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Adolescence as a critical window for developing an alcohol use disorder: Current findings in neuroscience

Kimberly Nixon* and Justin A. McClain
University of Kentucky College of Pharmacy

Abstract

Purpose of Review—Alcohol consumption during adolescence greatly increases the likelihood that an alcohol use disorder will develop later in life. Elucidating how alcohol impacts the adolescent brain is paramount to understanding how alcohol use disorders arise. This review focuses on recent work addressing alcohol's unique effect on the adolescent brain.

Recent findings—The unique and dynamic state of the developing adolescent brain is discussed with an emphasis on the developmentally distinct effect of alcohol on the dopaminergic reward system and corticolimbic structure and function. Reward neurocircuitry undergoes significant developmental shifts during adolescence, making it particularly sensitive to alcohol in ways that could promote excessive consumption. In addition, developing corticolimbic systems, including the prefrontal cortex and hippocampus, exhibit enhanced vulnerability to alcohol-induced damage. Disruption of white matter integrity, neurotoxicity and inhibition of adult neurogenesis may underlie alcohol-mediated cognitive dysfunction and lead to decreased behavioral control over consumption.

Summary—In adolescents, alcohol interacts extensively with reward neurocircuitry and corticolimbic structure and function in ways that promote maladaptive behaviors that lead to addiction. Future work is needed to further understand the mechanisms involved in these interactions. Therapeutic strategies that restore proper reward neurochemistry or reverse alcohol-induced neurodegeneration could prove useful in preventing emergence of alcohol use disorders.

Keywords

Adolescence; Alcohol Use Disorders; Alcoholism; Neurodegeneration; Adult Neurogenesis

Introduction

Adolescence, defined as ages 10-19 by the World Health Organization [1], represents the developmental transition to adulthood during which the brain is in a unique and dynamic state. This stage is marked by increased novelty seeking and risk-taking behavior as adolescents experiment with adult aspects of life, including the initiation of alcohol use. By twelfth grade, 73% of adolescents have experimented with alcohol while 30% have been drunk within the past month [2]. Further, more than half of 12-17 year-olds who consume alcohol, binge drink (>5/4 drinks for males and females respectively) [2]. Unfortunately, alcohol use during adolescence increases the risk for developing an alcohol use disorder (AUD) [3]. Elucidating the neurobiology of this risk is considered critical to understanding how AUDs develop. To date, two overlapping hypotheses have emerged to explain why adolescence is a critical time for developing an AUD. First, the adolescent brain responds

*Corresponding Author: Kimberly Nixon, Ph.D. Department of Pharmaceutical Sciences The University of Kentucky College of Pharmacy 725 Rose Street Lexington, KY 40536-0082 Phone (859) 323-3038 Fax: (859) 323-3575 kim-nixon@uky.edu.

uniquely to alcohol, which may result in fewer physiological cues to self-regulate intake [4]. Second, the adolescent brain exhibits an enhanced sensitivity to many alcohol effects, especially neurodegenerative effects of alcohol that dysregulate behavioral control systems and lead to addiction [5-7]. This review highlights current discoveries that support these neurobiological theories of how AUDs develop in adolescents.

Adolescent's unique response to alcohol promotes excessive intake

Adolescents respond to the effects of alcohol distinctly from adults [4]. Adolescents are less sensitive to negative effects of alcohol, including cues that influence self-regulation of intake, but are more sensitive to positive effects, which may serve to reinforce or promote excessive intake [4]. The distinct response of adolescents has both pharmacodynamic and pharmacokinetic components such that age-related differences in alcohol (ethanol) absorption and metabolism must be considered when examining these differences [8]. Specifically, it takes a larger dose of alcohol for an adolescent to achieve similar blood alcohol concentrations as an adult [7]. However, well-controlled animal studies have shown that despite similar blood alcohol concentrations, adolescents demonstrate enhanced sensitivities or vulnerabilities to many aspects of alcohol use and abuse [9,10]. The following sections highlight recent work that examines how the adolescent's unique response to alcohol may promote the development of an AUD.

