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# The Role of Early Life Stress as a Predictor for Alcohol and Drug Dependence

**Mary-Anne Enoch, M.D.**

## Abstract

**Rationale—**Genetic and environmental influences on the development of alcohol and drug dependence are equally important. Exposure to early life stress, that is unfortunately common in the general population, has been shown to predict a wide range of psychopathology, including addiction.

**Objective—**This review will look at the characteristics of early life stress that may be specific predictors for adolescent and adult alcohol and drug dependence and will focus on studies in humans, non-human primates and rodents.

**Results—**Experiencing maltreatment and cumulative stressful life events prior to puberty and particularly in the first few years of life is associated with early onset of problem drinking in adolescence and alcohol and drug dependence in early adulthood. Early life stress can result in permanent neurohormonal and hypothalamic-pituitary-adrenal axis changes, morphological changes in the brain and gene expression changes in the mesolimbic dopamine reward pathway, all of which are implicated in the development of addiction. However, a large proportion of children who have experienced even severe early life stress do not develop psychopathology indicating that mediating factors such as gene-environment interactions and family and peer relationships are important for resilience.

**Conclusions—**There appears to be a direct pathway from chronic stress exposure in pre-pubertal children via adolescent problem drinking to alcohol and drug dependence in early adulthood. However, this route can be moderated by genetic and environmental factors. The role that gene-environment interactions play in the risk-resilience balance is being increasingly recognized.

### Keywords

abuse; addiction; alcohol; corticotropin; dopamine; gene expression; glucocorticoid; HPA axis; stress; VTA

## Introduction

Alcoholism is a common psychiatric disorder that has devastating consequences for afflicted individuals, their families and for society in general. The lifetime prevalence of alcoholism (alcohol dependence and abuse) is 30% (Hasin et al. 2007). It is well established that the heritability (the genetic component of the variance) of alcoholism is around 50%; similarly, the heritability of cocaine and opiate addiction is around 60 – 70% (Goldman et al. 2005). Therefore genetic and environmental influences on the development of addictive disorders are equally important although the proportions of risk may vary according to societal

Corresponding author: Mary-Anne Enoch M.D., NIH/NIAAA/DICBR/LNG, 5625 Fishers Lane, Room 3S32, MSC 9412, Bethesda, MD 20892-9412, Tel: 301-496-2727, Fax: 301-480-2839, maenoch@niaaa.nih.gov.

groups. For example, in populations exposed to severe current and historical trauma such as some Native American tribes and Australian aboriginal groups, environmental stressors can swamp genetic influences.

An important risk factor for alcoholism or drug dependence is having a parent with the disorder. A prospective New Zealand birth cohort of nearly 1000 individuals has shown that family history is a strong predictor of alcohol and drug dependence and is associated with a more recurrent course, worse impairment but not younger age of onset (Milne et al. 2009). It is a well established fact that stressors experienced in childhood, particularly childhood maltreatment, are also predictors of adult psychopathology, including addiction to alcohol and drugs. Although the genetic risk for externalizing disorders, including alcohol and drug dependence, transmitted from parents to child influences both the likelihood that the child will be exposed to early life stress and will develop the disorder, nevertheless numerous studies, some of which are described below, have shown that stressors in childhood have an independent effect on the risk for adult alcohol and drug dependence (Anda et al. 2002; Eaves et al. 2010; Verona and Sachs-Ericsson 2005).

This review will look at exposure to early life stress as a specific predictor for adolescent and adult alcohol and drug dependence and will focus on studies in humans, non-human primates and rodents that have shown that early life stress is associated with neurohormonal and hypothalamic-pituitary-adrenal (HPA) axis changes, morphological changes in the brain and gene expression changes in the mesolimbic dopamine (DA) reward pathway, all of which are implicated in the development of addiction. A large proportion of children who are exposed to early life stress do not go on to develop psychopathology therefore this review will discuss risk-resilience factors, including gene-environment interactions. Other pertinent questions will be addressed in this review: are there factors that maximize the effects on addiction vulnerability such as the nature of the stressor (childhood maltreatment, stressful life events), specificity of stressors for addiction, acute or chronic exposure, severity, timing (critical time period for influence on brain development?) and sex differences in effects of stressors?

## Alcoholism and Drug Dependence; Definition and Prevalence

Addiction to alcohol and drugs has been described as a perpetual cycling of preoccupation and anticipation, binge/intoxication and withdrawal/negative affect (Koob 2003). The essential features of addiction are loss of control over consumption, obsessive thoughts about the drug and continuation of use despite knowledge of negative health and social consequences (American Psychiatric Association 1994). Both positive (euphoric) and negative (anxiolytic) reinforcement are features of addiction. Negative reinforcement tends to become the driving force as the disease progresses.

Results from a nationally representative sample of U.S. adults (NESARC, N = 43,093) have shown that the prevalence of lifetime DSM-IV alcohol dependence (AD) and alcohol abuse (a less severe from of addiction) is 12.5% and 17.8% respectively (Hasin et al. 2007). Lifetime alcohol use disorders (abuse + dependence, AUD) are twice as common in men (42%) as women (19.5%) (Hasin et al. 2007). The same survey looked at the prevalence of dependence and abuse across classes of drugs including cocaine, cannabis, heroin and other opiates, tranquilizers, sedatives, stimulants, hallucinogens and inhalents/solvents. The prevalence of lifetime DSM-IV drug dependence was 2.6% and drug abuse was 7.7%. Unlike AD, the prevalence of drug dependence was similar in men (3.3%) and women (2.0%) (Compton et al. 2007). Since AUD is a much more widespread problem in society, this addiction will be the predominant focus of this review.

