HHS Public Access

Author manuscript

Int Rev Neurobiol. Author manuscript; available in PMC 2022 October 06.

Published in final edited form as:

Int Rev Neurobiol. 2021 ; 160: 281–304. doi:10.1016/bs.irn.2021.08.005.

Consequences of Adolescent Alcohol Use on Adult Hippocampal Neurogenesis and Hippocampal Integrity

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Abstract

Alcohol is the most commonly used drug among adolescents. Their decreased sensitivity to self-regulating cues to stop drinking coincides with an enhanced vulnerability to negative outcomes of excessive alcohol drinking . In adolescents, the hippocampus is one brain region that is particularly susceptible to alcohol-induced neurodegeneration. While cell death is causal, alcohol effects on adult neurogenesis also impact hippocampal structure and function. This review describes what little is known about adolescent-specific effects of alcohol on adult neurogenesis and its relationship to hippocampal integrity. For example, alcohol intoxication inhibits neurogenesis persistently in adolescents but produces aberrant neurogenesis after alcohol dependence. Little is known, however, about the role of adolescent-born neurons in hippocampal integrity or the mechanisms of these effects. Understanding the role of neurogenesis in adolescent alcohol use and misuse is critical to our understanding of adolescent susceptibility to alcohol pathology and increased likelihood of developing alcohol problems in adulthood.

Keywords

Adolescence; Alcohol; Alcoholism; Ethanol; Hippocampus; Neurogenesis; Neural stem cell

Adolescence is often defined by a propensity for risk-taking and reward-seeking behavior, such as alcohol use. Unique qualities of the adolescent brain make this transitional period between childhood and adulthood of especially high risk for the development of an alcohol use disorder (AUD; Nixon & McClain, 2010; Spear, 2018). Though the factors involved are numerous and complex, slow-to-mature behavioral control centers coupled with a low sensitivity for negative effects of alcohol intoxication manifest as ease to drink to excess, the key risk factor for developing an AUD (Bava et al., 2010). Unfortunately, adolescents are *more* sensitive to many of the consequences of excessive alcohol consumption. Adolescents diagnosed with an AUD show not only cognitive impairments, but also neurodegeneration with only a few years of consumption (Nagel, Schweinsburg, Phan, & Tapert, 2005). Indeed, the hippocampus, known for its role in learning and memory, appears to be a particular target of alcohol toxicity in the adolescent (White & Swartzwelder, 2004). The

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hippocampus is also one region that continues to generate and incorporate newly born neurons through adulthood, or adult neurogenesis, a process that is how well-accepted for its role in hippocampal integrity and function (Denoth-Lippuner & Jessberger, 2021; Imayoshi et al., 2008). Adolescent-specific effects of alcohol consumption on the various aspects of adult neurogenesis may underlie the adolescent's susceptibility to hippocampal degeneration and dysfunction, although this nascent research area has many gaps in knowledge (Crews, Mdzinarishvili, Kim, He, & Nixon, 2006; Crews & Nixon, 2009; McClain, Hayes, Morris, & Nixon, 2011; McClain, Morris, Marshall, & Nixon, 2014; Morris, Eaves, Smith, & Nixon, 2010). As is explored in this chapter, binge patterns of alcohol consumption (including extreme binge drinking) in and around the adolescent period, coupled with the distinct vulnerability of the developing brain, leads to lasting effects on adult neurogenic processes and thus hippocampal integrity and function.

1. Alcohol use in adolescence

Adolescence, roughly defined as ages 10-19, is the time when most drug experimentation first occurs but also corresponds to a uniquely dynamic period of brain development and maturation (Jaworska & MacQueen, 2015; Sussman & Arnett, 2014). Alcohol is the most commonly used drug among 12-20 year olds, with 19% reporting drinking and 11% reporting binge drinking in the previous 30 days (SAMHSA, 2020). Binge drinking is a pattern of high alcohol consumption that raises the blood alcohol concentration (BAC) to 80 mg/dL or above (Alcoholism, 2012). Among college freshmen surveyed for drinking in the previous 2 weeks, 41% of men and 34% of women reported binge drinking, while 20% of men and 10% of women reported consuming two or three times the binge drinking threshold per occasion (White, Kraus, & Swartzwelder, 2006). Although adolescents may drink less often than adults, they consume a larger number of drinks each time they initiate (SAMHSA, 2020). For example, 18-24 year olds in the U.S. reported an average of 9.5 drinks per binge episode (Naimi, Nelson, & Brewer, 2010), which well exceeds the 4/5-drink threshold that defines adult binge drinking for women and men respectively (NIAAA, 2012). Furthermore, when compared to adults, adolescents require a fewer number of drinks to reach a 0.08 BAC, the binge drinking threshold, which is due in part to a smaller body size (Donovan, 2009). As such, rates of binge drinking in adolescents may be underestimated because these definitions are based on adult size and intake (Chung, Creswell, Bachrach, Clark, & Martin, 2018).

