

Adolescence: Booze, Brains, and Behavior

Peter M. Monti, Robert Miranda, Jr., Kimberly Nixon, Kenneth J. Sher, H. Scott Swartzwelder, Susan F. Tapert, Aaron White, and Fulton T. Crews

This article represents the proceedings of a symposium at the 2004 Research Society on Alcoholism meeting in Vancouver, British Columbia, Canada, organized and chaired by Peter M. Monti and Fulton T. Crews. The presentations and presenters were (1) Introduction, by Peter M. Monti; (2) Adolescent Binge Drinking Causes Life-Long Changes in Brain, by Fulton T. Crews and Kim Nixon; (3) Functional Neuroimaging Studies in Human Adolescent Drinkers, by Susan F. Tapert; (4) Abnormal Emotional Reactivity as a Risk Factor for Alcoholism, by Robert Miranda, Jr.; (5) Alcohol-Induced Memory Impairments, Including Blackouts, and the Changing Adolescent Brain, by Aaron M. White and H. Scott Swartzwelder; and (6) Discussion, by Kenneth Sher.

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ALCOHOL MISUSE AND alcohol-related problems are prevalent among adolescents. In a recent survey, nearly one third of 12th graders reported getting drunk in the past month (Johnston et al., 2003) and 6% of high school students met DSM-IV diagnostic criteria for an alcohol use disorder (Rohde et al., 1996). Furthermore, despite high rates of alcohol use, adolescents tend to underestimate the risk involved with heavy drinking (Deas et al., 2000). Thus, it is curious that compared with adult drinking, we know relatively little about adolescent drinking and its consequences (Monti et al., 2001).

One consequence of alcohol use during adolescence that is of increasing concern is its effects on brain function and development. Although similar concerns exist for the effects of other drugs, including nicotine, for the most part, these are beyond the scope of the present article. Although studies have examined adolescent alcohol misuse from psy-

chosocial and behavioral perspectives, relatively few investigations have targeted the acute and prolonged neurobiological impact of alcohol use during this developmental period (Monti et al., 2001).

Adolescence is a time of substantial neuromaturation that involves important changes in numerous brain regions, including the hippocampus, prefrontal cortex, and limbic system structures. Similarly, there are rapid changes in neurotransmission and plasticity. Such developmental changes can result in certain vulnerabilities for the adolescent brain (Dahl, 2004). It is essential that we learn more about the consequences of early drinking on brain development. In addition, investigations into how dysfunction in specific brain regions or systems may confer liability for the development of alcohol problems during adolescence are of primary importance.

Given recent technological developments in human laboratory and animal model research of alcohol use and adolescent brain function, it seemed timely to host a forum of experts with the intent of bridging the gap between what have quickly become two disparate literatures. Thus, this symposium considered neurobiological, biobehavioral, and psychological mechanisms related to adolescent drinking in humans and rats. Emphasis was placed on innovative approaches and models to studying the complexities of adolescent drinking and its relationship to brain function with the hope of guiding future inquiries into the neurobiological and biobehavioral mechanisms that might be involved.

ADOLESCENT BINGE DRINKING CAUSES LIFE-LONG CHANGES IN BRAIN

Fulton T. Crews and Kim Nixon

Adolescence is the transitional period between childhood and adult maturity. Puberty is a part of adolescence when gonadal hormones increase, but adolescence represents a broader period associated with increases in social

Veterans Affairs Medical Center (PMM), Brown University, Providence, Rhode Island; Center for Alcohol and Addiction Studies (PMM, RM), Brown University, Providence, Rhode Island; University of North Carolina (KN, FTC), Chapel Hill, North Carolina; Midwest Alcoholism Research Center (KJS), University of Missouri, Columbia, Missouri; Duke University Medical Center and Durham VA Medical Center (HSS, AW), Durham, North Carolina; and VA San Diego Healthcare System and University of California (SFT), San Diego, California

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Reprint requests: Peter M. Monti, PhD, Brown University, Box G-BH, Providence, RI 02912; Fax: 401-444-1888; e-mail: Peter_Monti@brown.edu.

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behavior, high activity, high risk taking, and sensation/novelty seeking. The high levels of adolescent social behavior, risk taking, and sensation/novelty seeking likely promote experimentation with alcohol and other drugs. Increased peer-directed social interactions and elevations in exploratory and risk-seeking behaviors is a characteristic of adolescence that occurs in many species, including rats and humans (Spear, 2000). Increased affiliation with peers and exploration of novel areas, behaviors, and reinforcers may be important for youths to develop skills and behaviors that are necessary for independent survival away from a family unit and adult success.

In humans, adolescence is commonly defined as the second decade of life, although some include the early 20s. In rats, commonly cited times for adolescent onset are postnatal days (PNDs) 28 to 42 (Spear, 2000). This timing includes the growth spurt, sexual puberty, emergence of rats from the protected nest burrow in the wild, adolescent play fighting, and increased social interactions and other behaviors associated with adolescence (Spear, 2000). Evolution among species in which group interactions promote survival likely includes behaviors associated with forming interpersonal bonds as well as exploratory behavior to expand the species beyond the initial family unit. The brain continues to change in adolescence, suggesting that adolescent behavior may be driven by biological changes in brain with the maturation of brain and behavior representing continuing development between childhood and adulthood.

The adolescent brain is undergoing rapid changes in neurotransmission and plasticity, making it unique from the adult brain. For example, neurogenesis, the formation of new brain cells, is greater in adolescent (PNDs 30–40) than in adult rat (PNDs >60) brain. The prefrontal cortex (PFC), an area involved in higher cognitive abilities, is larger in adolescents than in adults, with PFC volume declining in adolescent humans (Jernigan et al., 1991) and rats (van Eden et al., 1990). There is a marked developmental loss of synapses, assumed to be glutamatergic exci-

tatory inputs to PFC (Zecevic et al., 1989), during adolescent maturation in humans and nonhuman primates (Huttenlocher, 1984; Zecevic et al., 1989). Similarly, NMDA glutamate receptor density increases in rats just before adolescence, peaking during adolescence with receptor density 45 to 80% higher in various adolescent brain regions than that found in adults (Insel et al., 1990; Saransaari and Oja, 1995). Glutamate and particularly the glutamate-NMDA receptor are known to contribute to neurodegeneration through delayed neurotoxicity. Thus, the neurochemical, cellular, synaptic, and structural organization of the adolescent brain differs from the adult brain in a manner that may make it more vulnerable to disruption.