Decreased Response to Adverse Effects

Adolescents have consistently been found to be less sensitive to many of the negative effects of alcohol [4]. For example, adolescents have decreased sensitivity to the intoxicating effects of alcohol, such as alcohol-induced sedation and motor impairment [11]. Furthermore, adolescents display reduced sensitivity to aspects of "hangover," specifically alcohol withdrawal-induced social depression and anxiety [12,13]. Although some groups have found a reduced severity in alcohol withdrawal symptoms such as seizures [14,15], the reduced severity may be due to developmental differences in ethanol pharmacokinetics [8]. When blood alcohol concentrations are similar, withdrawal severity [16] and withdrawal-induced anxiety [17] are identical between adult and adolescent rats. However, developmental differences in alcohol's pharmacodynamic effects on GABAergic neurotransmission should also be considered. Adolescent sensitivity to alcohol sedation and/or withdrawal relies upon GABAergic neurotransmission; but, adolescent GABA_A receptors are less sensitive to ethanol-induced potentiation of GABA_A-mediated inhibitory currents [18]. As adverse effects of alcohol may serve as cues to halt intake or prevent future excessive intake, the adolescent's reduced sensitivity to these effects, whether pharmacodynamic or pharmacokinetic, could facilitate excessive alcohol consumption and thus increase the risk for developing an AUD [4].

Increased Response to Positive Effects

Although adolescents respond less to alcohol's aversive effects, they are more sensitive to many positive and rewarding effects of alcohol. For instance, alcohol mediates appetitive second-order conditioning in adolescent but not adult rats, suggesting greater reinforcing properties of alcohol [19]. Adolescents, but not adults, will self-administer enough alcohol to induce tachycardia, an effect linked to alcohol's hedonic value [20,21]. Thus, the rewarding effects of alcohol may be greater in adolescents than adults, which may promote future alcohol seeking behavior [19-21]. This idea is supported by studies where alcohol exposure during adolescence enhanced novelty seeking and influenced conditioned place preference in adulthood, both of which are predictors of alcohol seeking behavior [22,23]. Adolescents are also more sensitive to the social facilitation effects of alcohol, an important factor in adolescent human expectancies about alcohol and adolescent drinking behavior

[24]. A mere passive social interaction with an intoxicated rat increases alcohol self-administration [25], which supports that the enhanced positive effects of alcohol in adolescence can drive alcohol consumption in adulthood [22,23]. The underlying neurobiology responsible for the adolescent's enhanced sensitivities likely involves the mesocorticolimbic reward system, recent reports on which are discussed below.

During adolescence, the enhanced drive to explore, take risks, and experiment with novel aspects of life are thought to be due to a “disparate developmental trajectory” between the mesocorticolimbic reward and frontal cortical executive control systems [26,27]. The refinement of these systems during adolescence is extensive. In the prefrontal cortex (PFC), significant glutamatergic pruning decreases cortical volume, while cholinergic and dopaminergic innervation increase to adult levels [4,27,28]. In addition, a sharp peak in dopamine levels within the nucleus accumbens occurs in late adolescence before falling to adult levels [23,27,29].

The unique developmental state of these systems parallels the unique response of the adolescent brain to alcohol. Acute alcohol exposure causes a robust increase in dopamine release within the nucleus accumbens [30], an effect that is most pronounced during adolescence [27,31]. This enhancement in dopamine release is consistent with the greater rewarding effects of alcohol in adolescents [19-21]. Alternatively, previous alcohol exposure significantly alters the dopamine response to an acute dose of alcohol [27]. In adolescents, alcohol exposure may interfere with development of the mesolimbic reward system, resulting in increased basal accumbal dopamine release and decreased dopamine D2 receptor expression [27,29,31]. Importantly, these changes are accompanied by a decrease in alcohol-evoked dopamine release upon subsequent alcohol exposure [27]. Decreased dopamine release and D2 receptor expression may create a hypodopaminergic state that *reduces* alcohol's rewarding effect. This state is reminiscent of Reward Deficiency Syndrome that arises when the reward system under-responds to natural or drug rewards and is hypothesized to increase reward seeking behaviors, such as risk taking and novelty seeking [32]. This idea is supported by observations that alcohol-induced changes to the dopaminergic system correlate with increased alcohol seeking behavior and voluntary consumption by adult rats that were exposed to alcohol at adolescence [23,31]. In these models, adults appear less sensitive to alcohol's effects on dopamine release and D2 receptor expression [27,31], indicating that the unique developmental state of the adolescent mesocorticolimbic reward system makes it particularly vulnerable to alcohol and risk for addiction.

