Infusing Neuroscience Into the Study and Prevention of Drug Misuse and Co-Occurring Aggressive Behavior

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The etiology of behavioral precursors to substance misuse and aggression is viewed from the perspective of a developmental, multifactorial model of complex disorders. Beginning at conception, genetic and environmental interactions have potential to produce a sequence of behavioral phenotypes during development that bias the trajectory toward high-risk outcomes. One pathway is theorized to emanate from a deviation in neurological development that predisposes children to affective and cognitive delays or impairments that, in turn, generate dysregulatory behaviors. The plasticity of these neurobiological systems is highly relevant to the prevention sciences; their functions are reliant upon environmental inputs and can be altered, for better or for worse, contingent upon the nature of the inputs. Thus, social contextual factors confer significant influence on the development of this neural network and behavioral outcomes by increasing risk for, or protecting¹ against, dysregulatory outcomes. A well-designed intervention can exploit the brain’s plasticity by targeting biological and social factors at sensitive time points to positively influence emergent neurobiological functions and related behaviors. Accordingly, prevention research is beginning to focus on perturbations in developmental neural plasticity during childhood that increase the likelihood of risky behaviors and may also moderate intervention effects on behavior. Given that the more complex features of neurobiological functions underlying drug misuse and aggression (e.g., executive cognitive function, coping skills, affect regulation) do not coalesce until early adulthood when prefrontal-limbic brain networks consolidate, it is critical that mechanisms underlying developmental risk factors are identified. An empirically driven prevention approach, thus, may benefit from consideration of (i) the type, effect, and developmental timing of the environmental impact on the brain, and (ii) the type and

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¹The reader is reminded that these two concepts, which are often noted in the literature, are all too often inadequately delineated in terms of their dimensions (linear, nonlinear), their “demands,” the critical necessary conditions (endogenous as well as exogenous ones, and both micro and macro) which are necessary for either of them to operate (begin, continue, become anchored and integrate, change as de facto realities change, cease, etc.) or not to and whether their underpinnings are theory-driven, empirically based, individual, and/or systemic stakeholder bound, based upon “principles of faith,” etc. Such understanding is necessary if these posited processes are not to remain as yet additional shibboleths in a field of many stereotypes. Hills’s criteria for causation are a useful consideration. These were developed in order to help assist researchers and clinicians determine if risk factors were causes of a particular disease or outcomes or merely associated. Editor’s note 1204
effect on brain function, and developmental timing of the intervention. This translational approach promises to eventually offer some direction for the design of effective interventions to prevent drug misuse and concomitant aggression.

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**Introduction**

A multitude of factors, from the genetic to the social environmental, directly impact the brain to influence the expression of psychological and behavioral disturbances which commonly precede substance use disorder (SUD) and related psychopathology, particularly aggressiveness (see Chambers et al., 2003; Spear, 2000; Tarter et al., 1999 for reviews). Various aspects of brain function may constitute a formidable liability to both substance misuse and aggression. Interactions between compromised brain function and deleterious environmental conditions (e.g., deprivation, poverty, traumatic stress, and prenatal drug exposure) further compounds that risk. The relationship between neurobiological and environmental processes is interactive, fluid, and cumulative in their ability to influence an individual’s developmental progress and alter subsequent behavioral outcomes. Given the codependent relationship between these processes, brain function is now believed to be malleable via manipulations of the environment in ways that may decrease liability for psychopathology. Research that explores these relationships and ways in which interventions can redirect this developmental track may substantially advance both the science and practice of prevention of substance misuse. Accordingly, interventions directed at promoting normal neurological development would most likely have preventative benefits.

**Altering Pathways to Substance Misuse**

While we know a great deal about the effects of socio-environmental conditions on propensity to certain behavioral disorders, only recently have discoveries in the field of neuroscience linked brain function with a predisposition for substance misuse and related high-risk behaviors. Research has clearly established that the origins of brain and behavioral dysfunction are both genetically and environmentally determined (McGuire, Neiderhiser, Reiss, Hetherington, and Plomin, 1994; O’Connor, Reiss, McGuire, and Hetherington, 1998b; Pike, Hetherington, Reiss, and Plomin, 1996; Reiss et al., 1995); thus, their presence can cumulatively alter an individual’s developmental trajectory to influence subsequent development and behavioral outcomes. Several markers indicative of brain dysfunction have been identified and associated with particular behaviors such as aggressiveness that characterize liability for substance misuse. For example, studies suggest that individuals prone to substance misuse possess a greater number of deviations in particular genes (i.e., polymorphisms) that affect the activity and metabolism of the neurotransmitters serotonin, norepinephrine, and dopamine than those that do not (see Fishbein, 1998). Also, physiological, neuropsychological, and neuroimaging studies implicate dysfunction of particular brain regions in several aspects of vulnerability to drug addiction and related behaviors, including impaired judgment, conduct disorder (CD), sensation-seeking, attention deficits, and impulsivity (see Raine, 1993). All of these aspects of brain function are at least partially alterable by our environment in ways that may increase or decrease liability for substance misuse. Thus, it is critical that prevention research begin to explore these relationships and devise ways in which prevention programs can redirect this developmental track.
Research-based prevention programming should focus on optimizing the potential of individuals in the context of prevailing social and biological conditions. Under optimal socio-environmental circumstances, a responsive social system supports and encourages constructive choices, lifestyles, and opportunities. And on an individual level, the necessary internal controls are present to select and sustain a productive path. The potential to take advantage of existing external resources, make adaptive choices, and reach potentialities depend upon executive decision-making and rational thought capacities—functions modulated within the central nervous system (CNS). In the dual absence of favorable external resources and developmentally appropriate brain function, high-risk or maladaptive behavior more likely becomes the default option. In general, therefore, research-based prevention strategies must achieve the following three goals: (1) to structure the environment to be more responsive to human needs and expand the availability of constructive choices and opportunities, (2) to optimize brain functioning, and (3) to introduce an intervention that will have an impact on one or both of these processes when they are somehow in deficit.

To effectively accomplish these goals, the relationship between environmental and biological liabilities must be better understood. This identification process will generate a better understanding not only of how environmental conditions influence brain function but also how genes and aspects of brain function moderate the social environment. Such information will more fully explain why some individuals are susceptible to substance misuse and aggression, i.e., more likely to choose to alter brain function via “abusable drugs”2 and engage in related risky behaviors than others under certain conditions. There is ample research demonstrating the role of innate strengths and vulnerabilities in propensity for substance misuse and the external environment’s contribution to behavioral disorders through its impact on brain function.

Based on the above discussion, it is evident that neuroscience research can contribute, in several important ways, toward substance misuse prevention.

1. Delineation of neurobiological vulnerabilities may be useful for identifying high-risk youths.
2. Identification of the environmental factors that potentiate expression of these vulnerabilities enables the design of ecological preventions which promote health development.
3. Application of neuron-rehabilitation techniques in a variety of settings to enhance neurodevelopment, thereby preventing expression of risk-enhancing psychological characteristics.

The discussion begins with a conceptual perspective for explorations of the brain–environment relationship. Then, a review of the literature is presented specific to the role of genetics and neurobiological factors and the impact of environmental factors on brain function and behavioral outcomes, including exposure to adverse conditions from the prenatal environment through adulthood. In conclusion, implications of the neuroscience research for prevention strategies are discussed and a prospective research agenda is proposed.

2The often used nosology “drugs of abuse” is both unscientific and misleading in that (1) it mystifies and empowers selected active chemicals into a category whose underpinnings are neither theoretically anchored nor evidence-informed and is based upon “principles of faith” held and transmitted by a range of stakeholders representing a myriad of agendas and goals, and (2) active chemical substances of any types—“drugs”—are used or misused; living organisms can be and are all–too often abused. Editor’s note
Neurologic Factors Predisposing to Substance Misuse and Aggressiveness

Figure 1 illustrates how genes interact with both common and unique facets of the environment to produce traits across neurochemical, neurophysiological, and neuropsychological levels of biological organization. Many of these traits are consequent to gene–environment interactions and have been implicated in the risk for substance misuse and other risky behaviors.

