

ADULT COGNITIVE FUNCTIONING IN ADOLESCENT-ONSET AND  
PERSISTENT ALCOHOL USE DISORDERS IN MEN

A THESIS  
SUBMITTED TO THE FACULTY OF  
UNIVERSITY OF MINNESOTA  
BY

Jordan Corrie Sparks

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS  
FOR THE DEGREE OF  
MASTER OF ARTS

William Iacono

May 2013



## Abstract

Alcohol use disorders (“AUDs”) have a high prevalence rate, are heterogeneous, and are associated with deficits in executive abilities, learning, and memory. The literature on adolescent AUD and adult cognitive functioning is limited, and no prospective study has simultaneously examined how an AUD-onset during a neurologically-vulnerable period, persistence of use in adulthood, and an interaction of these processes may attenuate or exacerbate cognitive issues. This study used two AUD subtypes commonly employed to characterize the heterogeneity in AUD presentation – the adolescent-onset and persistent subtype – to address these questions, and also relied on measures of behavioral disinhibition and intellectual functioning ascertained during childhood to address the concern that the relationship between AUDs and later-cognitive functioning may be subject to confounding. It was hypothesized that premorbid childhood risk factors would relate to both AUD subtype and adult cognition, that both an adolescent-onset and a persistent course of AUD would relate to cognitive deficits in adulthood, and that accounting for premorbid risk factors would attenuate this relationship. A community sample of 650 men born in Minnesota was assessed at six visits occurring between age 11 and age 29 and divided into AUD groups of adolescent-onset persisters and desisters, adult-onset persisters and desisters, and controls. Both AUD-membership and age 29 cognitive performance were associated with risk factors that preceded AUD-onset; when accounting for premorbid risk, there was scant evidence that AUDs were associated with cognitive deficits. Future research of AUDs and cognition should account for premorbid risk factors.

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## Chapter 1.

### Literature Review

#### 1.1 Introduction

Maladaptive alcohol use represents a significant area of public health concern due to the ubiquity of alcohol use disorders and the constellation of associated detrimental outcomes. Results from the National Epidemiologic Survey on Alcohol and Related Conditions revealed a lifetime prevalence rate for alcohol use disorders (“AUDs”) over 30% (Hasin, Stinson, Ogburn, & Grant, 2007) with a much higher rate (42%) in men. With such a high prevalence rate, AUDs represent a heterogeneous group most accurately conceptualized as a continuum of severity rather than a dichotomous category (Hasin et al., 2003). In an effort to more precisely characterize the *range* of possible AUD presentations and effectively match individuals to treatments, researchers have long examined AUDs in terms of subtypes that provide more detail about the course of the disorder. Two well-supported subtypes include the adolescent-onset subtype, reflecting whether an individual has an AUD-onset during adolescence, and the persistent subtype, reflecting whether an individual’s AUD does not remit after emerging adulthood.

A separate literature has examined the nature of the cognitive deficits associated with AUDs and, interestingly, has revealed that whether an individual *misuses alcohol during adolescence* and whether they fail to *desist from use* may be important factors in predicting deficits. However, there is scant literature that has addressed both of these processes simultaneously, limiting conclusions about their unique associations with adult cognition and potential interactions. As such, the aforementioned subtypes may be useful

in investigating the processes that contribute to AUD-related cognitive impairment. This study seeks to test the association between adult cognitive functioning and both the adolescent-onset and persistent AUD subtypes. Further, it seeks to determine whether this association is accounted for by risk factors that precede AUD-onset.

## **1.2 Significant Features of Subtype Typologies: Onset & Persistence**

### ***1.2.1 Onset Subtype***

In the last fifty years, many typologies for problematic alcohol use have been offered; the most well-known include Jellinek's work on alcoholism "species," Cloninger's Type I and Type II, and Babor's Type A and Type B (reviewed in Gunzerath, Hewitt, Li, & Warren, 2011). Age of AUD onset is frequently used to characterize these different typologies. Individuals with an early onset of alcohol dependence in adolescence experience increased levels of alcohol consumption, a higher incidence of antisocial personality disorder, a higher probability of other substance misuse, lower educational achievement, more legal problems, more familial conflict, increased comorbidity with psychiatric disorders, lower likelihood of seeking help following diagnosis, and more severe levels of dependence, including longer duration of alcohol dependence episodes, more frequent episodes, and a wider range of dependence symptoms (Hicks, Iacono, & McGue, 2010; Hingson, Heeren, & Winter, 2006; Johnson, Cloninger, Roache, Bordnick, & Ruiz, 2000; Moss, Chen, & Yi, 2007; Rohde, Lewinsohn, Kahler, Seeley, & Brown, 2001; Wills, Sandy, Yaeger, & Shinar, 2001).

### ***1.2.2 Persistent Subtype***

According to the National Survey on Drug Use and Health (2011), the prevalence of AUDs increases from 4.5% among 12-17 year olds to 15.6% among 18-25 year olds; it subsequently decreases to 5.9% after age 25. Some of these key differences in prevalence can be explained by the decreasing rate of new AUD cases in the mid-twenties (Dawson et al., 2005; Hingson et al., 2006; Li, Hewett, & Grant, 2004). However, another contributor to the difference in prevalence is that many individuals in their mid-twenties “desist” from their AUD. For example, Dawson et al. (2005) found in their study of adults previously diagnosed with alcohol dependence that over 43% of individuals 18-29 were still dependent at follow-up, whereas only 22% of individuals age 30-44 were still dependent. Desistance most typically occurs in the later-20s, leading individuals who persist with their AUDs beyond this point to be dubbed “developmentally deviant” by some researchers (Copeland et al., 2012). While the correlates underlying AUD persistence have not been as thoroughly investigated as the adolescent-onset subtype, the extant literature suggests that desistance is associated with new role obligations (e.g., marriage, children, leaving college and entering the workforce) (Bachman et al., 2002; Copeland et al, 2012; Littlefield, Sher, & Wood, 2010; Leonard and Rothbard, 1999; O’Malley, 2004; O’Malley & Johnston, 2002; Staff et al., 2010; Yamaguchi & Kandel, 1985).

### **1.3 Alcohol and Cognitive Functioning**

Approximately 50% of the 20 million individuals in the United States with alcohol dependence exhibit some cognitive impairment (Oscar-Berman & Marinkovic,

2003), typically presenting as deficits in executive abilities, learning, and memory (Green et al., 2010; Tedeschi et al., 2012). Consistent with these findings, neuroimaging studies suggest that the brain regions associated with these cognitive abilities – the frontal cortical areas and limbic region – are particularly vulnerable to alcohol’s neurotoxic effects (Beresford et al, 2006; Moselhy, Georgiou, & Kahn, 2001; Oscar-Berman & Marinkovic, 2003; Pfefferbaum, Sullivan, Mathalon, & Lim, 1997).