Recent findings in adolescent models emphasize that the contributions of other neurotransmitters to reward systems should not be overlooked. Glutamatergic, cholinergic, and opiodergic pathways each play important roles in regulating the dopaminergic reward system [30,33]. In rodents, repeated ethanol exposure reduces hippocampal glutamate dehydrogenase 1 and phosphorylation of the NR2B subunit of glutamatergic N-methyl-D-aspartate receptors in the frontal cortex, hippocampus, and nucleus accumbens of adolescent, but not adult rats [31,34]. These changes within reward neurocircuitry support the idea that alcohol-mediated changes in glutamatergic neurotransmission during adolescence may contribute to the development of an AUD [35]. Further, blockade of μ -opioid receptors inhibits alcohol-mediated social facilitation in adolescent rats, which links the endogenous opioid system to rewarding effects of alcohol in this age group [36]. Alcohol also enhances midbrain choline acetyltransferase activity in adolescent mice, suggesting that alcohol increases midbrain cholinergic innervation [37]. This could have important consequences for reward since ventral tegmental acetylcholine is required for alcohol-induced dopamine release into the nucleus accumbens [30]. Potential interactions between

these neurotransmitter systems warrant further study as they could hold important clues regarding the enhanced sensitivity of the adolescent reward response to alcohol.

Enhanced susceptibility to alcohol-induced neurodegeneration leads to addiction

While adolescents appear less sensitive to effects that limit consumption, they exhibit increased sensitivity to the amnesic effects of alcohol intoxication [6] and are more vulnerable to alcohol-induced neurodegeneration [7,38]. Adult alcoholics suffer from a variety of cognitive impairments that are thought to reflect defects in central nervous system integrity, including hallmark reductions in brain volume (neurodegeneration) from both corticolimbic grey matter degeneration and altered white matter integrity [39]. Alcohol-induced neurodegeneration occurs in regions that control behaviors that may lead to addiction such that repeated exposure to the high blood alcohol levels characteristic of binge drinking is thought to be one of the critical steps in the downward spiral towards an AUD [38,39]. Unfortunately, these regions of the adolescent brain are more susceptible to the degenerative effects of excessive alcohol intake. For example, adolescents meeting diagnostic criteria for an AUD exhibit cognitive deficits that correspond to hippocampal and PFC volume reduction despite only a few years of excessive drinking [40-45]. The consistent reports of degeneration in adolescent hippocampus are intriguing as adults with AUDs do not reliably show hippocampal degeneration [46]. Given the role of the PFC and hippocampus in behavioral inhibition systems, alcohol-induced damage to these regions could increase impulsive behavior, lead to poor-decision making and therefore promote further excessive alcohol consumption [47].

Adolescent susceptibility to degeneration may be due to multiple mechanistic factors that impair integrity or decrease volume. First, the adolescent brain is still developing, such that alcohol may have teratogenic effects that appear as degeneration in regions such as the PFC, mesolimbic system and hippocampus [7,38,48]. Second, alcohol is neurotoxic in many of these regions and past structural work has shown that some regions of the adolescent brain have greater sensitivity to alcohol neurotoxicity [7,9,49].

White Matter Integrity

Diffusion tensor imaging studies have shown that adolescent binge drinking damages white matter tracts throughout the brain, including the principle fiber tracts leaving the hippocampus and those interconnecting the PFC [50,51]. Damage severity correlated positively with withdrawal severity and estimated blood alcohol concentrations [50], which underscores the risk associated with binge drinking, the most common drinking pattern in adolescents [2]. Consistent with white matter damage, functional studies measuring event-related potentials revealed delayed responses to auditory stimuli in binge drinking college freshman, effects which are hypothesized to reflect impaired stimulus perception and decision making processes [52]. The extent of this effect is alarming given that the delays resembled those recorded from alcohol-dependent adults, even though subjects had not yet progressed to AUD criterion [52].

