

Addiction: Childhood Trauma, Stress and the Biology of Addiction

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ABSTRACT

Rather than choice, chance or genetic predetermination, it is childhood adversity that creates the susceptibility for addiction.

Humans and animals require nurturing from a caregiver in order to survive. When a child does not receive consistent, secure interactions, or experiences painfully stressing ones, maldevelopment results. *In vivo* studies have shown that marked alterations in neurotransmitter systems occur within one week of separation from the mother, whereas animals receiving various kinds of nurturing contact during their infancy have shown more efficient brain circuitry for reducing anxiety as adults. Moreover, *in vivo* studies have demonstrated that animals exposed to prenatal stress exhibit characteristics of drug addiction, alcoholism and increased risk of self-administration of drugs.

Early trauma has consequences for how human beings respond to stress. Trauma in children, such as sexual, physical or emotional abuse or abandonment alter the child's physical stress mechanisms and, as a result, the child is more reactive to stress throughout their adult life. Studies of drug addicts find high percentages patients have experienced childhood trauma of various sorts, including physical, sexual and emotional abuse.

The three dominant brain systems in all addictions—the opioid attachment-reward system, the dopamine-based incentive-motivation apparatus and the self-regulation areas of the prefrontal cortex—are all exquisitely fine-tuned by the environment. To various degrees, in all addicted persons these systems are not functioning properly

Accordingly, this article explores the relationship between childhood emotional loss or trauma and addiction, demonstrating a fourth brain-body system implicated in addiction: the stress-response mechanism.

Keywords: Addiction, Trauma, Stress, Development, Vulnerability

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INTRODUCTION

According to the National Survey on Drug Use and Health (NSDUH), it is estimated that 22.6 million Americans have a substance dependency or abuse problem.¹ Alcohol is reported to be the most widely used intoxicant in the United States, with increased rates seen during teenage years. Marijuana is the most abused drug in the United States, followed by prescription painkillers, with other drugs used to a lesser extent. Substance dependence or abuse reportedly peaks in adults aged 18 to 25.¹

Various stressors experienced in early childhood have been shown to alter the development and functioning of different areas of the brain. The present review summarizes the impact of early environmental stress and trauma as risk factors for addiction.

THE ROLE OF NURTURING AND RELATIONSHIP ATTACHMENTS IN THE DEVELOPING CHILD

Happy, attuned emotional interactions with parents stimulate a release of natural opioids in an infant's brain.² This endorphin surge promotes the attachment relationship and the further development of the child's opioid and dopamine circuitry.² In contrast, stress reduces the numbers of both opiate and dopamine receptors.² Healthy growth of these crucial systems—responsible for such essential drives as love, connection, pain relief, pleasure, incentive and motivation—depends, therefore, on the quality of the attachment relationship.^{3,4} When circumstances do not allow the infant and young child to experience consistently secure interactions or, worse, exposure to many painfully stressing ones, maldevelopment often results.⁵

Dopamine levels in a baby's brain fluctuate, depending on the presence or absence of the parent.⁶ A study in four-month-old monkeys showed that major alterations of dopamine and other neurotransmitter systems occurred after only six days of separation from their mothers. "Loss of an important attachment appears to lead to less of an important neurotransmitter in the brain. Once these circuits stop functioning normally, it becomes more and more difficult to activate the mind."⁷

In vivo studies have demonstrated that social-emotional stimulation is necessary for the growth of the nerve endings that release dopamine and for the growth of receptors to which dopamine needs to bind in order to do its work.⁸ Adult rats and mice kept in long-term isolation have a reduced number of dopamine receptors in the midbrain incentive circuits and, notably, in the frontal areas implicated in addiction.⁹ Rats separated from their mothers at an early stage display permanent disruption of the dopamine incentive-motivation system in their midbrains. Abnormalities in this system play a key role in the onset of addiction and craving. Predictably, in adulthood these maternally deprived animals exhibit a greater propensity to self-administer cocaine.¹⁰ In another study, rat pups deprived of their mother's presence for only one hour a day during their first week of life grew up to be much more eager than their peers to take cocaine on their own demonstrating that extreme deprivation is not required for the occurrence of this behaviour.¹¹ The presence of consistent parental contact in infancy is one factor in the normal development of the brain's neurotransmitter systems; the absence of it makes the child more vulnerable to "needing" drugs of abuse later in life to supplement what their brain is lacking. Another key factor is the *quality* of the contact the parent provides, which in large part, is dependent on the parent's mood and stress level.

