HHS Public Access

Author manuscript

Neurobiol Learn Mem. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

Neurobiol Learn Mem. 2020 July ; 172: 107234. doi:10.1016/j.nlm.2020.107234.

The effects of adolescent alcohol exposure on learning and related neurobiology in humans and rodents

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Abstract

Adolescent alcohol use is a widespread problem in the United States. In both humans and rodents, alcohol can impair learning and memory processes mediated by forebrain areas such as the prefrontal cortex (PFC) and hippocampus (HC). Adolescence is a period in which alcohol use often begins, and it is also a time that can be uniquely sensitive to the detrimental effects of alcohol. Exposure to alcohol during adolescence can cause persisting alterations in PFC and HC neurobiology that are linked to cognitive impairments, including changes in neurogenesis, inflammation, and various neurotransmitter systems in rodent models. Consistent with this, chronic adolescent alcohol exposure can cause PFC-dependent learning impairments that persist into adulthood. Deficits in adult HC-dependent learning after adolescent alcohol exposure have also been reported, but these findings are less consistent. Overall, evidence summarized in this review indicates that adolescent exposure to alcohol can produce long-term detrimental effects on forebrain-dependent cognitive processes.

Keywords

Adolescence; alcohol; learning; memory; prefrontal cortex; hippocampus

1. United States adolescent drug use and cognition

Alcohol is the most commonly used drug of abuse among adolescents (Johnston *et al.*, 2018). Twenty-four percent of adolescents use alcohol by the eighth grade, and around sixty percent use alcohol before graduating high school (Johnston *et al.* 2018). Additionally, adolescents display different patterns of alcohol use than adults. Adolescents generally consume alcohol less frequently, but they usually consume larger amounts of alcohol per occasion than adults (Substance Abuse and Mental Health Services Administration [SAMHSA], 2011). These episodes of high alcohol intake are referred to as binge drinking

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CRediT Author Statement

Laurel Seemiller: Conceptualization, Writing - Original draft

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episodes. Approximately 1 in 4 people over the age of 11 report binge alcohol use in the past month (SAMHSA, 2018). In 2018, fourteen percent of 12th graders admitted to binge drinking, which the study defined as having five or more drinks in a row on one or more occasions in the previous two weeks (Johnston *et al.*, 2018). Binge drinking can have serious consequences, including increases in traffic accidents, violent behavior, suicide, and increased risk to develop alcohol use disorders (Stolle *et al.*, 2009; Addolorato *et al.*, 2018). Because of the prevalence and extent of adolescent alcohol use, it is critical to study its immediate and long-term consequences.

Adolescence can be defined as a transitional period between childhood and adulthood. It is accompanied by changes in numerous behaviors, some that may be responsible for the transition to independence associated with adulthood. For example, time spent interacting with peers and risk-taking behaviors drastically increase during adolescence (Spear, 2000). Examples of typical adolescent risk-taking behaviors include disobeying parents, school misconduct, antisocial behaviors, and substance use (Maggs *et al.*, 1995). While all of these behaviors can have long-term consequences, adolescent substance use is especially dangerous as it predicts adult addictive disorders (Rohde *et al.*, 2001; Brook *et al.*, 2002). Exposure to drugs of abuse during adolescence can cause other long-lasting behavioral changes. For example, persistent learning and memory deficits can be seen after adolescent drug exposure (Hanson *et al.*, 2011; Portugal *et al.*, 2012; Mooney-Leber & Gould 2018). Drug-induced changes in cognition can have a wide range of consequences, including an increased propensity for drug addiction (for review, see Gould, 2010).

Adolescent risk-taking can be attributed to differential development of subcortical limbic regions and the prefrontal cortex (PFC). Subcortical limbic regions are more developed than the PFC during adolescence (Casey *et al.*, 2008). Limbic development, specifically in the nucleus accumbens, can drive the seeking of novel experiences. The PFC circuitry that normally controls these impulses is underdeveloped at this point and cannot adequately regulate risk-taking in adolescence. As the PFC develops, so does executive control, and this development is thought to gradually reduce risk-taking behavior as adolescents reach adulthood (Casey *et al.*, 2008). Additionally, the PFC and the hippocampus (HC) are important substrates of learning and memory processes (Dias & Aggleton, 2000; Smith & Milner, 1981), and they develop at different rates. The HC and related cognitive processes seem to be mostly developed by mid-childhood or adolescence (Ofen et al., 2007; Ghetti et al., 2010; Ofen et al., 2012; Shing et al., 2016), while the PFC continues developing through late adolescence into adulthood (Giedd et al., 1999; Sowell et al., 1999; Gogtay et al., 2004). Because the PFC and HC are still developing during adolescence, learning processes modulated by these regions may be more vulnerable to detrimental effects of adolescent risk-taking and drug use (Broadwater & Spear, 2013; Spear, 2015).

2. Alcohol's behavioral effects and pharmacology

Alcohol is the most commonly abused recreational drug (SAMHSA, 2015). Its behavioral impacts are wide-ranging, including both rewarding and aversive effects that influence its abuse liability. Alcohol can produce acute stimulating effects such as euphoria and social facilitation (King *et al.*, 2011). Its negative acute effects include nausea, sedation, motor

incoordination, and cognitive impairments (Weissenborn & Duka, 2003; Brumback *et al.*, 2007; King *et al.*, 2011; Acheson *et al.*, 1998). Chronic alcohol use is associated with additional, often severe, consequences. Some may become addicted to alcohol and experience withdrawal symptoms such as headaches, nausea, tremors, depression, and irritability during periods of abstinence (Stewart & Brown, 1995). They may also experience lasting changes in mood and impaired learning after periods of alcohol use (Brière *et al.*, 2014; Brandt *et al.*, 1983). However, recovery of psychomotor skills and short-term memory has been seen after prolonged abstinence from long-term alcohol use (Brandt *et al.*, 1983). This suggests that some lasting behavioral consequences of alcohol exposure are reversible.

Alcohol primarily acts as an agonist on γ-aminobutyric acid $(GABA)_A$ receptors (see Kumar *et al.*, 2009 for review). GABA is the primary inhibitory neurotransmitter of the central nervous system and plays a role in countless important brain processes (McCormick, 1989). Alcohol also antagonizes N-methyl-D-aspartate (NMDA) receptors, a subtype of glutamate receptors, that contribute to excitatory neurotransmission (Lovinger *et al.*, 1990). These receptors are involved in synaptic plasticity and learning and memory (Artola & Singer, 1987). In addition to modulating $GABA_A$ and NMDA receptor function, alcohol also influences AMPA, kainate, glycine, and nicotinic acetylcholine receptor function (Lovinger, 1993; Weiner *et al.*, 1999; Mihic *et al.*, 1997; Cardoso *et al.*, 1999). AMPA and kainate receptors are important components of glutamatergic signaling (for review, see Bettler & Mulle, 1995), and glycine is important in inhibitory neurotransmission (Werman *et al.*, 1968). Alcohol therefore suppresses the activity of the central nervous system while simultaneously affecting a number of other signaling molecules that can have diverse effects on cognition.

