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RESEARCH REPORT

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Alcohol use and brain morphology in adolescence: A longitudinal study in three different cohorts

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Abstract

Alcohol consumption is commonly initiated during adolescence, but the effects on human brain development remain unknown. In this multisite study, we investigated the longitudinal associations of adolescent alcohol use and brain morphology. Three longitudinal cohorts in the Netherlands (BrainScale $n = 200$, BrainTime $n = 239$ and a subsample of the Generation R study $n = 318$) of typically developing participants aged between 8 and 29 years were included. Adolescent alcohol use was self-reported. Longitudinal neuroimaging data were collected for at least two time points. Processing pipelines and statistical analyses were harmonized across cohorts. Main outcomes were global and regional brain volumes, which were a priori selected. Linear mixed effect models were used to test main effects of alcohol use and interaction effects of alcohol use with age in each cohort separately. Alcohol use was associated with adolescent's brain morphology showing accelerated decrease in grey matter volumes, in particular in the frontal and cingulate cortex volumes, and decelerated increase in white matter volumes. No dose–response association was observed. The findings were most prominent and consistent in the older cohorts (BrainScale and BrainTime). In summary, this longitudinal study demonstrated differences in neurodevelopmental trajectories of grey and white matter volume in adolescents who consume alcohol compared with non-users. These findings highlight the importance to further understand underlying neurobiological mechanisms when adolescents initiate alcohol consumption. Therefore, further studies need to determine to what extent this

Abbreviations: FOV, field of view; MRI, magnetic resonance imaging; NTR, Netherlands Twin Registry; TE, echo time; TI, inversion time; TR, repetition time.

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reflects the causal nature of this association, as this longitudinal observational study does not allow for causal inference.

KEYWORDS
adolescent alcohol use, adolescent development, brain, cortex, neuroimaging

1 | INTRODUCTION

Alcohol consumption is commonly initiated during adolescence, which is defined as the developmental period during which children transition to adulthood and develop personal social goals. Even though the law does not allow alcohol consumption/purchase below age 18 years, in the Netherlands, last-month prevalence of alcohol use in adolescents aged 12–16 years was 42.7% (de Looze et al., 2017). In Europe, the average last-month prevalence of adolescent alcohol use is 48%, varying from 9% to 68% (ESPAD-Group, 2016). This high prevalence of alcohol use among adolescents and young adults is worrying as the brain undergoes significant structural and functional changes in this specific developmental period. Generally, grey matter volume decreases after puberty, which has been linked to elimination of weak synaptic connections (Huttenlocher & Dabholkar, 1997) or to increased myelination in the lower layers of the cortex (Gogtay & Thompson, 2010). Also, white matter fibres continue to develop to allow more efficient and rapid communication between brain regions (Giedd, 2004; Lebel & Beaulieu, 2011). Healthy adolescent brain development is essential for optimal neurocognitive performance, with deviations in maturational trajectories (e.g. changes in brain volume, cortical thickness and myelination) linked to problems with cognitive, emotional and social functioning (Bos et al., 2018; Casey et al., 2008; Nagy et al., 2004).

Although animal studies have demonstrated that alcohol use in adolescence induces neurodegeneration (Crews et al., 2000, 2004; Pascual et al., 2007) and inhibition of neurogenesis (Crews et al., 2006), it remains to be determined to what extent alcohol use in human adolescents relates to changes in developmental brain trajectories. Preliminary longitudinal studies demonstrated alterations in adolescent brain development due to excessive exposure to alcohol could have functional consequences throughout life (reviewed in Squeglia, Jacobus, & Tapert, 2014). Indeed, prospective studies with long follow-up (>8 years) showed that binge drinking or excessive drinking (as well as alcohol withdrawal and hangover symptoms) has been linked to poor performance on visuospatial and memory abilities, and attention problems in adolescents and young adults (Hanson et al., 2011; Tapert et al., 2002). Further, several studies suggest that adolescents with alcohol use disorder or who frequently engage in binge drinking show reduced grey matter volumes, typically in frontal, parietal and temporal cortices, limbic regions (e.g. hippocampus) and the cerebellum (Ewing et al., 2014; Lisdahl et al., 2013; Medina et al., 2008; Nagel et al., 2005; Pfefferbaum et al., 2018; Squeglia, Rinker, et al., 2014; Sullivan et al., 2019). Interestingly, recent reviews of longitudinal studies show that some of these regional decreases in grey matter predate alcohol use (e.g. in the anterior cingulate and prefrontal cortex), while there are also regionally specific alterations in grey matter development that are consequences of alcohol use (e.g. in frontal, temporal and subcortical regions) (Spear, 2018; Squeglia & Cservenka, 2017; Squeglia & Gray, 2016). However, the above-mentioned studies have mostly focused on binge drinking, excessive alcohol use or adolescents with a (history of) alcohol use disorder and used relatively small sample sizes (often $n < 100$), although most adolescents in the general population are light-to-moderate drinkers. Limited information is available on whether a smaller amount of alcohol drinking is also associated with

