The Adolescent Brain and the College Drinker: Biological Basis of Propensity to Use and Misuse Alcohol*

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ABSTRACT. *Objective:* This article reviews the literature on adolescent brain development and considers the impact of these neural alterations on the propensity to use and misuse alcohol. *Method:* Neural, behavioral and hormonal characteristics of adolescents across a variety of species were examined, along with a review of the ontogeny of ethanol responsiveness, tolerance development and stress/alcohol interactions. *Results:* The adolescent brain is a brain in transition. Prominent among the brain regions undergoing developmental change during adolescence in a variety of species are the prefrontal cortex and other forebrain dopamine projection regions, stressor-sensitive areas that form part of the neural circuitry modulating the motivational value of alcohol and other reinforcing stimuli. Along with these characteristic brain features, adolescents also exhibit increased stressor responsivity and an altered sensitivity to a variety of ethanol effects. Findings are mixed to date as to whether exposure to ethanol during this time of rapid brain development alters neurocognitive function and later propensity for problematic ethanol use. *Conclusions:* Developmental transformations of the adolescent brain may have been evolutionarily advantageous in promoting behavioral adaptations to avoid inbreeding and to facilitate the transition to independence. These brain transformations may also alter sensitivity of adolescents to a number of alcohol effects, leading perhaps in some cases to higher intakes to attain reinforcing effects. These features of the adolescent brain may also increase the sensitivity of adolescents to stressors, further escalating their propensity to initiate alcohol use. Additional investigations are needed to resolve whether ethanol use during adolescence disrupts maturational processes in ethanol-sensitive brain regions. (*J. Stud. Alcohol,* Supplement No. 14: 71-81, 2002)

TO NEGOTIATE with success the developmental transition from youth to maturity, adolescents of many species must survive the risks and stresses of this passage while obtaining the skills necessary for independence. Although certain attributes of human adolescents are unique and not evident in other species, other characteristic features are expressed by adolescents of diverse species and may have been evolutionarily adaptive in helping adolescents conquer this critical transition.

Characteristics of Adolescence in Humans and Other Animals

The process of adolescence is not synonymous with puberty. Adolescence includes the entire transition from childhood to adulthood; puberty is a more discrete phase during which the physiological and neuroendocrine alterations associated with sexual maturation occur. Puberty is only one of the ontogenetic alterations occurring during adolescence, with the timing of this phase within the broader framework of adolescence varying notably among human adolescents (e.g., Dubas, 1991).

The temporal boundaries of adolescence are elusive. It is difficult in any species to characterize when the first transition of adolescence begins to emerge and the last remnant still persists. In humans, adolescence is commonly defined as the second decade of life (Petersen et al., 1996), with ages up to 25 years considered late adolescence by some researchers (Baumrind, 1987). In rats, commonly cited times for the onset of adolescence are postnatal days 28-32 (P28-32), with offsets between P38-55 (e.g., Ojeda and Urbanski, 1994), although this timing is somewhat disputed (Odell, 1990) and may depend on growth rate (Kennedy and Mitra, 1963). Spear and Brake (1983) operationally defined "periadolescence" as the age period around the time of sexual maturation when age-specific behavioral and psychopharmacological discontinuities were evident. Using this criterion, the age period of approximately P28-42 in rats was conservatively designated as periadolescence, with animals of this age showing numerous neurobehavioral alterations from significantly younger (pre- or postweanling) animals as well as more mature (P60 and older) animals. Adolescence in monkeys typically occurs in the age range of 2-4 years (see Lewis, 1997).

Hormonal concomitants of adolescence

Puberty represents a reactivation, after a prolonged period of suppression during the childhood/juvenile period, of pulsatile release of gonadotropin-releasing hormone that was evident perinatally. This reinstatement of pulsatile release of gonadotropin-releasing hormone induces pulsed release of follicle-stimulating hormone and luteinizing hormone, which in turn stimulate release of gonadal hormones

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(e.g., testosterone in males and estrogen in females) (e.g., Brooks-Gunn and Reiter, 1990). Pulsatile release of growth hormone also increases more than 10-fold during the growth spurt of adolescence (Gabriel et al., 1992). Surprisingly, many of the characteristic behavioral features of adolescence discussed below do not seem to be associated in any simple fashion with puberty-related increases in gonadal hormones (e.g., Susman et al., 1987), but rather may be driven largely by maturational changes in the nervous system (reviewed in a later section; see also Spear, 2000).

