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Earlier Alcohol Use Onset Prospectively Predicts Changes in Functional Connectivity

Tam T. Nguyen-Louie, M.S.¹, Alan N. Simmons, Ph.D.², Lindsay M. Squeglia, Ph.D.³, M. Alejandra Infante, Ph.D.², Joseph P. Schacht, Ph.D.³, and Susan F. Tapert, Ph.D.^{1,2,*}

¹San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, California, USA

²University of California San Diego, Department of Psychiatry, La Jolla, California, USA

³Medical University of South Carolina, Department of Psychiatry and Behavioral Sciences, Charleston, South Carolina

Abstract

Background—Half of all new alcohol initiates are between 12–17 years old. This is a period of intense neurodevelopment, including changes in functional connectivity patterns among higher-order function areas. It is crucial to understand how alcohol-related neurotoxicity may be influenced by drinking onset age.

Design—This study prospectively examined the effects of age of first drink on frontoparietal context-dependent functional connectivity (cdFC) during a visual working memory task. Youth 13.5 years of age ($SD=1.2$) underwent a neuropsychological and neuroimaging session before drinking initiation and at follow-up six years later. Hierarchical linear regressions examined if youth with earlier ages of onset for first and weekly alcohol use showed higher follow-up cdFC between the dorsolateral prefrontal cortex and posterior parietal cortex regions of interest and whole-brain exploratory regions, controlling for pre-drinking cdFC. Higher follow-up cdFC was hypothesized to be correlated with poorer performances in neuropsychological performance.

Results—Exploratory whole brain analyses showed that, as hypothesized, earlier ages of weekly drinking onset were associated with higher cdFC between the bilateral posterior cingulate and cortical and subcortical areas implicated in attentional processes, which was in turn associated with poorer performance on neuropsychological tasks of attention, $p<.05$. No relationship between age of onset and cdFC between the two ROIs were found.

Conclusion—Earlier ages of weekly alcohol use initiation may adversely affect neurodevelopment by reducing developmentally appropriate integration of attentional circuits during a cognitive challenge. Delaying the onset of weekly alcohol use patterns well after early adolescence may reduce the risk for harm of alcohol use on the brain.

Keywords

anticorrelations; alcohol use; alcohol onset; context dependent functional connectivity

*Corresponding author: Susan F. Tapert, Ph.D.; University of California San Diego, 9500 Gilman Drive (0603), La Jolla, California, 92093, United States.

Introduction

Adolescent neuromaturation has been linked to environmental factors such as alcohol exposure (Greenough et al. 1987), typically the first and most commonly used substance among youth (Johnston et al. 2017). In 2015, 13,000 people began using alcohol each day, half of whom were between 12-17 years of age (Lipari et al. 2016). Alcohol may interact with and disrupt neurodevelopmental processes in adolescence, which are complicated by different maturation rates of brain structures and circuits (Somerville 2016).

An earlier age of alcohol use onset is associated with more psychosocial difficulties (Falk et al. 2008; Hawkins et al. 1997; Shrier et al. 1997) and increased likelihood of developing psychiatric and other substance use disorders (SUD) (Kessler et al. 1997; Rohde et al. 1996; SAMHSA 2013). Considering the dynamic neuromaturational processes taking place throughout adolescence, it is crucial to understand the effects of alcohol on the developing brain and its relationship with age at drinking onset. Evidence suggests that the impact of alcohol use onset on neurodevelopment is not a uniform process but may selectively affect certain circuitries and processes. Earlier onset of alcohol use disorder (AUD) is associated with smaller hippocampal volumes (De Bellis et al. 2000), suggesting that earlier onset may be more deleterious for brain development. Among youth who initiated drinking between 10-16 years of age, an earlier age of alcohol use onset has been found to be associated with increased resting-state functional connectivity between the nucleus accumbens and prefrontal, right inferior parietal, and medial temporal regions (Weissman et al. 2015). While these and other findings (Spadoni et al. 2013) suggest that increased resting-state functional connectivity represents a negative outcome of alcohol use, other studies have shown that youth with positive family history of alcohol use disorder showed lower functional connectivity between frontal and cerebellar and parietal regions (Herting et al. 2011; Wetherill et al. 2012). Another study found no difference in cerebral blood flow among individuals with AUD onset prior to versus after 20 years of age (Demir et al. 2002).

In addition to examining age of first drink (AFD) as a predictor of neurocognition, the effects of age of *weekly* drinking onset (AWDO; i.e., the age at which an individual first begins drinking on a more frequent, or weekly basis) (Brown et al. 1998) on neural development may also be an important public health interest. Youth who have initiated ongoing regular patterns of alcohol use are at greater risk for increased rates of conduct disorder, negative drinking consequences, and other substance use (Grant et al. 2005; Pechansky et al. 2004). One may expect that even among those who initiated alcohol use at the same age, individuals with less frequent drinking would not likely show the same neurocognitive changes as continuous drinkers. Examination of first and weekly drinking onset ages allows for a more comprehensive understanding of how such effects may differ for individuals who recently initiated drinking versus sustained moderate-heavy drinkers.

The aims of this study were threefold. First, examine the prospective influence of AFD and AWDO after initiation of alcohol use (i.e., follow-up) on cdFC between the DLPFC and PPC regions of interest (ROIs), controlling for pre-drinking (i.e., baseline) cdFC. Second, examine the influence of AFD and AWDO on follow-up cdFC among other regions of the

brain in exploratory whole brain analyses, controlling for cdFC between the same regions at baseline. Third, ascertain if, and how, follow-up cdFC, an index of neural functioning, may be associated with behavioral and cognitive correlates of adolescent alcohol use: externalizing symptomology, drinking frequency and duration, and neuropsychological performance. The DLPFC and PPC were chosen as ROIs due to their continued maturation throughout adolescence (Østby et al. 2009), which offers an opportunity to examine a circuitry that has not yet reached full development. Secondly, these regions may be particularly vulnerable to alcohol (Tapert et al. 2004; Wager and Smith 2003). Binge drinkers, compared to controls, exhibit greater activation in frontal and parietal regions to VWM tasks (Campanella et al. 2013; Maurage et al. 2013; Schweinsburg et al. 2011; Wetherill et al. 2013). Substance-naïve youth with AUD family history show lower correlations in activation patterns during VWM tasks (i.e., context-dependent functional connectivity [cdFC]) between the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) (Wetherill et al. 2013).

