Gene Function is Responsive to Social Interaction: Implications for Practice

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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).

Gene Function is Responsive to Social Interaction: Implications for Practice

* Is gene function independent of the environment, or is it responsive to the environment, including social environments?
* Theories of genetic predisposition to “mental health disorders” tend to implicate DNA and conceal the importance of the social environment.
* However, even when heredity has been shown to be a factor in the development of human behaviour, researchers have failed to explain this by genes alone. “Heredity” is not synonymous with “genetics.” The case of the missing heredity (Maher, 2008, p. 18)?

Gene Function is Responsive to Social Interaction

* Genes and environments interact with each other, and epigenetic responses to the environment are capable of directing gene expression.
* "Genetic determinism has died a quiet death" (Simons et al., 2011, p. 883)
* Thus, we now know that we may alter our gene function by changing our environments!

Gene Function is Responsive to Social Interaction: Implications for Practice
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.
* "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).

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.”
* In this presentation, I use a language of responses.
* For further information regarding the distinction between effects and responses please see Wade (1999).

Diagnostic Categories

* Research designs use diagnostic categories that denote psychopathology (“mental illness”).
* However, diagnostic criteria tend to lack analysis of context, and thus may be particularly problematic in cases where human suffering is a response to adversity.

From “A Gene For . . .” to G x E

* 1980 to 2005: 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).
* From 1996 onward, a shift to genetic association studies (genes associated with an increased incidence of a disorder).
* 2002 – a paradigm shift to gene-environment interaction (G x E) studies.
* Results are exciting, but misinterpretations carry serious ethical implications.

“Genetic Vulnerability”

* Claims that common genetic variations (frequencies of 25-80%) 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);
* “Warrior gene” (Lea & Chambers, 2007);
* “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 Do These Claims Suggest?

* Best case scenario for those with genetic variations (alleles) said to convey vulnerability or risk is that they will have the same outcomes as others as long as environmental conditions are favourable.
* Worst case scenario: Those with risk alleles suffer more when environments are 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).
* Lack of social support is one of the strongest risk factors for PTSD following severe adverse events (Brewin et al., 2000; Ozer et al., 2008).

Implications of Claims of Genetic Vulnerability

* Conceal the importance of social responses.
* Suggest that distress following adversity is a result of an intrinsic biological deficiency.
* Suggest a solution may be to use pharmacological interventions to alter gene function.
* Suggest those with genetic vulnerability may be resistant to therapy.
* After all, how easy is it to mend shattered glass?
* However, a growing body of research supports an alternative view.

Paradigm Shift

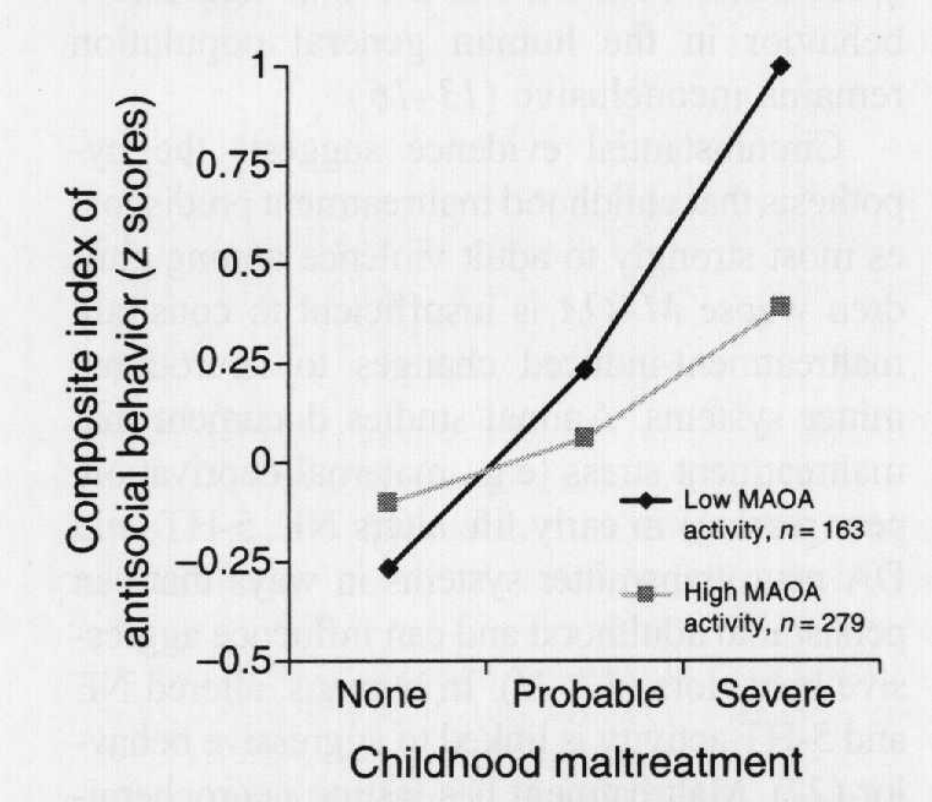
* Caspi et al. (2002)studied monoamine oxidase A (MAOA), which degrades serotonin, dopamine, and norepinephrine (Shih et al., 1999).
* There are high-activity (MAOA-H) and low-activity (MAOA-L) MAOA alleles located only on the X chromosome. (Caspi, 2002).

MAOA-L Allele Frequencies				
New Zealand Caucasians	African Americans	Maori	Taiwanese	Chinese
37%	58%	56%	61%	56%
Caspi et al. (2002)	Lea & Chambers (2007)	Lea & Chambers (2007)	Lu et al. (2002)	Lung et al. (2011)

Paradigm Shift

* Caspi et al. (2002) proposed that “childhood maltreatment predisposes most strongly to adult violence among children whose MAOA is insufficient to constrain maltreatment-induced changes to neurotransmitter systems” (p. 851).
* 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.

Maltreatment + MAOA-L

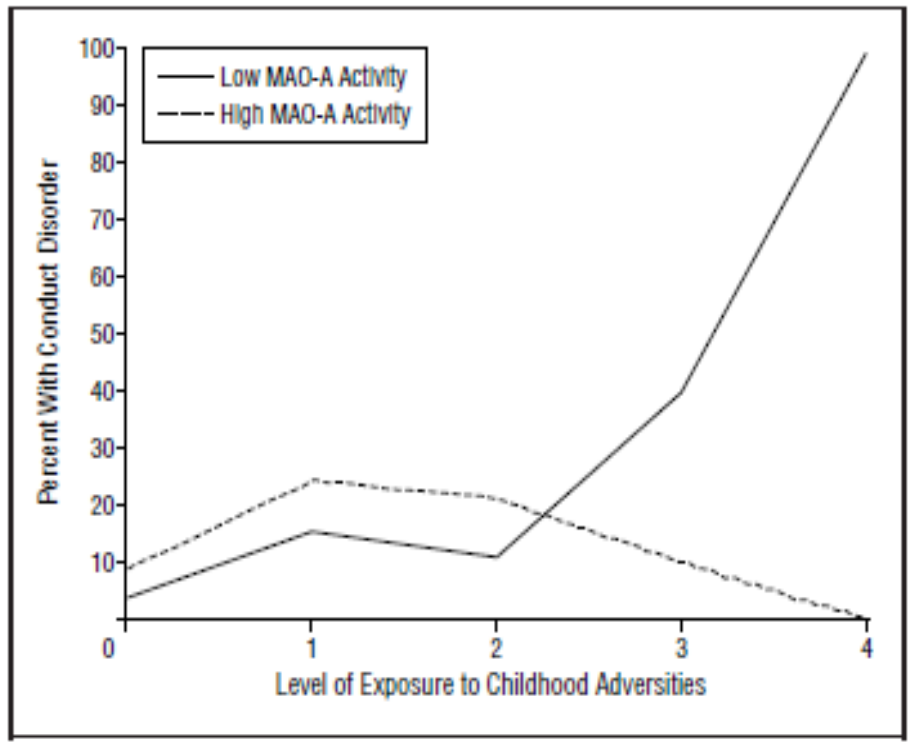


No direct relationship between MAOA activity and antisocial behaviour.