Behavioral characteristics of adolescence

Adolescents of a variety of species differ behaviorally from younger and older individuals on a number of dimensions consistent with a developmental trajectory toward the goal of independence. Adolescent rats exhibit increases in exploration and novelty seeking relative to other aged rats (e.g., Spear et al., 1980; for review, see Spear, 2000). They also spend more time in social interactions with conspecifics (Fassino and Campbell, 1981; Primus and Kellogg, 1989). Sex differences in behavior also begin to emerge in adolescence, with some of these differences being driven in part by organizational influences of pubertal hormones (e.g., Beatty and Fessler, 1977; Brand and Slob, 1988). Human adolescents likewise exhibit increases in social behavior (Csikszentmihalyi et al., 1977), as well as a disproportionate amount of reckless behavior, sensation seeking and risk taking relative to individuals at other ages (Arnett, 1992). Together such age-related modifications in behavior are consistent with the need of the adolescent to explore novel domains and establish new social relationships during the process of achieving parental independence. Across most mammalian species, adolescence is associated with emigration of male and/or female adolescents away from the natal group into unknown territory, a strategy thought to have been evolutionarily advantageous for species to avoid the detrimental effects of inbreeding (e.g., see Schlegel and Barry, 1991).

Adolescents also seemingly exhibit age-related alterations in the way they respond to motivational stimuli. Human adolescents exhibit an increase in negative affect and depressed mood relative to younger or older individuals (e.g., Larson and Asmussen, 1991). In addition to greater negative affect, adolescents seemingly experience and expect to experience positive situations as less pleasurable than younger or older individuals. Between late childhood and adolescence, the number of reports of feeling happy drops by 50%; even when engaged in the same activities, adolescents find them less pleasurable than do adults (Larson and Richards, 1994). Thus human adolescents appear to show some degree of anhedonia, seeming to attain less positive impact from stimuli with moderate to low incentive value. As a consequence, adolescents may be predisposed to pursue new appetitive reinforcers through increases in risk taking and novelty-seeking behaviors, including alcohol and drug use.

In animal studies, adolescents also have been shown to exhibit characteristic alterations in psychopharmacological sensitivity suggestive of a temporary hyposensitivity of one or more dopamine (DA) systems during adolescence. For example, adolescent rats are less sensitive than their younger or older counterparts to the acute stimulatory effects of catecholaminergic agonists such as amphetamine and cocaine, but conversely are more sensitive to the DA antagonist haloperidol (for references and discussion, see Spear and Brake, 1983). Indeed, alterations in mesocorticolimbic DA systems are a particular hallmark of the adolescent brain, as discussed in the next section.

Neural alterations during adolescence

The adolescent brain is unique and in a state of transition as it undergoes both progressive and regressive changes (for review, see Spear, 2000). One brain region prominently altered during adolescence across a variety of species is the prefrontal cortex, an area thought to subserve higher cognitive abilities such as the bridging of temporal delays in memory (e.g., Diamond, 1991). For example, absolute prefrontal cortex volume declines in adolescence in humans (Jernigan et al., 1991) as well as in rats (van Eden et al., 1990). Substantial synapse elimination occurs during adolescence in the prefrontal cortex and other cortical regions in humans (Huttenlocher, 1984) and in nonhuman primates (Zecevic et al., 1989). At least a portion of this synapse elimination in the prefrontal cortex appears to be associated with the marked developmental loss of presumed glutaminergic excitatory input (Zecevic et al., 1989). In contrast, DA input to the prefrontal cortex in nonhuman primates increases during adolescence to peak at levels well above those seen earlier or later in life (Rosenberg and Lewis, 1994; for review, see Lewis, 1997). Increases in prefrontal cortex DA input through adolescence are also evident in rats (Kalsbeek et al., 1988). Cholinergic innervation of the prefrontal cortex likewise increases in adolescence to reach mature levels in rats (Gould et al., 1991) and humans (Kostovic, 1990).