The measurable or observable expression of a neurobiological or behavioral trait is referred to as a “phenotype.” Biological and psychological phenotypes develop during childhood via interaction with the environment to culminate in the outcomes of substance misuse and aggression. These interactions take two forms: (1) selection, in which a particular phenotype (e.g., novelty-seeking) biases motivation toward situations where substance use is opportune and aggression is either provoked or appears “advantageous”; and, (2) contagion, in which the environment impacts on the phenotype (e.g., aggression) to bias pathways toward substance use. Thus, understanding the role of neuroscience in etiology and prevention must incorporate and integrate information about gene by environment (G × E) and phenotype by environment (P × E) processes.

Neurogenetics

The “genotype” is the complement of genes inherited from parents, although genetic mutations or recombinations during embryonic development also contribute to an individual’s genetic complement. Phenotypes result from the interaction between the genotype and environment, i.e., gene functions are mediated and moderated by environmental influences and subsequently expressed in biological processes and behavioral outputs. For example, neurogenetic mechanisms, such as brain chemistry traits, are genetically designed with respect to the synthesis and metabolism of brain chemicals, the number of receptor sites present, and the activity of competing or regulating enzymes. Nevertheless, environmental inputs and experiences can modify the expression of affected genes, thereby altering behavioral outcomes for better or for worse. Understanding this interactive process translates into the ability to redirect behavior by introducing particular experiences, directive training and opportunities that influence critical neurobiological functions. Thus, although gene functions cannot be “reprogrammed” by altering the molecular genetic structure to change behavioral outcomes, their expression (e.g., gene activities) can be manipulated. Genes establish the framework for brain function while the environment customizes and fine-tunes it.

Neurogenetic factors increase liability for substance misuse and comorbid aggressiveness by influencing related, core phenotypes that are associated with and antedate the
eventual behavioral outcome, such as temperament, personality traits, patterns and orientations of behavior, and relationships. Phenotypes known to be genetically influenced that are related to and predictive of both substance misuse and aggressiveness include poor decision-making skills, impulsivity, cognitive deficits, attention deficits, high activity levels, sensation or novelty-seeking, symptoms of CD, negative affect, risky decision-making, poor conditionability, lack of pain avoidance responses, abnormal levels of arousal, and low verbal ability. Several of these phenotypes have been associated with particular neurogenetic mechanisms, such as irregularities in neurotransmitter function and hormone responses, and genetic variants (see Cloninger, Svrakic, and Przybeck, 1993; Fishbein, 1998; Raine, 1993; Vanyukov et al., 2004). Prevention strategies will be most effective if they focus on these underlying phenotypes, in conjunction with particular forms of environmental stimulants and supports as indicated by the needs of targeted individuals and their neighborhoods.

Neurobiological conditions are, therefore, mutable; although genes underlie their expression, they are environmentally influenced and can be altered via environmental manipulations. Since genetic risks are expressed through vulnerability or heightened sensitivity to adverse environmental factors, genetic traits can be either suppressed or enhanced in response to environmental inputs. No individual is predestined strictly by virtue of their genes or their biology to high-risk behaviors; environmental conditions carry significant weight in this equation.

Neurochemistry

Multiple neurotransmitter systems have been implicated in the risk for substance misuse and aggressiveness via ways in which they contribute to liability phenotypes. The most widely studied system, the mesolimbic dopaminergic system, has been shown to be integral for drug-induced reinforcement and behavioral self-regulation (Cabib, Oliverio, Ventura, Lucchese, and Puglisi-Allegra, 1997; Maldonado, 2003) and is directly altered by both stress and drug misuse (Kalivas and Duffy, 1989; Koob and LeMoal, 1997; Piazza and LeMoal, 1996). The serotonergic system has been strongly implicated in the modulation of affect and behavior self-control (Petty, Davis, Kabel, and Kramer, 1996). In addition, the opioid system is critical for mediation of hedonic (pain and pleasure) mechanisms that underlie high-risk behaviors in general (Koob, 2003). In effect, the risk for substance misuse and aggression has a strong neurochemical basis involving multiple transmitters. Research has not yet explored whether modification of these transmitter systems in childhood reduces substance misuse risk, with the exception of evidence recently accrued demonstrating that pharmacological treatment of attention deficit hyperactivity disorder, at time accompanied by aggressive behavior, is effective for lowering substance misuse risk (Mannuzza, Klein, and Moulton, 2003). Prevention researchers and practitioners need to keep pace with the emergence of findings from etiological investigations as they may inform intervention design.

While pharmacological interventions would appear to be an obvious candidate for manipulating neurotransmitter functions, other strategies are also fertile topics for exploration. It is widely recognized, for example, that experience impacts neurochemical processes. For example, a decline in brain serotonin activity and alterations in dopaminergic systems occur in conjunction with stress (Davis, Suris, Lambert, Heimberg, and Petty, 1997; Fichtner, O’Connor, Yeoh, Arora, and Crayton, 1995; Graeff, Guimarães, De Andrade, and Deakin, 1996; Southwick et al., 1997; van der Kolk, 1997). Low serotonin level is associated with poor self-control and negative affect (Flory, Manuck, Matthews, and Muldoon, 2004) and altered dopamine activity is associated with novelty-seeking (Lusher, Chandler, and Ball,
2001). Not surprisingly, heightened sensitivity to the reward from abusable drugs, and even engaging in high sensation behaviors such as aggression, is increased with low levels of serotonin and altered dopamine activity (Gordon, 2002; Vazquez, Eskandari, Zimmer, Levine, and Lopez, 2002). Thus, high levels of stress in genetically susceptible individuals can trigger neurochemical changes leading to substance misuse and other risky behaviors. The strong association between a history of adversity in substance misusers and individuals with CD and criminal behavior, and the tendency to relapse and/or recidivate with reoccurring stress may be at least partially explained by the influence of stress on neurotransmitter systems. Thus, traumatic experiences directly affect biological traits, which can subsequently increase risk for substance misuse and risky behaviors. One might anticipate that methods to normalize neurotransmitter activity, either environmentally or pharmacologically, may reduce sensitivity to drugs and sensation-seeking in general. In effect, linking a targeted intervention to the neurotransmitter mechanisms underlying risk behavior liability may reduce the risk for adverse outcome.

**Neurophysiology**

Psychophysiological activities in the brain (i.e., neurophysiology), in general, reflect its level of arousal and efficiency of information processing, and are measured using electrophysiological instruments (e.g., electroencephalogram or EEG) that detect the brain’s electrical activity in various regions. One of the most frequently reported neurophysiological features of both substance misuse risk and aggression is attenuated amplitude of the P300 wave of the event-related potential (Bauer and Hesselbrock, 2003; Bernat, Hall, Steffen, and Patrick, 2007; Palomo, Kostrzewa, Beninger, and Archer, 2004). This waveform is an indicator of physiological inhibition and cognitive information processing. Notably, research findings point to low P300 amplitude that is especially marked in the prefrontal cortex (PFC) of the cerebrum (Segalowitz and Davies, 2004). This brain region is integral to maintaining self-regulation, suggesting that the poor behavioral self-control and low capacity for modulation of emotion in high-risk youths may be due to disrupted functioning in the PFC (Bechara, Tranel, Damasio, and Damasio, 1996; Frith and Dolan, 1997; Kandel and Freed, 1989; Post and Weiss, 1997; Volavka, 1995).

Additional psychophysiological studies that assessed risk factors specifically in drug misuse are suggestive of a relationship with behavioral problems that oftentimes precede drug misuse, notably aggression (see McCaul et al., 1991; Newlin and Thomson, 1991; Raine et al., 1999). Skin conductance (SC) responses and heart rate (HR) are reflective of emotional arousal in response to cognitive, emotional, and social stimuli. Increased SC responses (amplitude and frequency) indicate heightened emotional states, responsivity to environmental stimuli, and behavioral disinhibition, while reduced SC responses suggest diminished emotional arousal (Brutus et al., 1986; Elliott, 1992; Volavka, 1995). Low SC activity in response to emotional stimuli may compromise the execution of socially appropriate or effective behavior, i.e., sufficient physiological arousal may be required to motivate appropriate behavioral responses to emotional cues. Low SC responsivity has been related to risky behaviors often exhibited by drug misusers (Iacono et al., 1996). Finn et al. (1994) found that men at risk for substance misuse disorders exhibited relatively fewer SC responses to a tone signaling the advent of an electric shock. Heightened autonomic activity may adversely affect processing of cognitive stimuli (Braggio et al., 1991). Atypical SC responses may reflect impaired regulation of emotion by the PFC (Critchley et al., 2000; Damasio et al., 1990; Hazlett et al., 1993; Raine, 1993; Raine et al., 1991). For example,
patients with prefrontal damage who are insensitive to future outcomes as measured by the Iowa Gambling Task (a measure of executive decision-making; Bechara et al., 1996) fail to show anticipatory SC responses unlike healthy controls (Bechara et al., 1996).