All mammalian mothers—and many human fathers, as well—give their infants sensory stimulation that has long-term positive effects on their offspring's brain chemistry.¹² Such sensory stimulation is necessary for the human infant's healthy biological development. Premature babies who have to live in incubators for weeks or months have faster brain growth if they are stroked for just ten minutes a day.

Humans hold and cuddle and stroke; rats lick as a form of nurturing. A study found that rats whose mothers had given them more licking and other kinds of nurturing contact during their infancy had, as adults, more efficient brain circuitry for reducing anxiety.¹³ They also had more receptors on their nerve cells for benzodiazepines, natural tranquillizing chemicals found in the brain.¹³

In more recent experiments, the infants of mothers who were not naturally as “affectionate” were transferred to the more nurturing mothers, they grew to be adults with more efficient brain apparatus for reducing anxiety, suggesting that these differences are not genetic, but rather are environmental.⁶

Parental nurturing determines the levels of other key brain chemicals, too—including serotonin, the mood messenger enhanced by antidepressants like Fluoxetine (Prozac, Eli Lilly, Indiana). Peer-reared monkeys, separated from their mothers, have lower lifelong levels of serotonin than monkeys brought up by their mothers.¹⁴ In adolescence these same monkeys are more aggressive and are far more likely to consume alcohol in excess. Similar effects are seen with other neurotransmitters that are essential in regulating mood and behaviour, such as norepinephrine.^{15,16} Even slight imbalances in the availability of these chemicals are manifested in aberrant behaviours like fearfulness and hyperactivity, and increase the individual’s sensitivity to stressors for a lifetime. In turn, such acquired traits increase the risk of addiction.

Another effect of early maternal deprivation appears to be a permanent decrease in the production of oxytocin, one of our emotional modulation chemicals.^{17,18} Oxytocin regulates social recognition and affiliation and modulates mood, anxiety and aggression. Use of illicit substances can alter the oxytocin-dopamine interaction. The interaction between oxytocin and dopamine may also be involved in drug-seeking behaviour.¹⁹

Not only can early childhood experience lead to a dearth of “good” brain chemicals; it can also result in a dangerous overload of others. Maternal deprivation and other types of adversity during infancy and childhood result in chronically high levels of the stress hormone cortisol. In addition to damaging the midbrain dopamine system, excess cortisol shrinks important brain centres such as the hippocampus—a structure important for memory and for the processing of emotions—and disturbs normal brain development in many other ways, with lifelong repercussions.^{20,21} Another major stress chemical that is permanently overproduced after insufficient early maternal contact is vasopressin, which is implicated in hypertension.¹⁸

A child’s capacity to handle psychological and physiological stress is completely dependent on the relationship with their parents. Infants have no ability to regulate their own stress apparatus, leading to death due to stress if they are never picked up. The capacity is acquired gradually through maturation and is dependent on relationships with caregivers. A responsive, predictable nurturing adult plays a key role in the development of healthy stress-response neurobiology.²²

Kraemer *et al.*, stated that “maternal contact alters the neurobiology of the infant.”²³ Maternal contact does not only refer to mothers, but rather extends to primary caregivers, regardless of gender. Children who suffer disruptions in their attachment relationships will not have the same biochemical milieu in their brains as their well-attached and well-nurtured peers. As a result their experiences and interpretations of their environment, and their responses to it, will be less flexible, less adaptive and less conducive to health and maturity. Their vulnerability will increase, both to the mood-enhancing effect of drugs and to becoming drug dependent. Animal studies have shown that early weaning can have an influence on later substance intake: rat pups weaned from their mothers at two weeks of age had, as adults, a greater propensity to drink alcohol than pups weaned just one week later.²⁴

Inborn temperamental traits interact with deficiencies in the nurturing environment to produce susceptibility to addiction.²⁵ “This interaction is particularly important in the developmental critical periods of the first years of life, during which the maturing brain is most sensitive to environmental influences.”²⁵

THE ROLE OF CHILDHOOD TRAUMA AND SUSCEPTIBILITY TO ADDICTION

Epidemiological studies revealing the typical childhood of the hardcore drug addict have been reported widely but, it seems, not widely enough to have had the impact they ought to on mainstream medical, social and legal understandings of drug addiction.²⁶

