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Neurobiological mechanisms of early life adversity, blunted stress reactivity and risk for addiction

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Abstract

Blunted stress reactivity resulting from early exposure to stress during childhood and adolescence may increase vulnerability to addiction. Early life adversity (ELA) affects brain structure and function and results in blunted stress axis reactivity. In this review, we focus on the underlying neurobiological mechanisms associated with a blunted response to stress, ELA, and risk for addictive disorders. ELA and blunted reactivity are accompanied by unstable mood regulation, impulsive behaviors, and reduced cognitive function. Neuroimaging studies reveal cortical and subcortical changes in persons exposed to ELA and those who have a genetic disposition for addiction. We propose a model in which blunted stress reactivity may be a marker of risk for addiction through an altered motivational and behavioral reactivity to stress that contribute to disinhibited behavioral reactivity and impulsivity leading in turn to increased vulnerability for substance use. Evidence supporting this hypothesis in the context of substance use initiation, maintenance, and risk for relapse is presented. The effects of ELA on persons at risk for addiction may lead to early experimentation with drugs of abuse. Early adoption of drug intake may alter neuroregulation in such vulnerable persons leading to a permanent dysregulation of motivational responses consistent with dependence.

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Keywords

Stress reactivity; Early life adversity; Addiction risk; Neurobiological mechanisms; HPA axis

1. Introduction

Exposure to adverse circumstances during childhood and adolescence may lead to poor health outcomes in adulthood. In the behavioral realm, ELA is associated with future maladaptive behaviors including abuse of alcohol and other substances (SUD), compulsive

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gambling, and risk-taking behaviors (Carroll et al., 2017; Duffy et al., 2018; Ellis et al., 2020; Schilling et al., 2007; Sinha 2008). In this review, we focus on the underlying neurobiological mechanisms associated with a blunted response to stress, early life adversity (ELA), and risk for addictive disorders. ELA broadly denotes exposure early stressors including low socioeconomic status, physical and sexual abuse, significant family disruption, and lack of nurturing (Lovallo et al., 2012). The pathways leading from ELA to poor health behaviors and addiction are not well understood, although dysregulation of the stress axis appears to have a central role. In addition, there is evidence indicating that ELA exerts its impact on behavioral and mental health by triggering changes in the developing brain (Acheson et al., 2014b; Lim et al., 2020; Meaney et al., 2002; Miguel et al., 2019; Tomalski and Johnson 2010). Evidence points to diminished communication between the prefrontal cortex and brain reward centers along with the hypothalamus and brainstem leading to modification of stress reactivity, behavioral control, and regulation of affect. These modifications collectively appear to increase the likelihood of behavioral risk-taking resulting in increased risk for substance use disorders (SUD). We note that not all persons exposed to ELA have adverse outcomes and some that manifest protective characteristics including adaptive coping and problem-solving skills as noted in recent papers (Ellis et al., 2020; Hoffmeister et al., 2019; Malhi et al., 2019; Romeo 2015; Rutter 2013).

Substantial evidence has emerged supporting ELA as a precursor to blunted stress reactivity (Carroll et al., 2017). Evidence is also emerging that specific genetic polymorphisms may confer vulnerabilities to ELA that confer enhanced risk of SUD. Behavioral and mechanistic evidence indicates that ELA can permanently modify neurobiological processes including communication pathways to and from the hypothalamus and brainstem resulting in abnormal regulation of the stress axis (Kataoka et al., 2020). Observational studies show that blunted stress reactivity resulting from ELA is associated with a tendency toward high-risk behaviors including drug use. Other evidence suggests that ELA, blunted stress reactivity, and poor emotional and behavioral regulation involve impaired prefrontal communication with reward centers in ways that may increase the reward value of abused drugs (Koob and Le Moal 2008; Koob and Schulkin 2019). At present the nature of the above relationships are understood at a correlational level but the precise mechanisms are not fully developed. We review the current state of work, point to areas in need of attention, and provide a heuristic model to aid in our focus on these questions as described in Fig. 1.

2. Stress response and regulation

Activation of the stress axis by physical and psychological challenges is represented by rapid increases of catecholamines, driven by sympathetic nervous system activity, and of cortisol and beta-endorphin, controlled by the hypothalamic-pituitary-adrenocortical axis (HPA) (Akil et al., 1984; al'Absi et al., 2006a,b; al'Absi et al., 2004). Although cortisol and beta-endorphin release are key signals of HPA response to threats to homeostasis, it is often overlooked that both substances also regulate the stress axis by preventing excessive activation of the central nervous system and peripheral systems (de Kloet et al., 2005). By extension, blunted stress axis reactivity to stressor exposure can impair the ability of the system as a whole to regulate the impact of those same challenges.