Recent functional studies suggest that excessive alcohol intake during adolescence has far greater consequences than previously considered [53]. Functional magnetic resonance imaging studies that assess neural activity by measuring blood oxygen level dependent (BOLD) signals have revealed abnormalities in the brain's response despite normal performance on some tasks [53,54]. Even more disturbing are recent findings that binge-drinking adolescents who do *not* meet criteria for AUDs show slight, but detectable cognitive impairments when compared to their non- or social-drinking peers [55]. For

example, binge-drinking adolescents performed only marginally poorer on a simple verbal learning test compared to age-matched controls but showed *increased* neural activation in frontal, parietal and cingulate cortices during this task [55]. The consistent finding that BOLD responses are increased in adolescents with alcohol problems during different working memory-type tasks have lead the authors to hypothesize that the frontal lobe memory systems may compensate for deficiencies in medial temporal lobe function [54,55]. This suggestion is consistent with several studies that have shown degeneration in temporal lobe structures in adolescents with AUDs [42-44].

Grey Matter Degeneration

Animals models have been necessary to understand the mechanism of alcohol effects on the integrity of these systems and provide more direct links between alcohol intake, behavioral impairments and neurodegeneration [7]. Although it is well established that alcohol has an enhanced amnestic effect on learning and memory performance in adolescent rats [6,56], only recently has it been shown that excessive alcohol exposure results in greater or more persistent effects on learning and memory in the adolescent [57,58]. Although the neurobiology of these hippocampus-dependent impairments is not clear, they correlate to hippocampal degeneration in human adolescent AUDs [44]. However, adolescent susceptibility to alcohol-induced cell death was only reported in frontal-anterior cortical regions [9]. Even though hippocampal degeneration is consistently reported in human adolescent AUDs, observations of hippocampal cell death in animal models are limited [10]. This discrepancy has lead to the exploration of additional mechanisms of degeneration.

Alcohol Effects on Neural Stem Cells

It is well-accepted that neural stem cells produce new neurons in the dentate gyrus of the hippocampus throughout life as an integral process to hippocampal structure and function [59]. Recent work suggests that alcohol effects on neural stem cells may underlie the susceptibility of the adolescent hippocampus to alcohol-induced degeneration [10,38]. Acutely, alcohol inhibits adult neurogenesis by reducing neural stem cell proliferation [38]. However, in models of an AUD, alcohol both impairs neural stem cell proliferation and reduces survival of newborn neurons [10]. By our estimates, alcohol inhibition of adult neurogenesis eliminates thousands of hippocampal neurons, whereas cell death only eliminates a few hundred. This loss is due to the developmental state of the adolescent brain where the number of new neurons produced is many-fold higher than in adults [60]. Thus, because of the higher rate of neurogenesis in adolescents, a greater number of cells are “lost” (never born or survive) due to alcohol as opposed to adults [10,38]. The enhanced vulnerability of the adolescent brain to alcohol-induced effects on a form of plasticity is consistent with recent observations that adolescent rats demonstrate more persistent alcohol effects for many plasticity-related and cytoskeletal proteins [34,49]. Considering that hippocampal neurodegeneration is more consistently observed in adolescents with AUDs than adults, alcohol inhibition of adult neurogenesis - or degeneration through lack of cell generation - may explain the vulnerability of the adolescent hippocampus to alcohol-induced neurodegeneration [38].

Conclusions

In summary, recent studies continue to show that corticolimbic systems, such as the PFC, mesolimbic reward system and hippocampus, are undergoing significant developmental transitions during adolescence that make them primary targets for alcohol-induced structural and functional changes [5,7,26,38]. The adolescent's decreased response to the negative aspects of alcohol consumption (motor impairment, sedation, anxiety, and social depression) coupled with increased or altered response to the positive and rewarding effects of alcohol

may promote excessive intake. Repeated exposure to excessive intake and the adolescent's enhanced susceptibility to alcohol-induced damage - whether through toxicity, teratogenicity, or other effects on plasticity - further dysregulates behavioral control of consumption. Thus, the adolescent's unique response to alcohol combined with increased susceptibility to alcohol-induced neurodegeneration interact to facilitate excessive alcohol consumption, the hallmark of an AUD. However, the mechanisms behind the adolescent's unique response to and consequences of alcohol use/abuse are not well understood. Additional research is desperately needed to understand the responses and consequences of alcohol exposure on the dynamic and developing adolescent brain. Because AUDs commonly begin in adolescence and AUDs affect over 8% of the U.S. population [61], research is critical to public health in order to better prevent and reduce the prevalence of AUDs.

