

WHY THE DIFFERENT FORMS OF GENE-ENVIRONMENT INTERPLAY MATTER

By
Michael Rutter

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

EFFECTS OF GENES

Dynamic process in which the effects of a single gene are influenced by multiple inherited DNA elements and by the actions of environments and of random stochastic variation.

HOW GENES WORK



↑ ↑ ↑
Impact of transacting
and cis-acting factors,
enhancers and
silencers (all made up
of DNA)

Influenced by other
genes and cell
environments

Genetic influences

← Environmental influences and
chance effects

Gene Expression

STRATEGIES FOR STUDYING NONGENETIC EFFECTS ON GENE EXPRESSION IN THE BRAIN

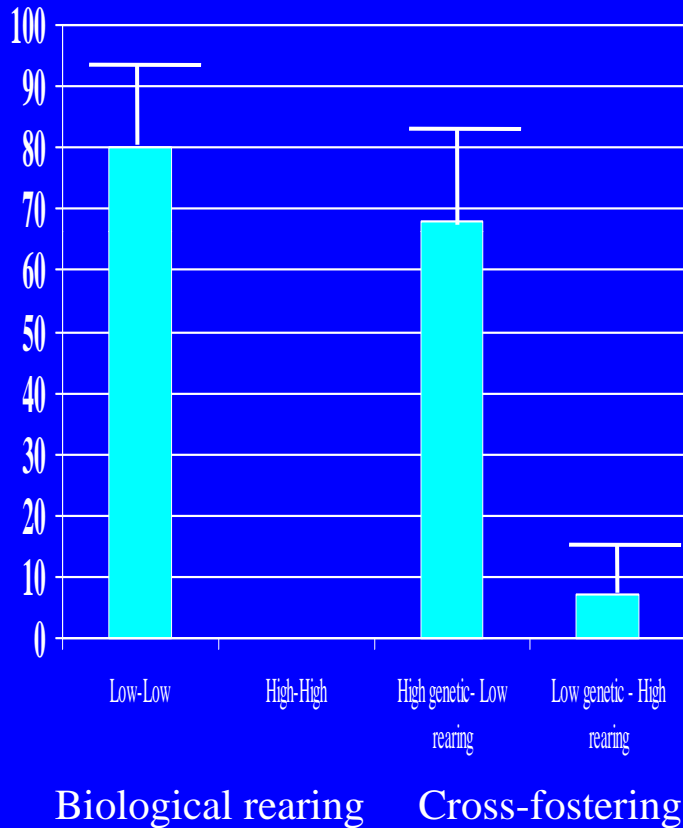
1. Examination of DNA methylation patterns in MZ twins discordant for some trait/disorder
2. Examination of gene expression in post-mortem brain specimens from contrasting clinical groups and controls
3. Experimental animal studies

RAT STUDIES OF MICHAEL MEANEY ET AL.

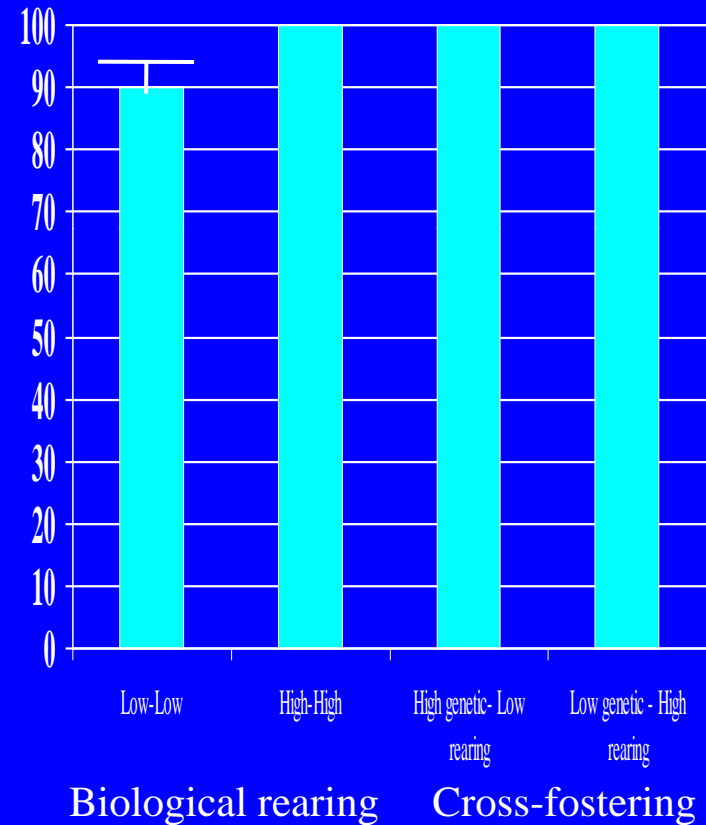
1. Observation that lactating mother rats differed markedly in licking/grooming archback nursing of neonatal rat pups
2. These maternal differences associated with offspring differences in behavior, neuroendocrine response to stress, and neurotransmitters
3. Cross-fostering design to determine if offspring differences 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

GENE EXPRESSION FINDINGS FROM CROSS-FOSTERING STUDY (from Weaver et al., 2004)

5' CpG dinucleotide



3' CpG dinucleotide



MODELS FOR VARIATIONS IN HERITABILITY ACCORDING TO ENVIRONMENTAL CIRCUMSTANCES I

(from Shanahan & Hofer, 2005)

1. Relative variation model

(Predicts that heritability will go DOWN in the context of a massive environmentally mediated risk effect and, conversely, that environmental effects will account for less of the variance in the context of a major genetic risk effect)

2. Stress-diathesis model reflecting GxE

(Predicts that heritability will go UP in the context of environmental risk because it will incorporate GxE)

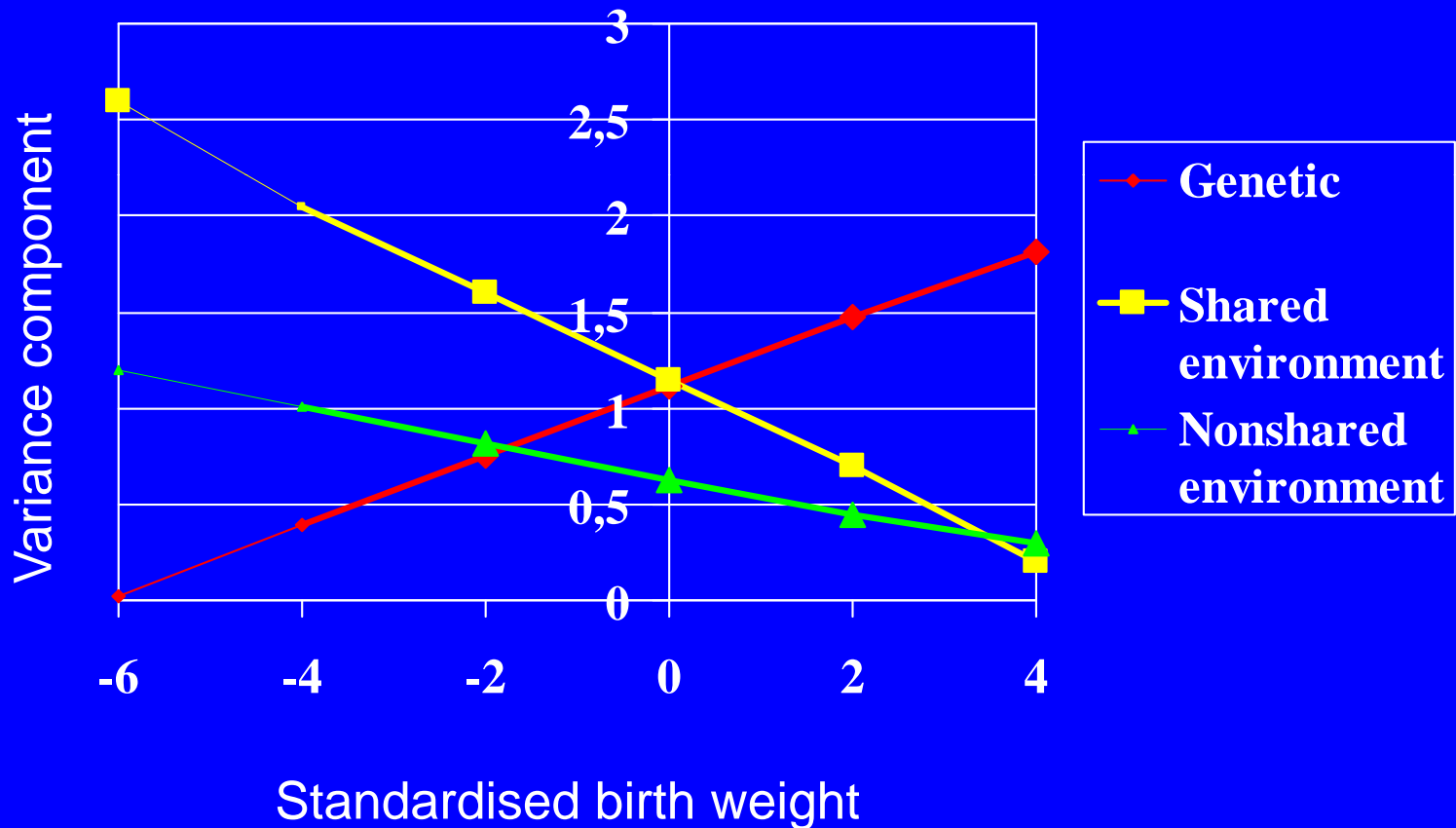
MODELS FOR VARIATIONS IN HERITABILITY ACCORDING TO ENVIRONMENTAL CIRCUMSTANCES II

(from Shanahan & Hofer, 2005)