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

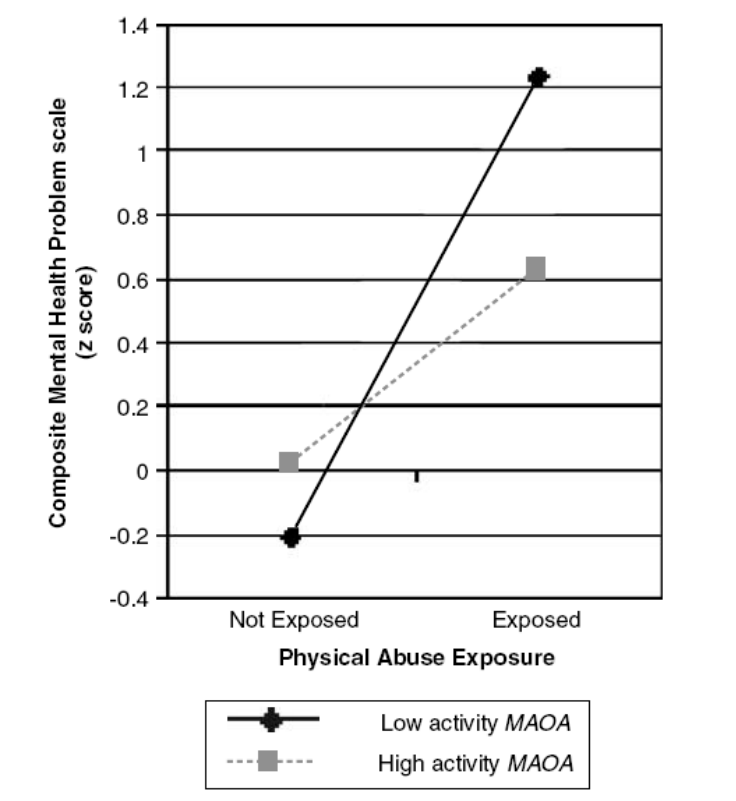
Composite index of antisocial behavior as a function of MAOA activity and a childhood history of maltreatment (Caspi et al., 2002, p. 852).

Foley et al. (2004) Acknowledge the Intersection!



"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 alleles associated with higher levels of distress and aggression after physical abuse.
- Significant main effect of MAOA activity in the *opposite direction*!

Diathesis-Stress vs. Differential Susceptibility vs. Differential Responsiveness

* Belsky and colleagues (Belsky, Bakermans-Kraneneburg, & van IJzendoorn, 2007; Belsky et al, 2009; Belsky & Pluess, 2009)
* Much psychiatric genetic research is based on the diathesis-stress model (sensitivity to stress)
* Differential susceptibility to environmental influences (susceptibility to both positive and negative influences)
* Vulnerability genes/risk alleles vs. plasticity genes
* I prefer the terms differential responsiveness and responsiveness alleles.

Recent Meta-Analysis

* Byrd and Manuck (2013) conducted a meta-analysis of studies testing the interaction of MAOA genotype with childhood adversities on antisocial outcomes in predominantly non-clinical samples.
* Across 20 male cohorts, early adversity was more strongly associated with antisocial outcomes for those carrying MAOA-L than for those carrying MAOA-H.

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.

A Responsiveness Gene

* MAOA-L has been referred to as the “Warrior Gene” (Lea & Chambers, 2007).
* Research suggests it would be more accurately portrayed as responsiveness gene – associated with increased responsiveness to social interactions: both adverse and beneficial.

The Serotonin Transporter (5-HTT)

* 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

Both 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%

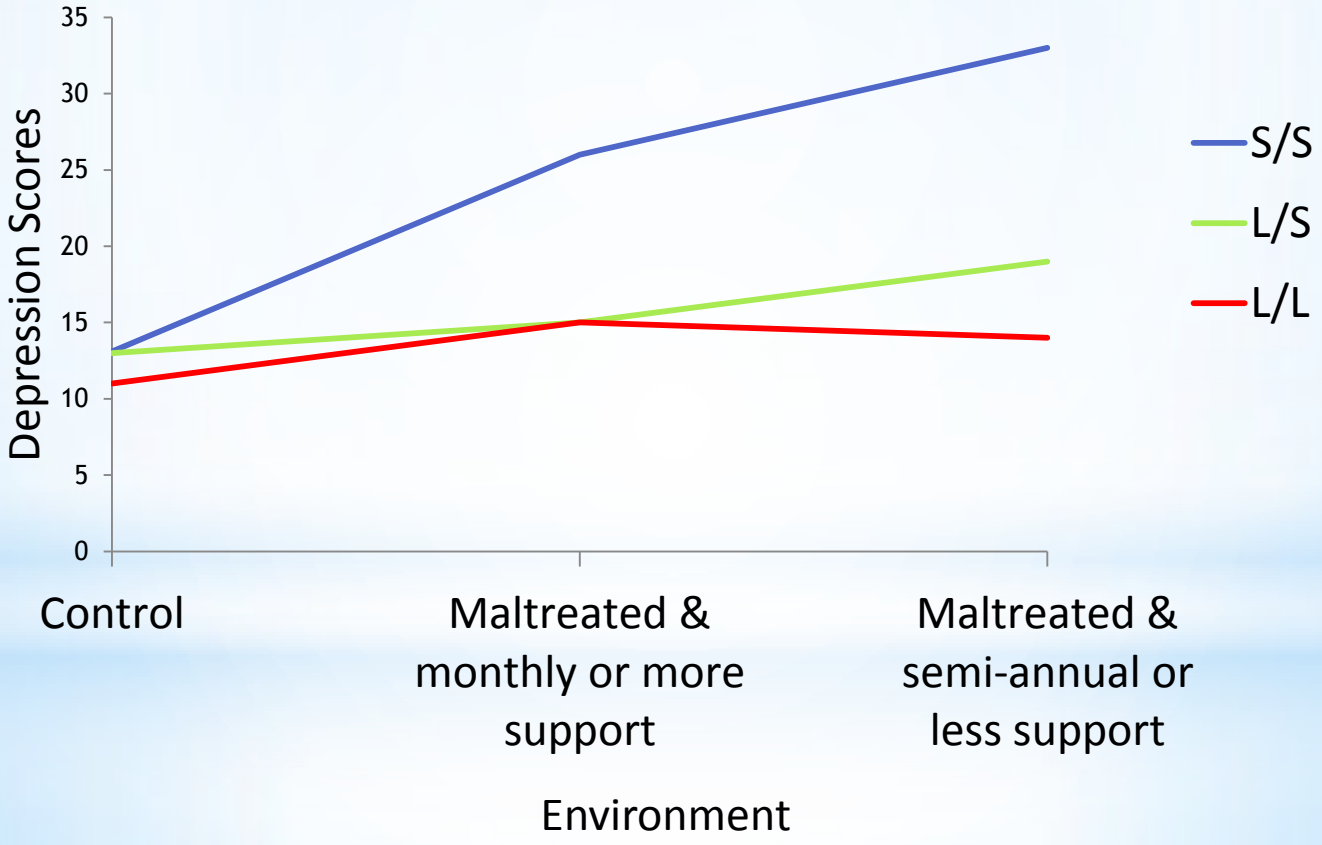
5-HTTLPR Genotype Frequencies in a Caucasian Population (Caspi et al., 2003)		
S/S	S/L	L/L
17%	51%	31%

Serotonin Transporter (5HTT) and G x E Interactions

* 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.
* 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.

