An Integrative Perspective on the Etiology of Substance Use

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Nicole J. Roberts and Diana Fishbein

Introduction to the "Ecobiodevelopmental" Framework

Persons who initiate use and later develop substance dependence transition through a number of stages, including experimental or social use, escalation, maintenance, abuse, and eventually addiction (Kandel, 2002). These pathways, however, are not without significant fluctuations in usage and desistance patterns. Subgroups of users may never escalate while maintaining moderate use for decades; others may experience intermittent periods of cessation with some abstaining permanently. And still others escalate rapidly and develop substance-abuse disorders (SUD). Determining which experimental users will continue on a path to abuse and dependence is an age-old question that has compelled researchers and practitioners to better understand, predict, and appropriately intervene in these distinct etiological pathways.

The "ecobiodevelopmental" theoretical framework, founded on an integration of behavioral science fields, is helpful in understanding variations in substance-use pathways. This model views human behavior as emerging from the biological imbedding of social and physical environmental conditions (Shonkoff et al., 2012). Individual-level characteristics, such as personality and genetics, interact with experiences and exposures to socio-environmental factors to directly affect the developing brain's structure and function (Duncan & Murnane, 2011; NRC & IOM, 2009; Yoshikawa, Aber, & Beardslee, 2012). This inherent "experience dependence" of the brain means that the nature of conditions to which individuals are exposed—optimal versus suboptimal—influences the resultant behavior. An abundance of positive experiences, such as protective factors (e.g., family support, well-equipped schools), can strengthen neural connections underlying self-regulation, impulse control, and executive decision-making. In reverse, however, negative or adverse exposures can translate to impairments in the developing child's ability to regulate behavior and emotions (Glaser, 2000; McEwen & Morrison, 2013). And importantly, exposures and experiences have differential effects on social, psychological, and neural processes contingent upon the developmental stage, which have functional and behavioral implications (Adler & Rehkopf, 2008).

N. J. Roberts (✉)
The Pennsylvania State University, University Park, PA, USA
e-mail: njr175@psu.edu

D. Fishbein
Program for Translational Research on Adversity and Neurodevelopment, The Pennsylvania State University, University Park, PA, USA
e-mail: dfishbein@psu.edu

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This framework further accounts for the immediate "microlevel" (e.g., family) and surrounding "macro-level" (e.g., neighborhood) factors that influence the development and prevalence of behavior through their effects on individual functioning in multiple domains. While specific influential factors vary between individuals, and no factor alone is sufficient to lead to substance use and abuse, there is likely some critical combination of the number of risk influences present and protective influences that are absent that makes the difference between having a brain primed for substance abuse versus one that is not. Reaching this threshold can be achieved by any number of potential combinations of external and personal factors and thus will be unique for each individual. Nevertheless, brain development is so exquisitely sensitive to psychosocial experiences that their effects on the way the brain develops and functions are observable and those effects, in turn, have a direct impact on a child's ability to self-regulate and, in turn, his or her susceptibility to substance use and abuse. Prevention programming and policy have the potential to strengthen protective influences and reduce exposure to or minimize the effects of negative influences, thus redirecting development away from risky behaviors such as substance abuse.

The aim of this chapter is threefold. First, we describe the independent association of person-level, microlevel, and macro-level influences on substance use as sources of vulnerability and resilience. This evidence is then placed into the context of a developmental and integrative framework on the etiology of substance abuse (see Fig. 3.1). Finally, we discuss the translational implications of this model for identifying developmental windows of opportunity for prevention and intervention programs to curb substance use during key periods when initiation is both most common and most detrimental to development (i.e., early adolescence).

Figure 3.1 exhibits the two main categories of factors conferring risk for substance misuse, genes and the environment. Genetic variants are displayed as switches, either "on" or "off." Environmental influences are presented as dials, turned up or down depending on experience. The combination of switches and dials crosses a liability threshold priming the brain for substance misuse. As shown, the functional relationship between factors is not linear, and some environmental dials confer resiliency and may attenuate the effects of the particular genetics.

Person Level

Fundamental characteristics of individuals play a significant role in determining who will use, misuse, and, in some cases, become addicted to substances, and who will abstain or desist at points in the pathway. Consideration of these roles is important for three reasons. First, genetic variations, neurobiological integrity, personality, emerging stress, and coping responses help to determine an individual's responses to the prevailing social and environmental influences, contributing to eventual outcomes. Personal level characteristics have been shown to predict or moderate outcomes, and they interact with environmental influences in unique and complex ways. Second, knowledge regarding these characteristics is critical in helping to determine what preventive and treatment interventions may have the greatest potential to benefit any given individual or subgroup. This information can also identify opportunities during development for implementing the most effective prevention strategies. And third, we can expect to see favorable changes in these characteristics if the intervention positively influences its targets: a mediation effect. Below we describe those characteristics consistently found to be associated with risk for various substance-abuse pathways, and thus have been implicated in their etiology.