These vulnerable areas change considerably during adolescence. The limbic system increases in volume and the frontal regions decrease (Giedd, 2004; Giedd, 2008). This plasticity may leave the adolescent brain *especially* susceptible to alcohol’s effects (Ehlers & Criado, 2010; Guerri & Pascual, 2010). Animal studies (Crews, Mdzinarishvili, Kim, He, & Nixon, 2006; Markwiese, Acheson, Levin, Wilson, & Swartzwelder, 1998) and brain imaging studies (De Bellis et al, 2000; De Bellis et al, 2005; Medina et al., 2008; Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007) all point to this conclusion. Further, neuropsychological performance studies (e.g., Brown, Tapert, Granholm, & Delis, 2000; Brown & Tapert, 2004; Ferrett, Carey, Thomas, Tapert, & Fein, 2010; Squeglia, Spadoni, Infante, Meyers, & Tapert, 2009; Ziegler et al., 2005) demonstrate that adolescents who use alcohol problematically exhibit cognitive deficits. How adolescent use relates to *adult* cognitive functioning is less studied, although some prospective studies have found that adolescents with heavy drinking histories continue to display cognitive deficits into adulthood (e.g., Tapert, Granholm, Leedy, & Brown, 2002).

A key question is how desistence from problematic drinking may relate to adult cognitive outcomes. In adult drinkers, abstinence has been demonstrated to ameliorate associated cognitive deficits, but it is unclear how these findings may vary depending on an individual's history of adolescent drinking. In two prospective longitudinal studies, individuals with a history of adolescent AUD were given a cognitive assessment in adulthood, with a specific focus on whether individuals who persisted in their use displayed impaired cognitive functioning compared to individuals who remitted. AUDs predicted deficits in verbal learning and memory irrespective of desistence in adulthood; further, recent use predicted poorer executive functioning and attention (Hanson, Cummins, Tapert, & Brown, 2011a; Hanson, Medina, Padula, Tapert, & Brown, 2011b). However, these studies did not examine how persistence might interact with age of AUD onset, as there were no individuals with an adult AUD-onset in the sample. In summary, there is a small body of literature surrounding later life cognitive outcomes associated with AUD-persistence and adolescent AUDs, but a systematic effort to examine the unique effects of each subtype on adult cognition is needed.

#### **1.4 Preexisting Risk Factors and AUD Subtypes**

If AUD subtypes are etiologically-related to risk factors that precede the onset of drinking and these risk factors *also* predict adult cognitive functioning, an association between AUD subtypes and cognitive functioning is subject to confounding. The literature raises concern about such a confounder, suggesting that the adolescent-onset subtype, and to some extent the persistent subtype, are associated with premorbid

“behavioral disinhibition” – i.e. “an inability to inhibit socially undesirable or restricted actions” (Iacono, Malone, & McGue, 2008) – that may also relate to adult cognition.

#### ***1.4.1 Adolescent-Onset Subtype***

It is well-established that early misuse of alcohol is associated with a propensity for behavioral disinhibition in preadolescence and an increased risk for externalizing disorders (e.g., antisocial personality disorder, childhood disruptive disorders, and other substance use disorders) (Holdcraft, Iacono, & McGue, 1998; Iacono, Carlson, Malone, & McGue, 2002; Sringeri, Rajkumar, Muralidharan, Chandrashekar, & Benegal, 2008). Further, all of these disorders can be linked to a latent “EXT” factor, which is highly heritable (Hicks et al., 2007). Thus, individuals with an adolescent-onset AUD are at increased risk for possessing this general EXT liability, and the etiology of their disorder likely stems (in part) from a common genetic propensity for behavioral disinhibition. There is also evidence that this general EXT liability may ground some of the same kind of cognitive impairments that are related to alcohol’s neurotoxic properties. For example, children and adolescents who go on to experience antisocial and substance use problems exhibit premorbid deficits in verbal ability and executive functioning (reviewed in Moffitt, 1993; Tapert, Baratta, Abrantes, & Brown, 2002). Executive functioning deficits have even been observed in preschool children with externalizing problems (Thorell & Wahlstedt, 2006). Finn et al. (2009) demonstrated that cognitive problems in individuals with adolescent-onset AUD were not uniquely related to alcohol problems, but rather a general liability for externalizing behaviors. These findings raise the possibility that any

association between adolescent-AUD and cognitive issues may be attributable to deficits associated with externalizing that existed premorbidly prior to the onset of drinking.

### ***1.4.2 Persistent Subtype***

Far less is known about the relationship between behavioral disinhibition and a persistent course. For example, in the Copeland et al. (2012) study, some variables traditionally associated with behavioral disinhibition and an adolescent-onset AUD predicted a persistent course (e.g., police contact) while others did not. Hicks et al. (2010) found that when adjusting for the effects of an adolescent-onset subtype, several measures of behavioral disinhibition at age 17 predicted a persistent course at age 29. In sum, there is clear evidence that a propensity for behavioral disinhibition is associated with the adolescent-onset subtype, and some limited evidence to suggest that it may be associated with the persistent subtype as well. As such, in investigating how AUD subtypes relate to adult cognitive functioning, it is critical to consider potentially confounding effects. Utilizing measures of risk that are assessed *before* the onset of alcohol use initiation is the most convincing in this regard, as it ensures that none of these risk measures could have been influenced by alcohol use.

## **Chapter 2.**

### **Current Study**

#### **2.1 Hypotheses**

The current study aims to extend the past literature by testing three related hypotheses. First, given concern that studies of AUDs and cognitive functioning are at risk for confounding by a general liability for externalizing, this study will investigate the

extent to which *specific AUD subtypes* are subject to this problem by examining how adolescent-onset and persistent AUDs relate to premorbid childhood disinhibitory risk and cognitive functioning. It is hypothesized that both the adolescent-onset subtype and persistent subtype will be associated with premorbid disinhibitory risk (*Hypothesis 1a*) and baseline cognitive functioning (*Hypothesis 1b*). Further, it is hypothesized that disinhibitory risk (and baseline childhood cognitive functioning) will be associated with adult cognitive functioning (*Hypothesis 1c*).

Secondly, this study seeks to determine if there is a unique relationship between each of the AUD subtypes and adult cognitive functioning. Specifically, based on the previous literature, it is hypothesized that individuals with an adolescent-onset AUD will demonstrate deficits in memory, learning, and working memory at age 29 compared to controls and individuals with an adult-onset AUD (*Hypothesis 2a*), and individuals with a persistent course of AUD will demonstrate greater deficits in working memory compared to controls and desisters (*Hypothesis 2b*).

As a follow-up to the first two hypotheses, to investigate whether the association with AUD subtypes and adult cognitive functioning is inconsistent with a causal explanation, it is hypothesized that after adjusting for premorbid risk, the relationship between the subtypes and adult cognitive functioning will be attenuated but still detectable (*Hypothesis 3*).

## **2.2 Methodology**

### **2.2.1 Sample**

The sample for this study was drawn from participants in the Minnesota Twin

Family Study (MTFS). The MTFS is a longitudinal, population-based study of twins born in the state of Minnesota. The sample was recruited via state birth records spanning 1972 to 1984. Addresses for over 90% of all twin births were located with public databases. Participants were contacted and their eligibility (no physical or mental disability, located within one day's drive) was assessed. Eighty-three percent of those eligible agreed to participate. The ethnic composition of the sample was representative of the population of Minnesota during the years ascertained (approximately 98% Caucasian). Mean years of education ranged from 13.7 years in mothers to 14.0 years in fathers. The male sample consists of 666 twin pairs (including three triplets) first assessed at age 17 (older cohort) or at age 11 (younger cohort). The current investigation utilized the younger cohort for a total sample of 757.