3. Human cognitive deficits after adolescent alcohol exposure

Acute and repeated alcohol exposure during adolescence or young adulthood can impair learning and memory during these periods (Acheson *et al.*, 1998; Brown *et al.*, 2000; Hanson *et al.*, 2011; Thoma *et al.*, 2012). In humans, 21- to 24-year-olds are more susceptible than 25- to 29-year-olds to acute alcohol-induced disruptions in semantic and figural memory (Acheson *et al.*, 1998). Furthermore, after three weeks of abstinence from alcohol, alcohol-dependent adolescents show impaired performance in the Wechsler Intelligence Scale for Children-Revised (WISC-R) Vocabulary, Information, Similarity, and Coding subtests. California Verbal Learning Test for Children (CVLT-C) retention rates and visual reproduction retention rates are also impaired in alcohol-dependent adolescents after a three-week abstinence period (Brown et *al.*, 2000). Heavy alcohol use in adolescence has been linked to poorer memory in the California verbal learning test during adolescence (Hanson *et al.*, 2011). These findings suggest that verbal learning, verbal retention, and nonverbal retention are affected by heavy alcohol use and/or alcohol dependence in adolescence. Adolescent alcohol use has also been linked to adolescent deficits in executive function and attention after two days of abstinence from alcohol use (Thoma *et al.*, 2012).

Executive function deficits have also been reported in 18-year-old subjects after adolescent alcohol exposure, as measured by working memory in the N-back task (Mahedy *et al.*, 2018). However, young adult working memory deficits have not been observed consistently.

Others have reported no adult working memory deficits measured by the Amsterdam Neuropsychological Task after adolescent alcohol exposure (Boelema *et al.*, 2015). These inconsistent findings may be due to the differences in tasks used to assess working memory. Ages of alcohol exposure and cognitive testing also differed between these studies. N-back task performance was assessed in subjects that were 18 years of age and exposed to alcohol around 15 years of age, and Amsterdam Neuropsychological Task performance was measured in adolescents that were 11–19 years old and exposed to alcohol at variable adolescent ages (Mahedy *et al.*, 2018; Boelema *et al.*, 2015). Because learning circuitry is still developing throughout adolescence, it is likely that alcohol exposure can affect learning processes differently in different stages of adolescence (Broadwater & Spear, 2013; Spear, 2015). Therefore, differences in timing of alcohol exposure and in learning assessment tasks may contribute to the different effects of adolescent alcohol exposure on adult learning. The cognitive consequences of adolescent alcohol exposure may be better studied in rodent models, in which the timing of alcohol exposure and later testing can be carefully controlled.

4. Rodent PFC-mediated learning after adolescent alcohol exposure

The PFC is primarily responsible for executive function, which includes selfregulation to align actions with goals (Miller & Cohen, 2001). The PFC is an important component of cognitive flexibility and is known to be impacted by alcohol exposure during adolescence (Dias & Aggleton, 2000; De Bellis *et al.*, 2005; Medina *et al.*, 2008). The following sections of this review will describe short-term (present during adolescence) and long-term (present during adulthood) consequences of adolescent alcohol exposure on PFC-dependent cognitive behaviors.

4.1. Trace fear conditioning and contextual fear extinction

Adolescent alcohol exposure affects numerous PFC-dependent memory tasks, including both contextual fear extinction and trace fear conditioning. Fear conditioning is a common learning paradigm in which subjects are trained to associate an initially neutral conditioned stimulus, such as a context or tone, with a naturally aversive unconditioned stimulus, like a mild footshock. This conditioning paradigm relies on similar neural regions in rodents and humans (Delgado *et al.*, 2006). In classical cued fear conditioning, the shock is presented during the auditory cue so that there is no gap between stimuli. Trace fear conditioning is a form of fear conditioning in which there is a temporal gap, or a trace interval, between the offset of the tone and the onset of the shock. This paradigm recruits PFC-dependent working memory processes in addition to HC-dependent declarative memory processes (Connor & Gould, 2016). Adolescent rats show more severe deficits in trace fear conditioning than adults when given acute alcohol before training in this task (Hunt & Barnet 2016). This contrasts what has been reported for contextual fear conditioning, in which subjects are trained to associate an aversive stimulus with the context in which they experienced that stimulus. Adolescent rats show less severe acute alcohol-induced contextual fear learning deficits than adults (Land & Spear, 2004; Broadwater & Spear 2013; Hunt & Barnet, 2016). Because trace fear conditioning is PFC-dependent and contextual fear conditioning is primarily HC-dependent (Connor and Gould 2016; Logue et al. 1997), increased

susceptibility to ethanol deficits in trace fear learning may suggest that the adolescent PFC is more susceptible than the adolescent HC to the effects of acute alcohol.

Fear extinction is a reduction in fear response after repeated re-exposure to the conditioning context or cue without co-exposure to the aversive stimulus. Contextual fear extinction depends on the PFC in addition to the HC and amygdala (Morgan *et al.*, 1993; Quirk & Mueller, 2008). Contextual fear extinction in adult rats has been shown to be impaired after intermittent alcohol exposure during adolescence (Broadwater & Spear, 2013). This demonstrates that contextual fear extinction is another PFC-dependent learning process that is impaired by adolescent alcohol exposure. Importantly, in this same study, cued fear extinction was not impaired by adolescent alcohol exposure. This could suggest that a region, such as the HC, that is engaged by contextual and not cued fear learning processes is responsible for observed contextual fear extinction deficits. It is possible that damage to the PFC acts in combination with damage to the HC to cause contextual fear extinction deficits. Because cued fear extinction is HC-independent (Phillips & LeDoux, 1992), it may be that damage to the PFC after adolescent alcohol exposure is insufficient to impair cued fear extinction. Contextual fear extinction can be used to understand the persistence of fear memories in anxiety disorders such as post-traumatic stress disorder (Milad *et al.*, 2006). If adolescent alcohol exposure reduces adult fear extinction (Broadwater & Spear, 2013), this could imply an increased susceptibility to anxiety disorders (Milad *et al.*, 2006). This is consistent with other pre-clinical findings suggesting that adolescent alcohol exposure can increase anxiety-like behaviors in adults (Pandey *et al.*, 2015; Kyzar *et al.*, 2016).

4.2. Object Recognition

Deficits in novel object recognition (NOR) after repeated adolescent alcohol treatment have been documented in numerous studies (Pascual *et al.*, 2007; Vetreno & Crews, 2015; Wolstenholme *et al.*, 2017). The NOR test measures time exploring novel and familiar objects to determine memory of the familiar; rodents will spend more time exploring novel objects. This is a valuable way to measure learning in a task that is neither aversive nor appetitive (Ennaceur & Delacour, 1988; Antunes & Biala, 2012). Variation in the timing between training and testing, herein referred to as the delay, can affect the neural circuitry involved in this task. It has been suggested that shorter delays require the PFC, while longer delays may depend more on the perirhinal cortex and HC (Warburton & Brown, 2015). Studies in rats have shown that lesions to the perirhinal cortex impairs NOR performance with delays longer than 5 minutes, but have little effect with a shorter NOR delay (Norman & Eacott, 2004). Other areas modulate related aspects of object recognition such as the entorhinal cortex, which may be involved in object-context associations (Wilson *et al.*, 2013). Alcohol can produce neurodegeneration of the entorhinal cortex (Obernier *et al.*, 2002), which suggests other parts of the circuitry involved in NOR could be disrupted. One study in mice tested both short (5 minute) and long (1 hour) delay NOR and found that only short-delay NOR showed a deficit in adulthood after adolescent alcohol exposure, suggesting that NOR deficits may be PFC-related (Wolstenholme *et al.*, 2017). Consistent with this finding, a study in rats using a short 1-minute delay also observed adult NOR deficits after adolescent alcohol treatment (Pascual *et al.*, 2007). While the neurocircuitry mediating NOR may not be fully characterized (Warburton & Brown, 2015), converging

evidence of deficits in PFC-mediated tasks after adolescent alcohol exposure (Coleman *et al.*, 2011; Vetreno *et al.*, 2012; Broadwater & Spear, 2013) suggests that alterations in PFC function may play a role in NOR deficits after adolescent alcohol exposure. These deficits can persist into adulthood (Wolstenholme *et al.*, 2017; Pascual *et al.*, 2007).

