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Adolescent neurobehavioral characteristics, alcohol sensitivities, and intake: Setting the stage for alcohol use disorders?

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Abstract

The transition to adolescence is characterized by rapid biological transformations that include not only the hormonal and physiological changes of puberty but also dramatic changes in the brain as well. Similar neural and physiological changes are associated with the transition from immaturity to maturity across a variety of mammalian species, along with a variety of common adolescent-typical behavioral characteristics. Among the neural systems undergoing alterations during adolescence are those that modulate sensitivity to a variety of alcohol effects, potentially increasing the propensity for relatively high levels of adolescent alcohol use, which in turn may set the stage for later alcohol use disorders. This article reviews research on adolescent alcohol sensitivities and suggests possible implications of these findings for the frequent initiation and relatively high levels of alcohol intake seen at this age.

Keywords

adolescent; animal models; alcohol; brain development; social facilitation; rewarding stimuli; aversive stimuli

Adolescence is a time of marked change, as the ways and appearance of childhood are gradually transformed into the adult form. A multitude of factors, including cultural, economic, and psychosocial influences, play major roles in the expression and pace of adolescence, as well as in the manner adolescents are viewed and treated by the adults around them (e.g., Enright et al., 1987; Schlegel, 2009). Recognition of these critical influences does not, however, diminish the strong biological underpinnings of adolescence. Biological transformations of adolescence include the relatively restricted temporal period of puberty that culminates in sexual maturation, along with other hormonal and physiological changes, including a considerable growth spurt. Unequivocal evidence has emerged over the past decade that adolescence is also characterized by notable, regionally-specific developmental transformations in the brain.

These neural transformations, along with pubertal hormonal changes and other physiological transitions of adolescence, are not only characteristic of human adolescence but are seen during the transition from immaturity to maturity in other mammalian species as well (see Spear, 2000, 2010, for a review and references). Likewise, certain common behavioral characteristics of human adolescents—including increases in risk-taking and novelty-seeking, elevations in peer-directed social interactions, and greater per-occasion alcohol consumption

than seen in adults--are often seen in other species as well during this developmental transition (see Spear, 2000, 2010; Gardner & Steinberg, 2005; Steinberg, 2008). These fundamental biological and behavioral similarities across species suggest that the biological roots of adolescence are deeply embedded in our evolutionary past. Such across-species similarities in basic neurobehavioral features of adolescence provide reasonable face and construct validity to support the use of basic animal models to explore facets of adolescent neurobehavioral function (see Spear, 2000, for discussion). This is not to imply, however, that basic science studies are always generalizable to humans; the rich complexity of human brain and behavioral function during adolescence (or any other point in the lifespan) defies detailed modeling in other species. Yet judicious use of animal models can be used to supplement and extend neuroimaging, neuropsychological, and behavioral studies of human adolescents (Spear, 2000), especially when exploring manipulations and levels of analysis that are ethically or technically not amenable to study in humans, including for instance, administration of alcohol challenges to young adolescents.

The goal of this article is to review research exploring adolescent alcohol sensitivities and consider possible implications of these findings for the frequent initiation and relatively high levels of alcohol intake seen at this age. The discussion will begin by briefly highlighting some of the major transformations seen in the adolescent brain and the possible functional implications of these transformations, with a focus on age-related alterations in sensitivity to various effects of alcohol. Generalizability of these sensitivity patterns to other drugs and nondrug stimuli will also be considered before addressing the possible contribution of these age-typical sensitivities for emergence of alcohol use disorders among vulnerable adolescents.

Neural transformations of adolescence

During adolescence, portions of the immature brain are pruned away to reveal a “leaner,” more efficient adult brain. This regionally specific developmental sculpting is seen in terms of the relative amount of brain area devoted to cell bodies and their processes--termed “gray matter” (e.g., Sowell et al., 2002), and in the number of connections (synapses) between nerve cells (e.g., Rakic et al., 1994). In contrast, increases are seen during adolescence in the production of myelin, a fatty, sheathing material that insulates nerve processes (axons) and appears white in unstained tissue, leading to developmental increases in brain “white matter” (Benes et al., 1994). Myelination speeds the flow of information along axonal pathways, and thus, via selective myelination of pathways connecting distant brain regions (Salami et al., 2003), patterns of neural activity are shifted during adolescence from a bias toward a predominance of relatively local influences to the emergence of networks involving more distant brain regions (e.g., Rubia et al., 2007).