Heart rate is also a reliable and noninvasive measure of nervous system activation during acute stress similar to one experienced during performance of complex cognitive tasks and may be altered after exposure to chronic psychosocial and environmental stressors (Sinha et al., 1998; Szabo, 1993). Psychophysiological studies suggest that these cardiac measures may be risk factors in drug misuse (McCaul et al., 1991; Newlin and Thomson, 1991; Raine et al., 1999) and aggression-proneness (Lorber, 2004). In fact, low resting HR may be the best replicated biological correlate of child antisocial and aggressive behavior (Raine, Brennan, Farrington, 1997), which is a strong precursor for early drug use (Giancola and Parker, 2001; Mannuzza and Klein, 2000). Lower HR reactivity has also been linked to aggression in a cross-sectional study of children (Pitts, 1997). In 16- to 18-year-old boys during exposure to aversive stimuli, HR was lower and SC responses were higher who did not modulate their coping styles effectively (Taylor et al., 1999). The investigators interpreted this finding as reflecting the role autonomic processes may play in exerting inhibitory control over behavioral responses with protective effects against risky behaviors. Low HR may contribute to blunted behavioral and physiological responses to various tasks, which are thought to be outwardly expressed as reduced responsiveness to socially meaningful stimuli.

To date, prevention methods have not been developed to modify neurophysiological functioning. Indeed, there is evidence demonstrating that high-risk youths exhibit deviations on standard EEG assessment and other physiological indices (Raine, 1993). Whether these deviations normalize with effective prevention efforts is not known.

**Neurocognition (Neuropsychology)**

By far, the strongest evidence pointing to neurological disturbance or developmental delay in high-risk youths emanates from neuropsychological research. The executive cognitive functions (ECF) are higher-order neuropsychological skills that have been found deficient in youths at high risk for both substance misuse and aggressive behavior. These cognitive functions, primarily localizable to the dorsolateral and orbitofrontal regions of the PFC, are integral to supervisory regulation of emotion and behavior. The specific ECF processes include strategic thinking, attention control, working memory, self-monitoring behavior during goal-directed motivation, and assessing the consequences of behavior (Fishbein, 2000a; Giancola et al., 1996; Shafer and Fals-Stewart, 1997).

Notably, poor ECF capacity has also been reported in youths with conduct problems who are well known to be at high risk for substance misuse (Aytaclar et al., 1999; Blume et al., 1999; Giancola et al., 1996, 1998; Moss et al., 1997; Tarter et al., 1995; Weinberg, 2001). This impairment has also been theorized to comprise the core deficit in attention deficit hyperactivity disorder (ADHD) (Barkley, 1997), which magnifies the risk for substance misuse and SUD. Concomitant to strategic thinking, the ADHD and/or CD child engages in risky behaviors featured by aggression, impulsivity, and poor decision-making competence. Furthermore, low ECF capacity impedes the ability to interpret social cues during interpersonal interactions, undermines the ability to generate alternative socially adaptive behavioral responses, and executes a response necessary to avoid or cope with stressful interactions (Giancola, 1995).

Like all complex traits, ECF capacity is the product of gene–environment interactions. Research has not, to date, elucidated the genetic polymorphisms which contribute to
variation in these capacities in the population. Exacerbating environmental factors, such as stimulus deprivation and stress (Mizoguchi et al., 2000; Skosnik et al., 2000), appear to mitigate development of ECF capacities. Hence, ECF deficits are more prevalent in children domiciling in low-income and high-crime neighborhoods and dysfunctional families (Noble, Norman, and Farah, 2005). The multifaceted origins of ECF deficits notwithstanding, it is clear that the effectiveness of approaches to prevent drug misuse and aggressive behavior prevention can be enhanced by implementing interventions that promote the acquisition of these capacities.

Executive cognitive function processes do not operate in isolation but in conjunction with neural mechanisms integral to regulation of motivation and emotion. Thus, the dorsolateral and orbitofrontal PFC are intimately integrated with other regions of the PFC, the anterior cingulate, and limbic structures (e.g., amygdala, hippocampus, nucleus accumbens, and insula) to coordinate behavioral and emotional self-regulation. Accordingly, a lesion, dysfunction, or developmental delay in the frontal cortico-limbic circuitry is manifested as disturbances that span cognition, emotion, and behavior. These disturbances are diverse with the most pronounced features consisting of disinhibited behavior, gregariousness, impulsivity, irritability, and aggressiveness (see Kandel and Freed, 1989). These latter characteristics, which likely have their basis in suboptimal neurological functioning, are well known to amplify the risk for substance misuse.

This neurobehavioral perspective has many ramifications for substance misuse prevention. Development and function of the PFC and its circuitry with limbic regions are exquisitely sensitive to psychosocial and environmental influences (Bremner et al., 1999; Bremner et al., 2000; Critchley et al., 2000). Given that environmental stress impedes neuromaturation and, in turn, development of ECF skills (Bremner, 1999; Steckler and Holsboer, 1999), it would appear heuristic to devise interventions that reduce stress, which accordingly would diminish the risk for or severity of these characteristics. Child abuse and neglect are two well-recognized stressors that magnify the risk for substance misuse and aggression through their effects on brain chemistry, physiology, and cognition (Sinha, 2001). Interventions in the environment that optimize neurocognitive development would, thus, likely have a preventative impact.

A novel strategy for prevention involves the application of cognitive neurorehabilitation strategies commonly used to treat frontal lobe head injuries. Although this is a promising approach for the prevention of high-risk behaviors, it has yet to be implemented despite the emergence, in the past few years, of interventions that enhance the cognitive regulation of emotion and behavior. The virtual absence of these prevention strategies reflects the current Zeitgeist in drug misuse and aggression research wherein neurologic mechanisms are not typically considered in appraising the child's risk. However, as discussed above, neurodevelopmental processes are integral to the expression of risk-enhancing behaviors and emotions which augment the risk for substance misuse. Overall, suboptimum maturation of the PFC (cognition) and its neural connections with limbic structures (emotion) may provide a parsimonious explanation of the failure of youths at high risk to acquire the capacities integral to cognitive, emotional, and behavioral self-regulation. Applying neurorehabilitation strategies to improve may be a potent prevention strategy.

**Neurobehavioral Model of Substance Misuse**

Raine, Brennan, Farrington, Mednick, (1997) proposed a dynamic model for understanding the etiology of behavior disorders which has ramifications for prevention. In their model,
biological and psychosocial risk and protective factors interact in a dynamic, fluctuating, and ongoing process to determine the likelihood of a behavioral outcome. The outcome can also, in a feedback loop, affect risk and protective conditions to further strengthen or weaken risk status. For example, a child with ADHD is commonly difficult to manage. Parents without child-rearing skills, who harshly or inconsistently punish the child, exacerbate the child’s risk for the subsequent development of antisocial behavior (O’Connor, Deater-Deckard, Fulker, Rutter, and Plomin, 1998a; O’Connor et al., 1998b). The child may react to such parenting with hostility and defiance, providing further fuel for a negative developmental outcome. The results may be quite different for a learning disabled child in the presence of a supportive home with appropriate intervention. In effect, each phenotype via interactions with multiple facets of the environment portends risk for subsequent behavioral outcomes in the context of emergent risk and protective factors. A complementary developmental model aligned with a behavior genetic framework has also been proposed (Vanyukov et al., 2003). In this model, each outcome biases the developmental process toward successive outcomes. As discussed, deficient capacity or deviant neurological functioning predisposes to negative outcomes via disrupted interactions with the environment.

A developmental approach is consistent with widely accepted drug misuse prevention principles (Hawkins and Catalano, 1995). These authors point out that the most promising strategies for the prevention of alcohol and other drug problems focus on risk and protective factors, encompassing all levels of biobehavioral functioning and multiple spheres of the child’s social ecosystem. Through an understanding of the child’s particular vulnerability, interventions can be devised which enable inculcation of capacities to reduce substance misuse risk and concomitant, often antecedent, aggressive behaviors.

