Published in final edited form as:

Alcohol Clin Exp Res. 2017 December ; 41(12): 2082–2092. doi:10.1111/acer.13503.

Earlier Alcohol Use Onset Predicts Poorer Neuropsychological Functioning in Young Adults

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Abstract

Background—Neurodevelopment may be shaped by environmental factors such as alcohol intake. Over 20% of U.S. high school students begin drinking before age 14, and those who initiated drinking before age 14 are four times more likely to develop psychosocial, psychiatric, and substance use difficulties than those who began drinking after turning 20. Little is known, however, about how the age of alcohol use onset influences brain development.

Methods—This study prospectively examined the effects of alcohol use onset age on neurocognitive functioning in healthy adolescent drinkers ($N=215$). Youth were administered a neuropsychological battery before substance use initiation ($M = 13.6$ years, $SD = 0.8$), and on average 6.8 years later ($M = 20.2$ years, $SD = 1.5$). Hierarchical linear regressions examined if earlier ages of onset for first and regular (i.e., weekly) alcohol use adversely influenced neurocognition, above and beyond baseline neurocognition, substance use severity, and familial and social environment factors.

Results—As hypothesized, an earlier age of first drinking onset predicted poorer performance in the domains of psychomotor speed and visual attention ($p < .05$, $N = 215$) and an earlier age of weekly drinking onset predicted poorer performances on tests of cognitive inhibition and working memory, controlling for baseline neuropsychological performance, drinking duration, and past-year marijuana use ($p < .05$, $N = 127$). No relationship between age of first and weekly drinking onset was found with verbal learning and memory and visuospatial ability.

Conclusion—This is the first study to assess the association between age of adolescent drinking onset and neurocognitive performance using a comprehensive test battery. This study suggests that early onset of drinking increases risk for alcohol-related neurocognitive vulnerabilities and that initiation of any or weekly alcohol use at younger ages appears to be a risk factor for poorer subsequent neuropsychological functioning. Findings have important implications for public policies related to the legal drinking age and prevention programming. Further studies are needed

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to replicate these preliminary findings and better understand mediating processes and moderating conditions.

Keywords

alcohol onset; neuropsychology; longitudinal; adolescents

Introduction

Although the rate of alcohol use among adolescents in the United States (U.S.) has decreased over the past decade (Johnston et al., 2017a), the early ages at which youth initiate drinking remains an area of particular concern. One in five U.S. high school students begin drinking by 13 years old (Eaton et al., 2012; SAMHSA, 2013), and the average age of first alcohol use among individuals aged 12–49 in the U.S. is 17.6 (Lipari et al., 2016). In 2015, approximately 13,000 individuals tried alcohol for the first time within the past year, half of whom were between 12–17 years of age. This initiation rate is twice that of the second most common intoxicant, marijuana (Lipari et al., 2016). An earlier age of alcohol use onset is associated with increased likelihood of developing a substance use disorder (SUD), as 16% of adults who first drank before age 14 develop an alcohol use disorder (AUD), compared to 4% who initiate after 20 (SAMHSA, 2013). Early alcohol use initiation is also linked to more psychosocial difficulties (Falk et al., 2008; Hawkins et al., 1997; Shrier et al., 1997) and increased risk for psychiatric disorders (Kessler et al., 1997; SAMHSA, 2013).

Continued alcohol use appears to have a lasting effect on multiple neuropsychological domains. Adolescent drinkers, compared to non-drinking controls, show poorer performances on tasks of attention, memory, information processing, visuospatial ability, language abilities, motor speed, and executive functioning (Thoma et al., 2011; Boelema et al., 2016; Brown et al., 2000; Ferrett et al., 2010; Montgomery et al., 2012). Youth who consume 10 or more drinks in one occasion may be at greater risk for poorer functioning in verbal learning and memory compared to moderate non-binge drinkers who consume less than five drinks per occasion, even after controlling for pre-drinking performances (Nguyen-Louie et al., 2016). Drinkers 18–20 years old, with longer durations of lifetime use, exhibit poorer performances on tasks of visuomotor coordination and mental flexibility (Day et al., 2013) and continued problematic alcohol use has been found to be related to greater and more rapid declines in cognitive performance in heavy drinkers (Hanson et al., 2011). A recent prospective study examined the linear quantitative relationship between 11 individual substance use behaviors (e.g., past-year and 3-month frequency and quantity, post-drinking effects) and 19 neuropsychological task variables, controlling for age, socioeconomic status (SES), gender, drinking status (i.e., control, moderate, heavy drinkers), and baseline cognitive functioning in 234 participants (Nguyen-Louie et al., 2015). More past year heavy episodic drinking days, more overall drinking days, and higher maximum drinks per occasion were predictive of poorer follow-up verbal memory. More past month alcohol use days predicted poorer visuospatial ability, and more instances of hangover/post-drinking effects predicted poorer performance in psychomotor speed. Together, these results suggest that youth with sub-diagnostic alcohol use symptomology may still be at risk for developing subtle, but detectable, neuropsychological changes after alcohol use begins and escalates.

This is an important public health consideration. In 2012, 43% of youth aged 12–25 reported current alcohol use, but only 9% met criteria for AUD (SAMHSA, 2013). It is possible that young drinkers who do not meet diagnostic criteria for AUD (American Psychiatric Association, 2000) may still exhibit subtle cognitive difficulties.

