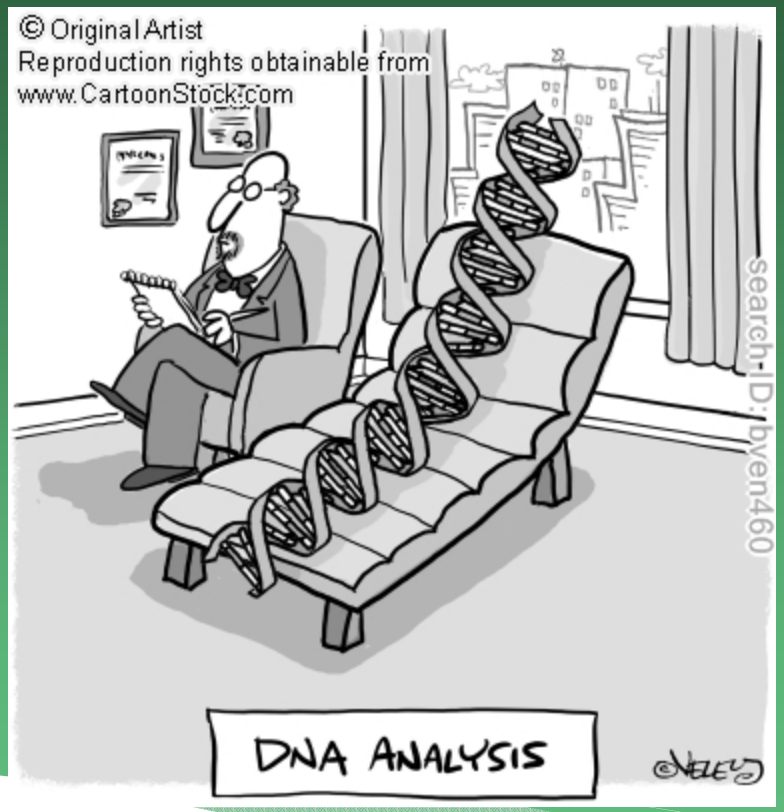
Studying Stress, Neurobiology and Development
Genetics and epigenetics



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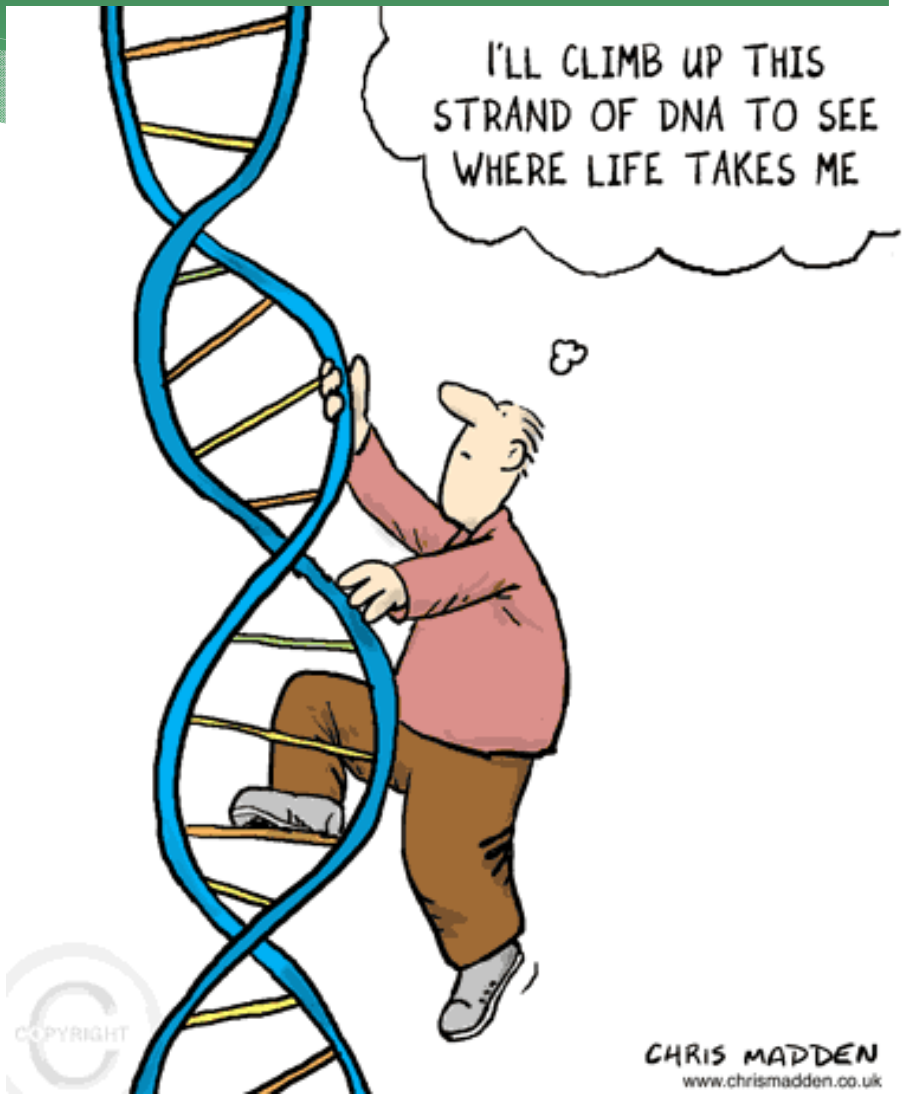
E. James Anthony, 1974

* "..to clarify the concepts of risk, vulnerability and resilience, I have used the analogy of three dolls made of glass, plastic and steal and exposed to the same risk- the blow of a hammer. The first doll breaks down completely, the second shows a dent that it carriers permanently, and the third doll gives out a fine metallic sound. Of course the outcome for the three dolls would be different if their environments were different…..."

Gene x Environment

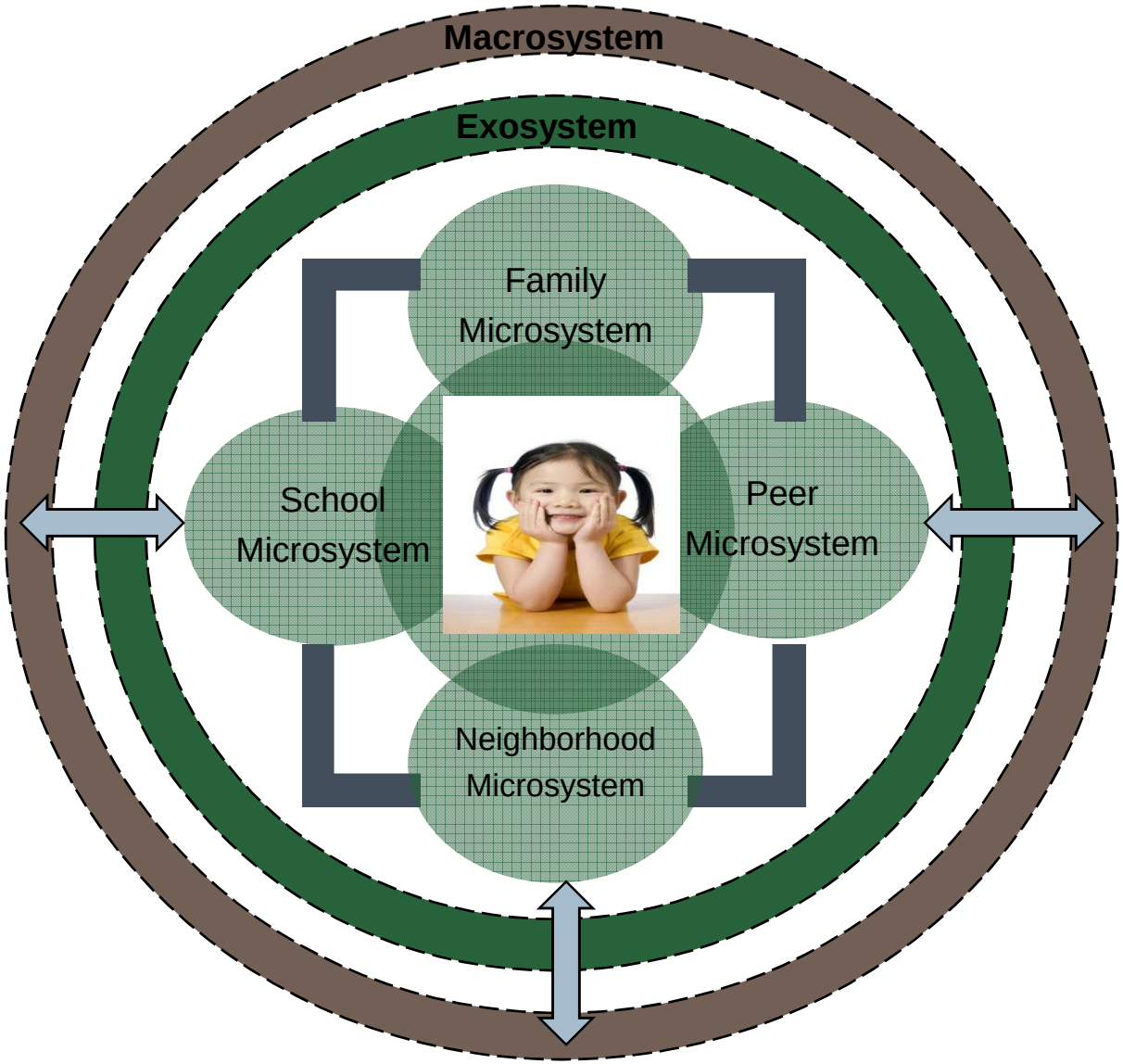
* Defining the “E”
* Defining the “G”
  * Single genes
  * Single SNPs
  * GWAS, rare variants
  * Cumulative genetic impact



