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What is This?
The Teenage Brain: Adolescents and Alcohol

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Abstract
The high levels of alcohol consumption characteristic of adolescence may be in part biologically based, given that elevated consumption levels are evident during this developmental transition in other mammalian species as well. Studies conducted using a simple animal model of adolescence in the rat have shown adolescents to be more sensitive than adults to social facilitatory and rewarding effects of alcohol but less sensitive to numerous alcohol effects that may serve as cues to limit intake. These age-specific alcohol sensitivities appear related to differential rates of development of neural systems underlying different alcohol effects, as well as to an ontogenetic decline in rapid brain compensations to alcohol, termed acute tolerance. In contrast, these adolescent-typical sensitivities to alcohol do not appear to be notably influenced by pubertal increases in gonadal hormones. Although data are sparse, there are hints that similar alcohol sensitivities may be seen in human adolescents, with this developmentally decreased sensitivity to alcohol’s intoxicating effects possibly exacerbated by genetic vulnerabilities also characterized by an insensitivity to alcohol intoxication, thereby perhaps permitting especially high levels of alcohol consumption among vulnerable youths.

Keywords
adolescent, alcohol, puberty, intoxication, rodent model

Alcohol use becomes normative during adolescence and reaches high levels in some youths. Among twelfth graders, more than one in four report binge use of alcohol (defined as consumption of five or more drinks in one drinking episode) within the past 2 weeks (Johnston, O’Malley, Bachman, & Schulenberg, 2008). In a recent field study conducted in a college bar area, alcohol consumption levels of young underage and legal drinkers averaged eight standard drinks, overall mean breathalyzer levels were above the cutoff for drunk driving (>80 mg per 100 ml of blood), and 75% of the individuals scored above the standard cutoff for risky alcohol consumption on the Alcohol Use Disorders Identification Test (Celio, Vetter-O’Hagen, Lisman, Johansen, & Spear, 2011). Indeed, on average, adolescents drink more than twice as much as adults per drinking occasion (Substance Abuse and Mental Health Services Administration, 2006). Consequences of adolescent alcohol use can be devastating, not only in terms of immediate effects of intoxication—such as alcohol-related automobile accidents and other injuries (see, e.g., National Institute on Alcohol Abuse and Alcoholism, 2004–2005)—but also in terms of potential longer-lasting effects. Early use of alcohol is associated with an increased probability of later alcohol or drug dependence (Grant & Dawson, 1998), and amount of use has been correlated with certain neural and neuropsychological measures, although causality cannot be conclusively determined from such correlational analyses (see Clark, Thatcher, & Tapert, 2008, for discussion).

Despite the importance of determining contributing factors to and consequences of alcohol use among adolescents, ethical concerns against administering alcohol to underage individuals have constrained empirical studies investigating these issues in youths and have led some researchers to study these issues using simple animal models of adolescence. When defined as the transition from a state of immaturity and parental dependence to one of relative independence and sexual maturity, adolescence is a developmental transition widely identifiable across mammalian species. During this transition, similar biological changes are seen across mammalian species, including rises in sex-related hormones and other physiological transformations of puberty, alterations in release of other hormones, a growth
spurt, and notable transformations in the brain. Maturation extends through adolescence in frontal regions (e.g., the prefrontal cortex) that are important for cognitive control (see Casey & Jones, 2010), with these developmental immaturities sometimes proving seemingly insufficient to countermand activity in subcortical emotion- and reward-relevant regions (e.g., the amygdala and nucleus accumbens) that may be especially reactive to socially arousing and emotional circumstances during adolescence (see Spear, 2011b).

Along with these neural transformations are a variety of behavioral proclivities that are seen across a variety of mammalian species, including an increasing focus on and time spent interacting socially with peers and increases in novelty-seeking, risk-taking, sensation-seeking, and related behaviors (see Spear, 2010). Likewise, the propensity for enhanced alcohol consumption during adolescence is seen not only in humans but in other mammalian species as well (e.g., Doremus, Brunell, Rajendran, & Spear, 2005), thereby suggesting that this propensity may in part have evolutionarily conserved, neurobiological roots and supporting the use of simple mammalian (e.g., rodent) models to study alcohol and other drugs in adolescence. Of course, the use of alcohol and other drugs among adolescents is determined by multiple factors, only some of which are amenable to study in laboratory animals. Hence, the appropriateness, validity, and applicability of the animal model needs to be carefully considered—a point to which I return after reviewing alcohol studies using a simple animal model of adolescence in the rat.

