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Early Life Stress and Substance Use Disorders: The Critical Role of Adolescent Substance Use

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Abstract

Early life stress (ELS) is a well-established risk factor for many psychiatric and medical disorders, including substance use disorders (SUDs). The relationship between ELS and SUDs is complex and there are likely multiple pathways from ELS to adverse substance use outcomes. The association between ELS and substance use emerges in adolescence. Adolescence is a critical period in development during which substance exposure markedly increases risk for SUDs. Therefore, this review focuses on the literature supporting the hypothesis that ELS increases risk for the development of SUDs through its influence on adolescent substance use. We discuss studies substantiating the role of ELS in adolescent substance use and explore how internalizing and externalizing psychopathology may be antecedents of substance use in adolescence. We examine clinical work suggesting ELS sculpts the Hypothalamic-Pituitary-Adrenal (HPA) Axis and developing brain—particularly subcortical brain regions that underlie stress response, mesocorticolimbic brain systems associated with reward sensitivity, and prefrontal regions that underlie executive control—in a way that increases risk for adolescent substance use and SUDs. We further explore how substance use during adolescence alters structure and function of these same systems, and how brain changes following ELS and adolescent substance use may independently, additively, or interactively contribute to risk for addiction. We conclude by discussing how the current literature can inform interventions aimed at reducing risk for SUDs in individuals with a history of ELS.

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1. Introduction

Early life stress (ELS)—defined as childhood maltreatment (sexual, physical, and emotional abuse and physical and emotional neglect) and household dysfunction—is highly prevalent. Fifty-three percent of adults have experienced ELS prior to the age of 18 (Green, McLaughlin et al. 2010). ELS is a major public health concern and increases risk for a wide range of psychiatric and medical illnesses (Nemeroff 2016, Lippard and Nemeroff 2020), including substance use disorders (SUDs) (Kirsch, Nemeroff et al. 2020). The landmark Adverse Childhood Experiences (ACE) study (N=17,337) found number of ACEs 'dose-dependently' related to greater risk for alcoholism and drug abuse. ACEs were associated with 65% of population attributable risk for alcoholism, 50% for drug abuse, and 78% for intravenous drug use (Dube, Felitti et al. 2003). Anda and colleagues (2006) also demonstrated a graded relationship between ELS and risk for alcohol use disorders; individuals having experienced four or more categories of ELS possessed a 7.2-fold increase in risk for developing an alcohol use disorder (Anda, Felitti et al. 2006). This relationship has since been replicated by a large number of retrospective cross-sectional studies (Enoch 2011). Prospective, longitudinal studies have also emerged, and have begun to establish the temporality of this association (Shin, Edwards et al. 2009, Skeer, McCormick et al. 2009, Kisely, Mills et al. 2020, Kisely, Strathearn et al. 2020). Decades of preclinical work also supports an association between ELS and SUDs, thereby strengthening inferences about the causality of this relationship (Higley, Hasert et al. 1991, Kosten, Miserendino et al. 2000, Huot, Thrivikraman et al. 2001, Kosten, Sanchez et al. 2004, Kosten, Zhang et al. 2006, Vazquez, Penit-Soria et al. 2006, Moffett, Vicentic et al. 2007).

ELS impacts each stage of the addiction cycle, from compulsive drug seeking and use, to loss of control over limiting intake, and to the emergence of negative emotional states (Kirsch, Nemeroff et al. 2020). ELS has been associated with an earlier onset of addiction and a more pernicious illness course marked by increased risk of relapse and poor treatment response. Patients with a SUD and a history of ELS remain abstinent for shorter periods of time (Greenfield, Kolodziej et al. 2002), relapse more often (Heffner, Blom et al. 2011, Van Dam, Rando et al. 2014), and are less adherent to treatment (Jaycox, Ebener et al. 2004), compared to patients with a SUD who do not have a history of ELS. The association between ELS and increased risk for SUDs is observed across a broad range of substances of abuse, including alcohol, cannabis, nicotine, opioids, and cocaine (Le Moal and Koob 2007, Sinha 2008, Pilowsky, Keyes et al. 2009, Enoch 2011, Garami, Valikhani et al. 2019). Despite this significant public health concern, the exact mechanisms by which ELS is translated into risk for SUDs is not entirely understood. A wealth of literature supports the hypothesis that ELS shapes neurobiological development in a way that increases risk for addiction (Andersen and Teicher 2009). Indeed, ELS-related neurobiological differences are strikingly similar to those observed in individuals with SUDs. The pathway from ELS to

SUDs, however, is complex and likely mediated and moderated by a plethora of internal and external factors.

The current review focuses on evidence supporting the hypothesis that ELS increases risk for the development of SUDs through its influence on adolescent substance use. The association between ELS and substance use emerges in early adolescence (Tonmyr, Thornton et al. 2010, Brajović, Bellis et al. 2019)—a vulnerable period during which exposure to substances of abuse is more likely to increase risk for SUDs (Orlando, Tucker et al. 2004, King and Chassin 2007). As a high proportion of individuals with ELS are exposed to substances of abuse during this vulnerable window, adolescent substance use may be a critical intermediate step in the pathway from ELS to SUDs. We discuss the literature substantiating the relationship between ELS and adolescent substance use and explore psychological and neurobiological pathways by which ELS may confer risk for adolescent substance use. We further examine how substance use during the adolescent period may uniquely increase risk for the development of SUDs. We conclude by discussing future areas of research and opportunities for intervention aimed at reducing risk for the development of SUDs following ELS through intervention during adolescence.

2. ELS and Adolescent Substance Use

2.1 Age of Substance Use Initiation

ELS is associated with a younger age of substance use and abuse initiation compared to what is observed in typical development (Andersen and Teicher 2009). Earlier age of first substance use is robustly associated with progression towards heavy substance use and increased risk for SUDs (Grant, Stinson et al. 2001, Englund, Egeland et al. 2008, Richmond-Rakerd, Slutske et al. 2017). For example, alcohol use before the age of 15 increases risk for alcohol use disorders by 40% (SAMHSA, 1999). Longitudinal research supports a causal role of early substance use initiation and subsequent development of SUDs (Irons, Iacono et al. 2015). Large scale studies have documented associations between ELS and early age of substance use initiation (Harrison, Fulkerson et al. 1997, Dube, Felitti et al. 2003, Ompad, Ikeda et al. 2005, Mills, Alati et al. 2014, Sartor, Grant et al. 2018), with these findings observed across sociocultural contexts (Ramos-Olazagasti, Bird et al. 2017). Bensley and colleagues (1999) found past physical and sexual abuse was associated with more than a 12-fold increase in the odds that regular drinking or marijuana use occurred by the age of 10 (Bensley, Spieker et al. 1999). Another study found childhood neglect was associated with early onset of smoking and alcohol use in a large (N=5158) prospective birth cohort (Mills, Alati et al. 2014). In a nationally representative sample of 3,592 young adults, Rothman and colleagues (2008) showed ACEs predict early onset drinking (initiation prior to the age of 15) (Rothman, Edwards et al. 2008). This association remained significant when controlling for parental and peer alcohol use and parental attitudes toward drinking. The study also found drinking initiation occurred after the age of 20 in young adults without a history of ACEs. There appears to be an inverse dose-response relationship between number of ACEs and age of substance use initiation. For example, Dube and colleagues (2006) found that for every ACE, the likelihood of having initiated alcohol and illicit drugs by the age of 14 increased 2- to 3-fold (Dube, Miller et al. 2006). Harsh parenting, parental

substance abuse, and poor parental verbal reasoning have also been prospectively linked with early substance use initiation (Kaplow, Curran et al. 2002, Dodge, Malone et al. 2009).