Environment

* Life events
* History of abuse
* History of neglect
* Cumulative exposure
* Additional factors
  * Community
  * School
  * Household stress
  * caregiving

Bronfenbrenner's Ecological Theory



Levels of evidence for G x E

* Cellular and molecular level studies
  * Does polymorphism result in changes in expression/function consistent with phenotypic associations?
* Animal models- knock outs, genetically engineered
  * Does animal phenotype reflect human associations?
* Observation of associations within specific populations
  * Replication across studies
    * Sample size, power and meta- analysis
* Neuroscience and biological phenotypes
  * Does polymorphism have influence on underlying neural substrates?

Developmental Issues

* Changes in gene expression over development
  * http://www.brainspan.org/rnaseq/search?type=user_selections
* Changes in environment influence over time

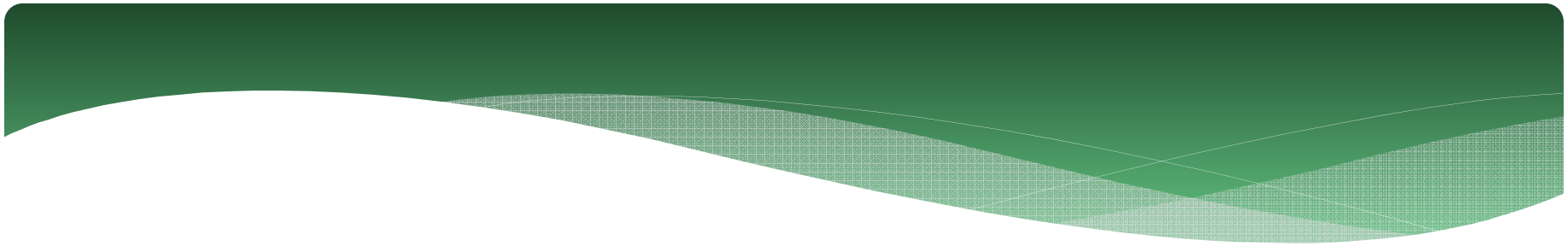
Genes linked to early adversity/care

* 5HTT
* CRHR1
* GR

* BDNF
* MAOA
* GABA

* DAT
* DRD2
* DRD4
* COMT

* AVP
* Oxytocin



Gene → Outcome

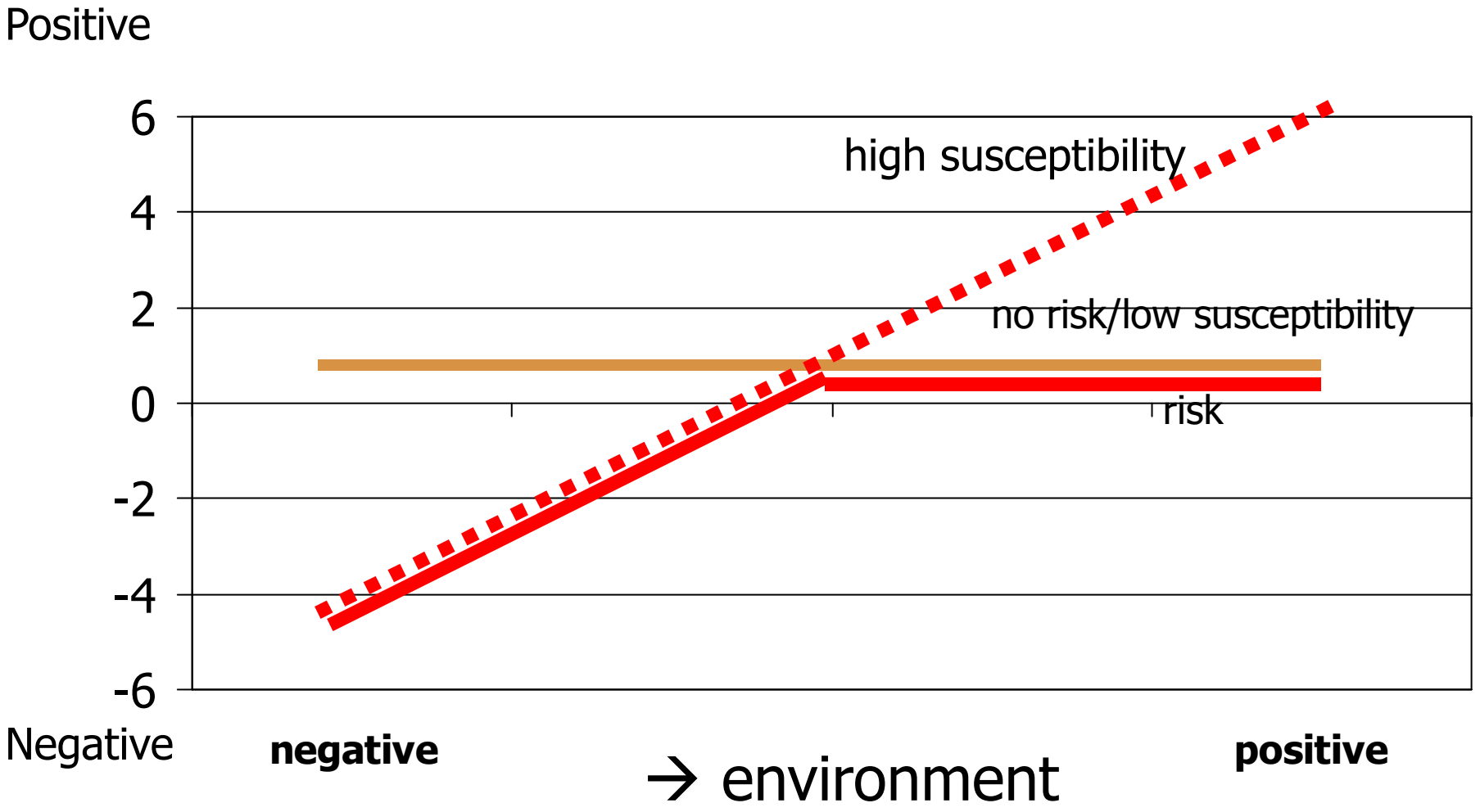
Gene x Environment → Outcome

Gene x Environment → Stress reactivity → Outcome

Gene x Environment
- Differential Susceptibility ★
- Biological Sensitivity to Context ★
- Mismatch Hypothesis
- Adaptive Calibration Model