Because binge drinking is common among adolescent humans, we investigated the effects of binge drinking on adolescent brain compared with adult rat brain. Although both adolescents and adults show binge drinking-induced brain damage, adolescents are unique in having considerable damage to frontal association cortex, anterior piriform, and perirhinal cortices, areas that correspond to orbital frontal and temporal cortical areas in human brain. Adults showed no binge-induced degeneration in these frontal regions (Fig. 1) (Crews et al., 2000). Other brain regions also showed differential binge-induced brain damage. Although the mechanism of binge-induced brain damage is not precisely known, alcohol preferring (P) rats show greater binge-induced brain damage and decreased formation of phospho-mitogen-activated protein kinase than nonpreferring (NP) rats, suggesting that ethanol-induced changes in cellular signaling pathways contribute to increased binge-induced brain damage (Crews and Braun, 2003). Both adolescents and P rats are resistant to the sedative effects of ethanol, as are humans who are at risk for developing alcoholism (Schuckit and Smith, 1996), suggesting that low sedative responses may be secondary to decreased changes in cellular signaling pathways that predispose to both the development of alcoholism and binge

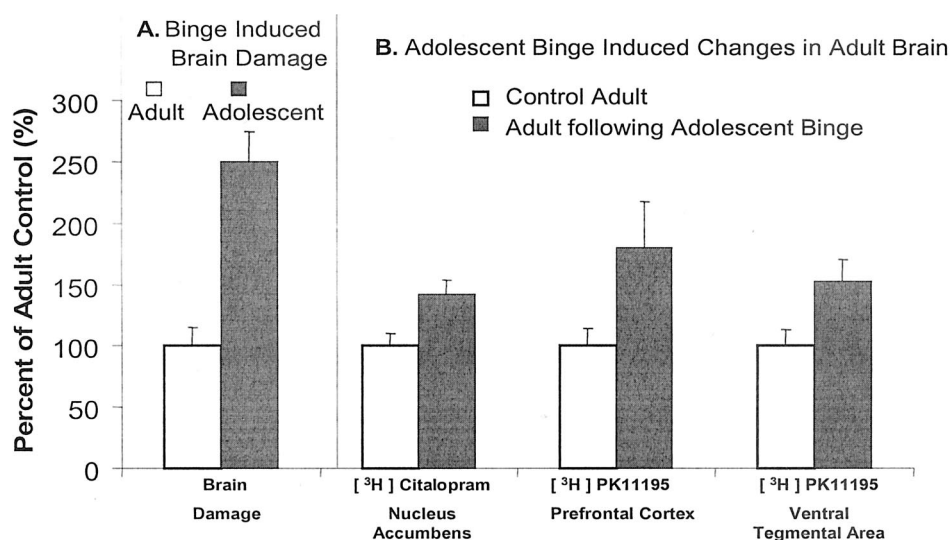


Fig. 1. Binge alcohol administration induced changes in adolescent and adult brain. All animals received intragastric binge alcohol administration during adolescence, e.g., PNDs 33 to 37. Binge administration involves 4 days of multiple dosing achieving high blood levels (see Crews et al., 2000; Knapp and Crews, 1999; Obernier et al., 2002a,b; Rudolph et al., 1997, for details). (A) A comparison of neuronal damage as assessed by argyrophilic silver stain found that adolescent juvenile rats had much greater forebrain damage than adults (Crews et al., 2000). (B) In adults (PND 90), after adolescent binge treatment (PNDs 33–37), there are increases in [³H] citalopram and [³H] PK11195 binding, suggesting permanent changes in serotonergic innervation and microglia after adolescent binging (Crews, 1999; Crews et al., 2000, 1998; Obernier et al., 2002a,b).

drinking-induced neurodegeneration. Similarly, adolescents are more sensitive to ethanol inhibition of neurogenesis (Mdznarishvili et al., 2002), possibly also related to differences in ethanol effects on cellular signaling in adolescents compared with adults. Thus, adolescents are more sensitive to the neurotoxic effects of binge drinking and ethanol inhibition of neurogenesis than are adults.

The biogenic amine-containing neurons of the brain, including dopamine and serotonin, are dynamically changing in the adolescent brain. Dopamine input to PFC increases during adolescence to peak levels well above those seen earlier or later in life (Kalsbeek et al., 1988; Rosenberg and Lewis, 1994). Dopamine neurotransmission contributes to reward and euphoria, and it is possible that the euphoric behavior of adolescents is related to high levels of brain dopamine that are found in adolescence. Dopaminergic systems undergo substantial reorganization during postnatal development (from childhood through adolescence). Dopamine D₁ and D₂ receptor levels in the striatum of juveniles are 30 to 50% higher than those found in adults in both humans (Seeman et al., 1987) and rats (Gelbard et al., 1989; Teicher et al., 1995). The peak in D₁ and D₂ receptor binding during adolescence and the decline toward adulthood is much more pronounced in the striatum than in the nucleus accumbens (Teicher et al., 1995). Not all dopamine receptors show this overproduction and pruning, with juveniles having only 40% of adult dopamine D₃ receptor levels in striatal and accumbens regions (Stanwood et al., 1997). The dopamine transporter also undergoes a period of development in mesolimbic and mesocortical brain regions, with levels significantly lower in preadolescent rats and increasing to adult levels during adolescence (Coulter et al., 1996). Thus, there is a substantial developmental change in dopamine innervation during adolescence.

Serotonergic systems also undergo reorganization during postnatal development (from childhood through adolescence). In humans, as in the rat, 5-HT neurons are generated prenatally (Lauder, 1990; Lauder and Bloom, 1974; Lidov and Molliver, 1982; Nobin and Bjorklund, 1973; Olson et al., 1973; Wallace and Lauder, 1983). Brain 5-HT levels peak early in life, then decrease to adult levels (Hedner et al., 1986; Toth and Fekete, 1986) following a developmental pattern in the PFC similar to that of dopamine (Goldman-Rakic and Brown, 1982). Most 5-HT receptor subtypes are expressed prenatally, and reorganization of the serotonergic system could mediate trophic actions of 5-HT on neuronal and nonneuronal cells that contribute to adolescent brain maturation (Hellendall et al., 1992; Hillion et al., 1993; Johnson and Heinemann, 1995; Lauder and Krebs, 1978; Morilak and Ciaranello, 1993; Roth et al., 1991). Postnatal reorganization of developing serotonergic projections is exemplified by transient dense serotonergic innervation of the cerebral cortex in the rat (D'Amato et al., 1987; Hedner et al., 1986) and ferret (Voigt and de Lima, 1991), as well as transient innervation patterns in the rat basal forebrain (Dinopoulos et al., 1997), lateral genic-

ulate body (Dinopoulos et al., 1995), and superior colliculus (Dori et al., 1998). Reorganization of serotonergic innervation in specific brain regions is also suggested by changing postnatal expression patterns of the 5-HT transporter (Hansson et al., 1998; Lebrand et al., 1998).

In a recent experiment, we investigated the effects of adolescent binge ethanol administration on the distribution of the 5-HT transporter in adults using [³H] citalopram (Fig. 1). It is interesting that adult rats that had been treated with our binge treatment as adolescents had more [³H] citalopram binding in several brain regions than normal control rats (Crews and Braun, 2003; Crews et al., 1998; Obernier et al., 2002b). These findings suggest that disruption of adolescent brain by binge drinking results in long-term permanent changes in serotonergic innervation in adult brain (Fig. 2). Altered serotonergic innervation and possibly reduced synaptic serotonin as a result of increased transporter density could contribute to altered sleep patterns, impulsivity, satiation, and other behaviors associated with serotonergic function.