Genetic Susceptibilities and Personality Traits

Genetic susceptibility to substance use and abuse encompasses heritable factors which are believed to influence the trajectory of initiation and progression to addiction, including severity of

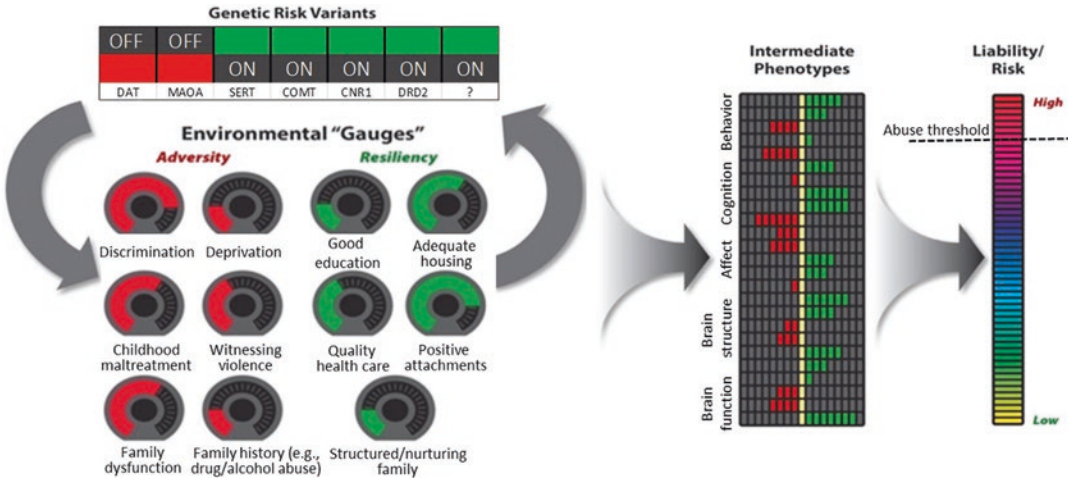

Fig. 3.1 Accumulative model of risk for substance misuse

dependence and risk of relapse (Kreek, Nielsen, Butelman, & LaForge, 2005). By identifying genetic risks that contribute to dependence, we can begin to dissect the various ways in which genes contribute to the transition from escalation to dependence in the context of environmental influences (Bierut, 2011; Vink, Willemsen, & Boomsma, 2005). Critically, studying the genetic components of substance use poses numerous challenges, such as precise phenotypic characterization of individuals, consideration of ethic/cultural backgrounds (as different backgrounds yield differences in allelic frequencies), and achieving sufficient effect sizes (Kreek et al., 2005). Thus, the findings are intriguing and provide a framework for understanding essential gene by environment interactions, but much remains to be explored.

That said, studies suggest that the search for genetic variants affecting substance use should consider the neurobiological systems and phenotypic traits they influence. Genetic variants exert a wide range of actions across multiple functions and characteristics, such as the genetic variation that leads to particular personality traits or the liability to externalizing disorders consistently implicated in the use and abuse of substances (Kendler, Prescott, Myers, & Neale, 2003). The putative role of the dopamine D_2 receptor gene, DRD2, in substance abuse and addiction susceptibility is a case in point (see Le Foll, Gallo, Le Strat, Lu, & Gorwood, 2009 for review). Single-nucleotide polymorphisms (SNPs) in DRD2, for example, have been found to predict specific behavioral traits pertaining to reward sensitivity and inhibitory control, endophenotypes implicated in addiction vulnerability (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007; Klein et al., 2007). Variation in these genetically modulated personality dimensions, particularly impulsivity and novelty seeking, may contribute to the initiation of substance use as well as the transitions from initial to intermittent to regular substance use, the transition from abuse to addiction, and the propensity for repeated relapse after achieving satiety (Kreek et al., 2005). For example, cigarette smokers have been found to exhibit higher levels of novelty/sensation seeking compared to nonsmokers (Zuckerman & Kuhlman, 2000). Individuals with these traits tend to seek highly stimulating and risky situations and show less anxiety in anticipation of the consequences of their behavior (see Kreek et al., 2005). Postmortem studies of the human brain have begun to reveal the link between certain genes and these endophenotypes. Molecular characterizations reveal associations between particular SNPs, including DRD2, and expression in areas of the brain (e.g., the amygdala) linked to these endophenotypes has been implicated in increased risk for addiction (Jutras-Aswad et al., 2012).

Importantly, similar to environmental factors, genetic influences also have differential impacts on these complex behaviors at different developmental stages (Kendler et al., 2003; Li, 2006). Normative development during adolescence is characterized by increased rates of impulsivity and novelty seeking, in part due to dramatic, largely genetically modulated fluctuations in hormone levels that affect brain development and other systems. However, the subgroup of adolescents who exhibit an especially high level of any combination of these personality traits are at heightened risk to abuse substances. Lerman and Niaura (2002) propose that genetic influences on addiction susceptibility are mediated partly by individual differences in comorbid personality traits, as well as individual differences in the reinforcing effects of substances. In effect, it is critical that prevention programs are devised to specifically redirect this developmental track and identify positive outlets that are sufficiently reinforcing.

Behavioral and Mental Health

Internalizing symptoms (e.g., post-traumatic stress disorder [PTSD], depression, anxiety), externalizing behaviors (e.g., conduct disorder [CD], attention-deficit hyperactivity disorder [ADHD], oppositional defiant disorder [ODD], antisocial personality disorder [ASPD]), and mental health conditions have a significant heritable component and are strongly and consistently related to the risk of substance abuse (for review see Armstrong & Costello, 2002). Individuals with these disorders are more likely to use substances and at an earlier age than those without such disorders (De Bellis, 2002; Liddle et al., 2004). Adolescents and adults are also at heightened risk for continued substance use to manage their psychiatric symptoms and for being resistant to substance-abuse treatment (Tomlinson, Brown, & Abrantes, 2004).