Diathesis-Stress vs. Differential Susceptibility

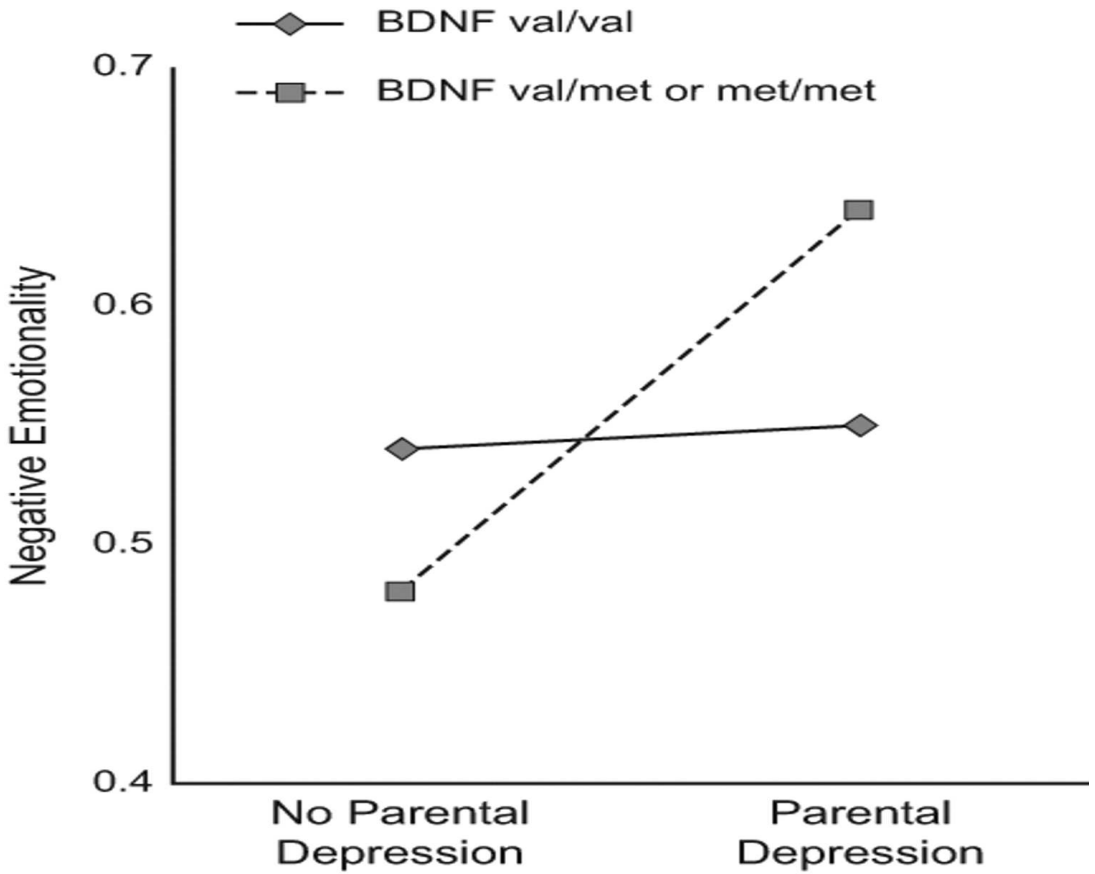
Bakermans-Kranenburg & Van IJzendoorn, 2006



Plasticity genes

* 5httlpr
* MAOA
* DAT
* DRD4
* DRD2
* BDNF

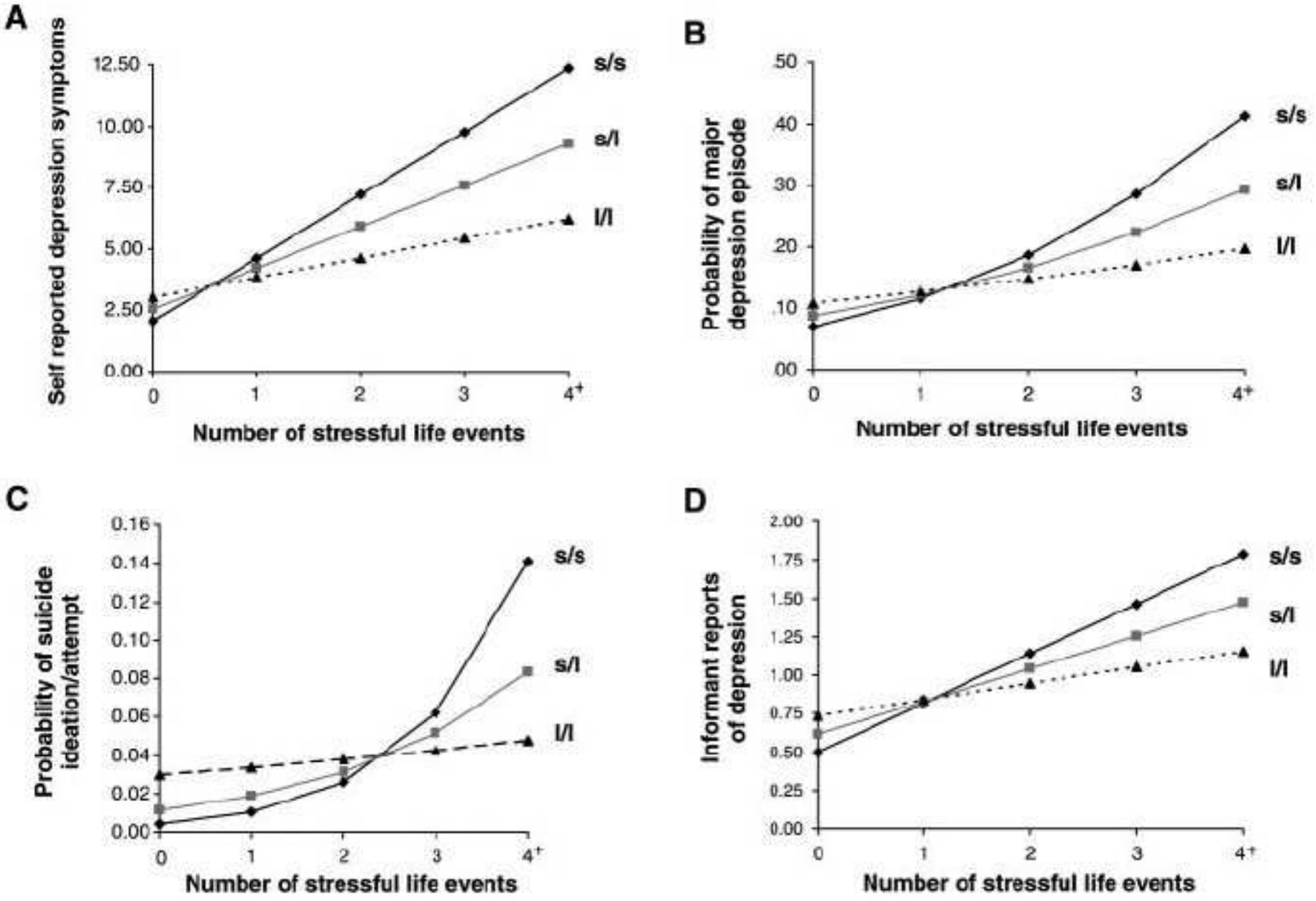
Parental Depression and Negative Emotionality in 3-Year Olds Moderated by BDNF



