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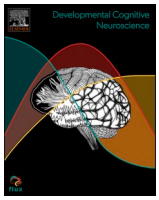

A longitudinal study of the relationship between alcohol-related blackouts and attenuated structural brain development

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ABSTRACT

Purpose: Alcohol-related blackouts (ARBs) are common in adolescents and emerging adults. ARBs may also be indicative of persistent, alcohol-related neurocognitive changes. This study explored ARBs as a predictor of altered structural brain development and associated cognitive correlates.
Methods: Longitudinal growth curve modeling estimated trajectories of brain volume across 6 years in participants from the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) study (n = 800, 213 with lifetime ARB history). While controlling for demographics and overall alcohol use, ARB history was analyzed as a predictor of brain volume growth in regions associated with alcohol-related cognitive change. Post hoc analyses examined whether ARBs moderated relationships between brain morphology and cognition.
Results: ARBs significantly predicted attenuated development of fusiform gyrus and hippocampal volume at unique timepoints compared to overall alcohol use. Alcohol use without ARBs significantly predicted attenuated fusiform and hippocampal growth at earlier and later timepoints, respectively. Despite altered development in regions associated with memory, ARBs did not significantly moderate relationships between brain volume and cognitive performance.
Conclusion: ARBs and overall alcohol use predicted altered brain development in the fusiform gyrus and hippocampus at different timepoints, suggesting ARBs represent a unique marker of neurocognitive risk in younger drinkers.

1. Introduction

Alcohol-related blackouts (ARBs) are a common neurocognitive consequence of alcohol use, with up to 35 % of adolescents and 60 % of young adults reporting past-year and lifetime ARBs, respectively (Lorkiewicz et al., 2022; Rose and Grant, 2010). ARBs typically occur due to a rapid rise in blood alcohol concentration, and are associated with binge drinking and related behaviors common among younger drinkers (Hartzler and Fromme, 2003). Compared to binge drinking alone, ARBs are strongly associated with poor psychosocial functioning (Haas et al., 2019), academic or occupational achievement (Hingson et al., 2016), and mental health outcomes (Miller et al., 2020; Wilhite and Fromme, 2015), as well as higher risk for alcohol use disorder (Yuen et al., 2021). Of particular importance, ARBs are also related to adverse neurocognitive outcomes independent of overall alcohol use (Wetherill and Fromme, 2016).

Characterized by anterograde amnesia for part or all of a drinking event, ARBs reflect ethanol's acute disruption of long-term potentiation (i.e., transfer of sensory information from short to long-term storage) within the hippocampus (White, 2003) and dysfunction of frontal networks involved in memory consolidation and retrieval (Rose and Grant, 2010). In addition to acute deficits, emerging literature suggests ARBs are also indicative of persistent alcohol-related neurocognitive changes. Cross-sectionally, ARBs are associated with lower performance on

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attention, executive function, prospective memory, and verbal memory tasks (Min et al., 2019; Zamroziewicz et al., 2017), though samples differ in age and severity of lifetime alcohol use. In a recent longitudinal analysis of adolescents and emerging adults, ARBs predicted attenuated development of cognitive functions related to facial recognition and visual recall compared to alcohol use without ARBs (Lorkiewicz et al., 2022). Independent of overall alcohol use, ARBs are also associated with self-reported cognitive concerns among young adults (Linden-Carmichael et al., 2023), indicating that in addition to laboratory-based behavioral findings, ARBs are related to distinct cognitive changes apparent in everyday life.

Literature has not thoroughly examined underlying neurobiological changes associated with ARBs in adolescents and young adults. Existing research demonstrating associations between ARBs, certain genetic profiles (Nelson et al., 2004), and preexisting frontoparietal network dysfunction (Wetherill et al., 2012, 2013; Wetherill and Fromme, 2016) suggests some individuals are more susceptible to ARBs than others. MRS studies further illustrate relationships between ARBs and low glutathione (i.e., a primary CNS antioxidant; Chitty et al., 2014), N-acetyl-aspartate (i.e., NAA; marker of neuronal integrity), and GABA (Silveri et al., 2014) concentrations, indicating increased susceptibility to oxidative stress and untoward neurocognitive consequences of binge drinking in some or all individuals. In young adult binge drinkers without alcohol use disorder or neurological vulnerabilities, low NAA concentrations were only found in subjects reporting ARBs, highlighting ARBs as a unique marker of adverse alcohol-related effects on neuronal integrity (Silveri et al., 2014). Indeed, ARBs may be associated with morphological brain changes due to heavy drinking during critical stages of neural development (Hermens and Lagapoulos, 2018) given that binge drinking adolescents experience more frequent ARBs as adults despite reductions in alcohol use (Marino and Fromme, 2016). However, while one study in college students found that ARBs predicted a larger two-year decline in hippocampal volume compared to alcohol use alone (Meda et al., 2018), there is a paucity of research further characterizing structural correlates of ARBs. Additional work is therefore needed to determine whether higher ARB incidence represents neurotoxic effects of binge drinking that persist beyond intoxication.

Taken together, current literature suggests ARBs are a unique indicator of lasting cognitive and neurobiological changes in younger drinkers independent of alcohol consumption indices. Nevertheless, ARB correlates are largely defined within the context of alcohol intoxication, and associations between ARBs and persistent neurotoxic effects of alcohol and subsequent structural and behavioral sequelae are not fully established. More research is needed to clarify the relationship between ARBs and lasting morphological brain changes in neurologically healthy drinkers given that altered neural development can have significant functional consequences later in life. ARBs may be particularly relevant to identifying at-risk adolescents and emerging adults given high rates of binge drinking and adverse effects of alcohol on the developing brain in regions undergoing significant maturation (Crews et al., 2016; Silveri, 2012; Squeglia et al., 2009a; Sullivan et al., 2020). Moreover, identifying novel targets for early detection and intervention of problematic alcohol use is important since alcohol-related neurocognitive changes are often subtle and difficult to measure in younger cohorts.

The purpose of this study was to further characterize ARBs as a predictor of persistent, alcohol-related morphological brain changes in adolescents and emerging adults. To expand findings from our prior longitudinal analysis (Lorkiewicz et al., 2022) in which ARBs predicted changes in facial recognition and delayed visual recall (i.e., cognitive domains sensitive to adolescent binge drinking; Lees et al., 2020), we aimed to determine whether ARBs predicted changes in underlying brain structures independent of alcohol use quantity and frequency. In adolescents and emerging adults, we examined growth in structural brain volume in five regions associated with the facial recognition (Gur et al., 1997, 2002) and visual learning and memory (Melrose et al., 2013; Mock et al., 2023) tasks explored in our prior study that were also sensitive to negative effects of heavy, intermittent alcohol use (Jones and Nagel, 2019; Mashhoon et al., 2014; Squeglia et al., 2014, 2015). Latent growth curve modeling analyzed relationships between ARBs and structural MRI data from the longitudinal National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) study across six years. Given NCANDAs accelerated longitudinal design, development of the fusiform gyrus, hippocampus, amygdala, superior frontal gyrus, and posterior cingulate gyrus regions was studied over multiple periods. We hypothesized that participants with ARB histories would have attenuated development (i.e., slower growth rates over time) across all regions, particularly at later timepoints, compared to drinkers without ARB histories. In regions where ARBs predicted altered development, post hoc analyses aimed to a.) examine associations between brain volume and cognitive task performance in an exploratory fashion and b.) analyze whether ARB history moderated the relationship between brain volume and cognition. We hypothesized that the interaction between ARBs and regional brain volumes would be significantly associated with lower task performance.

2. Method

2.1. Study sample

The current study analyzed data from 800 adolescents and emerging adults (i.e., ages 12–21 years at study entry) recruited as part of the NCANDA study. Participants with available structural MRI data from at least two follow-up assessments were included in analyses. A data distribution agreement was obtained from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to access NCANDA data on 03/31/2023. Publicly available data from the sixth-year data release (i.e., baseline through sixth annual follow-up assessment) related to structural neuroimaging, neuropsychological task performance, substance use, and demographics were downloaded from www.cnslab.stanford.edu/data using the Sage Bionetworks Synapse 2023 portal.

NCANDA recruited participants from five assessment sites in the United States (i.e., Duke University, Oregon Health & Science University [OHSU], University of Pittsburgh, SRI International, and University of California San Diego [UCSD]). To evaluate substance use during a range of critical developmental stages, NCANDA utilized an accelerated longitudinal design (Duncan et al., 1996, 2006) and oversampled individuals ages 12 through 15 years at risk for alcohol use initiation (i.e., drinking before age 15, family history of substance use disorder, ≥ 1 externalizing or ≥ 2 internalizing symptoms; Squeglia et al., 2017; Zucker et al., 2008). Baseline inclusion criteria were age 12 through 21 years, English fluency, and residence < 50 miles from each assessment site. Exclusion criteria included MRI contraindications, vision or hearing impairment, lack of parental consent, medications impacting brain function or blood flow, certain medical conditions (i.e., those impacting MRI results, brain development, or study participation), early psychiatric disorders interfering with protocol completion (i.e., including substance use disorders), parental history of psychotic disorder not associated with substance use, and developmental or severe learning disorder. Full description of the NCANDA study's including inclusion and exclusion criteria is described in Brown et al., (2015).

While most NCANDA participants had limited substance use exposure at baseline, 17 % were allowed to exceed baseline age-adjusted thresholds for alcohol, nicotine, and marijuana use (National Institute on Alcohol Abuse and Alcoholism, 2011; Substance Abuse and Mental Health Services Administration, 2012) to broaden the range of substance use severity and allow for future comparison groups. Subjects allowed to exceed baseline substance use thresholds tended to be older (i.e., 60 % were ages 18–21) and report earlier age of alcohol use onset (i.e., 25 % drank before age 15; Brown et al., 2015). Current analyses included participants who exceeded baseline substance use thresholds given our longitudinal focus on ARBs which are associated with heavier episodic

alcohol use.

Prior to study enrollment and participation at each annual follow-up visit, all participants underwent informed consent procedures in which adult participants or parents of minor participants provided written informed consent and minor participants provided assent. The Institutional Review Boards of each site approved all NCANDA study protocols. At baseline and annual follow-up visits, all participants completed neuropsychological testing (Sullivan et al., 2016), a comprehensive psychosocial and psychodiagnostic interview (Brown et al., 2015), and multimodal magnetic resonance imaging (MRI) of the brain (Pfefferbaum et al., 2016; Pohl et al., 2016). Full description of NCANDA's MRI protocol and baseline neuroimaging results are described in Pfefferbaum et al. (2016). The neuropsychological battery protocol and associated baseline cognitive results are shown in Sullivan et al. (2016).

2.2. Measures

2.2.1. Demographics

Demographic data were collected at baseline and each annual follow-up (see Brown et al., 2015 for full description of demographic measures). In the current study, demographic factors associated with variation in brain volume were analyzed longitudinally as covariates including age (Pfefferbaum et al., 2013), biological sex (Paus, 2010; Sowell et al., 2007), ethnicity (Bakken et al., 2011; Pfefferbaum et al., 2016), and socioeconomic status (SES; McLoyd, 1998). MRI manufacturer was also included as a covariate in longitudinal analyses based on prior NCANDA studies that suggest controlling for manufacturer reduces variability in MR metrics (Kwon et al., 2018; Pohl et al., 2016). In longitudinal models, age was centered on 12 years (i.e., youngest possible age at study entry) to aid in interpretation and analyzed as a continuous, time-varying covariate (i.e., varies at each timepoint) with fixed factor loadings to control for the direct correlation between age and brain volume. Baseline data for biological sex (i.e., male versus female) and race/ethnicity (i.e., white versus non-white[1]) were analyzed as time-invariant covariates (i.e., group inclusion did not change over time). Baseline SES was analyzed as a continuous, time-invariant covariate defined as highest level of parental education for either parent, an estimate that is less sensitive to changes in family income due to geographical location, and was centered on median level of parental education (Akshoomoff et al., 2014; Brown et al., 2015).

2.2.2. Self-reported substance use

ARB history and overall alcohol use were assessed at baseline and each annual follow-up using the Customary Drinking and Drug Use Record (CDDR), an interviewer-administered instrument measuring current and past alcohol and other substance use (Brown et al., 1998, 2015). The current study defined ARB history as experiencing at least one ARB within the past year (i.e., yes versus no) measured by the single CDDR item: "*In the past year, have there been periods of time that later you could not remember while drinking alcohol/under the influence?*" (Schuckit et al., 2015; Wetherill et al., 2013). Past-year ARB history was included as a dichotomous, time-varying covariate and main predictor of interest in longitudinal models and post-hoc analyses. To better identify whether ARBs predict changes in structural brain development, overall alcohol use was analyzed as a covariate and defined based on a quantity and frequency metric. Specifically, past-year alcohol use quantity was measured by the single CDDR item: "*During the past year, in the average 24-hour period you were drinking, how many alcoholic drinks did you have*?". Alcohol use frequency was measured by the single CDDR item: "During the past year, how many days did you drink alcohol?". Past-year quantity and frequency data were multiplied together to create a final quantity-frequency index (Sobell and Sobell, 1995) of overall alcohol use included as a continuous, time varying covariate in longitudinal models.