Dysregulation of the stress axis is likely to represent long term modification of structures including the nucleus accumbens, amygdala and hippocampus along with their connections to key brainstem structures including the locus coeruleus, raphe nuclei, and ventral tegmental nuclei, all of which receive opioid neuronal projections leading to the stimulation of dopaminergic neurons, inhibition of CRF activity neurons within the PVN and adrenergic neurons within the locus coeruleus (Bruijnzeel 2009; Drolet et al., 2001; Zhou et al., 2008). The interaction of these systems represents a nexus that could help us understand the role of stress and reward regulation in risk for substance use (Chong et al., 2006; Oswald and Wand 2004; Wand et al., 2002; Wand and Schumann 1998). In particular, emerging research is providing insights into the means by which ELA leads to risk-related behavioral tendencies (Gianoulakis 1996, 2004). In light of the complex network involving the endogenous opioid system, we have explored the role of the opioid system in understanding the blunted stress response in tobacco addiction (al'Absi and Bongard, 2006; al'Absi et al., 2004; al'Absi et al., 2008; Ceballos et al., 2007; France et al., 2005a; b; France et al., 2007; Shaw and al'Absi 2010) using the opioid blocker, naltrexone.

We observed a consistent reduction of HPA response to opioid blockade during stress in abstinent smokers, suggesting reduced opioid tone during tobacco withdrawal as evidenced by HPA stress response (al'Absi et al., 2020). This seems to be reversed by acute use of tobacco suggesting that nicotine may produce its reinforcing effects in part by its effects in the opioid-HPA stress response regulation.

3. Early life adversity and vulnerability to addiction

Several lines of evidence point to relationships among blunted stress reactivity, ELA, and proneness to addiction. Population studies and national surveys in the USA have shown that exposure to two or more adverse experiences during childhood significantly increases risk for alcohol and drug abuse (Pilowsky et al., 2009) across ethnic and racial groups (Ducci et al., 2009; Koss et al., 2003; Robin et al., 1997). Children exposed to ELA begin use of alcohol and drugs at an earlier age than persons not exposed to ELA (Anda et al., 1999; Dube et al., 2003; Hyman et al., 2006; Hyman and Sinha 2009), and early-onset alcohol and drug use is associated with increased risk for abuse and dependence in adulthood (Agorastos et al. 2018, 2019; Englund et al., 2008; Kessler et al., 2005).

In earlier work, we observed blunted cortisol reactivity to laboratory stressors in a group of male veterans hospitalized for alcoholism (Errico et al., 1993). In a later study, we showed that blunted reactivity was not due to disruption of basal cortisol secretion, suggesting that the HPAC was functionally intact in alcoholic patients, instead suggesting alterations in brain systems mediating responses to the environment including the mesolimbic system (Lovallo et al., 2000). Since the stressors we employed were largely psychological in nature, we surmised that the source of the observed blunted reactivity was likely to be due to diminished communication from the prefrontal cortex to brain regions associated with response to reward and punishment and activation of the stress axis.

We next examined a large group of healthy young adults with a family history of alcoholism (FH+) who were social drinkers and found that they too had blunted cortisol and heart

rate responses to psychosocial stressors (Lovallo et al., 2019b). We then found that the largest contributor to blunted reactivity was the degree of prior exposure to ELA (Lovallo et al., 2012). Not surprisingly, FH + persons are more often exposed to ELA than their FH– counterparts (Vincent et al., 2017), and FH + show a greater degree of blunted reactivity following ELA exposure than do FH– (Lovallo et al., 2019b). Research has shown that blunted stress reactivity predicts risk for SUD and proneness to relapse following withdrawal and treatment (al'Absi et al., 2003; Gilbert et al., 1997; Kirschbaum et al., 1994; Kirschbaum et al., 1993a; b; Tsuda et al., 1996). For example, our laboratory has examined stress reactivity during initial phases of a smoking cessation attempt and examined the extent to which these changes predicted risk for relapse Results indicate that blunted HPA (cortisol and ACTH) as well as beta endorphin, prolactin, and blood pressure responses during withdrawal predict shorter time to relapse (al'Absi et al., 2005).

4. Mechanisms of the blunted stress response

Several mechanisms may contribute to the dysregulated stress response, including changes in both central brain processes and peripheral feedback loops that may have resulted from developmental alterations and chronic dysregulation of these systems (al'Absi, 2018; Eddie et al., 2020). These modifications are likely to result is altered motivational and behavioral reactivity to external stimuli.