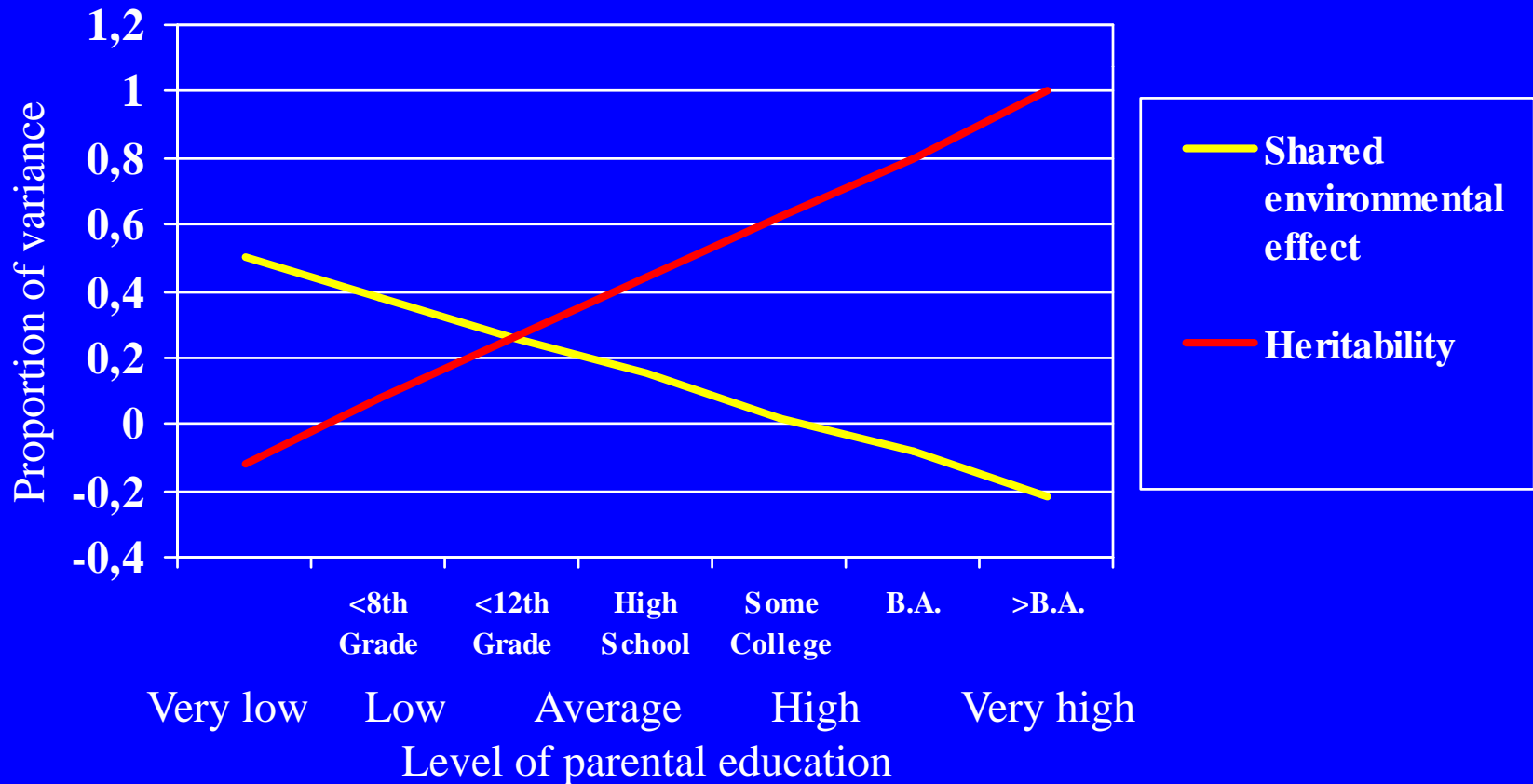
3. Bioecological model proposing that advantageous proximal environments actualise genetic influences
(Predicts that heritability will go DOWN in the context of environmental constraints)
4. Environmental constraints/opportunities model
(Predicts that heritability will go UP in the context of good opportunities and DOWN in the context of environmental constraints)

GENE-BIRTHWEIGHT INTERACTION AND PROBLEM BEHAVIOR

(from Wichers et al., 2002)

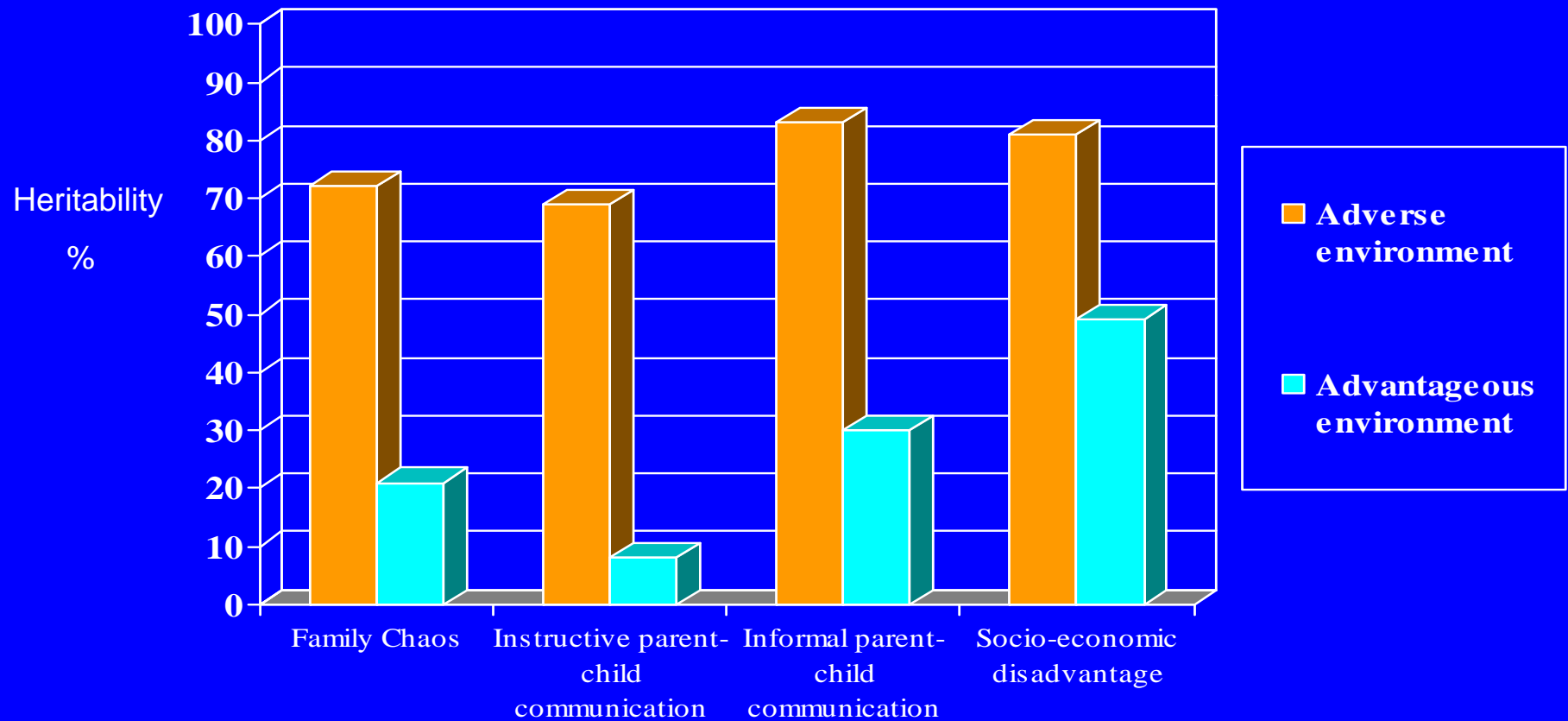


RELATIONS BETWEEN GENETIC AND SHARED ENVIRONMENTAL VARIANCE COMPONENTS EFFECTS ON IQ BY LEVEL OF PARENTAL EDUCATION (from Rowe et al., 1999)



HERITABILITY VARIATION FOR VERBAL ABILITY ACCORDING TO ENVIRONMENTAL EXTREMES

(from Asbury et al., 2005)



SOCIETAL MODERATORS OF HERITABILITY I

a) Tested by cohort effects

e.g. heritability for age at first intercourse (Dunne et al., 1997) greater in those born between 1952 and 1965 than in those born between 1922 and 1952

in women 49% vs 32%

in men 72% vs 0%

(difference attributed to greater sexual tolerance but why big difference in men but small difference in women?)

SOCIETAL MODERATORS OF HERITABILITY II

- b) Tested by variation in some broad social variable
e.g. heritability of adolescent alcohol use

60% in areas of high migration

vs

16% in areas of low migration

(difference attributed to difference in degree of social control, but no measure of control)

CONCLUSIONS ON VARIATIONS IN HERITABILITY

1. Replication needed before there can be any conclusions on the generality of the type of effect found
2. Important reminder that heritability estimates are time and sample specific
3. The dimension of variation in environmental risk is not necessarily entirely mediated environmentally
4. The variation does not imply an interaction between a specific susceptibility genetic allele and a specific risk environment
5. There are several different mechanisms that could be operative (including the effects of restriction in range)

Gene-environment correlations refer to genetic effects on individual differences in **liability to exposure** to particular environmental circumstances.

(Background is the extensive evidence that environmental risk exposure is far from randomly distributed)

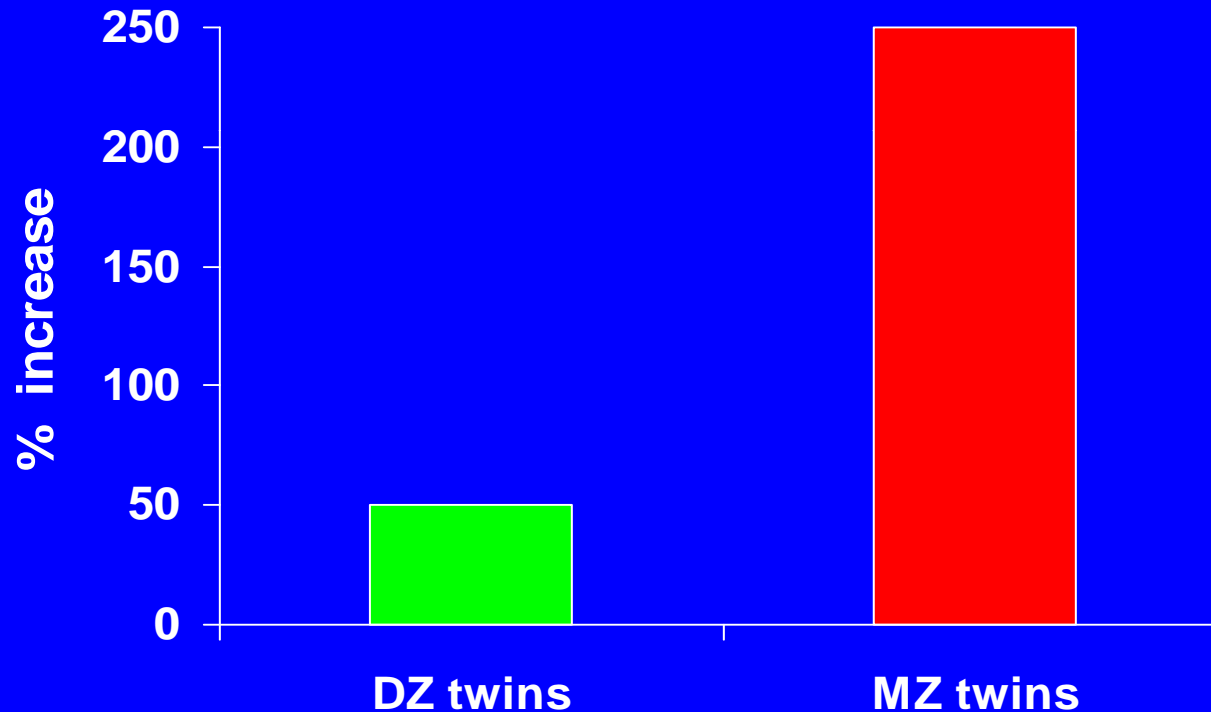
Gene-environment interactions concern genetically influenced individual differences in the **sensitivity** to specific environmental factors.

