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Review

# Adolescent alcohol exposure and persistence of adolescent-typical phenotypes into adulthood: A mini-review

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ABSTRACT

Alcohol use is typically initiated during adolescence, which, along with young adulthood, is a vulnerable period for the onset of high-risk drinking and alcohol abuse. Given across-species commonalities in certain fundamental neurobehavioral characteristics of adolescence, studies in laboratory animals such as the rat have proved useful to assess persisting consequences of repeated alcohol exposure. Despite limited research to date, reports of long-lasting effects of adolescent ethanol exposure are emerging, along with certain common themes. One repeated finding is that adolescent exposure to ethanol sometimes results in the persistence of adolescent-typical phenotypes into adulthood. Instances of adolescent-like persistence have been seen in terms of baseline behavioral, cognitive, electrophysiological and neuroanatomical characteristics, along with the retention of adolescent-typical sensitivities to acute ethanol challenge. These effects are generally not observed after comparable ethanol exposure in adulthood. Persistence of adolescent-typical phenotypes is not always evident, and may be related to regionally specific ethanol influences on the interplay between CNS excitation and inhibition critical for the timing of neuroplasticity.



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## 1. Introduction

Alcohol is the most widely used recreational drug, and most people in the U.S. begin to use alcohol during adolescence or young adulthood. According to nationwide surveys, by approximately 14 years of age, alcohol use has become normative among youth in the United States, with about 75% of 12th graders and 85% of college students reporting that they have tried alcohol. Some of this consumption reaches high levels, with 10% of 8th graders, 25% of 12th graders and >40% of college students reporting that they had consumed five or more drinks in a row during the last two weeks (Johnston et al., 2006). This prevalence of high risk drinking occurs at a developmental period when the brain is undergoing rapid changes in structure and function that could make it especially vulnerable to negative consequences of alcohol exposure (Dahl, 2004; Monti et al., 2005). Epidemiological studies have shown that

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adolescence and young adulthood are the periods of greatest risk for the onset of alcohol abuse and that adult abuse of alcohol is strongly (although not necessarily causally) associated with young age at drinking onset (Dawson et al., 2008; Sher and Gotham, 1999). Thus, evaluating the acute and chronic effects of ethanol on the adolescent brain and behavior may be of great value in understanding the development of alcohol abuse disorders. Studies with laboratory animals such as the rat have proved particularly useful in this regard given ethical constraints limiting experimental investigation of ethanol effects in youth, and the seeming number of neurobehavioral characteristics shared among adolescents across mammalian species (see Spear, 2010; Brenhouse and Andersen, 2011, for review). Reminiscent of human adolescents, adolescent rats also often exhibit elevated ethanol intake relative to their adult counterparts (e.g., Doremus et al., 2005; Vetter et al., 2007).

During the past several decades, it has become clear that significant development and remodeling occurs in the brain throughout adolescence and into early adulthood, with this developmental interval characterized by various neural and behavioral phenotypes that differ notably from those seen at other ages (see Spear, 2000, 2010; Brenhouse and Andersen, 2011). Among the notable alterations in neurobehavioral function seen during adolescence relative to younger and older ages are alterations in responsiveness to a variety of drugs (e.g., see Adriani and Laviola, 2004). One particularly well-investigated drug is alcohol (ethanol), with substantial research demonstrating that acute ethanol induces different effects on both neural and behavioral function during adolescence than are evident at maturity. For example, adolescent rats show greater ethanol-induced memory impairment in the Morris water maze and in a discrimination task than do adults (Land and Spear, 2004; Markwiese et al., 1998). Similarly, humans in their early 20s are more sensitive to the effects of ethanol on both semantic and figural memory tasks than those in their late 20s (Acheson et al., 1998). Acute ethanol has been shown to more potently suppress both NMDA receptor-mediated synaptic activity (Swartzwelder et al., 1995b) and the induction of long-term potentiation (LTP)(Swartzwelder et al., 1995a) in hippocampal slices from adolescent animals compared to those from adults. Adolescents are also uniquely sensitive to the social facilitation effects of ethanol relative to their adult counterparts (e.g., Varlinskaya and Spear, 2002). Conversely, adolescent rats are less affected than are adult rats to most other ethanol effects. These include ethanol's sedative (Little et al., 1996; Silveri and Spear, 1998), motor impairing (Little et al., 1996; White et al., 2002a,b), social inhibitory (Varlinskaya and Spear, 2002) and aversive (Anderson et al., 2010) effects, as well as ethanol's impact on γ-aminobutyric acid (GABA) type A ($GABA_A$) receptor-mediated inhibition (Li et al., 2003, 2006; Yan et al., 2010; but see Yan et al., 2009). Therefore, it is now clear that acute ethanol affects both behavioral and neural function differently in adolescents than adults, although whether ethanol sensitivity is augmented or attenuated during adolescence is dependent on the specific function being tested.

