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The role of genetics in stress effects on health and addiction

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Abstract

Advances in stress research have yielded new insights into how stress exposure, in combination with genetics, can contribute to poor health outcomes. We review these topics with a special emphasis on early life stress and vulnerability to addiction. The direct effects of stress and our compensatory responses can modify our physiology and behavior during future stress episodes. These consequences can influence health, including an increased propensity for addiction. The relation between stress and health is not uniform across individuals. Some people succumb to stress-related disorders while others are resilient. Specific genetic polymorphisms affect how an individual appraises and responds to stress, potentially mediating the impact of stress on health. These genetic vulnerabilities can influence responses to the external environment, shape motivated behavior, and have an impact on health throughout life.

Stress and health

Stress impacts the organism throughout life; work from animal models as well as human development has demonstrated lasting effects of stress from prenatal development through old age. Severe early trauma (e.g. sexual or physical abuse) is among the factors that most consistently predicts development of psychopathology, including addiction (see Ref. [1]). These effects were first appreciated via experimental animal studies of prolonged (three or more hours) maternal deprivation [2*]. These deprived animals showed patterns of stress hyperreactivity in adulthood, including increased autonomic and neuroendocrine responses and increased preference for alcohol [3]. Such effects on stress reactivity and behavior are not limited to severe maltreatment. Rats raised by mothers who show low levels of maternal care (e.g. maternal licking and grooming), but no outright deprivation, show similar effects [4]. Importantly, these animals' experience falls well within the normal distribution of exposure to maternal care. By contrast, animals exposed to higher levels of maternal care, but still within the normative range, show a more resilient pattern of stress reactivity, as well as reduced indices of depression and anxiety-like behaviors (e.g. lower indices of depression-like psychomotor behavior, reduced startle reactivity; [4]).

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Similar patterns have been observed in human populations. Exposure to outright child abuse and neglect is associated with greater adult stress reactivity, along with increased incidence of depression, anxiety, and substance abuse as adults (see Ref. [1] for review). As with the normal distribution of maternal care in rodents, variation along the normal distribution in stress experience and parental care also exerts significant effects on mental and physical health outcomes in human populations [5]. Research from the Adverse Childhood Experiences (ACES) study demonstrates a graded effect of the number of childhood negative experiences and negative adult health outcomes [6]. More recent work has documented that adversity that does not rise to the level of abuse (e.g. six-month separation from mother or father before the age of 15) also has strong negative impacts on physical health, mental health, and addiction outcomes [7]. One proposed mechanism for the influence of such adversity on health is through the stress system.

Stress reactivity is not uniform

The stress reactivity hypothesis [8,9] purports that exaggerated cardiovascular and neuroendocrine reactivity has negative health consequences. This hypothesis held sway in stress research for many years, but more recently, scholars have begun to appreciate that stress hypo-reactivity may serve as a marker for negative health outcomes as well [10,11,12]. A recent meta-analysis showed that exposure to early life adversity was consistently associated with a reduced cortisol stress response in adulthood [13]. Such findings have led to the appreciation that a robust stress response — neither too high, nor too low — represents the healthiest reactivity pattern [10].

The special case of addiction

Blunted cortisol and autonomic nervous system activity serves as a risk factor for the development of addiction [11,14]. Abnormal stress physiology is related to greater addiction severity, cravings, poor treatment outcome, and greater likelihood of relapse after treatment in alcohol use disorder [15]. Early life stress may lead to addictive behaviors through effects on both stress physiology as well as the mesolimbic dopamine reward system [16]. These effects may be especially pronounced in people who have experienced early life stress [17,18].

Genetic association studies of stress and addiction

Addiction, like many behavioral health outcomes, is the result of environmental and genetic variables that affect an individual over the course of a lifetime. Twin studies have established that the heritability, or proportion of the variation in the population trait of addiction, ranges between 40%–70% [19]. This leaves considerable variation left to environmental influences. Initiation of drug taking behavior is more under environmental influences, while progression to addiction is more associated with genetic influences (see Ref. [20] for review).

