQ**

Genes involved in metabolism of fatty acids

Genes regulated by fatty acids

Genes with known location

Known functional polymorphisms / Haplotypes?

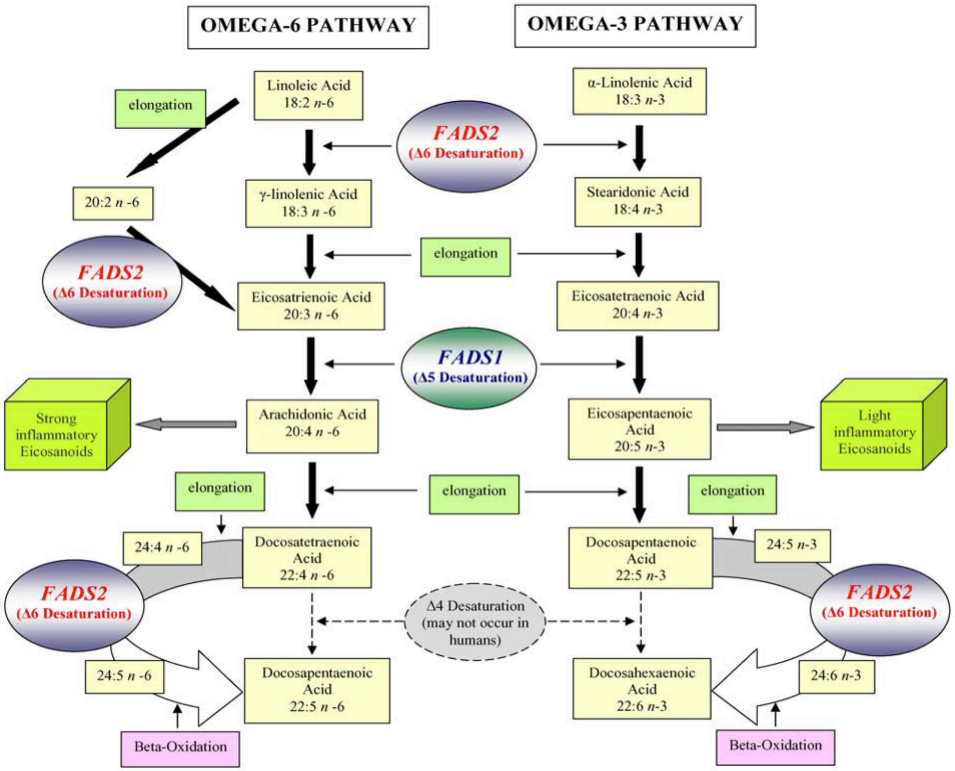
Yes

1) Is functional effect or association relevant to investigation?
2) Is the MAF sufficient for analysis?

No

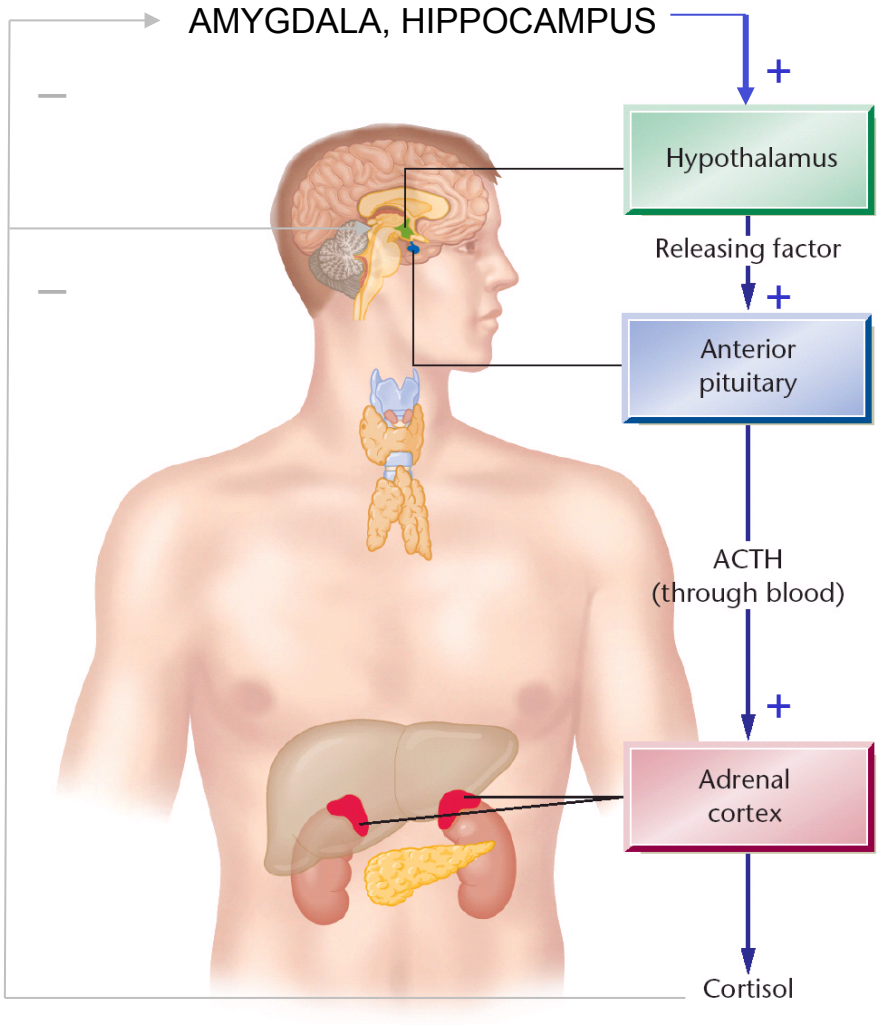
1) LD Markers HAPMAP
2) Nonsynonymous SNPs
3) VNTRs

Adding genes to the equation: Breastfeeding, fatty acids, and brain development



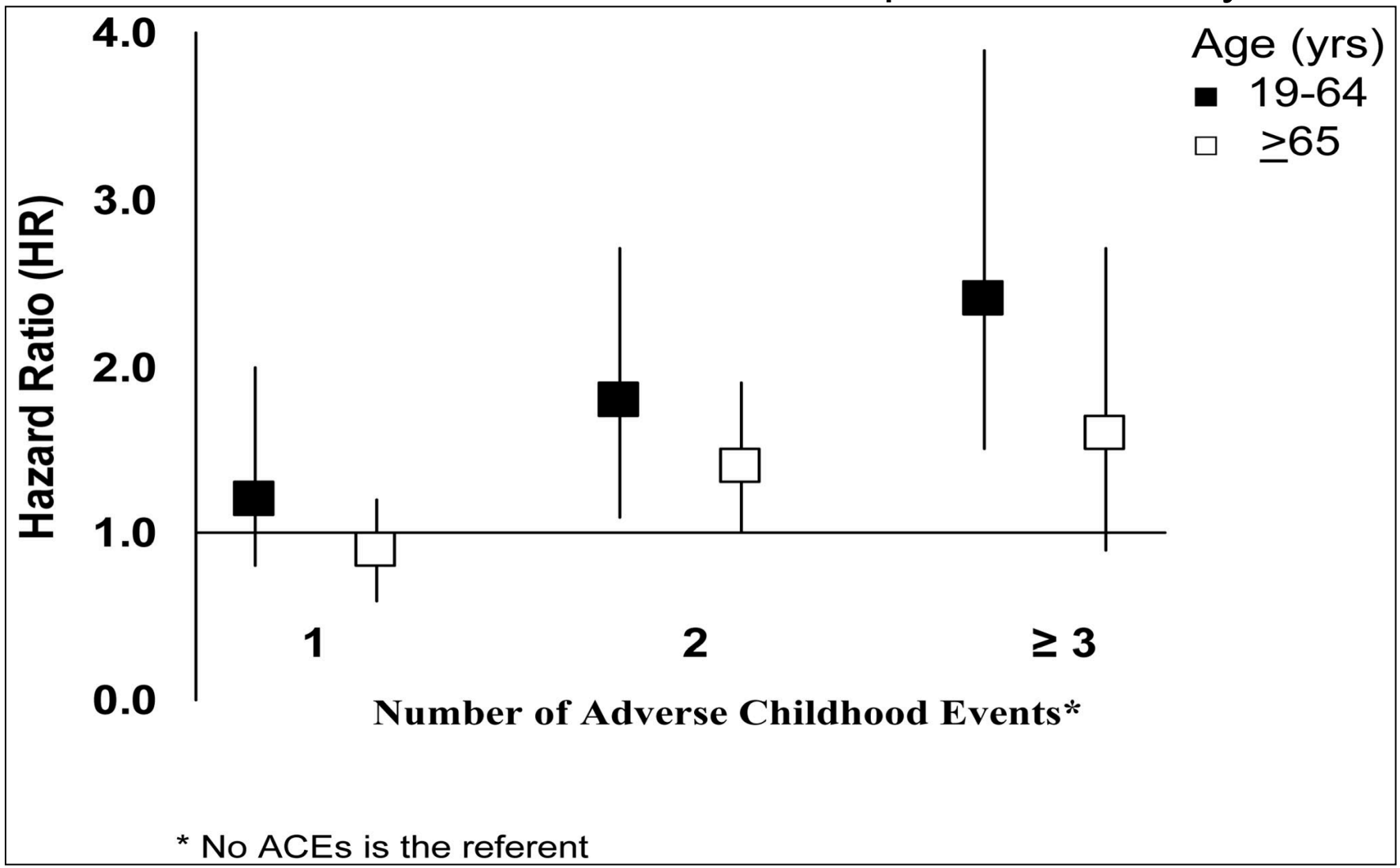
MALTREATMENT

AND THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS



Gunnar M (2007) *Annu Rev Psychol*

Adverse childhood stress events predict autoimmune diseases
From the Adverse Childhood Experiences Study.



