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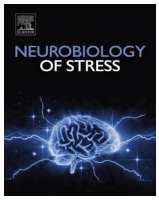

Alcohol and stress exposure across the lifespan are key risk factors for Alzheimer's Disease and cognitive decline

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ABSTRACT

Alzheimer's Disease and related dementias (ADRD) are an increasing threat to global health initiatives. Efforts to prevent the development of ADRD require understanding behaviors that increase and decrease risk of neurodegeneration and cognitive decline, in addition to uncovering the underlying biological mechanisms behind these effects. Stress exposure and alcohol consumption have both been associated with increased risk for ADRD in human populations. However, our ability to understand causal mechanisms of ADRD requires substantial preclinical research. In this review, we summarize existing human and animal research investigating the connections between lifetime stress and alcohol exposures and ADRD.

1. Introduction

Alzheimer's disease (AD) is currently the sixth leading cause of death in the United States (Skaria, 2022), with an anticipated doubling of the rate of diagnoses in the next few decades (Alzheimer's Disease Facts and Figures, 2022). A clinical diagnosis of AD can include a range of major to minor neurocognitive impairments, depending on how symptoms (including cognitive decline one to two standard deviations from the mean on a formal assessment of cognition) interfere with one's ability to live independently (Diagnostic and Statistical Manual of Mental Disorders, 2023). While AD has a clear genetic risk factor and some pathological markers of the disorder such as amyloid beta peptide (Aβ) aggregation and neurofibrillary tangles have been identified, it still remains a major unsolved brain disorder (Goedert and Spillantini, 2006). In the United States, The Department of Health and Human Services (HHS) has instituted a National Plan to Address Alzheimer's Disease (2023) with six overarching goals to prevent future AD and cognitive decline as well as to better serve families coping with AD and related dementias (ADRD). This initiative includes a focus on promoting healthy aging and reducing risk factors for ADRD. However, accomplishing this goal will take a comprehensive understanding of the genetic, environmental, and societal risk factors that contribute to the development of ADRD – which can occur decades before disease onset. Here, we review how two major risk factors – alcohol consumption and stress exposure – interact across the lifespan to influence healthy aging and cognition. We summarize major evidence for the interacting risks of alcohol and stress on cognitive decline in both clinical work and animal models as well as provide suggestions for future avenues of research.

Alcohol and stress exposure can each have immense ramifications at the individual and societal levels. Alcohol is thought to account for over $250 billion in societal costs in the United States per year (CDC, 2019), with 1 in 8 deaths attributable to alcohol (Esser et al., 2022). Comparable yearly costs of about $300 billion per year are attributed to stress (American Psychological Association, 2017) – without even considering their compounding and synergistic effects. Stress and alcohol use can have a bidirectional relationship at all stages of the human lifespan, and both stress and alcohol consumption have been further exacerbated during the global COVID-19 pandemic (Barbosa et al., 2021). While stress exposure may influence the likelihood of both alcohol use and alcohol relapse, alcohol use can also change the response to stressful

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experiences. In some cases, these effects can be modulated by biological sex, gender, and mood, but this can be inconsistent across age groups. It is important to note that there are neural adaptations to repeated drug use, and because of this, stress and drug interactions can also vary with different stages of drug use such as initial use, continuation, withdrawal, and relapse (Koob, 2017). Thus, the relationship between stress and alcohol use is complex and varies across the lifespan. The following sections review literature examining the relationships between stress and alcohol use in humans and animal models. Importantly, though meaningful and comprehensive correlational assessments have been conducted, very little neurobiological work on the relationship between alcohol use, stress, and cognitive decline has been conducted in humans.

Some human studies have begun uncovering the contributions of alcohol and stress to neurodegeneration in patients and post-mortem brain tissue. Necropsies of chronic alcohol users have revealed significant atrophy of white matter (de la Monte, 1988; Harper et al., 1985). Mixed results have been seen regarding the effects of alcohol consumption on other markers of AD – while recent studies have replicated the previous findings of a relationship between alcohol and white matter lesions, they do not see significant Aβ deposits via PET scan with alcohol consumption in patients not diagnosed with clinical dementia (Koch et al., 2020). Some work has shown no correlation between beer consumption and Aβ (Kok et al., 2016). Though this study only evaluated men, it did also replicate findings of genetic risk for Aβ development. It is likely that a causal link between alcohol and AD is more complicated than just alcohol's effects on Aβ pathology. For example, a strong emerging line of evidence is linking the relationship between alcohol and pathological Aβ to neuroinflammation (Venkataraman et al., 2017).

In addition to biological markers, alcohol use has been associated with negative behavioral and cognitive outcomes related to ADRD. Some evidence suggests that heavy alcohol drinking can accelerate the onset of AD, with one study showing that a history of heavy drinking (>2 drinks per day) among individuals diagnosed with AD was associated with earlier onset of the disease by 4 years relative to those who consumed fewer than 2 drinks per day (Harwood et al., 2010). In this same study, the effect of drinking was exacerbated among patients with a genetic predisposition for AD (APOE genotype). Among individuals diagnosed with AD, faster rates of cognitive decline have been reported among heavy drinkers relative to abstainers and mild-moderate drinkers (Heymann et al., 2016). Thus, heavy alcohol use can lead to an accelerated onset and progression of AD – an effect that is worsened when combined with genetic risk factors. More broadly, alcohol use is also a risk factor for developing dementia. A large retrospective cohort study was conducted using discharge data from French national hospitals, analyzing the relationship between alcohol-related diagnoses and later diagnoses of dementia (Schwarzinger et al., 2018). They found a strong association between early onset dementia (diagnosis before age 65) and alcohol use. Additionally, this study found alcohol use to be significantly associated with other risk factors for dementia onset, such as tobacco smoking, obesity, high blood pressure, hyperlipidemia, diabetes, and cerebrovascular disease.