The prevalence and timing of these and other maturational changes in adolescent brain are regionally specific (and in some cases, sex-specific) (e.g. Lenroot & Giedd, 2006; Lenroot et al., 2007). Such regional differences can be seen at a number of levels, ranging from molecular changes evident only in invasive studies of laboratory animals to age-related changes in relative brain volumes, gray-matter volumes, and ratios of white/gray matter that are widely evident during adolescence across species. For instance, in human imaging studies, developmental declines in gray matter have been shown to occur earlier in sensory and motor regions of the cortex than in prefrontal cortex (PFC) and other cortical association areas thought to play critical roles in impulse control, response suppression, and other cognitive control functions that fall under the rubric of “executive functions” and whose development is prolonged into late adolescence and beyond (Gogtay et al., 2004; Lenroot & Giedd, 2006; Østby et al., 2009; see Casey et al., 2008, and Zucker et al., 2011, for reviews).

Considerable developmental change also occurs during adolescence in cortical and subcortical brain regions critical for modulating responding to natural rewards (e.g., social stimuli, novelty, food), as well as to the rewarding properties of alcohol and other drugs with abuse potential. Of particular importance are developmental changes in limbic regions such as the nucleus accumbens and amygdala, along with projections of the critical reward-relevant neurotransmitter, dopamine (DA) to these regions and the PFC (see Doremus-Fitzwater et al., 2010, for review). Given these changes, it would be surprising indeed if adolescents did not differ from those at other ages in the way they responded to natural rewards, as well as to alcohol and other drugs.

Relative to adults, adolescents also display developmentally enhanced activity in portions of the major excitatory neurotransmitter system in brain, the glutamate neurotransmitter system and its associated N-methyl-D-aspartic acid (NMDA) receptor system (e.g., Kasanetz & Manzoni, 2009), while at the same time displaying developmental immaturity in certain components of the brain's major inhibitory neurotransmitter system, the gamma-aminobutyric acid (GABA) system (e.g., Brooks-Kayal et al., 2001; Yu et al., 2006). These characteristics of the adolescent brain could influence adolescent responsiveness to alcohol as well, given that alcohol-related blockade of glutamate NMDA receptor action and stimulation of GABA systems are thought to be critical for contributing to the intoxicating effects of alcohol (see Eckardt et al., 1998; McBride & Li, 1998). Indeed, as discussed below, adolescents differ markedly from adults in their sensitivity to a variety of effects of alcohol.

Adolescent-typical patterns of alcohol/drug sensitivity

Experimentation with alcohol use during adolescence becomes normative in many cultures, with a majority of adolescents in the United States reporting that they have tried alcohol by about 14 years of age (e.g., Johnston et al., 2008). When adolescents use alcohol, they tend to drink substantial amounts, with 10% of 8th graders, 22% of 10th graders, and 26% of 12th graders in the United States reporting consumption of five or more drinks in a row within the past two weeks (Johnston et al., 2008) and adolescents in some European countries reporting binge-drinking rates that are even two to three times higher (Ahlström & Österberg, 2004). On average, adolescents drink more than twice as much per drinking episode as do adults (SAMHSA survey data, 2006).

To the extent that adolescent sensitivity to alcohol use is in part biologically based and related to adolescent-typical neural characteristics that have to some extent been evolutionarily conserved across species, it might be expected that not only human adolescents but adolescents of other species as well would consume more alcohol per occasion, on average, than do adults. Under a variety of circumstances, they, in fact, do. For instance, in a simple model of adolescence in the rat, adolescents have often been found to voluntarily drink two to three times more alcohol than do adults (e.g., Doremus et al., 2005; Vetter et al., 2007; but see also Bell et al., 2006). Such basic science studies have shown that adolescent rats also differ from adults in their sensitivity to a variety of alcohol effects. However, as discussed below, whether adolescents are more or less sensitive to alcohol than are adults varies notably with the specific alcohol effect that is targeted.