The presence of mental and behavioral health disorders may exacerbate the role of poor or maladaptive stress reactivity patterns in developmental pathways to substance abuse. Individuals with internalizing disorders tend to have higher levels of arousal in brain systems responsible for stress responses which may lead to a tendency to self-medicate the symptoms of anxiety and depression (Hussong, Jones, Stein, Baucom, & Boeding, 2011). For those with externalizing disorders, there tends to be a low level of arousal in these systems, which has been associated with a relative lack of regard for consequences and a need for additional stimulation. The likelihood of effectively meeting social challenges due to these internal states is diminished as doing so requires intact neurocognitive and emotional functions (see below), which are often compromised in psychiatric disorders (Kovacs & Goldston, 1991).

Neurological Development

One pathway to substance use and abuse is believed to originate in a deviation or delay in neurological development which is thought to underlie problem (especially risky) behaviors that often precede substance use. Understanding the neurobiological contribution to the etiology of substance use involves characterization of brain maturational processes occurring during adolescence that are associated with substance use, such as reduced inhibitory control and increased reward sensitivity.

While substance abuse is the result of a developmental process beginning in the prenatal period and lasting until one's mid to late 20s, national survey data indicate that initiation is most common in mid-adolescence and that, for the subgroup that escalates, substance abuse peaks during the transition into young adulthood (SAMHSA, 2011). Critically, new social challenges (e.g., increased autonomous decision-making) facing adolescents coincide with complex changes in brain wiring and connectivity taking place throughout this time which have implications for adaptive decision-making and ability to self-regulate behavior and emotion (Giedd et al., 1999; Gogtay et al., 2004). In effect, some degree of impulsivity, risk-taking, and sensation-seeking is normative during adolescence; however, a heightened level of risk-taking

may extend from a combination of social circumstances and nonnormative neurodevelopmental immaturity or dysfunction.

Neurobiological development during adolescence occurs transitionally rather than as a single snapshot in time (Casey, Jones, & Hare, 2008). The prefrontal cortex (PFC), responsible for executive cognitive functions (ECF) (e.g., decision-making, impulse control, working memory), is still under construction. A central function of ECFs is to shield long-term goals from temptations afforded by short-term benefits that often lead to negative consequences (Munakata et al., 2011). Somerville and Casey's dual-system process model (2010) demonstrates how prefrontal "top-down" cognitive regulation over subcortical regions is somewhat functionally disconnected throughout adolescence; subcortical, limbic structures which modulate affect and emotional responses to social cues mature earlier than PFC regions. As a result, adolescents are naturally biased by emotional impulses relative to cognitive control. Through both the natural course of development and environmental experience, the functional connectivity between these regions is strengthened and provides a mechanism for increasing top-down modulation of the subcortical systems (Hare et al., 2008).

In addition, ventral striatal reward processing circuits show rapid maturation during the adolescent years, reflected by an increase in the salience of a potential reward (Geier & Luna, 2009; Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011; Somerville, Jones, & Casey, 2010). This heightening of reward sensitivity may play a unique role in substance-use initiation rates in early to mid-adolescence and may be exaggerated in the subgroup that escalates use. Subsequent use of substances may exacerbate some adolescents' already heightened ventral striatum response resulting in a strengthening of the substance's reinforcing properties (Hardin & Ernst, 2009). In line with this increase in reward sensitivity, a greater tendency to sensation/novelty seeking is typical during this developmental period (Steinberg et al., 2008). Compounding these neurological liabilities are early puberty and erratic hormone levels, as well as detrimental environmental conditions, such as stress, adversity, maltreatment, and other negative experiences that compromise neurodevelopment and can cause measurable dysfunction in these systems.

Another aspect of neurodevelopment shown to exert an influence on substance-abuse propensity is prenatal exposure to substances, considered both as a direct and mediating mechanism. Prenatal and early exposure to cigarette smoke has been shown to increase children's propensity to smoke, become dependent on nicotine, and exhibit externalizing (conduct problems such as aggression) and internalizing (e.g., depression, anxiety) symptoms (Cornelius, Goldschmidt, & Day, 2012; Piper & Corbett, 2011). Prenatal drug and alcohol exposure is associated with subsequent behavioral problems in the offspring in childhood and adolescence, including eventual substance abuse (DiNieri et al., 2011; Sithisarn, Granger, & Bada, 2012). Alterations in neurological systems associated with self-regulation, reward, and motivation in the fetus, due to the properties of the drug(s) pregnant women use, appear to be the mechanism by which prenatal drug exposure affects the child. The effects of these sorts of prenatal exposures on mental health and behavior will tend to exacerbate any preexisting susceptibilities to use, abuse, and develop addiction to a substance(s).

In sum, regardless of the source of delayed or deficient neurodevelopment, the eventual imbalance between social demands and emergent neurobiological systems during adolescence may lead to heightened vulnerability to substance use and escalation (Casey & Jones, 2010). This evidence has direct implications for the design of intervention components that target this period of development. For example, strategies that focus on incorporating risky and exciting activities (e.g., rock climbing) may provide adolescents with positive ways of obtaining needed stimulation (Perry et al., 2011). In addition, mounting evidence shows that physical activity and programs that include mindfulness have direct neurobehavioral effects; both appear to protect against PFC-mediated impulsivity and drug-use vulnerability (see Perry et al., 2011). Indeed,

prevention programs are emerging that target individual-level personality and cognitive factors reflective of underlying neural mechanisms, such as impulsivity and cognitive and emotion regulatory deficits (Conrod et al., 2013).