The consensus from the human literature is that the complicated relationship between stress and alcohol experiences favors maladaptive outcomes related to cognitive decline and neurodegeneration later in life. Stress can precipitate alcohol use and vice versa, but the details of this depend on a long list of moderators including genetics, sex and gender, social environment, and mood. This is further complicated by the distinct stages of alcohol use and addiction that can influence stressors, along with the variety of types of stressors that exist and the stage of life during which these experiences occur. Such complications make it difficult to fully understand the complexities and mechanisms of stress and alcohol effects on neurocognitive outcomes in humans, much of which is only available as a retrospective analysis. Importantly, such analyses do not provide a route to understanding the underlying biological changes and mechanisms involved. Thus, animal models of stress and alcohol use are necessary to better understand the neurobiological underpinnings of neurodegenerative diseases that develop across the lifespan. Here, we review the effects of alcohol, stress, and combined alcohol and stress on cognitive outcomes in both human and rodent models, and at distinct timepoints in development. Importantly, when reviewing the human literature, language specific to the original manuscripts regarding sex and gender are recapitulated here (and further addressed in the discussion).

2. Adolescents

2.1. Overview of adolescence

Adolescence is a period of development in part characterized by increased risk-taking and greater social association with peer groups (Nelson et al., 2005; Steinberg, 2004). For many adolescents, the combination of peer influence and elevated risk-taking promotes drug use, including alcohol consumption (Loke and Mak, 2013; Ohannessian and Hesselbrock, 2007). Adolescence is also a critical period of brain development (Larsen and Luna, 2018), due to the sensitive neurobiological, morphological, and connectivity changes that occur in the developing cortex. These neurodevelopmental processes, which often must occur at a fixed point in development, may be uniquely vulnerable to disruption by external stimuli, such as drug use or social stressors - making adolescence a sensitive period of development during which alcohol and stress can disrupt the growth and maturation of an already vulnerable cortex.

Approximately 21% of adolescents of ages 14–15 report having consumed at least one alcoholic drink sometime in their lives (SAMHSA, 2023), with the likelihood of alcohol consumption increasing substantially in late adolescence. A study conducted over the course of two decades (1991–2011) found that approximately 70% of 12th grade students reported alcohol use in the past 12 months, and around 30% of students reported having been drunk in the past 30 days (Patrick and Schulenberg, 2014). Importantly, the gender gap in alcohol consumption has narrowed in recent years with increasing rates of consumption among women, with women already at a greater risk of developing ADRD (White et al., 2015). Because of this, it is important to consider how early life (adolescent) exposure to alcohol and stress contributes to long-term brain health and behavior. In both clinical and preclinical studies adolescents tend to drink more than adults per occasion. This can be associated with maturational and developmental events occurring in the adolescent brain (Spear, 2018). Since adolescence is a critical period, stress and alcohol consumption during this time can have detrimental and long-lasting effects. Our ability to study this in longitudinal human studies, and with biological depth, is limited, so rodent studies are of particular importance for addressing these questions.

Most mammal species, including rodents, experience a developmental period with parallels to human adolescence (Laviola et al., 2003). Rodents exhibit adolescent-like characteristics similar to humans around their second month of development (Laviola et al., 2003; Marco et al., 2011; Spear, 2000). Like humans, rodents in this period of development exhibit increased interest in social interactions (Panksepp, 1981) and increased risk-taking behavior (Laviola et al., 2003), including elevated alcohol consumption (Tambour et al., 2008). Many preclinical studies examine stress and alcohol effects on rodents during this developmental period to better understand the biological underpinnings of adolescent vulnerabilities and use a wide variety of stress and alcohol models (Burke and Miczek, 2014; Crowley et al., 2019).

Both human and rodent adolescents are more prone to binge-like alcohol consumption patterns than adults. This is clear in clinical studies (Patrick and Schulenberg, 2014) and mirrored in pre-clinical research, where adolescent rodents often consume more alcohol per session than adults (Tambour et al., 2008). In the human literature, some of this has been attributed to adolescent vulnerability to social pressures, as the perception that parents, friends, and members of an individual's social groups are consuming large quantities of alcohol is a

risk factor for adolescent binge drinking (Haugland et al., 2012; Scholly et al., 2014; Van Damme et al., 2016). Adolescents are also more prone to risk-taking in general, further supporting risky drug use (Steinberg, 2004). In addition, clinical and preclinical research supports the idea that adolescents may feel more positive short-term effects of alcohol (Pautassi et al., 2008; Spear, 2014). Adolescents may also be less sensitive to the unpleasant symptoms of hangovers (Varlinskaya and Spear, 2004) and alcohol's sedative effects (Moy et al., 1998; Silveri and Spear, 1998). All of these factors (social and biological) support problematic patterns of binge drinking among adolescents.

Adolescents also experience unique stressors compared to adults, in part due to the unique social changes that happen during this period of development. For example, a longitudinal assessment found that conflicts with parental figures were a common source of stress among younger adolescents (15 years old on average), but this was significantly reduced at follow-up one year later (average age over 16) in the same subjects (Timko et al., 1993). Others report a similar reduction in family conflict in later adolescence (Montemayor, 1983). This is likely related to the typical pattern of development where peer relationships become more important throughout adolescence, likely drawing attention away from family conflicts as peer conflicts develop. Animal models effectively mimic these unique adolescent social stressors through paradigms involving chronic variable social stressors (mixed novel cage mates and solo housing), social defeat paradigms, and physical restraint stress (for review, see Burke and Miczek, 2014).

In summary, the adolescent period, due in part to rapid brain development and to specific behavioral and social conditions, may be uniquely vulnerable to stress and alcohol. This is further complicated by how stress and alcohol exposures may interact during this stage of life.

