Published in final edited form as:
Child Adolesc Psychiatr Clin N Am. 2010 July ; 19(3): 479–492. doi:10.1016/j.chc.2010.03.003.

Neurobiology of Adolescent Substance Use Disorders: Implications for Prevention and Treatment

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Keywords

Neurobiology; Adolescence; Substance Use; Treatment; Prevention

Adolescence marks an important developmental period of neurobiological change, with heightened vulnerability to substance use. Indeed, greater severity in progression of drug usage in adolescence has been observed, with higher dependency rates during this developmental period [1]. Adolescents also show greater experimental use and report higher rates of substance use disorders (SUDS) [2], suggesting potential neurobiological vulnerability to substance use or a critical period in adolescent development. Early substance use may influence later social and occupational functioning [3], as well as physical and psychological health [4,5], with earlier onset of substance use predicting greater addiction severity and morbidity with other clinical disorders in adulthood [6]. Consequently, an improved understanding of the neurobiology of adolescent substance use initiation and development of SUDs should facilitate advances in prevention and treatment during adolescence.

This review is organized into three sections. The authors first consider the neurobiology of adolescent decision-making and how this contributes to initiation of substance use prior to maintained use and abuse or dependence. Second, the authors present the empirical research which has started to identify neurobiological differences in structural and functional neuroanatomy in adolescents with SUDs and healthy controls. Finally, in the third section, the authors consider the implications of structural and functional differences for prevention and treatment of adolescent SUDs.

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The neurobiology of adolescent decision-making

Behavioral tests have been used to investigate decision-making in laboratory settings. One such paradigm, the Iowa Gambling Task (IGT), was developed to investigate why individuals with stroke lesions in specific brain areas (e.g., the ventromedial prefrontal cortex) exhibited poor performance in real-life measures of functioning while not displaying impairment on standard neuropsychological tests [7]. Adults with drug addictions have been shown to perform disadvantageously on the IGT (that is, selecting larger immediate rewards despite longer term losses and not learning to change this behavior over time), and performance has been associated with real-life measures of functioning (e.g., disadvantageous performance has been positively associated with unemployment; [8]). However, decision-making tasks like the IGT involve multiple components including risk/reward assessment, strategic learning, and cognitive flexibility. In making decisions, the valence, probability, and magnitude of potential outcomes should be considered [9]. Impaired consideration of any of these processes may lead to engagement in risky behavior such that immediate rewarding outcomes drive decision-making regardless of future (potentially negative) outcomes. As such, it has been hypothesized that such dysfunctions in decision-making serve to underscore the development of substance use disorders [10]. Thus, additional tasks that probe specific components of decision-making can be used to fractionate the construct and better understand the relationships of the core components to adolescent substance use behaviors.

Risk/reward assessment as it contributes to decision-making has been investigated from a behavioral neuroeconomic perspective. Specifically, temporal discounting (or delay discounting) paradigms have been used to investigate reward preferences as they relate to substance use behaviors [11]. Delay discounting refers to the selection of small immediate rewards over larger delayed rewards, with higher rates of discounting demonstrated by individuals scoring high on measures of impulsivity [12]. Adults with SUDs typically show a rapid discounting of rewards, tending to prefer smaller, immediate rewards over larger, delayed ones [13]. As compared with adults, adolescents have been found to discount rewards more rapidly [14], with heavy alcohol drinking adolescents discounting more than light alcohol drinking adolescents [15]. Individual differences in the ability to delay gratification and select larger delayed rewards over smaller immediate ones have been demonstrated in youth as young as three to four years of age [16], suggesting that the propensity to exhibit self-control in the setting of appetitive stimuli may manifest early in life. As related to adolescent SUDs, more rapid temporal discounting has been related to drug use initiation [17], patterns of consumption (e.g., number of cigarettes smoked among adolescent and young adult smokers;[18]) and treatment outcome among adolescents seeking to cease tobacco smoking [19].

