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ALCOHOL (RF LEEMAN, SECTION EDITOR)

Alcohol Consumption in Adolescence: a Translational Perspective

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Abstract Alcohol use becomes normative in adolescence and sometimes reaches high levels. Studies have shown that both adolescent rats and their human counterparts often drink two to three times more ethanol per occasion than adults, suggesting potential evolutionarily conserved, biological contributors. These elevated intakes may be promoted by neural changes that increase adolescent sensitivity to desired ethanol effects while attenuating sensitivity to undesired consequences likely serving as cues to moderate intake; while based primarily in rodent work, similar (albeit limited) findings are available in humans, suggesting some consilience—i.e., comparability in findings across species. A variety of neural, cognitive, behavioral, and affective alterations, along with an elevated propensity for elevations in later alcohol use, have been reported after repeated ethanol exposure in both species. In those cases where roughly comparable measures have been used across species, signs of consilience are often apparent. Such emerging consiliences may help to guide future research efforts in this understudied and rapidly evolving research area.

Keywords Adolescent · Ethanol · Alcohol · Human · Rodent · Rat

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Introduction

Alcohol use typically begins during adolescence. This use becomes normative by about 14 years of age in the USA, with a majority of youth reporting that they have at least tried alcohol (EtOH) [1]. Although adolescents drink EtOH less often than do adults, when they do drink, their consumptions are greater than adults, with the average number of drinks per occasion reported to be about twice as high in adolescents than adults [2]. Some of this use reaches high levels, with 10 and 25 % of 8th- and 12th-grade students reporting binge drinking (consumption of 5+ drinks within a drinking episode) within the past 2 weeks in the USA [1], and twofold to threefold greater rates of binge drinking reported among adolescents in some European countries [3]. Some adolescents report especially high consumptions, with >10 % of 18 year olds in the USA endorsing consumption of ten or more drinks and >5 % reporting 15+ drink consumption per drinking episode in the past 2 weeks [4•].

Elevated levels of EtOH consumption are evident not only in human adolescents, but also in animals undergoing this developmental transition in other species as well. For instance, adolescent rats, like their human counterparts, often drink two to three times more per drinking occasion than do adults (e.g., [5, 6], but see also [7]). These across-species similarities support the suggestion that this developmental elevation in intake is related in part to evolutionarily conserved biological factors. Indeed, when defined as the transition from parental dependence to relative independence, adolescence is a developmental period evident in all mammalian species. There are similar goals for this transition across species (such as gaining the skills necessary for survival in adulthood and for reproductive success) as well as similar biological changes that include the temporally restricted processes of puberty, along with other hormonal changes, transformations in the brain, and a growth

spurt. Particularly notable among the changes occurring in the adolescent brain is the marked pruning of synaptic connections between neurons in some brain regions as well as the continued elaboration, modification, and refinement of neuronal signaling systems, including myelination of pathways that link different brain regions, thereby speeding information flow across these regions (see [8] for review). These brain changes are regionally specific and include not only the oft-discussed delayed maturation of prefrontal cortex critical for cognitive control [9], but also subcortical transformations, including enhanced reactivity of limbic regions critical for motivational responding and the processing of rewarding, arousing, and emotionally provoking stimuli [10, 11]. Given these adolescent-associated brain transformations, it is not surprising that age-specific behavioral alterations are evident as well, with, for instance, adolescent-associated elevations in peer-directed social behavior and in risk-taking and sensation/novelty-seeking evident during adolescence across a variety of species (see [8] for review). Of course, there are striking species differences in lifespan, and hence, the length and timing of adolescence vary accordingly. Although the precise onset and offset of adolescence are as difficult to characterize in other species as in humans, the early/mid-adolescent period (~10–17 years in humans) may subsume roughly the 28–42 postnatal day (P) period in rodents, with late adolescence (~18–25 years in humans) extending from ~P42 to 55 [12, 13].

These cross-species similarities in brain and behavior during adolescence, including elevated levels of per occasion EtOH use, provide the opportunity to examine potential contributors and consequences of adolescent EtOH use in ways that are not possible when studying human adolescents—e.g., through the use of EtOH challenge studies, invasive neural assessments, and empirical studies of long-term consequences of repeated exposure to EtOH during adolescence. Of course, the rodent brain is much less complex than that of humans, and hence, studies in laboratory animals cannot be used to model all aspects of neural, behavior, and psychopharmacological function in humans during adolescence (or at any other point in the lifespan). But, whenever comparable across-species data exist, areas of potential consilience (similar findings across species) will be considered here (see [14], for discussion of consilience in EtOH phenotypes). Because of the rapid accumulation of work in the area, this review will not attempt to be comprehensive but will focus instead on representative findings. In areas where other recent reviews are available, findings will be only briefly summarized, and readers are encouraged to consult these reviews for further detail and references. Most of the rodent work to date has been conducted in rats; cited instances where mice were investigated will be noted accordingly.

Contributors to Early Drinking: Adolescents Differ from Adults in Their Sensitivity to EtOH in Ways That May Promote Use and Encourage High Levels of Use

Studies using rodent models have revealed a number of potential contributors to the elevated EtOH intake of adolescents, including notable age differences between adolescents and adults in their sensitivity to acute effects of EtOH. For instance, relative to adults, adolescents are more sensitive to the social facilitatory and rewarding effects of EtOH (e.g., [15–17] for data in rats, but see also [18] for contrasting findings in a mouse study). Enhanced facilitatory and rewarding effects could make EtOH consumption particularly desirable for adolescents. Adolescents unfortunately are also more vulnerable than adults to the disrupting effects of acute EtOH exposure on spatial memory and hippocampal brain plasticity (e.g., long-term potentiation) [19]. In contrast to these few instances of enhanced EtOH sensitivities, adolescents are relatively insensitive when compared with adults to most other effects of EtOH, including acute consequences of intoxication that likely serve as cues to limit intake. These effects include adolescent insensitivities to the social impairing effects of higher doses of EtOH as well as to EtOH's motor impairing, sedative, and aversive effects [15, 20–22]. EtOH is also a less effective discriminative cue for adolescents, suggesting that adolescents are less able to detect the presence of EtOH within the body (i.e., its subjective, interoceptive effects) than their mature counterparts [23].

Neural Contributors to These EtOH Sensitivities These adolescent-typical EtOH sensitivities are not simply related to age-related differences in pharmacokinetics [24], but rather seemingly reflect developmental differences in expression of acute (within session) tolerance [25], along with differential rates of development of neural systems underlying these various acute effects. For example, consistent with functional actions of EtOH as a glutamate NMDA-receptor antagonist and gamma-aminobutyric acid (GABA) agonist, similar ontogenetic patterns of psychopharmacological sensitivity are seen to NMDA-R antagonists and GABA agonists as to EtOH—data consistent with the hypothesis that developmental alterations in these neural systems contribute to adolescent-typical EtOH sensitivities. For instance, analogous to the biphasic, inverted J-shaped (low-dose rise from baseline, higher-dose decline past baseline) dose–response curve for EtOH's effects on social behavior seen during adolescence (see Fig. 1), the NMDA-R antagonist MK-801 and the NR2B receptor subtype-specific antagonist ifenprodil likewise induce both low-dose stimulatory and higher-dose inhibitory effects on social behavior during adolescence [26, 27]. Again, reminiscent of the EtOH data, the stimulation of social behavior by low doses of these drugs was only evident in adolescents and

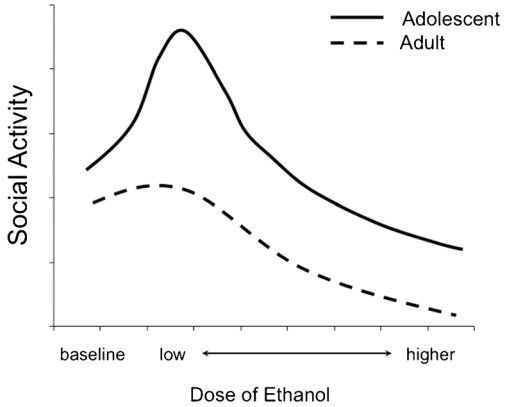

Fig. 1 Acute effects of EtOH on overall social activity of adolescent and adult rats tested in a familiar test environment (adapted from [15])

not adults, with adults being more sensitive than adolescents to the aversive and social impairing effects of NMDA antagonists [26–28] and to the anxiolytic effects of a partial $GABA_A$ receptor agonist [29]. Swartzwelder and colleagues have shown that the greater vulnerability of adolescents to EtOH-induced memory impairment and disruptions in synaptic plasticity may be related to greater induction of $GABA_A$ receptor-mediated tonic inhibition by EtOH in the hippocampus of adolescents than adults [30]. Magnetic resonance spectroscopy (MRS) studies also have revealed maturational changes in the GABA system in human adolescents that have likewise been suggested to contribute to adolescent-specific EtOH sensitivities [31]. Other neural systems may also contribute to adolescent-typical EtOH sensitivities, including opioid receptor systems. EtOH-related social facilitation appears mediated in part through EtOH-induced activation of mu opioid receptors [32], whereas resistance of adolescents to EtOH's aversive properties may be related in part to attenuated sensitivity of adolescents to kappa opioid effects [33].