On the one hand, adolescents are often *less* sensitive than adults to certain undesired effects of alcohol that likely serve as cues to limit intake. For instance, basic animal studies have found that, following intoxicating doses of alcohol, adolescents are *less* sensitive than adults to alcohol-related disruptions in motor behavior (Silveri & Spear, 2001; White et al., 2002), social impairment (e.g., Varlinskaya & Spear, 2006), sedation (Moy et al., 1998; Silveri & Spear, 1998), and general aversive effects (Vetter-O'Hagen et al., 2009), as well as to

“hangover”-related elevations in anxiety (Varlinskaya & Spear, 2004; Doremus-Fitzwater & Spear, 2007). Although ethical concerns preclude analogous studies in humans, in one older study, Behar and colleagues (1983) did administer alcohol challenges to 8- to 15-year-olds and noted 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” (p. 407).

Evidence is building that part of the insensitivity to alcohol-related intoxication seen in adolescents may be related to the propensity of the adolescent brain to adapt very quickly to the presence of alcohol within a given exposure episode--a phenomenon termed “acute tolerance” (Mellanby, 1919). Basic science studies have shown that this rapid, within-session adaptation to a variety of intoxicating effects of alcohol is much more prevalent in young organisms than in adults (e.g., Silveri & Spear, 1998; Varlinskaya & Spear, 2006) and may be related in part to the developmentally enhanced expression of glutamate NMDA receptor systems discussed earlier (Silveri & Spear, 2004). Acute tolerance is not the entire story, however, in that blocking expression of acute tolerance does not eliminate expression of age differences in alcohol sensitivity (Silveri & Spear, 2002, 2004).

It is also possible that adolescents’ relative resistance to alcohol intoxication could be related in part to age differences in how much and how quickly alcohol gets into and out of their systems. However, the available evidence suggests that this is unlikely to be a significant contributor. Adolescents, with their faster resting metabolic rate, do tend to metabolize alcohol and other substances slightly faster than do adults. Yet even when this difference is significant, it is generally insufficient to account for the attenuated sensitivity of adolescents to alcohol (see Spear, 2007) and is seemingly difficult to relate to the *increased* sensitivity that adolescents show to other alcohol effects.

For instance, adolescent rats, like their human counterparts (e.g., Beck et al., 1993), are very sensitive to the social facilitation induced by relatively low doses of alcohol, whereas such alcohol-related social stimulation is not normally seen in adult rats (e.g., see Spear & Varlinskaya et al., 2005). Several recent studies have suggested that adolescent animals may also find alcohol to be generally more rewarding than do adults (Pautassi et al., 2008; Ristuccia & Spear, 2008), although work in this area is just beginning, and the data to date are mixed (see Dickinson et al, 2009).

Animal studies have also shown adolescents to be more sensitive than adults to alcohol-induced disruptions in brain plasticity indexed via the capacity to show adaptive increases in neuronal activation in response to prior neuronal stimulation--a form of plasticity termed “long-term potentiation” (Pyapali et al., 1999). Enhanced sensitivity to alcohol-induced memory impairments during adolescence has been seen not only in terms of performance differences between adolescent and adult rats in a spatial-memory task (Markwiese et al., 1998) but also in terms of performance differences between 21- to 24-year-old college students and individuals several years their senior (25 to 29 years of age) on both verbal and nonverbal memory tasks (Acheson et al., 1998).

Thus, findings derived largely from basic science studies have indicated that alcohol is experienced differently by adolescents and adults, and similar hints can be found in the limited human research literature as well. Adolescents are primed to be particularly sensitive to alcohol’s social-facilitatory and (possibly) rewarding effects, while being more resistant than adults to its aversive, sedating, motor-impairing, and socially suppressive consequences. As mentioned earlier, these differential ontogenetic sensitivities may be related in part to the developmentally enhanced portions of the glutamate excitatory system and developmentally immature components of GABA inhibitory systems that are

characteristic of the adolescent brain. Developmental alterations in other neurotransmitter systems upon which alcohol exerts its effects (e.g., opiate, cannabinoid, and DA systems) may also contribute to adolescent-related alcohol sensitivities. There is evidence, for example that certain components of the opiate system contribute to alcohol-related social facilitation seen in rats during adolescence (Varlinskaya & Spear, 2010). It is also possible that some adolescent-typical sensitivities to alcohol may reflect broad developmental alterations in DA projection systems and their neural targets in the nucleus accumbens, PFC, and amygdala that affect the processing of multiple types of rewards (see Doremus-Fitzwater et al., 2010, for review). Indeed, the adolescent alcohol data are reminiscent of other findings showing adolescent-typical patterns of sensitivities to appetitive (positively rewarding) and aversive properties of natural rewards and drugs other than alcohol.

