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ORIGINAL ARTICLE

Adolescent Binge Drinking Is Associated With Accelerated Decline of Gray Matter Volume

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Abstract

The age- and time-dependent effects of binge drinking on adolescent brain development have not been well characterized even though binge drinking is a health crisis among adolescents. The impact of binge drinking on gray matter volume (GMV) development was examined using 5 waves of longitudinal data from the National Consortium on Alcohol and NeuroDevelopment in Adolescence study. Binge drinkers ($n = 166$) were compared with non-binge drinkers ($n = 82$ after matching on potential confounders). Number of binge drinking episodes in the past year was linked to decreased GMVs in bilateral Desikan–Killiany cortical parcellations (26 of 34 with $P < 0.05/34$) with the strongest effects observed in frontal regions. Interactions of binge drinking episodes and baseline age demonstrated stronger effects in younger participants. Statistical models sensitive to number of binge episodes and their temporal proximity to brain volumes provided the best fits. Consistent with prior research, results of this study highlight the negative effects of binge drinking on the developing brain. Our results present novel findings that cortical GMV decreases were greater in closer proximity to binge drinking episodes in a dose–response manner. This relation suggests a causal effect and raises the possibility that normal growth trajectories may be reinstated with alcohol abstinence.

Key words: adolescence, alcohol, binge drinking, brain development, cortical volume

Introduction

Adolescence is a critical developmental stage when experimentation with alcohol and other substances is often initiated. Alcohol remains the most widely used substance during adolescence with 19%, 38%, and 52% reporting past-year alcohol use by 8th, 10th, and 12th grade, respectively (Johnston et al. 2020). Although adolescents generally consume alcohol with less frequency than adults, among those who report drinking, the majority engages in binge drinking (Substance Abuse and Mental Health Services Administration 2020), defined by the National Institute on Alcohol Abuse and Alcoholism (2004) as a pattern of drinking alcohol that brings the blood alcohol concentration to 0.08 g/dL or higher, which typically corresponds to consuming 5 or more drinks for men and 4 or more drinks for women within a 2-h period. Findings from the most recent Monitoring the Future survey show 14% of adolescents in the 12th grade had engaged in binge drinking in the past 2 weeks, and data from the 2019 National Survey on Drug Use and Health show 5% of adolescents aged 12–17 had engaged in past month binge drinking. Binge drinking has been identified as particularly risky for adolescents, with far more severe consequences compared with adults, including deviation from normal brain development (Zhao et al. 2021), structural and functional brain alterations (Jones et al. 2018), neuropsychological deficits (Carbia et al. 2018), and increased risk for developing alcohol as well as other substance use disorders (Chassin et al. 2002). The burden of excessive alcohol use alone on US society is estimated to be over 223 billion dollars per year (Bouchery et al. 2011).

During adolescence, the brain goes through significant maturational and organizational changes (Mills et al. 2016; Pfefferbaum et al. 2016; Tamnes et al. 2017). Structural magnetic resonance imaging (MRI) studies have shown region-specific variation of cortical development from childhood through early adulthood, with sensorimotor and occipital brain regions maturing first, followed by limbic regions important for rewards and emotion, and higher order cortical association areas, including the prefrontal cortex maturing later in development (Gogtay et al. 2004; Khundrakpam et al. 2013; Krongold et al. 2017; Sotiras et al. 2017; Nadig et al. 2021). The asynchronous development of brain regions, particularly the difference in timing of the development of the reward and control systems, may explain why adolescents are prone to risk-taking behaviors (Crews et al. 2007; Casey et al. 2008). At the same time, given the extensive nature of neurodevelopment during this period, the adolescent brain may be especially vulnerable to intoxicants such as alcohol.

Findings from cross-sectional studies have shown gray matter differences in binge drinking college-age adolescents compared with their nondrinking peers, including smaller volumes in the frontal lobe (Kvamme et al. 2016) and cerebellum (Lisdahl et al. 2013). By contrast, others have found larger cortical volumes in college-age binge drinkers compared with nondrinkers, including regions of the prefrontal cortex, anterior cingulate (Doallo et al. 2014), and ventral striatum (Howell et al. 2013). Greater gray matter density in the left middle frontal gyrus among college-age binge drinkers compared with nondrinkers was also reported in a more recent study (Sousa et al. 2017). Sex differences in the effect of binge drinking on brain structure have also been documented, perhaps related to sex-related differences in genetic vulnerabilities or neurotoxic sensitivities (Kvamme et al. 2016).

