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Differential Susceptibility to Environmental Influences

Jay Belsky

17 November 2010

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OUTLINE

I. Evolutionary Foundations
II. Diathesis-Stress vs. Differential Susceptibility
III. Evidence
    A. Phenotypic: Negative Emotionality
    B. Endophenotypic: Physiological Reactivity
    C. Genetic
        1. 5-HTTPLR, MAO, DRD4, ESR1
        2. Beyond Single Genes
IV. Unknowns in the differential-susceptibility equation

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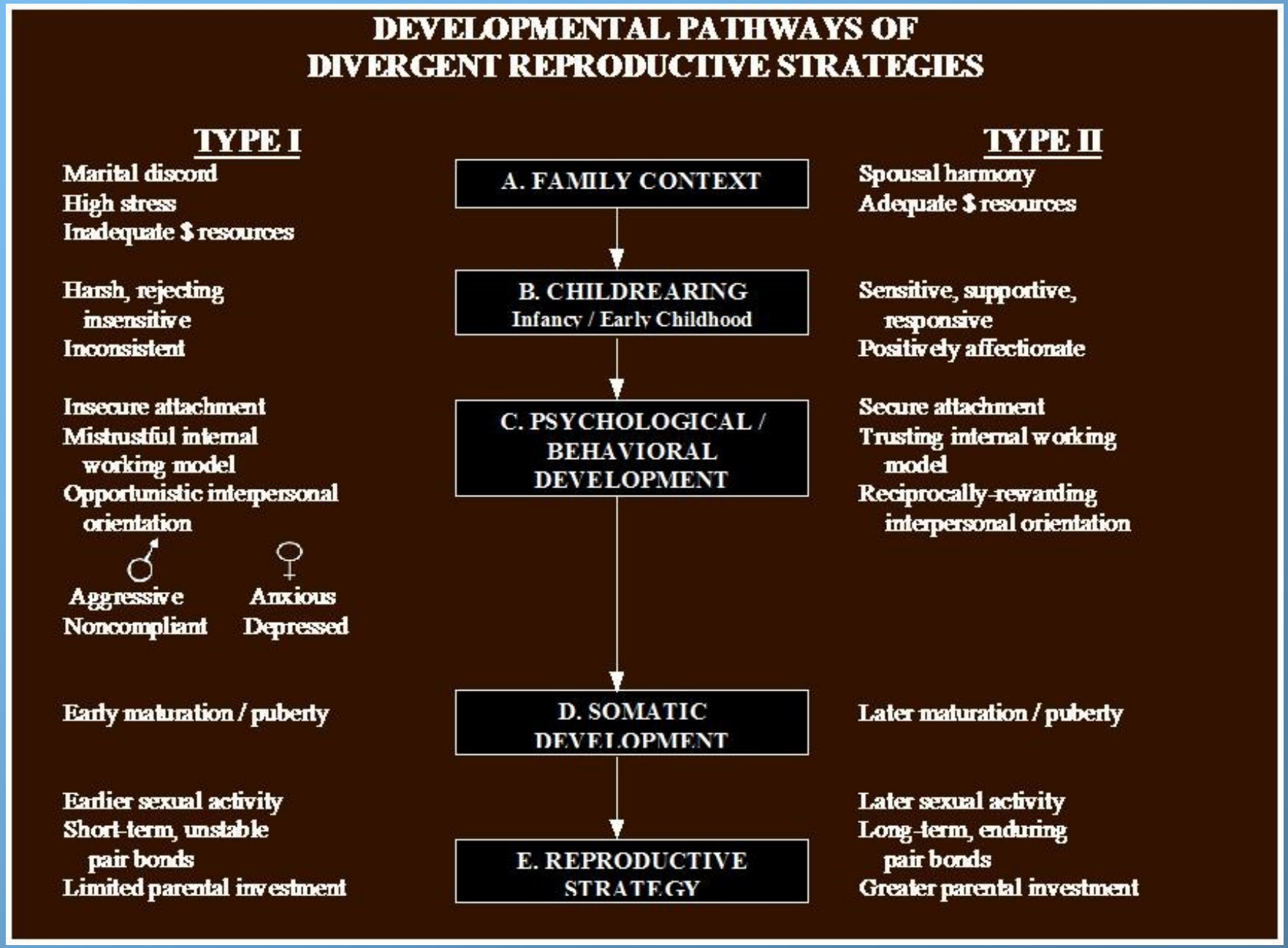
EVOLUTIONARY FOUNDATIONS

DEVELOPMENTAL PATHWAYS OF DIVERGENT REPRODUCTIVE STRATEGIES



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BEHAVIOR-GENETIC CHALLENGE: GENETIC MEDIATION "MASQUERADING" AS ENVIRONMENTAL EFFECTS

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WHY—not how--WOULD NATURAL SELECTION CRAFT AN ORGANISM WHOSE FUTURE FUNCTIONING IS INFLUENCED BY ITS EARLIER EXPERIENCES?

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POSSIBLE SOLUTION: CONDITIONAL *AND* ALTERNATIVE REPRODUCTIVE STRATEGIES

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AN EVOLUTIONARY ARGUMENT

Because the future is inherently uncertain, parents cannot know for certain—either consciously or unconsciously—what rearing strategies and practices will prove most beneficial to their offspring's long-term well being, including their own and their children's reproductive fitness, the ultimate "target" of natural selection. This is just as true today as it was in the ancestral environmentS in which humans evolved (i.e., EEAs, not EEA).

Because it was possible, then, for parents to inadvertently lead their children down figurative if not literal dead ends—because the future turned out different from what was (consciously or unconsciously) anticipated--it would have benefited parents to "hedge their bets" by bearing children whose development was more and less likely to be influenced by the rearing environment.

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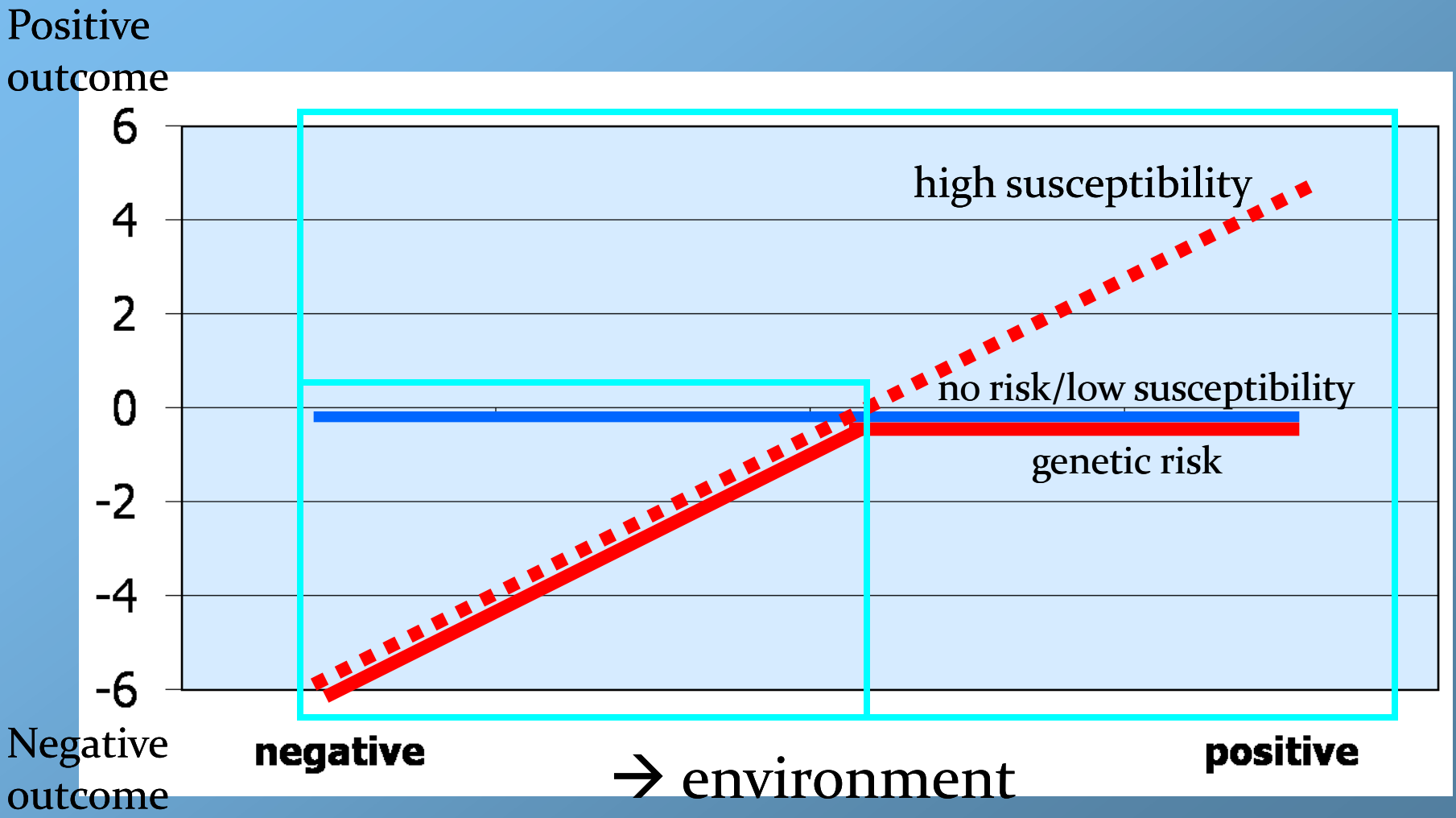
HOW DIFFERENTIAL SUSCEPTIBILTY DIFFERS FROM DIATHESIS STRESS

Diathesis-Stress vs. Differential Susceptibility



Bakermans-Kranenburg & Van IJzendoorn (2007) *JCPP, 48*, 1160-1173

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It's one thing to posit differential susceptibility, but is there any evidence?

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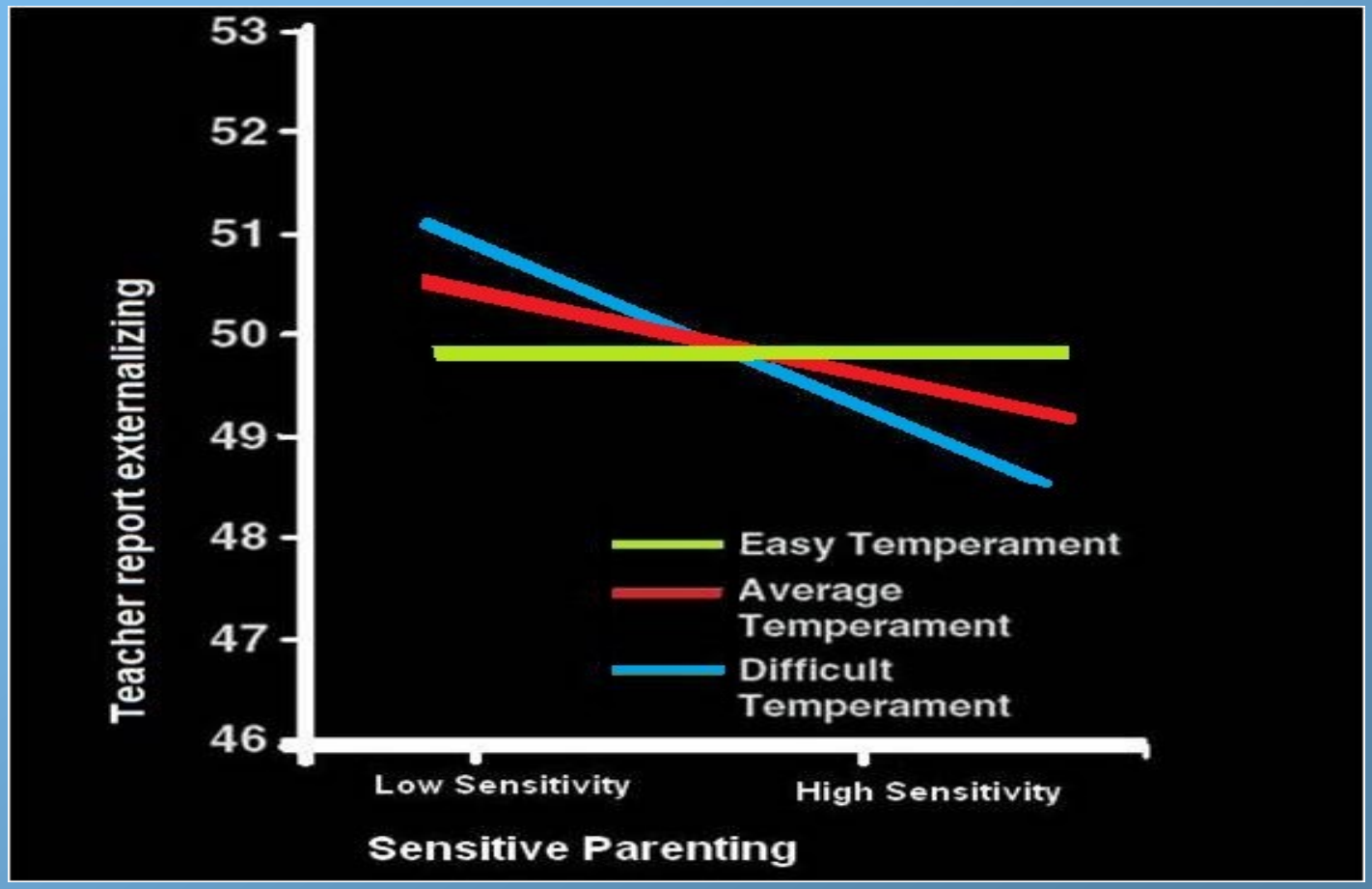
INFANT TEMPERAMENT AS A SUSCEPTIBILITY MARKER

Observed Parenting and Teacher-Rated Behavior Problems in Kindergarten



Bradley, R. H., & Corwyn, R. F. (2008). Infant temperament, parenting, and externalizing behavior in first grade: a test of the differential susceptibility hypothesis. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 49*(2), 124-131.

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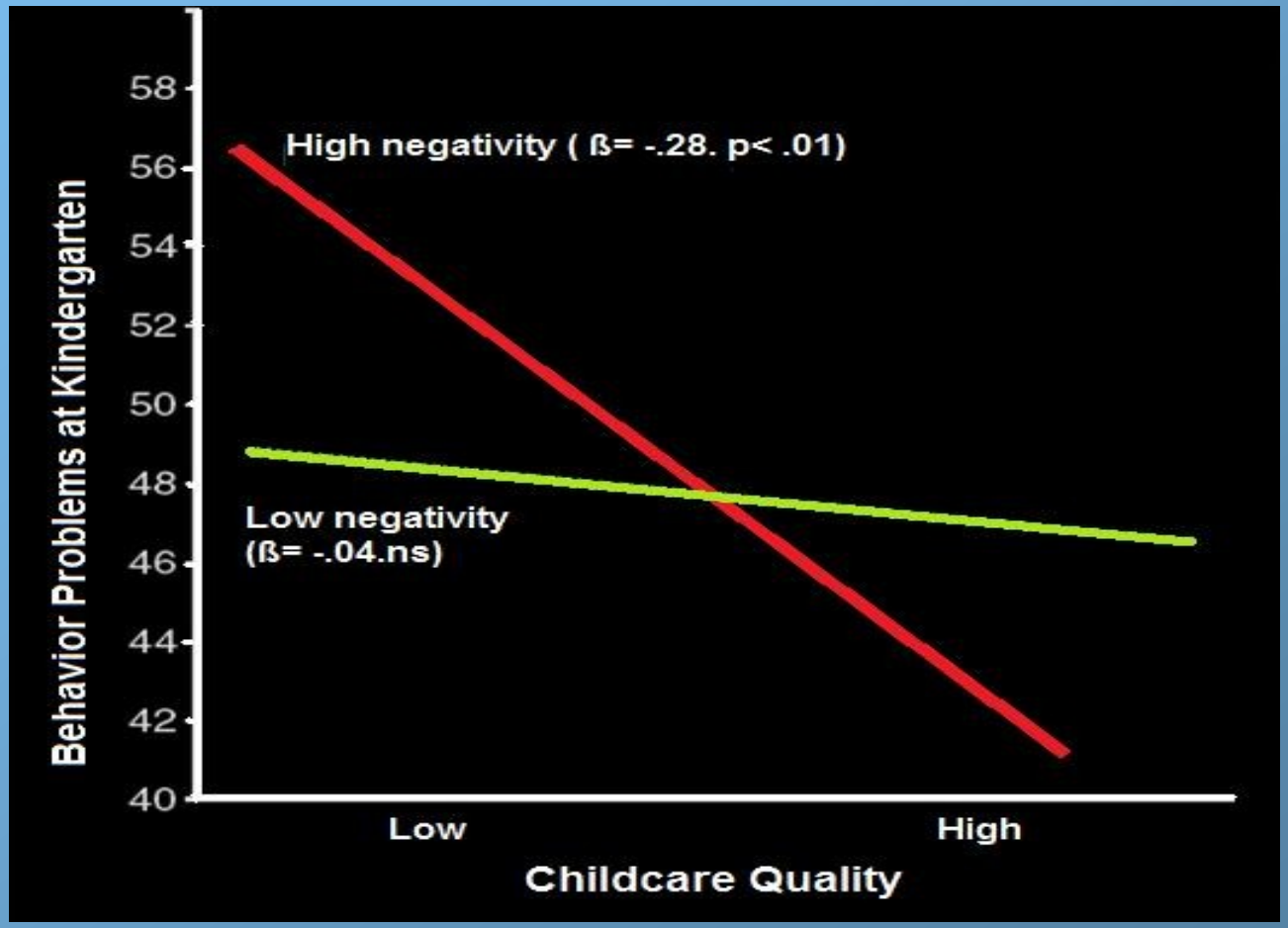
Observed Quality of Child Care and Teacher-Rated Behavior Problems in Kindergarten



Pluess, M., & Belsky, J. (2009). Differential Susceptibility to Rearing Experience: The Case of Childcare. *Journal of Child Psychology and Psychiatry and Allied Disciplines*.