Maturational changes during adolescence are also evident in other brain regions such as the hippocampus of rodents (Dumas and Foster, 1998; Wolfer and Lipp, 1995) and humans (Benes, 1989). Alterations evident in the hypothalamus include qualitative differences in norepinephrine (NE) release evident in adolescents relative to younger or older rats, along with pharmacological alterations consistent with the suggested emergence in adolescence of inhibitory alpha-2 NE autoreceptors (Choi and Kellogg, 1992; Choi et al., 1997).

Dopaminergic systems undergo substantial reorganization during adolescence. More than one-third to one-half of the DA D_1 and D_2 receptors present in the striatum of juveniles are lost by adulthood in both humans (Seeman et al., 1987) and rats (Gelbard et al., 1989; Teicher et al., 1995). This peak in D_1 and D_2 binding during adolescence and subsequent decline is much more pronounced in the striatum than in the nucleus accumbens (Teicher et al., 1995) and in male rats than in female rats (Andersen et al., 1997b). Not all DA receptors show this overproduction and pruning, with juveniles having only 40% of adult-typical DA D_3 receptor levels in striatal and accumbens regions (Stanwood et al., 1997). The DA transporter likewise undergoes a protracted period of development in mesolimbic and mesocortical brain regions, with only about 70% of adult uptake levels being seen prior to adolescence onset in rats (Coulter et al., 1996).

Developmental events during adolescence may alter the relative balance of DA activity between the prefrontal cortex and striatal or mesolimbic terminal regions, resulting in a greater predominance of DA activity in the prefrontal cortex during early adolescence. As mentioned previously, DA input to the prefrontal cortex increases during adolescence in nonhuman primates (Rosenberg and Lewis, 1994) and rats (Kalsbeek et al., 1988). Basal DA synthesis peaks in rat prefrontal cortex early in adolescence and subsequently wanes, while synthesis is low at this time in nucleus accumbens and subsequently increases (Andersen et al., 1997a). Similar data are obtained from estimates of DA turnover (Teicher et al., 1993). Interestingly, although the prefrontal cortex is seemingly devoid of synthesis-modulating autoreceptors in adulthood (e.g., Galloway et al., 1986), convincing evidence has been obtained for a transient expression of DA autoreceptor-like modulation of DA synthesis in the prefrontal cortex early in life that disappears during adolescence (Andersen et al., 1997a; Teicher et al., 1991).

A shift in the balance of DA activity from the nucleus accumbens to the prefrontal cortex early in adolescence would seemingly result in a relative DA deficiency at this time in the accumbens, a mesolimbic brain region critical for modulating the salience of various incentive stimuli, including alcohol and other drugs of misuse (e.g., Koob, 1992). Functional DA deficits in the accumbens and related mesolimbic brain regions have been linked to a reward deficiency syndrome. Individuals with this syndrome have been postulated to "actively seek out not only addicting drugs but also environmental novelty and sensation as a type of behavioral remediation of reward deficiency" (Gardner, 1999, p. 82). It remains to be determined whether adolescents, because of age-related shifts in the balance of DA activity among mesocorticolimbic brain regions, might show a transient "reward deficiency syndrome" that is milder although qualitatively similar to that hypothesized to be characteristic of abstinent drug users and other at-risk adults. Consistent with this speculation is evidence (previously discussed) that human adolescents show signs of anhedonia, as well as findings that adolescent animals exhibit a reduced sensitivity to certain effects of drugs such as alcohol when compared with their adult counterparts (see discussion below).

Clearly, the brain of the adolescent is in transition. Neural regions showing prominent alterations during adolescence include the prefrontal cortex as well as other forebrain DA projection regions. Given the importance of these brain areas in modulating reward efficacy of reinforcing drugs (Koob, 1992), sensitivity to the environment and stressors (e.g., Dunn and Kramarcy, 1984) and the association between the two (e.g., Goeders, 1997; Piazza et al., 1991), it is not surprising that adolescents vary notably from more mature animals in their responsivity to ethanol, stressors and their interaction, as discussed in the sections below.

Ontogeny of Responsivity to Ethanol

Prevalence of alcohol use in adolescents

In the 2000 Monitoring the Future Survey of the National Institute on Drug Abuse (Johnston et al., 2001), 43% of 8th graders, 65% of 10th graders and 73% of high school seniors reported that they had used alcohol in the past year. About 8% of 8th graders, 24% of 10th graders and 32% of 12th graders also reported getting drunk on one or more occasions during the past month. Clearly, many adolescents use alcohol, with evidence of excessive use emerging in some individuals.