(Background is the extensive evidence of huge individual differences in vulnerability to all manner of environmental hazards)

TYPES OF GENE-ENVIRONMENT CORRELATION (rGE)

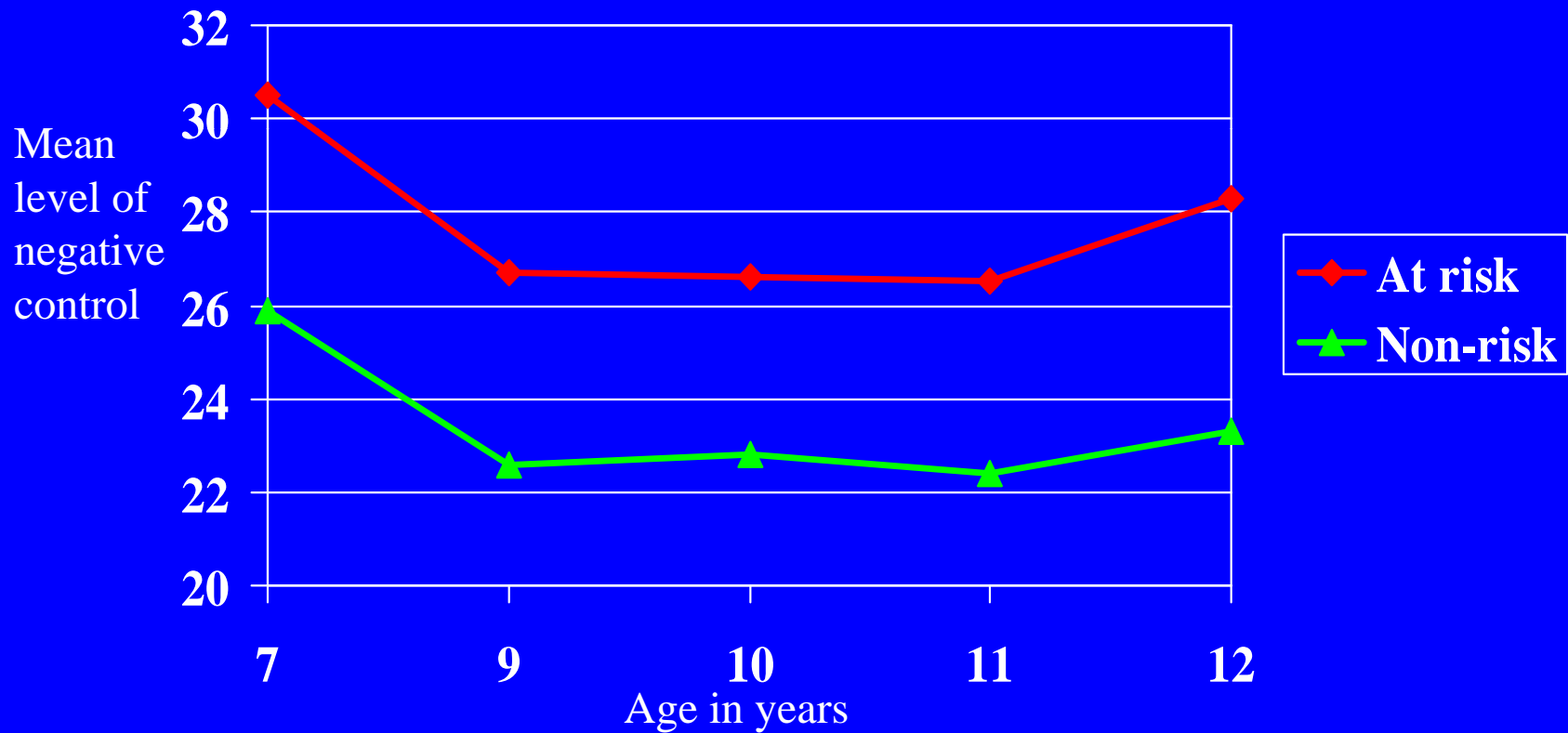
- Passive: Parental genes influence parental behaviors that play a role in determining the kind of rearing environment that they provide
- Active: Child genes influence child behaviors that play a role in determining how children shape and select their environments
- Evocative: Child genes influence child behaviors that play a role in evoking different types of responses in other people

THE INCREASE IN ONE TWIN'S RISK FOR DIVORCE IF THE CO-TWIN HAD BEEN DIVORCED (from Jockin et al., 1996)



Source: Minnesota Twin Registry

ADOPTIVE CHILDREN'S GENETIC STATUS AND ADOPTIVE PARENTS' NEGATIVE CONTROL (O'Connor et al., 1998)



ROLE OF GENES IN EVOCATIVE EFFECT OF CHILDREN'S DISRUPTIVE BEHAVIOR AND NEGATIVE PARENTING BY ADOPTIVE PARENTS

(from O'Connor et al., 1998)

Correlations between 'externalizing' behavior and
negative parenting

Before partialling out
genetic risk

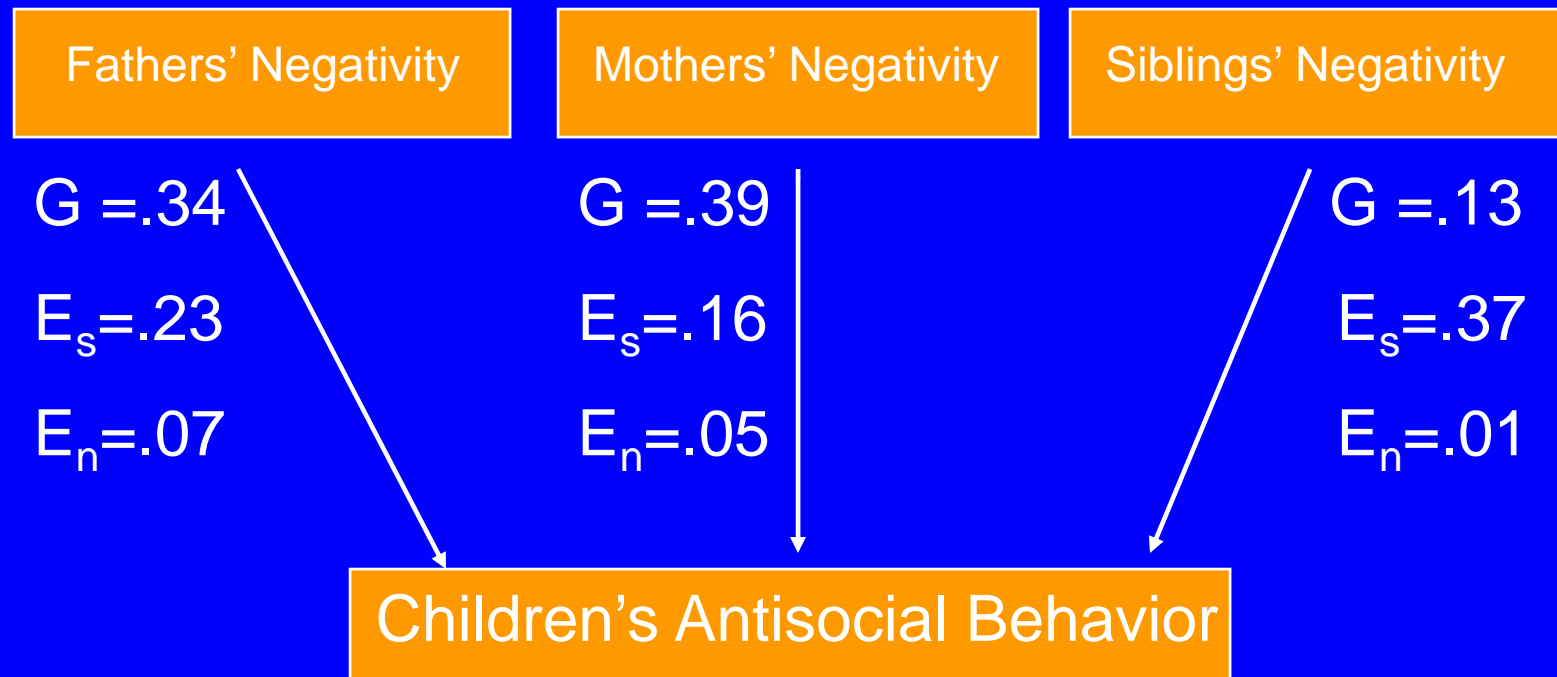
.35

After partialling out
genetic risk

.31

FAMILY NEGATIVITY AND ANTISOCIAL BEHAVIOR

(Data from Pike et al, 1996)



G = Path coefficient for genetic route

E_s = Path coefficient for shared environmental effect

E_n = Path coefficient for non-shared environmental effect

CHILD EFFECTS ON CORPORAL PUNISHMENT AND ON PHYSICAL MALTREATMENT (from Jaffee et al., 2004)