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Bibliography

1. Organization, WH. Highlights: Child and Adolescent Health and Development Progress Report 2006-2007. WHO Press; Geneva, Switzerland: 2008. p. 20
2. Johnston, LD.; O'Malley, PM.; Bachman, JG.; Schulenberg, JE. Monitoring the Future national survey results on drug use, 1975-2006: Volume I, Secondary school students. National Institute on Drug Abuse; Bethesda, MD: 2007.
3. Grant BF, Dawson DA. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *J Subst Abuse*. 1997; 9:103-110. [PubMed: 9494942]
4. Spear LP, Varlinskaya EI. Adolescence. Alcohol sensitivity, tolerance, and intake. *Recent Dev Alcohol*. 2005; 17:143-159. [PubMed: 15789864]
5. Crews F, He J, Hodge C. Adolescent cortical development: a critical period of vulnerability for addiction. *Pharmacol Biochem Behav*. 2007; 86:189-199. [PubMed: 17222895]
6. White AM, Swartzwelder HS. Hippocampal function during adolescence: a unique target of ethanol effects. *Ann N Y Acad Sci*. 2004; 1021:206-220. [PubMed: 15251891]
7. Spear LP. Assessment of adolescent neurotoxicity: rationale and methodological considerations. *Neurotoxicol Teratol*. 2007; 29:1-9. [PubMed: 17222532]
8. Walker BM, Ehlers CL. Age-related differences in the blood alcohol levels of Wistar rats. *Pharmacol Biochem Behav*. 2009; 91:560-565. [PubMed: 18940195]
9. Crews FT, Braun CJ, Hoplight B, et al. Binge ethanol consumption causes differential brain damage in young adolescent rats compared with adult rats. *Alcohol Clin Exp Res*. 2000; 24:1712-1723. [PubMed: 11104119]
- 10**. Morris SA, Eaves DW, Smith AR, Nixon K. Alcohol inhibition of neurogenesis: A mechanism of hippocampal neurodegeneration in an adolescent alcohol abuse model. *Hippocampus*. 2009 [This study was the first to show that alcohol effects on neural stem cells may be the primary mechanism by which the hippocampus degenerates and in adolescent alcohol use disorders. Notably, the effect of alcohol on neural stem cells may also underlie the enhanced vulnerability of the adolescent hippocampus to alcohol-induced neurodegeneration.]
11. Little PJ, Kuhn CM, Wilson WA, Swartzwelder HS. Differential effects of ethanol in adolescent and adult rats. *Alcohol Clin Exp Res*. 1996; 20:1346-1351. [PubMed: 8947309]
12. Doremus TL, Brunell SC, Varlinskaya EI, Spear LP. Anxiogenic effects during withdrawal from acute ethanol in adolescent and adult rats. *Pharmacol Biochem Behav*. 2003; 75:411-418. [PubMed: 12873633]