4.1. Alteration in HPA regulation and signaling

The greater sensitivity to ELA seen in FH + persons may reflect some combination of their increased exposure as well as a genetic diathesis reflecting their family history (Lovallo et al., 2019b). Although gene-by-environment interactions remain to be explored in depth, several findings in the Family Health Patterns Project point to genetic vulnerabilities in relation to FH + status, ELA exposure, and phenotypic tendencies reflecting risk for alcoholism, including early adoption of drinking prior to age 15.

Gene alleles associated with cortisol trafficking in the brain may be associated with poor working memory and blunted HR reactivity in relation to a history of ELA (Lovallo et al. 2016, 2019a). FKBP5 is a molecular cochaperone that contributes to the functional status of the glucocorticoid receptor (GR) and to the quality of corticosteroid signaling that is modified in the G-to-A single nucleotide polymorphism (SNP), rs9296158. Compared with FKBP5, GG homozygotes (N = 118), A-allele carriers (N = 132) without psychiatric morbidity had progressively worse performance on the Stroop color-word task with histories of increasing levels of ELA exposure (Genotype × ELA, $F = 5.14$, $P = 0.007$), indicating a G × E interaction on working memory in early adulthood. In addition, heart rate response to mental stress was diminished in AA/AG-allele carriers ($F = 5.15$, $P = 0.024$) having greater ELA exposure. Given the greater impact of stress levels of cortisol on GR receptor function in carriers of the A allele, ELA may affect the prefrontal cortex and, by extension, its interactions with external stimuli and subsequent impact on the limbic system and stress axis during development in A-allele carriers in agreement with work by others (Buchmann et al., 2014; Lapp et al., 2019; VanZomeren-Dohm et al., 2015).

Another avenue of vulnerability to ELA appears in studies of polymorphisms in the gene for catechol-O-methyltransferase (COMT) and altered dopaminergic signaling in the prefrontal cortex (Abraham et al., 2020). We have shown that differences in prefrontal DA availability known to occur in met vs. val/val carriers of the COMT val158met polymorphism (rs4680) are differentially reactive in HPA stress reactivity and differentially vulnerable to ELA, and in addition met-carriers are prone to early alcohol intake and smoking, showing that the met polymorphism not only renders individuals sensitive to ELA but that this sensitivity translates into a significant effect on health behaviors (Lovallo et al., 2019c). Neuroimaging of brain response to reward feedback shows greater effects in met-allele carriers exposed to ELA, also suggesting differential sensitivity to ELA in met carriers (Boecker-Schlier et al., 2016). As noted by Goldman, "The higher activity Val158 allele is predicted to reduce dopamine levels in the frontal cortex because levels of the dopamine transporter are low in this region. Consistent with the role of dopamine in the tuning of frontal cortical function, the Val158 allele and Val158 haplotypes have replicably been linked to frontal lobe function" (Goldman et al., 2005). Some work implies a greater increase in frontal DA availability in val homozygotes against their presumed lower baseline (Serrano et al., 2019). Met carriers show a gene-dose effect greater response to unpleasant stimuli in the limbic system (left hippocampus, right amygdala, right thalamus), connected prefrontal areas (bilateral ventrolateral prefrontal cortex, right dorsolateral prefrontal cortex), and the visuospatial attention system (bilateral fusiform gyrus, left inferior parietal lobule) relative to val homozygotes (Smolka et al., 2005). A review of rodent literature shows an impact of ELA on DA availability in the striatal region (Bonapersona et al., 2018). Our work and others agree that one or two copies of the COMT met allele render individuals more sensitive to ELA than their val/val counterparts (Abraham et al., 2020; Boecker-Schlier et al., 2016). These studies point to a gene × environment interaction between the COMT val158met allele and ELA resulting in altered responses to motivational cues that may enhance risk for SUD. The COMT polymorphism seems to warrant more extensive investigation of the impact of ELA on the stress axis and in relation to health behaviors in both animal models and clinical populations (Lonsdorf et al., 2011).

4.2. Network disruption cortical-subcortical integration

4.2.1. Structural evidence—Human neuroimaging studies demonstrate that ELA and blunted stress reactivity may relate to altered structure of the cerebral cortex (Busso et al. 2017a, 2017b). To our knowledge, there have only been two studies examining the associations between cardiovascular stress reactivity and grey matter volume (Gianaros et al., 2008; Trotman et al., 2019). The studies suggest, in healthy populations, higher levels of cardiovascular stress reactivity are associated with lower amygdala and hippocampal volume (Gianaros et al., 2008; Trotman et al., 2019). A more extensive line of research has specifically focused on the influence of ELA and brain structure. Research suggests ELA is associated with alternations in corticolimbic brain structures that have also been associated with neuroendocrine and autonomic control such as the anterior cingulate cortex, prefrontal cortex, amygdala, hippocampus (Beissner et al., 2013; Bremner et al., 1997; Gianaros and Wager 2015; Ginty et al., 2017; Gorka et al., 2014; McLaughlin et al., 2019; Myers 2017; Teicher et al., 2016; Thayer et al., 2012). Both animal and human studies demonstrate that ELA alters the normal course of brain development, particularly for

