The role of resilience in the relationship between stress and alcohol

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ABSTRACT

Stress plays a well-documented role in alcohol consumption and the risk for developing alcohol use disorder. The concept of resilience - coping with and successfully adapting to stressful life experiences – has received increasing attention in the field of addiction research in recent decades, and there has been an accumulation of evidence for resilience as a protective factor against problematic alcohol consumption, risk for alcohol use disorder, disorder severity, and relapse. The conceptual and methodological approaches used in the generation of this evidence vary considerably across investigations, however. In light of this, we carried out this review in order to provide a more thorough understanding of the meaning and scope of resilience, what factors contribute to resilience, how it is measured, and how it relates to alcohol-associated phenotypes. Implications for treatment through the use of resilience-building interventions are likewise discussed, as well as implications for future research on the role of resilience in the etiology and clinical outcomes of alcohol use disorder.

1. Introduction

Exposure to stressful events is a fairly universal experience, but how an individual responds to such events, both initially and in succeeding exposures, varies considerably. For some individuals, repeated exposures to stress result in maladaptive changes in physiology and behavior that increase risk for adverse health outcomes. For others, however, these exposures trigger coping responses and positive adaptations that mitigate risk for adverse health outcomes. The latter set of individuals are often described as "resilient". Resilience, broadly defined as positive or successful adaptation to stressful life experiences (Herrman et al., 2011), unquestionably contributes to interindividual variability in the response to stress and its aftermath, yet research on resilience has long taken a backseat to research on stress vulnerability, particularly in the area of neurobiology of stress and addiction. Stress is a well-documented risk factor for alcohol misuse and alcohol use disorder (Keyes et al., 2011, 2012; Sinha, 2022), and growing evidence suggests that resilience to stress is a protective factor against problematic alcohol use (Cusack et al., 2023). Resilience is a multidimensional construct (Connor and Davidson, 2003; Shevell & Denov, 2021) and as such, many sources of resilience have been identified in the literature encompassing psychological, social, environmental, and biological factors (Brown et al., 2023a; Charney, 2004; Haglund et al., 2007; Herrman et al., 2011; Wu et al., 2013). Many of these same factors have also been linked to risk for

alcohol and other substance use disorders. Thus, a more thorough understanding of resilience-based factors, and of ways to foster and promote resilience in individuals, offers a valuable contribution to alcohol use disorder (AUD) research.

In this review, we examine the concept of resilience and the relationship of resilience to problematic alcohol use and AUD. We begin by examining the definition and scope of resilience as it applies to health research in the broader sense, as well as the specific relationship of resilience to stress, including exposure to childhood maltreatment. We then review the various psychological, behavioral, environmental, and biological sources of resilience that have been identified in the literature. Current evidence concerning the relationship between resilience and various alcohol-related phenotypes, including AUD, is then examined. Finally, we discuss important implications for prevention and intervention strategies that may benefit individuals diagnosed with AUD.

2. What is resilience?

2.1. Definition

Numerous definitions of resilience have been put forth over the years, but in general they all reflect a fundamental theme: resilience is coping with and positively adapting to adversity, trauma, or stress

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(Brown et al., 2023a; Herrman et al., 2011; Luthar et al., 2000; Yehuda et al., 2006b). This definition combines three key elements: 1) exposure to adversity, which can include physical, emotional, social, and other types of stressors, 2) coping with the adversity, or managing stressful situations in order to maintain normal functioning, and 3) positive adaptation, entailing changes that are ultimately advantageous rather than maladaptive to the individual. Notably, exposure to adversity is a fundamental feature that distinguishes resilience from overall positive psychological functioning (Denckla et al., 2020). Leading conceptual models build on this definition by portraying resilience as a *capacity*, a *process*, and an *outcome* (Brown et al., 2023a; Choi et al., 2019; Denckla et al., 2020; Masten, 2001; Masten and Tellegen, 2012; Southwick et al., 2014). *Capacity* refers to the collection of traits, characteristics, and environmental and community resources that predispose an individual for resilience. Capacity is not a static construct, and can vary across contexts as well as over time. *Process* refers to the dynamic response to an adverse event, involving the interplay between capacity and the context and severity of the stressor. The response can range from no perturbation at all (i.e. resistance), to a recovery to baseline, or to a recovered state that is an improvement over baseline, considered positive adaptation (Brown et al., 2023a). Process also encompasses repeated exposures to stress over time, with successive exposures potentially furthering positive adaptation and growth in resilience capacity. *Outcome* refers to the end result of the process and includes, but is not limited to, absence of negative consequences on health and maintenance of positive functioning (Choi et al., 2019). In mental health and addiction research, resilience is often viewed as the absence of psychopathology despite exposure to significant adversity (Alim et al., 2012). However, individuals with a disorder but who exhibit lower severity and/or fewer symptoms, despite exposure to significant adversity, are often described as demonstrating "relative resilience" (Choi et al., 2019). As we hope this review will show, relative resilience turns out to be an important concept in the etiology of AUD, especially.

2.2. Relationship of resilience to stress

Current concepts of resilience converge on the notion that resilience can only be defined in the context of exposure to adversity. Adversity can take on many forms, including physical or emotional trauma, neglect, financial insecurity, and natural disasters, among others. Such exposures typically invoke the stress response, resulting in both physiological and behavioral sequelae. A key point about resilience is that it is not the opposite of stress, nor the absence of stress; rather, resilience is reflected in how an individual responds to stress. Everyone experiences stress, but not everyone has the same capacity for resilience. It is these individual differences in response that define both risk and resilience.