Adolescents are not immune to the development of dependence and may exhibit a variety of alcohol dependence symptoms, including evidence of ethanol tolerance, escalated patterns of use and difficulty in cutting down or quitting (Pollock and Martin, 1999). Once adolescents become dependent on alcohol, their rates of relapse approximate those of alcoholic adults, despite the much shorter chronicity of alcohol use in the adolescent (Brown, 1993). Escalation of alcohol use may be unusually rapid during adolescence. Compared with individuals initiating drug use in adulthood, adolescent-onset individuals had "accelerated dependency courses, with shorter times from first exposure to dependence for alcohol and cannabis and shorter times between their first and second dependencies" (Clark et al., 1998, p. 120).

Adolescent rats display two to three times higher levels of ethanol intake relative to their body weights than do more mature animals (Brunell et al., 2001; Lancaster et al., 1996), although ethanol preference per se does not peak until well into adulthood (around 5 months of age [Goodrick, 1967; Parisella and Pritham, 1964]). The notably different ontogenetic conclusions reached when using gram-per-

kilogram intake versus percentage of total fluid to index ethanol consumption seemingly reflect ontogenetic differences in total fluid consumption, with adolescent rats exhibiting greater overall fluid (and food) consumption than adults. Indeed, during the adolescent growth spurt, caloric intake relative to body weight is greater than at any other time in the life span (e.g., Nance, 1983). Adolescent humans also exhibit elevated metabolic activity and developmental hyperphagia (e.g., Ganji and Betts, 1995; Post and Kemper, 1993), with heavy alcohol use often being "adolescence-limited" (e.g., Bates and Labouvie, 1997).

The elevated consummatory patterns of adolescence could contribute to high levels of ethanol intake by these growing individuals relative to their body weight. As discussed below, adolescents might be able to sustain comparatively large ethanol intakes due to their relative insensitivity to the sedative and locomotor incoordinating effects of ethanol, which may be in part related to their greater propensity to develop acute and functional tolerance relative to more mature organisms.

Acute responsivity to alcohol

Studies using a variety of measures in laboratory animals have observed increases in ethanol sensitivity from infancy through adolescence and into adulthood, with further increases in sensitivity during the aging process (e.g., York and Chan, 1993). This early insensitivity to many ethanol effects is evident despite slower rates of ethanol metabolism in younger animals (e.g., Silveri and Spear, 2000; Zorzano and Herrera, 1989) and is evident using measures such as lethal dose (Hollstedt and Rydberg, 1985), motor impairment (Hollstedt et al., 1980; Moy et al., 1998), hypothermia (Silveri and Spear, 2001; Spiers and Fusco, 1991), anxiolytic effects (Varlinskaya and Spear, 2001) and ethanol-induced hypnosis (Ernst et al., 1976; Little et al., 1996; Silveri and Spear, 1998). These findings, however, are not ubiquitous (e.g., Keir and Deitrich, 1990).

Whether a similar insensitivity to various ethanol effects is evident prior to maturity in humans is unknown, with research in this area limited by ethical constraints. Even if it were possible to conduct controlled studies of ethanol responsivity in children and adolescents, interpretation of across-age data would be complicated by issues such as history of prior use, ethanol tolerance and intoxicated practice effects. On the one hand, it could be argued that an adolescent insensitivity to ethanol effects would be inconsistent with the high incidence of morbidity and mortality during adolescence (Irwin and Millstein, 1992) due in part to risk behaviors involving alcohol use (e.g., drinking and driving) (Donovan, 1993). On the other hand, a relative insensitivity to ethanol effects could contribute to the high incidence of heavy episodic drinking among adolescents. In the year 2000 data from the Monitoring the Future Study, 14.1% of 8th graders, 26.2% of 10th graders and 30.0% of 12th graders reported drinking five or more drinks in a row within the past 2 weeks. Surprisingly, these percentages at the two younger ages were higher than those reporting drunkenness, with only 8.3% of 8th graders and 23.5% of 10th graders indicating that they were drunk on one or more occasions during the past month (comparable data for 12th graders was 32.3%). To the extent that these data are accurate, fewer young to mid-adolescents reported being drunk than drinking five or more drinks in a row, findings consistent with a relative insensitivity to ethanol intoxication among younger adolescents when compared with more mature individuals. Alternatively, these survey data could reflect inflation of alcohol consumption or inaccuracies in perception or reporting of intoxication among younger adolescents.