Studies of drug addicts repeatedly find extraordinarily high percentages of childhood trauma of various sorts, including physical, sexual and

emotional abuse.²⁶ One group of researchers was moved to remark that “our estimates . . . are of an order of magnitude rarely seen in epidemiology and public health.”²⁶ Their research, the renowned ACE (Adverse Childhood Experiences) study, looked at the incidence of ten separate categories of painful circumstances—including family violence, parental divorce, drug or alcohol abuse in the family, death of a parent and physical or sexual abuse—in thousands of people. The correlation between these figures and substance abuse later in the subjects’ lives was then calculated. For each adverse childhood experience, or ACE, the risk for the early initiation of substance abuse increased between two- and fourfold. Subjects with five or more ACEs had seven to ten times greater risk for substance abuse than those with none.²⁶

Dube *et al.*, concluded that nearly two-thirds of injection drug use can be attributed to abusive and traumatic childhood events.²⁶ A third or more were college graduates, and most had at least some university education.²⁶ In clinical practice, childhood trauma percentages may run close to one hundred percent. Not all addicts were subjected to childhood trauma, just as not all severely abused children grow up to be addicts. However, clinical experience has shown that a majority of hardcore injection users were subjected to childhood trauma.²⁷

According to a review published by the [U.S.] National Institute on Drug Abuse in 2002, “the rate of victimization among women substance abusers ranges from 50% to nearly 100% . . . Populations of substance abusers are found to meet the [diagnostic] criteria for post-traumatic stress disorder . . . those experiencing both physical and sexual abuse were at least *twice* as likely to be using drugs than those who experienced either abuse alone.”²⁸ Alcohol consumption has a similar pattern: those who had suffered sexual abuse were three times more likely to begin drinking in adolescence than those who had not. For each emotionally traumatic childhood circumstance, there is a two- to threefold increase in the likelihood of early alcohol abuse. Dube *et al.*, concluded “Overall, these studies provide evidence that stress and trauma are common factors associated with consumption of alcohol at an early age as a means to self-regulate negative or painful emotions.”²⁹

Many addicts self-medicate to soothe their emotional pain—but more than that, their brain development was sabotaged by their traumatic experiences. The systems subverted by addiction—the dopamine and opioid circuits, the limbic or emotional brain, the stress apparatus and the impulse control areas of the cortex—are not able to develop normally in such circumstances.

The affects on brain development of some specific kinds of childhood trauma are known. For example: the vermis, a part of the cerebellum at the back of the brain, is thought to play a key role in addictions because it influences the dopamine system in the midbrain. Imaging of this structure in adults who were sexually abused as children reveals abnormalities of blood flow, and these abnormalities are associated with symptoms that increase the risk for substance addiction.³⁰ In one study of the EEGs of adults who had suffered sexual abuse, the vast majority had abnormal brainwaves, and over a third showed seizure activity.¹⁸

The brains of mistreated children have been shown to be smaller than normal by 7 or 8 % with below-average volumes in multiple brain areas, including the impulse-regulating prefrontal cortex; in the corpus callosum (CC), the bundle of white matter that connects and integrates the functioning of the two sides of the brain; and in several structures of the limbic or emotional apparatus, whose dysfunctions greatly increase vulnerability to addiction.³¹ In a study of depressed women who had been abused in childhood, the hippocampus (the memory and emotional hub) was found to be 15 % smaller than normal. The key factor was abuse, not depression, since the same brain area was unaffected in depressed women who had not been abused.³²

The CC, as noted, facilitates the crucial collaboration between the brain’s two halves, or hemispheres.³³ Not only have the CCs of trauma survivors been shown to be smaller; there is evidence of a disruption of functioning there as well. The result can be a “split” in the processing of emotion: the two halves may not work in tandem, particularly when the individual is under stress.^{34,35} One characteristic of borderline personality disorder, a condition with which substance abusers are very commonly diagnosed, is a kind of flip-flopping between idealization of another person and intense dislike,

even hatred. There is no middle ground, where both the positive and the negative qualities of the other are acknowledged and accepted.³⁶

It has been suggested that our “negative” views of a person are stored in one hemisphere and our “positive” responses, in the other.³⁷ The lack of integration between the two halves of the brain would mean that information from the two views, negative and positive, is not melded into one complete picture. As a result, in intimate relationships and in other areas of life, the afflicted individual fluctuates between idealized and degraded perceptions of themselves, people and the world.¹¹ This sensible theory, if proven, would explain a lot not only about drug-dependent persons, but also about many behavioral addicts.