Longitudinal studies suggest that accelerated decline in cortical volumes may result from heavy alcohol use during adolescence (Squeglia et al. 2014; Squeglia et al. 2015; Meda et al. 2017; Pfefferbaum et al. 2018). A study by Squeglia et al. (2014) examined brain development before and after initiation of heavy drinking, showing alcohol-associated reduction in subcortical regions as well as inferior and middle temporal structures. In another study (Meda et al. 2017), participants were categorized as heavy or light drinkers based on number of binge drinking episodes in the previous 26 weeks, with subjects in the heavy binge drinking group showing an increased rate of gray matter decline, primarily in fronto-striatal regions. Using 3 waves of data from the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA), Pfefferbaum et al. (2018) examined the impact of adolescent heavy drinking on brain trajectories of gray and white matter volumes. That study compared brain trajectories of those who at the 2-year follow-up remained no/low drinkers versus those who had initiated moderate or heavy drinking by this time point. Results indicated smaller volumes of frontal, cingulate, and total gray matter in heavy drinkers compared with those in the no/low drinking group. As in Squeglia et al. (2014), youth were classified based moderate or heavy drinking pattern as opposed to binge drinking status. Understanding the impact of binge drinking on adolescent brain development of specific brain regions has important implications given the association between neurobiological changes at the structural and functional level to cognitive and behavioral changes (Jones et al. 2018).

To date, the age- and time-dependent effects of binge drinking on adolescent brain development have not been well characterized. Large-scale longitudinal studies with several years of data collection are needed to explicate the effects of binge drinking, including its proximal and longer-term effects on the brain. To begin to address these issues, the present study expands on the Pfefferbaum et al. (2018) analysis in 3 ways. First, we assessed the relationship of adolescent binge drinking with gray matter volume (GMV) trajectories across 5 extant waves of longitudinal data from the NCANDA study, encompassing a longer time period, broader age ranges, and a larger variation in drinking behaviors than in prior reports using NCANDA data. Second, we leveraged the NCANDA cohort sequential design to assess whether strength of any associations of binge drinking with GMV trajectories varied by baseline age. Third, we examined whether models that are sensitive to number of binge drinking episodes ("dose") and temporal proximity of binge drinking to outcomes would explain more variation than models that incorporate binge drinking in other ways (as discrete indicators and/or as cumulative measures). Based on previous findings, we predicted that binge drinking would lead to a steeper decline in GMV, particularly in frontal and cingulate regions than would be detected in no-to-low drinkers. NCANDA's large sample size, number of longitudinal assessments, and cohort sequential design thus allow for an unprecedented investigation into the nature of the association of adolescent alcohol use and subsequent trajectories of cortical GMV development across adolescence and into young adulthood.

Materials and Methods

Participants

Data came from the NCANDA. The NCANDA cohort consists of 831 12–21 year-olds enrolled across 5 sites (Duke University, University of Pittsburgh Medical Center [UPMC], Oregon Health & Science University [OHSU], University of California San Diego [UCSD], and SRI International) and followed for 5 years (Brown et al. 2015). Participants were recruited through local schools

and targeted catchment-area calling. The study follows a cohort sequential design, which recruited youth in 3 age bands (12–14, 15–17, and 18–21 years), enabling examination of a broad developmental window due to between-subject variation in baseline age ("age cohort"). Prior to study entry, most of the sample had not engaged in binge drinking ($n = 121$). Youth at risk for heavy drinking (i.e., early experimentation with alcohol, family history of substance use disorder, externalizing or internalizing symptoms) were overrecruited and comprised 50% of the baseline sample.

Exclusion criteria included lack of English fluency, MRI contraindications, serious medical conditions (e.g., traumatic brain injury [TBI] with loss of consciousness >30 min), noncorrectable sensory impairments, current serious Axis I psychiatric disorder that may influence study completion (e.g., psychosis), and early developmental problems (e.g., known exposure to prenatal alcohol or other drugs) (Brown et al. 2015). The research protocol was approved by the Institutional Review Boards at each site. At each visit, participants (or the parent or legal guardian for minors) provided written informed consent, and written informed assent was obtained from minors. Participants and their parents were compensated for participation.

After informed consent, at baseline and each follow-up year participants completed a comprehensive assessment of substance use, psychiatric symptoms, functioning in major life domains, neuropsychological testing, and neuroimaging (Brown et al. 2015). This included the Customary Drinking and Drug use Record (Brown et al. 1998) to characterize past and current alcohol and other substance use, reported on past-year use frequency, maximum number of drinks in a drinking episode, and number of binge drinking episodes (i.e., 5 or more drinks for males or 4 or more drinks for females on an occasion). The number of binge drinking episodes in the prior year at each annual follow-up assessment was the primary (longitudinal) independent variable of interest.

Participants who reported having had at least one lifetime binge episode at baseline ($n = 121$) were excluded from analyses. Because the focus of this paper is longer-term temporal variation in binge drinking, we also excluded participants who had not completed all 5 (baseline and 4 annual follow-up) visits to allow sufficient within-person assessments of binge drinking to characterize its association with concurrent and subsequent GMVs. (Note, we performed sensitivity analyses of the impact of this and other design decisions on resulting associations.) This resulted in a final pool of $n = 344$ subjects for analyses. Of these, $n = 178$ (52%) reported never having had a binge drink episode over the 5 visits and $n = 166$ (48%) reported binge drinking at least once during the study period subsequent to baseline. Participant characteristics are reported in Table 1.