2.2 Heavy Use

ELS has also been associated with heavy adolescent substance use (i.e., binge drinking). Using data from the US National Longitudinal Study of Adolescent Health (n=12,478 adolescents), Shin and colleagues found that childhood maltreatment prior to the age of 11 increased risk for adolescent (ages 12-18 years) binge drinking (Shin, Edwards et al. 2009). In a separate study of 8503 adolescents from the National Longitudinal Study of Adolescent Health, Shin and colleagues (2013) also showed childhood neglect and physical abuse was associated with faster increases in heavy episodic drinking and persistently elevated heavy episodic drinking across adolescence and young adulthood (Shin, Miller et al. 2013). Hamburger and colleagues (2008) similarly observed a link between childhood sexual abuse and heavy episodic drinking in males (Hamburger, Leeb et al. 2008). Bensely and colleagues (1999) found childhood physical and sexual abuse was associated with an 8-fold increase in risk for heavy drinking in 8th grade (Bensley, Spieker et al. 1999). Studies have also examined the impact of ELS on cigarette smoking, marijuana use, and polysubstance use. Mills and colleagues' (2014) aforementioned prospective birth cohort study also found childhood neglect was associated with heavy smoking (and alcohol use) in adolescence (Mills, Alati et al. 2014). In a subset of youth (n=903) from the Longitudinal Studies of Child Abuse and Neglect, Yoon and colleagues (2020) found ELS predicts longitudinal trajectories of marijuana and alcohol use (Yoon, Shi et al. 2020). Specifically, emotional abuse during early childhood and physical abuse during adolescence was associated with marijuana and alcohol use trajectories with increasing use observed across ages 12, 16, and 18. Shin and colleagues (2010) found adolescent girls with a history of childhood sexual abuse were five times more likely to be heavy polysubstance users (including alcohol, cannabis, amphetamine, and hallucinogens) compared to those without a history of childhood sexual abuse (Shin, Hong et al. 2010).

2.3 Implications for SUDs

While adolescent substance use appears to increase risk for development of SUDs across the lifespan (DeWit, Adlaf et al. 2000, Englund, Egeland et al. 2008, Tonmyr, Thornton et al. 2010, Brajović, Bellis et al. 2019), it may be uniquely associated with early-onset SUDs. Early onset of SUDs is associated with a more severe illness course characterized by more severe dependence (Hingson et al., 2006), more severe and frequent withdrawal complications (Le Strat et al., 2008), and higher rates of co-occurring psychopathology, including psychotic and mood disorders (Subodh et al., 2019). ELS is associated with a faster transition from substance use to SUDs (Larance, Gisev et al. 2018) and is more prevalent in individuals with early-onset SUDs (before the age of 25), compared to individuals with late-onset SUDs (Dom, De Wilde et al. 2007). DuMont and colleagues (2007) found 56% of young adults who experienced court-documented cases of physical abuse or neglect or sexual abuse between ages 0 and 11 met criteria for alcohol or drug abuse or dependence by young adulthood (DuMont, Widom et al. 2007). In a large-scale (N=1421) longitudinal study, Skeer and colleagues (2009) showed individuals having experienced five or more adverse childhood experiences were seven- to ten-fold

more likely to exhibit illicit drug use problems and addiction in late adolescence and emerging adulthood (Skeer, McCormick et al. 2009). Overall, childhood maltreatment has been associated with up to an 8.3-fold increase in risk for youth alcohol and cannabis use disorders (Kilpatrick, Acierno et al. 2000, Scott, Smith et al. 2010, Copeland, Angold et al. 2012).

The studies discussed above indicate exposure to ELS shifts initiation of substance use to younger ages and increases heavy adolescent substance use. Adolescence is a critical period of development during which drug exposure is more likely to lead to dependence (Orlando, Tucker et al. 2004, King and Chassin 2007). Taken together, this work may suggest early and heavy adolescent substance use acts as an intermediate step between ELS and SUDs. While few studies have directly tested this pathway, Skinner and colleagues' (2012) longitudinal study followed 332 participants from childhood (18 months to 6 years old) to adulthood (31-41 years old) and found the influence of childhood sexual abuse on adult substance use problems was fully mediated by adolescent alcohol use and depression (Skinner, Hong et al. 2016). Widom and colleagues (2007) found women with documented cases of childhood physical abuse, sexual abuse, and/or neglect prior to age 11 were at greater risk for alcohol abuse or dependence in young adulthood (age 29), compared to non-maltreated women, and that alcohol abuse or dependence in young adulthood mediated the relation between childhood abuse and/or neglect with excessive drinking in middle adulthood (age 40) (Widom et al., 2007). Another prospective longitudinal study of 585 families showed a direct effect of physical abuse (before the age of 5) in females on substance use at age 12, with substance use at age 12 mediating the relationship between physical abuse and substance use at ages 16 and 24 (Lansford, Dodge et al. 2010). Additional longitudinal studies directly testing the mediating role for adolescent substance use on the link between ELS and SUDs are needed, as results could have serious implications for informing prevention and early intervention strategies aimed at delaying onset and quantity of substance use in maltreated youth.

3. Pathways from ELS to Adolescent Substance Use: Internalizing and Externalizing Psychopathology

The psychological antecedents of adolescent substance use in maltreated youth marks an area of research that has received considerable attention. Studies aiming to identify potential pathways from ELS to adolescent substance use and SUDs have focused on the mediating role of internalizing and externalizing symptoms. Indeed, ELS is a well-established risk factor for internalizing (i.e., major depression, bipolar disorder, and anxiety disorders) and externalizing (i.e., disruptive behavioral disorders and conduct problems) psychopathology, and for their comorbidity with SUDs in adolescence (Weinberg, Rahdert et al. 1998, Cicchetti and Rogosch 1999, Kessler, McLaughlin et al. 2010, Lippard and Nemeroff 2020). Rates of ELS are especially high in individuals with SUDs and comorbid internalizing/externalizing psychopathology. Wu and colleagues (2010) found that 95% of individuals with comorbid SUDs and mental health problems had experienced a traumatic event during childhood (Wu, Schairer et al. 2010). While findings are mixed—and there is more than one pathway to this comorbidity—prospective data has suggested psychopathology can precede

substance use and SUDs in adolescents (Costello 2007, Wittchen, Fröhlich et al. 2007). The subsequent sections will discuss literature examining internalizing and externalizing pathways to adolescent substance use and SUDs following ELS. It is important to keep in mind that these pathways are complex in that they are not mutually exclusive and may even bidirectionally interact to contribute to substance use outcomes.

3.1 Internalizing Psychopathology

Studies have provided empirical support for an internalizing pathway from ELS to adolescent substance use. For example, Shin and colleagues (2020) found depression symptoms mediated the association between childhood maltreatment and problem drinking in young adulthood (Shin, Ksinan Jiskrova et al. 2020). Another study showed childhood maltreatment prospectively predicted cigarette use at age 16 via internalizing symptoms at age 14 (Lewis, Kotch et al. 2011). ELS is also associated with high rates of post-traumatic stress disorder (PTSD) symptoms in adolescence (De Bellis and Zisk 2014), and PTSD symptoms have been consistently found to mediate the relationship between childhood maltreatment and problematic adolescent/young adult substance use (Klanecky, McChargue et al. 2016). The antecedents of adolescent substance use in individuals experiencing internalizing, including PTSD, symptoms following ELS is an active area of investigation; a greater understanding of these precursors is essential for informing interventions.

Substance use coping motives mark one commonly observed antecedent of adolescent substance use in individuals with internalizing symptoms and history of ELS. Large-scale studies have found individuals with a history of ELS are more likely to use substances to cope with problems than individuals without a history of ELS (Harrison, Fulkerson et al. 1997, Grayson and Nolen-Hoeksema 2005, Rothman, Edwards et al. 2008). Coping motives are associated with problematic substance use in adolescence/young adulthood, and with risk for development of SUDs (Merrill et al., 2014). A recent study by Shin and colleagues (2020) found childhood maltreatment was indirectly associated with alcohol-related problems in young adults (n=208) via coping motives (Shin, Jiskrova et al. 2020). Another study of 314 young adults found childhood emotional abuse was associated with higher levels of negative emotionality, which in turn predicted coping drinking motives and problematic drinking (Mezquita, Ibáñez et al. 2014). PTSD symptoms following ELS are also associated with substance use coping motives. For example, Park and colleagues (2019) found childhood maltreatment was associated with posttraumatic stress symptoms, post-traumatic stress symptoms predicted higher coping motives, and coping motives predicted higher levels of alcohol misuse in adolescence (n=564) (Park, Thompson et al. 2019). Similarly, Hannan and colleagues (2015) found childhood sexual abuse was associated with PTSD, PTSD predicted drinking to regulate emotional experiences, which was then associated with alcohol-related problems in females during college (n=579) (Hannan, Orcutt et al. 2015). As substance use coping motives is a well-established risk factor for problematic substance use, interventions aimed at promoting more effective methods for managing negative affect may be especially beneficial in reducing problematic alcohol use in individuals with a history of ELS.