Adolescents are less sensitive to many of the acute effects of alcohol and specifically cues that aid in self-regulation of alcohol drinking. For example, adolescents are not as sensitive to the sedative and locomotor effects of alcohol (Little, Kuhn, Wilson, & Swartzwelder, 1996), and its suppressive activity on social interaction requires higher doses (Varlinskaya & Spear, 2002). Accordingly, in young rats, less sensitivity to the interoceptive effects of alcohol is suggested from findings that alcohol serves as a less effective cue in an operant drug discrimination task (Anderson & Spear, 2014). In conditioned taste aversion experiments, adolescents require higher ethanol doses than adults need to induce aversion (Anderson, Varlinskaya, & Spear, 2010; Vetter-O'Hagen, Varlinskaya, & Spear, 2009). Adolescents' relative ease in reaching the same BAC coupled with low sensitivity to impairment could explain why human studies reveal not only binge drinking but drinking

levels above and beyond a typical binge termed “high intensity drinking” or “extreme binge drinking” in this age group (Patrick et al., 2013; Patrick & Terry-McElrath, 2017). Adolescents also exhibit attenuated anxiogenic effects following alcohol withdrawal, though withdrawal severity is similar to adults when blood ethanol concentrations are similar (Doremus, Brunell, Varlinskaya, & Spear, 2003; Morris, Kelso, Liput, Marshall, & Nixon, 2010; Varlinskaya & Spear, 2004). Alarmingly, adolescent consumption can result in these insensitivities continuing into adulthood, in a process termed the “lock-in effect” (Spear & Swartzwelder, 2014). Taken together, the lack of sensitivity to these effects allows adolescents to ingest large amounts of ethanol with fewer aversive effects, increasing the likelihood of drinking to excess (Towner & Varlinskaya, 2020).

2. Enhanced susceptibility of adolescents to the consequences of excessive drinking

While adolescents are less susceptible to many of the negative effects of alcohol intoxication that typically serve to regulate their alcohol intake, they are more sensitive to many of the consequences of excessive alcohol drinking than adults. Heavy drinking damages the brain, a consequence of excessive consumption which is thought to contribute to developing an AUD (Crews & Nixon, 2009). Adolescents may be uniquely susceptible to alcohol induced brain damage compared to adults, especially in regions known to develop during adolescence (Crews, Braun, Hoplight, Switzer, & Knapp, 2000; Monti et al., 2005). MRI studies demonstrate that adolescent heavy drinkers experience widespread reductions in both white and gray matter, with most studies supporting decreased volume in certain subcortical and cortical regions (Feldstein Ewing et al., 2014; Squeglia et al., 2014). Such alcohol use can damage major white matter pathways (Bava et al., 2010), including limbic and cortical projection fibers (McQueeny et al., 2009). Alcohol can also blunt increases in white matter that typically occur over adolescent development, notably in regions critical for executive control (Luciana, Collins, Muetzel, & Lim, 2013; Vargas, Bengston, Gilpin, Whitcomb, & Richardson, 2014). The hippocampus, a predominantly gray matter region critical for learning and memory that also contributes to other addiction processes (Tannenholz, Jimenez, & Kheirbek, 2014), is reduced in volume in adolescents with an AUD compared to healthy teens (Nagel et al., 2005). Greater hippocampal volume loss is associated with adolescents who drank starting at younger ages (De Bellis et al., 2000) and who consumed more alcohol per drinking episode (De Bellis et al., 2005). This enhanced susceptibility to damage by those who drink at younger ages parallels their increased risk of developing an AUD (Grant & Dawson, 1997).

Neurotoxicity associated with heavy alcohol consumption during adolescence can have behavioral consequences that stretch into adulthood and therefore influence the perpetuation of alcohol problems as adults (Crews et al., 2019; Lees, Meredith, Kirkland, Bryant, & Squeglia, 2020). Animal studies indicate that adolescent alcohol exposure leads to increased susceptibility to stress in later life (Boutros et al., 2018; Torcaso, Asimes, Meagher, & Pak, 2017). Various aspects of executive functioning can be severely impaired as well, with adult rats exposed to alcohol in adolescence demonstrating persistent impairments in cognitive flexibility (Fernandez & Savage, 2017), reversal learning deficits (Coleman, He, Lee, Styner,

& Crews, 2011), and increased resistance to extinction of ethanol-seeking behavior (Gass et al., 2014). Especially alarming are reports of increased impulsive behaviors in adult rats exposed to alcohol as adolescents (Ehlers, Criado, Wills, Liu, & Crews, 2011). In humans, positive correlations have been made between heavy alcohol consumption during adolescence and increased impulsivity later on (White et al., 2011). Thus, loss of executive control and increased impulsivity due to alcohol induced brain damage during adolescence likely increases the likelihood of developing an AUD (Crews & Boettiger, 2009).