changes in brain morphology. We used three relatively large independent representative cohorts of typically developing children, adolescents and young adults to investigate associations of (light-to-moderate) adolescent alcohol use and brain morphology using longitudinal assessments. Based on the above-mentioned literature, we considered global volumes, including total brain volume, total grey and white matter, as well as regional volumes, including frontal, cingulate and subcortical grey matter volumes as main outcomes. We hypothesized that adolescent alcohol use will be associated with pre-existing differences in brain volumes as well as with changes over time in grey and white matter development.

2 | MATERIALS AND METHODS

2.1 | Setting and design

The current study used data from three independent cohorts in the Netherlands: BrainScale $n = 200$, BrainTime $n = 239$ and a selected subsample [based on the availability of two magnetic resonance imaging (MRI) scans] of the Generation R study $n = 318$. All studies were approved by the local Medical Ethics Committee or Central Committee on Research Involving Human Subjects of the Netherlands, and all studies were performed in accordance with the Declaration of Helsinki. Written informed consent and assent was obtained from all participants (i.e. adolescents and their parents in case of minors).

2.2 | BrainScale

Brain Scale is an acronym for 'Brain Structure and Cognition: an Adolescent Longitudinal Twin Study into the Genetic Etiology of Individual Differences' (van Soelen et al., 2012) and is a collaboration between UMC Utrecht and the Netherlands Twin Registry (NTR) (Ligthart et al., 2019). A subcohort of 330 children from 112 families participating in the NTR was invited for neuroimaging, cognitive, hormonal and behavioural assessments. Families from birth cohorts 1995–1996 were selected based on zygosity of the twins, and whether the twins had an older brother or sister close in age (i.e. aged less than 14 years).

2.3 | BrainTime

The BrainTime study is a large longitudinal research project of normative brain development using an accelerated design, conducted at Leiden University, The Netherlands (Peters & Crone, 2017). Participants (8–25 years old at time point 1) were recruited through local schools and advertisements ($N = 299$). All participants were right-handed, reported normal or corrected-to-normal vision, and no history of past or current neurological or psychiatric disorders.

2.4 | The Generation Study

The Generation R Study is a population-based birth cohort in Rotterdam, the Netherlands (Kooijman et al., 2016). All participants were born between April 2002 and January 2006 in Rotterdam, and follow-up is ongoing. In the current study, a small subgroup of children who underwent the neuroimaging assessment twice was included. Neuroimaging data collection at 13 years at the time of the analyses was still ongoing, so we included children that were a first data set before a temporary 'datalock' which consisted children with MRI scans collected up to September 2017.

Extended information on the design, setting, inclusion and exclusion criteria are found in the Text S1.

2.5 | Adolescent alcohol use

All three cohorts collected information on adolescent alcohol use with questionnaires (Table S1). These questionnaires addressed whether participants ever drank alcohol (yes/no) and if so, whether the participants were ever drunk (ever drunk/never drunk). Additionally, information on frequency of alcohol consumption was collected in all three cohorts, with questions in BrainScale and the Generation R Study also distinguishing between weekday use and weekend use. In BrainScale, at the second and third measurement children were additionally asked to report on the average amount of alcohol on weekdays and weekend days (7-point scale ranging from <1 to >20 glasses) and on the frequency of drinking alcohol (7-point scale ranging from less than once a year to daily). In the BrainTime project, participants filled out a questionnaire in which they indicated how much they drink on average when they drink, how much they drank last month and total lifetime alcohol use (Ames et al., 2007). Past month alcohol use in number of glasses was measured using a 10-point scale (0, 1–2, 3–4, 5–6, 7–10, 11–15, 16–20, 21–30, 31–50 & >50). To create a scale variable, the ordinal data on quantity of alcohol use were converted by calculating the mean of the answer; thus, the scales were recoded as the average of the two numbers, that is, for 31–50, 40.5 was used ... (and for >50, 51 was used) (Peters et al., 2017). In the Generation R Study, the teenagers (age ± 13 years) reported about their alcohol use, whether they drank more than three glasses

at one occasion, and what their average number of alcoholic drinks was during week or weekend days on a 4-point scale ranging from less than one glass to more than three glasses. All participants were asked at what age they consumed alcohol for the first time.

3 | NEUROIMAGING

3.1 | Image acquisition

In all cohorts, to minimize head motion, participants were familiarized with the scanner environment using a mock scanner, their heads were fixated using foam pillows, and the importance of lying still was emphasized to participants in between scan sequences. Participants with an incidental structural brain abnormality were excluded from the analyses.