Hayden, E. P. et al. (in press). Psychological Science. .2010;0956797610385357

5HTTLPR

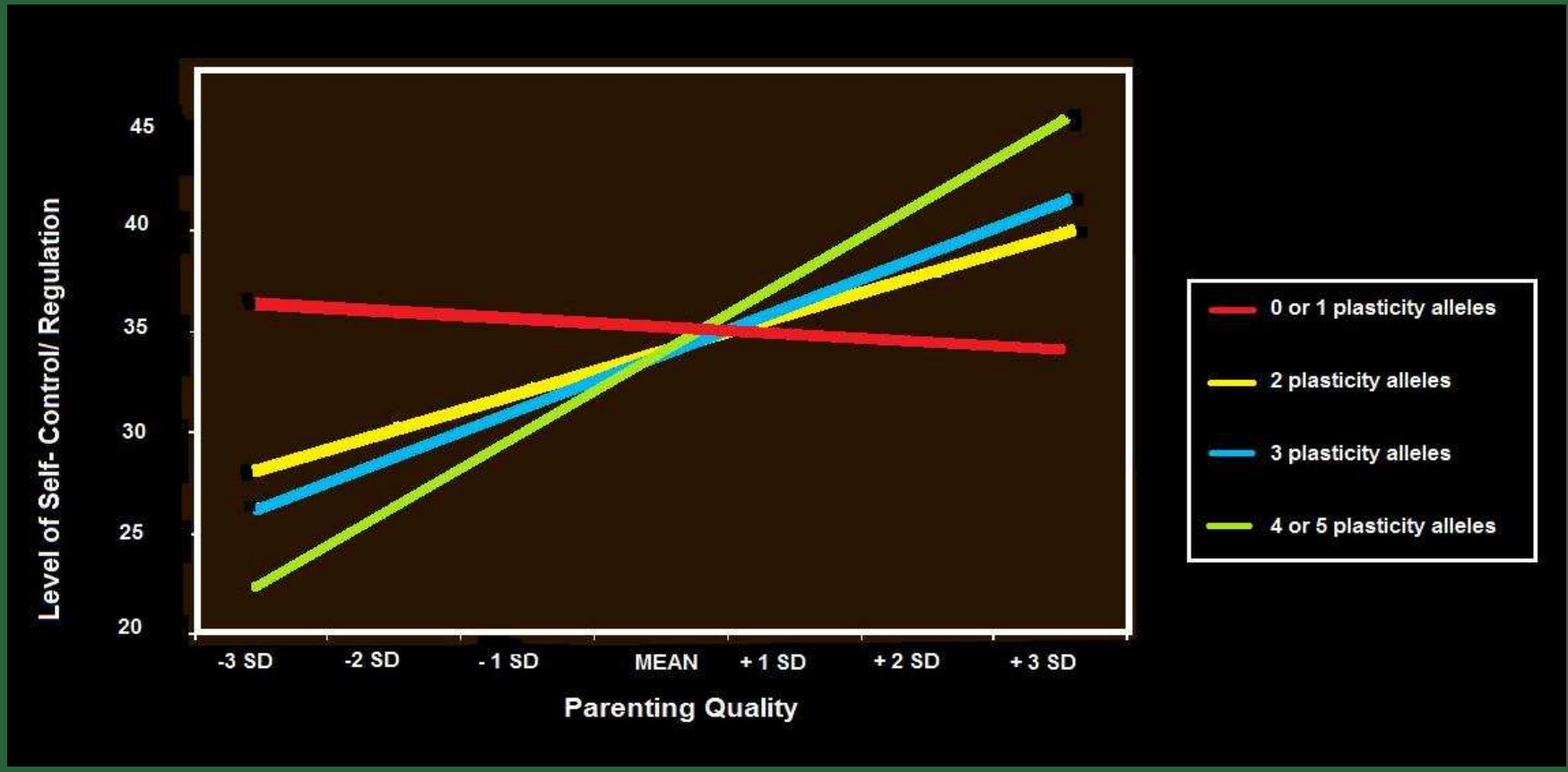
* 44 base pair repeat in the promoter region
  * Short allele decreased expression of 5HTT
  * L/L increased uptake of 5HT
* Evolutionary context
  * Only in humans and macaques
  * “weed primates”


A
Self reported depression symptoms
12.50
10.00
7.50
5.00
2.50
0.00
0
1
2
3
4+
Number of stressful life events
s/s
s/l
l/l
B
Probability of major depression episode
.50
.40
.30
.20
.10
.00
0
1
2
3
4+
Number of stressful life events
s/s
s/l
l/l
C
Probability of suicide ideation/attempt
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0
1
2
3
4+
Number of stressful life events
s/s
s/l
l/l
D
Informant reports of depression
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4+
Number of stressful life events
s/s
s/l
l/l

BEYOND SINGLE GENES: CUMULATIVE GENETIC PLASTICITY....

THEORETICAL MODEL OF GENETIC-PLASTICITY GRADIENT

Parenting and Adolescent Self-Control Regulation DAT, DRD2, DRD4, 5htt, MAOA



Belsky, J., & Beaver, M. (2011). Cumulative-Genetic Plasticity, Parenting and Adolescent Self-Control/Regulation. *Journal of Child Psychology & Psychiatry*.

Bucharest Early Intervention Project

Intervention Effects on Indiscriminant Social Behavior Among Institutionalized Romanian Children Moderated by Cumulative Genetic Plasticity: 5-HTTLPR *and* BDNF (CAUG: Care as Usual Group; FCG: Foster Care Group

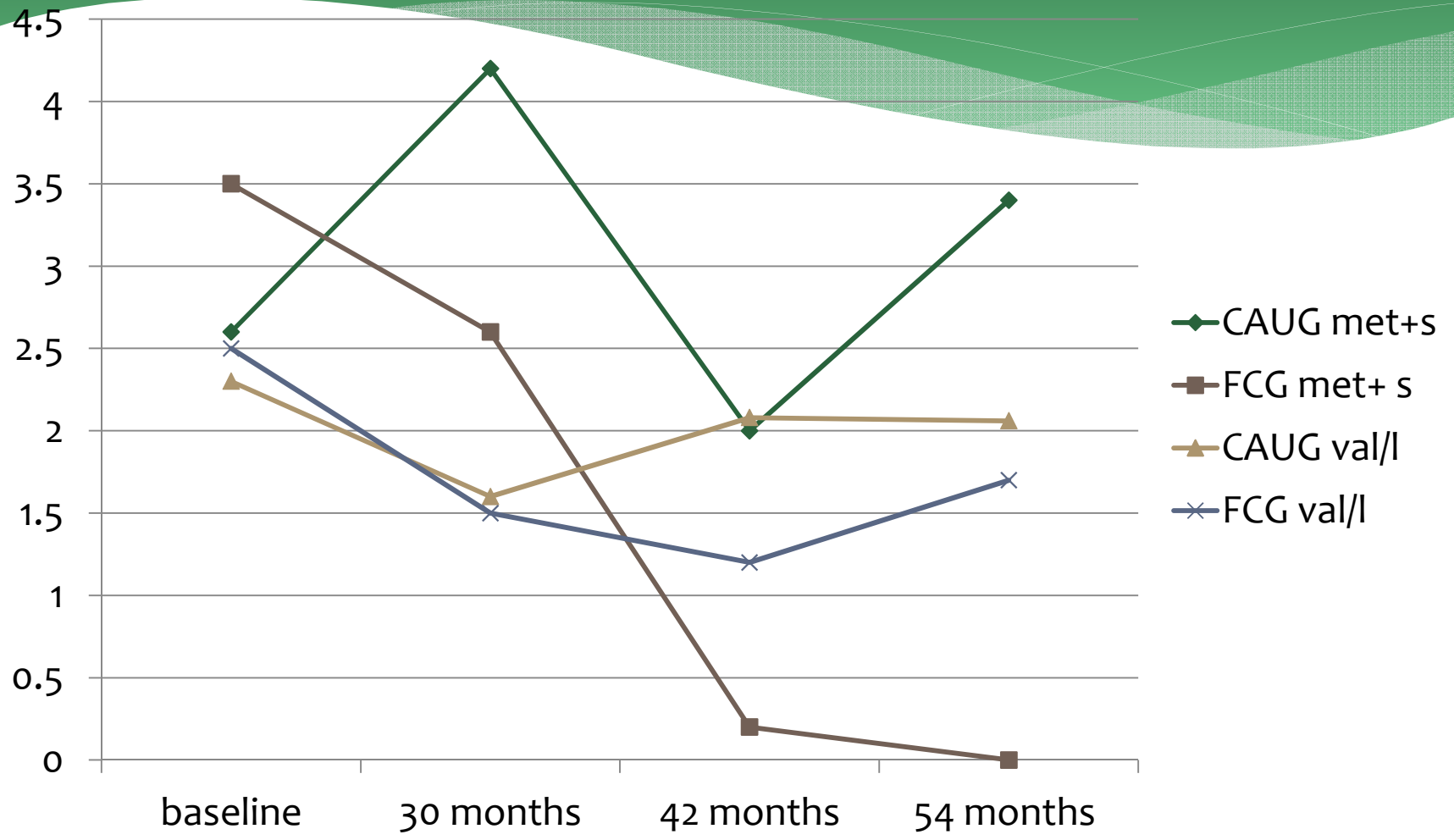
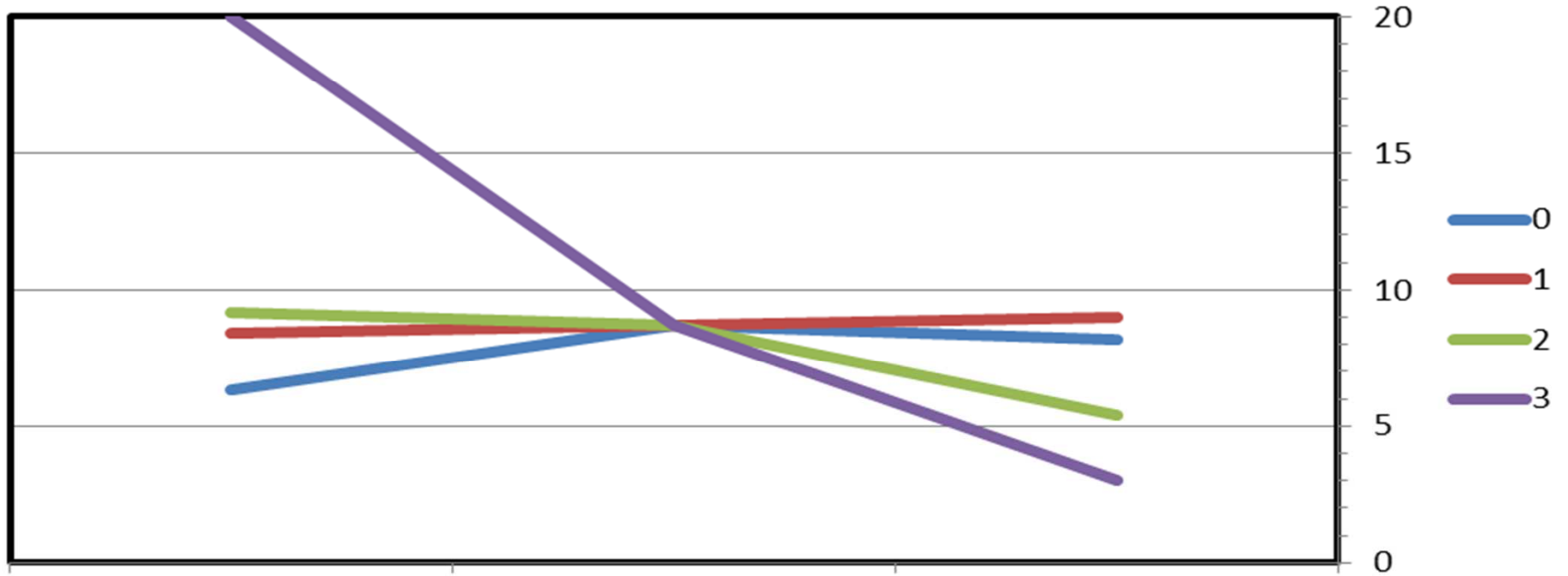