Binge drinkers (participants with a binge drinking episode at any of the visits) were then matched with non-binge drinkers (subjects with no binge drinking episodes at any visit) on potential confounders, including sex, age, race/ethnicity, highest level of education completed by either parent, site, and baseline (pre-binge drinking) intracranial volume (ICV). Matching was performed via a genetic search algorithm, implemented in the R package Matching using the Match function (Sekhon 2011; Sekhon and Grieve 2012; Diamond and Sekhon 2013). Because the pool of non-binge drinkers to select from was only slightly larger than the number of binge drinkers, we performed matching with replacement to improve the post-match balance on these potential confounders, although each matched subject appears only once in analyses even if they were selected in more than one match. Table 1 displays the pre- and post-match summaries of potential confounders of binge and non-binge drinkers, generally demonstrating improved balance for potential confounders. We report the number of times controls appeared in matches in Table 1. All matching variables were also included in subsequent analyses to control for any residual imbalances.

MRI Data Acquisition and Analysis

A high-resolution structural MRI protocol and the use of 3 T scanners were consistent across sites. Three sites (UCSD, SRI, and Duke University) used GE MR750 and 2 sites (UPMC and OHSU) used Siemens TIM-Trio scanners. T_1-weighted and T_2-weighted images were acquired in the sagittal plane. NCANDA used the same acquisition protocols for the Siemens and the same for GE sites (see (Pfefferbaum et al. 2016; Pfefferbaum et al. 2018) for details). The resulting structural MRIs were processed by the same pipeline (Pfefferbaum et al. 2018) resulting in image inhomogeneity corrected, skull stripped T_1-weighted MRI and corresponding ICV defined according the SRI24 atlas (Rohlfing et al. 2010; Rohlfing et al. 2014). The skull stripped images were first processed via cross-sectional FreeSurfer (Fischl 2012) followed by the longitudinal stream (Reuter et al. 2012) to the estimate the GMVs of cortical regions of interest (ROIs) defined according to the Desikan–Killiany atlas (Desikan et al. 2006). For each of the 34 ROIs, the volumes (expressed in mm^3) were combined across hemispheres to produce one value. We initially performed sensitivity analyses to assess left and right hemisphere volumes separately for each of the 34 R0Is (i.e., 68 regions total) and found little difference between left and right hemispheres. We thus decided to present results of the bilaterally averaged results here.

Statistical Analyses

Primary analyses consisted of 34 separate linear mixed-effects models (LMEs), one for each bilaterally averaged Desikan–Killiany GMV ROI as the dependent variable, each standardized to have zero mean and unit standard deviation (SD). The primary independent variable of interest was "number of binge drinking episodes in the prior year" ($binge_{ij}$) for the ith subject at the jth visit ($j = 1, \ldots, 5$). Because of the long tail in number of episodes (Fig. 1), $binge_{ij}$ was log transformed (after adding one to avoid taking the log of zero) and then mean centered at zero. Age was entered into the LME as 2 terms to reflect the cohort sequential aspect of the NCANDA study design. Between-subject variation in ages was captured by the baseline age of the subject across the 5 visits (age_{0i}). Within-subject change in age ($age_{d,ij}$) was captured by subtracting age_{0i} from the ith subject's age at visit j. Each of these terms ($binge_{ij}$, age_{0i}, and $age_{d,ij}$) was entered into LMEs along with their 2-way interactions. Random intercepts were included for subject and for family. Variables used in matching were also included as fixed effects to control for any residual imbalances after matching. We assessed the significance of binge drinking on GMVs by fitting the same model without $binge_{ij}$ or its interactions and using a Likelihood Ratio Test (LRT). All reported LRT P values were 2-sided and Bonferroni-corrected for 34 comparisons ($P = 0.05/34 = 0.0015$).

We next performed a second set of analyses by comparing model fits of coding binge drinking in several ways to examine the degree to which temporal proximity or "dose" (number of binge drinking episodes) was relevant for predicting differences

Table 1 Participant characteristics (% or mean) for subjects with at least one binge drinking episode during the study period (binge drinkers) versus those with no binge drinking episodes (controls) before and after matching on baseline covariates

Sex (% male)	Binge drinkers ($n = 166$) 53.0	Before matching controls ($n = 178$) 49.4	Post-matching controls ($n = 82$)* 54.9
Baseline visit age in years (SD)	16.5 (1.9)	15.0 (2.4)	15.9 (2.4)
Site			
Site A (%)	7.8	12.9	14.6
Site B (%)	10.2	7.9	8.5
Site C (%)	14.5	22.5	13.4
Site D (%)	24.7	21.9	28.0
Site E (%)	42.8	34.8	35.4
Race			
Asian (%)	7.8	5.6	9.8
Caucasian (%)	80.7	70.0	81.7
African-American	6.6	18.0	1.2
Other (%)	4.8	6.7	7.3
Socioeconomic status+ (SD)	17.0 (2.3)	16.2 (2.7)	16.9 (2.2)
Baseline ICV++ (SD)	0.1 (1.0)	−0.2 (1.0)	0.1 (0.9)

*Matching done with replacement. Number of matches of each non-binge drinking subject with a binge drinking subject: 0: $n = 96$; 1: $n = 39$; 2: $n = 23$; 3: $n = 8$; 4: $n = 7$; 5: $n = 2$; 6: $n = 2$; 7: $n = 1$. Note: multiply matched participants only appear once in this table and in analyses. No differences are significant post-matching.
+Highest level of education achieved by either parent at baseline.
++Total ICV standardized to have zero mean and unit variance.