Various mechanisms underlie the brain matter loss in the neurobiological and behavioral consequences of excessive alcohol consumption. In general, drinking to excess can cause neuronal death (Walker, Barnes, Zornetzer, Hunter, & Kubanis, 1980), with a variety of hypotheses on the mechanisms involved, as has been reviewed elsewhere (Cortez, Rodgers, Kosten, & Leasure, 2020; Crews & Nixon, 2009; Guerri & Pascual, 2019; Lees et al., 2020; Melbourne, Thompson, Peng, & Nixon, 2019). In adolescence, a combination of greater cell death after alcohol dependence (e.g. Crews et al., 2000) in combination with derangement in ongoing developmental processes (Giedd et al., 1999; Morris, Eaves, et al., 2010; Vargas et al., 2014) underlies the enhanced susceptibility to degeneration (Nixon & McClain, 2010). For regions such as the hippocampus, a particular target of alcohol effects (White & Swartzwelder, 2004), the adolescent-specific effects of alcohol on the processes of adult neurogenesis may underlie the susceptibility of this region to alcohol toxicity.

3. Adult neurogenesis

Adult neurogenesis is the mechanism by which new neurons are generated, which is now accepted to occur throughout the lifespan of an organism (Denoth-Lippuner & Jessberger, 2021; Gebara et al., 2016; Toda, Parylak, Linker, & Gage, 2019). The two best-accepted brain areas that contain niches conducive to neurogenesis throughout the life of an organism are the hippocampus and the lateral ventricles, specifically the subgranular zone of the dentate gyrus (SGZ) and the subventricular zone (SVZ), respectively (Altman & Das, 1965; Doetsch, Garcia-Verdugo, & Alvarez-Buylla, 1999; Gage, 2000; Gould, 1999). Adult neurogenesis has been observed within the hippocampus of all mammals, including humans (Boldrini et al., 2018; Eriksson et al., 1998; Spalding et al., 2013), with recent debate on the extent adult neurogenesis in humans generally resolved (Kempermann et al., 2018). While the role of SVZ neurogenesis in humans and mammals has been less clear, adult neurogenesis appears to play a key role in hippocampal structure and function (Clelland et al., 2009; Imayoshi et al., 2008; Sahay et al., 2011; Shors et al., 2001; for review see Denoth-Lippuner & Jessberger, 2021; Imayoshi et al., 2008; Kempermann, Song, & Gage, 2015; Olsufka, Peng, Newton, & Nixon, 2018; Snyder & Cameron, 2012; Snyder & Drew, 2020; Toda et al., 2019).

There are four major components to adult neurogenesis: 1) proliferation of stem or progenitor cells, 2) differentiation into a neuronal fate 3) migration, and 4) survival / integration into hippocampal circuitry. The initial birth of a new neuron within the SGZ, originates with what prior studies have identified as true neural stem cells (NSCs): type 1 radial glial-like cells that maintain stemness or the capacity to generate both newborn neurons but also astrocytes (Bonaguidi et al., 2011; Goncalves, Schafer, & Gage, 2016;

Olsufka et al., 2018). These cells are identified by the presence of astrocytic markers such as glial fibrillary acidic protein (GFAP; Bonaguidi et al., 2011) and are typically found in a quiescent, or non-actively dividing state. Provocation by both internal or external stimuli can drive activation of NSCs, identified by the presence of the endogenous proliferation marker Ki67 (Gardella et al., 2002), which results in the asymmetrical division of NSCs and the creation of intermediate neural progenitor cells (NPCs; Seri, Garcia-Verdugo, McEwen, & Alvarez-Buylla, 2001). Fate-restricted differentiation of these NPCs ultimately results in the generation of newborn dentate gyrus granule cells that migrate through the granule cell layer and may ultimately integrate into hippocampal circuitry (Esposito et al., 2005; Kronenberg et al., 2003; Palmer, Takahashi, & Gage, 1997; Seri et al., 2001). While full hippocampal integration of these newborn neurons takes months (Laplagne et al., 2006), around three weeks post cell birth, axonal projections can be detected in the mossy fiber pathway to the CA3 region of the hippocampus (Hastings, Seth, Tanapat, Rydel, & Gould, 2002) and dendritic connections to the perforant path (Toda et al., 2019) . Furthermore, the expression of immature neuronal markers, such as doublecortin, PSA-NCAM, and NeuroD1, declines as mature neuronal markers, like NeuN and Prox1 begin to emerge (Bonfanti, 2006; Brown et al., 2003; Karalay et al., 2011; Lavado, Lagutin, Chow, Baker, & Oliver, 2010).