STRESS RESPONSE MECHANISMS

Early trauma also has consequences for how human beings respond to stress throughout their lives, and stress has everything to do with addiction. Stress is a physiological response mounted by an organism when it is confronted with excessive demands on its coping mechanisms, whether biological or psychological. It is an attempt to maintain internal biological and chemical stability, or *homeostasis*, in the face of these excessive demands. The physiological stress response involves nervous discharges throughout the body and the release of a cascade of hormones, chiefly adrenaline and cortisol. It affects virtually every organ, including the heart and lungs, the muscles and, of course, the emotional centres in the brain. Cortisol itself acts on the tissues of almost every part of the body, in one way or another. It is an important part of the infinitely intricate system of checks and balances that enables the body to respond to a threat.

At a conference on stress at the U.S. National Institutes of Health, researchers defined stress “as a *state of disharmony or threatened homeostasis*.”³⁴ According to such a definition, a stressor “is a *threat, real or perceived, that tends to disturb homeostasis*.”³⁸ Ultimately all stressors represent the absence of something that the organism perceives as necessary for survival—or its threatened loss. The threat itself can be real or perceived. The threatened loss of food supply is a major stressor. So is the threatened loss of love—for human beings. “It may

be said without hesitation that for man the most important stressors are emotional.”³⁹

Early stress establishes a lower “set point” for a child’s internal stress system: such a person becomes stressed more easily than normal throughout their life. Dr. Bruce Perry* stated in an interview that “a child who is stressed early in life will be more overactive and reactive. He is triggered more easily, is more anxious and distressed. Now, compare a person—child, adolescent or adult—whose baseline arousal is normal with another whose baseline state of arousal is at a higher level. Give them both alcohol: both may experience the same intoxicating effect, but the one who has this higher physiological arousal will have the added effect of feeling pleasure from the relief of that stress. It’s similar to when with a parched throat you drink some cool water: the pleasure effect is much heightened by the relief of thirst.”⁴⁰

The hormone pathways of sexually abused children are chronically altered.⁴¹ Even a relatively “mild” stressor such as maternal depression—let alone neglect, abandonment or abuse—can disturb an infant’s physical stress mechanisms.⁴² Add neglect, abandonment or abuse, and the child will be more reactive to stress throughout their life. A study published in *The Journal of the American Medical Association* concluded that “a history of childhood abuse per se is related to increased neuroendocrine [nervous and hormonal] stress reactivity, which is further enhanced when additional trauma is experienced in adulthood.”⁴³

A brain pre-set to be easily triggered into a stress response is likely to assign a high value to substances, activities and situations that provide short-term relief and less interest in long-term consequences. In contrast, situations or activities that for the average person are likely to bring satisfaction are undervalued because, in the addict’s life, they have not been rewarding—for example, intimate connections with family. This shrinking from normal experience is also an outcome of early trauma and stress, as summarized in a recent psychiatric review of child development:

“Neglect and abuse during early life may cause bonding systems to develop abnormally and compromise capacity for rewarding interpersonal relationships and commitment to societal and cultural

values later in life. Other means of stimulating reward pathways in the brain, such as drugs, sex, aggression, and intimidating others, could become relatively more attractive and less constrained by concern about violating trusting relationships. The ability to modify behaviour based on negative experiences may be impaired.⁴⁴

Hardcore drug addicts, whose lives invariably began under conditions of severe stress, are all too readily triggered into a stress reaction. Not only does the stress response easily overwhelm the addict's already challenged capacity for rational thought when emotionally aroused, but also the hormones of stress "cross-sensitize" with addictive substances. The more one is present, the more the other is craved. Addiction is a deeply ingrained response to stress, an attempt to cope with it through self-soothing. Maladaptive in the long term, it is highly effective in the short term.⁴⁵

Predictably, stress is a major cause of continued drug dependence. It increases opiate craving and use, enhances the reward efficacy of drugs and provokes relapse to drug-seeking and drug-taking.⁴⁶ "Exposure to stress is the most powerful and reliable experimental manipulation used to induce reinstatement of alcohol or drug use."⁴⁷ "Stressful experiences increase the vulnerability of the individual to either develop drug self-administration or relapse."⁴⁸

