# Genetic Vulnerability or Genetic Responsiveness?

# Implications for Social Responses to Violence

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"Contrary to many fears, genetic research is serving to only underscore the importance of the social environment, not diminish it" (Way & Taylor, 2010, p. 111).

# Genetic Vulnerability or Genetic Responsiveness? Implications for Social Responses to Violence

* How can genetic research inform social responses to violence?
* Theories of genetic predisposition to “mental health disorders” tend to conceal the importance of the social environment.
* However, even when heredity has been shown to be a factor, researchers have not been able to explain this by genes alone. “Heredity” is not synonymous with “genetic.” Where is the “missing heredity” (Maher, 2008)?
* Genes and environments interact and epigenetic responses to the environment direct gene expression.
* “Genetic determinism has died a quiet death” (Simons et al., 2011, p. 883)
* Thus, we may alter our gene function by changing our environments!

# Genetic Vulnerability or Genetic Responsiveness? Implications for Social Responses to Violence Outline

* Gene- environment interaction (G x E) research.
* Framework for critical analysis of G x E research.
* Epigenetic research: Changes in gene expression that are not related to differences in DNA sequence.
* Implications for therapy and other social responses to violence.
* "Genetic research is serving to only underscore the importance of the social environment, not diminish it" (Way & Taylor, 2010, p. 111).

# Effects or Responses

* Language of effects – determinism – cause and effect e.g., “environmental causes” and “genetic effects.”
* Language of responses – agency – e.g., “epigenetic responses.”
* Language confusion in the literature e.g., “Neuroplasticity refers to the ability of the brain to be molded by experiences or to remodel itself as a response to injury” (Rutter, 2012, p. 17150).
* For further information regarding the distinction between effects and responses please see Wade (1999).

# Diagnostic Categories

* Research designs use diagnostic categories that denote pathology.
* “Limited validity” (Uher & Rutter, 2012)
* DSM-IV-TR: If a syndrome or pattern is “expectable” given the context, it is not a dysfunction (APA, 2000, p. xxxi).
* I use diagnostic categories out of necessity when referring to research results.

# From “A Gene For . . .” to G x E

* 1980 to 2005: The search for a gene for mental disorder.
* Human Genome Project completed in 2003.
* Attempts to identify single genes involved in causation of psychiatric disorders.
* These attempts failed to identify any single locus that was unequivocally replicated (Burmeister et al., 2008).
* Genome-wide association studies.
* Gene-environment interaction studies.
* Serious ethical implications.

# “Genetic Vulnerability”

* Claims that common (with frequencies of 25-80%) genetic variations convey vulnerability to stress (Caspi & Moffitt, 2006).
* “Genetic risk” (Bakermans-Kranenburg & van Ijzendoorn, 2011),
* “Most vulnerable genotypes” (Kaufman et al., 2006),
* “High-risk genotype” (Brody et al., 2009, p. 657).
* “Genetic defect” (Morse, 2011, p. 207)
* “In theory, 5-HTTLPR S-carriers are characterized by the stable trait of negative affectivity that is converted to psychopathology only under conditions of stress, just as glass is always characterized by the trait of brittleness but shatters only when a stone is thrown” (Caspi et al, 2010).

# What Does This Suggest?

* Best case scenario for those with so-called vulnerability or risk alleles is the same outcomes as others as long as environmental conditions are favourable.
* Worst case scenario: Those with risk alleles suffer more when environment is adverse.
* No possible benefits of carrying these alleles.
* However, much is concealed by this perspective.

# Social Responses

* Negative social responses following severe adverse events are associated with more intense and prolonged distress (Andrews et al., 2003; Brewin et al., 2000; Campbell et al., 2001).
* Brewin et al. (2000) found in a meta-analysis of 14 separate risk factors for Posttraumatic Stress Disorder (PTSD) in trauma-exposed adults that lack of social support was the strongest risk factor.

# Implications of Claims of Genetic Vulnerability

* Conceals the importance of social responses.
* Suggests that those labelled as genetically vulnerable are intrinsically/biologically deficient.
* Suggests a solution may be to use pharmacological interventions to alter gene function.
* Suggests these people may be resistant to therapy.
* How easy is it to mend shattered glass?
* However, a growing body of research supports an alternative view.

# Paradigm Shift

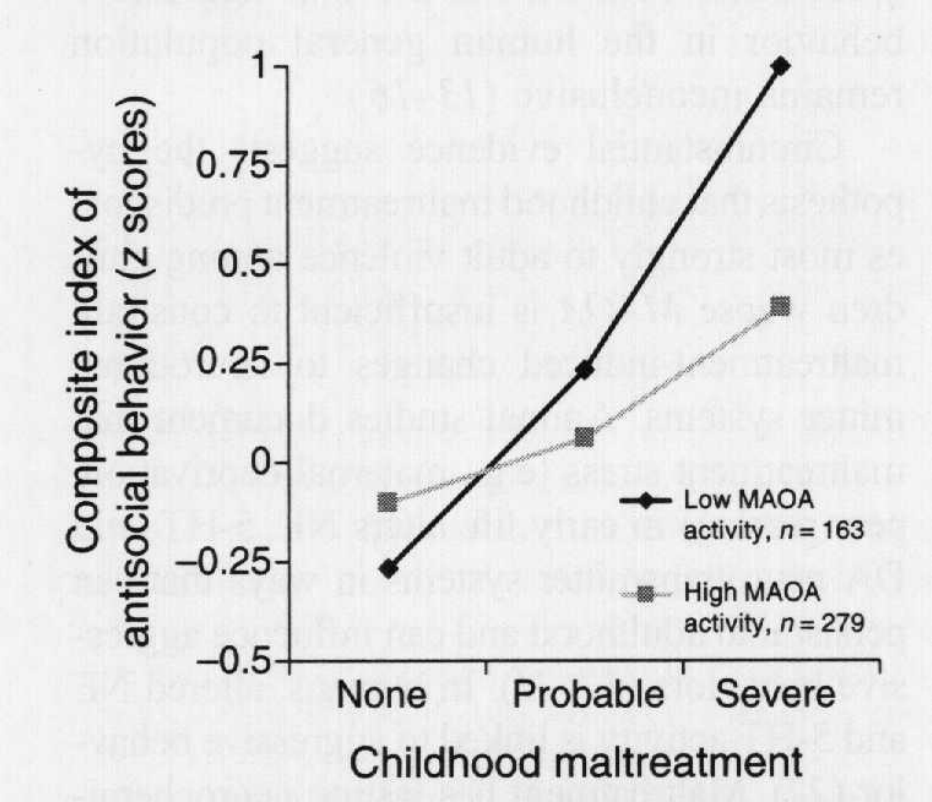
* Caspi et al. (2002): now cited over 2700 times (Google Scholar, 2013).
* Monoamine oxidase A (MAOA) degrades serotonin, dopamine, and norepinephrine (Shih et al., 1999). There are high-activity (MAOA-H) and low-activity (MAOA-L) MAOA alleles located on the X chromosome. Thus males have only one copy of the gene (Caspi, 2002).
* They proposed that "childhood maltreatment predisposes most strongly to adult violence among children whose MAOA is insufficient to constrain maltreatment-induced changes to neurotransmitter systems."

| MAOA-L Allele Frequencies | | | |
|---|---|---|---|
| Caspi et al. (2002) New Zealand Caucasians | Foley et al. (2004) USA | Haberstick et al. (2005) USA | Kim-Cohen et al. (2006) UK |
| 36.9% | 29.38% | 36% | 33.7% |

# Longitudinal Study

* Caspi et al. (2002) studied a New Zealand birth cohort (Dunedin Multidisciplinary Health and Development Study) of 442 males who had been followed from ages 3 to 26 with assessments at ages 3, 5, 7, 9, 11, 13, 15, 18, and 21 years. “Between ages of 3 and 11 years, 8% of the study children experienced “severe” maltreatment, 28% experienced “probable” maltreatment, and 64% experienced no maltreatment” (p. 852).
* Information from independent sources was used to ascertain outcomes. A composite index of antisocial behaviour (z scores) was developed based on assessments conducted at age 26.