Subsequent follow-ups occurred (approximately) at age 14 ("FU1"), age 17 ("FU2"), age 20 ("FU3"), age 24 ("FU4"), and age 29 ("FU5"). Two individuals were excluded from the original intake due to physical limitations. A parallel sample of female twins was also recruited, but at the time of this study, they had not completed the FU5 visit. When individuals were unable to attend follow-up assessments, abbreviated phone interviews were attempted. The average age at each wave was 11.7 (SD=0.4), 14.8 (SD=.5), 18.0 (SD=.7), 22.0 (SD=.7), 25.3 (SD=.7), and 29.4 (SD=.7). At the time of analyses, participation rates were 92% (FU1), 86% (FU2), 84% (FU3), 86% (FU4), and 86% (FU5). All participants provided informed consent/assent at each wave of data collection, with parents providing consent for minors. For more detail about the MTFS

design, aims and sample, see Iacono, McGue, & Krueger, 2006; Iacono, Carlson, Taylor, Elkins, & McGue, 1999.

### ***2.2.2 Designation of AUD Subtype***

At the age 17, age 20, age 24, and age 29 assessments, trained MTFS staff with Bachelor's or Master's degrees in psychology interviewed each participant and assessed for the presence of substance use disorders. DSM-IV was the most current diagnostic system at the time of the age 17 assessment. At age 17, lifetime symptoms were assessed and incorporated a report from the individual's parent; at subsequent visits, diagnoses were based only on symptoms occurring since the last assessment.

For the purposes of this investigation, an individual was considered to have met criteria for AUD at a given assessment if they endorsed *two or more* symptoms of an AUD. Alcohol dependence and abuse symptoms are mutually exclusive in the DSM-IV framework, so this definition would have incorporated individuals with just abuse symptoms, just dependence symptoms, or both abuse and dependence symptoms. This categorization scheme was utilized for several reasons. The diagnostic constructs outlined in the DSM significantly impact public health and policy, affecting how insurance benefits are allocated, informing eligibility for treatment, and defining a target for research. It is valuable to use such pragmatically-rich constructs when possible. A categorical classification system is straightforward and simple, incurring a parsimonious advantage, but is also highly correlated with other continuous measures of alcohol consumption, as demonstrated in the Hicks et al. (2010) study that used the same subtype classification scheme with DSM-III-R symptoms. Importantly, Hicks et al. (2010)

demonstrated that using a threshold of two symptoms increased the study's power but still allowed for the detection of meaningful differences between subtype groups. Of note, the proposed criteria for the updated DSM-V diagnosis of alcohol use disorder also includes a two-symptom threshold and combines the categories of abuse and dependence into one overarching disorder (American Psychiatric Association, 2012).

Using this conceptualization, individuals were divided into groups based on the presence of AUD at age 17 through age 29. With respect to age of onset, if individuals first met criteria by FU2, they were designated "adolescent-onset" cases. If individuals first met criteria by FU3 or FU4, they were designated "adult-onset" cases. With respect to a persistent course, if individuals continued to meet criteria at FU5, they were designated a "persistent" case. If individuals endorsed zero symptoms at FU5, they were designated a "desistent" case. Finally, if individuals did not meet criteria for AUD at *any* assessment, they were designated a "control" case. Of note, some subjects who did not attend an assessment were still assigned membership into a group because if an assessment was missed, the following assessment covered the time elapsed since the last completed one, thus making it possible to obtain diagnostic information covering the time of the missed assessment.

Attrition analyses revealed that 1) individuals missing FU5 diagnostic information were not more likely to be designated "adolescent-onset" or "adult-onset" cases and 2) were not significantly different on age 11 indicators of behavioral and cognitive functioning. The categorization scheme successfully classified 84% of those eligible (N=545) – adolescent-onset persistent group, N=47, adolescent-onset desistent group,

N=67, adult-onset persistent group, N=59, adult-onset desistent group, N=91, control group, N=281. The remaining individuals were not categorized because 1) they endorsed one symptom of AUD at FU5 (N=55), making it unclear if they were persistent or desistent cases, because 2) they met criteria for AUD for the first time at FU5 (N=12), or because 3) they missed an earlier follow-up that made their symptom endorsement trajectory ambiguous (N=38).

### ***2.2.3 Measures of Alcohol Consumption***

To validate the use of the adolescent-onset and persistent-course categorization scheme, several continuous measures of alcohol consumption were included. At age 11, each individual and his parent reported on the individual's history of alcohol consumption via the Diagnostic Interview for Children and Adolescents – Revised (“DICA-R”) (Reich, 2000; Welner, Reich, Herjanic, Jung, & Amado, 1987). Measures included whether or not the child had ever taken an alcoholic drink or become intoxicated, scored positive if either the parent or child answered yes. At age 17 and 29, individuals received the modified version of the expanded Substance Abuse Module of the Composite International Diagnostic Interview (Robins, Babor, & Cottler, 1987). At age 17, measures included whether the individual had ever used alcohol and ever been intoxicated, frequency of drinking during the previous 12 months (reported in T-score metric), the number of lifetime intoxications, the largest number of drinks consumed in 24 hours, and the average number of drinks per use during the previous 12 months. These measures were repeated at age 29, where individuals were asked specifically about their consumption since the previous assessment. For measures that are only meaningful

for individuals who previously used alcohol (e.g., ever been intoxicated), analyses excluded non-drinkers. Several of the drinking variables exhibited marked skew and were log-transformed. The maximum number of drinks consumed in 24 hours was capped at 50 and lifetime intoxications were capped at 100.

## ***2.2.4 Measures of Age 11 Behavioral and Cognitive Functioning***

### *2.2.4.1 DSM-III-R Symptoms*

The DICA-R was used to assess DSM-III-R symptoms of attention-deficit hyperactivity disorder, oppositional defiant disorder and conduct disorder at age 11. Subjects were assessed for lifetime symptoms, and caregivers reported on each individual. A symptom was considered present if either the primary caretaker or subject endorsed it. Symptoms were coded as present at the “definite” or “probable” level. Probable symptoms were weighted half as much (0.5) as definite symptoms. Due to considerable skew, symptom counts were log-transformed.

### *2.2.4.2 Academic Problems*

Each subject and his parent completed scales assessing academic motivation (e.g., enjoys school, seems engaged) and various academic behavioral problems (e.g., received detention, sent home from school) at age 11. For each scale, parent and child report were averaged and converted to a T-score metric.

### *2.2.4.3 Delinquent Behavior Inventory*

The delinquent behavior inventory (“DBI”) is a 36-item scale of delinquent behaviors (Gibson, 1967). If the individual had engaged in the behavior at least once in their lifetime at age 11, they responded “yes.” Examples of these behaviors include

deliberately littering, going to see an X-rated movie, cutting classes, breaking into a store, using a fake ID, etc. A parent also reported on these behaviors, and this report was averaged with the self-report. The score was log-transformed due to marked skew.

#### 2.2.4.4 *Composite*

A composite measure of age 11 behavioral risk factors was created by averaging standard scores on each of the aforementioned measures (DSM-III-R symptoms, academic issues, DBI).

#### 2.2.4.5 *Wechsler Intelligence Scale for Children - Revised*

Brief measures of cognitive ability were taken at age 11. Subjects completed four subtests from the *Wechsler Intelligence Scale for Children - Revised* (WISC-R, Wechsler, 1974) tapping verbal and perceptual reasoning skills. The verbal and perceptual subtests were averaged and prorated to form a verbal and perceptual IQ measure.