Environmentally Induced Neurobiological Changes Predisposing to Substance Misuse

Stress is a multifaceted process involving perception, interpretation, response, and adjustment to harmful, threatening, or challenging events (Lazarus and Folkman, 1984). The pattern and efficacy of an individual’s responses to stress have been related to the propensity for substance misuse and related high-risk behaviors (De Bellis, 2002; Kreek, Schlussman, Bart, Laforge, and Butelman, 2004; Nemeroff, 2004). With respect to prevention, four facets of stress adaptations merit serious consideration: (1) nature and severity of the events that cause stress; (2) cognitive and emotional processes involved in appraising the events; (3) biological responses and adaptations; and, (4) behavioral (coping) and cognitive responses to the stressor (Sinha, 2001). Cumulative exposure to stress can exhaust available internal and external resources that lead to maladaptations both in response to daily challenges and to future acutely stressful events, thus exerting long-term effects on behavioral pathways. Notably, stress and abusable drugs activate the same neural networks, sensitizing the individual to their effects, and increasing both maladaptive stress responses, drug-seeking, and other high-risk behaviors such as aggression (Kalivas and Duffy, 1989; Kreek and Koob, 1998; Piazza and LeMoal, 1996; Saal et al., 2003). Piazza and LeMoal (1998) have proposed that stress “primed” the brain reward pathway, making it more vulnerable to the positive (mood enhancing) and negative (stress relief) reinforcement of continued drug use. Accordingly, it would appear critical to devise prevention interventions, which both reduce exposure to stress and attenuate stress responsiveness so that sensitivity to drug effects and high sensation-seeking behaviors is likewise minimized.
Importantly, severe stressors, particularly in childhood, compromise the development and function of cognitive, emotional, and behavioral regulatory processes subserved by the PFC and its network with limbic structures (Davidson, 1994; deHaan et al., 1994). Chronic exposure to stressors also disrupts neuroendocrine functioning so that elevated levels of stress hormones (e.g., cortisol; Huether, 1998) induce neurological injury evidenced anatomically as reduced hippocampal volume and functionally as impaired memory and decision-making (Nelson and Carver, 1998; Sapolsky, 1996). Psychophysiological studies also show effects of stress on autonomic responses, such as HR, which, when perturbed, are associated with poor behavioral and emotional regulation and cognitive and coping skill deficits (Gunnar and Nelson, 1994; Sinha et al., 1998; Szabo, 1993). The life course trajectories of adolescents that include initiation and escalation of drug use, as well as aggressive behavior, are also shown to be influenced by the extent to which they experience stress (Cottler et al., 2001; De Bellis, 2002; Giaconia et al., 2000; Gollan, Lee, and Coccaro, 2005; McFarlane, 2000).

The model depicted in Figure 2 illustrates that stress adaptations (defined by neurocognitive and emotional regulatory functions), physiological reactivity, and sensitivity to stress stimuli, are all integral to effective coping. Thus, stress is a salient factor in high-risk behavior prevention due to its potentially hazardous effect on neurocognitive processes. These processes include strategic thinking, risk appraisal, decision-making, and memory registration concomitant to frontal-limbic disruption. Inasmuch as the PFC does not functionally mature until late adolescence or early adulthood, there is a prolonged period during which cortical plasticity can be exploited to potentiate acquisition of ECF capacities. Prevention research and practice has yet to comprehensively incorporate stress modification procedures that take into account neurological effects on sensitivity to drug response and

![Figure 2. Pathways from stress exposures to drug use transitions.](image-url)
behavioral self-regulation. By maximizing the functioning of ECF capacities subserved by the PFC, prevention approaches may exert a much greater effect.

In summary, environmental factors, especially stress, interact with neurobiological vulnerability to determine the risk for both substance misuse and aggressive behavior. Considered in developmental context, preventions directed at modifying the quality of this interaction must accommodate (1) individual differences in neurobiological functioning spanning biochemical, physiological, and cognitive processes and their changing status during neuromaturation, (2) individual differences in stress responses and adaptation as they relate to susceptibility to risk behaviors, and (3) manifold pathways in which person–environment interactions bias the developmental trajectory to substance use initiation and acceleration leading to risky behaviors.

**Developmentally Specific Liability Factors for Substance Misuse and Aggression**

**Prenatal Influences**

Quality of the intrauterine environment is predictive of anatomical, cognitive, psychiatric, and behavioral outcomes (Glover, 1997). Nutritional intake, substance use, and the mother’s mental state and stress levels during pregnancy are among the most potent factors affecting fetal development. Many investigations have documented an association between the fetal environment and long-term outcomes. Lou et al. (1994) compared the offspring of high- and low-stressed pregnant women. Stress and smoking during pregnancy were independently associated with younger gestational age, lower birth weight, and smaller head circumference. Importantly, stress was also negatively associated with scores on the neonatal neurological examination. However, the extent to which compromised neurological functioning via interaction with the environment promotes development of behavior problems remains to be determined. Nevertheless, it is salient for preventionists to note that babies who require extensive parenting resources and skills beyond parental capabilities due to the child’s disturbances are less likely to have effective parent–child bonding, which in severe cases leads to abuse and neglect. These latter parent–child relationship problems are well known to amplify substance misuse and aggressive behavior risk. In effect, the child’s suboptimum neurologic status, with its concomitant behavioral difficulties, challenges caregiver competence and investment, thereby biasing the ontogenetic trajectory toward poor outcomes.

It has also been shown that prenatal exposures to “abusable drugs” may lead to disrupted neurotransmitter function, including development of tolerance and sensitization at the time of birth, which predisposes to voluntary consumption and other conduct problems, including aggression by early adolescence (Allan, Wu, Paxton, and Savage, 1998; Battaglia, Cabrera, and Van de Kar, 1995; Howard and Takeda, 1990; Legido, 1997; Slotkin, 1998). Thus, another prenatal factor fostering later risky behaviors may be drug-induced neurologic injury of the fetus. Neurological injury may manifest in a variety of cognitive (e.g., learning disability, attention problems), behavioral (e.g., poor self-control), and affective (e.g., irritability) disturbances that promote deviant development leading to risky behaviors. Low functional capacity of ECF in self-regulation of emotion and behavior may, in effect, have a teratogenic basis. Importantly, neurobiological effects are strongly dependent upon the quality of home environment. The prevailing lifestyle can complicate the outcome for the developing child (Azuma and Chasnoff, 1993; Brooks-Gunn, McCarton, and Hawley, 1994). Conditions which often exist in the homes of children exposed prenatally to “drugs
of abuse” include a chaotic environment, a lack of appropriate stimulation, lack of parenting skills, mother with impaired mental functioning by virtue of her addiction, inappropriate developmental modeling, as well as abuse and neglect. The presence of these conditions increases the likelihood of further impairments to intellectual capability and social-ethical behavior.

Two practical strategies involve reducing exposure to stress and avoidance of drug and alcohol use during pregnancy. Prenatal interventions may be especially salient for the genetically predisposed fetus as indicated by research that stress during pregnancy activates genes linked to psychological disorders (Benes, 1997; Kaufer, Friedman, Seidman, and Soreq, 1998; Smith, Kim, Van Oers, and Levine, 1997; Stabenau, 1977; Van Os and Selten, 1998) via abnormal neurodevelopment (Kaufer et al., 1998; Senba and Ueyama, 1997).

**Perinatal Influences**

Common complications during the perinatal process (between the 7th month of pregnancy to 28 days after birth) include prematurity, hypoxia, infectious disease, prolapsed cord during delivery, and irregular heart beat in the child. Piquero and Tibbets (1999), in a thorough overview of the research, conclude that there is an association between perinatal factors and risk for antisocial behavior. Significantly, Piquero and Tibbetts theorize that perinatal complications may interact with the social environment to induce neuropsychological deficits, which, in turn, impede normative socialization. Inasmuch as the baby’s characteristics influence the quality of parenting that is received, it is important to implement family and rehabilitative interventions at this stage to establish normal development. This may be especially pertinent to prevention science given the plasticity of the brain in early stages of development, which provide an optimal opportunity for intervention. To date, research has not incorporated information about perinatal events in the design of prevention programs.