## Early Life Stress; Definition and Prevalence

For the purposes of research, early life stress can be compartmented into childhood maltreatment and stressful life events (SLE) although in reality there is considerable overlap between the two (see below). The degree of risk for adult psychopathology tends to be correlated with the severity of childhood maltreatment (see below) and the number of childhood SLE (Afifi et al. 2008; Enoch et al. 2010a; Jaffee et al. 2007; Pilowsky et al. 2009). Cumulative SLE experienced in adulthood have also been shown to have pathological effects (Blomeyer et al. 2008; Caspi et al. 2003; Covault et al. 2007; Schmid et al. 2009). Children tend to experience SLE alongside family members and friends. In contrast, childhood maltreatment: physical abuse and neglect, emotional abuse and neglect and sexual abuse (CSA), is directed at children and can be experienced in isolation and over an extended period of time (Goldman et al. 2003; Goodman-Brown et al. 2003).

Exposure to SLE is common in the general population; for example, a nationally representative U.S. sample of 9282 adults, The National Comorbidity Survey Replication (NCS-R), reported that 53% of adults had experienced some kind of stressor before the age of 18 (Green et al. 2010), the most common being parental divorce (17.5%), family violence (14%), economic adversity (11%), parental death (10%) and mental illness (10%). Childhood maltreatment is also common although reported prevalence varies depending on several factors including definition (Caspi et al. 2010), population sampled (Simpson and Miller 2002), survey methods (Arnow 2004) and whether data is obtained longitudinally or retrospectively. Most studies on early life stressors have been performed retroactively, therefore recall bias can be an issue. It has been shown that individuals, particularly over the age of 65, often under-report when questioned retroactively about exposure to childhood abuse (Fergusson et al. 2000; Green et al. 2010). Bearing this in mind, data from the NCS-R reveals the following prevalences: physical abuse 8.4%, CSA 6%, and parental neglect 5.6% (Green et al. 2010). Higher prevalences have been reported in other studies. A general population survey showed that 31% of men and 21% of women reported a history of childhood physical abuse while 4% of men and 13% of women had been exposed to CSA (Holmes and Slap 1998; Macmillan et al. 1997). A random U.S. sample of 935 individuals revealed that 22% of men and 20% of women reported childhood physical abuse and 14% of men and 32% of women reported CSA whereas 21% had experienced both types of abuse (Briere and Elliott 2003). In a retrospective cohort study on 17,337 adult U.S. HMO members, contact CSA was reported by 16% of men and 25% of women (Dube et al. 2005). In a U.S. nationally representative sample of approximately 1000 women aged 21 and older, prevalence rates for CSA (Russell criteria) experienced below the age of 18 ranged from 15% to 26% (Vogeltanz et al. 1999). Some populations experience even higher rates of childhood maltreatment. A study across six Native American tribes with high rates of lifetime AD reported that 35–70% of men and 40–56% of women had experienced physical abuse in childhood; 17–40% of men and 24–53% of women had been exposed to CSA and 13–40% of men and 30–49% of women had experienced childhood emotional abuse (Koss et al. 2003). Similarly, in a Southwestern American Indian tribe, clinical interviews elicited the fact that 14% of men and 49% of women had experienced contact CSA, more than half before the age of 10 and more than half with intercourse (Robin et al. 1997).

Children who are subjected to early life stress are often exposed to multiple stressors (Dong et al. 2004; Ney et al. 1994) Childhood maltreatment often emerges from disturbed and disrupted family backgrounds (Mullen et al. 1996). The NCS-R revealed that 95% to 88% of individuals who had experienced parental neglect and physical abuse respectively, and 72% exposed to sexual abuse had been subjected to multiple early life stressors (Green et al. 2010). Older studies have generally reported on only one or two forms of childhood maltreatment, notably CSA and physical abuse, but more recent studies have used newly

developed measures including the Childhood Trauma Questionnaire (Bernstein et al. 2003) and the Early Trauma Inventory (Bremner et al. 2007) to assess various maltreatment types and their cumulative effect.

### Timing of Early Life Stressors

The type of abuse may be confounded with age or developmental stage. It appears that in humans, cortisol activity is particularly sensitive to the quality of nurturing during the first year of life and therefore it is likely that emotional neglect will have the largest impact at this time (Gunnar and Donzella 2002). Sexual abuse is usually experienced at a later developmental stage. Kaplow and Widom (2007) reported that in a group of nearly 500 children with documented cases of neglect and sexual abuse, the age of onset for sexual abuse was significantly later (8.4 (SD = 2.6) years) than neglect (5.9 (SD = 3.3 years). Likewise, of those women in a U.S. nationally representative sample who had experienced CSA, 13.5% were 5 years and younger, 25% were age 6–8 years and 23% were age 9–11 years (Vogeltanz et al. 1999).

Longitudinal studies have shown that maltreatment at less than age 5 years is related to greater psychopathology in adulthood, including anxiety and depression, than maltreatment experienced at later ages (Kaplow and Widom 2007; Keiley et al. 2001; Lansford et al. 2007).

A study of 7500 girls and boys from the Avon Longitudinal Study of Parents and Children (ALSPAC), U.K., a community-representative cohort study of children followed from pre-birth onwards, showed that in both sexes, exposure to family adversity and SLE in the first three years of life predicted hyperactivity and conduct problems at age 4, persisting until at least age 7 (Enoch et al. 2010a). The New Zealand longitudinal study has shown that hyperactivity and conduct problems at age 3 predict AD at age 21 (OR = 2.7 [95% CI, 1.2–6.2]) (Caspi et al.1996). Likewise, hyperactivity and conduct problems in boys aged 8 predict frequent drunkenness 10 years later (Niemela et al. 2006) and externalizing behavior in pre-pubertal boys predicts adult AUD (Englund et al. 2008). Therefore by extension the ALSPAC study implies that SLE and family adversity in the first few years of life predicts adult AUD. However, another longitudinal study showed that for maltreatment, age of onset at any particular time in the interval of 0 – 11 yrs was not predictive of alcohol or drug abuse or dependence (Kaplow and Widom 2007).