Dube et al. 2009 (*Psychosomatic Medicine*)

Childhood Maltreatment

AGE 3-11 in Dunedin cohort

Maternal rejection (14%)

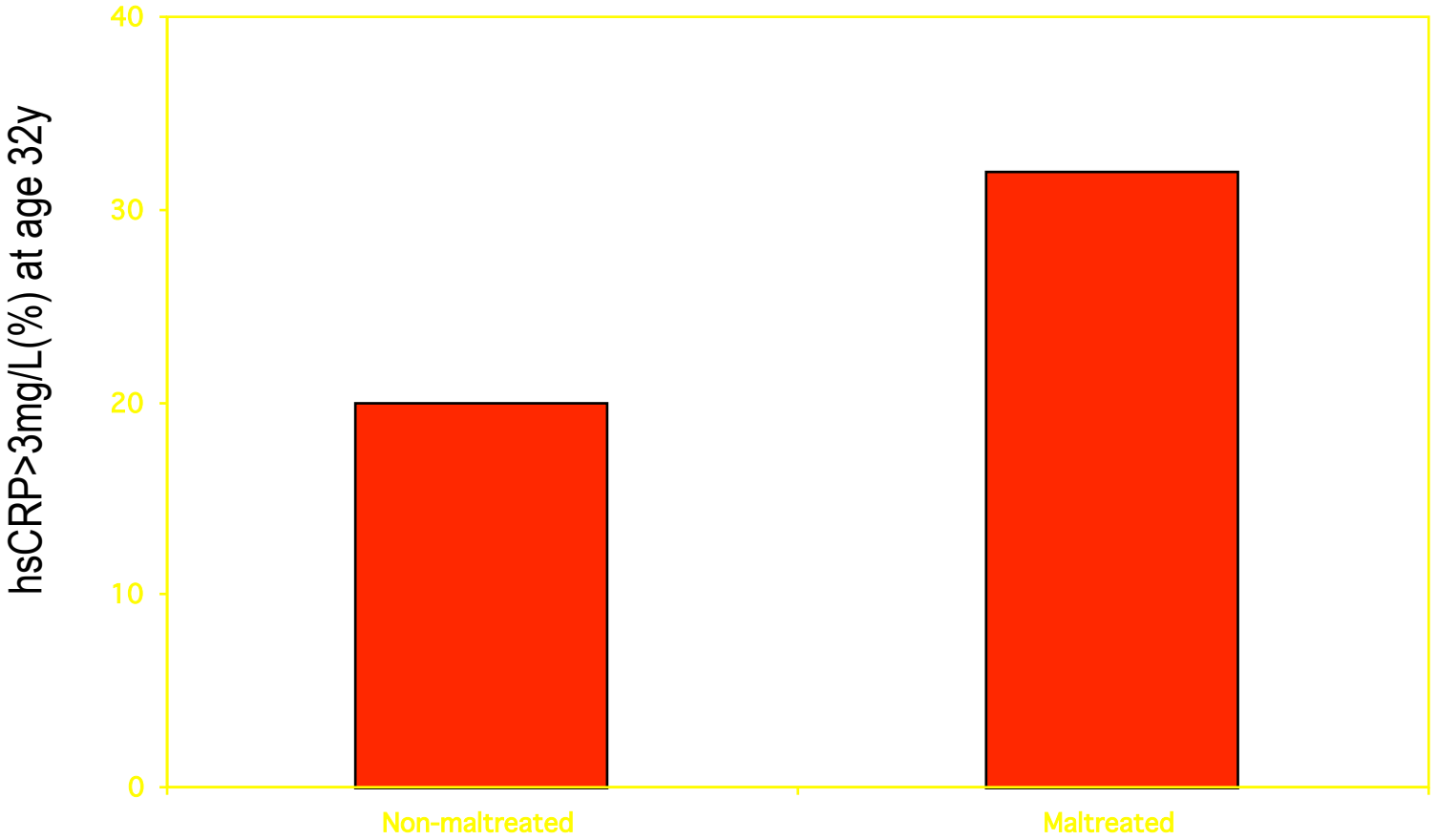
Harsh discipline (10%)

Caregiver changes (6%)

Physical abuse (4%)

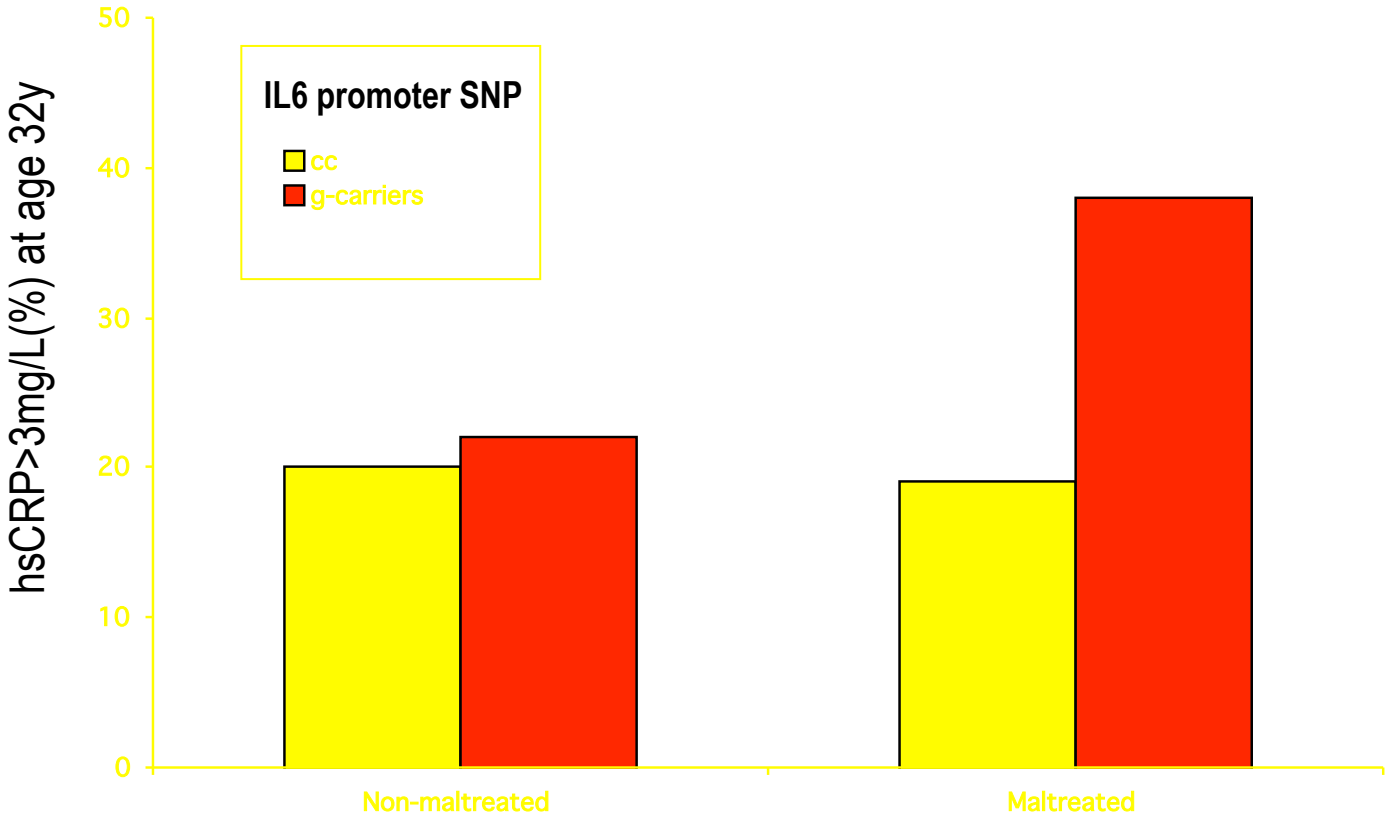
Sexual abuse (12%)

Childhood maltreatment predicts age-32 Inflammation: C-reactive protein



Danese, Caspi et al. (2007) PNAS

IL6 GENOTYPE x MALTREATMENT > ADULT INFLAMMATION: Gene x Environment interaction (in search of replication)



Danese et al. (in preparation)