Corporal punishment $h^2 = 25\%$

Physical maltreatment $h^2 = 7\%$

Antisocial behavior $h^2 = 73\%$

Genetic factors account for 86% of the covariation between corporal punishment and antisocial behavior

Genetic factors account for 0% of the covariation between physical maltreatment and antisocial behavior

Shared environmental effects account for 74% of the covariation between corporal punishment and physical maltreatment

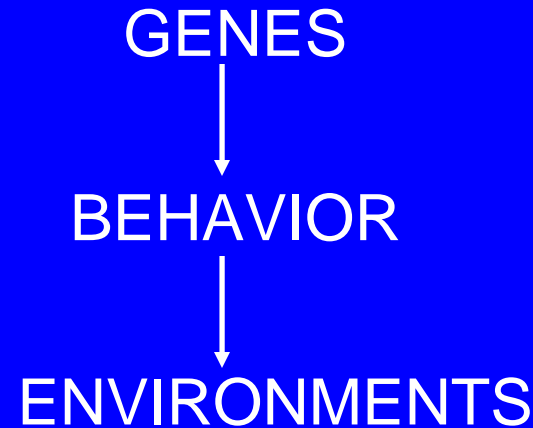
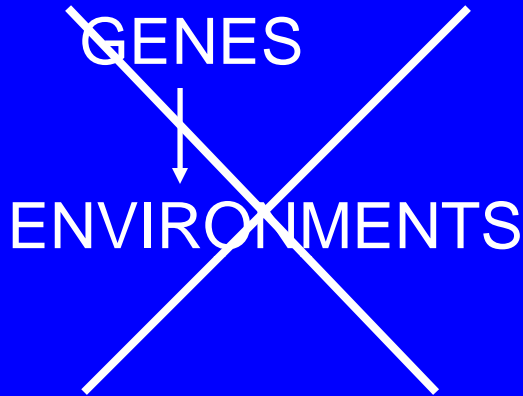
IMPLICATIONS OF EXPOSURE TO RISK ENVIRONMENT FINDINGS I

1. There is no point in searching for individual susceptibility genes for specific environments because the effects of genes are on behavior rather than on environments (other than indirectly)
2. The key research question concerns the types of parent and of child behavior that have environmental effects and the causal mechanisms involved in such effects. The extent to which individual differences in such behaviors are genetically influenced is a meaningful question but, in most circumstances, it is the secondary question and not the primary one

IMPLICATIONS OF EXPOSURE TO RISK ENVIRONMENT FINDINGS II

3. The one crucial genetic aspect concerns the fact that the findings mean that part of the risk effects associated with adverse environment or stress experiences are likely to involve genetic mediation. The possibility means that environmental research must use designs to take that into account

GENETIC EFFECTS ON THE LIABILITY TO EXPOSURE TO DIFFERENT SORTS OF ENVIRONMENTS



i.e. Key question is which parental and child behaviors influence variation in environmental risk exposure and how these effects are mediated

The question of the extent to which such behaviors are genetically influenced is secondary and has few clinical implications

BACKGROUND TO STUDIES OF GENETIC EFFECTS ON INDIVIDUAL DIFFERENCES IN SUSCEPTIBILITY TO RISK ENVIRONMENTS

Marked individual variation in response to all types of environmental hazard studied – whether physical or psychosocial.

Such variation evident in closely controlled experimental studies in both humans and other animals so that the variation is not just an artefact of differences in initial risk.

This applies to both minor environmental hazards and extremely serious hazards.

KEY REASONS FOR EXPECTING G x E FOR PSYCHOPATHOLOGY I

1. Evolutionary considerations

Genetically influenced variations in the response of organisms to environmental challenges constitutes the raw material for natural selection.

2. Developmental considerations

Biological development at the individual level involves adaptations to the environmental conditions that prevail during the formative period of development; it is implausible that genetic factors do not play a role in moderating that process.

KEY REASONS FOR EXPECTING G x E FOR PSYCHOPATHOLOGY II

3. Environmental considerations

Both human and animal studies consistently reveal great variability in individuals' behavioral responses to a variety of environmental hazards. To argue that response heterogeneity is not influenced by genes would require the assumption that responsiveness to the environment is uniquely outside the sphere of genetic influence.

4. Biological considerations

Numerous examples of G x E in biology and increasingly also in medicine.

NEED TO STUDY GENE-ENVIRONMENT INTERACTION THROUGH SPECIFIC HYPOTHESES ON MECHANISMS

1. In present state of knowledge, choose proximal environmental risk factor for which there is good evidence of substantial, environmentally-mediated, risk effects, and good measures of the risk feature but, for which, there is major individual variation in response, i.e. start with environmental factor
2. Choose phenotype with multifactorial causation but with substantial heritability and evidence that gene-environment interaction likely
3. Choose susceptibility gene with some evidence of real effect, and with plausible impact on a possible causal pathway, but not with a strong deterministic effect

DUNEDIN MULTIDISCIPLINARY HEALTH AND DEVELOPMENT STUDY

Birth cohort of 1037 children in New Zealand (South Island)