13. Varlinskaya EI, Spear LP. Acute ethanol withdrawal (hangover) and social behavior in adolescent and adult male and female Sprague-Dawley rats. *Alcohol Clin Exp Res.* 2004; 28:40–50. [PubMed: 14745301]
14. Chung CS, Wang J, Wehman M, Rhoads DE. Severity of alcohol withdrawal symptoms depends on developmental stage of Long-Evans rats. *Pharmacol Biochem Behav.* 2008; 89:137–144. [PubMed: 18207224]
15. Acheson SK, Richardson R, Swartzwelder HS. Developmental changes in seizure susceptibility during ethanol withdrawal. *Alcohol.* 1999; 18:23–26. [PubMed: 10386661]
16. Morris SA, Kelso ML, Liput DJ, et al. Similar withdrawal severity in adolescents and adults in a rat model of alcohol dependence. *Alcohol.* 2010; 44 in press.
17. Slawewski CJ, Roth J, Gilder A. Neurobehavioral profiles during the acute phase of ethanol withdrawal in adolescent and adult Sprague-Dawley rats. *Behav Brain Res.* 2006; 170:41–51. [PubMed: 16563530]
18. Li Q, Wilson WA, Swartzwelder HS. Developmental differences in the sensitivity of hippocampal GABAA receptor-mediated IPSCs to ethanol. *Alcohol Clin Exp Res.* 2003; 27:2017–2022. [PubMed: 14691391]
- 19*. Pautassi RM, Myers M, Spear LP, et al. Adolescent but not adult rats exhibit ethanol-mediated appetitive second-order conditioning. *Alcohol Clin Exp Res.* 2008; 32:2016–2027. [PubMed: 18782343] [This important study adds to emerging data indicating that adolescents may experience greater reward in response to alcohol than adolescents. The increased sensitivity to alcohol's rewarding effects could contribute to increased susceptibility to alcoholism.]
20. Doremus-Fitzwater TL, Varlinskaya EI, Spear LP. Motivational systems in adolescence: Possible implications for age differences in substance abuse and other risk-taking behaviors. *Brain Cogn.* 2010; 72:114–123. [PubMed: 19762139]
- 21*. Ristuccia RC, Spear LP. Adolescent and adult heart rate responses to self-administered ethanol. *Alcohol Clin Exp Res.* 2008; 32:1807–1815. [PubMed: 18657128] [Stimuli that activate the brain's dopamine reward system cause an increase in heart rate. The authors use this measure to determine the intensity of alcohol reward, showing that adolescents find acute alcohol more rewarding than adults.]
22. Stansfield KH, Kirstein CL. Chronic cocaine or ethanol exposure during adolescence alters novelty-related behaviors in adulthood. *Pharmacol Biochem Behav.* 2007; 86:637–642. [PubMed: 17395255]
- 23*. Maldonado-Devincci AM, Badanich KA, Kirstein CL. Alcohol during adolescence selectively alters immediate and long-term behavior and neurochemistry. *Alcohol.* 2010; 44 in press. [This work shows that exposure of an alcohol-naïve adolescent animal to an alcohol-intoxicated peer increases alcohol seeking behavior and repeated alcohol exposure during adolescence causes long-lasting behavioral changes that persist into adulthood. This is important because it shows that adolescents are more vulnerable to alcohol's behavioral effects that act to promote consumption.]
24. Varlinskaya EI, Spear LP. Acute effects of ethanol on social behavior of adolescent and adult rats: role of familiarity of the test situation. *Alcohol Clin Exp Res.* 2002; 26:1502–1511. [PubMed: 12394283]
- 25*. Maldonado AM, Finkbeiner LM, Kirstein CL. Social interaction and partner familiarity differentially alter voluntary ethanol intake in adolescent male and female rats. *Alcohol.* 2008; 42:641–648. [PubMed: 18922665] [The authors show that exposure of an alcohol-naïve animal to an alcohol-intoxicated peer increases subsequent self-administration of alcohol by the observer, signifying the importance of peer influence in initiation of alcohol use in adolescents.]
26. Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *Am J Psychiatry.* 2003; 160:1041–1052. [PubMed: 12777258]
- 27*. Philpot RM, Wecker L, Kirstein CL. Repeated ethanol exposure during adolescence alters the developmental trajectory of dopaminergic output from the nucleus accumbens septi. *Int J Dev Neurosci.* 2009; 27:805–815. [PubMed: 19712739] [This found that repeated alcohol exposure increases basal dopamine levels, but decreases the magnitude of dopamine release when alcohol

is administered during early adolescence. Decreased dopamine response to alcohol could result enhance the drive to consume alcohol.]