Mechanisms extending beyond coping motives may also contribute to co-occurring internalizing psychopathology and substance use following ELS. Stress sensitization, for example, is well documented in mood disorders (Dienes et al., 2006) and may be another mechanism by which ELS increases risk for substance use in adolescents exhibiting internalizing symptoms. Young-Wolff and colleagues (2012) observed a relationship between childhood maltreatment and greater stress-related drinking even after controlling for mood-related symptoms (Young-Wolff, Kendler et al. 2012). Additionally, stress and reward systems have been found to interact (Koob 2008), and differences in stress sensitivity may alter the rewarding properties of drugs of abuse. Indeed, studies have found individuals with mood and anxiety disorders report drinking to enhance euphoric mood (Norberg et al., 2010, McDonald and Meyer, 2011). There also appears to be shared risk factors (i.e., genetic variation) for mood and SUDs. The internalizing pathway from ELS to SUDs is undoubtedly complex, and recent work has shown it is moderated by various internal and external factors, not limited to, but including genetics, biological sex, parental and peer context, intergenerational effects, and race and ethnicity (Box 1). More work is needed to better delineate the mechanisms by which internalizing symptoms may increase risk for adolescent substance use following ELS, as results could have important implications for prevention and early intervention strategies.

3.2 Externalizing Psychopathology

There is also compelling evidence in support of an externalizing pathway from ELS to adolescent substance use and SUDs. Externalizing symptoms are typically characterized by high levels of behavioral disinhibition (Gorenstein and Newman 1980). Externalizing behaviors have been found to mediate the relationship between adolescent/young adult alcohol and cannabis use problems. In a 10-year prospective study, Handley and colleagues (2017) showed childhood conduct problems mediated the effect of childhood maltreatment on problematic alcohol use in emerging adulthood (Handley, Rogosch et al. 2017). Shin and colleagues (2019) found behavioral dysregulation mediated the association between childhood emotional abuse and problematic alcohol use in young adulthood (Shin, Jiskrova et al. 2019). Another study demonstrated a developmental pathway by which childhood maltreatment related to less adaptive childhood personality functioning, followed by externalizing problems in preadolescence, and the development of cannabis abuse and dependence symptoms in adolescence (Oshri, Rogosch et al. 2011). A prospective study following 1421 adolescents, from ages 10 to 22, found impulsivity-related externalizing problems (i.e., aggression, delinquency) partially mediated risk for SUDs following early life familial conflict (Skeer, McCormick et al. 2009). Externalizing psychopathology has also been linked to an earlier age of substance use initiation. For example, in a sample of 1,105 youth enrolled in the Longitudinal Studies of Child Abuse and Neglect, Proctor and colleagues (2017) found externalizing behavior problems in middle childhood (age 8) mediated the relationship between childhood neglect and/or sexual abuse (prior to age 6) and younger age of alcohol and marijuana initiation (Proctor, Lewis et al. 2017). Interestingly, Doan and colleagues' (2019) recent longitudinal study found externalizing behaviors (i.e., aggression) buffered the detrimental effects of ELS on psychological dysregulation/allostatic load (measured through cortisol levels, urinary epinephrine and norepinephrine, resting systolic and diastolic blood pressure, and body mass index) at ages 9, 13, and 17 (Doan et

al., 2019). The authors reasoned such externalizing behaviors that are typically considered maladaptive may actually, in some circumstances, be adaptive in that these behaviors can be an effective form of stress regulation. Another interpretation is that externalizing behaviors may be an adaptive response to ELS in the short term, but ultimately confer risk for adverse substance use and clinical outcomes later in life. One limitation is that the study did not examine substance use, which could directly impact these measures of allostatic load. This counterintuitive finding highlights the need for longitudinal studies with longer follow-up periods to clarify mechanisms of risk versus resiliency.

3.3 Interactions between Internalizing and Externalizing Symptoms: Impulsivity

Internalizing and externalizing pathways to adolescent substance use and SUDs are not mutually exclusive. Indeed, co-occurring internalizing and externalizing symptoms are commonly observed in adolescents, and symptoms may even bidirectionally interact to increase risk for substance use and ultimately SUDs. Impulsivity is a symptom characteristic of externalizing psychopathology and has been proposed as a common transdiagnostic marker observed across internalizing disorders (i.e., bipolar disorder, major depression, anxiety disorders) (Strakowski et al., 2010, Fields et al., 2021). ELS is associated with elevated levels of impulsivity (Elam, Wang et al. 2016), and impulsivity is a major risk factor for the initiation of substance use, heavy episodes of substance use, and addiction (Dawes 1997). The role of impulsivity may be especially salient in adolescence, as studies have found impulsivity traits peak at this developmental stage (Argyriou et al., 2018). Consequently, the role of impulsivity in the relationship between ELS and adolescent substance use and SUDs has received considerable attention (Shin, Lee et al. 2015, Proctor, Lewis et al. 2017, Kim, Hwang et al. 2018).

Negative urgency, or impaired self-control in the face of negative emotionality, is one facet of impulsivity that has consistently been related to adolescent substance use in individuals with a history of ELS (Stautz and Cooper 2014, Shin, McDonald et al. 2018). In a community sample of young adults, Shin and colleagues (2015) found negative urgency mediated the relationship between childhood emotional abuse and frequency of alcohol use, binge drinking, and alcohol use disorders in young adults (Shin, Lee et al. 2015). Similarly, Wardell and colleagues (2016) found the relationship between childhood maltreatment and alcohol and cannabis use problems in adolescence was mediated by negative urgency (Wardell, Strang et al. 2016). Additional facets of impulsivity, including positive urgency (impulsivity in the face of positive emotions) and sensation seeking also appear to mediate the relationship between childhood maltreatment and alcohol and cannabis use (Kim, Hwang et al. 2018, Oshri, Kogan et al. 2018). Co-occurring internalizing symptoms may exacerbate impulsive tendencies and consequently increase substance use. For example, Oshri and colleagues (2018) found the association between childhood maltreatment and alcohol use problems via impulsive decision making was modulated by acute stress response reactivity, measured by heart rate variability (Oshri, Liu et al. 2018). Another study found negative urgency mediated the relationship between depression and alcohol use problems in 143 college students (Gonzalez et al. 2011). Recently, studies have tested psychological interventions/techniques aimed at reducing impulsivity in healthy and substance using and dependent individuals (Martínez-Loredo and Fernández Hermida, 2019). While more work

is needed, these techniques have garnered promising experimental support and may be especially relevant in minimizing substance use outcomes in adolescents with a history of ELS.

4. Hypothalamic-Pituitary-Adrenal (HPA) Axis Changes Associated with ELS and Substance Use

4.1 HPA Axis

ELS is associated with altered HPA axis basal functioning and stress reactivity (Heim and Nemeroff 2001, Lupien, McEwen et al. 2009). The prevailing view is that individuals with ELS show HPA axis hyperactivity in childhood (Danese and McEwen 2012), and consequent HPA axis hypoactivity in adolescence that persists throughout adulthood (Miller, Chen et al. 2007, Trickett, Noll et al. 2010, Doom, Cicchetti et al. 2014, Kaess, Whittle et al. 2018). Stress and stress reactivity play critical roles in the initiation and maintenance of substance use. HPA axis dysregulation is observed in individuals with SUDs, and studies have found cortisol levels influence drug self-administration, drug reinforcement (i.e., subjective “high”), withdrawal symptoms, and stress-induced craving and relapse (Sinha 2001, Cleck and Blendy 2008). Lower cortisol release has also been linked to enhanced motivation for substance use (Sinha 2001). Blaine and colleagues (2019) found lower cortisol response to stress and drug cues predicted greater alcohol consumption during an alcohol taste test in moderate and heavy social adult drinkers (Blaine, Nautiyal et al. 2019). Moss and colleagues (1999) observed a blunted cortisol response to stress in prepubertal sons of fathers with a SUD, with lower anticipatory cortisol response associated with cigarette smoking and marijuana use in adolescence (Moss, Vanyukov et al. 1999). Suppressed cortisol secretion in the face of stress is also associated with enhanced drug motivation and self-administration in individuals with and without a SUD (Blaine and Sinha 2017).