2.2. Adolescent stress and alcohol interactions

Adolescent stress is consistently associated with both initiation (Dube et al., 2006) and use of alcohol (Hussong and Chassin, 1994). Studies report associations between alcohol consumption and strained social relationships, negative life events, family conflict, unemployment, and parental neglect among youth and adolescents (Baer et al., 1987; Gebeyehu and Srahbzu Biresaw, 2021; Hammarström, 1994; Labouvie, 1986). There may be some sex and gender differences in this relationship, as studies report that positive relationships between stress or emotional pain and alcohol use are stronger in young women than young men (Beck et al., 1995; Byrne & Mazanov, 1999), which could be driven by differences in actual stressors, as well as the perception of and response to stressors between groups. Byrne and Mazanov (1999) found support for the former option, as they observed gender differences in the kinds of stressors that were reported. However, some studies do not find associations between early life stress and alcohol use (Iakunchykova et al., 2015). Importantly, few human studies can define causality between stress exposure and alcohol consumption. One study found a positive association between adverse childhood experiences (defined in this study as abuse, neglect, and household dysfunction) and alcohol initiation by age 14, in addition to a weaker positive relationship with alcohol initiation later in adolescence (Dube et al., 2006). Cumulatively, these findings provide support for stress precipitating alcohol use and alcohol use increasing the likelihood of stress, which may be greater among young women.

Various moderating factors have been proposed for the relationship between stress and alcohol consumption in youth and adolescents. Some evidence suggests that positive peer influences may protect against problematic drinking patterns (Liu et al., 2014). Adolescents experiencing both depression and impulsivity may also be more likely to increase drinking in response to stress (Hussong and Chassin, 1994). Age might also contribute importantly to the association between stress and alcohol use. One study found that the association between stress and drinking gets weaker between late adolescence (teenage years) and early adulthood (twenties; Aseltine and Gore, 2000). Such factors may be meaningful contributors to alcohol use vulnerability during youth and adolescence.

Stress-induced relapse may be less common in adolescents than in adults (Brown et al., 1989). A study in adolescents experiencing a range of substance use issues found the presence of other people and social pressures to be most predictive of relapse, with about 60% of relapses involving direct social pressures to use a drug. In contrast, attempting to cope with a negative affect state was reported in only one third of adolescent relapses. However, others have found negative emotional states to be associated with adolescent relapse in populations with comorbid psychiatric disorders (Ramo et al., 2005). Future studies can better examine the relationship between stress and alcohol use relapse among adolescents, and preclinical studies may aid in understanding the mechanisms underlying these phenotypes.

In rodents, adolescent alcohol exposure has been shown to alter numerous stress responses (Allen et al., 2016; Kim et al., 2019; Varlinskaya et al., 2017, 2020). Behaviorally, exposure to alcohol during adolescence has been associated with increased anxiety-like behavior in adulthood (Varlinskaya et al., 2017, 2020). These behavioral changes are likely in part a consequence of known changes in major stress-related physiological responses. For example, adolescent intermittent alcohol exposure protocols have been reported to increase adult hypothalamic–pituitary–adrenal (HPA) axis reactivity as measured by corticosterone (CORT) production (Kim et al., 2019; Varlinskaya et al., 2017). Chronic intermittent alcohol exposure during adolescence has also been shown to sensitize prefrontal microglial CD11b responses induced by acute stress (Walter et al., 2017). Further, a study of adolescent alcohol vapor exposure in male rats revealed a reduction in the CORT response to an acute alcohol challenge in adulthood (Allen et al., 2016). Thus, adolescent alcohol exposure may produce lasting changes in stress responses to later alcohol exposures. Alcohol exposure during adolescence can produce changes in brain circuits related to both stress and cognitive decline (Sicher et al., 2022) – and importantly, these changes can be extremely long-lasting, reaching well into adulthood despite abstinence during adulthood (Sicher et al., 2023).

Various adolescent-specific stress paradigms have also been shown to affect alcohol consumption. Adolescent social stress, meant to mimic the social instability often experienced by human adolescents, led to elevated binge-like alcohol consumption in adult mice (Caruso et al., 2018). Some research suggests, however, that stress effects on drinking are sensitive to sex and age. For example, a study in adolescent and adult male and female Wistar rats examining the effects of repeated restraint stress on alcohol consumption found that stress increased alcohol intake among adolescent females, but decreased alcohol intake in adult females and adolescent males (Wille-Bille et al., 2017). Thus, stress effects on alcohol exposure are nuanced depending on adolescent age and sex. In addition, adolescents are often exposed to other pharmaceuticals that may interact with both stress and alcohol (Crowley et al., 2014). These interactions may be important when considering how alcohol and stress may contribute to cognitive decline.

2.3. Adolescent alcohol and stress effects on cognitive decline and related phenotypes

The disruption of normative adolescent development via stress and/or alcohol use has been implicated in the development of numerous psychiatric disorders (Brière et al., 2014; Fergusson et al., 2013; Goodyer et al., 1985; Guessoum et al., 2020; Pedrelli et al., 2016; Rohde et al., 2001), and impaired cognitive functioning (Daughters et al., 2013; Ferrett et al., 2010; Parada et al., 2012; Rahdar and Galván, 2014; Sullivan et al., 2016). It has been argued that early life adversity, such as adolescent alcohol or stress exposure, may prime the brain for accelerated aging and associated dysfunction (Chaudhari et al., 2022). Few studies have attempted to directly link adolescent alcohol or stress exposure to lifespan cognitive decline due to obvious difficulties in tracking subjects across an entire lifespan, although some have argued

for the high likelihood that early life adversity accelerates brain aging and decline (Chaudhari et al., 2022). However, more research has separately examined the effects of adolescent alcohol or stress on early adult cognitive performance and its neurobiological correlates. These studies and their implications for long-term cognitive outcomes are discussed here.

2.3.1. Adolescent alcohol effects on cognitive decline

A growing body of literature, largely from the NADIA consortium, is directly assessing whether adolescent alcohol exposure can promote cognitive decline or neurodegeneration in late adulthood (Crews et al., 2019). One study in male Sprague-Dawley rats indicated that adolescent alcohol exposure could impair spatial learning in the Morris Water Maze when tested at multiple timepoints throughout the lifespan (Matthews et al., 2017). A later study in male and female Sprague-Dawley rats tested whether the cognitive effects of adolescent intermittent alcohol exposure differed between sexes and between different cognitive tasks (non-spatial learning, spatial learning, and behavioral flexibility in a water maze) at similar protracted time points (Matthews et al., 2022). Here, they found that behavioral flexibility was impaired across both sexes, but some sex-specific cognitive changes were observed. Intriguingly, a significant reduction in survival likelihood later in life was seen in males and not females, indicating a lasting effect of adolescent alcohol exposure on overall health and longevity in males.