Although such studies have provided crucial information about age differences in the acute effects of ethanol between adolescents and adults, a perhaps even more pressing question is whether the adolescent is at greater or lesser risk for long-term changes in neurobehavioral function after repeated ethanol exposure. Studies of spatial learning in the radial arm maze have shown that adolescent intermittent ethanol (AIE) exposure but not chronic intermittent ethanol (CIE) exposure in adulthood, results in greater long-term sensitivity to the memory-impairing effects of acute ethanol in the absence of any evidence of changes in baseline learning ability (Risher et al., 2013a; White et al., 2000). In contrast, Silvers and colleagues showed that AIE exposure across the 20-day period of adolescence in the rat markedly reduced the efficacy of ethanol to impair spatial learning in the Morris water maze 24 h after the last in the series of chronic ethanol doses (Silvers et al., 2003, 2006), though it is likely that those outcomes were related to withdrawal, tolerance, or both, rather than reflecting an enduring change in ethanol sensitivity. Sircar and Sircar (2005) reported that five consecutive days of ethanol exposure during adolescence resulted in spatial learning deficits in the Morris water maze up to 25 days after the last ethanol treatment, independent of subsequent ethanol challenge. Fear retention deficits have also been observed 25 days following AIE but not the same length of time following CIE exposure (Broadwater and Spear, 2013). Outside the domain of learning, AIE but not CIE has been shown to produce a long lasting decrease in the sensitivity of rats to the sedative/motor-impairing effects of acute ethanol (White et al., 2002b) and, when administered early in adolescence, to increase ethanol consumption in adulthood and enhance motivation for ethanol (Alaux-Cantin et al., 2013). At the cellular level, AIE (but not comparable ethanol exposure in adulthood) was found to produce an enduring decrease in the magnitude of GABA receptor-mediated tonic current in dentate granule cells (Fleming et al., 2012, 2013) which is critical for maintaining the balance of excitation and inhibition within hippocampal circuits. Moreover, although both AIE and CIE decreased A-type potassium current ($I_A$) in GABAergic hippocampal interneurons, this effect was notably more pronounced after AIE (Li et al., 2013).

Despite the relatively limited amount of work to date assessing later effects of repeated exposure to ethanol during adolescence, a few common themes have begun to emerge. The emphasis of this mini-review is on one such theme: emerging across-study commonalities in AIE effects characterized by the persistence of adolescent-typical phenotypes into adulthood. That is, after adolescent exposure to ethanol, certain characteristics of adolescence continue to be expressed developed after their normal ontogenetic decline, and are evident in adulthood, weeks after termination of the adolescent exposure period. Persisting adolescent phenotypes after AIE prominently include retention of adolescent-typical sensitivities to ethanol. These effects can be manifest as either increases or decreases in responsiveness to ethanol challenge in adulthood, so it is important to distinguish persistence of an adolescent-typical response to ethanol from ethanol tolerance *per se*. As outlined in the sections below, examples of persisting adolescent phenotypes have emerged with behavioral and cognitive measures as well as electrophysiological and other neural characteristics, although it is important to point out that certainly not all consequences of AIE reflect the persistence of an adolescent phenotype. For some measures, particularly those that require extensive amounts of training, it may not be possible to assess similarity of the AIE effect to an adolescent phenotype because temporal constraints may limit the ability to assess the adolescent-typical phenotype within the short time-span of adolescence in rodents (i.e., the 2 week period from roughly postnatal day [P] 28–42 as early/mid adolescence, and ~ the next 2 weeks [P43–55] as late adolescent/emerging adulthood – see Spear, 2000; Vetter-O'Hagen and Spear, 2012). Without clear characterization of the adolescent phenotype, it is of course not possible to determine whether this phenotype is retained into adulthood after AIE. The notion that AIE results in the retention of certain adolescent phenotypes into adulthood also seemingly implies that similar findings would not emerge from ethanol exposure at a time when the adolescent phenotype was no longer evident (i.e., after CIE). Only a subgroup of adolescent exposure studies to date have included comparison groups of animals given comparable exposure in adulthood, but in those studies that have, the expression of adolescent-like phenotypes has principally been found to be specific to AIE, and not evident following comparable CIE (see Table 1).

It is important to note that no one adolescent exposure regimen is necessary to produce these persisting adolescent-like phenotypes, with evidence for such effects reported across a number

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