Strategic steps for research into measured GxE

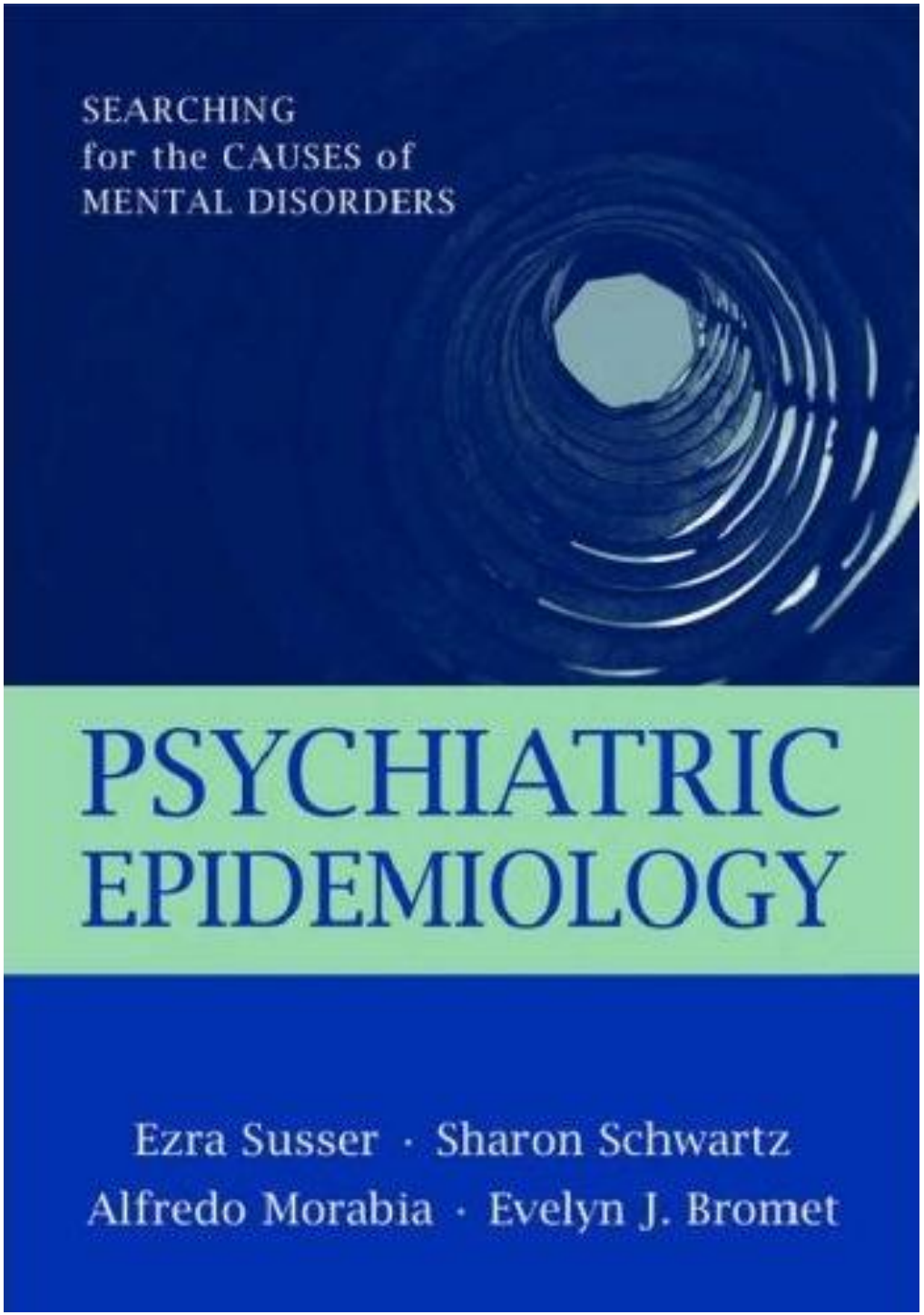
Step 1: Identifying and measuring the candidate environmental pathogen

Step 2: Identifying candidate susceptibility genes

Step 3: Testing for an interaction

Step 4: Replication and beyond

Moffitt et al. 2005 (*Arch Gen Psychiatry*);
Moffitt et al. 2006 (*Perspectives on Psych Science*)

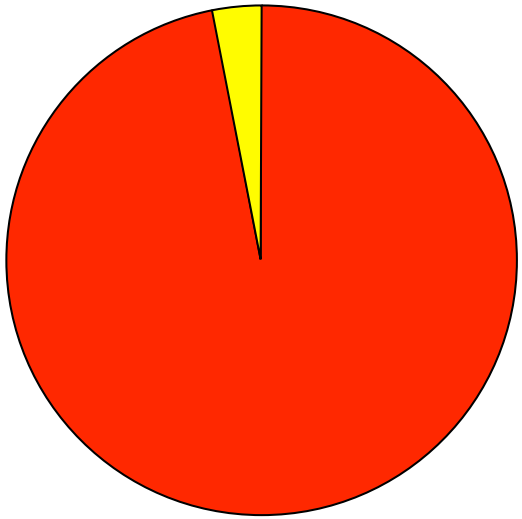

SEARCHING
for the CAUSES of
MENTAL DISORDERS
PSYCHIATRIC
EPIDEMIOLOGY
Ezra Susser · Sharon Schwartz
Alfredo Morabia · Evelyn J. Bromet

Genes, environment, and the value of prospective cohort studies

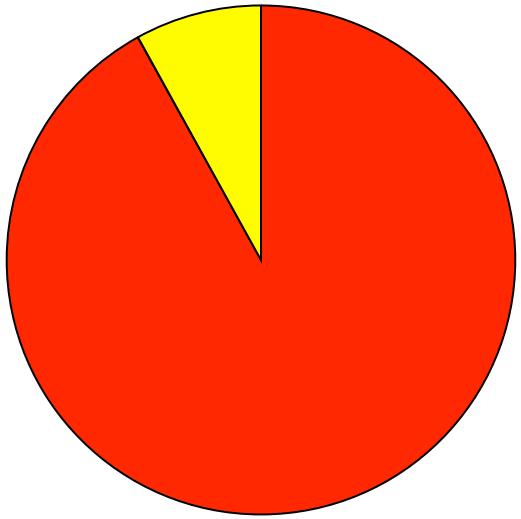
- Accurately represents population variation in:
  - Genotype
  - Environmental exposure
  - Disorder
  - Healthy controls
- Prospective + longitudinal
  - Unbiased, premorbid exposure information
  - Cumulative exposures
  - Timing of disorder relative to exposure
- Multiple disease outcomes
- Clinical utility (for diagnostics or therapeutics)

Manolio, Bailey-Wilson & Collins, 2006 (*Nat Rev Genet*)

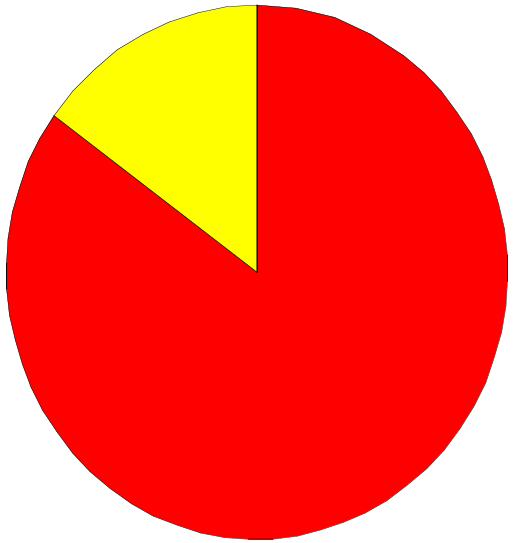
Modest attributable risk for prediction of schizophrenia-spectrum disorder in a birth cohort