A more recent study in Sprague-Dawley rats tested whether chronic intermittent alcohol exposure (administered during adolescence via gavage) could disrupt anxiety-related behavior, spatial learning, and behavioral flexibility 18 months after alcohol administration (Matthews et al., 2023), with the protracted behavioral timepoint roughly corresponding to an age around the 60s when compared to the human developmental time scale (Ghasemi et al., 2021). At this protracted timepoint, there were no effects on anxiety-related behavior, but males (and not females) experienced deficits in spatial learning and impaired behavioral flexibility in the Morris Water Maze. This replicated previously observed sex-specific cognitive effects by the same group (Matthews et al., 2022). Interestingly, researchers also tested microglia activation at these time points and did not find an effect of alcohol exposure, suggesting that protracted behavioral deficits were not driven by continuous microglia activation, though this does not rule out long-lasting downstream effects of immediate microglia activation at the time of drinking.

The behavioral deficits observed in late life after adolescent alcohol exposure in rodents suggests underlying neurobiological changes that have not yet been well-characterized. One likely contributor to behavioral deficits is alcohol-induced changes in brain-derived neurotrophic factor (BDNF). A study in male Wistar rats tested the influence of adolescent intermittent alcohol exposure on adult BDNF in the hippocampus and prefrontal cortex (Scheidt et al., 2015). While no changes were observed in the prefrontal cortex, BDNF levels were reduced in the adult hippocampus. It is likely that this creates or is associated with an impairment in neuroplasticity, which drives hippocampus-associated learning deficits, such as spatial learning impairments observed in other studies (Matthews et al., 2023).

Some work has directly investigated the impacts of adolescent alcohol exposure on long-term outcomes related to AD and neuroinflammation (Barnett et al., 2022). Intermittent intragastric alcohol doses were administered to adolescents of a mouse line prone to amyloid and tau phenotypes comparable to human AD (3xTg-AD mouse line). This study examined intracellular (Aβ42) levels, which do not constitute amyloid pathology, but may highlight differences in amyloid processing. At timepoints in late adulthood, amyloid (Aβ42) and tau pathology were exacerbated in alcohol-treated subjects, particularly in females, and anxiety-related behaviors and memory deficits were also increased among alcohol treated subjects. Intriguingly, treatment with minocycline, an antibiotic with anti-inflammatory effects, throughout adolescent alcohol treatments was sufficient to prevent some amyloid and tau changes in addition to some of the behavioral consequences of adolescent alcohol.

It is likely that adolescent alcohol exposure induces neuroinflammation which consequently drives cell death, and this is particularly devastating for outcomes associated with cholinergic cells of the basal forebrain. Numerous studies have shown that adolescent intermittent alcohol exposure can lead to a reduction in cholinergic markers in the basal forebrain (Crews et al., 2021; Swartzwelder et al., 2015; Vetreno et al., 2014, 2020; Vetreno and Crews, 2018). This decrease in cholinergic signaling has been associated with increases in proinflammatory measures, and treatment of alcohol-exposed subjects with anti-inflammatory interventions such as exercise and indomethan were sufficient to prevent both cholinergic and inflammatory deficits (Vetreno et al., 2020; Vetreno and Crews, 2018). Importantly, others have found that adolescent alcohol exposure-associated deficits in the basal forebrain cholinergic system are correlated with behavioral pathologies, such as increased exploratory behaviors (Ehlers et al., 2011). Because degeneration of cholinergic neurons in the basal forebrain and cognitive changes are hallmarks of human AD pathology (Ma et al., 2020), these changes are likely important in the lifetime development of ADRD.

The shorter lifespan of rodents compared to humans make them a critical model for understanding the biological relationship between early consumption of alcohol and cognitive decline. While some evidence suggests that some long-term cognitive effects of adolescent alcohol consumption vary by sex (Matthews et al., 2022, 2023), it is important to consider that this also likely varies by genetic background. Studies examining short-term cognitive effects of acute alcohol exposure during adolescence have shown interactions between sex and genetic background to produce unique alcohol-associated learning deficits (Seemiller et al., 2022, 2023; Seemiller and Gould, 2021). Importantly, while the literature directly assessing adolescent alcohol exposure and cognitive decline is sparse, much of it points toward a key relationship warranting further investigation.

2.3.2. Adolescent stress effects on cognitive decline

While little work has been conducted on adolescent stress and late life cognitive outcomes, one study testing the effects of adolescent stress exposure on cognitive performance found compelling persistent effects of adolescent chronic social stress on multiple important outcomes later in life (Sterlemann et al., 2010). Male mice underwent a chronic stress paradigm during adolescence and were assessed for lasting cognitive deficits. Twelve months after cessation of chronic stress, deficits were observed in spatial memory and not social or object recognition memory. These cognitive deficits were accompanied by an impairment in long-term potentiation (LTP) in hippocampal CA1 electrophysiological recordings, a downregulation of hippocampal BDNF, and a likely decrease in dentate gyrus synaptic number or size, as measured by a decrease in synaptophysin expression. In support of this finding, others reported that female Wistar rats that underwent a social stress paradigm during adolescence showed impaired cognitive flexibility in early adulthood driven by long-lasting changes in synaptic strength in the hippocampus (Hyer et al., 2021). Other work has thematically replicated these findings, suggesting that adolescent stress can have lasting effects on cognition and memory well into adulthood, long after the stressor has ceased (Chaby et al., 2015). Importantly, emerging evidence suggests behavioral manipulations such as dietary changes can protect against early-life stress induced cognitive decline in rodents (Provensi et al., 2019).