Adolescent brain development seems to be important for the maturation of brain structure and behavior. Binge drinking-induced damage to the forebrain likely represents the loss of neurons that contribute to circuitry that ultimately forms the forebrain structures, particularly prefrontal cortex, that drive executive functions such as impulse inhibition and goal setting. Damage to these structures likely results in altered maturation. The increase in serotonergic transporters in adults after adolescent binge administration is one example of how brain structure is altered. In addition, we have found increases in the density of [³H]-PK11195 binding after binge administration in adults, both after adult binge administration and adolescent binge administration (Fig. 1) (Obernier et al., 2002b). This ligand binds to the peripheral benzodiazepine receptor and is found particularly in microglia (Stephenson et al., 1995). Thus, the presence of increased [³H] PK11195 binding may represent an inflammatory marker that is permanently up-regulated after binge administration. Increased density of serotonin transporters and microglial markers suggest that the adult brain has been permanently altered by adolescent binge administration.

The studies summarized above support the hypothesis that there is a permanent change in adult brain structure after adolescent binge drinking. The adolescent brain is highly plastic and undergoing maturation that is disrupted by alcohol. The unique sensitivity of the adolescent forebrain results in increased forebrain damage at just the time the forebrain is maturing. Our finding of increased damage likely results in a permanent loss of neurons and a permanent increase in resident microglia. Both of these changes could contribute to altered forebrain function. Increased microglia might predispose to increased responses to neuroinflammation later in life. The increased forebrain damage in binge drinking adolescents could stimulate sprouting of serotonergic neurons as well as other neurons that result in

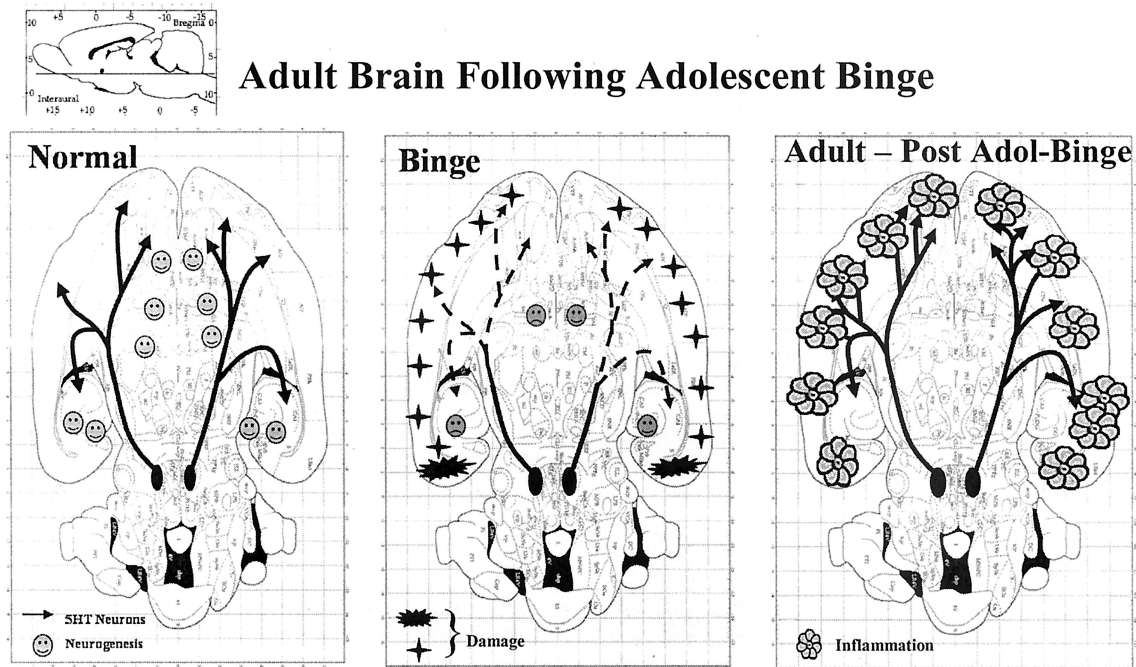


Fig. 2. Schematic diagram illustrating permanent changes in adult brain resulting from adolescent binge drinking. Shown is a schematic diagram of the brain represented as a horizontal section of brain through limbic cortical regions (see upper left diagram indicating location of horizontal section). Normal brain has serotonergic projections that originate in mid-brain raphe nuclei and project to forebrain and other regions as indicated by the dark branching arrows projecting up from nuclei (oval). Normal brain also contains stem-progenitor cells in hippocampus and forebrain (happy faces). Binge treatment decreases stem-progenitor cells, may disrupt serotonergic projections, and damages brain as indicated by crosses and blobs. Adult brain after adolescent binge administration (adult-post Adol-Binge) has more serotonin transporters, possibly as a result of changes in serotonergic innervation, and has inflammatory markers (flowers) throughout the brain that likely result from responses to injury as a result of adolescent binge administration.

altered wiring of the brain. Also, the loss of stem-progenitor cells could result in long-term changes in adult brain structure. These permanent changes in brain could contribute to behavioral changes that alter the life course of individuals, including promoting the progression to alcohol dependence. Additional studies are needed to understand the effects of ethanol on adolescent brain maturation.

FUNCTIONAL NEUROIMAGING STUDIES IN HUMAN ADOLESCENT DRINKERS

Susan F. Tapert

As described previously, alcohol use is common during adolescence, yet we are just beginning to understand how heavy drinking during youth affects brain development. As substantial neuromaturation continues throughout adolescence, adolescents may be differentially affected by heavy drinking as compared with adults.

Studies of neurocognition in adolescents with alcohol use disorder (AUD) have demonstrated some decrements in problem solving (Moss et al., 1994), verbal and nonverbal retrieval (Brown et al., 2000), visuospatial skills (Tapert and Brown, 1999), and working memory (Tapert et al., 2002), particularly among youths who report experiencing alcohol withdrawal symptoms (Tapert and Brown, 1999; Tapert et al., 2002). However, it has been unclear whether these performance abnormalities reflect underlying neural

impairment. Functional magnetic resonance imaging (fMRI) is a safe approach for observing brain response to cognitive or affective tasks and stimuli by taking advantage of the paramagnetic qualities of deoxygenated blood, which serves as an endogenous contrast agent.

We compared brain response to a moderately difficult spatial working memory task between teens with AUD ($n = 15$) and those with little alcohol experience ($n = 19$) after 5 or more days of abstinence. No participant had a history of psychiatric or other substance use disorder. Boys and girls with AUD showed *increased* parietal response compared with control teens, despite similar task performance (Tapert et al., 2004b). This suggests that in the early stages of AUD, the brain may compensate for subtle alcohol-induced disturbances by recruiting additional neural resources, resulting in more intense and widespread activation. In contrast, women who were aged 18 to 25 and had AUD since adolescence showed significantly *diminished* frontal and parietal response to the same spatial working memory task, as well as less accurate performance relative to demographically similar control subjects (Tapert et al., 2001). The findings with young adults raises the possibility that as heavy drinking continues, neural injury may increase, the brain may no longer be able to compensate for the disruption, and performance may begin to show impairments.