corticolimbic brain structures (Card et al., 2005; Davidson and McEwen 2012; Harden et al., 2016; Malter Cohen et al., 2013; Pechtel and Pizzagalli 2011; Shonkoff 2010; Teicher et al., 2016; Tottenham and Sheridan 2009) and alternations in cortical structures in adulthood (Cassiers et al., 2018; Jensen et al., 2015; Paquola et al., 2016; van Harmelen et al., 2010). In a study comparing individuals with a history of childhood maltreatment to those with no history, maltreatment was associated with decreased structural connectivity from the anterior cingulate with other areas in a network of regions important in emotional regulation, attention, and social cognition (Teicher et al., 2014).

Diffusion tensor imaging (DTI) studies have also shown reduced fractional anisotropy in individuals with a history of ELA (Choi et al., 2009; Lim et al., 2020; Teicher et al., 2010; Tendolkar et al., 2018). In a study examining individuals exposed to ELA, participants who developed post-traumatic stress disorder symptoms had decreased FA compared to those who did not develop symptoms (Fani et al., 2012), suggesting white matter integrity may be an important risk marker for psychopathology. DTI measures also show impaired integrity of myelinated fiber pathways in the PFC (anterior corona radiata) in relation to impulsive tendencies (Peper et al., 2013) and in studies of FH + subjects from two of our data sets (Acheson et al., 2014b). In FH + persons with no psychiatric history, the degree of myelinated fiber functional impairment was associated independently with FH + history in these studies, one on children 11–14 years of age and the other in young adults averaging 23.5 years of age, with each sample being significantly correlated with the number of alcoholic first-degree relatives (rs = 0.4) (Acheson et al. 2014a, 2014b). Although the foregoing studies did not have sufficient statistical power to examine ELA in the FH + population, a recent meta-analysis of ELA exposure showed widespread white matter microstructural abnormalities in the fornix, corpus callosum, and optic radiations linking fronto-limbic connections to areas presumably involved in conveying and processing aversive experiences (Lim et al., 2020). White matter abnormalities suggest a source of further work examining a direct impact of ELA on brain development and a source of interaction between ELA exposure on vulnerable genotypes affecting development of glial cells responsible for myelinated pathways. We suspect that further work on larger subject samples will allow an examination of white matter structural abnormalities and behavioral and emotional dysregulation contributing to SUD risk. There is also a role for sex-related hormones with changes in cortical-subcortical communication. For example, high levels of testosterone are associated with reduced cortico-subcortical communication (Peper et al., 2011). For example, high testosterone levels over time may attenuate white matter tracts between frontal and striatal regions, which may have chronic effects on reward and threat processing (e.g. increased impulsivity) (Peper et al., 2013).

4.2.2. Resting state functional evidence—Studies of ELA and resting state functional connectivity compliment studies of white matter abnormalities. Both sets of studies suggest that ELA alters connectivity in areas associated with stress circuitry. ELA is associated with reduced functional connectivity between the prefrontal cortex and limbic regions, including the amygdala, in humans (Birn et al., 2014; Grant et al., 2014; Herringa et al., 2013; Kraynak et al., 2019) and animals (Guadagno et al., 2018; Yan et al., 2017).

4.3. Blunted reactivity and cortico-limbic function

Reviews and meta-analyses have confirmed cortical and limbic areas associated with visceral control (anterior cingulate cortex, medial prefrontal cortex, hippocampus, insula, and amygdala) are core components of a network of forebrain systems involved in stressor-evoked cardiovascular reactivity (Gianaros and Wager 2015; Ginty et al., 2017; Myers 2017; Shoemaker and Goswami 2015; Thayer et al., 2012) and addiction reward circuitry (Eddie et al., 2020). Three studies in healthy young adults demonstrate lower cardiovascular reactivity in relation to reduced activation in these same brain regions. Lower blood pressure reactivity was associated with reduced stressor-evoked amygdala activation (Gianaros et al., 2008) and anterior cingulate cortex activation (Gianaros et al., 2005) in these samples. In a study comparing individuals with blunted and exaggerated cardiovascular reactivity, we demonstrated that blunted reactivity was associated with reduced stressor-evoked activation in the anterior mid-cingulate cortex and insula and greater deactivation in the amygdala and posterior cingulate (Ginty et al., 2013).