3.2 | BrainScale

In the BrainScale cohort, all brain images were collected on a 1.5 Tesla Philips Achieva Scanner (Philips, Best, The Netherlands) using the same protocol at all time points (Brouwer et al., 2012). The scanning protocol included a 3D whole head T1-weighted scan [Spoiled Gradient Echo, echo time (TE) = 4.6 ms, repetition time (TR) = 30 ms, flip angle 30°, 160–180 contiguous coronal slices of 1.2 mm, in-plane resolution 1×1 mm^2 & acquisition matrix 256×256].

3.3 | BrainTime

In the BrainTime study, all images were collected on a Philips Achieva TX 3.0T scanner (Philips, Best, The Netherlands), while using a standard whole-head coil. A high-resolution 3D T1 anatomical scan was acquired with the following sequence parameters: TR = 9.76 ms, TE = 4.59 ms, flip angle = 8°, 140 slices, voxel size = $0.875 \times 0.875 \times 1.2$ mm, field of view (FOV) = $224 \times 177 \times 168$ mm.

3.4 | The Generation R Study

An overview of the imaging procedure in the Generation R cohort, sequences, and quality assessment has been described previously (White, Muetzel, et al., 2018). All images in the Generation R cohort were acquired on a 3 Tesla GE MR750W Discovery scanner (GE Healthcare, Milwaukee, WI, USA) using an eight-channel head coil. After a localizer, T1-weighted structural images were acquired with an inversion recovery-prepared fast spoiled gradient recalled sequence. The following sequence parameters were used with the GE option BRAVO: TR = 8.77 ms, TE = 3.4 ms, inversion time (TI) = 600 ms, Flip Angle = 10°, FOV = 220 mm × 220 mm, Acquisition Matrix = 220 × 220, slice thickness = 1 mm, number of slices = 230, voxel size = 1 mm × 1 mm × 1 mm, ARC Acceleration = 2.

3.5 | Structural image processing

Structural images were processed through the FreeSurfer analysis suite, version 6.0 (Fischl, 2012). Freesurfer morphometry has demonstrated good test–retest reliability across scanner manufacturers and field strengths (Han et al., 2006; Reuter et al., 2012). In summary, non-brain tissue was removed, voxel intensities were normalized for B1 inhomogeneity, whole-brain tissue segmentation was performed, and a surface-based model of the cortex was reconstructed. Global metrics of volume (i.e. total brain volume, total cortical grey matter volume, white matter volume and total ventricular volume) and subcortical grey matter measures were extracted.

3.6 | Quality assurance

Freesurfer output was visually inspected in all cohorts. In brief, visual inspection comprises inspection of the white and pial surface representations for all subjects for accuracy against the brain image at a number of slices in different plains, that is, axial, coronal and sagittal. Also, movement or other artefacts were identified. Image data sets not suitable for analysis were excluded from the final samples. All cohorts inspected the data visually, which was agreed upon harmonization. However, the procedure of quality assurance was slightly different in each cohort. In the BrainScale cohort, the data were checked by using visual and outlier inspection. For BrainTime, visual inspection was also performed and aided by an automated quality tool, Qoala-T (Klapwijk et al., 2019). In the Generation R cohort, Freesurfer output data were visually inspected and an automated tool was used to verify the visually inspected data (White, Jansen, et al., 2018). None of the cohorts attempted to fix the scans with suboptimal segmentation (e.g. the use of manual control points). All children with poor scanning quality (mostly due to motion) were excluded from the analyses. In the Brainscale study, 5% (at T3) to 10% (at T1) of the scanned subjects had bad scanning quality,

In BrainTime 1% (at T3) to 10% had poor image quality and in the Generation R Study, approximately 20% of the subjects had poor image quality.

3.7 | Statistical analysis

Statistical analyses were performed in the same way in all three cohorts separately, that is, data were not pooled or meta-analysed because of the heterogeneity of populations, designs, MRI scanners and measurements in the three cohorts. First, data were inspected and transformed or recoded if needed. The Generation R cohort had data on two time points, whereas the BrainTime and BrainScale study had neuroimaging data at three time points available (see Table 1). Based on the number and frequency of adolescents that drank alcohol and comparability of the data across the three cohorts, we used a dichotomized approach for alcohol use (ever drinking vs. never drinking) as the independent variable. Additionally, we categorized alcohol use in three groups: intoxication (being drunk), versus ever drinking (without ever being drunk) versus never drinkers. To model the shape of individual growth curves, we used linear mixed model analyses (also termed 'random effects', 'multilevel modelling' or hierarchical linear model analyses) to test the associations of adolescent alcohol use (ever vs. never) and brain morphological outcomes. This method expands on multiple regression analyses and is suited for longitudinal data, because it considers the repeated-nature of the data, and controls for the dependency in measures within individuals (i.e. nested data). Change scores were not calculated, because linear mixed models consider all data including individual differences in intercepts. For formula used, see Text S2.