The specific role of newborn cells has been suggested through studies that examined the immediate early gene, c-Fos, in newborn neurons. In response to the hippocampal-dependent spatial learning and memory task, the Morris water maze, an increased activation and preferential recruitment of newborn neurons has been observed (Kee, Teixeira, Wang, & Frankland, 2007). Furthermore, behavioral studies have implicated hippocampal neurogenesis in cognitive flexibility (Burghardt, Park, Hen, & Fenton, 2012; Toda et al., 2019). For example, impaired spatial memory retention has been observed with inhibition of adult hippocampal neurogenesis (Imayoshi et al., 2008; Snyder, Hong, McDonald, & Wojtowicz, 2005), while increases in adult neurogenesis improved the ability to distinguish between two similar contexts, also known as pattern separation (Sahay et al., 2011). While these studies suggest the relevance of hippocampal neurogenesis to the structure and function of the hippocampus, factors or conditions that impact any aspect of the neurogenesis such as injury, sex, or age, similarly result in alterations to hippocampal-related behavior.

4. Alcohol and adult neurogenesis in adolescents

Differences between adolescents and adults

Neurogenesis, specifically newborn cell production, in the dentate gyrus peaks early after birth, around postnatal day (PND) 6 in rats and declines significantly throughout adolescence and into adulthood (Altman & Das, 1965; Schlessinger, Cowan, & Gottlieb, 1975; Snyder, 2019). Adult hippocampal neurogenesis is around 6-14% of its maximum between PND 20-30 (PND 28 a commonly accepted onset of adolescence) and 3% by PND 120 (Snyder, 2019). Furthermore, the number of proliferating cells in the dentate gyrus decreases significantly between PND 35 and PND 63-70 (Cameron & McKay, 2001). Thus, baseline adult neurogenesis and NPC proliferation differs for adolescent and adult animals.

This difference forces comparisons to only be of relative percent change from age matched controls.

Adult neurogenesis has been shown consistently to be decreased by alcohol intoxication in adolescent rats in a variety of ethanol exposure models (Briones & Woods, 2013; Broadwater, Liu, Crews, & Spear, 2014; Crews et al., 2006; Ehlers, Oguz, Budin, Wills, & Crews, 2013), but also in adolescent mice (Lacaille et al., 2015) and rhesus monkeys (Taffe et al., 2010). Differences are seen in how the neurogenic niche is affected, indicating that the length of exposure, ethanol concentration, and timing of neurogenesis measurement are all important factors when considering the overall impact of ethanol on adult neurogenesis. In addition, each aspect of neurogenesis, proliferation, differentiation, migration, and integration (e.g. Figure 1) must be studied separately in order to understand how alcohol produces its effects. Starting with proliferation, acute exposures to ethanol dose-dependently decrease proliferation in both adult and adolescent rats (Crews et al., 2006; Nixon & Crews, 2002). While this effect appears to be exaggerated in adolescents, with larger decreases in proliferation from age matched controls compared to adults, methodological differences in the exogenous proliferation marker BrdU, muddy this interpretation (Crews et al., 2006; Nixon & Crews, 2002). Adults received two non-saturating (Cameron & McKay, 2001) 100mg/kg BrdU injections 45- and 105-minutes following ethanol while adolescents received one saturating 300mg/kg injection 30-minutes following ethanol. Notably, acute alcohol did not decrease proliferation in either adult or adolescent mice (Lacaille et al., 2015). Results in a binge model of alcohol dependence and AUD in which animals receive three daily intragastric gavages of ethanol for four days (PND 35-38 in adolescent rats; approximately PND 70 in adults), are quite different from acute effects. After ethanol dependence but notably while the animals are still intoxicated, overall decreases in both NPC proliferation and neurogenesis are observed (Morris, Eaves, et al., 2010; Nixon & Crews, 2002) but the decreases in proliferation are reportedly *smaller* in adolescents compared to adults following the last dose of ethanol (Morris, Eaves, et al., 2010; Nixon & Crews, 2004). Again, methodological differences in the exogenous marker, BrdU, and lack of direct comparisons cloud interpretations: the timing of the BrdU injections differ slightly between studies though the rats received the same (300 mg/kg) dose which could explain the differences. Thus, more work is needed and specifically direct comparisons and the inclusion of additional endogenous markers of proliferation in order to fully understand how ethanol produces its effects on the components of adult neurogenesis.