More rapid temporal discounting has been cited as a core feature of impulsivity, a construct linked to adolescent SUDs [20]. Impulsivity has been defined as “a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or others.” (p. 1784) [21] Impulsivity thus is a complex, multi-faceted construct containing elements that overlap with core components of addiction [22], and one that can be deconstructed to probe the relationships between specific aspects of impulsivity and SUDs [23,24]. Impulsivity may lead to increased substance use or alternatively substance use may promote impulsivity, and longitudinal studies support each notion, particularly in animal models in which environmental factors may be more carefully controlled [25-28]. Such animal studies also suggest that adolescence substance exposure may promote risky decision-making later in life [28]. Taken together, these data indicate a complex relationship between impulsivity and substance use behaviors that is developmentally sensitive.

Additional constructs (e.g., novelty seeking, sensation seeking, and risk-taking) that are linked to impulsivity may relate to decision-making and engagement in substance use behaviors. Behavioral risk-taking may be assessed through such tests as the balloon analogue risk task (BART; [29]) in which a computer-simulated balloon is presented on each trial and participants are instructed to pump up the balloon, with each pump being worth a point. Repeatedly pumping the balloon increases points earned but also increases the chances the balloon will pop and those points will be lost. Thus the participant has to decide when to stop pumping and collect the points accrued. Adolescent performance on the BART positively correlates with measures of risky behavior, including substance use [30]. Although the BART and laboratory measures of temporal discounting represent examples of behavioral assessments of adolescent risk-taking, these assessments are limited to the level of description. Thus it is necessary to move beyond this descriptive level to a neurobiological level of understanding adolescent risky behavior and substance use.

There is an apparent *paradox* of adolescence [31] wherein executive functions and decision-making are comparable to adult levels, but adolescence is marked by risky behaviors such as substance use, even with prior knowledge of the consequences of this behavior [31,32]. Understanding this paradox is possible through probing the neurobiology of decision-making in adolescence, and this has highlighted the role of two core neurobiological networks important in the emergence of risky behavior [33]. The first, a cognitive control system, which consists of prefrontal and parietal regions, as well as the anterior cingulate, facilitates executive functioning. The second, affective system, includes regions which are important to processing reward and social and emotional salience, including but not limited to the amygdala, ventral striatum, orbitofrontal cortex, medial prefrontal cortex, and the superior temporal sulcus. Note that this dissociation between an affective and cognitive system has also been conceptualized as a dissociation between an activational system and an inhibitory system, with delayed development of the inhibitory system and the dominance of the activational system contributing to the engagement in risky behaviors like substance use (e.g., [20,34]).

Consequently, to understand risky behavior and the onset of substance use, it is important to consider the developmental maturity of both the affective and cognitive networks. With this in mind, a neurobiological model of adolescent brain development has been proposed wherein during adolescent development, limbic systems develop earlier than prefrontal cortical ones, and thus behavior is preferentially driven by the more mature limbic system rather than the immature prefrontal cortical system [35]. As prefrontal regions mature, a shift in decision-making occurs such that these frontal regions exert greater top-down cognitive control over contributions from the affective limbic system. Individual differences in multiple aspects, as may relate to specific genetic or environmental factors, may exert influences on these processes during development.

An important component of the limbic system relevant to this discussion is the nucleus accumbens, which is located in the ventral striatum and is sensitive to the anticipation of reward [36]. In adults, ventral striatal activation correlates with risky behavior [37]. Compared to children and adults, ventral striatal activation associated with the anticipation of reward is heightened in adolescents during a computer-based reward task [38]. This finding converges with others (e.g., [39]) demonstrating increased sensitivity to reward in adolescence, particularly as reflected in ventral striatal activations [40]. At the same time, the protracted development of prefrontal cortical control regions is evident by weaker activity in this area in adolescents (and children) compared to adults in anticipatory reward tasks [38], and it is likely that these frontal regions are important in both the representation [41] and updating [42] of reward information, and being important for decision-making in general. Taken together, existing neurobiological data suggest heightened sensitivity to

reward in adolescents. Furthermore, relatively diminished top-down control over limbic structures may provide a neurobiological rationale to explain heightened risk-taking behavior in this developmental epoch [35].