First, global metrics (i.e. total brain volume, total white and grey matter, and cerebellar volume) were used as outcomes, as well as cortical volumes of frontal and cingulate brain regions that were a priori selected based on the existing literature (reviewed in Spear, 2018; Squeglia & Cservenka, 2017; Squeglia & Gray, 2016). In addition, subcortical grey matter structures part of the mesolimbic (reward) system (caudate, putamen, nucleus accumbens, amygdala and hippocampus) were analysed. Left and right hemispheres were separately analysed. In the same way, the association of adolescent drunkenness [categories: intoxication (being drunk) vs. ever drinking vs. never drinking] and brain morphological outcomes were assessed. As an additional sensitivity analyses, both

TABLE 1 Descriptive statistics of the study populations in the three cohorts

	BrainScale[a]			BrainTime			The Generation R Study		
	T1	T2	T3	T1	T2	T3	T1	T2	T3
N	161	157	200	239	228	215	318	318	—
Age mean (SD)	9.9 (1.3)	13.0 (1.4)	18.0 (1.4)	14.2 (3.6)	16.4 (3.6)	18.2 (3.8)	10.5 (0.7)	13.5 (0.2)	—
Age range	9.0–15.0	11.7–18.0	16.8–22.9	8.0–24.6	9.9–26.6	11.9–28.7	9.5–12.0	12.7–14.5	—
Sex, % (*n*)									
Male	44.1 (71)	48.4 (76)	48.0 (96)	46.0 (110)	47.8 (109)	46.0 (99)	49.4 (157)	49.4 (157)	—
Female	55.9 (90)	51.6 (81)	52.0 (104)	54.0 (129)	52.2 (119)	54.0 (116)	50.6 (161)	50.6 (161)	—
IQ mean (SD)	103.9 (13.9)	101.9 (14.8)	104.2 (13.1)	109.4 (10.5)	108.2 (10.2)	—	103.1 (14.7)[b]	—	—
Ever alcohol (%, *n*)									
Yes	0 (0)	55.4 (87)	97.5 (195)	41.4 (99)	61.8 (141)	75.3 (162)	—	14.8 (47)	—
No	100 (156)	44.6 (70)	2.5 (5)	58.6 (140)	38.2 (87)	24.7 (53)		85.2 (271)	—
Ever drunk, % (*n*)									
Yes	0 (0)	10.8 (17)[c]	81.0 (162)[c]	17.6 (42) [c]	43.9 (100)[c]	58.1 (125)	—	1.6 (5)	—
No	100 (156)	72.6 (114)	18.0 (36)	76.6 (183)	55.7 (127)	41.9 (90)	—	98.4 (313)	—
Mean age of first drink (SD)			14.9 (1.2)			14.5 (1.8)	—	11.9 (1.6)	—

Note: In the Generation R cohort, information on alcohol use in participants was collected at the 13 years assessment.

Abbreviation: SD, standard deviation.

[a]In the BrainScale study, the number of subjects at T3 is higher than the number of subjects at T2, because at T2 children more children had braces.

[b]Intelligence in Generation was collected at the age of 6 years of age (which is prior to the neuroimaging assessment at T1).

[c]Some percentages do not count up to 100% due to a small number of missing data.

in BrainScale and BrainTime, categories of frequency were used as predictors to assess a dose–response association with the outcomes. In Generation R, this was not possible, as there was little variation in the frequency of alcohol use. All models included age (repeated) and sex of the participants. To keep the models as similar as possible across cohorts, no other covariates were included, except for BrainScale in which an additional random factor was included to account for family relations. We also provided the results with an additional adjustment for ICV (Table S5).

BrainScale, BrainTime and the Generation R Study used different instruments to collect sociodemographic information, requiring different models for each cohort, and this would complicate cross-cohort comparison. The Generation R cohort had data on two time points, whereas the BrainTime and BrainScale study had neuroimaging data on three time points available (see Table 1). Because of this, we did not investigate non-linear associations that would need data on more time points. In addition, children with only one measurement were not included in the analyses to retain the longitudinal design.

A false discovery rate (FDR) multiple comparisons correction (Benjamini–Hochberg procedure) was applied for the three main outcome domains (1) global metrics, (2) frontal and cingulate cortical metrics, and (3) subcortical grey matter metrics.

3.8 | Sensitivity analyses

To compare the results of the cohorts with older participants (BrainScale and BrainTime) with the results of the cohort with younger participants (the Generation R Study), we reran the same models with children in the age range 12 and 16 years in the two cohorts with older participants (BrainScale and BrainTime).

3.9 | Code or software

All sites used R (Rflow/RStudio GUI) including the nlme-package for the longitudinal mixed effects analyses and other packages for statistics testing (e.g. fdrtool) and visualization (e.g. ggplot2) of the results.