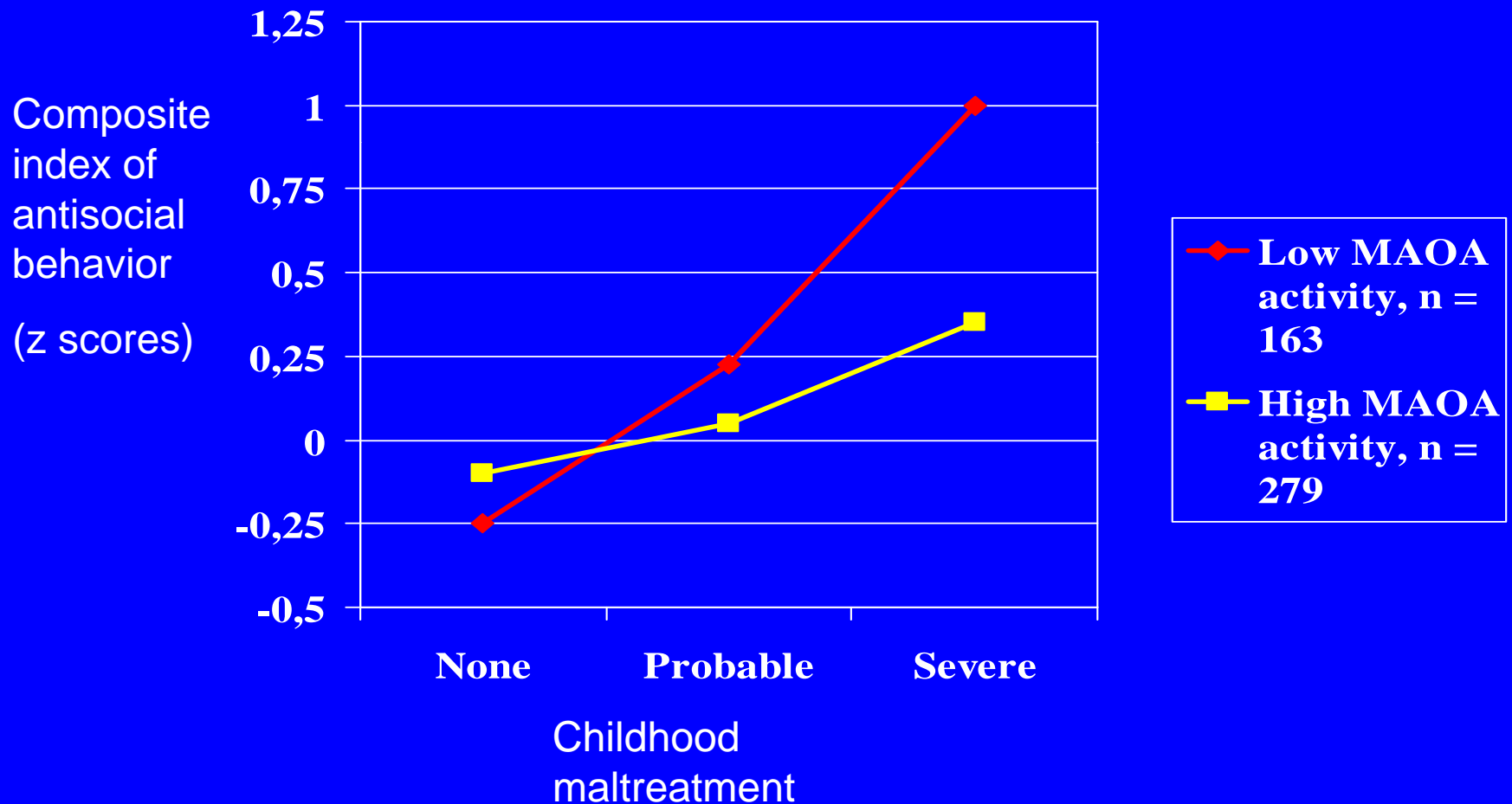
Established at age 3 years

Assessments at 3, 5, 7, 9, 11, 13, 15, 18, 21 and 26 years

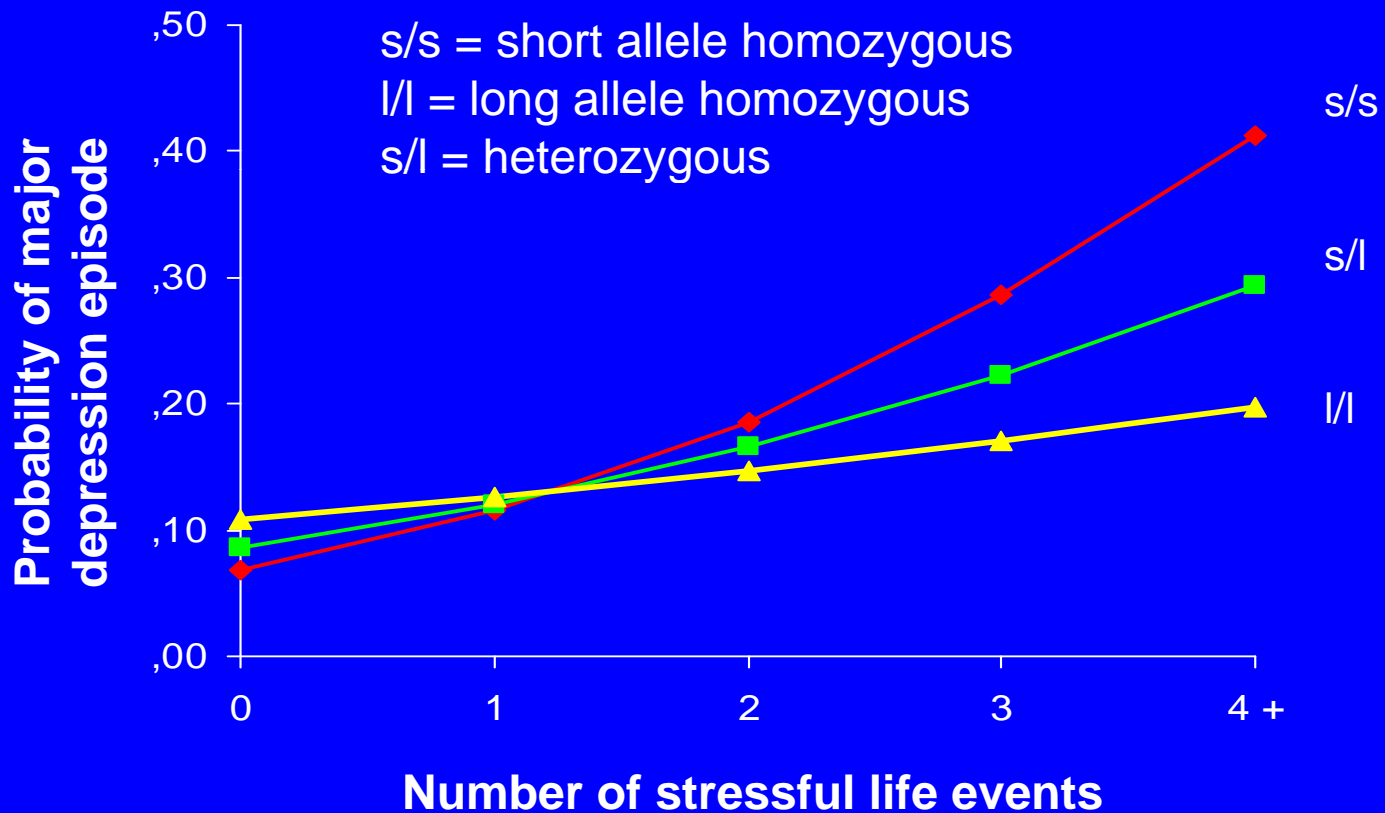
Rich range of self-report, interview, parent report and teacher report measures

DNA (93% blood and 7% buccal swabs)

ANTISOCIAL BEHAVIOR AS A FUNCTION OF MAOA ACTIVITY AND A CHILDHOOD HISTORY OF MALTREATMENT (from Caspi et al., 2002)

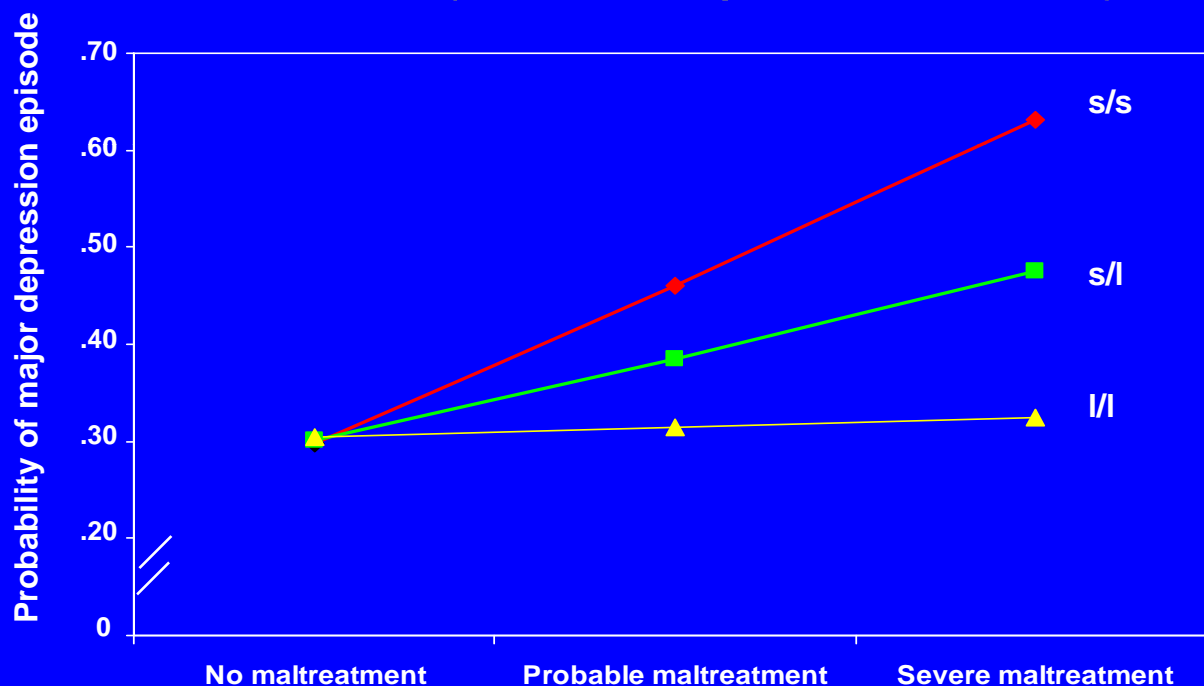


EFFECT OF LIFE STRESS ON DEPRESSION MODERATED BY 5-HTT GENE (from Caspi et al., 2003)



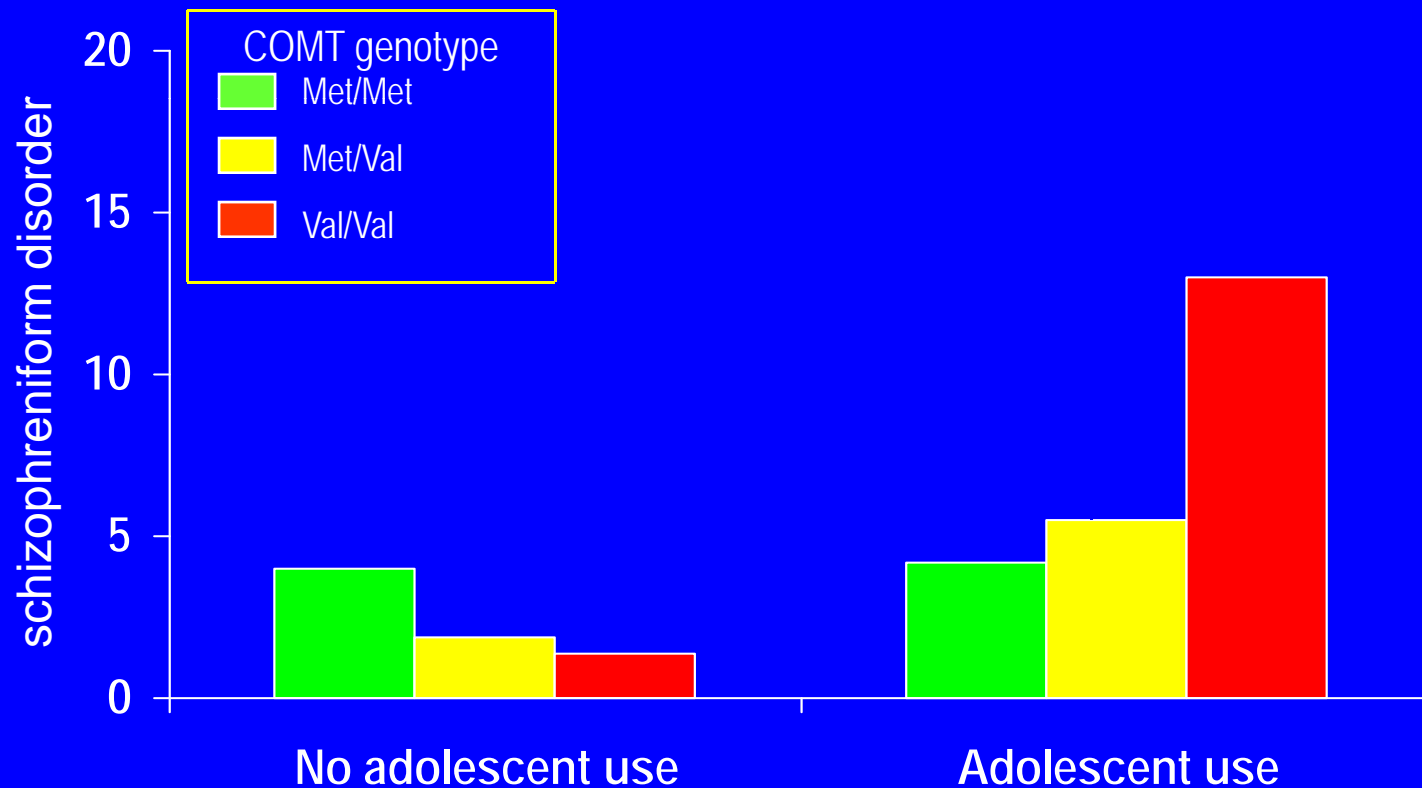
EFFECT OF MALTREATMENT IN CHILDHOOD ON LIABILITY TO DEPRESSION MODERATED BY 5-HTT GENE

(from Caspi et al., 2003)



s/s = short allele
homozygous
l/l = long allele
homozygous
s/l =
heterozygous

SCHIZOPHRENIA SPECTRUM DISORDER: CANNABIS USE INTERACTS WITH GENOTYPE (Caspi et al., 2005)