## Early Life Stress as a Predictor of Psychopathology

Numerous studies have shown that childhood maltreatment and SLE predict a wide range of adverse physical and emotional health outcomes, psychopathology including alcoholism and drug dependence, socioeconomic disadvantage and an increased risk for physical assault and rape in adulthood (Arias 2004; Arnow 2004; Bulik et al. 2001; Caspi et al. 2002; De Bellis 2002; Dube et al. 2005; Hyman and Sinha 2009; Kendler et al. 2000; Poulton et al. 2002; Simpson and Miller 2002; Sinha 2001; Walker et al. 1999; Yuan et al. 2006). The NCS-R study identified three meaningful factors: (a) maladaptive family functioning, including parental substance abuse, criminality, domestic violence, childhood abuse and neglect; (b) parental death and other loss and (c) parental divorce, both with associated economic adversity. The maladaptive family functioning stressors were the strongest correlates of onset of psychopathology (Green et al. 2010). Little specificity has been found for the association of particular types of childhood maltreatment and SLE with particular psychiatric disorders (Green et al. 2010; Kendler et al. 2000). Also, a study in 17,337 U.S. HMO members has shown that the long-term impact of CSA on multiple health and social problems is similar for both men and women (Dube et al. 2005).

Predictably, the severity of childhood maltreatment is positively correlated with poorer outcomes in adulthood (Arnow 2004; Bulik et al. 2001; Caspi et al. 2002; Ducci et al. 2009; Kendler et al. 2000; Robin et al. 1997). For example, in a population based sample of 1411 female adult twins, 30% reported CSA of whom 8% reported severe CSA (intercourse before age 16) and this group of women experienced a greater risk for psychopathology: the adjusted odds ratios for non-genital – penetration, respectively were: AD, OR = 3.2 – 6.5; drug dependence, OR = 3.6 – 6.6; development of ≥ 2 disorders, OR = 1.4 – 4.8 (Kendler et al. 2000). In Southwestern American Indians, men and women exposed to severe CSA were more likely to be diagnosed with more than three psychiatric disorders (Robin et al. 1997) and in African American substance dependent, treatment-seeking men, greater severity of childhood maltreatment was associated with a greater likelihood of polysubstance abuse (Ducci et al. 2009). Chronic childhood maltreatment can have more deleterious effects than 'one-off' episodes as illustrated by a longitudinal study of 113 African American women with documented CSA that found that multiple incidents of CSA, more than the characteristics of such abuse, were predictors of heavy alcohol use and binge drinking in adulthood, even after controlling for parental drinking behavior (Jasinski et al. 2000).

## Relationship between Early Life Stress and Alcohol/Drug Dependence

Numerous studies have demonstrated a link between retrospectively documented childhood stressors and alcohol and drug dependence (Arnow 2004; De Bellis 2002; Dodge et al. 1990; Ducci et al. 2009; Heffernan et al. 2000; Hyman et al. 2006; Nelson et al. 2006; Nelson et al. 2010; Pilowsky et al. 2009; Verona and Sachs-Ericsson 2005). Data from the general population NESARC study showed that experiencing two or more childhood SLE compared with none, significantly increased the risk for AD after controlling for socieodemographic and other variables (adjusted OR = 1.4 [95% CI, 1.1–1.8]) (Pilowsky et al. 2009). In treatment seeking African American men with substance dependence, the odds ratios for risk of developing alcohol, cocaine or heroin dependence after exposure to childhood maltreatment ranged from 3.2 to 4.2 (Ducci et al. 2009). In a Southwestern American Indian tribe with a high prevalence of AD, CSA in women significantly increased the risk for lifetime AD (OR = 2.1 [95% CI, 1.2–3.6]) and drug dependence (OR = 4.2 [95% CI, 2.2–7.8]) (Robin et al. 1997). A study in of 1362 individuals from six American Indian tribes with a high lifetime prevalence of AD found that, in men, childhood exposure to physical and sexual abuse was associated with an increased risk of AD: OR = 1.6 [95% CI 1.1–2.3] whereas for women, all forms of abuse and neglect increased the risk of AD [OR = 1.6 – 2.4] (Koss et al. 2003). In this study, 29% of men had experienced 4 or 5 maltreatment categories and these individuals had a 3 fold greater risk of AD; 35% of women had experienced 4 or 5 maltreatment categories of maltreatment and had a 7 fold greater risk of AD (Koss et al. 2003).

### Sex Differences

There appears to be considerable evidence for an association between childhood maltreatment and AD or drug dependence in women but fewer positive studies in men (reviewed in Simpson and Miller 2002 and Widom et al. 2006). For example, a longitudinal cohort study (N = approximately 900) of children with court documented cases of childhood (0 – 11 yrs) sexual and physical abuse and neglect followed through to middle age (40 years) showed that childhood maltreatment predicted the development of AD in women but not men (Widdom et al. 2007). For women, a composite risk factor (prostitution/homelessness/delinquency/crime/poor school performance) together with another risk factor (PTSD) mediated the pathway from childhood maltreatment to middle-aged drug use (White and Widom 2008; Wilson and Widom 2009). For men, neither childhood maltreatment nor the mediating factors predicted adult drug use (Wilson and Widom 2009). A general population sample drawn from the National Comorbidity survey showed that childhood

maltreatment accounted for the relationship between parental and offspring externalizing behavior in women but not men (Verona and Sachs-Ericsson 2005). Severity of childhood emotional abuse has been correlated with increased risk for substance abuse in both sexes (Hyman et al. 2006) and an increased risk of relapse in cocaine dependent women but not men (Hyman et al. 2008). However, in the Virginia Adult Twin Study of 3527 men it was reported that men who had experienced childhood maltreatment before age 15 were 1.7 times more likely to meet criteria for AUD than men not exposed to maltreatment, and this association was attributable to environmental adversity that was shared between twins (Young-Wolff et al. 2010). Further longitudinal studies are needed before it can be determined whether childhood maltreatment is indeed a stronger predictor of AUD and drug dependence in women than in men.