Stress Exposures and Physiological Reactivity

Stress is a major common denominator across neurobiological, physiological, psychological, and environmental domains implicated in susceptibility to substance use, escalation, relapse, and treatment resistance. "Stress" refers to processes involving perception, appraisal, and response to harmful, threatening, or challenging external events or conditions, known as "stressors," such as poverty, prenatal exposures, child maltreatment, divorce, and bereavement (Pechmann, Levine, Loughlin, & Leslie, 2005). Numerous studies have demonstrated associations between increasing levels of emotional and physiological stress and decreases in behavioral control, higher levels of impulsivity, and high levels of maladaptive behaviors, including substance use (e.g., Hayaki, Stein, Lassor, Herman, & Anderson, 2005; Greco & Carli, 2006; Fishbein et al., 2006; Hatzinger et al., 2007). There is also substantial evidence to support the role of stress in substance-use pathways (e.g., Fishbein et al., 2006; Lee, Neighbors, & Woods, 2007; Simons-Morton & Chen, 2006). Early-life adversity, in particular, is markedly associated with increased risk for substance use, abuse, and dependence (Dube et al., 2003). This fundamental relationship is clearly demonstrated by results of the Adverse Childhood Experiences (ACE) study; results claimed that population-attributable substance-use risk associated with early-life adversity was 50% for substance abuse, 65% for alcoholism, and 78% for intravenous drug use (Chapman et al., 2004; Dube et al., 2003), suggesting that very early development sets the stage for response to initiation by primary biological, psychological, and social responses to initiation.

Similar to all other risk factors, exposure to stress has differential effects on social, psychological, and neural functioning, contingent upon the developmental stage of exposure (Adler & Rehkopf, 2008). In fact, repeated and/or severe exposure to stressors compromises the development of neural systems that underlie social, behavioral, cognitive, and emotional functioning in profound and enduring ways (Davidson, 1994; Pechtel & Pizzagalli, 2011). Andersen and Teicher (2008) argue that early-life stress predisposes individuals to abuse substances via alterations in immature neurophysiological systems that have yet to come on board. Then later in adolescence, when these emergent systems become increasingly functional, the damage is expressed in heightened risk for psychopathology. With greater levels of stress, changes in brain circuitry—which largely occur in the prefrontal cortex (Teicher et al., 2010)—lower behavioral and cognitive control, demonstrating that regulatory brain pathways are targets of brain stress chemicals (see Sinha, 2001 for a review).

More specifically, stress exposures disrupt hormonal systems (e.g., cortisol) that regulate these functions (Huether, 1998); chronically elevated levels of stress hormones can impair learning, memory, decision-making, and other functions that normally support self-regulation of behavior (Nelson & Carver, 1998). Studies also show effects of stress on physiological responses such as heart rate and skin conductance that, when disrupted, are associated with poor behavioral and emotional regulation and cognitive and coping skill deficits (Lovallo, 2012). These physiological and behavioral stress responses activate the same neural systems underlying the positive reinforcing effect of drugs (Koob & Le Moal, 1997), potentially reinforcing drug-taking behaviors. As a result, when an individual experiences a great deal of stress or adversity, these neurologically based processes are affected and lead to poor ability to cope with stress, both behaviorally and physiologically. In these cases, there is often impaired coordination between social, cognitive, psychological, emotional, and biological responses; such impairments have been found to increase drug-seeking behavior (Robinson & Berridge, 2000). As a result, drug taking may

occur as a maladaptive response to stressful experiences.

In sum, the changes in biological and psychological processes induced by stress are strongly related to early onset of substance use (Sinha, 2001) and may predict the escalation of drug use, relapse, and intractability. Recognizing the increased risk for substance use in people who have experienced early-life stressors is critical to guide prevention efforts designed to both prevent the exposure and counteract the potential subsequent negative consequences by teaching children ways in which to cope with early-life stress in healthy ways.

Microlevel Influences

Substance use cannot be understood or addressed without understanding the social context within which individuals grow, develop, and interact. This section considers not only liability factors that influence problem behavior, but also environmental conditions that may insulate individuals from negative outcomes.

Parenting and Family Functioning

The home environment is the single most profound influence on early child development in multiple domains of functioning (NRC & IOM, 2013). Parenting and family continue to be important through adolescence when youth begin to have more autonomy and opportunities for either prosocial or risky behaviors (Ernst & Mueller, 2008). The effects of a chaotic home environment, ineffective parenting, and lack of mutual attachment are particularly impactful on overall child outcomes (Springer, Sheridan, Kuo, & Carnes, 2007). The regulatory skills children need to resist substance use and other problem behaviors are instilled early in life, suggesting that a favorable home environment may confer protection against negative outcomes.

The strength of parental influence on substance use has been well documented (e.g., Lippold, Greenberg, Graham, & Feinberg, 2014; Wood, Read, Mitchell, & Brand, 2004). The quality of parenting has been found to interact with factors such as psychological well-being, exposure to stress, and social support in predicting general antisocial behavior, as well as substance use (NIDA No. 94-4212, 1997). Parenting techniques that foster healthy development (e.g., appropriate discipline practices, warmth, affection, secure attachment, involvement, limit setting, and monitoring) are protective (Mayberry, Espelage, & Koenig, 2009; Velleman, Templeton, & Copello, 2005). For example, Lippold et al.'s (2014) results demonstrated that parent efforts to monitor youth in Grade 6 predicted substance use in Grade 8. In addition, their findings suggest that the monitoring process may be influenced by the quality of the parent-youth relationship; within warmer relationships, parent attempts to solicit information from youth may be perceived more positively by youth.