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WHAT ABOUT DADS?

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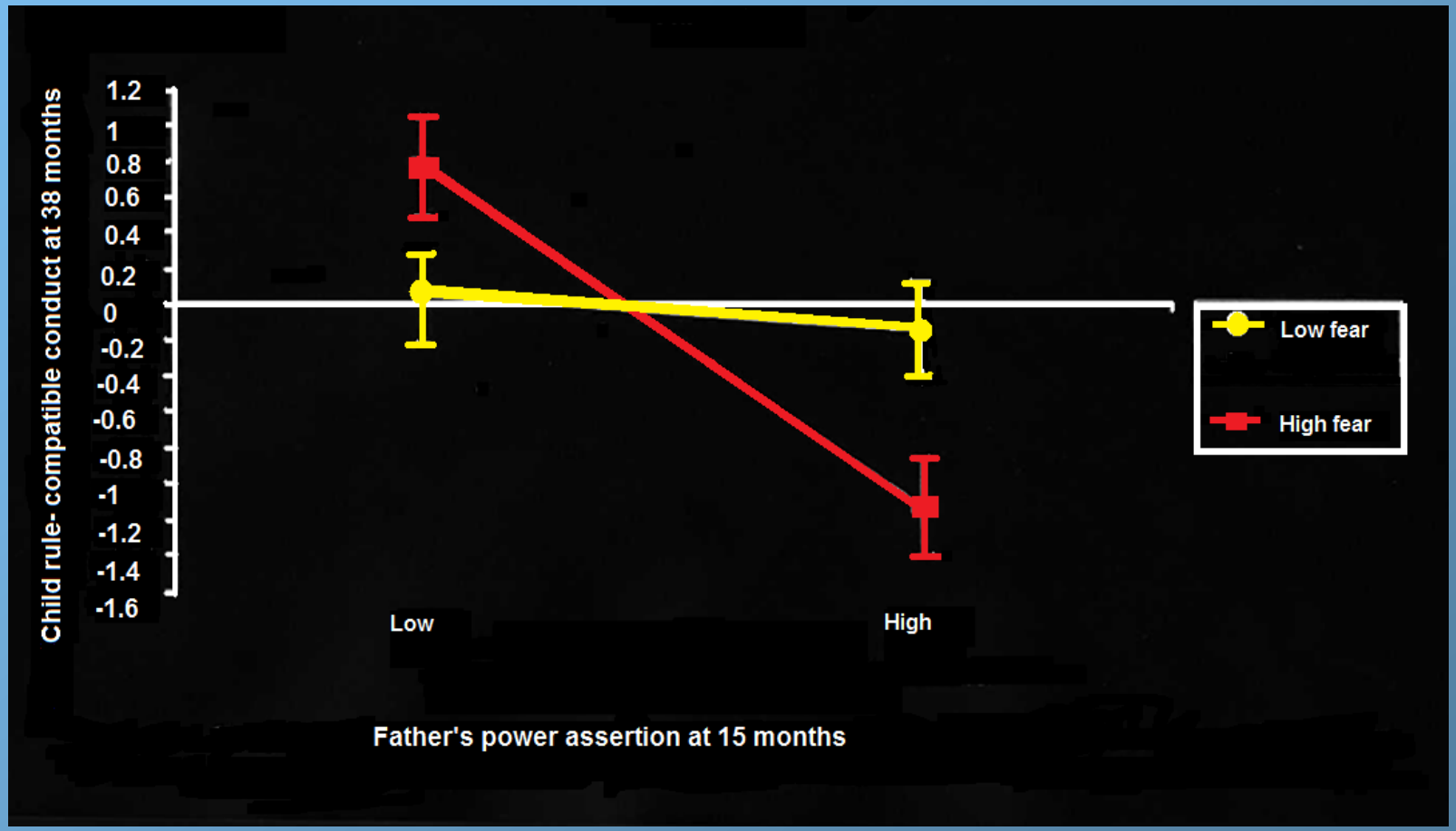
Observed Paternal Power Assertion (15 months) and Child Rule-Compatible Conduct (38 months)



Kochanska, G., Aksan, N., & Joy, M. E. (2007). Children's fearfulness as a moderator of parenting in early socialization: Two longitudinal studies. *Developmental Psychology, 43*(1), 222-237.

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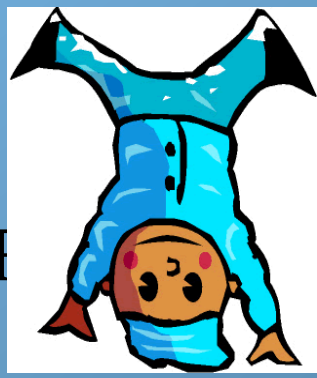
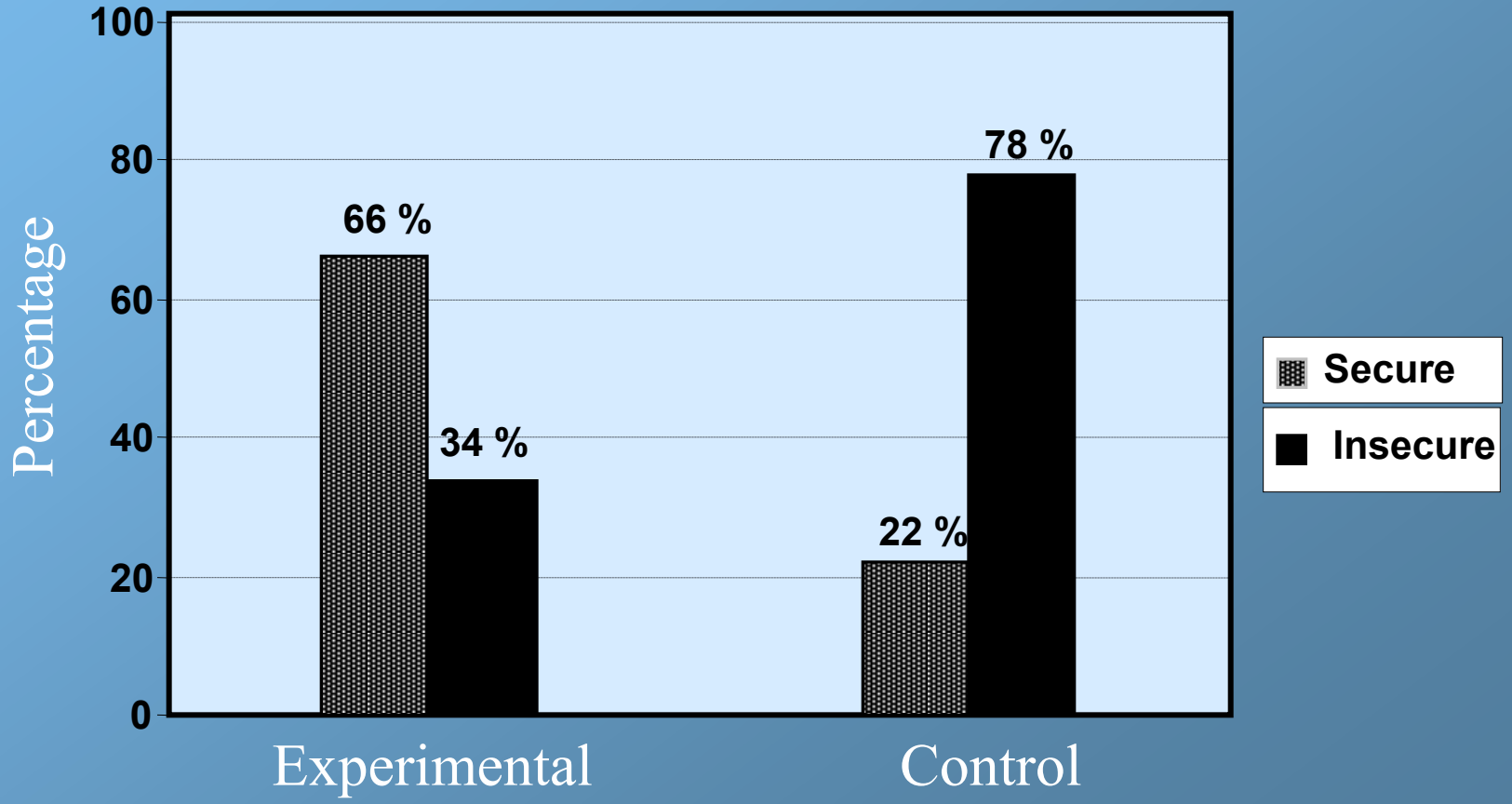
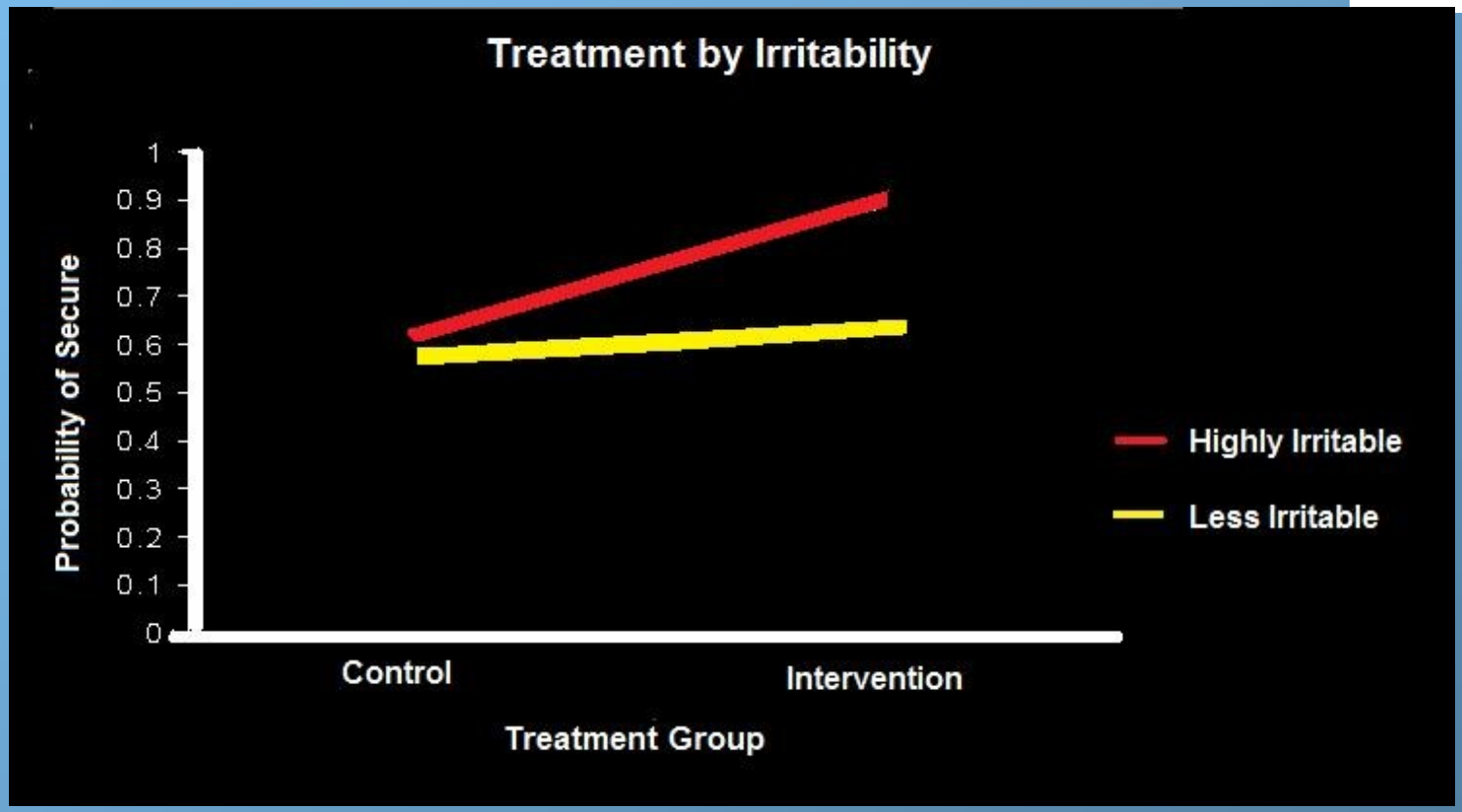


ATTACHMENT SECURITY AS FUNCTION OF EXPERIMENTAL-CONTROL TREATMENT

(van den Boom, 1990, 1994)



Experimental Enhancement of Maternal Sensitivity via Circle of Security: Effects on Attachment Security



NOTE: Only highly irritable newborns included in study; those labelled "highly irritable" met van den Boom (2004) criteria; but "less irritable" group still more irritable than many other newborns included in sample.

Cassidy, J., et al. (in press). Enhancing infant attachment security: An examination of treatment efficacy and differential susceptibility. *Development & Psychopathology*.

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BEYOND TEMPERAMENT: *Endophenotypes as Moderators of Environmental Effects (Boyce & Ellis, 2005)*

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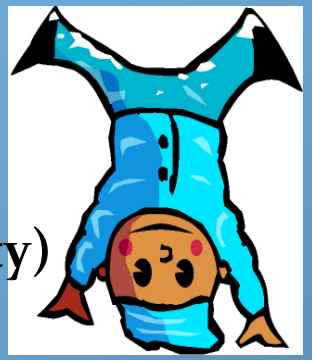
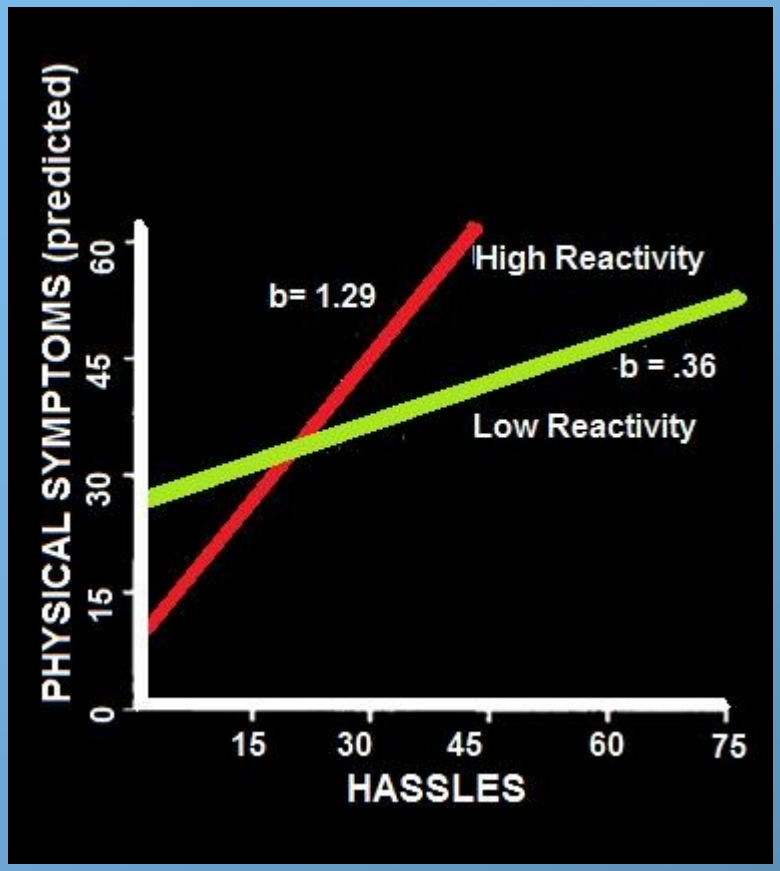
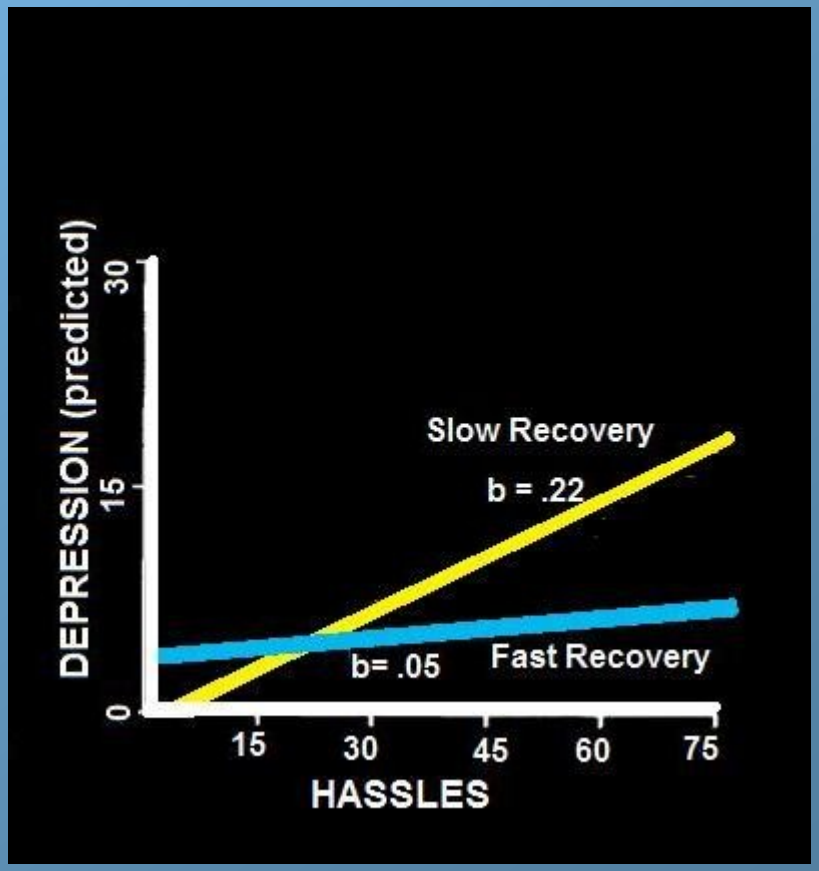


Daily Hassles, Physical Health & Depression (Blood Volume Pulse Amplitude and Heart Rate Reactivity)





Gannon, L., Banks, J., Shelton, D., & Luchetta, T. (1989). The mediating effects of psychophysiological reactivity and recovery on the relationship between environmental stress and illness. *Journal of Psychosomatic Research, 33*(2), 167-175.