2.2.3. Neuropsychological task performance

Post hoc analyses examined continuous neuropsychological task performance scores. NCANDA's full neuropsychological battery consisted of computerized and traditional (i.e., paper and pencil) measures administered at baseline and each annual follow-up. Measures were selected based on reliability, minimization of practice effects, and adequate validity for age (see Sullivan et al., 2017 for detailed description of test selection). Computerized tasks comprised of subtests from the Web-Based Computerized Neurocognitive Battery (WebCNP) that calculates raw accuracy and time scores for each subtest and individual subtest trial (Gurr et al., 2010). The current study analyzed data from one WebCNP subtest, the Penn Facial Memory Test (FMT), and one traditional task, the Rey Complex Figure Test (RCFT), based on previous findings in the NCANDA sample that ARBs significantly and independently predicted task performance in domains of facial recognition and visual learning and memory (Lorkiewicz et al., 2022). Given that demographic covariates were controlled for in all post hoc analyses, raw scores were considered an accurate representation of current cognitive task performance in the absence of demographic or standardized corrections.

Raw accuracy scores from the WebCNP FMT immediate and delayed recognition trials were analyzed separately. On the FMT, participants were shown 20 digitized faces one at a time and asked to identify target faces among 20 distractor items immediately and 20 min later (Moore et al., 2015). For both trials, participants were asked if they had seen each face before using a four-choice scale (i.e., "*definitely not*," "*probably not*," "*probably yes*," "*definitely yes*;" (Gur et al., 2012). Total scores for immediate and delayed recognition trials were defined as total true positive responses, ranging from 20 to 40. Raw scores from the traditional, RCFT copy, immediate recall, and delayed recall trials were also analyzed separately (Rosenbloom et al., 2009). For the RCFT copy trial, participants were asked to copy a complex geometric figure on a piece of paper as precisely as possible to encode visual information. Copy trial performance also measures other cognitive processes necessary for task completion such as psychomotor, visuospatial, and executive functions (Corwin and Bylsma, 1993; Strauss et al., 2012). Immediate and delayed recall trials require participants to draw the same figure from memory 3 and 27 min after the copy trial, respectively (Meyers and Meyers, 1995). Total scores for all three RCFT trials were calculated as the number of correctly drawn figure details, ranging from 0 to 36.

2.3. MRI data acquisition and analysis

The NCANDA study collected T1-weighted images in the sagittal plane using a 3 Tesla General Electric (GE) Discovery MR750 system at three assessment sites (i.e., UCSD, SRI, and Duke University) and a 3 Tesla Siemens TIM TRIO system at two sites (i.e., UPMC and OHSU). GE sites used an Array Spatial Sensitivity Encoding Technique (ASSET) for parallel and accelerated imaging with an 8-channel head coil and acquired an Inversion Recovery-Spoiled Gradient Recalled (IR-SPGR) echo sequence (TR = 5.904 ms, TI = 400 ms, TE = 1.932 ms, flip angle = 11°, NEX = 1, matrix = 256 × 256, FOV = 24 cm, slice dimensions = 1.2 × 0.9375 × 0.9375 mm, 146 slices). Siemens sites used a 12-channel head coil and parallel imaging and temporal acceleration with iPAT and acquired an MPRAGE sequence (TR = 1900 ms, TI = 900 ms, TE = 2.92 ms, flip angle = 9°, NEX = 1, matrix = 256 × 256, FOV = 24 cm, slice dimensions = 1.2 × 0.9375 × 0.9375 mm, 160 slices). The same acquisition protocols were used between Siemens and GE sites. Full

[1] While the NCANDA sample includes a diverse range of race/ethnicities, a detailed analysis of all racial/ethnic categories within longitudinal models was not performed due to unequal sample sizes between categories resulting in model instability and a lack of power. The race/ethnicity variable was therefore dichotomized to ensure this information was included in longitudinal models in some capacity. Nonetheless, descriptive statistics were calculated for all groups and are described herein.

description of protocols and baseline imaging characteristics are described elsewhere (Pfefferbaum et al., 2016; Sullivan et al., 2017b).

To obtain volume estimates, T1-weighted images from all sites were processed by the same pipeline by correcting for image inhomogeneity, skull stripping T1-weighted images, and corresponding intracranial volume (ICV) defined by the SRI24 atlas (Pfefferbaum et al., 2018; Rohlfing et al., 2010, 2014). Imaging processing conducted as part of the NCANDA protocol is described elsewhere in more depth (Pfefferbaum et al., 2016, 2018). Skull stripped images were subsequently processed using FreeSurfer v6.0 via cross-sectional segmentation into grey matter (GM), white matter, and cerebrospinal fluid (CSF; Fischl, 2012). Generation of an unbiased, within-subject template for guiding longitudinal segmentation estimated the grey matter volume (GMV) of cortical regions of interest (ROIs; Reuter et al., 2012) defined according to the Desikan et al. (2006).

From this pipeline, the current study analyzed total volumes (mm^3) for five ROIs: the fusiform gyrus, hippocampus, amygdala, superior frontal gyrus, and posterior cingulate. ROIs were identified based on regions that are both a) involved in facial recognition (Haist and Anzures, 2017) and visual learning and memory (Leech and Sharp, 2014; Rosen et al., 2018; Slotnick et al., 2003) as well as b) known to be negatively impacted by heavy, intermittent alcohol use in adolescents and young adults (Jones et al., 2018; Squeglia et al., 2014). The superior frontal gyrus and posterior cingulate were specifically chosen due to the visual learning and memory task analyzed (e.g., RCFT) that includes a learning trial requiring aspects of visual attention and executive function (Hai et al., 2022; Sugiura et al., 2005). We initially performed sensitivity analyses to examine left and right hemisphere volumes individually and did not find significant differences between hemispheres. Consequently, brain ROIs were combined across hemispheres to create one value for each ROI volume. Resulting bilateral ROIs were analyzed separately in longitudinal models as the main outcome measures of interest.

2.3.1. Outlier detection

Based on prior NCANDA studies, case-wise outlier detection was used to identify and exclude brain ROIs with a volume of 2.9 standard deviations below or above the sample mean across all timepoints of interest (Infante et al., 2022). Outlier estimates ranged from 3 to 11 cases between all ROIs. Visual inspection of data for age and quantity-frequency index variables also resulted in exclusion of 4 additional cases resulting in a final sample of 800 participants.

2.4. Data analysis

IBM SPSS Version 29 was used to calculate cross-sectional, descriptive statistics and bivariate comparisons for demographics and overall alcohol use in participants with (i.e., reported a past-year ARB history at any timepoint) and without (i.e., past-year ARB history was not reported at any timepoint) a lifetime ARB history. Two-tailed, independent samples *t*-tests compared continuous variables (i.e., age, SES, and overall alcohol use) and chi-square (χ^2) tests of independence compared categorical variables (e.g., sex, and race/ethnicity).

2.4.1. Longitudinal models

Longitudinal analyses were conducted using *MPlus* Version 8.6 with the robust Full Information Maximum Likelihood (FIML) algorithm for missing data (Muthén and Muthén, 1998). A series of latent growth curve models were specified to estimate developmental trajectories of brain volume in five ROIs across six waves of data collection (i.e., baseline through fifth annual follow-up). Separate growth models were fit for data from each ROI, with both linear and quadratic functions considered during model selection. Goodness of model fit was based on interpretability and the following indices: Root Mean Squared Error of Approximation (RMSEA ≤ 0.08), Standard Root Mean Square Residual (SRMR ≤ 0.08), Comparative Fit Index (CFI ≥ 0.90), and Chi-Square (χ^2) Test of Model Fit where higher *p*-values and lower χ^2 values suggest relatively better fit between models (Hancock and Mueller, 2013; Hancock and Freeman, 2001; Muthén and Muthén, 1998). Best fit models for all five ROIs followed linear functions and are represented by the following series of multilevel regression equations:

$$Y_{it} = \beta_{0i} + \beta_{1i} \times Time_t + \epsilon_{it} \quad (1)$$

$$\beta_{0i} = \gamma_{00} + \zeta_{0i} \quad (2)$$

$$\beta_{1i} = \gamma_{10} + \zeta_{1i} \quad (3)$$

At the individual level (1), Y_{it} represents observed brain volumes for each individual *i* at time *t*. Terms β_{0i} and β_{1i} refer to individual intercepts (i.e., brain volume at baseline when $Time_t = 0$) and rates of change in brain volume per unit increase in time (i.e., slope), respectively. Assessment occasion (i.e., annual follow-up) is reflected by $Time_t$, and ϵ_{it} is residual error, or deviations of individual brain volumes from volume predicted by the model. At the population level (2, 3), γ_{00} and γ_{10} represent average intercept and slope. Factors ζ_{0i} and ζ_{1i} reflect random effects, or individual deviations from the average intercept and slope, respectively.

In addition to adequate fit statistics, linear functions allowed for flexibility in model parameters to account for individual differences in growth trajectories at various timepoints. That is, given NCANDA's accelerated longitudinal design, development in the current sample spans both adolescence and early adulthood, resulting in variation in brain growth between subjects during distinct developmental periods. Moreover, literature suggests that growth rates during specific developmental stages differ between brain regions (Chen et al., 2022; Lynch et al., 2019; Russell et al., 2021; Vijayakumar et al., 2016). To control for regional and age-specific variance in volume and more accurately examine ARBs as a predictor of brain development, modification indices were generated to specify expected drops in χ^2 values (i.e., improvement in model fit) when model constraints were applied. Consistent with common practice (Hancock and Mueller, 2013), modifications were made to model parameters for each ROI based on fit statistics and theoretical framework from developmental literature. Specifically, modifications capture a.) individual age-related differences in initial and final brain volume that impacted growth rates over time and b.) region-specific differences in growth rate associated with final volume estimates (i.e., periods of development are associated with more rapid growth at different times in each ROI). Fit statistics for final, best fit growth models for each ROI are displayed in Table 1. Table 2 displays intercept and slope factor estimates for final models.

Final growth models for each ROI were used to analyze ARBs as a predictor of brain development over six years. After growth model specification, covariates were included as independent variables in each multivariate model in a stepwise fashion as follows: 1) demographics, 2) MRI manufacturer, and 3) overall alcohol use. ARB history was included last as the main predictor of interest. All models included brain volume as the dependent variable. Individual level regression equations can be modified as follows to include (4) time-invariant and (5) time-varying covariates:

Table 1
Fit Index Statistics for Final Linear Growth Models. *Note*. Fit index statistics reflect final growth model fit following application of parameter modifications. RMSEA = Root mean square error of approximation; SRMR = Standardized root mean square residual; CFI = Comparative fit index; χ^2 = Chi-square test of model fit.

Model	RMSEA	SRMR	CFI	χ^2 (*p*-value)
Fusiform gyrus	0.047	0.009	0.998	30.649 (0.001)
Hippocampal	0.006	0.016	1.000	14.409 (0.420)
Amygdala	0.021	0.037	0.999	20.483 (0.152)
Superior frontal gyrus	0.042	0.019	0.996	30.706 (0.002)
Posterior Cingulate	0.021	0.003	1.000	16.291 (0.178)

Table 2
Intercept and Slope Parameter Estimates for Linear Growth Models. *Note:* ROI = Region of Interest; Est = Unstadardized parameter estimate; SE = Standard error; Parameter estimates reported as parameter estimate (SE).

	Intercept					Slope				
Brain Volume ROI	*Est*	SE	*p*-value	95 % CI		*Est*	SE	*p*-value	95 % CI	
Fusiform Facial Gyrus	326.484	1.386	< 0.001	323.767	329.201	−1.284	0.092	< 0.001	−1.464	−1.104
Hippocampus	99.118	0.331	< 0.001	98.469	99.767	0.170	0.011	< 0.001	0.148	0.191
Amygdala	32.177	0.111	< 0.001	31.959	32.395	0.037	0.007	< 0.001	0.023	0.051
Superior Frontal Gyrus	546.686	2.348	< 0.001	542.084	551.288	−0.232	0.108	0.031	−0.444	−0.020
Posterior Cingulate	27.766	0.176	< 0.001	27.421	28.111	−0.097	0.008	< 0.001	−0.113	−0.081

$$Y_{it} = (\pi_0 + \beta_0 X_i) + (\pi_1 + \beta_1 X_i) T_{it} + \epsilon_{it} \quad (4)$$

$$Y_{it} = (\pi_0 + \beta_0 X_i) + (\pi_1 + \beta_1 X_i) T_{it} + \gamma Z_{it} + \epsilon_{it} \quad (5)$$

where X_i and Z_{it} represent time-invariant (e.g., demographics, MRI manufacturer) and time-varying covariates (e.g., age, overall alcohol use, ARB history), respectively. Intercept (i.e., baseline brain volume) and slope (i.e., volume growth) factors are depicted as π_0 and π_1, respectively. In Eqs. (4) and (5), β_0 and β_1 reflect the effect of time-invariant covariates on the initial brain volume and growth. The γ coefficient represents the effect of time-varying covariates on brain volume independent of the overall growth trajectory modeled by π_0 and π_1.

2.4.2. Missing data

Analyses of missing data between baseline and fifth annual follow-up found a five-year, six-occasion retention rate of approximately 55 % (i.e., subjects without any missing data). Sample size at each annual follow-up for all brain ROIs was similar. No significant relationships were found between dropout and ARB history or overall alcohol use at any timepoint. The FIML estimator in *MPlus* uses all available data without excluding cases by listwise deletion and provides unbiased estimates of model parameters under the conditional missing at random assumption (Duncan et al., 2013; Ferrer et al., 2005; Mcardle and Hamagami, 1992). Since FIML only estimates missing data for dependent variables, multiple imputation (i.e., number of imputations = 10) accounted for missing data on all independent variables (Enders, 2022) for longitudinal models only.