### 2.2.5 *Measures of Adult Cognitive Functioning*

#### 2.2.5.1 *Rey Auditory Verbal Learning Test*

The Rey Auditory Verbal Learning Test (“RAVLT”) was administered at age 29. In the RAVLT (Rey, 1964; Schmidt, 1996; Spreen & Strauss, 1998), the participant is read a list of 15 words and asked to repeat back as many as they can remember (“Trial 1”). This process is repeated four times. Subsequently, the participant is read another list of 15 words (“Trial B”), asked to repeat back words from the second list, and then asked to repeat back words from the original list (“Trial 6”). After a delay interval, the participant is again asked to generate words from the original list (“Delay”).

The advantage of this assessment tool is that it taps several different areas of functioning, including short-term verbal memory, verbal learning, and post-interference recall (Rosenberg, Ryan, & Prifitera, 2009). Measures of RAVLT performance are total performance across all five learning trials (converted to a T-score metric), number of words recalled on Trial 1, Trial B, and the delay trial, number of words gained over the five learning trials (Trial 5 – Trial 1), proactive interference (Trial B – Trial 1), retroactive interference (Trial 6 – Trial 5), number of words forgotten at delay (Delay – Trial 6), and learning across all trials (converted to a T-score metric). As discussed above, verbal memory and learning represent one area of functioning demonstrated to be sensitive to alcohol's effects. RAVLT performance has been used in numerous studies in which it successfully indexed known problems with hippocampal function (e.g., Manns, Hopkins, Reed, Kitchener, & Squire, 2003), even correlating with the microstructure integrity of the hippocampus prior to volumetric changes (van Norden et al, 2012).

#### 2.2.5.2 *Digit Span*

The Digit Span subtest from the *Wechsler Adult Intelligence Scale, Revised* (WAIS-R, Wechsler, 1981) was administered at age 29. In Digit Span, participants are read a series of numbers and asked to repeat them back. The length of the series gradually increases over subsequent trials. Subjects are scored based on their overall accuracy as well as the span of the longest list they correctly remembered. Subjects are also asked to repeat the series of numbers backwards via the same procedure. Measures included are total performance on Digit Span Forward (“DSF”) and Digit Span Backward (“DSB”) as well as combined overall performance, scored via a scaled score metric, and

the highest span correctly reported on DSF and DSB. Of import for these purposes, DSF and DSB appear to tap different neuropsychological abilities. While DSF has been dubbed a measure of an individual's auditory memory capacity, as well as language skills, DSB involves additional processing demands of working memory, as the individual has to maintain the information in the short-term auditory-memory store even longer and subsequently manipulate it (Hale, Hoepfner, & Fiorello, 2002; Sattler & Ryan, 2009). Indeed, DSB has been demonstrated to predict a range of deficits in sustained attention, working memory, and executive functioning (Hale et al., 2002). Neuroimaging studies have established that the neural correlates of working memory are in the prefrontal cortex, one of the areas vulnerable to alcohol's effects (Curtis & D'Esposito, 2003; Linden, 2007).

### **2.3 Analytic Strategy**

Because twins tend to be more similar to each other than two randomly selected individuals, implementing a traditional analysis of variance test would violate the assumption that all observations are independent and essentially assume there is more unique information in the data than there actually is; as a result, the estimated standard errors of the parameter estimates would likely be too small (Zeger & Liang, 1992). Linear mixed models were used to account for the correlated nature of the observations. Linear mixed models include random effects that are associated with specific units drawn from the population randomly (Pinheiro & Bates, 2000). In the current study, for each continuous outcome variable of interest at each follow-up visit, a linear mixed-model with AUD persistence and onset status as fixed effects and family-group as a random

effect was run using the lme4 package in “R” (Bates & Maechler, 2013). This analytic strategy was analogous to the one implemented in Hicks et al. (2010). First, each alcohol-use trajectory group was compared to the control group for each variable of interest. Subsequent analyses focused exclusively on individuals classified into the four alcohol-use trajectory groups and allowed for the identification of the *unique* effects associated with persistence and desistence (i.e., the results for persistence were adjusted for the effects of onset and the results for onset were adjusted for the effects of persistence) and their interaction. Interaction terms with  $p \geq .05$  were dropped from the model. Eta squared values from uncorrected ANOVAs were calculated since linear mixed models do not have a standardized measure of effect size. Eta squared represents the proportion of unique variation attributable to a given predictor (Cohen, Cohen, West, & Aiken, 2003; Pierce, Block, & Aguinis, 2004). Cohen (1988) outlined that values of .01, .06, and .14 represent the lower limits of small, medium, and large effect sizes, respectively.

Parallel analyses were performed for categorical variables with an extension of the generalized linear model that accommodates correlated data by accounting for the correlation in the formulas that produce standard errors using a robust “sandwich” estimator. GLM is appropriate when the outcome variable is not normally distributed, as is the case for diagnostic outcomes. These analyses were conducted using generalized estimating equations in the Statistical Package for the Social Sciences (Version 17.0). The individual’s age at the age 17 and age 29 assessments were entered as a covariate for all analyses. Due to the large number of analyses, only results where  $p < .01$  were

considered statistically-significant, although associations with  $p < .05$  are noted in the tables.

### **Chapter 3.**

#### **Results**

First, the results pertaining to measures of alcohol consumption are presented; subsequently, results pertaining to each of the hypotheses are reviewed.

#### **3.1 Measures of Alcohol Consumption**

As seen in Table 1, at age 11, there was a trend-level association with the adolescent-onset course where individuals classified in the adolescent-onset groups were approximately twice as likely to have tried alcohol as individuals in the adult-onset groups. However, the age 11 rate of alcohol usage was quite low in each of the AUD trajectory groups (17 out of 114 adolescent-onset individuals had tried alcohol – 15% – versus 10 out of 150 adult-onset individuals – 7%). The *vast majority* of participants in the AUD groups and the control group had not tried alcohol. Analyses were not conducted on the intoxication measures due to virtually no reports of intoxication among the AUD groups. Only one individual in the control group who had drunk before reported being intoxicated.

By age 17, the majority of individuals in each of the AUD trajectory groups and the control group had used alcohol, and the majority of those who used alcohol had been intoxicated. Individuals in the adolescent-onset groups were different from the controls on every measure of consumption, while individuals in the adult-onset groups were not as consistently distinguishable. Among individuals classified in AUD groups, an

adolescent-onset was associated with excessive drinking for every continuous measure of alcohol consumption. The persistent-course was also uniquely associated with two features of consumption – number of lifetime intoxications and frequency of drinking. At the age 29 assessment, an adolescent-onset was no longer uniquely associated with any of the consumption measures, and the persistent-course was associated with all of them. In sum, the subtype designations captured meaningful differences in consumption at the relevant developmental time periods and suggested that risk measures taken at age 11 were largely “premorbid” because only 27 individuals in the AUD groups (10% of the total) had tried alcohol by age 11, and of those, none reported drinking to intoxication.

### **3.2 Hypothesis One**

To test the hypothesis that premorbid childhood risk factors are associated with the adolescent-onset and persistent-use subtypes, a number of indices of behavioral disinhibition and cognitive performance were assessed at age 11. Each trajectory group was compared to controls; subsequently, main effects for differences on these indices with respect to onset and persistence were examined among those with AUD. If this hypothesis was correct, one would expect clear differences from controls in at least three trajectory groups (adolescent-onset persistent, adolescent-onset desistent, adult-onset persistent) and main effects for both persistence and onset within the AUD groups. (To confirm that the small minority of individuals who reported a history of drinking at age 11 were not driving the results, analyses were repeated with these individuals excluded, and the pattern of findings was unchanged.)