Relevance of These Laboratory Animal Data to EtOH Intake of Human Adolescence Collectively, such studies using animal models of adolescence suggest that the high levels of EtOH intake seen during adolescence may be related to developmental changes in adolescent brain that increase sensitivity of adolescents to desired, social-stimulatory and rewarding effects of EtOH, while attenuating their sensitivity to undesired consequences of EtOH that presumably serve to moderate drinking. Yet, the critical question remains of how relevant these data are for human adolescents. Of course, empirical studies examining responses to acute EtOH challenge are difficult to conduct in youth who are under legal drinking age. What limited data are available, however, are reminiscent of those obtained in the studies with laboratory animals (see Table 1). For instance, although individuals of all ages often drink under social circumstances, social context is of particular importance for adolescents, with human adolescents reporting that they consume EtOH mostly for social

Table 1 Adolescents differ from adults in their sensitivity to acute EtOH effects, findings largely documented in studies in laboratory animals but confirmed where studied in human adolescents

Adolescents are more sensitive than adults to EtOH's stimulatory and brain plasticity- and memory-impairing effects
Animal studies seen with
-EtOH-induced social facilitation
-EtOH's rewarding properties
-EtOH-induced disruption in brain plasticity indexed via long-term-potentiation
-EtOH-induced memory disruption
Human studies seen with
-Particular importance of EtOH's social facilitatory effects
-EtOH's stimulatory effects
-EtOH-induced memory disruption
Adolescents are less sensitive than adults to many other EtOH effects likely serving as cues to moderate drinking
Animal studies seen with
-EtOH-induced aversive effects
-Social inhibitory effects at higher EtOH doses
-EtOH-induced sedation
-EtOH-induced motor impairment
-EtOH-induced subject (discriminative stimulus) effects
Human studies seen with EtOH-induced intoxication indexed via
-EtOH-induced motor impairment
-EtOH-induced subject effects

References are provided in text and in cited review articles

reasons—i.e., to facilitate social behavior and make these interactions more enjoyable [34, 35]. Likewise, using ecological momentary assessment methods, adolescent humans were found to be more sensitive to the stimulant effects of EtOH than were adults [36]. Furthermore, reminiscent of the greater sensitivity of adolescents than adults to the memory-impairing effects of EtOH in rats, humans during late adolescence (i.e., early 20s) were observed to be more sensitive to EtOH-induced memory impairment than young adults (individuals in their late 1920s) [37].

In terms of EtOH's intoxicating and impairing effects, the literature seems to be limited to an older (1983) study conducted in the USA of 8–15-year-old boys who were challenged with a dose of EtOH that produced blood EtOH levels (BECs) in the moderate intoxicating range (i.e., BECs of 34–35 mg%) [38]. After giving the boys a battery of subjective and objective (e.g., motor impairment and balance) tests of intoxication, the researchers noted that they "were impressed by how little gross behavioral change occurred in the children… after a dose of EtOH which had been intoxicating in an adult population" ([38], p.407). These results are all the more impressive when considering that the boys in this study were thought to be EtOH naïve and receiving their first "intoxicating experience" in the study, whereas at least some of the

adults assessed earlier using the same test battery likely had developed some EtOH tolerance due to prior EtOH use.

Vulnerability Factors Normal developmental insensitivities to the impairing and intake-moderating consequences of EtOH may interact with other vulnerability factors to promote and encourage heavier drinking during adolescence. Indeed, low initial sensitivity to EtOH intoxication is a known risk factor for problematic EtOH involvement and increases the risk of future alcoholism [39]. There is a genetic component to this attenuated sensitivity, with youth having a family history of alcoholism long known to exhibit a lower sensitivity to EtOH impairment [40, 41], and strains of mice and rats bred for high EtOH preference and intake likewise showing attenuated sensitivity to EtOH's aversive effects (see [42] for review). Stressors may serve as an additional vulnerability factor that alters EtOH sensitivity in a similar way. Repeated exposure to stressors has been reported to increase EtOH intake in developing and adult mice and rats [43–45] while conversely decreasing sensitivity to the impairing effects of EtOH [46]. Thus, stressor exposure may further exacerbate typical developmental insensitivities to intake-moderating effects and may interact with other vulnerabilities to precipitate heavier drinking. Indeed, studies in both humans and rodents have shown that genetic factors notably interact with stressors to influence EtOH consumption (for review, see [45]). These stressor influences may be exerted even early in development, with chronic postnatal stress of infant and juvenile rats reported to increase EtOH intake early in adolescence [47] and childhood maltreatment serving as a risk factor for early initiation of EtOH use and later alcohol use disorders (AUD) [48].

Reminiscent of the greater sensitivity of adolescents than adults to the rewarding and social stimulatory effects of EtOH seen in rodent studies [15–17], family history-positive individuals have also been observed to be more sensitive to the stimulatory and rewarding effects of EtOH than those without a family history of alcoholism [41, 49]. Repeated stressor exposure has also been found to restore sensitivity to the social facilitatory effects of EtOH after the ontogenetic decline in this adolescent-typical EtOH-induced behavior [50]. Thus, it appears that attenuated sensitivities to EtOH's suppressant/intoxicating effects, along with enhanced sensitivity to EtOH's rewarding and stimulatory effects, not only are characteristic of adolescents, but are also evident in individuals with genetic vulnerabilities and perhaps prior stressful experiences. Consistent with this perspective, heavier drinkers have been reported to experience stronger stimulant relative to sedative effects, with the opposite being evident in lighter drinkers [51]. This combination of normal developmental EtOH sensitivities may combine with other similar sensitivities in genetically or experientially vulnerable adolescents to precipitate high levels of use.

Indeed, recent field studies have helped to highlight the remarkably high consumption levels evident in college-aged individuals. For instance, in a series of field-based studies of drinkers recruited outside bars in an area frequented by students (mean age ~19–20 years), individuals averaged about eight drinks consumed at the time of assessment during the drinking occasion. Approximately 70 % of the individuals assessed had BECs (indexed via breathalyzer) in the binge range (i.e., ≥80 mg% as defined by the National Institute on Alcohol Abuse and Alcoholism [NIAAA]) [52]. Average BECs were approximately 90 mg% and reached as high as 290–320 mg% in some individuals [53, 54, 55•]. These BECs were all the more impressive when considering that only individuals who were able to fill out a multi-page survey while standing could be recruited, thereby excluding the more intoxicated individuals from study. Seventy-five percent of these individuals also scored in or above the range for risky drinking on the Alcohol Use Disorders Identification Test (AUDIT), a test that focuses on adverse drinking consequences over the past year [53]. Other evidence for potential residual effects of prior adolescent EtOH use also emerged in this field work, with chronic EtOH consumption, independent of the acute effects of intoxication, found to be associated with deleterious effects on a test of cognitive flexibility (Trail Making) [55•]. Although these field studies were not specifically designed to assess lasting consequences of the surprisingly high levels of EtOH use in this predominately college-age population, these findings hint of possible enduring effects of prior EtOH exposure, setting the stage for the work presented in the sections to follow.