2.4.3. Post hoc analyses

A series of post hoc analyses were conducted to evaluate whether ARB history moderated relationships between brain volume and cognition. First, exploratory analyses were conducted to determine whether brain volume trajectories were associated with cognitive task performance. Growth models for ROIs in which ARBs significantly predicted changes in volume trajectories were analyzed after inclusion of cognitive data. Specifically, FMT (i.e., immediate and delayed recognition total scores) and RCFT (i.e., copy, immediate recall, and delayed recall total scores) scores were included as explanatory variables of interest in select models. Total scores for individual trials from both cognitive measures were analyzed separately in each model. Covariates (i.e., age, sex, race/ethnicity, SES, MRI manufacturer) were included in the aforementioned stepwise fashion. Cognitive task performance was included last. Overall alcohol use and ARB history were not included in exploratory post hoc analyses.

Second, moderation analyses were conducted using *IBM SPSS* Version 29 PROCESS toolbox (Version 2.4; Hayes, 2017) to test whether the interaction between ARB history and regional brain volume impacted cognitive task performance. Of note, the RCFT was phased out of NCANDA's battery after the fourth annual follow-up assessment, resulting in a relatively smaller number of participants who completed the RCFT, the FMT, and reported an ARB history at later timepoints. Moderation analyses were therefore conducted in a subset of participants between ages 16–18 who completed all cognitive tasks and reported a history of ≥ 1 ARB at any timepoint (n = 68). An age range of 16–18 years was chosen due to an increase in ARB frequency across the NCANDA cohort and to control for changes in brain development occurring in early adulthood. Fig. 1 displays age distributions for individual participants from the final study sample (n = 800) with and without past-year ARB histories across six years of data collection. If a subject had an ARB history at multiple timepoints between ages 16–18, data were analyzed for the timepoint at which the individual was the oldest given prior NCANDA findings that ARBs predicted cognitive changes at later timepoints (Lorkiewicz et al., 2022).

Due to a smaller sample size used in post hoc moderation analyses, case-control matching was performed using *IBM SPSS* Statistics Version 29 (Rose and Van Der Laan, 2009) to identify an equivalent control group of individuals without a past-year ARB history at any timepoint (n = 68) based on factors known to influence performance on cognitive tasks including age (i.e., 16–18 years; Gur et al., 2012), biological sex (Sullivan et al., 2017a), and SES (Noble et al., 2015). Final moderation models (n = 136) included cognitive task performance as the dependent variable, brain volume as the independent variable, and ARB history as the moderating factor. Bootstrap inference for model coefficients (i.e., 5000, CI = 95 %; Hayes, 2017) was used and continuous variables that defined interaction products were mean centered (Hayes, 2017). NCANDA assessment site was included as a separate covariate given previously documented associations with cognition (Akshoomoff et al., 2014; Gur et al., 2012; Lorkiewicz et al., 2022; Sullivan et al., 2017a) and was effects coded as a five-level categorical variable using UCSD as the reference site. Descriptive data for NCANDA assessment sites and ARB history are discussed in Lorkiewicz et al. (2022). Moderation analyses were only conducted at timepoints in which ARBs significantly predicted altered development.

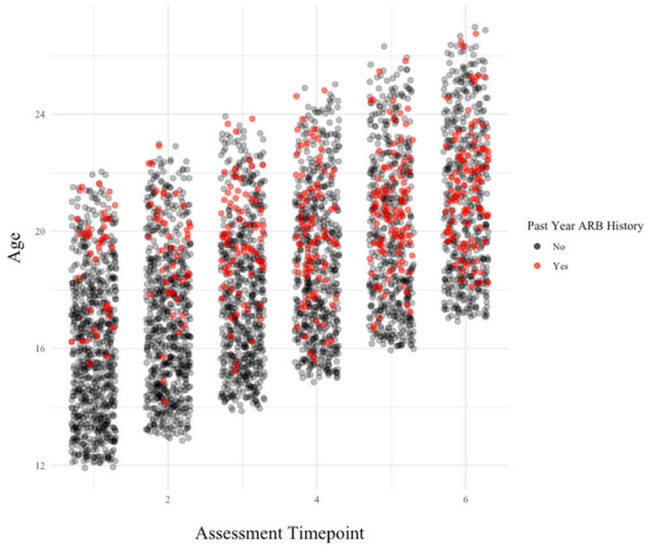

Fig. 1. Age Distribution of Individuals in the Final Sample (n = 800) with and without ARB Histories. *Note.* Participants with (i.e., red dot) and without (i.e., black dot) a past-year ARB history are shown distributed by age (y-axis) at each timepoint (x-axis).

3. Results

3.1. Sample characteristics

Descriptive data for age, ARB characteristics, and overall alcohol use are shown in Table 3. At baseline, 4.62 % of the total sample ($n = 37$) reported an ARB history within the past year compared to 15.87 % ($n = 100$) by year 5. Among participants with a past-year ARB history at any timepoint (i.e., lifetime ARB history; $n = 213$), 56.8 % reported 1 ARB and 10.8 % reported ≥ 3 ARBs at baseline. By year 5, 39.8 % reported 1 ARB and 28.4 % reported ≥ 3 ARBs in the past year. Additionally, 54.5 % of participants with a lifetime ARB history reported ARBs at multiple timepoints whereas 45.5 % reported ARBs at one timepoint. Individuals with an ARB history tended to be older ($ps < 0.001$) and report greater overall alcohol use ($ps < 0.001$) compared to participants without an ARB history at any timepoint. Earlier age of alcohol use onset was also significantly correlated with earlier age of first ARB ($r = 0.379$, $p < 0.001$).

Demographic characteristics for participants with and without a lifetime ARB history are presented in Table 4. Individuals with a lifetime ARB history were 50.23 % female, 77.93 % White, and had relatively high SES (i.e., average highest parental education was 17.13 years). Significant differences in ethnicity were found between individuals with and without a lifetime ARB history at all timepoints ($ps < 0.01$) except year 6 such that a greater proportion of White participants experienced ARBs compared to non-White individuals. Sex[2] significantly differed between participants with and without a lifetime ARB history only at year 5 ($\chi^2 = 4.94$, $p = 0.017$), with a greater number of males reporting past-year ARB history. SES did not differ by lifetime ARB history at any timepoint.

3.2. ARBs as a predictor of structural brain development

Results from final, multivariate growth models analyzing ARBs as a predictor of brain volume development are presented in Table 5. In the fusiform gyrus, ARBs independently and significantly predicted attenuated volume growth at year 5 ($Est = -0.897$; SE = 0.399; $p = 0.025$) compared to individuals without an ARB history. Among individuals without an ARB history, overall alcohol use predicted attenuated growth in fusiform gyrus volume at years 3 ($Est = -0.281$; SE = 0.087; $p < 0.001$) and 4 ($Est = -0.282$; SE = 0.081; $p < 0.001$). In the hippocampus, ARBs significantly and independently predicted attenuated volume growth at years 3 ($Est = -0.218$; SE = 0.107; $p = 0.042$) and 5 ($Est = -0.325$; SE = 0.129; $p = 0.012$) compared individuals without an ARB history. Among participants without an ARB history, overall alcohol use predicted attenuated growth in hippocampal volume at year 5 ($Est = -0.071$; SE = 0.026; $p = 0.005$).

ARBs were not significantly associated with growth trajectories of amygdala, superior frontal gyrus, or posterior cingulate volume at any timepoint. However, among individuals without an ARB history, overall alcohol use predicted attenuated growth in amygdala volume at year 3 ($Est = -0.034$; SE = 0.015; $p = 0.029$), attenuated growth in superior frontal gyrus volume at baseline ($Est = -0.796$; SE = 0.357; $p = 0.026$), and attenuated growth in posterior cingulate gyrus volume at year 4 ($Est = -0.021$; SE = 0.010; $p = 0.039$). Brain volume trajectories for each ROI with 95 % confidence intervals in participants with and without ARB histories at any timepoint are displayed in Fig. 2. Trajectories are based on final models including demographic and alcohol use covariates.

3.3. Associations between brain volume and cognition

Since ARBs significantly predicted attenuated fusiform gyrus and hippocampal development, cognitive task performance was included as a potential explanatory factor in multivariate, linear growth models for these ROIs only. Within the fusiform gyrus, lower RCFT immediate recall performance was associated with attenuated volume growth at baseline ($Est = -0.040$; SE = 0.016; $p = 0.015$), year 1 ($Est = -0.027$; SE = 0.012; $p = 0.029$), year 2 ($Est = -0.033$; SE = 0.013; $p = 0.015$), and year 5 ($Est = -0.060$; SE = 0.026; $p = 0.018$). Similarly, lower RCFT delayed recall performance was associated with attenuated growth in fusiform gyrus volume at baseline ($Est = -0.045$; SE = 0.017; $p = 0.008$), year 1 ($Est = -0.031$; SE = 0.013; $p = 0.018$), year 2 ($Est = -0.039$; SE = 0.014; $p = 0.006$), and year 5 ($Est = -0.074$; SE = 0.028; $p = 0.008$). RCFT copy trial performance was not significantly associated with trajectories of fusiform gyrus volume at any timepoint.

Within the hippocampus, lower RCFT immediate recall performance was associated with attenuated volume growth at baseline ($Est = -0.012$; SE = 0.005; $p = 0.029$) only. RCFT delayed recall performance was associated with attenuated hippocampal volume growth at baseline ($Est = -0.014$; SE = 0.005; $p = 0.008$) and year 4 ($Est = -0.016$; SE = 0.008; $p = 0.039$). RCFT copy trial performance was not significantly associated with trajectories of hippocampal volume at any timepoint. Unstandardized parameter estimates for RCFT performance in fusiform gyrus and hippocampal growth models are shown in Supplemental Table 1. Performance on FMT immediate and delayed recognition trials was not significantly associated with fusiform gyrus or hippocampal volume at any timepoint. Unstandardized parameter estimates for FMT performance in fusiform gyrus and hippocampal growth models are displayed in Supplemental Table 2.

3.4. The Interaction Effect of ARBs and Brain Volume on Cognition

Moderation analyses were conducted in a subset of case control matched participants with and without a lifetime ARB history ($n = 136$). Based on results from initial exploratory analyses, moderation analyses examined hippocampal volume at year 4 and fusiform volume at year 5 including only RCFT trial performance as independent variables since RCFT, but not FMT performance, was associated with changes in hippocampal and fusiform gyrus development. To create a single robust metric of visual recall, total RCFT immediate and delayed recall trial scores were averaged to generate a visuospatial memory composite score that was included as a dependent variable in moderation analyses. Hippocampal and fusiform gyrus volumes were included as independent variables in separate RCFT memory composite analyses. Separate moderation analyses were conducted using RCFT copy trial performance as the dependent variable to explore moderation effects on both learning (e.g., RCFT copy trial) and memory (i.e., immediate and delayed RCFT recall trials). Similarly, hippocampal and fusiform gyrus volume were included as independent variables in RCFT copy trial analyses. All analyses included past-year ARB history as the moderating factor.

Results for moderation analyses including fusiform gyrus volume as the independent variable are shown in Table 6 and depicted in Fig. 3 (i.e., panels a and b). The interaction between ARB history and fusiform gyrus volume was not significantly associated with the RCFT memory composite or the RCFT copy trial score.

Results for moderation analyses including hippocampal volume as the independent variable are shown in Table 7 and depicted in Figure 3 (i.e., panels c and d). Similarly, the interaction between ARB history and hippocampal volume was not significantly associated with RCFT

[2] While literature generally suggests women are more susceptible to ARBs than men (Rose and Grant, 2010), studies show men report higher ARB incidence in the context of greater alcohol use (Voloshyna et al., 2018). To clarify this relationship, a series of one-way ANOVAs were conducted to determine if men consumed more alcohol than women using the quantity-frequency index. Results found men drank significantly more at year 5 ($F[1784] = 7.23$, $p = 0.007$) and year 4 ($F[1792] = 4.64$, $p = 0.03$). Overall alcohol use did not significantly differ between men and women from baseline to year 3. These results suggest men report more ARBs at year 5 due to greater overall alcohol use.

Table 3
Descriptive Data for Age, ARB Characteristics, and Overall Alcohol Use in the Final Sample (n = 800). *Note.* Percentages are based on the total sample at each assessment timepoint for all variables except Age of First ARB and ARB Frequency which are based on individuals reporting ARB history at that timepoint (n = 213). [‡]Reported as n (%); [†]Reported as M (SD). [a]Past-year average number of drinks per 24-hour drinking occasion; [b]Number of drinking days in the past year. [+]Value does not change over time.

Characteristic	Baseline (n = 800)	Year 1 (n = 744)	Year 2 (n = 697)	Year 3 (n = 668)	Year 4 (n = 617)	Year 5 (n = 630)
Age[†]	16.15 (2.50)	17.11 (2.49)	18.07 (2.46)	19.12 (2.51)	20.16 (2.52)	21.17 (2.50)
ARB History[‡]						
Yes	37 (4.62)	43 (5.78)	70 (10.04)	82 (11.91)	94 (15.23)	100 (15.87)
Age of First ARB[+†]	19.47 (1.89)					
ARB Frequency[‡]						
1	21 (56.8)	21 (48.8)	32 (45.7)	40 (50.0)	41 (44.6)	39 (39.8)
2	12 (32.4)	10 (23.3)	19 (27.1)	20 (25.0)	24 (26.1)	31 (31.6)
≥ 3	4 (10.8)	12 (27.9)	19 (27.1)	20 (25.3)	27 (29.3)	28 (28.4)
Age of Alcohol Use Onset[+†]						
Yes	16.95 (2.24)					
Overall Alcohol Use[†]						
Quantity[a]	0.84 (1.90)	1.15 (2.05)	1.39 (2.05)	1.67 (3.32)	1.71 (2.21)	1.83 (2.05)
Frequency[b]	4.15 (14.96)	6.02 (16.50)	11.27 (26.67)	16.06 (34.63)	21.49 (41.53)	29.39 (49.29)

Table 4
Demographic Characteristics in the Final Sample (n = 800) for Participants with and without Lifetime ARB History. *Note.* [a]Past-year ARB history at any timepoint; [b]No past-year ARB history at any timepoint; [‡]Reported as n(%); [†]Reported as M(SD) and is defined as highest level of parental education (i.e., number of years).