Conversely, parenting behaviors that are harsh, restrictive, inconsistent, hostile, and/or high in conflict can often lead to negative behavioral outcomes in children (Barrett & Turner, 2005). Among children exposed to these negative parenting qualities, there is a 2–4 times higher likelihood of mental and physical health issues compared to national norms (Herrenkohl, Lee, Kosterman, & Hawkins, 2012). At the extreme of parenting behavior, abuse, neglect, and domestic violence, in particular, threaten every aspect of children's development. Additionally, parental substance abuse, which is often associated with poorer quality of parenting, has repeatedly been a strong predictor of substance use in adolescence (e.g., De Micheli & Formigoni, 2002; Madu & Matla, 2003). In addition to parenting, various aspects of the family environment can influence the child's subsequent substance-use behavior, including structure, family cohesion, family communication, and family management (see Velleman et al., 2005). Family processes that tend to be most effective are those with limited levels of stress exposure and coercion (Barrett & Turner, 2006). Additionally, higher levels of substance use have been found in adolescents from single-parent families, consistent with studies reporting that dual-parent families afford

protection against substance use (e.g., Adlaf, Ivis, Smart, & Walsh, 1996). This finding could be due to the lack of a protective presence of an additional person in the home which can buffer the child from stress exposure and lack of monitoring.

In response to these reports, family-based preventive interventions recognize that many aspects of the family context play an important part in socializing children to adjust to the demands and pressures of the social environment. Preventing poor outcomes (e.g., mental, emotional, and behavioral problems, substance use) in children often involves parent skill training, relieving the stressors and mental health problems of caregivers, and trauma prevention and trauma-informed treatment strategies (Shay & Knutson, 2008).

A needs assessment of 129 parents discovered that parents did not know how to identify "teachable moments," and they lacked the appropriate requisite language when trying to speak about substance issues with their children (Velleman, Templeton, & Copello, 2005). The National Survey of Children's Health (2003) reported that there is a significant relationship between parental communication of their disapproval of substance use and less subsequent use by their child. Together, these findings suggest that prevention programs should incorporate an educational component which teaches parents the extent to which their own behavior influences young people's use of substances, and ways in which they can initiate and carry out conversations with their child about substance use. Indeed, prevention programs (e.g., "Preparing for the Drug Free Years") have begun to incorporate such educational components (Kosterman, Hawkins, Haggerty, Spoth, & Redmond, 2001).

Schools and Educational Opportunities

The quality of the school environment, its teachers, curriculum, and students' social networks in school are major socializing influences on student learning and behavior (Bond et al., 2007; Cleveland, Feinberg, Bontempo, & Greenberg, 2008). At a very basic level, attendance in school protects against poor outcomes on multiple levels, and may exert a particularly powerful effect for children with self-regulatory problems (Christle, Jolivette, & Nelson, 2005). In addition, unqualified teachers, ineffective teaching practices, and low-quality curricula confer significant additional risks, leading to academic failure (Christle et al., 2005; Darling-Hamond, 2000). Lack of a good education and poor classroom management set the stage for lower levels of cognitive functioning, poor social skills, high levels of stress, and perceptions of inadequacy and failure (Engle & Black, 2008), each of which is implicated in risk for substance abuse. And eventually, a poor-quality education results in an inability to compete in the workforce and obtain jobs that pay a good wage (Campbell, Ramey, Pungello, Sparling, & Miller-Johnson, 2002), factors also associated with substance abuse.

Effectively teaching students the academic and social skills necessary to succeed in school and in life requires that schools also address the special needs of children with social, learning, mental health, and emotional issues that could interfere with success in the classroom (Adelman & Taylor, 1999). Lack of support within the schools for these children often means that disadvantaged or special-needs youth fail to receive the attention they require to overcome their challenges. Absent adequate educational support and/or targeted school programs, learning disabilities, and mental health problems increase the risk for substance abuse (Mason et al., 2010).

Another aspect of school influences is the important role of school connectedness. Research suggests that youth are more likely to have mental health problems and an increased likelihood to use substances in their later years of schooling when they report low school connectedness and interpersonal conflict in early secondary school (Bond et al., 2004; Catalano, Oesterle, Fleming, & Hawkins, 2004). Bond et al. (2007) found that young people in grade 8 who were socially connected, but not connected with school, were more likely to become regular smokers and use marijuana 2 years later, suggesting that students who do not have good school connectedness,

regardless of their social relationships, are at greater risk for engaging in subsequent substance-use behaviors. A child's attachment to school appears to be a component of resilience, indicating that effective and responsive teachers, evidence-based curriculum, and classroom reinforcements may play an important role in substance-abuse prevention.

Peer Influences

There is a strong association between adolescent substance use and contact with drug-using peers. Research suggests that there may be social aspects of adolescent substance use in that other adolescents provide a unique source of access, reinforcement, and opportunity to use drugs (Kirke, 2004; Simons-Morton & Farhat, 2010). Urberg, Luo, Pilgrim, and Degirmencioglu (2003) and others have questioned the extent to which peer influence is responsible for adolescent substance use, claiming that there is a difference between *selection* and *influence* of friends. Adolescents tend to be similar to their friends with respect to behaviors, attitudes, and personality traits (Urberg, Değirmencioğlu, Tolson, & Halliday-Scher, 1995; Urberg et al., 2003), and similarities appear to be present even before friendships are established. Studies have proposed models suggesting that adolescents who choose substance-using friends may differ from those who do not. The quality of the friendship seems to also be a factor in determining the extent an individual may be influenced by a friend; a high-quality relationship may be more valued by the adolescent, who then may be more likely to change their behavior to please the friend. Better friends also may spend more time together, resulting in more modeling and emulation of deviant behavior. Additionally, the weight of their influence may be a function of other factors, such as parental monitoring, school rules regarding off-campus access during school hours, and so forth. Regardless of the difference between *selection* and *influence* of a friend, a more complete understanding of these complementary processes will greatly assist prevention science in developing ways to decrease the risk factors associated with acquiring and having substance-using friends (Prinstein & Wang, 2005; Tragesser, Aloise-Young, & Swaim, 2006).

