Alcoholism: A Life Span Perspective on Etiology and Course

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Alcoholism is a disorder involving problems with the use of alcohol such that the consumption becomes compulsive and/or negatively affects the person's health, personal relationships, and ability to fulfill major role obligations (e.g., work, family). For over 30 years, the disorder was defined by the Diagnostic and Statistical Manual (DSM) disorders of *alcohol dependence* and *abuse*. Dependence involves physiological addiction (tolerance or withdrawal) and/or compulsive alcohol use, where use is continued despite problems of physical and mental health as well as impairment in social, family, and job responsibilities. Alcohol abuse involves less severe drinking problems, including hazardous use (e.g., drunk driving) and social problems (e.g., legal problems due to drinking), but not physiological dependence. There is little evidence, however, to justify the distinction between symptoms of abuse and dependence (Borges et al., 2010). Rather, problematic alcohol use seems best conceptualized as a continuum ranging from heavy use to severe symptoms. As such, the broader term alcohol use disorder (AUD) is now used in the recently published, latest edition of the DSM (DSM-5), which we also use to refer to the general condition of problematic alcohol use over time.

From a developmental psychopathology perspective, AUD occupies a special place among other disorders for a number of reasons. The first is common to all substance use disorders, but not other forms of psychopathology, namely, that the deviant behavior occurs in conjunction with an external object. As such, a distinguishing feature of AUD is that the availability, regulation of use, and patterns of use within the social context have direct impact upon the development of the disorder. For example, AUD is not a high-prevalence disorder in abstinent Muslim countries, but it may become a problem for those with high-risk profiles who emigrate or travel. Related to availability, prevalence of AUD has been shown to vary with the overall the use structure of the larger social system in which it is embedded (Reich, Cloninger, Van eerdewegh, Rice, & Mullaney, 1988). Thus, when consumption rates are higher, there is a lower threshold for moving into problem activity because access is easy and the cue structure for continued use is also more common. Under these conditions, population rates for AUD increase. Conversely, when social controls are tighter and the normative structure is more abstinence orientated, rates of AUD decrease.

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Second, alcohol is a drug of everyday use and occupies a special place in the social order that ties patterns of use and abuse to other stages of the life cycle more tightly than most other psychiatric disorders. Ethanol is the world's most domesticated psychoactive drug. It is heavily sought after for its pharmacological effects and in the form of beer and wine is one of the world's most common foods and celebratory substances. Thus, alcohol's use structure is heavily embedded in the fabric of the majority of modern societies. It is a drug of courting, recreation, and relaxation and also the drug with which we sometimes mourn.

Third, because alcohol is embedded in the fabric of everyday life, both alcohol use and AUD are superimposed upon the ongoing life structure. Therefore, patterns of AUD differ as a function of life course variations upon which alcohol involvement is overlaid (Zucker, 1998). Therefore, an understanding of AUD needs to take account of the life cycle variations that co-occur with age, affect availability, and to a degree either proscribe or prescribe use with shifts in role structure. Thus, many of the trends in epidemiological data are explained by this life cycle variation, but this underlying variation is often not sufficiently emphasized.

Finally, a notable advantage in understanding etiological course is that AUD cannot occur prior to the discrete event of initiation of alcohol use. This allows for a clear separation between preexisting risk factors and factors that may either be confounded with the symptoms of the disorder or involve different expressions of the same underlying risk structure. Also, substance use disorders have a relatively late onset, with early-onset cases typically emerging in middle to late adolescence. By that point in the life course, there has been substantial development of personality structure and exposure to environmental risks. This provides the opportunity to track individual differences in the underlying risk structure for lengthy periods both before and after initiation, which assists in delineating the causal role of various risk factors contributing to the development and maintenance of AUD.

To do justice to the complexity of the biopsychosocial matrix of risk obviously requires more space than is available here. To manage this limitation, after a brief review of epidemiology, we address several topics critical to understanding AUD including heterogeneity of course, developmental trends, early risk factors with a focus on behavioral disinhibition/dysregulation, and genetic and environmental influences including gene–environment interplay. We also provide a brief discussion of the neurobiology of addiction. A recurrent theme is the need to disaggregate risk into two domains: one involving nonspecific risk factors shared between AUD and other impulse control disorders, and the other involving risks that are specific to AUD.

Epidemiology

Table 29.1 summarizes findings from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) for the 12-month and lifetime prevalence rates for DSM-IV alcohol abuse and dependence (Hasin, Stinson, Ogburn, & Grant, 2007). NESARC was conducted in 2001–2002 and included 43,093 respondents age 18 to over 65. In order to give a broader perspective on the alcohol problem, we also present rates for illicit drug abuse and dependence (Compton, Thomas, Stinson, & Grant, 2007). A number of points about these prevalence rates are of importance:

1. Alcohol abuse and dependence are much more common than illicit drug use disorders.
2. Among males, 4 in 10 have at some point in their lives met abuse or dependence criteria.
3. Gender differences are significant and approximate 2:1 for both abuse and dependence.
4. Illicit drug use disorders are substantially less of an issue than alcohol abuse/dependence with a ratio of 12-month alcohol to drug disorder of over 4:1.
5. Illicit drug use disorders are to a large degree superimposed upon AUDs given that a minority of 12-month drug disorders occur without a concomitant AUD diagnosis.