Importantly, a gap in the literature does not address the longitudinal influence of age of first drink and perhaps more importantly, AWDO on neurocognitive functioning in adolescents, accounting for differences in functional connectivity prior to alcohol use onset. Some longitudinal evidence suggests that from childhood to adolescence and adulthood, cortical and subcortical anticorrelations increase in select regions (Barber et al. 2013). Anticorrelations, also referred to as negative functional connectivity, describe a neurological event in which BOLD activity in two regions are negatively correlated (i.e., have a negative correlation coefficient) (Chen et al. 2011). The most prominent findings of increased anticorrelations as a function of age have involved regions implicated in attention and working memory (Barber et al. 2013; Chai et al. 2014), particularly the DLPFC and associated regions including the PPC. The increase in negative correlations between the DLPFC and other regions during working memory cognitive tasks have been proposed to represent an increase in resource allocation efficiency during competing attentional demands (Chai et al. 2014). Thus, proliferation of anticorrelations in key regions may represent a normal course of circuitry maturation over time, and deviations from this pattern (e.g., decreased anticorrelations) were hypothesized to reflect aberrant neurocognitive functioning. Weissman and colleagues (2015) previously showed that adolescent drinkers with an earlier age of alcohol use onset exhibit higher functional connectivity. In the current study, it was hypothesized that, above and beyond baseline cdFC, an *earlier* AFD and AWDO would linearly predict *higher* (i.e., less negative) cdFC between ROIs (DLPFC and PPC) and among exploratory regions at follow-up. Greater externalizing symptomology, drinking frequency, and drinking duration have consistently been shown to be associated with risky drinking and poorer neurocognitive performances (Finn et al. 2009; Nguyen-Louie et al. 2015; Squeglia et al. 2009). Thus, it was hypothesized that higher externalizing symptomology, higher drinking frequency, higher duration, and poorer neuropsychological performance would be associated with higher follow-up cdFC, which represented a less favorable neurocognitive outcome. This prediction was supported by prior evidence showing that these indices have been associated with poorer neuropsychological functioning (e.g., younger age, positive AUD family history) and increased cdFC (Spadoni et al. 2013).

Methods

Procedures

Data for the current study came from a larger longitudinal neuroimaging study on adolescent substance use (R01 AA13419). At baseline, participants between ages 12-15 were recruited from San Diego area public schools in 2002-2010 (Nguyen-Louie et al. 2015; Squeglia et al. 2011). Potential participants were screened by trained psychometrists; consent and assent were obtained from parents and youth. Eligible participants were administered a detailed interview, comprehensive neuropsychological battery, and magnetic resonance imaging (MRI) scan at baseline and follow-up. Parents were privately interviewed using parallel measures.

Baseline exclusionary criteria—At baseline, individuals were excluded if parental or youth report indicated >10 lifetime drinking occasions, >2 drinks per week, >5 lifetime marijuana use occasions, any marijuana use in the past three months, >1 cigarette per week, or any other intoxicant or psychotropic medication use. Based on parental and youth report, other exclusionary criteria included: (1) prenatal exposure to any intoxicant; (2) chronic medical illness; (3) neurological or psychiatric disorder except for oppositional defiant or conduct disorder (American Psychiatric Association 2000); (4) loss of consciousness of >2 minutes; (5) learning or intellectual disability; (6) parental history of psychiatric disorders other than SUD; (7) non-correctable auditory or visual problems; (8) left handedness; (9) birth prior to 35th gestational week; (10) current pregnancy; (11) alcohol or drug intoxication on day of testing; (12) inadequate English; (13) MRI contraindications (N=295).

Follow-up eligibility—Inclusion criteria at follow-up for the current study were: (1) youth must have initiated alcohol use (i.e., have had at least one standard drink) by follow-up; (2) have available VWM blood oxygenation level dependent (BOLD) data at baseline and follow-up; and (3) have available substance use, demographic, and mental health self-report data at baseline and follow-up. For the present study, 133 met these criteria. Among these individuals, 73 transitioned into weekly drinking (i.e., consumed at least one standard drink of alcohol at least once a week for six or more consecutive months) and 60 did not (see Table 1, 2). The overall followup rate exceeded 95% as of 2017.

Measures

Substance use measures—The Customary Drinking and Drug Use Record (Brown et al. 1998) was administered at baseline and follow-up to assess pattern and severity of alcohol, nicotine, marijuana, and other recreational drug use. The Timeline Followback (TLFB; Medina et al. 2007; Sobell and Sobell 1992; Sobell et al. 1979) examined past 30-day frequency and quantity of substance use. Drinking duration was defined as the number of years youth engaged in alcohol use between drinking onset and follow-up, inclusive. Past year drinking frequency was defined as the number of drinking days in the past year prior to follow-up.

Externalizing symptomology—Youth level of externalizing symptomology was 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 normed indices of Externalizing (i.e., Rule-Breaking Behavior and Aggressive Behavior Problems) problems, with higher scores indicating more symptoms.