2.3.3. Adolescent alcohol and stress interactions and cognitive decline

Human literature suggests a bidirectional relationship between adolescent stress and alcohol use (Dube et al., 2006; Ramo et al., 2005). Thus, it is important to examine how these experiences may act in concert to promote maladaptive cognitive changes. Some common themes emerge among studies examining the effects of adolescent

alcohol and stress on cognitive decline and neurodegeneration-associated markers. First, the literature provides robust support for persistent adolescent alcohol and stress-induced cognitive deficits, ranging from spatial learning to behavioral flexibility and impulsivity (Boutros et al., 2017; Matthews et al., 2017, 2022, 2023; Sterlemann et al., 2010). This is also seen when alcohol and stress exposure are combined. For example, one study in male Wistar rats examined how adolescent intermittent alcohol exposure and neonatal maternal separation when experienced separately or together could change adult attentional processes and impulsive behaviors in the five-choice serial reaction time task (Boutros et al., 2017). They observed nuanced effects of alcohol and maternal separation stress on measurements of impulsive behavior and attention, where stress impaired compulsivity and alcohol exposure did not. Attention was enhanced by stress, alcohol, and combined stress and alcohol exposures. The authors speculated that the magnitude of these changes is likely sensitive to dose and duration. As has been pointed out previously, learning deficits mediated by brain regions that are still developing during adolescence, such as the prefrontal cortex, are more consistently affected by adolescent alcohol or stress (Seemiller and Gould, 2020). Changes have also been seen in learning-associated neurobiological measures, such as hippocampal LTP (Sterlemann et al., 2010). Hippocampal BDNF has been reported to be downregulated in aged subjects after either adolescent alcohol (Scheidt et al., 2015) or stress exposure (Sterlemann et al., 2010). These findings accumulate to paint a broader picture of adolescent developmental insults priming the brain for reduced neuroplasticity throughout aging.

Exposure to alcohol in adolescence affects both brain structure and function that can facilitate the development of psychiatric disorders (Lees et al., 2020) and neurodegenerative diseases (Araujo et al., 2021). Vast clinical and preclinical studies have shown that alcohol consumption during adolescence can negatively impact behavioral patterns during adulthood such as increase adult alcohol drinking, disinhibition, and social anxiety. It can also affect different cellular and molecular mechanisms that can have deleterious effects on adult synapses, neurogenesis, gene expression, overall cognition, and sleep (Crews et al., 2016; Peñasco et al., 2020; Sánchez-Marín et al., 2022). Future work should attempt to link the behavioral and molecular changes seen following adolescent alcohol and stress exposure to known markers of AD pathology in humans. Importantly, a greater emphasis on neuroinflammation will mirror the findings in humans and provide a greater mechanistic understanding to these interacting diseases (Barnett et al., 2022; Walter and Crews, 2017).

3. Adults

3.1. Overview of adulthood

While adolescence is widely considered to be a period of rapid change, adulthood can also consist of continuous transitions related to employment, education, relationships, and living arrangements (Matud et al., 2020). These changes can be associated with negative emotional states, and alcohol can be a rapid and accessible tool for coping with them, with strong reinforcing effects (Koob et al., 2020). There are different stages of adulthood, and each is associated with a slightly different collection of stressors and drug use behaviors. The following sections will summarize studies done during all stages of life after the adolescent period.

Different patterns of alcohol use can be established during emerging adulthood where different biopsychosocial variables play a role in maintaining alcohol use throughout life. (Maggs and Schulenberg, 2004). Over the past decade, rates of alcohol use in both younger and older adults have been considerably increasing, reaching its highest level in 2022 (Patrick et al., 2023). However, this trend seems to be more prominent in middle-aged and older adults than among younger drinkers, and accelerating drinking rates have been greater for women than for men (White, 2020).

Adulthood can have numerous periods of adaptation to new scenarios, and when the demands of the environment surpass our ability to confront these changes it can result in psychological stress (Koolhaas et al., 2011). Adults deal with a variety of pressures and high expectations related to relationships, education, work careers and family. These events are a normal part of life, however, for some people they can become stressful and exacerbate or prolong other chronic strains (Matud et al., 2020). Furthermore, individuals have different strategies for coping with stress and these can influence physical and mental health (Billings and Moos, 1981; Folkman and Lazarus, 1980). For example, some may use alcohol as a stress coping mechanism (Koob et al., 2020). The following section will review stress and alcohol interactions such as these in more detail.

3.2. Adult stress and alcohol interactions

Positive associations have been observed between stress and alcohol consumption in adult populations across a broad range of stressors – some of which are unlikely to occur in adolescents and are unique to adults (Bradstock et al., 1988; José et al., 2000; Metcalfe et al., 2003; Montgomery et al., 1998; Richman et al., 1996; Rospenda et al., 2000). Montgomery et al. (1998) report a positive relationship between unemployment and drinking, while Metcalfe et al. (2003) similarly report a positive association between occupational stress and alcohol consumption. Studies with other stress assessments such as perceived workplace harassment and workplace abuse also report that higher stress predicts greater alcohol intake (Richman et al., 1996; Rospenda et al., 2000). A telephone survey of US women found that reports of interpersonal stress were positively associated with binge drinking (Bradstock et al., 1988). These findings provide support for a positive association between stress and alcohol use among adults.

In contrast, a noteworthy study in a Dutch population by José et al. (2000) examined a variety of stressors and their relationship to drinking and found more complex relationships between stressors and alcohol use. Questionnaires and personal interviews were used to collect information about stressful life events and alcohol-related behaviors. Some stressors, like unfavorable employment status and financial difficulties, had positive associations with abstinence in both men and women. However, in separate analyses, being divorced was positively associated with both abstinence and heavy drinking when compared to light or moderate drinking among men. In women, being divorced had a positive association with heavy drinking and a negative association with abstinence. These results indicate that some stressors may be more likely to predict extremes of alcohol consumption behaviors, such as abstinence or heavy drinking, and this may be different between men and women. Stress effects on drinking patterns may rely on individual susceptibility and stressors can promote positive or negative changes in drinking behaviors depending on interactions of multiple personal factors and is likely dependent on the individual's preexisting relationship with alcohol prior to a stressful event.