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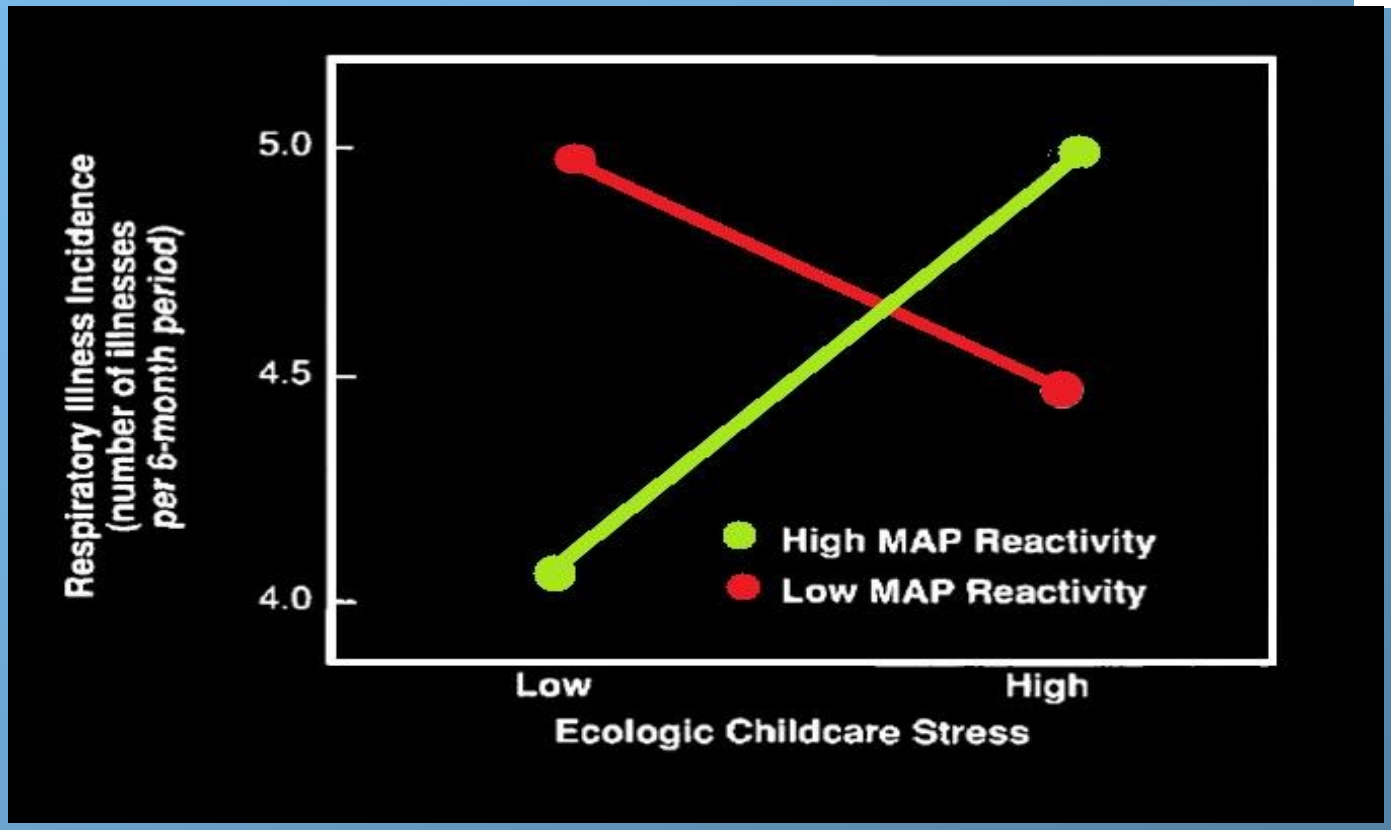
Childcare Stress and Respiratory Illness
(Mean Arterial Blood Pressure Reactivity)



Boyce, W., Chesney, M., Alkon, A., Tschann, J., Adams, S., Chesterman, B., Cohen, F., Kaiser, P., folkman, S., & Wara, D. (1995). Psychobiological reactivity to stress and childhood respiratory illnesses: Results from two prospective studies. *Psychosomatic Medicine, 57,* 411-422.

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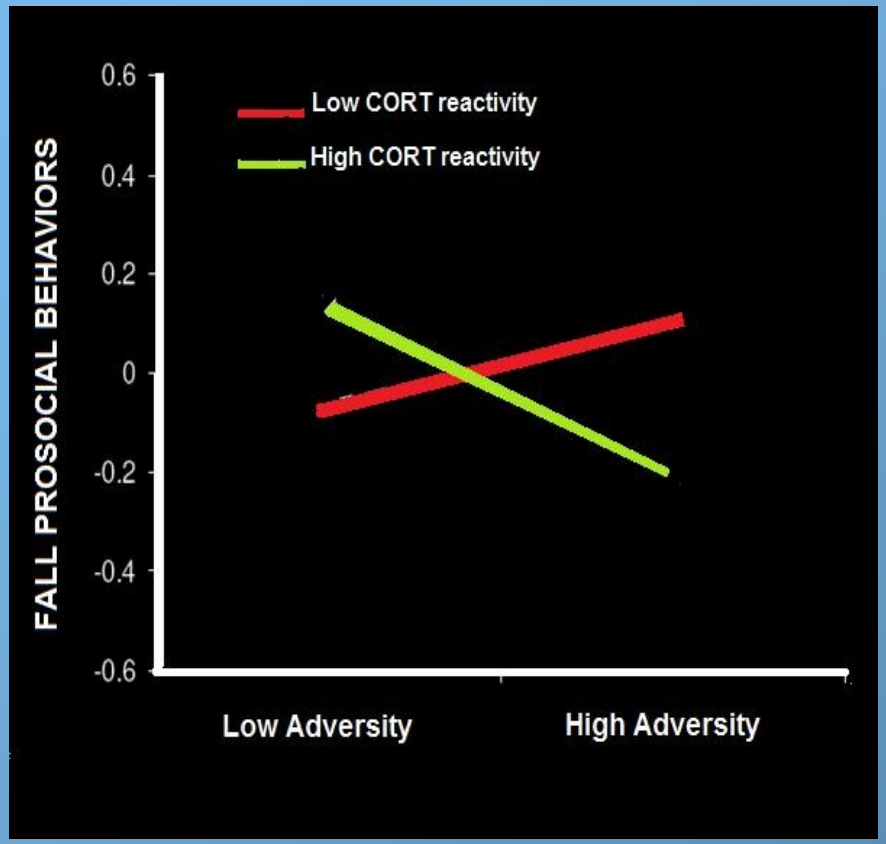
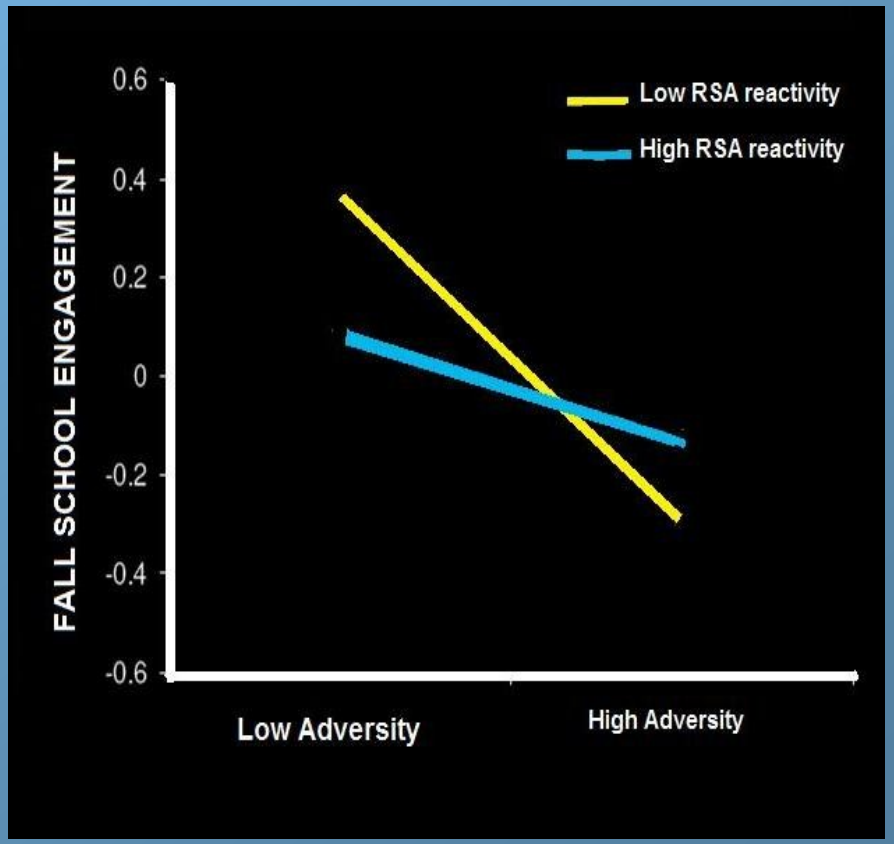
Family Adversity, Socio-emotional Behavior and School Readiness

(Cortisol and Respiratory Sinus Arrhythmia Reactivity)





Obradovic, J., Bush, N. R., Stamperdahl, J., Adler, N. E., & Boyce, W. T. (2010). Biological Sensitivity to Context: The Interactive Effects of Stress Reactivity and Family Adversity on Socio-emotional Behavior and School Readiness. *Child Development*.

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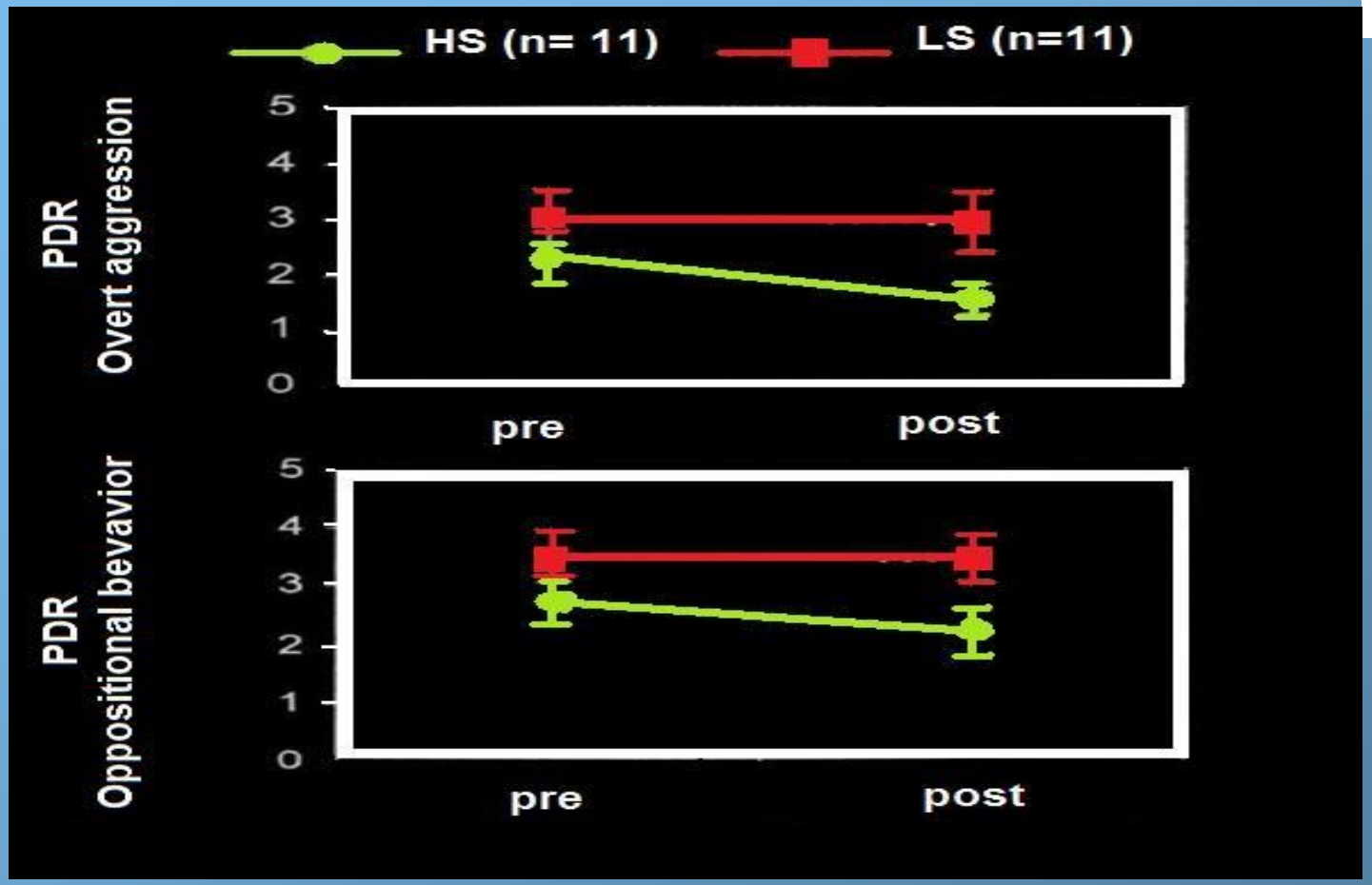
Intervention for Children with Disruptive Behavior Disorder

(Cortisol Stress Reactivity: HS=Highly Reactive)



Pre- and postrtreament comparison of Parent Daily Report (PDR) Overt Aggression scores and Oppositional Behavior scores in high cortisol stress responsivity (HS) and low cortisol stress responsivity (LS) in disruptive behavior disorder subgroups

Van de Wiel et al. (2004). Cortisol and treatment effect in children with disruptive behavior disorder: A preliminary study. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*, 1011-1018.

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BEYOND TEMPERAMENT AND PHYSIOLOGY:

Genes as Moderators of Environmental Effects (GXE)

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The 5-HTTPLPR Gene

The serotonin-transporter gene (5-HTTP) is a good gene to consider because there is some evidence that infants carrying the short (vs. long) allele are more negatively emotional as newborns (Auerbach et al., 2005). Short alleles have also been linked to depression in females and vulnerability to the depression fostering effects of negative life events in adulthood (Caspi et al., 2003).

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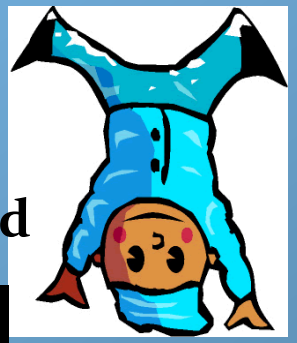
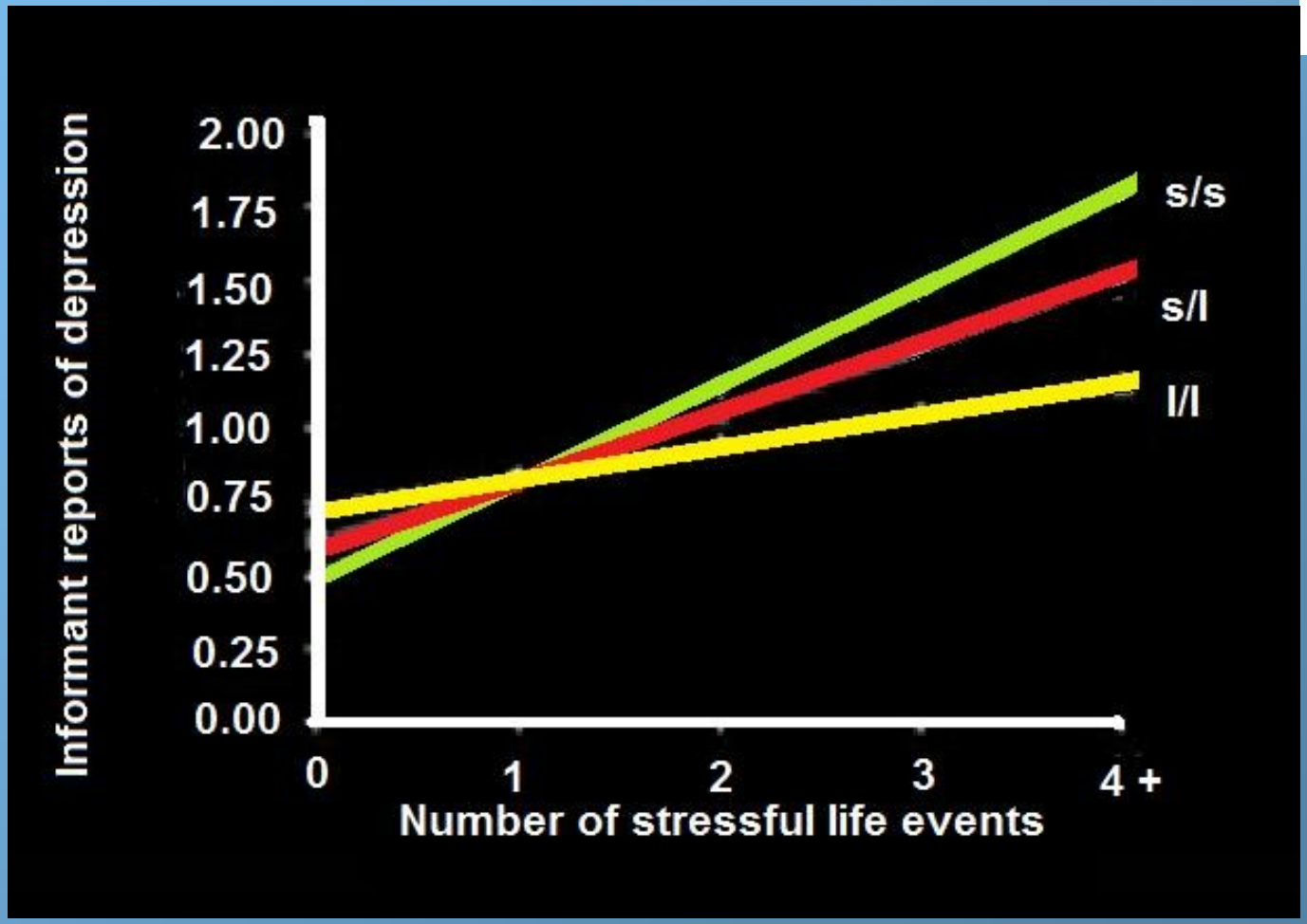


Stressful Life Events and Depression in Young Adulthood



Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mil,l J., Martin, J., Braithwaite, A. & Poulton, R (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5 HTT gene. Science, 301, 386-389.