Consequences of Adolescent Drinking

There is substantial evidence that use of EtOH by adolescent youth is associated with a variety of neurocognitive alterations and affective disorders. What is less clear, however, is the extent to which these associations are causal in either direction or whether they are each are promoted by some third factor [56]. Retrospective cross-sectional studies have been used to determine the temporality of the observed alterations (i.e., whether EtOH use or the target alteration/disorder appeared earlier), although temporal primacy in itself is not sufficient to establish causality [57]. Prospective longitudinal studies are beginning to emerge and are an important advance for establishing causal relationships between adolescent EtOH use and later consequences. Animal models can also be used to determine consequences of adolescent EtOH exposure. Studies in laboratory animals such as the rat have a number of particular advantages in this endeavor, including the capacity to design empirical studies that specifically manipulate EtOH exposure at the target time(s) during development while holding all other variables constant. With short lifespans and

correspondingly brief adolescent periods, data also can be generated in rodent studies much more rapidly than the multiple years required for longitudinal studies in developing youth.

In the sections below, both human cross-sectional and longitudinal data will be examined, as well as empirical studies conducted predominantly in rats. The focus will be on areas of consilience—i.e., convergence in findings from studies with humans and laboratory animals. Such efforts can sometimes be challenging, in part due to the frequent use of different types of assessments across species, as well as to dissimilarities in the relative timing of the assessments (i.e., often during adolescence while use continues in human studies versus in adulthood after a post-exposure recovery period in rodent studies). Nevertheless, a number of signs of possible consiliences are emerging in the data to date (see Table 2)

Neural Alterations

Assessing possible neural consiliences in consequences of adolescence EtOH exposure is often challenging, given across-species differences in level of analysis and techniques used. For instance, imaging techniques typically used in human work provide data on large populations of neurons whereas basic neurobiological studies in laboratory animals often use electrophysiological, neuroanatomical, and molecular studies to probe specific neuronal populations and their structure, signaling systems, adaptations, and functions at a cellular level. Before turning to the issue of potential neural consiliences in instances where possibly comparable across-species data are available, finding from studies in humans and laboratory animals will be briefly discussed.

Human Studies Imaging studies examining the effects of adolescent EtOH use on brain structure and function have been recently summarized in several excellent reviews (e.g., [58, 59••]), and hence, only a few common themes will be highlighted here. Decreases in volume of grey matter (cell-enriched regions) have been observed in a number of brain regions of EtOH-abusing youth, including the hippocampus, prefrontal cortex, and cerebellum, along with sex-specific alterations in cortical thickness, although it is unclear from these

Table 2 Across-species consequences of repeated adolescent exposure to EtOH, with areas of potential consilience, apparent non-consilience, and study gaps noted

Effect	Animal studies	Human studies
Neural alterations	↓ Neurogenesis	–
	↓ Cholinergic markers basal Forebrain	–
	Disrupted epigenetic regulation	–
	Neuroimmune activation	–
	NR	*Decreases in prefrontal cortex volume*
	–	fMRI alterations in task-related brain activation
	↓ Hippocampal volume	↓ Hippocampal volume
	↓ White matter integrity (*With ↓ mean diffusibility* [*MD*])	↓ White matter integrity (*With ↓ typically in fractional anisotropy; ↑ MD*)
	Alterations in glutamate/GABA systems	alterations in glutamate/GABA systems
Cognitive/behavioral	Disinhibition (↑ risky choice)	–
	Persistence of adolescent-typical EtOH Sensitivities	–
	NA	↓ Performance language tasks
	Executive function (EF) deficits	EF deficits
	(*NOT on attention*, *memory tasks*, but seen w.r.t. ↓ cognitive flexibility, include ↓ reversal acquisition/set-shifting) –	(*Evident attention*, *memory tasks*, ↓ cognitive flexibility) –
	–	↓ Performance visuospatial tasks
Affective measures	↑ Depression (may not be long-lasting)	↑ Depression (may not be causally related)
	↑ Anxiety (social and non-social anxiety)	↑ Anxiety (temporally delayed)
Later EtOH use and AUDs	–	↑ Incidence of AUDs
	↑ Later EtOH consumption	↑ Incidence of EtOH use and problematic Use

Findings in italics reflect areas of potential non-consilience. References are provided in text and in cited review articles

– Little studied to date, *NR* not reliably reported, *NA* non-applicable

largely cross-sectional studies if these alterations preceded or were a consequence of that use. Decreases in volume of white matter (regions enriched in myelinated axons) along with decreases in integrity/health/function of white matter indexed through diffusion tensor imaging (DTI) have also been reported that may both precede and become exacerbated with use. Functional magnetic resonance imaging (fMRI) studies have revealed intriguing timing-related differences in brain activation during cognitive tasks among adolescents with a history of heavy EtOH use, with increases in task-related brain activation among those relatively early in their drinking history (thought to perhaps reflect compensatory increases in effort to permit performance at control levels), whereas those with a longer drinking history showed less brain activation in these same brain regions and performed worse on the tasks.

Studies in Laboratory Animals A variety of persisting brain alterations have been observed in adulthood after repeated exposure to EtOH during adolescence (adolescent intermittent EtOH [AIE]), typically at doses producing BECs above the binge level (i.e., >80 mg%). Highlights of a few findings replicated across laboratories include lasting decreases in neurogenesis and increases in apoptosis (programmed cell death) in both rats and mice [60, 61], as well as decreases in cholinergic neuron markers in basal forebrain [62•], alterations in epigenetic regulation [63, 64], and neuroimmune activation [65, 66] in specific brain regions reported in studies with rats.

Summary and Areas of Possible Consilience Studies in both humans and laboratory animals have observed neural alterations after adolescent EtOH exposure, effects that animal studies have shown to last well into adulthood. Although rare to date, there are a few areas where the dependent measures targeted are similar enough across species to permit consideration of possible neural consiliences. For instance, hippocampal volume reductions have been reported not only in human studies [67] but also in rodents [68] following extensive EtOH exposure during adolescence. DTI studies of white matter permit another area of potential consilience given recent work with DTI in rats [69]. In this study, long-lasting alterations in white matter integrity were observed in adulthood after repeated EtOH exposure during adolescence [69], findings reminiscent of the alterations in white matter integrity reported in human adolescents with high levels of EtOH use (see [70] for review). It should be noted, however, that the decreases in mean diffusibility (MD) seen in rats by Vetreno et al. [69], while similar to some DTI findings in adolescent EtOH abusers [71], differ from the more typical decreases in fractional anisotropy (FA) and increases in MD observed in these adolescents [70]. While this could reflect a species difference, other suspects include study variations in brain regions examined, history and extent of EtOH exposure, length of abstinence pre-scanning, assessment age, and comorbid disorders or other drug use in human studies. Neurochemical consequences of EtOH exposure during adolescence provide another example of possible emerging consiliences. Among the neurotransmitter systems whose development has been shown to be disrupted by AIE in rodent studies are the primary excitatory and inhibitory neurotransmitter systems in brain—glutamate (glu) and GABA [72, 73]. Using MRS to examine neurochemistry of human brain, emerging binge drinkers with a history of EtOH-induced blackouts likewise were found to exhibit attenuated levels of glu and GABA [74], findings reminiscent of the rodent AIE findings. Thus, although limited, where across-species comparisons are possible, intriguing signs of potential consiliences have emerged in these data.

Cognitive/Behavioral

Human Studies As was the case with the neural literature, the literature on cognitive consequences of adolescent use in humans has been recently summarized (e.g., see [59]), and hence, major findings will be only briefly highlighted here. Heavy drinking during adolescence has been associated with subtle cognitive alterations, including attenuated performance on language, learning, and visuospatial tasks, as well as deficits in attention, memory, and other executive functions. While most of these deficits were initially observed in cross-sectional studies and, hence, causal relationships could not be definitely established, several more recent longitudinal investigations have found that history of EtOH use during adolescence does predict later poorer performance on these types of tasks.