Entire Cohort



Adolescent-onset cannabis users



Adolescent cannabis users homozygous for *COMT* valine allele

Source: Dunedin Longitudinal Study

Strategic steps for research into measured GxE

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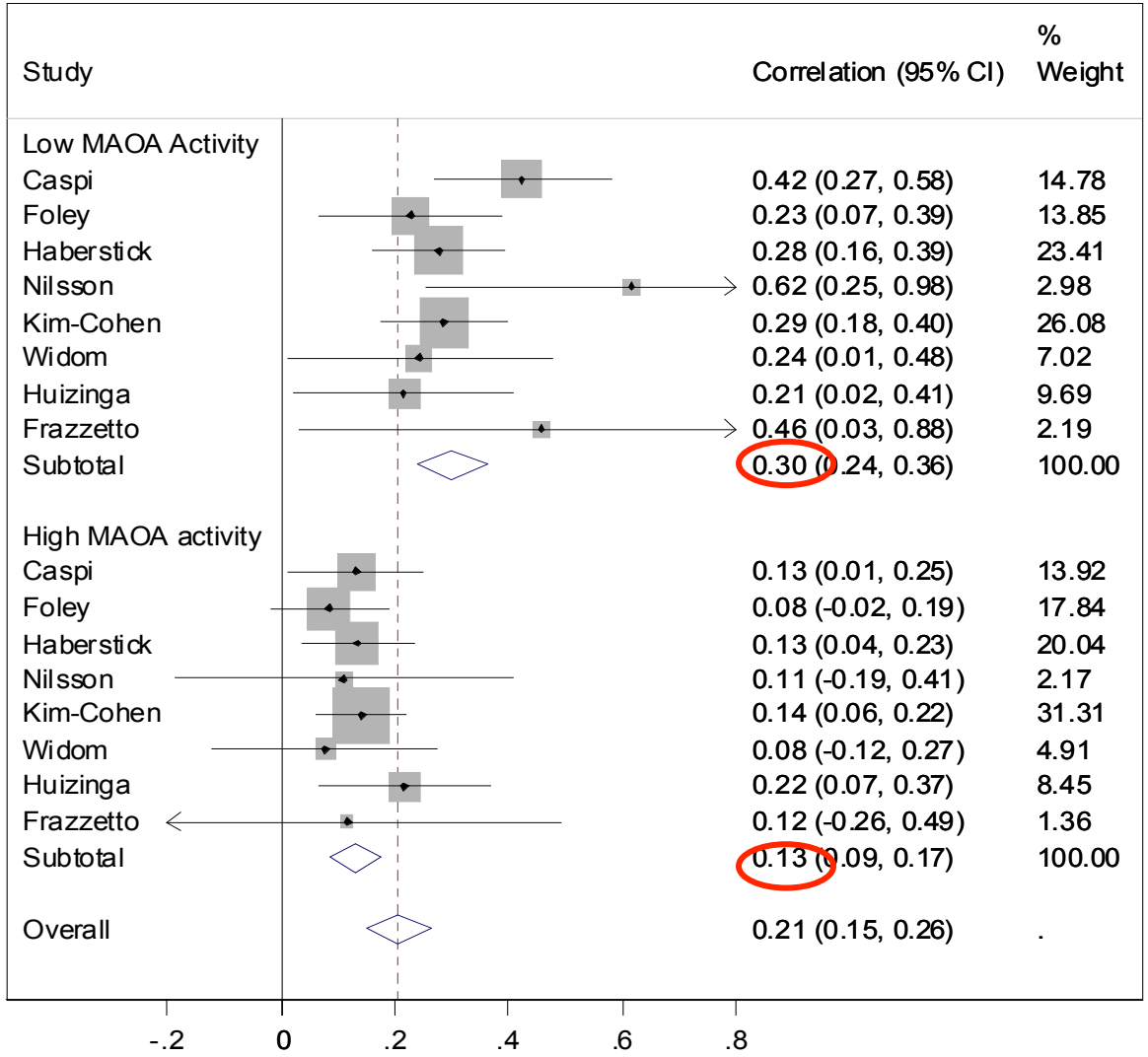
Moffitt et al. 2005 (*Arch Gen Psychiatry*);
Moffitt et al. 2006 (*Perspectives on Psych Science*)

REPLICATIONS?

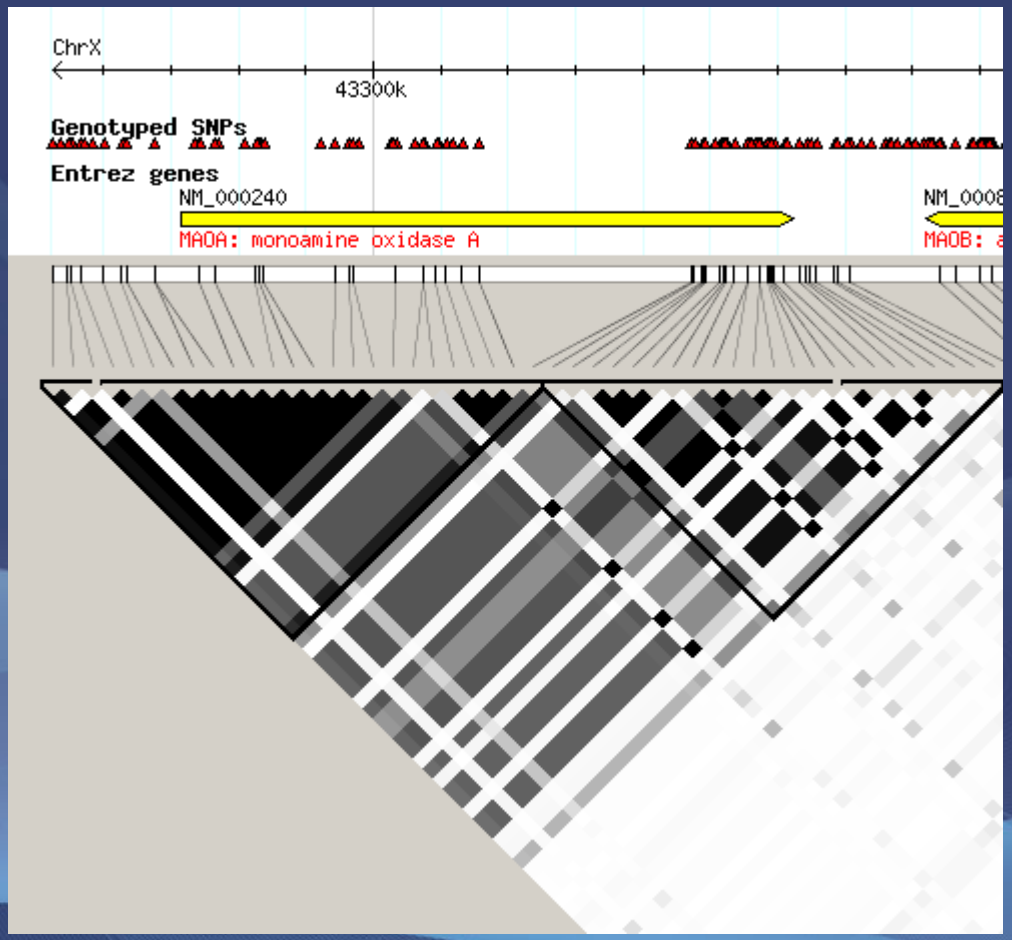
Finding	Positive findings	Failures
MAOA x maltreatment > antisocial disorders (2002)	11	4
5-HTT x life stress > depression (2003)	33	7
COMT x cannabis > psychosis (2005)	3	1
FADS2 x breastfeeding > IQ (2007)	2	-

META-ANALYSIS:
Correlation between maltreatment & antisocial outcome by *MAOA* genotype

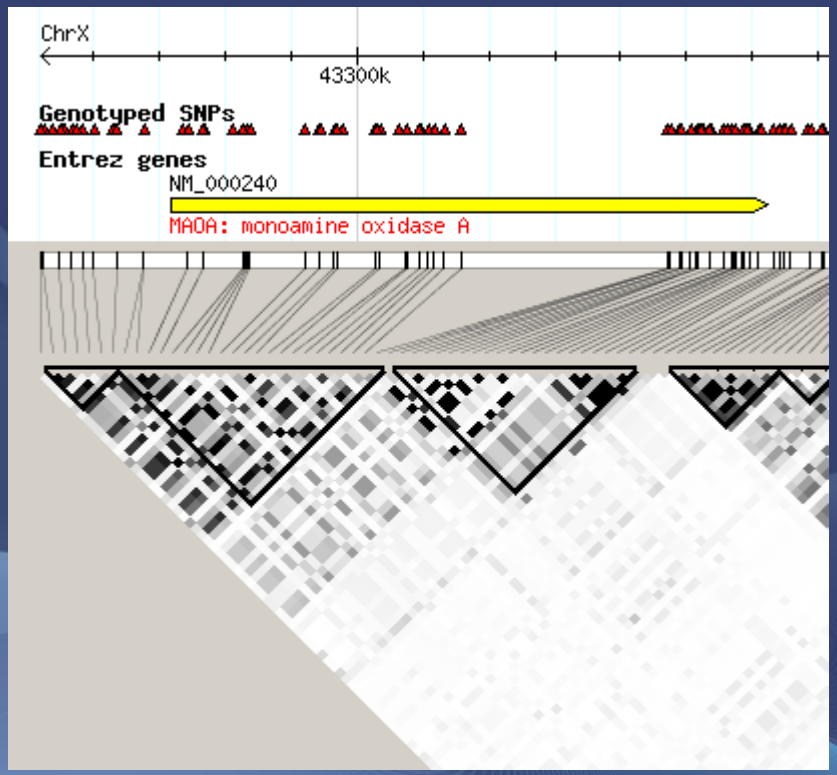


Taylor & Kim-Cohen, 2007 (*Dev & Psychopathology*); Kim-Cohen et al., 2006 (*Mol Psychiatry*)