4.3. Cognitive flexibility and serial reaction time tasks

Rodent studies demonstrate that exposure to alcohol during adolescence leads to long-term deficits in PFC-dependent reversal learning (Coleman *et al.*, 2011; Vetreno & Crews, 2012). When tested in the Morris Water Maze, adult mice that were treated with alcohol during adolescence had deficits in reversal learning, or learning new escape conditions from a water maze (Coleman *et al.*, 2011). Deficits in adult mice and rats exposed to alcohol during adolescence have also been seen in Barnes maze reversal learning, where subjects re-learn escape conditions in a dry spatial maze (Vetreno & Crews, 2012; Coleman *et al.*, 2014). Set-shifting tasks, in which rodents are trained and then retrained to respond to different cues for food rewards, also serve as a measure of cognitive flexibility. Impairments in this task have been observed in adult rats treated with alcohol in adolescence (Gass *et al.*, 2014). The 5-choice serial reaction time task (5-CSRTT) can be used to assess impulsivity and cognitive flexibility in rodents (Robbins, 2002). Subjects are trained to nose-poke the location of light stimuli and are subsequently rewarded with food pellets, and their ability to sustain attention between different locations over numerous trials is assessed. The serial reaction time task is thought to be dependent on the PFC, cingulate cortex, and striatum (Robbins, 2002). Adult impairments in cognitive flexibility indicated by more timeout responses in the 5-CSRTT have also been observed after adolescent alcohol exposure in rats (Semenova, 2012). Reports of such deficits in maze reversal learning, set-shifting tasks, and the 5-CSRTT suggest that adolescent alcohol exposure can produce long-lasting deficits in reversal learning and cognitive flexibility.

Notably, impairments in cognitive flexibility have not been consistent across learning paradigms. Studies in rats using the 5-CSRTT have found that adult cognitive flexibility during this task is impaired (Semenova, 2012) or unaffected (Boutros *et al.*, 2017) after adolescent intermittent alcohol. Adult performance in the 2-choice reaction time task is actually improved after adolescent alcohol exposure (Slawecki, 2006). It has been suggested that the different performance seen between 5-choice and 2-choice reaction time tasks is related to task difficulty, as changing stimulus durations can change alcohol's effects on serial reaction time tasks (Semenova, 2012). The following section will discuss how changing task difficulty by introducing an acute alcohol challenge can influence performance in a serial reaction time task.

4.4. PFC-dependent cognition after adult acute alcohol challenge and prior adolescent alcohol exposure - Serial Reaction Time Task

Exposure to alcohol during adolescence can change susceptibility to acute alcohol-induced changes in adult cognitive faculties. Acute alcohol treatment in adult rats can impair attentional performance, increase impulsive responding, and decrease cognitive flexibility in the 5-CSRTT (Semenova, 2012). However, adults exposed to alcohol during adolescence have been reported to be less susceptible to acute alcohol-induced attentional impairments in

5-CSRTT. An acute alcohol exposure decreased correct responses and increased omissions in subjects with no history of prior alcohol exposure. However, in subjects that were treated intermittently with alcohol during adolescence, an acute alcohol exposure did not impair these measures of attentional performance. Without an alcohol challenge, subjects exposed to alcohol during adolescence demonstrated comparable numbers of omissions and correct responses to water-treated subjects (Semenova, 2012). This finding suggests that exposure to intermittent alcohol during adolescence can alter adult susceptibility to acute alcohol-induced cognitive deficits.

4.5. Summary of PFC-dependent learning

A converging body of evidence in rodent models suggests that repeated alcohol exposure during adolescence can impair PFC-dependent learning tasks in adulthood (Hunt & Barnet, 2016; Barnet & Spear, 2013; Pascual *et al.*, 2007; Vetreno & Crews, 2015; Wolstenholme *et al.*, 2017; Coleman *et al.*, 2011; Vetreno & Crews, 2012; Gass *et al.*, 2014; Semenova, 2012). Adult PFC-dependent cognitive behaviors after adolescent alcohol exposure are summarized in Table 1. These impairments have been observed primarily in assessments of novel object recognition (Pascual *et al.*, 2007; Vetreno & Crews, 2015; Wolstenholme *et al.*, 2017) or cognitive flexibility (Coleman *et al.*, 2011; Vetreno & Crews, 2012; Coleman *et al.*, 2014; Gass *et al.*, 2014; Semenova, 2012). These findings in rodents recapitulate the deficits in executive function seen in young adult humans after alcohol exposure during adolescence (Mahedy *et al.*, 2018), providing strong evidence that adolescent alcohol exposure has long-term effects on PFC function.

5. Adolescent alcohol effects on PFC structure and neurobiology

In both adult and adolescent humans, alcohol use has been associated with changes in PFC volume (Pfefferbaum *et al.*, 1997; De Bellis *et al.*, 2005; Medina *et al.*, 2008; Luciana *et al.*, 2013; Squeglia *et al.*, 2015). Studies in adult males and females after alcohol exposure have shown that alcohol use is associated with smaller PFC volume (Pfefferbaum *et al.*, 1997; Kubota *et al.*, 2001). Studies in adolescents have shown that alcohol can disrupt frontal cortical maturation (De Bellis *et al.*, 2005; Medina *et al.*, 2008; Luciana *et al.*, 2013; Squeglia *et al.* 2015; Pfefferbaum *et al.*, 2016; Pfefferbaum *et al.*, 2018). Frontal lobe maturation has been linked to adolescent performance in learning and memory tasks (Sowell *et al.*, 2001). Normal PFC development in adolescence consists of reductions in gray matter, due to pruning processes, and increases in white matter, due to increases in myelination (Giedd *et al.*, 1999; Pfefferbaum *et al.*, 2013; Pfefferbaum *et al.*, 2016; Pfefferbaum *et al.*, 2018). However, some report different patterns of white matter development, suggesting that PFC white matter volume remains consistent or decreases in a sex-dependent manner (Nagel *et al.*, 2006). Most studies report that adolescent alcohol users have reduced PFC volume (De Bellis *et al.*, 2005; Medina *et al.*, 2008; Luciana *et al.*, 2013), with reduced PFC white matter volume (De Bellis *et al.*, 2005; Medina *et al.*, 2008; Pfefferbaum *et al.*, 2018) and accelerated PFC gray matter reduction (Squeglia *et al.*, 2015; Pfefferbaum *et al.*, 2018). Medina and colleagues (2008) observe a sex difference in alcohol's impact on PFC volume, with adolescent females experiencing decreases and adolescent males experiencing increases in PFC volume after alcohol exposure. This sex difference is not observed in the longitudinal

study by Squeglia and colleagues (2015). Still, this potential sex difference calls for a more thorough investigation of the effects of adolescent alcohol exposure on learning in female human and rodent subjects. Converging reports of impaired adolescent PFC maturation after alcohol exposure suggest that altered PFC neurobiology likely contributes to altered cognitive performance observed after adolescent alcohol exposure (Brown *et al.*, 2000; Hanson *et al.*, 2011; Thoma *et al.*, 2012; Mahedy *et al.*, 2018).