Figure 1: Externalizing Symptoms by Genetic Plasticity Gradient



One more step…

* Gene x Environment- with stress reactivity

ANS and HPA
finding the tipping point

Asymmetric:

Reactivity in RSA no reactivity in cortisol

Reactivity in cortisol no RSA reactivity

Symmetric:

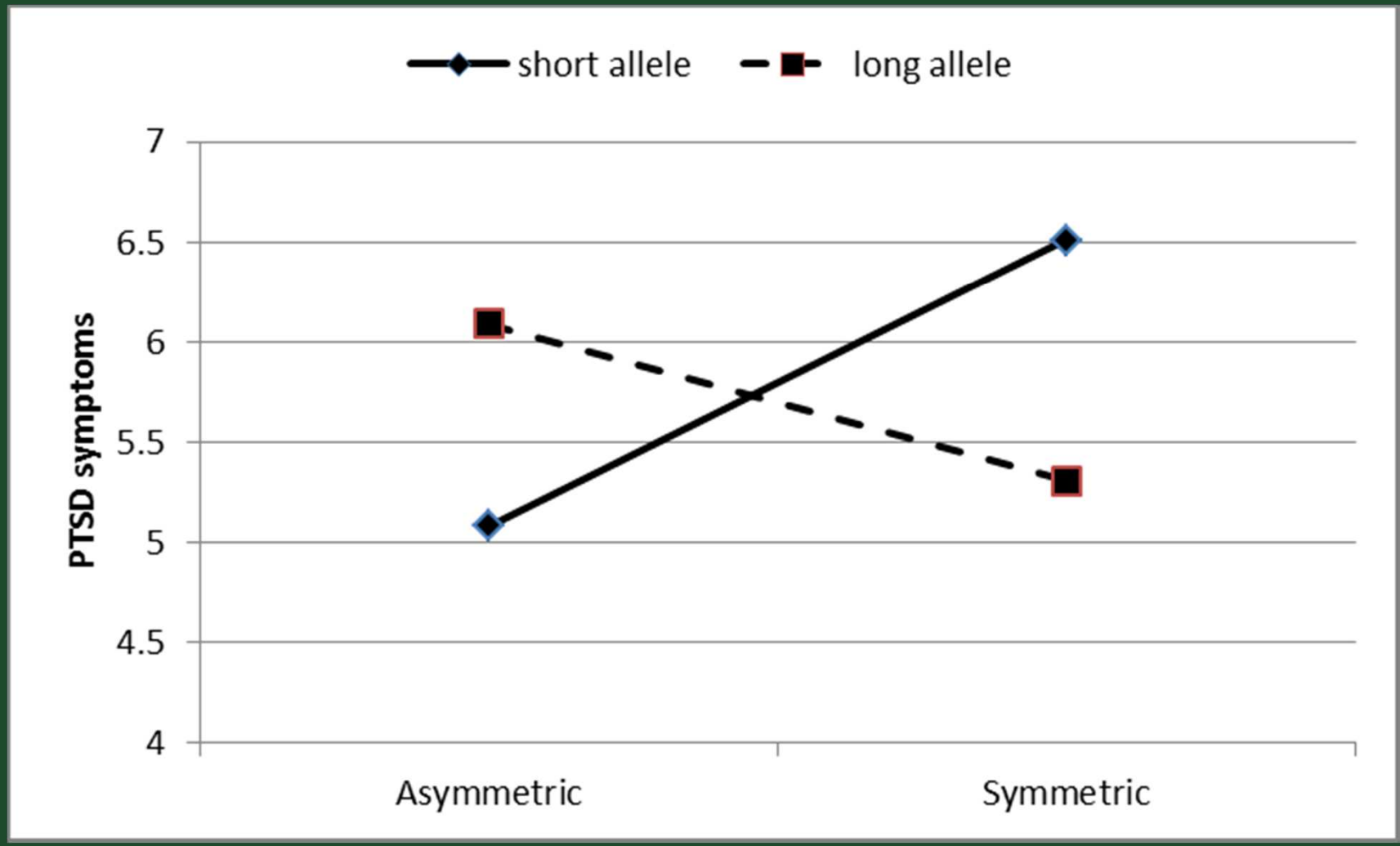
Reactivity in RSA

Reactivity in cortisol

Stress reactivity x genotype

n=141	B	SE	R^2 change	p
Reduced model:			.054	.27
gene*cortisol	-1.92	1.18		.11
gene*RSA	-0.52	1.28		.68
cortisol*RSA	1.90	1.22		.12
3-way Interaction model:			.044	**.05**
gene*cortisol	-1.17	1.20		.13
gene*RSA	0.19	1.29		.89
cortisol*RSA	-2.25	2.02		.45
gene*cortisol*RSA	6.40	2.51		**.01**