Considerably less is known about how the age at which an individual begins drinking influences subsequent neurocognitive functioning. Among adult drinkers, those with an early age of AUD onset (<25 years old) performed better than those with late onset (≥ 25 years old) on tests of executive functioning, memory, and attention (Joos et al., 2013). Yet another study found no difference in cognitive performance among individuals with early, late, and very late (≥ 45 years old) AUD onset (Kist et al., 2014; Demir et al., 2002). Similarly, Bjork et al. (2004) reported that in adults, age of heavy drinking onset (i.e., consumed 90 drinks in one month) was negatively correlated with years of heavy drinking, self-reported impulsivity, and aggressive behaviors, but was not significantly related to a measure of immediate and delayed memory. To date, no prospective study has examined the influence of age of first drinking onset (i.e., the age of first consuming at least one standard drink) on adolescent neurocognitive functioning. Importantly, few studies have examined age of onset as a ratio-scale (e.g., age in years) rather than as an ordinal-scale variable (e.g., early, late, and very late onset groups).

When examining age of first drinking onset (AFDO), one must consider the variability in drinking patterns. For example, an individual who consumed her first drink at age 14 but has less than 10 drinking occasions per year is likely at lower risk for poor cognitive performance than a counterpart who initiated at 14 years and has 52 drinking occasions per year. Further, youth who tried alcohol once and thereafter abstain from drinking are not expected to show the same neurocognitive changes as continuous drinkers, even among those with equivalent AFDO. Thus, in addition to examining AFDO as a predictor of neurocognition, it may be relevant to examine the age of *regular* drinking onset (i.e., the age at which an individual first begins drinking on a regular, or weekly, basis, and has engaged in consistent weekly drinking for six or more continuous months) (Brown et al., 1998). Youth who initiated ongoing patterns of alcohol use are at greater risk for psychosocial difficulties than occasional drinkers, as evidenced by increased rates of conduct disorder, negative drinking consequences, and other substance use (Pechansky et al., 2004; Grant et al., 2005). Considering the dynamic neuromaturation processes taking place throughout adolescence (Østby et al., 2009), it is crucial to understand if, and how, alcohol-related neurotoxicity may be influenced by the age at which youth begin drinking. Examination of both age of first drinking onset and age of weekly drinking onset (AWDO) allows for a more comprehensive understanding of how such effects may differ for individuals who recently initiated drinking versus sustained moderate-heavy drinkers.

This study aimed to longitudinally examine the influence of first (onset age range 10–20; follow-up age range: 18–25) and weekly (onset ages 14–23; follow-up ages: 18–26) alcohol use onset on follow-up neuropsychological performance in a large prospective cohort of adolescents ($N=215$), controlling for baseline (i.e., pre-onset) neuropsychological performance and other biological and environmental factors. Earlier ages of first and weekly

drinking onset were hypothesized to linearly predict worse performances in neuropsychological measures.

Materials and Methods

Procedures

Data for this study were a subsample of an existing larger longitudinal study on neurocognitive effects of substance use in adolescents (R01 AA13419). In the parent study, participants were recruited between 2003 – 2010 through flyers sent to households of students attending San Diego area public middle schools (Squeglia et al., 2011; Nguyen-Louie et al., 2015). Potential participants between ages 12–15 were screened by trained bachelor- and master-level psychometrists. Parents and youth provided written consent and assent, respectively. Eligible participants were administered a detailed interview while parents underwent a similar, parallel screen (see Initial Screen below). Youth and parents were then followed annually after baseline in the parent study (annual follow-up rates each year following initial recruitment were 99%, 99%, 98%, 98%, 97%, 95%, 90%, 91%, and 94%, with an overall average follow-up rate of 95.7%). Each participant was administered a comprehensive neuropsychological battery and MRI scan at baseline and follow-up.

Exclusionary criteria for entering the larger study included: prenatal alcohol (2 or more drinks a given week) or illicit drug exposure; birth prior to 35th gestational week; history of any neurological or DSM-IV (American Psychiatric Association, 2000) Axis I disorder, head trauma or loss of consciousness (>2 minutes), chronic medical illness, learning or intellectual disability, psychoactive medication use; inadequate English comprehension; and non-correctable sensory problems. Potential participants were also excluded if they had 10 total lifetime drinking days, 3 lifetime experiences with marijuana, 5 lifetime cigarette uses, and history of other intoxicant use (Squeglia et al., 2009a). All participants were asked not to use alcohol and other recreational drugs for at least 24 hours prior to the study, confirmed with breath alcohol concentration and urine drug screen in the laboratory. The study protocol and procedures were approved by the University of California San Diego Human Research Protections Program.

The parent study initially enrolled 295 adolescents. Follow-up neuropsychological data was obtained 4.7 years, on average, after the onset of first drinking and 3.1 years after the onset of weekly drinking (6.8 years after initial enrollment). The total sample size of the current study included $N = 215$ adolescents who had transitioned into at least one full drink. Among them, 127 individuals had transitioned into weekly alcohol use by their 2016 follow-up (see Table 5).

Measures

Initial screens—At baseline, the study was briefly described to youth and parents interested in the project by phone. The study purpose, procedures, potential risks and benefits and issues relating to confidentiality were reviewed, and eligibility criteria were assessed. Brief functioning and demographic information were obtained to assess for exclusionary criteria. Eligible participants (youth and parents) were then administered a

detailed clinical interview with the measures below. At follow-up, youth and parents were administered similar forms to assess changes in social functioning and demographics factors.

Substance use measures: The Customary Drinking and Drug Use Record (CDDR; Brown et al., 1998) is a structured interview that examines the pattern and severity of alcohol, nicotine, marijuana, and other drug use (amphetamines, barbiturates, hallucinogens, benzodiazepines, cocaine, inhalants, opiates, ecstasy, ketamine, gamma-hydroxybutyric acid, phencyclidine, and recreational use of prescription drugs). Age of onset, average and peak frequency and quantity of use, withdrawal symptoms, and DSM-IV (American Psychiatric Association, 2000) and DSM-5 (American Psychiatric Association, 2013) SUD criteria were assessed at the follow-up time point (after initiation of use).