Although studies using animal models have documented that adolescents are resistant to many ethanol effects, they are conversely more sensitive to certain restricted effects of ethanol—specifically ethanol-induced disruptions of hippocampal plasticity and memory. Swartzwelder et al. (1995a,b) found that hippocampal slices from preadolescent (P15-25) rats were more sensitive than adult slices to ethanol disruption of both N-methyl-D-aspartate (NMDA)-mediated excitation as well as stimulus-induced long-term potentiation. Behaviorally, P30 adolescent rats were found to be more impaired than adult rats by ethanol in a hippocampally related spatial memory task in the Morris maze, whereas nonspatial performance was unaffected by ethanol at either age (Markwiese et al., 1998). Somewhat similar age-related memory disruptions by ethanol have been reported in humans, with early postadolescent (21- to 24-year old) adults showing more ethanol-induced disruption of memory acquisition on both semantic and figural memory tasks than slightly older (25- to 29-year old) individuals (Acheson et al., 1998). Thus, although reduced sensitivity to motor impairing, anxiolytic and sedative consequences of ethanol (see above) may permit adolescents to consume greater amounts of ethanol, this exposure may have more adverse effects on hippocampally related memory processing than later in life.

Taken together, the animal data show that the mosaic of behavioral sensitivities to different ethanol effects vary between adolescents and adults, with adolescents showing greater sensitivity to ethanol-induced impairments of cognitive performance and long-term potentiation, but less sensitivity to ethanol-related sedative, motor impairment and anxiolytic effects. These divergent patterns of sensitivities may represent differential development of neural systems underlying different cognitive and behavioral consequences of ethanol. For example, although ethanol-induced disruption of spatial memory appears to be linked to developmental changes in hippocampal glutamate/NMDA systems (see Swartzwelder et al., 1995a,b), developmental immatu-

rity in brain gamma-aminobutyric acid (GABA) systems rather than ontogenetic alterations in NMDA systems appears to contribute in part to the lower sensitivity of adolescent animals to the sedative effects of ethanol (Moy et al., 1998; Silveri and Spear, in press).

Tolerance development

Differential sensitivity to various ethanol effects between adolescents and adults may also be attributable in part to possible ontogenetic differences in the capacity to develop ethanol tolerance. For example, the resistance of young organisms to ethanol's hypnotic effects has been shown to be related in part to the tolerance that develops within a given ethanol exposure period. This form of within-session tolerance is called acute tolerance and is very prevalent early in life, declining to reach adult levels only during late adolescence (Silveri and Spear, 1998). This ontogenetic decline may be specific to acute tolerance, with forms of tolerance that emerge only following repeated ethanol exposures showing different ontogenetic patterns. For example, Silveri and Spear (1999) reported that preweanling and adolescent rats showed no evidence of rapid tolerance (tolerance developing with 24-48 hours after repeated ethanol exposures) to ethanol-induced sleep, whereas such tolerance was evident in adults. On the other hand, following multiple ethanol exposures, adolescents have been reported to exhibit more chronic tolerance to ethanol-induced hypothermia than adult rats (Swartzwelder et al., 1998). The sometimes greater propensity for adolescent animals to develop these compensatory adaptations to ethanol may contribute to their relative resistance to many ethanol effects relative to their more mature counterparts. Yet it remains to be determined whether similar adaptations would be evident in human adolescents. Empirical research of this nature would be difficult to conduct given ethical constraints on exposing human children and adolescents to ethanol even on a single occasion, let alone repeatedly.

Stress, Adolescence and Alcohol Misuse

Stress and adolescence

Navigating the developmental transition toward independence is often stressful for human adolescents, and indeed adolescents appear to experience a greater number of negative life events than preadolescents (Larson and Asmussen, 1991). In addition to the actual frequency of life stressors possibly being greater in adolescence than at other ages, adolescents may also respond differently to stress than individuals at other ages. This perhaps should not be surprising, given that stressors selectively activate many of the neural systems undergoing developmental change during adolescence (for review, see Spear, 2000), including mesocorticolimbic DA projections implicated in modulating the reward value of drugs (Dunn and Kramarcy, 1984).