Neuropsychological battery—A comprehensive neuropsychological battery was administered at baseline and follow-up to assess cognitive functioning. The battery included: Digit Vigilance Test (Lewis and Rennick 1979); Delis-Kaplan Executive Function System (D-KEFS; Delis et al. 2001) Color Word Interference (CWI) and Trail Making (TMT) subtests; California Verbal Learning Test - Second Edition (CVLT-II; Wechsler 1997); Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler 1999) Block Design subtest; Wechsler Adult Intelligence Scale - Third Edition (WAIS-III; Delis et al. 2000) Coding and Digit Span subtests; and the Rey- Osterrieth Complex Figure task (Rey and Osterrieth 1993).

To reduce Type I error, correlational analyses with a false discovery rate of $q\text{-value} = 0.05$ (see below) between cdFC and neuropsychological performance were conducted with raw scores from a small subset of nine tests among the larger neuropsychological battery. These tests were chosen based on their expected association with visual working memory functioning (Nguyen-Louie et al. 2015; Strauss et al. 2006): Digit Vigilance Test, D-KEFS Trail Making Test Visual Scanning and Color Naming subtests, WAIS-III Digits Backward, Digits Forward and Arithmetic, WASI Block Design, Complex Figures task - copy, and CVLT-II List B.

Imaging—Participants were scanned in a 3-Tesla GE Discovery MR750 short bore Excite-2 MR system with an 8- channel phase-array head coil. A sagittally acquired spoiled gradient recalled sequence was used (field of view [FOV]= 24 cm, 256×192 interpolated to 256×256 matrix, .94×.94×1 mm voxels, 176 slices, repetition time [TR]= 8 ms, echo time [TE]=4.8 ms; flip angle [FA] = 12,7;26 duration). Field map acquisitions employed two different TEs to assess field inhomogeneities and signal distortions under the same parameters as echo-planar image acquisition. This information was applied to the functional MRI (fMRI) acquisitions to minimize warping and signal dropouts (4 minutes total). BOLD fMRI signal was measured with T2*-weighted axially acquired echo-planar imaging sequences (FOV=24 cm, 64×64 matrix, 3.75×3.75×3.8 mm voxels, 32 slices, 256 repetitions, TR = 2000 ms, TE=30 ms, FA = 90, ramped bandwidth 250 KHz). Task stimuli were back projected from a laptop to a screen at the foot of the scanner bed visible via an angled mirror attached to the head coil. Accuracy and reaction time data were logged with a response box designed for MRI studies. Each task was identical for all participants.

Visual Working Memory fMRI task—A parametric visual working memory (VWM) task serves as an ideal paradigm with which to explore the neurotoxic effects of alcohol. VWM tasks have been shown to be sensitive to adolescent alcohol use (Peeters et al. 2014), particularly involving frontoparietal areas (Chafee and Goldman- Rakic 2000; Wetherill et al. 2012). The VWM task (see Figure 1) consisted of 30 trials of an array of 2, 4, or 6 colored dots presented briefly (100 ms, see Figures 1 and 2). After a 1,000ms delay, the subsequent trial presented the same number of dots in the same location that were either the same color array (50% of arrays) or one-color different. For each trial, participants pressed “1” if the color array was identical, and “2” if not. The human working memory system can

hold three to four distinct pieces of information at a given moment (Paulus et al. 2006); thus, the 6-dot condition was considered higher than most people's working memory span, and the 2-dot condition was within most people's working memory load capacity. The measure of interest was the difference in cdFC during the 6-dot relative to the 2-dot array (high load vs. low load condition), interpreted as cdFC between ROIs and exploratory regions in response to increasing working memory load. A larger, more positive, cdFC fit coefficient was interpreted as higher positive temporal correlation between ROIs or exploratory whole-brain analysis regions to complete the 6-dot trials.

Data Analysis

Regions of interest analysis—All baseline and follow-up imaging data were processed and analyzed using the Analysis of Functional NeuroImages software (AFNI; afni.nimh.nih.gov). Motion (i.e., three rotational and three linear displacement parameters) was estimated for each participant and used to control for task-related analyses (Bandettini et al. 1993). Outliers from 2 times the mean absolute deviation of each voxel time series (*3dToutcount*) was inspected for each participant. Acquisitions with outliers making up >3% of the brain volume were also excluded from further analysis. On the remaining data, significant outliers in the voxel time series data were replaced using *3dDespike*. Time series data were then temporally aligned and co-registered to a maximally stable base volume with an iterated least squares algorithm (*3dvolreg*) (Cox and Jesmanowicz 1999). Spatial smoothing was applied using a Gaussian filter (full-width half maximum 6 mm with *3dBlurToFWHM*). The time series for each task condition (2-, 4-, and 6-dot) was entered as a regressor and convolved with an ideal hemodynamic response function in a general linear model (GLM; *3ddeconvolve*) (Cohen et al. 1997), covarying for baseline, linear trends and motion correction parameters (x,y,z, roll, pitch, yaw). The first three repetition times (TRs) were ignored, as were censored volumes as specified above. For each voxel, results of the GLM included: 1) a fit coefficient representing signal change between 6- and 2-dot conditions, 2) percent signal change and 3) threshold (T) statistics. Each individual's functional and anatomical data sets were co-registered and warped to standardized Talairach space (Talairach and Tournoux 1988) to reduce effects of anatomical variability (*3dAllineate*). Functional data were resampled into isotropic (3 mm³) voxels (*3dfractionize*). Co-registration was examined for each subject (*3dABoverlap*). Four participants were removed from analysis due to excessive motion in greater than 15% of repetitions and misalignment of greater than 10% after realignment attempts were unsuccessful (AFNI's *align_epi_anat.py*).