Indeed, the examination of the endogenous active cell cycle marker, Ki67 (Kee, Sivalingam, Boonstra, & Wojtowicz, 2002) revealed that ethanol may affect proliferation differently in adults versus adolescents after alcohol dependence. BrdU, which is taken up during S phase of the cell cycle, is decreased in both adults and adolescents (Morris, Eaves, et al., 2010). However, Ki67, which is expressed across all active division portions of the cell cycle, is not decreased in adolescents after the 4-day binge, while it is decreased in adult animals (Crews et al., 2006; McClain et al., 2011; Morris, Eaves, et al., 2010). This difference led to subsequent experiments which found that ethanol dependence shortens the cell cycle, and the S-phase specifically, of neural stem and progenitor cells in adolescence leading to an expansion of the neural progenitor cell pool (McClain et al., 2011). This difference appears to return to normal a week after binge exposure when adolescent rats show a reactive burst

in hippocampal neurogenesis, as the proportion of cells in each phase of the cell cycle was not different between alcohol exposed and control animals.

The adolescent intermittent ethanol (AIE) model is another common model of ethanol exposure that has been used to study the effects of ethanol on adult neurogenesis. AIE exposure differs from the 4-day binge in that it does not induce physical dependence, produces transient, lower BECs (in the range of 150-190 mg/dL at PND 38, measured 1 hr after ethanol administration) and perhaps mimics adolescent weekend drinking. During AIE, animals typically receive ethanol 2-days on and 2-days off starting early in adolescence and ending in early adulthood. In this model, animals were sacrificed 3 days after the last ethanol dose (and 2 hrs after BrdU injection) and thus show no difference in proliferation consistent with alcohol's inhibitory effect during intoxication (Nixon, 2006), but do display decreased numbers of stem and progenitor cells (Liu & Crews, 2017). One report found less neurogenesis one day following AIE (Vetreno & Crews, 2015) while another found no difference three days following AIE (Liu & Crews, 2017). After protracted abstinence, however, adolescent AIE animals have been shown consistently to have decreased proliferation and neurogenesis (Liu & Crews, 2017; Sakharkar et al., 2016; Swartzwelder et al., 2019; Vetreno & Crews, 2015, 2018). In agreement with AIE models, after chronic ethanol vapor exposure, NPC proliferation and neurogenesis as assessed by doublecortin and Ki67 immunoreactivity is also persistently decreased following two- and eight-weeks of abstinence (Ehlers, Liu, Wills, & Crews, 2013). This extended decrease of neurogenesis appears counter to that seen in the 4-day binge in which decreased neurogenesis is transient and returns to baseline after reactive increases in neurogenesis (Geil et al., 2014; Nickell et al., 2017). Differences in neurogenesis levels in protracted abstinence may reflect differences in exposure times or when neurogenesis is measured in these two models, but also a differential impact of the development of dependence and therefore withdrawal seizures on the components of neurogenesis. Long-term or repeated exposures to excessive alcohol may result in multiple cycles of reactive neurogenesis, resulting in depletion of the stem cell pool. Indeed, stem cell depletion from hyperactivation has been shown to occur in seizure models (Sierra et al., 2015). Thus a major gap in our understanding is how and why decreased neurogenesis persists into adulthood following some types of adolescent ethanol exposure, but not in all models.

Only two studies to date have directly compared adult and adolescent animals. One in mice utilized a single binge-like exposure of three IP injections in one day or a multiple binge-like exposure of three one day binges in five-day intervals (Lacaille et al., 2015). Though only one marker was used to assess cell proliferation (BrdU), results showed that adolescents with multiple binges had decreased proliferation while the single binge exposure adolescents and all adults did not differ from controls. The other study in rats utilized a 1 day on and 2 day off variant of AIE (Broadwater et al., 2014). Using this model, Broadwater et al. (2014) found that four weeks after the final dose of ethanol, animals did not differ in the number of proliferating cells in adolescence or adulthood, but intriguingly AIE exposed adolescents had significantly decreased neurogenesis as measured by doublecortin expression while adults did not. This study suggests that alcohol has long-term effects on the neurogenic niche that also impacts the integration and survival of newborn neurons (Zou & Crews, 2012).