**Postnatal Influences**

The brain is the organ through which the child transacts with the external environment and processes information from the internal milieu (e.g., hunger). The behavioral, cognitive, and emotional patterns of an individual established early in life may thus potentially have lifespan consequences. The quality of interactions between the environment (e.g., relations with the mother) and the developing brain, as discussed below, comprises the framework for elucidating the acquisition of biobehavioral characteristics that amplify or suppress the child’s risk for substance misuse and aggression.

This information on child development as a product of interactive and constantly changing conditions is especially important for devising effective preventions. For example, temperament characteristics of infants reflect, to a large degree, genetically determined neurological processes. A difficult temperament, such as oppositional behavior or aggression, negatively interacts with suboptimal or deleterious environmental conditions (e.g., poor or inadequate parenting) and the child is subsequently placed at risk for later developing conduct disorder. This disorder consists of a more crystallized pattern of behavior than temperament alone and possibly a focalized underlying neurological disturbance. CD further provokes negative interpersonal interactions. Thus, as child matures, there are different neurological and environmental processes at different points in development that need to be accounted for in understanding the trajectory to high-risk behaviors. Accordingly, prevention programs need to be tailored to the child’s level of neuromaturation at that given time point, and address the particular risk factors at hand as they provide opportunities for redirecting that trajectory.
At the outset, the bond between caregiver and child provides sensory and social stimulation necessary for brain development. Notably, the brain continues to form neural connections during the first year of life during which time approximately 50% of all learned responses in life are established. Infants who do not receive an appropriate level of social stimulation or develop a secure attachment with a primary caregiver are at elevated risk for aggressiveness, attention deficit disorder, anxiety, emotional disturbances and social withdrawal. In the absence of adequate levels of early social stimulation, children lack the foundation to deal with the rigors of daily life and its stressors. All of these childhood characteristics reflect a neuroregulatory disturbance and increase the risks for poor behavioral outcomes.

Many factors could underlie poor mother–child bonding. Low socioeconomic status may require the mother to work outside the home and thus not have time for effective bonding. A large number of children in the sibship (i.e., many brothers and sisters) also diminishes bonding opportunities with each child. Parental psychopathology is a common feature of children who develop behavioral problems. Parents with mental disorder may be less able to emotionally invest in their children or have adequate parenting skills. Lack of knowledge regarding the importance of physical stimulation of the child and verbal interaction are obstacles to normal development in offspring. Importantly, these types of interactions are modifiable.

Sensory stimulation is also essential for optimum neuromaturation (Kuhn and Schanberg, 1998). The acquisition of perceptual and cognitive capacities is not equally paced during development but rather occurs in spurts during “critical” periods of brain maturation. Stimulus-deprived babies are less responsive to their environments, which, if sustained, results in learning impairments along with other neurobehavioral disturbances (Holsboer, 1989; Kempermann, Kuhn, and Gage, 1998; Kuhn and Schanberg, 1998; McEwen, 1997; Stokes, 1995). Some data have been reported indicating that prepubertal children at high risk for SUD have a higher rate of learning disability compared with low-risk children (Cosden, 2001). Besides neurocognitive disturbances, stimulus deprivation predisposes to deviant behavior problems due to poor emotional self-regulation. Aggression and depression (Agid et al., 1999; Kuhn and Schanberg, 1998; Post and Weiss, 1997; Siegel et al., 1993) augment substance misuse risk and are sequelae of chronic stimulus deprivation. An obvious intervention is to expose the baby to a stimulating environment so as to engage neurocognitive and neurological processes. Available findings indicate that neurological enhancement resulting from early childhood stimulation persists through adulthood (Kuhn and Passig et al., 1996; Meaney et al., 1991; Pham, Soderstrom, Henriksson, and Mohammed, 1997; Pham et al., 1997; Risch, 1997; Schwartz and Goldman-Rakic, 1990; Weisglas-Kuperus, Baerts, Smrkovsky, and Sauer, 1993).

Numerous other postnatal influences may also negatively impact on neurological development. For instance, many studies have demonstrated an association between physical abuse experienced during childhood and subsequent risk for substance use and aggressive behavior (Connor, Doerfler, Volunigs, Steingard, and Mellonli, 2003; Maxfield and Widom, 1996). This risk may be partially related to alterations in neurotransmitter activity and stress hormone levels (Kaufman et al., 1997; Lemieux and Coe, 1995; Lewis, 1992). Moreover, physical abuse has been linked to developmental lags in neural connectivity and neurophysiological abnormalities (Ito, Teicher, Glod, and Ackerman 1998; Ito et al., 1993; Shin et al., 1997; Stein et al., 1997; Teicher et al., 1997). Heightened hormone release (e.g., glucocorticoids) consequent to child abuse and other traumatic events may be another mechanism biasing development to high-risk behaviors (McEwen, 1997; McEwen et al., 1995; Sapolsky, 1996; Smith, 1996; Uno et al., 1994). Notably, injury to the hippocampus resulting
from high levels of stress hormone release in response to severe stress impedes memory and other cognitive processes that influence the risk for conduct problems for reasons discussed above. Later in life, stress experienced during childhood has long-term adverse psychosocial effects, including low self-esteem and social competency and acquiescence (De Goeij, Dijkstra, and Tilders, 1992; Gust et al., 1991; Higley, Suomi, and Linnoila, 1991; Kraemer, Ebert, Schmidt, and McKinney, 1989; Oates, Forrest, and Peacock, 1985; Sapolsky, 1989; Sapolsky and Mott, 1987; Virgin and Sapolsky, 1997). Thus, for a variety of reasons, child abuse amplifies the risk for conduct problems via effects on neurobiological systems that alter effective coping and behavioral self-regulation.

Importantly, however, these influences are not unidirectional. The child’s characteristics impact on the quality of parenting which may manifest as abuse or neglect. In effect, the child may unwittingly exacerbate existing developmental lags in neurological function that ensues from a poor quality relationship with caregiver. For example, a difficult temperament in the child reflecting unstable neurobiological functioning (manifested by sudden changes in mood, circadian dysregulation, low attention control, and excessive activity) are at high risk for poor parenting that in turn may compromise neurodevelopment (O’Connor et al., 1998a,b). A difficult temperament has been shown to be related to heightened risk for aggression and substance misuse (Moffitt, 1993; Moffitt, Caspi, Harkness, and Silva, 1993). The point to be emphasized, however, is that postnatal neurodevelopment is the product of child–environment interactions. The interactions are reciprocal; that is, the child’s characteristics influence selection of risk in promoting environments and the quality of the environment further impacts on multiple levels of developing neurological organization. Because functioning is modifiable, interventions can be devised which prevent risky behaviors by altering the quality of interactions between the child and the environment.

There is further evidence that severe stress during adolescence can damage coping responses by disrupting neurotransmitter responses (Gerra et al., 1998; Ryan, 1998). Parental divorce, for example, has been associated with neuroendocrine changes in adolescents (Gerra et al., 1993). Parental divorce can have serious psychological and behavioral consequences during childhood, including problems in peer relationships and a high incidence of aggressive behavior and alcohol consumption. These studies suggest that resulting disorders may be due to changes in the secretion patterns of neurohormones induced by the stress of the parental divorce, thereby reducing adaptation to stress in the adolescent. Fortunately, several factors offer some protection from these deleterious conditions, including quality of the home life, relationships with others, and intimate bonds.

In summary, social experiences affect psychological processes and can alter neurobiological traits and states. Both acute social stressors that are severe, and chronic social stressors from mild to severe, may produce measurable and long-standing changes in several biological systems that influence behavior. Exposure to highly stressful situations lead to excessive release of stress hormones, which, in turn, heighten sensitivity of the mesolimbic dopamine reward system; the same system which mediates the rewarding effects of drugs of abuse and sensation-seeking behaviors, such as aggressiveness (Bardo, Donohew, and Harrington, 1996; Cools and Gingras, 1998; Horger and Roth, 1996). Heightened sensitivity of this system may, thus, increase susceptibility to high-risk behaviors (Phillips, Roberts, and Lessov, 1997; Piazza and Le Moal, 1996, 1998). Damage to key brain structures has also been associated with stress, producing irregularities in brain function and contributing to learning deficits, mood disturbances, drug misuse, tension, depression, and an inability to cope with external stressors which are all associated with propensity to substance misuse and impulsive–aggressive behavior. On the other hand, the extent to which a stressor has an impact on any given individual is also contingent on the unique characteristics and
perceptions the individual brings to the situation. Fortunately, the ability of the social environment to alter biological systems is reflective of the malleability of these systems and their outcomes.