Studies in Laboratory Animals Notable specificity has been found in the persisting cognitive effects of AIE exposure in animal studies. Learning of a variety of tasks typically has been found to be largely unaffected. In contrast, reliable disruptions in cognitive flexibility have been reported when indexed using a variety of measures and tasks, including decreases in set-shifting [75] and in reversal acquisition [76]. Signs of disinhibition have been also reported on various tasks [77] along with increases in risky choice [78]. One surprising effect that has been observed across a diversity of measures and laboratories is an AIE-induced persistence of adolescent-typical phenotypes into adulthood (see [79•] for review). These persisting adolescent-like effects are sometimes evident in adulthood in terms of baseline behavioral, cognitive, and electrophysiological characteristics. Particularly pronounced, though, is the AIE-induced persistence into adulthood of many of the adolescent-typical sensitivities to EtOH discussed earlier (such as attenuated sensitivity to aversive and accentuated responsiveness to rewarding effects of EtOH ([80, 81]; see [79•] for review).

Summary and Areas of Possible Consilience Signs of disruptions in cognitive function after adolescent EtOH exposure have been reported in both studies with humans and laboratory animals, although the types of tasks affected may reflect somewhat different constructs. Learning deficits observed in human studies have rarely been reported in animal experiments, although across-species alterations in executive-type functions (cognitive control, behavioral flexibility) are suggestive of potential consiliences. Reminiscent of the animal literature showing an AIE-induced persistence of adolescent-like sensitivities to EtOH, amount of adolescent use by university students was found to be positively related to reward and inversely related to aversive sensitivity [82]. This was a cross-sectional study, however, and given evidence discussed earlier that similar alterations represent a vulnerability factor in individuals with a family history of alcoholism, longitudinal work would be needed to determine whether reports of altered EtOH sensitivity could bidirectionally reflect not only premorbid factors but also consequences of adolescent EtOH exposure.

Affective Measures

Human Studies It has long been known that there is substantial co-morbidity between AUDs and the affective disorders of anxiety and depression [57, 83, 84]. The degree to which these associations reflect causal relationships and, if so, which most often reflects the primary disorder is still controversial. In the case of mood disorders, whereas a few studies have not found significant comorbidity between depression and EtOH problems when other covariates are considered, reports of positive associations predominate. Some studies report that depression is primary and predicts later EtOH problems while others have found that problematic use of EtOH predicts later depression, with evidence building for frequent reciprocal positive associations between the two, with each serving as a risk factor for the other [85]. The association of EtOH use with later depression may not require expression of an AUD per se, with drinking frequency in early adolescence prospectively associated with depression later in adolescence [86]. The relationship between depression and EtOH problems appears to be particularly strong in early to mid-adolescence—which could varyingly reflect particular vulnerabilities of early adolescence or the greater severity of early onset cases. Some sex differences have been reported with, for instance, relationships between depression and levels of EtOH use reported to be particularly marked early in adolescence in females [85] and AUD more likely to precede the onset of depression in males than in females [57].

There is likewise diversity in the reported directional relationships between EtOH abuse and anxiety, perhaps exacerbated in this case by differences across studies in whether one or more separable disorders (social anxiety disorder (SAD), panic, phobias, general anxiety disorder (GAD), etc.) were examined or whether they were grouped together, with perhaps these disorders having different causal relationships with AUD and substance abuse disorders [87]. Anxiety has been reported to often precede abuse disorders, with SAD and social phobia sometimes noted as a particular vulnerability factor [88, 89]. Sex differences are sometimes apparent, with, for instance, SAD and GAD in early adolescence associated with later adolescent EtOH use in females but not males [90]. Conversely, there is also evidence that EtOH abuse and dependence can promote later expression of anxiety disorders [57, 83]. Sex differences were again apparent, with men, for example, reported to be more likely than women to have EtOH abuse that preceded the onset of GAD [57]. Bidirectional associations between anxiety disorders and EtOH use could initiate a "feed-forward cycle," with anxiety symptoms inducing EtOH use for its anxiolytic effects, while that EtOH use may further exacerbate anxiety symptoms [83].

Of particular relevance to considerations of lasting consequences of adolescent EtOH exposure, in cases where AUDs occurred prior to the later emergence of depression or anxiety, expression of the affective disorder typically occurred "temporally distal" to problematic use, with, for instance, lag times of 7–16 years reported from the onset of AUD (typically by late adolescence) to the later expression of GAD and depression in young adulthood [57]. Such long lag times may make it difficult to assess affective consequences of adolescent alcohol use and abuse in a timely manner in human longitudinal studies, suggesting the potential value of studies in laboratory animals for the assessment of these long-term consequences of adolescent EtOH exposure.

Studies in Laboratory Animals Indeed, affective alterations have frequently been reported in rodent AIE studies. Depression-like symptoms (e.g., decreases in sucrose preference used as an index of anhedonia; immobility in the Porsolt swim test) have been observed [91, 92], although this effect was sometimes found to recover with time following termination of the AIE exposure [92]. Reliable AIE-associated increases in general and social anxiety have been reported by a number of groups in adulthood, well after the end of the exposure period [64, 92, 93]. When sex differences have been examined, the elevation in social anxiety after AIE was evident in males, but not females [93], findings somewhat reminiscent of data showing that GAD was more likely to have been preceded by EtOH abuse in men than women [57].

Summary and Areas of Possible Consilience There is substantial evidence for co-morbidity between affective disorders and AUDs. In the human literature, the temporal nature of this association is often characterized by the emergence of affective disorders that precedes the development of problematic use. There is also compelling data, mirrored by the animal data

(especially in the case of anxiety), that repeated EtOH exposure may also increase the risk of affective disorders—suggesting that there may be, in some cases, a bidirectional, positive feedback relationship. Exploring later affective consequences of EtOH, however, may sometimes prove challenging in longitudinal human studies, given the often decade or longer lag between emergence of AUDs and later expression of anxiety disorders, thereby increasing the reliance on animal models for timely assessment of alterations in affect and their neural underpinnings after adolescent EtOH exposure.

Later EtOH Use and AUDs

Human Studies Early initiation of drinking has long been associated with an increased incidence of developing AUDs [94], although whether associations between age at first drink and later problems still hold when pre-existing risk factors are considered has been questioned [95]. Delay from first use to first intoxication may be an additional variable of importance to consider [96], suggesting that developmental timing of exposure to actual pharmacological consequences of EtOH may be critical. Indeed, EtOH use during early and mid-adolescence has been reliably associated with later problematic use of EtOH. For instance, use of EtOH beginning prior to 15 years of age was associated with an increased likelihood of the later emergence of both EtOH abuse and dependence [97], whereas level of EtOH consumption between 15 and 19 years was predictive of amount of EtOH use in adulthood, with heavy drinking during that age range related to later AUDs and dependence [98]. These data are consistent with the suggestion that high levels of adolescent EtOH exposure, especially early in adolescence, increase later EtOH use and problems associated with that use, though additional longitudinal studies are needed to derive compelling causal inferences.

Studies in Laboratory Animals Studies in laboratory animals have been used to examine effects of adolescent EtOH exposure per se on later voluntary consumption of EtOH. Findings are mixed, with reports of AIE-induced increases in later EtOH intake contrasting with others finding no increases; influential variables may include the route by which adolescents were exposed to ETOH, familiarity of the EtOH drinking solution, and timing of the adolescent exposure [99]. The latter point is reminiscent of the human literature, with, for instance, EtOH exposure during early–mid-adolescence reported to increase free-choice EtOH consumption in adult rats, an effect not observed with EtOH exposure later in adolescence [100].

Summary and Areas of Possible Consilience There is compelling evidence from the human literature that adolescent use relatively early in adolescence is associated (albeit not necessarily causally) with later increases in EtOH consumption and a greater incidence of AUDs. While the findings to date examining AIE effects on later EtOH intake in rodents are mixed, the limited available evidence on timing of adolescent exposure has revealed findings similar to that seen in humans, revealing a possible area of consilience in these data.