Table 29.1 Lifetime and 12-month prevalence of DSM-IV substance use disorders

	Total		Male		Female	
Disorder	Lifetime	12 months	Lifetime	12 months	Lifetime	12 months
Alcohol abuse without dependence	17.8	4.7	24.6	6.9	11.5	2.6
Alcohol dependence	12.5	3.8	17.4	5.4	8.0	2.3
Alcohol abuse/dependence combined	30.3	8.5	42.0	12.4	19.5	4.9
Drug abuse	7.7	1.4	10.6	2.0	5.2	0.8
Drug dependence	2.6	0.6	3.3	0.9	2.0	0.4
Drug abuse/dependence combined	10.3	2.0	13.8	2.8	7.1	1.2

Source from Hasin et al. (2007) and Compton et al. (2007) National Epidemiologic Survey on Alcohol and Related Conditions and are weighted non-institutionalized United States population percentage estimates for persons 18 years or older

6. The visibility of illicit drug use disorders is likely because they are more dramatic, hence socially compelling; because they appear more of a threat to the social order (e.g., because of their links with crime and the belief that they may be less responsive to treatment); and because societal costs involved in interdiction and treatment are proportionately much larger.

Related to the these points, AUD is nationally one of the most prevalent psychiatric disorders with approximately 30 % of the population reporting symptoms sufficient for either an abuse or dependence diagnosis at some point during their lives. Thus, the set of problems encompassed by this disorder is an extraordinarily large one. At the same time, when examining the disorder from a developmental perspective, among all those who meet the AUD criterion, there is substantial heterogeneity of onset and course. Such variation has been identified at least as far back as Carpenter (1850), and because the variation continues to emphasize the point that "one size does not fit all," there have been periodic attempts to classify the heterogeneity.

Heterogeneity of Course and Phenotype

Babor's (1996) review of this literature noted that different classification schemes identify two consistent "types," with different etiologies and symptom presentations. One type is characterized by early onset, physical aggression, more severe dependence symptoms, a denser positive family history—suggesting a stronger genetic basis—and more personality disturbance. The other is characterized by later onset of alcohol dependence, a slower disease course, fewer social complications, less psychological impairment, and a better prognosis. More recent studies using factor analytic and cluster analytic techniques continue to identify these two forms, but a number of others have also been identified. The unearthing of this larger spectrum of course heterogeneity is due to the newer studies' use of samples that are less chronic, improved statistical methodology, and utilization of functional characteristics rather than symptoms to make the differentiation. Leggio, Kenna, Fenton, Bonefant and Swift (2009) provide a comprehensive tally of the current array.

Developmental Trends

Only in the past generation has significant attention been paid to the earlier developmental manifestations of these course variations by utilizing prospective course information to more accurately characterize course variation. This work has focused more on course of heavy drinking than on AUD symptoms. Reviewing this literature, Maggs and Schulenberg (2005) note that virtually all of the studies identify four pathways of heavy use: a chronic/severe and continuing trajectory, a mild low-level binging and symptom group, an initially severe use group that drops off with entry

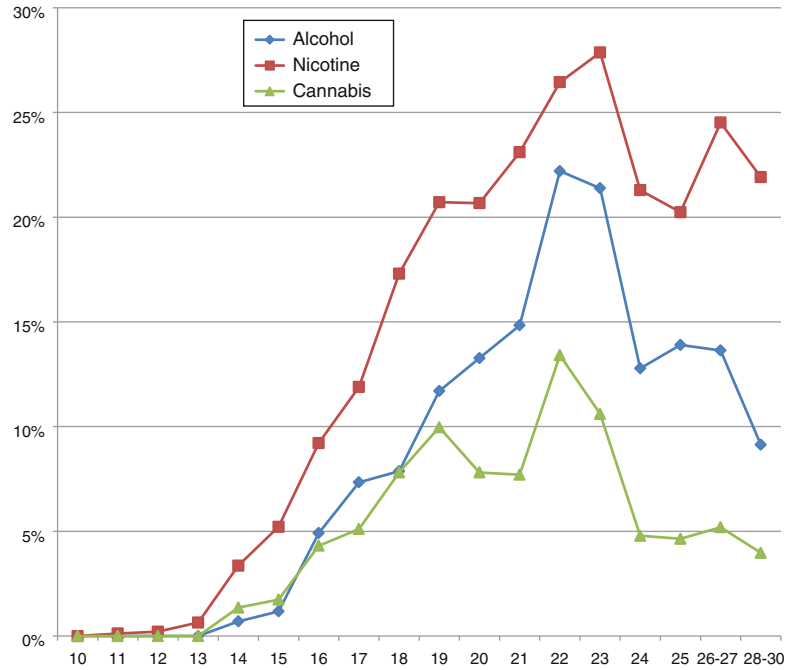

Fig. 29.1 Prevalence of alcohol, nicotine, and cannabis use disorder by chronological age in the longitudinal twin, adoption, and family studies of the Minnesota Center for Twin and Family Research ($N = 5{,}001$). Each substance use disorder was defined as the presence of three or more symptoms of abuse or dependence according to DSM-III-R criteria, the current diagnostic system when the earliest studies began. Participants reported on the symptoms over the past 3 years

into early adulthood, and one that begins in adolescence and escalates over time into adulthood. The later-onset path for this last group is not well understood.

There are also normative developmental trends in age of onset, escalation, and decline of the prevalence of AUD over the life course. To illustrate this patterning, we report data from the longitudinal Minnesota Twin Family Study (Iacono, McGue, & Krueger, 2006). Approximately 5,000 individuals began participating in this study as either children or adolescents and have been followed until about age 30 reporting on patterns of substance use every 3–5 years. Fairly large and representative samples are available for almost each year between ages 10 and 30 to track developmental trends in the prevalence of substance use disorders.