The cycle of experiencing and re-experiencing stress is a dynamic process in which adaptations occur with each exposure (i.e., allostasis) (McEwen, 1998; McEwen et al., 2015). These changes can be either detrimental or beneficial, depending on the individual and the context of the stress exposure. Resilience can be considered a successful allostatic response, which in the short-term can provide stability, and in the longer-term, help develop the ability to withstand challenges to the system. The foundation of an individual's stress response is established in childhood, with the development of neural and endocrine systems (e. g., the hypothalamic pituitary adrenal or HPA axis) beginning prenatally and continuing up through adolescence (Engel and Gunnar, 2020). As such, experiences during development can have a lasting impact on the functioning of these systems. A vast amount of literature shows that exposure to extreme or recurring stress during childhood can negatively impact the functioning of the HPA axis, with concomitant adverse effects on both physical and mental health (Smith and Pollak, 2020). However, not all children exposed to significant stress during childhood exhibit negative consequences, and exposure to mild and manageable forms of stress during childhood can actually promote healthy development of the stress response (e.g., stress inoculation) (Feder et al., 2019; Haglund

et al., 2007; Rutter, 2013; Wu et al., 2013). Thus, the foundation of individual resilience is likewise established in childhood. The study of resilience actually originated, in part, from research on disadvantaged and maltreated children (Garmezy, 1985; Graber et al., 2015; Herrman et al., 2011; Luthar et al., 2000; Masten et al., 1999; Masten and Tellegen, 2012; Rutter, 2012). Investigators studying children at high risk for psychopathology due to disadvantages and early adversity observed substantial variation in developmental outcomes among these children, with some maintaining "competence" at home and in school, exhibiting "stress resistance", and "positive adaptation" (Garmezy, 1993; Masten and Tellegen, 2012; Werner, 1992). These concepts evolved into what we now identify as resilience, and research relating to resilience has since expanded beyond the field of developmental psychology to include adults, with the recognition that resilience is not a fixed or static entity, but a dynamic interactive process that takes place across the lifespan. This is because stress is continually experienced across an individual's lifetime. How and to what degree an individual responds to each stressful occurrence is dependent on a number of factors, the nature and impact of which shifts over time as a person grows and progresses through life.

2.3. Scope of resilience

Recent advances in the study of resilience recognize both the multi-level and multidimensional nature of resilience. Resilience is developed and utilized not only at the individual level, but at the family, community, and societal levels as well (Brown et al., 2023a; Denckla et al., 2020; Herrman et al., 2011). Ideally, studies of resilience involve integrative approaches that incorporate factors across these multiple levels; however, the optimal methods for applying such approaches are still a work in progress (Brown et al., 2023b; Shevell & Denov, 2021). Within the mental health and addiction field, individual-level resilience has been the primary focus; however, even individual-level resilience is itself multidimensional, comprising behavioral, psychological, environmental, and biological and components. In the broader sense, individual resilience encompasses both *psychological resilience* and *biological (or physiological) resilience*. Psychological resilience alludes to cognitive and emotional capabilities, behaviors and coping mechanisms, and environmental factors that impact individual mental well-being in the face of adversity. Psychological resilience can also be viewed as an outcome, reflected in either high levels of wellbeing, or low levels of illbeing (Hofgaard et al., 2021). Sources of psychological resilience include personality traits (e.g., neuroticism, extraversion, openness, agreeableness, and conscientiousness) (Costa and McCrae, 2002), positive emotionality, cognitive flexibility and reappraisal, and adaptive coping strategies (e.g., active coping, task-oriented coping, exercise) (Alim et al., 2008, 2012; Arida and Teixeira-Machado, 2020; Campbell-Sills et al., 2006; Dijkstra and Homan, 2016; Gloria and Steinhardt, 2016; Haglund et al., 2007; Iacoviello and Charney, 2020; Linnemann et al., 2022; Oshio et al., 2018; Ramchandani et al., 2018; Schwandt et al., 2023; Southwick et al., 2015; Wu et al., 2013). Environmental factors that contribute to psychological resilience include social support from family and peers, influential role models, and community health and resources (e.g., stable employment, adequate income and housing, access to health and social services) (Gil-Rivas and Kilmer, 2016; Herrman et al., 2011; Iacoviello and Charney, 2020; Ozbay et al., 2007; Shevell & Denov, 2021; Southwick et al., 2005; Ungar, 2011).

Biological resilience involves the physiological systems that are known to be impacted by stress, including but not limited to neurobiological, neuroendocrine, hormonal, and immune systems (Charney, 2004; Feder et al., 2019; Haglund et al., 2007; Charney, 2004; Feder et al., 2019; Haglund et al., 2007). The central organ of adaptation to stress is the brain, which is characterized by a significant capacity for structural and functional plasticity during both early development and adulthood (Karatsoreos and McEwen, 2013). Not surprisingly, brain structures involved in the response to stress, such as the hippocampus,