It is important to note findings with regards to HPA axis activity following ELS are mixed, with a number of studies documenting HPA axis hyperactivity in adolescents and adults with a history of ELS (Nemeroff 2016). Many of these studies, however, have focused on individuals with psychopathology, including major depression and borderline personality disorder, and a history of ELS (Heim et al., 2000, Heim et al., 2001, Heim et al., 2002, Carpenter et al., 2004, Fernando et al., 2012). Such psychopathology is associated with HPA axis dysregulation (particularly hyperactivity) (Varghese and Brown, 2001), and may confound findings. Interestingly, HPA axis hyperactivity has also been linked to heavier substance use (Piazza and Le Moal, 1996, Fahlke et al., 2000, de Wit et al., 2007, Huizink et al., 2009). This suggests multiple pathways to substance use following ELS, with HPA axis hyperactivity potentially driving substance use in individuals with psychopathology. Indeed, Andersen and Teicher (2008, 2009) theorized the link between ELS and SUDs may be mediated in part by a highly reactive HPA axis and using substances to cope with negative affect (Andersen and Teicher 2008, Andersen and Teicher 2009). While findings are mixed, this literature does converge to suggest HPA axis dysregulation—both hypo- and hyperactivity—serves as a biomarker of risk for substance use and development of SUDs in individuals with ELS. Substance use during adolescence and clinical factors

(i.e., internalizing and externalizing symptoms) associated with ELS may contribute to dysregulation of HPA axis function (Alink, Cicchetti et al. 2012) and possibly discrepant findings.

Heavy substance use, particularly during adolescence, directly alters HPA axis functioning (Blaine and Sinha 2017). Alcohol, for example, stimulates the HPA axis, and heavy, chronic alcohol use is associated with changes in HPA negative feedback that typically result in a blunted response to acute stress (Lovallo 2006, Becker 2017). Despite the high rates of ELS reported in individuals with SUDs, few studies have directly examined the influence of ELS history. A recent study attempted to address this by investigating HPA axis functioning in alcohol dependent and healthy control adults with and without a history of childhood maltreatment (Muehlhan, Höcker et al. 2020). While alcohol dependent adults showed lower cortisol response to a Trier-Social-Stress-Test compared to healthy controls, childhood maltreatment was not associated with cortisol differences within the alcohol dependent group. Interestingly, healthy controls with a history of childhood maltreatment exhibited a lower cortisol response to stress, compared to controls without childhood maltreatment. Results could suggest alcohol dependence influences HPA axis functioning in a way that may mask differences in the HPA axis due to childhood maltreatment. It is also possible lower cortisol response to stress in healthy controls with a history of childhood maltreatment acts as a resiliency factor. Another study reported adrenocorticotropic hormone (ACTH) levels negatively correlated with childhood trauma questionnaire (CTQ) scores in alcohol dependent patients during acute withdrawal (day 14 after admission to a detoxification unit) (Schäfer et al., 2010), suggesting ELS and associated changes in HPA axis function may relate to differences in withdrawal and ultimately risk of relapse. ELS has been associated greater rates of relapse and poor treatment response (Heffner, Blom et al. 2011, Van Dam, Rando et al. 2014), and results could suggest differences in HPA axis activity following detoxification may be one mechanism contributing to this. Additional work investigating HPA axis functioning prior to the development of SUDs and across different phases of addiction is needed to delineate the role(s) of the HPA axis in risk for the development of SUDs following ELS, and interactions between adolescent substance use and ELS on HPA axis function and development and maintenance of SUDs.

5. Neurobiological Changes Associated with ELS and Substance Use

ELS is associated with brain changes that may heighten risk for the development of SUDs. These brain differences are strikingly similar to differences in the brain observed in individuals with SUDs. Specifically, ELS has been found to interfere with typical development of subcortical brain regions—including the amygdala and hippocampus—involved in the stress response, mesocorticolimbic brain system associated with reward processing and sensitivity (Teicher, Samson et al. 2016), and prefrontal cortical (PFC) regions that underlie executive control (Lupien, McEwen et al. 2009). These brain systems develop and mature throughout childhood and adolescence and are highly sensitive to stress; even brief periods of stress exposure can result in significant structural remodeling (Arnsten 2009, Hart and Rubia 2012). Preclinical work supports a causal relationship between ELS and neural alterations and has uncovered potential stress-induced remodeling processes (i.e., reduced dendritic length and branching, decreased spine density, and

suppressed neurogenesis) (Arnsten 2009, Holmes and Wellman 2009, Lupien, McEwen et al. 2009). These neurobiological systems play critical roles in addiction-related behaviors, with differences in their structure and function enhancing risk for SUDs. In their stress-incubation/corticolimbic developmental cascade hypothesis, Andersen and Teicher (2009) proposed neurobiological changes associated with ELS predispose individuals to use drugs at an earlier age compared to the age of onset observed in populations without a history of ELS (Andersen and Teicher 2009). The brain continues to develop and mature during adolescence, rendering the adolescent brain highly susceptible to substance-related neurodegeneration (White and Scott Swartzwelder 2005, Crews and Nixon 2009, Jacobus and Tapert 2013). Thus, adolescent substance use may continue to shape these neurobiological systems in a way that further increases risk for SUDs (figure 1).

5.1 Stress Response: Amygdala and Hippocampus

ELS is associated with enduring alterations in brain regions that regulate the HPA axis and stress response. The amygdala and hippocampus mark two critical structures that bidirectionally interact with the HPA axis and are highly sensitive to ELS. Studies have consistently observed an effect of ELS on amygdala structure, though both increases and decreases in amygdala volume following ELS have been reported (Teicher, Samson et al. 2016). Oshri and colleagues (2019) attempted to address this discrepancy using high-resolution segmentation algorithms to assess volume of specific amygdala nuclei in emerging adults (Oshri, Gray et al. 2019). The group found higher ACE scores were associated with reduced right amygdala volume, and specifically basolateral and central-medial segments. While findings suggest ELS is associated with lower right amygdala volume, it is likely the influence of ELS on brain structure is complicated by additional factors like time and type of stress exposure. Teicher and colleagues proposed early exposure may result in amygdala enlargement, while later exposure may result in volume reduction and hypothesized this may stem from modifications to the developmental processes taking place at the time of exposure (i.e., overproduction of dendrites, axonal terminals, synapses, and receptors in early to middle childhood versus pruning of these processes during adolescence and early adulthood) (Teicher and Samson 2016, Teicher, Samson et al. 2016, Teicher and Khan 2019). Findings with respect to ELS and hippocampal morphometry are more consistent, with reduced hippocampal volume (Bremner et al., 1997, Vythilingam et al., 2002) and decreased adult hippocampal neurogenesis (Ming and Song, 2005) consistently observed in individuals with a history of ELS.