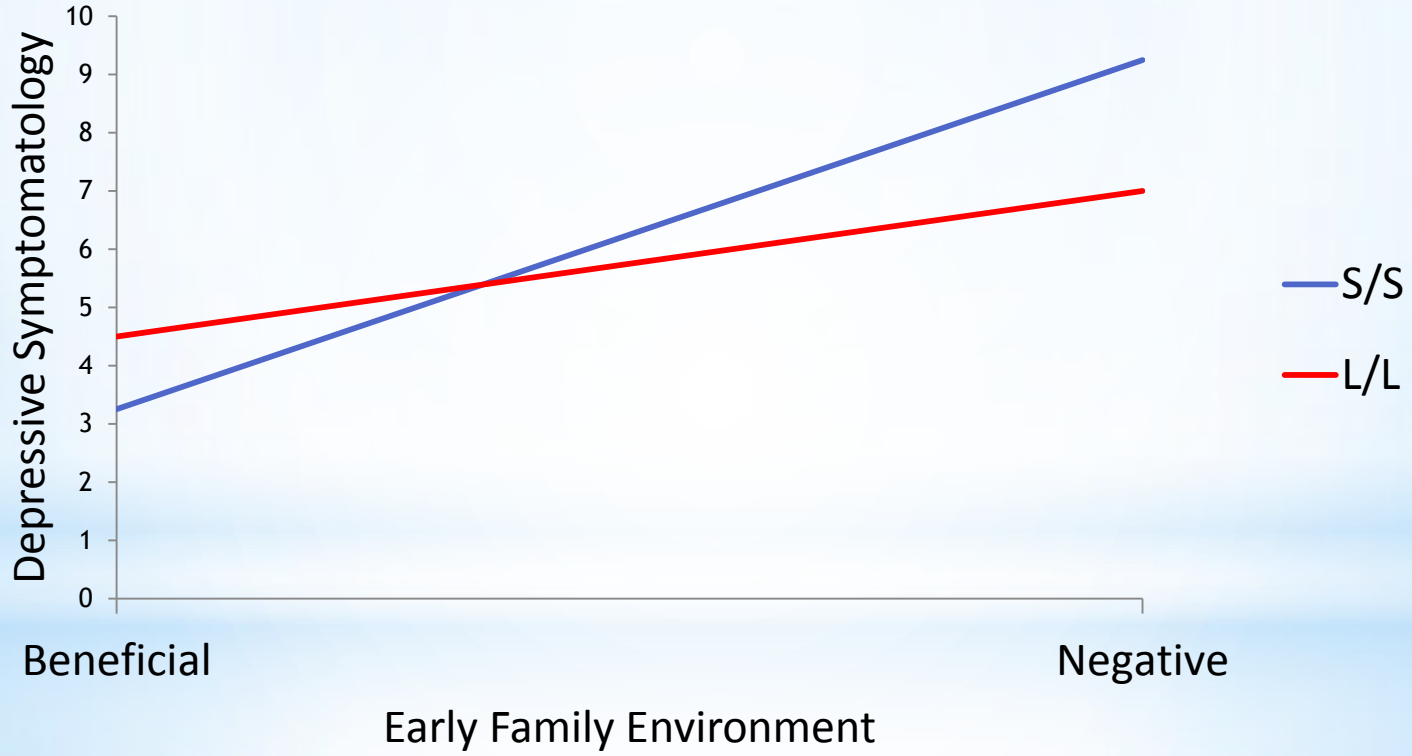
Gene x Maltreatment x Social Support

Kaufman et al. (2004) examined 5-HTTLPR x maltreatment x social support interactions.



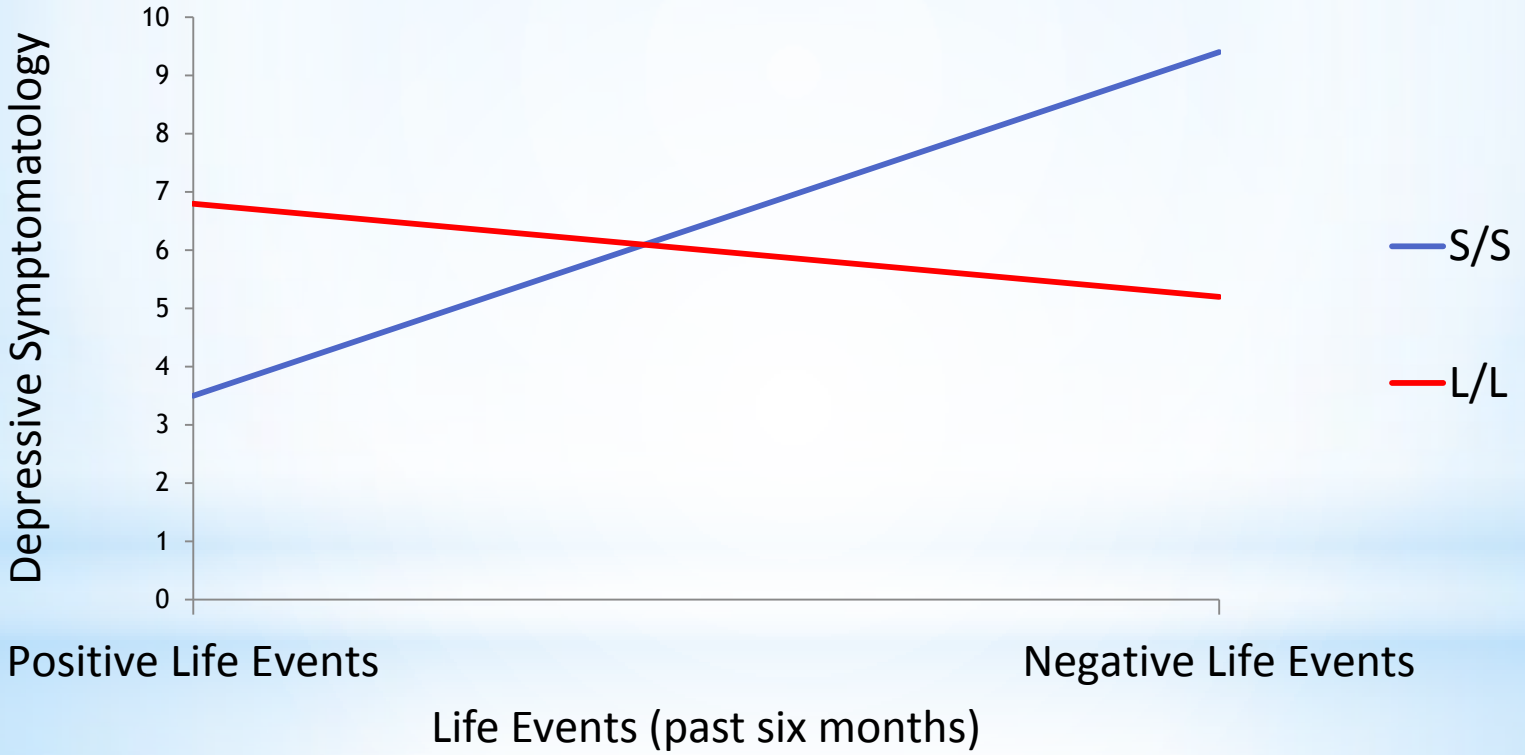
5-HTTLPR X Enriched Environment

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)