The Timeline Followback (TLFB; Medina et al., 2007; Sobell and Sobell, 1992; Sobell et al., 1979) examined detailed frequency and quantity of substance use during the past 30 days. Youth were administered the TLFB two times at the follow-up appointment post-initiation of use: during the detailed phone interview and at the neuropsychological assessment appointment. Information from both TLFB sources and CDDR were then integrated and coded by trained psychometrists to ensure reporting accuracy at follow-up.

Demographics: The Family History Assessment Module (FHAM; Rice et al., 1995) was administered to youth and parent at baseline and follow-up to assess family history of SUD of first-(i.e., biological parents) and second-degree (i.e., biological grandparents, siblings, aunts, and uncles) relatives. Data from the FHAM provided a continuous familial history density measure, calculated as the weighted sum of all first-(i.e., biological parents and siblings, weighted 0.5) and second-degree relatives (i.e., biological grandparents, aunts, and uncles, weighted 0.25) who endorsed two or more SUD symptoms (Zucker et al., 1994).

The Hollingshead Index of Social Position score (Hollingshead, 1965), an index of SES calculated using socioeconomic background information (i.e., educational attainment, occupation, and salary), was collected from the parent at baseline and each follow-up time point until the youth had transitioned to financial independence, at which time this was completed by the youth on their own occupation and educational attainment. The present analyses used the baseline report from the parent as a reflection of the youth's rearing background. Higher values indicate lower SES.

Externalizing symptomology: Youth level of externalizing symptomology were assessed with the parent report Child Behavior Checklist (Achenbach, 1991) at baseline, and, at follow-up, the parallel Adult Self Report (for ages 18 or older; Achenbach and Rescorla, 2003) to obtain continuous normed indices of Externalizing (i.e., Rule-Breaking Behavior and Aggressive Behavior Problems) problem symptoms. Higher scores indicated more symptoms.

Neuropsychological test measures: A comprehensive neuropsychological battery was administered at baseline and follow-up to assess cognitive functioning. At baseline, the assessment battery included: Delis-Kaplan Executive Function System (D-KEFS; Delis et

al., 2001) Color Word Interference (CWI) and Trail Making (TMT) subtests; California Verbal Learning Test - Children's Version (CVLT-C; Delis et al., 1994); Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) Block Design subtest; Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 1991) Digit Symbol-Coding and Digit Span subtests; and the Rey-Osterrieth Complex Figure task (Rey and Osterrieth, 1993). At follow-up, participants 18 years and older were administered the adult versions of the CVLT - Second Edition (CVLT-II; Wechsler, 1997) and Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Delis et al., 2000) Coding and Digit Span subtests. At follow-up, youth were administered the Taylor Complex Figures task (Hubley, 1996) as an alternate form complex figure.

Data Analyses

Data reduction of neuropsychological test battery—To reduce potential Type I error and redundancy among outcome measures, raw scores for 26 neuropsychological test variable were subjected to a principle components analysis using varimax rotation with Kaiser normalization for each of the four time points (see Tables 1, 3, and 4): baseline and follow-up for participants who transitioned into any alcohol use ($N = 215$), and baseline and follow-up for participants who transitioned into weekly alcohol use ($N = 127$). Nearly identical factor structures were confirmed with oblique, direct oblimin, rotation. Thus, all following analyses were conducted using the varimax rotation structure. Only factors with eigenvalues greater than 1.0 were retained for interpretation. Results yielded six latent factors (i.e., cognitive domain) that were generally consistent with prior factor analytic structures (Squeglia et al., 2009b; Nguyen-Louie et al., 2015; Squeglia et al., 2014; Santos et al., 2015; Mirsky et al., 1991): verbal learning and memory, cognitive inhibition, psychomotor speed, working memory, visual attention, and visuospatial ability. After determining the loading structure of each cognitive domain, neuropsychological test raw scores were transformed into z-scores for each time point based on the respective sample and corresponding standard deviations. Z-scores within each of the six cognitive domains were then averaged to create final composite z-scores for each time point. All time to completion measures (i.e., D-KEFS Color Word Interference and Trails Making Test, Digit Vigilance Test tasks) were multiplied by -1 ; after transformation, higher scores indicated better performance for all neuropsychological domains. Internal consistency was assessed with Cronbach's alpha coefficients (see Table 2, Table 3).

Covariates and moderators—To account for pre-drinking neurocognitive functioning, analyses controlled for baseline neuropsychological performances on corresponding tasks. To better understand the effects of AFDO and AWDO on neurocognition, independent of other substance use related risk factors, analyses also controlled for the duration of drinking years, past year drinking frequency, past year tobacco and marijuana use frequency and recency of marijuana use. Drinking duration was defined as the number of years between onset and follow-up in which participants were not classified as a control (i.e., have consumed ≥ 2 drinks per occasion and ≥ 10 drinking occasions in the past year). Past year drinking frequency was defined as the number of drinking days in the past year prior to follow-up. Past year tobacco and marijuana use indicated the number of days participants have used tobacco and cannabis within the past year, respectively. Marijuana use recency

assessed the number of days since the last use occasion prior to neurocognitive testing. At follow-up, 76% of participants had used marijuana at least once in their life, and marijuana use recency ranged from 2–1828 days prior to follow-up neuropsychological testing. Marijuana use recency for youth who have not transitioned into any marijuana use by follow-up was coded 2000. Identical follow-up analyses that coded recency of marijuana use for non-users as “missing” with list-wise deletion of missing data in regression models showed no changes in significance or directionality and minimal changes in beta coefficients.