Reactivity and genotype

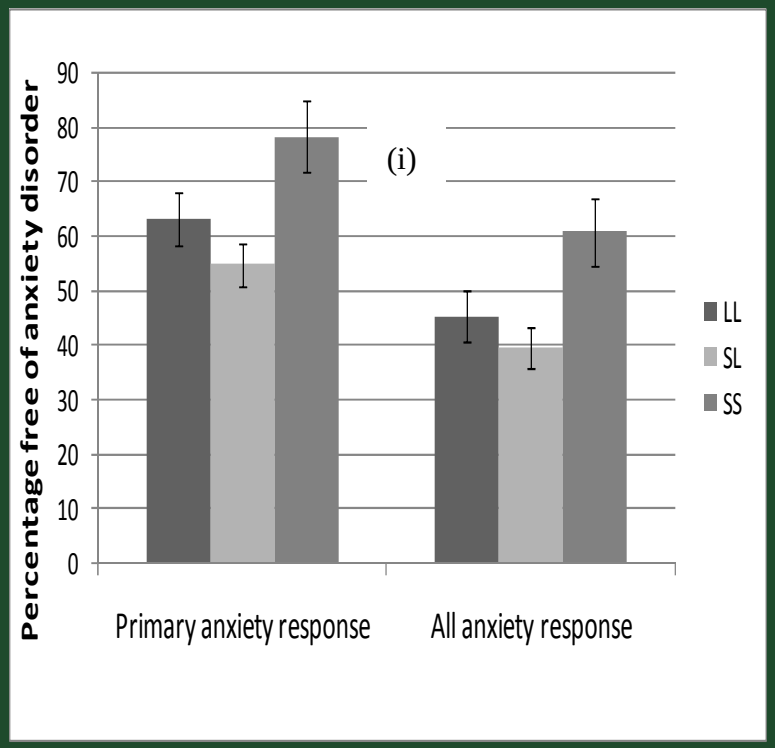


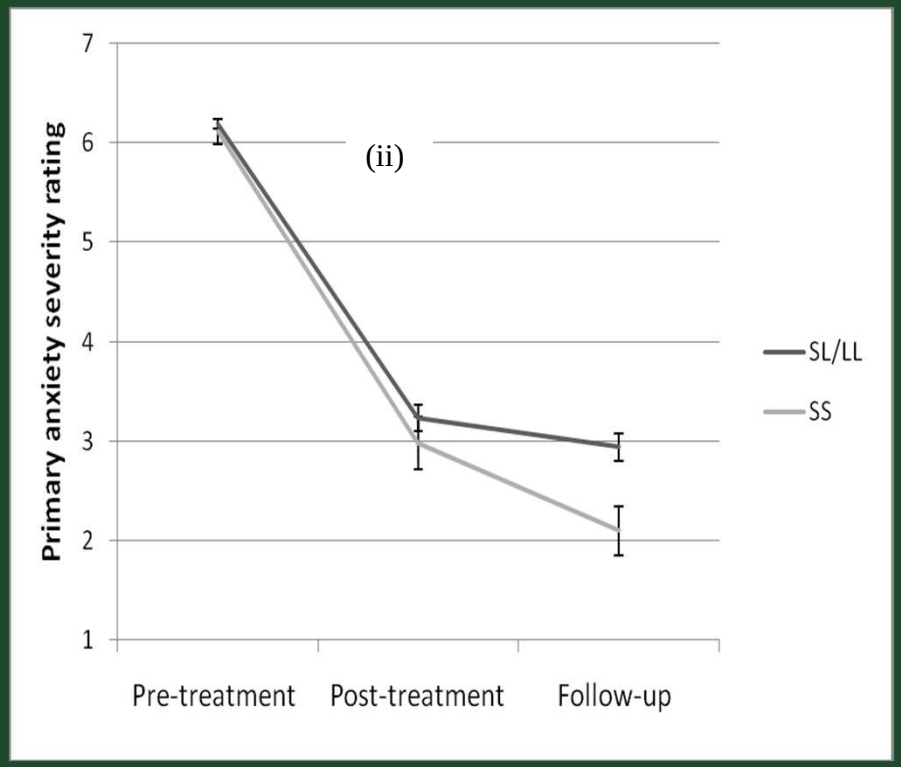
Genetic plasticity and treatment outcome:
therapy genetics 101

CHILDREN'S RESPONSE TO CBT MODERATED BY 5HTTLPR

(i) Proportion of children free of (a) their primary anxiety disorder and (b) all anxiety disorders at follow-up by *5HTTLPR* genotype.

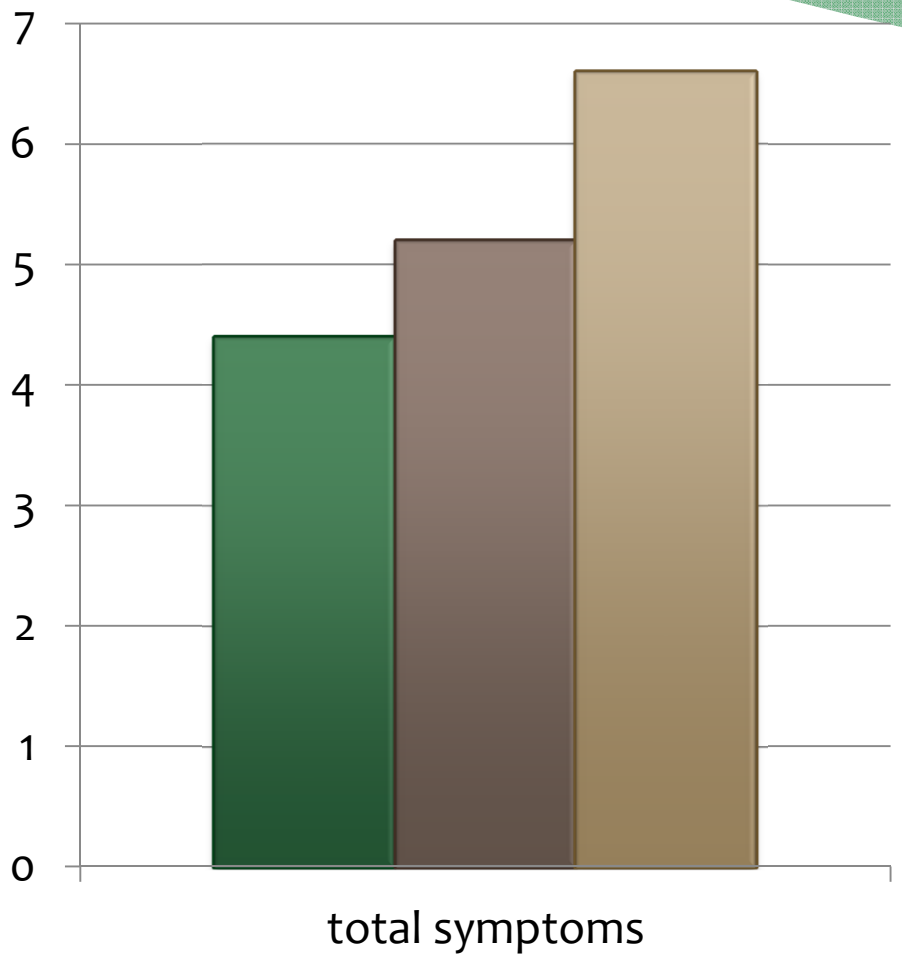
(ii) Symptom severity of primary diagnosis at each time point, as a function of genotype.