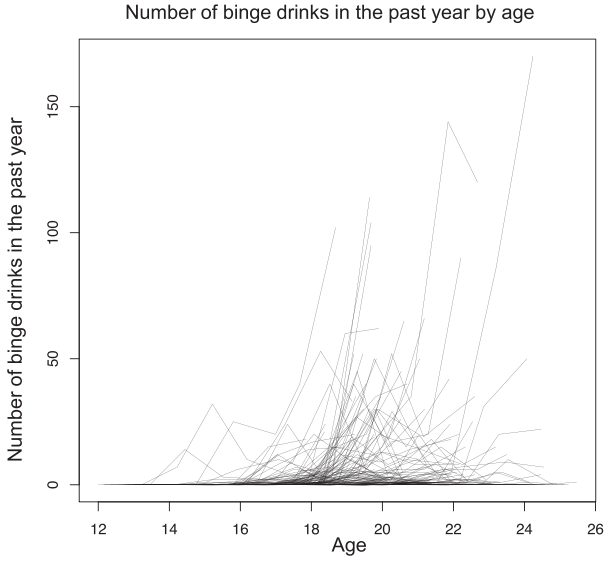

Figure 1. Number of binge drinking episodes in the prior year by age ($N = 242$).

in GMVs between binge drinkers and non-binge drinkers. Coding binge drinking episodes as an indicator (yes/no) removes any information about dose, whereas coding binge drinking episodes as a cumulative measure removes information about temporal proximity. Specifically, we fit these models: M0) a base model without any binge drinking variable; M1) number of binge drinking episodes in the prior year ($binge_{ij}$,), identical to the primary analyses, which preserves temporal proximity and dose information; M2) cumulative number of binge drinking episodes ($binge\_cum_{ij}$), equal to the log-transformed sum of the number of current and past binge drinking episodes; M3) $binge\_cat_{ij}$, equal to one if the participant had one or more binge drinking episodes in the last year and zero otherwise; M4) current or past binge drinking ($binge\_past_{ij}$), equal to one if the participant had a binge drinking episodes at the current visit or at any past visit and zero otherwise; M5) ever binge drank ($binge\_ever_i$) equal to one if the participant had at least one binge drink in any visit (including future visits) and zero otherwise; and M6) log-transformed total number of binge drinking episodes across all 5 visits ($binge\_tot_i$). These different ways of coding binge drinking were entered into separate LMEs (7 coding × 34 volumes = 238 total models) for each of the GMV's as described above for $binge_{ij}$ and the fits were compared using the Akaike Information Criterion (AIC, (Akaike 1974). All statistical analyses were conducted using R Version 3.6.3. (R Core Team 2020).

Results

Demographic characteristics of the sample at baseline ($N = 344$) by binge drinking status are presented in Table 1. After matching with replacement, the final sample consisted of 242 subjects: 166 binge drinkers with mean (SD) age 16.5 (1.9) years, 53% male, and 82 non-binge drinkers with mean age 15.9 (2.4) years, 54% male. Table 2 gives the distribution of binge drinking by age cohort for each yearly follow-up assessment. Figure 1 displays a spaghetti plot of binge drinking trajectories across all 5 yearly assessments. Information on participants' cannabis and tobacco use can be found in Supplementary Table 1.

In the first set of 34 LMEs, the LRTs of models with $binge_{ij}$ versus models without binge, 26 were significant after a Bonferroni correction. LME fixed-effect regression coefficient estimates for the main parameters of interest (along with their Wald test P values and 95% confidence intervals) as well as the overall model LRT statistics, and P values are presented in Table 3. Fixed effects including all covariates are presented in Supplementary Tables 2–6.

Spaghetti plots of trajectories and model fits for superior frontal GMV are displayed in Figure 2 (fits for the all Desikan ROIs, qualitatively similar, are shown in the Supplementary Figures 1–5). In all models, GMVs were smaller as a function

Table 2 Mean number (range, SD) of binge drinking episodes in past year by post-baseline follow-up year (Year 1 to Year 4 follow-up) by age cohort for $N = 166$ participants with at least one binge drinking episode over the NCANDA study period to date