Social and environmental factors were included as potential covariates in initial analyses to account for possible social rearing effects on neurocognitive performances. Familial density of SUD and SES were examined, as youth from higher SES households and of lower familial SUD density are more likely to perform better on neuropsychological tests (Raizada and Kishiyama, 2010; Roberts et al., 1999; Hill et al., 2000). Externalizing symptomology has been associated with risky drinking and poorer cognitive functioning (Finn et al., 2009) and was therefore examined in initial analyses as a potential covariate. Age at follow-up was examined as a possible covariate to account for age-related differences in neuropsychological performance. Gender was considered as a possible moderator, as prior studies have found differences in cognitive performance between adolescent boys and girls (Mormile and Hunt, 2016). Models were first estimated with all proposed moderator, covariates and the independent variable of interest (i.e., AFDO or AWDO). All hierarchical regression analyses were carried out in SPSS (Rel. 21.0.0. 2012. IBM, Chicago, IL).

Power analysis—Using G-Power (Vogel et al., 2001), *a priori* analyses suggested that a total sample size of $N = 52$ was needed to achieve power of $1 - \beta = .80$ (medium effect size of $f = .40$, two-tailed $\alpha = .05$) with one variable of interest (i.e., AFDO or AWDO) and a total of nine potential predictors (i.e., nine possible covariates) in a linear regression model. A total sample size of $N = 107$ is needed to achieve the same parameters in a model with all nine predictors included.

Multiple comparisons—Correction for multiple comparisons was carried out based on the false discovery rate controlling procedure (Benjamini and Hochberg, 1995) with q -value = 0.05 (corrected p -value) using the *multproc* package (Newson, 2003) in Stata (Version 14; StataCorp LP, College Station, TX). Nominal (uncorrected) p -values are also presented for comparison.

Hypothesis testing—The effect of AFDO and AWDO on follow-up neuropsychological functioning was examined using hierarchical linear regressions. Each neuropsychological domain was analyzed in a separate model. AFDO and AWDO were examined in different models as independent predictors, assessing and controlling for the nine previously described covariates and gender. Initial models included all potential moderator and covariates described above; those that did not account for any significant variance in the outcome variable and/or independent variable were removed from the final models. Baseline neuropsychological performance, a robust predictor of follow-up performances (Nguyen-Louie et al., 2015; Tapert et al., 2002), was entered in step 1 of the regression, followed in step 2 with other covariates that showed significant relationship with either

neuropsychological outcome or age of onset. In step 3, AFDO or AWDO was entered into the regression model to examine its association with cognitive performances at follow-up above and beyond covariates. For neuropsychological domains that showed significant associations with age of onset, follow-up hierarchical regressions were conducted to better understand this association for each individual neuropsychological test that comprised each latent domain. Effects sizes were assessed using R^2 (full model) and R^2 (increase in variance accounted for at each step).

Results

Description of Sample

At baseline, participants ($N=215$) were between 12–15 years of age ($M=13.6$, $SD=0.77$). The subsample that later initiated weekly drinking ($N=127$) was statistically equivalent in age at baseline as the total sample (AWDO youth baseline age: $M=13.7$, $SD=0.79$). At follow-up, participants were on average age 20.2 ($SD=1.48$); the subsample who transitioned into weekly drinking ($N=127$) was $M=21.3$ years of age ($SD=1.76$) at follow-up.

On average, the age of first drinking onset in the whole sample was $M=16.1$ years ($SD=2.04$, range=10.00 – 22.83). Youth who later transitioned into weekly drinking had their first standard drink at $M=15.6$ years of age ($SD=2.0$), while youth who never initiated weekly drinking ($N=88$) were significantly older at the time of first drinking onset, $M=16.9$ years of age ($SD=1.9$; $T_{213}=4.57$, $p<.0001$). The average age of weekly drinking onset was $M=18.4$ years ($SD=1.70$, range=14.00 – 23.17). Ages of onset were consistent with epidemiological studies, in which the age of alcohol use initiation was 17.6 years overall (Lipari et al., 2016) and 16.2 years for those who initiated prior to age 21 (SAMHSA, 2013), see Table 5.

Relationship among Predictors at Follow-up

AFDO was significantly correlated with AWDO, follow-up age, SUD familial density, drinking duration, externalizing symptomology, past year tobacco, alcohol, and marijuana use days, $ps<.01$, but not with SES or marijuana use recency (see Table 3, 4 and 6). AWDO was significantly correlated with follow-up age, externalizing symptomology, and past year tobacco and alcohol use days ($ps<.01$) but not with SUD familial density, SES, drinking duration, and marijuana use days and recency. AFDO and AWDO were the most highly correlated predictors ($r=.56$), followed by drinking duration and follow-up age ($r=.49$). These associations remained significant after multiple comparisons correction with a false discovery rate of $q = .05$. Sensitivity analyses suggested minimal concern for multicollinearity among predictors. In final models reported below, the variance inflation factor of predictors ranged from 1.01 to 1.35 (tolerance range: 0.74–0.99). AFDO, AWDO, and neuropsychological performances within each domain at baseline and follow-up time points did not differ between boys and girls ($ps > .05$).

Age of first drinking onset—AFDO was a significant predictor of outcome neuropsychological data only if the model also accounted for drinking duration. Drinking duration did not account for any significant variance in the outcome of interest,

neuropsychological performance. That is, drinking duration exhibited a statistical suppression effect on AFDO. No moderating effects of gender were found.

An earlier AFDO predicted worse visual attention functioning at follow-up ($\hat{\beta} = .106$, $T_{214} = 2.0$, $p = .048$), controlling for baseline visual attention and drinking duration (see Figure 1). In step 1, baseline visual attention accounted for 47.2% of the variance of follow-up visual attention functioning ($\hat{\beta} = .697$, $T_{214} = 14.0$, $p < .001$); in step 2, drinking duration did not account for any additional variance ($\hat{\beta} = .055$, $T_{214} = 1.0$, $p = .308$); in step 3, adding AFDO increased overall R^2 to 48.3%. No interaction effects were found; all other covariates were non-significant and removed from the final model. Follow-up hierarchical regressions of individual neuropsychological tests in this domain showed that an earlier AFDO predicted worse performance on D-KEFS CWI Word Reading above and beyond covariates ($\hat{\beta} = .116$, $T_{214} = 2.05$, $p = .042$; $R^2 = .414$; R^2 AFDO = .011). No relationships between AFDO and other subtests in this domain were detected at $p < .05$.