Stressful experience has been the focus of a great deal of research as an environmental influence on substance use and abuse (see Ref. [21,22]). The relation of stress and addiction demonstrates the challenges inherent in behavioral genetics research. Both stress reactivity

and addiction are the result of a combination of genetic and environmental influences that ultimately impact one's physiology and behavior in a variety of ways [16]. Behavioral genetics researchers distinguish between gene-environment correlations and gene-environment interactions [23]. Gene-environment correlations describe the situation in which one's genetics influence the type of environment one may be exposed to. Gene-environment interactions, by contrast, include the situation in which one's genes predispose how much a particular environment affects one's outcomes. In the case of addiction, a gene-environment correlation would be demonstrated by one's temperament influencing one's choice of peer group and therefore exposure to addictive substances. An example of a gene-environment interaction in addiction would be a predisposition to experience greater reward in response to drug administration, which leads to greater drug seeking and drug taking behavior.

Candidate gene $\times$ stress interaction

Certain genetic variants may increase susceptibility to neurobehavioral disorders, especially in combination with stressful life experience [24]. These studies of gene $\times$ environment interactions are challenging because of the need to test large sample sizes, and the sometimes weak influence of individual genes on adult outcomes, as seen in failures to replicate some high-profile findings [25]. Nevertheless, the potential to uncover connections between genetic variation and the impact of stressful experience in producing maladaptive behaviors is a compelling area of research that will benefit from refinements in methodology. These include the use of larger sample sizes, incorporating a greater understanding of epigenetic processes [26–28], the use of genome-wide association studies, as well as the inclusion of polygenic scores [25]. Here, we highlight recent work on two candidate genes that, in combination with early life stress, may influence adult behavior and risk for addiction (Figure 1).

Glucocorticoid receptor variation—The stress hormone cortisol regulates the function of all bodily tissues. Its increased production during stress is essential for controlling the stress response, and its feedback to the central nervous system influences such processes as risky decision making [29,30] and the formation of emotional memories [31,32]. The foregoing processes depend on how effectively cortisol acts on target cells via the glucocorticoid receptor (GR) system [28]. Recent work indicates that a genetic variant of a protein designated FK506 binding protein-5 (FKBP5), can affect the efficiency of cortisol's binding with the GR and the ease of cortisol's transport into the cell nucleus. Persons carrying two copies of the A-allele of the FKBP5 gene have decreased cortisol actions at target cells. This reduces cortisol's negative feedback at the central nervous system prolonging cortisol release during stress. This imbalance in cortisol regulation may increase the risk of neuropsychiatric disorders [29,30]. One consequence is that A-allele carriers may be vulnerable to the long-term effects of stress encountered during childhood and adolescence. In a study of healthy adults, A-allele carriers who reported experiencing greater levels of early life adversity (ELA) showed blunted cardiac reactivity to mental stress and they displayed mild alterations in working memory compared to A-allele carriers with no history of ELA [33]. Although studies of this sort are considered preliminary, they

illustrate potential $G \times E$ processes by which early life stress can have a disproportionate impact on some individuals resulting in negative health outcomes.

Catecholamine variation—A second example of potential $G \times E$ processes concerns the regulation of the catecholamine neurotransmitters norepinephrine and dopamine. These transmitters have long been of interest in mental health research because they are essential for normal communication between the prefrontal cortex and limbic system [34]. Their synaptic actions are regulated by the enzyme catechol-*O*-methyl-transferase (COMT). Some individuals carry a single-nucleotide polymorphism of the *COMT* gene that substitutes the amino acid valine (val) for methionine (met) at coding position 158. This val158met polymorphism results in val/val carriers having faster synaptic breakdown of dopamine in key brain areas involving communication between the limbic system and prefrontal cortex, with potential implications for health and behavior [35]. A recent study showed increased sensitivity to the early environment in met/met carriers, who showed progressively smaller cortisol responses to stress after experiencing greater levels of ELA [36^{**}]. Such a relationship was not observed in val/val homozygotes. This blunted cortisol reactivity in met/met carriers exposed to early stress may impact processes that depend on normal cortisol regulation following periods of acute stress. Accordingly, vulnerable individuals exposed to ELA may be at increased risk for disorders of motivated behavior, including risk for addiction.