In Fig. 29.1, the prevalence rates of substance use disorders in the Minnesota Twin Family Study sample are presented for the three most widely used substances in the United States: alcohol, nicotine, and cannabis. Substance use disorders were defined as 3 symptoms of abuse or dependence according to DSM-III-R criteria (the diagnostic system that was current when the study began). Based on these data, substance use disorders first emerge in a small subset of people around ages 14–15, followed by a steep rise in the prevalence rates of each disorder through adolescence until rates peak at ages 21–23. Around age 24, there is a notable decline in the prevalence of each disorder. Nicotine dependence is always the most common substance use disorder. AUD and cannabis use disorder have similar prevalence rates until about age 20, whereupon there is a dramatic increase in AUD that outpaces that of cannabis use disorder. During the late 20s, nicotine dependence and cannabis use disorder decline to relatively stable prevalence rates of slightly over 20 % and about 5 %, respectively. In contrast, AUD continues to decline out to age 30 to a prevalence rate of slightly less than 10 %. Given the lifetime prevalence rates reported from the NESARC, it would appear that the vast majority of people who meet criteria for a substance use disorder will first do so before age 30.

These patterns suggest that (1) nonspecific risk processes likely underlie the emergence and rapid escalation of each substance use disorder

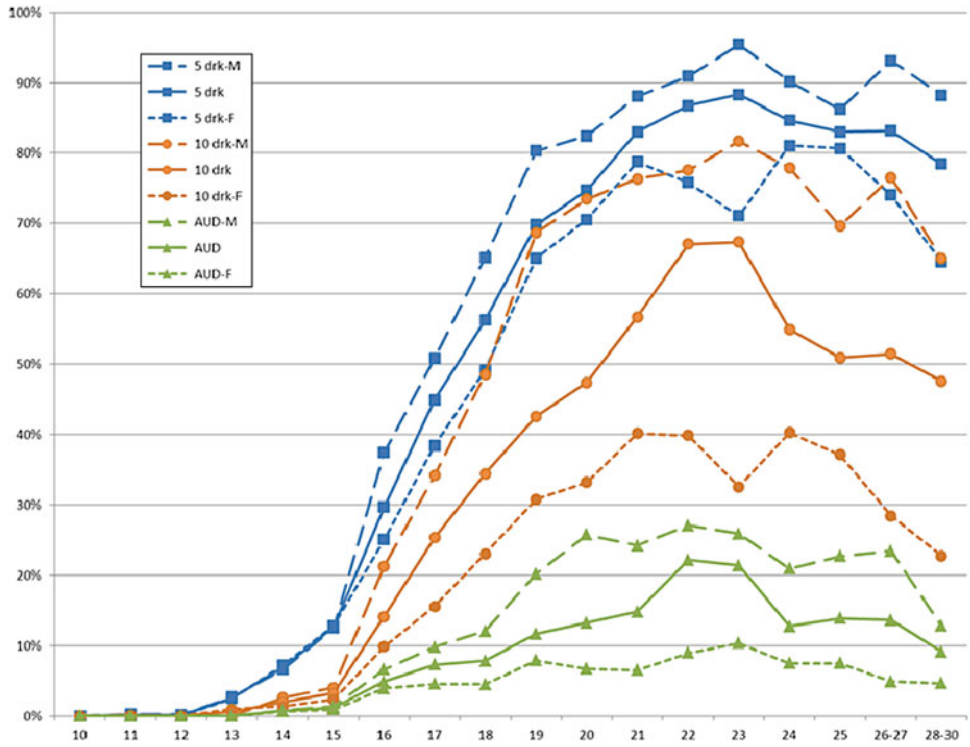

Fig. 29.2 Prevalence of alcohol use disorder and binge drinking defined as 5+ and 10+ drinks in a 24-h period as function of chronological age in the Minnesota Center for Twin and Family Research sample. Prevalence rates are also provided separately for men and women

in late adolescence and young adulthood and (2) similar general processes likely underlie the reductions in substance use disorders beginning in the mid-20s, though the rate of this decline differs across substances. Differences in legal status and psychoactive effect across the substances undoubtedly account for many of the differences in prevalence. Specifically, the sale and purchase of tobacco and alcohol are both legal, which contributes to their higher prevalence rates relative to cannabis. In terms of psychoactive effects, nicotine is associated with greater physiological dependence than alcohol, but persistent nicotine dependence has weaker associations with psychosocial impairment than persistent AUD. As such, tobacco is harder to quit using than alcohol, but nicotine dependence is easier to live with than AUD, hence the higher prevalence rate for nicotine dependence than AUD, especially as people transition into middle adulthood.

A major premise of this volume is that adult disorders do not emerge full-blown in adulthood, but rather are the endpoint of a process that culminates over time for which childhood precursors and risk factors can be identified. To illustrate this, Fig. 29.2 presents the rates for two measures of binge drinking (consuming either 5 or 10 drinks in a 24-h period)—markers of problematic alcohol use that typically precede AUD symptoms—along with the prevalence rates for AUD. Rates are reported separately for males and females to illustrate the large gender differences for both use and disorder.

These data illustrate that by middle adolescence there is a subset of individuals who are already exhibiting problematic alcohol use that portends later AUDs. For example, by age 15 over 10 % of the sample reported consuming 5 drinks on one occasion, and by age 16 over 20 % of males reported consuming 10 drinks on one occasion. The increases in drinking are so dramatic

that heavy drinking is essentially normative by age 19 and ubiquitous by age 23. While not everyone who engages in heavy drinking goes on to develop AUD, heavy drinking provides the necessary context as the rates of AUD closely track those of binge drinking, especially binges of 10 or more drinks. Also note the dramatic gender differences in the rates of larger binges and AUD. By age 18, the rate for women who reported a binge of 5 drinks is equal to the rate for men who reported a binge of 10 drinks, and the rate of AUD in men is over twice that of women; these gender differences persist at least to age 30. Men it seems literally drink twice as much as women.