Stress also diminishes the activity of dopamine receptors in the emotional circuits of the forebrain, particularly in the Nucleus Accumbens, where the craving for drugs increases as dopamine function decreases.⁴⁹ Literature has identified three factors that universally lead to stress for human beings: *uncertainty, lack of information and loss of control*.⁵⁰

To these we may add *conflict that the organism is unable to handle and isolation from emotionally supportive relationships*. Animal studies have demonstrated that isolation leads to changes in brain receptors, and increased propensity for drug use in infant animals and in adults reduces the activity of dopamine-dependent nerve cells.^{11,51} Unlike rats reared in isolation, rats housed together in stable social groupings resisted cocaine self-administration.⁵²

Human children do not have to be reared in physical isolation to suffer deprivation: emotional isola-

tion will have the same effect, as does stress on the parent.

SELF-AWARENESS OF CHILDHOOD EXPERIENCES

Some hold beliefs that addicts invent or exaggerate their stories to earn sympathy or to excuse their habits. However, many addicts tell their life histories reluctantly, only when asked and only after trust has been established—a process that may take months, even years. Often they see no link between childhood experiences and their self-harming habits. If they speak of the connection, they do so in a distanced manner that still insulates them against the full emotional impact of what happened.

Research shows that the vast majority of physical and sexual assault victims do not spontaneously reveal their histories to their doctors or therapists.⁵³ Rather, there is a tendency to forget or to deny pain. One study followed up on young girls who had been treated in an emergency ward for proven sexual abuse.⁵⁴ When contacted seventeen years later as adult women, 40% of these abuse victims either did not recall or denied the event outright. Yet their memory was found to be intact for other incidents in their lives.

CONCLUSION

Early developmental trauma and exposure to stressors produce numerous neurobiological abnormalities including changes in neural circuit function which may manifest in dependence or substance abuse. This review of the literature demonstrates that the stress-response mechanism is involved in addiction. Abandonment, neglect, or abuse (emotional, physical or sexual) can alter physical stress mechanisms and the child often becomes more reactive to stress throughout their life. Substance abuse or dependence is related to stress response in an attempt to self-soothe.

Childhood emotional loss and trauma, then, provide both the experiential, psychoemotional and physiological template for addiction.

DISCLOSURE OF INTERESTS

Dr. Maté has nothing to disclose.