Interestingly, one of the ways in which peers *appear* to influence one another is through the idea of "pluralistic ignorance" (Prentice & Miller, 1993). In other words, a subgroup of adolescents have a general belief that more individuals are engaging in substance use than actually are and, in turn, they themselves are more likely to then use substances (Prinstein & Wang, 2005; Tragesser, Aloise-Young, & Swaim, 2006). Conversely, those who believe that substance use will have harmful consequences are less likely to use. For example, a survey conducted by the Center of Addiction and Substance Abuse found that teens who viewed substance use favorably in terms of the benefits of substance use (e.g., popularity, weight control, self-medication, stress relief) were more likely to smoke, drink, and use other drugs than those who perceived use less favorable or had stronger perceptions of risk (CASA, 2011).

Understanding the contextual factors that increase or attenuate susceptibility to peer influence is crucial for the development of prevention and intervention programs. Research on the role of peers suggests that programs need to focus their efforts broadly on the multiple social contexts in which adolescents behave, and not just on peer influence, to be most successful.

Macro-Level Influences

The Neighborhood and Physical Environment

Social conditions in neighborhoods have important implications for risk for substance use; they shape social norms, enforce patterns of social control, influence perception of the risk of substance use, and effect psychological and physiological stress responses (Shonkoff & Phillips, 2000). Informal social controls and norms are vital and embraced for maintaining neighborhood viability, including issues such as observable

violence, child maltreatment, and public consumption of illegal drugs, among other risky behaviors. In particular, decades of research have demonstrated that the risk for substance use is related to the prevailing norm toward substance use in the social environment (Elek, Miller-Day, & Hecht, 2006).

One aspect of neighborhood influence is the perception of social cohesion—an indicator of attachment to and satisfaction with the neighborhood and its residents and, thus, involves trust and support for one another in a community. Socially cohesive neighborhoods allow parents to depend on each other for help when needed to maintain norms for positive social behavior and communication in the neighborhood, and support each other in guiding children and adolescents. High social cohesion has been suggested to be associated with lower substance use among adolescents (Winstanley et al., 2008), fewer perceived youth drug problems (Duncan, Duncan, & Strycker, 2002), and lower drug-related mortalities (Anderson & Baumberg, 2006a, 2006b).

Another influential factor is the extent to which the neighborhood is perceived as disorganized or disordered—an area characterized by vandalism, abandoned buildings and lots, graffiti, noise, and dirt. The neighborhood context has been found to be particularly influential for low-income urban youth due to the high level of exposure to drug activity, disorder, and violence in their neighborhoods, all of which may influence substance use (Furr-Holden et al., 2011). Indeed, Lambert, Brown, Phillips, & Ialongo (2004) found that perceptions of neighborhood disorganization in grade 7 predicted increased tobacco, alcohol, and marijuana use in grade 9 among urban black youths. Additionally, Buu et al. (2009) reported that children whose neighborhoods became more stable from early childhood to adolescence tended to develop fewer alcohol-use disorder symptoms relative to children who remained in disorganized neighborhoods. Many aspects of the physical design of the environment can also harm young people's overall development (Leventhal & Brooks-Gunn, 2000; Shonkoff & Phillips, 2000), social relations, and crime, all of which have implications for substance use. Decayed and abandoned buildings, ready access to alcohol and drugs, urbanization of the area, and neighborhood deprivation are associated with drugs, crime, violence, and accidents. High level of exposure to toxic substances (e.g., heavy metals, in utero alcohol, lead, cadmium, mercury, manganese, arsenic) is another aspect of the physical environment that can harm overall development. During the prenatal period and early childhood, such exposures have been strongly and consistently linked to functional deficits (e.g., cognitive dysfunction and psychological disorders; Bellinger, 2012), and later risk for substance abuse, as well as other forms of psychopathology. Lead exposure, in particular, at even only moderately elevated levels, has been shown to lead to mental retardation, and lower levels have been related to hyperactivity and violence in children. Although the research is scant with respect to their direct association with substance use, exposures are more definitively related to personal characteristics (e.g., psychiatric disorders, lack of impulse control, cognitive deficits) that are known to increase the risk for substance abuse (Andrade et al., 2014).

The media is one of the most insidious influences on social norms and other messages that are favorable toward substance use (Feinstein, Richter, & Foster, 2012). Adolescents in particular spend a great deal of time being entertained by television, movies, radio, the Internet, magazines, smartphones, and social media cites. In essence, these messages can make substance use appear to be normative behavior and can alter attitudes about the safety of substance use. As such, social media has been repeatedly linked to initiation of substance use (see Feinstein et al., 2012).

Income/Resources

Over the past few decades, a growing body of evidence has been amassed to help us better understand how overall conditions in impoverished communities lead to considerable delays or deficits in child and adolescent development (see Blair, 2010). Impoverished neighborhoods with a

high rate of single-parent families, racial segregation, inequality (based on race, sex, or other characteristics), homelessness, transiency, and poorly equipped school and teachers are profound risk factors for substance use, along with high levels of child abuse, infant mortality, school dropout, academic failure, crime, delinquency, and mental illness.