# Maltreatment + MAOA-L

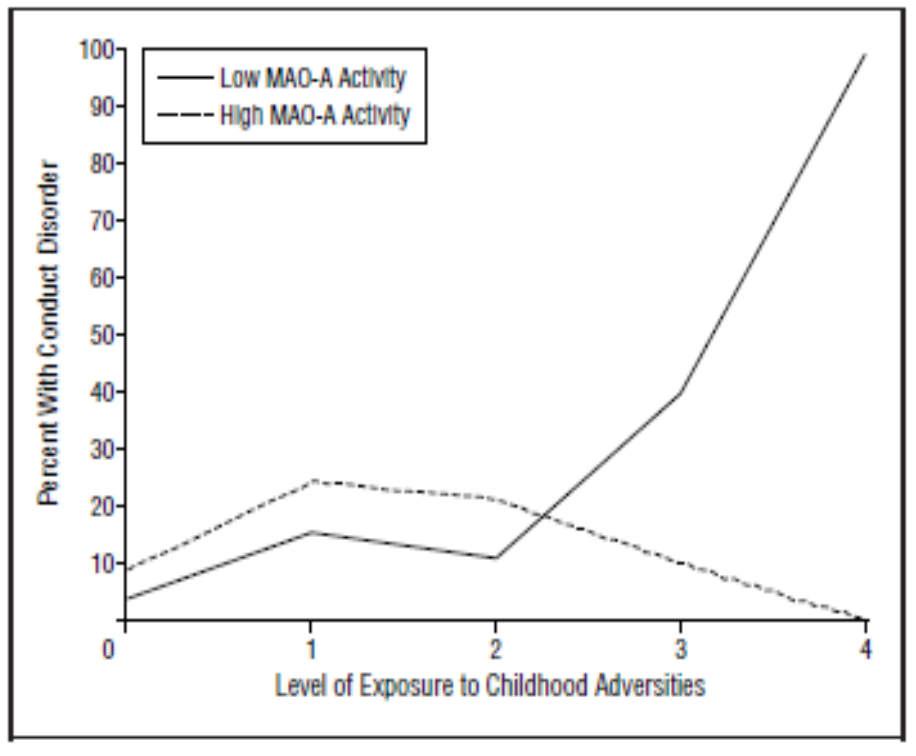



Caspi et al. (2002) found no direct relationship (main effect) between MAOA activity and composite index of antisocial behaviour.

However, those carrying the MAOA-L allele and exposed to maltreatment showed significantly higher levels of antisocial behaviour.

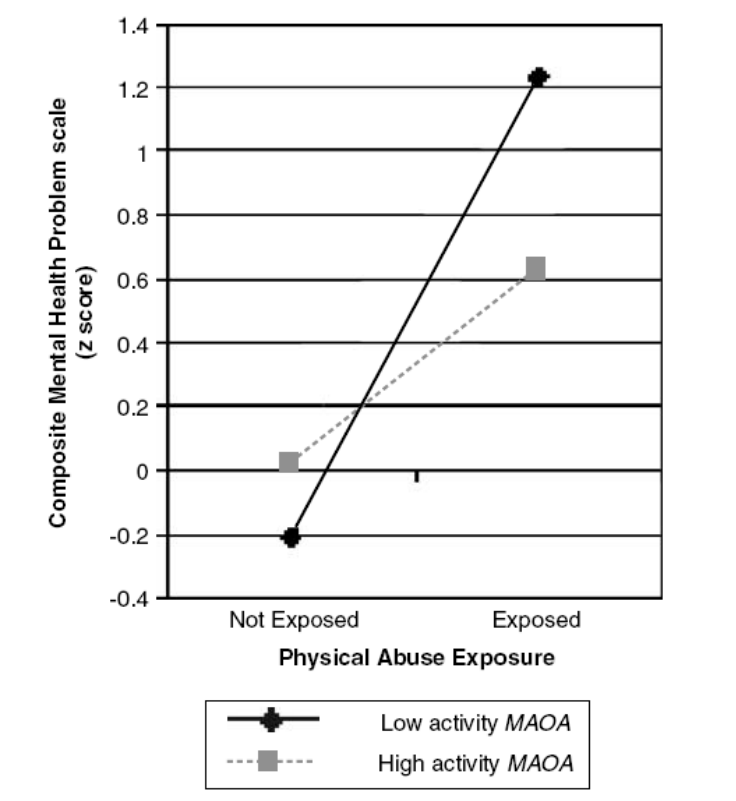
Composite index of antisocial behavior as a function of MAOA activity and a childhood history of maltreatment (Caspi et al., 2002, p. 852).

# Foley et al. (2004) Acknowledge the Intersections!




"This is an important finding because it suggests that specific genotypes may be associated with increasing or decreasing risks for psychiatric disorder contingent on environmental exposures" (Foley et al., 2004, p. 742).

# More Intersecting Lines!




(Kim-Cohen et al., 2006, p. 907)

- Kim-Cohen et al. (2006) studied the relationship between MAOA alleles, physical abuse, and aggression in 975 seven-year-old boys in the UK.
- MAOA-L activity allele associated with higher levels of distress and aggression after physical abuse.
- Significant main effect of MAOA activity in the *opposite direction*!
- Meta-analysis of 5 studies also found G x E interaction for MAOA.
- "These findings provide the strongest evidence to date suggesting that the MAOA gene influences vulnerability to environmental stress" (p. 903).

# Diathesis-Stress vs. Differential Susceptibility vs. Differential Responsiveness

* Belsky and colleagues (Belsky, Bakermans-Kraneneburg, & van IJzendoorn, 2007; Belsky et al, 2009; Belsky & Pluess, 2009)
* Diathesis-stress model vs. differential susceptibility to environmental influences (both positive and negative)
* Vulnerability genes/risk alleles vs. plasticity genes
* I prefer the terms differential responsiveness and responsiveness alleles.

# What happens at severe to extreme levels of trauma?

Weder et al. (2009) found that children with severe to extreme levels of traumatic experiences had high aggression scores, regardless of MAOA genotype.

# Additional MAOA Studies Showing A Cross-Over

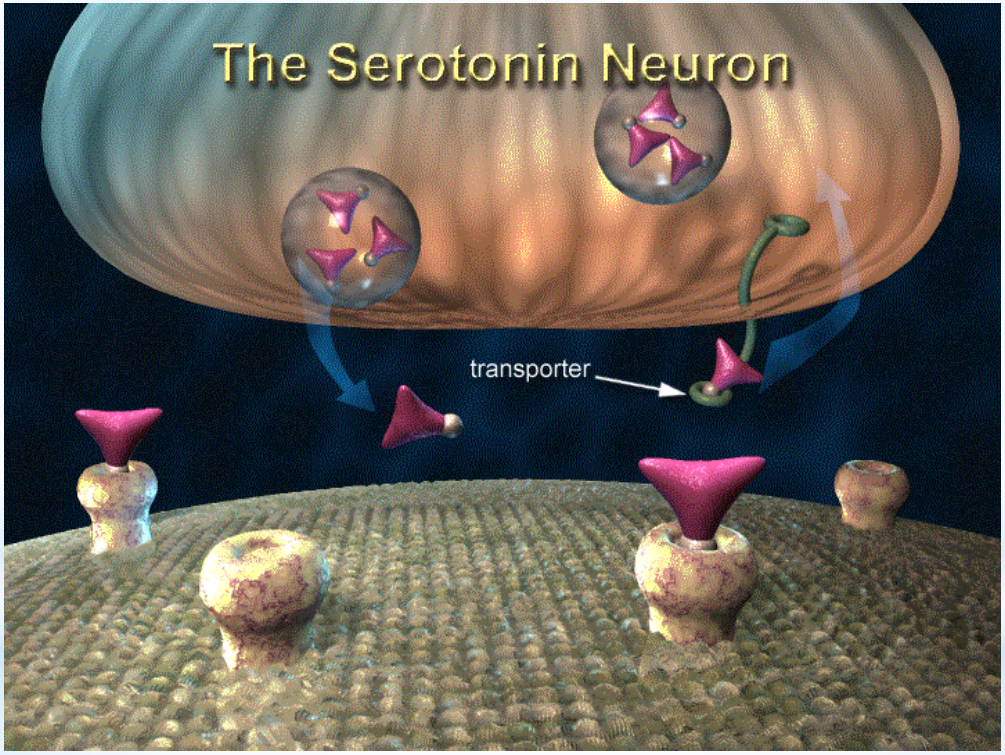
* Belsky & Pluess (2009) identified 7 studies showing a cross-over with those carrying MAOA-L alleles showing higher levels of distress when exposed to adversity and lower levels of distress in supportive environments than those carrying MAOA-H alleles.

# G x E and Testimony at Criminal Trials

* G x E presented in over 200 trials (Feresin, 2009).
* Jail term for murder decreased in Italy after testimony that the man convicted carried 5 genes linked to violent behaviour, including MAOA (Feresin, 2009).
* American jury reduced a charge for murder from “felony murder” (carrying the death penalty) to “voluntary manslaughter” (32-year sentence), largely based on testimony that the offender carried the “warrior gene” (MAOA-L) (Hagerty, 2010)
* Questions of agency: “Genes, environments, and their interactions do not commit crimes: acting people commit crimes” (Morse, 2011, p. 209).
* Group data are not necessarily relevant for individuals.
* “G x E evidence can be a knife that cuts both ways, supporting both mitigation and aggravation” (Morse, 2011, p. 231).
* Morse (2011) refers to “a genetic defect that caused a monoamine oxidase A (MAOA) deficiency” (p. 207).
* Responsiveness to rehabilitation?