Characteristic	Lifetime[a] ARB History (n = 213)	No Lifetime[b] ARB History (n = 587)
Female[‡]	107 (50.23)	311 (52.98)
Male[‡]	106 (49.76)	276 (47.02)
Ethnicity[‡]		
Native American/ American Indian	1 (0.47)	2 (0.34)
Asian/Pacific Islander	15 (7.04)	48 (8.17)
African American/Black	13 (6.10)	84 (14.31)
White/Caucasian	166 (77.93)	404 (68.82)
Multiracial/Other	18 (8.45)	49 (8.34)
SES[†]	17.13 (2.35)	16.66 (2.53)

memory composite score or the RCFT copy trial score. However, the interaction between ARB history and hippocampal volume approached significance (p = 0.069) in the RCFT memory composite model.

4. Discussion

In participants from the NCANDA study, longitudinal growth models were used to analyze ARBs as a predictor of brain volume development over six years in five ROIs. These data are the first to show that ARBs significantly predicted attenuated development in brain regions associated with alcohol-related cognitive change in adolescents and emerging adults. Specifically, we found that individuals with an ARB history demonstrated attenuated hippocampal and fusiform gyrus growth. These effects remained significant after controlling for overall alcohol consumption and demographic factors known to impact neurocognitive development, suggesting ARBs are a unique indicator of abnormal brain morphology in some or all younger drinkers. Post hoc analyses found that ARB history did not significantly moderate the relationship between brain volume and cognitive task performance. However, a trend towards significance suggested individuals with ARB histories did not benefit from greater brain volume during visual recall performance, and may be at risk for cognitive change later in life.

4.1. ARBs as a predictor of structural brain development

In fusiform gyrus models, ARBs significantly predicted attenuated development at year 5 above and beyond effects of overall alcohol use. Conversely, overall alcohol use in the absence of ARBs significantly predicted altered fusiform gyrus development relatively earlier, at years 2 and 3. This pattern is consistent with epidemiological literature positing that correlations between early onset alcohol use and more frequent ARBs in adulthood are related to altered developmental brain trajectories (Marino and Fromme, 2016). Current models of fusiform gyrus growth therefore suggest ARBs represent greater vulnerability to alcohol use later in development in individuals who previously drank at levels associated with altered brain morphology. In this regard, our findings extend epidemiological data to show that adolescent binge drinking may result in neural sensitivity to alcohol use in specific brain regions and subsequent ARBs.

Exact neurobiological mechanisms underlying the relationship between ARBs and fusiform gyrus growth are unclear. Consistent with our model in the NCANDA sample, literature shows that development of fusiform gyrus volume follows a linear trajectory from early childhood to middle adulthood (Haist and Anzures, 2017) and is potentially vulnerable to alcohol use during several developmental periods. Within this context, continued alcohol use throughout adolescence may alter fusiform development and, in turn, increase neurocognitive sensitivity to ARBs and perhaps more persistent behavioral sequelae during future drinking episodes. While longitudinal research is limited on how alcohol consumption affects fusiform gyrus development in adolescents, current results are consistent with existing functional MRI data demonstrating reduced blood-oxygenation-level-dependent (BOLD) responses in the left fusiform gyrus among adolescents with alcohol use disorder compared to abstinent youth (Tapert et al., 2004). Neurobehavioral sequelae of early alcohol use within the fusiform gyrus may therefore include both abnormal morphology and function, particularly later in development with continued drinking, reflecting risk for potentially deleterious, alcohol-related effects in this region. Future research is needed to identify precise neurobiological mechanisms of alcohol neurotoxicity during fusiform gyrus development as well as functional or cognitive correlates of ARBs that may be more relevant later in life.

We also found ARBs predicted attenuated hippocampal development at years 3 and 5, suggesting ARBs are a marker of hippocampal vulnerability to alcohol use relatively earlier in development than the fusiform gyrus. These results extend literature reporting hippocampal sensitivity to alcohol use across the lifespan (Crews et al., 2016), including associations between early age-of drinking-onset and lower hippocampal volume (De Bellis et al., 2000; Jones et al., 2023). Further, hippocampal development follows both linear and non-linear trajectories during different stages, with rapid increases in volume occurring early in adolescence followed by plateaus in late adolescence and early adulthood (Lynch et al., 2019). That is, the hippocampus is particularly susceptible to alcohol neurotoxicity during early adolescence given marked proliferation and growth. ARBs may therefore be a sensitive indicator of early changes in hippocampal morphology related to

Table 5
Unstandardized Estimates for Overall Alcohol Use and ARB History in Final Growth Models. *Note.* ROI = Region of interest; Est = Unstandardized parameter estimate; SE = Standard error. Unstandardized parameter estimates reflect anticipated change in outcome for every unit change in each covariate at that timepoint while controlling for overall growth trajectory (i.e., population level slope and intercept factors). Final multivariate linear growth models include brain volume as the dependent variable, past-year ARB history as the independent variable of interest, and all covariates (i.e., age, gender, ethnicity, SES, MRI manufacturer, and overall alcohol use).

Brain ROI	Timepoint	Overall Alcohol Use					ARB History				
		Est	SE	*p*-value	95 % CI		*Est*	SE	*p*-value	95 % CI	
Fusiform Gyrus	Baseline	−0.014	0.111	0.827			0.048	0.439	0.913		
	Year1	−0.140	0.100	0.162			−0.105	0.393	0.790		
	Year2	−0.281	0.087	0.001	−0.451	−0.110	0.427	0.322	0.185		
	Year3	−0.282	0.081	0.001	−0.441	−0.123	−0.073	0.321	0.821		
	Year4	−0.186	0.100	0.064			−0.182	0.439	0.678		
	Year5	−0.153	0.092	0.097			−0.897	0.399	0.025	−1.679	−0.115
Hippocampus	Baseline	0.059	0.037	0.109			−0.027	0.144	0.852		
	Year1	0.006	0.038	0.882			−0.079	0.129	0.543		
	Year2	−0.025	0.032	0.440			−0.087	0.121	0.469		
	Year3	−0.038	0.024	0.113			−0.218	0.107	0.042	−0.428	−0.008
	Year4	−0.053	0.028	0.053			−0.076	0.128	0.553		
	Year5	−0.071	0.026	0.005	−0.122	−0.020	−0.325	0.129	0.012	−0.578	−0.072
Amygdala	Baseline	0.019	0.026	0.460			−0.081	0.114	0.477		
	Year1	−0.017	0.024	0.485			−0.052	0.095	0.580		
	Year2	−0.021	0.018	0.221			0.032	0.072	0.658		
	Year3	−0.034	0.015	0.029	−0.063	−0.005	0.067	0.070	0.340		
	Year4	0.014	0.017	0.409			−0.134	0.087	0.123		
	Year5	−0.014	0.087	0.501			0.001	0.096	0.994		
Superior Frontal Gyrus	Baseline	−0.796	0.357	0.026	−1.496	−0.096	−1.587	0.933	0.089		
	Year1	−0.133	0.235	0.570			0.086	0.870	0.921		
	Year2	−0.047	0.167	0.780			−0.077	0.580	0.894		
	Year3	−0.094	0.177	0.594			0.459	0.656	0.450		
	Year4	−0.036	0.168	0.831			−0.984	1.067	0.357		
	Year5	−0.356	0.185	0.054			0.500	1.039	0.630		
Posterior Cingulate	Baseline	−0.001	0.020	0.955			−0.015	0.067	0.818		
	Year1	0.020	0.017	0.229			−0.014	0.053	0.794		
	Year2	−0.008	0.011	0.499			0.030	0.040	0.459		
	Year3	−0.013	0.010	0.171			0.017	0.042	0.691		
	Year4	−0.021	0.010	0.039	−0.041	−0.001	0.072	0.047	0.128		
	Year5	−0.019	0.010	0.056			−0.082	0.054	0.125		

drinking, even prior to cumulative effects of alcohol use. Since the NCANDA sample largely consists of individuals without alcohol use disorder history, these data demonstrate neural vulnerability to drinking levels that do not meet criteria for dependence or substance use disorder at certain developmental stages. We also found that alcohol use predicted attenuated hippocampal growth at year 5 in the absence of ARBs, suggesting earlier drinking at any quantity or frequency may confer neural sensitivity to alcohol later in development, given that hippocampal growth typically plateaus over time and is therefore less vulnerable to alcohol use (Crews et al., 2016).

Conversely, ARBs did not significantly predict changes in amygdala, posterior cingulate, or superior frontal gyrus development. Non-significant results may be related to several factors, including period of development during which each structure experiences significant acceleration or deceleration in growth. Patterns of normal brain developmental differ by region or structure, with changes shown to be more pronounced in anterior vs. posterior cortical areas and inconsistent in subcortical regions (Sullivan et al., 2011). Specifically, supratentorial and CSF volumes increase with age (Sullivan et al., 2011), white matter volumes steadily increase into early adulthood, and cortical grey matter volumes increase until the first decade of life but decline afterward (Pfefferbaum et al., 1994). Similar patterns are found in the NCANDA sample, with rates of reductions in grey matter and increases in white matter decelerating with age (Pfefferbaum et al., 2016, 2018). Importantly, periods of significant growth represent windows of vulnerability to substance use (Squeglia et al., 2014). In our study, we found ARBs significantly predicted attenuated development in the hippocampus and fusiform gyrus but not the amygdala, posterior cingulate, or superior frontal gyrus. It is possible that heavy drinking did not systematically coincide with relevant periods of neurofunctional growth in regions where ARBs did not significantly predict development and/or the impact of alcohol may not have manifested yet.

Additionally, the nature of susceptibility to alcohol use differs within each brain region (Oscar-Berman and Marinkovic, 2007; Sullivan and Pfefferbaum, 2005). In the amygdala, for instance, studies show that alcohol-related abnormalities are characterized by disrupted circuitry or functional connectivity with regions such as the orbitofrontal cortex (Gorka et al., 2013) rather than reductions in volume related to alcohol neurotoxicity. Further, in the context of research showing posterior cingulate abnormalities (e.g., reduced volume and cortical thinning; Pfefferbaum et al., 2016; Squeglia et al., 2014) in adolescent binge drinkers and frontal dysfunction in binge drinkers and chronic alcoholics (Infante et al., 2022; Sullivan et al., 2010), ARBs may not be an effective way to predict neurocognitive risk in these regions relative to other alcohol use metrics. As such, ARBs appear to differentially predict neurocognitive risk due to alcohol use in some regions but not others. More studies exploring ARBs as a marker of abnormal development in additional regions will aid in better characterizing ARBs as a useful marker of neurocognitive risk in younger drinkers and provide additional clarity on alcohol's impact on brain development.

Of note, overall alcohol use in the absence of ARBs predicted attenuated amygdala, superior frontal gyrus, and posterior cingulate growth at baseline, year 3, and year 4, respectively. Findings of widespread cortical and subcortical abnormalities in younger drinkers with a range of alcohol consumption histories are consistent with prior literature (Jones et al., 2018). In particular, current data from superior frontal gyrus models showing overall alcohol use predicted altered volume at baseline are consistent with alcohol studies in adolescents that suggest some youth may have pre-existing frontal characteristics making them assailable to alcohol use and risky drinking behaviors (Squeglia et al., 2012; Wetherill et al., 2013; Whelan et al., 2014). Given that we did not find an effect of alcohol consumption at later timepoints within this