Adolescent Alcohol Sensitivity

Like their human counterparts, adolescent rats typically voluntarily consume 2 to 3 times more alcohol than do adults (e.g., Doremus, Brunell, Rajendran, & Spear, 2005). Adolescent rats not only consume more alcohol but differ in their sensitivity to various acute effects of alcohol when compared with adults. As summarized in the appendix, the nature of this developmental difference varies with the alcohol effect examined. For a few restricted effects of alcohol, adolescent rats are more sensitive than adults. These findings include data from Swartzwelder’s group that adolescent rats are more vulnerable than adult rats to alcohol-induced disruptions in memory and in brain plasticity (indexed via long-term potentiation—i.e., an increase in transmission of signals between neurons after prior stimulation of those neurons; see White & Swartzwelder, 2005, for review). There is also emerging evidence that adolescent rats may be more sensitive than adults to the rewarding effects of alcohol (Pautassi, Myers, Spear, Molina, & Spear, 2008; Ristuccia & Spear, 2008). In basic animal studies, adolescents have also been shown to be uniquely sensitive to alcohol-induced social facilitation. Under familiar, low-stress circumstances, social behavior is stimulated by alcohol in adolescent but not adult rats (Varlinskaya & Spear, 2002). This alcohol-induced social facilitation in adolescent rats is specific to social behavior and not evident in terms of overall activity, and it can be seen both with adolescent-typical (play fighting) and adult-typical (social investigation—i.e., body sniffing) social behaviors.

In marked contrast to these few enhanced alcohol sensitivities, adolescents have been shown in animal studies to be notably less sensitive than adults to a variety of other alcohol effects—many of which seemingly serve as cues to help regulate intake. Effects of alcohol to which adolescent rats are relatively resistant include the suppression of social behavior that begins to emerge at moderate doses of alcohol (Varlinskaya & Spear, 2002), as well as alcohol-induced motor impairment (Silveri & Spear, 2001), disruption of locomotion (Little, Kuhn, Wilson & Swartzwelder, 1996), and sedation (Silveri & Spear, 1998). Using conditioned taste aversions, Vetter-O’Hagen, Varlinskaya, and Spear (2009) likewise found adolescents to be more resistant to the aversive effects of alcohol, with adolescent rats requiring more alcohol than adults to develop an aversion to a novel taste paired with alcohol. Animal studies have also shown adolescent rats to be less likely than adults to display certain “hangover” symptoms during the postintoxication recovery period, including hangover-related increases in anxiety (Varlinskaya & Spear, 2004).

At least some of these adolescent-typical sensitivities may extend beyond alcohol. For instance, relative to adults, adolescents are more sensitive to the rewarding and less sensitive to the aversive properties of not only alcohol but also other drugs, including nicotine (Shram, Funk, Li, & Le, 2006; Wilmouth & Spear, 2004), cocaine, and amphetamine (Brenhouse & Andersen, 2008; Infurna & Spear, 1979), and even appetitive and aversive taste stimuli (Wilmouth & Spear, 2009). Such adolescent-typical reward/aversion biases may reflect very basic reward and motivational systems undergoing transformation during adolescence (e.g., see Spear, 2011b, for review).

Contributors to Adolescent-Typical Alcohol Sensitivities

One potential explanation for age-related alterations in alcohol sensitivity could be developmental changes in how rapidly alcohol gets in and out of the system, although this possibility seems unlikely to be able to explain both the attenuated and accentuated sensitivities that adolescents show to different effects of alcohol. Adolescents do tend to have higher metabolic rates than adults, and age differences in alcohol levels are occasionally observed, although such differences are generally insufficient to account for the altered alcohol sensitivity of adolescents. For instance, adolescent rats given a sedative dose of alcohol not only recover in about half the time as do adults given the same dose but also recover at higher brain levels of alcohol, which suggests that their brains are more resistant to the sedative properties of alcohol (Silveri & Spear, 1998). Findings such as these support the
conclusion that adolescent-typical alcohol sensitivities are not simply a function of pharmacokinetic differences but rather reflect age differences in brain sensitivity to alcohol.