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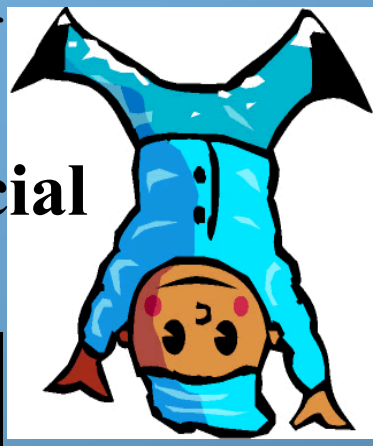
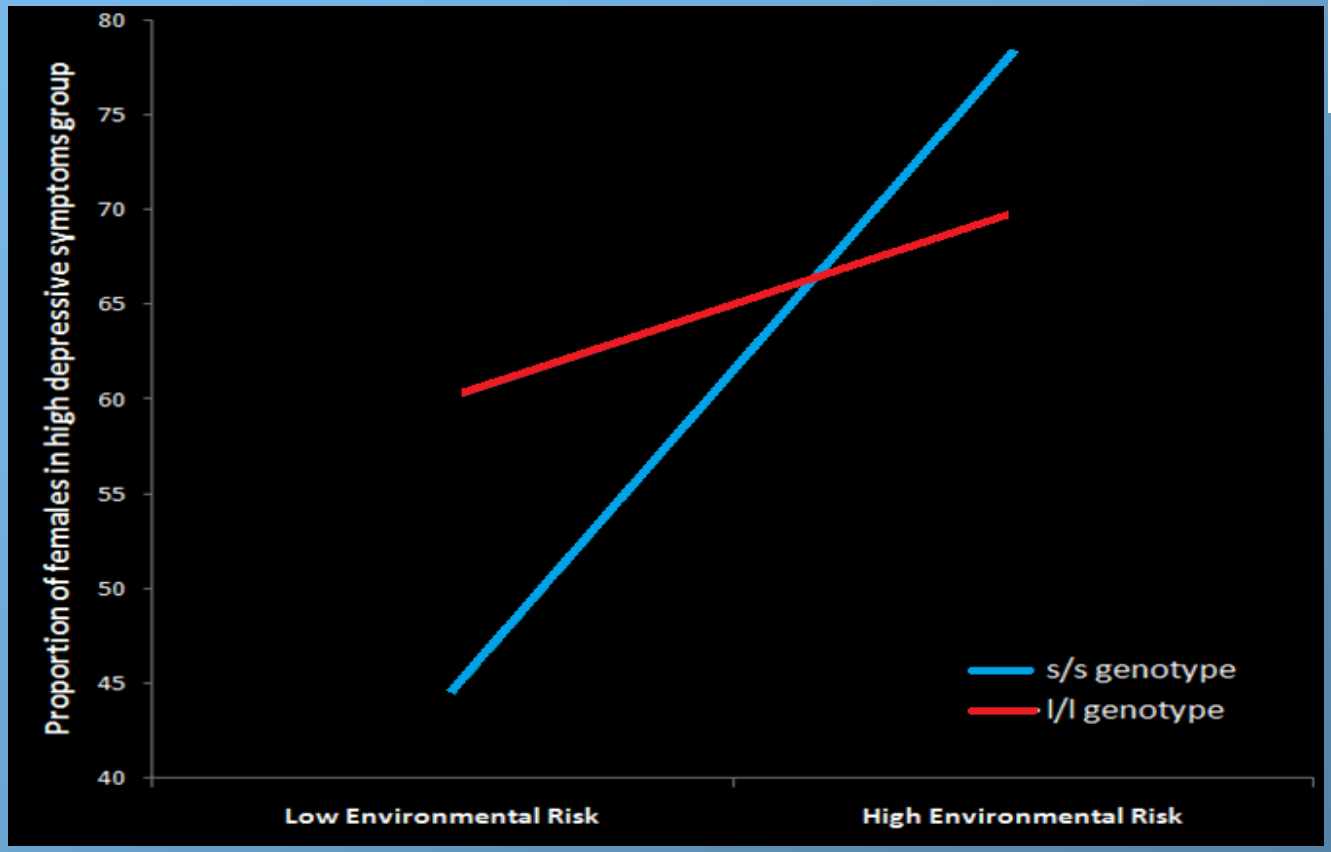


Family Risk (SES, Adverse Life Events, Social Adversity) and Adolescent Depression

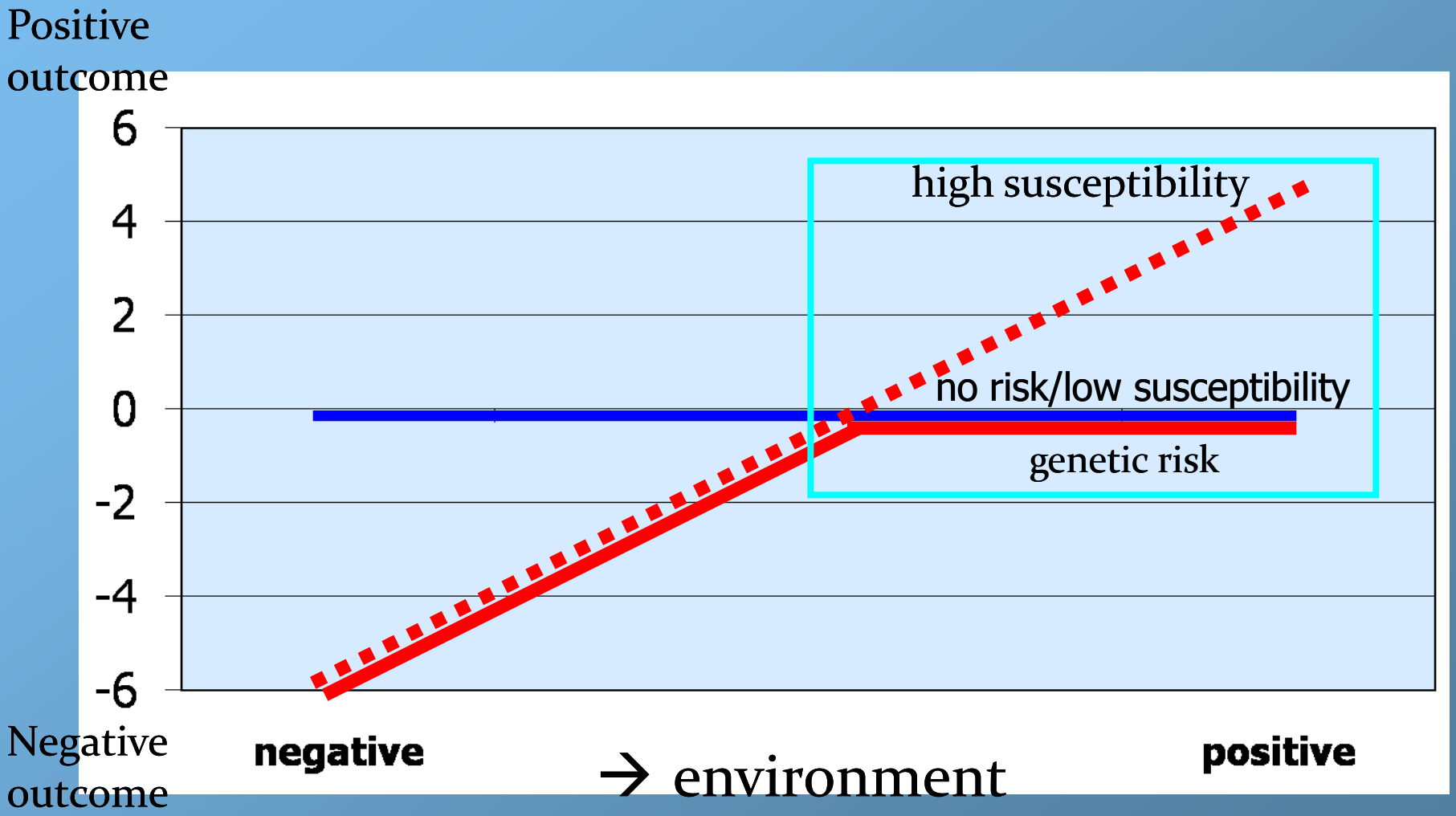


Eley et al., (2004) data re-graphed and re-evaluated by Belsky et al. (2009)

Eley, T. C., Sugden, K., Corsico, A., Gregory, A. M., Sham, P., McGuffin, P., et al. (2004). Gene-environment interaction analysis of serotonin system markers with adolescent depression. *Molecular Psychiatry, 9*, 908-915.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummet, B., & Williams, R. (2009). Vulnerability Genes or Plasticity Genes? M*olecular Psychiatry, 14*, 746-754.

Diathesis-Stress vs. Differential Susceptibility



Bakermans-Kranenburg & Van IJzendoorn (2007) *JCPP, 48*, 1160-1173

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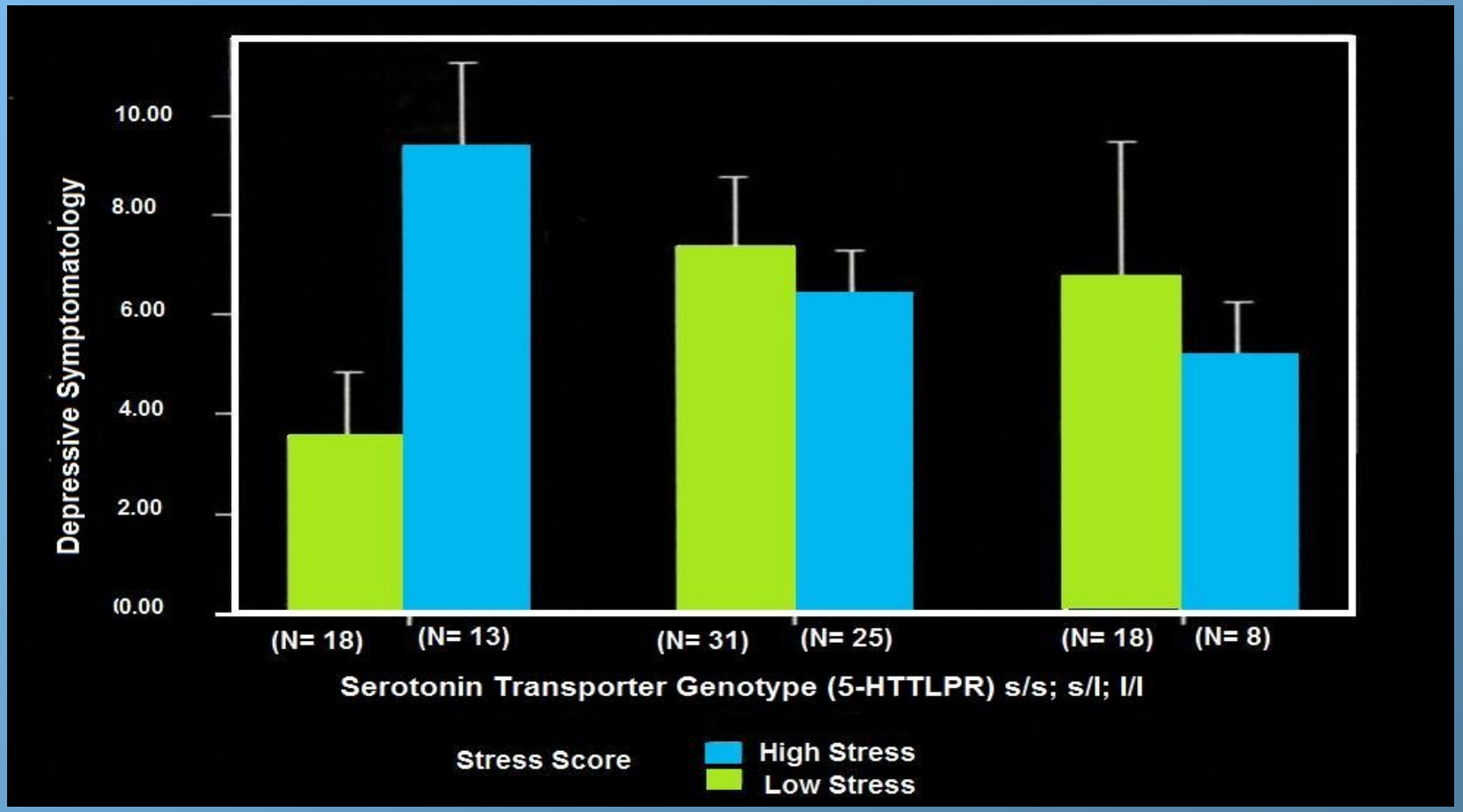
Recent Life Events and Depression in Young Adulthood



Taylor, S. E., Way, B. M., Welch, W. T., Hilmert, C. J., Lehman, B. J., & Eisenberger, N. I. (2006). Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. Biological Psychiatry, 60(7), 671-676.

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Perceived Racial Discrimination and Conduct Problems

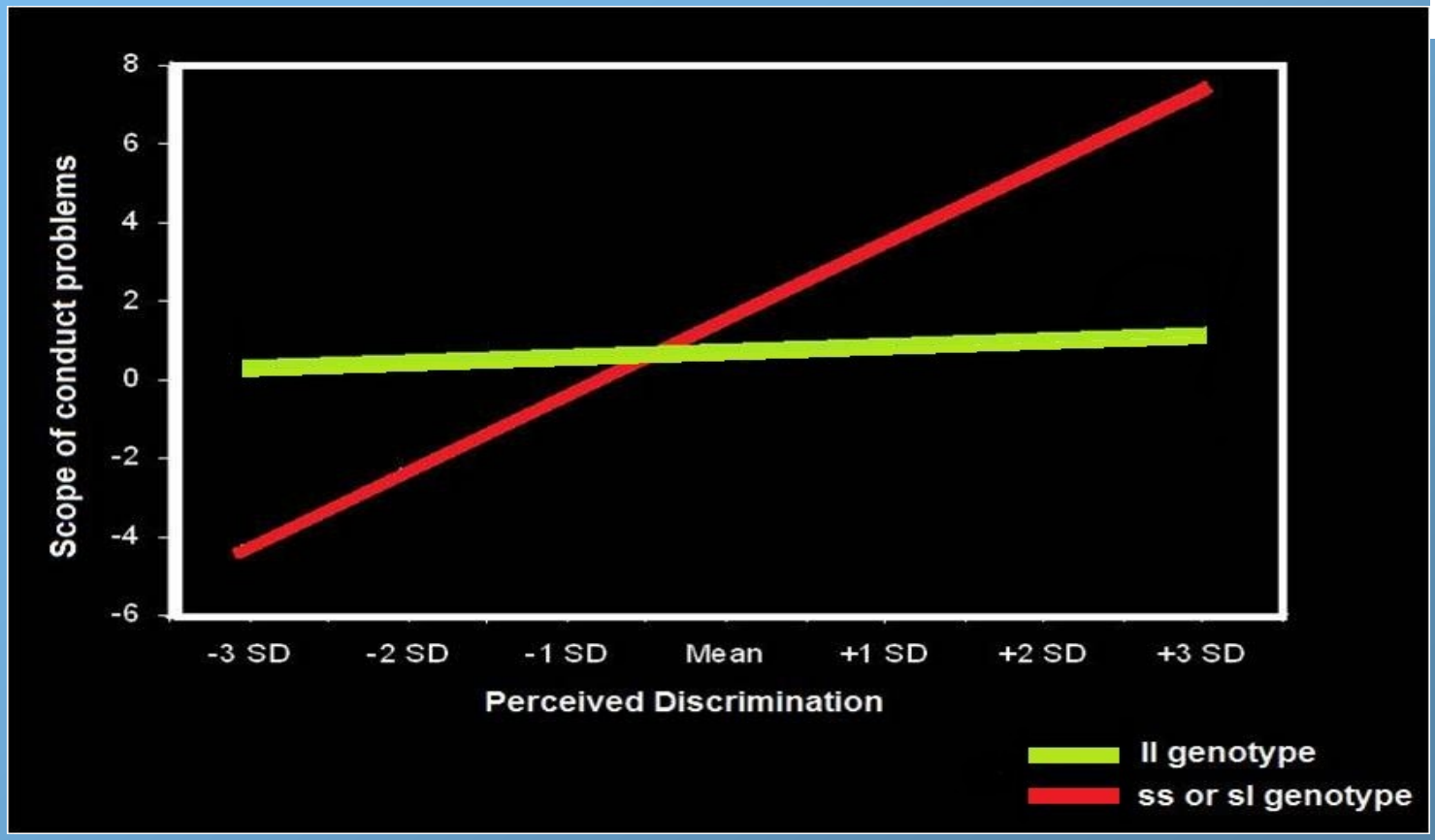

Figure 2. Results of the analysis for male youths only. Slopes of conduct problems for levels of perceived discrimination, ranging from -3 to +3 standard deviations from the sample mean, plotted separately for male youths with the *ll* genotype and male youths with the *ss* or *sl* genotype.