Studies in adults have suggested that female individuals may be more susceptible to alcohol-related brain injury

than male individuals (Hommer et al., 2001), which could be due to hormonal fluctuations, differences in alcohol metabolism, or sex-specific drinking patterns. Some evidence suggests that adolescent girls incur more alcohol-related neurocognitive deficits than adolescent boys (Moss et al., 1994). Our recent fMRI investigations have observed a greater magnitude of brain response difference to a spatial working memory task between female adolescents with and without AUD than the difference observed between male adolescents with and without AUD. This may indicate that girls with AUD are somewhat more vulnerable to alcohol-related neural dysfunction than are boys on a memory for locations task.

A complication in studying the effects of alcohol on brain functioning is that teenagers who drink often use other drugs and nicotine. Marijuana, stimulants, inhalants, and dissociative drugs all have been associated with neurocognitive decrements in adolescents (e.g., Tapert and Brown, 1999). Brain response to a spatial working memory task was examined in 15 teens with comorbid marijuana and alcohol use disorders, 15 teens with AUD and limited drug use, and 19 nonusing control subjects. Exclusionary criteria were history of medical, neurological, or psychiatric disorders, and groups were similar on demographic variables. Groups performed similarly on the task, but youths with comorbid marijuana use and AUD showed reduced temporal and increased frontal activation relative to control subjects and to teens with AUD only. This pattern suggests that, despite substance involvement of as little as 2 years, heavy marijuana and alcohol consumption during adolescence seems to be associated with aberrant brain response to spatial working memory, and the degree of abnormality in frontal regions is greater with concomitant alcohol and marijuana involvement. We also examined brain functioning in 12 adolescents with AUD and varying levels of nicotine involvement. During fMRI acquisition, participants were given a pattern recognition task, and no relations were found between brain response and quantity, frequency, or recency of nicotine use. However, teens who started smoking at younger ages performed more poorly on memory tests and showed a decreased fMRI response in frontal areas and increased response in occipital regions, which may indicate altered recruitment of brain areas associated with visual processing.

The previously described studies all have been cross-sectional, and it is very possible that differences between adolescents with and without AUD may be attributable, at least in part, to factors that predate the onset of drinking. Compared with youths without family histories of AUD (FHN), family history–positive (FHP) youths have shown neuropsychological abnormalities (Sher et al., 2000; Tapert and Brown, 2000). Using fMRI, we examined 11 FHP and 10 FHN 12- to 14-year-olds with no previous substance involvement. During fMRI acquisition, youths performed a go/no-go task to evaluate brain response during inhibition. Groups performed similarly on the task, but FHP

youths showed less activation on no-go (inhibition) trials relative to go trials in prefrontal, occipital, and parietal regions (Schweinsburg et al., 2004). These preliminary findings suggest that a family history of AUD may be associated with less brain response to inhibition during adolescence, which may underlie disinhibition problems that relate to the development of AUD.

To understand the extent to which familial factors contribute to the neural abnormalities seen in adolescents with AUD, FHN and FHP adolescents with and without AUD ($n = 7$ per group; groups matched on age, sex, and socioeconomic background) were compared on fMRI brain response as participants performed a pattern recognition task. Overall, FHP adolescents showed less response in bilateral frontal regions, and, among FHN youths, those with AUD showed compensation in frontal areas as evidenced by more brain response despite equivalent task performance. However, among FHP youths, those with AUD did not show a compensatory response but demonstrated less activation, especially in the inferior parietal lobule. These preliminary results suggest that family history of AUD may be associated with attenuated brain response to a pattern recognition task, especially in frontal regions, whereas adolescent AUD may be more associated with abnormalities in parietal regions (see Fig. 3). In sum, adolescent drinkers with family histories of AUD may be at particular risk for neurocognitive inefficiency.

fMRI has helped characterize neural response to alcohol cue exposure among adults with AUD. We examined the neural substrates of cue reactivity in 15 teenagers with AUD and 15 demographically similar nonabusing teens (Tapert et al., 2003). During fMRI acquisition, adolescents were shown pictures of alcoholic beverage advertisements and visually similar nonalcoholic beverage ads. Compared with control subjects, teens with AUD demonstrated dramatically increased brain response to alcohol ads relative to nonalcohol beverage ads in many brain regions, especially areas linked to positive emotion, visual attention, and reward. Teens who had AUD and reported greater alcohol consumption and more intense desires to drink showed the largest neural response to the alcohol ads. It is possible that these media cues may interfere with effective coping strategies and influence continued drinking among teens with AUD. Using the simpler stimulus of words, fMRI response of college-age young women with and without AUD were compared as they viewed alcohol-related and nonalcohol words. Although findings were more mixed than in the pictures study, young women with AUD showed significantly more brain response in the nucleus accumbens area while viewing alcohol words relative to nonalcohol words, whereas control subjects did not show differences in this critical reward region (Tapert et al., 2004a).

In summary, emerging research suggests subtle but important neurocognitive disadvantages among adolescents with AUD as compared with those without AUD. fMRI studies suggest that adolescents with AUD have brain re-

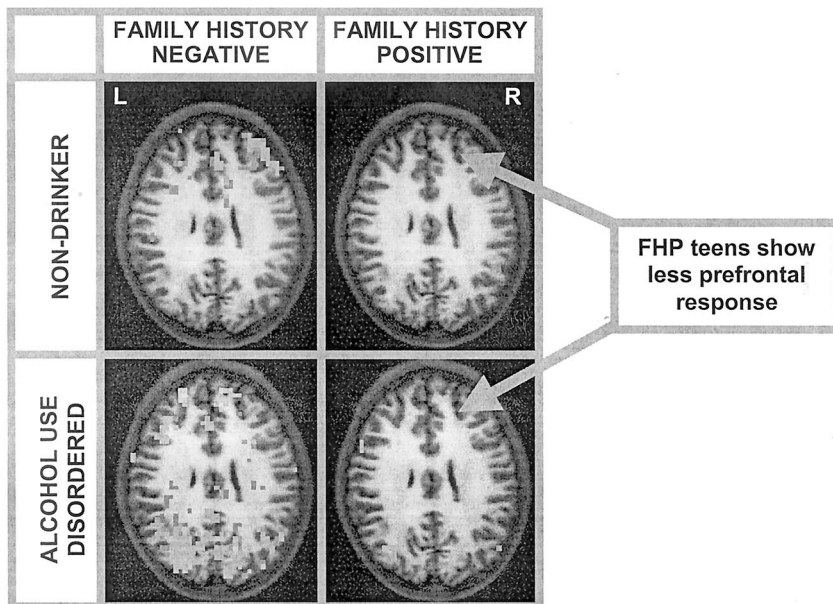


Fig. 3. Brain response to pattern recognition task among four groups of 15- to 17-year-old adolescents: (1) no family history of AUD, no personal AUD; (2) family history of AUD, no personal AUD; (3) no family history of AUD, personal AUD; and (4) family history of AUD and personal AUD ($n = 7$ per group; groups were similar on age, sex, and socioeconomic status). Orange regions show brain regions that activated during a pattern recognition task relative to baseline.

sponse abnormalities while performing challenging cognitive tasks yet enhanced brain response when viewing alcohol cues such as advertisements. Important methodological considerations for this area of study include concomitant other substance use and familial risk factors for developing AUD. Ultimately, longitudinal studies are needed to ascertain the extent to which adolescent drinking produces disturbances in brain development and thinking and memory skills and the risk for future alcohol problems.