amygdala, insula, hypothalamus, medial prefrontal cortex (mPFC), and the anterior cingulate cortex (ACC), are also implicated in resilience (Burt et al., 2016; Cornwell et al., 2023; Eaton et al., 2022; Fonseca et al., 2021; Levone et al., 2015; McEwen et al., 2015; van der Werff et al., 2013; van der Werff, van den Berg, et al., 2013). The stress circuit also interacts with other systems the promote resilience, including reward, emotion regulation, cognitive control, fear conditioning, and reconsolidation and extinction (Charney, 2004; Eaton et al., 2022; Feder et al., 2019; Holz et al., 2020; Moreno-Lopez et al., 2020; Rodman et al., 2019; van der Werff, van den Berg, et al., 2013). Hormones and neurotransmitters that provide critical communication within and between the brain and body also play a key role, including not only adrenocorticotropic hormone (ACTH), corticotropin releasing hormone (CRH), and cortisol, but also other metabolic hormones, thyroid hormones, sex hormones, oxytocin, brain derived neurotrophic factor (BDNF), serotonin (5-HT), dopamine, dehydroepiandrosterone (DHEA), neuropeptide Y (NPY), endocannabinoids, lipocalin-2 (LCN2), and tissue plasminogen activator (tPA) (Charney, 2004; Fonseca et al., 2021; Horn et al., 2016; McEwen, 2007, 2010; McEwen et al., 2015; Morgan et al., 2000; Russo et al., 2012; Sajdyk et al., 2008; Thorsell, 2010; Yehuda et al., 2006a). Biological resilience is also evidenced by genetic factors, with twin studies estimating the heritability of psychological resilience at ~31% (Amstadter et al., 2014; Sheerin et al., 2021). Many of the candidate genes associated with psychological resilience are closely aligned with the neurobiological factors just highlighted (Alim et al., 2008; Belsky and Hartman, 2014; Cicchetti and Rogosch, 2012; Ryan and Ryznar, 2022; Feder et al., 2019; Niitsu et al., 2019; Park et al., 2021; Terock et al., 2019; Zhou et al., 2008)}, while genome-wide association studies (GWAS) of resilience in humans are only just emerging, identifying loci in the doublecortin-like kinase 2 (DCLK2), kelch-like family member 36 (KLHL36), and solute carrier family 15 member 5 (SLC15A5) genes (Stein et al., 2019). Finally, epigenetic changes such as DNA methylation, histone modifications, and the actions of microRNAs, have emerged as potential predictors or correlates of both stress and resilience (Ryan and Ryznar, 2022; Smeeth et al., 2021). Existing research has largely identified epigenetic changes associated with exposure to early life stress (Burns et al., 2018), and thus not directly related to resilience *per se*. However, the impact of early life stress on the epigenome may be moderated by genetic variation, for example the FKBP5 gene is one of several key candidates in this regard (Klengel and Binder, 2015; Klengel et al., 2013; Wiechmann et al., 2019; Ryan and Ryznar, 2022).

It is important to recognize that psychological and biological resilience are not mutually exclusive. Physiological processes and mechanisms provide the underlying foundation for the cognitive and emotional processes that contribute to psychological resilience. Even so, the lion's share of research on resilience, especially in the field of mental health and addiction, has focused on psychological resilience and in fact, the term "resilience" is often used synonymously with psychological resilience (Denckla et al., 2020).

3. Assessment of resilience

Resilience is most often assessed using psychometric assessments or scale-based questionnaires, and as many as 20 different scales have been identified in existing literature (Mao et al., 2020). While there is no consensus on a "gold standard", the three most commonly used scales are the Connor Davidson Resilience Scale (CD-RISC 25) (Connor and Davidson, 2003), the Brief Scale of Resilience (BRS) (Smith et al., 2008), and the Resilience Scale for Adults (RSA) (Friborg et al., 2003). These three scales were also identified as possessing the best psychometric ratings (Windle et al., 2011). Of these scales, the CD-RISC and the BRS have been utilized most often in studies of alcohol consumption and AUD. The CD-RISC assesses multiple components of psychological resilience, with most items assessing resilience capacity (e.g., hardiness, tenacity, self-efficacy, tolerance of negative affect, faith and optimism, sense of purpose, close and secure relationships), although a few items

gauge more process oriented aspects of resilience (e.g., adaptability, ability to bounce back, coping with stress making one stronger). Notably, the CD-RISC was originally developed as a clinical measure to be used to assess treatment response, and data from a small clinical sample with PTSD showed that individuals who responded to treatment showed a significant increase in CD-RISC score pre-to post-treatment (Connor and Davidson, 2003). Thus, the CD-RISC could be utilized in the same context for those seeking treatment for AUD. In addition to the original 25-item CD-RISC, there is also a brief version with 10-items (CD-RISC 10) (Campbell-Sills and Stein, 2007) and a 2-item version (CD-RISC 2) (Vaishnavi et al., 2007).

The Brief Resilience Scale (BRS), with only 6 items, was designed specifically to measure the perceived ability to bounce back, rather than specific characteristics and resources associated resilience. The items ask respondents to gauge their ability to bounce back after stress, and the length of time it takes to recover from stress. Thus, the BRS is primarily a measure of resilience process rather than capacity. Unlike the CD-RISC, it assumes a unidimensional construct of resilience, and does not include any context related to external support from family or the community. However, the BRS score is correlated with relevant physical (e.g., pain, fatigue) and mental health (negative affect, perceived stress) measures even when accounting for other measures of resilience (including the CD-RISC), suggesting this measure of resilience has a distinct relationship with health outcomes (Smith et al., 2008). Two additional scales that have been utilized in relation to alcohol-associated phenotypes include the Essential Resilience Scale (Chen et al., 2016), and the Bidimensional Resilience Scale (Hirano, 2010), but these have not been widely used beyond the specific populations samples for which they were developed.