Studies have also shown amygdala and hippocampus hyperactivity in individuals with a history of ELS (Teicher, Samson et al. 2016, VanTieghem and Tottenham 2018), with recent work suggesting such hyperactivity may mediate the relationship between ELS and HPA axis dysfunction. Seo and colleagues (2019) found increased amygdala and hippocampal reactivity to acute stress mediated the relationship between lifetime trauma exposure and lower morning cortisol levels in healthy adults (Seo, Rabinowitz et al. 2019). Another study by Seo and colleagues (2014) found ELS was associated with stress induced hyperactivity of the amygdala and hippocampus, as well as of the insula and striatum, but hypoactivity of the orbitofrontal cortex (OFC) (Seo, Tsou et al. 2014). Lower PFC, including OFC, volume and activity is consistently observed in individuals with a history of ELS (Teicher,

Samson et al. 2016, Kirsch, Tretyak et al. 2021). The PFC, particularly the OFC, shares reciprocal connections with the amygdala and hippocampus, and plays an integral role in regulating these regions' response to stress (VanTieghem and Tottenham 2018). The PFC is highly sensitive to the effects of HPA dysregulation; the region has a high density of stress-susceptible glucocorticoid receptors, and both elevated and suppressed levels of glucocorticoids have been linked to disruptions in PFC development through mechanisms including apoptosis, myelination delays, inappropriate pruning, and decreases in brain growth factors (McEwen 2007, De Bellis and Zisk 2014). Lower PFC volume and activity could result in compromised top-down control of these subcortical regions, and ultimately a sensitized stress response. Indeed, a number of studies have observed differences amygdala-PFC and hippocampus-PFC functional connectivity in individuals with a history of ELS (Herringa, Birn et al. 2013, Marusak, Martin et al. 2015, Thomason, Marusak et al. 2015, VanTieghem and Tottenham 2018). For example, Peverill and colleagues (2019) found adolescents with a history of child abuse exhibited stronger negative amygdala - ventromedial PFC functional connectivity during an emotional regulation task compared to adolescents without this history (Peverill, Sheridan et al. 2019).

Amygdala, hippocampus, and PFC structural and functional differences in individuals with a history of ELS have been associated with adolescent/young adult substance use (Kirsch, Nemeroff et al. 2020). The aforementioned study by Oshiri and colleagues (2019) found reduced basolateral amygdala volume partially mediated the positive relationship between ACE scores and greater alcohol use, anxiety and depressive symptoms in young adults (Oshri, Gray et al. 2019). The insula, another region found to be highly sensitive to the effects of early life stress (Edmiston et al., 2011, Hart and Rubia, 2012, Lim et al., 2018), has also been associated with adolescent/young adult substance use. Kirsch and colleagues (2021) found childhood maltreatment correlated with lower insula gray matter volume, which was associated with greater frequency of cannabis use (Kirsch, Tretyak et al. 2021). Lower insula gray matter volume also related to greater quantity of alcohol use only in adolescents/young adults with familial risk for bipolar disorder, suggesting familial— possibly genetic—risk factors may influence substance use outcomes following ELS. Studies also indicate functional changes observed within these regions following ELS increase risk for substance use problems in adolescence/young adulthood. Sinha and colleagues (2016) found sustained ventromedial PFC hypoactivity to stress predicted higher levels of maladaptive coping behaviors, including binge alcohol intake, in young adults (Sinha, Lacadie et al. 2016). Peverill and colleagues (2019) found stronger negative amygdala - ventromedial PFC functional connectivity during emotional regulation in individuals with a history of ELS was associated with higher levels of concurrent internalizing and externalizing symptoms and with higher levels of externalizing symptoms two years later (Peverill, Sheridan et al. 2019). The authors conclude ELS may result in brain adaptations that allow for rapid identification of environmental threats, but ultimately result in greater emotional reactivity and difficulty modulating emotions. Acute alcohol administration attenuates amygdala and insula reactivity to emotional stimuli and weakens amygdala – ventral PFC functional connectivity during emotional processing and insula – ventral PFC functional connectivity during rest (Gilman, Ramchandani et al. 2008, Sripada, Angstadt et al. 2011, Gorka, Fitzgerald et al. 2013, Gorka, Phan et al. 2018). Thus, acute

alcohol appears to alter activity within brain regions that show altered function following ELS. ELS-associated changes in function may interact with the effects of acute alcohol to contribute to motives for alcohol use. Several imaging studies have proposed functional connectivity changes following ELS may actually be adaptive and promote resiliency (Gee, Gabard-Durnam et al. 2013, Herringa, Burghy et al. 2016). For example, Kaiser and colleagues (2018) found women previously exposed to ELS showed increased variability in amygdala - subgenual anterior cingulate cortical (ACC) functional connectivity, with greater variability associated with improved mood and less blunting of the stress response (Kaiser, Clegg et al. 2018). Longitudinal studies are needed to disentangle mechanisms of risk versus resiliency. Taken together, work suggests ELS-related brain differences may predate substance use, and differences associated with greater substance use may occur through ELS-related alterations brain regions that subserve emotional and stress regulation. The role(s) of adolescent substance use on neurophysiological differences following ELS warrants more attention.

Adolescent substance use also has neurotoxic effects on the amygdala, hippocampus, and PFC. These brain regions may be uniquely vulnerable to substances during this time because the PFC, and connections between the PFC and the amygdala/hippocampus, continue to mature throughout adolescence and young adulthood (Silveri, 2012). Neuroimaging studies have consistently found adolescents who meet criteria for alcohol use disorders and who engage in sub-diagnostic heavy drinking show lower PFC and hippocampal volume and differences in functional activation of these regions, compared to non-using adolescents (De Bellis, Clark et al. 2000, Nagel, Schweinsburg et al. 2005, Medina, McQueeny et al. 2008, Jacobus and Tapert 2013). Additionally, a wealth of preclinical work suggests excessive alcohol consumption during adolescence compromises cortical and glial cell survival in the amygdala, hippocampus, and PFC, along with alterations in white matter tracts connecting these regions (White and Scott Swartzwelder 2005, Crews and Nixon 2009). For example, Taffe and colleagues (2010) found daily alcohol consumption reduced hippocampal neurogenesis and increased hippocampal neural degeneration in adolescent primates (Taffe, Kotzebue et al. 2010). These brain changes may further perpetuate a negative cycle, ultimately resulting in addiction (Jacobus, Squeglia et al. 2013). Adolescent psychopathology may also perpetuate this negative cycle. Whittle and colleagues (2013) found the presence of Axis I psychopathology during adolescence marks one mechanism by which ELS has continuing effects on amygdala and hippocampal brain development (Whittle, Dennison et al. 2013). Overall, data indicate both ELS and adolescent substance use influence development of the neurobiological systems underlying the stress response—in strikingly similar ways—and likely interact to contribute to addiction-related outcomes. Large scale longitudinal studies beginning prior to substance use are needed to disentangle mechanisms that contribute to risk for initiation of, and transition to, SUDs. The Adolescent Brain Cognitive Development (ABCD) study, for example, is an ongoing landmark study that is collecting neuroimaging data on 10,000 healthy children beginning at the age of 9-10 and following the cohort into early adulthood in order to track brain growth and investigate how environmental factors—including stressors (e.g., abuse, neglect, household challenges, parental substance use) and substance use—influence brain development and behavioral outcomes. The study collects stress-related measures that capture the domains included in

the landmark ACE study (Dube et al., 2003, Hoffman et al., 2019) and investigates these experiences at the individual, family, peer, and community levels in youth participants as well as in their parents/guardians at each study visit. The ABCD study is uniquely positioned to investigate how stress and substance use prospectively relates to adolescent development.

Despite the high rates of ELS in SUDs, few studies have investigated the neural correlates of ELS in individuals with SUDs. Van Dam and colleagues (2014) found hippocampal gray matter volume deficits in individuals with SUDs were uniquely associated with childhood maltreatment (Van Dam et al., 2014). Bachi and colleagues (2018) observed decreased OFC volume in individuals with cocaine use disorders and a history of ELS compared to diagnostic controls with no ELS history (Bachi, Parvaz et al. 2018). Results suggest the possibility that hippocampal and PFC neural differences that distinguish clinically healthy controls from individuals with SUDs are more robust in, or possibly even restricted to, individuals with a history of ELS (Opel et al., 2014, Teicher et al., 2016). More work focused on understanding if and how the neural consequences of ELS confound and/or interact with those observed following heavy substance use is needed.