Alcohol inhibition of neurogenesis impairs hippocampal integrity

Alterations to neurogenesis following adolescent drinking can have lasting impacts on the brain, and especially to hippocampal integrity and cognitive function. Studies using human subjects allow a glimpse into lasting structural changes that can occur after adolescent drinking. For example, Pfefferbaum at al. (2018) recruited 483 no- or low-drinking adolescents and conducted MRI scans at the beginning of the study and also at 1 and 2 years later. Subjects who had initiated heavy drinking during the course of the study showed rates of frontal cortical gray matter degeneration above and beyond subjects who were no- or low-drinkers. Additionally, hippocampal volume loss was greater in adolescents who started drinking at a younger age, and who consumed more alcohol each time they drank (De Bellis et al., 2000; De Bellis et al., 2005).

In mice, adolescent binge alcohol exposure led to reduced neurogenesis accompanied by impaired short-term memory, effects which were not observed in adult mice (Lacaille et al., 2015). In rats, adolescent alcohol exposure is linked to an increase in anhedonia and behavioral despair during withdrawal/abstinence along with reduced BrdU+ immunoreactivity in the dentate gyrus (Briones & Woods, 2013). However, administration of a brain-derived neurotrophic factor (BDNF) receptor agonist (TrkB) restored neurogenesis and ameliorated the depression-like symptoms. AIE exposed adolescent rats also display anxiety-like behavior (Loxton & Canales, 2017; Sakharkar et al., 2016), which coincides with histone deacetylase (HDAC) increases though decreases in histone H3 acetylation at the BDNF exon IV promoter in the hippocampus (Sakharkar et al., 2016). Treatment with the HDAC inhibitor trichostatin A reversed histone acetylation deficits and recovered the anxiety-like behavior, providing evidence of epigenetic disturbances to a pro-neurogenic trophic factor promoter following adolescent alcohol use. In a separate study, AIE impaired adult object recognition memory, and interestingly, memory for objects was positively correlated with doublecortin immunoreactivity in the both the dorsal and ventral dentate gyrus while latency to enter the center of the testing arena (thigmotaxis, a measure of anxiety-like behavior) was negatively correlated with ventral dentate gyrus doublecortin immunoreactivity (Vetreno & Crews, 2015). Taken together, these studies suggest how sensitive cognitive and emotional health is to the long-term anti-neurogenic effects of adolescent drinking.

Reactive neurogenesis after alcohol dependence

After the hippocampus has experienced an insult such as trauma (Dash, Mach, & Moore, 2001; Yu, Zhang, Liebl, & Kernie, 2008), seizure (Cho et al., 2015; Parent et al., 1997), ischemic stroke (Jin et al., 2006; Liu, Solway, Messing, & Sharp, 1998) or alcohol dependence (Geil et al., 2014; Hansson et al., 2010; Mandyam & Koob, 2012; Nawarawong, Nickell, Hopkins, Pauly, & Nixon, 2021; Nixon & Crews, 2004; Somkuwar et al., 2016), a phenomenon known as “reactive neurogenesis” occurs, during which there is a surge in progenitor cell proliferation followed by an increase in newborn neurons (Molowny, Nacher, & Lopez-Garcia, 1995). Although reactive neurogenesis has most often been studied in the context of injury, it has also been observed in response to naturally occurring apoptosis (Larson, Thatra, Lee, & Brenowitz, 2014), suggesting it plays an important part in homeostatic regulation of cell birth and death. Evidence of reactive neurogenesis has been

observed in both adults and adolescent models of alcohol dependence which suggests that hippocampal damage or excitation upon withdrawal may be the fundamental cause of this striking event (Hansson et al., 2010; McClain et al., 2014; Nawarawong et al., 2021; Nixon & Crews, 2004; Somkuwar et al., 2016).

Reactive neurogenesis can be beneficial to recovery or aberrant, depending on the condition, and perhaps the degree of hippocampal activation incurred during insult. For example, seizures appear to initially abolish neurogenesis by biasing neural stem cells to differentiate into astrocytes, while sub-seizure levels of excitation enhance both new neuron and new astrocyte formation (Sierra et al., 2015). With similar alcohol withdrawal seizures following the 4-day binge, there is a reactive increase of neurogenesis in abstinence for both adult and adolescent animals (McClain et al., 2011; Nickell et al., 2017; Nixon & Crews, 2004). Reactive proliferation first occurs peaking seven days following the last dose of ethanol (Hayes et al., 2018; Nixon, Kim, Potts, He, & Crews, 2008) with similar two-fold increases in actively proliferating progenitor cells (BrdU+/Sox2+ co-labeled cells) at T7 in both adults and adolescents (Hayes et al., 2018; Nickell et al., 2017). Also by T7, the percentage of cycling cells in each phase of the cell cycle are similar for 4-day binge alcohol exposed versus controls in adults versus adolescents. Qualitatively, however, there could be age differences in the percentage of cells in each phase with adults having 60% of actively dividing cells estimated to be in G1 while adolescents have only 40%. This may not be surprising given the expected age-related decline in neurogenesis that occurs (Altman & Das, 1965). Although withdrawal severity and specifically seizure severity based on overt behavior appears to be similar between adults and adolescents, the driver of reactive neurogenesis may differ between the age groups. In adolescents, ethanol shortens the cell cycle during ethanol dependence (McClain et al., 2011) possibly as a means of amplifying type 2 progenitor cells (Nickell et al., 2017). In adults, however, reactive proliferation at T7 results from activating type 1 radial glial-like NSC out of quiescence (Hayes et al., 2018). This type-1 NSC activation is not observed in adolescents at T7, though other time points have not been examined as exhaustively as they have in adults (Nickell et al., 2017). The extent of activated type 1 NSCs has implications for exhaustion of the stem cell pool, potentially explaining long term decreases in NSC proliferation or adult neurogenesis (Sierra et al., 2015).