An alternative method for assessing resilience is the use of data driven techniques. Person-centered approaches such as latent class analysis (LCA) and latent profile analysis (LPA) have been used to identify subgroups of resilient individuals based on good versus poor functioning across a set of variables (Han et al., 2022; Janousch et al., 2022; Masten, 2001; Ramchandani et al., 2018). Similarly, growth mixture modeling (GMM) has been used to examine resilience trajectories over time (e.g., (Infurna and Grimm, 2017; Martz et al., 2018). One method that has recently been applied in several studies of mental health and AUD is discrepancy-based (or residual-based) psychiatric resilience (Amstadter et al., 2016; Cusack et al., 2021; Sheerin et al., 2019; Sheerin et al., 2021; Sheerin et al., 2021). Essentially, a broad measure of internalizing symptoms, or other measure of psychological distress, is regressed against a measure of stress or trauma load (e.g., the number of lifetime stressful or traumatic events experienced), the residuals are extracted and multiple by −1 (for ease of interpretation) and treated as resilience "scores". Resilience is thus quantified as the difference between an individual's actual and expected functioning, given existing stress or trauma load, with greater positive residuals reflecting a lower level of distress than "expected" (i.e., resilient), and greater negative residuals reflecting a higher level of distress than expected (i.e., non-resilient) (Sheerin et al., 2019).

The assessment of biological resilience is inherently more complex due to the variety of systems proposed to play a role in resilience, and the various techniques that are required to measure the functioning of these systems. Accordingly, there is no single, integrated method that can effectively measure biological resilience capacity. System-specific measures, such as dexamethasone/corticotropin-releasing hormone testing to assess the HPA-axis stress response, have been utilized in this context, with recent evidence suggesting that a "resilient" response involves rapid activation of cortisol secretion (on-switch) followed by appropriate termination of secretion (off-switch) (de Kloet and Joels, 2023). Structural, functional, and resting-state neuroimaging methodologies are also useful tools for identifying brain-based resilience phenotypes, with a focus on circuitry implicated in resilience such as reward, fear conditioning and arousal, memory, and regulation of emotion (Haglund et al., 2007; Holz et al., 2020; Martz et al., 2018; van

der Werff, van den Berg, et al., 2013). Of note, recent efforts have attempted to identify combinations of markers across physiological, neuroendocrine, psychological and behavioral indicators of stress reactivity, which together provide an integrated readout that may improve the power to characterize and predict resilience to stress (Lau et al., 2021). These holistic approaches may help identify individuals at risk for maladaptive coping responses to stress as well as those that might carry traits and features that confer resilience, and potentially uncover underlying mechanisms of these resilient characteristics.

4. Resilience and alcohol use disorder

Given the abundance of evidence linking stress to alcohol consumption and the development of AUD (Blaine and Sinha, 2017; Keyes et al., 2011, 2012; Peltier et al., 2019; Ramchandani et al., 2018; Sinha, 2022), it stands to reason that resilience also plays an important role. Even with the recognition of resilience as a crucial area of research in the field of alcohol (Alim et al., 2012), studies of resilience in relation to alcohol use and AUD specifically are limited, especially considering the substantial proliferation of research on resilience in the overall scientific literature in recent decades (Denckla et al., 2020). A scoping review of resilience and alcohol use in the U.S. published in 2023 (Cusack et al., 2023) resulted in only 14 articles from 2010 to 2022 that met review criteria. It should be noted that this review was limited to studies of psychological/trait resilience. However, given the aforementioned difficulty in quantifying an overall measure of biological resilience, it should come as no surprise that most studies of resilience in AUD have focused on psychological resilience, the exception being a handful of studies investigating neuroimaging- and genetic-based resilience. Of note, the onset of the COVID-19 pandemic in 2020 resulted in a distinct rise of the number of studies on resilience and its relationship to alcohol use, among other mental health outcomes. This is especially significant given the wide-spread effects of the pandemic on stress and mental health across the globe. Notwithstanding methodological variation in the assessment of resilience, the overall picture from existing research is that higher resilience is associated with lower alcohol consumption, less problematic alcohol use, fewer alcohol-related consequences, reduced risk of developing AUD, endorsement of fewer AUD criteria and, among those with AUD, reduced disorder severity and lower risk of relapse.

4.1. Alcohol consumption

The majority of studies investigating the relationship of resilience to routine alcohol use have found that higher resilience is associated with reduced alcohol consumption. This association has been investigated primarily in non-clinical samples, and has been demonstrated as early as childhood and adolescence. Wong et al. (2006), using an adaptation of the California Child Q-Sort (Block and Block, 1980) which relies on observer/clinician ratings of personality and behavioral adaptations to generate measures related to behavioral control and "resiliency", found that children with higher levels of resilience at age 3–5 years were less likely to use alcohol by age 14. On the other hand, initial resilience showed no association with the likelihood of getting drunk by age 17. Several studies of college student samples have linked increased resilience to lower alcohol consumption. Johnson et al. (2011) found a negative correlation between CD-RISC score and alcohol consumption levels, measured on a scale from abstaining to binge drinking, in a small college sample from the Midwest, while Elton et al. (Elton et al., 2021) found a negative association between CD-RISC score and binge drinking, measured by a score combining information on speed of drinking and frequency of drinking to get drunk (Townshend and Duka, 2002). In this latter study, in which the sample included students with and without a family history of AUD., the association between resilience and binge drinking score was stronger in individuals with a family history of AUD (Elton et al., 2021).

Several studies of college students conducted during the COVID-19 pandemic lockdown highlight the role of resilience in the context of a highly stressful global event. Three studies utilizing the Brief Resilience Scale (BRS) found either an overall decrease or no change in alcohol consumption from before to during the COVID-19 pandemic, with resilience as one of several predictors of changes in consumption. Wattick et al. (2021) found a modest association between resilience and decreased alcohol consumption after accounting for a larger association between moving back home and increased alcohol consumption. Zysset et al. (2022) found that higher BRS score was associated with decreased likelihood of increased consumption during the pandemic, while Rubio et al. (2023) found that among regular drinkers, lower resilience was associated with an increase, rather than a decrease, in consumption. Tam et al. (2023), using the 10-item CD-RISC, found that while there was no direct effect of resilience on drinking among Chinese college students, there was an indirect effect on drinking through anxiety symptoms, whereby resilience was associated with less anxiety and consequently, reduced drinking. Conversely, Cusack et al. (2022), who used a residual-based measure of resilience by regression internalizing symptoms against lifetime trauma exposure, found no association between this measure and alcohol consumption among college students impacted by the COVID-19 pandemic.