Early Risk Factors

I. Behavioral Disinhibition

Although the prevalence of AUD begins its ascent in late adolescence, increased risk for AUD can be detected at much younger ages. Like many disorders, a family history of AUD is a robust predictor of AUD and also suggestive of genetic influences. Family history, however, does not rule out environmental influences, as genetic and environmental influences are confounded when biological parents raise their own children. Family history then is only a proxy for risk, the mechanisms of which require further explication. Moreover, not all families with an alcoholic parent contain the same levels of risk, and in some, the vulnerability components may be largely absent. Designs that leverage family history—most notably children of alcoholic parents studies—can be especially helpful by comparing individuals who differ on family history of AUD on a number of variables to identify potential risk pathways. One long-term high-risk study, the Michigan Longitudinal Study, has been following a large number of families with either an alcoholic father or control families in which neither parent had an alcohol or illicit drug use disorder, for over 25 years beginning when the children were 3–5 years old (Zucker et al., 2000). They found that even at ages 3–5, children of an alcoholic parents exhibited significantly more internalizing (anxiety, depression) and externalizing (aggression, rule breaking) problems than children of nonalcoholic parents, indicating risk mechanisms for AUD are present long before even the initiation of alcohol use.

Several lines of evidence including long-term longitudinal studies of high-risk (e.g., children of alcoholic parents) and epidemiological samples have demonstrated a robust association between childhood externalizing behavior and an earlier age of initiation of substance use, heavy use, and onset of substance use disorders in general, not just for alcohol (Armstrong & Costello, 2002). At the diagnostic level, externalizing behavior is typically operationalized as one of the disruptive behavior disorders (conduct disorder, oppositional defiant disorder, attention deficit hyperactivity disorder) or as scores on problem behavior checklists (aggression, rule breaking). As such, rather than antisocial behavior per se, the broader temperament trait of **behavioral disinhibition**—defined as an inability to inhibit socially undesirable or restricted behavior—is the key childhood risk factor for later problematic substance use (Iacono, Malone, & McGue, 2008; Zucker, Heitzeg, & Nigg, 2011). The phenotypic or observable manifestations of behavioral disinhibition are typically referred to as **"externalizing,"** which includes disinhibited personality traits, disruptive behavior disorders, substance use disorders, and antisocial behavior.

The conceptualization of a behavioral disinhibition liability provides a model of general and specific risk processes for AUD. Most notably, this model helps to account for the high rates of co-occurrence or comorbidity between AUD and other substance use disorders as well as with antisocial behavior and disinhibited personality traits. AUD and other addictions rarely occur in isolation, but rather tend to be part of a profile of correlated externalizing features. Conceptually then, persons who exhibit multiple externalizing disorders are simply higher on the behavioral disinhibition dimension. A meta-analysis of several epidemiological studies comprising over 23,000 individuals that modeled the structure of 10 common mental disorders found that the covariance among AUD, illicit drug use disorders, and the

child and adult symptoms of antisocial personality disorder was best modeled by a single underlying externalizing factor (Krueger & Markon, 2006; also see Kendler, Prescott, Myers, & Neale, 2003). Juxtaposed to this externalizing factor was a latent "internalizing" factor that accounted for the comorbidity among unipolar mood and anxiety disorders. Specific risk processes then differentiate these general liability dimensions into the specific disorders and accounts for why people manifest some disorders and not others.

II. Early Onset of Use

Another early risk factor for AUD is the age at which individuals first use alcoholic beverages. Persons who have their first use before age 15 are approximately four times more likely to meet criteria for alcohol dependence in adulthood relative to persons who first tried alcohol at age 20 or later (Grant & Dawson, 1997). Consistent with a model of nonspecific risk processes, earlier age of first use (<15 years old) has frequently been identified as an intermediate outcome associated with behavioral undercontrol, disruptive behavior disorders, and academic problems in preadolescence, which then predicts not only AUD but also nicotine dependence, illicit drug dependence, and antisocial personality disorder in adulthood (McGue, Iacono, Legrand, Malone, & Elkins, 2001). It also is associated with a more rapid progression to and longer duration of alcoholism, greater difficulty achieving abstinence, and more severe symptom profiles of AUD.

III. Negative Affectivity/Internalizing

In addition to behavioral disinhibition, there is a long history of work indicating an internalizing or negative affect pathway to AUD (Hussong, Jones, Stein, Baucom, & Boeding, 2011; Zucker, 2006). The major evidence for an internalizing pathway comes from a small number of prospective studies showing a relationship between internalizing symptoms in childhood and an AUD outcome in adulthood (Caspi, Moffitt, Newman, & Silva, 1996; Hawkins, Catalano, & Miller, 1992; Kellam, Brown, Rubin, & Ensminger, 1983; Kellam, Ensminger, & Simon, 1980). Indirect evidence for an internalizing pathway is also suggested by the elevated rates of comorbidity between AUD, major depression, and some anxiety disorders (Hasin et al., 2007), as well as the moderate correlation ($r=0.50$) between the latent internalizing and externalizing dimensions (Krueger & Markon, 2006). Also, personality traits that tap negative emotionality such as neuroticism are elevated in both internalizing disorders and AUD (Krueger, Caspi, Moffitt, Silva, & McGee, 1996). The longitudinal evidence for a direct childhood internalizing pathway, however, is mixed, especially after controlling for comorbid externalizing (Chassin, Pitts, DeLucia, & Todd, 1999; Costello, Erkanli, Federman, & Angold, 1999; Kaplow, Curran, Angold, & Costello, 2001). Although the prospective studies already noted find a positive association between internalizing and substance use disorders, others find a null or negative association (Kaplow et al., 2001; Masse & Tremblay, 1997). Possibly the association between internalizing and AUD is a function of greater symptom severity, or it may only operate as a moderator of externalizing characteristics.