An earlier AFDO predicted worse psychomotor speed at follow-up ($\hat{\beta} = .137$, $T_{214} = 2.6$, $p = .042$), controlling for baseline psychomotor speed and drinking duration. In step 1, baseline psychomotor speed accounted for 40.2% of the variance in follow-up psychomotor speed ($\hat{\beta} = .642$, $T_{214} = 12.2$, $p < .001$); in step 2, drinking duration did not account for any additional variance ($\hat{\beta} = -.058$, $T_{214} = -1.0$, $p = .304$); in step 3, adding AFDO increased overall R^2 to 41.1%. No interaction effects were found; all other covariates were non-significant and removed from the final model. Follow-up hierarchical regressions of individual neuropsychological tests in this domain showed that an earlier AFDO predicted worse performance on D-KEFS TMT Motor Speed above and beyond covariates ($\hat{\beta} = .205$, $T_{214} = 3.3$, $p < .001$; $R^2 = .189$; R^2 AFDO = .042). No relationships between AFDO and other subtests in this domain were detected at $p < .05$.

Age of weekly drinking onset—An earlier AWDO predicted worse working memory at follow-up ($\hat{\beta} = .304$, $T_{126} = 2.59$, $p = .014$), controlling for baseline working memory and past year marijuana use (see Figure 1). In step 1, baseline working memory accounted for 33.8% of the variance of follow-up verbal working memory ($\hat{\beta} = .590$, $T_{126} = 5.04$, $p < .001$); in step 2, past year marijuana use accounted for an additional 2.2% ($\hat{\beta} = -.116$, $T_{126} = -2.0$, $p = .033$); in step 3, adding AWDO increased overall R^2 to 45.1%. No interaction effects were found; all other covariates were non-significant and removed from the final model. Follow-up hierarchical regressions of individual neuropsychological tests in this domain showed that, above and beyond covariates, an earlier AWDO predicted worse performances on Digit Span Backwards ($\hat{\beta} = .317$, $T_{126} = 2.28$, $p = .028$; $R^2 = .206$; R^2 AWDO = .099). No moderating effects of gender were found. No relationships between AWDO and other subtests in this domain were detected at $p < .05$.

An earlier AWDO predicted worse cognitive inhibition ability at follow-up ($\hat{\beta} = .313$, $T_{126} = 2.26$, $p = .030$), controlling for baseline cognitive inhibition, past year marijuana use, and recency of marijuana use. In step 1, baseline cognitive inhibition accounted for 15.7% of the variance of follow-up verbal working memory ($\hat{\beta} = .355$, $T_{126} = 2.57$, $p = .014$); in step 2, past year marijuana use ($\hat{\beta} = .221$, $T_{126} = 1.93$, $p = .013$) and recency of marijuana use ($\hat{\beta} = .215$, $T_{126} = 1.94$, $p = .015$) accounted for an additional 3.6%; in step 3, adding AWDO

increased overall R^2 to 30.7%. No interaction effects were found; all other covariates were non-significant and removed from the final model. Follow-up hierarchical regressions of individual neuropsychological tests in this domain showed that, above and beyond covariates, an earlier AWDO predicted worse performances on D-KEFS TMT Switching ($\hat{\beta} = .302$, $T_{126} = 2.35$, $p = .024$; $R^2 = .363$; R^2 AWDO = .084). No moderating effects of gender were found. No relationships between AWDO and other subtests in this domain were detected at $p < .05$.

Discussion

This study aimed to ascertain the effects of alcohol on neuropsychological performance as a function of the age at which youth began any drinking (i.e., AFDO) and began drinking on a regular, weekly basis (i.e., AWDO). Six neuropsychological domains, comprised of 26 individual test scores, were assessed. As hypothesized, youth who began drinking at earlier ages (i.e., lower AFDO) were more likely to perform worse on tasks that have traditionally been associated with “lower level” cognitive abilities (i.e., psychomotor speed and visual attention) (Lezak, 2004). Adolescents with ongoing alcohol use have been found to be at greater risk for psychosocial difficulties (Pechansky et al., 2004). For the first time, the current results suggest that individuals who initiate weekly drinking at earlier ages may also be at greater risk for poorer performances on “higher-order” cognitive abilities (i.e., executive functioning and working memory). Further, no interaction effects were found, suggesting that the effects of AFDO and AWDO may be robust across gender, family history, SES, externalizing symptomology, and drinking and marijuana use history. No relationship between AFDO and AWDO were found with verbal learning and memory and visuospatial ability, possibly because these cognitive domains reach near adult-level maturation comparatively earlier in life (Gathercole, 1998; Ardila and Rosselli, 1994), or the impact of drinking may be consistent throughout adolescence.

The current study offers additional evidence to support the deleterious effects of early adolescent alcohol use. Taken together, results suggest that earlier ages of drinking onset are related to, and may act as a risk factor for, poorer neuropsychological functioning in young adult drinkers. It has been suggested that cognitive development continues until 30 years of age (Sowell et al., 2003; Craik and Bialystok, 2006). Behaviorally and neuroanatomically, executive functions such as impulsivity, inhibition, problem solving, and decision making continue to develop until 20–29 years old (De Luca et al., 2003). Different areas of the brain follow different trajectories of neural development and pruning processes (Giedd et al., 1999; Østby et al., 2009; Somerville, 2016). Thus, grouping individuals with AFDOs under 25 (Joos et al., 2013) together likely overlooks a range of neurodevelopmental processes that occur within this time.