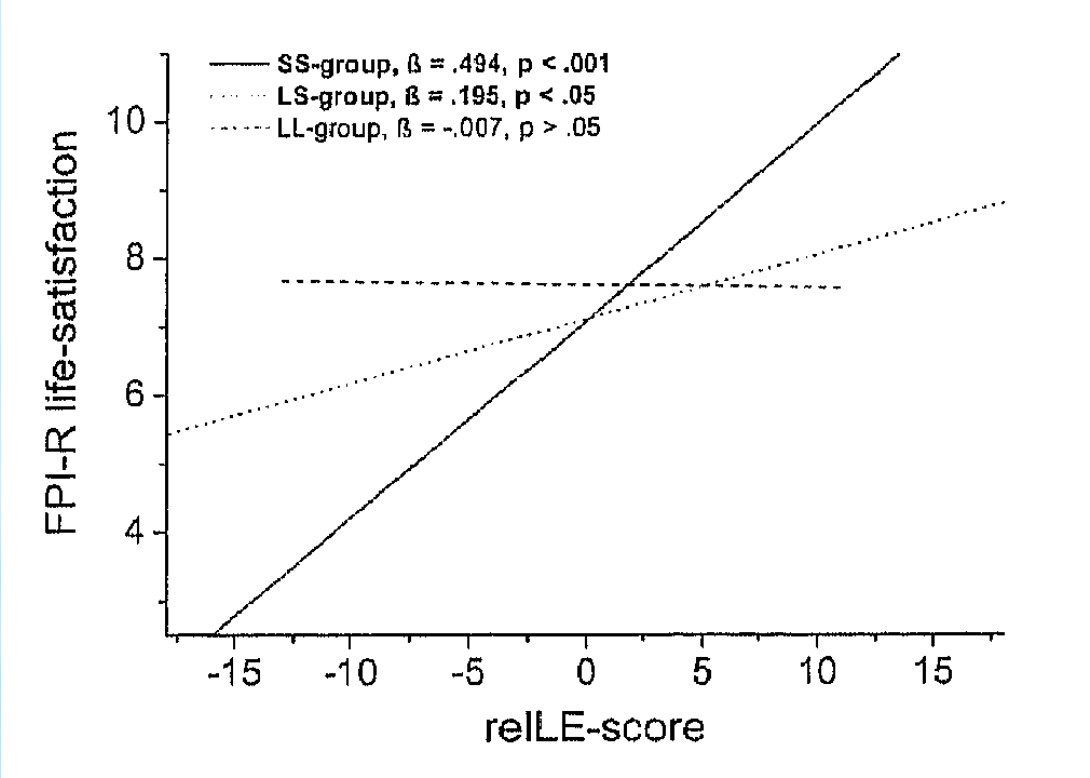


Differential Responsiveness to Social Environment!

* In a subsequent analysis, Way and Taylor (2010) found the interaction between *social* events (e.g., breaking up with a romantic partner, conflict with family or friends, or death of a loved one) and the S/S genotype was significantly associated with depressive symptomatology.
* There was no interaction between *non-social* life events (e.g., receiving a low grade in class, job loss, being in a car accident) and S/S genotype.
* **"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).

Life Satisfaction

(Kuepper et al. 2012, p. 645)



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

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

What do Meta-Analyses say About 5-HTTLPR-Environment Interactions?

* A meta-analysis of 54 studies 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 (Karg et al., 2011).
* Van IJzendoorn, Belsky, and Bakermans-Kranenburg (2012) conducted a meta-analysis of child and adolescent 5-HTTLPR x environment studies.
  * 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.

Cumulative Genetic Responsiveness

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

Simons et al. (2012, p. 16)

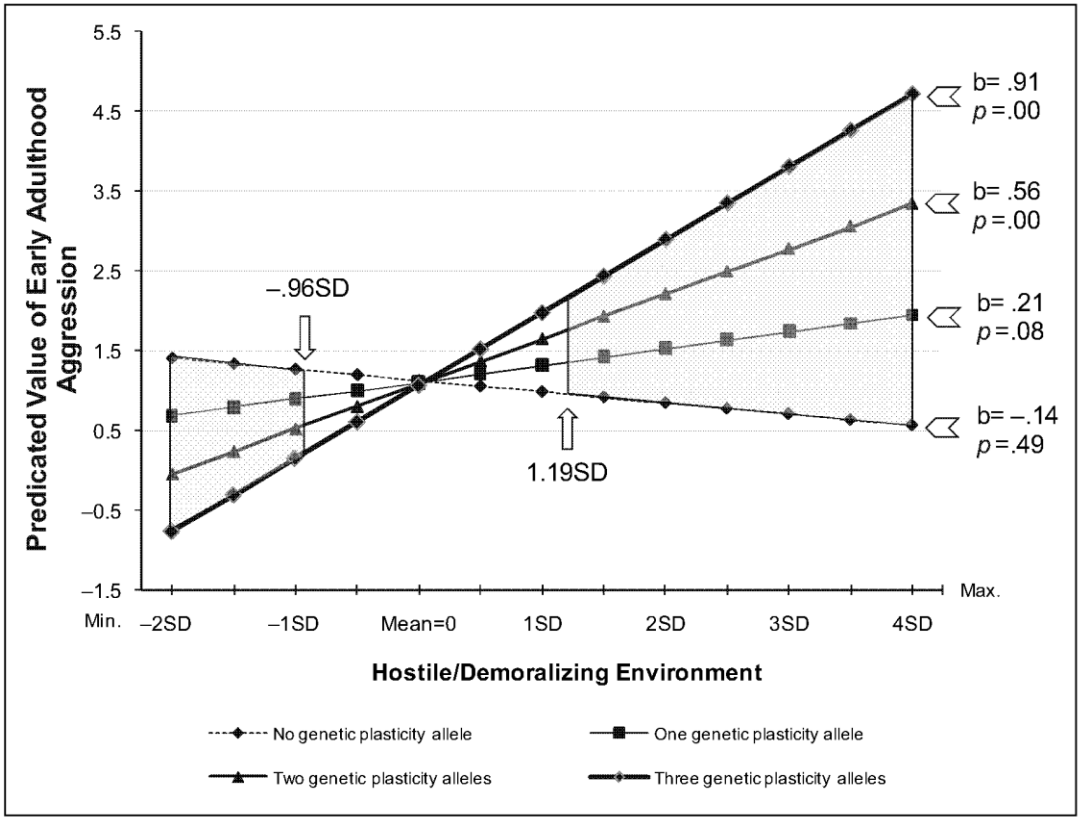


Figure 2. The effect of hostile/demoralizing environment on aggression by number of genetic plasticity alleles with Johnson–Neyman confidence bands. The gray areas are significant confidence regions.

Serotonin Transporter and Therapy

Three studies have shown greater responsiveness to psychotherapy among those with serotonin transporter short alleles (Brody et al., 2009; Eley et al., 2012; Fox et al., 2011)

Framework for Critical Analysis of G x E Research

When researchers make claims of genetic vulnerability to stress, 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.

Implications for Practice

* We may contest pathologizing of those who carry common genetic variations.
* Those who are most distressed in response to adversity may also be most likely to respond to therapeutic social interventions.
* Everything we do to reduce hostile/demoralizing environments may contribute to reductions in violence.

Implications for Practice

* Subjecting those who are highly responsive to social environments to incarceration in hostile and demoralizing prison settings, may increase risk for future violence.
* Consider implementing respectful and compassionate responses to those who have been maltreated and show aggression.

Implications for Practice

* Those who are most responsive to social interactions may be interested in highly contextualized forms of therapy.
* An example of such a therapeutic approach is Response-Based Therapy (Wade, 1999; see also responsebasedpractice.com)

Epigenetic Responses

“Epigenetic” derives from the Greek *epi* meaning ‘‘upon’’ and *genetics.* Epigenetics has been defined as functional modifications to DNA that do not involve an alteration of DNA sequence. (Meaney, 2010).

DNA Methylation

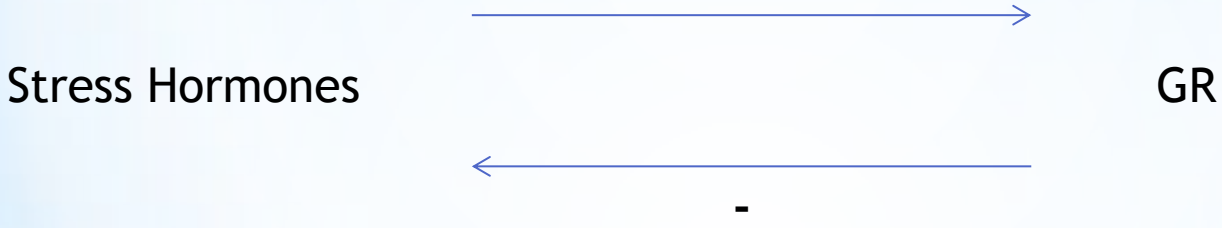
When methyl groups attach to key DNA sequences, genes become inaccessible.

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.