Rodent studies have given some insight into the long-term neurobiological changes that occur after adolescent alcohol exposure. Functionally, studies have demonstrated that PFC synaptic transmission and intrinsic excitability are altered in adult subjects exposed to alcohol during adolescence (Kroener *et al.*, 2012; Trantham-Davidson *et al.*, 2017; Salling *et al.*, 2018). The medial PFC (mPFC) has important dopaminergic and GABAergic connections that undergo pruning during adolescence (Teicher *et al.*, 1995; Tseng & O'Donnell, 2006). Adolescent alcohol has been shown to interrupt this development, causing reduced dopamine D_1 receptor modulation of intrinsic firing and D_1 receptor modulation of evoked NMDA currents in prelimbic pyramidal cells. Fast-spiking interneurons also exhibited reduced intrinsic excitability and modulation by D_1 receptors. D_2 receptor function appeared to be unaffected by alcohol exposure (Trantham-Davidson *et al.*, 2017). Another recent study expanded upon these findings and demonstrated that adult mPFC pyramidal neurons also display reduced intrinsic excitability after adolescent alcohol exposure (Salling *et al.*, 2018). It is suggested that alcohol exposure may arrest normal development of intrinsic excitability during adolescence (Salling *et al.*, 2018).

Some evidence suggests that adult neuroimmune markers are dysregulated after adolescent alcohol exposure (Vetreno & Crews, 2012). Specifically, adult levels of high-mobility group box 1 and Toll-like receptors 3 and 4 were increased in adolescent alcohol-exposed adult rats (Vetreno & Crews, 2012). These findings are consistent with the known pro-inflammatory effects of alcohol treatment in adult rodents (Qin *et al.*, 2008). Inflammatory pathways are known to influence abundance of brain-derived neurotrophic factor (BDNF), an important contributor to neuroplasticity (Lapchak *et al.*, 1993). Importantly, persistent reductions in PFC BDNF have been reported in adult rodents after adolescent alcohol exposure (Fernandez *et al.*, 2016). However, another study reported that BDNF levels returned to normal after protracted abstinence (Fernandez *et al.*, 2017). While the duration of alcohol-induced BDNF alterations is unclear, it is possible that temporary reductions in BDNF levels could produce lasting downstream consequences. Both reductions in BDNF and altered inflammatory processes can impair learning and memory (Linnarsson *et al.*, 1997; Boitard *et al.*, 2014), making it likely that these neurobiological changes are linked to cognitive deficits seen after adolescent alcohol exposure.

In summary, in humans, adolescent alcohol exposure has been found to disrupt PFC maturation (De Bellis *et al.*, 2005; Medina *et al.*, 2008; Luciana *et al.*, 2013; Squeglia *et al.* 2015; Pfefferbaum *et al.*, 2016; Pfefferbaum *et al.*, 2018). Exposure to alcohol during adulthood has also been linked to reduced PFC volume (Pfefferbaum *et al.*, 1997; Kubota *et al.*, 2001). Rodent studies have shown that synaptic transmission and intrinsic excitability within the PFC are altered after adolescent alcohol exposure (Kroener *et al.*, 2012; Trantham-Davidson *et al.*, 2017; Salling et al. 2018). These findings suggest that adolescent

alcohol may halt or slow different aspects of PFC development, which could contribute to the persistent adolescent-like behavior, such as increased impulsivity, that is typically observed in adulthood after adolescent alcohol exposure (Spear & Swartzwelder, 2014). Increases in inflammatory markers and decreases in BDNF have also been reported in the PFC after adolescent alcohol exposure (Vetreno & Crews, 2012; Fernandez *et al.*, 2016; Fernandez *et al.*, 2017). Many or all of these neurobiological changes are likely to contribute to deficits in cognitive flexibility and working memory after adolescent alcohol exposure.

6. Rodent HC-mediated learning after adolescent alcohol exposure

The HC is an important component of spatial memory and memory consolidation processes (Smith & Milner, 1981). The HC and learning behaviors dependent upon this region are also affected by adolescent alcohol exposure (De Bellis *et al.*, 2000; Nagel *et al.*, 2005; Broadwater & Spear, 2013). The following sections examine the immediate and long-term effects of adolescent alcohol exposure on HC-related cognitive function.

6.1. Contextual fear conditioning

As described previously, contextual fear learning involves the association of an aversive stimulus with a context. It is known to be HC-dependent and impaired by alcohol in rodents (Logue *et al.*, 1997; Wehner & Radcliffe, 2004; Gould, 2003; Tipps *et al.*, 2015). Adolescent rats are less susceptible to HC-dependent contextual fear learning deficits after an acute alcohol challenge than adults (Land & Spear 2004; Broadwater & Spear, 2013; Hunt & Barnet, 2016). Cued fear learning, in which subjects associate an aversive stimulus with an auditory cue, is HC-independent (Kim & Fanselow, 1992; Logue *et al.*, 1997) and more resistant to alcohol-induced deficits in both adolescent and adult mice and rats, suggesting a HC-specific effect of alcohol on contextual fear conditioning (Gould, 2003; Broadwater & Spear, 2013). Adult contextual fear learning in rats has been shown to be impaired after early adolescent, and not adult, intermittent alcohol exposure (Broadwater & Spear, 2013). These findings suggest that, while adolescents may be less susceptible to acute alcohol-induced contextual learning deficits, they are more susceptible to long-term intermittent alcohol-induced contextual learning deficits in adulthood (Broadwater & Spear, 2013).

6.2. Object Recognition

As discussed in relation to PFC-dependent learning, chronic adolescent alcohol exposure can result in adult deficits in NOR (Pascual *et al.*, 2007; Vetreno & Crews, 2015; Wolstenholme *et al.*, 2017). One study found that these deficits were present after a short (5 minute) delay but not a long (1 hour) delay between NOR training and testing, suggesting that deficits in NOR can be attributed to the PFC and not the perirhinal cortex and HC (Wolstenholme *et al.*, 2017). In support of this, another study using long delays between training and testing (24 hours and 7 days) did not report adult rat NOR impairments after adolescent alcohol exposure (Fernandez & Savage, 2017). However, a different study using a long 24 hour delay reported adult rat NOR deficits after adolescent alcohol exposure (Vetreno & Crews, 2015). Notably, NOR performance in this study positively correlated to HC neurogenesis markers after adolescent alcohol exposure (Vetreno & Crews, 2015). This finding suggests a role for the HC in novel object recognition deficits caused by exposure to

alcohol during adolescence. Differences in alcohol treatments or NOR paradigms, such as the delay duration between training and testing, may contribute to differing reports of NOR performance after adolescent alcohol exposure.