28. Azam L, Chen Y, Leslie FM. Developmental regulation of nicotinic acetylcholine receptors within midbrain dopamine neurons. *Neuroscience*. 2007; 144:1347–1360. [PubMed: 17197101]
29. Philpot R, Kirstein C. Developmental differences in the accumbal dopaminergic response to repeated ethanol exposure. *Ann N Y Acad Sci*. 2004; 1021:422–426. [PubMed: 15251921]
- 30*. Soderpalm B, Lof E, Ericson M. Mechanistic studies of ethanol's interaction with the mesolimbic dopamine reward system. *Pharmacopsychiatry*. 2009; 42(Suppl 1):S87–94. [PubMed: 19434560] [The authors review ethanol's effects on the dopamine reward system focusing on pharmacological action of ethanol on cholinergic and glycine receptors.]
- 31**. Pascual M, Boix J, Felipo V, Guerri C. Repeated alcohol administration during adolescence causes changes in the mesolimbic dopaminergic and glutamatergic systems and promotes alcohol intake in the adult rat. *J Neurochem*. 2009; 108:920–931. [PubMed: 19077056] [This study correlates adolescent alcohol exposure with adult consumption and provides intriguing data examining dopamine and glutamate release, neurotransmitter receptor expression, and epigenetics. Data suggests that repeated alcohol exposure during adolescence suppresses D2 receptor expression which could act to drive alcohol consumption and increase the risk for addiction.]
32. Blum K, Chen AL, Braverman ER, et al. Attention-deficit-hyperactivity disorder and reward deficiency syndrome. *Neuropsychiatr Dis Treat*. 2008; 4:893–918. [PubMed: 19183781]
33. Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci*. 2006; 29:565–598. [PubMed: 16776597]
- 34*. Hargreaves GA, Quinn H, Kashem MA, et al. Proteomic analysis demonstrates adolescent vulnerability to lasting hippocampal changes following chronic alcohol consumption. *Alcohol Clin Exp Res*. 2009; 33:86–94. [PubMed: 18945221] [A classic proteomics approach is used to show that alcohol consumption during adolescence alters the expression of numerous proteins, lasting into adulthood.]
35. Carpenter-Hyland EP, Chandler LJ. Adaptive plasticity of NMDA receptors and dendritic spines: implications for enhanced vulnerability of the adolescent brain to alcohol addiction. *Pharmacol Biochem Behav*. 2007; 86:200–208. [PubMed: 17291572]
- 36*. Varlinskaya EI, Spear LP. Ethanol-induced social facilitation in adolescent rats: role of endogenous activity at mu opioid receptors. *Alcohol Clin Exp Res*. 2009; 33:991–1000. [PubMed: 19302088] [This work demonstrates that mu opioid receptors mediate alcohol-induced social facilitation in adolescents. Since, this response is considered rewarding, pharmacological inhibition of mu opioid receptors may be a potential therapy aimed at reducing alcohol consumption in this age group.]
- 37*. Ribeiro-Carvalho A, Lima CS, Filgueiras CC, et al. Nicotine and ethanol interact during adolescence: effects on the central cholinergic systems. *Brain Res*. 2008; 1232:48–60. [PubMed: 18692029] [This is the first study the effect of alcohol on the developing adolescent cholinergic system and shows that alcohol enhances midbrain cholinergic innervation.]
38. Nixon K, Morris SA, Liput DJ, Kelso ML. Roles of neural stem cells and adult neurogenesis in adolescent alcohol use disorders. *Alcohol*. 2010; 44 in press.
39. Crews FT, Nixon K. Mechanisms of neurodegeneration and regeneration in alcoholism. *Alcohol Alcohol*. 2009; 44:115–127. [PubMed: 18940959]
40. Brown SA, Tapert SF, Granholm E, Delis DC. Neurocognitive functioning of adolescents: effects of protracted alcohol use. *Alcohol Clin Exp Res*. 2000; 24:164–171. [PubMed: 10698367]
41. De Bellis MD, Narasimhan A, Thatcher DL, et al. Prefrontal cortex, thalamus, and cerebellar volumes in adolescents and young adults with adolescent-onset alcohol use disorders and comorbid mental disorders. *Alcohol Clin Exp Res*. 2005; 29:1590–1600. [PubMed: 16205359]
42. De Bellis MD, Clark DB, Beers SR, et al. Hippocampal volume in adolescent-onset alcohol use disorders. *Am J Psychiatry*. 2000; 157:737–744. [PubMed: 10784466]
43. Medina KL, Schweinsburg AD, Cohen-Zion M, et al. Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. *Neurotoxicol Teratol*. 2007; 29:141–152. [PubMed: 17169528]