Baseline age cohort (years)	Mean number of binge drinking episode in the past year (range, SD)			
	Year 1	Year 2	Year 3	Year 4
Cohort 1 (12–14)	1.4 ([0,25], 4.7)	2.3 ([0,32], 6.3)	2.9 ([0,40], 7.1)	8.6 ([0,102], 16.9)
Cohort 2 (15–17)	0.7 ([0,12], 1.7)	4.4 ([0,45], 8.6)	7.5 ([0,60], 12.2)	15.5 ([0,114], 23.7)
Cohort 3 (18–21)	3.7 ([0,20], 6.2)	5.9 ([0,52], 10.6)	12.7 ([0,144], 27.2)	18.1 ([0,170], 36.4)

Table 3 LME coefficients of interest and *P* values for GMV in ROIs

Desikan region	LRT* (*P* value)	log(binge drinking episodes in past year + 1)		log(binge drinking episodes in past year+1) × baseline age	
		β	*P* value	β	*P* value
Frontal lobe					
Superior frontal	59.2 (<0.001)	−0.05	<0.001	0.01	<0.001
Rostral middle frontal	36.3 (<0.001)	−0.05	<0.001	0.01	<0.001
Caudal middle frontal	70.5 (<0.001)	−0.05	<0.001	0.02	<0.001
Pars opercularis	46.5 (<0.001)	−0.03	<0.001	0.01	<0.001
Pars triangularis	33.5 (<0.001)	−0.04	<0.001	0.01	0.002
Pars orbitalis	37.6 (<0.001)	−0.05	<0.001	0.01	0.002
Lateral orbitofrontal	19.5 (<0.001)	−0.04	<0.001	0.01	0.006
Medial orbitofrontal	8.7 (0.034)	−0.03	0.006	0.01	0.129
Precentral	45.8 (<0.001)	−0.03	<0.001	0.02	<0.001
Paracentral	31.1 (<0.001)	−0.03	<0.001	0.01	<0.001
Frontal pole	18.6 (<0.001)	−0.06	<0.001	0.01	0.076
Parietal lobe					
Superior parietal	26.4 (<0.001)	−0.03	0.002	0.01	<0.001
Inferior parietal	30.0 (<0.001)	−0.04	<0.001	0.01	<0.001
Supramarginal	47.2 (<0.001)	−0.05	<0.001	0.01	<0.001
Postcentral	29.2 (<0.001)	−0.03	0.004	0.01	<0.001
Precuneus	24.6 (<0.001)	−0.03	0.001	0.01	0.002
Temporal lobe					
Superior temporal	38.6 (<0.001)	−0.04	<0.001	0.01	<0.001
Middle temporal	36.1 (<0.001)	−0.06	<0.001	0.01	0.007
Inferior temporal	37.0 (<0.001)	−0.05	<0.001	0.01	0.005
Banks of the superior temporal sulcus	26.9 (<0.001)	−0.03	<0.001	0.01	0.002
Fusiform	30.8 (<0.001)	−0.03	<0.001	0.01	0.001
Transverse temporal	12.2 (0.007)	−0.02	0.044	0.01	0.019
Entorhinal	7.6 (0.056)	−0.02	0.029	0.00	0.341
Temporal pole	14.1 (0.003)	−0.04	0.003	0.01	0.112
Parahippocampal	10.7 (0.014)	−0.01	0.0448	0.00	0.127
Occipital lobe					
Lateral occipital	27.6 (<0.001)	−0.04	<0.001	0.01	0.002
Lingual	23.2 (<0.001)	−0.03	<0.001	0.01	0.013
Cuneus	21.8 (<0.001)	−0.02	0.003	0.01	0.004
Pericalcarine	19.1 (<0.001)	0.01	0.174	0.01	0.019
Cingulate					
Rostral anterior cingulate	17.7 (0.001)	−0.02	0.042	0.01	0.003
Caudal anterior cingulate	5.8 (0.124)	−0.00	0.754	0.00	0.313
Posterior cingulate	8.5 (0.036)	−0.01	0.256	0.00	0.479
Isthmus	6.7 (0.086)	−0.01	0.062	0.00	0.146
Insula	17.4 (0.001)	−0.02	0.002	0.00	0.110

*LRT is for full model with respect to a base model with the same covariates but without binge drinking or its interactions with baseline age or change in age. Full model results including covariates are included in Supplementary Tables 2–6.
Cells shaded in gray shows significance after Bonferroni correction ($P = 0.05/34 = 0.0015$).

of both, age_{0i} and $age_{d,ij}$. In 33 of 34 LMEs, the main effects of $binge_{ij}$ were negative (20 with $P < 0.05/34$, with the remaining 14 not significantly different from zero). The 2-way interactions of $binge_{ij} \times age_{m,i}$ were positive for all models (with 12 of 34 having *P* values $< 0.05/34$), indicating attenuated association of volumes with number of binge drinking episodes in older subjects. Subsequent models including the 3-way interaction of age_{0i} and $age_{d,ij}$ and $binge_{ij}$ (not shown) did not significantly improve fits for any