Other object recognition tasks have been shown to be impaired in adulthood by adolescent alcohol exposure in rats (Swartzwelder *et al.*, 2015). Adolescent alcohol exposure caused adult deficits in a modified spatial-temporal object recognition task (stOR). In this task, training involves the introduction of two sets of objects one hour apart. One hour after the second set of objects is introduced, familiar objects from both sessions are reintroduced in old and new locations. Adult mice treated with alcohol during adolescence spent more time exploring the older objects than saline controls. Deficits were not seen in spatial task components, which could suggest that hippocampal learning was not affected by adolescent alcohol exposure. However, Swartzwelder and colleagues (2015) suggest that the complexity of temporal task components may have been required to expose alcohol-induced impairments. The idea that complex learning challenges are required to reveal deficits caused by adolescent alcohol exposure will be explored further in a later section.

6.3. Maze-learning

Other tasks have been used to assess HC-dependent learning after adolescent alcohol exposure. Conditional discrimination learning in a Y maze is a HC-dependent task in which rodents are trained to choose visually distinctive arms for food rewards (Murray & Ridley, 1999; Pascual *et al.*, 2007). Intermittent alcohol treatment during adolescence in rats has been shown to impair adolescent and adult performance in this task (Pascual *et al.*, 2007). Other studies have suggested that some HC-dependent learning is not affected by adolescent alcohol exposure. Radial arm maze learning, for example, assesses working memory by testing a rodent's ability to collect rewards from arms of a maze quickly without repeating entry into those arms. While many brain regions can contribute to this task, it is thought to be associated with HC function (Jarrard, 1993; Floresco *et al.*, 1997). In adult rats, radial arm maze learning has been reported to be unaffected by adolescent alcohol exposure using standard measures of learning (Risher *et al.*, 2013). Spontaneous alternation is another HC-dependent task in which rodents explore a maze and revisits into previous arms are recorded as a measure of memory (Johnson *et al.*, 1977). Spontaneous alternation in a plus maze during adulthood is not impaired by adolescent alcohol exposure in rats (Fernandez *et al.*, 2017). These findings suggest that adolescent alcohol may have task-specific effects on adult maze-learning, impairing some (Pascual *et al.*, 2007) but not other (Risher *et al.*, 2013; Fernandez *et al.*, 2017) maze-learning tasks.

The acquisition phase of the Morris Water Maze, in which rodents learn escape conditions, is also HC-dependent (Morris *et al.*, 1982). In rats, an acute alcohol exposure causes more severe Morris Water Maze acquisition deficits in adolescents than in adults (Markwiese *et al.*, 1998). However, inconsistent effects of intermittent adolescent alcohol exposure on water maze acquisition have been reported (Sircar *et al.*, 2009; Sircar & Sircar, 2005; Coleman *et al.*, 2011; Silvers *et al.*, 2006). While some studies in rats have reported adolescent and adult deficits in Morris Water Maze acquisition after adolescent intermittent alcohol treatment (Sircar *et al.*, 2009; Sircar & Sircar, 2005), other studies in rats and mice

have reported that intermittent alcohol does not affect this task in adolescents or adults (Coleman *et al.*, 2011; Silvers *et al.*, 2006). Similarly, learning spatial escape conditions of a dry Barnes maze in adulthood has also been reported to be unaffected after adolescent alcohol exposure in rats (Vetreno & Crews, 2012; Fernandez *et al.*, 2017). Differences in maze protocols or alcohol administration paradigms between laboratories may be responsible for these different effects.

6.4. HC-dependent cognition after adult acute alcohol challenge and prior adolescent alcohol exposure

Findings from studies in rats using acute alcohol challenges support the idea that adult learning deficits after adolescent alcohol may only be revealed during more complex learning tasks and challenges (Swartzwelder *et al.*, 2015; White *et al.*, 2006; Risher *et al.*, 2013). Some adult HC-dependent learning tasks are unaffected by adolescent alcohol exposure during normal conditions, but more sensitive to alcohol challenges during adulthood (White *et al.*, 2006; Risher *et al.*, 2013). Adult learning in a radial arm maze, for example, is typically unaffected by adolescent alcohol exposure (White *et al.*, 2006; Risher *et al.*, 2013), but an acute alcohol treatment prior to this task can impair learning (White *et al.*, 2006; Risher *et al.*, 2013). While adolescent alcohol exposure did not alter adult learning by itself in this task, it did increase adult vulnerability to an acute alcohol challenge in this same task (White *et al.*, 2006; Risher *et al.*, 2013). Contrary to these findings, it has also been reported that adolescent alcohol exposure protects adults from acute alcohol-induced learning impairments in the Morris Water Maze acquisition test. In rats that were treated with water during adolescence, an acute alcohol treatment in adulthood impaired memory acquisition in the Morris Water Maze. Subjects that were treated with alcohol throughout adolescence did not experience acute alcohol-induced acquisition impairments when tested one day after cessation of chronic alcohol treatment (postnatal day 50). However, this effect was reduced over time. When these subjects were challenged 12 days after cessation of intermittent alcohol treatment (postnatal day 62), they experienced acute alcohol-induced deficits similar to the intermittent water-treated group, suggesting that protection from acute alcohol-induced acquisition deficits caused by adolescent alcohol exposure may not be long-lasting (Silvers *et al.*, 2006).

It is unclear why adolescent alcohol exposure could decrease alcohol sensitivity in Morris Water Maze acquisition (Silvers *et al.*, 2006) and increase alcohol sensitivity in radial arm maze learning (White *et al.*, 2006; Risher *et al.*, 2013) when alcohol exposures occurred during similar age ranges between studies. One possible explanation is that intermittent alcohol exposure has different effects on acute alcohol sensitivity after brief or extended periods of abstinence from alcohol. Consistent with this idea, decreased adult sensitivity to an alcohol challenge on HC-dependent learning was reported 1 day after cessation of chronic treatment (Silvers *et al.*, 2006), no effect on learning was reported 12 days after chronic treatment (Silvers *et al.*, 2006), and increased sensitivity was reported 20 days after chronic treatment (White *et al.*, 2006; Risher *et al.*, 2013). This would suggest that a history of intermittent alcohol exposure in adolescence can make adults differentially susceptible to acute alcohol-induced cognitive deficits, depending on the time elapsed since adolescent alcohol treatment.

6.5. Summary of HC-dependent learning

Studies consistently report that adolescents are less susceptible to acute alcohol-induced contextual learning deficits than adults (Land & Spear, 2004; Broadwater & Spear, 2013; Hunt & Barnet, 2016). Intermittent alcohol exposure during adolescence can also produce long-term contextual learning deficits (Broadwater & Spear, 2013). While the role of the HC in NOR is debated (Warburton & Brown, 2015), it is clear that adult performance in this learning task can also be affected by adolescent alcohol exposure (Pascual *et al.*, 2007; Vetreno & Crews, 2015; Wolstenholme *et al.*, 2017). It has been reported that exposure to alcohol during adolescence can alter sensitivity to acute alcohol challenges on HC-dependent learning tasks in adulthood (White *et al.*, 2006; Risher *et al.*, 2013; Silvers *et al.*, 2006), with sensitivity increasing over time. Effects of adolescent alcohol exposure on other HC-dependent tasks are inconsistent (Pascual *et al.*, 2007; Risher *et al.*, 2013; Fernandez *et al.*, 2017; Sircar *et al.*, 2009; Sircar & Sircar, 2005; Coleman *et al.*, 2011; Silvers *et al.*, 2006). Adult HC-dependent learning after adolescent alcohol exposure is summarized in Table 2. These findings suggest that alcohol's long-term effects on the HC may be more nuanced or less robust than its previously discussed effects on the PFC.