Stress has also been associated with relapse from alcohol addiction (Brown et al., 1989; Hall et al., 1990). Stress can increase alcohol craving (Fox et al., 2007; Litt et al., 1990) and subsequently increase the likelihood of alcohol use. This relationship may be moderated by other individual risk characteristics. A study of adult men abstinent from alcohol found that stressors predicted relapse, but psychosocial factors such as coping skills and social networks were protective from stress effects on relapse (Brown et al., 1995). However, the previously described study by Hall et al. (1990), which included nicotine and alcohol users, found only a positive association between retrospective, and not prospective, stress scores and relapse, suggesting that stress may not be entirely causal of relapse.

The interaction between stress and alcohol consumption is complex. Stress can co-activate the reward system and the hypothalamic-pituitary adrenal (HPA) axis where multiple brain structures, neuropeptides and

neurotransmitters interact with each other to foster stress-related substance misuse (McKee et al., 2011). Stress has been associated with all phases of alcohol use disorder (AUD) including drinking initiation, maintenance, and relapse for both men and women. However, adult women seem to be more prone to stress-alcohol interactions compared to men (Peltier et al., 2019). It has been theorized that during negative emotional states, alcohol can be used as a way for coping with stress and may be an initial starting point for entering the addiction cycle via self-medication (Koob, 2017). For example, during COVID-19 pandemic approximately 1 in 4 adults reported using alcohol as a way of coping with stress (Stress in America, 2021). In another survey, it was reported that adults who have experienced symptoms of anxiety, loneliness, and depression were almost four times more likely to increase their consumption of alcohol (Eastman et al., 2021). Importantly, when a person develops AUD, the numerous symptoms associated with withdrawal from the drug can trigger stress responses and increase the probability of alcohol consumption (Koob et al., 2020), establishing a feedback loop between stress and alcohol consumption.

Collectively, these findings provide support for bidirectional relationships between stress and alcohol exposure during adulthood. The following sections will outline adult-specific vulnerabilities to alcohol stress in addition to their impact on cognitive decline and associated neuropathology.

3.3. Adult alcohol and stress effects on cognitive decline and related phenotypes

3.3.1. Adult alcohol effects on cognitive decline

While evidence suggests alcohol use during adolescence appears to be largely detrimental to overall health, there are mixed findings about the effects of adult alcohol consumption on neurodegeneration and cognitive decline. Recent work has described the relationship between alcohol and cognitive decline as likely U-shaped, with low to moderate alcohol consumption supporting cognition and higher alcohol consumption being detrimental to cognition (Zhang et al., 2020). It has been discussed that alcohol can have protective effects in mild and moderate doses (Krivanek et al., 2021). In light to moderate doses, alcohol may have protective effects for cognitive decline and reduce the risk of dementia (Ganguli et al., 2005; Krivanek et al., 2021). For example, preclinical and epidemiological data have shown that at low doses alcohol can diminish the damage done by Aβ accumulation and can be associated to a decrease in AD prevalence (Peng et al., 2020).

However, at higher concentrations, alcohol's effects are the opposite and can increase the risk for developing neurodegenerative diseases. Its consumption can promote dysregulation in the adult brain, and high consumption patterns such as binge drinking (defined as 4 for women, or 5 for men, alcoholic drinks within a 2 h period and reaching clinical intoxication levels) seem to be more associated with cognitive decline than lower alcohol consumption patterns (Grønkjær et al., 2019; Han and Jia, 2021; Sabia et al., 2014; Zhang et al., 2020). This might be further moderated by drinking patterns and preferred alcoholic beverage (Han and Jia, 2021).

Several studies utilizing preclinical mouse models of AD have demonstrated the effects of alcohol exposure on AD biomarkers and behaviors relating to cognition (Day et al., 2023; Hoffman et al., 2019; Huang et al., 2018). In a study using a mouse line (APP23/PS45) that is susceptible to AD-related pathologies, alcohol exposure increased expression of amyloid precursor protein (APP), beta-site APP cleaving enzyme 1, and Aβ 40 & 42; additionally, alcohol exposure exacerbated learning and memory impairments (Huang et al., 2018). However, in another AD mouse model (APP/PS1), it was found that ethanol exposure does not alter APP protein levels or metabolism (Day et al., 2023). Alcohol consumption also worsened cognitive function in the 3xTg-AD model and increased the production of Aβ 42 compared to Aβ 40 in the prefrontal and lateral entorhinal cortices, as well as increasing tau protein expression in the amygdala, lateral entorhinal, and medial prefrontal cortices (Hoffman et al., 2019). Alcohol exposure in the APP/PS1 model exacerbated reductions in brain mass (Day et al., 2023). Alcohol exposure in APP/PS1 mice increased the frequency of smaller amyloid plaques in the hippocampus and cortex, however it is unclear if these changes in plaque size contribute to Aβ pathology.

Although promising work has been done to elucidate how alcohol consumption can lead to neurodegeneration, this interaction is still not well understood. There are different mechanisms that could be contributing to neurodegeneration, including, but not limited to, oxidative stress, neuroinflammation, and excitotoxicity. Importantly, the effect of alcohol on cognitive outcomes further interacts with diseases that independently influence cognition, such as the prevalence or absence of hypertension (Yen et al., 2022). These opposing effects of alcohol are mirrored in pre-clinical literature. A recent study showed that high alcohol preferring (cHAP) mice which drank alcohol for 7 months exhibited an increase in oxidative stress, neuroinflammation, and neurodegeneration (Xu et al., 2019). However, in the same study it was also shown that chronic alcohol drinking promoted neurogenesis in the dentate gyrus and subventricular zone of the hippocampus in female cHAP mice. In APP/PS1 mice, alcohol exposure alters NMDA and $GABA_A$ receptor gene expression, which highlights the potential of alcohol to induce excitotoxicity (Day et al., 2023).