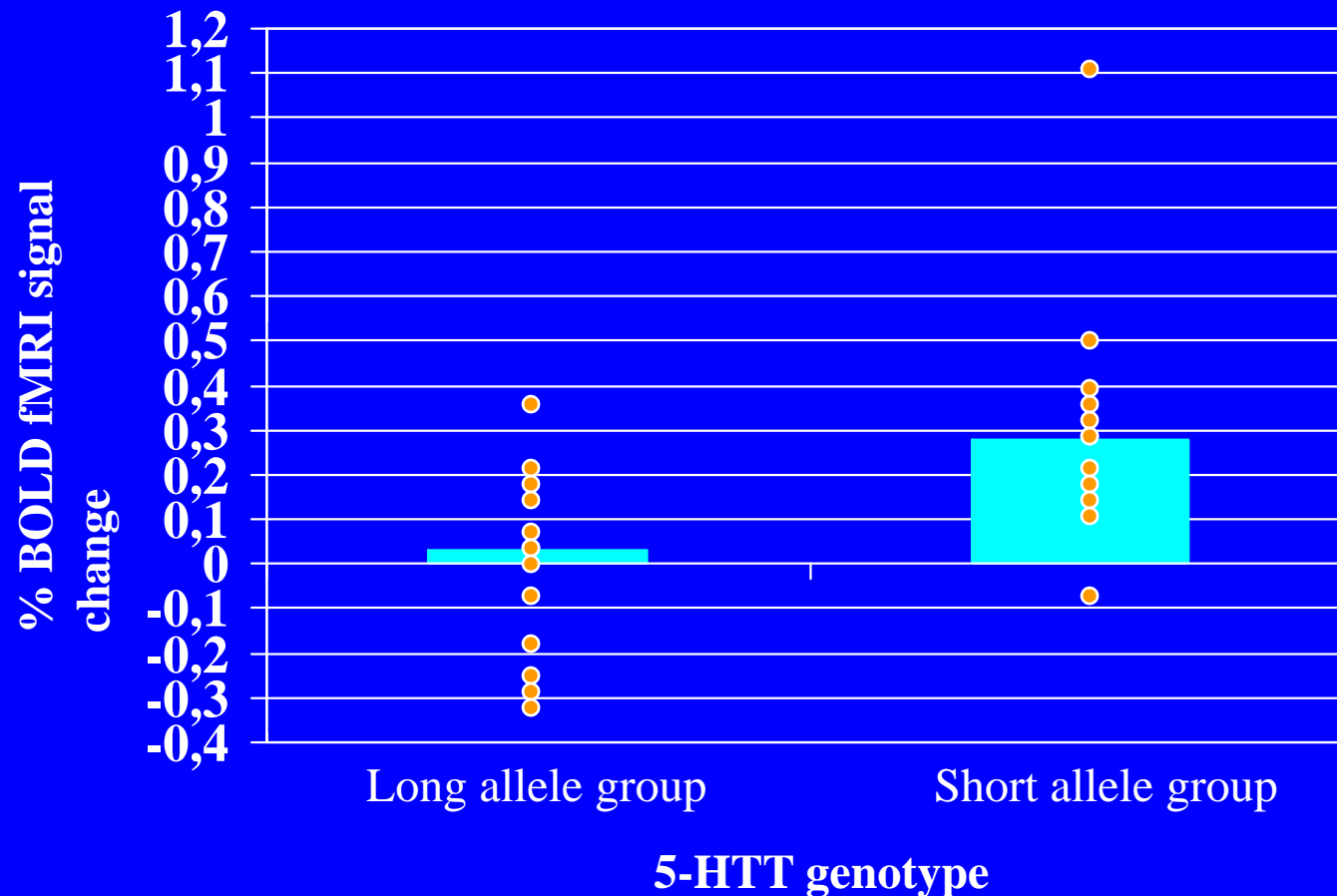
THREE KEY METHODOLOGICAL CHALLENGES TO G X E FINDINGS I

1. Could the interaction reflect G x G interaction rather than G x E? (Strategy is to repeat analysis with the same environmental factor using a timing that could not reflect environmental mediation because it followed the onset of disorder)
2. Could the interaction represent a scaling artefact? (Strategy is to repeat the analysis with a genetic polymorphism with similar scaling features and then to repeat the analysis with a phenotype with similar scaling features – in each case choosing ones without the same biological pathway expectation)

THREE KEY METHODOLOGICAL CHALLENGES TO G X E FINDINGS II

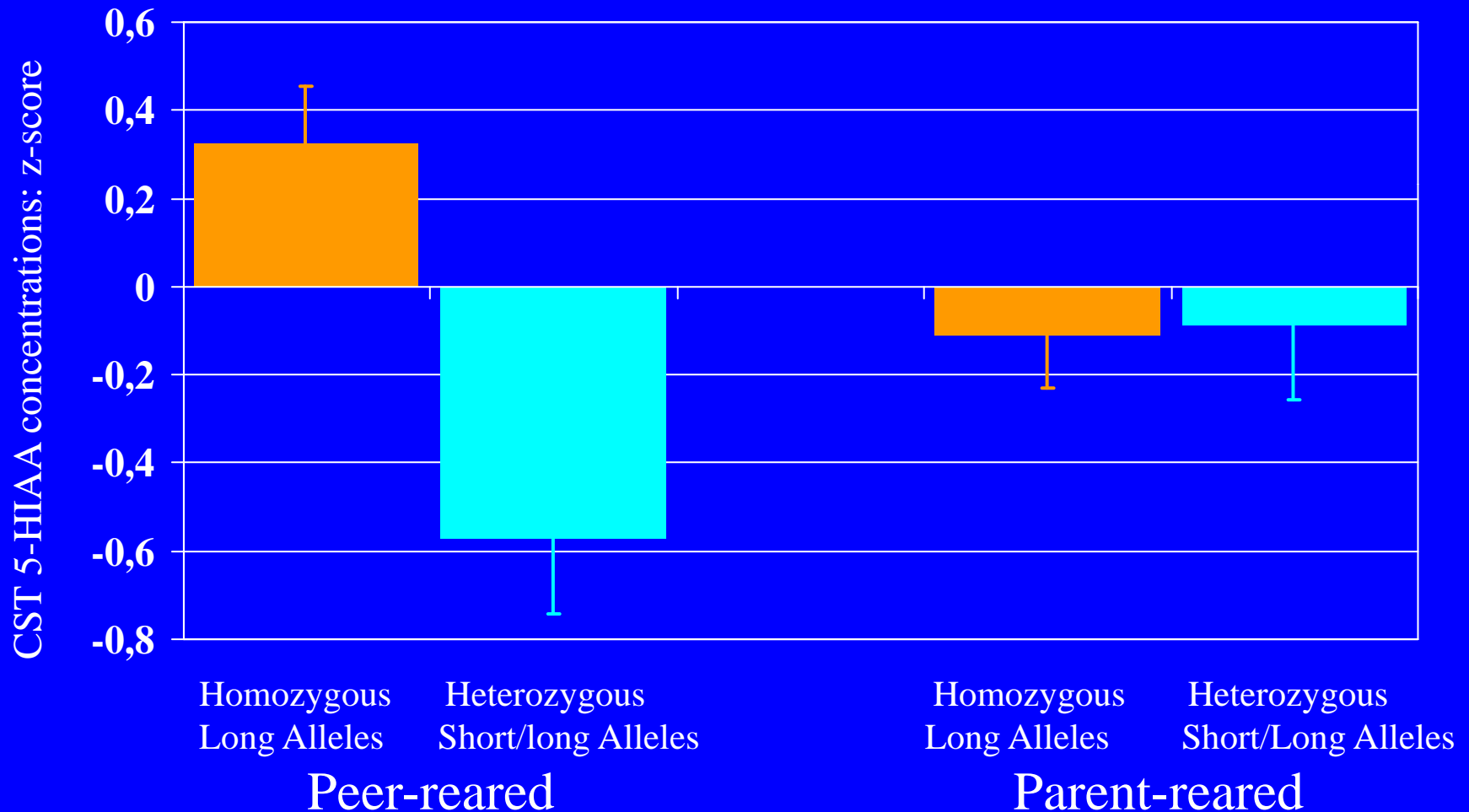
3. Is there other evidence (human or animal) on the postulated biological underpinning? (Need to use multiple biological strategies to test different aspects of the postulated mechanisms)

EFFECTS OF 5-HTT GENOTYPE ON RIGHT AMYGDALA ACTIVATION IN RESPONSE TO FEARFUL STIMULI (from Hariri et al., 2002)



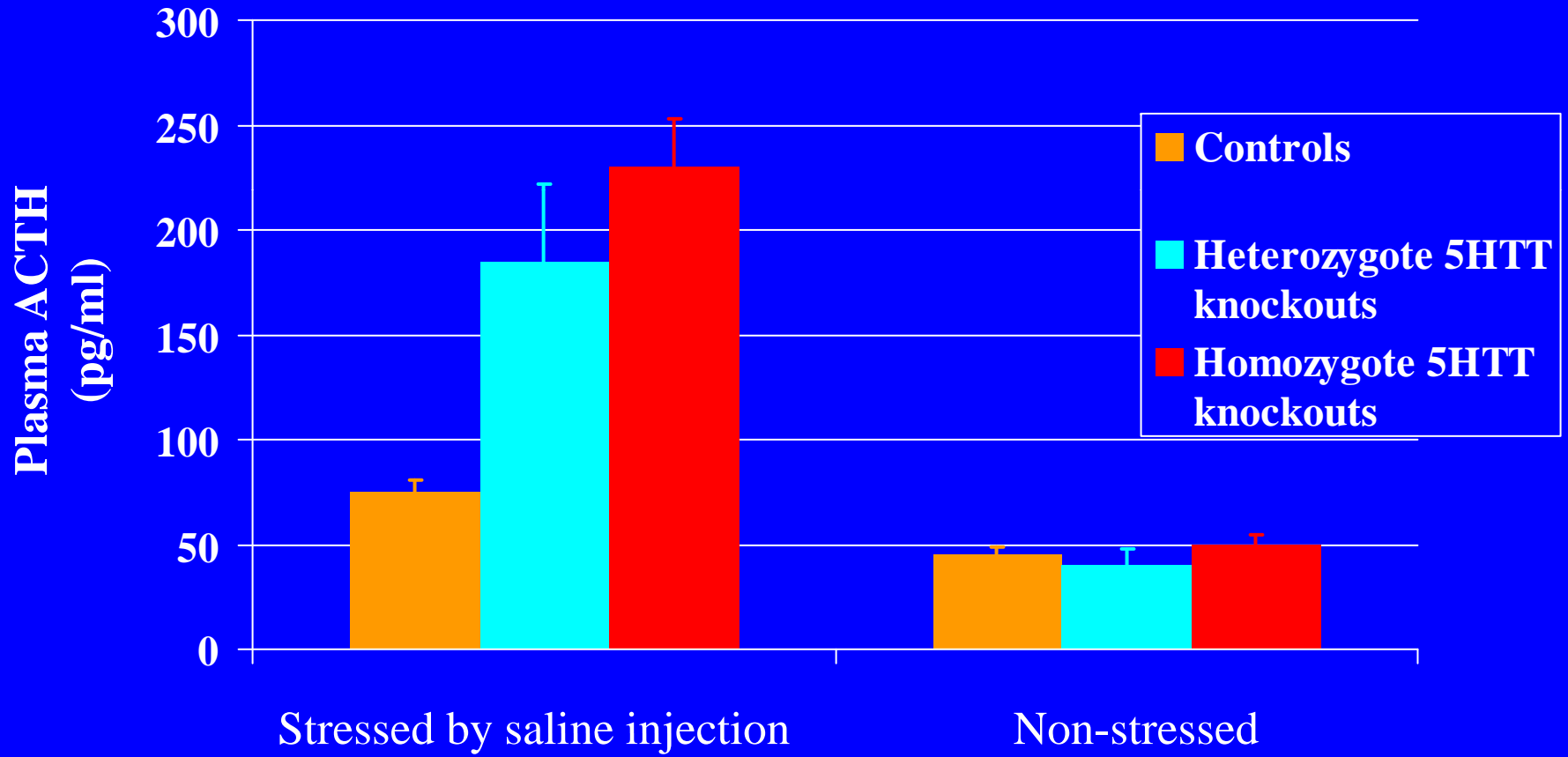
EFFECTS OF SEROTONIN TRANSPORTER GENE AND PATTERN OF REARING ON CENTRAL SEROTONIN FUNCTIONING