ABNORMAL EMOTIONAL REACTIVITY AS A RISK FACTOR FOR ALCOHOLISM

Robert Miranda, Jr.

Advances in affective neuroscience indicate that individual differences in emotional reactivity may confer liability for alcohol dependence and other substance use disorders. Emotion holds a central position in determining how the brain regulates behavior. Through integration with cognitive processes, emotion plays an important role in learning and memory, evaluating variable environmental contingencies, and motivating adaptive behavior (Damasio, 1994; Ekman and Davidson, 1994). Central regulation of behavior involves specific frontal lobe systems acting in concert with subcortical circuits. Of the five frontal-subcortical circuits identified (Litcher and Cummings, 2001), the orbito-frontal (OF) circuit is principally involved in the determination of contextually appropriate behavioral responses. The OF cortex comprises the most ventral regions of the prefrontal cortex and is critically intertwined with the amygdala in both anatomy and function. It is through its close connection with the amygdala that this brain region integrates the sensory characteristics of biologically significant stimuli and generates affective responses (Zald and Kim, 2001). With memory-related structures, stimulus

characteristics are evaluated against previous experience and adaptive approach and avoidance behaviors are motivated. Lesions to OF circuitry are postulated to disconnect frontal monitoring systems from subcortical emotional input (Eslinger and Damasio, 1985), which is manifested in poor control over behavior and prominent emotional lability (Litcher and Cummings, 2001). Patients with damage specific to OF regions exhibit socially inappropriate behavior, irritability, and lack of judgment and demonstrate aggressive and perseverative behaviors (for review, see Starkstein and Kremer, 2001).

Heritable or acquired dysfunction of these central processes has been implicated in a variety of psychiatric disorders, particularly conditions that involve inappropriate or maladaptive responses to signals for reward or punishment (e.g., Davidson et al., 2002). Mounting evidence suggests that the behavioral patterns exhibited by adults and adolescents with notable antisocial traits, which are characterized by persistent aggressive and impulsive behavior and failure to adhere to societal norms, may be a marker for underlying deficits in emotional reactivity and related impairment in frontal-limbic processes. Independent lines of investigation have similarly suggested that dysfunction in central processes that serve emotional reactivity are also related to alcohol dependence through mechanisms such as poor self-control, poor behavioral regulation, and impaired decision making (Finn et al., 2000; Mazas et al., 2000).

Human laboratory studies have increasingly used the startle reflex (SR) to investigate emotional processes in relation to psychopathology among clinical populations. The SR includes muscle contractions, heart rate acceleration, and electrodermal changes that aid in escape or avoidance of danger (Graham, 1979). Loud or rapid-onset probe stimuli cause brainstem auditory pathways to act on spinal motor systems (Davis, 1992). The eye blink electromyo-

gram (EMG) is a robust index of auditory SR. The core SR can be altered by emotion-related activity in more rostral areas, including the amygdala. The blink EMG is a useful indicator of an individual's emotional processing; contractions of the eye blink reflex are enhanced by unpleasant stimuli and diminished by pleasant ones (Bradley and Lang, 2000). SRs to auditory probes are increased by presenting an aversive conditioned stimulus (Brown et al., 1951), viewing emotionally negative photographs and film clips (Jansen and Frijda, 1994; Lang et al., 1990), and imagining emotionally negative scenes (Witvliet and Vrana, 1995). Positive pictures have been shown consistently to reduce SR magnitudes (Bradley et al., 1991; Cuthbert et al., 1996). The SR can be similarly elicited by acoustic, cutaneous, and photic stimulation (Landis and Hunt, 1939). Affective modulation of startle is robust to repetition, maintaining itself within and between days, although overall startle magnitude may decline (Bradley et al., 1993; Cuthbert et al., 1996). Modulation of the startle EMG is controlled by outputs from the central nucleus of the amygdala to brainstem motor areas (Davis, 1992). Amygdala stimulation enhances acoustic SR in rats and rabbits (LeDoux et al., 1988), and lesions of the central nucleus of the amygdala block the acquisition or expression of fear-potentiated startle (Davis, 1992). Patients with amygdalar lesions fail to show SR enhancement to aversive slides (Angrilli et al., 1996). The role of amygdaloid activity in startle modulation provides a useful backdrop for testing skeletal-motor expression of emotional reactivity.

Individual differences in emotion-modulated SR have been reported. Incarcerated male psychopaths failed to show the typical potentiated SR while viewing unpleasant picture stimuli and, instead, showed diminished SR to both pleasant and unpleasant pictures relative to neutral photographs (Patrick et al., 1993). Phobic individuals, relative to nonphobic control subjects, have shown exaggerated SRs while viewing pictures of phobic-specific stimuli (Hamm et al., 1997). Limited data also suggested that people with severe depression lack the expected diminution and instead show potentiation in the SR elicited during pleasantly valenced slides (Allen et al., 1999). Collectively, these findings suggest that affective modulation of the SR is sensitive to psychological dispositions and is a useful tool for objectively comparing emotional processing across individuals and diagnostic groups (Cook, 1999).

We have completed two studies using the emotion-modulated startle paradigm (EMS) to examine physiological reactivity in relation to alcohol dependence. In the first study (Miranda et al., 2002), we tested the hypothesis that relative to family history-negative individuals (FH-), young adults with a positive paternal history of alcoholism (FH+) have altered emotional reactivity to environmental cues. We tested 30 FH+ and 30 FH-, 15 male individuals and 15 female individuals in each group; the mean age of the sample was 19 years. Results indicated that FH- showed the normal linear increase in the eye blink EMG

component of the SR, with response strength increasing from pleasant to neutral to unpleasant stimuli (negative > neutral > positive). In contrast, FH+ did not show the typical potentiation of EMG to the unpleasant stimuli. Groups did not differ in ratings of slide pleasantness or activation, ruling out the likelihood that these differences were due to altered experience of the slides among the FH+. In this study, we also examined temperament variables and conduct problems as they related to SR. Although FH+ had significantly greater antisocial tendencies, our hypothesis that these behaviors would share significant common variance with abnormal affective modulation of startle was not upheld. Given that the antisocial behavior endorsed by this sample was within the normative range, deviance in antisocial and conduct characteristics may not have been sufficient to evaluate their impact on affective modulation of startle.