Potential mechanisms

The foregoing discussion suggests that ELA can have different consequences for individuals that carry-specific genetic polymorphisms. The examples above deliberately focused on genotypes that affected the regulation of key brain systems that control emotional responses to the environment, particularly responses occurring during periods of acute stress. These structures include the hypothalamus, hippocampus and amygdala, and ventro-medial prefrontal cortex [37]. Collectively, these brain structures shape our emotional responses to the environment, including cognitive appraisals and coping strategies, and they establish our physiological reactions during periods of stress. Not surprisingly, these alterations may increase the likelihood of some persons to engage in risky behaviors, leading to greater experimentation with alcohol, recreational drugs, or gambling and therefore potentially greater risk for addictions. A growing body of evidence shows that persons with deficient physiological responses to stress are at particular risk for disorders involving impulsive behavior and addiction. It may be the case that blunted autonomic and hormonal responses during stress may result in reduced bodily signs of danger, thereby reducing avoidance of threats in the environment. The accompanying figure (from Ref. [7]) illustrates pathways by which genetically vulnerable persons exposed to ELA may be at greater risk for negative health outcomes.

Future directions

The research discussed here illustrates one model for studying stress and its impacts on health. Key points of focus are: first, exposure to stress during periods of development spanning childhood and adolescence, second, genetic variations that affect brain systems

engaged with memory formation, emotional response, and decision making, and third, study of health outcomes that engage with these same brain systems and health behaviors, including but not limited to, the addictions. Studies of life stress exposure and health indicate that the impact of stress on health may have pervasive effects on health behaviors [38,39]. Challenges for future research will be to determine the mechanisms by which early life experience is translated into longlasting changes in the nervous system and their impact on health behavior. The examples provided here focused on known genetic polymorphisms. Future studies should extend established animal research on epigenetic processes [28] by which stress exposure during early life alters gene expression to humans (see Ref. [27]). Further advances in genetics, including the use of genome-wide association studies combined with the predictive power of polygenic scores [23*] may allow for more accurate prediction of how our genes and environments come together to shape our well-being.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Heim C, Shugart M, Craighead WE, Nemeroff CB: Neurobiological and psychiatric consequences of child abuse and neglect. *Dev Psychobiol* 2010, 52:671–690. [PubMed: 20882586]
2. Levine S: Maternal and environmental influences on the • adrenocortical response to stress in weanling rats. *Science* 1967, 156:258–260.
This is a classic article on the role of the environment on stress physiology. The research that launched a new field of inquiry in psychobiology.
[PubMed: 6021047]
3. Huot RL, Thrivikraman KV, Meaney MJ, Plotsky PM: Development of adult ethanol preference and anxiety as a consequence of neonatal maternal separation in Long Evans rats and reversal with antidepressant treatment. *Psychopharmacology (Berl)* 2001, 158:366–373. [PubMed: 11797057]
4. Meaney MJ: Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annu Rev Neurosci* 2001, 24:1161–1192. [PubMed: 11520931]
5. O'Donnell KA, Gaudreau H, Colalillo S, Steiner M, Atkinson L, Moss E, Goldberg S, Karama S, Matthews SG, Lydon JE et al.: The maternal adversity, vulnerability and neurodevelopment project: theory and methodology. *Can J Psychiatry* 2014, 59:497–508. [PubMed: 25565695]
- 6 •. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Marks JS: Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the Adverse Childhood Experiences (ACE) study. *Am J Prev Med* 1998, 14:245–258.
This is a classic demonstration of the prevalence and negative impact of early adverse experience on health. The authors reported on the negative effects of early adverse experience on a host of physical and mental health outcomes.
7. Lovallo WR: Early life adverse

[PubMed: 9635069]

7. Lovallo WR: Early life adversity reduces stress reactivity and enhances impulsive behavior: implications for health behaviors. *Int J Psychophysiol* 2013, 90:8–16. [PubMed: 23085387]
8. Chida Y, Steptoe A: Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: a meta-analysis of prospective evidence. *Hypertension* 2010, 55:1026–1032. [PubMed: 20194301]
9. Lovallo WR, Gerin W: Psychophysiological reactivity: mechanisms and pathways to cardiovascular disease. *Psychosom Med* 2003, 65:36–45. [PubMed: 12554814]
- 10 • al'Absi M: Stress and addiction: when a robust stress response indicates resiliency. *Psychosom Med* 2018, 80:2–16.