5.2 Reward Processing and Sensitivity: Mesocorticolimbic Brain Systems

ELS has been associated with altered reward sensitivity and differences in the mesocorticolimbic dopaminergic pathway, the brains' reward system (Guyer, Kaufman et al. 2006). Altered behavioral and neural sensitivity to rewards is a well-established risk factor for the development of SUDs. While findings are mixed, studies suggest reduced reward sensitivity in individuals with a history of ELS. For example, Dillon and colleagues found childhood maltreatment was associated with a decreased positive subjective response to reward-predicting cues, as well as lower globus pallidus activation during a monetary incentive delay task (Dillon, Holmes et al. 2009). Additional fMRI studies have also supported blunted basal ganglia activity to anticipated rewards following ELS (Hanson, Albert et al. 2016, Teicher, Samson et al. 2016). Using a monetary incentive delay task, Boecker and colleagues (2014) observed an inverse relationship between ELS and ventral striatum and putamen activation during reward anticipation in young adults (Boecker, Holz et al. 2014). Mehta and colleagues similarly found blunted striatal responses during reward anticipation in adolescents who were adopted from Romanian institutions (Mehta, Gore-Langton et al. 2010). Imaging studies have also identified ELS-related structural differences in mesocorticolimbic regions involved in reward processing (Edmiston, Wang et al. 2011). Specifically, structural alterations in the OFC and ACC (Kelly, Viding et al. 2013, Kirsch, Tretyak et al. 2021), striatum (Cohen, Grieve et al. 2006, Edmiston, Wang et al. 2011), and in the white matter of fronto-striatal pathways (Behen, Muzik et al. 2009) have been reported in individuals with a history of ELS. Preclinical studies provide support for a causal role of ELS on reward hyposensitivity (Pryce, Dettling et al. 2004).

ELS is also associated with altered sensitivity to the subjective effects of substances, i.e., levels of drug-induced euphoria (Wand, Oswald et al. 2007). Studies have suggested a positive association between ELS and mesocorticolimbic dopamine release in response to acute drug administration. For example, Oswald and colleagues (2014) found amphetamine

self-administration induced a stronger dopamine response in the ventral striatum of individuals with a history of childhood adversity compared to those without a history of adversity (Oswald, Wand et al. 2014). Stronger dopamine response to substance administration may enhance the reinforcing properties of drugs of abuse and increase risk for substance use (Piazza and Le Moal 1996). While the etiology underlying differences in sensitivity to substances following ELS is not entirely understood, neurobiological models have proposed interactions between stress and reward systems, such that neuroadaptations within the stress systems of the brain alter sensitivity to the rewarding properties of substances of abuse (Koob 2008). Cortisol, for example, has been found to influence reward sensitivity and drug self-administration through its interaction with the mesocorticolimbic reward system. Dopamine neurons in mesocorticolimbic brain regions express high levels of glucocorticoid receptors and are highly influenced by cortisol release in response to acute stress. In fact, increased HPA axis activity has been shown to mediate the relationship between ELS and greater mesocorticolimbic dopamine release following acute substance use (Meaney, Brake et al. 2002). For example, Pruessner and colleagues (2004) found healthy young adults with a history of low parental care exhibit a stronger cortisol response to a stress task, with levels of cortisol release positively associated with ventral striatum dopamine levels (Pruessner, Champagne et al. 2004). Another study found cortisol response following amphetamine administration was associated with dopamine binding in the ventral striatum and self-reported amphetamine-induced euphoria (Wand, Oswald et al. 2007). Aberrant amygdala reactivity during emotional processing may also contribute to differences in reward sensitivity in adolescents with a history of ELS (Marusak, Martin et al. 2015). Preclinical work supports a causal relationship; this work has shown suppression of corticosterone release decreases levels of dopamine under basal conditions and in response to stress and substance use (Piazza and Le Moal 1996, Barrot, Marinelli et al. 2000). While the aforementioned studies suggest greater cortisol release in response to acute stress may enhance dopamine release following acute drug administration, preclinical studies have also shown that chronic cortisol treatment may result in decreased sensitivity to the interceptive effects of drugs (Besheer, Fisher et al. 2012). Reward system functioning changes with age, and it is possible acute and chronic changes in cortisol differentially affect reward system functioning.

There appear to be important age-related differences in sensitivity to drugs of abuse. Specifically, studies support age-related increases in behavioral sensitivity to the effects of alcohol, including sedation, motor impairment, and hypothermia (Silveri, 2012). Adolescents exhibit reduced sensitivity to the effects of alcohol on these factors, which may result in greater levels of consumption. It is possible that adolescents with a history of ELS experience greater sensitivity to the euphoric effects of substances and reduced sensitivity to the sedative and motor impairing effects of substances, ultimately rendering these individuals at greater risk for heavy substance use. Experimental studies directly testing this hypothesis are needed. Despite their dampened behavioral sensitivity to substances, adolescents are highly susceptible to substance-related neurotoxicity. Therefore, serious efforts should be made to reduce heavy substance use during this critical developmental period. Cognitive behavioral alcohol intervention programs targeting an individual’s specific pre-existing vulnerability (i.e., level of response to alcohol) has shown some success in

improving alcohol use outcomes in adolescents and young adults (Schuckit et al., 2012, Schuckit et al., 2015, Schuckit et al., 2016), although more research is needed. A better understanding of the pre-existing differences in substance sensitivity in adolescents with a history of ELS may offer new and fruitful directions for intervention programs.

5.3 Executive Function: Prefrontal Cortex

The PFC underlies a wide range of emotional and executive processes that are fundamental for proper neuropsychosocial functioning. Earlier, we discussed the PFC's—particularly the OFC, ACC, and ventral PFC—critical role in regulating the stress response, and how disruptions in development of these prefrontal regions following ELS may contribute to a dysfunctional stress response and ultimately addiction liability. The PFC, including both ventral and dorsal prefrontal regions, also plays a critical role in a wide range of higher-order executive functions, including attentional and cognitive processes, behavioral control, impulsivity, working memory, and decision making (Goldstein and Volkow 2011, Girotti, Adler et al. 2018). There is a wealth of literature linking ELS with impaired executive functioning, including decreased working memory, attention, and inhibitory control (Holmes and Wellman 2009, Hart and Rubia 2012). These executive functions are also suggested to play a critical role in addiction onset and illness course, and deficits have been associated with a more severe clinical course characterized by increased craving, greater drug use, denial of illness, and increased risk of relapse (Goldstein and Volkow 2011, Blaine and Sinha 2017).

Preclinical studies have linked PFC dendritic changes—i.e., reduced dendritic length, branching, and spine density following ELS in preclinical models—with impairments in attentional and working memory processes (Arnsten 2009). HPA axis activity appears to influence executive function. Lyons and colleagues (2000) found excessive cortisol exposure impairs PFC function and inhibitory control in monkeys (Lyons et al. 2000), suggesting differences in stress response may also affect brain regions that underlie higher-order executive processes. Indeed, ELS is reported to be associated with greater stress-related cognitive impairments (Kuehl et al., 2020), and human fMRI studies have observed differences in PFC activation during tasks of executive functions. Mueller and colleagues observed greater PFC, including dorsal ACC and inferior PFC, activity during a cognitive (stop signal) task in adolescents with ELS compared to adolescents without a history of ELS (Mueller et al., 2010). Mueller and colleagues found correct, versus incorrect, responses recruited the inferior PFC more strongly in adolescents with a history of ELS compared to those without this history. These results may suggest inefficient processing and/or a compensatory mechanism in adolescents with ELS.