In addition to representing a period of neuronal maturation, adolescence is also characterized by increased vulnerability to stress. With the neuronal maturation of cortical and limbic structures during adolescence, the developing brain may be especially sensitive when exposed to stressors [43], which may increase the likelihood of substance use. Animal studies have proved fruitful in understanding the effects of stress on brain development, implicating regions including the amygdala, prefrontal cortex (PFC), and hippocampus [44]. Although there is limited knowledge about the effects of stress on adolescent amygdala and PFC structure and function, the effects of stress on the adolescent hippocampus have been more thoroughly investigated. In adults, stress exposure reduces dendritic branching in the hippocampus, but can be reversed with the prolonged absence of the stressor; however, in the adolescent hippocampus, more extensive volume reductions have been observed which appear longer lasting although delayed in their onset [43]. Animal work has also shown that chronic stress reduces PFC function and synaptic plasticity between the PFC and the hippocampus [45]; moreover, these physiological changes appear accompanied by impairments in measures of working memory and behavioral flexibility. Taken together, animal studies have demonstrated a vulnerability of the prefrontal cortex (and hippocampus) to stress, and this vulnerability may be heightened during adolescence. These data coupled with human limbic and frontal cortex findings suggest unique neural correlates of adolescence even before substance use initiation and dependence. In the next section of this review, we consider the structural and functional changes which have been reported in human adolescent SUDs.

Adolescent substance use disorders: Brain structure

Much of our knowledge of the neurobiology of SUDs is drawn from studies sampling adults. However, adolescence represents an important period of neuronal maturation, characterized by increases in myelination and initial aborization and then pruning of gray matter [46]. Further, evidence suggests that the adolescent brain is more vulnerable to the effects of substance use [47], with animal studies showing that substance use in adolescent rats disturbs neuroendocrine functioning [48]. Consequently, studies in adults with SUDs may not provide adequate insight into the neurobiology of adolescent SUDs, limiting treatment and prevention options and identifying the need for research during adolescence in this field. Advances in techniques such as magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) have provided a unique opportunity to probe structural differences which may exist in adolescent SUDs. Arguably, three brain regions have received the most attention in this regard: The hippocampus, corpus callosum, and frontal cortex.

Hippocampus

Hippocampal structure has been implicated in learning and memory [49], and evidence from animal studies has shown sensitivity of the hippocampus to neurotoxicity [48]. Initial work [50] showed reduced left and right hippocampal volumes in adolescents with alcohol use disorders (AUDs) relative to controls, in the absence of any volumetric differences in corpus callosum, grey and white matter, amygdala, and cerebrum. Furthermore, these decreases in hippocampal volume were significantly correlated with the age of onset and duration of AUDs, suggesting a direct association between the development of AUDs and hippocampal volume reduction. In a subsequent study, when recruiting adolescents with no additional co-morbid disorders, only left hippocampal volume reductions in adolescents with AUDs were observed [51]. In a separate study, increases (rather than decreases) in left hippocampal volume have been reported in adolescents using both marijuana and alcohol relative to

adolescents using just alcohol [52]. However, these populations appear more reflective of regular substance users than individuals with formal SUDs; nonetheless, these findings suggest a complex influence of multiple substance use on adolescent hippocampal structure.

Corpus callosum

Increases in myelination occur during adolescent brain development [46], and thus research has investigated the integrity of the corpus callosum in adolescents with SUDs, although with seemingly conflicting results. DTI research [53] has revealed that the integrity of white matter tracts in adolescents with AUDs, compared to controls, is reduced in the splenium and body (at statistical trend level) of the corpus callosum, with the integrity of the white matter tracts showing significant relationships with AUD characteristics such as duration of heavy drinking and withdrawal symptoms. However, group differences in callosal white matter between adolescents with AUDs and controls have not been reported elsewhere [50,54]. Furthermore, increases (versus decreases) in white matter integrity have been reported in the anterior corpus callosum in adolescents with AUDs, suggesting premature myelination rather than neurotoxicity [54].