# The Serotonin Transporter (5-HTT)

Serotonin, (5-hydroxytryptamine; 5-HT), is a neurotransmitter involved in the regulation of several processes within the brain, including mood, aggression, sleep, appetite, and anxiety.




National Institute on Drug Abuse. (n.d.). *The neurobiology of ecstacy (*MDMA), Retrieved October 10, 2008 from http://www.drugabuse.gov/Pubs/Teaching/Teaching4/Teaching3.html

# Serotonin Transporter Alleles

* Long (L) and short (S) alleles of 5-HTT gene-linked polymorphic region (5-HTTLPR) have been identified (Heils et al, 1996).
* The S allele has been associated with decreased 5HTT function (Lesch, 1996) relative to the L allele.

# Prevalence of 5-HTT Genotypes in World-Wide Populations

S and L alleles are common throughout the world (Gelernter et al., 1997; Hu et al., 2006).

| 5-HTTLPR S-Allele Frequencies | | | |
|---|---|---|---|
| African Americans | European Americans | Native Americans | Japanese |
| 25% | 40% | 65% | 80% |

| 5-HTTLPR Genotype Frequencies (Caspi et al., 2003) | | |
|---|---|---|
| S/S | S/L | L/L |
| 17% | 51% | 31% |

# Serotonin Transporter (5HTT) x Environment?

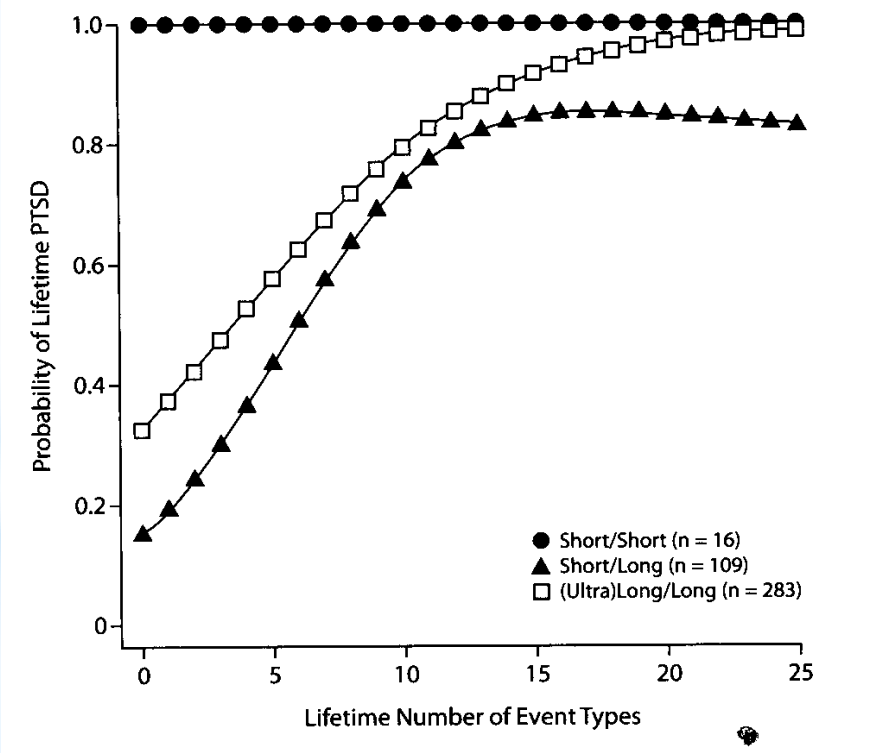
* Caspi et al (2003) conducted a G x E study looking at variations of the serotonin transporter gene and exposure to childhood maltreatment and stressful life events.
* This study has now been cited over 4700 times (Google Scholar, 2013)!

Caspi et al. (2003) found

* No “main effect” of 5-HTTLPR genotype on outcome of depression.
* G x E interaction: Childhood maltreatment and 5-HTTLPR S allele interact to increase risk for depression.
* G x E interaction: Stressful life events and 5-HTTLPR S allele interact to increase risk for depression.

# Responses to Genocide

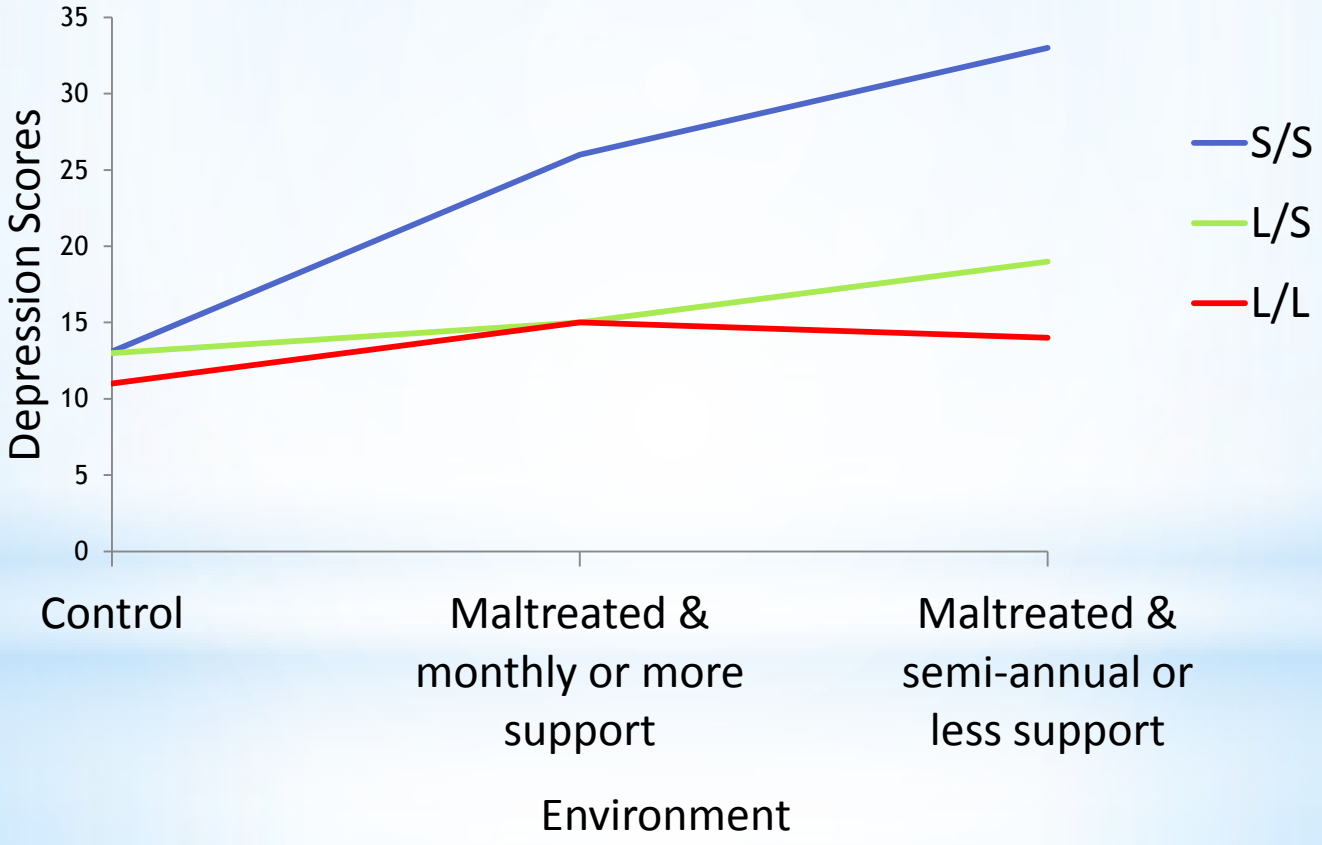
Kolassa et al. (2010) studied 408 Rwandan genocide survivors and found that though survivors with the S/S 5-HTTLPR genotype developed PTSD after fewer traumatic exposures, no influence of genotype was evident at high levels of traumatic exposure.