Studies have begun to explore neural contributors to age differences in brain sensitivity to alcohol. Unlike most other drugs, alcohol acts widely throughout the brain and interacts with multiple neurotransmitter systems, including the major inhibitory and excitatory neurotransmitters and their receptor systems: gamma aminobutyric acid (GABA) and GABA<sub>A</sub> and GABA<sub>B</sub> receptors, and glutamate and n-methyl-d-aspartate (NMDA) receptors, respectively. Adolescent-typical alcohol sensitivities appear to be related in part to ontogenetic changes that occur through adolescence in these and other alcohol-sensitive neurotransmitter systems, such as the opiate and dopaminergic systems. For example, social facilitatory effects of alcohol during adolescence appear related in part to mu opiate receptors, given that mu-receptor-specific opiate antagonists block this adolescent-specific effect (Varlinskaya & Spear, 2009). Unusually potent inhibition by alcohol of developmentally overexpressed NMDA receptors has been suggested to contribute to the greater sensitivity of adolescents to alcohol-induced disruptions in long-term potentiation (see White & Swartzwelder, 2005, for review), whereas attenuated sedative effects of alcohol appear related in part to delayed development of the GABA system (Silveri & Spear, 2002).

Attenuated alcohol sensitivities of adolescents also appear related in part to the very rapid onset of compensatory processes in their brains that serve to partially counter alcohol’s effects—a phenomenon termed acute tolerance (see Silveri & Spear, 2001, for further discussion and references). This rapid decline in alcohol sensitivity occurs within a single alcohol exposure and can be indexed in various ways, all generally based on the expression of less impairment at later points than earlier in the intoxication period relative to the amount of alcohol that is present at those times. When tested using measures such as alcohol-induced sedation (Silveri & Spear, 1998, 2002) and social inhibition (Varlinskaya & Spear, 2006), adolescent rats often exhibit notable acute tolerance under test conditions that do not support expression of acute tolerance in adults. This rapid adaptation, however, does not appear to be solely responsible for the attenuated alcohol sensitivities of adolescents, given that disrupting expression of acute tolerance in adolescents by blocking NMDA receptors does not eliminate age differences in alcohol sensitivity (Silveri & Spear, 2002, 2004).

Potentially important contributors to adolescent-typical alcohol sensitivities are changes related to puberty. Some neural transformations of adolescence may be puberty-dependent and driven by rising gonadal hormone levels, whereas other changes, particularly in hypothalamic regions and associated forebrain regulatory areas, may predate puberty and help precipitate pubertal processes. Still other alterations may be associated with maturational changes unrelated to puberty. For instance, consider developmental changes during adolescence in the dopamine (DA) system, a neurotransmitter system thought to be critical for processing of rewarding stimuli. There is evidence for both gonadal hormone-dependent and hormone-independent development within the DA system, with prepubertal gonadectomy, for instance, blocking postadolescent declines in DA release from DA cell bodies in the substantia nigra (Knoll, Miklya, Knoll, & Dalló, 2000) while not affecting developmental declines in density of D1 and D2 subtypes of the DA receptor in striatum (Andersen, Thompson, Krenzel, & Teicher, 2002).

One challenge when attempting to parse puberty-dependent versus puberty-independent processes in studies with humans is that, in contrast to the many biomarkers of pubertal status, there is no good proxy of non-puberty-related maturational state. Age, though typically used, is likely only marginally effective at best, given well-known differences in developmental rate that likely impact the relative maturational rate of both pubertal and nonpubertal processes. As research identifies aspects of cognition and behavior unrelated to pubertal status, it is possible that maturational changes in these measures (or neural alterations correlated with these functional changes) could perhaps be used to index general, non-puberty-related maturational rate.