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

Glucocorticoid Receptors (GR)



Licking, Grooming, and GR Methylation

* Weaver et al. (2004) found that at the end of the first week of life, the glucocorticoid receptor gene was unmethylated in the pups of high-licking-grooming (high-LG) mothers, but methylated in the pups of low-LG mothers.
* McGowan et al. (2011) found methylation changes in many other genes revealing “a clustered yet specific and patterned response” (p. e14739).

Licking, Grooming, and Learning

* Pups raised by low-LG mothers showed decreased learning and memory, decreased object recognition, and decreased hippocampal synaptic density.
* 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. (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, memory, and hippocampal synaptic plasticity.
* Pups of low LG mothers demonstrate enhanced capacity for defensive responses when exposed to 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

* 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 environmental enrichment. (Champagne & Meaney, 2006).

Advantages and Disadvantages of Defensive Responses

Meaney (2010) points out that while defensive responses to stress (e.g., increased vigilance and enhanced avoidance learning) are adaptive, persistent activation of these responses may lead to increased risk of chronic illness.

Advantages and Disadvantages of Low Stress Responsivity

However, “insufficient activation of defensive responses under conditions of threat also compromises health and is associated with chronic fatigue, chronic pain, posttraumatic stress disorder, and hyperinflammation” (Meaney, 2010, p. 54).

A Fine Line

Meaney (2010) concludes, “We walk a fine line here” (p. 54). The appropriate level of stress reactivity for an individual will vary according to the prevailing level of environmental demand. Thus, “there is no single, ideal level of stress reactivity across all populations” (p. 54).

What then is Ideal Parenting?

"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" (Meaney, 2010, p. 67).

Intergenerational Transmission Through the Germline

- F1 mice were exposed to unpredictable maternal separation
- F1 males (but not females) were more immobile in response to adversity
- Epigenetic alternations in germline genes related to emotions and behaviour

F2 males showed epigenetic alterations in germline genes

- F2 females (but not males) were more immobile in response to adversity
- Epigenetic changes in brain

F3 males (but not females) were more immobile in response to stress

(Franklin et al., 2010)

Human Correlate of Licking and Grooming

* Early maternal care in rodents is analogous to the 3rd trimester of human gestation.
* Increased third trimester depressed/anxious mood in human mothers was associated with increased GR methylation in cord blood mononuclear cells collected at birth.
* This was associated with increased salivary cortisol change scores following a stress test challenge (involving visual stimuli) at three months of age (Oberlander et al., 2008).

Epigenetics, Pregnancy, and Intimate Partner Violence

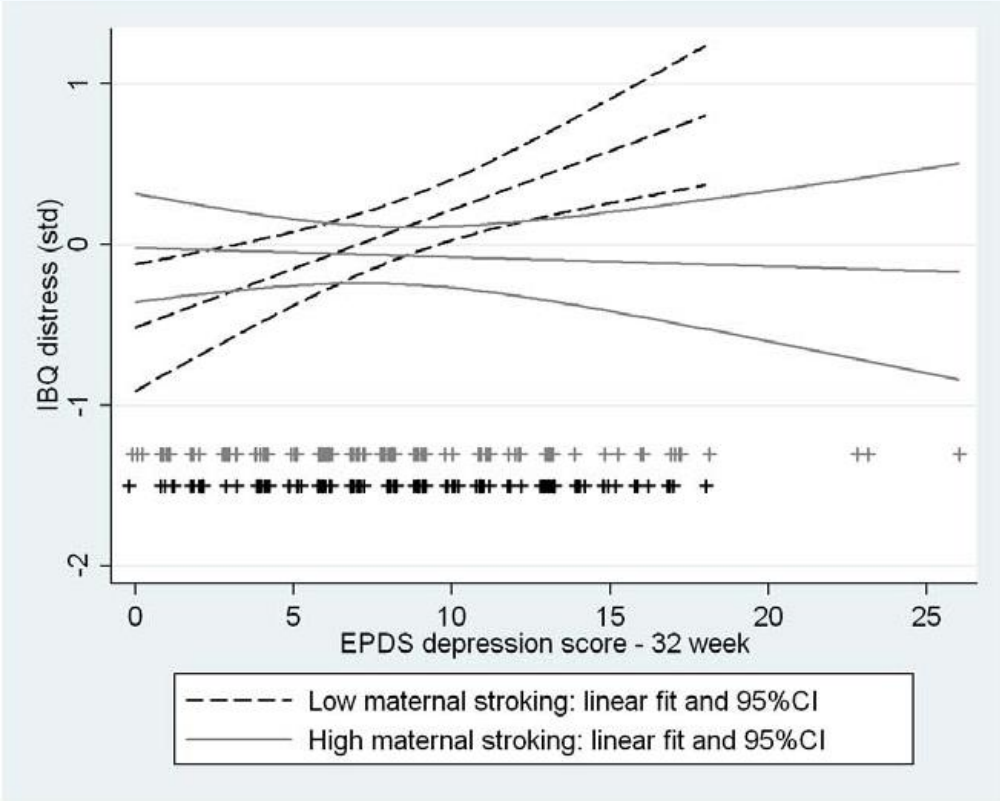
* Radtke et al. (2011) examined methylation status of the GR gene in blood samples from mothers and their children ages 10-19 and assessed for intimate partner violence (IPV).
* IPV during pregnancy, but not before or after pregnancy, was associated with increased methylation of the GR in children.

Human Prenatal Depression, Maternal Stroking, and Infant Distress

Sharp and colleagues (2012)

* Maternal pre- and post-natal depression
* Significantly correlated with infant negative emotionality at age 29 weeks,
* Only in the presence of low-frequency maternal stroking.

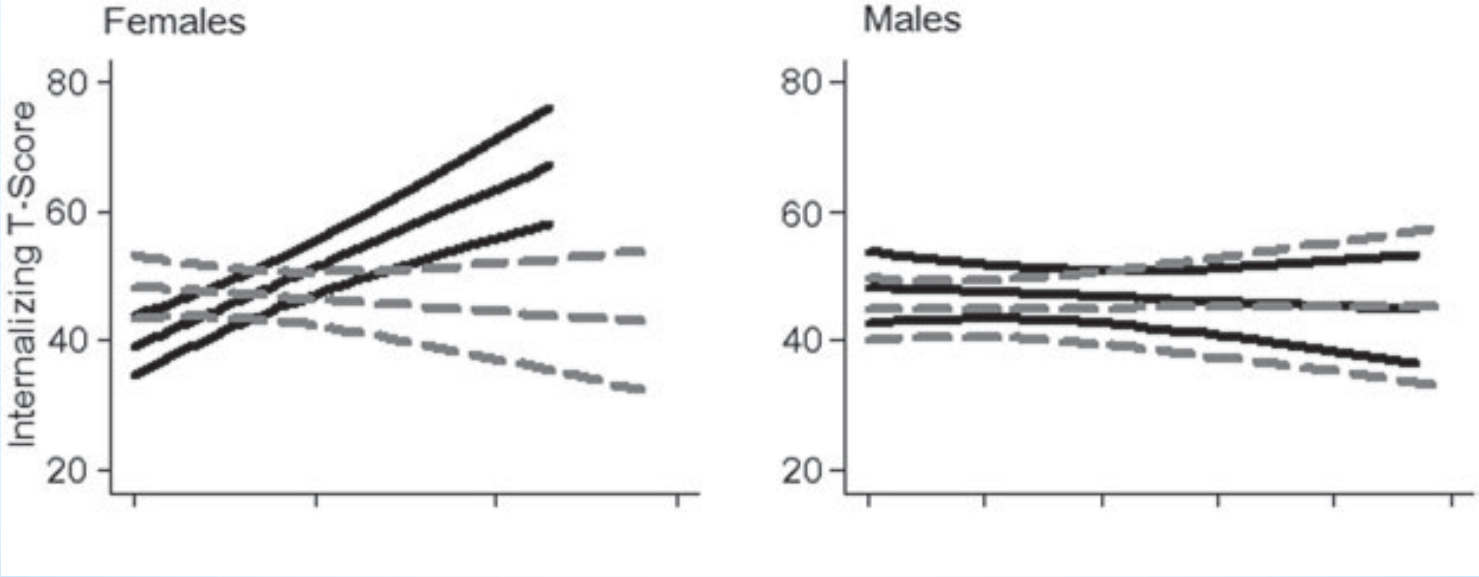
Maternal Depression Scores, Stroking, and Infant Distress (Sharp et al., 2012, p. 8)



Human Prenatal Anxiety, Maternal Stroking, and Infant Distress

* Sharp et al. (2015) investigated children age 2.5 years.
* When mothers experienced prenatal anxiety, their daughters (but not their sons) where more likely to show increased internalizing (emotionally reactive, anxious/depressed, somatic complaints, and withdrawal) scores only in the presence of low maternal stroking.