Context-dependent functional connectivity analysis—Context-dependent functional connectivity was assessed using the psychophysiological interaction (PPI) method (Friston et al. 1997; Gitelman et al. 2003; Jo et al. 2010), which estimates the inter-region neuronal temporal connectivity as a function of the VWM task (i.e., 6-2 dot contrast). The average time series was extracted for the seed ROI, DLPFC, defined as Talairach atlas-based regions (Talairach and Tournoux 1988): Brodmann area (BA) 46, ventral BA 9, and posterior BA10 (Zhou et al. 2007). Trends were removed (*3dDetrend*). These seed time series were then deconvolved into neural timing with a gamma basis function (*Waver* and *3dTfitter*). To examine changes in functional connectivity between regions as a function of the VWM 6-2

dot contrast, a PPI regressor was created by multiplying the deconvolved time series (i.e., “the physiological” neural activity) with the behavioral task (i.e., the “psychological” task) and then re-convolved with a gamma basis function. The resulting interaction terms (i.e., $\text{glt } 6-2 \text{ dot}$) and a main task effect regressor (i.e., detrended time series across all conditions) were entered into a GLM that included the regressors from the task-based fMRI analysis (see above). Additional regressors were included to model the six motion parameters and baseline, linear, quadratic, and cubic trends (i.e., $\text{polort } 4$). The first three TRs were ignored. An atlas-based anatomical mask was applied for the PPC (i.e., the superior parietal cortex, supramarginal gyrus and angular gyrus) (Cabeza et al. 2008) in order to examine cdFC between the DLPFC and PPC, masking out all other brain regions. The resulting PPI parameter (Fisher z-transformed correlation coefficients) of interest represented the measure of cdFC between the DLPFC and all other regions of the brain under the VWM task 6-2 dot contrast. PPI parameters representing the cdFC between the two ROIs (R^2) were transformed into correlation coefficients (i.e., R) and then, to account for skewness and deviations from a normal distribution, into Fisher’s Z .

Linear regressions were conducted in AFNI (*3dMVM*) to test the hypothesis that AFD and AWDO significantly predicts cdFC between the DLPFC and PPC at the follow-up time point, above and beyond baseline (i.e., pre-drinking) differences in cdFC between these ROIs. Two linear regressions models were tested, one for each independent variable of interest (i.e., AFD or AWDO). Each model included one voxel-wise covariate (*vVars* option in the *3dMVM* analysis program): baseline cdFC (i.e., Fisher’s Z) between the DLPFC and PPC. Generalized h^2 (GES) effect size estimates were computed using the *GES* option in the *3dMVM* program. Eta-squared values were interpreted as the proportion of variance in follow-up cdFC independently accounted for by each predictor and covariate. Follow-up age and past-year marijuana use days were initially considered as a possible covariates and gender was initially considered as a possible moderator. Results remained consistent with these predictors in the model; they were therefore removed in final models to increase degrees of freedom and power.

Whole-brain exploratory analyses—Exploratory cluster-based analyses were conducted to test the hypothesis that age of onset (AFD and AWDO) significantly predicts cdFC between brain regions other than *a priori* specified ROIs at the follow-up time point. To control for multiple comparisons and Type I error, noise smoothness in the x, y, and z dimensions was first estimated (*3dFWHMx*) with a Gaussian and mono-spherical autocorrelation function (acf). Parameters from this model were then entered into Monte Carlo simulations (*3dClustSim*, bug fixed version) that accounted for the estimated smoothing to determine cluster size thresholds that met the following criteria: bi-sided thresholding, first-nearest neighbor clustering, uncorrected (per-voxel) $p < .001$, and corrected (whole volume) $\alpha = .05$. Based on these calculations, only regions with >7 voxels were retained in fMRI and functional connectivity group-level analysis.

To determine seed regions for cdFC analysis, two exploratory whole-brain regression analyses (i.e., a separate regression for each predictor of interest: AFD and AWDO) were first conducted in AFNI (*3dMEMA*) to determine clusters that showed a significant relationship between BOLD activation to the VWM task (6-2 dot contrast) and age of onset.

Functional masks were created for regions that showed a significant relationship in BOLD activation with age of onset and applied to each participant's follow-up and baseline BOLD dataset. Each functional cluster was then used as the seed in follow-up cdFC analyses. Analysis for cdFC followed an identical plan as in ROI-based analyses, described above.

Behavioral and cognitive correlates of cdFC—Zero-order correlations (Pearson's r) were conducted to examine the bivariate association between age of onset (AFD and AWDO) and follow-up substance use (past year average and peak drinks per occasion and binge drinking days, past year marijuana use days, and past year other drug use days). Correlations were also conducted to examine the bivariate association between follow-up cdFC (i.e., Fisher's Z) and externalizing symptomology, drinking frequency and duration, and neuropsychological performance on nine tests. Fisher's Z values for each significant cluster in linear regression analyses ($3dMVM$, described above) were averaged across voxels for each subject and region, extracted, and exported into Stata Version 14; StataCorp LP, College Station, TX). Correlations were performed using the *corr* command. Correction for multiple comparisons was carried out based on the false discovery rate controlling procedure (Benjamini and Hochberg 1995) with q -value = 0.05 using the Stata *multproc* package (Newson 2003). Uncorrected p -values are also presented for comparison.

Results

Description of Sample

At baseline, 5% of participants ($n=7$) had consumed at least one standard drink of alcohol. At follow-up, all 133 individuals had transitioned into alcohol use (i.e., consumed 1 standard drink on 1 occasions), and among them, 73 had transitioned into weekly alcohol use (see Table 1 and 2).