7. Adolescent alcohol effects on HC structure and neurobiology

In humans, alcohol use during adulthood and adolescence has been associated with smaller HC volumes (De Bellis *et al.*, 2000; Nagel *et al.*, 2005). A recent longitudinal study in college students found that a greater alcohol use index was associated with an accelerated decline of HC and para-hippocampal gray matter volume. This decline was associated with poor performance in the California Verbal Learning Test (Meda *et al.*, 2018). These findings importantly suggest a causal link between alcohol use and decreased HC volume. It is important to note that some studies report no association between HC volume and alcohol dependence (Lee *et al.*, 2007; Fein *et al.*, 2013). One recent meta-analysis suggests that the inconsistency between adult studies may be due to variability in sample sizes and a small effect size (Wilson *et al.*, 2018). The study also found that the association of problematic alcohol use with reduced HC volume increases with age. As older subjects have generally been using alcohol for longer periods of time, this likely suggests that longer duration of alcohol use leads to more severe HC injury. Alternatively, an increased susceptibility to alcohol damage with age could suggest that adolescents are less sensitive than adults to alcohol-induced HC damage (Wilson *et al.*, 2018).

Rodent studies have suggested mechanisms responsible for HC damage after alcohol exposure. HC-related learning deficits are often attributed to reductions in HC neurogenesis or increased HC cell death (Vetreno & Crews, 2015) and alterations in cholinergic signaling (Mohapel *et al.*, 2005). Cholinergic signaling from the basal forebrain is critical for learning and memory processes (Blokland, 1995; Mohapel *et al.*, 2005). It has been shown that intermittent alcohol exposure during adolescence can lead to a reduction of cholinergic markers in the basal forebrain (Ehlers *et al.*, 2011; Vetreno *et al.*, 2014; Vetreno *et al.*, 2018). This reduction may indicate reduced cholinergic signaling to the HC after exposure to alcohol during adolescence, which could underlie some alcohol-induced learning deficits.

Reductions in neurogenesis have also been linked to alcohol-induced learning deficits (Vetreno & Crews, 2015). Numerous reports have shown that adolescent or adult alcohol exposure can alter adult HC neurogenesis (Vetreno & Crews, 2015; Sakharkar *et al.*, 2016; He *et al.*, 2005). The adolescent brain is particularly vulnerable to alcohol-induced reductions in neurogenesis (Crews *et al.*, 2006) and therefore likely to be more vulnerable to behavioral consequences associated with changes in neurogenesis. Consistent with this idea, it has been shown that adult HC neurogenesis after adolescent alcohol exposure positively correlates with performance in an object recognition memory task (Vetreno & Crews, 2015). However, findings have been inconsistent as to whether adolescent alcohol affects adult neurogenesis. Some studies show decreases in adult neurogenesis and cell proliferation (Vetreno & Crews, 2015; Sakharkar *et al.*, 2016), while some show no effects of adolescent alcohol on adult cell proliferation (Broadwater *et al.*, 2014). Broadwater and colleagues found decreases in doublecortin, a marker of neurogenesis, that they attributed to increases in death of immature neurons and not decreases in neurogenesis itself (2014). Differences in reports of cell proliferation may be attributed to differences in alcohol administration paradigms. Those that reported decreases in cell proliferation used two-day on/two-day off treatment patterns (Vetreno & Crews, 2015; Sakharkar *et al.*, 2016), while Broadwater and colleagues (2014) administered alcohol every 48 hours. Different findings of altered cell proliferation after unique alcohol treatment paradigms could imply that the patterns of alcohol exposure may differentially influence adult cell proliferation in the HC.

HC neuronal loss is seen in adult rodents treated with alcohol during adolescence, and this cell death is thought to play a role in adult cognitive deficits after adolescent alcohol (Risher *et al.*, 2015). Glutamate toxicity could contribute to observed cell death (Olney, 1969; Choi, 1992). In support of this idea, rodent electrophysiological studies have shown that adolescent intermittent alcohol can increase NMDA receptor-mediated currents in HC CA1 pyramidal cells (Swartzwelder *et al.*, 2017). Adolescent intermittent alcohol can also lower the threshold for the induction of HC long-term potentiation (Risher *et al.*, 2015). These changes could drive neuronal loss after adolescent alcohol through increased glutamate signaling at potentially toxic levels.

Human studies have demonstrated that adolescent alcohol exposure can lead to reductions in adolescent and adult HC volume (De Bellis *et al.*, 2000; Nagel *et al.*, 2005). Rodent studies have suggested that impaired cholinergic input (Ehlers *et al.*, 2011; Vetreno *et al.*, 2014; Vetreno *et al.*, 2018), reduced neurogenesis and cell proliferation (Vetreno & Crews, 2015; Sakharkar *et al.*, 2016; He *et al.*, 2005), and cell death (Risher *et al.*, 2015) may contribute to damaged adult HC after adolescent alcohol exposure. These biological changes in adulthood likely contribute to impairments in HC-dependent learning. Reduced HC volume after alcohol in adolescence has been linked to poor performance in verbal learning tasks (Meda *et al.*, 2018), and neurogenesis after adolescent alcohol in rodents has been positively correlated to performance in object recognition memory task (Vetreno & Crews, 2015). These findings suggest that adolescent alcohol exposure can cause long-lasting HC damage, and this is likely related to reported deficits in HC-dependent cognitive behaviors.

8. Important mediating factors of adolescent alcohol's long-term effects

As outlined within this paper, adolescent alcohol exposure has the potential to affect a range of learning phenotypes. Converging evidence points to the PFC and HC as potential mediators of these effects. Broadly, deficits in adult PFC-related cognitive flexibility have been reported after adolescent intermittent alcohol exposure (Coleman *et al.*, 2011; Vetreno *et al.*, 2012; Broadwater & Spear, 2013). Adult HC-dependent cognitive impairments after adolescent alcohol exposure have also been reported, but these findings are inconsistent between studies (Pascual *et al.*, 2007; Risher *et al.*, 2013; Fernandez *et al.*, 2017; Sircar *et al.*, 2009; Sircar & Sircar, 2005; Coleman *et al.*, 2011; Silvers *et al.*, 2006). Detection of persistent deficits in HC-dependent learning after adolescent alcohol exposure seems to be largely dependent upon task and treatment paradigms. Variation in abstinence periods prior to learning assessment, administration patterns, and age of treatment likely contribute to inconsistent reports of HC-related learning deficits.