REFERENCES

1. Substance Abuse and Mental Health Services Administration, Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings, NS-DUH Series H-41, HHS Publication No. (SMA)11-4658. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2011.
2. Schore AN. Affect regulation and the origin of the self. Hillsdale, NJ: Lawrence Erlbaum Associates, 1994, 142.
3. Esch T, Stefano GB. The Neurobiology of Love. *Neuro Endocrinol Lett.* 2005, 26(3):175-92.
4. Pedersen CA. Biological aspects of social bonding and the roots of human violence. *Ann N Y Acad Sci.* 2004, Dec;1036:106-27.
5. Schwarz ED, Perry BD. The post-traumatic response in children and adolescents. *Psychiatr Clin North Am.* 1994, Jun;17(2):311-326.
6. Mate G, *Scattered: How Attention Deficit Disorder Originates And What You Can Do About It*, Penguin Group (USA), 1999
7. Dubovsky SL. Mind body deceptions: The psychomatics of everyday Life. New York: W.W. Norton, 1997, 193.
8. Lehmann K, Grund T, Bagorda A, Bagorda F, Grafen K, Winter Y, Teuchert-Noodt G. Developmental effects on dopamine projections and hippocampal cell proliferation in the rodent model of postweaning social and physical deprivation can be triggered by brief changes of environmental context. *Behav Brain Res.* 2009, 205(1):26-31.
9. Blanc G, Hervé D, Simon H, Lisoprawski A, Glowinski J, Tassin JP. Response to stress of mesocortico-frontal dopaminergic neurons in rats after long-term isolation. *Nature.* 1980, 284(5783):265–267.
10. Meaney MJ, Brake W, Gratton A. Environmental regulation of the development of mesolimbic dopamine systems: A neurobiological mechanism for vulnerability to drug abuse? *Psychoneuroendocrinology.* 2002, 27(1-2):127–138.
11. Gordon HW. Early environmental stress and biological vulnerability to drug abuse. *Psychoneuroendocrinology.* 2002, 27(1-2):115–126.
12. Sapolsky RM, Uno H, Rebert CS, Finch CE. (1990). Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *Journal of Neuroscience.* 10, 2897-2902.
13. Caldji C, Tannenbaum B, Sharma S, Francis D, Plotsky PM, Meaney MJ. Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. *Proc Natl Acad Sci U S A.* 1998, 95(9):5335–5340.
14. Higley JD and Linnoila M. Low central nervous system serotonergic activity is traitlike and correlates with impulsive behaviour. *Ann NY Acad Sci.* 1997, 836:39-56.
15. Clarke AS, Hedeker DR, Ebert MH, Schmidt DE, McKinney WT, Kraemer GW. Rearing experience and biogenic amine activity in infant rhesus monkeys. *Biol Psychiatry.* 1996, 40(5):338–52.
16. Higley JD, Hasert MF, Suomi SJ, Linnoila M. Nonhuman primate model of alcohol abuse: Effects of early experience, personality, and stress on alcohol consumption. *Proc Natl Acad Sci USA.* 1991, 88(16): 7261–7265.
17. Heim C, Young LJ, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. Lower CSF oxytocin concentrations in women with a history of childhood abuse. *Mol Psychiatry.* 2009, 14(10):954-958.
18. Teicher MH. Wounds that time won't heal: The neurobiology of child abuse. *Cerebrum: The Dana Forum on Brain Science.* 2000, 2(4).
19. McGregor IS, Callaghan PD, Hunt GE. From ultrasocial to antisocial: a role for oxytocin in the acute reinforcing effects and long-term adverse consequences of drug use. *Br J Pharmacol.* 2008, 154(2):358-368.
20. Mello AF, Mello MF, Carpenter LL, Price LH. Update on stress and depression: The role of the hypothalamic-pituitary-adrenal (HPA) axis. *Rev. Bras. Psiquiatr.* 2003, 25(4); see also
21. Kraemer GW, Ebert MH, Schmidt DE, McKinney WT. A longitudinal study of the effect of different social rearing conditions on cerebrospinal fluid norepinephrine and biogenic amine metabolites in rhesus monkeys. *Neuropsychopharmacology* 1989, 2(3): 175–189.
22. Perry B and Pollard R. Homeostasis, stress, trauma and adaptation: A neurodevelopmental view of childhood trauma. *Child and Adolesc Psychiatr Clin N Am.* 1998, 7(1): 33–51, viii.
23. Kraemer GW, Ebert MH, Schmidt DE, McKinney WT. Strangers in a strange land: A psychobiological study of infant monkeys before and after separation from real or inanimate mothers. *Child Dev.* 1991, 62(3):548–566.
24. Pohorecky LA. Interaction of ethanol and stress: Research with experimental animals:—An update. *Alcohol & Alcoholism.* 1990, 25(2/3): 263–276.
25. Goodman A. Sexual addiction: Nosology, diagnosis, etiology and treatment. In: Lowinson JH, et al. *Substance Abuse: A Comprehensive Textbook*. Philadelphia: Lippincott Williams & Wilkins, 2005, 318.
26. 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.
27. Wang Z, Du J, Sun H, Wu H, Xiao Z, et al. (2010) Patterns of Childhood Trauma and Psychological Distress among Injecting Heroin Users in China. *PLoS ONE* 5(12):e15882.