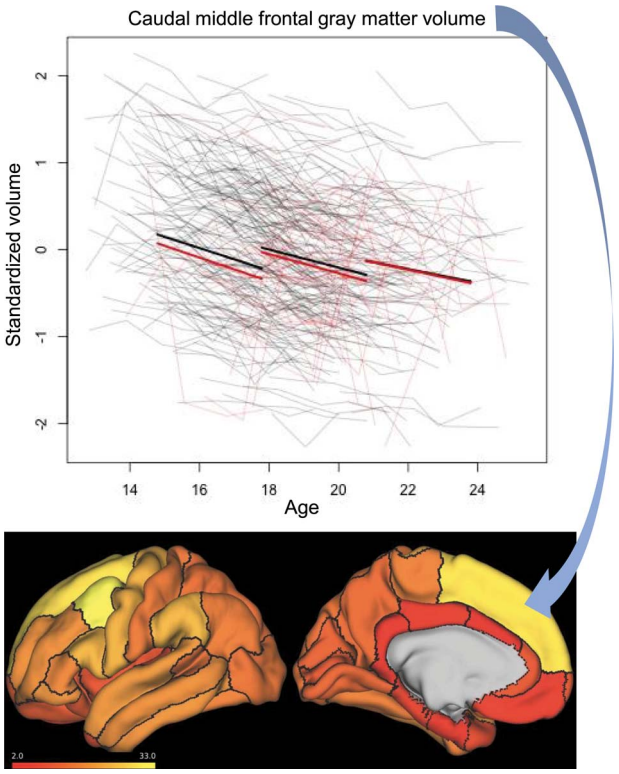

Figure 2. Left panel: Caudal middle frontal GMV trajectories for non-binge drinkers (black) and binge drinkers (red). Plots for all 34 bilaterally averaged Desikan regions, qualitatively similar, are displayed in Supplementary Figures 1–5. Heavy lines are predicted mean trajectories from LMEs for non-binge drinkers (heavy black line) and binge drinkers (heavy red line) for the 3 age cohorts (12–14 years, 15–17 years, 18–21 years at baseline). Note: baseline age was entered as a continuous variable in LMEs, the division into age cohorts is for display purposes only. Right panel: $-\log_e$(P value) from LRT for 34 bilaterally averaged Desikan regions outlined in black. The color coding indicates regions showing significant GMV declines related to binge metrics, where brighter yellow indicates stronger effects.

of the 34 regions. Sensitivity analyses examining left and right Desikan ROIs separately (also not shown) revealed no systematic differences between hemispheres.

We examined the potential differential effects of binge drinking for males and females by including an interaction of sex with $binge_{ij}$ and testing these versus models with no interaction using LRTs. None of the interactions were significant (unadjusted $Ps = 0.04–0.97$). We also examined whether TBIs, childhood trauma (Adverse Childhood Experiences Scale [ACES]), or psychopathology (Achenbach System of Empirically Based Assessment [ASEBA]) accounted for differences in binge versus non-binge drinkers in GMVs. When rerunning base models including these 3 covariates and testing the addition of binge drinking ($binge_{ij}$), LRTs gave identical results (26 of 34 Desikan GMVs significant after Bonferroni correction). Distributions of TBIs, ASEBA, and ACES are given in the Supplementary Tables. Finally, sensitivity analyses of the full sample (non-binge drinking at baseline but no exclusion for not completing all 5 visits and no matching but including the matching variables as covariates, $n = 710$) were consistent with the results based on the participants with all 5 visits.

The AIC results of the second set of LMEs are presented in Table 4. For each set of 6 models including binge drinking (M1–M6), the AIC for the base model M0 was subtracted to highlight the improvement of model fit of including binge drinking from the model with no binge drinking term: lower (here, more negative) AIC indicates better model fit than that for M0. The temporally proximal dimensional model (M1) was the best fitting for 26 of 34 regions. Of the remaining regions, 6 had M2 as the best-fitting model (though AICs for these models were close to that of M1). For the remaining 2, M3 was the best-fitting model. Besides M0, the worst-fitting models were thus M4–M6. In summary, including both "dose" and temporal proximity were conjointly informative and strongly improved upon fits of models ignoring this information for most outcomes.

Discussion

The goal of this study was to build on existing research to advance our understanding of the age- and time-dependent effects of binge drinking on adolescent brain development. Using 5 waves of longitudinal data from the NCANDA study with its cohort-sequential design, we examined the extent to which binge drinking in adolescence disturbs the development of regional GMVs. We specifically focused on binge drinking given the high rates of binge drinking among adolescents (Substance Abuse and Mental Health Services Administration 2020), preliminary evidence for the negative effects of binge drinking on the adolescent brain (Jones et al. 2018), and the limited longitudinal neuroimaging studies in this area. We found that binge drinking was associated with decrease GMVs relative to non-binge drinkers. Specifically, our results revealed greater number of binge drinking episodes in the prior year was associated with decline in 26 of 34 regions, with the strongest effects in the frontal lobe. Contrary to our hypothesis, after correction for multiple comparisons, we did not find significant effects of binge drinking in cingulate regions. Differences in methodological approaches including the careful matching procedure used in the current study and measure of binge drinking as a continuous variable might account for some of the observed differences. Further, we found the association between GMVs and binge drinking was attenuated among older participants. Finally, findings from our comparative analyses revealed that models coding binge drinking as a dimensional, temporally proximal variable better fit the data versus models ignoring this information. Taken together, these results provide evidence for a dose–response relationship of binge drinking with greater reduction in GMVs in younger than older youth and evidence for time-dependent associations, with temporally proximal number of binge drinks more predictive of reduced gray matter than cumulative or total lifetime binge drinks.