Adolescent-typical sensitivities to other drug and nondrug stimuli

There is mounting evidence that adolescents differ from adults in their sensitivity to the appetitive/aversive properties of not only alcohol but other drugs of abuse as well. For instance, adolescent animals have often been found to be more sensitive to the rewarding properties of cocaine than are adults (e.g., Badanich et al., 2006; Brenhouse et al., 2008, Zakharova et al., 2009; although see also Aberg et al., 2007), but less sensitive than mature animals to the aversive properties of another psychomotor stimulant, amphetamine (Infurna & Spear, 1979). Likewise, when compared with their adult counterparts, adolescent animals are characterized by both an enhanced sensitivity to the rewarding properties of low doses of nicotine and a greater resistance to the aversive properties of higher nicotine doses (Vastola et al., 2002; Shram et al., 2006; Torres et al., 2008). Basic science studies have also shown adolescents to be less sensitive to the aversive effects of tetrahydrocannabinol (THC), one of the major cannabinoids in marijuana (Schramm-Sapota et al., 2007), while being more sensitive to cannabinoid-induced disruptions in cognitive performance (Cha et al., 2006). A propensity for adolescents to be more sensitive to the rewarding properties of certain natural stimuli, including novelty (Douglas et al., 2003) and social conspecifics (Douglas et al., 2004), has been reported as well. Moreover, when assessing oral reactivity as an index of hedonic affect to taste stimuli, adolescents have been reported to exhibit not only greater positive taste responses to palatable sucrose solutions but also reduced negative taste reactions to the aversive taste of quinine (Wilmouth & Spear, 2009).

Thus, enhanced appetitive and attenuated aversive sensitivities are seen during adolescence not only to alcohol but to other drugs and natural stimuli as well, suggesting potential commonalities in their neural substrates. Likely neural candidates include, for instance, the marked adolescent-typical alterations in DA projections and reward-relevant forebrain recipients of this input that were discussed earlier (see Doremus-Fitzwater et al., 2010, for review). Substantial work is still needed, however, to characterize the nature of these and other neural alterations during adolescence and to determine how these transformations contribute to adolescents processing rewards and aversive stimuli differently than do adults. .

Implications of adolescent-typical alcohol sensitivities: potential risk factors for problematic alcohol use?

To the extent that these findings of adolescence-related alcohol sensitivities derived largely from studies with laboratory animals hold for human adolescents, what are the implications for problematic adolescent alcohol use? Why would it matter if adolescents are relatively insensitive to alcohol intoxication? The data are clear on this point. Although there are multiple genetic influences on alcohol use and dependence (see Dick, 2011), a decreased sensitivity to the intoxicating effects of alcohol has long been deemed a major risk factor for problematic alcohol involvement, with “a lower sensitivity to moderate doses of alcohol”

being associated with “a significant increase in the risk of future alcoholism, perhaps through increasing the chances that a person will drink more heavily” (Schuckit, 1994, p. 184). Sons of alcoholic fathers characteristically exhibit attenuated responses to the intoxicating and aversive effects of alcohol (along with possibly an increased sensitivity to the euphoric, rewarding effects of ethanol) (e.g., Begleiter & Porjesz, 1999; Schuckit, 1994). Likewise, rodent lines selectively bred for high alcohol intakes typically are insensitive to the aversive and sedating effects of alcohol (e.g., Green & Grahame, 2008).