Prenatal Anxiety, Internalizing Scores, and Maternal Stroking

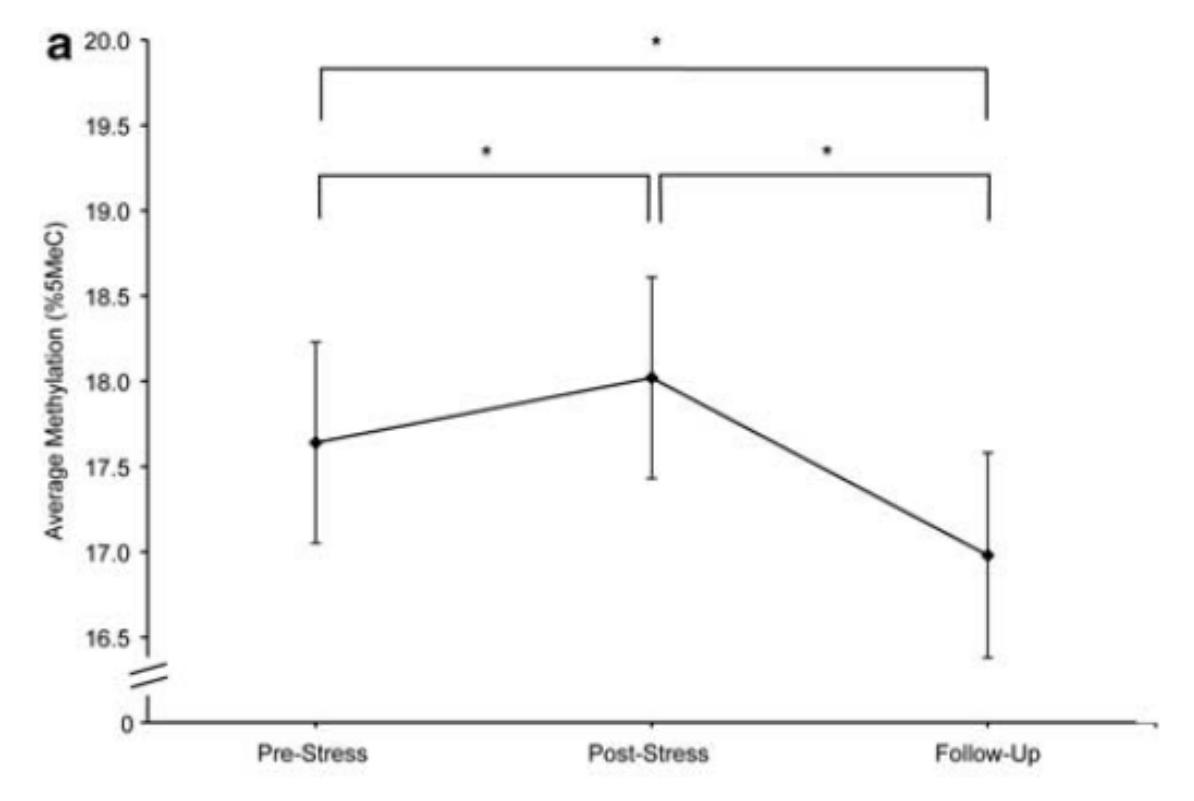


High and low stroking with 95% confidence intervals for 2.5 years Child Behavior Checklist scores plotted against 32 weeks gestation maternal anxiety. High stroking is indicated by the grey dashed line, low stroking by the solid black line. (Sharp et al., 2015, p. 279)

Rapid DNA Methylation Changes

* Adults participated in a stress test.
* Blood samples were drawn before, 10 minutes after, and 90 minutes after the stress test (Unternaehrer et al., 2012).

Oxytocin Receptor Gene Methylation Changes in Response to Acute Stress



Average mean DNA methylation levels in $OXTR_1$ at pre-stress, post-stress, and 90 minute follow-up. (Unternaehrer et al., 2012, p. e150)

Epigenetic Responses to Psychotherapy

* Perroud et al. (2013) measured methylation of the brain-derived neurotrophic factor (BDNF) gene, (which codes for BDNF, a protein involved in neurodevelopment), in leukocytes of participants diagnosed with borderline personality disorder (BPD).
* I-DBT treatment responders showed decreases in the methylation status of BDNF from pre- to post-treatment. Those showing the best response to treatment achieved the same BDNF methylation levels as control subjects.

Epigenetic Responses to Psychotherapy

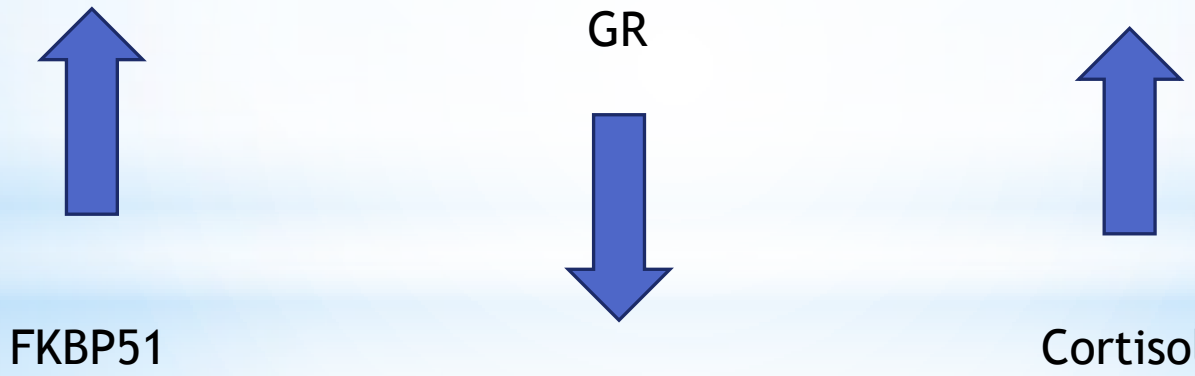
* Yehuda et al. (2013);
* 16 combat veterans enrolled in prolonged exposure therapy for PTSD;
* Evaluated prior to 12-week treatment, post-treatment, and at 3-month follow up;
* 8 treatment responders and 8 non-responders.

Stable GR Methylation Profiles

* PTSD is associated with low plasma cortisol levels,
* Increased GR responsiveness reduces cortisol levels,
* GR methylation levels remained stable across the 6 months of the study (Yehuda et al., 2013).

Another Gene on the Scene

* FKBP51 reduces GR responsiveness, thus increasing the stress response.
* Low FKBP51 expression in PTSD has been associated with low plasma cortisol and increased PTSD severity (Yehuda et al., 2013).



Dynamic Epigenetic Changes

* Methylation levels of FKBP51 decreased from pre-treatment to follow up in treatment responders.
* The authors suggest that, though their findings are preliminary, successful psychotherapy may alter epigenetic status (Yehuda et al., 2013).

Implications for Practice

* The more psychiatric genetic research tries to identify genetic and/or epigenetic contributions to human distress, the more it reveals the importance of social interactions.
* In order to understand people's responses, we need to understand their social environments/interactions.

Implications for Practice

* Provides reason for optimism: Positive social responses (e.g., maternal stroking of infants, psychotherapy) may be associated with reversal of epigenetic responses to stress.
* The overriding message of G x E and epigenetic research is that, in order to reduce human suffering, we must improve the quality of human social environments.