### Supporting Evidence from Animal Studies

Drug self-administration in animals is a robust model for drug abuse liability in humans (Koob 2009). Early life stress has been shown to affect alcohol consumption in adult rhesus macaque monkeys and alcohol, cocaine and morphine consumption in rodents (Higley et al. 1991; Huot et al. 2001; Moffett et al. 2007; Schwandt et al. 2010; Vazquez et al. 2006; reviewed in Sinha 2001). Peer reared monkeys (subjected to early life maternal separation) consume significantly more alcohol than mother-reared monkeys under non-stress conditions when alcohol is freely available. This behavior could be regarded as analogous to ‘drinking to cope’ in humans (Higley et al. 1991).

## The Association between Early Life Stress and Early Onset Problem Drinking

The effect of early life stress on adult AD may result from the earlier effect on adolescent problem drinking. Several studies have demonstrated the influence of childhood stressors on early age of onset of drinking and on binge drinking (≥ 5 drinks/occasion in any two week period). A survey of a probability sample of 3592 U.S. current or former drinkers reported that childhood stressors including physical abuse and sexual abuse were predictors of early onset (≤ 14 yrs) drinking, controlling for parental and peer alcohol use and parental attitudes toward drinking (Rothman et al. 2008). A study of 8417 adult HMO members, including 4 successive birth cohorts dating back to 1900, who completed a survey about adverse childhood experiences showed that early life stressors, including abuse and neglect, were strongly associated in with early onset of alcohol use in a ‘dose response’ relationship in all 4 cohorts demonstrating that this association has been stable over a long period of time (Dube et al. 2006). An earlier age of first alcohol use has been associated with childhood emotional abuse in both sexes and additionally sexual abuse and overall maltreatment in women (Hyman and Sinha. 2006). Retrospective questionnaire data from the U.S. National Longitudinal Study of Adolescent Health (AddHealth) (N = 12,748), showed that the co-occurrence all types of childhood maltreatment (< 11years) increased the risk for adolescent (ages 12 – 18 years) binge drinking, controlling for age, sex, ethnicity, parental alcoholism and monitoring (Shin et al. 2009). Another study showed that individuals exposed to childhood abuse were substantially more likely to report that they drank to cope during the first year of alcohol use (Rothman et al. 2008), a predictor of the development of alcohol problems (Grayson and Nolen-Hoeksema. 2005).

Early age of onset (< 15 years) of alcohol use predicts adult AD (Englund et al. 2008; Grant et al. 2001). A large (N = 11,261) U.K. longitudinal study has shown that adolescent binge drinking at age 16 predicts numerous adverse outcomes in adulthood (age 30) including AD (OR = 1.6 [1.3–2.0]) and illicit drug use (OR = 1.4 [1.1–1.8]) (Viner and Taylor 2007). Another UK longitudinal study (N = 2000) showed that, after adjustment for other teenage

predictors, frequent drinking at age 14–15 years (OR = 3.1 [1.2–7.7]) and antisocial behavior (OR = 2.4 [1.2–5.1]) predicted AD at age 20–21 years (Bonomo et al. 2004). A total of 5% of boys and girls aged 12 – 17 years have a diagnosis of AUD. The peak prevalence is at age 18 – 23 years when 20% of men and 10% of women have a current diagnosis of AUD (Harford et al. 2005; Bonomo et al 2004). By the ages of 23 years, 50% of all alcoholics have developed their symptoms (Kessler et al. 2005). Therefore adolescence and young adulthood is a risk period for problem drinking and the subsequent development of AUD, particularly for children who have experienced maltreatment.

## Effects of Early Life Stress on Stress Circuitry and the Mesolimbic Dopamine Reward Pathway

Stress induces secretion of the glucocorticoid hormones cortisol in human and non-human primates and corticosterone in rodents. The activation of the HPA axis, central corticotrophin releasing hormone (CRH) and peripheral catecholamine systems in response to acute stress are essential for survival, however chronic activation of these stress response systems results in increased risk for numerous physiological problems as well as vulnerability to psychopathology such as anxiety, depression and addiction to alcohol and drugs (Sapolsky et al. 2000).

### Long-term Effects of Early Life Stress on Stress Circuitry

A longitudinal study that investigated the developmental course of basal, morning cortisol in 84 females with confirmed familial CSA and 89 female controls at six points from age 6 to 30, showed attenuation in cortisol activity starting in adolescence with significantly lower levels of cortisol by early adulthood in abused females (Trickett et al. 2010). Other studies have also shown that adults who have experienced childhood maltreatment have low basal cortisol levels (Tarullo and Gunnar 2006). These findings in humans are supported by studies in rhesus macaque monkeys that have shown that early life stress (repetitive maternal separation) results in a flattened diurnal rhythm of cortisol secretion (Sanchez et al. 2005).