The normal developmental insensitivity of adolescents to the intoxicating effects of alcohol may not only interact with genetically related insensitivities but may also be exacerbated by the induction of chronic tolerance to alcohol, with human survey data reporting a high prevalence of tolerance among adolescent drinkers (Grant et al., 2007) and basic science studies suggesting that under some circumstances, adolescents develop at least as much chronic tolerance with repeated exposures to alcohol as do adults (Varlinskaya & Spear, 2007). Work in laboratory animals suggests that a history of prior stressor exposure may further lower sensitivity to the intoxicating properties of alcohol (Doremus-Fitzwater et al., 2007). Thus, typical adolescent insensitivities to the aversive and intoxicating effects of alcohol may combine with alcohol insensitivities induced by genetic history, prior stressors, and tolerance associated with repeated use to potentially serve as triple or quadruple “whammies,” thereby promoting high levels of alcohol use--such as might be seen when individuals with a family history of alcoholism and living in stressful circumstances begin to drink early and persistently in adolescence (see Spear, 2010, for further discussion). Conversely, those adolescents who, because of genetic background (perhaps in interaction with environmental circumstances), retain relatively greater sensitivity to alcohol’s intoxicating effects would seemingly be relatively protected from these potential “whammies” and less likely to develop persistent, “binge”-like use patterns. It remains to be seen whether there are environmental manipulations that could potentially serve as protective factors by bolstering adolescents’ sensitivity to ethanol intoxication, thereby decreasing their propensity to drink heavily.

Avoidance of high levels of consumption during drinking episodes is of importance during adolescence, given that high levels of alcohol exposure can expose adolescents to a whole raft of potential problems. These include alcohol-related disruptions in memory and brain plasticity to which, as discussed earlier, adolescents are especially sensitive. There are also mutual synergisms between alcohol use and risk-taking, with underage alcohol use, in particular, being both an expression of risk-taking in itself and a facilitator of other risky behaviors (e.g., driving while intoxicated or with someone who is intoxicated, engaging in unwanted or unintended sexual activity).

There may be longer-lasting consequences of repeated exposure to alcohol during adolescence as well. Substantial research has shown that the younger individuals are when they begin to drink, the more likely they are to develop risky drinking patterns, display later stress-induced drinking, and become dependent on alcohol (e.g., Grant & Dawson, 1997; Ehlers et al., 2006; Young et al., 2006). Alterations in regional brain volumes, white-matter integrity, and brain activation patterns during cognitive tasks also have been reported in youth after one to two years of binge drinking (Squeglia et al., 2009). Some of the neural differences seen among individuals with a history of high levels of adolescent alcohol use may be associated with toxicity due to the early alcohol exposure itself (e.g., reductions in the size of the limbic region known as the hippocampus), whereas other changes (e.g., decreases in PFC volume) may reflect premorbid characteristics that serve to increase risk for early alcohol use (e.g., De Bellis et al., 2005). Thus, early use of alcohol may not necessarily be causal in producing these neural alterations or the elevated risk for dependence, although findings from several recent longitudinal studies provide preliminary

evidence for lasting consequences of early use of alcohol and other drugs (e.g., Odgers et al., 2008). Definitive evidence is still needed to convincingly demonstrate that adolescent alcohol use is causal in producing lasting neural alterations and later abuse or dependence (see Clark et al., 2008). Controlled experiments with laboratory animals may prove helpful in determining whether brain development in adolescence is particularly vulnerable to alcohol toxicity. Some studies with laboratory animals have reported that exposure to alcohol during adolescence can exert long-term influences on the brain (e.g., Crews et al., 2000; Slotkin et al., 2002; Hargreaves et al., 2008; Sabeti & Gruol, 2008) and elevate intake of alcohol in adulthood in some cases (e.g., Rodd-Henricks et al., 2002), with some evidence of age-specific differences in the timing of exposure during the broad adolescent period as well (Sabeti & Gruol, 2008). These basic science studies are at their early stages, however, and may not always have been designed in a way to determine whether observed effects are specific to adolescence and evident at pharmacological relevant doses (see Spear, 2010, for discussion).

Summary and Conclusions

The physiological changes of adolescence, including the marked sculpting of the brain during adolescence, have roots that appear deeply embedded in our evolutionary past. Evidence is discussed that adolescent sensitivity to alcohol use is in part biologically based and related to adolescent-typical neural characteristics that result in a relative insensitivity to intoxicating and aversive effects of alcohol and likely other drugs of potential abuse. These adolescent-typical alcohol insensitivities may combine with genetic and environmental risk or protective factors to influence the likelihood of adolescents' drinking heavily and developing a pattern of elevated alcohol use that may set the stage for later alcohol use disorders. Additional basic research and human studies are needed to explore how these adolescent-typical alcohol sensitivities may be modulated by various risk and protective factors, determine the implications of these developmental insensitivities for elevated alcohol exposure during adolescence, and assess whether there are lasting, developmentally specific consequences of that exposure.

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