Conclusions and Future Directions

Animal studies have shown adolescents to vary markedly from adults in their sensitivity to various EtOH effects. These altered developmental sensitivities include enhanced sensitivity to rewarding and socially facilitating effects that may help promote intake, along with attenuated sensitivity to aversive, sedative, intoxicating effects that likely serve as cues to limit intake. This developmental pattern of EtOH sensitivities may combine with similar patterns induced by genetic risk factors as well as prior exposure to stressors to promote high levels of EtOH use, particularly among vulnerable individuals, that may in turn exert lasting consequences.

Indeed, repeated high levels of EtOH use among human adolescents, as well as exposures that produce BECs in the binge range or higher in laboratory animals, have been reported to be associated with a variety of neural, cognitive, behavioral, and affective consequences, along with increases in later EtOH intake and the probability of abuse in some instances. Despite the frequent focus on different levels of analysis and use of dissimilar assessment measures across species, when roughly comparable measures were available, signs of consilience between the human and rodent literature often were apparent. At this early stage in the study of lasting consequences of adolescent EtOH exposure, there are considerable gaps in the literature, as well as hints from potential consiliences that could help direct future efforts. To give a few examples, in animal studies to date, there has been little emphasis on systematic exploration of exposure timing in AIE effects [101•] or on assessment of AIE effects on a broader variety of intake measures, including later induction of EtOH dependency. Conversely, in human work to date, there has been little focus on exploring potential retention of adolescent-typical phenotypes into adulthood that has emerged as a prominent consequence of AIE in the animal literature. Only limited work in either humans or laboratory animals has explored the role of genetics, stressors, and their interaction for influencing adolescent EtOH sensitivities and the consequences of repeated exposure to EtOH during adolescence.

Another area of emerging interest is the area of withdrawal frequency. Studies with human adolescents have shown that frequency of prior withdrawals perhaps serves as a more sensitive predictor of adverse effects than the amount of EtOH exposure per se (see [59••]). Similar findings have also been

reported in mice, with intermittent EtOH exposure in early adolescence producing more pronounced alterations than a similar amount of EtOH exposure given continuously [102]. These findings are reminiscent of studies showing similar adverse consequences of multiple withdrawals/detoxification periods in adult alcoholics [103] and following chronic episodic (versus continuous) EtOH exposure in adult mice [104], and hence, further studies are needed to determine whether the intermittency of EtOH exposure and withdrawal plays a more critical role for induction of later deficits in adolescents than adults.

Further work in these and other areas will be critical to determine factors contributing to the high levels of EtOH use during adolescence, the consequences of that use, and the neural underpinnings of these effects. Several large efforts are currently underway, including two national consortiums funded by NIAAA, one focused on lasting neural, behavioral, and cognitive consequences of adolescent alcohol exposure in laboratory animals (the Neurobiology of Adolescent Drinking in Adulthood [NADIA]) and the other focusing on repeated neural and cognitive assessments of youth prior to and after initiation of alcohol use (the National Consortium on Alcohol and NeuroDevelopment in Adolescence [NCANDA]—see [105]. There is also a recently initiated extensive multi-site study on Adolescent Brain Cognitive Development (ABCD) funded by the National Institutes of Health that is designed to assess consequences of substance abuse during adolescence on brain development in ~10,000 children, with assessments conducted beginning prior to initiation of use and at regular intervals thereafter. Emerging consiliences derived from these ongoing group efforts and work from other laboratories will yield critical new data to facilitate development of effective education, prevention, and intervention efforts designed to decrease the frequency of adolescent EtOH use and the risks of harm from that use.

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Compliance with Ethical Standards

Conflict of Interest Linda Spear declares no conflict of interest.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the future: national results on adolescent drug use. NIH Publication No. 08–6418. 2008:1–70
2. Substance Abuse and Mental Health Service Administration. Office of Applied Statistics. The national survey on drug use and health report—quantity and frequency of alcohol use among underage drinkers. 2008; Rockville, MD
3. Ahlstrom SK, Ősterberg EL. International perspectives on adolescent and young adult drinking. Alcohol Res Health. 2004;28:258–68.
4.• Patrick ME, Schulenberg JE, Martz ME, Maggs JL, O'Malley PM, Johnston LD. Extreme binge drinking among 12th grade students in the United States: prevalence and predictors. JAMA Pediatr. 2013;167(11):101–25. doi:10.1001/jamapediatrics.2013.2392. **This study provides evidence that alcohol intake by adolescents may be notably higher than the 5+ drinks of binge drinking, with 1 in 10 high school seniors reporting consumption of 10+ drinks per drinking episode in the past 2 weeks, and 1 in 20 reporting consumptions of 15+ drinks**.
5. Doremus TL, Varlinskaya EI, Spear LP. Factors influencing elevated alcohol consumption in adolescent relative to adult rats. Alcohol Clin Exp Res. 2005;29(10):1796–808. doi:10.1097/01.alc.0000183007.65998.aa.
6. Vetter CS, Doremus-Fitzwater TL, Spear LP. Time-course of elevated ethanol intake in adolescent relative to adult rats under continuous, voluntary-access conditions. Alcohol Clin Exp Res. 2007;31(7):1159–68. doi:10.1111/j.1530-0277.2007.00417.x.
7. Bell RI, Rodd ZA, Sable HJK, Schultz JA, Hsu CC, Lumeng L, et al. Daily patterns of ethanol drinking in peri-adolescent and adult alcohol preferring (P) rats. Pharmacol Biochem Behav. 2006;83:35–46. doi:10.1016/j.pbb.2005.12.004.
8. Spear LP. Adolescent neurodevelopment. J Adolesc Health. 2013;52 Suppl 2:S7–13. doi:10.1016/j.jadohealth.2012.05.006.
9. Casey BJ, Getz S, Galvan A. The adolescent brain. Dev Res. 2008;28:62–77. doi:10.1016/j.dr.2007.08.003.
10. Ernst M, Fudge JL. A developmental neurobiological model of motivated behavior: anatomy, connectivity and ontogeny of the triadic nodes. Neurosci Biobehav Rev. 2009;33:367–82. doi:10.1016/j.neubiorev.2008.10.009.
11. Spear LP. Rewards, aversions and affect in adolescence: emerging convergences across laboratory animal and human data. Dev Cogn Neurosci. 2011;1(4):392–400. doi:10.1016/j.dcn.2011.08.001.
12. Arnett JJ. Emerging adulthood: the winding road from the late teens through the twenties. New York: Oxford University Press; 2004.
13. Vetter-O'Hagen CS, Spear LP. Hormonal and physical markers of puberty and their relationship to adolescent-typical novelty-directed behavior. Dev Psychobiol. 2012;54(5):523–35. doi:10.1002/dev.20610.
14. Leeman RF, Heilig M, Cunningham CL, Stephens DN, Duka T, O'Malley SS. Ethanol consumption: how should we measure it? Achieving consilience between human and animal phenotypes. Addict Biol. 2010;15(2):109–24. doi:10.1111/j.1369-1600.2009.00192.x.
15. Varlinskaya EI, Spear LP. Acute effects of ethanol on social behavior of adolescent and adult rats: role of familiarity of the test