4 | RESULTS

4.1 | Descriptive statistics

Table 1 shows the descriptive statistics of the study population of participants with alcohol use data and neuroimaging outcomes. The BrainScale cohort had MRI data (that passed quality assurance) on three time points in 157 to 200 participants aged 9.9 to 18 years on average. Males and females were roughly evenly distributed in the sample. BrainTime also had MRI data on three time points of 215 to 239 participants with a mean age of 14.2 to 18.2 years with an even distribution of males and females in the sample. The Generation Study had data on two points in 318 participants with a mean age range of 10.5 to 13.6. Boys and girls were approximately even distributed. In the supporting information, we provide the average volumes of global, cortical and subcortical per cohort at each time point (Table S2).

4.2 | Alcohol use

For adolescent alcohol use in each cohort, Table 1 shows the number of participants with lifetime alcohol use. In BrainScale at T1 (mean age 9.9 years, range 9–15 years), none of the participants consumed alcohol, whereas at the last assessment, almost all children drank alcohol at least occasionally, with mean age of the first drink 14.9 years. In BrainTime at T1 (mean age 14.2 years, range 8–24.6), 41.4% of the participants had drank alcohol, and at T3 (mean age 18.2 years, range 11.9–28.7 years), 75.3% of the participants had drank alcohol; the average age of the first drink was 14.5 years. In Generation R, the proportion of alcohol drinking participants was lower; 21.2% of the participants had drunk alcohol with a mean starting age of 11.6 years.

In addition, the three cohorts also collected information about how much alcohol participants drank. In the Brainscale cohort, at the second assessment, about half of the cohort had never drank alcohol, whereas 9% reported regular use (on average 3.8 glasses per day, ranging from 1 to 20, consumed on weekend days). At the third assessment, 14% of subjects reported alcohol use on week days (on average 2.8 glasses, ranging from 1 to 10) and 82% reported alcohol use on weekend days (on average 6.2 glasses, ranging from 1 to 21 glasses). In the BrainTime cohort, participants on average drank 11.35 glasses of alcohol (*SD* 11.9 with a median 3–4 glasses) over a period of the last 30 days at the first assessment, 15.03 glasses of alcohol (*SD* 15.7 with a median 7–10 glasses) at the second assessment and 16.6 glasses of alcohol (*SD* 16.4 with a median of 7–10 glasses) at the third assessment. In the Generation R cohort, almost all children on average drank less than one glass on week or weekend days (99.9% and 93.8%, respectively).

4.3 | Association of adolescent alcohol use and global brain volumes

First, we examined the associations of alcohol use (ever/never) and global brain volumes (Table 2). Effect estimates represent the main effect and interaction effect estimates (interaction of alcohol*age) with standard errors and (corrected) p values. The results show that adolescent alcohol use was associated with accelerated decreases in global brain volumes (interaction effects). In the BrainScale sample, adolescent alcohol use was associated with an accelerated decrease in total grey matter. In BrainTime, adolescent alcohol use was associated with an accelerated decrease in total brain volume and ventricular volume. White matter trajectories in alcohol using and non-using participants were slightly different: alcohol-using participants show a decelerated increase in white matter, in particular in the BrainScale cohort as compared with non-using participants (see plots in Figure S1). In the Generation R cohort, the effect estimates of alcohol use (with age) and total grey and white matter (and corpus callosum) were negative, but the associations did not reach significance.

4.4 | Association of adolescent alcohol use and regional cortical volumes

Next, we tested the associations between adolescent alcohol use and pre-defined regional cortical volumes. Figure 1 shows main and interaction effect estimates of the associations of adolescent alcohol use and a priori selected regional cortical volumes. In the BrainScale cohort (yellow coloured regions in Figure 1a), adolescent alcohol use was associated with accelerated decreases (negative interaction effect of alcohol with age) in the bilateral frontal superior, rostral middle frontal and lateral orbitofrontal cortex. In the BrainTime cohort (green coloured regions in Figure 1a), adolescent alcohol use was related with accelerated decrease of the caudal anterior cingulate cortex, but an accelerated increase in the isthmus cingulate cortex. Interestingly, in both BrainScale and BrainTime, adolescent alcohol use was associated with an accelerated decrease in the caudal middle frontal region (blue coloured regions in Figure 1a). In the Generation R cohort, adolescent alcohol use was related to an increase in the left caudal anterior cingulate, but this association did not survive the correction for multiple testing (Figure 1b). In addition, Figure 1b shows that there are several associations of adolescent alcohol use and volumes of the frontal cortex (main effects), suggesting larger frontal volumes in adolescent alcohol users. As an example, Figure 1c (plots) additionally shows the full distribution of data in the left superior frontal region across the two alcohol use categories (ever vs. never) and time points in the three cohorts. All exact effect estimates are shown in Table S3.