In general, adolescents appear to respond with greater negative affect to circumstances in their environment than do children and adults (Larson and Richards, 1994). They also typically find the circumstances of their lives to be more anxiety provoking and stressful. For example, using electronic diaries to monitor moods and certain behaviors of 14-year olds, Whalen et al. (2001) found that even adolescents who scored low on externalizing and depression measures reported feeling anxious more than one-third of the time and stressed about 25% of the time.

In behavioral studies with laboratory animals, adolescents often have been observed to be more susceptible to stressors than adults. For example, adolescent rats show more stress-induced immobility during forced swim testing (Walker et al., 1995) or in the presence of intermittent footshock (Campbell et al., in preparation) than do adults. As another example, Stone and Quartermain (1997) found that chronic exposure to social stress (placement in the cage of an isolated adult male for 5 minutes daily for 5 days) or a daily period of restraint stress had a greater impact on adolescent mice (P28-32) than on adult male mice, suppressing food intake and body weight gain in adolescents but not adults. In this study, the chronic social stress was also observed to increase anxiety (indexed by a suppression of time spent on the open arms of an elevated plus maze) in the adolescents but not the adult mice.

Exposure to a stressor activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in a cascading sequence of hormone release from the hypothalamus (corticotropin-releasing factor), pituitary (adrenocorticotropic hormone [ACTH]) and adrenals (corticosterone in rats; cortisol in humans). Whereas some research has reported that there are developmental increases in HPA activity through adolescence in humans (Kiess et al., 1995), the ontogeny of stress-induced activation of the HPA system and associated neurobehavioral consequences has been most systematically examined in laboratory animals. Peak ACTH and corticosterone responses to stress generally increase during ontogeny to reach an asymptote in rats around adolescence, at least in males (Bailey and Kitchen, 1987; Meaney et al., 1985a; Ramaley and Olson, 1974; Rivier, 1989; Walker et al., 1986). Adolescent rats have also been reported to exhibit more prolonged stress-induced increases in corticosterone than adults (Choi and Kellogg, 1996; Goldman et al., 1973; Sapolsky et al., 1985). This delayed poststress recovery presumably reflects immature feedback regulation mediated in part by glucocorticoid receptors in the hippocampus (e.g., Meaney et al., 1985a,b). Thus adolescence may be associated with a greater overall corticoid response to stress, with this stress-induced increase being elevated relative to younger animals and prolonged relative to adults.

Although little explored, the nervous system also appears to respond differently to stressors during adolescence than at younger or older ages. For example, Choi and Kellogg (1996) observed a blunted hypothalamic NE response to stress in late adolescent rats (P42), a transition between the increased stress-related NE utilization seen in early adolescence (P28) and the decreased utilization seen in adulthood. A similar adolescent transitional period was seen in terms of autonomic reactivity to stressor stimuli in the peripheral nervous system. Whereas preweanling rat pups exhibited heart rate bradycardia to an aversive stimulus, heart rate tachycardia emerged by adolescence, with this increased heart rate mediated by parasympathetic withdrawal in adolescents but primarily by sympathetic activation in adults (Kurtz and Campbell, 1994).

Thus, along with the presumed increase in the number of stressors to which adolescents are exposed as they navigate this critical developmental transition, the way adolescents respond to stressors may vary hormonally, behaviorally and neurally from that of other aged organisms.

Stress and alcohol consumption in adolescents

The apparent increase in the number of stressors to which adolescents are exposed and their age-typical responses to such stressors have been postulated to contribute to the frequent initiation of alcohol and other drug use in adolescence (e.g., Pohorecky, 1991; Wagner, 1993) as well as to the frequent emergence in adolescence of schizophrenic symptomatology in vulnerable individuals (Walker and Diforio, 1997). Indeed, alcohol use among adolescents has been shown to be predicted by stressors such as prior abuse, victimization and other negative life events (Kilpatrick et al., 2000; Sussman and Dent, 2000); negative school-related events (Unger et al., 2001); neighborhood stress (Scheier et al., 1999); and parental conflict and peer relationship problems (Aseltine and Gore, 2000). Coping strategies may interact with levels of stress in predicting alcohol-related problems (Laurent et al., 1997), with alcohol use suggested to be one of a number of "maladaptive ways to cope with stress" (Scharf, 1999).