Task Performance

No significant differences in performance were detected on the VWM task for the 2-dot condition between baseline and follow-up ($N=133$). On average, participants were correct on 93% of trials at baseline 94% of trials at follow-up. On the 6-dot condition, participants were significantly more accurate ($p<.0001$) and responded at a quicker rate at follow-up (82% accuracy rate) compared to baseline (77% accuracy rate). Among participants who had transitioned into weekly drinking ($n=73$), significant effects of time were found for performances on both the 2-dot ($p=.03$) and 6-dot ($p=.0001$) conditions, with better performance at follow-up than baseline. On the 6-dot condition, weekly-drinker participants were correct on 78% of trials at baseline and 82% at follow-up. Among nonweekly drinkers at follow-up ($n=60$), participants performed significantly better at follow-up (83% correct) than baseline (78% correct) on the 6-dot condition only ($p=.0002$). No significant differences in task performance (i.e., % correct and reaction time) were found between youth who remained occasional drinkers (i.e., have not transitioned into weekly drinking) and weekly drinkers, $p>.05$ (see Table 3).

Regions of Interest Analyses

AFD and AWDO did not significantly predict follow-up cdFC during the VWM task 6-2 dot contrast between the two *a priori* ROIs (DLPFC and PPC) at follow-up.

Whole-brain Analyses

Exploratory analyses showed that earlier AWDO predicted higher BOLD response during VWM 6 vs. 2 dot at follow-up in the bilateral posterior cingulate, bilateral medial frontal gyrus, and right superior temporal gyrus (see Figure 2, Table 4). These five regions served as seeds in whole-brain exploratory cdFC analyses. An earlier AWDO was not associated with lower BOLD response during the VWM 6 vs. 2 dot at follow-up in any region. No exploratory whole-brain cdFC analyses were conducted to examine the relationship between AFD and follow-up cdFC, as no regions showed significant differences in 6-2 dot BOLD activation as a function of AFD.

Seed: right posterior cingulate—Controlling for baseline cdFC between corresponding regions, earlier AWDO predicted *higher* cdFC between the right posterior cingulate to the: right middle frontal gyrus ($F(1,70) = -14.52$, AWDO $h^2 = .17$, baseline cdFC $h^2 = .05$), right inferior parietal lobule ($F(1,70) = -13.64$, AWDO $h^2 = .16$, baseline cdFC $h^2 = .03$), and left lingual gyrus ($F(1,70) = -14.43$, AWDO $h^2 = .17$, baseline cdFC $h^2 = .01$) (see Figure 3, Table 5).

Seed: left posterior cingulate—Controlling for baseline cdFC between corresponding regions, earlier AWDO predicted *higher* cdFC between the left posterior cingulate to the: right inferior frontal gyrus ($F(1,70) = -13.3$, AWDO $h^2 = .16$, baseline cdFC $h^2 = .04$), right anterior cingulate gyrus ($F(1,70) = -14.4$, AWDO $h^2 = .17$, baseline cdFC $h^2 = .07$), right posterior precuneus ($F(1,70) = -15.4$, AWDO $h^2 = .18$, baseline cdFC $h^2 = .02$), and left lingual gyrus, ($F(1,70) = -14.6$, AWDO $h^2 = .17$, baseline cdFC $h^2 = .02$) (see Figure 4, Table 5).

No significant relationship between AWDO and cdFC were found with the bilateral medial frontal gyrus and right superior temporal gyrus as seed regions.

Behavioral and cognitive correlates of cdFC—Youth who initiated first and weekly drinking at earlier ages were more likely to have more binge drinking occasions ($ps < .05$), more drinks per occasion ($ps < .01$), and more drug use days ($ps < .01$) in the past year at follow-up. Higher follow-up cdFC was correlated with higher externalizing symptomology, for the right posterior cingulate (seed) and the right middle frontal gyrus ($r = .27$, uncorrected $p = .03$) and the left lingual gyrus ($r = -.33$, uncorrected $p = .004$). Higher follow-up cdFC between the right posterior cingulate (seed) and right inferior parietal lobule was associated with poorer performances on Digits Forward ($r = -0.27$, uncorrected $p = .03$), Rey-Osterrieth figural copy ($r = -0.29$, uncorrected $p = .02$), and CVLT-II List B ($r = -0.28$, uncorrected $p = .02$). Higher follow-up cdFC between the left posterior cingulate (seed) and left lingual gyrus was associated with poorer performance on Digits Forward ($r = -0.29$, uncorrected $p = .02$). Pairwise correlations were no longer significant after adjusting for a false discovery rate of $q = 0.05$ (Benjamini and Hochberg 1995). Drinking frequency

and duration, and performance on other neuropsychological tasks (i.e., TMT Visual Scanning, Digits Backward, Block Design, and Arithmetic) were not correlated with cdFC, and higher cdFC was not linked to less psychopathological symptoms or better neurocognitive performance for any variable.

Discussion

This study examined the prospective effects of AFD and AWDO on context-dependent functional connectivity to ascertain how the latter index of neural functioning may be associated with behavioral and cognitive correlates of adolescent alcohol use. AFD and AWDO were not associated with cdFC between the hypothesized ROIs (DLPFC and PPC) at follow-up. However, exploratory whole-brain analyses suggested that an earlier age of weekly drinking onset predicted *higher* (i.e., more positive) cdFC between the bilateral posterior cingulate and cortical (i.e., right frontal, right parietal, left lingual areas) and subcortical (i.e., right cingulate precuneus) regions, above and beyond any pre-existing differences in cdFC between corresponding regions prior to initiation of significant alcohol use. Further, *higher* cdFC may be associated with *higher* externalizing symptomology and poorer neuropsychological performances, suggesting that higher cdFC may be a less favorable cognitive outcome. This study was the first to examine the effects of AWDO on functional connectivity, and additionally, to control for baseline cdFC, allowing for consideration of any pre-morbid differences in neurocognition. These findings represent an important advancement in the understanding of alcohol use onset age and its effects on neurocognitive functioning in high-functioning adolescents with minimal co-occurring medical or psychiatric distress.