(from Bennett et al., 2002)



EFFECTS OF 5HTT KNOCKOUT ON PLASMA ACTH UNDER STRESS AND NO-STRESS CONDITIONS

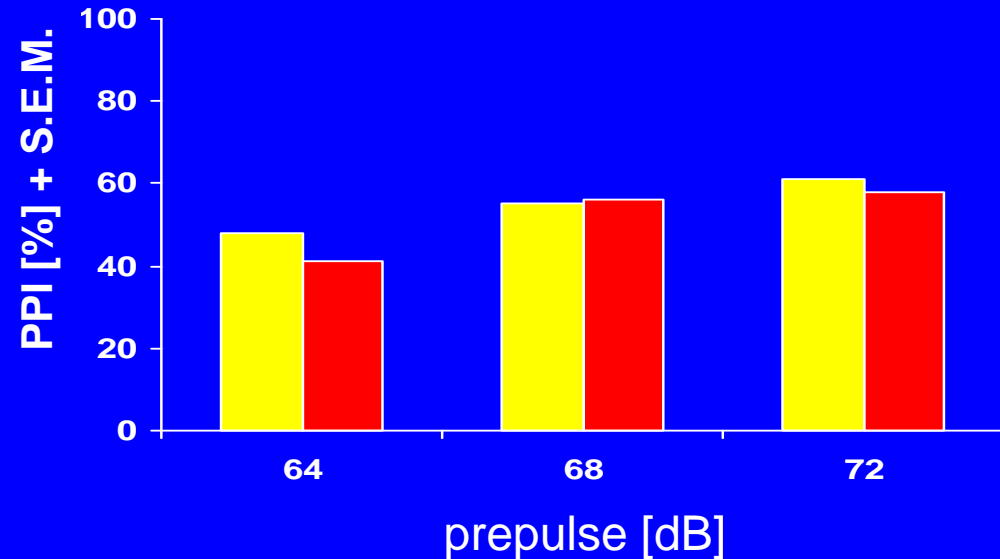
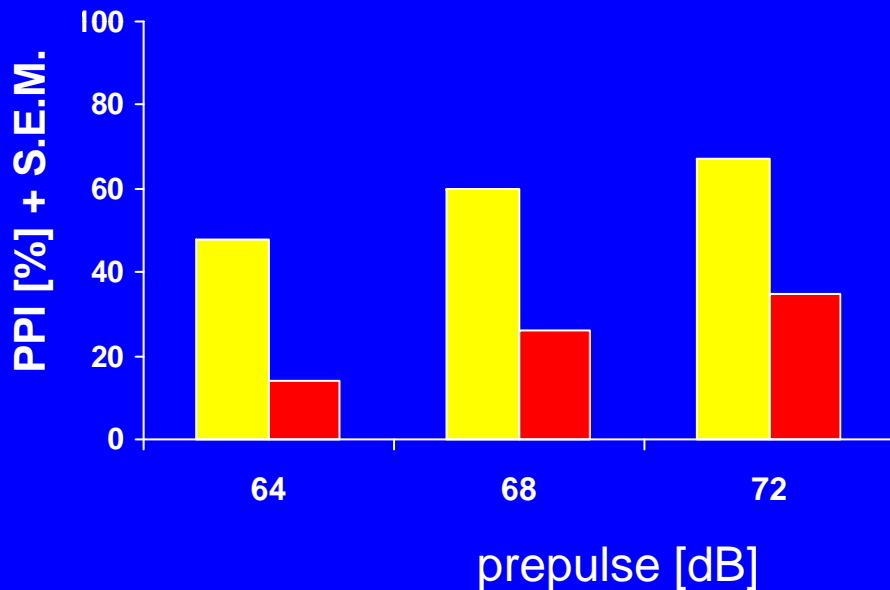
(from Murphy et al., 2001)



PUBERTAL, BUT NOT ADULT, CANNABIS TREATMENT IMPAIRS COGNITION (e.g. PPI, recognition memory)

Pubertal cannabinoid
treatment

Adult cannabinoid
treatment



■ Control ■ Cannabinoid
treatment

Schneider & Koch, 2003 (*Neuropsychopharmacology*)

IMPLICATIONS OF INTERACTION BETWEEN AN IDENTIFIED SUSCEPTIBILITY GENE AND MEASURED RISK ENVIRONMENT

Suggests that the postulated biological mechanism may be valid and that the gene and measured environment operate on the same causal pathway

ERA OF SIMPLY MEASURING HERITABILITY IS OVER AND NOW THERE IS THE OPPORTUNITY TO STUDY CAUSAL PROCESSES

Note that if the interest is in causal pathways (and I think that it should be), there must be use of focussed specific hypotheses, and molecular genetic strategies must be combined with other biological methodologies. Most crucially, the genetic research must move beyond the search for susceptibility genes “for” mental disorders, it must include a study of environmental risk mechanisms, and there must be study of the several forms of gene-environment interplay

WHY THE DIFFERENT FORMS OF GENE-ENVIRONMENT INTERPLAY MATTER

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WHY IS BEHAVIORAL GENETICS SOMETIMES VIEWED AS CONTROVERSIAL? I

1. Supposed problems with twin and adoptee studies
(but problems dealt with satisfactorily in good modern studies)
2. Fraud and bias
(There are examples of both – e.g. Burt – but the conclusions are much the same if these findings are excluded)
3. The neglect of social influences as a consequence of an over-emphasis of genetic effects
(This is a risk, as shown by genetic evangelism, but a key message of genetics is that gene-environment interplay is crucial)

WHY IS BEHAVIORAL GENETICS SOMETIMES VIEWED AS CONTROVERSIAL? II

4. Scepticism over the notion that there could be genes for behaviors that are manifestly social
(Of course, there could not be a gene for crime or divorce but genes can and do affect the propensity to behave in ways that increase the likelihood of particular social behaviors)
5. The inappropriateness of neurogenetic determinism
(Claims of direct genetic effects are unjustified; also, everything cannot be reduced to the molecular level. Nevertheless, reductionism is appropriate with respect to attempts to derive simplifying principles and to identify both organisational constructs and causal pathways)

GENETIC INFLUENCES ON MENTAL FUNCTIONING ARE SUBSTANTIAL

Strong Genetic Effect Heritabilities

Approximate

%

Autism

90

Schizophrenia

80

Bipolar Disorder

80

Attention deficit/hyperactivity

70

Intelligence

60

GENETIC INFLUENCES ON MENTAL FUNCTIONING ARE SUBSTANTIAL

<u>Moderate/Modest Genetic Effect</u> <u>Heritabilities</u>	<u>Approximate</u> %
Major depression	40
Generalized anxiety	30
Parenting	30
Life events	20

CAN THESE HERITABILITIES BE RELIED ON AS VALID FINDINGS?

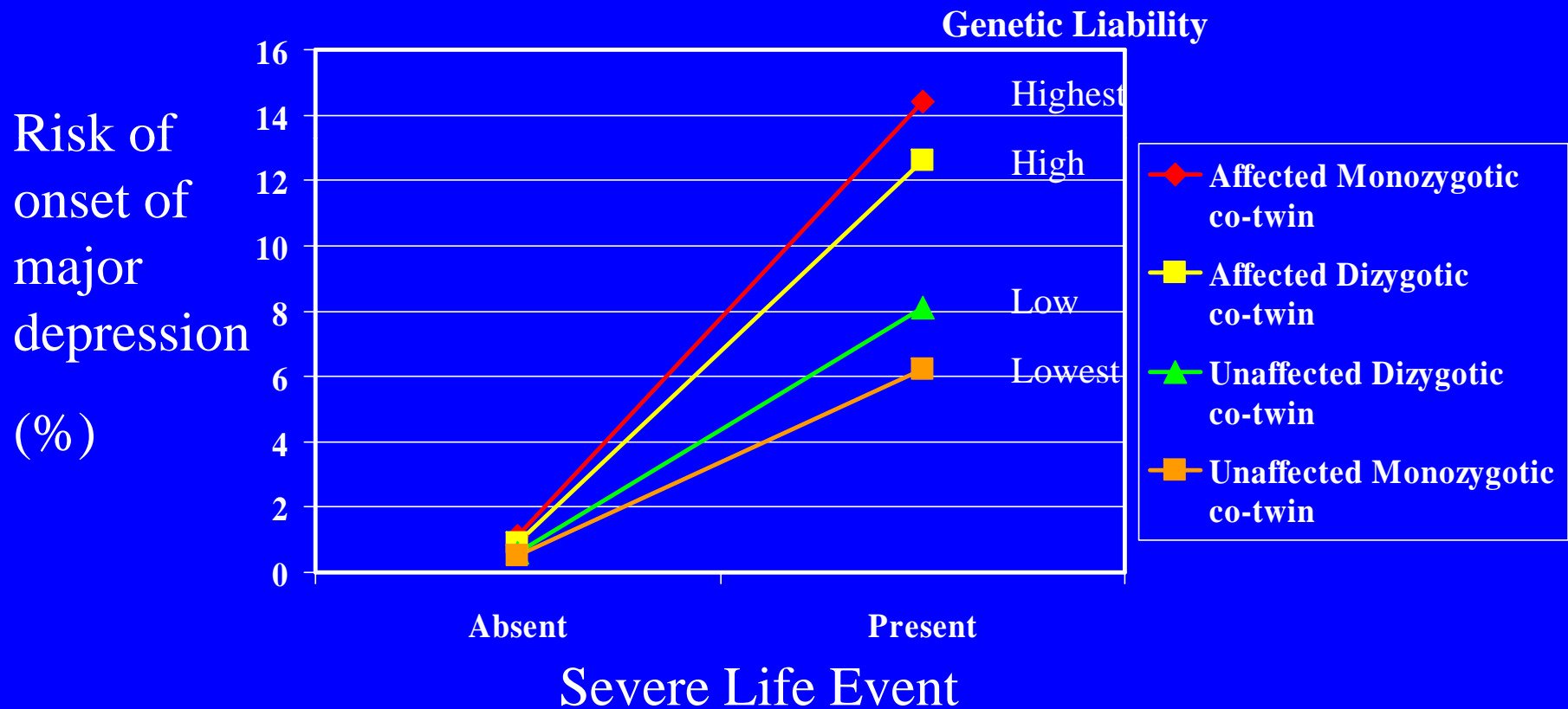
YES, there is plenty of replicated evidence from high quality studies