28. Gordon HW. Early environmental stress and biological vulnerability to drug abuse. *Psychoneuroendocrinology*. 2002, 27(1-2): 115–126.
29. Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WH, Anda RF. Adverse childhood experiences and the association with ever using alcohol and initiating alcohol use during adolescence. *J Adolesc Health*. 2006, 38(4): 444.e1-10 .
30. Anderson CM, *et al*. Abnormal T2 relaxation time in the cerebellar vermis of adults sexually abused in childhood: Potential role of the vermis in stress-enhanced risk for drug abuse. *Psychoneuroendocrinology*. 2002, 27(1-2):231–244.
31. De Bellis MD, Baum AS, Birmaher B, Keshavan MS, Eccard CH, Boring AM, Jenkins FJ, Ryan ND. A.E. Bennett Research Award. Developmental traumatology. Part I: Biological stress systems. *Biol Psychiatry*. 1999, 45(10):1259–1270.
32. Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, Brummer M, Staib L, Vermetten E, Charney DS, Nemeroff CB, Bremner JD. Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry*. 2002, 159(12): 2072–2080.
33. Teicher MH, Ito Y, Glod CA, Andersen SL, Dumont N, Ackerman E. Preliminary evidence for abnormal cortical development in physically and sexually abused children using EEG coherence and MRI. *Ann N Y Acad Sci*. 1997, 821:160-175.
34. Sternberg EM, Chrousos GP, Wilder RL, Gold PW. The stress response and the regulation of inflammatory disease. *Ann Intern Med*. 1992, 117(10):854-856.
35. Trull TJ, Sher KJ, Minks-Brown C, Durbin J, Burr R. Borderline personality disorder and substance use disorders: a review and integration. *Clin Psychol Rev*. 2000 Mar;20(2):235-53.
36. Widiger TA, Trull TJ. *Borderline and narcissistic personality disorders*. H Adams, P Sutker (Eds.), Comprehensive handbook of psychopathology (2nd ed), New York. Plenum Press. 1993, pp. 371–394.
37. Lane, R.D., and L. Nadel, ed. *Cognitive Neuroscience of Emotion*. Oxford University Press. New York, 2000, p. 233-237
38. Kusnecov A and Rabin BS. Stressor-induced alterations of immune function: Mechanisms and issues. *Int Arch Allergy Immunol*. 1994, 105(2):107-121.
39. Selye H. *The stress of life.*, rev. ed. New York: Mac-Graw-Hill, 1978, 4.
40. Perry, Bruce. Senior Fellow at the Child Trauma Academy, Houston, Texas. Interview.
41. De Bellis MD, Chrousos GP, Dorn LD, Burke L, Helmers K, Kling MA, Trickett PK, Putnam FW. Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. *J. Clin Endocrinol Metab*. 1994, 78(2):249-255.
42. Essex MJ, Klein MH, Cho E, Kalin NH. Maternal stress beginning in infancy may sensitize children to later stress exposure: Effects on cortisol and behaviour. *Biol Psychiatry*. 2002, 52(8):776-784.
43. Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, Miller AH, Nemeroff CB. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA*. 2000, 284(5):592–597.
44. Pedersen CA. Biological aspects of social bonding and the roots of human violence. *Ann N Y Acad Sci*. 2004, 1036:106–127.
45. Sinha R, Shaham Y, Heilig M. Translational and reverse translational research on the role of stress in drug craving and relapse. *Psychopharmacology (Berl)*. 2011;218(1):69-82.
46. Gardner EL. Brain-reward mechanisms. In: Lowinson JH, . *Substance abuse: A comprehensive textbook*. Philadelphia: Lippincott Williams & Wilkins, 2005, 72.
47. Brady KT and Sonne SC. The role of stress in alcohol use, alcoholism treatment, and relapse. *Alcohol Res Health*. 1999, 23(4):263–271.
48. Piazza PV and Le Moal M. Pathophysiological basis of vulnerability to drug abuse: Role of an interaction between stress, glucocorticoids, and dopaminergic neurons. *Annu Rev Pharmacol Toxicol*. 1996, 36:359–378.
49. Papp M, Klimek V, Willner P. Parallel changes in dopamine D2 receptor binding in limbic forebrain associated with chronic mild stress-induced anhedonia and its reversal by imipramine. *Psychopharmacology (Berl)*. 1994, 115(4):441–446.
50. Levine S and Ursin H. What is stress? In: Brown MR, Koob GF and Rivier C. Stress, neurobiology and neuroendocrinology. New York: Marcel Dekker, 1991, 3–21.
51. Blanc G, Hervé D, Simon H, Lisoprawski A, Glowinski J, Tassin JP. Response to stress of mesocortico-frontal dopaminergic neurons in rats. *Nature*. 1980, 284(5753):265–267.
52. Schenk S, Lacelle G, Gorman K, Amit Z. Cocaine self-administration in rats influenced by environmental conditions: Implications for the etiology of drug abuse. *Neurosci Lett*. 1987, 81(1-2):227–231.
53. Jacobson A. Physical and sexual assault histories among psychiatric outpatients. *Am J Psychiatry*. 1989, 146(6):755–758.
54. Williams LM. Recall of childhood trauma: A prospective study of women’s memories of child sexual abuse. *J Consult Clin Psychol*. 1994, 62(6): 1167–1176.
- *Bruce D. Perry, M.D., Ph.D., is an internationally-recognized authority on children in crisis. Dr. Perry is the Provincial Medical Director in Children’s Mental Health for the Alberta Mental Health Board. In addition, he is the Senior Fellow of the ChildTrauma Academy ([www. ChildTrauma.org](http://www.ChildTrauma.org)),