4.5 | Association of adolescent alcohol use and subcortical volumes

Finally, alcohol × age interactions were examined for subcortical volumes. Figure 2 shows that adolescent alcohol use was associated with accelerated decreases or less prominent increase in amygdala, (bilateral) hippocampus and caudal volumes. Again, the results were consistent across BrainTime and BrainScale. No associations were observed between adolescent alcohol use and subcortical grey matter structures in the Generation R cohort. All exact effect estimates are shown in Table S4.

4.6 | Intoxication and dose–response analyses

A remaining question concerned whether the observed alcohol-brain associations were dose-dependent (Figure 3). Figure 3 shows the results of intoxication (being drunk) versus ever drinking versus never drinking, respectively in relation to the brain morphological outcomes. When comparing cortical volumes of participants who were ever intoxicated versus participant who never drank alcohol or were never drunk (not intoxicated, but used alcohol), we observed that intoxication was associated with smaller volumes in several frontal and cingulate cortices. However, no clear dose response associations between the number of glasses of alcohol used and differences or changes in brain volumetric measures were observed. In order to examine whether the associations were not only driven by the young adults, analyses were restricted to children in the age range 12 and 16 years. These supplemental analyses showed similar results (data not shown).

5 | DISCUSSION

In general, our findings indicate that adolescents who use alcohol showed structural brain differences in brain volumes (in a priori selected regions) and accelerated decrease in brain volumes over time relative to adolescents who have not used alcohol. These associations were

TABLE 2 The association of adolescent alcohol use and global brain volumes (main and interaction effects estimates)

	BrainScale			BrainTime			The Generation R Study		
Global brain volumes	**Estimate (SE)**	***P* value**	***P* (FDR corrected)**	**Estimate (SE)**	***P* value**	***P* (FDR corrected)**	**Estimate (SE)**	***P* value**	***P* (FDR corrected)**
Main effect estimates									
Intracranial volume	−1904.6 (26,313.2)	0.94	0.94	165,108.2 (20,258.4)	<0.01	<0.01	−31,529.3 (36218.7)	0.38	0.64
Grey matter	54,759.1 (11,281.0)	<0.01	<0.01	5004.8 (8690.3)	0.56	0.56	−14,103.4 (14,701.9)	0.34	0.64
White matter	36,716.7 (9174.2)	<0.01	<0.01	41,119.6 (7252.9)	<0.01	<0.01	1174.0 (9598.5)	0.90	0.90
Corpus callosum	430.4 (93.7)	<0.01	<0.01	821.9 (148.0)	<0.01	<0.01	49.7 (116.6)	0.67	0.84
Ventricular volume	−563.3 (801.2)	0.48	0.60	1573.6 (619.9)	0.01	0.01	1251.3 (1266.5)	0.32	0.64
Interaction effect estimates									
Intracranial volume	120.5 (2054.4)	0.95	0.95	−10,814.6 (1364.1)	<0.01	<0.01	1194.3 (2526.5)	0.64	0.64
Grey matter	−4091.6 (880.8)	<0.01	<0.01	−1011.1 (585.2)	0.08	0.08	−515.3 (974.4)	0.60	0.64
White matter	−2998.3 (716.3)	<0.01	<0.01	−2729.2 (488.4)	<0.01	<0.01	−743.9 (542.6)	0.17	0.64
Corpus callosum	−33.6 (7.3)	<0.01	<0.01	−53.5 (10.0)	<0.01	<0.01	−7.0 (7.7)	0.36	0.64
Ventricular volume	41.2 (62.6)	0.51	0.64	−97.1 (41.7)	0.02	0.03	61.4 (77.5)	0.43	0.64

Note: Linear mixed models were used to test the associations of adolescent alcohol use and repeated brain morphological outcomes. Effect estimates represent the main effect, that is, the difference in volume (intercept, in mm^3) in the alcohol-using participants versus non-users (reference). Effect estimates represent the interaction effect, that is, the increase or decrease in volume over time (slope, in mm^3/year) in the alcohol-using participants versus non-users (reference). All models were adjusted for age and sex.

Abbreviation: FDR, false discovery rate.