In a second study (Miranda et al., 2003), we tested the hypothesis that abnormalities in emotional reactivity previously reported among individuals with alcohol dependence (AD) would be more pronounced among people with AD and comorbid antisocial personality disorder (ASPD). Participants were administered structured clinical interviews and categorized into the following groups: (1) AD only (no conduct problems in childhood or adolescence; $n = 24$); (2) AD-ASPD ($n = 17$); or (c) social drinkers with no lifetime or current substance use disorder, conduct disorder, or ASPD ($n = 21$). For determining the reliability of an interviewer's diagnostic decisions, taped interviews were rerated by a second doctoral-level clinician. To be eligible, participants were in overall good health, reported no history of traumatic brain injury or hearing difficulties, and were not taking central nervous system-acting medication for at least 30 days before participation. All participants tested negative on a urine toxicology screen and reported specific knowledge that their mother was abstinent from alcohol during pregnancy. The exclusion of people with certain psychiatric conditions was based on evidence of abnormal SR among individuals with certain psychopathologies and served to increase internal validity. Exclusion criteria included *lifetime* bipolar I or II disorder, agoraphobia, a psychotic disorder, posttraumatic stress disorder, obsessive compulsive disorder, or an eating disorder. Participants did not meet criteria for a *current* Axis I disorder, with the exception of social phobia ($n = 3$). Analyses indicated that the AD and control groups showed the expected linear trend (negative > neutral > positive), whereas individuals in the ASPD/AD group showed no emotion modulation of the SR (negative \cong neutral \cong positive). Group differences were not accounted for by subclinical depressive or anxious symptoms, psychopathy, or cognitive abilities.

There were no significant relationships between startle modulation across each of the three valence conditions and quantity or frequency of alcohol consumption or symptom severity of alcohol dependence. However, blunted SR to

the unpleasant slide set was associated with an early onset of regular alcohol use and a higher density of familial alcoholism among individuals with alcohol dependence. Given that age of first regular alcohol use and familial alcoholism have been associated with antisocial traits, we conducted a hierarchical linear regression analysis wherein SR was regressed on family density scores, age of first regular alcohol use, and ASPD among alcohol-dependent individuals. Both age of onset of regular alcohol use and ASPD status but not family history of alcoholism contributed significant and unique variance in predicting SR during the unpleasant slide set.

Taken together, these studies suggest that blunted emotional reactivity, as a result of dysfunction in frontal-limbic regions, may confer liability for the development of substance use disorders among adolescents. This is consistent with prospective studies that have begun to show that abnormalities in emotional reactivity and related frontal-limbic dysfunction, as indicated by blunted stress cortisol secretion (Moss et al., 1999) and low amplitude of the P300 component of the event-related potential (Berman et al., 1993; Iacono et al., 2002; McGue et al., 2001), predict initiation of drug-related behaviors among adolescents. Future work should evaluate whether the association between antisocial behavior during adolescence and adulthood and alcoholism may be explained, in part, by abnormalities in emotional reactivity and related frontal limbic dysfunction.

ALCOHOL-INDUCED MEMORY IMPAIRMENTS, INCLUDING BLACKOUTS, AND THE CHANGING ADOLESCENT BRAIN

Aaron M. White and H. Scott Swartzwelder

Adolescence is a stage of development perhaps best described as a metamorphosis. Individuals enter as children who are dependent on those around them for survival and exit as adults capable who are of surviving on their own. Profound physical and psychological changes occur during this period. The stage is marked by increased social activity, conflict with parents and siblings, sexual maturation, exploration, and risk taking. The specific age range during which this transition occurs varies on the basis of both individual and environmental factors but can encompass the entire second decade of life or longer (for review, see Dahl, 2004).

For an individual to acquire the repertoire of skills necessary to survive on one's own, an incredible amount of learning must take place. Not surprising, recent research indicates that the adolescent brain is essentially built to learn (for review, see White and Swartzwelder, 2004). The enhanced plasticity observed during adolescence provides the opportunity for important experiences to shape the individual in long-lasting ways. At the same time, recent studies suggest that it might render adolescents particularly vulnerable to the effects of drugs that disrupt plasticity. Alcohol is one such drug.

Alcohol is well known for its ability to disrupt memory formation. Alcohol produces what Ryback (1971) referred

to as a continuum of encoding deficits. As the dose of alcohol increases, so does the magnitude of the impact of alcohol on memory formation. For instance, a few drinks might make it more difficult for one to learn a new person's name. Several more drinks might completely impair one's ability to remember ever having met the person at all. The inability to remember events that occurred while drinking is commonly referred to as a *blackout*.

The specific mechanisms by which alcohol impairs memory are still under investigation. However, it seems likely that alcohol does so, at least in part, by disrupting neural plasticity in the hippocampus. The hippocampus is centrally involved in the formation of autobiographical memories (for review, see White et al., 2000). Damage to the hippocampus or just to a layer of cells known as pyramidal cells can render an individual incapable of forming new memories for facts and events. Substantial evidence indicates that NMDA receptors, glutamate receptor subtypes, play a critical role in experience-dependent changes in hippocampal pyramidal cell activity. Drugs that block NMDA receptor function in the hippocampus prevent plasticity in these circuits and also disrupt memory formation.

In awake, freely behaving rats, alcohol essentially shuts off hippocampal pyramidal cell activity (White et al., 2000). In slices of hippocampal tissue, alcohol blocks the activation of NMDA receptors (Swartzwelder et al., 1995) and interferes with the establishment of long-term potentiation (LTP) (Pyapali et al., 1999), an electrophysiological model of neural plasticity thought to reflect the types of changes that occur during learning.

Recent research clearly indicates that the adolescent hippocampus is particularly vulnerable to alcohol-induced blockade of NMDA receptor functioning and the establishment of LTP. Far less alcohol is needed to antagonize the activation of NMDA receptors (Swartzwelder et al., 1995) and disrupt LTP (Pyapali et al., 1999) in hippocampal tissue from adolescents than from adults.

At the behavioral level, there is some evidence that adolescents are more vulnerable than adults to the impact of alcohol on memory formation, although much more work needs to be done in this area. In rats, one task that is commonly used to assess learning and memory requires rats to locate a platform that is submerged an inch or so beneath the surface of the water in a big circular tub known as the Morris water maze. The ability to learn this task is sensitive to changes in activity in the hippocampus, providing an easy way to assess whether drugs that disrupt hippocampal function also disrupt learning that is dependent on this structure. Markwiese et al. (1998) observed that adolescent rats are more vulnerable than adults to alcohol-induced learning impairments in this task. It is interesting that using an appetitive learning task in which the incentive to perform was provided by food reward rather than escape from a stressful situation, as in the Morris water maze, Rajendran and Spear (2004) observed an opposite pattern. That is, adult rats exhibited larger alcohol-induced impair-

ments than adolescents. Again, more work clearly needs to be done in this area.

It is difficult to determine whether adolescent and adult humans are differentially sensitive to the effects of alcohol on learning and memory. For obvious legal and ethical reasons, this research has not been carried out in young adolescent humans. However, there is some evidence for age-related impairments. A study by Acheson et al. (1998) found that people in their early 20s are more vulnerable to alcohol-induced memory impairments than those in their late 20s. Although people in their early 20s are arguably at the upper threshold of the adolescent age range, it is certainly reasonable to expect that younger individuals would be at least as sensitive to alcohol-induced memory impairments as those in their early 20s and perhaps more so.