Perceiving events as being stressful may be of particular importance in exacerbating the already elevated propensity of human adolescents to exhibit alcohol use and other drug-taking behavior (Baer et al., 1987; Deykin et al., 1987; Tschann et al., 1994; Wills, 1986; but see also Hansell and White, 1991). After peer substance use, the next most powerful predictor of adolescent alcohol and drug use was found by Wagner (1993) to be levels of perceived stress, with the appraisal of events as being stressful of more importance than the absolute number of such events. Adolescents, especially younger adolescents, may be particularly prone to these stressor effects. In her review of the literature on stress effects on alcohol consumption in humans, Pohorecky (1991) concluded that stress is most convincingly associated with alcohol consumption in adolescence, with more mixed findings evident in studies conducted in adults. Using a linear growth curve analysis to examine age differences in drinking across five waves of data from a community sample of adolescents, Aseltine and Gore (2000) observed the strongest association between stress and drinking among younger adolescents, with the relationship weakening during the late teens and twenties.

Factors contributing to the stress-induced increase in propensity for ethanol use are still being explored. Although the interaction of stress and ethanol intake is complex (for review, see Pohorecky, 1990), stress hormones may play a role. Corticosterone levels in rats generally have been positively related to rates of self-administration of ethanol or other drugs, with adrenalectomy suppressing ethanol consumption (Fahlke et al., 1994) and stress-induced elevations in corticosterone increasing ethanol consumption (e.g., Bowers et al., 1997). Stressors may also enhance the rate of tolerance development to ethanol (Maier and Pohorecky, 1986), thereby indirectly increasing ethanol consumption capacity.

Taken together, the data available to date support the suggestion that the stressors of adolescence along with age-specific neural and hormonal responses to these stressors may contribute to the initiation of ethanol use during adolescence and the emergence of high levels of use among particularly stressed (or stress vulnerable) individuals.

Does Adolescent Alcohol Exposure Alter Ongoing Processes of Brain Development?

As discussed previously, the adolescent brain is a brain in flux. Many of the brain areas undergoing dramatic developmental change during adolescence are sensitive to ethanol. Ethanol use during adolescence may alter the developmental processes ongoing in these brain regions and hence may have different consequences than similar amounts of ethanol exposure in adulthood. Several recent studies in laboratory animals have supported this possibility. For example, following a 4-day period of multiple ethanol intubations (resulting in exposures of 9-10 g/kg/day), adolescent rats were found to exhibit substantially more ethanol-induced damage in brain regions including the frontal cortex than similarly treated adults (Crews et al., 2000). Rats exposed chronically to ethanol over a 20-day period that included much of the adolescent period were reported subsequently to exhibit a larger impairment in working memory following acute ethanol challenge than adults who were similarly exposed to ethanol (White et al., 2000). These data extend earlier findings in rats showing long-lasting alterations in cognitive functioning following chronic ethanol exposure during adolescence (Osborne and Butler, 1983). Exposure to ethanol vapor for 5 or 10 days has

recently been reported to alter parietal and hippocampal electroencephalogram activity in adolescent rats (Slawecki et al., 2001), whereas the opportunity to consume alcohol voluntarily during adolescence was found to increase later aggressive behavior in male golden hamsters (Ferris et al., 1998; Shtiegman et al., 1997). Whether similar effects would be seen with comparable exposures later in life is unknown in these latter studies, given the absence of adult comparison groups. Nevertheless, it appears from the limited amount of evidence available to date that alcohol exposure during adolescence in laboratory animals may not only disrupt puberty-associated increases in reproductive endocrinology in males (Cicero et al., 1990) and females (Dees et al., 1990), but also may induce long-term alterations in neurobehavioral function as well.