Studies of adolescent girls and adults free of psychopathology have shown that childhood maltreatment is associated with blunted reactivity to acute psychosocial stress (Carpenter et al. 2007; MacMillan et al. 2009), and, in the adult dataset, diminished cortisol response in the dexamethasone/corticotropin releasing hormone (DEX/CRH) test (Carpenter et al. 2009). However, other studies report that adults exposed to childhood maltreatment have elevated ACTH or cortisol responses to psychological stressors (Tarullo and Gunnar 2006; Preussner et al. 2004). It is difficult to disentangle reasons for these differences since they may be attributed to concomitant psychopathology, adult stressors, genetic vulnerability etc. For example, variation in the *CRHR1* gene has been shown to interact with childhood maltreatment to predict cortisol response to the DEX/CRH test (Tyrka et al. 2009). It is interesting to note that a blunted HPA axis response to stress has been found in family history positive non-alcoholics and alcoholics (Dai et al. 2005, 2007); boys with persistent antisocial behavior, a predictor for adult substance abuse (Snoek et al. 2004) and women with high neuroticism, a risk factor for psychopathology including alcoholism (Oswald et al. 2006). Thus a blunted stress response may indicate vulnerability to addiction.

Studies in rats have established that the quality of maternal care (grooming, licking of pups, arched back nursing) in the first two weeks of life influences the development of individual differences in behavioral and HPA responses to stress in offspring (Caldji et al. 2000; Liu et al. 1997). Early rearing conditions can permanently alter the developmental set-point of central CRH systems (Plotsky et al. 2005). Poor maternal contact in early life, akin to emotional neglect of children, results in adult rats having increased plasma ACTH and

corticosterone response to stress, reduced hippocampal glucocorticoid receptor (GR) mRNA expression, diminished glucocorticoid feedback sensitivity and greater HPA axis activation (Liu et al. 1997; Weaver et al. 2001, 2004; Weaver 2009). Stress-induced corticosterone secretion by the adrenal gland activates the GR, a ubiquitous transcription factor that influences gene expression by directly binding to hormone-responsive elements or by interacting with other transcription factors such as NF-κB (Meijer 2006). The maternally deprived offspring's response to stress in adulthood is due to reduced gene transcription resulting from hypermethylation of a GR exon $1_7$ promoter region (Weaver et al. 2004). Likewise, a study in humans of postmortem hippocampus shows that suicide victims exposed to childhood maltreatment have decreased levels of GR (*NR3C1*) mRNA as well as mRNA transcripts bearing the GR $1_F$ splice variant and increased cytosine methylation of an *NR3C1* promoter (McGowan et al. 2009).

## Long-term Effects of Early Life Stress on the Mesolimbic Dopamine Reward Pathway

Stress can affect neuronal plasticity, particularly in the limbic system (Sapolsky 2003). Evidence is emerging that early life stress (maternal separation or handling) in rats has significant, long-lasting effects on the mesolimbic dopamine (DA) pathway that is fundamental to the drug-induced sensation of pleasure that acts as positive reinforcement. This "reward" pathway originates in the ventral tegmental area (VTA) of the midbrain and projects to the nucleus accumbens (NAc) (in the ventral part of the striatal complex), the limbic system and the orbitofrontal cortex. The amygdala, hippocampus and medial prefrontal cortex send excitatory projections to the NAc. Alcohol and drug intake is associated with increased synaptic DA in the NAc and elsewhere in the reward pathway Morphometric analyses show a decreased volume of this reward system in abstinent alcoholics (Makris et al. 2008).

A study of dexamethasone treatment, a model of stress exposure, in rats during the first week of life shows that the survival or phenotypic expression of VTA DA neurons is profoundly influenced by exposure to glucocorticoid hormones at times when endogenous levels are normally low (McArthur et al. 2005). Likewise, the stress of disruption in early postnatal rearing conditions can lead to profound and lasting changes in the responsiveness of mesocorticolimbic DA neurons to stress and psychostimulants in adult rats (Brake et al. 2004). Acute stress or psychostimulant drug administration increases extracellular DA levels in the NAc whereas repeated exposure to stressor or drug increases both the magnitude and duration of NAc DA responses to psychostimulants (Kalivas 1993; Meaney et al. 2002). One explanation for the altered response to drugs may be that repeated episodes of early life stress (maternal separation) decreases DA transporter (DAT) expression in the NAc resulting in a greater responsiveness to DAT blockers such as cocaine (Brake et al. 2004; Meaney et al. 2002; Moffett et al. 2007). Inactivation of *NR3C1*, the GR gene, throughout the brain in mice results in decreased stress-related behavior and decreased motivation to self-administer cocaine (Deroche-Gamonet et al. 2003). Moreover, selective ablation of *NR3C1* and therefore GR in mouse DA receptive neurons (but not in DA releasing neurons) markedly decreases DA cell firing and the motivation of mice to self-administer cocaine (Ambroggi et al. 2009). Interestingly, although the GRs regulate both cocaine self administration and anxiety, these two behaviors are independent and dissociable (Ambroggi et al. 2009).

The few studies in humans are consistent with the findings of preclinical studies in rodents. Healthy young college students who reported low parental care showed a significantly increased cortisol response to a psychosocial stress task that was highly correlated with the release of DA in the ventral striatum, as measured in a positron emission tomography [11C]raclopride study (Pruessner et al. 2004). In an fMRI study of young adults who had experienced verified emotional, physical or sexual abuse before age 14, maltreatment was

associated with blunted subjective responses to reward-predicting cues together with dysfunction in left basal ganglia regions implicated in reward-related learning and motivation (Dillon et al. 2009). These findings are consistent with the hypothesis that early life stress affects the DA system since DA neurons that project to the basal ganglia are susceptible to stress-related dysfunction and are critical for incentive motivation (Dillon et al, 2009). Studies in rats have also shown that early life stress can cause changes in the reward/reinforcement systems in brain (Matthews and Robbins 2003).