There is an emerging consensus that alcohol consumption impacts cognition through increased inflammation. Alcohol consumption can increase oxidative stress processes which can lead to changes in immune response. These changes can promote glutamate excitotoxicity through upregulation of glutamate receptors (Kumar et al., 2016) and can also compromise astrocytic function which can result in a decrease in glutamate reuptake (Ayers-Ringler et al., 2016). Post-mortem assessments of brain tissue from humans with AUD have found associations between oxidative and ER stress-associated signaling pathways, proinflammatory responses, and neuronal cell death, supporting the relationship between alcohol use, oxidative stress, neuroinflammation, and neurodegeneration in human subjects (Crews et al., 2013; Qin et al., 2023; Vetreno et al., 2021). Furthermore, alcohol use is associated with compromised white matter (Yalcin et al., 2017) and brain atrophy in MRI studies (Mukamal et al., 2001). Alcohol consumption can also, via both direct and indirect pathways, trigger pro-inflammatory effects within the brain - leading to neurodegeneration and decreased adult neurogenesis (Anand et al., 2023). It can also compromise the integrity of the blood brain barrier by increasing oxidative stress in endothelial cells (Haorah et al., 2005) complementing work in other *in vitro* studies (Carrino et al., 2021). Though the nature of alcohol's effects varies by dose, it is clear that alcohol exposure can alter key biological pathways, such as neuroinflammation, which creates risk for neurodegeneration and cognitive decline.

3.3.2. Adult stress effects on cognitive decline

There is growing evidence linking prolonged exposure to stress and glucocorticoid signaling to neurodegeneration and cognitive decline (Vyas et al., 2016). In humans, it has been found that people who experience overwhelming lifetime events that can lead to chronic stress, such as spousal caregiving and widowhood, are more likely to exhibit cognitive decline (Wu-Chung et al., 2022). In preclinical studies, it has been found that chronic stress exposure can affect newborn cells (Borcel et al., 2008) and BDNF signaling (Niknazar et al., 2016) in the hippocampus and impair spatial memory. Similarly, in a recent study, using rats that were isolated and underwent a protocol of chronic stress, it was found that social isolation induced epigenetic changes associated to BDNF, memory impairment and anxiety-like behaviors (Viana Borges et al., 2019). In glial cells, chronic stress can compromise microglia morphology, heterogeneity, and protein expression of different cytokines which ultimately can lead to stress-related pathologies such as anxiety, depression, sleep disorders and neurodegenerative diseases (Musazzi and Marrocco, 2016; Picard et al., 2021). Thus, the consensus across preclinical and clinical literature is that stress exposure by itself

can lead to cognitive decline and related neurobiological phenotypes.

3.3.3. Adult alcohol and stress interactions and cognitive decline

There are few studies examining stress and alcohol consumption interactions in the context of neurodegeneration. However, many models of voluntary alcohol exposure utilize single housing which can be a confounding known stressor (Crowley et al., 2019). One preclinical study examined the cognitive effects of separate and combined alcohol access and restraint stress over 28 days in adult mice (Rajput et al., 2017). In this study, stressed mice consumed more alcohol than non-stressed mice, and subjects in the stress and alcohol group had exacerbated oxidative stress and inflammatory signaling relative to stress-only and alcohol-only groups. Comparable cognitive deficits were observed between subjects exposed to stress and alcohol and subjects that were only stressed. While the behavioral phenotype suggests that there were comparable consequences of stress-only exposure when compared to combined stress and alcohol exposures, the biological measurements suggest that subjects given stress and alcohol exposures may be more susceptible to other long-term health impacts of the exposures.

Promising work has been done to elucidate the role of microglia cells in stress- and alcohol-induced damage to the nervous system. Stress and alcohol can promote microglia activation and therefore immune responses, which can lead to compromised neuronal integrity (Walter et al., 2017) and neurodegeneration. In both *in vitro* and *in vivo* experiments, it has been shown that after binge ethanol consumption, microglia and neuroimmune expression was upregulated (Walter and Crews, 2017). In different preclinical studies, it has been shown that alcohol consumption can induce neuroinflammation processes which can contribute to the AUD cycle through mechanisms related to toll-like receptors (de Timary et al., 2017). Importantly, following alcohol withdrawal, cytokine levels can also heighten during negative emotional states (Breese et al., 2008). However, it is important to note that this activation has also been linked to a homeostatic role rather than directly contributing to neurodegeneration (Marshall et al., 2013), suggesting different interactions of alcohol consumption, microglia activation, and neuroinflammation that could be contributing to neurodegeneration.

4. Discussion

Experiences with stress and alcohol vary dramatically throughout the lifespan and across individuals. Adolescents and adults are prone to different kinds of stressors, use alcohol in different patterns, and have different underlying neurobiology that make them uniquely susceptible to damage. For this reason, it is critical to conduct research investigating age-specific stress and alcohol experiences and to understand how they may contribute to disease etiology.

Major life stressors and experimentation with alcohol often begin during adolescence. As the brain is rapidly developing during this time, it is particularly sensitive to some of these exposures. A general trend in preclinical literature is that the prefrontal cortex, a region that is undergoing plasticity changes throughout adolescence and into adulthood, is particularly sensitive to alcohol. Consequently, behaviors dependent upon prefrontal functioning (such as behavioral flexibility) tend to be most robustly impaired by adolescent alcohol and stress. While few studies have directly compared adolescent alcohol and stress effects on adult cognitive functioning, evidence suggests they have both shared and unique effects on cognition (Boutros et al., 2017) – supporting the importance of studying them separately and together. While the underlying mechanisms for these cognitive changes are still being elucidated, it is likely that adolescent alcohol and stress exposure may promote cognitive decline and neurodegeneration via neuroinflammatory effects. One study found that adolescent alcohol exposure led to amyloid (Aβ42) and tau pathology in a mouse model of AD, but this and associated cognitive phenotypes were prevented by coadministration of an anti-inflammatory drug (Barnett et al., 2022). Such findings suggest that top candidates for the neurobiological mechanisms of adolescent alcohol- and stress-induced neurocognitive decline include neuroinflammation and plasticity-associated changes (see Fig. 1 for overview of overlap in neurocircuits implicated in stress, alcohol, and cognitive decline in major life stages).