Our results showing decreased GMVs concurrent with binge drinking episodes are consistent with prior longitudinal studies on moderate to heavy drinking youth (Squeglia et al. 2014; Squeglia et al. 2015; Meda et al. 2017; Pfefferbaum et al. 2018). The association of binge drinking with smaller GMVs may be mediated by neurotoxic effects related to accelerated gray matter pruning, as suggested by Pfefferbaum et al. (2018). Alternatively, preexisting differences may account for the association of brain developmental trajectories and binge drinking. In particular, preexisting vulnerabilities in the inhibitory control system have been associated with alcohol initiation and other risk-taking behaviors among adolescents (Norman et al. 2011; Whelan et al. 2012; Wetherill et al. 2013; Cheetham et al. 2014; Heitzeg et al. 2014). To minimize the potential effect of preexisting vulnerabilities, binge and non-binge drinker participants in the current

Table 4 AIC of 6 model comparisons of coding binge drinking

Desikan region (volume)	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Frontal lobe						
Superior frontal	−53.57	−53.12	−31.06	−30.04	−10.85	−11.47
Rostral middle frontal	−30.97	−29.20	−19.90	−18.79	−5.44	−4.33
Caudal middle frontal	−64.96	−59.07	−35.32	−36.69	−14.16	−14.99
Pars opercularis	−40.80	−38.33	−23.82	−20.65	−3.19	−3.77
Pars triangularis	−27.59	−24.71	−10.92	−10.33	−1.51	−2.28
Pars orbitalis	−32.40	−31.53	−19.22	−16.89	−11.08	−12.48
Lateral orbitofrontal	−14.14	−11.57	−8.91	−4.75	−2.08	−0.30
Medial orbitofrontal	−2.19	−3.75	0.81	0.97	2.44	3.03
Precentral	−40.53	−42.86	−26.04	−23.27	−3.83	−2.42
Paracentral	−25.30	−23.97	−15.49	−13.16	−1.24	−4.85
Frontal pole	−12.95	−14.60	−3.79	−2.96	2.98	0.99
Parietal lobe						
Superior parietal	−20.52	−16.50	−8.98	−7.96	−1.94	−2.73
Inferior parietal	−24.08	−19.06	−14.59	−10.96	−2.85	−3.83
Supramarginal	−40.67	−32.90	−21.53	−18.93	−3.76	−5.90
Postcentral	−22.53	−18.73	−13.02	−10.46	−2.06	−1.45
Precuneus	−18.45	−16.14	−11.09	−9.03	−1.47	−1.58
Temporal lobe						
Superior temporal	−32.41	−29.92	−16.55	−14.72	−4.31	−3.42
Middle temporal	−29.63	−21.62	−14.12	−11.39	−2.94	−1.15
Inferior temporal	−30.99	−26.99	−13.70	−10.08	0.42	−0.45
Banks of the superior temporal sulcus	−20.96	−16.18	−17.17	−16.33	−3.57	0.59
Fusiform	−24.80	−25.03	−10.59	−9.15	0.32	−1.47
Transverse temporal	−5.89	−7.79	−5.18	−7.61	2.63	2.58
Entorhinal	−1.69	−0.43	−1.24	1.32	2.80	1.69
Temporal pole	−8.22	−4.51	−0.76	2.91	3.81	3.81
Parahippocampal	−4.78	−7.40	−4.25	−3.52	3.79	3.22
Occipital lobe						
Lateral occipital	−21.34	−17.63	−7.72	−4.83	−2.57	−4.99
Lingual	−17.30	−15.26	−7.36	−5.55	−7.22	−5.95
Cuneus	−64.96	−11.33	−4.66	−4.06	−6.19	−9.20
Pericalcarine	−13.14	−9.15	−4.36	−6.17	−3.35	−1.27
Cingulate						
Rostral anterior cingulate	−11.44	−8.70	−2.38	−0.58	0.42	−1.40
Caudal anterior cingulate	0.60	0.40	0.40	−0.03	4.20	5.70
Posterior cingulate	−3.01	−3.09	−3.62	−1.13	1.38	0.46
Isthmus	−0.80	−0.50	1.17	2.93	0.75	2.31
Insula	−11.42	−10.01	−10.58	−4.86	−3.20	−5.74