Resilience had also been linked to reduced alcohol consumption during the COVID-19 pandemic in adult samples. Two studies of adult populations including individuals with and without HIV demonstrated that higher BRS score was associated with lower consumption overall, and that people living with HIV showed higher resilience and less alcohol use than those without HIV (Baum et al., 2022; Diaz-Martinez et al., 2021). Among community-dwelling adults in Australia, resilience measured with the 10-item CD-RISC was found to moderate the relationship between perceived stress and alcohol consumption, whereby adults with low resilience were more likely to increase their alcohol consumption with increased perceived stress (Tudehope et al., 2022).

Two studies focused on specific populations of women have also investigated the association between resilience and alcohol use. Among sexual minority women, CD-RISC score was negatively associated with alcohol use (Foley et al., 2022), while in a sample of older women (62 or older), those individuals with higher resilience according to the BRS were actually at greater odds of being a moderate drinker (1 or fewer drinks per day) compared to being a non-drinker (Springfield et al., 2020). The authors speculated that this unexpected finding might be linked to the possibility that women consider moderate alcohol use to be beneficial to health.

Of note, four studies using four different measures of resilience have found no association between resilience and alcohol consumption. Goldstein et al. (2013) found no association between CD-RISC score and either past year alcohol use or past year binge drinking among emerging adults, while Sanchez et al. (2022) found no association between BRS score and either peak alcohol consumption within 24 h or frequency of binge drinking in the past three months among Hispanic college students. In the latter study, however, there were modest negative associations between BRS score and two drinking motives - drinking to cope and conformity motives. Nishimi et al. (2022), using a categorical measure of resilience based on cross-tabulating binary variables of adversity exposure (yes/no) and psychological health (high/low), found no association with prevalence of moderate alcohol consumption ($\leq$7 drinks/week for women, $\leq$14 for men) compared to higher levels of consumption. Finally, Cusack et al. (2022) measured resilience among newly enrolled college students using a residual-based method regressing internalizing symptoms against lifetime traumatic events, and found that this "baseline" level of resilience did not moderate the impact of COVID-19 (e.g., worry, exposure to the virus, housing/food insecurity) on alcohol consumption when measured at a follow-up timepoint during the spring of 2020.

4.2. Problematic alcohol use

The role of resilience in problematic alcohol use, most commonly measured by the Alcohol Use Disorders Identification Test (AUDIT) (Babor, 1989), has been studied primarily in adults. Several of these studies have been carried out in military service members and veteran populations, where combat exposure and a higher than expected prevalence of PTSD reflect the significant adversity experienced by these individuals. In a study of combat veterans, Green et al. (Green et al. (2010) found that CD-RISC score was negatively associated with AUDIT score, even after controlling for trauma exposure and PTSD diagnosis. In a related study that included a longitudinal follow-up component, a similar relationship between resilience and problematic alcohol use in military veterans was found, with both resilience at baseline and change in resilience from baseline to one-year follow-up associated with a decrease in AUDIT score (Green et al., 2014). Using a residual-based psychiatric resilience measure regressing a measure of overall psychological distress against lifetime traumatic events, Sheerin et al. (2019) found a negative correlation between resilience and AUDIT score, independent of the effects of combat exposure and level of social support.

Among college students, resilience has been linked to a reduction in problematic alcohol use both directly and indirectly, although existing studies are limited to female students. Using an assessment called the Resilience Research Centre Adult Resilience Measure (RRC-ARM), with 28 items assessing resilience capacities and therefore similar to the CD-RISC, Lyvers et al. (2020) found that resilience was associated with reduced AUDIT score in a sample of Australian students as an indirect effect through university-related stress. In a large national sample of college students in the U.S., resilience measured with the CD-RISC 2 was directly negatively associated with problematic alcohol use, but was not found to mediate the relationship between experiencing sexual assault and problematic drinking (Firkey et al., 2023).

Resilience measured with the CD-RISC has also been shown to moderate the relationship of problematic alcohol use with both childhood trauma and negative affect among adults. In men and women with a history of childhood trauma, CD-RISC score moderated the effect of childhood trauma severity on AUDIT score, such that individuals high on resilience had lower AUDIT scores across increasing number of childhood abuse types (Wingo et al., 2014). Among community-dwelling older adults, CD-RISC measures of resilience were found to moderate the relationship between both depression and anxiety symptoms and AUDIT score (van Gils et al., 2022). In this study the authors evaluated three latent factors of the CD-RISC corresponding to 'personal competence', 'adaptability', and 'spirituality' and found that personal competence and spirituality moderated the relationship of both depression and anxiety with problematic alcohol use, such that individuals scoring high on these factors exhibited no increase in AUDIT score with increasing depression or anxiety symptoms. Adaptability, on the other hand, was found to only moderate the relationship between depression and problematic alcohol use.