On an individual level, poverty's influence on families and parenting can lead to harmful effects on child and youth development by increasing stress among parents and caregivers, by reducing their ability to invest in learning and educational opportunities, and by compromising their ability to be involved, patient, responsive, and nurturing parents to their children (Ginsburg, 2007). As previously described, all of these conditions—both individually and through their interaction—are risk factors for substance use. Indeed, many studies have demonstrated that economic adversity is associated with disruptions in parenting behaviors and that psychological distress in parents is linked to substance abuse in children (e.g., Jackson, Brooks-Gunn, Huang, & Glassman, 2000). Furthermore, the caregiving environment for low-income children is more likely to be disorganized and lacking in appropriate stimulation and support, thereby creating conditions that are stressful for children (Evans, 2004; Repetti, Taylor, & Seeman, 2002). And stress, in the context of an impoverished, unsupportive environment, impedes growth, leads to dysregulated physiological responses to stressful situations, increases risk for psychological disorders (e.g., depression, anxiety, and traumatic stress disorders), and compromises development of self-regulatory skills, key vulnerability factors in substance use.

Youth who experience poverty and/or a lack of resources are subject to a host of environmental and health factors including homelessness, street involvement, exposure to toxic substances, and work at a young age. As a result, there is a high incidence of behavioral and psychological problems, including use and abuse of substances, in these youth (Meltzer, Ford, Bebbington, & Vostanis, 2012; Nada & El Daw, 2010). In each of these scenarios, there is a lack of available services or supports (starting with assessments to identify and address particular needs) to lift children out of these circumstances (Marshall & Hadland, 2012). With increased availability of badly needed services for these children, plus political and healthcare involvement, there is potential for them to develop skills that would improve their chances of success in school and life, combatting many of the risk factors for substance abuse (Hudson & Nandy, 2012).

Public Policy/Government Influence

Despite governments' attempts to reduce disparity, certain racial, ethnic, income, and gender groups continue to receive differential treatment and have restricted access to the goods and services available in their society. Research has focused on understanding discrimination both as involving social processes that impact identifiable groups and as social acts experienced by individual members of that group. Discriminatory attitudes, policies, and practices limit the power, status, and wealth of these groups which contributes to patterns of social isolation and concentrated poverty (see Thompson, 2016). In turn, residents in these poor neighborhoods often tend to experience lower levels of physical and mental health, educational attainment, and employment, and exhibit higher levels of risk behaviors such as substance abuse compared to residents residing in more advantaged neighborhoods (Small & Newman, 2001).

The implications of discrimination and social exclusion for child development arise from both a structural and cultural perspective. Structural inequalities lead to adverse educational, health, and behavioral outcomes, and are largely due to differential access to material needs, such as adequate nutrition, quality housing and schools, as well as increased exposure to environmental toxins and hazards. Poor access to services and social supports and a lack of collective neighborhood efficacy compound the problem (Chou, 2012; Odgers et al., 2009; Saechao et al., 2012). Adding to the challenge is the lack of effective coping strategies that often characterize

disadvantaged children. These problems tend to be compounded in individuals with an immigrant status. Cumulative adversity in immigrants, including language and legal status barriers (Perreira & Ornelas, 2013), perceived discrimination (Tran, Lee, & Burgess, 2010), and acculturation issues have all been related to risk for substance abuse and mental health problems.

An Integrative Perspective of the Etiology of Substance Use

Both Shonkoff's et al. (2012) and Bronfenbrenner's (1997) seminal works were instrumental in developing an initial framework for conceptualizing contextual influences on development. They propose that development is shaped by a range of nested, contextual systems whose joint impact is remarkably influential in healthy development. A clear demonstration of this (Mayberry, Espelage, & Koenig, 2009) found that adolescents' views of their school and community were associated with the amount of substance use they report. Moreover, these contextual systems acted as protective factors in relation to negative peer pressure and negative parenting attitudes and behavior. Prevention practices and interventions that focus on the *interaction* of communities, school, peers, parents, and individual development, and how they can influence each other as protective or risk factors for substance use, abuse, and addiction, are most powerful (see Brody et al., 2006; Hecht et al., 2003; Pantin et al., 2003). Programs need to train socialization agents to be better at what they do (e.g., parenting, teaching) as socialization defines the interaction between an individual, micro- and macroenvironments, and final outcomes.

In addition, preventive programs and interventions would benefit from integrative services that simultaneously consider various contexts of development, and the complex interrelated needs of individuals. Protective factors need to be developed and honed in the individual's peer group and family, and in the communities and schools. To truly understand the etiology of substance use with the critical mindset of prevention, one must understand developmental sequencing and how the aforementioned factors interact during distinct stages of development. Several important differences across stages of development influence outcomes in individuals who are exposed to the abovementioned factors and who exhibit the personal characteristics that have been related to propensity to experiment, use, and abuse substances. Each stage of development, from prenatal to early adulthood, is associated with a certain expected range of intellectual ability; language development; cognitive, emotional, and psychological functioning; and social competency skills that need attention to prevent the onset of substance abuse. Effective interventions that focus on these developmental milestones have been mapped to each stage as described in the foregoing.

In infancy, responsiveness to the environment and caregivers' interactions, and vice versa, and learning how to be effective in having needs met are of great importance for successful outcomes (Mullany et al., 2012—Family Spirit and Nurse-Family Partnership). Later, in early childhood, language, cooperation, control of emotions, collective conscience (cooperation), social and emotional skills, and problem-solving begin to develop and predict later social competence (Dishion et al., 2008—Early Steps Family Check-Up). Maintaining attention, controlling emotions, social inclusivity, effective communication, and reception emerge in middle childhood (Riggs, Greenberg, Kusché, & Pentz, 2006—Promoting Alternative Thinking Styles and Good Behavior Game). And in adolescence, social and emotional skills to establish stable relationships, sensitivity to needs of others, conflict resolution, prosocial skills, and impulse control are integral to self-regulation of emotion and behavior, which are predictive of favorable outcomes in early adulthood (Botvin & Griffin, 2004—Life Skills Training). Relatedly, delaying initiation of substance use in adolescence can be considered a goal for prevention policy. Each factor described above has an impact on the tendency to begin using substances early in adolescence, which has been repeatedly associated with risk for escalation and eventual abuse and addiction (e.g.,

McCabe, West, Morales, Cranford, & Boyd, 2007).