Frontal Cortex

The importance of understanding structural abnormalities in frontal cortex in adolescent SUDs is evident from the executive dysfunction observed in substance dependent adults [55], as well as the later maturation of this region in adolescence [33]. Recent DTI research has begun to investigate substance use in adolescents as related to white matter tract integrity, identifying frontal and parietal circuits [56]. PFC total volume and white matter volume has been reported as significantly smaller in adolescents with AUDs as compared to those without [57]. Furthermore, PFC volume and gray matter volume in the PFC in this sample were related to alcohol characteristics, specifically the average amount of alcohol consumed at a given time. In a similar study, structural MRI examined frontal regions with specific interest in gender effects in adolescents with AUDs [58]. Adolescent girls with AUDs were found to have smaller PFC and white matter PFC volume relative to control girls, whereas adolescent boys with AUDs were found to have larger PFC and white matter PFC volume relative to control boys. Such an effect was not found previously [57], but important sample differences, including a younger cohort and co-morbid psychiatric disorder exclusion criteria present in the former study [58], may represent important differences.

Adolescent substance use disorders: Brain function

Several studies employing functional magnetic resonance imaging (fMRI) have begun to elucidate differences in brain function during different tasks in adolescent substance dependence. Evidence to suggest functional abnormalities between adolescents with SUDs and adolescents without have been drawn from three task domains: Executive functioning including working memory, cerebral perfusion at rest, and presentation of substance-related cues.

Working memory and executive functioning

Multiple studies have required participants to complete a spatial working memory task during fMRI. Distinct differences in functional brain activation emerged in adolescents with AUDs [59], who show reduced functional activity compared to controls in multiple areas including the left precentral gyrus, left inferior temporal and fusiform gyri, and bilaterally in the cerebellum. Greater activity was also found in bilateral parietal regions relative to control participants. Interestingly, functional differences in this task between adolescents with AUDs and those without were heightened in girls (versus boys), suggesting increased

neurobiological vulnerability to the effects of alcohol use in girls [60]. This result also converges with structural findings of the differential effects of alcohol use on PFC volume as a function of gender [58]. The differences in functional activity in both studies [59,60] are more compelling taking into consideration the absence of any behavioral difference in performance between the AUD and control adolescents in the spatial working memory task. This performance indifference suggests the involvement of compensatory neural mechanisms engaged during task performance. Indeed an earlier study [61] using the same task but completed by an older (aged 18-25 years) cohort of women with alcohol dependence observed poorer behavioral performance on the same spatial working memory task relative to controls, with reduced activity in parietal regions, accompanied by a reduction in activity in prefrontal regions (including right medial frontal gyrus and left superior frontal gyrus). These studies taken together suggest that alcohol dependence during adolescence manifests in subtle neurophysiological changes in the absence of specific behavioral impairments, although as this dependence continues through the course of development, increased brain dysfunction emerges that is accompanied by objective behavioral difficulties.

Recent research suggests that adolescents with marijuana and alcohol dependence (MAUD) show no behavioral differences relative to controls in spatial working memory; however, a wider network of dysfunction appears to emerge [62]. Specifically, relative to controls, adolescents with MAUD show increased activity in the dorsolateral prefrontal cortex, with reduced activity in the anterior cingulate, right inferior frontal and bilateral temporal regions. These findings are consistent with the notion that functional activity observed in adolescents with MAUD may reflect compensatory networks of activation needed to maintain behavioral performance. Also noteworthy in this study were the comparisons between adolescents with MAUDs and AUDs that revealed similar functional patterns of activation in frontal regions, although functional activity in adolescents with AUDs did not statistically differ from controls. These findings suggest a gradation of substance use effects on neurophysiology, with additive effects of poly-substance use having more detrimental consequences on functional brain activity.