Fourteen days after the last dose of ethanol, these reactive increases in NPC and/or NSC proliferation in the SGZ at T7 subsequently produce increased adult neurogenesis as measured by either doublecortin or NeuroD1 expression at T14 in adolescents and adults (Hayes et al., 2018; McClain et al., 2014; Nickell et al., 2017). The two-fold increase in newborn neurons holds through to T35 (BrdU pulse at T7, sacrificed at T35 “chase”) with a remarkably similar rate of neuronal differentiation (~82-84%) in both groups (McClain et al., 2014; Nixon & Crews, 2004). These similarities are for cells found in the SGZ and inner 1/3 of the granule cell layer where newborn cells are expected. As such, this is where the similarities end: adolescent rats have a striking pattern of ectopically expressed BrdU (T7), doublecortin (T14) and then Prox1 (T14), the transcription factor expressed in granule neurons (Karalay et al., 2011). Interestingly, ectopic neurogenesis was observed essentially only in those rats that experienced high withdrawal (McClain et al., 2014).

Ectopic neurogenesis has not been observed in adults, male, or female (Nawarawong, submitted) in the 4-day binge model nor any other alcohol model to our knowledge.

Results to date in adult animals have indicated that adult neurogenesis is a reparative process in adult rats (Nickell, Thompson, Pauly, & Nixon, 2020), however perhaps not in adult mice (Cuartero et al., 2019; Golub et al., 2015; Lee et al., 2019). In adolescents, reactive neurogenesis leads to increased ectopic migration of newborn cells in those rats with greater withdrawal severity (McClain et al., 2014), but this effect is not observed in adults (Nixon & Crews, 2004). Specifically, in adolescents, severe ethanol withdrawal was linked to an increase in Prox1+ cells in the hilus of the dentate gyrus (McClain et al., 2014); similarly, pilocarpine-induced seizures elicit ectopic Prox1+ cells in the hilus (Parent, Elliott, Pleasure, Barbaro, & Lowenstein, 2006) suggesting that for alcohol withdrawal, seizure is the key to this phenomenon. At the same time, seizures are linked to ectopic neural stem cells, aberrant neurogenesis, and pathogenesis in models of seizure (Cho et al., 2015; Parent et al., 1997). There is evidence that these hilar-ectopic cells can travel to and integrate into the hippocampal CA3 cell layer while still morphologically and electrophysiologically retaining the properties of a granule cell (Scharfman, Goodman, & Sollas, 2000), which is in line with recent work implicating a derangement in newborn neuron integration in alcohol withdrawal seizures (Lee et al., 2019). As such, it is possible that aberrant neurogenesis that occurs with alcohol dependence may be responsible for the long-term consequences of adolescent drinking.

5. Conclusions

There are multiple ways that alcohol exposure can potentially impact adult neurogenesis with discoveries in this relatively nascent field still being made on descriptive but important questions of effects on cell proliferation, expression of newborn neuron markers and new cell survival. Thus, even less is known about how alcohol affects this process in the adolescent brain. Major gaps in our knowledge also remain for understanding the role of adult neurogenesis in hippocampal pathology in alcohol dependence, specifically the contribution of newborn cells not only to normal hippocampal structure and function but also the recovery process from the damaging effects of excess alcohol consumption. The presence of ectopic newborn cells after binge exposure may explain the greater damage to the hippocampus in adolescents (McClain et al., 2014). Finally, no mechanistic studies have yet probed the role of these cells in damage or recovery processes in adolescents. Of the existing studies, it does sem clear that adolescent exposure has a more detrimental impact on adult neurogenesis than in adults. Whether that effect is through persistent impairment in newborn neuron production as is observed in AIE models (e.g. (Broadwater et al., 2014) or through aberrant neurogenesis after dependence (McClain et al., 2014), either or both mechanisms together have implications on long term hippocampal structure and function. Understanding the cellular signaling mechanisms unique to adolescents is important to our overall understanding of the harms of adolescent drinking.