Genetic Influences

Twin and adoption studies have demonstrated that genetic influences play an important role in the development of AUD (Goldman, Oroszi, & Ducci, 2005). For such biometric analyses, the variance of a trait is partitioned into additive genetic (a^2), shared or common environment (c^2), and non-shared or unique environment (e^2) components by comparing the similarity of individuals on the trait who differ in genetic relatedness (e.g., by comparing the similarity of monozygotic twins to that of dizygotic twins). The ratio of genetic variance to total variance is called the heritability estimate. The shared environment refers to environmental influences that contribute to similarity among relatives (e.g., being part of the same peer group that encour-

ages drinking). The non-shared environment refers to environmental influences that contribute to differences among relatives (e.g., having romantic partners that differ in attitudes toward substance use).

Twin studies consistently find that genetic influences account for approximately 45 % of the variance of AUD and measures of quantity and frequency in adulthood (Dick, Latendresse, et al., 2009; Dick, Prescott, & McGue, 2009; Goldman et al., 2005). The relative genetic and environmental influences are moderated by age, however, as initiation of alcohol use exhibits both moderate genetic and shared environmental influences as does quantity/frequency and AUD in adolescence (Dick, Latendresse, et al., 2009; Dick, Prescott, & McGue, 2009). Further, longitudinal studies have found that genetic influences increase and shared environmental influences decrease with age (Bergen, Gardner, & Kendler, 2007). This suggests that shared environmental influences are important to initiation and early drinking, but that genetic and non-shared environmental influences are determinative for long-term problematic alcohol use in adulthood.

Several multivariate twin studies have also established that there is substantial common variance in genetic influences among AUD, nicotine dependence, and illicit drug dependence, as well as with their precursive nonspecific risk components, namely, antisocial behavior and disinhibited personality traits (Button et al., 2006; Kendler, Meyers, & Prescott, 2007; Slutske et al., 1998, True et al., 1999). This work prompted the fitting of biometric factor models to estimate the heritability of the externalizing factor, which would identify the extent to which comorbidity among externalizing phenotypes was due to common genetic and environmental influences. These studies find that externalizing is highly heritable (70 % to 85 %) in late adolescence and young adulthood, with little or no shared environmental influences (Kendler et al., 2003; Krueger et al., 2002; McGue, Iacono, & Krueger, 2006). These estimates are typically higher than for any individual disorder, with the externalizing factor accounting for the majority of genetic variance in each disorder. Each substance use disorder, however, also exhibited specific genetic and non-shared environmental variance. These findings are consistent with a hierarchical model of risk, involving a highly heritable nonspecific risk factor, but with the final phenotypic expression of the nonspecific risk determined by environmental and genetic influences that are unique to each disorder.

Genetic influences on nonspecific risk also shift over the course of development. McGue et al. (2006) found that the covariance among five trait indicators of early adolescent problem behavior was only modestly heritable ($a^2 = 0.18$) with moderate shared environmental influences ($c^2 = 0.39$). However, the association between problem behavior at age 15 and the more heritable externalizing factor underlying adult disorders at age 20 ($a^2 = 0.75$) was entirely due to common genetic influences, suggesting genetic influences are particularly important to the stability of externalizing over time. Also, the impact of the general externalizing factor on individual substance use disorders appears to peak in late adolescence and decline thereafter as disorder-specific effects increase (Vrieze, Hicks, Iacono, & McGue, 2012). Most of the decline is attributable to the fact that externalizing accounts for less heritable variance of the individual disorders, while disorder-specific genetic and environmental effects increase with age. These findings are consistent with the interpretation that a highly heritable behavioral disinhibition liability leads to nonspecific substance use and externalizing behaviors in late adolescence, but that substance-specific risk factors increase in importance as people age, leading to a specialization in substance use and abuse over time.

Identifying specific genes that reliably account for this nonspecific genetic risk for externalizing disorders and for AUD is high on the current research agenda, but the actuality has yet to be fully realized. The most promising candidate gene may be the $GABA_A$ receptor α2 subunit (*GABRA2*) on chromosome 4. GABA is a major inhibitory neurotransmitter that is sensitive to ethanol including its anxiolytic effects (Grobin, Matthews, Devaud, & Morrow, 1998). *GABRA2* has now been associated with several externalizing

phenotypes including alcohol and drug dependence, antisocial personality disorder and conduct disorder, and an electrophysiological endophenotype. There is also some evidence that the effects of *GABRA2* are moderated by environmental context including parental monitoring and marital status (Dick, Latendresse, et al., 2009; Dick, Prescott, & McGue, 2009).

Given the abundant nonspecific genetic risk, it is somewhat ironic that the most replicable genes associated with risk for AUD are specific to alcohol sensitivity (Higuchi et al., 1994). Aldehyde dehydrogenase (ALDH) is the rate-limiting enzyme in the metabolism of ethanol, and the rate of its production varies as a function of ALDH genotype. The mutant form of *ALDH2* (*ALDH2*2* allele) is inefficient at converting acetaldehyde—a toxin and the initial metabolite of ethanol—into acetate. After consuming alcohol, carriers of the *ALDH2*2* allele experience flushing, nausea, and headaches due to the accumulation of acetaldehyde. As a result, individuals with more acetaldehyde inefficient alleles exhibit lower rates of AUD. Notably, the frequency of the *ALDH2*2* variant differs widely across ancestral populations, being common in certain East Asian populations but virtually absent in European populations, which helps to account for some of the historic differences in rates of AUD across world populations. Also, this genetic mechanism is specific to AUD, as demonstrated in a study that showed East Asian adoptees in the United States who carried the *ALDH2*2* allele were less likely to have problems with alcohol use, but not less likely to have ever tried alcohol; they also exhibited similar levels of nicotine and marijuana use and antisocial behavior as those without the *ALDH2*2* allele (Irons, McGue, Iacono, & Oetting, 2007).