Alcohol and drug intake is associated with complex changes in numerous neurotransmitters implicated in stress response including opioid peptides, cannabinoids, GABA, glutamate and serotonin (5-HT). 5-HT neurons originating in the dorsal and median raphe nuclei project to mesolimbic structures and may inhibit DA release. Exposure to early life stress (poor maternal care, brief maternal separations or handling) in rats results in alterations in opiate, serotonergic, DA and GABAA receptors (Mesquita et al. 2007; Moffett et al. 2007). The quality of maternal care over the first week of a rat's life affects GABAA receptor mRNA subunit expression. Compared with rats that had experienced good maternal care, rats exposed to poor nurturing had decreased mRNA levels of α1 subunits in hippocampus, medial prefrontal cortex, amygdala, and decreased β2, β3, γ1, γ2 but increased α3 and α4 mRNA levels in the amygdala. The fact that these effects were reversed by cross fostering shortly after birth suggests epigenetic origins (Caldji et al. 2003). Other investigators have shown that early life stress results in decreased $\alpha_1$ but increased $\alpha_2$ subunit expression in the hippocampus that results in changes in receptor function (Hsu et al. 2003).

Within the limbic behavioral stress response system, CRH is localized and co-synthesized within GABAergic neurons in the central amygdala and in this location CRH1 receptors have been shown to mediate enhancement of GABAergic synaptic transmission by alcohol (Nie et al. 2004). The activity of CRH in the VTA and its role in cocaine addiction is complex and not yet fully understood (Corominas et al. 2010; Wise and Morales. 2010). A recent study illustrates changes at the cellular level in adult rats exposed to the swim stress test. In the dorsal raphe 5-HT system, the CRH1 receptor is prominent on the plasma membrane and CRH2 is in the cytoplasm. In the stressed rats CRH2 changed locations to the plasma membrane and CRH1 tended to internalize. Because of this redistribution of receptors, neuronal responses to CRH in the dorsal raphe serotonergic system changed from inhibition to CRF2-mediated excitation (Waselus et al. 2009). If a similar CRH receptor redistribution in the limbic behavioral stress response system resulted from early life stress, this might affect neuronal responses to alcohol and cocaine.

Transcription factor cAMP response element binding protein (CREB) is a component of many neurotransmitter signaling cascades that regulate expression of many genes in the reward pathway. Stress, together with alcohol, cocaine, morphine and several other drugs of abuse activate CREB through phosphorylation. Chronic exposure to drugs and stress causes sustained activation of CREB that is associated with adaptation in the addictive process: reduction in reward (tolerance), and reduced sensitivity to stress (Barrot et al. 2002; Wand 2005). One study showed CREB induction in the postnatal rat hippocampus following maternal separation (Nair et al. 2007) but not another (Lippmann et al. 2007).

Early life maternal separation in rats has been shown to induce long term changes in BDNF expression with decreased BDNF in the hippocampus but increased BDNF in the VTA (Lippmann et al. 2007). Early maltreatment in rats produces persisting changes in methylation of BDNF DNA that results in altered BDNF gene expression in the adult prefrontal cortex (Roth et al. 2009). Chronic exposure to drugs also increases BDNF levels in the VTA. Elevated BDNF may be critical for vulnerability to addiction: an influential study has shown that infusion of BDNF into the VTA induces a shift from a dopamine-

independent to a dopamine-dependent opiate reward system (Vargas-Perez et al. 2009) involving a switch in the VTA GABAA receptors from inhibitory to excitatory signaling (Laviolette et al. 2004; Vargas-Perez et al. 2009).

## The Effects of Early Life Stress on Brain Morphometry

Childhood maltreatment has been associated with abnormalities in brain development, including a reduction in size of the corpus callosum (CC), the brain's most extensive white matter tract (Andersen et al. 2008; Teicher et al. 2004), together with other white tract abnormalities (Choi et al. 2009). Emotionally deprived rhesus macaque monkeys showed a diminution in CC volume in one study (Sanchez et al. 1998) but not another (Spinelli et al. 2009). The latter study showed that early life stress (peer rearing vs maternal rearing) was associated with enlargements of stress sensitive brain regions (vermis, dorsomedial prefrontal cortex, dorsal anterior cingulate cortex) without any apparent differences in the CC and hippocampus (Spinelli et al. 2009). Childhood maltreatment has been associated with attenuated development of the left neocortex, amygdala and hippocampus (Teicher et al. 2003) and smaller hippocampal volumes in adolescents (Rao et al. 2010) and adults but not in children (Woon et al. 2008). Dissociative symptom severity of CSA has been negatively correlated with hippocampal volume in women (Stein et al. 1997). Although smaller hippocampal volumes have been reported in alcoholics, this may be proportional to the overall reduction in brain volume (Agartz et al. 1999).

AUD in adults is associated with white matter volume loss and demyelination, particularly in the CC (Chanraud et al. 2007; Schulte et al. 2005) and this has implications for efficiency in interhemispheric processing. Heavy drinking during adolescence can impair brain development (Guerri and Pascual. 2010; Monti et al. 2005; Witt 2010). Disrupted CC microstructure is found in adolescent binge drinkers (McQueeny et al. 2009) and adolescent onset AUD (De Bellis et al. 2008). Hippocampal volume is reduced in adolescent onset AUD and correlates negatively with duration of drinking (De Bellis et al. 2000). Since childhood maltreatment is a predictor of adolescent binge drinking it would be very interesting to know whether disrupted CC microstructure and changes in the hippocampus results from both childhood maltreatment and the effects of alcohol on the developing adolescent brain and if so, whether there are additive effects of these two environmental stressors. Moreover, since alcoholics able to abstain from drinking for 8 months show extensive brain volume recovery, including of the CC (Cardenas et al. 2007), it would be interesting to see whether abstainers who had experienced childhood maltreatment show the same rate of recovery (or any recovery) of brain volume.