**Ramifications of Neuroscience Research for Prevention**

Neurological processes, via interaction with multiple facets of the environment, can be modified so as to maximize the child’s cognitive, emotional and behavioral characteristics, and quality of social adjustment. There are many downstream sequelae of neurobehavioral disturbances. In a facilitative context, these disturbances predispose to substance use initiation, misuse, and ultimately, for some, dependence. Aggression, which often antedates and remains comorbid with drug misuse for a significant subgroup, is another relevant outcome. At the broad conceptual level, an important prevention strategy thus entails potentiating the child’s neurological development. Toward this goal, environment interventions can be applied which catalyze morphological and functional development of the brain. As discussed above, research has demonstrated that the environment impacts in many ways on neurologic development and neuroendocrine functioning. By structuring the environment in a fashion that maximizes neurologic potential, the risk for adverse outcomes is accordingly reduced.

As a result of the burgeoning transdisciplinary research on antisocial behavior, we are closer to enacting prevention programs aimed at entire communities, neighborhoods, or schools which are at risk for exposure to socio-environmental hazards that are known to trigger or exacerbate biological disadvantages and increase the incidence of behavioral problems. Factors that may prove to be important contributors to relevant behavioral disorders could then be manipulated on a wide scale to prevent the onset of behavioral disorders in the general population. Early detection programs could be implemented by school systems and parents could be educated to recognize signs of impairment. Screening clinics, regulating environmental toxins, school programs, prenatal care facilities, and public educational programs are only a few of the preventative measures possible. The number of “risk” factors could, in essence, be reduced or minimized. In essence, communication and exchange between neuroscientists and prevention scientists and practitioners may help us to (a) characterize the myriad of neurobehavioral liability factors in a socio-environmental context, (b) disaggregate populations with behavioral disorders into relatively distinct subgroups based on prevailing liabilities and interacting conditions, (c) determine which interventions work best in particular subgroups, and (d) design interventions to correspond with developmental stage.

**Prevention Strategies to Increase Resiliency and Minimize the Impact of Risk Factors**

Several types of interventions have been shown to be effective for reducing the risk of behavioral disorders (see Botvin, Baker, Dusenbury, Botvin, and Diaz, 1995; Eggert, Thompson, Herting, Nicholas, and Dicker, 1994; Olds et al., 1998; Spoth et al., 1998; Thompson, Horn, Herting, and Eggert, 1997; Webster-Stratton and Hammond, 1997). It is noteworthy, however, that benefits accrue to only a subset of individuals. It remains to be determined which characteristics differentiate youths who respond favorably from those who do not. The research cited herein suggests that prevention effectiveness can be increased when the intervention targets an individual’s specific liabilities. In other words, environmental manipulations matched to an individual’s genotype may effectively reinforce more adaptive and normative phenotypes. On the other hand, even global, community- or school-wide
programs would be benefited by addressing environmental conditions which are universally “contraindicated.” For example, nowhere do we see a greater concentration of “environmental triggers” and adversity in low-income neighborhoods that contributes in substantial ways to maladaptive behaviors in interaction with genetic or biological traits. Thus, we may eventually be able to concentrate on and alleviate those social problems that are differentially and disproportionately distributed throughout our society, trigger underlying vulnerabilities, and lead to an increased prevalence of various behavioral disorders.

Programs that modify brain functioning to improve psychological self-regulation would appear to have promise for prevention of risky behaviors on a more individualized basis. Preventive interventions directed at reducing stress and psychological problems having a neurological substrate may thus have lasting benefit. Also, early interventions, from prenatal to preschool stages are likely to exert an influence before problems become magnified across the lifespan. Ameliorating neurological dysfunction via cognitive remediation, behavioral rehabilitation, psychoeducation, environmental enrichment, speech and language therapy, functional and integrative training, and alternative activities, would appear to be useful. To date, their efficacy has not been investigated. Specifically, interventions that modify brain functioning so as to enable acquisition of cognitive skills, regulate emotion, and behavior self-control would likely have long-term positive impact on reducing risk for poor behavioral outcomes.

Rehabilitation programs developed for patients with head injuries also have potential for application in the prevention of these risky behaviors. Several lines of evidence indicate that a dysfunction of the PFC with underlying impulsivity, executive cognitive dysfunction, aggressive behavior, inability to assess consequences, behavior disinhibition, and poor coping strategies, is a viable target for rehabilitation (see Bechara et al., 1996; Frith and Dolan, 1997; Kandel and Freed, 1989; Post and Weiss, 1997; Volavka, 1995). In addition, patients with PFC injury commonly have impaired decision-making and other neurocognitive deficits (Damasio, Grabowski, Frank, Galaburda, and Damasio, 1994). In individuals with brain injury, a functional disconnection between frontal cortical regions and limbic structures may underlie these deficits. In turn, these impairments may influence the choice to initiate substance use or disinhibition that often accompanies tendencies to engage in aggressive behavior. Targeting interventions to such impairments may thus diminish risk. Thus, neurorehabilitation strategies applied to treat traumatic brain injury of the PFC may be an effective preventive measure.

An example of a universal prevention strategy that incorporates neurobiological research was designed by Bardo et al. (1996). Studies have implicated the trait of sensation or novelty-seeking in propensity to use drugs and engage in antisocial behavior. Because high sensation seekers are “biologically prepared to attend to novel information more than low sensation seekers” (Bardo et al., 1996 p. 36), prevention strategies might incorporate messages that attract individuals with this biological predisposition. Donohew and colleagues (Donohew, Palmgreen, and Lorch, 1994; Lorch et al., 1994; Palmgreen et al., 1994) have implemented interventions that convey anti-drug messages using highly sensational program content with high-risk teens. Significant changes in attitudes toward drugs were incurred. Lesson learned from this research is that programs simply attempting to extinguish drug misuse may not be sufficient in high-risk populations; instead, treatment and prevention strategies should replace drug-seeking behaviors with new behaviors which are inconsistent with drug use (Bardo et al., 1996).

Other externally focused interventions aim to change the environment to minimize effects of existing dysfunctions and may also have primary preventative effects. Some examples are given which extend from the findings reported herein:
1. Reinforced interaction with a complex cognitive and sensory environment can both stimulate anatomical and biochemical plasticity and ameliorate some of the behavioral consequences of a stressful, inadequate, or deprived environment.

2. Mandatory parenting classes within the school curriculum, early detection and intervention strategies, and a better-equipped child welfare system can prevent child abuse. Therapeutic strategies that focus on the neurobiological effects of child abuse may improve integrity of affected neuroendocrine systems, hypersensitivity to stressors, and coping strategies.

3. Stress reduction and prevention programs, in some cases with adjunctive serotonergic agonists, may optimize serotonin activity levels in individuals exposed to chronic or high levels of environmental stress.

4. Parent training, postnatal home visitation, and family therapy are warranted in high-risk populations to mitigate the effects of fetal drug exposure and maternal stress.

5. Very early identification of children at risk and the provision of a stimulating and nurturing environment with strong social bonds are critical given that a significant amount of brain development occurs within the first year of life.

6. Adequate prenatal care, particularly for low-income populations, may reduce our reliance on the mental health and criminal justice systems given the association between pre- and perinatal complications and later conduct problems in offsprings.

Only a few studies have focused on the biological changes following environmental manipulations. The findings underscore the important role of brain plasticity. Klintsova, Matthews, Goodlett, Napper, and Greenough (1997) demonstrated that training improved motor performance in rats impaired by alcohol exposure. An expansion of synaptic connectivity was also observed. Popova et al. (1998) demonstrated that treatment of patients with phobic syndromes resulted in changes in neurophysiological activity. Weisglas-Kuperas et al. (1993) reported that stimulating the home environment enhanced cognitive and neurological development in high-risk children. Even simple interventions, such as increased handling of rat pups, potentiate neurologic development (Kuhn and Schanberg, 1998). The point to be made is that brain functioning can be modified by environmental manipulations.