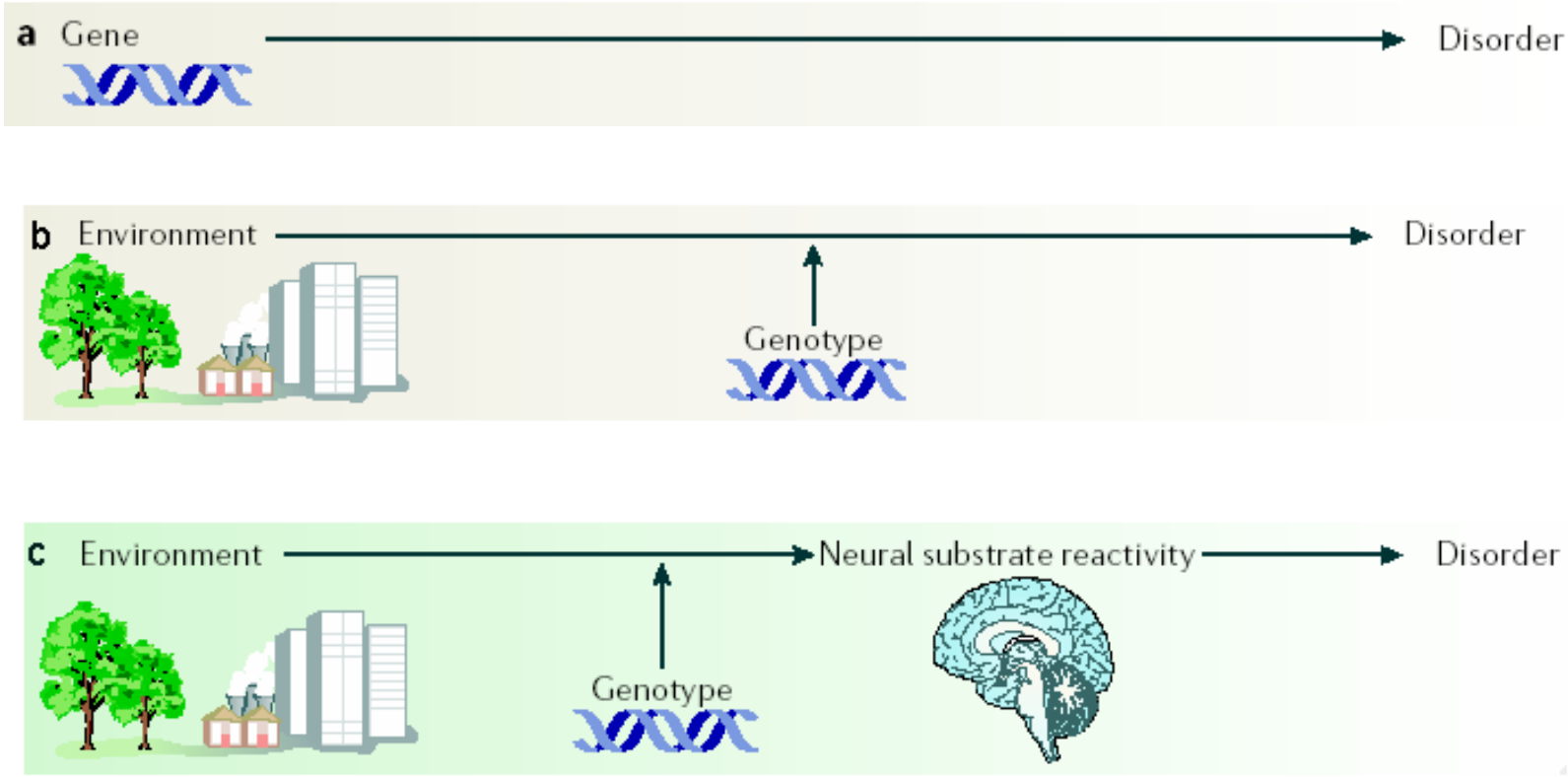
MAOA Haplotype Structure: Caucasians (Utah)



MAOA Haplotype Structure: Africans (Yoruba)



Beyond replication to understanding mechanisms

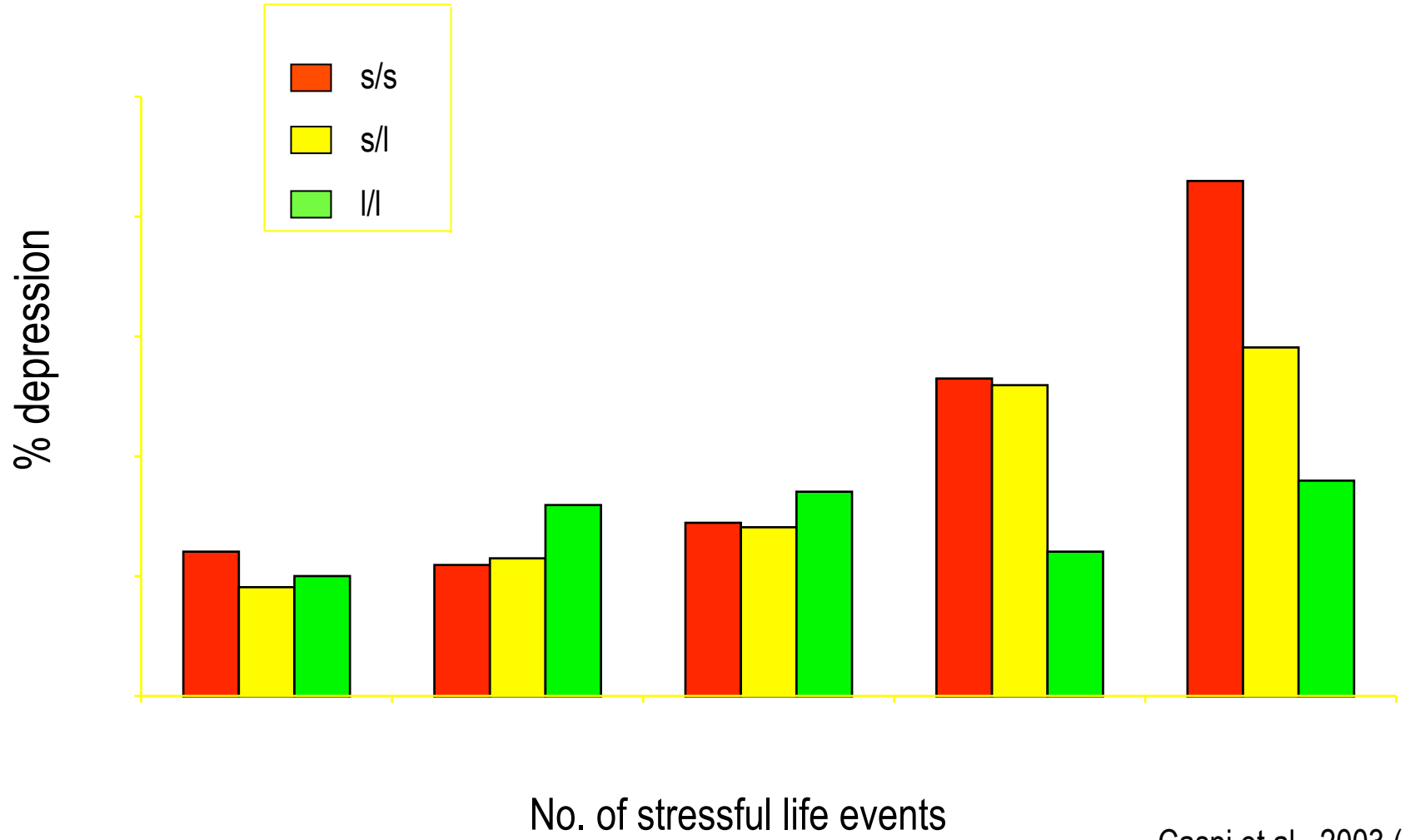


GxE research and experimental neuroscience: A new partnership

Caspi & Moffitt, 2006 (*Nature Reviews Neuroscience)*

Adult depression:

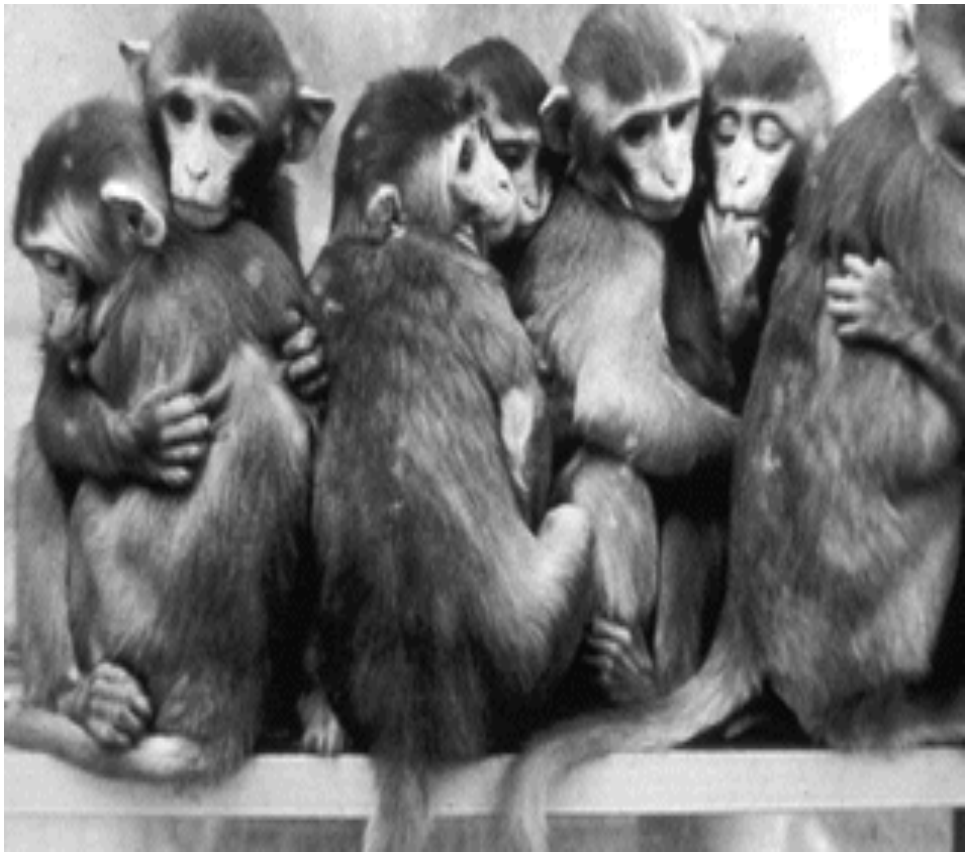
Life stress interacts with genotype (*5-HTT*)