These studies investigating spatial working memory reveal dysfunction in regions typically associated with cognitive control, including frontal, temporal, and parietal cortex. Additional research using an auditory memory (n-back) task has also revealed behavioral and neurobiological hippocampal dysfunction in adolescents frequently using both marijuana [63] and ecstasy [64]. Other studies have investigated the neurobiology of attentional control in adolescent substance users, particularly those with both SUDs and conduct problems (SCP; [65]). Consistent with other studies described above, activation differences were observed, often in the absence of behavioral deficits; for example, under conditions of attentional conflict, adolescents with SCP showed increased activation in multiple regions including bilateral hippocampal gyrus, superior frontal gyrus, thalamus, and the caudate.

Cerebral perfusion at rest

Important for understanding fMRI findings, which rely on blood flow measures during task performance, are the potential for existing differences in blood flow at rest. Resting cerebral perfusion in frontal regions have been examined in young women recruited from an existing adolescent substance abuse cohort and compared to control women [66]. Here it was found that although global differences in perfusion were absent, perfusion was less in prefrontal and parietal regions in the SUD cohort relative to control group. Such resting state differences may contribute to differences observed in the functional studies outlined above (those when engaged in spatial working memory tasks), although the contribution of age as a factor may need to be considered and this finding replicated in adolescents. Nevertheless it is interesting to note that such resting state differences can exist and future research will

benefit from determining how and whether changes in resting state manifest in functional and behavioral differences in adolescents with SUD.

Substance-related cues

The neural correlates of substance cue reactivity has been examined in adolescents with and without SUDs [67]. On each trial, participants were presented a single picture drawn from a series of advertisements containing either alcohol or non-alcohol-relevant cues, and these cues were personalized to suit the beverage preference of each individual participant. Responding was task-irrelevant, with participants making a discrimination response to the presence or absence of people in the advertisements. Adolescents with AUDs showed an overall increased activation in response to alcohol cues compared to controls. This functional increase was observed predominantly in frontal and limbic regions, areas which have previously been identified as important in processing emotionally and motivationally salient and rewarding stimuli [68]. This finding suggests that alcohol-related cues may be processed as rewarding by adolescents with AUDs. In studies that directly investigate reward processing, adolescents as compared with adults, including adolescents with a family history of alcoholism, have shown relatively diminished activation of the ventral striatum [69,70]. These findings resonate with studies of adults with AUDs in which relatively diminished ventral striatal activation is observed in the AUD group, and this diminished ventral striatal activation correlates with impulsivity measures [71,72].

Thus far we have reviewed both structural and functional evidence that points to neurobiological differences present in adolescents with SUDs relative to controls. We now turn our attention to considering the implications of these studies for the prevention and treatment of adolescent SUDs.

Implications for Prevention and Treatment

The evidence discussed above suggests that identifiable structural and functional abnormalities emerge in adolescents with SUDs, indicating the potential for prevention and treatment during this period. However, it is important to consider whether these abnormalities emerge as a consequence of substance use, or reflect preexisting differences that serve to increase vulnerability to initial substance use and subsequent abuse and dependence. On the one hand, substances such as alcohol may be exerting neurotoxic effects in cortical and subcortical regions, disrupting normative trajectories of neural myelination in adolescence. Indeed, the inhibitory effects of ethanol on N- methyl-D-aspartate (NMDA) receptors is such that it impairs excitatory glutamate neurotransmission [48] and the effects of alcohol on NDMA receptors has been hypothesized as a possible mechanism underlying reduced hippocampal volume in adolescent SUD (e.g.,[50]).

On the other hand, structural and functional abnormalities may represent pre-existing morbidity and vulnerability to the development of SUDs. One approach to teasing this apart with existing data sets would be to correlate age of onset of substance use and dependency with structural and functional data; presumably if these abnormalities were a consequence, rather than a cause, of substance use then there should be a numerical relation between neurobiology and chronology. The absence of such a relationship may instead speak to a pre-existing vulnerability to substance use. In the structural data for instance, PFC volume reduction was not related to age of onset [57] suggesting an initial volume deficit prior to substance use. Relating structure to function, existing research has also documented the importance of frontal regions in impulse control and decision-making [73], perhaps suggesting that these structural impairments may be a precursor to these behavioral and cognitive dysfunctions, and increase the likelihood of initial and maintained substance use [57]. As described above in an earlier section, animal data suggest a role for both pre-

existing vulnerabilities for substance use in substance-naïve individuals and that substance use leads to changes in behavior, mediated by functional and structural brain-based changes. Thus, it will be the goal of future research to investigate developmental interactions between substance use and adolescent (and adult) neurobiology.