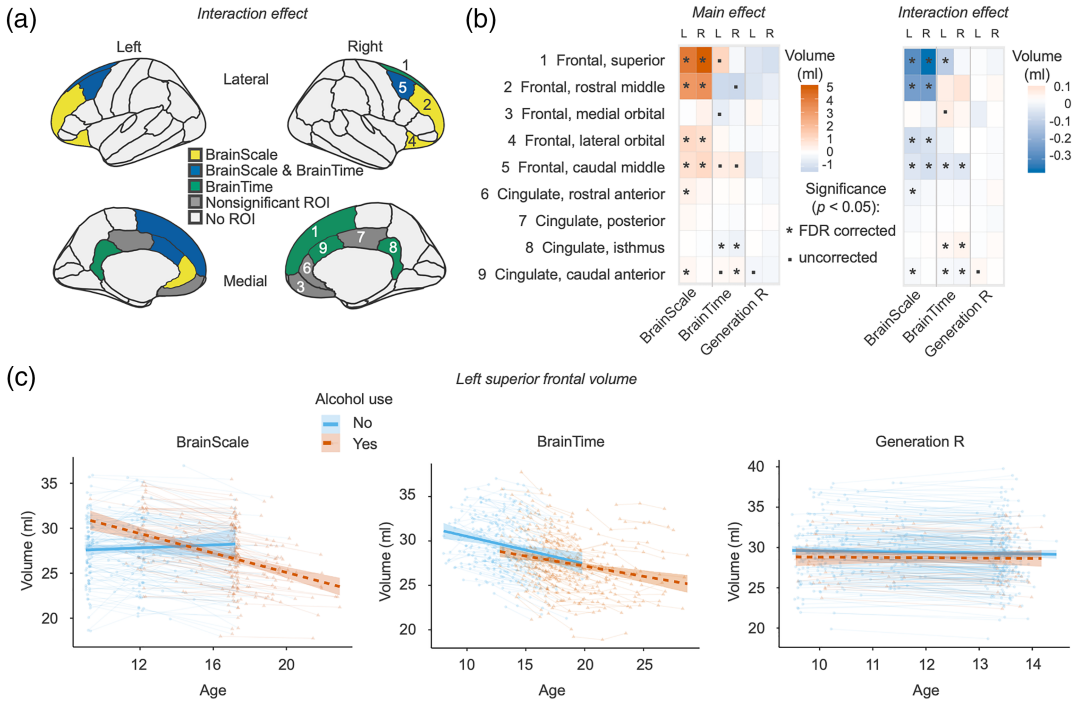

FIGURE 1 The association of adolescent alcohol use and cortical brain volumes (main and interaction effects) in the BrainScale, BrainTime and the Generation R Study. All volumes were converted from mm^3 to ml. Panel (a) shows the cortical brain regions that were found to be associated with the interaction effects in the three cohorts. Panel (b) shows the direction of the associations of adolescent alcohol use and cortical brain volumes found in the three cohorts in two correlograms (one for the main effects and one for the interaction effects). The specific effect estimates, uncorrected and FDR-corrected *p* values of panel (b) can be found in Table S3. Panel (c) shows the individual subject data for the left superior frontal volume in each cohort (never drinking vs. ever drinking). FDR, false discovery rate

found in both global (e.g. total grey matter volume), and regional volumes, but were most consistent in frontal and cingulate cortices and subcortical structures (i.e. amygdala, caudate and hippocampus) previously found to be involved in reward, memory and learning (Reynolds & Fletcher-Janzen, 2009). Also, in our study, intoxication (ever drunk) was associated with accelerated decrease in frontal and cingulate cortices. In addition, adolescent alcohol use was associated with a decelerated increase in white matter volume. In the three cohorts, there was no clear evidence for a dose–response association. The findings were most prominent and consistent in the older cohorts (BrainScale age range: 9.0–22.9 and BrainTime age range: 8.0–28.7), also when restricting the analyses to 12–16 years old participants. We did not observe any associations in the youngest cohort (the Generation R cohort age range: 9.5–14.5).

These findings are of great public health interest. Our results provide initial indications that adolescent alcohol use, even when drinking light-to-moderately (as compared with non-drinking), might be related to altered neurodevelopmental trajectories. Any alcohol use is associated with accelerated grey matter reductions or less increase in both global and regional brain volumes in two of the three samples. We did not observe this relation in a large group of younger adolescents who just starting drinking alcohol in small quantities (no regular alcohol use). This could be due to the younger age of the children, having less time points (thus a smaller age range of data collection) and the fact the children have not been using alcohol regularly or in large quantities. It has to be determined in future studies if incidental drinking at a young age indeed does not directly have an effect on brain volumes on the long-term. Our results indicate that continued use later in adolescence with a higher drinking frequency (i.e. intoxication) relate to accelerated decreases in cortical volumes too. However, it remains difficult to determine whether the observed associations are indeed directly induced by alcohol use. Alternative explanations, such as subtle pre-existing differences in neurodevelopmental trajectories before drinking onset cannot be ruled out. In addition, using our approach of similar statistical models in all cohorts, we were not able to correct for other confounders. For example, we did not adjust for socio-economic status. In other words, causal inference from these findings remains complicated because alcohol use is intertwined with other clinical, social and cognitive processes and no random allocation