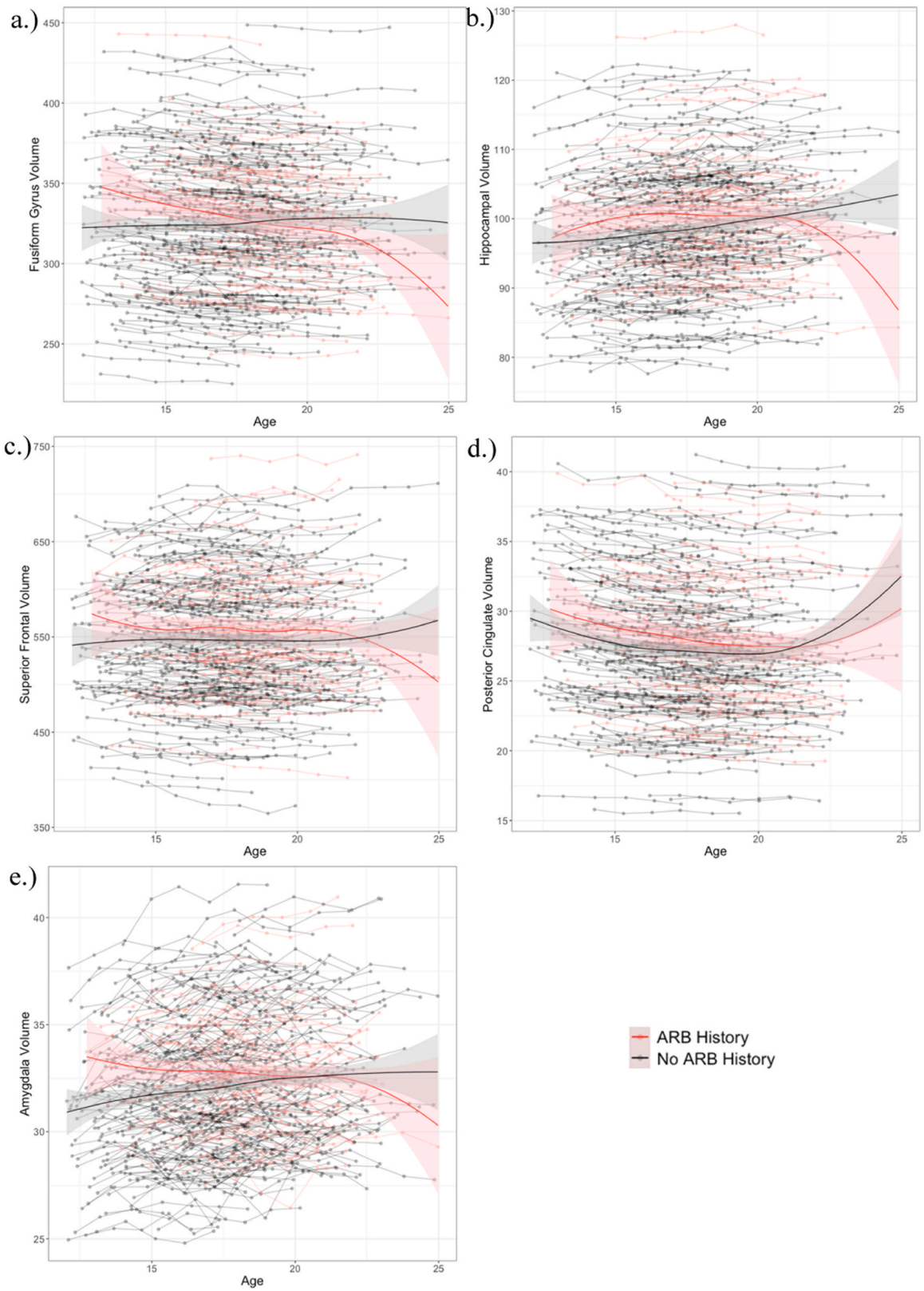

Fig. 2. Brain Volume Trajectories in NCANDA Study Participants with and without Lifetime ARB History. *Note.* Final growth models for (a) fusiform gyrus, (b) hippocampal, (c) superior frontal gyrus, (d) posterior cingulate, and (e) amygdala volumes (mm^3) are shown above. Y-axes reflect regional volumes divided by 100. X-axis reflects age at each timepoint. Participants with a history of ARBs at any assessment timepoint (i.e., baseline through year 5) are depicted by individual red trajectories. Participants without a history of ARBs at any assessment timepoint are depicted by individual black trajectories. Red and black bolded lines represent population level trends, or average growth of subjects with and without a lifetime history of ARBs, respectively.

Table 6
Moderation Analyses Examining Fusiform Gyrus Volume and RCFT Performance at Year 5. *Note.* *Interaction between fusiform gyrus volume and past-year ARB history; †Memory composite score created by averaging delayed and immediate recall trial total scores.

Model	Coefficient	SE	*t*-score	*p*-value	95 % CI	
RCFT Copy Trial						
Fusiform Volume	0.023	0.011	2.090	0.039	0.001	0.045
ARB History	−0.246	0.600	−0.409	0.683	−1.433	0.941
Interaction*	−0.004	0.015	−0.295	0.769	−0.034	0.025
RCFT Memory Composite†						
Fusiform Volume	0.049	0.017	2.698	0.008	0.012	0.080
ARB History	0.124	0.918	0.135	0.893	−1.692	1.940
Interaction*	−0.028	0.023	−1.218	0.225	−0.073	0.017

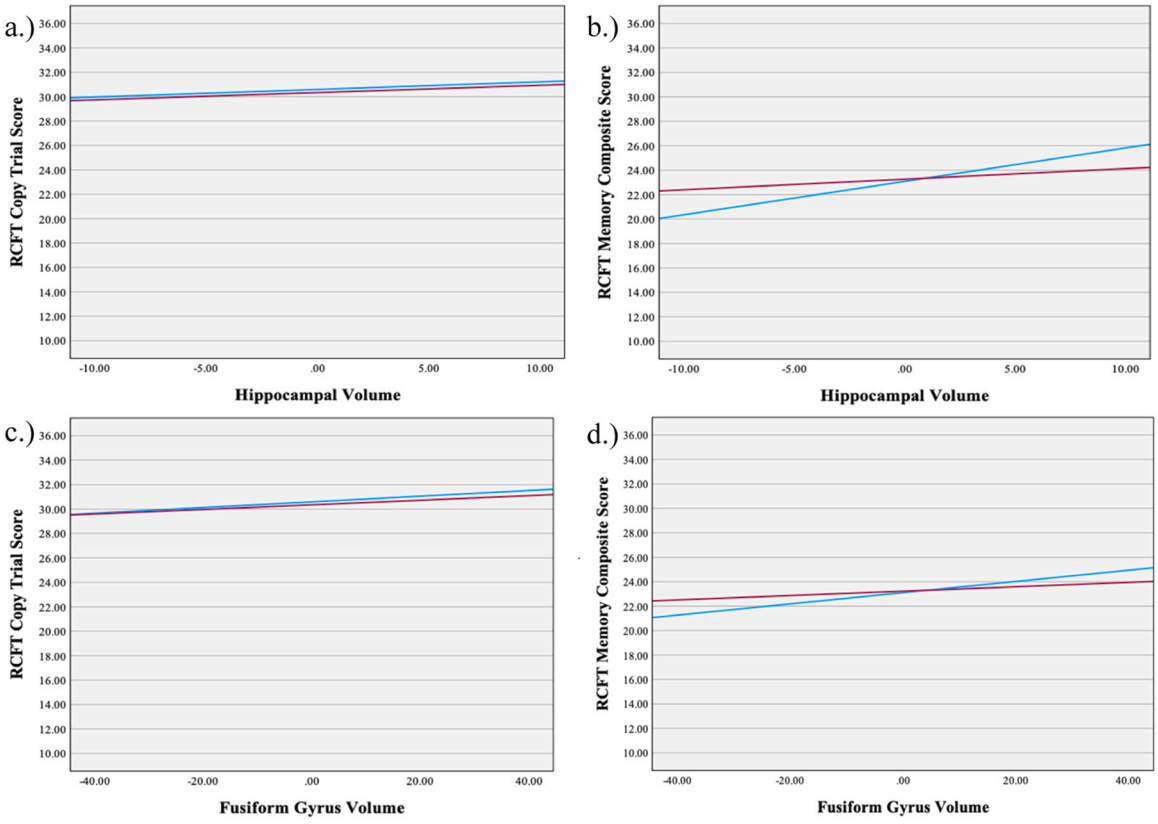

Fig. 3. Effects of ARB Moderation on Brain Volume and RCFT Performance. *Note.* Moderation trends are shown for analyses including RCFT performance as the dependent variable, brain volume as the independent variable, and past-year ARB history as the moderating factor. Models for hippocampal volume are shown in panels (a) and (b). Fusiform gyrus volume models are shown in panels (c) and (d). Red and blue lines represent subjects with and without past-year ARB histories, respectively. Intersecting lines in panel (b) highlights a trend toward significance ($p = 0.069$) for the interaction between ARB history and hippocampal volume in the RCFT memory composite model.

Table 7
Moderation Analyses Examining Hippocampal Volume and RCFT Performance at Year 4. *Note.* *Interaction between hippocampal volume and past-year ARB history; †Memory composite score created by averaging delayed and immediate recall trial total scores.

Model	Coefficient	SE	*t*-score	*p*-value	95 % CI	
RCFT Copy Trial						
Hippocampal Volume	0.062	0.051	1.210	0.228	−0.040	0.164
ARB History	−0.057	0.610	−0.421	0.675	−1.464	0.951
Interaction*	−0.003	0.069	0.039	0.968	−0.139	0.134
RCFT Memory Composite†						
Hippocampal Volume	0.273	0.076	3.606	0.004	0.123	0.423
ARB History	0.179	0.899	0.199	0.842	−1.599	1.957
Interaction*	−0.187	0.102	−1.836	0.069	−0.388	0.015

region, results may add to literature demonstrating that preexisting frontal abnormalities are more predictive of drinking initiation rather than an effect of alcohol itself (Wetherill et al., 2013).

4.2. The interaction effect of ARBs and brain volume on cognition

Despite altered structural development in regions associated with

facial recognition and visual recall, ARBs did not significantly moderate the relationship between brain volume and cognitive task performance. This finding could be related to several factors. First, a relatively smaller sample size used in moderation analyses may have had reduced power to detect subtle behavioral changes in neurologically healthy adolescents and emerging adults despite the use of matched samples. In contrast, our previous study analyzed behavioral data in individuals with ARB histories from the entire NCANDA cohort ($n = 106$) over five years, likely resulting in greater power to detect subtle changes in cognition.

Previously, we observed that ARBs significantly predicted attenuated development of facial recognition at earlier timepoints (Lorkiewicz et al., 2022). Relating this finding to our current study, ARBs predicted altered fusiform gyrus development at later timepoints, though did not significantly moderate the relationship between brain volume and cognition. A discrepancy in findings may be due to non-parallel developmental patterns of the fusiform gyrus compared to facial recognition and relative susceptibility of this region's structure and function to alcohol use. For instance, while fusiform gyrus volume increases linearly over time, development of facial recognition appears to be more nuanced. The ability to recognize human faces is present early in development, with infants able to identify faces and categorize specific facial features by 3–10 months (Bhatt et al., 2005; Quinn and Tanaka, 2009). Conversely, efficient recruitment of regions (e.g., amygdala, posterior cingulate, tempo-parietal regions) involved in more complex facial processing (e.g., recalling specific individuals, determining whether someone is threatening or trustworthy) continues to develop well into late adolescence (Gobbini and Haxby, 2007; Ishai et al., 2004; Nestor et al., 2011). Accordingly, heavy alcohol use can, to some extent, exert untoward effects on fusiform volume development during adolescence that may be functionally counteracted by effective compensation for neurostructural changes. Importantly, the presence of underlying ARB-related structural changes suggests that youth who black out are at risk for cognitive inefficiencies later in life. Moreover, the relationship between attenuated fusiform development and more complex aspects of facial recognition (e.g., emotionally charged faces) was not specifically explored, and may be of interest to future studies, particularly during adulthood or with continued alcohol use.

Additionally, we previously found that ARBs predicted attenuated delayed visual recall at later timepoints (Lorkiewicz et al., 2022). In post hoc moderation analyses, we observed cross-sectional trends consistent with the prior longitudinal results warranting further inquiry of whether ARBs moderate the relationship between hippocampal volume and delayed visual recall performance at later timepoints. This potential interaction effect between ARBs and brain volume on cognition should be tested in larger cohorts. Interestingly, the direction of current trends suggests subjects with past-year ARB histories did not necessarily benefit from larger hippocampal volume during a visual recall task. That is, larger brain volume did not result in better cognitive task performance, possibly reflecting less efficient cognitive functioning overall. Given a link between binge drinking and abnormal functional connectivity between the hippocampus and associated networks (Arienzo et al., 2019; Huntley et al., 2020), future longitudinal research should investigate whether experiencing ARBs is associated with abnormal hippocampal structure, function, and lower visual recall in younger drinkers, with age or continued alcohol use.

A lack of cognitive changes in the presence of underlying structural or functional abnormalities detected on imaging is also reported in prior ARB and binge drinking studies among youth (Squeglia et al., 2009a; Wetherill and Fromme, 2016). Our findings are consistent with the idea that cognitive changes tend to be subtle or absent despite underlying neurobiological changes in the developing brain. Altered brain structure or function in binge drinkers in the absence of overt cognitive impairment can suggest alternative or compensatory neural networks are being used to maintain optimal performance. It is also possible that brain regions outside the scope of this study are involved with performance on the RCFT. Future studies are needed to explore the relationship between ARBs, other brain regions, and performance on additional cognitive tasks during neurodevelopmentally sensitive periods. Given our cross-sectional focus on cognitive task performance in current analyses, exploring the dynamic relationships between longitudinal trajectories of cognition and regional brain volumes would also aid in our understanding of complex relationships between ARBs, structural brain development, and cognition in young drinkers. In this regard, future longitudinal studies should consider practice effects noted in prior NCANDA studies (Lannoy et al., 2022; Sullivan et al., 2017a) when interpreting potential effects of ARBs on neurocognition.

4.3. Strengths and limitations

The current study has several strengths, including the accelerated longitudinal design of NCANDA allowing for assessment of growth in multiple brain regions across several developmental periods. Longitudinal growth curve modeling also allowed for robust individual and population level comparisons within a diverse set of adolescents and emerging adults. These models provided flexibility to account for differences in growth during specific developmental periods while controlling for demographic factors that may impact brain development and retaining power to detect associations between ARBs and subtle volume changes over time. By including alcohol use quantity and frequency as a covariate in longitudinal analyses, we were also able to interpret ARB findings in a more nuanced way to determine how this phenomenon may aid in characterizing the impact of alcohol use on neurocognition in younger drinkers. Given the current focus on brain structure, future studies should consider how ARBs may be related to functional brain connectivity between regions negatively impacted by alcohol use and how potential connectivity changes may impact cognitive task performance.