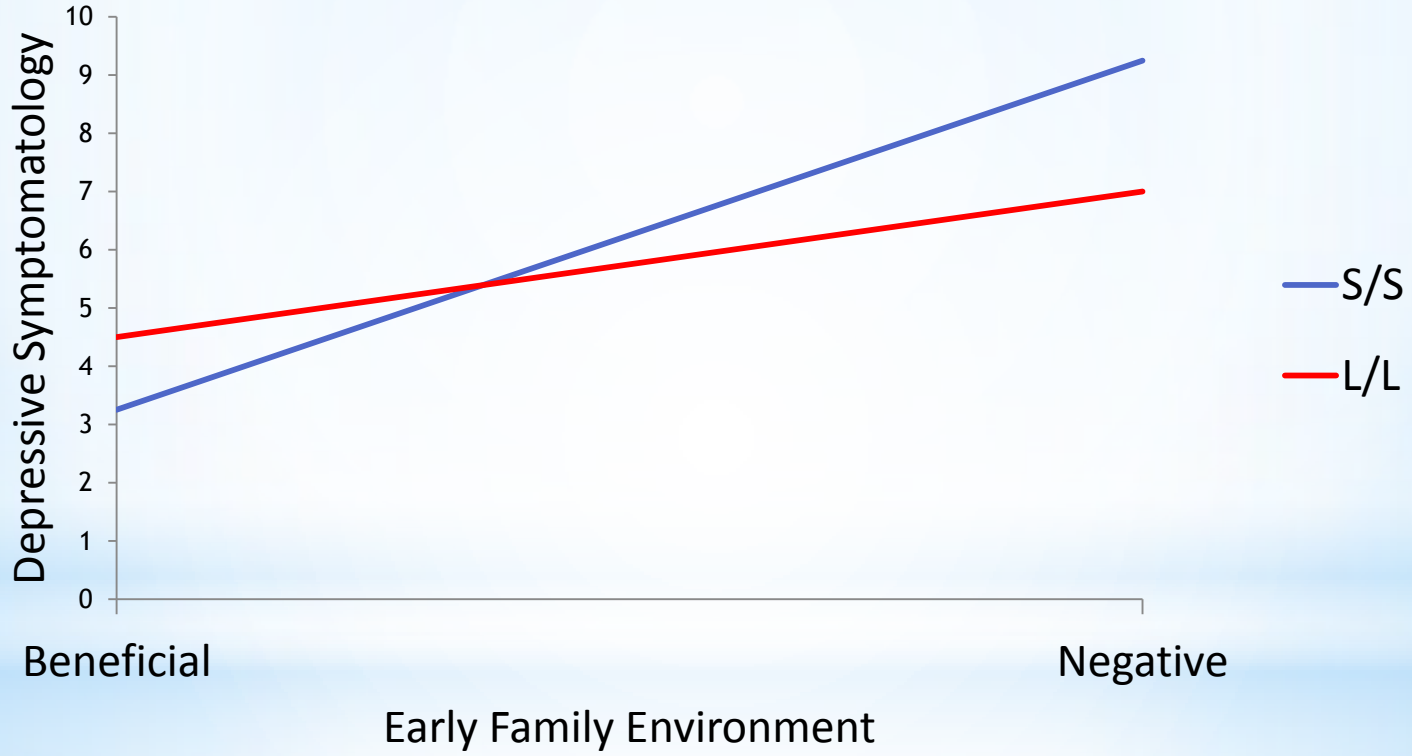

(p. 545)

# Gene x Maltreatment x Social Support

Kaufman et al. (2006) examined 5-HTTLPR x maltreatment x social support interactions.

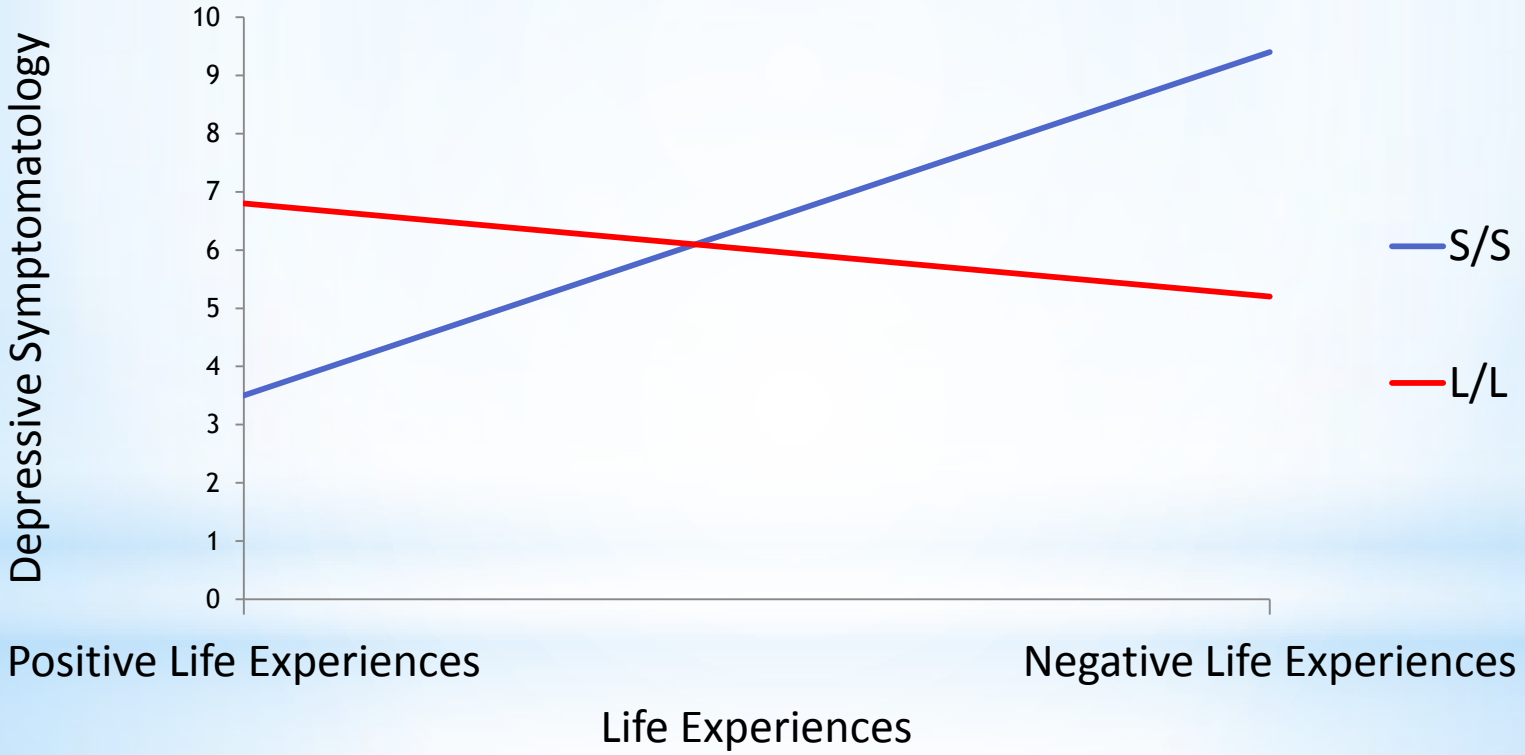


# Relationship of early family environment and 5-HTTLPR genotype to depressive symptomatology (adapted from Taylor et al., 2006)




Taylor et al. (2006) studied a non-clinical sample of 118 young adults.

# Relationship of current stress and 5-HTTLPR genotype to depressive symptomatology (adapted from Taylor et al., 2006)



# Differential Responsiveness to Social Environment!

* In a subsequent analysis, Way and Taylor (2010) found the interaction between *social* events and the S/S genotype was significantly associated with depressive symptomatology, but the interaction between *non-social* life events and S/S genotype was not.
* **"Genetic research is serving to only underscore the importance of the social environment, not diminish it"** (p. 111).

# Social Evaluation

* Way and Taylor (2010b) tested levels of salivary cortisol when performing stress tests i.e., presenting a speech and performing mental arithmetic tasks, in front of critical, supportive, or no audiences.
* Cortisol levels were highest for S/S genotypes, intermediate for S/L genotypes, and lowest for L/L genotypes, only in the critical audience condition.
* They concluded that S/S individuals might be especially sensitive to social evaluation.