Abbreviations

AIE	Adolescent Intermittent Ethanol

AUD	Alcohol Use Disorder
BAC	Blood Alcohol Concentration
BDNF	Brain-Derived Neurotrophic Factor
GFAP	Glial Fibrillary Acidic Protein
HDAC	Histone Deacetylase
NPC	Neural Progenitor Cell
NSC	Neural Stem Cell
PND	Postnatal Day
PFC	Prefrontal Cortex
SGZ	Subgranular Zone
SVZ	Subventricular Zone

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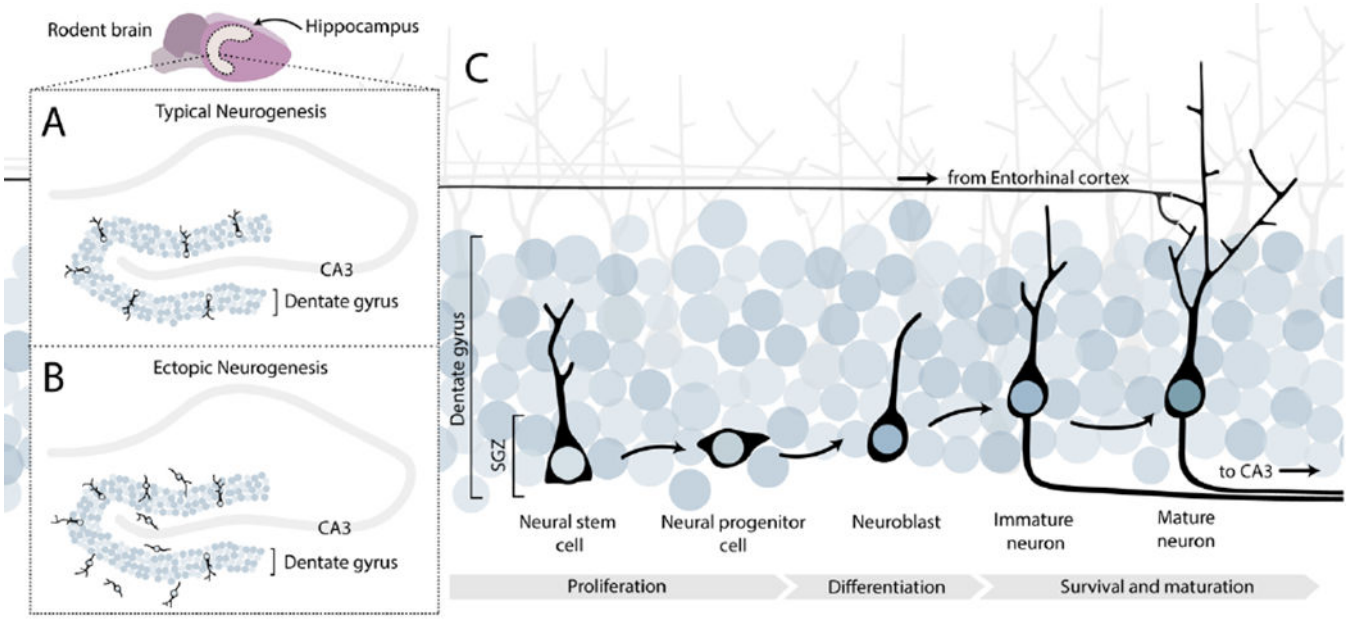

Figure 1:

In the rodent brain adult neurogenesis occurs in at least two regions, one of which is the hippocampus. (A) As part of normal brain functioning, new neurons are born in the subgranular zone of the dentate gyrus of the hippocampus. (B) In adolescent rats, reactive neurogenesis following ethanol administration leads to increased abnormal "ectopic" migration of newborn neurons. (C) Adult neurogenesis is a multi-step process that occurs over a time-span of several weeks. First, neural stem cells proliferate and differentiate into neural progenitor cells, which themselves can proliferate and differentiate into neuroblasts. Some neuroblasts will gradually mature into adult neurons and migrate into the dentate gyrus granule cell layer. As newborn cells mature, they extend their axons to the CA3 pyramidal cells of the hippocampus, while their dendrites elongate and ramify to receive inputs from the entorhinal cortex. Alcohol can potentially affect any one or multiple steps in its overall effect on adult neurogenesis.