Given these differential levels of competency throughout childhood and adolescence, the social and physical environmental factors outlined above are expected to have different effects on the individual depending upon their developmental stage. Similarly, the phase of development must be considered when targeting interventions to particular risk factors, populations, and settings, as the programs themselves will be received and processed differently given the level of maturity in these processes. For example, the development of ECFs is a multistage process starting in early childhood when the building blocks for these higher order cognitive functions begin to form, followed by a period of complex refinement in adolescence (Zelazo & Carlson, 2012). The more complex features of executive cognitive functions (ECF) such as problem-solving, goal-setting, impulse control, and working memory only begin to surface in adolescence and do not coalesce until early adulthood (Geier & Luna, 2009). During adolescence, demands for coping with competing social, cognitive, biological, and academic changes are high and have important long-term implications for the emergence of risk behaviors (Petersen, Leffert, & Graham, 1995; Pope et al., 2003; Thadani, 2002). Taking into account the level of development of ECFs along with prevailing social demands of the individual helps to determine what type of interventions will work best—in terms of being understandable and executable—during adolescence as opposed to early stages when ECFs are much less developed. Given the prominent role of ECF deficits as an etiological factor in substance abuse, these are important considerations. The same issues are relevant for social and physical environmental risk factors which will exert different effects from a risk standpoint depending on the developmental period of exposure, as well as personal characteristics such as psychological disorders which develop and evolve over time.

Research has begun to explore the interactions of many of these influences in an effort to understand how they interact, shape, and affect each other. There is evidence that peers moderate neighborhood effects, such that high levels of positive peer support lead to a decrease in deviant behavior for children who live in impoverished neighborhoods. And community/school contexts have been found to moderate the association between parent/peer factors and adolescent substance use even after taking into account the variance that parents, peers, school, and community have individually on substance use (Mayberry, Espelage, & Koenig, 2009). In sum, the earlier and the more multifaceted the intervention is, the more effectively we can redirect behavioral pathways, increase resiliency, and reduce exposure to the potentially long-term adverse effects of the above etiological conditions, including the early use of drugs itself. In all cases, an enriched environment, external supports, and high-quality education are essential at all ages.

Crucially, sustaining the effort over time is critical to exert positive effects into late adolescence and early adulthood with appropriately different goals and approaches. Adolescence and early adulthood are not too late for intervention given the tremendous amount of brain plasticity and maturation of cognitive and emotional regulatory functions that are taking place, providing a window of opportunity to improve outcomes, such as substance use, abuse, and addiction. Many mental health, emotional, and behavioral problems result from impulsive, sensation-seeking activities among teenagers. And in adulthood, influences on these behaviors persist and require ongoing attention to prevent further escalation of use, addiction, and relapse.

Translational Implications of Etiological Research

Considerable evidence indicates that the myriad of behavioral problems are preventable; based on that knowledge, several evidence-based programs (EBPs) have emerged from various disciplinary perspectives. EBPs that focus on socio-emotional and cognitive functioning, development of which is particularly vulnerable to adverse psychosocial and environmental influences, may redirect and possibly normalize

specific dimensions of a child's developmental pathway in behavioral, emotional, mental, and physical (e.g., brain function) domains. The effects of appropriately targeted interventions, even those that are universally implemented, may be particularly remarkable for children who are disadvantaged by poverty and other social ills. Research that integrates multiple disciplines to better understand influences and outcomes related to substance abuse have directed us toward solutions for these problems that target underlying mechanisms and not solely substance abuse, per se. It is vital that we address the factors that eventually lead to substance abuse prior to its development, the key behind prevention science.

Taking all the evidence together, the integrity of the way the brain develops from gestation through adolescence is a significant prerequisite for adaptive responses to socio-environmental challenges. Thanks to vast brain plasticity throughout childhood there is a great deal of variability in the way children develop in response to environmental inputs. This scenario throughout development provides an optimal window of opportunity for intervention. When neurodevelopment is on course or shows a trend toward improvement, overall intervention outcomes are likely to be favorable. In contrast, existing or emergent neurodevelopmental deficits or delays may compromise intervention effects, potentially explaining differential outcomes in response to even the most highly regarded and efficacious programs. A comprehensive evidence-based set of solutions (programs and policies) to prevent psychopathology and eventually substance abuse operate to enhance developmental indicators of brain function in multiple domains. This approach will, in turn, improve the ability to self-regulate behavior and reduce the risk for developing substance abuse.

Applying this integrative and developmental perspective will lead to significant advancements in our ability to prevent substance use and eventuality of abuse and addiction for some. Indeed, researchers have begun to incorporate cognitive training, mindfulness approaches, behavioral and environmental modifications, and other innovative strategies that target neurodevelopmental processes that contribute to substance abuse (Bryck & Fisher, 2012; Twamley, Narvaez, Becker, Bartels, & Jeste, 2008). There are many outstanding questions in this line of research; however, we do know enough about prevailing conditions that influence the risk for substance abuse to exert a positive impact now.

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