As mentioned previously, under some circumstances, alcohol can impair learning-related plasticity to such an extent that the individual is rendered incapable of recalling entire events that transpired while intoxicated. It was long assumed that such impairments, known as blackouts, primarily occurred in adult chronic alcoholics. However, it has become clear in recent years that blackouts are alarmingly common among young drinkers. White et al. (2002) surveyed 772 undergraduate college students (aged 18–22) regarding their experiences with blackouts. Fifty-one percent of the students who had ever consumed alcohol reported blacking out at some point in their lives, and 40% reported experiencing a blackout in the year before the survey. Among students who had consumed alcohol during the 2 weeks before the survey, 9.4% reported blacking out during this period. Students in the study reported that they later learned that they had participated in a wide range of events that they could not remember, including vandalism, driving an automobile, and having intercourse. Not surprising, the likelihood of blacking out in the 2 weeks before the survey was related to how heavily students drank (see Fig. 4).

In a subsequent study, White et al. (2004) interviewed 50 undergraduate students, all of whom had experienced at least one blackout, to gather more information about the factors related to blackouts. As in the previous study, students reported engaging in a range of risky behaviors during blackouts, including vandalism, getting into arguments and fights, and engaging in sexual activity. Estimated peak blood alcohol concentrations during the night of the last blackout were roughly 0.30% for men and 0.35% for women, well over the legal driving limit on blood levels of 0.08%.

As is common in studies of drinking among students, the studies discussed above measured students' drinking levels using survey instruments. Recent observations regarding how students define single servings of alcohol suggest that estimates of alcohol consumption using surveys likely underestimate actual drinking levels. White et al. (2003) recently published a study suggesting that college students define drinks more liberally than researchers and govern-

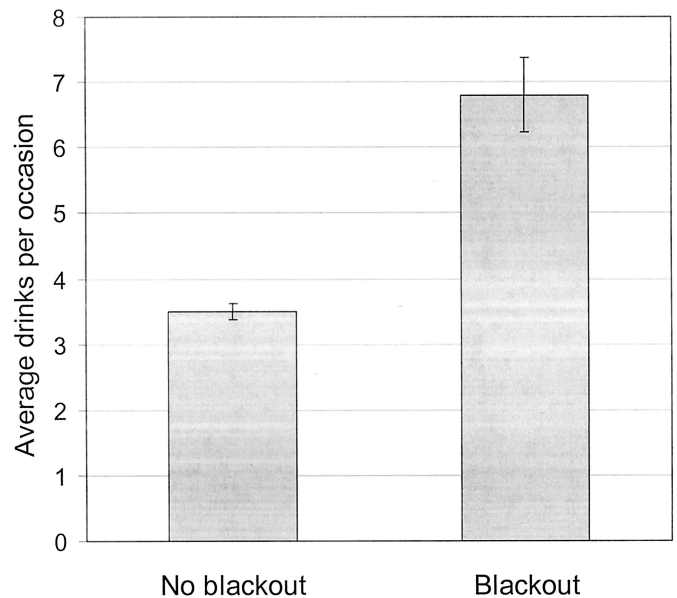


Fig. 4. As might be expected, the likelihood of experiencing an alcohol-induced memory blackout is clearly related to how heavily an individual drinks. The figure shows the average number of drinks consumed per occasion in the previous 2 weeks for college students who did or did not experience blackouts during this period. Students who did experience blackouts reported drinking roughly twice as many drinks per occasion as those who did not.

ment agencies. Students were asked to pour water into cups of different sizes and approximate the volumes of a standard beer, shot, or the amount of liquor in a mixed drink. In every task, students' drinks were significantly larger than the standard drink volumes used by the Harvard School of Public Health (Wechsler and Nelson, 2001), as well as the more liberal definitions used by the National Institute on Alcohol Abuse and Alcoholism and other government entities (Dufour, 1999). That students overestimate how much alcohol represents a standard drink strongly suggests that they underestimate their own levels of consumption. Such findings raise troubling questions about the validity of estimates of drinking levels and resulting blood alcohol concentrations that are based on self-reports and suggest that greater efforts should be made to educate students about the definitions of standard drinks.

In summary, adolescence is a stage of development in which a tremendous amount of learning takes place. The brain is essentially built to be shaped and molded by experience during this period. At the same time, the adolescent brain seems to be particularly vulnerable to the deleterious effects of alcohol on neuronal plasticity. Although it is extremely difficult to determine whether adolescent humans truly are more susceptible than adults to alcohol-induced learning and memory impairments, the available evidence is consistent with this hypothesis. At the very least, it has become clear that alcohol-induced memory impairments, including blackouts, are alarmingly common among young drinkers. Finally, studies regarding how college students define single servings of alcohol suggest that the reliance on survey methods to assess drinking levels might

be leading researchers to underestimate the magnitude of alcohol use among college-aged adolescents and young adults.

DISCUSSION

Kenneth J. Sher

It has long been recognized that for most individuals in the United States, initiation into alcohol use begins in adolescence. However, until recently, the extent of heavy alcohol consumption (e.g., frequent “binge” drinking) has not been fully appreciated. Population-based surveys (e.g., Johnston et al., 2002) indicate that excessive alcohol involvement is highly prevalent in late adolescence, despite that the purchase of alcoholic beverages by those under 21 is illegal. Perhaps even more concerning is the growing recognition that many adolescents who drink heavily meet syndromal criteria for AUDs (both alcohol abuse and alcohol dependence). Indeed, recent epidemiological studies suggest that the period of greatest risk for the onset of AUDs is the late teens and early 20s (Grant et al., 2004; Rohde et al., 1996; Sher and Gotham, 1999), in contrast to the long-held perception, based on treated populations, that alcoholism was a disorder that, for most affected individuals, took many years to develop and was more a condition of later adulthood.

Parallel to the realization that AUDs can be viewed, in large part, as a developmental disorder with peak prevalence during the late teens and early 20s was research on brain development that pointed to adolescence as a period characterized by many changes—changes so extensive that some have referred to as “remodeling.” As discussed by most of the papers in this symposium, such rapid development seems to represent a period of great sensitivity (and, in some cases, insensitivity) to both acute and long-term effects of alcohol on neurocognition. From the vantage point of developmental theory, alcohol-related deficits during key developmental periods are critical not only for the specific deficit itself but also for subsequent development, because each developmental period “sets the stage” for the next, increasing the possibility that these early deficits may “reverberate” over the course of later development. Clearly, long-term follow-up of adolescent drinking is needed to characterize both the persistence of specific deficits and the effects that these have on later development.

Why Did It Take so Long to Discover?

It is possible that the types of effects described in the papers by Crews and Nixon, Tapert, and White and Schwartzwelder may be discounted by some, especially by those who are most affected: adolescents and young adults who drink heavily but in a culture in which such excesses seem normative. Moreover, heavy drinking at this stage of the life span has been common for many years both in this culture and in others. If these deficits, even if subtle, are as

common as the current research suggests they might be, then why has it taken so long for researchers to document them? I believe that there are several reasons that it has taken so long for these possibly serious effects to be recognized.