An important, yet unexpected, finding of this study concerned drinking duration, which acted as a suppressor variable (Darlington, 1968) in the relationship between AFDO and neuropsychological outcomes. By definition, a suppressor variable is neither a mediator nor moderator (MacKinnon et al., 2000), but an independent variable having no significant correlation with the dependent variable (i.e., follow-up neuropsychological functioning). However, its inclusion in the model enhances the association between the predictor of

interest (i.e., AFDO) and dependent variable, evidenced by an increase in regression coefficient magnitude (Conger, 1974). Although drinking duration was not significantly associated with outcome psychomotor speed and visual attention, it was negatively correlated with AFDO ($r = -0.37$). Sensitivity analyses suggested little concern for multicollinearity among predictors in the regression models reported (AFDO Variance Inflation Factor = 1.16; tolerance = 0.86). Evidence suggests that neither AFDO nor duration alone is an accurate predictor of outcome cognitive performance in adolescents and young adults. Rather, it is the *interplay* between these indices that warrants significance. It is possible that the relationship between AFDO and cognition is intricately associated with the number of years drinking behavior has been engaged in (Weissman et al., 2015). Individuals who begin drinking at the same age but engage in different trajectories of subsequent drinking may show differential patterns of cognitive performances in later life. One may speculate that youth who began drinking earlier are more likely to have longer drinking durations between age of onset and adulthood. This, in turn, allowed for greater alcohol-related neurotoxicity and exposure over an extended period of time.

An important limitation of this study is that the interpretation of results should not be extrapolated to ages of onset earlier or later than those in this study, or to patterns of drinking beyond those observed. AFDO ranged from 10 to 22 years and AWDO from 14 to 23 years, thus, findings cannot be applied to ages of onset outside this range. It is possible that once adolescents reach adulthood and full neural maturation, alcohol initiation may no longer exhibit effects in the same direction or pattern. Likewise, drinking duration played an important suppressor role in modeling the effects of AFDO on neuropsychological performance. It is unclear how this relationship may evolve as drinking duration becomes longer. Another limitation of the study is the low Cronbach's alpha (Peterson, 1994) for working memory at baseline and follow-up and visuospatial ability at follow-up ($\alpha = .47 - .58$; see Table 2). While the neuropsychological tests that comprise these latent factors were consistent with previous findings (Squeglia et al., 2009b; Nguyen-Louie et al., 2015), the low internal consistency may, in part, account for null findings in these domains. Thus, interpretation should proceed with caution. Additionally, the sample is comprised largely of middle to upper-middle-class Caucasian youth, which is consistent with the surrounding geographic area but limits generalizability.

Caution should be used in the interpretation of the current results within the context of correlation versus causation. John Stuart Mill (1884) posited three necessary criteria for causal inference. First, the effect must temporally follow the cause; second, the cause and effect must be associated with each other; and third, other possible alternatives that may account for the relationship has been sufficiently ruled out or accounted for. The longitudinal design of this study increased the accuracy with which AFDO and AWDO were assessed and outcome neuropsychological performances were examined 4.7 years after the onset of first drinking and 3.1 years after onset of weekly drinking. Thus, temporal order between age of onset and neuropsychological outcome was established. Results of hierarchical regression analyses suggest that, at $p < .05$, age of onset is significantly related to outcome neuropsychological performance, satisfying Mill's criterion two. To control for extraneous factors that may influence either the dependent or independent variables of interest (i.e., criterion three), eight potential covariates were examined. Results were only considered

statistically significant if AFDO or AWDO were significant predictors of neuropsychological functioning above and beyond baseline functioning, marijuana use, alcohol use and duration, familial factors (e.g., SES, family history of SUD), and externalizing symptomology. Some factors that may account for neuropsychological performance that were not examined included motivation (i.e., during laboratory sessions) and quality of education and school systems. The neurocognitive effects of AWDO and AFDO are unlikely independent of tobacco and marijuana, commonly used among US adolescents (Johnston et al., 2017b). Further, initiation of alcohol (17.6 years), cigarettes (17.9 years) and marijuana (19.0 years) occur at around the same age (Lipari et al., 2016). To account for this, analyses controlled for use of tobacco and marijuana, and the rate of other substance use in this sample was minimal (<2.7% in the past year). However, the unique effects of AFDO and AWDO on neurocognition can only be arrived at statistically in the current study, given the high co-occurring rate of youth who have tried alcohol, tobacco, and marijuana at least once. To better control for other substance use, future studies should examine the age of alcohol use onset in participants with no comorbid use of any other substances. Overall, based on Mill's criteria for causal inference, the current study met two of three proposed criteria. Another important consideration is the distinction between statistical significance versus practical significance (Kirk, 1996). Although the relationship between age of alcohol use onset and cognitive outcomes reached the statistical threshold of $p < .05$, effect sizes of AFDO and AWDO were small. Thus, additional studies are needed to explore this important question, possibly in an animal model with a randomized design in which all extraneous factors inherent in human studies can be controlled for. Importantly, AWDO may be an important risk factor for alcohol-related neurotoxicity and warrants further examinations in future studies. Of particular interest would be a detailed examination of the differential effects of AFDO and AWDO (i.e., comparison of effect sizes for each index) on cognition and to replicate the current findings on possible selective effects of age of onset on certain cognitive domains while leaving others relatively unaffected.

Strengths of this study aided in the interpretation and bolster the robustness of the results. Importantly, participants were followed each year to assess past year and recent substance use. Data on age of onset were not obtained through error-prone retrospective recall in adults, but calculated by trained psychometrists as youth transitioned into alcohol use while enrolled in the study. Secondly, neurocognitive functioning was assessed at baseline, when youth have had no or minimal experience with alcohol. This allowed for the examination of the effects of alcohol on neurocognition, *controlling for each individual's premorbid cognitive functioning*. Baseline neuropsychological functioning has previously been shown to be the most consistent predictor of performance after alcohol use initiation (Nguyen-Louie et al., 2015; Tapert et al., 2002), accounting for 30–55% of variance in follow-up performance. Thus, cross-sectionally examining this phenomenon without considering pre-drinking cognitive functioning may lead to inaccurate attributions and overestimation of effect sizes when examining the effects of alcohol.