Brody, G.H., et al. (submitted). Perceived discrimination, 5-HTTLPR status, and conduct problems: A differential susceptibility analysis.

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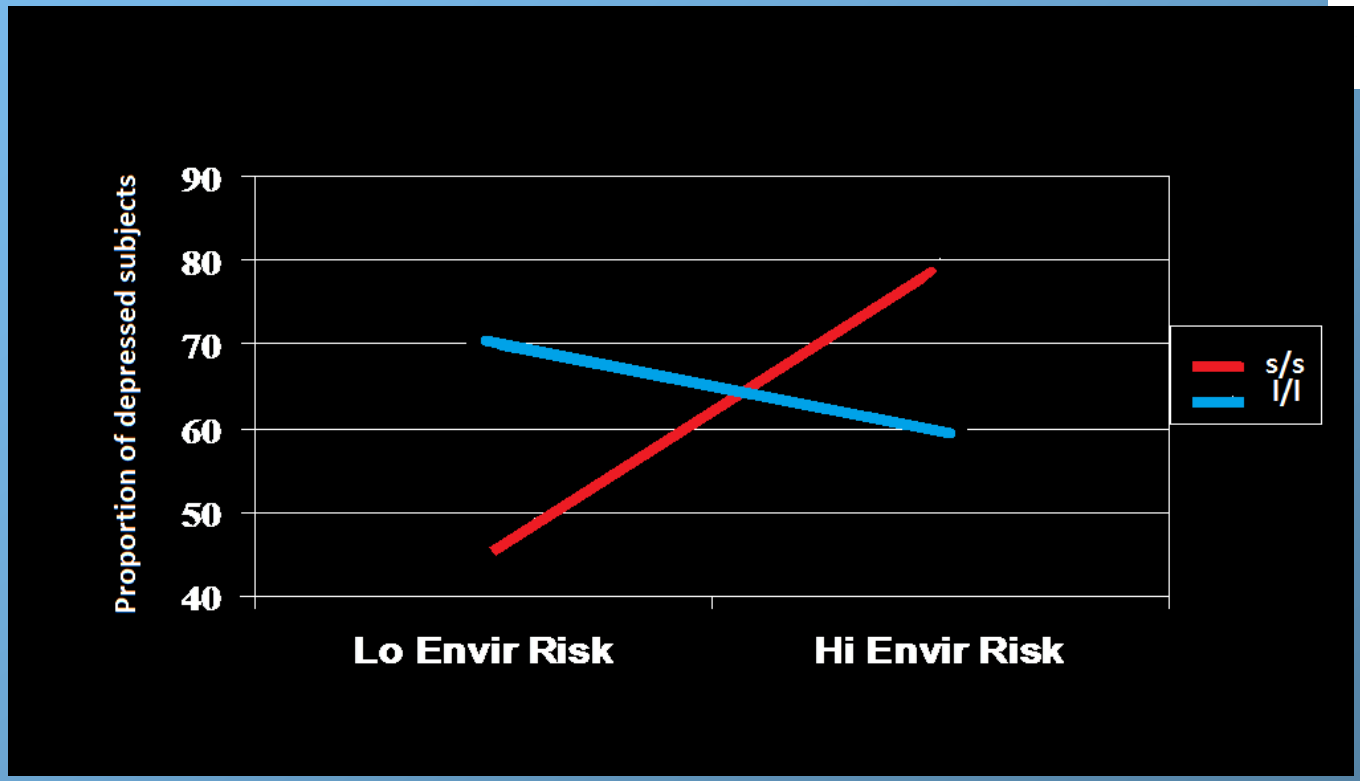
Caring for Alzheimer's Sufferer and Depression Symptoms in Female Caregivers



Original Brummett et al. (2008) data re-graphed by Belsky et al. (2009).

Brummett, B. H., Boyle, S. H., Siegler, I. C., Kuhn, C. M., Ashley-Koch, A., Jonassaint, C. R., et al. (2008). Effects of environmental stress and gender on associations among symptoms of depression and the serotonin transporter gene linked polymorphic region (5-HTTLPR). *Behavior Genetics, 38*, 34-43.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummet, B., & Williams, R. (2009). Vulnerability Genes or Plasticity Genes? *Molecular Psychiatry, 14*, 746-754.

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GXE:
The MAOA Gene

The MAOA gene is located on the X chromosome and encodes the MAOA enzyme, which metabolizes neurotransmitters such as norepinephrine, serotonin, and dopamine, rendering them inactive. Deficiencies in MAOA activity have been linked with aggression in mice and humans (i.e., low MAOA activity)—but like other studies looking at direct or main effects of genes on behavior, only inconsistently, perhaps due to GXE

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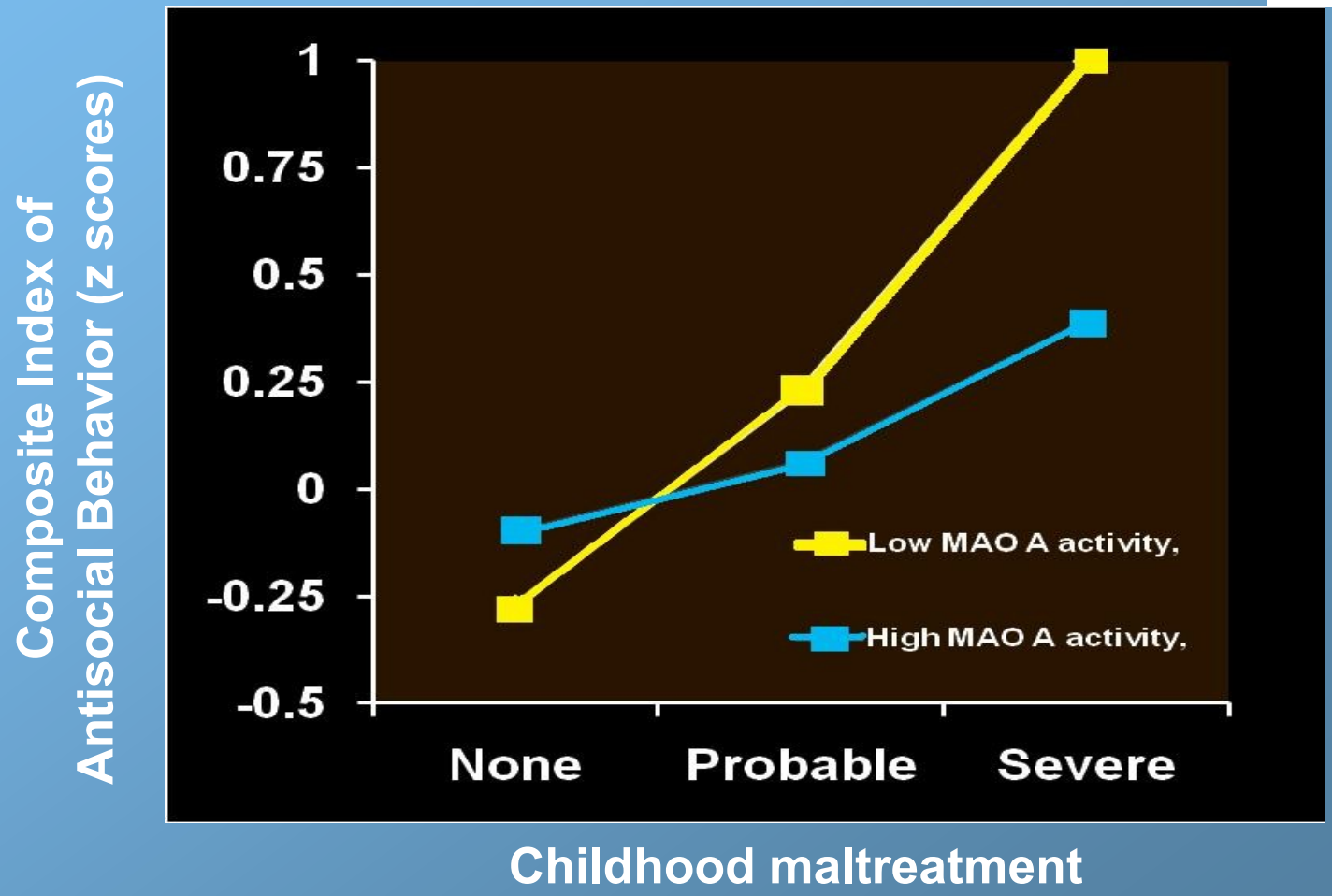
Child maltreatment and Antisocial Behavior



Caspi, A. et al. (2002). The role of genotype in the cycle of violence in maltreated children. Science, 297, 851-854.

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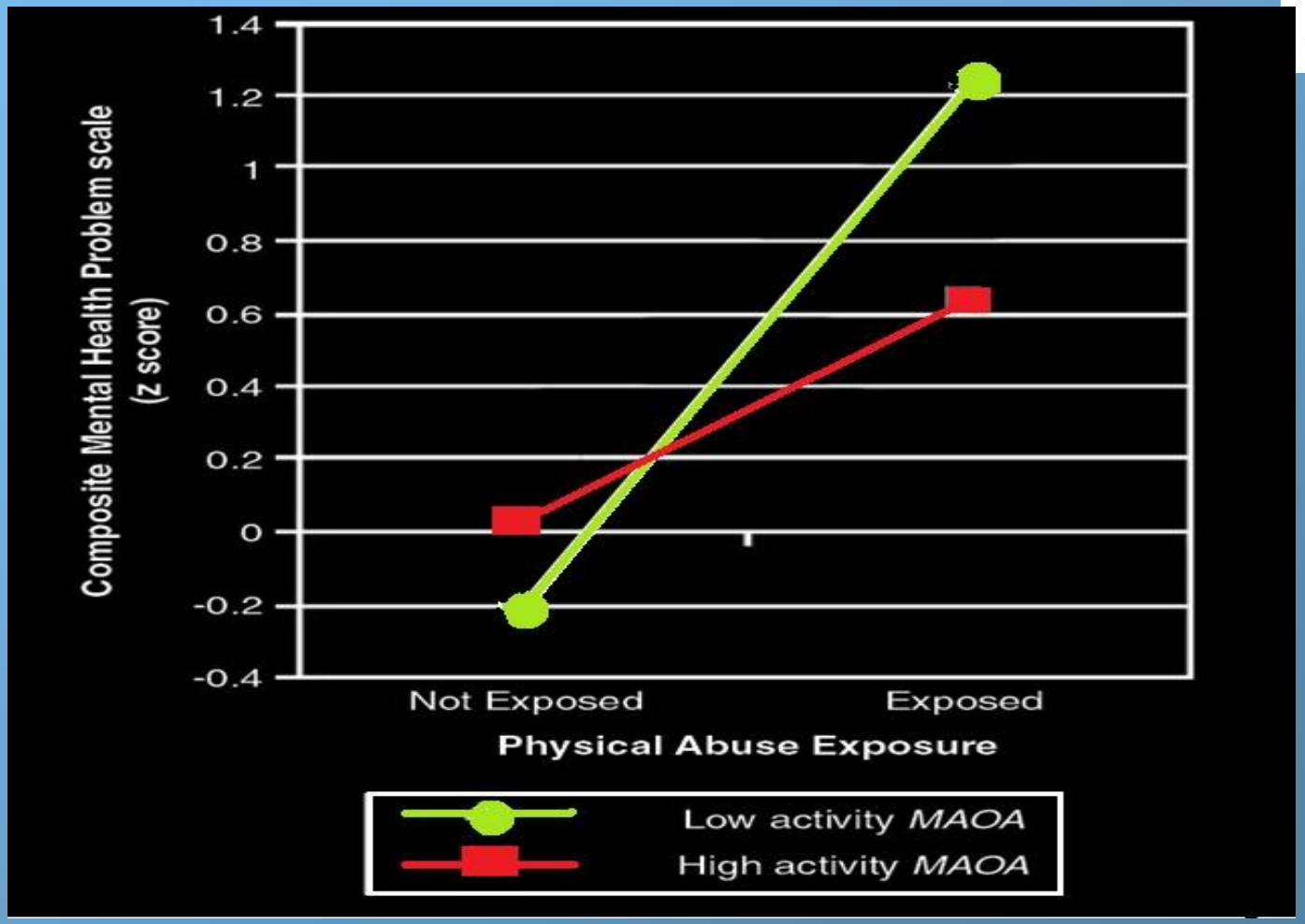
Physical Abuse and Mental Health Problems



Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I. W., et al. (2006). MAOA, maltreatment, and gene-environment interaction predicting children's mental health: new evidence and a meta-analysis. *Molecular Psychiatry, 11*(10), 903-913.

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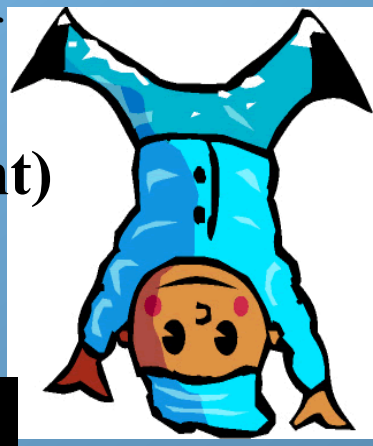
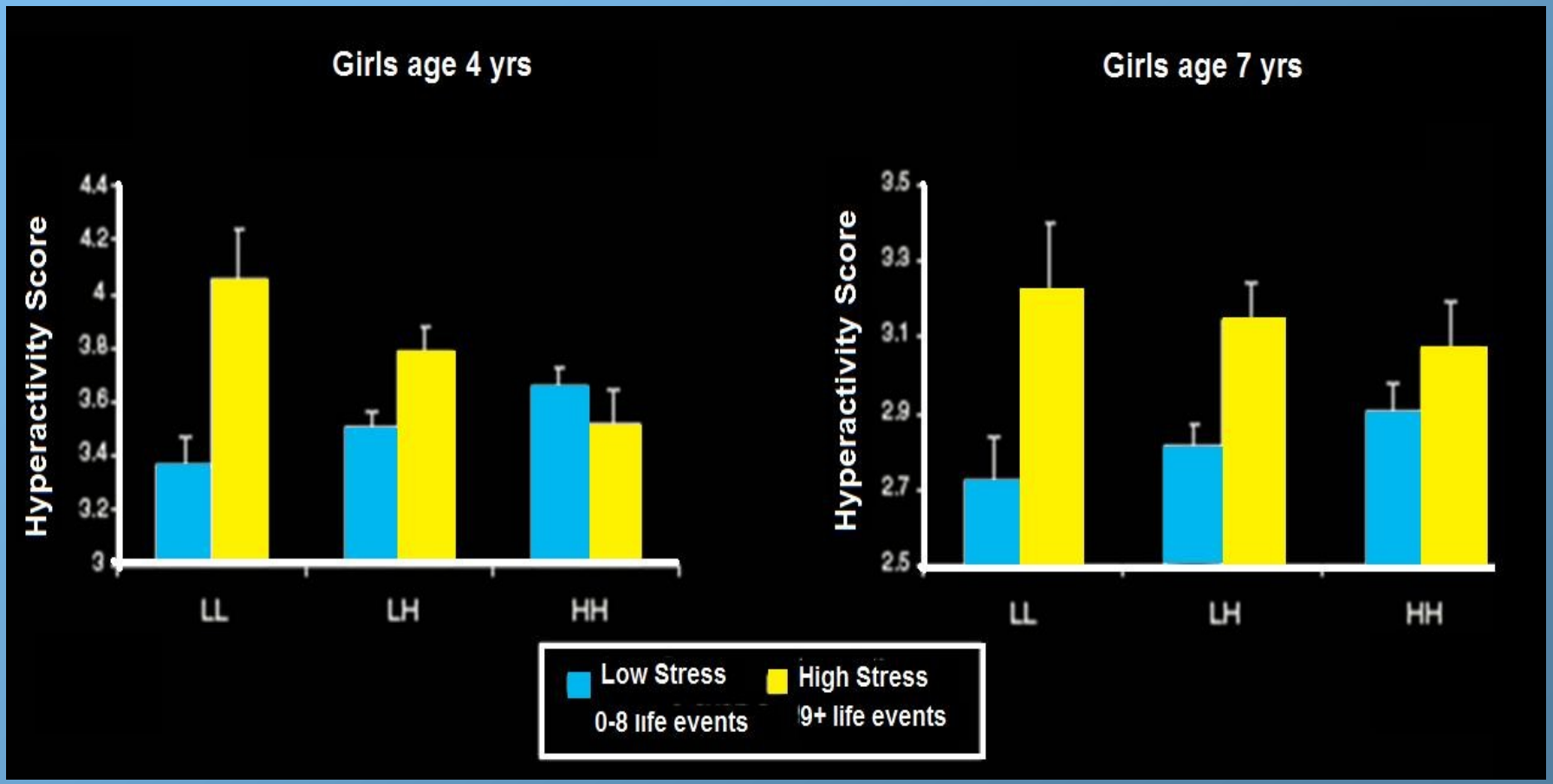


Psychosocial Risk (poor housing+maltreatment) and Violent Criminality

Nilsson, K. W., Sjoberg, R. L., Damberg, M., Leppert, J., Ohrvik, J., Alm, P. O., et al. (2006). Role of monoamine oxidase A genotype and psychosocial factors in male adolescent criminal activity. *Biological Psychiatry, 59*(2), 121-127.