First, it is likely that although it has long been known that adolescents drink, sometimes heavily, the actual extent of the prevalence and severity has only recently been documented by good, population-based epidemiology. As noted above, this is coupled with growing recognition that the adolescent brain may be especially vulnerable to the effects of alcohol and perhaps other neurotoxic substances. Moreover, research on the neuropsychological consequences of so-called “social drinking” in the 1970s initially suggested measurable impairment in neurocognition (e.g., Parker and Noble, 1977), but later studies indicated that these early reports were not replicable (Parsons, 1986). However, even though more recent studies suggest that even in nonclinical samples, heavy drinking is associated with a range of deficits (Parsons, 1998; Parsons and Nixon, 1998), suggesting a continuum of impairment, many researchers may remain skeptical of the extent and chronicity of findings given the earlier, controversial literature on “social drinking” effects. This is especially true because it seems that most neuropsychological impairment associated with alcohol dependence is reversible with the simple passage of time in abstinent individuals (i.e., time-dependent recovery) and/or with sufficient opportunity to regain lost ability with practice (i.e., experience-dependent recovery; see Goldman, 1983). The lessons from this earlier research should guide us with respect to characterizing dose-response relationships between alcohol consumption and neurocognitive impairment and to determining the extent that recovery of function occurs and under what circumstances.

What Else Do We Need to Know?

Not only do we need to know more about the general effects of alcohol on cognitive development, but also we need to know much more about individual differences that characterize who is most vulnerable (and, ultimately, why they are most vulnerable). Research reported here by Tapert and Miranda indicate that family history of alcoholism, indicating genetic risk, may be associated with premorbid differences in neurocognitive and neuroaffective processes that either persist independently or interact with early (and presumably later) alcohol-related brain injury, and this may be particularly true for those with behavioral evidence of poor executive functioning in adolescence. It also seems that there may be important sex-related differences (Tapert), and we still have much to learn about those specific ages or developmental substages that seem to represent windows of exceptional risk. In addition, there is increasing evidence that a range of neurotoxic exposures early in development may manifest later in development (e.g., Farber and Olney, 2003). Tapert’s paper highlights the impor-

tance of co-occurring marijuana use on neurocognitive dysfunction, and there is reason for concern about the possible enhanced harm associated with co-occurring marijuana and alcohol use. For example, there is now a body of consistent evidence indicating that marijuana use during adolescence seems to substantially increase the risk (~2-fold; e.g., Smit et al., 2004) for the development of schizophrenia and other serious psychotic illnesses, but it is not yet known whether heavy alcohol use throws fuel on the marijuana-instigated fire. Research (e.g., Lamers and Ramaekers, 2001) indicates that alcohol and marijuana interact synergistically, indeed in a dramatic way, to cause acute behavioral impairment, but we do not yet know whether these acute effects are correlated with the type of chronic deficits observed by Tapert and the effects that it has on later development.

Independent of direct neurotoxic effects, we also do not yet know to what extent alcohol use in adolescence affects normative development. As suggested by Baumrind and Moselle (1985), alcohol involvement during adolescence can preempt the development of a number of life skills that are necessary for adaptive adult functioning. For example, alcohol intoxication can create a false sense of intimacy between individuals and preempt the need to develop genuine intimacy skills. Related, individuals who use alcohol to cope with various social stressors that are inherent in adolescence (e.g., dating) may fail to develop those skills. Also, adolescence and young adulthood is a time of life when schooling plays a critical role in the accrual of human intellectual capital that determines, to a large degree, successful adaptation to the workplace and economic success (Sher and Gotham, 1999). It seems likely that heavy alcohol involvement (and more general deviance) conflicts with the intellectual growth opportunities afforded through educational and vocational training. Alcohol-related interference with full engagement in an educational curriculum may be particularly related to the development of higher intellectual functions such as critical thinking and reflective judgment that are known to be positively affected by higher education [although our own research to date has failed to find measurable deficits in these domains in college students (Wood et al., 2002)].

In the past few decades, there has been increasing recognition that many serious adult mental disorders have onset in childhood and are risk factors for heavy alcohol involvement, especially attention-deficit/hyperactivity disorder, schizophrenia spectrum disorders, and bipolar spectrum disorders (e.g., Sher et al., 2005). These same disorders also seem to be disorders of abnormal brain development, and the nature and the extent of alcohol's effects on the neurodevelopmental and clinical aspects of these disorders is clearly an extremely high priority for those who are interested in both adolescent alcohol use and severe mental illness.

Although it may be early to recommend specific pharmacological strategies for preventing adolescent alcohol-related brain damage, it is probably useful to consider various strat-

egies that are rational and may be worthy of clinical investigation. The most obvious are drugs that have been demonstrated to reduce consumption, such as naltrexone (but also, possibly, acamprosate) (Anton and Swift, 2003). With the development of depot forms of naltrexone (Bartus et al., 2003), it may be possible to have better compliance in adolescents than is possible with forms of administration that require daily dosing. Also, to the extent that alcohol seems to inhibit neurogenesis in certain brain areas (Crews and Nixon), medications that have potential neurotrophic effects [e.g., selective serotonin reuptake inhibitors (Castren, 2004), lithium (Gray et al., 2003)] may hold promise for protecting adolescent brains (although the risks associated with these types of treatments in adolescents should not be underestimated). Also, it is unknown to what extent various antioxidants may prove helpful in protecting young brains from alcohol-related insults. Finally, there is accumulating evidence that repeated withdrawal from alcohol can cause neurodegeneration in certain brain regions. Although frank withdrawal in adolescents is rare, it is unclear whether subsyndromal withdrawal may have similar effects and whether drugs that are neuroprotective for alcohol withdrawal [e.g., acamprosate] may prove to have a salutary effect.

Perhaps the greatest implication and challenge for the work described in these papers is how best to get youths to understand the potential harm related to drinking. Although a large proportion of young drinkers experience "problems" from drinking, perceiving oneself as having a drinking "problem" is relatively uncommon. In severe adult alcohol dependence, such lack of awareness is often viewed as denial by more traditional clinicians or as a form of anosognosia (by more neurologically oriented clinicians). However, it seems likely that in adolescence, many alcohol-related problems (e.g., blackouts, hangover, vomiting, unplanned sex) are so common that they are viewed as an inevitable part of the drinking experience. (For a discussion of traditional and contemporary views on self-awareness of drinking problems, see Sher and Epler, 2005) For this reason, it seems that intervention with this population needs to be very sensitive to the culture of the adolescent and young adult, and prevention messages and interventions need to be tailored accordingly. Individual and group motivational approaches that place a great deal of autonomy and choice on the role of drinking in one's life are promising (e.g., Masterman and Kelly, 2003; Monti et al., 2001, 2005), we need to develop a broader range of approaches, especially approaches that can be effective on a population-wide basis (Tappert et al., 2004a).

Should We Be Concerned?

We should be very concerned. The work presented here suggests that heavy alcohol consumption holds the potential to have enormous cost on the accrual of human capital. Moreover, those who are most likely to drink heavily are those who may be already most "handicapped" neurologi-

cally to begin with. Unfortunately, our ability to reduce or prevent underage drinking is modest and involves considerable effort, but the papers in this symposium suggest that developing and implementing more effective drinking reduction approaches should be of the very highest priority.

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