The presented findings may have important implications for public safety and policies related to alcohol use. Currently, the legal age of drinking in the United States is 21 years of age. However, the adolescent brain does not reach full maturity until around age 25 or later for some processes in some individuals (Østby et al., 2009). Alcohol initiation at a younger

age may disrupt the normal neurodevelopmental trajectory, resulting in immature brain function and deviations in neurocognition. Results suggest that there are no cut-offs for which alcohol use initiation is not deleterious to neurocognition between 10–23 years old. The legal drinking age of 21 marks a developmental and social, but not neurodevelopmental, transition into adulthood, thus it may not be a “safe” drinking age with regards to neurotoxicity. Another important implication of this study is the possibility of utilizing these and future results in individualized and targeted treatment for AUD. Currently, drinkers undergo similar treatments regardless of age of onset and developmental stage. As neurocognitive performance changes linearly with age of onset, treatment may be individualized based on the age the individual began drinking to increase efficacy. For example, current diagnostic criteria for AUD (American Psychiatric Association, 2013) takes into account recent use patterns, physiological and psychological dependence, disruptions to everyday functioning, and a general history of frequency and quantity of use, but not age of onset. Clinical interviews may help guide treatment such that individuals with earlier ages of onset may receive a greater level of care, as early onset has been found to be correlated with greater psychosocial difficulties and based on the current results, poorer psychomotor speed, attention, and cognitive inhibition.

Acknowledgments

Funding: This study was supported by National Institute on Alcohol Abuse and Alcoholism Grants R01 AA13419, U01 AA021695 (PI: Tapert), and F31 AA024389 (PI: Nguyen-Louie).

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Figure 1.

Results of hierarchical regression examining the effects of age of onset on neuropsychological performances in six cognitive domains.

Hierarchical regressions examined the effects of baseline (i.e., pre-drinking) performance in each neuropsychological domain at step 1, other covariates (i.e., follow-up age, substance use disorder familial density, socioeconomic status, externalizing symptoms, lifetime drinking duration, past year drinking and marijuana use days, number of days since last marijuana use) in step 2, and the predictor of interest (age of first drinking onset, $N=215$ or age of weekly drinking onset, $N=127$) in step 3. Positive regression coefficients indicate a positive relationship between age of onset with neuropsychological performance, such that higher ages of first or weekly drinking onset predicted better performance at follow-up 3–4 years after onset; negative regression coefficients indicate the opposite directionality.

AFDO = age of first drinking onset; AWDO = age of weekly drinking onset; MJ = marijuana; MJ recency = number of days prior to neuropsychological testing since last marijuana use occasion

* $p < .05$, above and beyond covariates

Table 1

Principal component analysis loading structure of follow-up neuropsychological test raw scores for youth who transitioned into any drinking ($N = 215$) Rotation method: Varimax with Kaiser normalization. All factor loadings < 0.300 are omitted for clarity. Identical structures, with similar coefficients, were obtained with baseline neuropsychological test scores for youth who transitioned into any drinking ($N = 215$), and for youth who transitioned into weekly drinking ($N = 127$) at baseline and follow-up.

Item	Factor						Factor Label
	1	2	3	4	5	6	
CVLT-II Long Delayed Cued Recall	.93						Verbal Learning & Memory
CVLT-II Long Delayed Free Recall	.91						
CVLT-II Short Delayed Cued Recall	.91						
CVLT-II Short Delayed Free Recall	.88						
CVLT-II List A Trial 1–5	.85						
CVLT-II List A Trial 5	.82						
CVLT-II List A Trial 1	.49				.35	.34	
D-KEFS CWI Discrepancy Score ^a	.79						Cognitive Inhibition
D-KEFS CWI Inhibition/Switching ^b	.77				.42		
D-KEFS CWI Inhibition ^b	.72				.40		
D-KEFS TMT Letter-Number Switching ^b	.52		.43	.35			
WAIS-IV Coding		.46					Psychomotor Speed
D-KEFS TMT Visual Scanning ^b		.44					
Digit Vigilance Test ^b		.74					
D-KEFS TMT Number Sequencing ^b		.70					
D-KEFS TMT Motor Speed ^b		.68	.31				
D-KEFS TMT Letter Sequencing ^b		.63					
		.51	.33				
WAIS-III Digits Backwards						.73	Working Memory
WAIS-III Digits Forward						.72	
WAIS-III Arithmetic						.70	
CVLT-II List B		.37				.38	

Item	Factor						Factor Label
	1	2	3	4	5	6	
D-KEFS CWI Word Reading ^b					.83		Visual Attention
D-KEFS CWI Color Naming ^b		.32			.74		
Rey-Osterrieth Complex Figures Copy Accuracy						.80	Visuospatial Ability
Rey-Osterrieth Complex Figures Delay Accuracy						.79	
WASI Block Design	.40					.50	

^aDiscrepancy score was calculated as the difference in raw scores (time to completion) between D-KEFS Color Word Interference conditions 4 (Inhibition) and 1 (Color Naming).

^bTime to completion; multiplied by −1; low values reflect worst/slower performance

CVLT-II = California Verbal Learning Test II; D-KEFS = Delis-Kaplan Executive Function System; WAIS = Wechsler Adult Intelligence Scale; WASI = Wechsler Abbreviated Scale of Intelligence; CWI = Color Word Interference; TMT = Trail Making Test.