If pre-existing structural and functional vulnerabilities can be considered risk factors to the development and maintenance of SUDs, then these neurobiological characteristics could potentially be used to identify those most at risk in adolescence and into adulthood. The pragmatics of neurobiological screening during adolescence though is limited, but brain-behavior relationships may be useful here. As detailed above, certain constructs such as impulsivity and related factors may contribute significantly to decision-making processes and engagement in risky behaviors, and if a strong association can be demonstrated between such behavioral measures and brain findings, then this could prove fruitful in identifying those individuals at greatest risk. An important caveat here though in understanding neural substrates of adolescent substance use is that part and parcel of adolescence are biological changes that promote novelty seeking and risk-taking which are adaptive in promoting independence from care-givers [2,31]. It is when these normative changes lead to more negative outcomes, with initial substance use leading to repeated substance use and dependence, that intervention is crucial. Nevertheless, identification of those individuals who may show atypical responses in behavioral measures of risk may still prove beneficial. This could be greatly facilitated by establishing relations between risk factors identified in behavioral measures and neurobiological changes in adolescent populations with SUDs. Indeed, prevention programs could identify those most at risk, targeting behavioral characteristics associated with risk rather than a more general intervention approach, and this has proven successful in changing the attitudes of young adults who report high scores on sensation seeking [74].

Relevant to findings in non-SUD adolescents understanding the contribution of reward sensitivity may also prove important here. According to the neurobiological model of adolescent brain development [35], the maturation of the limbic system with heightened reward sensitivity in conjunction with the protracted development of prefrontal cortex and immature cognitive control, suggests that an imbalance between the development of these two systems may be at the core of risk-taking behavior. Indeed, in healthy participants across development, activity in the ventral striatum positively correlated with an increased likelihood of self-reported engagement with risky behaviors [75]. Although this neurobiological approach speaks to a general increase in risk-taking behavior during this developmental period, intervention programs need to identify those adolescents more likely to engage in risky behaviors, potentially through reward sensitivity, who may be susceptible to the negative outcomes beyond the normative adolescent trajectory.

As described previously, substance-related cues are processed by the affective system similarly to motivationally rewarding cues in adolescents with SUDs, with increased responsiveness in frontal and limbic circuits to these cues [67]. Similarly in adult studies, substance use cues have been shown to influence neural activity in frontal and sub-cortical (e.g., thalamic) regions [76], thus converging with findings in adolescents. As such, the marketing and advertising of commonly used substances, such as alcohol and tobacco, warrant consideration, particularly as related to adolescents. Overlapping reward systems processing substances and non-substances also suggest the utility of treatment programs in replacing risk-taking behavior with other stimulating or novel behaviors which have rewarding outcomes but are not substance-based [74]. This could be completed in conjunction with interventions enhancing the rewarding value of naturally occurring reinforcers [77]. However, as these investigations are at very early stages and some prevention strategies with seemingly rational foundations have been shown not to be very

helpful in adolescents[78], additional research is needed to determine empirically the validity of such approaches.

It is also worthwhile to consider the role of gender in the development of adolescent SUDs. Findings of differential PFC structural volumes in boys and girls with AUDs [58], and functional differences during spatial working memory tasks [60], suggest gender differences in the neurobiological substrates of adolescent SUDs may be a significant factor [79,80]. Indeed, the pathways to substance use and dependence may differ significantly by gender; for example, women with AUDs use alcohol more to facilitate regulation of negative affect than men with AUDs [81]. Gender differences in psychopathology (for instance, adolescent girls have higher rates of mood disorders [82]; boys have higher rates of conduct disorder [83]) may also serve to demonstrate the importance of gender more generally in the development of clinical disorders, especially considering these disorders typically onset in adolescence and are highly co-morbid with substance use [20]. Consequently, structural and functional gender differences may reflect distinct mechanisms underlying substance use, and both screening and intervention programs should consider gender in order to optimize efforts.