44. Nagel BJ, Schweinsburg AD, Phan V, Tapert SF. Reduced hippocampal volume among adolescents with alcohol use disorders without psychiatric comorbidity. *Psychiatry Res.* 2005; 139:181–190. [PubMed: 16054344]
- 45*. Medina KL, McQueeney T, Nagel BJ, et al. Prefrontal cortex volumes in adolescents with alcohol use disorders: unique gender effects. *Alcohol Clin Exp Res.* 2008; 32:386–394. [PubMed: 18302722] [This study demonstrates that adolescent alcohol consumption interferes with normal prefrontal cortex development, but the effects are gender-dependent fashion. This is the first study to examine gender-specific structural effects of alcohol on the prefrontal cortex in human adolescents.]
46. Harper C. The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? *J Neuropathol Exp Neurol.* 1998; 57:101–110. [PubMed: 9600202]
- 47*. Crews FT, Boettiger CA. Impulsivity, frontal lobes and risk for addiction. *Pharmacol Biochem Behav.* 2009; 93:237–247. [PubMed: 19410598] [The authors describe the balance between impulsivity and executive function and how alcohol damages the frontal cortex, tipping the scale towards impulsive behavior. Increased sensitivity of adolescent to this damage and its potential consequences are discussed in this insightful review.]
48. Clark DB, Thatcher DL, Tapert SF. Alcohol, psychological dysregulation, and adolescent brain development. *Alcohol Clin Exp Res.* 2008; 32:375–385. [PubMed: 18241320]
49. Evrard SG, Duhalde-Vega M, Tagliaferro P, et al. A low chronic ethanol exposure induces morphological changes in the adolescent rat brain that are not fully recovered even after a long abstinence: an immunohistochemical study. *Exp Neurol.* 2006; 200:438–459. [PubMed: 16631170]
- 50*. McQueeney T, Schweinsburg BC, Schweinsburg AD, et al. Altered white matter integrity in adolescent binge drinkers. *Alcohol Clin Exp Res.* 2009; 33:1278–1285. [PubMed: 19389185] [The authors describe widespread disruption of white matter integrity in adolescents binge drinkers. This study is important because it shows that binge drinking with no history of alcohol use disorder has significant effects on brain structure.]
- 51*. Jacobus J, McQueeney T, Bava S, et al. White matter integrity in adolescents with histories of marijuana use and binge drinking. *Neurotoxicol Teratol.* 2009; 31:349–355. [PubMed: 19631736] [This work demonstrates that adolescents who binge drink, but do not meet AUD diagnostic criteria, display significant damage to white matter tracts. Depending on the location, alcohol's effect on white matter are altered when marijuana use is combined with binge drinking.]
- 52*. Maurage P, Campanella S, Philippot P, et al. Alcoholism leads to early perceptive alterations, independently of comorbid depressed state: an ERP study. *Neurophysiol Clin.* 2008; 38:83–97. [PubMed: 18423329] [This study identifies that short-term (9 months) binge drinking in late adolescence significantly alters auditory event-related potentials in a pattern resembling that found in chronic alcoholics. These results support the idea that adolescent binge drinking alters brain function in a way that could increase the risk of later alcohol abuse and dependence.]
53. Squeglia LM, Jacobus J, Tapert SF. The influence of substance use on adolescent brain development. *Clin EEG Neurosci.* 2009; 40:31–38. [PubMed: 19278130]
54. Tapert SF, Schweinsburg AD, Barlett VC, et al. Blood oxygen level dependent response and spatial working memory in adolescents with alcohol use disorders. *Alcohol Clin Exp Res.* 2004; 28:1577–1586. [PubMed: 15597092]
- 55*. Schweinsburg AD, McQueeney T, Nagel BJ, et al. A preliminary study of functional magnetic resonance imaging response during verbal encoding among adolescent binge drinkers. *Alcohol.* 2010; 44 in press. [The authors demonstrate that binge drinking adolescents that do not yet meet alcohol use disorder diagnostic criteria perform slightly worse on a simple verbal learning task and rely heavily on frontal and parietal regions to learn simple word pair associations, which may reflect alcohol-mediated disruption of medial temporal lobe function.]
56. Sircar R, Basak AK, Sircar D. Repeated ethanol exposure affects the acquisition of spatial memory in adolescent female rats. *Behav Brain Res.* 2009; 202:225–231. [PubMed: 19463705]
57. Schulteis G, Archer C, Tapert SF, Frank LR. Intermittent binge alcohol exposure during the peradolescent period induces spatial working memory deficits in young adult rats. *Alcohol.* 2008; 42:459–467. [PubMed: 18760715]

58. Sircar R, Sircar D. Adolescent rats exposed to repeated ethanol treatment show lingering behavioral impairments. *Alcohol Clin Exp Res.* 2005; 29:1402–1410. [PubMed: 16131847]
59. Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. *Cell.* 2008; 132:645–660. [PubMed: 18295581]
60. He J, Crews FT. Neurogenesis decreases during brain maturation from adolescence to adulthood. *Pharmacol Biochem Behav.* 2007; 86:327–333. [PubMed: 17169417]
61. Hasin DS, Stinson FS, Ogburn E, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry.* 2007; 64:830–842. [PubMed: 17606817]