Early Life (Event) Stress and Childhood Disinhibition



Enoch, M. A., Steer, C. D., Newman, T. K., Gibson, N., & Goldman, D. (2009). Early life stress, MAOA, and gene-environment interactions predict behavioral disinhibition in children. *Genes, Brain, and Behavior.*

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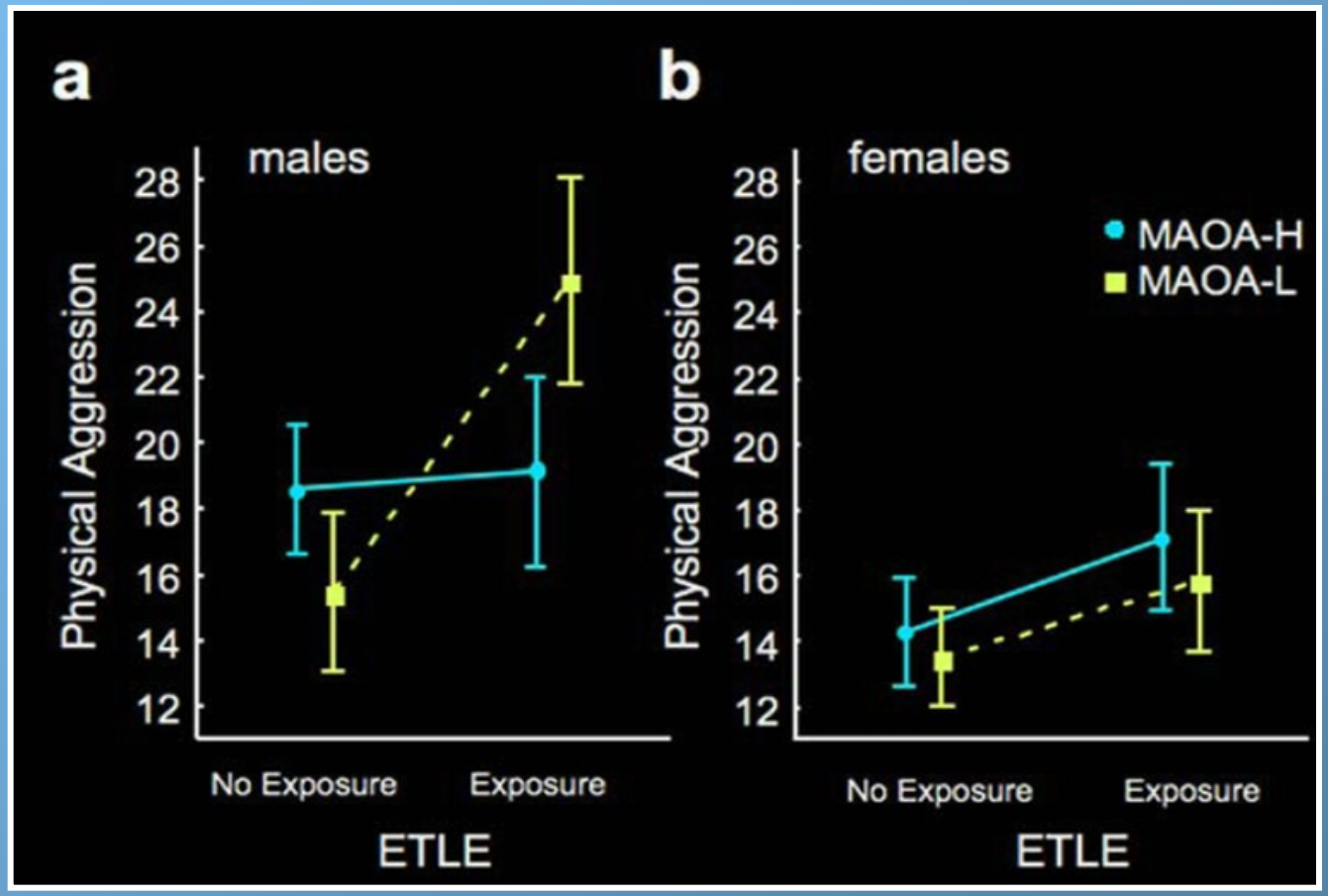
Early Trauma and Physical Aggression in Adulthood



Frazzetto, G., Di Lorenzo, G., Carola, V., Proietti, L., Sokolowska, E., Siracusano, A., et al. (2007). Early trauma and increased risk for physical aggression during adulthood: the moderating role of MAOA genotype. *PLoS ONE, 2*(5), e486.

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Sexual Abuse and Anti-Social Personality Disorder in Adult Women

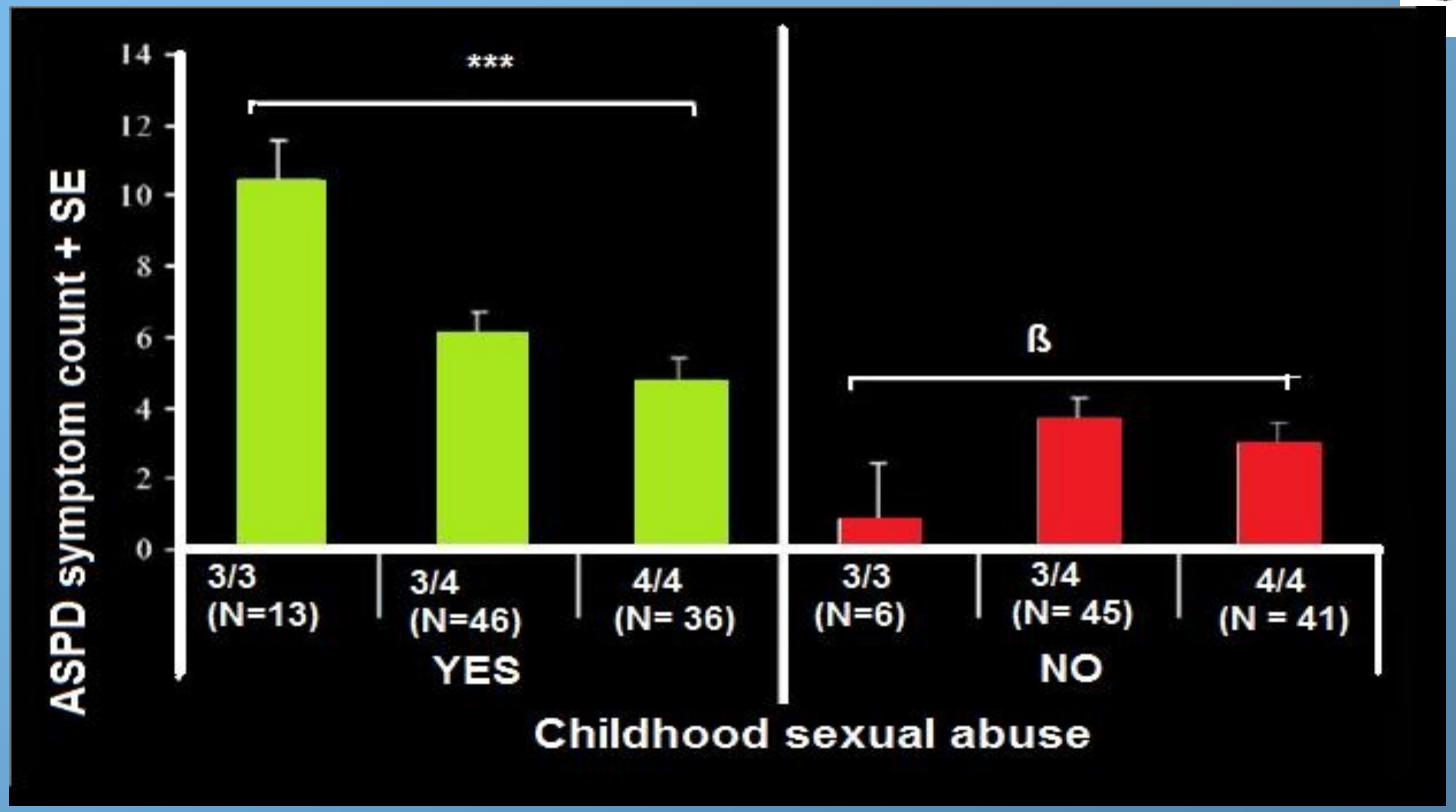

Figure 3 ASPD symptoms count is compared across the three MAOA-LPR genotypes separately within sexually molested ($N = 95$) and non-sexually molested participants ($N = 92$). 3/3 = homozygous for the low activity allele; 3/4 = heterozygous; 4/4 = homozygous for the high activity allele; β = regression coefficient; CSA = childhood sexual abuse. *** = $P < 0.001$.

Ducci, F., Enoch, M. A., Hodgkinson, C., Xu, K., Catena, M., Robin, R. W., et al. (2008). Interaction between a functional MAOA locus and childhood sexual abuse predicts alcoholism and antisocial personality disorder in adult women. Molecular Psychiatry, 13(3), 334-347.

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GXE:
The DRD4 Gene

The *DRD4* gene codes for a type of dopamine receptor, with the dopaminergic system involved in attentional, motivational, and reward mechanisms in the brain. One variant of this gene, the 7-repeat DRD4 allele, has been linked to lower dopamine reception efficiency, and thus to ADHD and externalizing problems in children, as well as behavioral difficulties, including substance abuse and aggression, in adulthood, .

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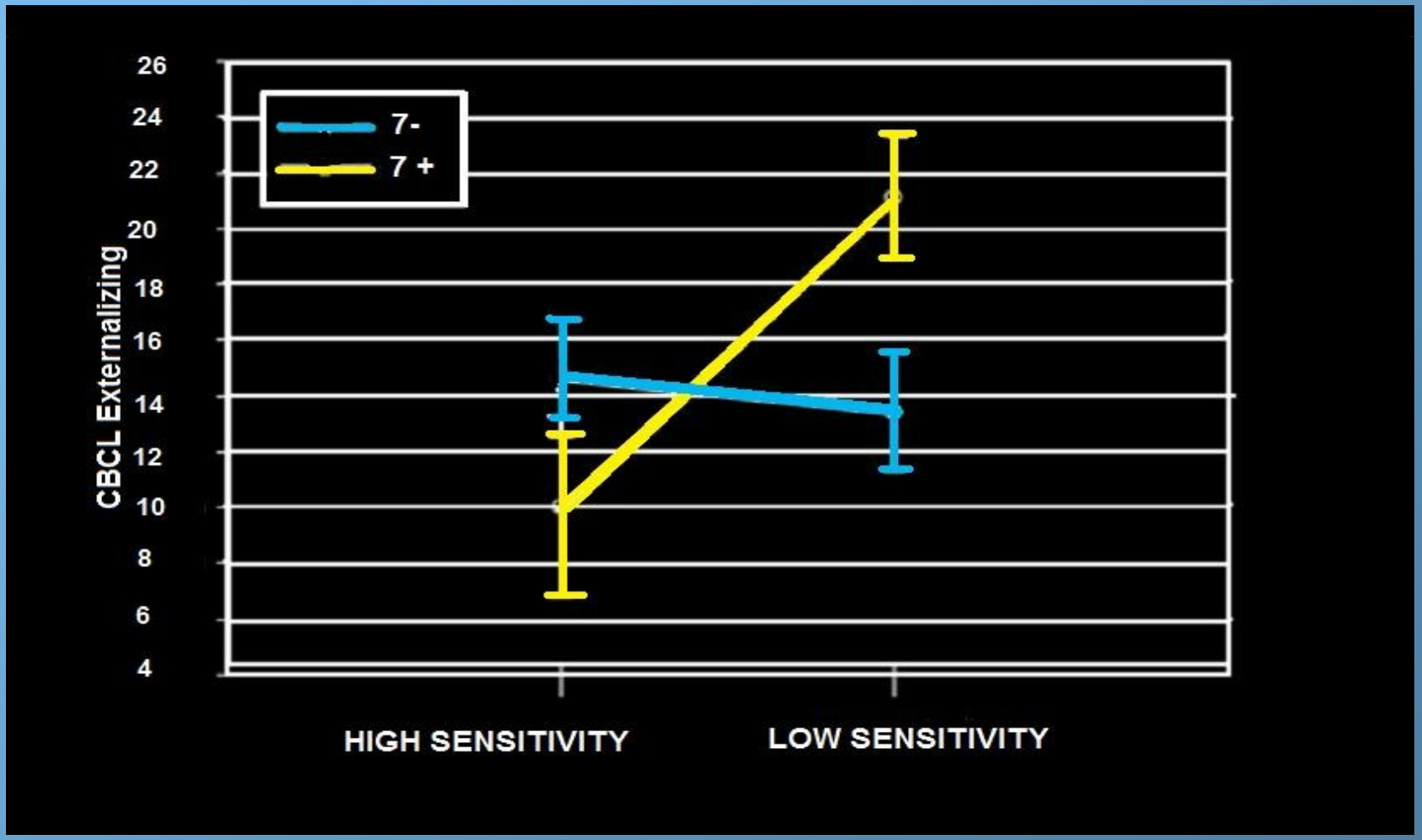

Fig: Externalizing scores (M. SE) of preschoolers with and without the DRD4 exon III 7-repeat allele experiencing sensitive or insensitive parenting.

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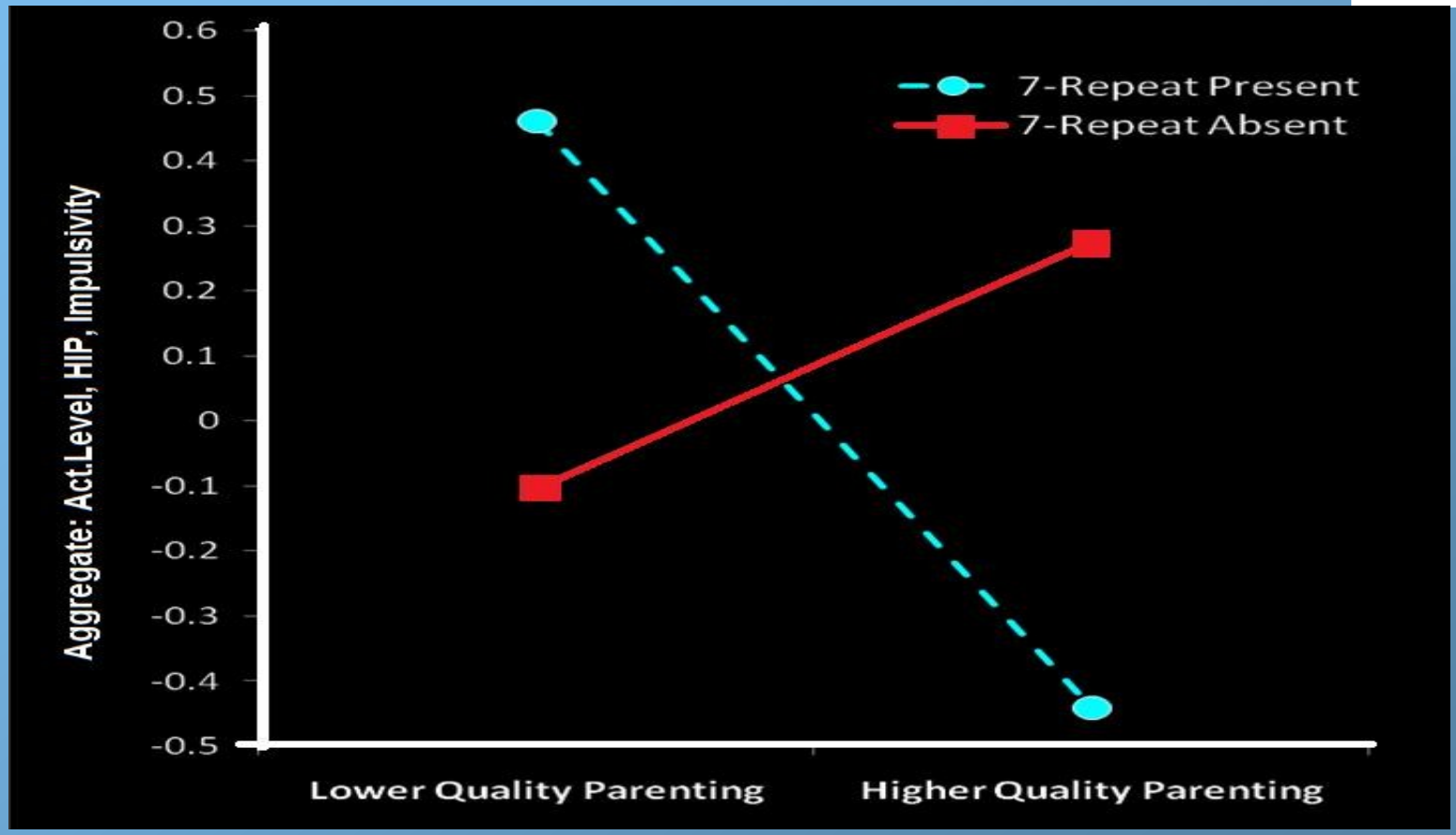
Parenting and Hyperactivity/ Impulsivity



Regraphing of Figure from Sheese, B. E., Voelker, P. M., Rothbart, M. K., & Posner, M. I. (2007). Parenting quality interacts with genetic variation in dopamine receptor D4 to influence temperament in early childhood. *Development and Psychopathology, 19*, 1039-1046.