In the context of psychological stressors, it is proposed that cortical and subcortical circuits associated with autonomic and neuroendocrine function generate anticipatory visceromotor commands to engender the cardiovascular and neuroendocrine system, via subcortical and brainstem cell groups, to prepare individuals to cope with the stressors (Gianaros and Wager 2015; Ginty et al., 2017). Individual differences in these forebrain appraisals may explain individual differences in cardiovascular and neuroendocrine stress responses. Failure to mount a stressor-evoked cardiovascular or neuroendocrine response may be caused by a 'visceral prediction error' or a mis-calibration between anticipatory commands and actual behavioral needs to cope with the stressor (Gianaros and Wager 2015; Ginty et al., 2017). Previous work has proposed a cardiovascular response to acute psychological stress is a marker of active coping (Obrist et al., 1978). It is possible that blunted cardiovascular responses to acute psychological stress are a result of forebrain appraisals predicting that less support is needed than is actually needed to cope with the stressor. Indeed, as mentioned earlier in this review, blunted reactivity has been associated with disorders associated with reduced motivation (Ginty et al., 2020).

While there is a substantial body of literature examining the impact of ELA on functional activation during emotion processing, inhibitory control, and reward processing tasks (for review see (Kraaijenvanger et al., 2020), there is scant research examining whether ELA is related to alternations in stressor-evoked activity within the brain regions shown to regulate cardiovascular and cortisol responses to stress. A study of 155 healthy adults demonstrated that childhood physical abuse was associated with reduced stressor-evoked activity in the subgenual anterior cingulate cortex, bed nucleus of stria terminalis, amygdala, and paraventricular nucleus of the hypothalamus (Banihashemi et al., 2015). Foster/adopted children with ELA had significantly less activation in the dorsal anterior cingulate cortex and dorsolateral prefrontal cortex compared with matched controls during a social stressor (Puetz et al., 2014). These two studies provide evidence that ELA is associated with altered stressor-evoked neural activity in areas associated with cardiovascular and neuroendocrine control. Given that ELA is associated with reduced cardiovascular and neuroendocrine activity and alterations in stressor-evoked neural activity, it is possible that ELA alters

the impact of forebrain appraisals of stress or threatening stimuli and results in 'visceral prediction errors' which result in reduced cardiovascular and neuroendocrine activity needed to behaviorally cope with the stressor. In the context of early life adversity, such alterations may be an adaptive "survival" response to external conditions that are out of the individual's control and cannot be escaped. However, these hypotheses have yet to be tested.

4.4. Genetic diathesis

The above studies implicating ELA, blunted stress reactivity, addiction risk, and addiction raise questions about genetic polymorphisms that may point to increased risk for addiction (Mueller et al., 2012). A number of such studies point toward genotypes possibly affecting neurochemical systems and brain regions associated with reward processes and behavioral regulation more generally (Blum et al., 2000; Coplan et al., 2011; Mueller et al., 2012; Ouellet-Morin et al., 2008). We have examined potential clustering of genetic polymorphisms in FH + young adults in relation to phenotypes associated with heightened risk for SUD. We found an association between ELA and neuroticism, harm avoidance, and symptoms of depression in persons carrying the gain-of-function polymorphism of the serotonin transporter gene SCL6A4 (Lovallo et al., 2014) consistent with other work showing enhanced startle reactivity in carriers of the short allele of the serotonin transporter gene (Armbruster et al., 2009). Other analyses showed impaired working memory and blunted heart rate stress reactivity in persons carrying the rs9296158 polymorphism of the gene for the molecular cochaperone, FKBP5, an allele that impairs glucocorticoid signaling in the central nervous system (Lovallo et al., 2016). Persons exposed to ELA who carry the high-activity polymorphism of the gene for COMT (rs4680, val158met) display blunted stress reactivity and begin drinking at an earlier age and experimenting with more drugs during adolescence (Lovallo et al. 2017, 2019c). Collectively, these studies suggest the value of examining these and related genotypes for main effects and interactions with FH status, ELA exposure, blunted stress reactivity and addictions (Lovallo et al., 2019c).

4.5. Sex differences in the stress response and risk for addiction

Research has demonstrated significant sex differences in different systems involved in regulating the stress response including the sympathetic system and HPA axis (al'Absi et al., 1999; al'Absi et al., 2004; Kirschbaum et al., 1995; RC et al., 2014). Sex steroids, such as estradiol, may mediate these differences (Allen and Matthews 1997; Kirschbaum et al., 1999; Steptoe et al., 1996). For example, suggested by observations showing that cortisol response to stress was similar between men and women in the luteal phase of the menstrual cycle, while women in the follicular phase showed a blunted response relative to men (Kirschbaum et al., 1999). Research also indicated sex differences in the pattern and level of regulation on the HPA stress response exerted by the endogenous opioid regulation (al'Absi et al., 2004; Chong et al., 2007; Uhart et al., 2006). Findings in humans extend preclinical evidence indicating sex differences in the sensitivity, quantity, and ratio of the different classes of opioid receptors (Hammer 1985; Hammer et al., 1994; Sershen et al., 1998) and observation in humans showing higher μ-opioid binding in women compared to men (Zubieta et al., 2002).