As seen in Table 2, at age 11, the hypothesis that premorbid risk factors might be related to AUD group membership was merited, in that each of the AUD groups differed from the controls on various measures (*Hypothesis 1a*). Both adolescent-onset groups were significantly different in their level of conduct disorder symptoms, and the adolescent-onset persistent group was also different in oppositional defiant disorder and academic problems. The persistent groups were different in their composite risk factor score, and with the exception of the adult-onset desistent group, all of the AUD groups were less academically-motivated than controls. Further, all of the AUD groups were significantly different from the controls on the delinquent behavior inventory. However, among individuals with AUDs, neither the adolescent-onset course nor the persistent-course was uniquely associated with any of these measures. In summary, the hypothesis was partially supported in that subtype membership did not discriminate among individuals with AUDs with respect to behavioral disinhibition, but there was evidence that AUD-membership in general related to preexisting differences from *controls*. Each trajectory group differed from the controls on at least one indicator, with individuals in the adolescent-onset groups and the persistent groups displaying the most differences.

With respect to subtype membership and age 11 cognitive functioning (*Hypothesis 1b*), as seen in Table 2, the adolescent-onset persistent group was significantly different on verbal IQ compared to controls. Among individuals with AUD, there was a trend-level interaction ( $F = 5.81$ ,  $df = 201.70$ ,  $p = .02$ ,  $\eta^2 = .024$ ) where individuals in the adolescent-onset persistent group had lower verbal IQ scores than other

AUD groups. Thus, the hypothesis was supported in that subtype membership was associated with age 11 cognitive performance.

To test the hypothesis that age 11 disinhibitory risk and cognitive functioning relate to age 29 cognitive functioning (*Hypothesis 1c*), a series of separate bivariate models were implemented where the behavioral risk factor composite, verbal IQ, and perceptual IQ were each used to predict the cognitive measures at age 29. As seen in Table 3, verbal and perceptual IQ were associated with almost all of the adult measures, while the composite was associated with measures of verbal learning and memory.

### 3.3 Hypothesis Two

To test the hypothesis that individuals with an adolescent-onset AUD demonstrate deficits in memory, learning, and working memory, and individuals with a persistent course of AUD demonstrate greater deficits in working memory, each trajectory group was compared to controls; subsequently, differences in cognitive performance at age 29 were examined with respect to subtype membership among individuals with AUDs. At age 29, as seen in Table 4, the adolescent-onset persistent group performed significantly worse than controls on several aspects of the RAVLT – total performance on all learning trials, words recalled on the interference trial, and words recalled on the delay trial.

There were also trend-level differences on Trial 1 performance and retroactive interference. Among the AUD groups, there were trend-level interactions for retroactive interference ( $F = 5.24$ ,  $df = 176.60$ ,  $p = .02$ ,  $\eta^2 = .027$ ) and delay trial score ( $F = 4.03$ ,  $df = 162.21$ ,  $p = .046$ ,  $\eta^2 = .023$ ) due to lower performances in the adolescent-onset persistent group compared to the other AUD groups. On the Digit Span test, there was a

trend-level difference between the adolescent-onset persistent group and the control group on DSB performance. Among the AUD groups, the persistent-course was associated with only a trend-level difference in DSB performance and overall Digit Span performance.

In summary, there was evidence in support of the hypothesis that adolescent-onset persistent individuals were different from the controls on measures of learning and memory; however, this did not extend to the adolescent-onset desistent group. The hypothesis that individuals with a persistent course would demonstrate working memory deficits was not supported.

### 3.4 Hypothesis Three

It was hypothesized that after adjusting for premorbid risk factors, the relationship between the subtypes and age 29 deficits in cognitive functioning would be attenuated but still apparent. As seen in Table 5, after adjusting for verbal IQ, perceptual IQ, and the behavioral risk factor composite, all of the previously-significant differences between the control group and the adolescent-onset persistent group on total score, words recalled on the interference trial, and words recalled on the delay were no longer significant (*RAVLT Total score*:  $F = 4.21$ ,  $df = 200.19$ ,  $p = .04$ ,  $\eta^2 = .014$ ; *RAVLT Trial B*:  $F = 1.73$ ,  $df = 231.99$ ,  $p = .19$ ,  $\eta^2 = .006$ ; *RAVLT Delay*:  $F = 3.86$ ,  $df = 203.40$ ,  $p = .05$ ,  $\eta^2 = .016$ ). Among the AUD groups, the adjustment for childhood risk factors further attenuated all of the previous trend-level effects (*RAVLT RIS interaction*:  $F = 4.24$ ,  $df = 172.31$ ,  $p = .04$ ,  $\eta^2 = .022$ ; *RAVLT Delay interaction*:  $F = 3.26$ ,  $df = 164.27$ ,  $p = .07$ ,  $\eta^2 = .013$ ; *DSB persistence*:  $F = 4.43$ ,  $df = 169.46$ ,  $p = .04$ ,  $\eta^2 = .026$ ; *Digit Span Total persistence*:  $F =$

4.30,  $df = 169.59$ ,  $p = .04$ ,  $\eta^2 = .024$ ). In summary, the first part of the hypothesis was supported in that accounting for premorbid risk attenuated the relationship between AUD group and adult cognition; however, the second part of the hypothesis was not supported in that none of these adjusted effects were statistically significant.

### **3.5 Summary**

The results demonstrated that age of AUD onset and persistence were associated with clear differences in how individuals used alcohol at age 17 and age 29. Persistence was associated with increased consumption at age 29 while an adolescent-onset was associated with increased consumption at age 17. At age 11, the AUD groups demonstrated premorbid differences from controls on measures of behavioral disinhibition and the adolescent-onset persistent group demonstrated differences from the controls on a measure of verbal intelligence. Further, these age 11 measures predicted performance on several measures of cognitive functioning at age 29. At age 29, compared to controls, members of the adolescent-onset persistent group performed significantly lower on various measures of verbal learning and memory, but these effects were no longer significant once adjusted for premorbid measures of age 11 functioning.

## **Chapter 4.**

### **Discussion**

#### **4.1 Cognitive Functioning**

A primary aim of this study was to determine if both the age of onset of AUD and the persistence of AUD into the late twenties were related to adult cognitive functioning. While there is a limited literature that has utilized prospective samples to examine the

association between either adolescent AUD or persistence with adult cognition, few studies have simultaneously addressed the contributions of each subtype and their interaction. Among the AUD groups, there were no statistically-significant effects; however, the adolescent-onset persistent group was significantly different from controls on a number of measures of verbal learning and memory. All effect sizes were small in magnitude. These findings extend the previous literature by demonstrating that cognitive differences in AUD groups are detectable in community samples and that accounting for subtype status affects the degree to which cognitive correlates can be identified.

Even before premorbid measures were taken into account, with the exception of the adolescent-onset persistent group, individuals in the AUD groups were indistinguishable from controls on measures of learning and memory. This is a promising finding for those who started using alcohol problematically in adolescence and were able to desist. It contrasts, however, with previous studies of individuals with an adolescent-onset desistent course (Hanson et al., 2011a; Hanson et al., 2011b) that revealed deficits of learning and memory in adulthood. However, these individuals were from a clinical sample of adolescents admitted to a treatment program for substance use, suggesting that their AUDs were more severe. Further, they were approximately three years younger when classified as desistent and cognitively-assessed, suggesting that they may have had less time to recover from alcohol's effects.