Caspi et al., 2003 (*Science*)

5HTT GxE in rhesus monkeys

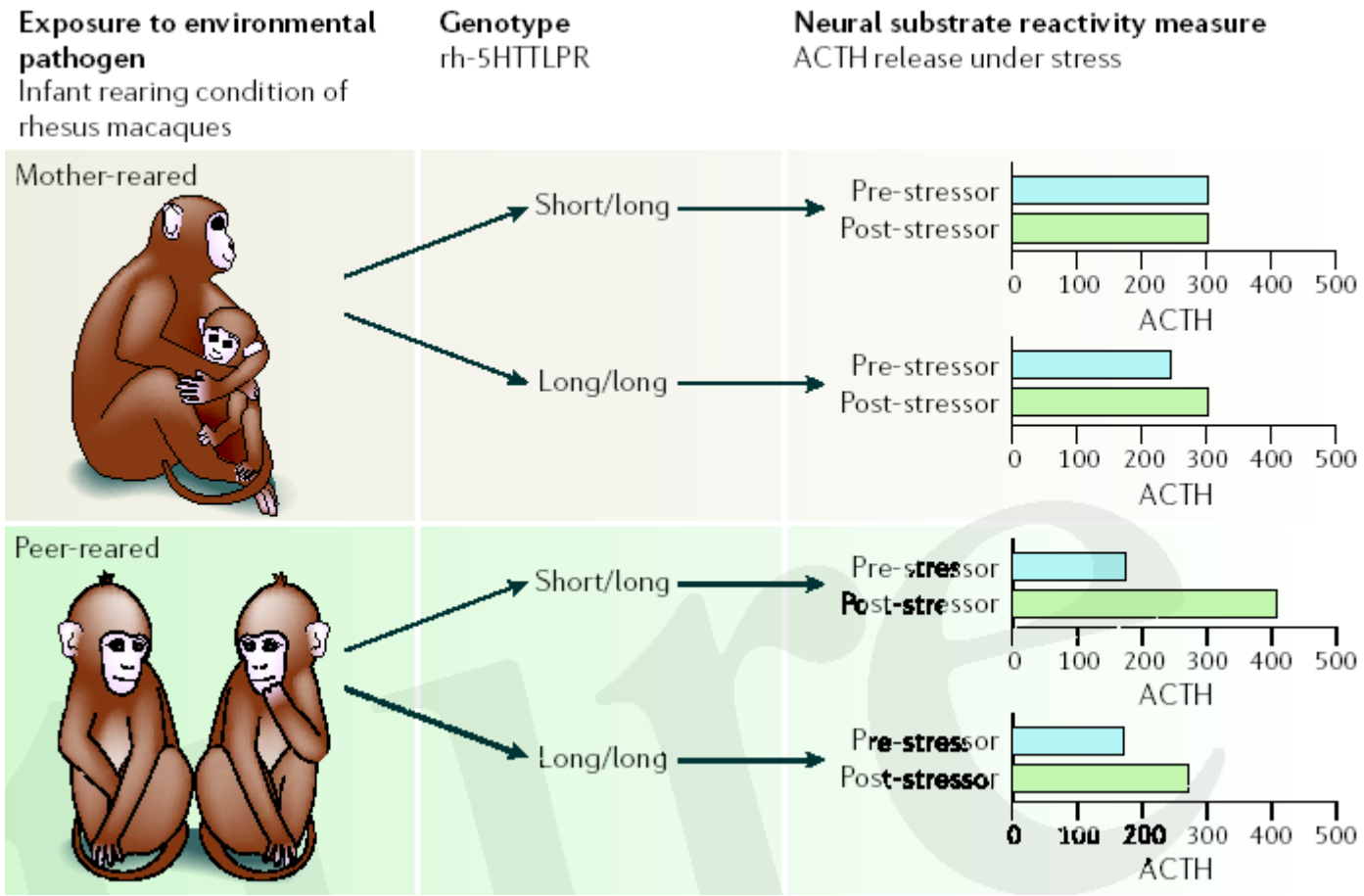
Normal Rearing



Stressful Rearing

Barr et al. 2004 (Biol Psychiatry)

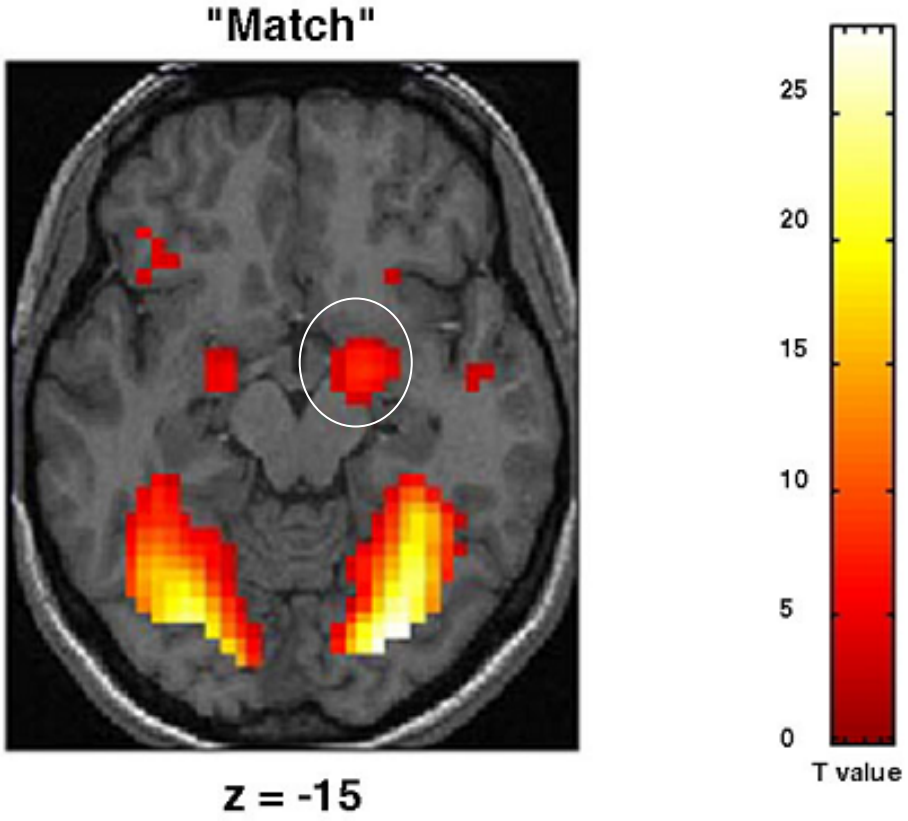
ACTH release after adult stress:
Infant rearing stress interacts with 5HTT genotype



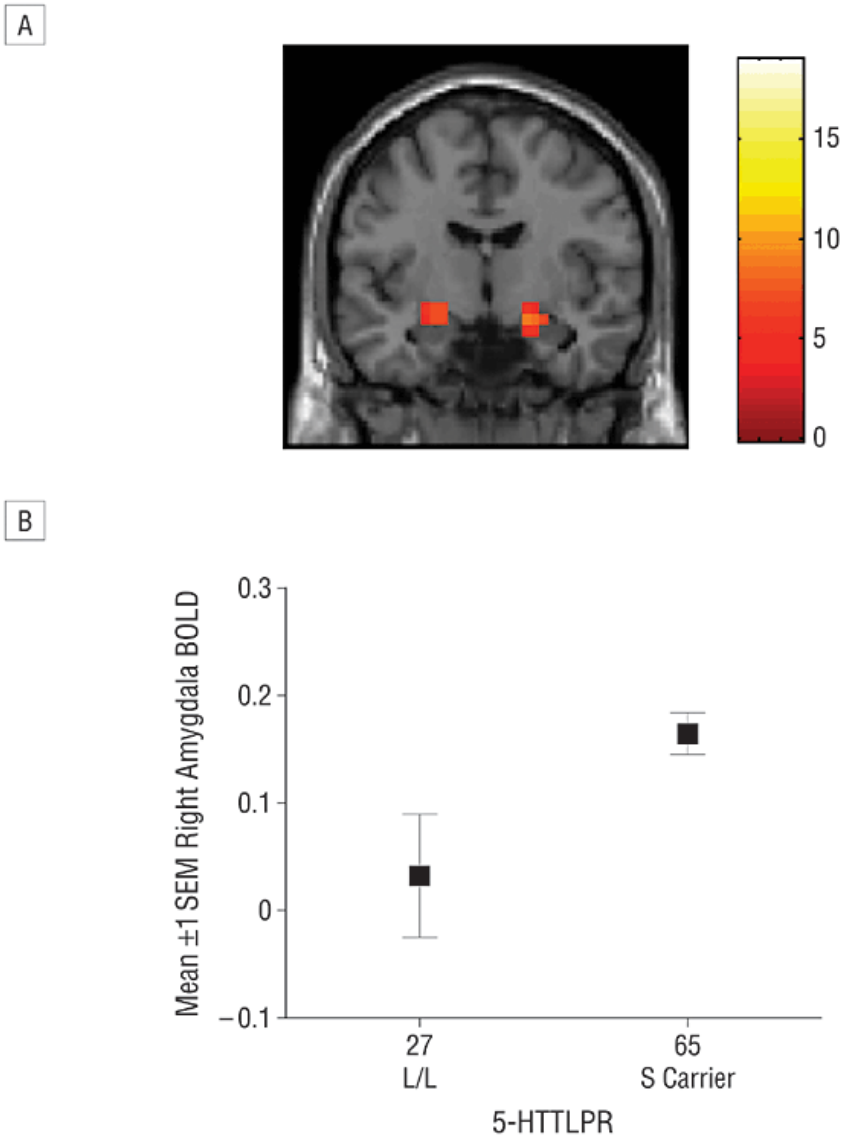
Barr et al. 2004 (Biol Psychiatry)