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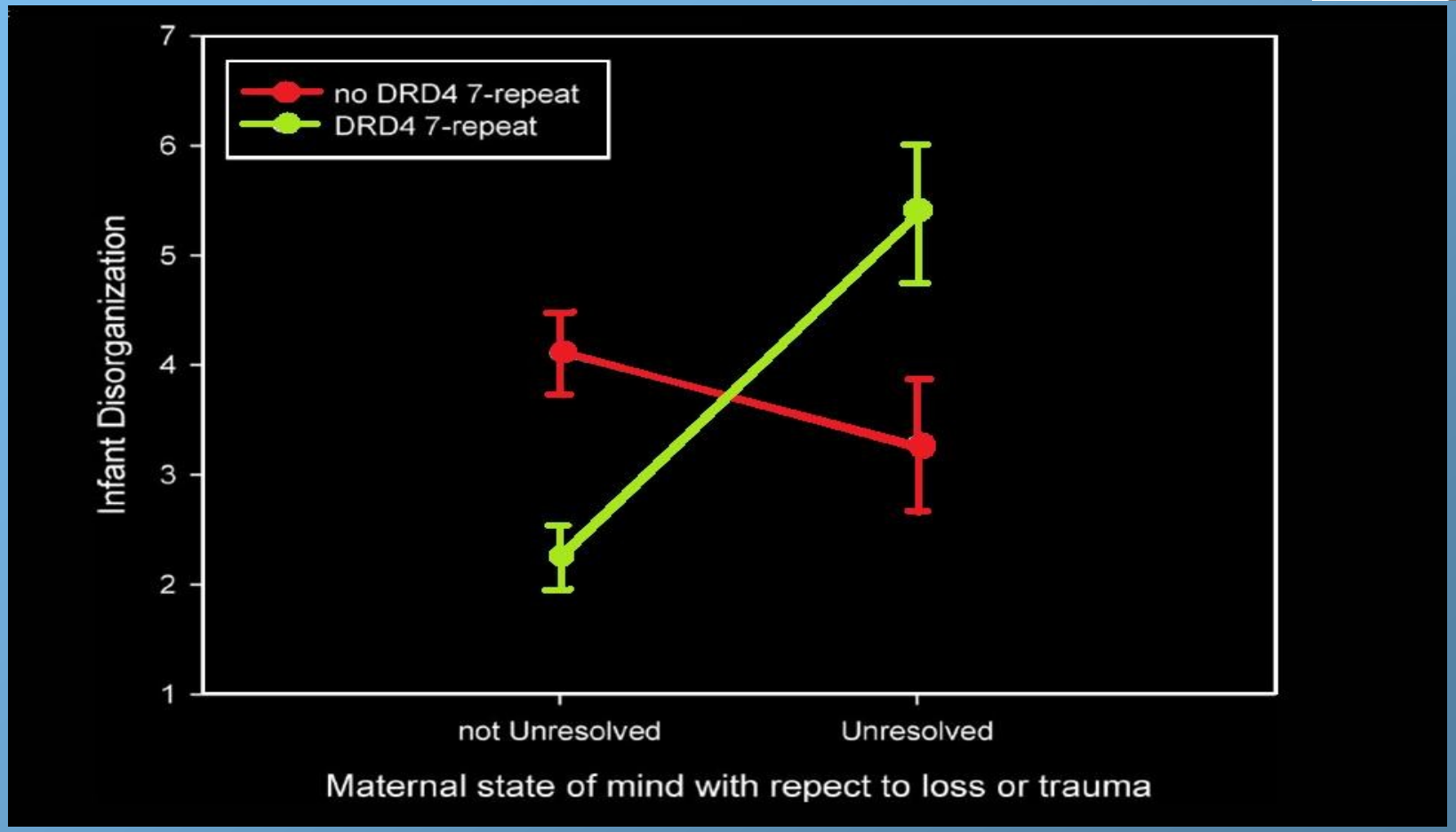
Maternal Unresolved Loss or Trauma & Disorganized Infant Attachment



van Ijzendoorn, M. H., & Bakermans-Kranenburg, M. J. (2006). DRD4 7-repeat polymorphism moderates the association between maternal unresolved loss or trauma and infant disorganization. *Attachment and Human Development, 8*(4), 291-307.

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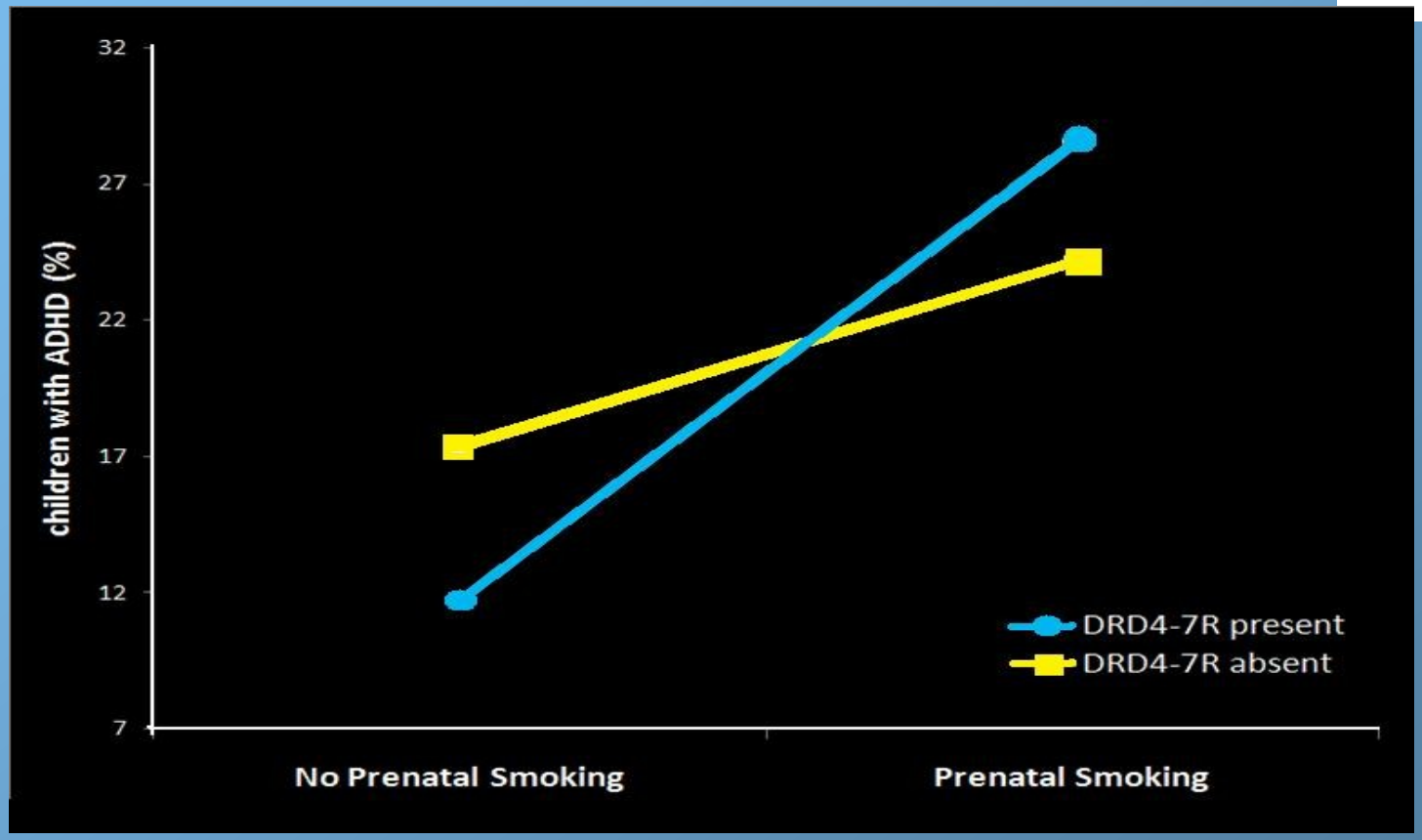
Prenatal Smoking & ADHD



Based on: Neuman RJ, Lobos E, Reich W, Henderson CA, Sun LW, Todd RD (2007): Prenatal smoking exposure and dopaminergic genotypes interact to cause a severe ADHD subtype. *Biological Psychiatry* 61:1320-8.

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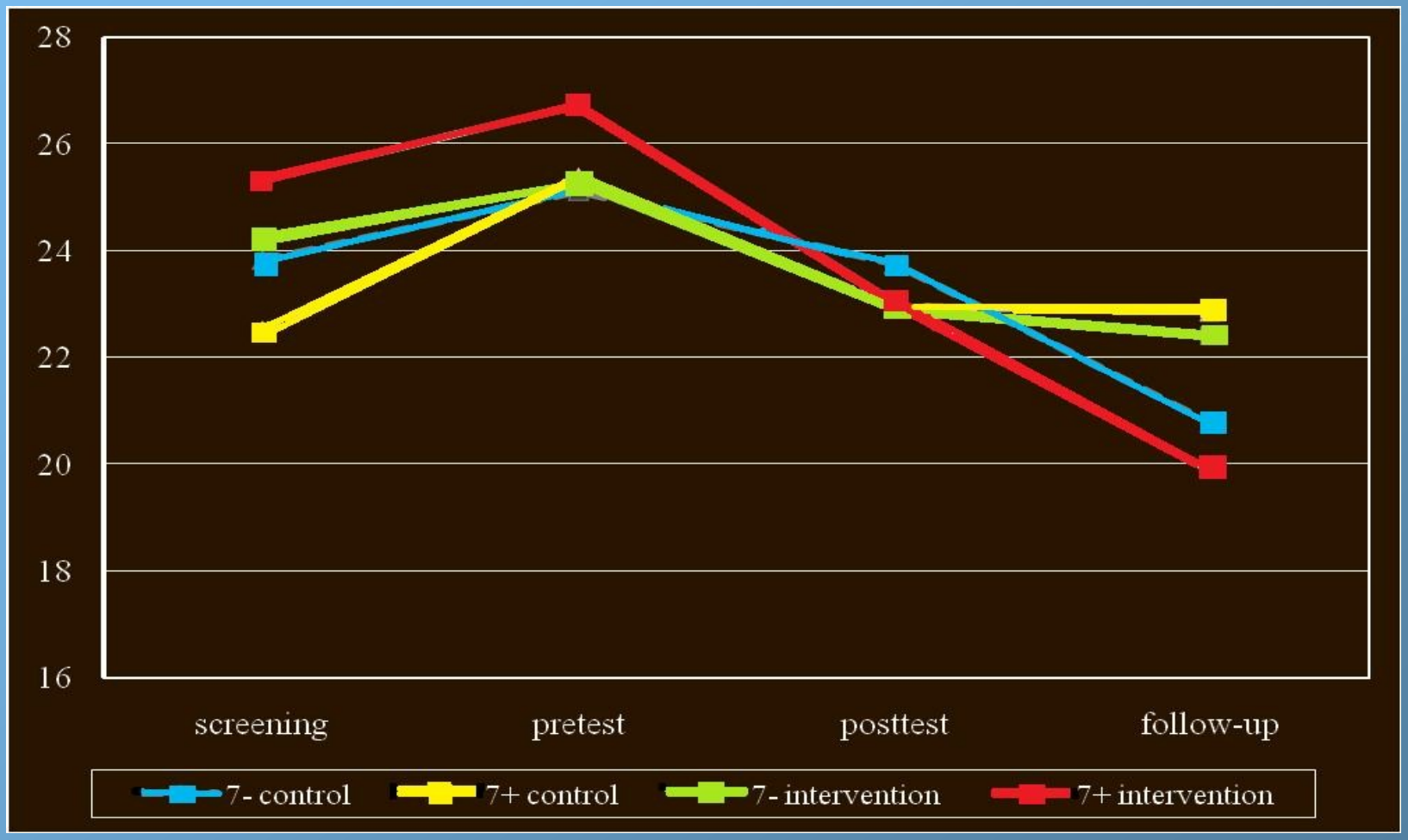
EXPERIMENTAL EVIDENCE OF GXE IN THE CASE OF PARENTING INTERVENTION

Development of Externalizing Behavior Over Time for Intervention and Control Groups by DRD47-Repeat Allele

CBCL externalizing



Source: Bakermans-Kranenburg et al. (2008). Experimental evidence for differential susceptibility: Dopamine D4 receptor polymorphism (DRD4 VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. *Developmental Psychology, 44, 293-300.*

Development of Externalizing Behavior Over Time for Intervention and Control Groups By DRD47-Repeat Allele

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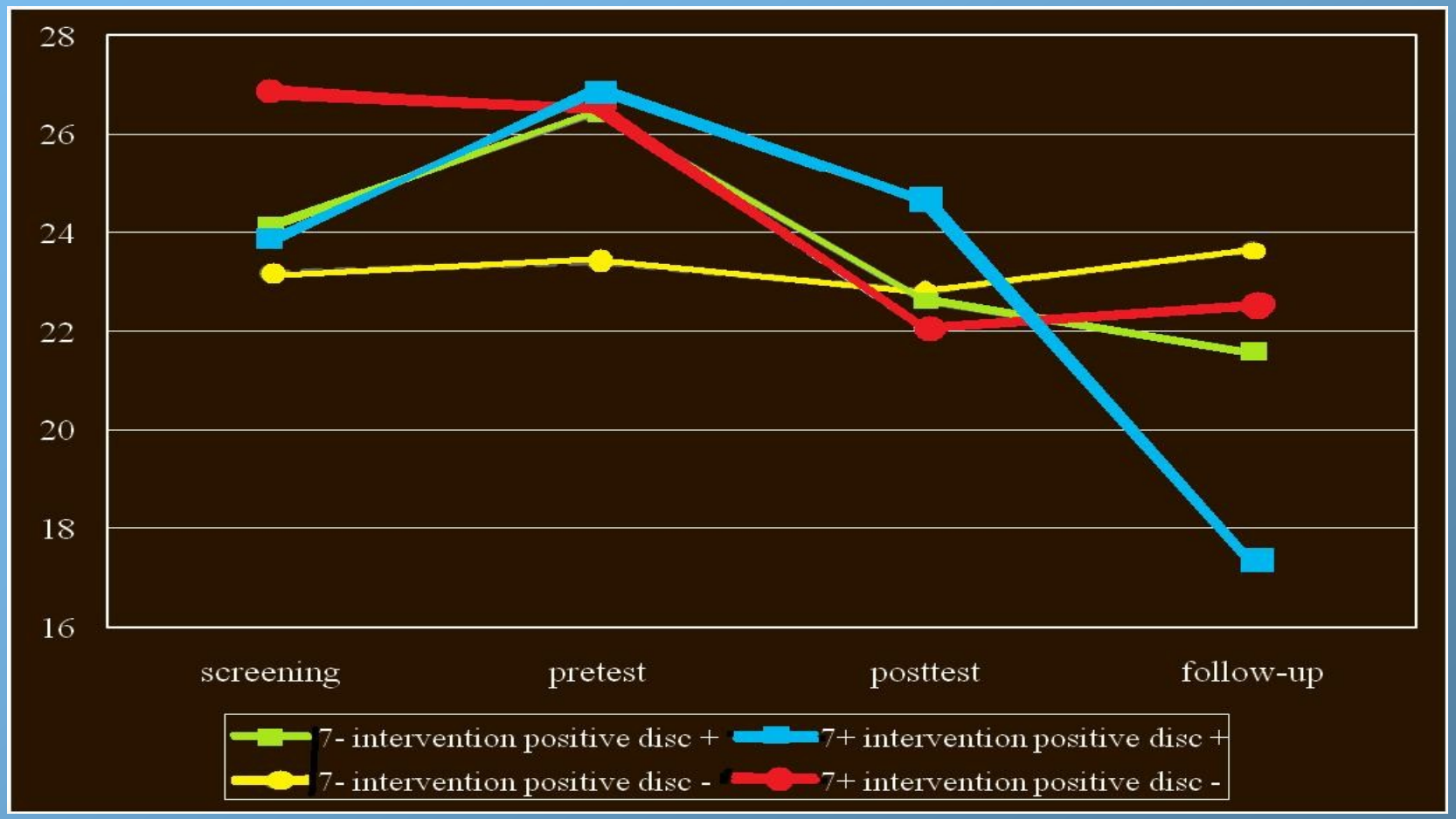

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Testing Belsky's (2000) Conditional vs. Alternative Reproductive Strategy Hypothesis: Estrogen Receptor-α (*ESR1*) Polymorphism as Moderator

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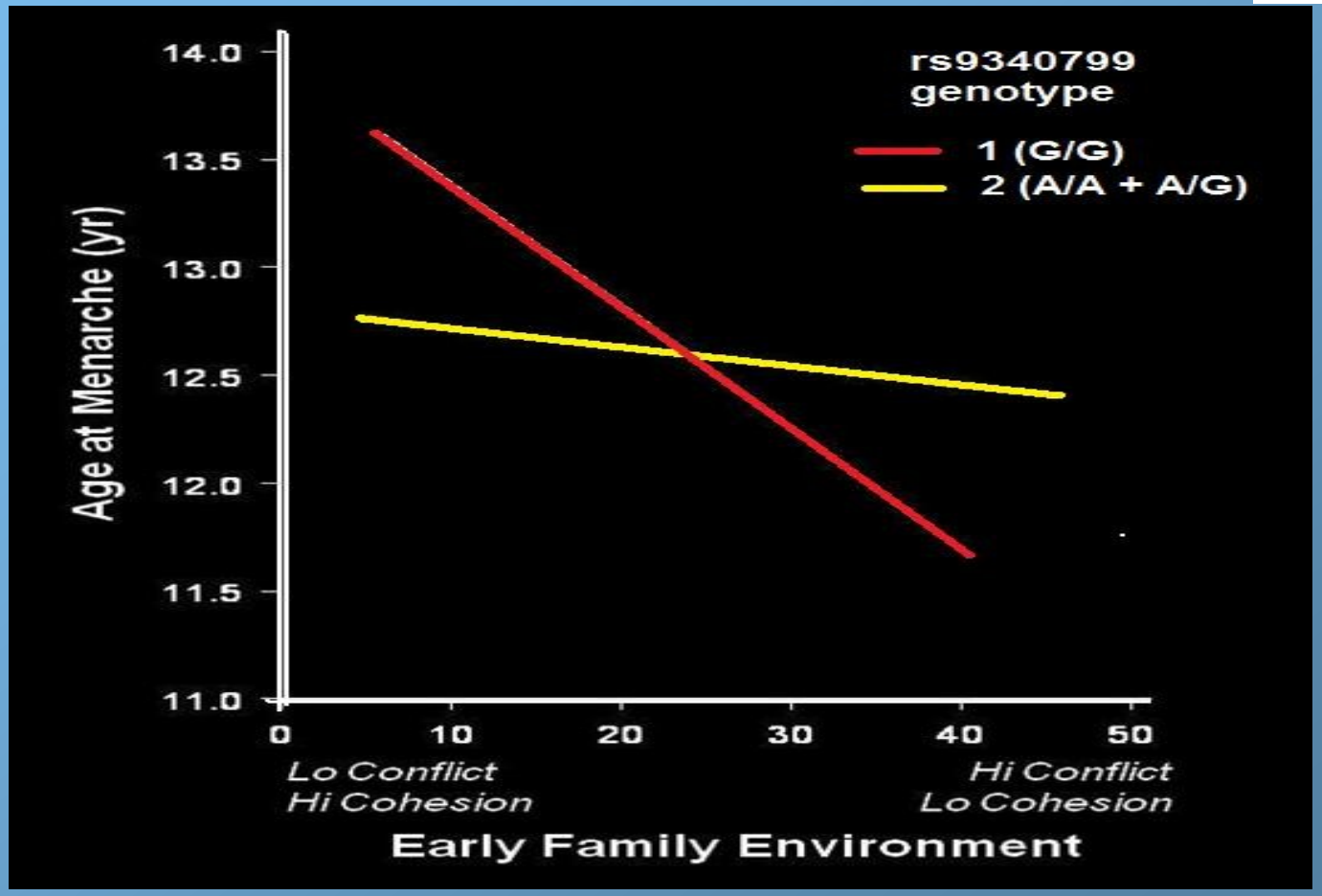
Early Family Environment and Age of Menarch



Manuck, S. et al. (in press). Reported Early Family Environment Covaries with Menarcheal Age as a Function of Polymorphic Variation in Estrogen Receptor-α (*ESR1*). *Development & Psychopathology*.