#### **4.2 Premorbid Risk Factors and Confounding**

Given the evidence linking AUDs with behavioral disinhibition, another aim of this study was to identify whether premorbid measures of cognitive functioning and

behavioral risk factors were confounders in the relationship between AUDs and adult cognition. Consistent with expectations, AUD groups displayed premorbid differences in cognitive functioning and disinhibitory risk compared to controls, with the adolescent-onset persistent group displaying the most differences. Further, the premorbid factors each predicted many aspects of adult cognitive performance.

When analyses were adjusted for baseline risk, there were no statistically-significant differences among the AUD groups and controls on measures of cognitive functioning. Given the lack of statistically-significant results, it would appear that the study's findings are not suggestive of a causal relationship between alcohol use disorders and cognitive deficits. However, one interesting issue in formulating this interpretation is that while several analyses involving cognitive performance were not significant, they were associated with small effect sizes. For example, after accounting for baseline risk factors, comparisons between the control group and the adolescent-onset persistent group on retroactive interference, total score, and words recalled on the delay yielded p-values ranging from .04 to .05, and  $\eta^2$  ranging from .014 to .016. Given the high prevalence of alcohol use disorders and the potential public health impact of a causal relationship between AUDs and cognitive functioning, it would be remiss to fail to discuss the potential import of these effects. Certainly, given their small magnitude (Cohen, 1988), their impact at an individual-level may be negligible, but even a very weak relationship could be costly to society at the population-level. As such, rather than concluding that the results are inconsistent with a causal association because of the lack of significant results, which may discourage future research on this important issue, the more critical

point to take from the current study is that future researchers interested in links between problematic drinking patterns and cognitive functioning should implement methods to address preexisting risk factors.

### **4.3 Validity of Subtype Designations**

The question arises as to whether the adolescent-onset and persistent subtype definitions utilized in this study were actually effective in capturing and categorizing the heterogeneous courses of AUDs. Of note, this is not the first study to utilize this categorization scheme. Hicks et al. (2010) identified psychosocial variables associated with an adolescent-onset and persistent AUD using the older MTFs cohort. The subtype designation was virtually identical to the one implemented in the current study, with the only difference laying in the use of DSM-III-R criteria to define the groups rather than DSM-IV. Hicks et al. (2010) identified meaningful differences in functioning that were associated with persistence and an adolescent-onset AUD.

In the current study, roughly one-quarter of individuals included in the AUD groups fell into each of the four cells (ranging from 18% for the adolescent-onset persistent group to 34% for the adult-onset desistent group). The continuous measures of alcohol consumption that were ascertained suggest that these designations were not arbitrary but encapsulated meaningful differences in how the subjects were using alcohol throughout their life course. While members of the adult-onset and persistent courses were not wholly indistinguishable from the controls at age 17, the adolescent-onset course was clearly associated with increased alcohol consumption on every measure of use. In contrast, at age 29, the persistent subtype was associated with increased measures

of consumption. Further, alcohol consumption was minimal at age 11, which helps to validate the baseline measures of behavioral disinhibition and cognitive functioning as “premorbid” predictors of AUDs. Certainly, more empirically-driven methods of describing different AUD courses could be implemented, but taken together, the pattern of alcohol consumption among the AUD groups in the current study and the findings of Hicks et al. (2010) suggest that these subtypes are helpful in AUD categorization and are a promising target for future studies of the specific characteristics associated with different AUD courses.

In the Hicks et al. (2010) study and the current study, there were similar patterns of alcohol consumption across the different AUD groups. Of the individuals participating at age 29, virtually the same percentage of individuals were classified as controls (43%) and comparable percentages were categorized into an alcohol use trajectory group (37% in Hicks et al., 41% in the current study). Given these similarities, the lack of clear association between AUD membership and cognitive functioning in the current study was especially striking because in the Hicks et al. (2010) study, AUD group membership was associated with numerous psychosocial issues at age 29. Compared to controls, individuals in the persistent groups displayed more antisocial behavior, had more legal and drug problems, had used and abused other substances excessively, had fewer prosocial peers and more antisocial peers, were more likely to be divorced, and had more sex partners. Further, individuals in the adolescent-onset groups had lower educational attainment and were more likely to have fathered a child early. Taken together with the current study, it appears that individuals with an adolescent-onset or

persistent AUD are at risk for psychosocial issues at age 29, but that these issues are not mediated by deficits in the cognitive domains assessed.

#### **4.4 Early Risk Factors for Subtype Membership**

While premorbid measures of behavioral disinhibition and cognitive functioning were investigated to determine if they might represent potential confounders in the relationship between AUD subtype and adult cognition, identifying predictors of different AUD trajectories represents an interesting inquiry in its own right. *Among individuals with AUD*, Hicks et al. (2010) identified a number of risk factors at age 17 that related to the adolescent-onset course, and several risk factors that were uniquely related to a persistent-course. In this study, however, no such risk factors emerged at age 11; instead, different AUD groups were only distinguishable from *controls*. This finding raises questions about the point in adolescence at which specific AUD trajectories can be reliably identified among individuals who will ultimately go on to develop AUD.

#### **4.5 Limitations**

This sample largely consisted of Caucasian individuals and was limited to the male gender, which limits the generalizability of results. Further, the AUD groups were drawn from a community sample, which likely diminished the capacity to identify individuals with more severe AUDs who might have demonstrated more dramatic deficits.

One clear limitation in this study was that the measures of cognitive functioning available at age 29 (RAVLT, Digit Span) tapped very limited domains of brain functioning (although importantly, they were areas of functioning thought to be sensitive

to alcohol's effects). Further, they were only available at one time point. As such, it was not possible to examine how performance changed over time depending on whether individuals persisted in their use or desisted.

Another limitation is the degree to which these analyses allowed for conclusions about causal processes connecting AUD subtypes with adult cognitive functioning. The inclusion of premorbidly-measured covariates that represent theoretically-plausible confounders is helpful in this regard, and certainly, utilizing a wider range of baseline measures and family background factors would have provided even more rigorous control. However, no amount of covariates eliminates the threat of unmeasured factors that may relate to both subtype membership and adult cognition.

#### **4.6 Future Directions and Conclusions**

The age 29 cognitive results in this study are encouraging, in that the majority of AUD individuals were indistinguishable from the control group on all of the measures assessed. One important avenue for future study is to repeat this design with females. Studies have suggested that among males and females who use at comparable rates, outcomes involving accidents, risky sexual behavior, brain atrophy, and cognitive performance may be more negative in women (Diehl et al., 2007; Flannery et al., 2007; King, Bernardy, & Hauner, 2003; Mann et al., 2005; Nolen-Hoeksema, 2004; Sugarman, DeMartini, & Carey, 2009).

The fact that *premorbid* verbal IQ had a stronger relationship with AUDs than any subsequent measure of adult cognition – and that this effect was specific to those with both an adolescent-onset and persistent use – illustrates the importance of taking a

longitudinal approach to understanding the relationship between AUDs and their cognitive correlates. Future studies should take into account the variability in AUD courses and the premorbid differences among AUD groups. Where these premorbid differences do not account for the relationship, methodological designs that allow for conclusions about causality, such as the discordant-twin design, should be implemented. Identifying the point at which premorbid risk factors can differentiate subtypes among individuals who will go on to develop AUD is also important and could assist in determining the etiological processes that incur risk for specific AUD subtypes.