This is a thorough review of the evolving view of the role of stress in the development of addiction.

Specifically highlights that an optimal stress response is associated with resiliency, while lower stress reactivity is indicative of risk

. [PubMed: 28834923]

11. Carroll D, Ginty AT, Whittaker AC, Lovallo WR, de Rooij SR: The behavioural, cognitive, and neural corollaries of blunted cardiovascular and cortisol reactions to acute psychological stress. *Neurosci Biobehav Rev* 2017, 77:74–86. [PubMed: 28254428]
12. Phillips AC, Ginty AT, Hughes BM: The other side of the coin: blunted cardiovascular and cortisol reactivity are associated with negative health outcomes. *Int J Psychophysiol* 2013, 90:1–7. [PubMed: 23454029]
13. Bunea IM, Szentágotai-Tar A, Miu AC: Early-life adversity and cortisol response to social stress: a meta-analysis. *Transl Psychiatry* 2017, 7:1274. [PubMed: 29225338]
14. Lovallo WR: Cortisol secretion patterns in addiction and addiction risk. *Int J Psychophysiol* 2006, 59:195–202. [PubMed: 16434116]
15. Sinha R: New findings on biological factors predicting addiction relapse vulnerability. *Curr Psychiatry Rep* 2011, 13:398–405. [PubMed: 21792580]
16. Enoch MA: The influence of gene-environment interactions on the development of alcoholism and drug dependence. *Curr Psychiatry Rep* 2012, 14:150–158. [PubMed: 22367454]
17. Keiley MK, Howe TR, Dodge KA, Bates JE, Pettit GS: The timing of child physical maltreatment: a cross-domain growth analysis of impact on adolescent externalizing and internalizing problems. *Dev Psychopathol* 2001, 13:891–912. [PubMed: 11771913]
18. Lansford JE, Miller-Johnson S, Berlin LJ, Dodge KA, Bates JE, Pettit GS: Early physical abuse and later violent delinquency: a prospective longitudinal study. *Child Maltreat*. 2007, 12:233–245. [PubMed: 17631623]
19. Goldman D, Oroszi G, Ducci F: The genetics of addictions: uncovering the genes. *Nat Rev Genet* 2005, 6:521–532. [PubMed: 15995696]
20. Kendler KS, Chen X, Dick D, Maes H, Gillespie N, Neale MC, Riley B: Recent advances in the genetic epidemiology and molecular genetics of substance use disorders. *Nat Neurosci* 2012, 15:181–189. [PubMed: 22281715]
21. Koob GF: A role for brain stress systems in addiction. *Neuron* 2008, 59:11–34. [PubMed: 18614026]
22. Milivojevic V, Sinha R: Central and peripheral biomarkers of stress response for addiction risk and relapse vulnerability. *Trends Mol Med* 2018, 24:173–186. [PubMed: 29396148]
- 23 • Chabris CF, Lee JJ, Cesarini D, Benjamin DJ, Laibson DI: The fourth law of behavior genetics. *Curr Dir Psychol Sci* 2015, 24:304–312.

A thorough, but accessible guide to behavior genetics research

. [PubMed: 26556960]

24. Halldorsdottir T, Binder EB: Gene × environment interactions: from molecular mechanisms to behavior. *Annu Rev Psychol* 2017, 68:215–241. [PubMed: 27732803]
25. Duncan LE, Keller MC: A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am J Psychiatry* 2011, 168:1041–1049. [PubMed: 21890791]