Studies in human subjects have shown that alcohol abstinence in alcohol-dependent individuals can improve working memory impairments caused by alcohol use (Petit *et al.*, 2017). Adolescents and young adults may be more likely to recover cognitive abilities after abstinence than older alcohol-dependent subjects, suggesting that age and alcohol abstinence duration may interact to mediate long-term consequences of alcohol use (Munro *et al.*, 2000; Tapert *et al.*, 2002). Rodent models also demonstrate that alcohol-induced cognitive impairments can be attenuated over time. A study in alcohol-dependent rats found that binge-like alcohol exposure caused deficits in spatial and recognition memory one week after treatment. Ten weeks after treatment, spatial memory impairments persisted, while recognition memory normalized to that of water-treated rats (Cippitelli *et al.*, 2010). These findings suggest that the impact of an alcohol abstinence period on the recovery of cognitive function can vary depending on the learning task and neural circuitry employed in the task. This may explain some inconsistencies between studies that find persistent cognitive impairments (Broadwater & Spear, 2013; Pascual *et al.*, 2007; Coleman *et al.*, 2011; Coleman *et al.*, 2014; Vetreno & Crews, 2012; Gass *et al.*, 2014; Vetreno &Crews, 2015; Wolstenholme *et al.*, 2017) or lack thereof (Slawecki, 2006; Boutros *et al.*, 2017) after adolescent alcohol exposure.

The term "intermittent" has been used to describe a variety of alcohol treatment paradigms. Some common alcohol treatment patterns include treatments once every 24 hours (Sircar *et al.*, 2009; Coleman *et al.*, 2011), once every 48 hours (Broadwater & Spear, 2013; White *et al.*, 2006; Silvers *et al.*, 2006), and once daily for two consecutive days followed by two abstinent days (Pascual *et al.*, 2007; Vetreno & Crews, 2012; Coleman *et al.*, 2014; Fernandez & Savage, 2017). However, the period of abstinence between alcohol exposures has been shown to be critical in determining the severity of adult phenotypes (Tapert *et al.*, 2002). For example, it has been reported that intermittent and chronic alcohol exposure paradigms can differentially affect later alcohol-related behaviors. Specifically, in adult and adolescent rodents, intermittent alcohol access patterns produce greater elevations in alcohol intake than chronic alcohol access patterns (Wise, 1973; Tomie *et al.*, 2006; Melendez, 2011; Kimbrough *et al.*, 2017). This effect is greater in adolescent subjects than in adult subjects (Melendez, 2011). While differential escalation effects may be attributed to factors specific

to voluntary alcohol drinking, such as conditioned taste aversion, other potential mediators such as acute withdrawal effects could be broadly relevant to behavioral changes reported after other intermittent alcohol exposure paradigms (for review, see Spear, 2020). These periods of acute alcohol withdrawal, and not just the periods of alcohol administration by themselves, are major causes of altered neurobiology that is linked to learning impairments. Decreases in neurogenesis, for example, can be caused by acute alcohol withdrawal (Nixon & Crews, 2002). While alcohol can be damaging in many ways, variation in acute alcohol withdrawal duration during alcohol administration paradigms undoubtedly produces variation in the severity of these phenotypes. This finding highlights the importance of alcohol administration patterns in determining alcohol's long-term effects.

Another explanation for inconsistent reports of learning deficits after adolescent alcohol exposure is the variable timing of adolescent alcohol exposure. It has been posited that adolescence consists of separable periods of vulnerability based on the brain regions that are differentially developing during those periods (Spear, 2015). Effects of alcohol on contextual fear conditioning, for example, can be variable depending on the stage of adolescence in which rats are exposed to alcohol. Intermittent alcohol exposure during early adolescence can impair adult contextual fear retention. Exposure during mid-late adolescence, however, leaves contextual fear retention unaffected while impairing contextual fear extinction (Broadwater & Spear, 2013). This may suggest that the HC is more vulnerable during early adolescence, while other regions that mediate fear extinction, such as the PFC, are vulnerable during late adolescence (Spear, 2015). This is consistent with current understanding of adolescent brain development, as the PFC is more plastic during late adolescence.

9. Conclusion

Overall, adolescent alcohol exposure has detrimental effects on brain development that translate into potential later life psychological challenges. These effects are not equal across behaviors and brain regions. Long-term cognitive deficits are associated with adolescent alcohol exposure, and PFC-dependent tasks are particularly sensitive to this effect. This most likely relates to the late developmental maturation of the PFC (Giedd et al., 1999; Sowell et al., 1999; Gogtay et al., 2004). Because the PFC is involved in executive function, this also suggests increased risk for mental health problems and antisocial behavior associated with executive function deficits (Morgan & Lilienfeld, 2000; Ogilvie *et al.*, 2011; Brower & Price, 2011; Willcutt *et al.*, 2005). Both adult mental health problems and antisocial behaviors are associated with adolescent alcohol use (Rohde *et al.*, 2001; Brière *et al.*, 2014).

Adolescent alcohol exposure can lead to impaired PFC morphology (Pfefferbaum *et al.*, 1997; De Bellis *et al.*, 2005; Medina *et al.*, 2008), PFC neurobiology (Vetreno & Crews, 2012; Fernandez *et al.*, 2017; Fernandez *et al.*, 2018), and PFC-related learning and cognition (Coleman *et al.*, 2011; Vetreno & Crews, 2012; Coleman *et al.*, 2014; Broadwater & Spear, 2013). Adolescent alcohol exposure can also produce impaired HC morphology (De Bellis *et al.*, 2000; Nagel *et al.*, 2005), HC neurobiology (Broadwater *et al.*, 2014; Risher *et al.*, 2015; Vetreno & Crews, 2015; Sakharkar *et al.*, 2016), and HC-related learning (Broadwater & Spear, 2013; Swartzwelder *et al.*, 2015; White *et al.*, 2006; Risher *et al.*,

2013). Impaired adult learning is sometimes reported as being more severe after adolescent alcohol exposure than after adult alcohol exposure (Broadwater & Spear, 2013; Markweise *et al.*, 1998; White *et al.*, 2006). Lasting HC-dependent learning impairments after adolescent alcohol exposure are not reported in all studies (Broadwater & Spear, 2013; Vetreno & Crews, 2015; Wolstenholme *et al.*, 2017; Fernandez & Savage, 2017; Swartzwelder *et al.*, 2015; White *et al.*, 2006; Risher *et al.*, 2013; Pascual *et al.*, 2007; Markwiese *et al.*, 1998; Silvers *et al.*, 2006; Sircar *et al.*, 2009; Sircar & Sircar, 2005; Coleman *et al.*, 2011). Some cognitive consequences of adolescent alcohol exposure have been shown to improve over prolonged abstinence (Cippitelli *et al.*, 2010; Munro *et al.*, 2000; Tapert *et al.*, 2002; Petit *et al.*, 2017), suggesting that duration of abstinence period before behavioral testing may account for variable findings between studies. Intermittent alcohol exposure patterns also vary between studies (Sircar *et al.*, 2009; Broadwater & Spear, 2013; Fernandez & Savage, 2017), creating differences in the amount of alcohol, duration of exposure, and number of alcohol withdrawal periods to which subjects are exposed. Additionally, behaviors dependent upon brain regions that develop at different rates throughout adolescence may be differentially susceptible to alcohol's harmful effects (Broadwater & Spear, 2013; Spear, 2015). Therefore, timing of exposure may play a critical role in determining the nature and severity of alcohol's cognitive consequences. These relevant mediating factors highlight the importance of continued study in this field. Overall, alcohol exposure during adolescence is problematic because it has been shown to impair adolescent and adult cognitive functioning and associated neural substrates (Brown *et al.*, 2000; Hanson *et al.*, 2011; Thoma *et al.*, 2012; Mahedy et al. 2018). Further exploration of how abstinence, adolescent age of exposure, and intermittence patterns mediate alcohol's effects will determine risk factors for long-term consequences of drug use. This will ultimately inform prevention and treatment plans for affected individuals.