situation. Alcohol Clin Exp Res. 2002;26(10):1502–11. doi:10.1111/j.1530-0277.2002.tb02449.x.
16. Pautassi RM, Myers M, Spear LP, Molina JC, Spear NE. Adolescent, but not adult rats exhibit ethanol-mediated appetitive second-order conditioning. Alcohol Clin Exp Res. 2008;32(11):1–12. doi:10.1111/j.1530-0277.2008.00789.x.
17. Ristuccia RC, Spear LP. Autonomic responses to ethanol in adolescent and adult rats: a dose–response analysis. Alcohol. 2008;42:623–9. doi:10.1016/j.alcohol.2008.002.
18. Dickinson SD, Kashawny SK, Thiebes KP, Charles DY. Decreased sensitivity to ethanol reward in adolescent mice as measured by conditioned place preference. Alcohol Clin Exp Res. 2009;33:1–6. doi:10.1111/j.1530-0277.2009.00950.x.
19. White AM, Swartzwelder HS. Age-related effects of alcohol on memory and memory-related brain function in adolescents and adults. In: Galanter M, editor. Recent developments in alcoholism, volume 17: alcohol problems in adolescents and young adults (pp 161–76). Hingham: Kluwer Academic Publishers; 2005.
20. Silveri MM, Spear LP. Decreased sensitivity to the hypnotic effects of ethanol early in ontogeny. Alcohol Clin Exp Res. 1998;22:670–6. doi:10.1111/j.1530-0277.1998.tb04310.x.
21. Anderson RI, Varlinskaya EI, Spear LP. Ethanol-induced conditioned taste aversion in male Sprague–Dawley rats: impact of age and stress. Alcohol Clin Exp Res. 2010;34:2106–15. doi:10.1111/j.1530-0277.2010.01307.x.
22. Ramirez RL, Spear LP. Ontogeny of ethanol induced motor impairment following acute ethanol: assessment via the negative geotaxis reflex in adolescent and adult rats. Pharmacol Biochem Behav. 2010;95(2):242–8. doi:10.1016/j.pbb.2010.01.013.
23. Anderson RI, Spear LP. Age differences in ethanol discrimination: acquisition and ethanol dose generalization curves following multiple training conditions in adolescent and adult rats. Alcohol Clin Exp Res. 2013;38(1):186–94. doi:10.1111/acer12255.
24. Spear LP. Assessment of adolescent neurotoxicity: rationale and methodological considerations. Neurotoxicol Teratol. 2007;29(1):1–9. doi:10.1016/j.ntt.2006.11.006.
25. Varlinskaya EI, Spear LP. Ontogeny of acute tolerance to ethanol-induced social inhibition in Sprague–Dawley rats. Alcohol Clin Exp Res. 2006;30(11):1833–44. doi:10.1111/j.1530-0277.2006.00220-x.
26. Morales M, Spear LP. The effects of an acute challenge with the NMDA receptor antagonists, MK-801, PEAQX, and ifenprodil, on social inhibition in adolescent and adult male rats. Psychopharmacology. 2013;231(8):1797–807. doi:10.1007/S00213-01303278-3.
27. Morales M, Varlinskaya EI, Spear LP. Low doses of the NMDA receptor antagonists, MK-801, PEAQX, and ifenprodil, induces social facilitation in adolescent male rats. Behav Brain Res. 2013;250:18–22. doi:10.1016/j.bbr.2013.04.050.
28. Ramirez RL, Spear LP. Sensitivity of adolescent and adult male rats to the dysphoric effects of the selective NMDA NR2B antagonist ifenprodil. San Diego: Society for Neuroscience; 2010.
29. Morales M, Varlinskaya EI, Spear LP. Anxiolytic effects of the $GABA_A$ receptor partial agonist, L-838,417: impact of age, test context familiarity, and stress. Pharmacol Biochem Behav. 2013;109:31–7. doi:10.1016/j.pbb.2013.05.004.
30. Fleming RL, Wilson WA, Swartzwelder HS. Magnitude and ethanol sensitivity of tonic $GABA_A$ receptor-mediated inhibition in dentate gyrus from adolescence to adulthood. J Neurophysiol. 2007;97(5):3806–11. doi:10.1152/jn.00101.2007.
31. Silveri MM. GABAergic contributions to alcohol responsivity during adolescence: insights from preclinical and clinical studies. Pharmacol Ther. 2014;143(2):197–216. doi:10.1016/j.pharmthera.2014.03.001.
32. Varlinskaya EI, Spear LP. Ethanol-induced social facilitation in adolescent rats: role of endogenous activity at mu opioid receptors. Alcohol Clin Exp Res. 2009;33(6):991–1000. doi:10.1111/j.1530-0277.2009.00920.x.
33. Anderson RI, Morales M, Spear LP, Varlinskaya EI. Pharmacological activation of kappa opioid receptors: aversive effects in adolescent and adult male rats. Psychopharmacology (Berl). 2013;231(8):1687–93. doi:10.1007/s00213-013-3095-8.
34. Read JP, Wood MD, Kahler CW, Maddock JE, Palfai TP. Examining the role of drinking motives in college student alcohol use and problems. Psychol Addict Behav. 2003;17:13–23. doi:10.1037/0893-164X17.1.13.
35. Kuntsche E, Knibbe R, Gmel G, Engels R. Why do young people drink? Clin Psychol Rev. 2005; 841–61. 10.1016/j.cpr.2005.06.002
36. Miranda Jr R, Monti PM, Ray L, Treloar HR, Reynolds EK, Ramirez J, et al. Characterizing subjective responses to alcohol among adolescent problem drinkers. J Abnorm Psychol. 2014;123(1):117–29. doi:10.1037/a0035328.
37. Acheson SK, Stein RM, Swartzwelder HS. Impairment of semantic and figural memory by acute ethanol: age-dependent effects. Alcohol Clin Exp Res. 1998;22(7):1437–42. doi:10.1111/j.1530-0277.1998.tb03932.x.
38. Behar D, Berg CJ, Rapoport JL, Nelson W, Linnoila M, Cohen M, et al. Behavioral and physiological effects of ethanol in high-risk and control children: a pilot study. Alcohol Clin Exp Res. 1983;7:404–10.
39. Trim RS, Schuckit MA, Smith TL. The relationships of the level of response to alcohol and additional characteristics to alcohol use disorders across adulthood: a discrete time survival analysis. Alcohol Clin Exp Res. 2009;33(9):1562–70. doi:10.1111/j.1530-0277.2009.00984.x.
40. Schuckit MA. A longitudinal study of children of alcoholics. Recent Dev Alcohol. 1991;9:5–19.
41. Quinn PD, Fromme K. Subjective response to alcohol challenge: a quantitative review. 2011; 35(10):1759–70. 10.1111/j.1530-0277.2011.01521.x.
42. Green AS, Grahame NJ. Ethanol drinking in rodents: is free-choice drinking related to the reinforcing effects of ethanol? Alcohol. 2008;42(1):1–11. doi:10.1016/j.alcohol.2007.10.005.
43. Lopez MF, Doremus-Fitzwater TL, Becker HC. Chronic social isolation and chronic variable stress during early development induce later elevated ethanol intake in adult C57BL/6J mice. Alcohol. 2011;45(4):355–64. doi:10.1016/j.alcohol.2010.08.017.
44. Skelly MJ, Chappell AE, Carter E, Weiner JL. Adolescent social isolation increases anxiety-like behavior and ethanol intake and impairs fear extinction in adulthood: possible role of disrupted noradrenergic signaling. Neuropharmacology. 2015;97:149–59. doi:10.1016/j.neuropharm.2015.05.025.
45. Spanagel R, Noori HR, Heilig M. Stress and alcohol interactions: animal studies and clinical significance. Trends Neurosci. 2014;37(4):219–27. doi:10.1016/j.tins.2014.02.006.
46. Varlinskaya EI, Doremus-Fitzwater TL, Spear LP. Repeated restraint stress alters sensitivity to the social consequences of ethanol in adolescent and adult rats. Pharmacol Biochem Behav. 2010;96:228–35. doi:10.1016/j.pbb.2010.05.011.
47. Odeon MM, Andreu M, Yamauchi L, Grosman M, Acosta GB. Chronic postnatal stress induces voluntary alcohol intake and modifies glutamate transporters in adolescent rats. Stress. 2015;18(4):427–34. doi:10.3109/10253890.2015.1041909.
48. Keyes KM, Hatzenbuehler ML, Hasin DS. Stressful life experiences, alcohol consumption, and alcohol disorders: the epidemiologic evidence for four main types of stressors. Psychopharmacology (Berl). 2011;218(1):1–17. doi:10.1007/S00213-011-2236-1.
49. Newlin DB, Thomson JB. Alcohol challenge with sons of alcoholics: a critical review and analysis. Psychol Bull. 1990;108(3):383–402. doi:10.1037/0033-2909.108.3.383.