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BEYOND SINGLE GENES: CUMUALTIVE GENETIC PLASTICITY?

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Plasticity Genes (DAT1, DRD2, DRD4, 5HTTLPR, and MAOA), Negative-Positive Mothering and Lack of Self Control in Adolescence

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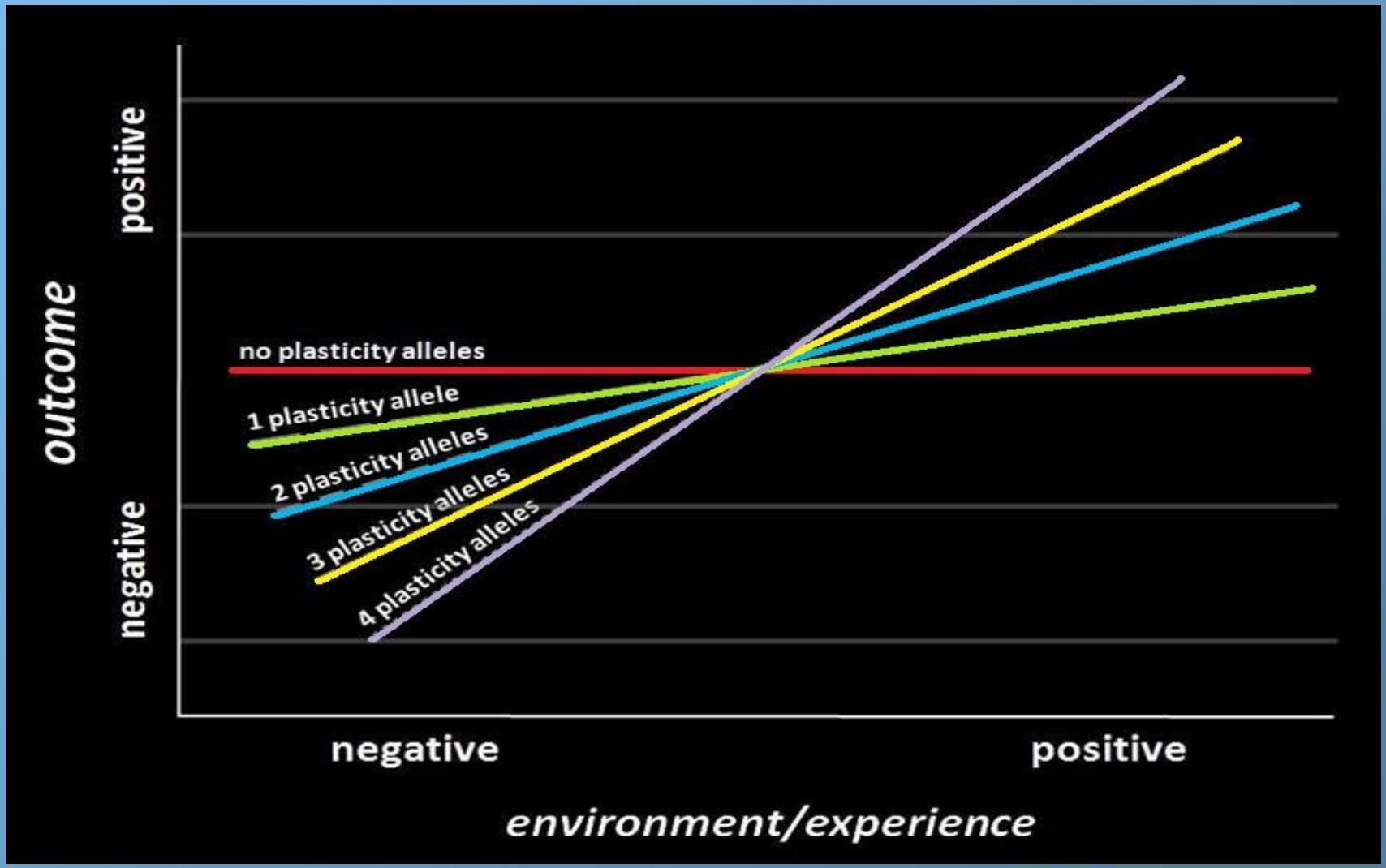
THEORETICAL MODEL OF GENETIC-PLASTICITY GRADIENT



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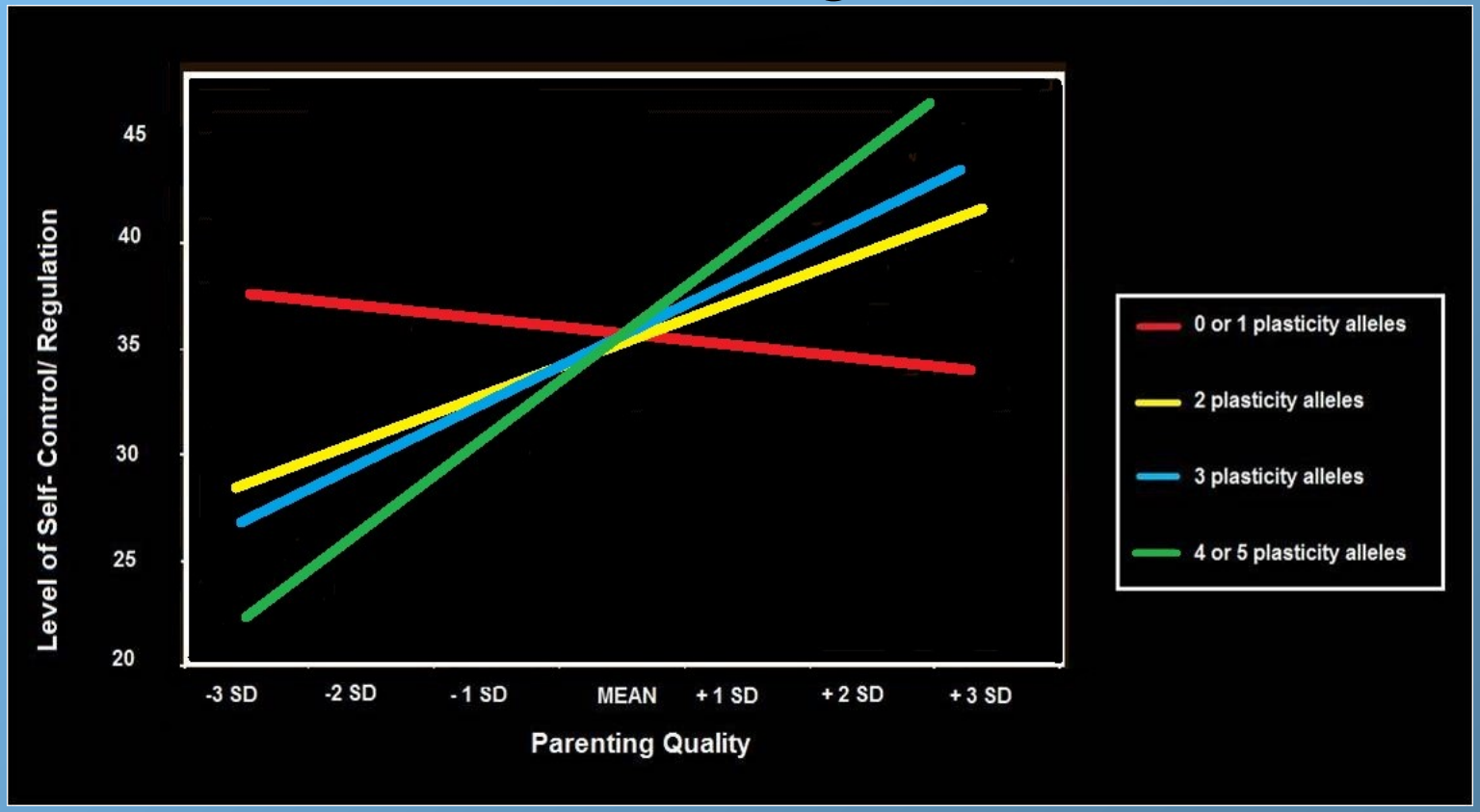
Parenting and Adolescent Boys' Self-Control Regulation



Belsky, J., & Beaver, M. (in press). Cumulative-Genetic Plasticity, Parenting and Adolescent Self-Control/Regulation. *Journal of Child Psychology & Psychiatry*.

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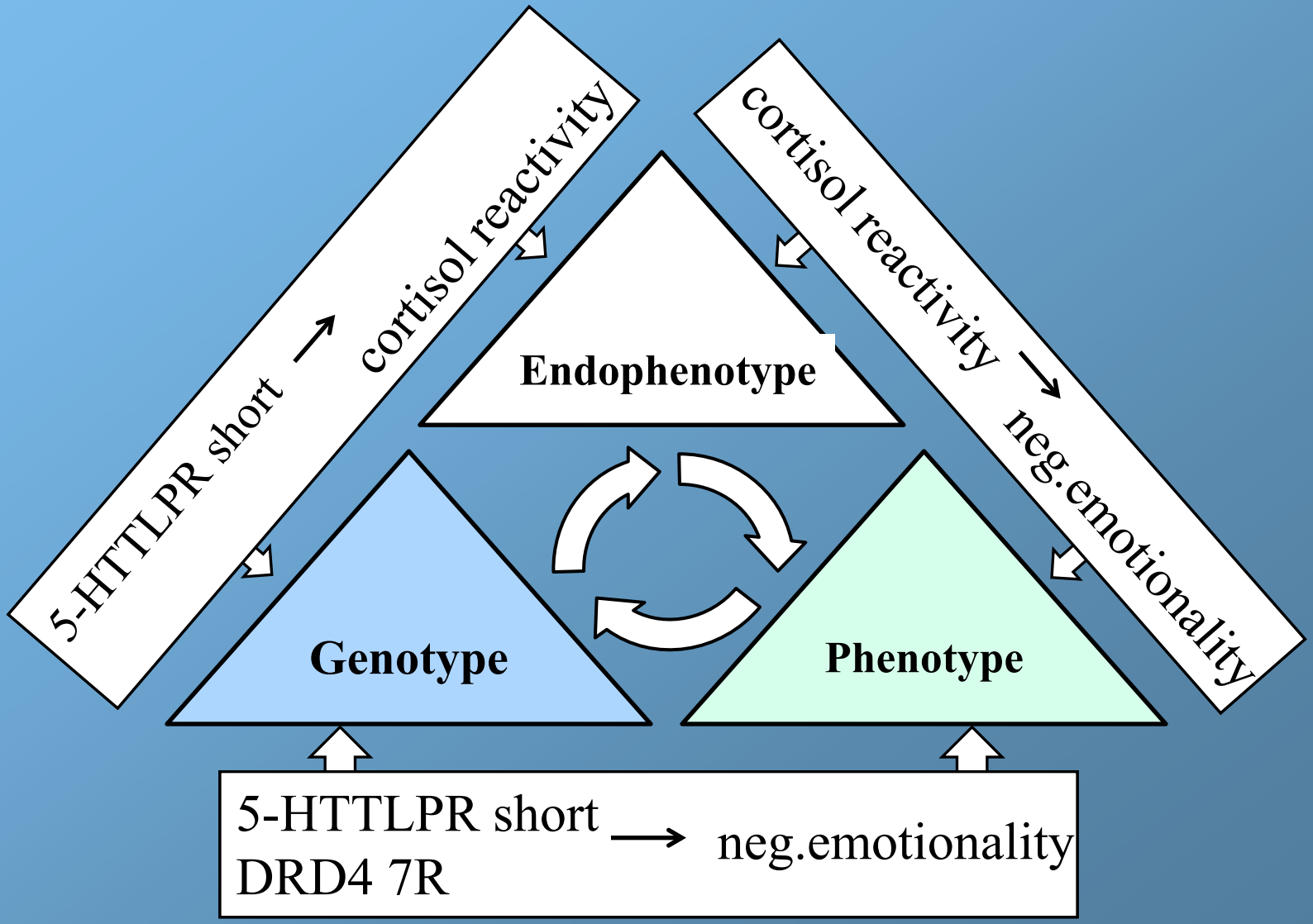
CONCLUSIONS

Are the same susceptible individuals being detected using different foci—temperament, physiology and genetics?

Mechanism of Susceptibility



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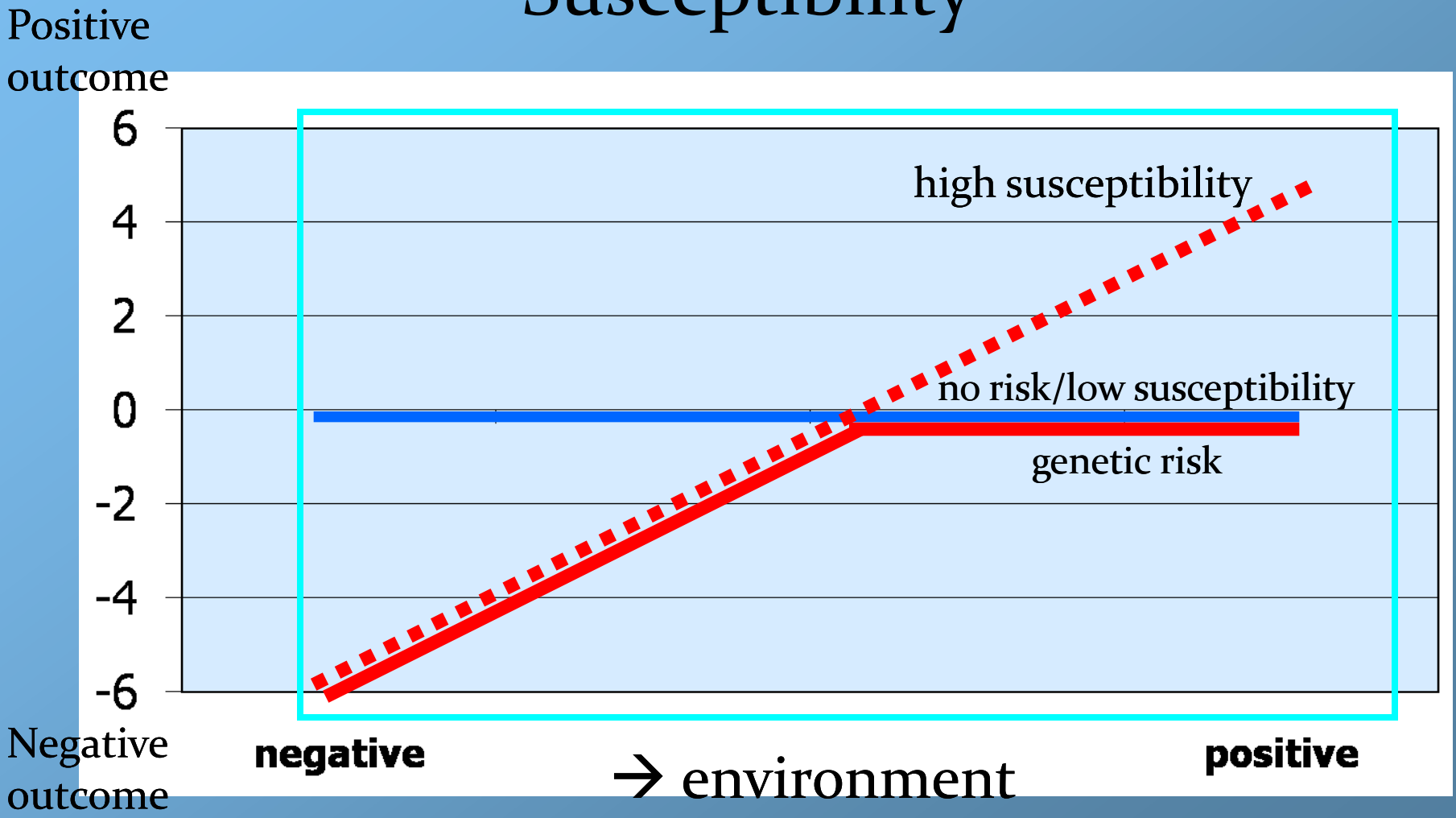
CONCLUSIONS (cont'd)

Need for empirical tests of differential susceptibility vs. diathesis stress, but to succeed in any such comparative analysis, it will be necessary to measure a broad range of environments—from unsupportive to supportive—and of developmental functioning, from poor to good.

Diathesis-Stress vs. Differential Susceptibility



Bakermans-Kranenburg & Van IJzendoorn (2007) *JCPP, 48,* 1160-1173

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CONCLUSIONS (cont'd)

--Language for "upside plasticity"?
--Domain specific or domain general?
--Mechanisms?
--Susceptibility: born or made or "born to be made"?
--GXE interaction or epigenetic mediation: E→G→Behavior
--Implications for Intervention: Efficacy vs. Equity?