In conclusion, this study implemented a longitudinal design that was innovative in examining cognitive correlates of four different AUD types varying in their onset and persistence into the late twenties. After accounting for potential confounding deficits, AUD group status was not significantly related to cognitive performance. This study provides further support that the adolescent-onset and persistent subtypes are valuable for capturing the heterogeneity inherent to alcohol-use disorders and highlights the importance of accounting for premorbid risk in examining deficits associated with AUDs.

**Table 1: Alcohol Consumption at Age 11, 17, and 29 by AUD Group**

Values in the left AUD group columns contain the means and standard deviations for each group on each measure; statistically-significant differences between the control group mean and AUD group mean are indicated via asterisk. For variables that were log-transformed, the means and SDs reflect raw values before transformation. Values in the right “Adolescent-Onset” and “Persistent-Course” columns contain the results of comparisons among the AUD groups. Effects that include an “onset x persistence” interaction term are italicized. Statistically-significant results are reflected via asterisk where “\*” indicates  $p < .01$  and “\*\*” indicates  $p < .001$ . Results where  $p < .05$  are also noted via “▲.”

	AUD Group					Adolescent-Onset		Persistent-Course	
	Control	Adolescent Persistent	Adolescent Desistent	Adult Persistent	Adult Desistent	Wald Chi-Square	Odds Ratio	Wald Chi-Square	Odds Ratio
<b>Age 11 Alcohol Consumption</b>									
Used alcohol	3.56%	12.77%	16.42%*	8.47%	5.49%	$\chi^2(1)=5.32$ ▲	2.48	$\chi^2(1)=.06$	.89
Been intoxicated	10.00%	0%❖	0%❖	0%❖	0%❖	❖	❖	❖	❖
<b>Age 17 Alcohol Consumption</b>									
Used alcohol	62.11%	100.00%❖	100.00%❖	81.25%▲	84.09%**	❖	❖	❖	❖
Been intoxicated	67.11%	100.00%❖	98.40%*	64.86%	77.14%	$\chi^2(1)=11.70$ *	33.78	$\chi^2(1)=.38$	.74
	❖ Analysis not completed due to quasi-complete separation in data								
						<b>F-test</b>	<b><math>\eta^2</math></b>	<b>F-test</b>	<b><math>\eta^2</math></b>
# of lifetime intoxications	10.24 (19.12)	58.59 (35.97)**	43.18 (36.37)**	18.83 (22.25)**	11.50 (17.74)	F(1, 161.87)= 66.90**	.255	F(1, 167.81)= 12.62**	.053
Average # of drinks per use last year	5.40 (2.51)	10.34 (4.41)**	9.25 (3.73)**	7.58 (3.78)▲	6.81 (3.01)▲	F(1, 130.75)= 18.76**	.109	F(1, 134.70)= 2.05	.013
Most # of drinks in 24 hrs during heaviest period	8.53 (6.19)	24.00 (7.26)**	22.18 (11.00)**	12.05 (10.84)	11.50 (7.68)*	F(1, 198.11)= 71.29**	.245	F(1, 201.35)= .20	.000
Frequency of drinking last year	45.21 (7.29)	59.39 (7.48)**	57.09 (10.38)**	52.19 (9.74)**	46.52 (7.08)	F(1, 194.25)= 46.18**	.181	F(1, 197.45)= 13.60**	.043

<b>Age 29 Alcohol Consumption</b>									
Average # of drinks per use during heaviest period	5.31 (3.80)	10.87 (4.93)**	8.84 (4.60)**	10.85 (5.22)**	8.15 (4.41)**	F(1, 216.12)= .97	.005	F(1, 223.10)= 15.54**	.065
Most # of drinks in 24 hrs during heaviest period	14.56 (8.07)	25.96 (8.54)**	21.78 (9.31)**	27.53 (9.64)**	21.66 (7.66)**	F(1, 230.97)= .04	.001	F(1, 231.00)= 19.47**	.077
Average # of drinks per use since last assessment	2.83 (1.90)	7.13 (3.54)**	3.71 (2.75)▲	6.24 (2.73)**	3.75 (2.41)*	F(1, 230.72)= .34	.001	F(1, 230.84)= 63.75**	.219
Average # of drinks per use last year	2.48 (1.89)	5.87 (4.21)**	3.40 (2.80)*	5.67 (3.57)**	3.47 (2.76)*	F(1, 225.68)= .22	.089	F(1, 226.99)= 20.71**	.089
Most # of drinks in 24 hrs since last assessment	9.23 (5.82)	20.26 (6.42)**	10.49 (4.96)▲	24.27 (9.72)**	11.43 (6.30)*	F(1, 227.24)= .31	.001	F(1, 227.98)= 156.58**	.393

**Table 2: Age 11 Behavioral Disinhibition and Cognitive Functioning by AUD Group**

Values in the left AUD group columns contain the means and standard deviations for each group on each measure; statistically-significant differences between the control group mean and AUD group mean are indicated via asterisk. For variables that were log-transformed, the means and SDs reflect raw values before transformation. Values in the right “Adolescent-Onset” and “Persistent-Course” columns contain the results of comparisons among the AUD groups. Effects that include an “onset x persistence” interaction term are italicized. Statistically-significant results are reflected via asterisk where “\*” indicates  $p < .01$  and “\*\*\*” indicates  $p < .001$ . Results where  $p < .05$  are also noted via “▲.”

	AUD Group					Adolescent-Onset		Persistent-Course	
	Control	Adolescent Persistent	Adolescent Desistent	Adult Persistent	Adult Desistent	F-test	$\eta^2$	F-test	$\eta^2$
<b>Age 11 Measures of Behavioral Disinhibition</b>									
DBI	.81 (1.21)	2.08 (1.99)**	1.86 (2.23)*	1.68 (2.27)**	1.18 (1.34)*	F(1, 178.81)= 2.70	.029	F(1, 173.88)= .23	.008
Academic problems	48.65 (9.54)	55.14 (11.71)*	51.58 (9.50)▲	51.23 (8.71)	49.97 (10.97)	F(1, 256.97)= 2.20	.012	F(1, 258.35)= 1.23	.010
Academic motivation	51.74 (9.08)	44.73 (10.69)**	48.51 (10.70)*	47.86 (10.28)*	50.47 (11.42)	F(1, 229.41)= 2.42	.015	F(1, 235.56)= 2.00	.023
ODD symptoms	2.18 (1.69)	3.65 (2.12)**	2.67 (2.37)	2.41 (2.07)	2.15 (1.67)	F(1, 228.20)= 2.86	.019	F(1, 234.81)= 3.39	.024
CD symptoms	.68 (1.10)	1.65 (1.74)**	1.27 (1.41)*	.94 (1.16)▲	.87 (1.11)	F(1, 236.56)= 2.95	.028	F(1, 241.13)= 1.42	.006
ADHD symptoms	1.82 (2.90)	2.84 (3.89)	2.37 (3.51)	2.08 (3.26)	2.07 (2.99)	F(1, 244.45) = .44	.003	F(1, 248.59)= .16	.001
Behavioral risk composite	-.23(.90)	.72(.88)**	.21(1.21)▲	.14 (1.01)*	-.05(1.10)	F(1, 230.22)= 3.91▲	.027	F(1, 236.74)= 1.41	.022
<b>Age 11 Measures of Cognitive Functioning</b>									
Verbal IQ	103.38 (14.33)	96.36 (11.75)*	102.38 (10.96)	103.20 (11.32)	100.81 (13.69)▲	<i>F(1, 208.85)= 3.04</i>	.011	<i>F(1, 227.24)= 0.92</i>	.004
Perceptual IQ	109.17 (14.46)	106.02 (12.13)	109.44 (16.32)	106.02 (16.43)	109.60 (13.64)	F(1, 252.22) = 0.01	.000	F(1, 256.43) = 2.63	.016

**Table 3: Age 11 Risk Factors Predicting Age 29 Cognitive Functioning**

Each column contains the coefficients for the results of separate bivariate models where the age 11 behavioral risk factor composite, verbal IQ, and perceptual IQ scores were each used to predict age 29 cognitive functioning. Statistically-significant results are reflected via asterisk where “\*” indicates  $p < .01$  and “\*\*” indicates  $p < .001$ . Results where  $p < .05$  are also noted via “▲.”