BUT

1. Heritability figures include the effects of gene-environment correlations and interactions; accordingly, they incorporate the co-action of genes and environments
2. Because they are population statistics, their value will change if either the gene pool or mix of environments alters
3. Heritability measures genetic effects on the population variance of traits, but it does not indicate how the genes operate and it does not mean that the genes operate on the trait itself (rather than on some intermediate variable)
4. Heritability is uninformative about the strength of the genetic effects on a trait at an individual level

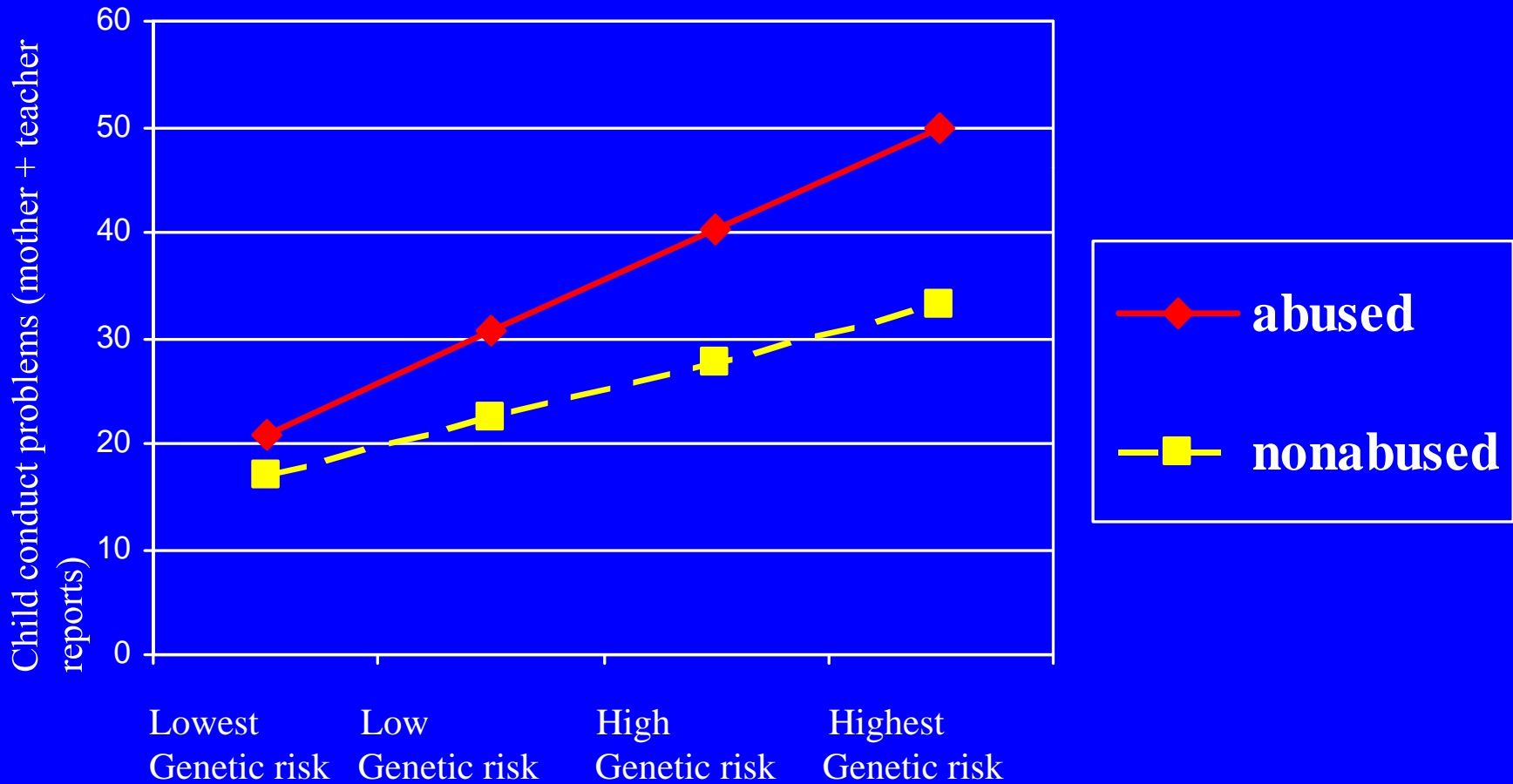
RESPONSE TO LIFE EVENTS AS A FUNCTION OF GENETIC LIABILITY

(from Kendler et al., 1995)



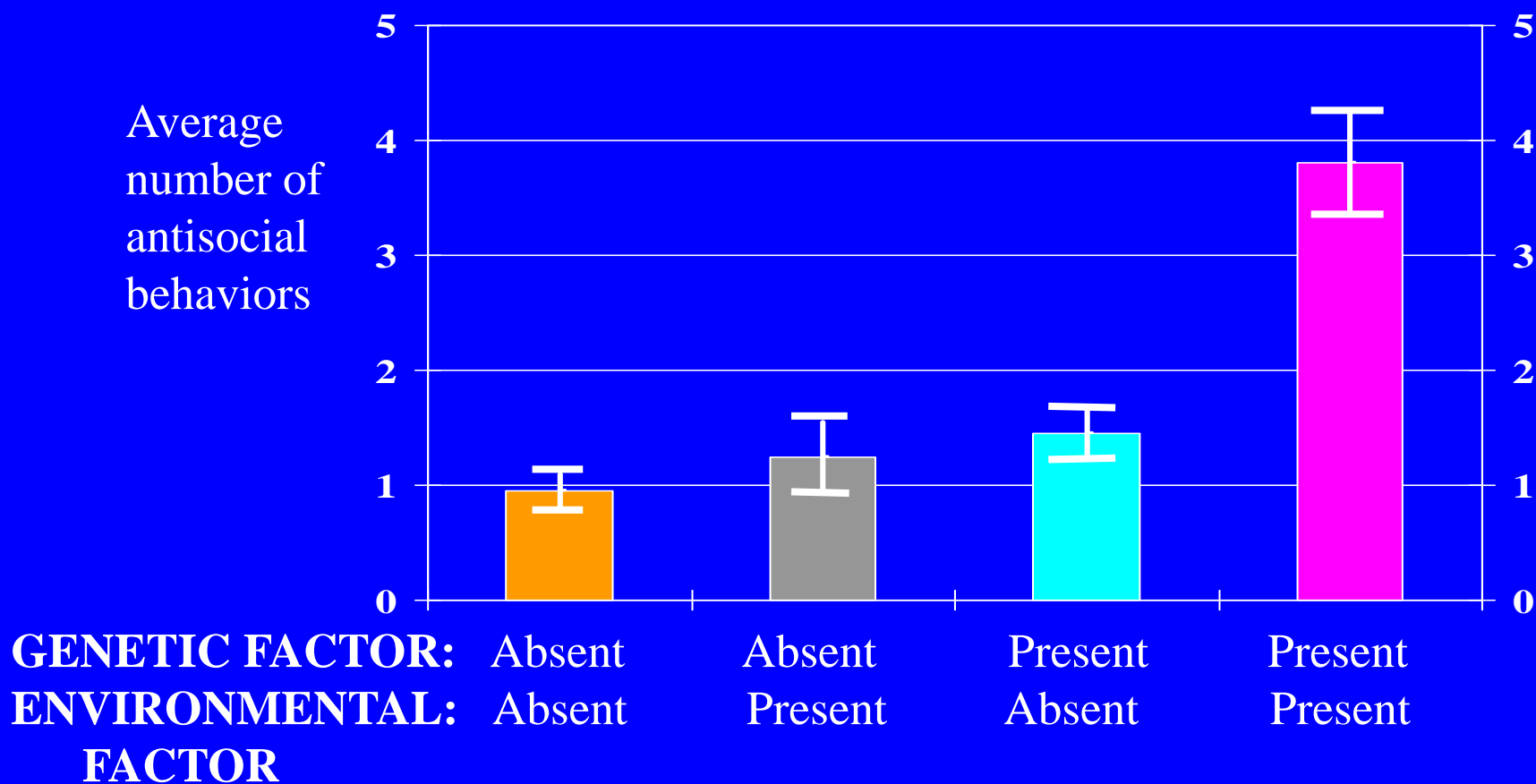
CHILD CONDUCT PROBLEMS AS A FUNCTION OF GENETIC RISK AND PHYSICAL MALTREATMENT

(from Jaffee et al., 2003)



GENE-ENVIRONMENT INTERACTION IN LIABILITY TO ANTISOCIAL BEHAVIOR

(From Cadoret, Cain & Crowe, 1983)



INTERACTION BETWEEN ANTISOCIAL PERSONALITY DISORDER BIOLOGIC BACKGROUND (ASP BIO) AND ADVERSE ADOPTIVE HOME ENVIRONMENT: EFFECT ON ADOLESCENT AGGRESSIVITY (n = 175) (Cadoret et al., 1995)