## Resilience to the Damaging Effects of Early Life Stress

Not all children who have been exposed to maltreatment go on to develop psychopathology, indicating that resilience and mediating factors play a role (Enoch 2006). In a prospective study using court documented and therefore presumably severe cases of childhood maltreatment (physical abuse, sexual abuse and neglect experienced from 0 – 11 years), 33.5% of adolescents (up to age 18) and 56% of young adults (18 or older) who had experienced childhood maltreatment met criteria for alcohol or drug abuse or dependence. Likewise, 46% of adolescents and 47% of young adults met criteria for anxiety disorders, depression, PTSD or antisocial personality disorder (ASPD) (DuMont et al. 2007). A community survey, the NCS-R, showed that retrospectively reported childhood stressors (SLE plus maltreatment) predicted 26% of substance use disorders with onset at ages 13–29 years (Green et al. 2010) but did not predict persistence of the disorders (McLaughlin et al. 2010). Likewise, at ages 13 – 19 years and 20 – 29 years childhood stressors respectively predicted 31% and 25% of mood disorders and 29% and 31% of anxiety disorders (Green et

al. 2010). Another large retrospective study showed that exposure to CSA accounted for approximately 13% of adult psychopathology, including substance dependence, but, once controlled for family factors, childhood physical abuse had only weak effects (Fergusson et al. 2008).

## Mediating Factors

After exposure to early life stress, women, African Americans and Hispanics have been shown to be more resilient to developing psychopathology than men and White, non-Hispanic individuals (DuMont et al. 2007; Schilling et al. 2007). Good parenting and parental monitoring decreases risk of psychopathology (DuMont et al. 2007, Lansford et al. 2006). Other factors that increase resilience include good peer relationships (Fergusson et al. 1999), no parental ASPD or substance dependence (Jaffee et al. 2007) and low family and neighborhood stress (Jaffee et al. 2007). Adolescent drinking (Dick et al. 2007) and cannabis use (Hyman and Sinha 2009) is strongly influenced by peer characteristics A longitudinal New Zealand study of 1000 individuals from birth to age 25 years reported that risk factors for adult illicit drug use and abuse/dependence included exposure to childhood abuse, parental illicit drug use, male sex, substance using peers, adolescent cannabis and alcohol use, novelty seeking and childhood conduct disorders (Fergusson et al. 2008), thereby confirming the results derived from retrospective studies. The strongest factor to reduce risk for the development of alcohol and drug dependence is a lack of access to alcohol and drugs, as is the case in certain religious communities. Another important risk-reduction factor is the inability to tolerate the aversive effects of alcohol, specifically the ‘flushing response’, as is the case in 50% of South East Asians who have genetic variants that result in absent or inefficient alcohol metabolizing enzymes (Edenberg 2007).

## Gene-Environment Interactions

The genetic risk for complex behavioral disorders such as alcohol and drug dependence is likely to derive from numerous genes, each with small to moderate effects. It is becoming increasingly apparent that variation in some genes, particularly stress-related genes, may only be a risk for psychopathology in individuals who have been exposed to early life stress. In contrast, stress-exposed individuals who lack the risk genetic variants may be resilient. Therefore interactions between genes and environment stressors (G x E) are likely to influence the risk – resilience balance for pathological behavior (Heath and Nelson 2002; Moffitt et al. 2005). For example, a study of over 1000 British twin pairs aged 5 years and their families found that the effect of physical maltreatment increased the risk for conduct problems by 24% in children at high genetic risk but by only 2% in children at low genetic risk (Jaffee et al. 2005). The Minnesota Twin Family Study also identified a G x E interactive effect on externalizing behaviors (ASPD and substance use) at age 17 years such that greater severity of adolescent stressors was associated with increased genetic risk for externalizing disorders (Hicks et al. 2009).

G x E interactions are most likely with stress-related genes, particularly those genes with a glucocorticoid response element (GRE) located within the promoter. After the publication of two key papers based on the previously mentioned longitudinal New Zealand cohort study that showed G x E effects of childhood maltreatment and the monoamine oxidase A gene (*MAOA*) on adult antisocial behavior in men (Caspi et al. 2002) and G x E effects of cumulative adult SLE and the serotonin transporter gene (*SLC6A4*) on depression (Caspi et al. 2003), numerous papers have been published showing interactive effects between stress genes and childhood maltreatment on depression, PTSD and suicidal behavior (for example: Binder et al. 2008, 2010; Bradley et al. 2008; Caspi et al. 2010 (review); Heim et al. 2009;Ressler et al. 2009; Roy et al. 2010; Polanczyk et al. 2009). A discussion of these and related papers is beyond the scope of this review. A few studies, discussed below, have

reported interactive effects between stress-related genes and childhood maltreatment or childhood and adult SLE on alcohol consumption and alcohol and drug dependence.

**CRHR1 and CRH—**The Mannheim Study of Children at Risk showed that there was an interaction between *CRHR1* SNP variation and adolescent SLE that predicted an earlier age of onset of drinking and heavy alcohol consumption (Blomeyer et al. 2008; Schmid et al. 2009). Similarly, a study of over 1000 Australian adults found that an interaction between CSA and a chr 17q21.31 haplotype that includes *CRHR1* predicted lifetime alcohol consumption (Nelson et al. 2010). Supporting evidence comes from a study in rats which showed that *CRHR1* genotype and expression interact with environmental stress to reinstate alcohol-seeking behavior (Hansson et al. 2006). Finally, a functional *CRH* promoter variant in rhesus macaque monkeys conferred increased stress reactivity and was associated with increased alcohol consumption in stress exposed (peer reared) animals (Barr et al. 2009).