It has been suggested that adolescence is a critical period for alcohol-related neural vulnerabilities, evidenced by decreased sensitivity to the adverse social and behavioral aspects of alcohol use coupled with increased sensitivity to its neurotoxic effects (Crews et al. 2016). In rodents, adolescents show decreased sensitivity to sedation, social inhibition, motor impairment, withdrawal, and taste aversion effects of alcohol (Doremus et al. 2003; Silveri and Spear 1998; Varlinskaya and Spear 2002; White et al. 2002). In general, young drinkers are less likely to experience the negative pharmacological and social effects of acute alcohol intoxication, a mechanism that, in adults, likely serves as experiential feedback to curb maladaptive drinking patterns (for review, see Crews et al. 2016). Further, adolescents may be at increased vulnerability for neurotoxic effects of alcohol. For example, ethanol dose-dependently reduces dendritic pruning in the somatosensory cortex (Chandler 2003) and neurogenesis in male adolescent rats in the forebrain and hippocampal areas while increasing widespread neuronal apoptotic markers (Crews et al. 2006; Morris et al. 2010).

Our results suggest that delaying weekly drinking until later in adolescence is associated with increased anticorrelated functional connectivity between the posterior cingulate and other regions during a visual working memory task, and anticorrelation appears linked to better neuropsychological performance and fewer externalizing symptoms. This is in line with prior studies that have consistently found anticorrelations with the posterior cingulate as seed in response to demanding attentional tasks (Fox et al. 2005; Kelly et al. 2008). Evidence suggests that throughout neurodevelopment, there is a global increase in negative

functional connectivity among brain regions, most notably in frontal and parietal areas implicated in attention and working memory (Barber et al. 2013; Chai et al. 2014). Longitudinal examinations of functional connectivity have found a reversal of phase as individuals mature into adolescence and adulthood, in which activation between regions initially show positive correlations in childhood but transition to negative correlations by adulthood (Barber et al. 2013; Stevens et al. 2009). Overall, this body of literature suggests that the normal course of development follows an increase in anticorrelations among cortical and subcortical regions as an individual ages. Based on our results, it is possible that the onset of regular alcohol use at an earlier age disrupts this typical trajectory. Youth with earlier AWDO were less likely to show anticorrelation cdFC than those who initiate weekly drinking at a later age, when the brain has undergone greater maturation (Gogtay et al. 2004). However, the literature on this phenomenon is in its infancy and requires further exploration.

A key unanticipated result was that no significant relationship between age of onset and cdFC between *a priori* ROIs (DLPFC and PPC) was found in the current analysis. Frontoparietal connectivity has been implicated in various aspects of alcohol use. For example, substance-naïve youth with a family history of AUD showed lower positive cdFC than those without (Wetherill et al. 2012). Among adult men, heavier drinkers showed lower resting- state frontoparietal functional connectivity compared to normal controls (Shokri-Kojori et al. 2016). Differences in methodology may account for the unexpected null findings with the specified ROIs in this study. Prior studies have focused either on heavy drinkers with AUD (De Bellis et al. 2000) or substance-naïve youth with and without AUD family history (Spadoni et al. 2013; Wetherill et al. 2012). In the current study, participants entered as healthy, nontreatment seeking adolescents who exhibited a range of drinking patterns at follow-up. It is possible that as a risk factor, age of onset exhibits differential effects on neural patterns than family history and drinking severity.

The current study utilized a VWM task (Luck and Vogel 1997) to explore the impact of AFD and AWDO on neurocognition. Working memory continues to develop and mature throughout adolescence and into adulthood (Crone et al. 2006; Isbell et al. 2015), providing an important construct for understanding the effects of alcohol use on neurodevelopment. It was not surprising that the regions in this study that showed significant differences in BOLD activation and cdFC in brain regions are areas that have previously been found to be important to vision and working memory, including the right frontal gyrus, right parietal lobule, cingulate gyrus, and lingual gyrus. Findings may represent part of a complex functional network among brain regions involved in attentional shift, possibly with the seed regions (bilateral posterior cingulate) acting to regulate these processes (Hampson et al. 2006). Earlier ages of weekly alcohol use initiation may adversely affect neurodevelopment by reducing developmentally appropriate integration of attentional circuits, as evidenced by reduction of anticorrelations between these regions. The right inferior frontal gyrus, for example, plays a role in attentional control and allocation to relevant stimuli (Corbetta and Shulman 2002; Hampshire et al. 2010). The right inferior and middle frontal gyri may be involved in a broader network implicated in reorienting to unexpected and endogenous stimuli (Corbetta and Shulman 2002; Shulman et al. 2009; Thiel et al. 2004) that occurs outside the focus of attention. The inferior parietal lobule, on the other hand, is involved in

vigilance and sustained attention together with the ventral frontal cortex (Singh-Curry and Husain 2009). Modulation of arousal state throughout the VWM task may be maintained through connectivity between the posterior and anterior cingulate gyri (Boly et al. 2012). Another key region, the lingual gyrus, is important for processing visual stimuli while the posterior precuneus contributes to episodic memory processes utilized for retrieval of previously seen stimuli required for successful completion of the task (Cavanna and Trimble 2006).

An important limitation of this study is that these results are exploratory in nature and were obtained using a data- driven approach. Although methods for clustering and thresholding were used (e.g., Monte Carlo simulations) to decrease Type I error, the process of selecting seed regions based on areas found to be activated in BOLD analysis is not free from bias. For example, regions that showed activation differences in relation to age of onset in BOLD analyses are also more likely to show an association with the same predictor in cdFC analyses. For these reasons, the reported effect sizes may be inflated, and should be interpreted with caution. Findings from the whole- brain exploratory analyses should be viewed as a foundation for future studies examining the relationship between age of onset and cdFC and additional research is needed to replicate these findings. A possible future direction is to examine group differences in cdFC among youth who have never consumed any alcohol (nondrinkers), youth with early AWDOs, and youth with late AWDOs. Based on the current results, we expect non-drinkers to display more anticorrelations than all drinker groups, and drinkers with late AWDO would show less anticorrelations than controls, but more anticorrelations than drinkers with early AWDO. If future results are in line with these predictions, this would provide further supporting evidence to suggest that early AWDO predicts poorer neurocognitive developmental outcomes.