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 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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References

Andrews, B., Brewin, C. R., Rose, S. (2003). Gender, social support, and PTSD in victims of violent crimes. *Journal of Traumatic Stress*, 16(4), 421-427.

Bagot, R. C., & Meaney, M. (2010). Epigenetics and the biological basis of gene x environment interactions. *Journal of the American Academy of Child & Adolescent Psychiatry, 49*(8), 752-771.

Bagot, R. C., van Hasselt, F. N., Champagne, D. L., Meaney, M. J., Krugers, H. J., & Joëls, M. (2009). Maternal care determines rapid effects of stress mediators on synaptic plasticity in adult rat hippocampal dentate gyrus. *Neurobiology of Learning and Memory*, *92*(3), 292-300. doi:10.1016/j.nlm.2009.03.004

Belsky, J., Bakermans-Kraneneburg, M. J., & van IJzendoorn, M. H. (2007). For better *and* for worse: Differential susceptibility to environmental influences. *Current directions in Psychological Science, 16*(6), 300-304.

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

Belsky, J. & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Pychological Bulletin, 135*(6), 885-908.

References Continued

Bredy, T. W., Zhang, T. Y., Grant, R. J., Diorio, J., Meaney, M. J. (2004). Peripubertal environmental enrichment reverses the effects of maternal care on hippocampal development and glutamate receptor subunit expression. *European Journal of Neuroscience*, *20*, 1355-1362.

Brewin, C. R., Andrews, B., & Valentine, J. D. (2000). Meta-Analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *Journal of Consulting and Clinical Psychology*, 68(5), 748-766.

Brody, G. H., Beach, S. R. H., Philibert, R. A., Chen, Y.-F., Murry, V. M. (2009). Prevention effects moderate the association of 5-HTTLPR and youth risk behavior initiation: Gene x environment hypotheses tested via a randomized prevention design. *Child Development, 80*(3), 645-661.

Burmeister, M., McInnis, M. G., & Zöllner. (2008). Psychiatric genetics: Progress amid controversy. *Nature Reviews. Genetics*, *9*(7), 527-540.

Byrd, A. L., & Manuck, S. B. (2013). MAOA, childhood maltreatment, and antisocial behavior: Meta-Analysis of a gene-environment interaction. *Biological Psychiatry, 75,* 9-17.

Cameron, N. M. (2011). Maternal programming of reproductive function and behavior in the female rat. *Frontiers in Evolutionary Neuroscience*, *3*(10), 1-10.

Campbell, R., Ahrens, C. E., Sefl, T., Wasco, S. M., & Barnes, H. E. (2001). Social reactions to rape victims: healing and hurtful effects on psychological and physical health outcomes. *Violence and Victims*, 16(3), 287-302.

References Continued

Caspi, A., Hariri, A. R., Holmes, A., Uher, R., & Moffitt, T. E. (2010). Genetic sensitivity to the environment: The case of the serotonin transporter gene and its implications for studying complex diseases and traits. *American Journal of Psychiatry, 167*(5), 509-527.

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., . . . Poulton, R. (2002). Role of genotype in the cycle of violence in maltreated children. *Science*, *297*(5582), 851-854.

Caspi, A. & Moffitt, T. E. (2006). Gene-environment interactions in psychiatry: joining forces with neuroscience. *Nature Reviews Neuroscience*, 7, 583-590.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., . . . Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301*(5631), 386-389.

Champagne, D. L., Bagot, R. C., van Hasselt, F., Ramakers, G., Meaney, M. J., de Kloet, E., & . . . Krugers, H. (2008). Maternal care and hippocampal plasticity: Evidence for experience-dependent structural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress. *The Journal of Neuroscience*, *28*(23), 6037-6045. doi:10.1523/JNEUROSCI.0526-08.2008

Clarke, H., Flint, A. S., Attwood, A. S., & Munafò, M. R. (2010). Association of the 5-HTTLPR genotype and unipolar depression: A meta-analysis. *Psychological Medicine, 40*, 1767-1778.

References Continued

Cooper, R. M., & Zubek, J. P. (1958). Effects of enriched and restricted early environments on the learning ability of bright and dull rats. *Canadian Journal of Psychology, 12*(3), 159-164.

Douglas Institute. (2012). *Michael Meaney, neuroscientist at the Douglas Institute, receives the Order of Canada*. Retrieved from http://www.douglas.qc.ca/news/1128/file_en/120214-release-meaney-order-canada.pdf

Eisenberger, N. I., Way, B. M., Taylor, S. E., Welch, W. T., & Lieberman, M. D. (2007). Understanding genetic risk for aggression: Clues from the brain's response to social exclusion. *Biological Psychiatry*, *61*(9), 1100-1108. doi:10.1016/j.biopsych.2006.08.007

Eley, T. C., Hudson, J. L., Creswell, C., Tropeano, M., Lester, K. J., Cooper, P., . . . Collier, D. A. (2012). Therapygenetics: The 5HTTLPR and response to psychological therapy. *Molecular Psychiatry, 17*, 236-241.

Ellis, B. J., Boyce, W., Belsky, J., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary–neurodevelopmental theory. *Development and Psychopathology*, *23*(1), 7-28. doi:10.1017/S0954579410000611

Foley, D. L., Eaves, L. J., Wormley, B., Silberg, J. L., Maes, H. H., Kuhn, J., & Riley, B. (2004). Childhood adversity, monoamine oxidase A genotype, and risk for conduct disorder. *Archives of General Psychiatry, 61*(7), 738-744.

Fox, E. Zougkou, K., Ridgewell, A., & Garner, K. (2011). The serotonin transporter gene alters sensitivity to attention bias modification: Evidence for a plasticity gene. *Biological Psychiatry, 70*, 1049-1054.

References Continued

Franklin, T. B., Russig, H., Weiss, I. C., Gräff, J., Linder, N., Michalon, A., . . . Mansuy, I. M. (2010). Epigenetic transmission of the impact of early stress across generations. Biological Psychiatry, 68, 408-415.

Gelernter, J., Kranzler, H., & Cubells, J. (1997). Serotonin transporter protein (SLC6A4) allele and haplotype frequencies and linkage disequilibria in African- and European-American and Japanese populations and in alcohol-dependent subjects. *Human Genetics*, *101*(2), 243-246.

Heils, A., Teufel, A., Petri, S., Stöber, G., Riederer, P., Bengel, D., & Lesch, K. (1996). Allelic variation of human serotonin transporter gene expression. *Journal of Neurochemistry*, *66*(6), 2621-2624.

Homberg, J. R., & Lesch, K.-P. (2011). Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry, 69*, 513-519.

Howard, S., Dryden, J., & Johnson, B. (1999). Childhood resilience: review and critique of literature. *Oxford Review of Education*, 25(3), 307-323.

Hu, X.-Z., Lipsky, R. H., Zhu, G., Akhtar, L. A., Taubman, J., Greenberg, B. D. . . . Goldman, D. (2006). Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *The American Journal of Human Genetics, 78*, 815-826.

References Continued

Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited. *Archives of General Psychiatry, 68*(5), 444-454.

Kaufman, J., Yang, B., Douglas-Palumberi, H., Grasso, D., Lipschitz, D., Houshyar, S., & . . . Gelernter, J. (2006). Brain-derived neurotrophic factor-5-HHTLPR gene interactions and environmental modifiers of depression in children. *Biological Psychiatry*, *59*(8), 673-680. doi:10.1016/j.biopsych.2005.10.026

Kaufman, J., Yang, B-Z., Douglas-Palumberi, H., Houshyar, S., Lipschitz, S., Krystal, J. H., & Gelernter, J. (2004). Social supports and serotonin transporter gene moderate depression in maltreated children. *Proceedings of the National Academy of Sciences,* 101, 17316-17321.

Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I. W., & Moffitt, T. E. (2006). MAOA, maltreatment, and gene-environment interaction predicting children's mental health: New evidence and a meta-analysis. *Molecular Psychiatry*, 11, 903-913.