**5-HTTLPR—**The 5-HT transporter regulates synaptic 5-HT availability and is sensitive to stress since the encoding *SLC6A4* gene has a GRE in the promoter region. It has been postulated that *SLC6A4* variation may to some extent, through influence on early life development of corticolimbic circuitry, modulate the capacity to cope with stress (Hariri and Holmes 2006). 5-HTTLPR is a common, functional variable number of tandem repeats in the *SLC6A4* promoter region. The variant low activity short ‘S’ allele is associated with an attenuated response to dexamethasone (Glatz et al. 2003), greater amygdala activity in response to fearful stimuli (Hariri et al. 2005) and impaired feedback circuitry for the extinction of negative affect (Pezawas et al. 2005). Thus the S allele is associated with a greater vulnerability to negative emotions when stressed. The S allele has been shown to predict early alcohol use in maltreated children entering out-of-home care (Kaufman et al. 2007) and the use of illicit drugs in adolescents who had experienced poor maternal care (Gerra et al. 2010). The S allele was associated with increased drinking and drug use in college students who had experienced multiple SLE (Covault et al. 2007). In contrast, results from the Mannheim Study of Children at Risk showed that in male participants only there was an interaction between either childhood adversity or early adulthood negative life events and the LL genotype that predicted hazardous drinking (Laucht et al. 2009). Other studies have also detected sex specific effects for 5-HTTLPR and adult SLEs (Armeli et al. 2008; Wust et al. 2009). Sex specific effects have also been detected in rhesus macaque monkeys: S allele carrier peer reared females consume more alcohol and progressively increase the levels of consumption over time compared with non S carriers (Barr et al. 2004).

**MAOA—**MAOA is a key enzyme for the degradation of 5-HT, DA and norepinephrine. Glucocorticoids enhance *MAOA* gene expression in human cells (Ou et al. 2006). Longitudinal G x E studieshave shown that childhood maltreatment (Caspi et al. 2002; Kim-Cohen et al. 2006; Widom and Brzustowicz 2006) and family adversity (Foley et al. 2004) interact with the MAOA-LPR low activity variant to predict childhood conduct disorder and adult antisocial behavior. In the ALSPAC longitudinal study, the low activity MAOA-LPR variant was associated with increased hyperactivity at age 7 years in children exposed to multiple SLE in the first 3 years of life (Enoch et al. 2010a). These longitudinal studies reflect possible indirect G x E interactive effects on alcohol and drug dependence since childhood hyperactive behavior and conduct disorders predict problem drinking and AD in later life (Caspi et al. 1996; Niemela et al. 2006). There is one retrospective study that shows a G x E effect on AD: in women from a Southwestern American Indian tribe, the MAOA-LPR low activity allele was associated with AD, particularly antisocial alcoholism, but only among women exposed to CSA (Ducci et al. 2008). Other retrospective studies have had mixed G x E results for antisocial behavior (Haberstick et al. 2005; Prichard et al. 2008; Prom-Wormley et al. 2009; Sjoberg et al. 2007; Young et al. 2006).

**GABRA2—**The *GABRA2* gene has been implicated in addiction (reviewed in (Enoch 2008). As discussed above, early life stress has been shown to alter *GABRA2* expression in adult rodents (Hsu et al. 2003). Therefore it is likely that an interaction between early life stress and *GABRA2* variation might influence alcohol and drug dependence. In a study of substance-dependent African American men, one commom *GABRA2* haplotype that tags African ancestry appeared to confer resilience to addiction, and one unlinked potentially functional SNP rs11503014 increased the risk of addiction (particularly to cocaine) but only in association with severe childhood maltreatment (Enoch et al. 2010b). A moderating effect of parental monitoring on the association of *GABRA2* with externalizing trajectories has been demonstrated in a longitudinal study of a community based sample monitored from ages 11 to 22 years (Dick et al. 2009).

## Conclusion

Exposure to early life stress, even to more severe forms such as physical and sexual abuse and emotional neglect, is common in the general population. The degree of risk for adult psychopathology tends to be correlated with the severity of childhood maltreatment and the number of childhood SLE. An important causal pathway that links early life stress to the onset of psychiatric disorders is the altered homeostasis in the HPA axis and the altered stress response circuitry that underlies many disorders including anxiety, depression, PTSD and addiction. There appears to be a direct pathway from chronic stress exposure in pre-pubertal children via adolescent problem drinking to alcohol and drug dependence in early adulthood that is independent of family history. Of course this can only occur in individuals exposed to the availability of alcohol or drugs. Early life stress may increase vulnerability to addiction through permanent effects on the expression of genes within the mesolimbic dopamine reward pathway. Early onset of problem drinking in stress-exposed children may exacerbate the deleterious effects on the developing brain. Since a large proportion of stress-exposed children do not go on to develop addiction, clearly resilience factors, including gene-environment interactions, are important. This review of the literature indicates that prevention should focus on early intervention in problem families to forestall maltreatment. Adolescence is a critically vulnerable time for the development of risky drinking habits and this is an area where prevention, through the development of positive family, peer and neighborhood mediating factors, is vital. A holistic approach to the treatment of alcohol and drug dependence is essential since treatment is unlikely to be effective unless underlying impediments such as early life stress are recognized and addressed.

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