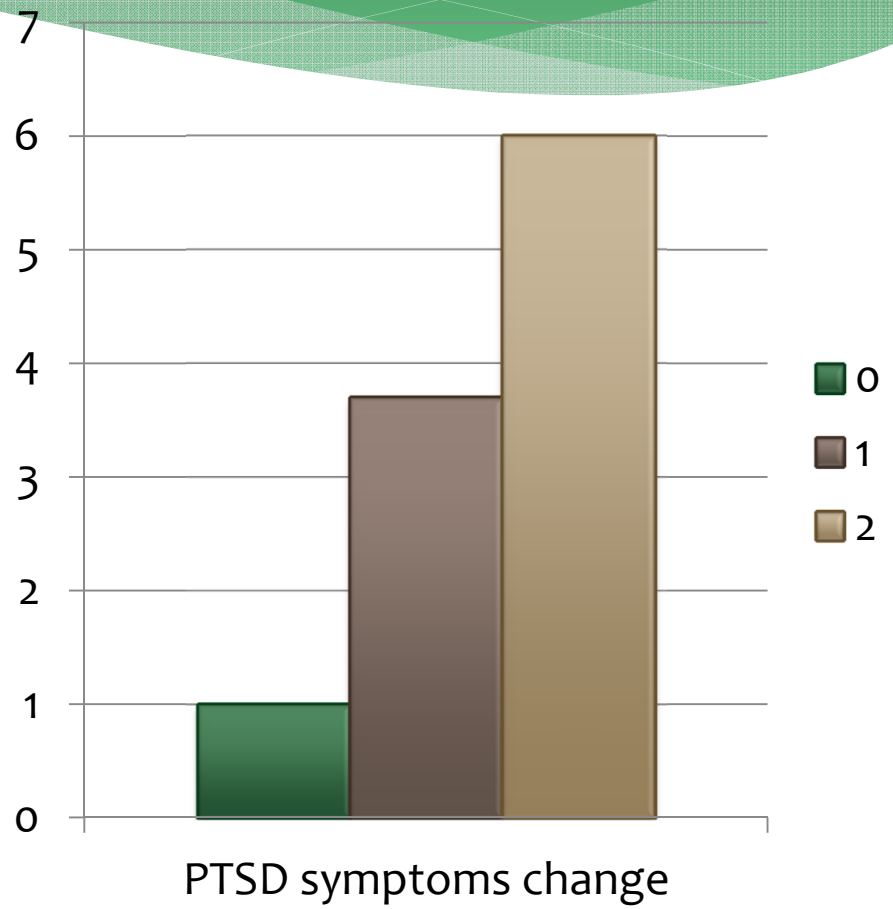


Eley, T.C. et al. (in press). Therapygenetics: The 5HTTLPR and response to psychological therapy. Molecular Psychiatry.

PTSD treatment and genetic plasticity



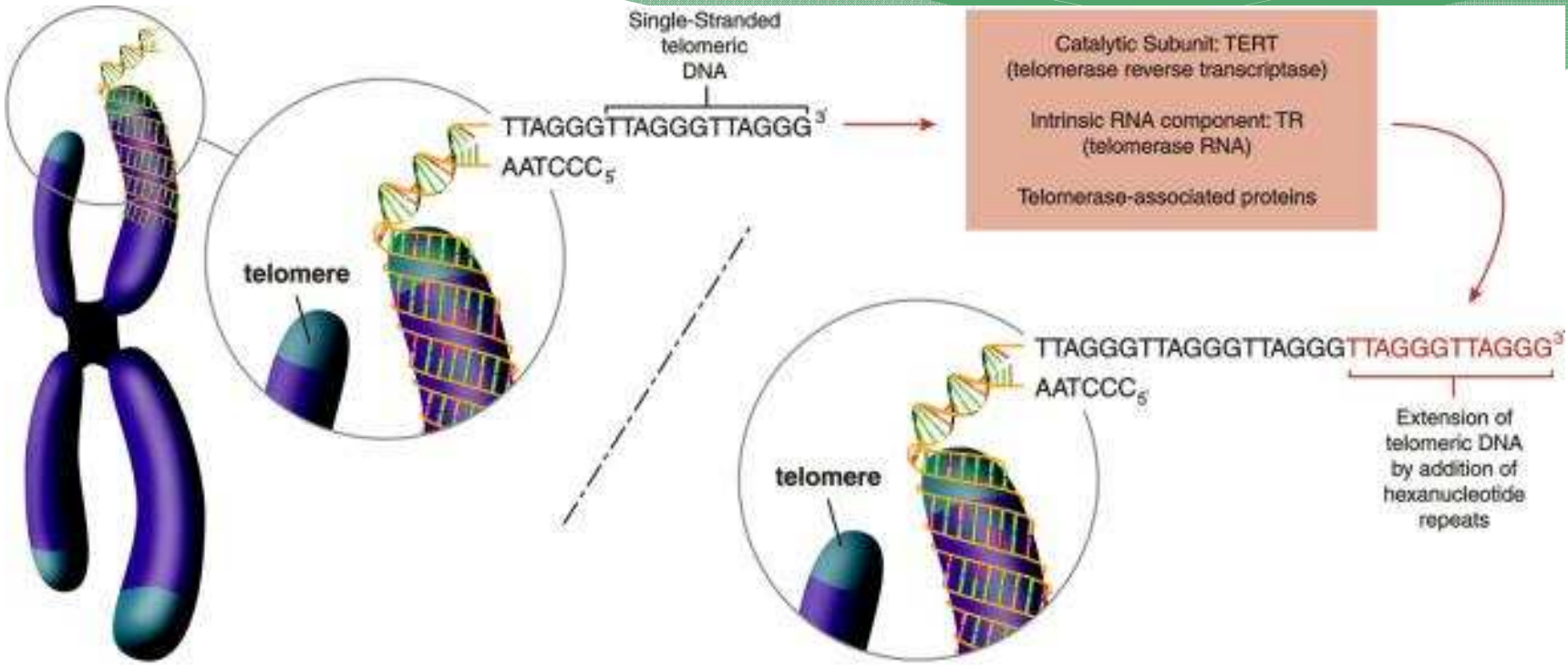
total symptoms



PTSD symptoms change

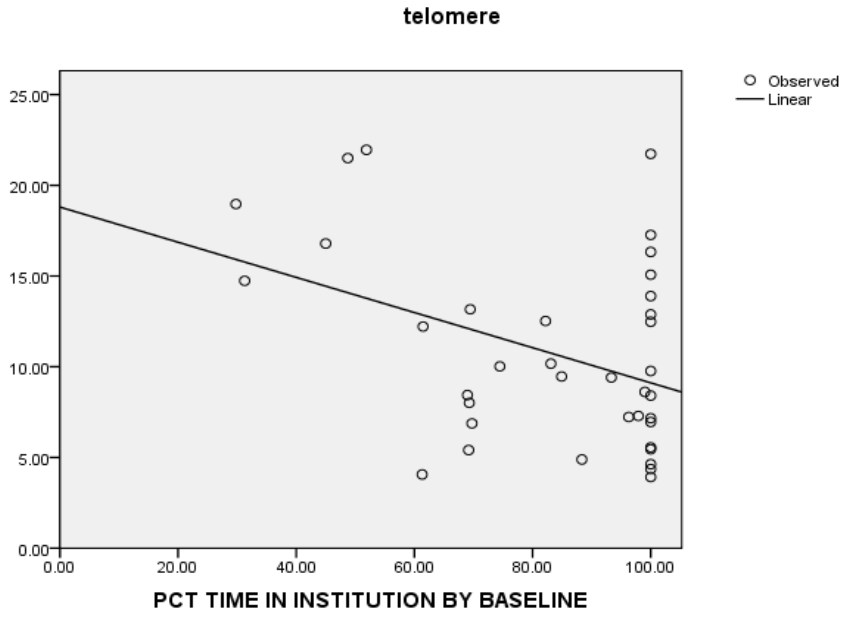

Nobel prize in Medicine '09
Don't cut it too short,
I don't wanna look old
Stripped Science
by Viktor S. Poór