A recent advance in gene association methodology has been the advent of genome-wide association studies that are able to interrogate a target phenotype on over one million single nucleotide polymorphisms (SNPs) of common variation (minor allele frequency >0.01). Findings from genome-wide association studies show that the effect for any individual SNP is small, and sample sizes in the many thousands are necessary to detect even a small number of risk SNPs that exceed genome-wide significance ($p < 5^{-8}$). An early genome-wide association study of alcohol dependence included over 1,500 male cases and 2,300 matched controls detected two SNPs on chromosome 2 in linkage disequilibrium with the peroxisomal trans-2-enoyl-coenzyme A reductase (*PECR*) gene, which is involved in fatty acid metabolism and primarily expressed in the liver (Treutlein et al., 2009). A much larger study of alcohol consumption ($N > 47{,}000$) detected an association with the autism susceptibility candidate 2 gene (*AUTS2*) (Schumann et al., 2011). The mechanism by which *AUTS2* effects alcohol consumption is unclear, but it has been linked with other neurobehavioral disorders in humans and alcohol sensitivity in animals. Of note, this study failed to detect an association with the *PECR* gene. Despite the advantage of scanning the whole genome and the possibility of generating novel leads for etiology then, it is clear that genome-wide association studies for alcohol use phenotypes are in their early stages, and extensive follow-up studies will be needed to delineate the causal chain from genotype to phenotype.

Environmental Risk and Person–Environment Transactions

AUD is also affected by a variety of environmental influences related to family, peer, school, and neighborhood contexts (Hawkins et al., 1992; Zucker, 2006). A family history of AUD, especially in combination with antisocial behavior, is associated with increased risk via various mechanisms involving both inherited risk and disorganization of the social environment (Puttler, Zucker, Fitzgerald, & Bingham, 1998). The link between externalizing and these contextual risk factors tends to follow a typical developmental sequence culminating in early initiation of substance use and escalation to substance use disorders by late adolescence (Granic & Patterson, 2006). This sequence has been called a developmental cascade, as exposure to one contextual risk factor increases the likelihood of exposure to

another, and involves transactions with person-level risk factors. Specifically, high-risk rearing environments are characterized by poor parent–child relationships, harsh and inconsistent discipline, lax parental monitoring, and parental substance abuse that provides children with access and models for use. Such ineffective parenting and family management practices combined with undercontrolled temperament traits then result in child conduct problems, which in turn are often followed by academic failure and disengagement and rejection by prosocial peers. Failure to bond with these socializing agents then increases the likelihood of depressed mood and hostility and deviant peer affiliation. Deviant peer affiliation sets the stage for an early initiation and rapid escalation of substance use in adolescence, as well as with concomitant adolescent problem behaviors (e.g., delinquency, precocious and risky sexual behavior; Jessor & Jessor, 1977). Reinforcing these processes are contextual factors such as family, money, and legal problems, parental conflict and divorce, and residence in neighborhoods characterized by high rates of poverty, crime, and residential instability, all of which have been associated with high rates of adolescent substance abuse (Appleyard, Egeland, van Dulmen, & Sroufe, 2005; Buu et al., 2009; Hawkins et al., 1992). Importantly, these contextual risk factors are nested, and exposure is disproportionately spread across the population, such that youth are typically exposed to not one but several of these risk factors (Appleyard et al., 2005; Hicks, South, DiRago, Iacono, & McGue, 2009; Zucker, 2006).

Exposure to environmental risk is also not independent of the child's characteristics, as the child's behavior both elicits responses from others and moves the child into circumstances that increase exposure to risk. For example, using an empirical approach, Hicks, Iacono, and McGue (2014) identified the childhood personality trait of socialization (conformity to rules and adult supervision and endorsement of conventional moral and ethical values) was most predictive of later substance use disorders in the Minnesota Twin Family Study sample. Additionally, socialization at age 11 was strongly correlated with several concurrent contextual risk factors associated with substance use disorders including deviant peer affiliation, academic failure and disengagement, poor parent–child relationships, and stressful life events.

Such person–environment transactions continue to be played out over the life course. A study by Buu et al. (2007) provides an example of this transactional process, wherein the residential migration patterns of sociodemographically matched families with or without an alcoholic father were tracked over a 12-year interval. Families with an alcoholic father were more likely to either remain in or migrate into a disadvantaged neighborhood (high crime, poverty, and residential instability). Conversely, men whose AUD was in remission tended to live in neighborhoods whose residential characteristics were indistinguishable from those of non-AUD men. Shifting the focus to the children of these men, Buu et al. (2009) found that these same characteristics of neighborhood disadvantage during early childhood (ages 3–5) predicted alcohol, nicotine, and marijuana symptoms as well as antisocial personality disorder and major depression in young adulthood (ages 18–20) even after controlling for family history of AUD.

While we have focused on nonspecific processes of both person-level and environmental risk, there are also alcohol-specific risk processes that are present at a young age. Social cognition studies have found that preschoolers in the general population have already learned two core alcohol use schemas of the larger culture, namely, that alcohol consumption is age graded (alcohol use is acceptable for adults but not for children) and also is sex typed (use is more common for adult males than for adult females) (Noll, Zucker, & Greenberg, 1990; Zucker, Kincaid, Fitzgerald, & Bingham, 1995). Noll et al. (1990) also established that the knowledge of alcoholic beverage use patterns is acquired in the home rather than through media exposure. Zucker et al. (1995) later showed this effect is heightened among high-risk families by virtue of a resident alcoholic parent; children of alcoholic parents were better than children of nonalcoholic parents in correctly identifying specific alcoholic

beverages. Also, the extent to which children attributed alcohol use to common life situations (picnics, family meals, school lunch, adult parties) was predicted by their parents' level of alcohol consumption. In short, children's alcohol schemas relating to both knowledge and use were more sophisticated in the families with an alcoholic parent and were more salient in families where the drinking was more common and therefore more visible.