There are several limitations to consider when interpreting findings from this study. ARBs were included as a yes/no indicator which captures past-year and/or lifetime ARB history at each timepoint. Patterns related to frequency and type of ARBs were therefore not evaluated. Given evidence that previously experiencing ARBs may put younger drinkers at risk for experiencing ARBs in the future (Marino and Fromme, 2016), exploring the impact of multiple ARBs or ARB frequency on neurocognition over time may be particularly relevant to the NCANDA sample as they progress through adulthood and incidence of ARBs may increase. Additionally, en bloc ARBs represent complete anterograde amnesia for a drinking event whereas fragmentary ARBs represent partial amnesia for a drinking event (White, 2003). Since en bloc and fragmentary ARBs are associated with unique brain structures and functions (Rose and Grant, 2010), future studies should consider how ARB type may predict altered neural development. Future studies should also consider the impact of age of first ARB and neurodevelopment. For instance, we found that most participants with ARB histories were older than 16 years of age, though a small subset of individuals reported blacking out prior to age 16. Given that earlier onset drinking is associated with consistent, untoward alcohol-related effects on brain development (Brown and Tapert, 2004; Nguyen-Louie et al., 2018), research is needed to determine whether ARBs prior to age 16 are associated with unique neurocognitive risk.

While our alcohol use metric consisted of both quantity and frequency of alcohol use, we did not examine binge drinking, per se. Despite frequent co-occurrence of the two constructs, ARBs are associated with unique predictors (Goncalves et al., 2018; Schuckit, 2017) and alcohol-related consequences (Hingson et al., 2016) compared to binge drinking alone. ARBs are also distinct from severe intoxication or unconsciousness that may result from binge drinking. During an ARB, an individual is consciously interacting with their environment without encoding relevant sensory information (i.e., do not form memories of the drinking event) due to alcohol's disruption of neurobiological mechanisms involved in learning and memory (White, 2003). Therefore, ARBs may predict unique neurocognitive changes even in the context of binge

drinking, though future research is warranted exploring the relationship between ARBs and brain development in a subset of binge drinkers to clarify the extent to which binge drinking contributes to these associations. Finally, while the NCANDA sample is demographically diverse, we did not closely examine race/ethnicity as a more nuanced variable in longitudinal models.

5. Conclusion

In conclusion, we found ARBs in adolescents and emerging adults predicted attenuated structural development in the fusiform gyrus and hippocampus independent of overall alcohol use. Despite altered development in regions associated with visual memory, ARBs did not significantly moderate relationships between brain volume and cognitive performance. However, given our prior findings that ARBs predict attenuated delayed recall later in development, non-significant trends suggest ARBs may moderate the relationship between hippocampal volume and visual recall. As such, these findings highlight ARBs as a marker of neurobiological sensitivity to alcohol use, though findings related to cognition are less clear. Further characterization of neurocognitive sequelae of ARBs in younger cohorts is warranted since attenuated development in brain regions involved in learning, memory, and processing of emotions may have an adverse impact on cognition and daily functioning later in life. Developmental studies should more consistently measure ARBs when evaluating drinking patterns in youth to identify individuals without alcohol use disorders at risk for neurobiological changes during development. This is particularly relevant given high incidence of ARBs in younger cohorts and positive perceptions associated with ARBs (Merrill et al., 2019; Riordan et al., 2019). Prevention and intervention efforts such as targeted education related to the nature of ARBs and their association with potentially adverse brain changes are recommended.

Author contributions

Sara A. Lorkiewicz contributed to conceptualization, methodology, formal analysis, visualization, writing the original draft of the manuscript, and review and editing of the manuscript; Eva M. Müller-Oehring contributed to conceptualization, methodology, investigation, visualization, and review and editing of the manuscript; Fiona C. Baker contributed to conceptualization, data curation, methodology, resources, funding acquisition, and review and editing of the manuscript; Brionne V. Elkins contributed to methodology, visualization, and review and editing of the manuscript; Tilman Schulte contributed to conceptualization, methodology, investigation, and review and editing of the manuscript.

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Data statement

Data used here can be accessed through submission of a data request and approval of a data distribution agreement from the National Institute on Alcohol Abuse and Alcoholism (NIAAA). These data were part of the public data releases

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CRediT authorship contribution statement

Eva M. Müller-Oehring: Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Sara A. Lorkiewicz:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Tilman Schulte:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Brionne V. Elkins:** Writing – review & editing, Visualization, Methodology. **Fiona C. Baker:** Writing – review & editing, Resources, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Akshoomoff, N., Newman, E., Thompson, W.K., McCabe, C., Bloss, C.S., Chang, L., Amaral, D.G., Casey, B.J., Ernst, T.M., Frazier, J.A., Gruen, J.R., Kaufmann, W.E., Kenet, T., Kennedy, D.N., Libiger, O., Mostofsky, S., Murray, S.S., Sowell, E.R., Schork, N., Jernigan, T.L., 2014. The NIH toolbox cognition battery: Results from a large normative developmental sample (PING). Neuropsychology *28* (1), 1–10. https://doi.org/10.1037/neu0000001.

Arienzo, D., Happer, J.P., Molnar, S.M., Alderson-Myers, A., Marinkovic, K., 2019. Binge drinking is associated with altered resting state functional connectivity of reward-salience and top down control networks. Brain Imaging Behav. *14*, 1731–1746. https://doi.org/10.1007/s11682-019-00107-6.

Bakken, T.E., Dale, A.M., Schork, N.J., 2011. A geographic cline of skull and brain morphology among individuals of European Ancestry. Cereb. Cortex *72* (1), 35–44. https://doi.org/10.1159/000330168.

Bhatt, R.S., Bertin, E., Hayden, A., Reed, A., 2005. Face processing in infancy: Developmental changes in the use of different kinds of relational information. Child Dev. *76* (1), 169–181. https://doi.org/10.1111/j.1467-8624.2005.00837.x.

Brown, S.A., Tapert, S.F., 2004. Adolescence and the trajectory of alcohol use: basic to clinical studies. Ann. N. Y. Acad. Sci. *1021* (1), 234–244. https://doi.org/10.1196/annals.1308.028.

Brown, S.A., Myers, M.G., Lippke, L., Tapert, S.F., Stewart, D.G., 1998. Psychometric evaluation of the customary drinking and drug use record (CDDR): a measure of adolescent alcohol and drug involvement. J. Stud. Alcohol *59* (4), 427–438. https://doi.org/10.15288/jsa.1998.59.427.

Brown, S.A., Brumback, T., Tomlinson, K., Cummins, K., Thompson, W.K., Nagel, B.J., De Bellis, M.D., Hooper, S.R., Clark, D.B., Chung, T., Hasler, B.P., Colrain, I.M., Baker, F. M., Prouty, D., Pfefferbaum, A., Sullivan, E.V., Pohl, K.M., Rohlfing, T., Nichols, N. B., Tapert, S.F., 2015. The national consortium on alcohol and neurodevelopment in adolescence (NCANDA): A multisite study of adolescent development and substance use. J. Stud. Alcohol Drugs *76* (6), 895–908. https://doi.org/10.15288/jsad.2015.76.895.

Chen, Y., Allison, O., Green, H.L., Kuschner, E.S., Liu, S., Kim, M., Slinger, M., Mol, K., Chiang, T., Bloy, L., Roberts, T.P.L., Edgar, J.C., 2022. Maturational trajectory of fusiform gyrus neural activity when viewing faces: from 4 months to 4 years old. Front. Hum. Neurosci. *16*, 917851. https://doi.org/10.3389/fnhum.2022.917851.

Chitty, K.M., Lagapoulos, J., Hickie, I.B., Hermens, D.F., 2014. The impact of alcohol and tobacco use on in vivo glutathione in youth with bipolar disorder: An exploratory study. J. Psychiatr. Res. *55*, 59–67. https://doi.org/10.1016/j.jpsychires.2014.03.024.

Corwin, J., Bylsma, F.W., 1993. Psychological examination of traumatic encephalopathy. Clin. Neuropsychol. *28* (1), 3–21. https://doi.org/10.1080/13854049308401883.

Crews, F.T., Vetreno, R.P., Broadwater, M.A., Robinson, D.L., 2016. Adolescent alcohol exposure persistently impacts adult neurobiology and behavior. Pharmacol. Rev. *68* (4), 1074–1109. https://doi.org/10.1124/pr.115.012138.

De Bellis, M.D., Clark, C.B., Beers, S.R., Soloff, P.H., Boring, A.M., Hall, J., Kersh, A., Keshavan, M.S., 2000. Hippocampal volume in adolescent-onset alcohol use disorders. Am. J. Psychiatry *157* (5), 737–744.

Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Kiliany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage *31* (3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021.

Duncan, S.C., Duncan, T.E., Hops, H., 1996. Analysis of longitudinal data within accelerated longitudinal designs. Psychol. Methods *1* (3), 236–248. https://doi.org/10.1037/1082-989X.1.3.236.

Duncan, S.C., Duncan, T.E., Strycker, L., 2006. Alcohol use from ages 9-16: a cohort-sequential latent growth model. Drug Alcohol Depend. *81* (1), 71–81.