The literature has described in detail the structural, functional, and behavioral development of the brain from early childhood to adulthood, and evidence suggests that alcohol negatively impacts adolescent neuromaturational processes. However, few studies have examined how these two processes -brain development and alcohol use initiation - interact. The current results suggest that alcohol impacts the temporally linked functioning of important brain areas. Earlier ages of weekly alcohol use initiation may adversely affect neurodevelopment by reducing developmentally appropriate anticorrelations in attentional circuits. Importantly, between 15-23 years, a weekly drinking onset age that is safe from deleterious neurocognitive effects has yet to be identified.

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Fig. 1. Example of Visual Working Memory task 2-dot condition
Task adapted from: Luck, S. J., & Vogel, E. K. (1997). The capacity of visual working memory for features and conjunctions. *Nature*, 390(6657), 279-281.

Fig. 2. Age of drinking onset and BOLD activation in whole-brain analyses

Regions (in green, circled for emphasis) that showed significant associations between blood oxygen-level dependent (BOLD) contrast response to a visual working memory task 6-2 dot contrast and age of weekly drinking onset (AWDO; $N=73$). Multiple comparisons correction was carried out with Monte Carlo simulations at a voxel-wise $p < .001$ and cluster $\alpha < .05$. Color bar indicates t-value scaling.

All regions showed a negative relationship, such that higher AWDO predicted decreased activation. No significant regions were found in the lateral left hemisphere. No significant relationship between age of first drink and BOLD contrast response was found ($N=133$).

Fig. 3. Relationship between age of weekly drinking onset and context-dependent functional connectivity with seed region right posterior cingulate ($N=73$)

Whole-brain analyses examining the relationship between age of weekly drinking onset (AWDO) and context-dependent functional connectivity (cdFC) in response to a visual working memory task 6-2 dot contrast. Three pairs of regions (seed: right posterior cingulate, bottom left) showed a significant negative relationship between cdFC and AWDO. Earlier AWDO predicted more positive cdFC six years after adolescents transitioned into weekly alcohol use, controlling for baseline cdFC among corresponding regions. Scatter plots depict linear relationship between cdFC (i.e., Fisher's Z-transformed correlation coefficients) and AWDO.

L = left hemisphere; R = right hemisphere

Fig. 4. Relationship between age of weekly drinking onset and context-dependent functional connectivity with seed region left posterior cingulate ($N = 73$)

Whole-brain analyses examining the relationship between age of weekly drinking onset (AWDO) and context-dependent functional connectivity (cdFC) in response to a visual working memory task 6-2 dot contrast. Four pairs of regions (seed: left posterior cingulate, bottom left) showed a significant negative relationship between cdFC and AWDO, controlling for baseline cdFC among corresponding regions.

L = left hemisphere; R = right hemisphere

Table 1

Demographic characteristics ($N=133$)

	All participants (N = 133)	M (SD) or % [Range] Non-weekly drinkers by follow-up (n = 60)	Weekly drinkers by follow-up (n = 73)
BL age*	13.5 (1.2)	13.2 (1.4)	13.8 (0.7)
FU age*	19.9 (1.3)	19.8 (1.2)	21.0 (1.7)
Age first drank*	16.4 (1.7) [Range: 11.0–21.3]	16.9 (1.6) [Range: 13.0–21.3]	15.6 (1.9) [Range: 11.0–20.1]
Age first drank weekly	—	—	18.4 (1.5) [Range: 15.0–23.2]
Years between BL and FU	6.0 (1.4) [Range: 2.0 – 9.0]	6.6 (1.6) [Range: 3.0 – 9.0]	7.2 (1.9) [Range: 2.0 – 9.0]
% Female	40%	40%	37%
Race/Ethnicity			
Caucasian*	62%	54%	71%
Latino/a	20%	25%	16%
Multiple races	11%	9%	11%
African American/Black	3%	5%	1%
Asian American*	4%	7%	0%

BL = baseline; FU = follow-up; significant group difference between non-weekly drinkers and weekly-drinkers at follow-up, $p < .05$

Table 2

Substance use behaviors at baseline and follow-up ($N = 133$)

	M (SD) or % [Range]		
	All participants ($N = 133$)	Non-weekly drinkers by follow-up ($n = 60$)	Weekly drinkers by follow-up ($n = 73$)
Baseline			
Tried alcohol	5%	2%	11%
Tried marijuana	<1%	0%	3%
Tried other drugs	0%	0%	0%
Follow-up			
Past year drinking days *	52.8 (58.5); $Mdn = 29.9$	19.9 (23.2); $Mdn = 14.0$	101.3 (66.8); $Mdn = 84.0$
Past year average drinks per occasion *	4.2 (2.8); $Mdn = 4.0$	3.2 (2.3); $Mdn = 3.0$	5.1 (2.8); $Mdn = 5.0$
Past year binge drinking days * ^a	26.3 (43.4); $Mdn = 7.0$	7.3 (11.9); $Mdn = 2.0$	48.0 (50.9); $Mdn = 40.0$
Past year drink days per month *	4.4 (4.9); $Mdn = 2.5$	1.7 (1.9); $Mdn = 1.2$	8.3 (5.6); $Mdn = 7.0$
Past year peak drinks per occasion *	8.1 (5.2); $Mdn = 2.0$	5.9 (3.9); $Mdn = 6.0$	10.6 (5.3); $Mdn = 10.0$
Past year marijuana use days *	49.3 (102.6); $Mdn = 2.0$	22.5 (63.1); $Mdn = 0.0$	76.7 (121.3); $Mdn = 10.0$
Past year other drug use days *	2.8 (8.7); $Mdn = 0.0$	0.6 (2.5); $Mdn = 0.0$	7.4 (14.4); $Mdn = 0.0$
Used marijuana in the past year *	60%	46%	71%
Used other drugs in the past year *	29%	14%	48%
Past year alcohol use classification *			
Non-drinker	5%	9%	0%
Infrequent drinker	15%	26%	3%
Moderate drinker ^c	77%	65%	89%
Mild Alcohol Use Disorder ^b	20%	0%	36%
Moderate Alcohol Use Disorder ^b	5%	0%	10%
Severe Alcohol Use Disorder ^b	3%	0%	5%