Finally, identifying those at risk for the development of adolescent SUDs to target intervention will benefit greatly from consideration of whether the implications of these findings are in standing within the realms of genetic or environmental contributions. Family studies have found that there are high concordance rates between substance-using children and parents, suggesting a heritable component to illicit drug use, with increased rates of adolescent substance use when parents are perceived as a substance user (see [84] for a review). Although this may suggest a genetic component, the familial environment with exposure (and potentially access) to drugs may reinforce substance using behaviors, specifically initiation of use. Genetic components are also important, with susceptibility and vulnerability to substance use and SUDs found to have substantial heritable contributions [85]. Furthermore, repeated substance use may alter the expression of specific genes involved in the pathophysiology of SUDs (e.g., [50]). Thus, it may be that genetic and environmental factors modulate substance use experimentation, and the complex transition from initiation to repeated use and subsequent dependence with specific periods, like adolescence, of particular neurodevelopmental vulnerability [84].

Conclusion

Adolescence is characterized by distinct neurobehavioral changes with more rapid development of limbic systems and relatively immature prefrontal cognitive systems that may promote risky behaviors and substance use. Research understanding the neurobiological substrates of SUDs has historically focused on adults, and findings from studies of adults may have limited applicability to adolescents. Recent studies are identifying distinct structural and functional differences in adolescents with SUDs, providing a biological basis for prevention and treatment programs. These data coupled with a better understanding of individual differences and their relation to brain structure and function will be important for the successful development and implementation of prevention and treatment before, during, and following adolescence.

Synopsis

Adolescence represents a unique period of development with neuronal maturation accompanied by increases in behavioral risk-taking. Although risky behavior is a likely marker of normative adolescent development, there is an early emergence of substance use disorders in this population. Indeed, adolescence represents a distinct period of

vulnerability to substance use initiation and transitions to substance abuse and dependence. Of recent interest has been understanding the neurobiology of adolescent substance use disorders, with adult studies being limited in their applicability to this developmentally sensitive maturation period and providing restricted insight into potential treatment and intervention. Therefore, the purpose of this review is two-fold; first, we review the neurobiology of adolescent substance use disorders; and second we consider the implications of these findings for prevention and treatment.

Acknowledgments

We are grateful to Naaila Panjwani for her assistance with the preparation of the manuscript.

Funding Sources and Disclosures This work was supported by the National Institutes of Health (NIH) grants R01 DA019039, R01 DA020908, RL1 AA017539, RO1 DA06025, R01 DA017863, R01 HD044796, R21 DA024232, P01 DA022446, P50 DA09241, P50 DA016556, UL1 DE19586, NIH Roadmap for Medical Research/Common Fund, the Office of Research on Women's Health, the Gustavus and Louise Pfeiffer Research Foundation, and the Anna Freud Centre (UK). This publication was also made possible by CTSA Grant Number UL1 RR024139 from the National Center for Research Resources (NCRR), a component of the NIH, and NIH roadmap for Medical Research. The contents of the manuscript are solely the responsibility of the authors and do not necessarily represent the official views of any of the funding agencies. Dr. Potenza has received financial support or compensation for the following: Dr. Potenza consults for and is an advisor to Boehringer Ingelheim; has consulted for and has financial interests in Somaxon; has received research support from the National Institutes of Health, Veteran's Administration, Mohegan Sun Casino, the National Center for Responsible Gaming and its affiliated Institute for Research on Gambling Disorders, and Forest Laboratories, Ortho-McNeil, Oy-Control/Biotie and Glaxo-SmithKline pharmaceuticals; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; has consulted for law offices and the federal public defender's office in issues related to impulse control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts.

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