# Life Satisfaction

(Kuepper et al. 2012, p. 645)

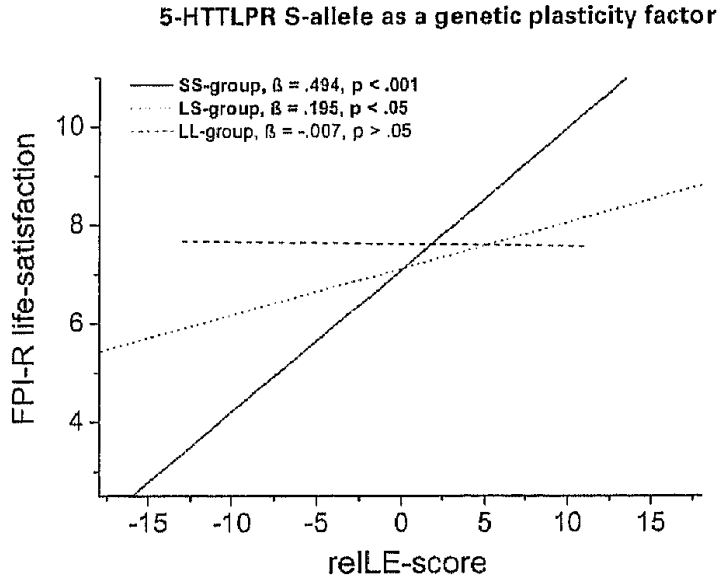



**Figure 1: relLE scores and life satisfaction association by genotype.** Regression lines depicting the association between relLE scores and life satisfaction, separated by genotype group.

RelLE = Relative Life Events = # positive life events - # negative life events.

Thus, for S carriers, positive life events may help to counter-balance negative ones.

# Hurricane Exposure, Social Support, and Posttraumatic Stress Disorder (PTSD)

* Individuals with the S/S 5-HTTLPR genotype and high hurricane exposure were more likely to develop PTSD *only* if they reported low levels of **social support** during the six months prior to the hurricane season (Kilpatrick et al., 2007).
* In the same study sample, the 5-HTTLPR S allele was associated with significantly *increased* risk of PTSD in **high-crime counties** (OR = 1.54) and *decreased risk* in low-crime counties (OR = .61) and a trend towards *increased* risk of PTSD in **high-unemployment counties** (OR = 1.46) and significantly *decreased risk* in low-unemployment counties (OR = .35) (Koenen et al., 2009).

# Sensitive Parenting

Based on the hypothesis that those carrying the S allele are more sensitive to their environments and that this may convey advantages in some environments, Mileva-Seitz et al. (2011) examined mothers' responses to their infants during a 30-minute recorded interaction with their six-month-old infants. Mothers with a 5-HTTLPR short allele showed more sensitive responses (as measured by indicators of cooperation, accessibility, and acceptance) than mothers who lacked the short allele.

# 5-HTTLPR and Therapy

* Brody et al. (2009) studied 641 African American youths and their parents randomly assigned to a control group or to participation in a program designed to increase nurturant-involved parenting practices.
  * Youth in the control group possessing a short allele (s/s or s/l) initiated risk behaviour (alcohol consumption, marijuana use, early sexual intercourse) at twice the rate of youths in the other three groups.
* Fox et al. (2011) engaged study participants in Attention Bias Modification (ABM) training designed to increase attention bias toward either negative or positive images. 5-HTTLPR S-carriers developed greater bias toward both negative and positive images than l-carriers. The authors conclude that S-allele carriers should gain the most from therapeutic interventions such as ABM.

# Therapygenetics

* Eley et al. (2012) published an article titled *Therapygenetics: The 5HTTLPR and response to psychological therapy.*
* They genotyped 359 children who were undergoing CBT for an anxiety disorder.
* Positive response was seen in 20% more children with the S/S genotype than in those with S/L or L/L genotypes.

# What do meta-analyses say?

* Diathesis-Stress Model: Karg et al. (2011) conducted a meta-analysis of 54 studies published prior to November 2009. Their study suggests there is cumulative and replicable evidence that 5-HTTLPR moderates the relationship between stress and depression with the S allele associated with increased stress sensitivity.
* Differential Susceptibility Model: Van IJzendoorn, Belsky, and Bakermans-Kranenburg (2012) conducted a meta-analysis of child and adolescent 5-HTTLPR x environment studies (41 effect sizes for 5-HTTLPR x negative environment and 36 effect sizes for 5-HTTLPR x positive environment). SS/SL carriers were significantly more vulnerable to *negative* environments then LL carriers and, in Caucasian samples, SS/SL carriers also profited significantly more from *positive* environmental input than LL carriers.

# The Benefits of Genetic Diversity

* Rhesus monkeys are the only primates other than humans to possess two 5-HTTLPR alleles (long and short) (Lesch et al, 1997).
* They also possess the greatest variability of the promoter region of MAOA (3 variants vs. 1 or 2) of all macaques studied (Wendland et al., 2006).
* Compared with other primates, both humans and rhesus monkeys can live in an extraordinarily wide range of physical habitats and social environments (Richard et al., 1989).
* "Maybe—just maybe—one of the secrets to the remarkable **resiliency shown at the species level** by rhesus monkeys and ourselves alike could actually be genetic *diversity*" (Suomi, 2006, p. 59).

# The 5-HTTLPR L Allele and Heart Disease

* While the long allele of the 5-HTTLPR has been characterized as protective and as conveying resilience, it is associated with higher rates of cardiovascular disease (Arinami et al., 1999; Bozzini et al., 2009; Coto et al., 2003; Fumeron et al., 2002).
* Interestingly, platelets possess serotonin transporters, take up and store serotonin, and release it in thrombotic events, promoting platelet aggregation (Lopez-Vilchez et al., 2009).

# Dopamine D4 Receptor (DRD4), Novelty Seeking, and ADHD

* The dopaminergic system is involved in attention, motivation, and reward mechanisms (Robins & Everitt, 1999).
* The 2-repeat (2R) and 7-repeat (7R) alleles demonstrate lower dopamine reception efficiency and have been associated with novelty seeking (Asghari et al., 1995; Ebstein et al., 1996; Benjamin et al., 1996, Reist et al., 2007) and risk for Attention Deficit Hyperactivity Disorder (ADHD) (Faraone et al., 2010; Leung et al., 2005).

| World-Wide DRD4 Allele Frequencies (Ding et al., 2002) | | |
|---|---|---|
| 2-repeat | 4-repeat | 7-repeat |
| 8.8% | 65.1% | 19.2% |

# Novelty Seeking and Migration

* 7-repeat allele probably arose as a rare mutational event approximately 40,000-50,000 years ago and increased quickly to high frequency through positive selection (Ding et al., 2002; Wang et al., 2004).
* Matthews and Butler (2011) propose that major rapid migrations out-of-Africa beginning about 50,000 years before the present (BP) selected for individuals with increased exploratory behaviour, novelty seeking, and risk taking (i.e., DRD4 2R and 7R).
* Ding et al. (2002) speculate that the very behaviours that may be selected for in individuals possessing a DRD4 7R allele may be considered inappropriate in typical classroom settings: Hence the diagnosis of ADHD.

# DRD4 and Differential Responsiveness

* Bakermans-Kranenburg and van Ijzendoorn (2011) conducted a meta-analysis of 15 studies examining G x E interactions involving dopamine-related genes (DRD2, DRD4, and dopamine transporter).
* Children with the supposed “risk” alleles were equally responsive to negative and supportive influences.

# DRD4 and Response to Social Intervention

Bakermans-Kranenburg et al. (2008) found that toddlers carrying the DRD4 7R allele had the highest scores for externalizing problems prior to an intervention program designed to promote **positive parenting and sensitive discipline** and the lowest scores at two-year follow up.

# Cumulative Genetic Responsiveness

* Simons et al. (2012)
* 208 African American males ages 20-21
* MAOA-L, 5-HTTLPR S, DRD4 7R genotype x harsh/demoralizing environment