50. Varlinskaya EI, Truxell EM, Spear LP. Repeated restraint stress alters to the social consequences of ethanol differentially in early and adolescent rats. Pharmacol Biochem Behav. 2013;113:38–45. doi:10.1016/j.pbb.2013.10.1016.
51. King AC, de Wit H, McNamara PJ, Cao D. Rewarding, stimulant, and sedative alcohol responses and relationship to future binge drinking. Arch Gen Psychiatry. 2011;68(4):389–99. doi:10.1001/archgenpsychiatry.2011.26.
52. NIAAA. Binge drinking defined. NIAAA Newsletter. 2004; 3:3.
53. Celio MA, Vetter-O'Hagen CS, Lisman SA, Johansen GE, Spear LP. Integrating field methodology and web-based data collection to assess the reliability of the alcohol use disorders identification test (AUDIT). Drug Alcohol Depend. 2011;119(1–2):142–4. doi:10.1016/j.drugalcdep.2011.05.035.
54. Celio MA, Usala JM, Lisman SA, Johansen GE, Vetter-O'Hagen CS, Spear LP. Are we drunk yet? Motor versus cognitive cues of subjective intoxication. Alcohol Clin Exp Res. 2013;38(2):538–44. doi:10.1111/acer.12276.
55.• Day A, Celio MA, Lisman SA, Johansen GE, Spear LP. Acute and chronic effects of alcohol on trail making test performance among underage drinkers in a field setting. J Stud Alcohol Drugs. 2013;74(4):635–41. **This field study documented average levels of alcohol consumption in the binge range among under-aged (18–20 year old) drinkers in a college bar area, and provided evidence that in this young population in the field, history of chronic alcohol consumption was associated with deleterious effects on executive functioning, independent of current level of intoxication**.
56. Brook JS, Richter L, Rubenstone E. Consequences of adolescent drug use on psychiatric disorders in early adulthood. Ann Med. 2000;32(6):401–7. doi:10.3109/07853890008995947.
57. Falk DE, Yi HY, Hilton ME. Age of onset and temporal sequencing of lifetime DSM-IV alcohol use disorders relative to comorbid mood and anxiety disorders. Drug Alcohol Depend. 2008;94(1–3):234–45.
58. Jacobus J, Tapert SF. Neurotoxic effects of alcohol in adolescence. Annu Rev Clin Psychol. 2013;9:703–21. doi:10.1146/annurev.clinpsy.050212.185610.
59.•• Squeglia LM, Jacobus J, Tapert SF. The effect of alcohol use on human adolescent brain structures and systems. Handb Clin Neurol. 2014; 501–10. 10.1016/B978-0-444-62619-6.00028-8. **This article provides a concise and excellent review of the effects of alcohol use on neurocognition in human adolescents, with a focus on data from neuropsychological and neuroimaging studies.**
60. Broadwater MA, Liu W, Crews FT, Spear LP. Persistent loss of hippocampal neurogenesis and increased cell death, following adolescent, but not adult, chronic ethanol exposure. Dev Neurosci. 2014;36(3–4):297–305. doi:10.1159/000362874.
61. Lacaille H, Duterte-Boucher D, Liot D, Vaudry H, Naasila M, Vaudry D. Comparison of the deleterious effects of binge drinking-like alcohol exposure in adolescent and adult mice. J Neurochem. 2015;132(6):629–41. doi:10.1111/jnc.13020.
62.• Vetreno RP, Broadwater M, Liu W, Spear LP, Crews FT. Adolescent, but not adult, binge ethanol exposure leads to persistent global reductions of choline acetyltransferase expressing neurons in brain. PLoS One. 2014;9(11):e113421. doi:10.1371/journal.pone.0113421. **This study conducted using an animal model of adolescence in the rat demonstrates that repeated exposure to alcohol during adolescence produces neural alterations that are not evident after equivalent exposure to ethanol in adulthood, suggesting that adolescence is a vulnerable period for alcohol neurotoxicity**.
63. Pascual M, DoCouto BR, Alfonso-Loeches S, Aguilar MA, Rodriguez-Arias M, Guerri C. Changes in histone acetylation in the prefrontal cortex of ethanol-exposed adolescent rats are associated with ethanol-induced place conditioning. Neuropharmacology. 2012;62(7):2309–19. doi:10.1016/j.neuropharm.2012.01.011.
64. Pandey SC, Sakharkar AJ, Tang L, Zhang H. Potential role of adolescent alcohol exposure-induced amygdaloid histone modifications in anxiety and alcohol intake during adulthood. Neurobiol Dis. 2015; pii: S0969-9961(15)00091-1. doi: 10.1016/j.nbd.2015.03.019.
65. Alfonso-Loeches S, Guerri C. Molecular and behavioral aspects of the actions of alcohol on the adult and developing brain. Crit Rev Clin Lab Sci. 2011;48(1):19–47. doi:10.3109/10408363.2011.580567.
66. Vetreno RP, Crews FT. Binge ethanol exposure during adolescence leads to a persistent loss of neurogenesis in the dorsal and ventral hippocampus that is associated with impaired adult cognitive functioning. Front Neurosci. 2015;9:35. doi:10.3389/fnins.2015.00035.
67. Welch KA, Carson A, Lawrie SM. Brain structure in adolescents and young adults with alcohol problems: systematic review of imaging studies. Alcohol Alcohol. 2013;48(4):433–44. doi:10.1093/alcalc/agt037.
68. Ehlers CL, Oguz I, Budin F, Wills DN, Crews FT. Peri-adolescent ethanol vapor exposure produces reductions in hippocampal volume that are correlated with deficits in prepulse inhibition of the startle. Alcohol Clin Exp Res. 2013;37(9):1466–75. doi:10.1111/acer.12125.
69. Vetreno RP, Yaxley R, Panaigua B, Crews FT. Diffusion tensor imaging reveals adolescent binge ethanol-induced brain structural integrity alterations in adult rats that correlate with behavioral dysfunction. Addict Biol. 2015. doi:10.1111/adb.12232.
70. Elofson J, Gongvatna W, Carey KB. Alcohol use and cerebral white matter compromise in adolescence. Addict Behav. 2013;38(7):2295–305. doi:10.1016/j.addbeh.2013.03.001.
71. DeBellis MD, Van Voorhees E, Hooper SR, Gibler N, Nelson L, Hege SG, Payne ME, MacFall J. Diffusion tensor measures of the corpus callosum in adolescents with adolescent onset alcohol use disorders. 2008; 32(3):395–404. 10.1111/j.1530-0277.2007.00603.x
72. Fleming RL, Li Q, Risher ML, Sexton HG, Moore SD, Wilson WA, et al. Binge-pattern ethanol exposure during adolescence, but not adulthood, causes persistent changes in $GABA_A$ receptor-mediated tonic inhibition in dentate granule cells. Alcohol Clin Exp Res. 2013;37(7):1154–60. doi:10.1111/acer.12087.
73. Silvestre De Ferron B, Bennouar KE, Kervern M, Alaux-Cantin S, Robert A, Rabiant K, et al. Two binges of ethanol a day keep the memory away in adolescent rats: key role for GLUN2B subunit. Int J Neuropsychopharmacol. 2015. doi:10.1093/jinp/pyv087.
74. Silveri MM, Cohen-Gilbert J, Crowley DJ, Rosso RM, Jensen JE, Sneider JT. Altered anterior cingulate neurochemistry in emerging adult binge drinkers with a history of alcohol-induced blackouts. Alcohol Clin Exp Res. 2014;38(4):969–79. doi:10.1111/acer.12346.
75. Gass JT, Glen Jr WB, McGonigal JT, Trantham-Davidson H, Lopez MF, Randall PK, et al. Adolescent alcohol exposure reduces behavioral flexibility, promotes disinhibition, and increases resistance to extinction of ethanol self-administration in adulthood. Neuropyschopharmacology. 2014;39(11):2570–83. doi:10.1038/npp.2014.109.
76. Coleman Jr LG, Liu W, Oguz I, Styner M, Crews FT. Adolescent binge ethanol treatment alters adult brain regional volumes, cortical extracellular matrix protein and behavioral flexibility. Pharmacol Biochem Behav. 2014;116:142–51. doi:10.1016/j.pbb.2013.11.021.
77. Acheson SK, Bearison C, Risher ML, Abdelwahab SH, Wilson WA, Swartzwelder HS. Effects of acute or chronic ethanol exposure during adolescence on behavioral inhibition and efficiency in

a modified water maze task. PLoS One. 2013;8(10):a77768. doi:10.1371/journal.pone.0077768.