Gene–Environment Interplay

The foregoing not only illustrates the importance of both genetic and environmental influences on the development of AUD but also indicates that the underlying mechanisms of risk are a function of gene–environment interplay rather than simply main effects of genes and environments. Two mechanisms of gene–environment interplay are gene–environment correlation and gene × environment interaction. Gene–environment correlation refers to the nonindependence between a person's genotype and the likelihood of exposure to environmental risk, such that those with higher genetic risk also tend to experience greater environmental risk exposure (Scarr & McCartney, 1983). Passive gene–environment correlations arise from parents providing both the genes and the rearing environments. The Buu et al. (2009) study finding that parental AUD was associated with residence in disadvantaged neighborhoods, which in turn increased risk for negative outcomes in offspring, is an example of such a passive gene–environment correlation.

As children transition into adolescence and gain greater autonomy in selecting their environments, active gene–environment correlations become more relevant mechanisms to the development of substance use and abuse, which also emerge during the same period (Bergen et al., 2007; Scarr & McCartney, 1983). Active gene–environment correlations primarily arise because heritable individual differences increase exposure to trait-congruent environments that then increase risk for substance use disorders. Hicks et al. (2013) used a longitudinal-twin design to delineate active gene–environment correlation processes over time, between the nonspecific risk (under)socialization trait at age 11, an environmental risk composite at age 14, and a composite of substance use disorders at age 17 involving alcohol, nicotine, and marijuana disorders. Low socialization predicted substance use disorders at age 17 but was also strongly correlated with environmental risk at age 14. Moreover, low socialization at age 11 predicted greater environmental risk at age 14, even after controlling for the stability of environmental risk from ages 11 to 14. In turn, environmental risk at age 14 mediated some—but not all—of the effect of low socialization at age 11 on substance use disorders at age 17. In fact, 78 % of the genetic correlation between childhood socialization and adolescent substance use disorders was mediated by environmental risk at age 14. That is, to the extent that (under)socialization accounts for heritable risk in substance use disorders, the mechanism is indirect, via increased exposure to high-risk environments.

Gene × environment interactions have also been documented for alcohol use and AUD and again emphasize that the importance of + genetic influences on alcohol use outcomes varies as a function of the environmental context. For example, in a Finnish study, Dick, Rose, Viken, Kaprio, and Koskenvuo (2001) demonstrated gene × environment interactions for areas with more young adults (more role modeling), greater social mobility, and higher regional alcohol sales, all of which encouraged a greater expression of genetic disposition to heavier use. Other investigators have found that genetic influences on alcohol initiation and alcohol use were weaker for adolescents who were highly religious (Koopmans, Slutske, van Baal, & Boomsma, 1999) and for women who were married (Heath, Jardine, & Martin, 1989), respectively. A common thread that may be operating across these environments is one of the greater social controls, such that more constrained environments depress the influence of genetic factors. Such an effect is not limited to alcohol; for example, genetic influences on smoking are attenuated in the context of high parental monitoring (Dick et al., 2007). A comprehensive

test of this hypothesis was carried out by examining the impact of six different environmental variables on the genetic influences of a composite of externalizing disorders in late adolescence (Hicks et al., 2009). For each environmental variable, genetic influences on externalizing were greatest in the context of greater environmental adversity. These findings are consistent with a general mechanism of gene–environment interplay for externalizing disorders, such that those with the greatest genetic risk were the mostly likely both to be exposed to environmental risk (gene–environment correlation) and to be most sensitive to the influences of environmental risk factors (gene × environment interaction).

Neurobiology of Addiction

AUD and problems of undercontrol more generally are associated with a number of neurocognitive deficits (Oscar-Berman, 2000). While prolonged substance use—especially chronic and heavy alcohol use—has neurotoxic effects, some neurocognitive deficits, most notably those involving deficits in control and inhibition, are present in those at high risk for substance use disorders even before symptoms are present and thus are indicative of an etiological role rather than a consequence of use (Corral, Holguin, & Cadaveira, 2003; Tarter et al., 2003). The neural underpinnings of these deficits involve regions of the brain that regulate the incentive motivation and effortful control networks (Bechara, 2005; Kalivas & Volkow, 2005; Robinson & Berridge, 2003; Wiers et al., 2007; Zucker et al., 2011). These systems are interconnected and exist in a dynamic tension such that an imbalance between the two provides a model for addictive behavior.

The incentive motivation network is responsible for scanning the environment for the anticipation of reward and detection of potential danger (Berridge & Robinson, 2008; Kalivas & Volkow, 2005). The network centrally involves the anterior cingulate cortex, as well as other structures including the ventral striatum, nucleus accumbens, and ventral tegmental area that are major dopaminergic or reward structures of the brain. The processes of the incentive motivation network are relatively automatic in that they do not require higher order mental resources and operate rapidly. It is sensitive to novelty and incentive cues that signal potential near-term reward or loss, orientating the organism by interrupting ongoing behavior. The incentive motivation network is distinct from the more basic appetitive systems that underlie motivations and emotions such as hunger or fear, which are sensitive to actual reward or loss rather than cues that signal their potential. The system orientates the organism to the incentive stimulus by inducing high arousal or excitement rather than by inhibiting previous behavior, while also activating attentional resources to the novel stimulus. The basic appetitive systems are sensitive to the psychopharmacological effects of drugs including addiction following drug ingestion. In contrast, the incentive motivation network becomes excessively activated following repeated failures to obtain the drug; thus, it is a liability marker for drug problems.

The incentive motivation network is functionally integrated with other brain structures that collectively constitute the effortful control network, notably the dorsolateral and orbitofrontal prefrontal cortex and inferior frontal gyrus (Miller & Cohen, 2001). Functionally, the effortful control network uses the information obtained from the incentive motivation network to guide responses, often by modifying an ongoing behavioral set. Effortful control involves the ability to regulate behavior to fit contextual demands and maintain a goal set by way of forming mental representations of a distal goal via working memory processes rather than by immediate incentives and cues. Effortful control likely reflects both activation in prefrontal cortical regions and suppression of activation in limbic regions, particularly the ventral striatum-nucleus accumbens structures.