# Simons et al. (2012, p. 16)

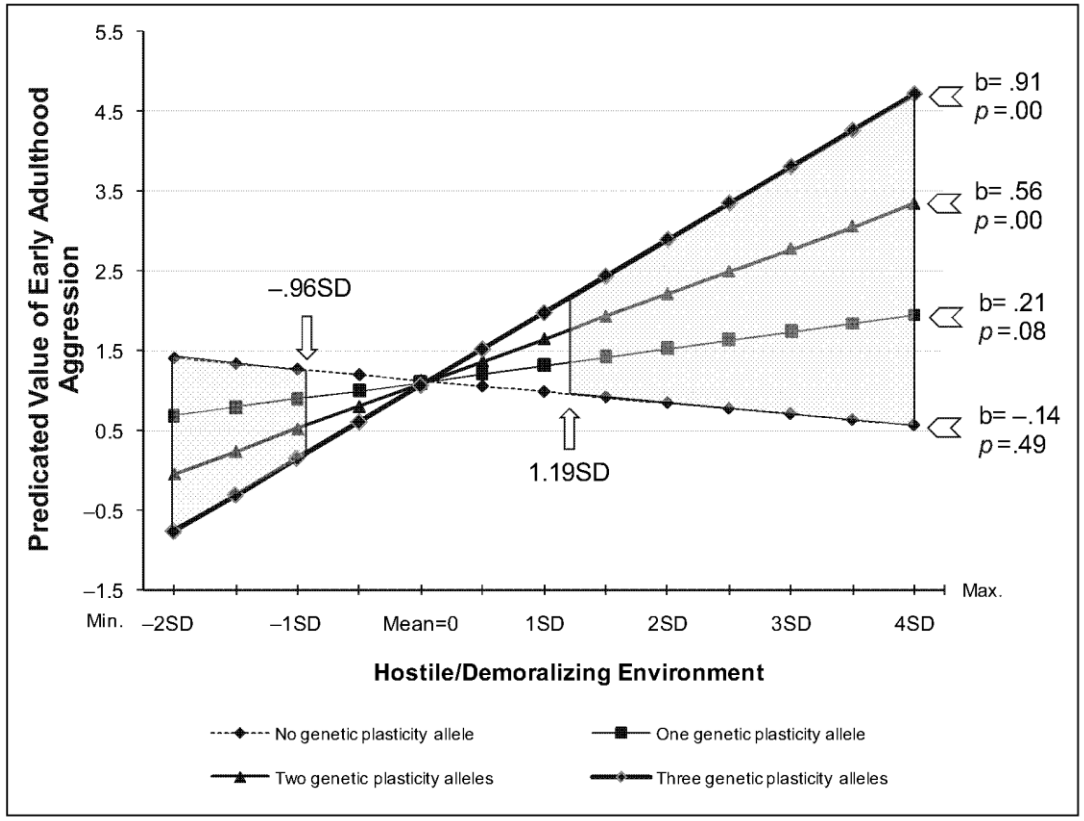



**Figure 2.** The effect of hostile/demoralizing environment on aggression by number of genetic plasticity alleles with Johnson–Neyman confidence bands. The gray areas are significant confidence regions.

# Vulnerability, Brittleness, Susceptibility, Plasticity, and Sensitivity

* Mileva-Seitz et al. (2011) conclude,

  > Genotypes with one or two S alleles have been regarded as 'vulnerability' genotypes . . . However, in the absence of early stress and perhaps even despite early stress, the S allele might in some contexts have adaptive advantages over the L allele. This fits well with the emerging theory that the S allele confers greater sensitivity to environmental signals (Taylor 2010), and that rather than a susceptibility allele, the S allele may be viewed as a plasticity allele (Belsky et al., 2009). Our results corroborate this view. (p. 329)

* I prefer the terms "responsive genotypes" (Way & Taylor, 2010, p. 110) and "differential responsiveness" because they reflect the active nature of responses to environment i.e., agency, whereas the other terms suggest passive states.

# Vantage Sensitivity

* No word to describe those who may benefit disproportionately from enriched environments.
* Pluess and Belsky (2012) found no term in English, French, German, Italian, Chinese, Czech, Spanish, Korean, or Polish.
* Manuck and associates (Manuck, 2011; Sweitzer et al., 2012) introduced the term *Vantage Sensitivity.*
* Pluess and Belsky (2012) summarize recent research that suggests the 5-HTTLPR S allele (7 studies) and the DRD4 7R allele (4 studies) convey vantage sensitivity across a variety of environmental exposures and outcome measures.

# Which Alleles Convey an Advantage? It Depends on the (Social) Environment, Outcome Measures, and Perspective (Individual vs. Population)

* Those with S 5-HTTLPR, MAOA-L, and/or DRD4 7R or 2R alleles appear to have a disadvantage in adverse environments and an advantage in enriched ones.
* At extreme levels of adversity, these differences disappear.
* Attributions of vulnerability and resilience may also vary depending on outcomes measured e.g., cardiovascular health.
* Variations may exist in outcomes that have not yet been measured.
* At a population level, diversity appears to convey advantage.

# Providing Genotype Results to Research Participants

* Wilhelm et al. (2009) offered 128 research participants (mean age 48 years) their 5-HTTLPR test results.
* Participants were provided with a summary of the Caspi et al. (2003) study along with possible limitations, including the potential future obligation to provide results to insurance companies.
* Those with the S/S genotype were told they were in the 20% who were potentially more emotionally reactive when confronted with a series of life events, with an increased risk (~twofold) for depression.
* Those with S/S showed higher distress after learning their results.

# What Happens With Medication?

* When those who experience distress following exposure to adversity, or those who are diagnosed with ADHD, are medicated, to what extent are we using drugs in an effort to fit people to their environments rather than attempting to create environments in which these people may thrive?
* What are the costs associated with these practices? How much diversity and potential is lost?
* Are we committing a form of "**pharmacological eugenics**" i.e., pharmacologically attempting to force one genotype to function like another?

# Summary

* "Genetic research is serving to only underscore the importance of the social environment, not diminish it" (Way and Taylor, 2010, p. 111).
* Genes and environments do not function *independently of* each other; they *interact with* each other.
* The serotonin transporter short allele (5-HTTLPR S), monoamine oxidase A low-activity alleles (MAOA-L), and the dopamine receptor D4 7-repeat (DRD4 7R) allele have been portrayed as conveying *vulnerability* to adversity (e.g., Caspi et al., 2002, 2003). This view suggests there are no advantages associated with these alleles and those carrying them may be resistant to treatment.
* However, a growing body of research suggests those carrying these alleles may demonstrate increased emotional and behavioural *responsiveness* (as suggested by measures of distress, aggression, life satisfaction, etc.) to *both* adverse *and* supportive social environments: They may suffer more when exposed to adversity and benefit more in supportive environments (e.g., Belsky & Pluess, 2009). Thus, they may be *more likely* to respond positively to therapy and other supportive social interventions.

# Summary Continued

* Differences in responses disappear at severe to extreme levels of adversity (Kolassa et al., 2010; Weder et al., 2009). Everyone is responsive to adversity, though thresholds may vary.
* Those carrying so-called “resilience alleles” e.g., 5-HTTLPR L, MAOA-H, and DRD4 4R, may respond to adversity in as-yet unmeasured ways.
* The 5-HTTLPR S, MAOA-L, and DRD4 2R and 7R alleles are common in worldwide populations and have apparently been maintained at high levels because they are associated with a balance of advantages and disadvantages that depend on environmental conditions. In addition, diversity in these genes may have been instrumental to our survival and adaptability as a species (Suomi, 2006). Thus, there is no one best allele or genotype!

# Implications for Practice

The results summarized

* Provide reasons to honour, value, and appreciate genetic diversity,
* Contest pathologizing of those who carry common genetic variations,
* Provide reason for hope that those who are most distressed in response to adversity may also be most likely to respond to therapeutic social interventions,
* Suggest those who are most responsive to their social environments may be interested in highly contextualized forms of therapy that acknowledge contextualized accounts of problems and their responses to those problems, support their capacity to address adverse situations and environments, and focus on developing contextualized solutions and social support. We might ask, “In what types of environment will this person be most likely to thrive?”

# Implications for Practice Continued

* Support respectful and compassionate responses to those who have been maltreated and show aggression. We might ask, “In what types of environment will this person be most likely to choose to change?”
* Suggest that Response-Based Therapy, developed by Allan Wade and colleagues (Wade, 1999), with its focus on contextualized analysis, interpersonal interactions, responses to adversity, and the situational logic of these responses, may be ideally suited to those who are highly responsive to their social environments.

# Implications for Practice Continued

## Controllable vs. Uncontrollable Stress

* Amat et al. (2005) note that the intensity of stress responses is related to the degree of behavioural control an organism has over a stressor. When a stressor was controllable, activity in the ventral medial prefrontal cortex inhibited the stress response in the dorsal raphe nucleus, thus blocking typical stress responses associated with uncontrollable stress. Could this be a key to the **physiology of successful psychotherapy**?
* Could it be that therapy and other social responses that contribute to a sense of mastery over social stressors may be particularly beneficial for those who show greater responsiveness to the social environment?

# Framework for Critical Analysis of Genetic and G x E Research

When researchers portray a specific genetic variation as detrimental, ask

* Is the genetic variation common?
* If it is common, what advantages might offset reported disadvantages?
* What outcome measurements (measures of both distress and wellbeing?) have been used?
* In what environments (restricted or broad, adverse and supportive?) have outcomes been examined?

If narrow outcome measures were used in restricted environments, results must be interpreted with extreme caution. Results of G x E research reflect group averages and may have limited applications to specific individuals.

# Future G x E Research

* How do L/L carriers respond to environmental adversity? Do they respond in ways that have yet to be measured?
* What is distress in L/L carriers a response to?
* Further research regarding responsiveness to treatment, especially with those who perpetrate violence.