Although adults show varied consumption patterns of alcohol and responses to stress compared to adolescents, there is still evidence that neurodegeneration and cognitive decline are impacted by these factors. Despite some potential beneficial effects at low and moderate doses, higher concentrations of alcohol consumption show an increased risk for neurodegenerative disease development (Krivanek et al., 2021). Similar to the effects noted in adolescents, alcohol and stress further

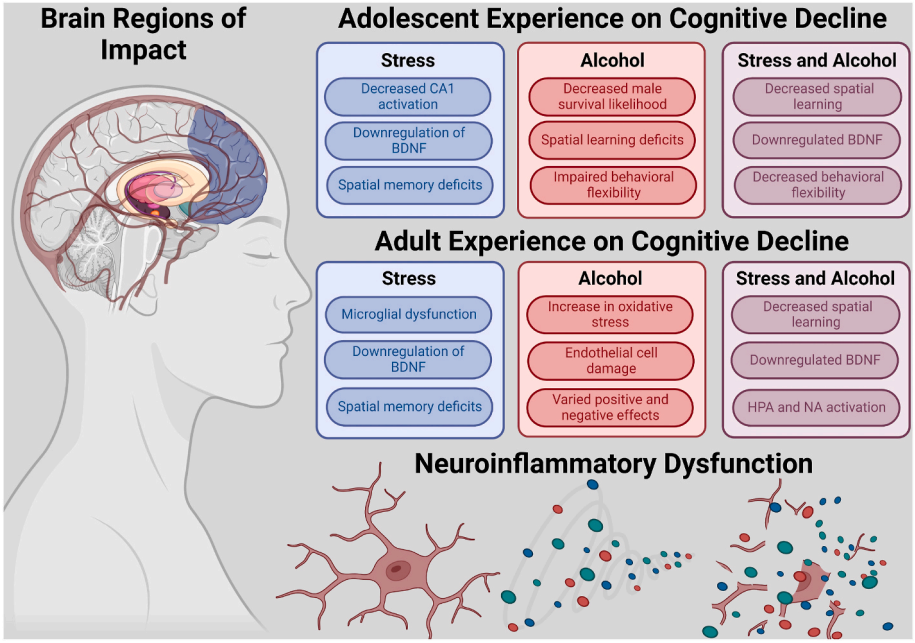

Fig. 1. Major themes and regions impacted by stress and alcohol throughout the lifespan.

neurodegenerative disease progression and cognitive decline through perturbations in neuroinflammatory responses. Recently, there has been progress made examining the role that alcohol can play on AD-like progression throughout a rodent's life course (Barnett et al., 2022). The impact of neuroinflammation on models of disease progression highlights an important potential role for microglial activation. Accumulation of Aβ can potentially impact overall microglial health (Streit, 2006). Future studies should continue to examine the effects that alcohol and stress have on neuroimmune functioning, specifically microglial functionality, and these studies should follow the life course of disease.

Studies of disease progression, specifically those relating to neurodegeneration, are inherently difficult due to logistical hurdles. However, there is a major hole in our understanding of neurodegenerative disease epidemiology and unmet need for greater solutions and treatments. Ongoing work is continuing to explore longitudinal studies that look to correlate adolescent stressors throughout adulthood and into healthy aging and making great progress in understanding the biological underpinnings of the interaction between alcohol, stress, and neurodegeneration. It should be noted that societal factors can also play an important role in the biopsychosocial theory of disease development and should also be considered moving forward. For example, marginalized groups such as women, transgender, non-binary, and Black Americans report higher binge alcohol consumption (Connolly and Gilchrist, 2020; Desalu et al., 2019; Guinle and Sinha, 2020). Racial discrimination, a notable stressor, can lead to higher levels of alcohol consumption in Black Americans (Desalu et al., 2019). Members of the transgender community, and non-binary individuals in particular, report higher levels of drinking (Connolly and Gilchrist, 2020). Self-reporting bias, usage level variation, and societal factors are all important assessment variables that influence the way we correlate alcohol and stress to neurodegeneration and cognitive decline, and ongoing work should consider a minority stress framework.

Investigation of the overlapping brain circuits impacted by alcohol and stress that contribute to cognitive decline can provide further insight into the mechanism of alcohol- and stress-induced risk for ADRD (Fig. 1). Continuing to understand how specific pathologies emerge in a brain-region specific fashion during the development of disease will be vital for identifying at-risk individuals early and understanding treatment options. Going forward, future work should also explore how alcohol and stress relate to emerging targets for ADRD including inflammatory markers, new genetic factors such as TREM2, and vascular contributions. While these are all stated areas of interested of the National Institute of Aging (NIA, 2017), more work is needed to integrate alcohol and stress risk factors into these domains.

The world is experiencing a global demographic transition as the population ages (Longevity, 2021). Not only has the number of older adults in the United States increased, but the amount of alcohol consumption in older drinkers is also growing (White et al., 2023). Older drinkers may have a set of age-related characteristics that can interact negatively with alcohol consumption such as chronic disease, daily medication, and decrease in overall quantity and quality of sleep (White et al., 2023) which ultimately can increase the risk of cognitive decline and neurodegeneration. Additionally, major collective stressors such as the COVID-19 pandemic have put the global population at greater risk for escalated drinking and other associated long-term health consequences including cognitive decline (Barbosa et al., 2021). Thus, better understanding the risk factors for cognitive decline and ADRD is of paramount importance.

Both stress and alcohol have been implicated as possible driving forces in cognitive decline and subsequent development of ADRD. Brain regions including, but not limited to, the prefrontal cortex (blue), nucleus accumbens (teal), and hippocampus (purple) are all impacted throughout a subject's lifespan by stress and alcohol (Fig. 1). Combined, stress and alcohol lead to neuroinflammatory dysfunction and potentially contribute to the etiology of AD. Figure inspired by and adapted from Maldonado et al. (2021) and created with BioRender.com.

CRediT authorship contribution statement

Laurel R. Seemiller: Conceptualization, Writing – original draft, Writing – review & editing. **Julio Flores-Cuadra:** Writing – original draft, Writing – review & editing. **Keith R. Griffith:** Writing – original draft, Writing – review & editing. **Grace C. Smith:** Writing – original draft, Writing – review & editing. **Nicole A. Crowley:** Conceptualization, Funding acquisition, Project administration, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

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