Perceptual processing of fearful faces engages the amygdala

"match the emotion"

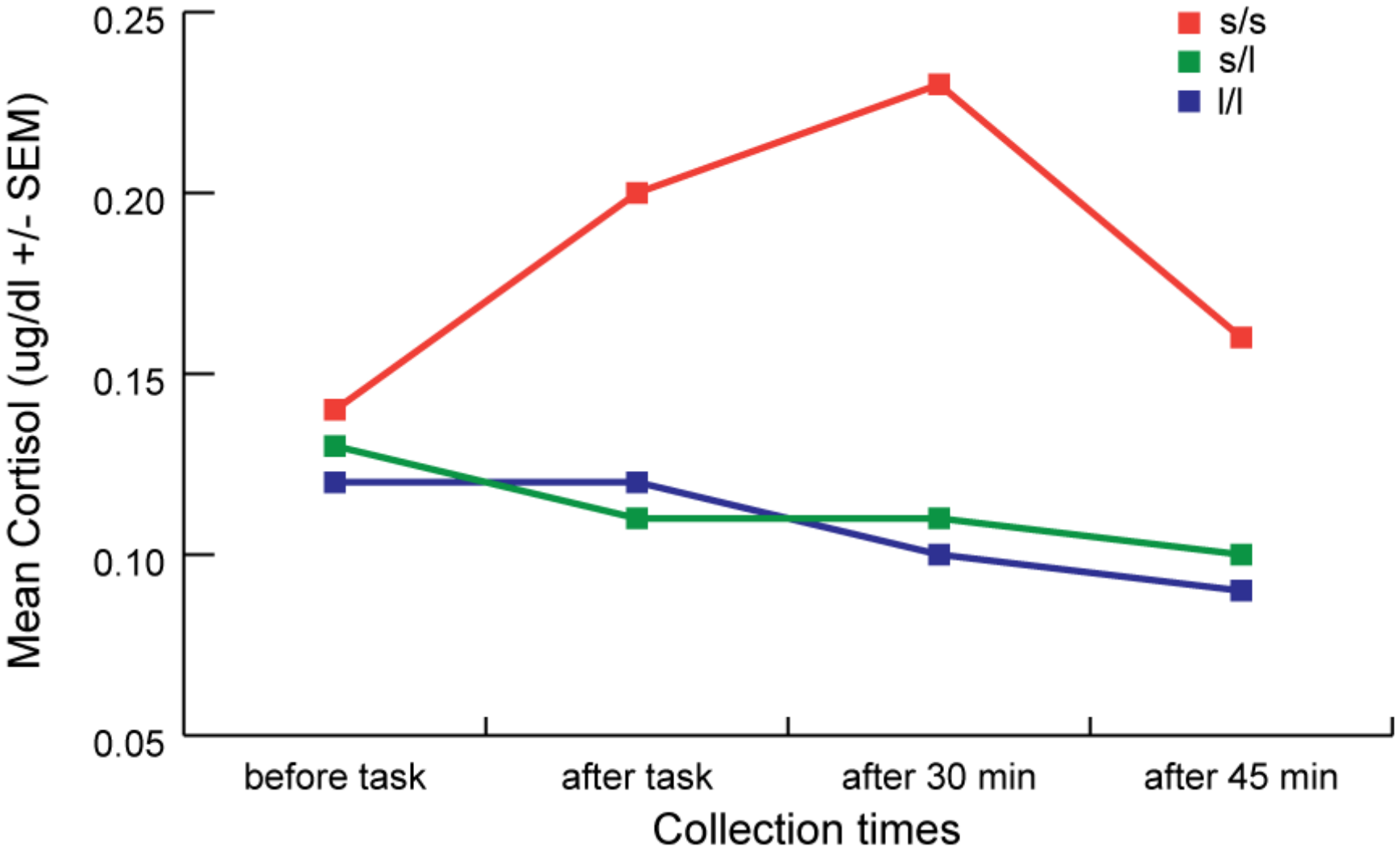


5-HTTLPR effects on amygdala reactivity to environmental threat



Hariri et al., 2002 (*Science*);
Hariri et al., 2005 (*Arch Gen Psychiatry*)

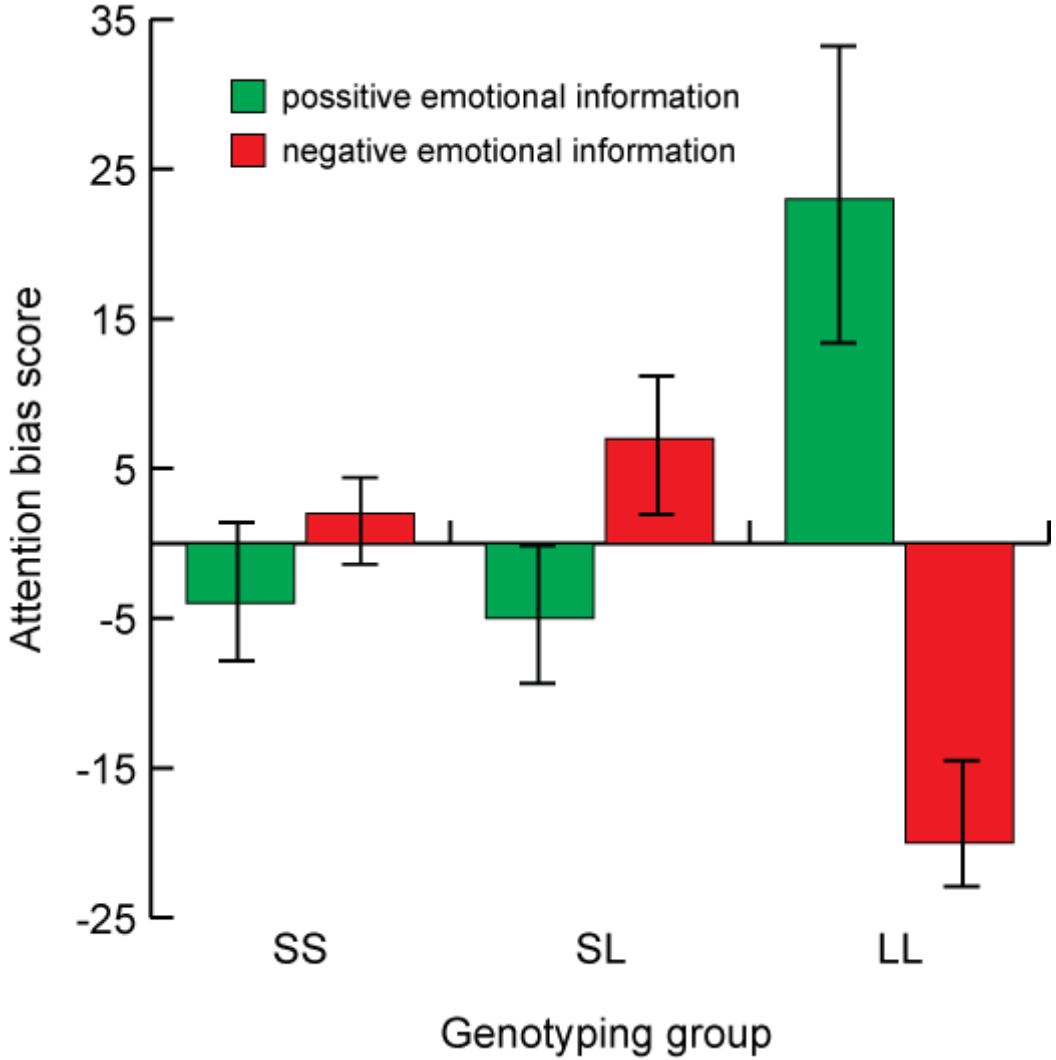
5HTT gene influences HPA Axis reactivity to a lab stressor