# Epigenetic Responses

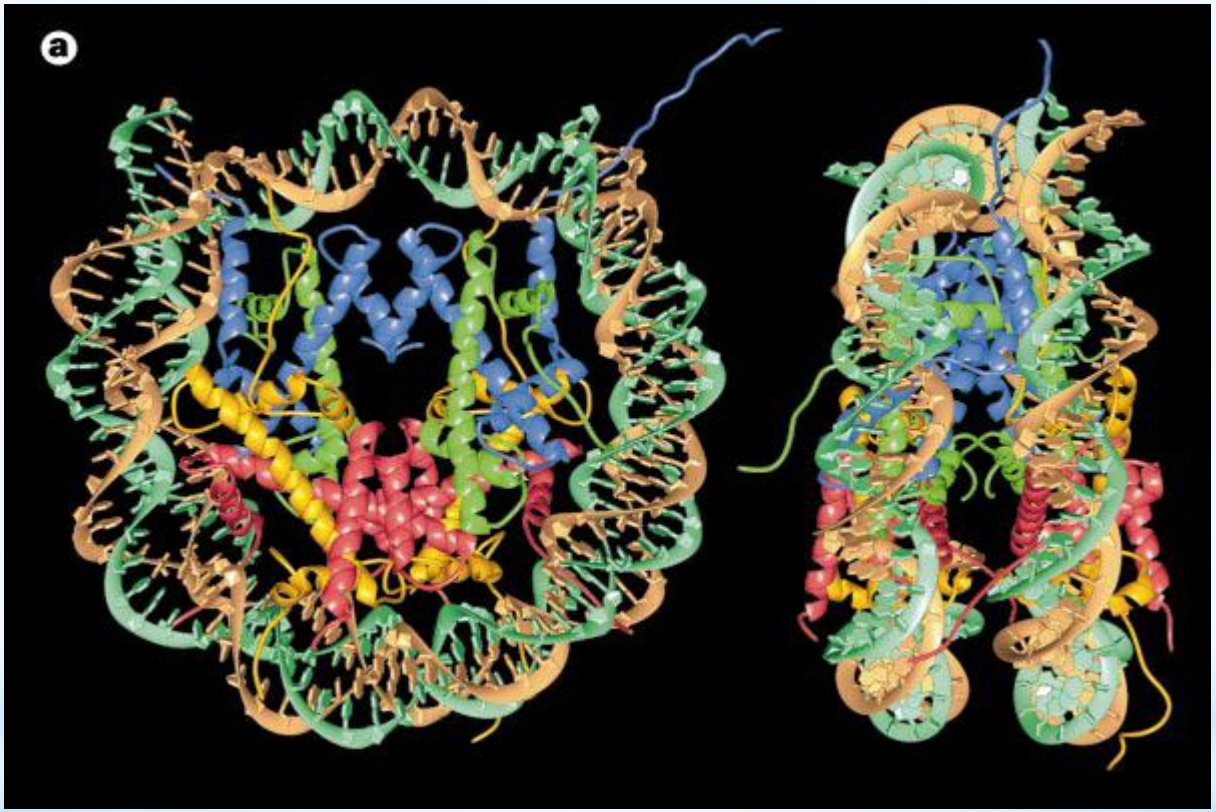
* The word *epigenetic* derives from the Greek *epi* meaning ‘‘upon’’ and *genetics.* Epigenetics has been defined as a functional modification to the DNA that does not involve an alteration of DNA sequence. (Meaney, 2010).
* Our DNA sequence does not change as our experiences change, but the way information stored in our DNA is *used* by our cells does change!

“All cellular processes derive from a constant dialogue between the genome and environmental signals” (Canadian epigenetic researcher, Michael Meaney, 2010).

# What Does DNA Look Like?

Retrieved from http://wallpapers.free-review.net/23__DNA.htm

# DNA, Histones, and Histone Tails




Nucleosome Core Particle: Crystallographic image of the nucleosome showing146 base pairs wrapped around a histone complex with histone tails protruding (from Luger, Mader, Richmond, Sargent, & Richmond, 1997).

# Cellular Responses and Resistance

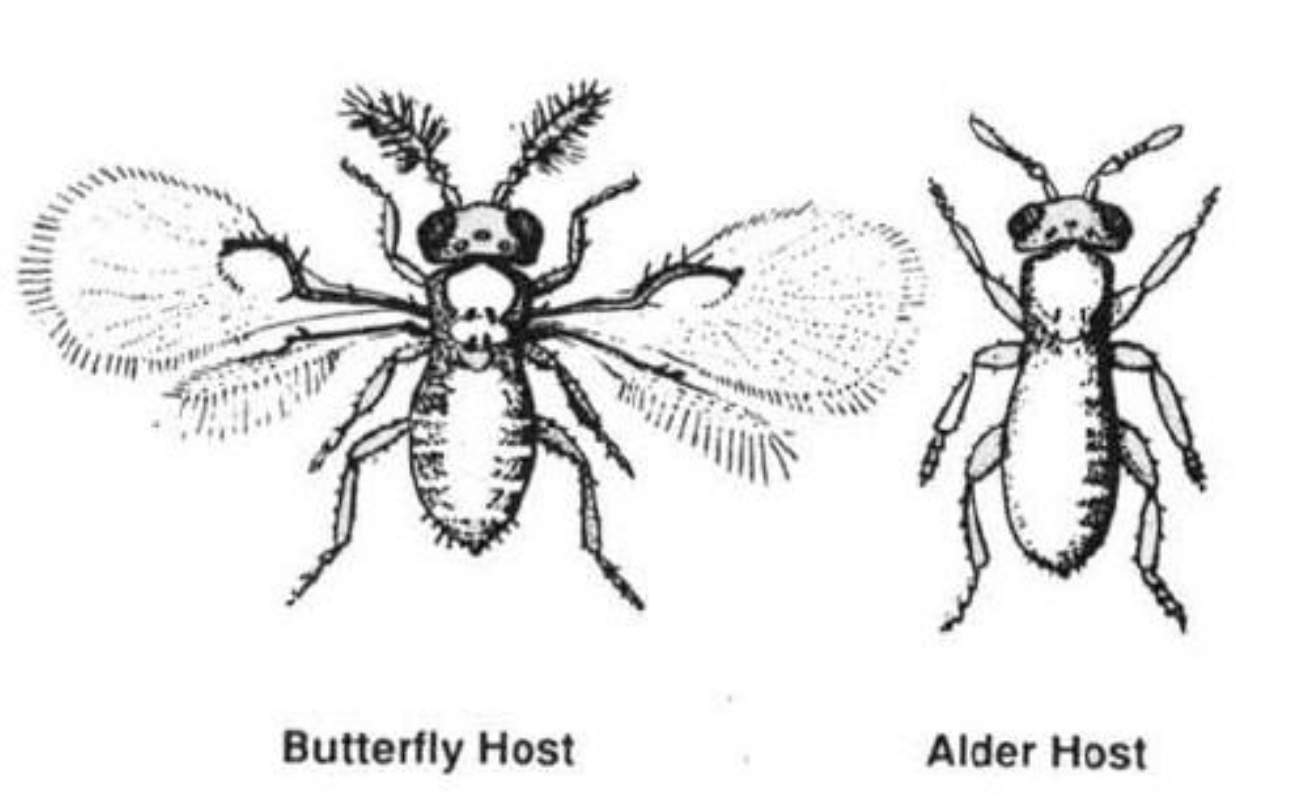
* Cell biologist Bruce Lipton (2005) provides the following example of cellular responses to the environment:

> I saw that endothelial cells, which are the blood vessel-lining cells I was studying, changed their structure and function depending on their environment. When, for example, I added inflammatory chemicals to the tissue culture, the cells rapidly became the equivalent of macrophages, the scavengers of the immune system. (Lipton, 2005, pp. 72-73)

* These cells *resisted* and *changed* their environment!

# The Environment Makes a Difference!

Gottlieb (1998) provides an example of dramatic differences in insects carrying the same DNA but exposed to different environments.




Alder fly

(http://en.wikipedia.org/wiki/Alderfly)

Minute parasitic wasp hatched on butterfly host compared with one hatched on an alder fly host. Adapted by Gottlieb (1998) from Wigglesworth (1964).

# One Gene, Diverse Proteins

* Epigenetic processes can use information contained in a single gene to produce multiple diverse protein products, even proteins with opposite functions! (Meaney, 2010, p. 47).

# What can we Learn from Rats?

* The amount of time rat mothers spend licking and grooming their pups varies during the first week of life. Weaver et al. (2004) found that at the end of the first week of life sites on the exon $1_7$ glucocorticoid receptor promoter region were unmethylated in the pups of high-licking-grooming (high-LG) mothers, but not in the pups of low-LG mothers.
* When glucocorticoid receptors are acted on by stress hormones, the stress response is dampened. Thus, decreased availability of glucocorticoid receptor genes due to increased methylation may result in increased stress responses.