Duncan, T., Duncan, S., Benjamin, L.A., 2013. An Introduction to Latent Variable Growth Curve Modeling: Concepts, Issues, and Applications, Second. Routledge.
Enders, C.K., 2022. Applied missing data analysis. Gilford Publications.
Ferrer, E., Salthouse, T.A., McArdle, J.J., Stewart, W.F., Schwartz, B.S., 2005. Multivariate modeling of age and retest in longitudinal studies of cognitive abilities. Psychol. Aging *20* (3), 142–422. https://doi.org/10.1037/0882-7974.20.3.412.
Fischl, B., 2012. FreeSurfer. NeuroImage *62* (2), 774–781. https://doi.org/10.1016/j.neuroimage.2012.01.021.
Gobbini, M.I., Haxby, J.V., 2007. Neural systems for recognition of familiar faces. Neuropsychologia *45* (1), 32–41. https://doi.org/10.1016/j.neuropsychologia.2006.04.015.
Goncalves, P.D., Smith, T.L., Antheneli, R.M., Danko, G., Schuckit, M.A., 2018. Alcohol-related blackouts among college students: Impact of low level of response to alcohol, ethnicity, sex, and environmental characteristics, *40* (2), 128–137. https://doi.org/10.1590/1516-4446-2016-2165.
Gorka, S.M., Fitzgerald, D.A., King, A.C., Phan, K.L., 2013. Alcohol attenuates amygdala–frontal connectivity during processing social signals in heavy social drinkers: a preliminary pharmaco-fMRI study. Psychopharmacology *229*, 141–154. https://doi.org/10.1007/s00213-013-3090-0.
Gur, R.C., Ragland, J.D., Mozley, L.H., Mozley, P.D., Smith, R., Alavi, A., Bilker, W., Gur, R.E., 1997. Lateralized changes in regional cerebral blood flow during performance of verbal and facial recognition tasks: Correlations with performance and "effort. Brain Cogn. *33* (3), 388–414.
Gur, R.C., Schroeder, L., Turner, T., McGrath, C., Chan, R.M., Turetsky, B.I., Alsop, D., Maldjian, J., Gur, R.E., 2002. Brain activation during facial emotion processing. NeuroImage *16* (3), 651–662. https://doi.org/10.1006/nimg.2002.1097.
Gur, R.C., Richard, J., Calkins, M.E., Chiavacci, R., Hansen, J.A., Bilker, W.B., Loughead, J., Connolly, J.J., Qiu, H., Mentch, F.D., Abou-Sleiman, P.M., Hakonarson, H., Gur, R.E., 2012. Age group and sex differences in performance on a computerized neurocognitive battery in children age 8-21. Neuropsychology *26* (2), 251–265. https://doi.org/10.1037/a0026712.
Gurr, R.C., Richard, J., Hughett, P., Calkins, M.E., Macy, L., Bilker, W.B., Brensinger, C., Gur, R.E., 2010. A Cognitive neuroscience based computerized battery for eficient measurement of individual differences: Standardization and initial construct validation. J. Neurosci. Methods *187* (2), 254–262. https://doi.org/10.1016/j.jneumeth.2009.11.017.
Haas, A.L., Lorkiewicz, S.A., Zamboanga, B.L., 2019. Replication of factors related to blackout incidence in US high school students: a brief report. Addict. Behav. *93*, 104–107. https://doi.org/10.1016/j.addbeh.2019.01.035.
Hai, T., Swansburg, R., Kahl, C.K., Frank, H., Stone, K., Lemay, J.F., MacMaster, F.P., 2022. Right superior frontal gyrus cortical thickness in pediatric ADHD. J. Atten. Disord. *26* (14), 1895–1905. https://doi.org/10.1177/10870547221110918.
Haist, F., Anzures, G., 2017. Functional development of the brain's face-processing system. Wiley Interdiscip. Rev.: Cogn. Sci. *8* https://doi.org/10.1002%2Fwcs.1423.
Hancock, G., Mueller, R., 2013. Structural Equation Modeling: A Second Course, 2nd ed. Information Age Publishing Inc.
Hancock, G.R., Freeman, M.J., 2001. Power and sample size for the root mean square error of approximation test of not close fit in structural equation modeling. Educ. Psychol. Meas. *61* (5), 741–758. https://doi.org/10.1177/00131640121971491.
Hartzler, B., Fromme, K., 2003. Fragmentary and en bloc blackouts: Similarity and distinction among episodes of alcohol-induced memory loss. J. Stud. Alcohol *64* (4), 547–550. https://doi.org/10.15288/jsa.2003.64.547.
Hayes, A.F., 2017. Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. Gilford Publications.
Hermens, D.F., & Lagapoulos, J. (2018). *Binge drinking and the young brain: A mini review of the neurobiological underpinnings of alcohol-induced blackout. 9*(Article 12). https://doi.org/doi:10.3389/fpsyg.2018.00012.
Hingson, R., Zha, W., Simmons-Morton, B., White, A., 2016. Alcohol-Induced blackouts as predictors of other drinking related harms among emerging young adults, *40* (4). https://doi.org/10.1111/acer.13010.
Huntley, E.D., Marusak, H.A., Berman, S.E., Zundel, C.G., Hatfield, J.R.B., Keating, D.P., Rabinak, C.A., 2020. Adolescent substance use and functional connectivity between the ventral striatum and hippocampus. Behav. Brain Res. *390*, 112678.
Infante, M.A., Eberson, S.C., Zhang, Y., Brumback, T., Brown, S.A., Colrain, I.M., Baker, F.C., Clark, D.B., De Bellis, M.D., Goldston, D.B., Nagel, B.J., Nooner, K.B., Zhao, Q., Pohl, K.M., Sullivan, E.V., Pfefferbaum, A., Tapert, S.F., Thompson, W.K., 2022. Adolescent binge drinking is associated with accelerated decline of gray matter volume. Cereb. Cortex *32* (12), 2611–2620. https://doi.org/10.1093/cercor/bhab368.
Ishai, A., Pessoa, L., Bikle, P.C., Ungerleider, L.G., 2004. Repetition suppression of faces is modulated by emotion. Proc. Natl. Acad. Sci. *101* (26), 9827–9832. https://doi.org/10.1073/pnas.0403559101.
Jones, S.A., Nagel, B., 2019. Altered frontostriatal white matter microstructure is associated with familial alcoholism and future binge drinking in adolescence. Neuropsychopharmacology *44* (6), 1076–1083. https://doi.org/10.1038/s41386-019-0315-x.
Jones, S.A., Lueras, J.M., Nagel, B.J., 2018. Effects of binge drinking on the developing brain. Alcohol Res.: Curr. Rev. *39* (1), 87–96 https://doi.org/PMC6104956.
Jones, S.A., Morales, A.M., Harman, G., Dominguez-Savage, K.A., Gilbert, S., Baker, F.C., de Zambotti, M., Goldston, D.B., Nooner, K.B., Clark, D.B., Luna, B., Thompson, W. K., Brown, S.A., Tapert, S.F., Nagel, B.J., 2023. Associations between alcohol use and sex-specific maturation of subcortical gray matter morphometry from adolescence to adulthood: Replication across two longitudinal samples. Dev. Cogn. Neurosci. *63*, 101294. https://doi.org/10.1016/j.dcn.2023.101294.
Kwon, D., Pfefferbaum, A., Sullivan, E.V., Pohl, K.M., 2018. Regional growth trajectories of cortical myelination in adolescents and young adults: longitudinal validation and functional correlates. Brain Imaging Behav. *14* (1), 242–266. https://doi.org/10.1007/s11682-018-9980-3.
Lannoy, S., Pfefferbaum, A., Le Berre, A.P., Thompson, W.K., Brumback, T., Schulte, T., Pohl, K.M., De Bellis, M.D., Nooner, K.B., Baker, F.C., Prouty, D., Colrain, I.M., Nagel, B.J., Brown, S.A., Clark, D.B., Tapert, S.F., Sullivan, E.V., Müller-Oehring, E. M., 2022. Growth trajectories of cognitive and motor control in adolescence: how much is development and how much is practice? Neuropsychology *36* (1), 44. https://doi.org/10.1037/neu0000771.
Leech, R., Sharp, D.J., 2014. The role of the posterior cingulate cortex in cognition and disease. Brain *137* (1), 12–32. https://doi.org/10.1093/brain/awt162.
Lees, B., Meredith, L.R., Kirkland, A.E., Bryant, B.E., Squeglia, L.M., 2020. Effect of alcohol use on the adolescent brain and behavior. Pharmacol. Biochem. Behav. *192*, 172906. https://doi.org/10.1016/j.pbb.2020.172906.
Linden-Carmichael, A.N., Mogle, J., Miller, S.E., 2023. Associations between blackout drinking and self-reported everyday cognition among young adults. Addict. Behav. *141*, 107653. https://doi.org/10.1016/j.addbeh.2023.107653.
Lorkiewicz, S.A., Baker, F.C., Müller-Oehring, E.M., Haas, A.L., Wickham, R., Sassoon, S. A., Clark, D.B., Nooner, K.B., Tapert, S.F., Brown, S.A., Schulte, T., 2022. A longitudinal examination of alcohol-related blackouts as a predictor of changes in learning, memory, and executive function in adolescents. Front. Psychiatry *13*, 866051. https://doi.org/10.3389/fpsyt.2022.866051.
Lynch, K.M., Shi, Y., Toga, A.W., Clark, K.A., Pediatric Imaging, Neurocognition and Genetics Study, 2019. Hippocampal shape maturation in childhood and adolescence. Cereb. Cortex *29* (9), 3651–3665. https://doi.org/10.1093/cercor/bhy244.
Marino, E.N., Fromme, K., 2016. Early onset drinking predicts greater level but not growth of alcohol-induced blackouts beyond the effect of binge drinking during emerging adulthood. Alcohol.: Clin. Exp. Res. *40* (3), 599–605. https://doi.org/10.1111/acer.12981.
Mashhoon, Y., Czerkawski, C., Crowley, D.J., Cohen-Gilbert, J.E., Sneider, J.T., Silveri, M.M., 2014. Binge alcohol consumption in emerging adults: anterior cingulate cortical "thinness" is associated with alcohol use patterns. Alcohol.: Clin. Exp. Res. *38* (7), 1955–1964. https://doi.org/10.1111/acer.12475.
Mcardle, J.J., Hamagami, F., 1992. Modeling incomplete longitudinal and cross-sectional data using latent growth structural models. Exp. Aging Res. *18* (3), 145–166. https://doi.org/10.1080/03610739208253917.
McLoyd, V.C., 1998. Socioeconomic disadvantage and child development. Am. Psychol. *53* (2), 185–204. https://doi.org/10.1037/0003-066X.53.2.185.
Meda, S.A., Hawkins, K.A., Dager, A.D., Tennen, H.A., Khadka, S., Austad, C.S., Wood, R. M., Raskin, S.A., Fallahi, C.R., Pearlson, G.D., 2018. Longitudinal effects of alcohol consumption on the hippocampus and parahippocampus in college students. Biol. Psychiatry.: Cogn. Neurosci. Neuroimaging *3* (7), 610–617. https://doi.org/10.1016/j.bpsc.2018.02.006.
Melrose, R., Harwood, D., Khoo, T., Mandelkern, M., Sulter, D.L., 2013. Association between cerebral metabolism and Rey–Osterrieth Complex Figure Test performance in Alzheimer's disease. J. Clin. Exp. Neuropsychol. *35* (3), 246–258. https://doi.org/10.1080/13803395.2012.763113.
Merrill, J.E., Miller, M.B., DiBello, A.M., Singh, S., Carey, K.B., 2019. How do college students subjectively evaluate "blackouts"?, *89*, 65–69. https://doi.org/10.1016/j.addbeh.2018.09.022.
Meyers, J.E., Meyers, K.R., 1995. Rey complex figure test under four different administration procedures. Clin. Neuropsychol. *9* (1), 63–67.
Miller, M.B., DiBello, A.M., Merrill, J.E., Neighbors, C., Carey, K.B., 2020. The role of alcohol-induced blackouts in symptoms of depression among young adults. Drug Alcohol Depend. *211*, 108027. https://doi.org/10.1016/j.drugalcdep.2020.108027.
Min, E.-J., Kim, S.-G., Lee, J.-S., Seo, B., Jung, W.-Y., Huh, S.-Y., Park, J.-H., Hong, C.-H., Yu, H.J., 2019. Difference in cognitive function by first onset age of alcohol inducced blackout and its duration. Clin. Psychopharmacol. Neurosci. *17* (4), 503–508. https://doi.org/10.9758/cpn.2019.17.4.503.
Mock, N., Balzer, C., Gutbrod, K., Jäncke, L., Wandel, J., Bonati, L., Trost, W., 2023. Nonverbal memory tests revisited: neuroanatomical correlates and differential influence of biasing cognitive functions. Cortex *164*, 63–76. https://doi.org/10.1080/13803390802317542.
Moore, T.M., Relse, S.P., Gur, R.E., Hakonarson, H., Gur, R.C., 2015. Psychometric properties of the penn computerized neurocognitive battery. Neuropsychology *29* (2), 235–246. https://doi.org/10.1037/neu0000093.
Muthén, L.K., Muthén, B.O., 1998. Mplus User's Guide, 8th ed. Muthén & Muthén.
National Institute on Alcohol Abuse and Alcoholism. (2011). Alcohol screening and brief intervention for youth: A practitioner's guide. *NIH Publication No. 11-7805*, *Bathesda, MD*(Author). https://doi.org/Retrieved from http:// www.niaaa.nih.gov/YouthGuide.
Nelson, E.C., Health, A.C., Bucholz, K.K., Madden, P.A.F., Fu, Q., Knopik, V., Lynskey, M. T., Whitfield, J.B., Statham, D.J., Martin, N.G., 2004. Genetic epidemiology of alcohol-induced blackouts. Arch. Gen. Psychiatry *61* (3), 257–263. https://doi.org/10.1001/archpsyc.61.3.257.
Nestor, A., Paut, D.C., Behrmann, M., 2011. Unraveling the distributed neural code of facial identity through spatiotemporal pattern analysis. Proc. Natl. Acad. Sci. *108* (24), 9998–10003. https://doi.org/10.1073/pnas.1102433108.
Nguyen-Louie, T.T., Simmons, A.N., Squeglia, L.M., Infante, M.A., Schact, J.P., Tapert, S. F., 2018. Earlier alcohol use onset prospectively predicts changes in functional connectivity. Psychopharmacology *235*, 1041–1054. https://doi.org/10.1007/s00213-017-4821-4.
Noble, K.G., Houston, S.M., Brito, N.H., Bartsch, H., Kan, E., Kuperman, J.M., Akshoomoff, N., Amaral, D.G., Bloss, C.S., Libiger, O., Schork, N., Murray, S.S., Casey, B.J., Chang, L., Ernst, T.M., Frazier, J.A., Gruen, J.R., Kennedy, D.N., Van Zijl, P., Sowell, E.R., 2015. Family income, parental education and brain structure in