Interventions targeted toward child’s specific liabilities as well as public health initiatives should, therefore, place more emphasis on incorporating members of the child’s social milieu into prevention programming. Given the important role of the caregiver in fostering healthy mental and physical development as mentioned previously, there is a dire need to include caregivers in preventive and treatment efforts in order to improve their efficacy. Caregivers can be taught both how to create a supportive environment for their child and reinforce preventive materials that are introduced given that a majority of the child’s time is often spent with their caregivers. Reinforcing and practicing the program’s curriculum outside the clinical or school environment are likely to increase the salience of prevention materials, which may be especially crucial for children with a high liability status.

To date, prevention practice has not systematically incorporated neuroscience information to reduce the risk for substance misuse and aggression by implementing interventions that enhance adaptive psychological capacity through enhancement of neurological functioning. Behavioral scientists are only beginning to discuss the need for an integrated approach toward prevention (see for example Codie et al., 1993; Lewis, 1992; Mayes, 1999). Thus, although several biological markers for substance misuse and aggressive behaviors and their interaction with environmental influences have been investigated, their clinical usefulness still must be more fully explored. While further research is needed, this report also highlights the many efforts, well supported by the literature, that could now be
undertaken, e.g., mandatory parenting classes, stress reduction, and cognitive neurorehabilitation. In sum, early intervention with at-risk children appears to be a powerful means for preventing future psychopathology (Carter et al., 2004).

**Future Research**

Research conducted in the past two decades has clearly demonstrated that environmental factors impact brain function. The specific factors and their timing in relation to ontogeny, however, remain to be determined with respect to the development of biobehavioral characteristics that predispose to substance misuse and aggression. Investigations are also required to identify the range of neurologic mechanisms associated with these high-risk behaviors across multiple levels of biobehavioral organization. Once these are understood, prevention strategies can be targeted to the particular liability, whether it is one or multiple disturbed neurochemical, neurophysiological, or neuropsychological functions. This prevention strategy closely aligns with medical practice wherein the intervention is linked to the causal mechanisms. Furthermore, because the environment interacts with genes to determine development of phenotypes (e.g., neurological and psychological characteristics), innovative prevention efforts would also appear to entail targeting interventions to those at highest risk.

There is a need for additional human studies since several of the most intriguing bits of evidence are generated from animal research that cannot be easily extrapolated. Furthermore, longitudinal designs are necessary to identify critical periods of neural sensitivity to environmental influences, to assess relative contributions of psychosocial stress and phenotypic predisposition (e.g., aggressiveness), and to distinguish consequences of drug usage from its precursors. Referring to animal models and recent human studies, prevention scientists can eventually design programs that directly target these effects to reverse or attenuate negative outcomes. For example, effects of prenatal drug exposure on cognitive function and related behaviors have yet to be fully delineated and remain controversial. Some reports provide evidence for both gross and subtle deficits as a result of prenatal cocaine exposure while others do not. Identification of drug effects on the growing fetus and child will lead to a better understanding of prenatal exposures and their possible influence on liability to risky behaviors. The prevention implications for such studies are substantial.

Future research questions pertaining to potential linkages between neurobiology and prevention sciences are many and varied, and include the following:

1. What are the neural substrates and their behavioral and temperamental manifestations in various forms of psychopathology?
2. What is the impact of the environment on these neurogenetic mechanisms?
3. What are the critical stages of development during which psychosocial stress differentially exerts its effects?
4. How can the assessment of environmental–neurobiological relationships contribute to the design of interventions that impact at critical points in the developmental trajectory to alter risk status?
5. If the genetic makeup sets the stage for responses to environmental input, can environmental interventions alter genetic expression of risk traits and the behavioral phenotype, and will the outcome of this impact be sufficiently measurable?
6. Can an integrated data set including both socio-environmental and neurobiological variables account for more of the variability in intervention response than the use of one set of variables alone?
7. What designs and methodologies can be employed to identify neural substrates amenable to prevent, intervene, and assess change over time?

One example of an integrated research design is the examination of changes in brain function in relation to behavioral change during treatment. Theoretically, the use of a combination of neuropsychological imaging (e.g., PET or fMRI) and behavioral measures before, during, and after an effective intervention will demonstrate a trend toward normalization over time. The same design can examine subgroups that do not respond favorably to identify underlying differences. Thus, the biological impact of prevention approaches can be determined by combining assessment techniques to discern change in both brain function and related behaviors.

The development of this proposed research agenda is predicated on findings generated from a multistage process of research. The purpose of the first phase of studies would be to identify underlying, causal mechanisms in psychopathology relating to drug misuse, such as aggressive behavior, depression, impulsivity, and sensation-seeking. The second phase involves the identification of protective factors that suppress vulnerability, including both internal (certain aspects of temperament, verbal intelligence, and cognitive function) and external (caregiver bonds, family stability, and targeted community services) resources. A third general area of research is to introduce a preventive intervention and assess its ability to alter vulnerability factors, both biological and behavioral. It is expected that intervention effectiveness will be directly related to (a) changes incurred in vulnerability markers, (b) the type and number of existing protective factors, and (c) the lack of immutability and/or severity of vulnerability conditions. Finally, fourth, research must address the ways in which protective factors moderate outcomes in the presence of inherent liabilities to high-risk behaviors. In such a rare but informative protocol, neurobiological measures are treated as independent variables in the initial stages of research, while in the later stages, neurobiological factors are manipulated as dependent variables to assess response to an intervention stimulus.

Research in neurobiology suggests that a sole focus on the social contributions to behavioral disturbances is insufficient. Nor is it adequate to simply examine neurobiological influences. Individual vulnerability and protective factors differentially relate to and are altered by environmental conditions to either heighten or minimize risk for poor behavioral outcomes. In accordance, a more comprehensive and effective approach to the science, treatment, and prevention of substance misuse and aggression involves exploration of the relationship between neurobiological and psychosocial forces. As a result of the ineffective, unidimensional, linear-based approaches of the past, we are now defaulting to the mental health and criminal justice systems with troubled individuals. Rather than ignoring the warning signs in childhood and waiting until adulthood to put into motion these systems, spending billions for legal remedies that do not produce favorable outcomes, the provision of sorely needed services and interventions to high-risk individuals can yield far greater benefits.

RÉSUMÉ

L’étiologie du comportement des précurseurs de toxicomanie et de l’agression est considérée dans la perspective d’un développement, multifactoriel modèle complexe de troubles. Début à la conception, la génétique et des interactions environnementales sont susceptibles de produire une séquence de phénotypes comportementaux au cours du développement que biais de la trajectoire à haut risque vers les résultats. Une voie est théorisé à émaner...
d'une déviation dans le développement neurologique des enfants qui prédispose à l'affectif et cognitif des retards ou des déficiences qui, à son tour, générer des comportements dysregulatory. La plasticité de ces systèmes neurobiologiques est très importante pour la prévention des sciences; leurs fonctions sont dépendantes de l'environnement sur les intrants et peut être modifié, pour le meilleur ou pour le pire, dépend de la nature des intrants. Ainsi, les facteurs contextuels sociaux conférer une influence notable sur le développement de ce réseau de neurones et les résultats du comportement en augmentant le risque de, ou de les protéger contre, dysregulatory résultats. A bien conçu d’intervention peuvent exploiter la plasticité du cerveau biologique en ciblant les facteurs sociaux et à des points sensibles de temps à exercer une influence positive sur les fonctions émergent neurobiologiques et les comportements. En conséquence, la prévention de recherche commence à se concentrer sur le développement des perturbations dans la plasticité neurale au cours de l’enfance qui augmentent la probabilité de comportements à risque et que mai également modérée intervention effets sur le comportement. Étant donné que la plus complexe dispose de fonctions neurobiologiques qui sous-tendent l’usage de drogues et de l’agression (par exemple, la fonction cognitive exécutif, habiletés d’adaptation, d’affecter le règlement) ne sont pas s’unir avant le début de l’âge adulte quand-préfrontal du cerveau limbique consolider les réseaux, il est essentiel que des mécanismes sous-jacents de développement des facteurs de risque sont identifiés. Un empirique approche axée sur la prévention, ainsi, bénéficier de mai l’examen de (i) le type, l’effet, le calendrier de développement et de l’impact sur l’environnement sur le cerveau, et (ii) le type, l’effet sur la fonction cérébrale, de développement et le calendrier de la intervention. Cette approche translationnelle promet d’offrir une orientation pour la conception d’interventions efficaces pour prévenir l’usage de drogues et concomitante agression.