(Image from Zang & Meaney, 2010, p. C3)

# Licking, Grooming, and Learning

* Pups raised by low-LG mothers showed decreased learning and memory in the Morris water maze, decreased object recognition, decreased hippocampal synaptic density, and decreased expression of the NR2A and NR2B subunits of the hippocampal N-methyl-D-aspartate (NMDA) receptor.
* These changes are related to licking and grooming and not genetics, as shown by cross-fostering.
* However, when these rats were exposed to environmental enrichment from days 22 to 70 of life, the previous decreases in cognitive function were reversed as was expression of the NR2A and NR2B subunits of the NMDA receptor. (Bredy et al., 2004)

# Licking, Grooming, Learning, and Environment

* Champagne et al. (2008) and Bagot et al. (2009) showed that under stressful conditions, pups of low-LG mothers outperformed those of high-LG mothers: They showed greater learning and memory and their hippocampal neurons demonstrated greater synaptic plasticity when exposed to stress hormones in doses mimicking stress-responses.
* Pups of low LG mothers demonstrate enhanced capacity for defensive responses when exposed to a threat, engage in less open-field exploration, reach puberty at an earlier age, show increased sexual receptivity, and spend more time mating (Cameron, 2011).
* Champagne et al. (2008) conclude that, “individual differences in outcome of early experience depend on environmental context in later life” (p. 6043).

# Intergenerational Transmission of Licking and Grooming

* Maternal responses to adversity are also transmitted across subsequent generations.
* High-LG mothers placed in stressful conditions during gestation become low-LG mothers and their female pups also demonstrate low-LG practices with their own litters.
* Low-LG mothers shift in the direction of high-LG mothers with an extensive period of peripubertal environmental enrichment. (Champagne & Meaney, 2006).
* This suggests a connection between environment, parenting, and pup outcome wherein pups' neurological development prepares them for success in their ambient environments.

# What then is Ideal Parenting?

Meaney (2010) affirms, “If indeed there is no single ideal phenotype, then it should follow *that there is no single ideal form of parenting*. If this conclusion has worth, then it leads us to question the wisdom of establishing parenting programs that foster parental skills based on studies of families rearing children under more favorable conditions” (p. 67).

# Twin Children and Methylation Changes

* DNA samples from 182 twins at ages 5 and 10.
* Measured methylation of promoter regions of 5-HTT, DRD4, and MAOA genes obtained from cheek cells.
* High levels of differences in DNA methylation between monozygotic twins.
* High levels of differences in within-person DNA methylation over a five-year period.
* Most of the observed changes in DNA methylation were attributable to environmental influences and were not heritable.
* DNA methylation may act as a biological marker of environmental exposure (Wong et al., 2010)

# Adults and Methylation Changes

* American cohort: Ages 5-72, DNA samples 16 years apart.
  * 40% showed at least 5% change in DNA methylation in either direction, and 10% showed ≥ 20% change.
* Iceland: DNA samples 11 years apart.
  * Ages 69-96 when the second sample was collected.
  * 65% showed a change of DNA methylation of at least 5% in either direction, with 8% showing changes ≥ 20%.
  * This suggests DNA methylation changes continue into advanced age (Bjornsson et al., 2008)

# Human Correlates of Licking and Grooming

* Early maternal care in rodents is analogous to the 3rd trimester of human gestation.
* Exon $1_F$ region of the human glucocorticoid receptor (GR) gene homologous to the exon $1_7$ region of the rat GR gene.
* Increased third trimester depressed/anxious mood in human mothers was associated with increased site-specific exon $1_F$ GR methylation in cord blood mononuclear cells collected at birth.
* This, in turn, was associated with increased salivary cortisol change scores following a stress test challenge at three months of age (Oberlander et al., 2008).

# Epigenetics, Pregnancy, and Intimate Partner Violence

* Radtke et al. (2011) examined methylation status of the exon $1_F$ region of the GR gene in whole blood samples from mothers and their children ages 10-19 and assessed for intimate partner violence (IPV).
* IPV during pregnancy, but not before or after pregnancy, was associated with increased methylation of the exon $1_F$ region in children.
* No association between IPV and mothers' exon $1_F$ methylation status.

# Epigenetics, Child Abuse, and Suicide

* McGowan et al. (2009) studied post-mortem brain tissue from 36 males ages 22-47:
  * 12 died of suicide and had history of childhood abuse,
  * 12 died of suicide and had no history of childhood abuse,
  * 12 did of other causes and had no history of childhood abuse.
* Hippocampal samples of those with a history of childhood abuse show increased methylation of the exon $1_F$ promoter of the glucocorticoid receptor.
* No assessment of social responses (analogous to environmental enrichment in rat studies).

# Epigenetics and Foster-Care Placement

* Whole-genome blood-sample DNA methylation profiles.
* 20 to 28 year olds.
* With and without histories of foster care placements.
* 173 differentially-methylated genes.
* Suggests broad methylation differences in response to early adverse experiences (Bick et al., 2012).

# Epigenetics and Affectionate Parenting

* Measures of maternal warmth and affection 5-10 years prior to the DNA methylation analysis.
* Adult children of mothers displaying warm, affectionate parenting showed decreased methylation of the glucocorticoid (GR) gene.
* Preliminary evidence that warm, affectionate parenting may be associated with long-term GR methylation profiles associated with moderation of stress responses (Bick et al., 2012).

# Where G x E Meets Epigenetics

* Beach et al. (2010) found that methylation levels upstream from the 5-HTT gene were significantly higher in lymphoblast cells from adults reporting childhood abuse than in those reporting no childhood abuse.
* Olsson (2010) measured 5-HTTLPR x 5-HTT gene promoter methylation x depression scores in adolescents.
  * No association between methylation and depression scores.
  * No association between 5-HTTLPR and depression scores.
  * High depression scores 5-times more common among those with high 5-HTT promoter methylation and S/S or S/L.

# Epigenetics Responses Summary

* DNA is not a blueprint that determines form and function. It is better conceptualized as a database i.e., information the cell either silences or retrieves as needed in complex responses to the environment.
* Responses to adversity commonly construed as indicators of pathology e.g., increased fearful responses, may be better conceptualized as making the best of a bad situation (Ellis et al., 2011).
* Epigenetic changes to the glucocorticoid receptor (GR) gene, resulting in increased stress responses, are seen in 10-19 year-olds who experienced intimate partner violence (IPV) while in utero (Radke et al., 2011).
* Epigenetic and behavioural responses to early adversity may be partially or fully reversed by later environmental enrichment (Bredy et al., 2004).
* Epigenetic changes occur throughout the lifespan (Bjornsson et al., 2008).
* If we wish to understand someone's responses, it may be necessary to obtain detailed information about their social and environmental contexts.

# Implications for Practice

* Given compelling evidence that there is constant dynamic interplay between the environment and responses to it all the way down to the level of gene transcription and protein synthesis, therapy methods that ignore individuals' interactions with their environments are likely to omit information required to understand individual responses and to miss opportunities to develop contextualized solutions.
* The fact that epigenetic changes to GR function resulting in increased stress responses are seen in 10-19 year-olds who experienced IPV while in utero suggests a need for improved responses to protect unborn children in cases of IPV.
* The overriding message of G x E and epigenetic research is that, in order to decrease human suffering, we must improve the quality of human social environments. This is likely to be far more productive than efforts focused on identifying and treating so-called genetic "vulnerability"!

# Where Science and Indigenous Wisdom Meet

In closing, I provide two quotes that show similarities between the findings of leading-edge epigenetic research and traditional indigenous wisdom.

# Understanding Function

The function of the gene can only be fully understood in terms of the cellular environment in which it operates. And the cellular environment, of course, is dynamic, changing constantly as a result of signals from other cells, including those that derive from events occurring in the external environment. Ultimately, function can only be understood in terms of the interaction between environmental signals and the genome (Meaney, 2010, p. 48).

# A Web of Infinite Relationships

Levan (2003) provides a strong statement of the importance of context from an Inuit perspective:

> Within Inuit, and perhaps all land-based indigenous cultures, all aspects of life are seen as connected to each other in a web of infinite relationships. No part of life is separate from another part. All animal species, all vegetation and mineral life are related to each other, and to the earth. Nothing and no one can be understood outside of their place within this larger web of relationships. It is not possible to understand one person, or one event, by itself, without putting that person or event in its full historical, biological and spiritual context. In fact, physical and emotional survival is totally dependent on a focused, thorough appreciation and respect for this web of relationships. (¶ 10)

# Author Note

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