A number of studies have recently examined neurocognitive function in human adolescents with a history of extensive alcohol use. Adolescents with alcohol use disorders had been reported to have smaller hippocampal volumes than comparison subjects, with these hippocampal volumes correlating positively with onset age and negatively with duration of the use disorder (De Bellis et al., 2000). Brown et al. (2000) recently observed subtle to modest neuropsychological impairments, including memory retrieval deficits, in alcohol dependent adolescents with a history of heavy drinking during early and mid-adolescence. It remains to be determined, however, whether these reported associations between alcohol use and neuropsychological impairments are causal and whether these findings are relevant for nonclinical populations of adolescents. Indeed, Bates and Tracy (1990) concluded from their assessments of cognitive functioning in a nonclinical sample of 18- to 24-year olds that "cognitive performance bears little direct relation to drinking behaviors in young nonclinical males and females" (p. 242).

When considering potential long-term consequences of adolescent alcohol use, an important issue is whether this exposure alters later sensitivity to, and patterns of, alcohol use. The data are mixed on this point both in studies conducted in humans and in laboratory animals. For example, findings in rodent studies showing that preweaning (Hayashi and Tadokoro, 1985) or postweaning (Ho et al., 1989) exposure to ethanol increases later ethanol preference are countered by results from several groups reporting no increase in later consumption following periods of ethanol exposure that include adolescence (Kakihana and McClearn, 1963; Parisella and Pritham, 1964; Tolliver and Samson, 1991).

Studies conducted in humans likewise present a mixed picture. Early onset of alcohol use has been reported in both prospective and retrospective studies to be a predictor of later problematic use and dependence on alcohol (Barnes and Welte, 1986; Deykin et al., 1987; Fergusson et al., 1994; Friedman and Humphrey, 1985; Grant and Dawson, 1997; Hawkins et al., 1997; Rachal et al., 1982; Robins and Przybeck, 1985) and other drugs (Deykin et al. 1987; Robins and McEvoy, 1990; Robins and Przybeck, 1985; Yamaguchi and Kandel, 1984). However, an association between early ethanol use and later problematic use is not always seen. For example, based on findings from four waves of longitudinal data obtained from a nonclinical population ranging in age from 15 to 31 years, Labouvie et al. (1997) concluded that early use of alcohol did not predict drug or alcohol use at either 20 or 30 years of age. Even if early alcohol consumption is found to predict later problematic use and dependence, it is possible that the early use may merely be serving as a marker of later ethanol problems rather than as a causal precursor. For example, in a study of human twins, Prescott and Kendler (1999) reported that the age of initiation of alcohol use was not a direct risk factor for alcoholism, but was an "alternative manifestation of vulnerability to problematic alcohol involvement" (p. 106).

Taken together, recent evidence supports the suggestion that high amounts of alcohol exposure during adolescence may disrupt critical ongoing processes of brain maturation and influence neurocognitive functioning. These findings, however, still need to be replicated and extended, and their relevance to more moderate patterns of alcohol use determined. Whether early exposure to alcohol during adolescence promotes greater ethanol use and probability of dependence later in life remains to be resolved, with mixed findings both in studies with humans as well as in work using animal models of adolescent alcohol exposure.

Concluding Comments

Alcohol is frequently used by adolescents prior to and during the early college years. This age is critical for study for several reasons. First, the brain of the adolescent is unique and differs from that of younger individuals and adults in numerous regions, including stressor-sensitive, mesocorticolimbic DA projections that are critical for modulating the perceived value of reinforcing stimuli, including use of alcohol and other drugs. These features of adolescent brain may predispose adolescents to behave in particular ways, increasing their sensitivity to stressors and their propensity to initiate alcohol use. Thus, like a number of adolescent behaviors, the predisposition for alcohol use may be in part biologically determined by age-specific neural alterations that continue into late adolescence.

Certainly, given the dramatic differences between the adolescent and the adult brain, it cannot be assumed that factors precipitating the initiation and escalation of alcohol use would be the same during the stressful period of adolescence as in adulthood. Among critical areas for further investigation is the rather paradoxical notion that adolescents may show a reduced sensitivity to many alcohol effects, perhaps supporting elevated intakes to attain

reinforcing effects and a potentially more rapid progression into dependence by adolescents relative to adults. Another important area for future inquiry is the potential long-term consequences of alcohol use during this time of rapid neural and endocrine maturation. It is often the case that rapidly changing systems are particularly vulnerable to disruption, and hence there may be unique long-term consequences of alcohol exposure during adolescence. Data are mixed on this point to date and further research is needed.

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