Gotlib et al. 2008 (*Biol. Psychiatry)*

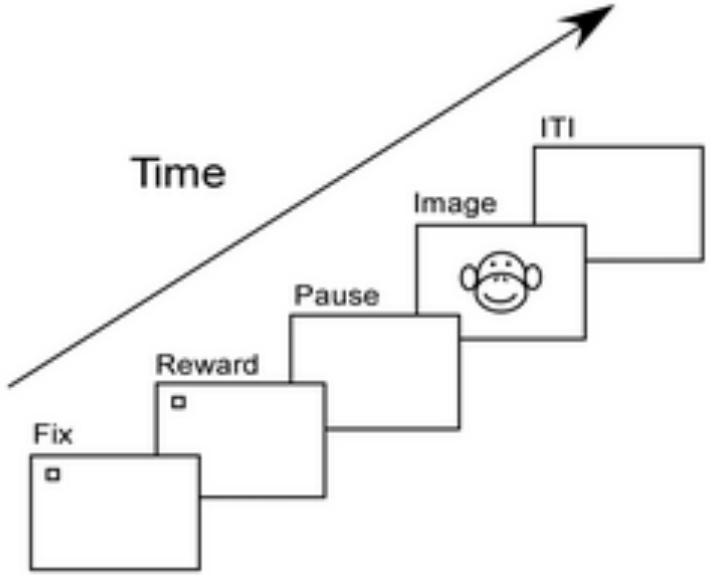
5HTT gene influences biased attention to emotional stimuli

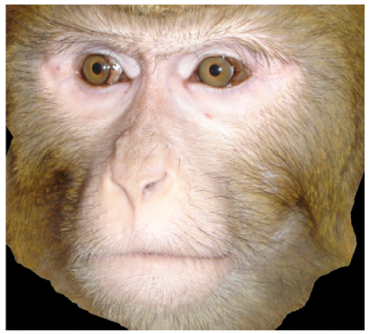
(mean attentional bias scores with standard errors as a function of genotype group and valence of the affective picture)

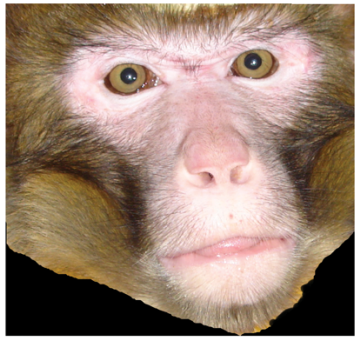


Fox E. et.al. 2009 (*Proc. R. Soc. B*)

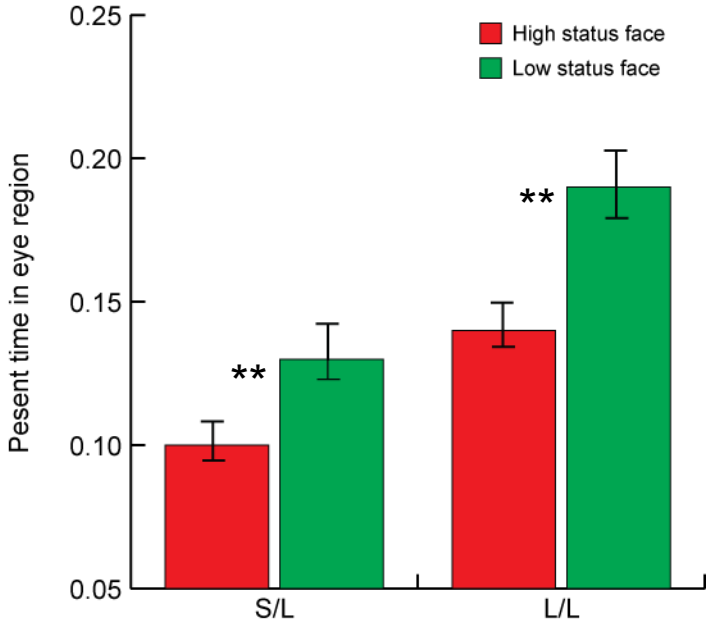
5HTT gene influences eye position and pupil diameter when observing social images

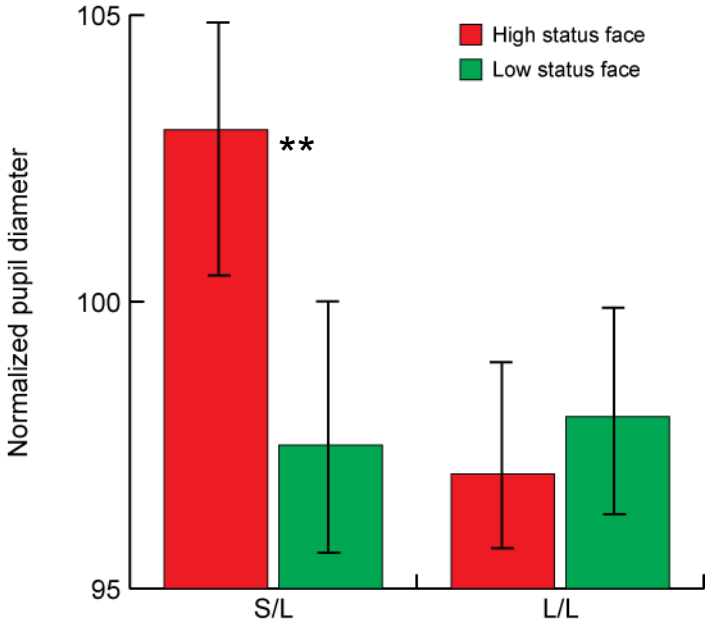






High status Low status

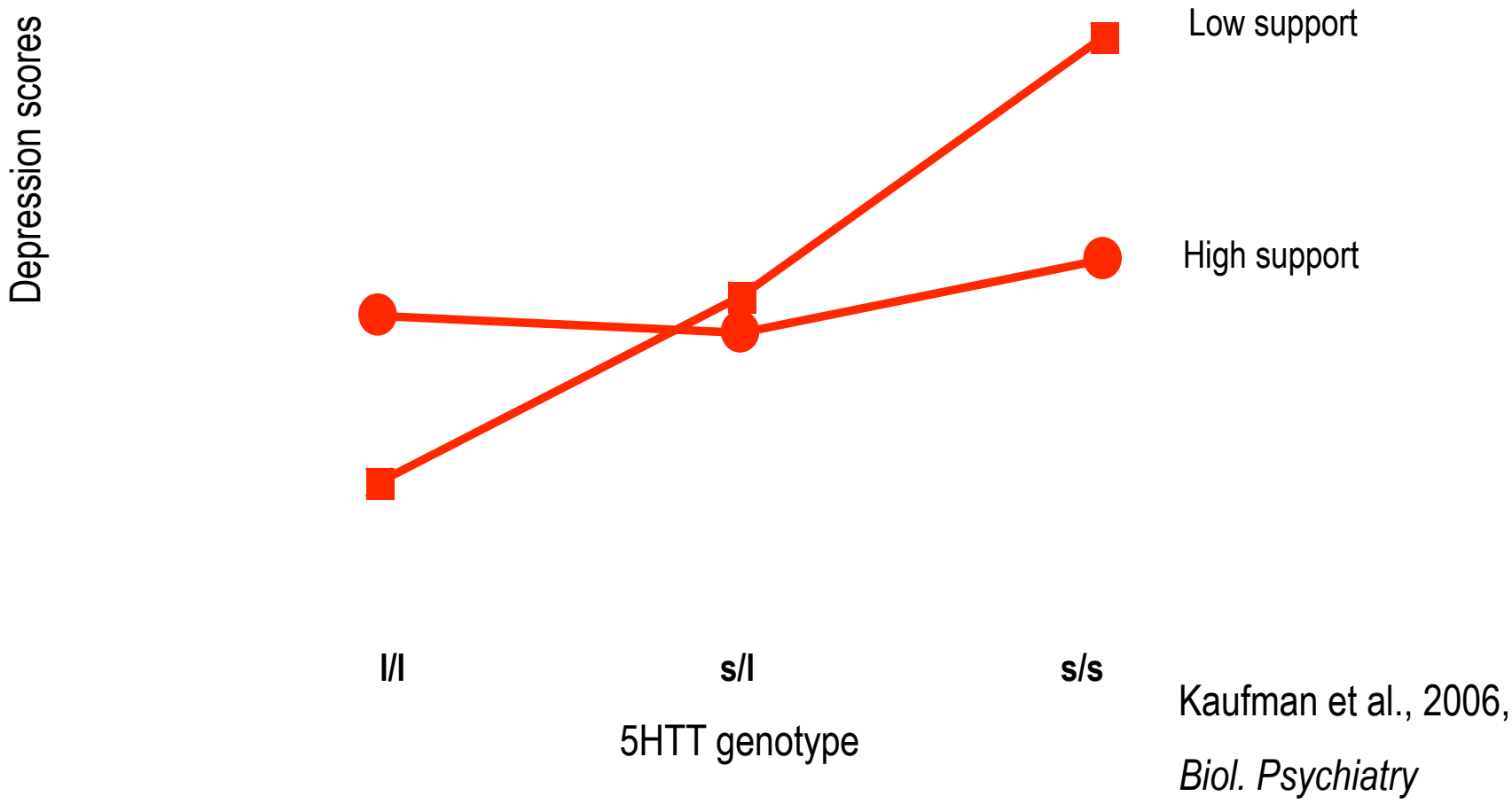




Watson et al. 2009 (*PlosOne*)

Genetic risk can be prevented: Among abused children….

social support protected children with the 5HTT risk genotype



Kaufman et al., 2006,

Biol. Psychiatry