Acknowledgements

This publication was supported, in part, by the National Institutes of Health (T32GM108563) and the Jean Phillips Shibley Endowment (T.J.G.). We would like to thank Dr. Janine Kwapis for her detailed review of this manuscript.

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Highlights

- Alcohol use during adolescence can have negative behavioral consequences
- Adolescent alcohol exposure impairs short- and long-term cognitive function
- Prefrontal biology and cognition are consistently impaired by adolescent alcohol
- Hippocampal learning and biology are also damaged by adolescent alcohol exposure
- Relevant human and rodent studies are summarized in this review article

Table 1:

Summary of adult PFC-dependent learning after adolescent alcohol exposure.

Species	Sex	Strain	Behavior	Dose	Treatment pattern	Treatment Duration	Adolescent age of treatment	Abstinence duration before testing	Age of testing	Effect on Learning	Paper
Rat	M	Sprague-Dawley	Context extinction	4 g/kg	Every 48 hours	21 days	PND 35–55	22 days	PND 70–90	Impaired	Broadwater and Spear 2013
Rat	M	Sprague-Dawley	Cued extinction	4 g/kg	Every 48 hours	21 days	PND 28–48	22 days	PND 70–90	No effect	Broadwater and Spear 2013
Rat	not listed	Wistar	NOR (1 min delay)	3 g/kg	2-day on/2-day off	14 days	PND 25–38	2 days and 22 days	PND 41 and 61	Impaired	Pascual et al. 2007
Mouse	M+F	DBA/2J	NOR (5 min delay)	4 g/kg	2-day on/2-day off	14 days	PND 29–42	24 days	PND 66+	Impaired	Wolstenholme et al. 2017
Mouse	M	C57BL/6 (Charles River)	MWM reversal learning	5 g/kg	Daily	10 days	PND 28–37	23 days	PND 60–72	Impaired	Coleman et al. 2011
Mouse	M	C57BL/6 (Charles River)	Barnes maze reversal	5 g/kg	2-day on/2-day off	10 days	PND 28–37	31 days	PND 68–91	Impaired	Coleman et al. 2014
Rat	M	Wistar	Barnes maze reversal	5 g/kg	2-day on/2-day off	31 days	PND 25–55	9 days	PND 64–75	Impaired	Vetreno and Crews 2012
Rat	M	Long-Evans	Set shifting	N/A, vapor	2-day on/2-day off	13 days	PND 28–41	49 days	PND 90	Impaired	Gass et al. 2014
Rat	M	Wistar	5-CSRTT	5 g/kg	Every 8 hours	4 days	PND 33–36	24 days	PND 60+	Impaired	Semenova 2012
Rat	M	Wistar	5-CSRTT	5 g/kg	2-day on/2-day off	30 days	PND 28–57	8 days	PND 65+	No effect	Boutros et al.2017
Rat	M	Sprague-Dawley	2-CRTT	N/A, vapor	Daily	14 days	PND 30–43	7 days	PND 50	Improved	Slawecki 2006
Rat	M	Sprague-Dawley	Set shifting	5 g/kg	2-day on/2-day off	30 days	PND 25–54	~21 days	PND 70–120	Impaired	Fernandez and Savage 2017

Table 2:

Summary of adult HC-dependent learning after adolescent alcohol exposure.

Species	Sex	Strain	Behavior	Dose	Treatment pattern	Treatment Duration	Adolescent age of treatment	Abstinence duration before testing	Age of testing	Effect on Learning	Paper
Rat	M	Sprague-Dawley	Contextual FC	4 g/kg	Every 48 hrs	21 days	PND 28–48	22 days	PND 70–90	Impaired	Broadwater and Spear 2013
Rat	M	Sprague-Dawley	Contextual FC	4 g/kg	Every 48 hrs	21 days	PND 35–55	22 days	PND 70–90	No effect	Broadwater and Spear 2013
Rat	M	Wistar	NOR (24 hr delay)	5 g/kg	2-day on/2-day off	31 days	PND 25–55	108 days	PND 163–165	Impaired	Vetreno and Crews 2015
Mouse	M+F	DBA/2J	NOR (1 hr delay)	4 g/kg	2-day on/2-day off	14 days	PND 29–42	24 days	PND 66+	No effect	Wolstenholme et al. 2017
Rat	M	Sprague-Dawley	NOR (24 hr and 7 day delay)	5 g/kg	2-day on/2-day off	30 days	PND 25–54	~21 days	PND 70–120	No effect	Fernandez and Savage 2017
Rat	M	Sprague-Dawley	Spatial-temporal object recognition task (stOR)	5 g/kg	2-day on/1 to 2-day off	16 days	PND 30–45	25 days	PND 70	Impaired	Swartzwelder et al. 2015
Rat	M	Sprague-Dawley	Radial arm maze	5 g/kg	Every 48 hrs	20 days	PND 30–49	20 days	PND 59	No effect	White et al. 2006
Rat	M	Sprague-Dawley	Radial arm maze	5 g/kg	2-day on/2-day off	20 days	PND 30–49	20 days	PND 71+	No effect	Risheret al. 2013
Rat	not listed	Wistar	Conditional discrimination (Y-maze)	3 g/kg	2-day on/2-day off	14 days	PND 25–38	2 days and 22 days	PND 41 and 61	Impaired	Pascual et al. 2007
Rat	M	Sprague-Dawley	MWM acquisition	5 g/kg	Every 48 hrs	20 days	PND 30–48	No abstinence	PND 29–43	No effect	Silvers et al. 2006
Rat	F	Sprague-Dawley	MWM acquisition	2 g/kg	Daily	5 days	PND 30–34	No abstinence	PND 30–34	Impaired	Sircar et al. 2009
Rat	M	Sprague-Dawley	MWM acquisition	2 g/kg	Daily	5 days	PND 30–34	No abstinence	PND 30–34	Impaired	Sircar and Sircar 2005
Mouse	M	C57BL/6J	MWM acquisition	5 g/kg	Daily	10 days	PND 28–37	23 days	PND 60–72	No effect	Coleman et al. 2011
Rat	M	Wistar	Barnes maze acquisition	5 g/kg	2-day on/2-day off	31 days	PND 25–55	9 days	PND 64–75	No effect	Vetreno and Crews 2012
Rat	M	Sprague-Dawley	Barnes maze acquisition	5 g/kg	2-day on/2-day off	30 days	PND 25–54	~21 days	PND 70–120	No effect	Fernandez and Savage 2017
Rat	M	Sprague-Dawley	Spontaneous alternation	5 g/kg	2-day on/2-day off	30 days	PND 25–54	~21 days	PND 70–120	No effect	Fernandez and Savage 2017