78. Boutros N, Semenova S, Liu W, Crews FT, Markou A. Adolescent intermittent ethanol exposure is associated with increased risky choice and decreased dopaminergic and cholinergic neuron markers in adult rats. Int J Neuropharmacol. 2014; 18(2) 10.1093/ijnp.pyu003

79.• Spear LP, Swartzwelder HS. Adolescent alcohol exposure and persistence of adolescent-typical phenotypes into adulthood: a mini-review. Neurosci Biobehav Rev. 2014;45:1–8. doi:10.1016/j.neubiorev.2014.04.012. **This mini-review presents evidence obtained from rodent students that after repeated ethanol exposure during adolescence, adults sometimes show phenotypic characteristics typical of adolescents; these "adolescent-like" neurobehavioral effects include expression of adolescent-typical sensitivities to acute ethanol challenge**.

80. Toalston JE, Deehan Jr GA, Hauser SR, Engelman EA, Bell RL, Murphy JM, et al. Reinforcing properties and neurochemical response of ethanol within the posterior ventral tegmental area are enhanced in adulthood by periadolescent ethanol consumption. J Pharmacol Exp Ther. 2014;351(2):317–26. doi:10.1124/jpet.114.21872.

81. Saalfield J, Spear LP. Consequences of repeated ethanol exposure during early or late adolescence on conditioned taste aversions in rats. Dev Cogn Neurosci. 2015;S1878–9293(15):00018–3. doi:10.1016/j.dcn.2015.01.004.

82. Jonker NC, Ostafin BD, Glashouwer KA, van Hemel-Ruiter ME, de Jong PJ. Reward and punishment sensitivity and alcohol use: the moderating role of executive control. Addict Behav. 2014;39(5):945–8. doi:10.1016/j.addbeh.2013.12.011.

83. Kushner MG, Abrams K, Borchardt C. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. Clin Psychol Rev. 2000;20(2):140–71.

84. Hussong AM, Jones DJ, Stein GL, Baucom DH, Boeding S. An internalizing pathway to alcohol use and disorder. Psychol Addict Behav. 2011;25(3):390–404. doi:10.1037/a0024519.

85. Marmorstein NR. Longitudinal associations between alcohol problems and depressive symptoms: early adolescence through early adulthood. Alcohol Clin Exp Res. 2009;33(1):49–59. doi:10.1111/j.1530-0277.2008.00810.x.

86. Edwards AC, Heron J, Dick DM, Hickman M, Lewis G, Macleod J, et al. Adolescent alcohol use is positively associated with later depression in a population-based U.K. cohort. J Stud Alcohol Drugs. 2014;75(5):758–65.

87. Marmorstein NR. Anxiety disorders and substance use disorders: different associations by anxiety disorder. J Anxiety Disord. 2012;26(1):88–94. doi:10.1016/j.janxdis.2011.09.05.

88. Pasche S. Exploring the comorbidity of anxiety and substance use disorders. Curr Psychiatry Rep. 2012;14:176–81. doi:10.1007/s11920-012-0264-0.

89. Black JJ, Clark DB, Martin CS, Kim KH, Blaze TJ, Creswell KG, et al. Course of alcohol symptoms and social anxiety disorder from adolescence to young adulthood. Alcohol Clin Exp Res. 2015;39(6):1008–15. doi:10.1111/acer.12711.

90. Zehe JM, Colder CR, Read JP, Wieczorek WF, Lengua LJ. Social and generalized anxiety symptoms and alcohol and cigarette use in early adolescence: the moderating role of perceived peer norms. Addict Behav. 2013;38:1931–9. doi:10.1016/j.addbeh.2012.11.013.

91. Briones TL, Woods J. Chronic binge-like alcohol consumption in adolescence causes depression-like symptoms possibly mediated by the effects of BDNF on neurogenesis. Neuroscience. 2013. doi:10.1016/j.neuroscience.2013.09.031.

92. Slawecki CJ, Thorsell A, Ehlers CJ. Long-term neurobehavioral effects of alcohol or nicotine exposure in adolescent animal models. Ann NY Acad Sci. 2004;1021:448–52. doi:10.1196/annals.1308.062.

93. Varlinskaya EI, Truxell EM, Spear LP. Chronic intermittent ethanol during adolescence: effects on social behavior and ethanol sensitivity in adulthood. Alcohol. 2014;48(5):433–44. doi:10.1016/j.alcohol.2014.01.012.

94. Grant BF, Dawson DA. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: results from the national longitudinal alcohol epidemiologic survey. J Subst Abus. 1997;9:103–10.

95. Marmaris W, McCambridge J. Age of first drinking and adult alcohol problems: systematic review of prospective cohort studies. J Epidemiol Community Health. 2014;68(3):268–74. doi:10.1136/jech-2013-203402.

96. Morean ME, Corbin WR, Fromme K. Age of first use and delay to first intoxication in relation to trajectories of heavy drinking and alcohol-related problems during emerging adulthood. Alcohol Clin Exp Res. 2012;36(11):1991–9. doi:10.1111/j.1530-0277.2012.01812.x.

97. Dawson DA, Goldstein RB, Chou SP, Ruan WJ, Grant BF. Age of first drink and the first incidence of adult-onset DSM-IV alcohol use disorders. Alcohol Clin Exp Res. 2008;32(12):2149–60. doi:10.1111/j.1530-0277.2008.00806.

98. McCambridge J, McAlaney J, Rowe R. Adult consequences of late adolescent alcohol consumption: a systematic review of cohort studies. PLoS Med. 2011;8(2), e1000413. doi:10.1371/journal.pmed.1000413.

99. Broadwater M, Varlinskaya EI, Spear LP. Effects of voluntary access to sweetened ethanol during adolescence on intake in adulthood. Alcohol Clin Exp Res. 2013;37(6):1048–55. doi:10.1111/acer.12049.

100. Alaux-Cantin S, Warnault V, Legastelois R, Botia B, Pierrefiche O, Vilpoux C, et al. Alcohol intoxications during adolescence increase motivation for alcohol in adult rats and induce neuroadaptations in the nucleus accumbens. Neuropharmacology. 2013;67:521–31. doi:10.1016/j.neuropharm.2012.12.007.

101.• Spear LP. Adolescent alcohol exposure: are there separable vulnerable periods within adolescence? Physiol Behav. 2015;148:122–30. doi:10.1016/j.physbeh.2015.01.027. **The thesis of this review is that effects of adolescent alcohol exposure may vary when that exposure occurs during early-mid adolescence from later in adolescence. Existing support for this emerging hypothesis is provided from both human data and studies using rodent models**.

102. Diaz-Granados JL, Graham DL. The effects of continuous and intermittent ethanol exposure in adolescence on the aversive properties of ethanol during adulthood. Alcohol Clin Exp Res. 2007;31(12):2020–7. doi:10.1111/j.1530-0277.2007.00534.x.

103. Duka T, Townshend JM, Collier K, Stephens DN. Impairment in cognitive functions after multiple detoxifications in alcoholic inpatients. Alcohol Clin Exp Res. 2003;27(10):1563–72. doi:10.1097/01.ALC.0000090142.11260.D7.

104. Lopez MF, Becker HC, Chandler LJ. Repeated episodes of chronic intermittent ethanol promote insensitivity to devaluation of the reinforcing effect of ethanol. Alcohol. 2014;48(7):639–45. doi:10.1016/j.alcohol.2014.09.002.

105. Brown SA, Brumback T, Tomlinson K, Cummins K, Thompson WK, Nagel BJ, et al. The National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA): a multisite study of adolescent development and substance use. J Stud Alcohol Drugs. 2015;76(6):895–908.