4.3. Alcohol-related consequences

Alcohol-related consequences refer to the negative effects on individual health and behavior due to excessive alcohol use. Although not as extensive as that for alcohol consumption, there is some evidence linking resilience to alcohol-related consequences. In a study of members of the U.S. National Guard, who according to some studies may actually experience greater overall stress than active duty military members, Morgan et al. (2018) found that higher CD-RISC score was associated with fewer alcohol-related consequences (e.g., drink driving, feeling sick, late for duty, physical fights, neglected work or home obligations, risky sexual behavior, tolerance to alcohol's effects, blackouts, and hangover). Furthermore, CD-RISC score moderated the relationship between number of stressors and alcohol-related consequences such that those with higher resilience experienced fewer consequences with

increasing stress. In the study by Sanchez et al. (2022) referenced earlier, while there was no relationship between BRS score and alcohol consumption, there was a negative association between BRS scores and alcohol-related consequences. Furthermore, resilience was found to moderate the relationships of both social drinking and enhancement drinking motives with alcohol-related consequences, with those high in resilience exhibiting few alcohol-related consequences even at high levels of drinking motives.

4.4. Alcohol use disorder

The role of resilience in the development of alcohol use disorder has been investigated using a variety of approaches and outcomes. For some, presence or absence of an AUD diagnosis is considered the main outcome of interest signifying resilience, but other outcomes such as the number of symptoms endorsed, severity of the disorder, and relapse risk among individuals treated for AUD have also been investigated. These outcomes are indicators of "relative resilience" among individuals either transitioning to or having already met criteria for AUD. Overall, individuals with a diagnosis of AUD tend to score lower on psychometric assessments of psychological resilience (CD-RISC and BRS) compared to healthy controls (Park et al., 2023; Sassoon et al., 2023; Schwandt et al., 2023). Studies explicitly investigating risk for AUD, on the other hand, have primarily utilized alternative measures of resilience. In an investigation using data from the National Epidemiologic Study on Alcohol and Related Conditions (NESARC), Overstreet et al. (2017) applied a residual-based quantification of psychological resilience, regressing PTSD symptom count on cumulative exposure to interpersonal traumatic events, and found that greater resilience was associated with decreased likelihood of AUD. In a study of members of the Norwegian military, psychological "hardiness", a primarily inherent characteristic purportedly related to resilience (Bartone, 1989), was found to be associated with decreased odds of developing AUD (Bartone et al., 2012). Subsequently, in a sample of Swedish twins, resilience-associated items of social maturity, interest, psychological energy, home environment, and emotional control extracted from a larger semi-structured interview, as well as a total resilience 'score', were associated with reduced risk for AUD (Long et al., 2017). This twin study also suggested a relationship between resilience and AUD risk that was due to both overlapping genetic (57%) and shared environmental factors (26%). Amstadter et al. (2016) likewise found genetic overlap between resilience and AUD when using a residual-based measure of resilience (regressing symptoms of depression, somatization, anxiety, and sleep difficulties against recent stressful life events), although the estimates for shared genetic and environment factors were lower (20% and 2%, respectively) than in the Swedish twin study. Correspondingly, GWAS, genome-wide complex trait analysis, and polygenic risk score (PRS) analyses have also revealed genetic overlap between resilience and AUD (Cusack et al., 2023).

In one of the few studies investigating a measure of biological resilience, Elton et al. (Elton et al., 2021) identified brain functional connectivity markers of resilience to AUD by examining individuals with AUD, their unaffected siblings (i.e., reflecting positive family history for AUD but with no disorder), and healthy controls. Resilience based phenotypes were identified based on 1) comparison between the three groups, whereby connections that were found to be different in unaffected siblings compared to both healthy controls and individuals with AUD were designated as potential resilience connections, and 2) canonical correlation analysis of both brain connectivity variables and behavior variables related to risk and resilience for AUD (e.g., personality measures, impulsivity and attention, positive and negative affect, social support, memory and cognition). The authors identified two resilience-based phenotypes reflecting lower attention problems/fewer internalizing symptoms and lower rule-breaking, which were correlated with connections among the brainstem, cerebellum, medial prefrontal cortex, striatum, insula, and medial temporal lobe. Resilience

phenotypes measured by both brain connectivity and behavior were associated with a reduced risk of AUD in this study.

Several investigations have examined the effects of residual-based psychiatric resilience on AUD symptom count, a metric that is regularly used to measure severity of AUD. Of note, however, not all individuals included in the relevant study samples actually met criteria for having the disorder. Two of these studies stand out by including a longitudinal component. The first of these (Cusack et al., 2021) was conducted among university students, with resilience measured at baseline (first semester enrollment) via residuals from regressing internalizing symptoms against lifetime traumatic events, and alcohol consumption, number of AUD symptoms, and new-onset traumatic experiences assessed at four yearly follow-up timepoints. No associations between baseline resilience and alcohol consumption were found at any of the time points; however, resilience was negatively associated with number of AUD symptoms in years 1 and 3. Resilience also moderated the effect of new-onset traumatic events on number of AUD symptoms in year 4, with the positive association between new onset events and AUD symptoms being attenuated in those with high resilience (Cusack et al., 2021). The second longitudinal study (Sheerin et al., 2021) utilized a sample from the Virgina Adult Twin Studies of Psychiatric and Substance Use Disorders (VATSPSUD), with baseline resilience at the first assessment wave measured using residuals from regressing internalizing symptoms against recent (past 90-day) stressful life events. Baseline resilience and new-onset stressful life events were negatively and positively associated, respectively, with number of AUD symptoms at the second assessment wave, however in this study there was no moderation of the effect of new-onset events by resilience. The longitudinal nature of these studies provide important information on the effects of resilience in the context of new-onset adversity, an element that is lacking in cross-sectional studies. However, the resilience measures were only collected at baseline, reflecting an assumption that these residual-based constructs of resilience are trait-like and relatively stable over time (Cusack et al., 2021).