Model 1: log of number of binge drinking episodes in the prior year (df = 20). Model 2: log of cumulative number of binge drinking episodes to current year (df = 20). Model 3: equal to one if any binge drinking episodes in past year and zero otherwise (df = 20). Model 4: equal to one if any binge drinking episodes at current or any past visit and zero otherwise (df = 20). Model 5: equal to one if any binge drinking episodes ever (including future visits) and zero otherwise (df = 20). Model 6: log of total number of binge drinking episodes across all 5 visits (df = 20). All AICs are with respect to Model 0 with no binge drinking variable included (df = 17). Cells shaded in gray are the lowest AICs for that particular region.

study were matched on various sociodemographic variables and total brain volume. Moreover, that temporal proximity of binge drinking improved model performance suggests the observed associations are not purely due to preexisting differences. Evidence from neuropsychological studies examining the effects of binge drinking provides support to the potential negative implications of the accelerated declines in GMV observed in this study and a potential for associated cognitive sequelae (Carbia et al. 2018; Lees et al. 2019). We found the strongest associations between effects of binge drinking and accelerated decline of GMV in frontal-executive control regions and in temporal lobe regions involved in memory processes. In line with our findings, deficits in various executive functioning domains have been observed among binge drinking adolescents and young adults (Goudriaan et al. 2007; Parada et al. 2012; Mota et al. 2013; Gil-Hernandez and Garcia-Moreno 2016; Gil-Hernandez et al. 2017). Similarly, studies have found binge drinking to be associated with memory deficits (Parada et al. 2011; Nguyen-Louie et al. 2016; Carbia et al. 2017).

Although the neurotoxic effects of alcohol on the developing brain have been widely reported, our study furthered prior findings by identifying a differential association of GMV with respect to age cohort. While an accelerated decline in GMVs among binge drinkers was observed across all age cohorts in contrast to their non-binge drinking peers, we found the association with binge drinking was accelerated in younger drinkers and attenuated in older youth. This attenuation of effects in older participants can be clearly observed in the model fits presented in Figure 2. Our results reinforce the increase risk of negative outcomes associated with early initiation of alcohol and in particular binge drinking.

This study has several strengths, including 5 yearly longitudinal assessments in a cohort sequential design, enabling ascertainment of age cohort and temporal and dose associations between binge drinking and brain development. Moreover, the large sample size allowed for matching on key sociodemographic factors and baseline (pre-binge drinking) total brain volume while maintaining adequate statistical power to estimate effects and test for associations.

Despite these strengths, our findings should be interpreted in light of limitations. Our study did not examine behavioral data to capture the longitudinal association between binge drinking episodes and cognition, nor how any effects of binge drinking on the brain may mediate this relationship. Additionally, as with all observational studies, there may be confounders we did not include in the analyses that bias observed associations between binge drinking and gray matter trajectories, including unobserved differences in confounding effects across age cohorts.

Site differences in GMVs were not completely accounted for by controlling for age, sex, parental education, and race. We thus included site in models along with these sociodemographic factors. Part of these site differences may have been due to scanner manufacturer (site A and D had a Siemens scanner and the others have a GE scanner), with Siemens scanners having consistently lower GMV estimates. Note, since each site has one scanner, controlling for site effects in analyses simultaneously controls for scanner effects.

Finally, there was insufficient within-subject variation among binge drinkers (e.g., onset of binge drinking followed by cessation) to enable direct assessment of the impact of abstinence on the potential for recovery of GMVs. However, the impact of abstinence on developmental trajectories will likely become estimable as the NCANDA study collects more annual follow-up assessments.

In summary, we found that binge drinking during adolescence resulted in accelerated decrease in GMVs above and beyond the expected decreases from the normal maturational process in youth. This decrease was greater in younger bingers and largely attenuated in later adolescence. Further, our novel findings that cortical GMV decreases were greater in closer proximity to reported drinking episodes in a dose–response manner suggests a causal effect and raises the possibility that normal growth trajectories may be reinstated with alcohol abstinence. Given the implications of our findings, future studies with additional time points and increased temporal variation in binge drinking patterns (including prolonged abstinence) will be needed to examine any potential recovery effects.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

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Notes

Data were collected from January 13, 2013 to January 15, 2019 study and were based on the formal locked data releases NCANDA_PUBLIC_4Y_REDCAP_V02* and NCANDA_PUBLIC_4Y_STRUCTURAL_V01**, which are distributed to the public according to the NCANDA Data Distribution agreement***.

* Pohl KM, Sullivan EV, Podhajsky S, Baker FC, Brown SA, Clark DB, Colrain IM, Goldston D, Nagel BJ, Nooner KB, Tapert SF, Pfefferbaum A. The NCANDA_PUBLIC_4Y_REDCAP_V02 Data Release of the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA). Sage Bionetworks Synapse. https://dx.doi.org/10.7303/syn24226662.

** Pohl KM, Sullivan EV, Pfefferbaum A. The NCANDA_PUBLIC_4Y_STRUCTURAL_V01 Data Release of the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA). Sage Bionetworks Synapse. https://dx.doi.org/10.7303/syn22216457.

*** https://www.niaaa.nih.gov/ncanda-data-distribution-agreement.

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