	<b>Age 11 Risk Measures</b>					
	<u>Behavioral risk factor composite</u>		<u>Verbal IQ</u>		<u>Perceptual IQ</u>	
	<b>B</b>	<b>R<sup>2</sup></b>	<b>B</b>	<b>R<sup>2</sup></b>	<b>B</b>	<b>R<sup>2</sup></b>
<b>Age 29 Rey Auditory Verbal Learning Test</b>						
Total score	-1.82**	.032	.24**	.123	.14**	.059
Trial 1	-0.20*	.019	.03**	.105	.01*	.029
Trial B	-0.29**	.026	.03**	.071	.02*	.029
Learning over trials	-0.68	.005	.05	.005	.08▲	.012
Learning curve (Trial 5 –Trial 1)	-0.13	.004	.004	.001	.01	.009
Proactive interference (Trial B –Trial 1)	-0.09	.002	.001	.000	.004	.001
Retroactive interference (Trial 6 – Trial 5)	.03	.000	.02**	.033	.005	.002
Words forgotten (Delay–Trial 6)	.001	.000	-.001	.000	.008	.007
Delay trial	-0.34▲	.014	.06**	.082	.04**	.053
<b>Age 29 Digit Span Test</b>						
Forward total	-0.23	.011	.06**	.103	.04**	.038
Forward max	-.11▲	.012	.02**	.083	.01**	.024
Backward total	-.29▲	.013	.07**	.107	.04**	.049
Backward max	-.14▲	.015	.03**	.101	.02**	.038
Total score	-.26	.015	.07**	.136	.04**	.058

**Table 4: Cognitive Functioning at Age 29 by AUD Group**

Values in the left AUD group columns contain the means and standard deviations for each group on each measure; statistically-significant differences between the control group mean and AUD group mean are indicated via asterisk. Values in the right “Adolescent-Onset” and “Persistent-Course” columns contain the results of comparisons among the AUD groups. Effects that include an “onset x persistence” interaction term are italicized. Statistically-significant results are reflected via asterisk where “\*” indicates  $p < .01$ , and “\*\*\*” indicates  $p < .001$ . Results where  $p < .05$  are also noted via “▲.”

	AUD Group					Adolescent-Onset		Persistent-Course	
	Control	Adolescent Persistent	Adolescent Desistent	Adult Persistent	Adult Desistent	F-test	$\eta^2$	F-test	$\eta^2$
<b>Age 29 Rey Auditory Verbal Learning Test</b>									
Total score	51.55 (10.06)	44.96 (10.92)**	49.26 (10.95)	49.14 (10.17)	49.11 (8.42)	F(1, 176.96)= .30	.002	F(1, 177.27)= 1.76	.012
Trial 1	5.98 (1.46)	5.28 (1.50)▲	6.00 (1.60)	5.78 (1.43)	5.76 (1.47)	F(1, 175.69)= .06	.000	F(1, 175.87)= 2.42	.013
Trial B	5.81 (1.95)	4.90 (1.37)*	5.68 (1.86)	5.40 (1.71)	5.45 (1.78)	F(1, 174.39)= .08	.000	F(1, 174.46)= 2.23	.012
Learning over trials	50.81 (10.20)	47.88 (8.40)	47.55 (10.39)	49.33 (9.54)	49.44 (9.78)	F(1, 173.70)= 1.18	.007	F(1, 174.00)= .001	.000
Learning curve (Trial 5 – Trial 1)	5.42 (2.29)	5.00 (1.73)	4.84 (2.20)	5.37 (1.95)	5.60 (2.26)	F(1, 174.30)= 2.23	.015	F(1, 177.77)= .000	.001
Proactive interference (Trial B – Trial 1)	-.17 (1.97)	-.38 (1.86)	-.35 (2.15)	-.37 (1.98)	-.31 (2.26)	F(1, 178.99)= .23	.001	F(1, 178.99)= .002	.000
Retroactive interference (Trial 6 – Trial 5)	-1.62 (1.73)	-2.28 (1.90)▲	-1.43 (1.39)	-1.76 (1.92)	-1.98 (1.66)	<i>F(1, 175.44)= .001</i>	.000	<i>F(1, 174.27)= 1.73</i>	.010

Words forgotten (Delay-Trial 6)	-83 (1.40)	-.74 (2.01)	-.62 (1.34)	-.78 (1.55)	-.75 (1.42)	F(1, 175.99)= .16	.001	F(1, 175.99)= .09	.001
Delay trial	8.96 (2.98)	7.26 (2.96)*	8.81 (2.72)	8.67 (2.94)	8.59 (2.87)	F(1, 169.47)= .80	.004	F(1, 169.81)= 1.61	.022
<b>Age 29 Digit Span Test</b>									
Forward total	9.98 (3.24)	9.32 (2.59)	10.18 (3.05)	9.93 (2.79)	10.61 (2.61)	F(1, 178.18)= 1.31	.009	F(1, 178.94)= 2.04	.015
Forward max	7.03 (1.30)	6.74 (1.02)	7.03 (1.09)	6.91 (1.09)	7.27 (1.01)	F(1, 178.78)= 1.82	.010	F(1, 178.92)= 3.55	.021
Backward total	10.32 (3.24)	8.97 (2.22)▲	10.51 (3.09)	9.47 (2.95)	10.15 (2.57)	F(1, 174.74)= .08	.000	F(1, 175.44)= 4.70▲	.031
Backward max	5.31 (1.46)	4.79 (1.12)	5.32 (1.45)	5.11 (1.43)	5.15 (1.18)	F(1, 175.64)= .002	.000	F(1, 174.28)= .70	.007
Total Score	10.85 (3.10)	9.79 (1.99)	11.03 (2.77)	10.33 (2.72)	11.11 (2.35)	F(1,175.99)= .19	.004	F(1,174.99)= 4.63▲	.030

**Table 5: Cognitive Functioning at Age 29 by AUD Group after Adjustment for Baseline Risk Factors**

For each of the Table 4 analyses where  $p < .05$ , this table includes the  $\eta^2$  after adjustment for premorbid risk factors.  $P < .05$  is noted via “▲”.

	Adolescent Persistent vs. Controls	Adolescent-Onset	Persistent-Course
<b>Age 29 Rey Auditory Verbal Learning Test</b>			
Total score	.014 ▲		
Trial 1	.006		
Trial B	.006		
Retroactive interference (Trial 6 – Trial 5)	.016 ▲	.000	.008
Delay trial	.016	.001	.013
<b>Age 29 Digit Span Test</b>			
Backward total	.001	.000	.026 ▲
Total Score		.001	.024 ▲

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