Research examining the interaction between sex and early life adversity on stress responses has produced mixed results, however. One study suggests there is a significant association between exposure to violence and blunted cortisol reactivity in males, but no significant association in females (Peckins et al., 2012). While other studies have demonstrated that although men tend to have a higher cortisol response to stress than females overall, there are no sex by ELA interactions (Lovallo et al., 2012; Trickett et al., 2014). A recent study in smokers reported that higher levels of ELA were associated with blunted stress responses in females and heightened responses in males (Hood et al., 2020). The general lack of consensus could be due to a number of factors. First, many studies examining the impact of ELA on stress reactivity use female only samples (Heim et al., 2001; Klumpers et al., 2004; MacMillan et al., 2009; Mielock et al., 2017; Voellmin et al., 2015). Second, ELA differentially impacts males and females depending on the timing of the adverse exposure; with males being more vulnerable than females to adversity that occur early in life (Hodes and Epperson 2019). Future research should aim to use samples that include both males and females and that record timing of ELA.

5. Discussion and conceptual integration

The cascade of ELA, blunted stress reactivity, impairments of motivated behavior (a phrase that broadly encompasses poor regulation of affect, attraction for immediate rewards, antisocial behavior, and poor cognitive function) are all associated with elevated risk for addictive behaviors. These risk factors may also vary as a function of genetic predisposition, as indicated by recent studies demonstration gene × environment interaction in shaping responses to motivationally relevant stimuli as well as the stress response and early adoption of drinking (Lovallo et al. 2016, 2019a). While it is currently unknown how these reactivity and behavioral propensities interact, we present here a model where we propose that ELA through initial changes in the brain can influence the manner by which information is processed and learning is developed. This also influence evaluative and emotional elaboration of stress as well as decision making and risk for impulsivity. Previous research has shown that traits such as impulsivity, sensation seeking, and disinhibition can influence the manner by which individuals respond to acute challenges and also increase propensity to engage in high-risk behaviors, such as substance use (Scarpa, 2015; Ginty et al., 2013; Lovallo et al., 2012; Phillips et al., 2013; Phillips et al., 2011).

Level of risk may be exacerbated or mitigated by various environmental and biological conditions and circumstances (Fig. 1). One of the outcomes of these upstream changes associated with ELA is dysregulation of the stress response (Carpenter et al. 2007, 2011; Lovallo et al., 2019b; Voellmin et al., 2015). Related work indicates that ELA and blunted reactivity may place otherwise healthy young adults at risk for drug abuse or for increased risk to relapse following cessation. Multiple mechanisms may mediate these effects including poor regulation of motivated behavior.

In conditions of ongoing stress and long-term effects of ELA on reward and stress response circuitry, drug use may have a potent reinforcing effect caused by its role in modulating the stress response. These effects, acutely, may also be facilitated by modifications in brain structures involved in emotional regulation and stress response. Chronically, this

may then lead to long-term effects on brain's motivational systems leaded to increased risk for maintenance of substance use. Our discussion here is therefore geared towards understanding the role of the chronic effects of ELA in altering the stress response and therefore increasing the risk for addiction. Indeed, much work in the field of substance use disorders has focused on studies of patients in treatment and in brain changes in animal models exposed to alcohol or other substances. The perspective presented here shows that similar changes in brain function and response to motivational stimuli may occur in healthy individuals thereby contributing to drug exposure, maintenance, and relapse (Koob and Le Moal 2008; Koob and Schulkin 2019; Zorrilla et al., 2014).

Our model assumes that in the face of stress and risk for drug use a robust stress and well-regulated recovery can be considered markers of resilience and the individual's ability to buffer the impact of early stress (al'Absi, 2018). This argument takes note of cortisol's important role as a regulator of brain function in the immediate aftermath of acute stress episodes. Elements involved in the stress response, biologically or behaviorally, may constitute immediate and delayed defense against stress-related threats, and therefore dysregulated response may reflect structural and functional problems in how we cope with demands that can be manifested by, for example, a disruption in integrating informational, physiological, and behavioral processes. The disruption of this systems coordination provides the impetus for subsequent risk for mental and substance use problems. Indeed, other research has linked dysregulated stress response and ELA with increased risk for engagement in risky behaviors such as smoking, binge drinking, risky driving, engaging in early sexual activity, and early and unintended pregnancy (Anda et al., 1999; Anderson 2017; Bentley and Widom 2009; Bogaert 2008; Culpin et al., 2014; Dietz et al., 1999; Gaydosh et al., 2018; Graber et al., 1995; Haller et al., 2014; Shin et al., 2013).