The role of pubertal hormones in adolescent-typical neurobehavioral function can be systematically examined in laboratory animals by examining consequences of prepubertal removal of the gonads. Researchers using this approach have found that animals that do not experience normal developmental increases in pubertal hormones exhibit deficits in later expression of a variety of reproductive behaviors and other adult-typical, sexually dimorphic behaviors (see Sisk & Zehr, 2005, for review). In contrast, we have found pubertal hormones to exert surprisingly modest influences on alcohol intake and sensitivity (Vetter-O’Hagen & Spear, 2011, 2012). For instance, gonadectomy in male (but not female) rats either prepubertally or in adulthood increased alcohol intake in adulthood—an increase largely reversed by testosterone replacement (Vetter-O’Hagen, Sanders, & Spear, 2011; Vetter-O’Hagen & Spear, 2011); this pattern of findings is consistent with an activation role of testosterone in adulthood rather than puberty-related processes. Moreover, neither prepubertal nor adult gonadectomy altered sensitivity to alcohol’s social inhibitory effects, although the microstructure of social behavior was affected in both male and female rats (Vetter-O’Hagen & Spear, 2012). Studies such as these support the suggestion that adolescent-typical alcohol sensitivities are not notably dependent on puberty-related processes.

**Relevance to Human Adolescent Alcohol Use and Emergence of Alcohol-Use Disorders**

Although available data are limited, studies conducted in human adolescents hint at age-related differences comparable to those
seen in laboratory animals. For instance, reminiscent of the alcohol-induced social facilitation seen in adolescent rats, social interactions are also of particular importance for facilitating drinking among youths (e.g., Kelly et al., 2012). Likewise, late-adolescent individuals in their early 20s were found to be more vulnerable to alcohol-induced disruptions in memory than were adults in their late 20s (Acheson, Stein, & Swartzwelder, 1998).

Conversely, in terms of intoxicating effects of alcohol that may serve as cues to moderate intake, insensitivities similar to those seen in adolescent rats were reported in an older study of 8- to 15-year-old boys given a battery of laboratory tests of intoxication, with the researchers noting that they “were impressed by how little gross behavioral change occurred in the children . . . after a dose of alcohol which had been intoxicating in an adult population” (Behar et al., 1983, p. 407).

Any adolescent insensitivity to intoxicating effects that normally help curb intake could contribute to the greater per-episode drinking seen among adolescents. Indeed, decreased sensitivity to alcohol’s intoxicating, aversive, and sedative effects has been shown in genetic studies in humans (e.g., Schuckit, 1994) and mice (Green & Grahame, 2008) to be a major risk factor for problematic alcohol use and enhanced alcohol intake. Thus, normal insensitivities to alcohol intoxication during adolescence may be exacerbated among genetically vulnerable individuals to encourage especially high levels of alcohol consumption, thereby elevating exposure of the still-developing brain of the adolescent to alcohol and potentially precipitating a variety of long-term consequences (see Spear, 2011a, for review).

### Appendix: Adolescent-Typical Alcohol Sensitivities Seen in Rats

Adolescent rats are more sensitive than adults to the following effects of alcohol:

- Impairment in brain plasticity and spatial memory (White & Swartzwelder, 2005)
- Social facilitation (Varlinskaya & Spear, 2002)
- Rewarding effects (Pautassi, Myers, Spear, Molina, & Spear, 2008; Ristuccia & Spear, 2008)

Adolescent rats are less sensitive than adults to the following effects of alcohol:

- Aversive effects (Vetter-O’Hagen, Varlinskaya, & Spear, 2009)
- Social inhibition (Varlinskaya & Spear, 2002)
- Sedation (Silveri & Spear, 1998)
- Motor impairment (Silveri & Spear, 2001)
- Disruption in locomotion (Little, Kuhn, Wilson, & Swartzwelder, 1996)
- Hangover effects (Varlinskaya & Spear, 2004)

### Recommended Reading


Spear, L. P. (2011a). (See References). An article discussing neurobehavioral characteristics of adolescence in relation to alcohol sensitivity and intake in more detail than the current article.

Spear, L. P. (2011b). (See References). A review of adolescent-typical sensitivities to rewarding and aversive properties of drugs and other stimuli, with data drawn from studies both in humans and laboratory animals.


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