References Continued

Kuepper, Y., Wielpuetz, C., Alexander, N., Mueller, E., Grant, P., & Hennig, J. (2012). 5-HTTLPR S-allele: A genetic plasticity factor regarding the effects of life events on personality? *Genes, Brain and Behavior, 11*, 643-650.

Lea, R., & Chambers, G. (2007). Monoamine oxidase, addiction, and the "warrior" gene hypothesis. *New Zealand Medical Journal*, *120*(1250). PMID: 17339897.

Lesch K. P., Bengel D., Heils A., Sabol S. Z., Greenberg B. D., Petri S., . . . Murphy D. L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274,* 1527–1531.

Levan, M. B. (2003). *Creating a framework for the wisdom of community: A review of victim services in Nunavut, Northwest and Yukon Territories.* Ottawa, Ontario, Canada: Department of Justice Canada. Retrieved July 4, 2007 from http://canada-justice.ca/en/ps/rs/rep/2003/rr03vic-3/rr03vic-3_02_01.html#212

Lopez-Vilchez, I., Diaz-Ricart, M., White, J. G., Escolar, G., & Galan, A. M. (2009). Serotonin enhances platelet procoagulant properties and their activation induced during platelet tissue factor uptake. *Cardiovascular Research, 84*(2), 309-316.

Lu, R. B., Lee, J.F., Ko, H.C., Lin, W.W., Chen K, & Shih J.C. (2002). No association of the MAOA gene with alcoholism among Han Chinese males in Taiwan. *Progress in Neuro-psychopharmacology & Biological Psychiatry, 26*(3), 457-61. PMID: 11999895.

Lung, F.W., Tzeng, D.S., Huang, M.F., Lee, M.B. (2011). Association of the MAOA promoter uVNTR polymorphism with suicide attempts in patients with major depressive disorder. *BMC Med Genet, 24*(12), 74. doi:10.1186/1471-2350-12-74.

Maher, B. (2008). Personal genomes: The case of the missing heritability. *Nature*, *456*(7218), 18-21.

References Continued

Mann, D. (2011, January 4). 'Depression gene' linked to response to stress: Study shows gene plays role in the ways people react to stressful events. *WebMD Health News.* Retrieved from http://www.webmd.com/depression/news/20110104/depresssion-gene-linked-to-response-to-stress

McGowan P. O., Suderman, M., Sasaki, A., Huang, T. C., Hallett, M., Meaney, M. J., & Szyf, M. Broad (2011). Epigenetic signature of maternal care in the brain of adult rats. *Plos One, 6* (2), e14739. doi:10.1371/journal.pone.0014739

Meaney, M. J. (2010). Epigenetics and the biological definition of gene x environment interactions. *Child Development*, 81(1), 41-79.

Oberlander, T. F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., & Devlin, A. M. (2008). Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics*, *3*(2), 97-106.

Ozer, E. J., Best, S. R., Lipsey, T. L., & Weiss, D. S. (2008). Predictors of Posttraumatic Stress Disorder in adults: A meta-analysis. *Psychological Trauma: Theory, Research, Practice, and Policy, S*(1), 3-36.

References Continued

Perroud, N., Salzmann, A., Prada, P., Nicastro, R., Hoeppli, M.-E., Furrer, S., . . . Malafosse, A. (2013). Response to psychotherapy in borderline personality disorder and methylation status of the BDNF gene. *Translational Psychiatry, 3*, e207.

Radtke, K. M., Ruf, M., Gunter, H. M., Dohrmann, K., Schauer, M., Meyer, A., & Elbert, T. (2011). Transgenerational impact of intimate partner violence on methylation in the promoter of the glucocorticoid receptor. *Translational Psychiatry, 1*e21, doi:10.1038/tp.2011.21

Science Daily. (2011, January 3) Resurrecting the so-called 'depression gene': New evidence that our genes play a role in our response to adversity. *Science Daily.* Retrieved from http://www.sciencedaily.com/releases/2011/01/110103161105.htm

Sharp, H., Hill, J., Hellier, J., & Pickles, A. (2015). Maternal antenatal anxiety, postnatal stroking and emotional problems in children: Outcomes predicated from pre- and postnatal programming hypotheses. *Psychological Medicine, 45*(2), 269-283.

Sharp, H., Pickles, A., Meaney, M., Marshall, K., Tibu, F., & Hill, J. (2012). Frequency of infant stroking reported by mothers moderates the effect of prenatal depression on infant behavioural and physiological outcomes. *Plos One, 7*(10), 1-10.

Shih, J., Chen, K., & Ridd, M. (1999). Monoamine oxidase: from genes to behavior. *Annual Review of Neuroscience*, 22, 197-217.

Simons, R. L., Lei, M. K., Beach, S. R. H., Brody, G. H., Philibert, R. A., & Gibbons, F. X. (2011). Social environment, genes, and aggression: Evidence supporting the differential susceptibility perspective. *American Sociological Review, 76*(6), 883-912.

References Continued

Simons, R. L., Lei, M. K., Stewart, E. A., Beach, S. R. H., Brody, G. H., Philibert, R. A., & Gibbons, R. X. (2012). Social adversity, genetic variation, street code, and aggression: A genetically informed model of violent behavior. *Youth Violence and Juvenile Justice, 10*(1), 3-24.

Sweitzer, M. M. Halder, I., Flory, J. D., Craig, A. E., Gianaros, P. J., Perrell, R. E., & Manuck, S. B. (2012). Polymorphic variation in the dopamine D4 receptor predicts delay discounting as a function of childhood socioeconomic status: Evidence for differential susceptibility. *Social Cognitive & Affective Neuroscience.* Doi:10.1093/scan/nss020

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.

Uher, R. (2008). The implications of gene-environment interactions in depression: Will cause inform cure? *Molecular Psychiatry, 13*, 1070-1078.

Unternaehrer, E., Luers, P., Mill, J., Dempster, E., Meyer, A. H., Staehli, S., . . . Meinischmidt, G. (2012). Dynamic changes in DNA methylation of stress-associated genes (OXTR, BDNF) after acute psychosocial stress. *Translational Psychiatry, 2*, e150.

Van IJzendoorn, M. H., Belsky, J., & Bakermans-Kranenburg, M. J. (2012). Serotonin transporter genotype 5HTTLPR as a marker of differential susceptibility? A meta-analysis of child and adolescent gene-by-environment studies. *Translational Psychiatry 2*e147. doi:10.1038/tp.2012.73

Wade, A. (1999). *Resistance to personal violence: Implications for the practice of therapy*. Unpublished doctoral dissertation, University of Victoria, Victoria, British Columbia, Canada. Retrieved from http://www.collectionscanada.ca/obj/s4/f2/ dsk2/ftp02/NQ47298.pdf

References Continued

Way, B. M., & Gurbaxani, B. M. (2008). A genetics primer for social health research. *Social and Personality Psychology Compass*, *2*(2), 785-816. doi:10.1111/j.1751-9004.2008.00084.x

Way, B. M., & Taylor, S. E. (2010). Social influences on health: Is serotonin a critical mediator? *Psychosomatic Medicine*, 72, 107-112.

Weaver, I. C. G., Cervoni, N., Champagne, F. A., Alessio, A. C., Sharma, S., Seckl, J. R., . . . Meaney, M. J. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience*, *7*(8), 847-854.

Wray, N. R., Pergadia, M. L., Blackwood, D. H. R., Renninx, B. W. J. H., Gordon, S. D., Nyholt, D. R., . . . Sullivan, P. F. (2010). Genome-wide association study of major depressive disorder: New results, meta-analysis, and lessons learned. *Molecular Psychiatry,17*(1), 36-48.

Yehuda, R., Daskalakis, N. P., Desarnaud, F., Makotkine, I., Lehrner, A. L., Koch, E., . . . Beirer, L. M. (2013). Epigenetic biomarkers as predictors and correlates of symptom improvement following psychotherapy in combat veterans with PTSD. *Frontiers in Psychiatry, 4*, 1-14.

Zhang, T.-Y., & Meaney, M. J. (2010) Epigenetics and the environmental regulation of the genome and its function. *Annual Review of Psychology, 61*, 439-466.