Neural and executive function consequences of ELS may also confound or interact with those observed in SUDs (Teicher and Khan 2019). In a recent study, De Bellis and colleagues (2019) aimed to test this hypothesis by examining how maltreatment history contributes to neurocognitive and brain structural differences in adolescent onset alcohol use disorders (De Bellis, Morey et al. 2019). Adolescents with alcohol use disorders and maltreatment scored lower in sustained attention, exhibited smaller anterior corpus callosum (the white matter tract that houses axons from the PFC and connects the left

and right hemisphere of the brain) and larger PFC (specifically left pars triangularis) volumes, compared to adolescents with alcohol use disorders but no maltreatment. Results suggest maltreatment may independently or additively contribute neurocognitive and neurostructural differences associated with adolescent alcohol use. Other forms of co-occurring psychopathology may also influence PFC structure and cognitive functioning in individuals with ELS. For example, Saleh and colleagues (2017) found the relationship between childhood trauma exposure and cognitive function and brain structure differs between individuals who do and do not develop depression (Saleh et al., 2017). Specifically, depressed subjects exhibited an inverse association between ELS exposure and processing speed and OFC volume, whereas non-depressed subjects showed the opposite relationship between ELS and processing speed and OFC volume. Some researchers hypothesize individuals with SUDs (and other psychopathology) with and without history of ELS represent clinically and neurobiologically distinct subtypes of SUDs (Teicher and Samson 2013). Additional work aimed at understanding specific ELS-related consequences on neurophysiology—including within stress, reward, and executive systems—and role(s) in SUD risk, onset, and recurrence/treatment and interactions with adolescent substance use is critical for informing interventions and treatments best suited for this population.

6. Summary and Future Directions

ELS is associated with increased risk for SUDs—an association substantiated by many large-scale cross-sectional and longitudinal studies. ELS-related substance use outcomes emerge in adolescence and manifest in the form of earlier substance use initiation and heavy substance use. Substance use during this critical developmental period contributes to risk for SUDs, particularly for early onset SUDs. As a high proportion of individuals with ELS are exposed to substances of abuse during this vulnerable window, adolescent substance use may be an intermediate step in the pathway from ELS to SUDs. Clinical studies have identified internalizing and externalizing psychopathology as antecedents of adolescent substance use in youth with a history of ELS. Of course, SUDs can also precede internalizing and externalizing psychopathology and contribute to development of internalizing/externalizing psychopathology, as discussed in this special issue (Lippard and Nemeroff, this issue). Despite the complexity of examining neural processes in humans, clinical studies have also consistently demonstrated associations between ELS and altered development of the HPA axis, subcortical brain regions that underlie the stress response, mesocorticolimbic brain systems associated with reward sensitivity, and PFC regions that underlie executive control. It is possible that ELS sculpts the developing brain in a way that increases risk for early onset and heavy adolescent substance use. Indeed, longitudinal studies suggest differences in PFC structure and function may actually occur prior to and predict adolescent substance use. For example, lower ACC volume and activation during response inhibition in substance-naive adolescents predicts alcohol use initiation, heavy adolescent alcohol use, and alcohol-related problems in adolescence (Norman, Pulido et al. 2011, Cheetham, Allen et al. 2014, Squeglia, Rinker et al. 2014). Lower OFC gray matter volume has also been found to prospectively predict initiation of cannabis use (Cheetham, Allen et al. 2012). It is widely accepted that substance use alters neural structure and function of these systems. Adolescence marks a period of high brain plasticity, rendering

the developing adolescent brain highly susceptible to the neurotoxic effects of drug exposure (Squeglia, Pulido et al. 2012, Pfefferbaum, Kwon et al. 2018). Substance use during this time may result in further brain changes that either independently, additively, or interactively contribute to risk for addiction in individuals with a history of ELS. Many of the large-scale studies substantiating the association between ELS, adolescent substance use, and SUDs relied on retrospective self-report measures of ELS and substance use. This is a considerable weakness in the literature, as the possibility of inaccurate recall and reporter bias cannot be excluded. Longitudinal studies with the power to disentangle temporal relations between ELS, substance use, adolescent brain development, and mechanisms that contribute to development and maintenance of SUDs have begun to emerge [e.g., ABCD, Environmental influences on Child Health Outcomes (ECHO) (Gillman and Blaisdell, 2018)]. These studies provide an unprecedented opportunity to further our understanding of the role of ELS on adolescent development, substance use, and interactions between brain development and substance use that may drive risk for SUDs.

6.1 Leveraging Protective Psychosocial Factors in Adolescence to Improve Outcomes

Adolescence marks a period of rapid development. While greater brain plasticity during this time may increase susceptibility to the effects of stress and substance use, it also makes it a critical window of opportunity for intervention (Romeo and McEwen, 2006). Studies have found psychosocial factors like living situation, parenting, environmental enrichment, social support all impact risk for SUDs in individuals with a history of ELS (Lansford, Malone et al. 2006, DuMont, Widom et al. 2007, Braithwaite, O'Connor et al. 2017, Cheong, Sinnott et al. 2017) and that this may occur, at least in part, through reversing ELS-related neurobiological changes. In a large sample (N=7047), Bellis and colleagues (2017) found following ELS, support from a trusted and always available adult during childhood decreased the prevalence of daily smoking and heavy alcohol use in adulthood (Bellis, Hardcastle et al. 2017). Shin and colleagues (2019) recently showed that high levels of paternal warmth weakened the association between childhood emotional abuse and alcohol-related problems (Shin, Wang et al. 2019). Supportive relationships with family members and peers teach healthy stress-coping strategies and foster healthy stress response systems. Improved childcare and alleviation of chronic stress is associated with a return to normal cortisol levels (Fries, Hesse et al. 2005, Gunnar and Quevedo 2008). Stress-induced morphological remodeling of the PFC and hippocampus also appear to be reversible following alleviation of chronic stress (Vyas, Pillai et al. 2004, Radley, Rocher et al. 2005). In a controlled study of Romanian orphans, Smyke and colleagues (2009) showed that children randomly assigned to a newly established system of higher-level foster care, as opposed to institutional care, exhibited lower levels of adverse clinical outcomes (Smyke et al., 2009) and a reversal of previously observed decreased white matter volume (Sheridan et al., 2012). Psychosocial interventions (i.e., trauma-focused cognitive behavioral therapy) have garnered empirical support and mark another avenue for further development (Cohen, Mannarino et al. 2006). Despite these promising results, more research is needed to investigate how psychosocial interventions and environmental enrichment can be most effective in reducing substance use outcomes in this population. For example, biological factors including genetics and sex influence substance use outcomes (box 1) and should be considered in intervention studies. Further, a focus on translating experimental findings

into clinical practice is needed to improve adverse substance use outcomes following ELS. ECHO is a nationwide large-scale study aimed to understand the effects of early environmental influences on child health and development (Gillman and Blaisdell, 2018). The study includes pediatric cohorts recruited during pregnancy, allowing for prospective examination of prenatal conditions (i.e., maternal obesity, depression, and drug use). The study is also unique in that includes both observational and interventional research branches. The interventional branch of the study offers children in medically underserved and rural populations access to enroll in clinical trials. This unprecedented study has prioritized "solution-oriented" research questions that can readily inform programs, policies, and practices based on research in children from diverse populations across the United States.

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Box 1.

Pathways from ELS to SUDs are complex and appear to be moderated by a multitude of factors. Not all individuals with a history of ELS develop SUDs; a greater understanding of how these factors moderate the relationship between ELS and SUDs could help us understand who is at greatest risk for adverse outcomes.

Genetic Variation:

It has become clear that genes interact with environmental stress to confer risk or resiliency to psychiatric outcomes (Moffitt 2005). Genetic studies have largely focused on how specific candidate genes interact with ELS to increase risk for SUDs. This literature suggests possessing certain genetic variants confers risk for psychopathology only in individuals who have experienced ELS. Conversely, lacking certain genetic variants may confer resilience to the effects of ELS. Variation within the corticotropin-releasing hormone receptor 1 (CRHR1) gene, for example, has been shown to interact with childhood and adolescent stressful events to predict age of drinking onset, progression to heavy alcohol consumption, and lifetime alcohol use (Blomeyer, Treutlein et al. 2008, Nelson, Agrawal et al. 2010, Schmid, Blomeyer et al. 2010). Variation in Solute Carrier Family 6 Member 4 (SLC6A4), the serotonin transporter promoter gene, is also reported to interact with ELS to increase risk for adverse alcohol and drugs use behaviors. Specifically, the short allele interacts with childhood maltreatment to predict early initiation of alcohol use (Kaufman, Yang et al. 2007) and use of illicit drugs (Gerra, Zaimovic et al. 2010). Additional work investigating the moderating role of genetic factors is critically needed to determine how genetic variation may put certain individuals at greater risk for adverse outcomes following ELS. To gain a more comprehensive understanding of these complex gene by environment interactions, studies should extend beyond investigating genetic polymorphisms of candidate genes and also focus on epigenetic changes and polygenetic risk.