RESUMEN

La etiología de la conducta precursores de uso indebido de sustancias y de la agresión se considera desde la perspectiva de un desarrollo, modelo multifactorial de los trastornos complejos. A partir de la concepción, genéticos y de las interacciones medioambientales tienen el potencial para producir una secuencia de los fenotipos conductuales durante el desarrollo que el sesgo hacia la trayectoria de alto riesgo los resultados. Una vía es la teoría de que proceden de una desviación en el desarrollo neurológico que predispone a los niños afectivo y cognitivo de los retrasos o impedimentos que, a su vez, generar dysregulatory comportamientos. La plasticidad de estos sistemas neurobiológicos es muy pertinente a la prevención de las ciencias; sus funciones son el medio ambiente depende de los insumos y puede ser modificado, para bien o para mal, depende de la naturaleza de los insumos. Así pues, los factores contextuales sociales confiere una influencia significativa en el desarrollo de esta red neuronal y de comportamiento por resultados aumenta el riesgo de, o proteger contra, dysregulatory resultados. Un bien diseñado intervención puede explotar el cerebro de la plasticidad de la orientación factores biológicos y sociales sensibles a los puntos de tiempo para influir positivamente en las funciones emergentes neurobiológicos y los comportamientos. En consecuencia, la prevención de investigación está empezando a centrarse en las perturbaciones en el desarrollo de la plasticidad neuronal durante la infancia que aumentan la probabilidad de que los comportamientos riesgosos y que también puede moderada intervención efectos en el comportamiento. Habida cuenta de que cuanto más complejas características de las funciones neurobiológicos subyacentes el uso de drogas y de la agresión (por ejemplo, el ejecutivo la función cognitiva, habilidades de afrontamiento,
afectan a la regulación) no se unen hasta principios de la edad adulta cuando prefrontal del cerebro límbico-la consolidación de las redes, es esencial que los mecanismos subyacentes al desarrollo de los factores de riesgo se identifican. Empíricamente una impulsada enfoque de prevención, por lo tanto, pueden beneficiarse de la consideración de (i) el tipo, el efecto, el desarrollo y la fecha de celebración del impacto ambiental en el cerebro, y (ii) el tipo, el efecto sobre la función cerebral, y el calendario de desarrollo de la intervención. Este enfoque traslacional a la larga promete ofrecer alguna orientación para el diseño de intervenciones eficaces para prevenir el uso de drogas y concomitante agresión.

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Glossary

**Autonomic nervous system**: Part of the peripheral nervous system that acts as a control system, maintaining homeostasis in the body. These activities are generally performed without conscious control or sensation. The ANS affects heart rate, digestion, respiration rate, salivation, perspiration, diameter of the pupils, micturition (urination), and sexual arousal.

**Brain reward pathway**: A collection of brain structures which attempts to regulate and control behavior by inducing pleasurable effects.

**Cortico-limbic circuitry**: Neuroanatomic feedback loops between the PFC and structures within the limbic system.

**Disinhibition**: Reduced capacity to edit or manage an immediate impulsive response to a situation.

**Dysregulation**: Poorly modulated emotional, behavioral, or cognitive responses.

**Ecological**: The environment of an organism.

**Executive cognitive function (ECF)**: Higher order neuropsychological skills, modulated by the PFC and its connections with the limbic system, including functions such as goal-directed behavior, problem solving, impulse control, attention, working memory, and social skills.

**Genetic Polymorphism**: Occurs when two or more clearly different phenotypes exist in the same population of a species where the frequency of the rarer form of gene(s) is greater than can be maintained by recurrent mutation alone.

**Genotype**: The complement of genes inherited from parents, although genetic mutations or recombinations during embryonic development also contribute to an individual’s genetic complement.

**Limbic system**: A set of brain structures including the hippocampus and amygdala and anterior thalamic nuclei and a limbic cortex that support a variety of functions including emotion, behavior, and long-term memory.

**Markers**: In this context, biological responses that correlate highly with certain features or attributes that are predictive of behavioral patterns.

**Mesolimbic dopaminergic system**: Neural pathways in the brain that links the ventral tegmentum in the midbrain to the nucleus accumbens, which is located in the striatum and is a part of the limbic system. It is one of the four major pathways where the neurotransmitter dopamine is found. The mesolimbic pathway is thought to be involved in producing pleasurable feeling and is often associated with feelings of reward and desire, particularly because of the connection to the nucleus accumbens, which is also associated with these states. As a result, this pathway is heavily implicated in neurobiological theories of addiction. However, recent research has pointed toward this pathway being involved in incentive salience rather than euphoric mood states.

**Neurobehavioral**: Behavioral orientations or tendencies that are thought to have a basis in neurological functions.

**Neuroendocrine system**: Cells that release a hormone into the circulating blood in response to a neural stimulus. They package the hormones in vesicles and send these packages via long processes (axons) to blood vessels. When stimulated (by hormones from the blood stream or neurons), the neuroendocrine cells secrete the hormones into the blood stream. The hormones then travel to their target cells and may stimulate, inhibit, or maintain function of these cells. The target cells may feed back information to these neurons that regulates further secretion.
Neurogenetic mechanisms: Genetically influenced neurological activities that influence various functions, such as cognition, behavior, and emotion.

Neurohormones: Hormones that influence brain function.

Neuroimaging: Use of various techniques to either directly or indirectly image the structure, function/pharmacology of the brain, e.g., PET and MRI.

Neuromaturation: Development of the brain throughout childhood and adolescence.

Neurorehabilitation: Strategies to improve functional consequences of head injuries that focus on rebuilding cognitive systems.

Neurotransmitters: Chemicals in the brain that are used to relay, amplify, and modulate signals between a neuron and another cell. A chemical can be classified as a neurotransmitter if it meets the following conditions: (1) There are precursors and/or synthesis enzymes located in the presynaptic side of the synapse; (2) the chemical is present in the presynaptic element; (3) it is available in sufficient quantity in the presynaptic neuron to affect the postsynaptic neuron; (4) there are postsynaptic receptors and the chemical is able to bind to them; (5) a biochemical mechanism for inactivation is present.

Opioid System: Contains chemical substances that have morphine-like actions in the brain and body. Its main function is to relieve pain. These agents work by binding to opioid receptors, which are found principally in the central nervous system and the gastrointestinal tract. The receptors in these two organ systems mediate both the beneficial effects, and the undesirable side effects.

Phenotype: The measurable or observable expression of a neurobiological or behavioral trait.

Plasticity: Changes that occur in the organization of the brain as a result of experience.

Precursor: A condition or factor that precedes and leads to the occurrence or manifestation of a particular trait or behavior.

Prefrontal cortex (PFC): The anterior (front) part of the frontal lobes of the brain, lying in front of the motor and premotor areas. This brain region has been implicated in planning complex cognitive behaviors, personality expression, and moderating correct social behavior. The basic activity of this brain region is considered to be orchestration of thoughts and actions in accordance with internal goals.

Psychopathology: The manifestation of behaviors and experiences which may be indicative of mental illness or psychological or behavioral impairment.

Serotonergic system: A neurotransmitter system that plays an important role in the modulation of anger, aggression, body temperature, mood, sleep, sexuality, appetite, and metabolism, as well as stimulating vomiting.

Skin conductance: Otherwise known as galvanic skin response (GSR) or electrodermal response, is a method of measuring the electrical resistance of the skin. There is a relationship between sympathetic activity and emotional arousal, although one cannot identify the specific emotion being elicited. The GSR is highly sensitive to emotions in some people. Fear, anger, startle response, orienting response, and sexual feelings are all among the emotions which may produce similar GSR responses.

Temperament: The innate aspects of an individual’s personality, such as introversion or extroversion.

Transdisciplinary: Research approaches that encompass and integrate perspectives and methodologies from various scientific disciplines.

Translational research: The “translation” of basic research into practicable and testable interventions for various groups and clinical populations.
References