A third study, also conducted on a sample from the VATSPSUD but without a longitudinal component, utilized a variation of the residual-based measure of psychiatric resilience measured at baseline and the phenotype of "alcohol resistance", or the number of AUD symptoms in relation to maximum alcohol consumption (Sheerin et al., 2021). In essence, high alcohol resistance, characterized by high consumption coupled with a low number of AUD symptoms, is conceived as a subtype of resilience that is specific to AUD. In this study, residual-based measures of both psychiatric resilience and alcohol resistance were generated using latent constructs of psychiatric risk and alcohol risk, which were then regressed on stressful life events and maximum alcohol consumption, respectively. A moderate-level genetic correlation (0.54) was observed between psychiatric resilience and alcohol resistance, indicating shared genetic underpinnings. Of note, however, both psychiatric resilience and alcohol resistance were characterized by relatively large estimates of unique environmental factors (67–71% and 74–75%, respectively), underscoring the contributions of individual experiences (e.g., peer influence), social and other external support sources, and learning processes to individual resilience (Sheerin et al., 2021).

Severity of AUD is also measured by assessments such as the Alcohol Dependence Scale (ADS) (Skinner and Horn, 1984), and existing evidence, including some of our own work, suggests resilience is negatively associated with this measure of severity. In a random sample of Chinese adults, resilience measured via the Essential Resilience Scale was negatively associated with AUD severity, and was found to moderate the association between stress, negative emotions, and AUD severity – specifically, the indirect effect of stress on AUD severity through anxiety and depression was attenuated among those with higher resilience scores (Wang and Chen, 2015). In our own work, we have examined resilience using both data-driven methods and the CD-RISC, and examined how these measures relate to AUD severity using the ADS. Applying latent class analysis to a sample of individuals with a history of

moderate to severe childhood trauma exposure, we identified three classes of individuals, with one class characterized by resilience-associated characteristics (i.e., low neuroticism coupled with high conscientiousness, low impulsivity, and reduced levels of negative affect). This class exhibited significantly lower ADS scores compared to the other two classes (Ramchandani et al., 2018). More recently, we analyzed resilience in two independent samples of adults using the CD-RISC, with one sample assessed in the context of the COVID-19 pandemic. In both samples, CD-RISC score was negatively associated with ADS score, with the strongest relationship observed among individuals diagnosed with AUD. We also observed an association between CD-RISC score and a reduction in failure to control drinking in the COVID-19 sample (Schwandt et al., 2023).

Finally, there is preliminary evidence linking resilience to relapse risk among individuals in treatment for AUD. Using the Bidimensional Resilience Scale (Hirano, 2010) developed in Japan, Yamashita et al. have found negative associations between both innate and acquired resilience and measures of relapse risk in a relatively small sample of AUD patients participating in self-help group meetings (Yamashita and Yoshioka, 2016; Yamashita et al., 2021). The relationship between resilience and relapse is one area that certainly warrants additional research, since stress is a known trigger for relapse (Blaine et al., 2017; Blaine and Sinha, 2017), and preventing relapse is one of the primary goals in treatment programs for AUD.

5. Implications for prevention and treatment

The research summarized above provides evidence supporting the role of resilience as a protective factor against the effects of stress on the development of AUD as a diagnosis, and as a mitigating factor influencing severity of the disorder and risk of relapse. Consequently, the potential exists for the application of resilience-building therapies and interventions to enhance the prevention and treatment of AUD. The goal of such interventions is not to reverse changes that have taken place in response to stress - although some pharmacological interventions might do this to some extent – rather, it is to provide prospective means of coping with adversity and fostering the ability to adapt in positive ways. Consistent with recommendations for AUD treatments in general (Boness and Witkiewitz, 2023; Koob, 2024; Litten et al., 2015; Lohoff, 2020), interventions to promote resilience can and should be tailored to meet individual needs, and ideally will integrate aspects of psychological, behavioral, and pharmacological interventions.

Psychological and behavioral approaches that could prove beneficial include cognitive behavioral therapy, with a focus on enhancing cognitive reappraisal and attention control (Southwick et al., 2015), mindfulness meditation, positive emotion exercises (e.g., maintaining a "gratitude" journal or writing about positive life experiences), coping skills training, learned optimism training, facilitating social interaction/social-support-seeking, and physical exercise (Alim et al., 2012; Feder et al., 2019; Garland et al., 2014; McEwen et al., 2015; Southwick et al., 2015; Wu et al., 2013). Strength-based interventions that build a sense of purpose and foster prosocial acts could also help build resilience (Hamby et al., 2021). Comprehensive resilience training programs such as stress inoculation training and hardiness training, which combine various techniques and often include several phases (e. g., education, skills acquisition, and practice) (Southwick et al., 2015) could also be employed.

There are at present several lines of evidence suggesting interventions that target specific components of resilience may improve treatment outcomes among those with AUD. A systematic review of determinants of relapse in individuals with AUD identified non-drinking social support networks, spirituality and a sense of meaning in life, and self-efficacy as protective factors against relapse (Sliedrecht et al., 2019). In an analysis of outcomes from the COMBINE and Project MATCH studies, Roos and Witkiewitz (Roos and Witkiewitz, 2016) showed that among individuals treated for AUD, those with a broad

range of coping skills that were used in a consistent manner had better treatment outcomes (i.e., higher percent days abstinent, fewer drinks per drinking day, and fewer alcohol-related consequences) compared to those with a narrow range of coping skills. Participants in a Mindfulness-Oriented Recovery Enhancement (MORE) program which integrates mindfulness training, cognitive restructuring, and elements of positive psychology administered across ten sessions in a residential setting, reported through narrative accounts an increase in self-awareness and enhanced ability to cope with emotional distress (such as guilt and shame), and a reduction in addictive impulses (Garland et al., 2012). In terms of practices geared towards social support, Network Support Treatment, a program developed to help AUD patients build a social network more supportive of abstinence, has been shown to improve abstinence outcomes and potentially increase self-efficacy and coping (Litt et al., 2009, 2016). In Korea, a Therapeutic Community Program, which utilizes a drug-free residential setting in the community, rather than in a hospital or medical setting, and which emphasizes mutual self-help and social support from the community to promote positive lifestyle changes, has been shown to increase resilience, reduce drinking, and promote positive lifestyle changes in individuals with AUD (Lee et al., 2019; Song et al., 2022).