One important consideration in understanding the role of ELA in altering the stress response and risk for addiction, is the timing of exposure to ELA, in addition to frequency and intensity. Indeed, research has demonstrated that different types of adversity are linked to specific psychological and behavioral consequences, and these in turn are mediated by specific rain mechanisms (Teicher and Khan 2019; Teicher and Parigger 2015). The type of adversity may also impact the trajectory of risk as well as severity (Teicher et al., 2016). Similarly age of exposure to adversity (i.e., timing) also determine the type of risk and severity of the consensus of this risk (Khan, McCormack, et al., 2015). The stress-response profile however has not been evaluated directly to examine the impact of these parameters and requires greater attention in the context of substance use disorders.

We note that our model focuses on the extant literature on adverse childhood experiences, such as physical and sexual abuse, but there remain other factors during early childhood that may impact risk and still need to be developed in the literature less attention has been paid to environmental factors including crowding, noise, and neighborhood safety. Indeed, recent work has proposed that active trauma (e.g., abuse) may have differential effects compared with trauma caused by environmental factors (e.g., SES; for reviews see: (Duffy et al., 2018; McLaughlin et al., 2014; McLaughlin et al., 2019). We have acknowledged this issue and added it as and topic for future research.

6. Future directions

An outgrowth of the discussion above is to identify resilience factors (see Fig. 1) that may buffer the impact of early life stress on vulnerability to addiction. Recent research provides encouraging data. Insight into the question of vulnerability and resilience comes from a limited number of analyses addressing the question of who avoids developing alcohol use disorders despite drinking relatively heavily. Resistance to addiction (Kendler and Myers 2015) was seen in persons with minimal exposure to ELA and who scored in the highly socialized range of CPI-So scores. Individuals who reported greater emotional stability, norm adherence, risk avoidance, and fewer family members with substance use disorders were more resistant to AUD despite higher alcohol intake (Hoffmeister et al., 2019). This analysis agreed in large measure with two analyses of larger groups of persons examined in an epidemiological study of risk for psychiatric disorders (Cooke et al., 2017; Dick et al., 2013).

Future research should also better define the amount of addiction vulnerability conferred by environmental factors during early life adversity, genetic risk factors, and the interaction of these two factors. To that end, although research over the last decade has advanced our understanding of clinical and neuronal markers of risk associated with the ELA, there is still much to be discovered about the specific trajectories of developmental risk across age and areas of the brain, both structurally and functionally, most influenced by this risk and predictive of addiction vulnerability. A host of phenotypes and endophenotypes have been linked to ELA and have also been shown to be related to drug use risk. Yet, the extent to which these markers mediate the influence of ELA on risk for addiction remains to be defined. In addition, these factors may also be influenced by early exposure to substance use, introducing another layer of complexity yet to be defined. Such efforts would provide a substantial growth in translating these rich data sets into the clinical context. Identification of early risk pathways provides a means of better understanding the progression toward changes in reward pathways that represent responses to consistent exposure to drugs of abuse (Koob and Schulkin 2019).

In light of the observation that blunted stress response is implicated in different stages of the addiction cycle, and research showing the link of dysregulated stress response with post-traumatic-stress disorder (PTSD), it is intriguing to propose that blunted stress response may be a nexus of risk for SUD-PTSD comorbidity, although no direct evidence available at this time. This may therefore be a fruitful line of research into understanding SUD-PTSD.

The literature to date points to additional directions focusing on the importance of developing targeted behavioral and psychosocial interventions and programs to mitigate the impact of exposure to high levels of early adversity. Such program may also increase bolstering components within existing intervention to specifically target factors mediating the impact of early life adversity on risk for substance use disorders or mental health comorbidity. For example, efforts to manage psychological reaction to emotional and environmental cues associated with history of adv cues associated with history of adversity should be investigated as potential preventive measures. To that end, we note the need for additional intervention to address intermediate risk pheno-types, such as blunted stress

reactivity, in the context of early life adversity. This may take integrated intervention approaches including pharmacological and psychological approaches targeting stress-related regulation processes.