Heuristically, the incentive motivation network can be thought of as a "bottom-up" process, while the effortful control network functions via "top-down" processes. As such the two systems are in dynamic tension to generate and modulate behavior (Zucker et al., 2011). An imbalance in activation between the two systems then leads to the loss

of control of drug use and addictive behavior. For example, especially strong activation of incentive motivation processes can overcome the inhibiting processes of the effortful control network. Alternatively, weak control processes will fail to inhibit or modulate even relatively modest incentive motivation drives. When modulation of incentive drives fails, undercontrolled behavior occurs and the individual goes forward with behavior despite a signal of potential problems (Heitzeg, Nigg, Yau, Zubieta, & Zucker, 2008). Ultimately, the extent to which drug (or other) cues provide greater activation of the incentive motivation network with relatively less activation of the effortful control network, an individual has less control over drug use behavior.

Developmentally, the reason adolescence is a period of high risk for substance use and abuse may be because maturation (or at least levels of activation) of the incentive motivation network outpaces that of the effortful control network (Spear, 2000). Limbic and striatal systems are relatively mature and responsive to cues, biasing behavior during adolescence. Thus, adolescents are especially sensitive to rewards and engage in high levels of exploratory and risk-taking behaviors, increasing risk for substance use and abuse. In contrast, areas such as the dorsolateral prefrontal cortex are some of the last brain regions to mature, contributing to the tendency to act impulsively and fail to delay gratification, appropriately modulate emotional reactivity, and consider the consequences of risky behavior. As prefrontal structures mature, nonspecific substance use and externalizing behavior decline, and substance-specific processes become more determinative in the persistence of problematic substance use.

Summary and Conclusion

Why some people lack the ability to moderate their intake of alcohol to the point that their use is compulsive and disrupts their ability to meet major life roles and responsibilities remains a complex question, but one where substantial progress has been made in finding an answer. AUD is an endpoint that will always be preceded by the initiation of alcohol use and regular drinking and that will only manifest after a period of heavy use. These are discrete mileposts, objectively assessed, and they occur relatively late in psychosocial development, all of which are advantages in identifying risk factors, developmental sequencing, contextual triggers and moderators, and causal structure. Much of the risk in childhood is nonspecific and is primarily the consequence of a broad and highly heritable behavioral disinhibition liability that increases risk not just for AUD, but for a spectrum of externalizing phenotypes including other substance use disorders, antisocial behavior, and disinhibited personality traits.

The behavioral disinhibition liability is expressed as several developmentally intermediate phenotypes prior to full-blown AUD in adulthood. At the personality level, early in life, it involves the trait of (under)socialization. At the behavioral level, its extreme phenotypic manifestation is in the form of the disruptive behavior disorders of childhood. In adolescence, the phenotype continues to involve disruptive behavior and rule breaking, but it also involves precocious substance use, usually including other drugs in addition to alcohol.

This liability also has a contextual parallel involving heightened exposure to conflictful and socially disorganized environments, which in turn provide poorer parental monitoring and a greater probability of parental abuse. Some of this elevated exposure is a direct outcome of niche seeking by individuals high in behavioral disinhibition. It also occurs as a result of passive, correlated environment effects which create a higher probability of exposure to the exacerbating environmental circumstances. We have elsewhere referred to this interconnected and overdetermined risk matrix as a "nesting structure" (Zucker et al., 2006), which changes the process model because the variable network is more likely to produce overlearning and coalescence of a risky behavioral repertoire.

At the neurobiological level, these disorders are largely a function of two interconnected brain systems, one of effortful control (primarily localized in the prefrontal cortex) and the other

involving incentive motivation (localized in the subcortical reward systems of the brain). These systems mature at different rates, and their imbalance in adolescence, as well as major changes in arousal regulation that occur during this interval, likely accounts for much of the dramatic increase in substance use and abuse in adolescence and young adulthood (Windle et al., 2008). The extent to which preadolescent differences in strength of these systems also play a role in creating individual differences in susceptibility to drug involvement remains unknown, but it is an issue of major interest to the research community at this time.

The generalized risk conferred by behavioral disinhibition and early environmental risk eventually gives way to substance-specific risk factors as people begin to specialize in their substance use and exhibit long-term problematic use. Though behavioral disinhibition is a core, early emerging pathway to AUD, the adult manifestations of the disorder are etiologically heterogeneous. Developmental specifiers of onset and persistence of AUD are helpful in identifying distinct etiological groups, with adolescent onset and persistent course past young adulthood indicative of severe psychopathology. Desistence, however, has substantial ameliorative effects, providing for recovery after even relatively severe substance abuse. Some of the correlates of desistence are known (e.g., marriage, parenthood, treatment), but the underlying mechanisms of effect require elaboration.

It is also instructive to note that when examining AUD as it occurs across the population, a substantial proportion of AUD individuals exhibit a "developmentally limited" form of the disorder (Zucker, 2006), where return to normative levels of use takes place without the assistance of treatment. At the same time, another subset of those moving into diagnosis in adolescence/early adulthood will remain involved in recurring and severe alcohol abuse throughout the life span and will leave a trail of personal and collateral damage that creates tragedy at the individual level and is responsible for major social and health costs at the societal level. For this subset, a return to moderate levels of consumption is not an option; the disorder needs to be regarded as a chronic and recurring disease, requiring monitoring and periodic intervention thereafter (McLellan, Lewis, O'Brien, & Kleber, 2000). The ability to identify these different developmental trajectories prior to the onset of first diagnosis is an essential task, which will bring the ultimate practicality of developmental science into the clinic and the community. Such work is currently under way, but still in its infancy (see NIAAA, 2011).

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