26. Lutz PE, Tanti A, Gasecka A, Barnett-Burns S, Kim JJ, Zhou Y, Chen GG, Wakid M, Shaw M, Almeida D et al.: Association of a history of child abuse with impaired myelination in the anterior cingulate cortex: convergent epigenetic, transcriptional, and morphological evidence. *Am J Psychiatry* 2017, 174:1185–1194. [PubMed: 28750583]
 27. Meaney MJ: Epigenetics and the biological definition of gene x environment interactions. *Child Dev* 2010, 81:41–79. [PubMed: 20331654]
 28. Turecki G, Meaney MJ: Effects of the social environment and stress on glucocorticoid receptor gene methylation: a systematic review. *Biol Psychiatry* 2016, 79:87–96. [PubMed: 25687413]
 29. Starcke K, Brand M: Decision making under stress: a selective review. *Neurosci Biobehav Rev* 2012, 36:1228–1248. [PubMed: 22342781]
 30. Weller JA, Buchanan TW, Shackelford C, Morganstern A, Hartman JJ, Yuska J, Denburg NL: Diurnal cortisol rhythm is associated with increased risky decision-making in older adults. *Psychol Aging* 2014, 29:271–283. [PubMed: 24955995]
 31. Wolf O, Atsak P, De Quervain D, Roozendaal B, Wingenfeld K: Stress and memory: a selective review on recent developments in the understanding of stress hormone effects on memory and their clinical relevance. *J Neuroendocrinol* 2016, 28:1–8.
 32. Buchanan TW, Lovallo WR: Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology* 2001, 26:307–317. [PubMed: 11166493]
 - 33 •• Lovallo WR, Enoch M-A, Acheson A, Cohoon AJ, Sorocco KH, Hodgkinson CA, Vincent AS, Goldman D: Early-life adversity interacts with FKBP5 genotypes: altered working memory and cardiac stress reactivity in the Oklahoma family health patterns project. *Neuropsychopharmacology* 2016, 41:1724–1732.
- This article demonstrates a gene by environment interaction between early life stress and a polymorphism related to the function of the glucocorticoid receptor such that A-allele carriers who reported experiencing greater early life adversity showed blunted cardiac reactivity to stress.
- [PubMed: 26632991]
34. Gatt JM, Burton KL, Williams LM, Schofield PR: Specific and common genes implicated across major mental disorders: a review of meta-analysis studies. *J Psychiatr Res* 2015, 60:1–13. [PubMed: 25287955]
 35. Enoch MA: The role of early life stress as a predictor for alcohol and drug dependence. *Psychopharmacology* 2011, 214:17–31. [PubMed: 20596857]
 - 36 •• Lovallo WR, Enoch M-A, Sorocco KH, Vincent AS, Acheson A, Cohoon AJ, Hodgkinson CA, Goldman D: Joint impact of early life adversity and COMT Val158Met (rs4680) genotypes on the adult cortisol response to psychological stress. *Psychosom Med* 2017, 79:631–637.
- These authors demonstrated a gene by environment interaction between early life stress and a polymorphism of the COMT gene, which controls catecholamine metabolism. Results showed a blunted cortisol response to stress in met/met carriers who had experienced high early life stress.
- [PubMed: 28452825]
37. Lovallo WR, Robinson JL, Glahn DC, Fox PT: Acute effects of hydrocortisone on the human brain: an fMRI study. *Psychoneuroendocrinology* 2010, 35:15–20. [PubMed: 19836143]
 38. Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WH, Anda RF: Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. *Pediatrics* 2003, 111:564–572. [PubMed: 12612237]
 39. Dube SR, Felitti VJ, Dong M, Giles WH, Anda RF: **The impact of adverse childhood experiences on health problems: evidence from four birth cohorts dating back to 1900.** *Prev Med* (37):2003:268–277. [PubMed: 12914833] ():

Figure 1.

A conceptual model that summarizes possible pathways through which the experience of stressful events in childhood and adolescence may alter emotional and behavioral response patterns and contribute to adverse health outcomes. Life experience is processed through brain regions that evaluate ongoing events and shape coping behaviors and their attendant bodily responses. These frontolimbic structures include key portions of the limbic system and the prefrontal cortex. The functional connectivity of these brain regions is highly modifiable by experience. Accordingly, there are at least three consequences of adverse experience-based on recent findings: **(a)** Stress reactivity is reduced; **(b)** Cognitive processing is shifted toward a focus on short term goals and a more impulsive response selection; and **(c)** Regulation of affect is less stable and prone to negative states. These three immediate consequences of modified frontolimbic functions may result in an impulsive behavioral style that includes a tendency toward risk taking. Over the lifetime, this behavioral style may have an impact on health through a tendency to use alcohol and other drugs (adapted from Ref. [7]).