Given the various neurobiological systems involved in resilience, there is considerable potential for a variety of pharmacological treatments to help promote resilience to stress. Several candidate pharmacological treatments for promoting resilience in PTSD, such as medications targeting the HPA-axis (e.g., mifepristone) and adrenergic and Neuropeptide Y systems, as well as ketamine and 3,4-Methylene-dioxymethamphetamine (MDMA), likewise have the potential to boost resilience in AUD patients (DePierro et al., 2019; Feder et al., 2019; Vendruscolo et al., 2015). Medications targeting the serotonergic and GABAergic systems such as tiagabine, fluoxetine, and sertraline, have already been associated with an increase in resilience, as measured by the CD-RISC, in individuals being treated for PTSD (Connor and Davidson, 2003; Davidson et al., 2005). Preclinical evidence suggests that L-4- Fluorophenylglycine, an inhibitor of neutral amino acid transporters ASCT1 and ASCT2 that are involved in D-serine transport, and kappa-opioid antagonists may provide clinical benefit to those with AUD by promoting stress resilience (Chavkin, 2018; Sung et al., 2022). Additional targets, based on the literature concerning the biological basis of resilience, include dopamine receptor agonists, monoamine oxidase inhibitors, dopamine reuptake inhibitors, CRF antagonists, oxytocin, and DHEA (Southwick et al., 2005; Wu et al., 2013). Notably, many of the neurobiological targets mentioned above are also implicated in the development of novel treatments for AUD, with a focus on pharmacological treatments directed at specific stages of the addiction cycle (binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation) (Koob, 2024).

6. Conclusions and implications for future research

Overall, the studies reviewed here provide reasonable and expanding evidence for resilience as a protective factor against the effects of stress and adversity on alcohol use and the development of AUD. Although not all studies investigated this explicitly, the effects of resilience on alcohol-related phenotypes were frequently revealed through indirect or interactive pathways, wherein measures of resilience mediated or moderated the effects of childhood trauma, current and lifetime cumulative stress, and negative affect on alcohol consumption and alcohol-related problems. This is consistent with the conceptualization of resilience as occurring specifically in the context of exposure to adversity. In this respect, recent studies conducted during the COVID-19 pandemic offer intriguing data on the role of resilience during a wide-spread, chronically stressful period of adversity that greatly affected mental well-being among individuals of all ages (Penninx et al., 2022; Theberath et al., 2022). That said, existing research on resilience in alcohol use disorder is still characterized by several limitations. First, resilience has primarily

been assessed as a capacity (e.g., CD-RISC or other measure) or as an outcome (e.g., residual-based measures of psychological functioning), most often taken at a single point in time. Further research is needed that evaluates resilience as a process, whether though 1) longitudinal investigations of changes in resilience over time, 2) experimental studies of change in how individuals respond to repeated psychological stressors and factors that contribute to positive trajectories of change, and/or 3) systematic evaluation of methodologies that encourage and strengthen resilience in individuals exposed to stress and trauma. Second, due to significant heterogeneity in how resilience has been assessed, comparison and replication of findings and generalization of results to the larger population is also limited. Greater harmonization of resilience measures is called for, a need that is recognized across health disciplines and not just within the field of alcohol and addiction. Third, generalizability is further limited by an overall lack of diversity within and among the study samples. Evidence suggests that rates of childhood trauma and other life stressors such as racism and discrimination are higher among minority populations (McLaughlin et al., 2009; Schwandt, 2023), however examinations of resilience specifically among these populations and how it relates to alcohol use and misuse are limited. Furthermore, the salience of specific resilience factors can vary as a function of cultural influences (Ungar, 2011). Fourth, sex differences in resilience and the impact of resilience on alcohol use need to be investigated more thoroughly, in light of well-documented sex differences in the response to stress (Heck and Handa, 2019; Hodes and Epperson, 2019), childhood trauma exposure (Lee and Chen, 2017; Moody et al., 2018; Saunders and Adams, 2014), stress-related alcohol use (Peltier et al., 2019), alcohol-related consequences (White, 2020) and prevalence of AUD (SAMSHA, 2021). Finally, existing research has focused primarily on individual-level resilience. More research is needed on how community factors and resources influence not only individual alcohol use, but success of community-based alcohol treatment programs and alcohol-related policies as well. To that end, the NIH resilience framework (Brown et al., 2023a) offers a design tool and roadmap for resilience research studies, with the ultimate goal of building an integrative approach that takes into account psychological, behavioral, and biological measures at the individual level as well as sociological and cultural elements from the community and societal levels (Brown et al., 2023b; Elwood et al., 2023).

CRediT authorship contribution statement

Melanie L. Schwandt: Writing – review & editing, Writing – original draft, Conceptualization. **Eva Cullins:** Writing – review & editing, Writing – original draft. **Vijay A. Ramchandani:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors have no conflicts of interest to report.

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