Telomeres

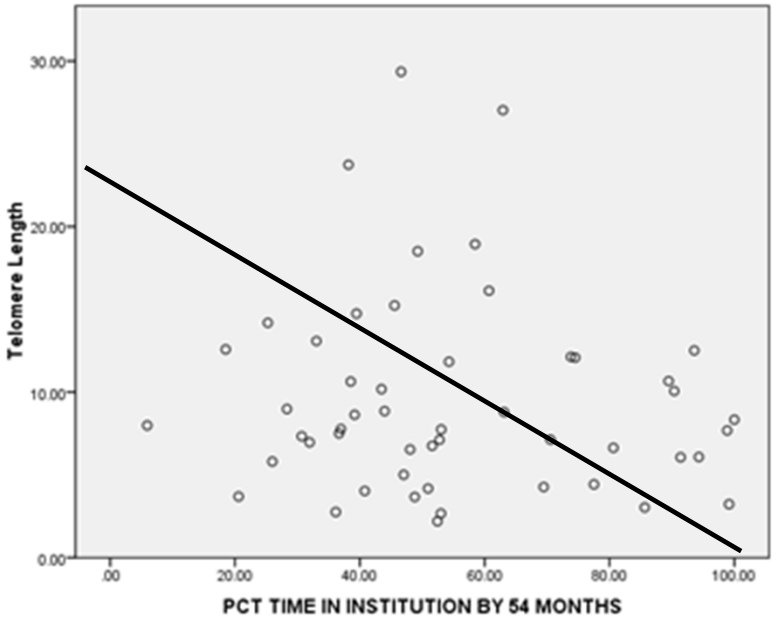

Single-Stranded telomeric DNA
TTAGGGTTAGGGTTAGGG 3'
AATCCC 5'
Catalytic Subunit: TERT (telomerase reverse transcriptase)
Intrinsic RNA component: TR (telomerase RNA)
Telomerase-associated proteins
telomere
TTAGGGTTAGGGTTAGGGTTAGGGTTAGGG 3'
AATCCC 5'
telomere
Extension of telomeric DNA by addition of hexanucleotide repeats

Telomere length and percent time

GIRLS: baseline



Boys: 54 months



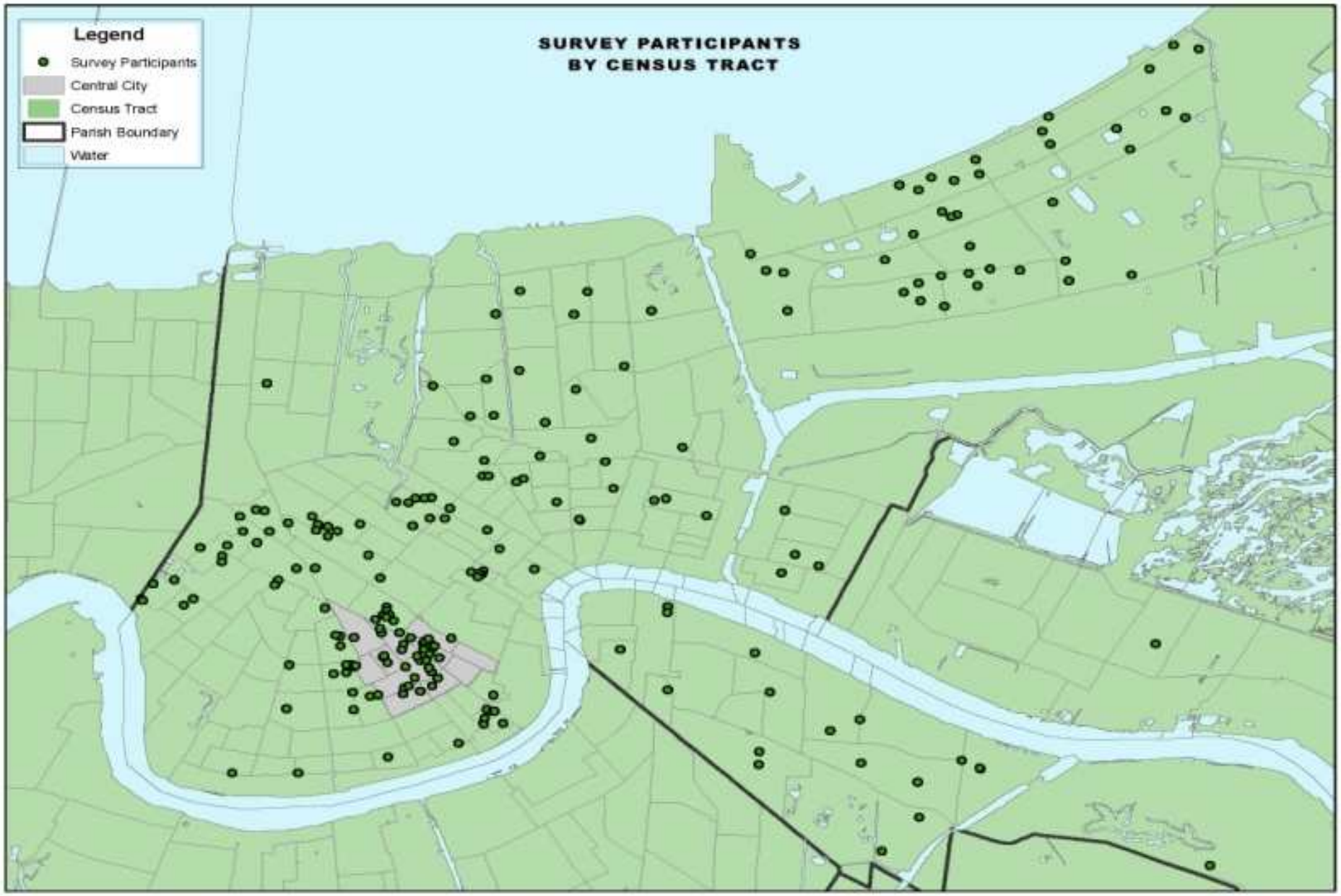
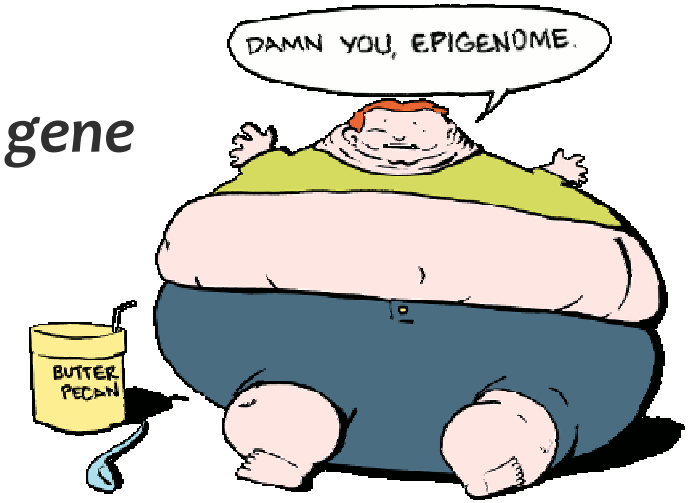

Legend
Survey Participants
Central City
Census Tract
Parish Boundary
Water
SURVEY PARTICIPANTS
BY CENSUS TRACT

Table 3. Neighborhood Adversity's Impact on Lower Telomere Length (N=52 tracts, N= 99 children)

		Model A	Model B	Model C
Neighborhood Adversity		High Disorder	Concentrated Disadvantage	Percent Below Poverty
	Adjusted Odds Ratio (95% Confidence Interval)			
High perceived disorder		★ **3.43 (1.22, 9.62)**	----	---
Concentrated disadvantage		**----**	1.10 (0.95, 1.28)	---
Percent below poverty		----	----	★ **1.02 (1.01, 1.04)**

Another layer: the Epigenome

* Evidence that early experience influences epigenome
  * Methylation
  * Histone acetylation
  * Chromatin structure
  * miRNA
  * Static vs labile effects
* ***Interactive/additional layer of influence on gene expression***



Genes associated with altered epigenetic marks and psychiatric outcomes

* **AVP
* COMT
* RELN
* **GR
* GABA-A
* PPIEL
* **POMC
* **ERα
* BDNF
* **GAD1

** indicates associated with early experience

Challenges to epigenetic studies

* Tissue specificity
* Developmental issues
* Power/Sample size
* Methodological

Use of genetic/epigenetics

* Explain individual differences in outcome
* Explain individual differences in recovery to intervention
* Neurogenetics- using genetics to understand neurobiology
* Epigenetic factors as an additional level of individual variation
* Vulnerability and resilience may be a matter of context
* Combining biophysiology, genetics, neuroscience to advance personalized treatment and development of novel interventions

The “d’s” to think about

* Development
* Different tissues
* Different polymorphisms
* Different environmental/care giving buffers
* Different treatments