Biological Sex:

Sex differences in pathways to adolescent substance use following ELS have been commonly observed (Hyman, Paliwal et al. 2008). Hudson and colleagues (2017) found childhood sexual abuse and adolescent problem drinking was mediated by anxiety and anger symptoms in females but only by anger symptoms in males (Hudson, Wekerle et al. 2017). Another study found coping-depression motives mediated the relationship between childhood abuse and alcohol consequences in women, but enhancement motives mediated the relationship in men (Goldstein, Flett et al. 2010). One possible explanation is that internalizing symptoms are more prevalent in females while externalizing symptoms, like anger and sensation seeking, are more prevalent in males. Indeed, sex-differences in the development of the corticolimbic circuitry that underlies emotional regulation has been observed in adolescents with a history of ELS (Colich et al., 2017). However, studies have also supported an externalizing pathway from ELS to adolescent substance use specifically in females (Bailey and McCloskey 2005). Understanding sex

differences in these pathways can help inform more targeted intervention in youth with a history of ELS.

Parental and Peer Context:

Parental and peer context influences adolescent substance use outcomes following ELS. Adolescence is characterized by increased time spent with peers and decreased time spent with parents (Spear 2000). This is also a time of greater autonomy and exposure to illicit substances. Adolescent peer relationships may result in exposure and high pressure to engage in illicit substance use, potentially through social motives or pressures (Tarter 2002, Brown, McGue et al. 2008). Indeed, affiliation with substance using peers is a predictor of adolescent substance use (Chuang, Ennett et al. 2005, Dubowitz et al., 2016). Despite this decrease in time spent with family, parents and parenting styles do appear to critically influence adolescent substance use behavior (Wood, Read et al. 2004). For example, maladaptive parenting styles may interact with childhood temperament and behavior (externalizing symptoms) to enhance risk for substance use (King, Iacono et al. 2004, Costello 2007, Zucker, Heitzeg et al. 2011, Chassin, Sher et al. 2013). A recent study observed a sequential association between childhood maltreatment, low levels of parental attachment, higher levels of involvement with pro-marijuana peers, and ultimately adolescent and adult marijuana use (Alex Mason et al., 2017). As discussed in *Summary and Future Directions*, supportive relationships with family and peers can act as a strong protective factor, as such relationships can teach healthy stress coping strategies and foster healthy stress responses.

Intergenerational Effects of ELS:

The adverse effects of ELS are multigenerational; they persist beyond an individual's lifespan and are transmitted to future generations (Cowan et al., 2016). Human studies have observed a greater risk of psychiatric illness in offspring of parents previously exposed to trauma. For example, grown children of Holocaust survivors—who were born after the war, or after their parents escaped to safety—show higher rates depression, anxiety disorders, and PTSD compared to Jewish adults without a Holocaust surviving parent (Yehuda et al., 2005). Preclinical studies provide experimental support for the hypothesis that behavioral and neurobiological consequences of ELS exposure are transmitted across generations (Fairbanks, 1996, Dias and Ressler, 2014). Parental behavior and epigenetic programming mark two potential mechanisms thought to underlie the intergenerational transmission of ELS (Cowan et al., 2016). As discussed, parenting style can have a profound influence on adolescent substance use as well as internalizing/externalizing behaviors. Maladaptive parenting, including emotional abuse and neglect (i.e., emotional disengagement), physical punishment and violence, and poor parental adjustment have been observed in parents with histories of ELS (Cowan et al., 2016). Such maladaptive parenting styles are a form of ELS and may increase risk for adverse substance use outcomes in their offspring. Epigenetic programming is one mechanism that may contribute to maladaptive parenting through experience-driven changes (Kundakovic and Champagne, 2015). For example, epigenetic changes in the neural circuitry thought to regulate parenting behavior (e.g., hypermethylation of the been associated with abusive and inattentive caregiving. Emerging evidence also suggests

epigenetic changes can be passed on to offspring via germline inheritance. While more research on the exact mechanisms of transmission is needed, future work should also aim to identify targets underlying intergenerational transmission to interrupt this cycle of transmission to future generations.

Race and Ethnicity:

Recently, studies have begun to investigate the role of ELS across different racial and ethnic groups. This work has suggested the vulnerability to the adverse effects of ELS may vary across race and ethnicity (Martin-Gutierrez et al., 2021). Studies have also identified stressors that may be unique to, or more prevalent among, specific racial or ethnic minorities. Racial discrimination, for example, is a stressor that begins early in life and is linked to worse health outcomes (e.g., depression, anxiety, and psychological distress) (Lewis et al., 2015, Williams, 2018). A longitudinal study of black adolescents (ages 10 – 12, N=714) in rural Georgia showed racial discrimination was associated with conduct problems and depressive symptoms (Brody et al., 2006). It is also suggested that structural racism can contribute to a stress proliferation process (Pearlin et al., 2005) where an initial stressor can initiate or exacerbate additional stressors. More research is critically needed to understand risk factors that may be unique to a specific race or ethnicity to develop tailored intervention strategies.

Highlights

- Early life stress (ELS) is related to adolescent substance use/disorders (SUDs)
- ELS and substance use are associated with brain changes that increase risk for SUDs
- Adolescent substance use may be an intermediate step in the path from ELS to SUDs
- Intervention during adolescence may effectively reduce substance use following ELS

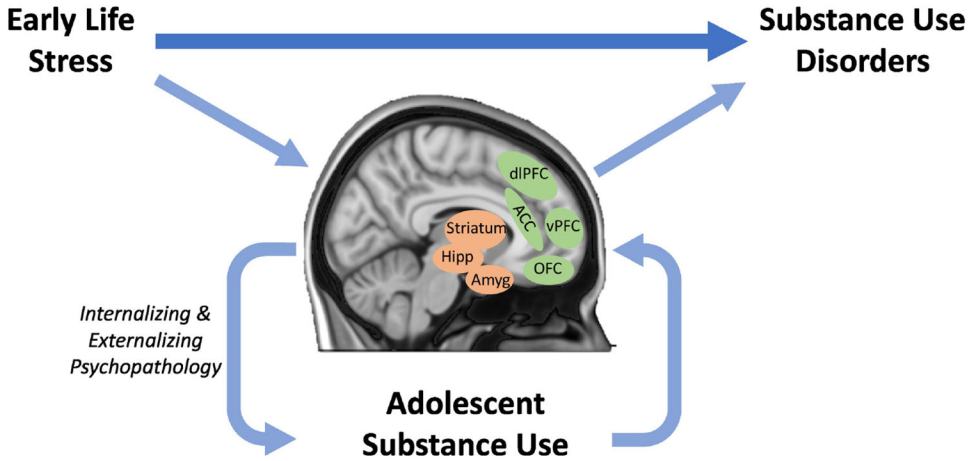

Figure 1.

Pathway from early life stress (ELS) to substance use disorders (SUDs) via adolescent substance use. ELS is associated with a large proportion of the population attributable risk for SUDs. While pathways to SUDs following ELS are complex and likely multifaceted, it is possible that ELS sculpts the developing brain in a way that increases risk for adolescent substance use, and substance use during this time results in further brain changes that either independently, additively, or interactively contribute to risk for SUDs. Internalizing and externalizing psychopathology may contribute to adolescent alcohol use following ELS. Both ELS and adolescent drug exposure have been related to differences in the structure and function of prefrontal and limbic-striatal regions, regions that are critically involved in the stress response, reward processing, and executive functions. dlPFC: dorsolateral prefrontal cortex; vPFC: ventral prefrontal cortex; OFC: orbitofrontal cortex; ACC: anterior cingulate cortex; Hipp: hippocampus; Amyg: Amygdala.