7. Conclusions

Recent studies have shown an impact of ELA on blunted stress reactivity in conjunction with vulnerability to addiction. The mechanisms connecting life history, blunted reactivity, and consequences of drug exposure aid our understanding of pathways to dependence in vulnerable persons and resilience in others. Our review here highlights the role of dysregulated stress response and the impact of ELA on vulnerability to drug use. Changes in specific stress and reward-related pathways provide avenues through which ELA may lead to blunted stress response, and how this dysregulated response may translate into increased risk for drug use. The recognition of the role of stress in initiating, maintaining, and increasing risk for drug relapse is now well accepted. This work must therefore be complemented by effort to develop intervention strategies that seek to mitigate this ongoing and delayed cost stress.

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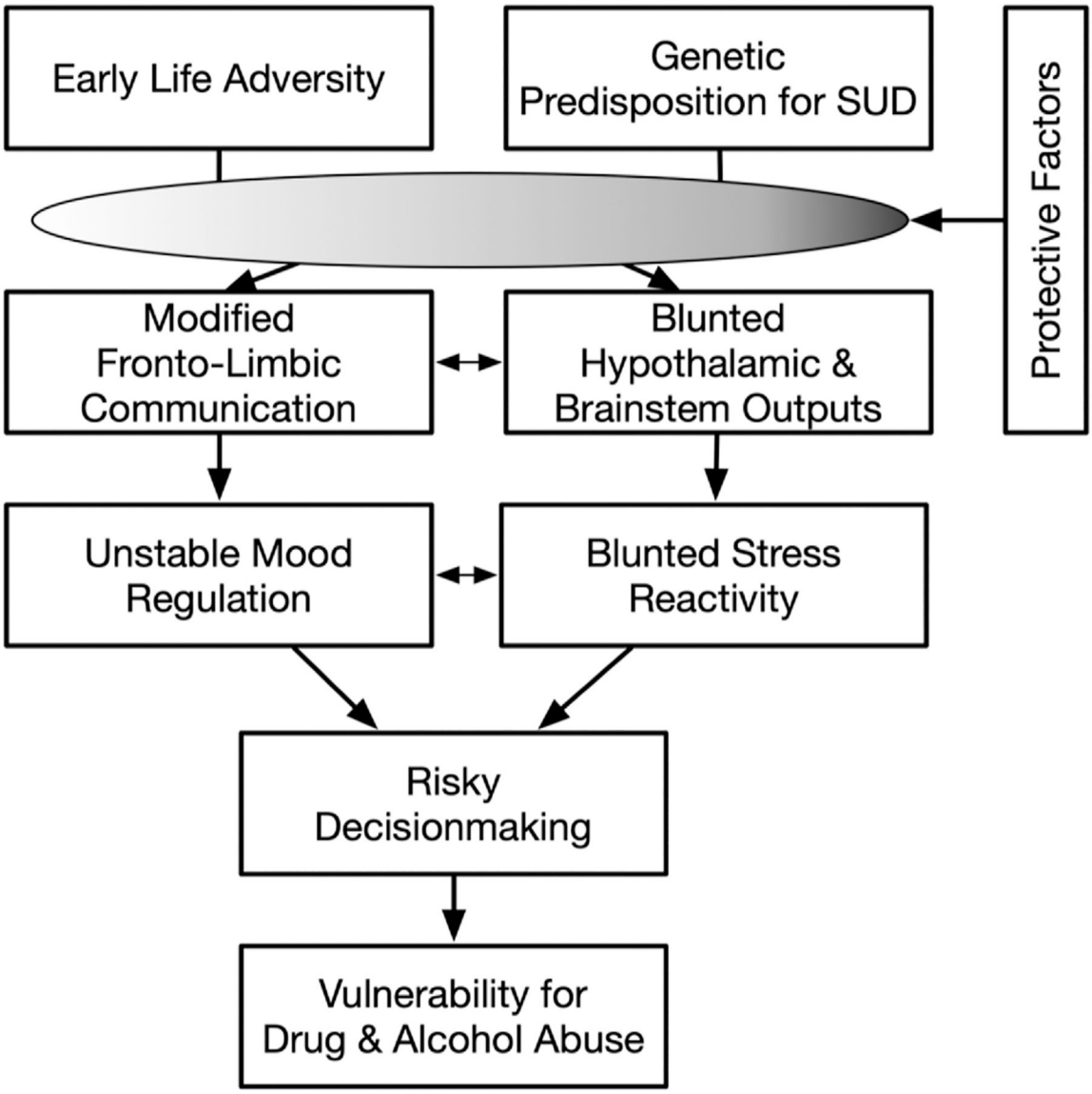

Fig. 1.

The influence of early life stress and genetic predisposition in modifying brain development and stress response systems leading to poor decision making and increased vulnerability for substance use. The gradient oval indicates that a range of protective factors may confer either low or high levels of protection to individuals, with the result that risk for substance use disorders is manifested to different degrees in downstream outputs.