* Significant group difference between non-weekly drinkers and weekly-drinkers at follow-up, $p < .05$

^a Consumed 5 drinks per occasion for men or 4 drinks per occasion for women

^b Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

^c Consumed no more than 2 drinks twice a week and no less than 4 drinks once a year; criteria based on Cahalan et al. (1969) and have been described in detail elsewhere (Nguyen-Louie et al., 2017)

Cahalan D, Cisin I, Crossley H. New Brunswick, NJ: Rutgers Center of Alcohol Studies; 1969. *American drinking practices*. Monograph No. 6.

Nguyen-Louie T.T., Courtney, K.E., Squeglia, L.M., Bagot, K., Eberson-Shumate, S., Migliorini, R., Alcaraz, A.R., Tapert, S.F., Pulido, C. (2017) Prospective changes in neural alcohol cue reactivity in adolescents at risk for alcohol use disorders. *Brain Imaging and Behavior*. Advance online publication. doi: 10.1007/s11682-017-9757-0

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Table 3

Visual Working Memory Task Performance

	Baseline	Follow-up
	M (SD) or % [Range]	
All participants (N = 133)		
2-dot condition		
% correct	93% (6.0) [68% – 100%]	95% (6.0) [61% – 100%]
Response time	2384.0 ms (185.3)	2213.2 ms (118.2)
6-dot condition		
% correct	77% (9.2) [52% – 100%]	82% (11.0) [52% – 100%]
Response time	2550.3 ms (190.2)	2354.5ms (143.1)
Non-weekly drinkers by follow-up (N = 60)		
2-dot condition		
% correct	94% (5.9) [68% – 100%]	95% (5.4) [77% – 100%]
Response time	2400 ms (193.9)	2195.0 ms (116.7)
6-dot condition		
% correct	78% (8.9) [55% – 97%]	83% (10.2) [61% – 100%]
Response time	2570.3 ms (186.1)	2340.3 ms (146.4)
Weekly drinkers by follow-up (N = 73)		
2-dot condition		
% correct	91% (6.0) [77% – 100%]	94% (6.1) [71% – 100%]
Response time	2373.0 ms (181.8)	2227.1ms (121.8)
6-dot condition		
% correct	78% (9.4) [52% – 100%]	82% (11.1) [75% – 100%]
Response time	2531.1 ms (192.8)	2364.0 (143.8)

Note. ms = reaction time in milliseconds

Table 4

Regions of significant visual working memory BOLD response contrast as a linear function of age of weekly drinking onset ($N=73$)

Anatomical Region	Talairach coordinates (RAI center of mass)			Cluster size (# voxels)
	x	y	z	
Whole-brain exploratory analyses				
R posterior cingulate	−8	63	14	31
R superior temporal gyrus	−43	27	5	9
R medial frontal gyrus	−1	−40	42	9
L posterior cingulate	10	57	17	8
L medial temporal gyrus	11	−28	42	7

Regions that showed significant changes in blood oxygen level dependent (BOLD) activation to visual working memory task 6-2 dot contrast in a linear regression model examining the relationship between age of weekly drinking onset and BOLD response (per-voxel $p<.001$, whole volume $\alpha=.05$). For all regions, an earlier age of weekly drinking onset predicted higher activation. No significant relationship was found between BOLD response and age of first drinking onset.

L=left hemisphere, R=right hemisphere

ROI= region of interest

RAI = coordinate system in which right, anterior, and inferior regions are depicted as negative x, y, and z coordinates, respectively

Table 5

Regions of significant differences in context-dependent functional connectivity as a linear function of age of weekly drinking onset ($N=73$) in whole-brain exploratory analyses

	Talairach coordinates (RAI center of mass)			
	x	y	z	Cluster size (# voxels)
Seed: R posterior cingulate				
R middle frontal gyrus	-28	-12	32	16
R inferior parietal lobule	-53	26	26	9
L lingual gyrus	26	80	-4	9
Seed: L posterior cingulate				
R inferior frontal gyrus	-38	-10	30	8
R anterior cingulate gyrus	-9	-24	40	9
R posterior precuneus	-21	64	23	8
L lingual gyrus	23	70	-4	7

Regions that showed significant changes in context-dependent functional connectivity (cdfC) with seed regions during a visual working memory task 6-2 dot contrast in a linear regression model examining the relationship between age of weekly drinking onset and whole-brain cdfC, controlling for baseline cdfC between corresponding regions (per-voxel $p < .001$, whole volume $\alpha = .05$). For all regions, an earlier age of weekly drinking onset predicted higher cdfC among respective regions, controlling for baseline cdfC among corresponding regions.

No significant relationship was found between cdfC and age of first drinking onset.

L=left hemisphere, R=right hemisphere

RAI = coordinate system in which right, anterior, and inferior regions are depicted as negative x, y, and z coordinates, respectively