children and adolescents. Nat. Neurosci. *18* (5), 773–778. https://doi.org/10.1038/nn.3983.
Oscar-Berman, M., Marinkovic, K., 2007. Alcohol: Effects on neurobehavioral funtions and the brain. Neuropsychol. Rev. *17* (3), 239–257. https://doi.org/10.1007/s11065-007-9038-6.
Paus, T., 2010. Sex differences in the human brain: a developmental perspective. Prog. Brain Res. *186*, 13–28. https://doi.org/10.1016/B978-0-444-53630-3.00002-6.
Pfefferbaum, A., Mathalon, D.H., Sullivan, E.V., Rawles, J.M., Zipursky, R.B., Lim, K.O., 1994. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Arch. Neurol. *51* (9), 874–887. https://doi.org/10.1001/archneur.1994.00540210046012.
Pfefferbaum, A., Rohlfing, T., Rosenbloom, M.J., Chu, W., Colrain, I.M., Sullivan, E.V., 2013. Variation in longitudinal trajectories of regional brain volumes of healthy men and women (ages 10 to 85 years) measured with atlas-based parcellation of MRI. NeuroImage *65*, 176–193. https://doi.org/10.1016/j.neuroimage.2012.10.008.
Pfefferbaum, A., Rohlfing, T., Pohl, K.M., Lane, B., Chu, W., Kwon, D., Nichols, N.B., Brown, S.A., Tapert, S.F., Cummins, K., Thompson, W.K., Brumback, T., Meloy, M.J., Jernigan, T.L., Dale, A., Colrain, I.M., Baker, F.M., Prouty, D., De Bellis, M.D., Sullivan, E.V., 2016. Adolescent development of cortical and white matter structure in the NCANDA sample: Role of sex, ethnicity, puberty, and alcohol drinking. Cereb. Cortex *26* (10), 4101–4121. https://doi.org/10.1093/cercor/bhv205.
Pfefferbaum, A., Kwon, D., Brumback, T., Thompson, W.K., Cummins, K., Tapert, S.F., Brown, S.A., Colrain, I.M., Baker, F.C., Prouty, D., De Bellis, M.D., Clark, D.B., Nagel, B.J., Chu, W., Park, S.H., Pohl, K.M., Sullivan, E.V., 2018. Altered brain developmental trajectories in adolescents after initiating drinking. Am. J. Psychiatry *175* (4), 370–380. https://doi.org/10.1176/appi.ajp.2017.17040469.
Pohl, K.M., Sullivan, E.V., Rohlfing, T., Chu, W., Kwon, D., Nichols, N.B., Zhang, Y., Brown, S.A., Tapert, S.F., Cummins, K., Thompson, W.K., Brumback, T., Colrain, I. M., Baker, F.C., Prouty, D., De Bellis, M.D., Voyvodic, J.T., Clark, D.B., Schrida, C., Pfefferbaum, A., 2016. Harmonizing DTI measurements across scanners to examine the development of white matter microstructure in 803 adolescents of the NCANDA study. NeuroImage *130*, 194–213. https://doi.org/10.1016/j.neuroimage.2016.01.061.
Quinn, P.C., Tanaka, J.W., 2009. Infants' processing of featural and configural information in the upper and lower halves of the face. Infancy *14* (4), 474–487. https://doi.org/10.1080/15250000902994248.
Reuter, M., Schmansky, N.J., Rosas, H.D., Fischl, B., 2012. Within-subject template estimation for unbiased longitudinal image analysis. NeuroImage *61* (4), 1402–1418. https://doi.org/10.1016/j.neuroimage.2012.02.084.
Riordan, B.C., Merrill, J.E., Ward, R.M., 2019. Can't wait to blackout tonight: An analysis of the motives to drink to blackout expressed on twitter, *43* (8), 1769–1776. https://doi.org/10.1111/acer.14132.
Rohlfing, T., Zahr, N.M., Sullivan, E.V., Pfefferbaum, A., 2010. The SRI24 multichannel atlas of normal adult human brain structure. Hum. Brain Mapp. *31* (5), 798–819. https://doi.org/10.1002/hbm.20906.
Rohlfing, T., Cummins, K., Chu, W., Nichols, N.B., 2014. N-CANDA data integration: Anatomy of an asynchronous infrastructure for multi-site, multi-instrument longitudinal data capture. J. Am. Med. Inform. Assoc. *21* (4), 758–762. https://doi.org/10.1136/amiajnl-2013-002367.
Rose, M.E., Grant, J.E., 2010. Alcohol-induced blackout phenomenology, biological basis, and gender differences. J. Addict. Med. *4* (2), 61–73. https://doi.org/10.1097/ADM.0b013e3181e1299d.
Rose, S., Van Der Laan, M.J., 2009. Why match? Investigating matched case-control study designs with causal effect estimation. Int. J. Biostat. *5* (1). https://doi.org/10.2202/1557-4679.1127.
Rosen, M.L., Sheridan, M.A., Sambrook, K.A., Peverill, M.R., Meltzoff, A.N., McLaughlin, K.A., 2018. The role of visual association cortex in associative memory formation across development. J. Cogn. Neurosci. *30* (3), 365–380. https://doi.org/10.1162/jocn_a_01202.
Rosenbloom, M.J., Sassoon, S.A., Pfefferbaum, A., Sullivan, E.V., 2009. Contribution of regional white matter integrity to visuospatial construction accuracy, organizational strategy, and memory for a complex figure in abstinent alcoholics. Brain Imaging Behav. *3*, 379–390. https://doi.org/10.1007/s11682-009-9080-5.
Russell, J.D., Marsee, M.A., Weems, C.F., 2021. Developmental variation in amygdala volumes: modeling differences across time, age, and puberty. Biol. Psychiatry.: Cogn. Neurosci. Neuroimaging *6* (1), 117–125. https://doi.org/10.1016/j.bpsc.2020.08.006.
Schuckit, M. (2017). *Predictors of Patterns of Alcohol-Related Blackouts Over Time in Youth From the Collaborative Study of the Genetics of Alcoholism: The Roles of Genetics and Cannabis*.
Schuckit, M.A., Smith, T.L., Heron, J., Hickman, M., Macleod, J., Munafo, M., Kendler, K. S., Dick, D.M., Davey-Smith, G., 2015. Latent trajectory classes for alcohol-related blackouts from age 15 to 19 in ALSPAC. Alcohol.: Clin. Exp. Res. *39* (1), 108–116. https://doi.org/10.1111/acer.12601.
Silveri, M.M., 2012. Adolescent brain development and underage drinking in the United States: Identifying risks of alcohol use in college populations. Harv. Rev. Psychiatry *20* (4), 189–200. https://doi.org/10.3109/10673229.2012.714642.
Silveri, M.M., Cohen-Gilbert, J., Crowley, D.J., Rosso, I.M., Jensen, J.E., Sneider, J.T., 2014. Altered anterior cingulate neurochemistry in emerging adult binge drinkgers with a history of alcohol-induced blackouts. Alcohol.: Clin. Exp. Res. *38* (4), 969–979. https://doi.org/10.1111/acer.12346.
Slotnick, S.D., Moo, L.R., Segal, J.B., Hart Jr., J., 2003. Distinct prefrontal cortex activity associated with item memory and source memory for visual shapes. Cogn. Brain Res. *17* (7), 75–82. https://doi.org/10.1016/S0926-6410(03)00082-X.
Sobell, L.C., Sobell, M.B., 1995. Alcohol consumption measures. Asssesing Alcohol Probl.: A Guide Clin. Res. *2*, 75–99.
Sowell, E.R., Peterson, B.S., Kan, E., Woods, R.P., Yoshi, J., Bansal, R., Xu, D., Zhu, H., Thompson, P.M., Toga, A.W., 2007. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb. Cortex *17* (7), 1550–1560. https://doi.org/10.1093/cercor/bhl066.
Squeglia, L.M., Jacobus, J., Tapert, S.F., 2009a. The influence of substance use on adolescent brain development. Clin. EEG Neurosci. *40* (1), 31–38. https://doi.org/10.1177/155005940904000110.
Squeglia, L.M., Pulido, C., Wetherill, R.R., Jacobus, J., Brown, G.G., Tapert, S.F., 2012. Brain response to working memory over three years of adolescence: influence of initiating heavy drinking. J. Stud. Alcohol Drugs *73*, 749–760. https://doi.org/10.15288/jsad.2012.73.749.
Squeglia, L.M., Rinker, D.A., Bartsch, H., Castro, N., Chung, Y., Dale, A.M., Jernigan, T.L., Tapert, S.F., 2014. Brain volume reductions in adolescent heavy drinkers. Dev. Cogn. Neurosci. *9*, 114–125. https://doi.org/10.1016/j.dcn.2014.02.005.
Squeglia, L.M., Tapert, S.F., Sullivan, E.V., Jacobus, J., Meloy, M.J., Rohlfing, T., Pfefferbaum, A., 2015. Brain development in heavy-drinking adolescents. Am. J. Psychiatry *172* (6), 531–542. https://doi.org/10.1176/appi.ajp.2015.14101249.
Squeglia, L.M., Ball, T.M., Jacobus, J., Brumback, T., McKenna, B.S., Nguyen-Louie, T.T., Sorg, S.F., Paulus, M.P., Tapert, S.F., 2017. Natural predictors of initiating alcohol use during adolescence. Am. J. Psychiatry *174* (2), 172–185. https://doi.org/10.1176/appi.ajp.2016.15121587.
Strauss, E., Sherman, E.M.S., Spreen, O., 2012. A compendium of neuropsychological tests: Administration, norms, and commentary, 3rd ed. Oxford University Press.
Substance Abuse and Mental Health Services Administration. (2012). Results from the 2011 national survey on druge use and health: Summary of national findings. *Vol. NSDUH Series H-44, Rockville, MD*(Author).
Sugiura, M., Shah, N.J., Zilles, K., Fink, G.R., 2005. Cortical representations of personally familiar objects and places: functional organization of the human posterior cingulate cortex. J. Cogn. Neurosci. *17* (2), 183–198. https://doi.org/10.1162/0898929053124956.
Sullivan, E.V., Pfefferbaum, A., 2005. Neurocircuitry in alcoholism: A substrate of disruption and repair. Psychopharmacology *180*, 583–594. https://doi.org/10.1007/s00213-005-2267-6.
Sullivan, E.V., Harris, R.A., Pfefferbaum, A., 2010. Alcohol's effects on brain and behavior. Alcohol Res. Health *33* (1–2), 127.
Sullivan, E.V., Pfefferbaum, A., Rohlfing, T., Baker, F.C., Padilla, M.L., Colrain, I.M., 2011. Developmental change in regional brain structure over 7 months in early adolescence: comparison of approaches for longitudinal atlas-based parcellation. NeuroImage *57* (1), 214–224. https://doi.org/10.1016/j.neuroimage.2011.04.003.
Sullivan, E.V., Brumback, T., Tapert, S.F., Fama, R., Prouty, D., Brown, S.A., Cummins, K., Thompson, W.K., Colrain, I.M., Baker, F.C., De Bellis, M.D., Hooper, S. R., Clark, D.B., Chung, T., Nagel, B.J., Nichols, N.B., Rohlfing, T., Chu, W., Pohl, K. M., Pfefferbaum, A., 2016. Cognitive, emotion control, and motor performance of adolescents in the NCANDA study: Contributions from alcohol consumption, age, sex, ethnicity, and family history of addition. Neuropsychology *30* (4), 449. https://doi.org/10.1037/neu0000259.
Sullivan, E.V., Lane, B., Kwon, D., Meloy, M.J., Tapert, S.F., Brown, S.A., Colrain, I.M., Baker, F.C., De Bellis, M.D., Clark, D.B., Nagel, B.J., Pohl, K.M., Pfefferbaum, A., 2017b. Structural brain anomalies in health adolescents in the NCANDA cohort: relation to neuropsychological test performance, sex, and ethnicity. Brain Imaging Behav. *11* (5), 1302–1315. https://doi.org/10.1007/s11682-016-9634-2.
Sullivan, E.V., Brumback, T., Tapert, S.F., Prouty, D., Fama, R., Thompson, W.K., Brown, S.A., Cummins, K., Colrain, I.M., Baker, F.M., Clark, D.B., Chung, T., De Bellis, M.D., Hooper, S.R., Nagel, B.J., Nichols, N.B., Chu, W., Kwon, D., Pohl, K.M., Pfefferbaum, A., 2017a. Effects of prior testing lasting a full year in NCANDA adolescents: Contributions from age, sex, socioeconomic status, ethnicity, site, family history of alcohol or drug abuse, and baseline performance. Dev. Cogn. Neurosci. *24*, 72–83. https://doi.org/10.1016/j.dcn.2017.01.003.
Sullivan, E.V., Brumback, T., Tapert, S.F., Brown, S.A., Baker, F.C., Colrain, I.M., Prouty, D., De Bellis, M.D., Clark, D.B., Nagel, B.J., Pohl, K.M., Pfefferbaum, A., 2020. Disturbed cerebellar growth trajectories in adolescents who initiate alcohol drinking. Biol. Psychiatry *87* (7), 632–644. https://doi.org/10.1016/j.biopsych.2019.08.026.
Tapert, S.F., Schweinsburg, A.D., Barlett, V.C., Meloy, M.J., Brown, S.A., Brown, G.G., Frank, L.R., 2004. BOLD response and spatial working memory in adolescents with alcohol use disorders. Alcohol.: Clin. Exp. Res. *28* (10), 1577–1586. https://doi.org/10.1097/01.ALC.0000141812.81234.A6.
Vijayakumar, N., Allen, N.B., Youssef, G., Dennison, M., Yücel, M., Simmons, J.G., Whittle, S., 2016. Brain development during adolescence: A mixed-longitudinal investigation of cortical thickness, surface area, and volume. Hum. Brain Mapp. *37* (6), 2027–2038. https://doi.org/10.1002/hbm.23154.
Voloshyna, D.M., Bonar, E.E., Cunningham, R.M., Ilgen, M.A., Blow, F.C., Walton, M.A., 2018. Blackouts among male and female youth seeking emergency department care, *44* (1), 129–139. https://doi.org/10.1080/00952990.2016.1265975.
Wetherill, R.R., Fromme, K., 2016. Alcohol-Induced blackouts: a review of recent clinical research with practical implications and recommendations for future studies. Alcohol.: Clin. Exp. Res. *40* (5), 922–935. https://doi.org/10.1111/acer.13051.
Wetherill, R.R., Schnyer, D.M., Fromme, K., 2012. Acute alcohol effects on contextual memory BOLD response: Differences based on fragmentary blackout history. Alcohol.: Clin. Exp. Res. *36* (6), 1108–1115. https://doi.org/10.1111/j.1530-0277.2011.01702.x.
Wetherill, R.R., Castro, N., Squeglia, L.M., Tapert, S.F., 2013. Atypical neural activity during inhibitory processing in substance-naïve youth who later experience alcohol-induced blackouts. Drug Alcohol Depend. *128* (3), 243–249. https://doi.org/10.1016/j.drugalcdep.2012.09.003.

Whelan, R., Watts, R., Orr, C.A., Althoff, R.R., Artiges, E., Banaschewski, T., Barker, G.J., Bokde, A.L., Büchel, C., Carvalho, F.M., Conrod, P.J., Flor, H., Fauth-Bühler, M., Frouin, V., Gallinat, J., Gan, G., Gowland, P., Heinz, A., Ittermann, B., the IMAGEN Consortium, 2014. Neuropsychosocial profiles of current and future adolescent alcohol misusers. Nature *512* (7513), 185–189.

White, A.M., 2003. What happened? Alcohol, memory blackouts, and the brain. Alcohol Res. Health *27* (2), 186–196.

Wilhite, E.R., Fromme, K., 2015. Alcohol-Induced blackouts and other negative outcomes during the transition out of college. J. Stud. Alcohol Drugs *76* (4), 516–524. https://doi.org/10.15288/jsad.2015.76.516.

Yuen, W.S., Chan, G., Bruno, R., Clare, P.J., Aiken, A., Mattick, R., Farrell, M., Kypri, K., Slade, T., Hutchinson, D., McBride, N., McCambridge, J., Boland, V., Peacock, A., 2021. Trajectories of alcohol-induced blackouts in adolescence: Early risk factors and alcohol use disorder outcomes in early adulthood. Addiction *116* (8), 2039–2048. https://doi.org/10.1111/add.15415.

Zamroziewicz, M., Raskin, S.A., Tennen, H.A., Austad, C.S., Wood, R.M., Fallahi, C.R., Dager, A.D., Sawyer, B., Leen, S., Pearlson, G.D., 2017. Effects of drinking patterns on prospective memory performance in college students. Neuropsychology *31* (2), 191–199. https://doi.org/10.1037/neu0000313.

Zucker, R.A., Donovan, J.E., Masten, A.S., Mattson, M.E., Moss, H.B., 2008. Early developmental processes and the continuity of risk for underage drinking and problem drinking. Pediatrics *121* (Suppl 4), S252–S272. https://doi.org/10.1542/peds.2007-2243B.