Table 2

Standardized Cronbach's alpha for principle components analysis factor loadings at baseline and follow-up

Factor Label	AFDO Sample (N=215)		AWDO Sample (N=127)	
	Baseline	Follow-up	Baseline	Follow-up
Verbal Learning & Memory	.92	.94	.91	.94
Cognitive Inhibition	.81	.84	.77	.82
Psychomotor Speed	.73	.76	.66	.71
Working Memory	.53	.65	.47	.62
Visual Attention	.79	.80	.80	.86
Visuospatial Ability	.58	.60	.57	.60

AFDO=age of first drinking onset; participants who have transitioned into any alcohol use and have had at least one standard drink

AWDO=age of weekly drinking onset; participants who have transitioned into weekly drinking onset (i.e., drinks one or more standard drink at least once a week for six or more continuous months).

Table 3

Bivariate correlations among cognitive domains at follow-up ($N = 215$)

	Verbal Learning & Memory	Cognitive Inhibition	Psychomotor Speed	Working Memory	Visual Attention	Visuospatial Ability
Verbal Learning & Memory	1	.36	.24	.35	.20	.32
Cognitive Inhibition		1	.51	.42	.51	.25
Psychomotor Speed			1	.26	.41	0.09
Working Memory				1	.37	.18
Visual Attention					1	0.10
Visuospatial Ability						1

Shaded cells: Significant Pearson's correlations at an uncorrected $p < .01$ and after multiple comparisons correction with false discovery rate of $q = .05$

Table 4

Bivariate correlations among cognitive domains and past-year alcohol and marijuana use at follow-up ($N=215$)

	Marijuana Use Days	Binge Drinking Days	Drinking Days	Alcohol Use Lifetime Duration
Verbal Learning & Memory	−0.04	−0.10	−0.06	−0.06
Cognitive Inhibition	0.05	0.05	−0.03	−0.09
Psychomotor Speed	0.14	0.02	0.08	−0.07
Working Memory	−0.10	0.03	0.01	0.03
Visual Attention	0.13	0.03	0.03	−0.04
Visuospatial Ability	−0.04	−0.03	−.14	−.15 [*] $p = .03$

Note:

* Significant Pearson's correlation coefficient at uncorrected p -value as indicated. No correlation was significant after correction for multiple comparisons at a false discovery rate of $q = 0.05$.

Table 5

Demographic characteristics at baseline and follow-up ($N=215$)

	M (SD) or % [Range]	
	Baseline	Follow-up
Age	13.6 (0.8)	20.2 (1.5)
Age first drank ($N=215$)	-	16.1 (2.0) [10.0–22.8]
Age first drank weekly ($N=127$)	-	18.4 (1.7) [14.00–23.2]
% Female	41%	-
% with family history of AUD ^a	28%	-
Lifetime conduct disorder	9%	-
Race		
Caucasian	67%	-
Latino/a	19%	-
Multiple races	8%	-
African American/Black	2%	-
Asian American	4%	-
Native Hawaiian/Pacific Islander	1%	-
Socioeconomic status	23.0 (14.1)	-
Tried alcohol (1 standard drink)	10%	100%
Tried tobacco	4%	67%
Tried marijuana	5%	76%
Tried other illicit drugs	0%	4%
Drank in the past year	9%	96%
Past year drinking days	0.4 (1.8)	65.4 (71.3)
Past year binge days ^b	0.0 (0.0)	31.7 (49.7)
Drinks per peak drinking occasion past 3-months	1.7 (1.1)	7.0 (4.6)
Days since last drink	119.5 (102.7) [30.0 – 365.0]	87.9 (252.9) [2.0 – 1920.0]
Past year marijuana use days	0.6 (1.2)	56.1 (105.7)
Days since last tobacco use ^c	397.8 (301.6) [60.0 – 998.0]	245.9 (469.1) [1.0 – 2555.0]
Days since last marijuana use ^c	223.9 (203.0) [14.0 – 730.0]	153.0 (291.0) [2.0–1828.0]
Past year alcohol dependence	0%	9%

	M (SD) or % [Range]	
	Baseline	Follow-up
Past year drug use classification (including marijuana)		
Non-user	97%	40%
Infrequent user	3%	21%
Moderate user	-	25%
Drug abuse (DSM-IV)	-	8%
Drug dependent (DSM-IV)	-	10%
Full sustained remission	-	1%

^a At least one first degree relative with an alcohol use disorder

^b Consumed 5 drinks per occasion for men or 4 drinks per occasion for women; calculated from $n = 91$ participants with available binge-drinking data

^c Calculated only for individuals who reported using marijuana ($n = 164$) or tobacco ($n = 144$) at least once in their lifetime

Socioeconomic status was assessed using the Hollingshead Index of Social Position score; AUD = alcohol use disorder

Table 6

Pearson’s correlation of predictors and covariates ($N = 215$)

	Past Year						
	AFDO	AWDO	Follow-up age	FH density	SES	Duration	Externalizing Symptomology
AFDO	1	.56**	.27**	-.20**	-.06	-.37**	-.33**
AWDO		1	.47**	-.13	.02	.03	-.28**
Follow-up age			1	-.08	.05	.49**	-.09
FH density				1	.26**	.23**	-.14*
SES					1	.04	.01
Duration						1	.26**
Externalizing Symptomology							1
Tobacco Use Days							
Drinking Days							
Marijuana Use Days							
Marijuana Use Recency							

Note:

** Pearson’s correlation coefficient, uncorrected $p < .01$;

* Pearson’s correlation coefficient, uncorrected $p < .05$

Shaded cells: Significant correlations after multiple comparisons correction with false discovery rate of $q = .05$

AFDO = age first drinking onset; AWDO = age weekly drinking onset; FH = familial density of substance use disorders; SES = Hollingshead socioeconomic index, higher scores indicate lower socioeconomic status; Marijuana Use Recency = number of days prior to neuropsychological testing since last marijuana use occasion for participants who have transitioned into marijuana use ($n = 164$).