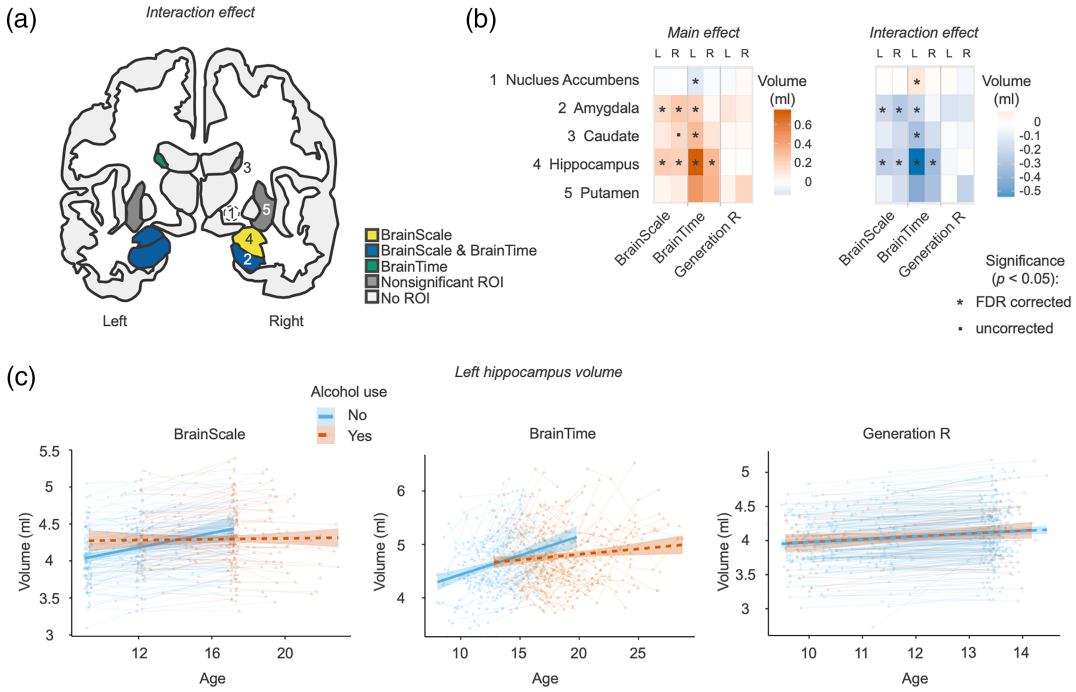

FIGURE 2 The association of adolescent alcohol use and subcortical brain volumes (main and interaction effects) in the BrainScale, BrainTime and the Generation R Study. All volumes were converted from mm^3 to ml. Panel (a) shows the subcortical brain regions that were found to be associated with the interaction effects in the three cohorts. Panel (b) shows the direction of the associations of adolescent alcohol use and subcortical brain volumes found in the three cohorts in two correlograms (one for the main effects and one for the interaction effects). The specific effect estimates, uncorrected and FDR-corrected *p* values of panel (b) can be found in Table S4. Panel (c) shows the individual subject data for the left hippocampus in each cohort (never drinking vs. ever drinking). FDR, false discovery rate

of alcohol use in adolescence (like in randomized controlled trials) is possible. Nevertheless, several mechanistic explanations for our findings could be possible.

First, the observed associations may be a direct cause of alcohol use. Evidence from animal models suggests that early exposure to alcohol sensitizes the neurocircuitry of addiction and contribute to adolescents' vulnerability to drug addiction. One of the proposed systems involved is the mesolimbic pathway. Sensitization of the mesocorticolimbic dopaminergic pathway, along with changes in the glutamatergic and dopaminergic neurotransmission, might mediate the vulnerability of adolescents to the long-term consequences of alcohol addiction (Guerri & Pascual, 2010). In addition, another proposed mechanism is neuroinflammation as alcohol activates specific pathways in glial cells leading to inflammatory responses with the production of cytokines and inflammatory mediators and neural damage (Guerri & Pascual, 2010). Whether these underlying systems are also implicated in the current studies needs further investigation.

Second, the current study suggests that intoxication was related to pre-existing (main effects) and subsequent differences (interaction effects) in the frontal and cingulate a priori selected regions of interest. Some have hypothesized that post-drinking withdrawal and hangover symptoms play a deleterious role in brain function, as these symptoms may be more detrimental than the quantity of alcohol consumed and may present a more accurate marker of personal drinking quantity (Squeglia, Jacobus, & Tapert, 2014). Hangover symptoms have been found to be predictive of worsened attention and visuospatial function (Tapert et al., 2002), and withdrawal symptoms were negatively associated with learning and memory performance (Mahmood et al., 2010).

Finally, it is possible that adolescent alcohol use merely represents an aspect of risk-taking behaviour and that the alterations in brain morphology we observed are epiphenomena of risk-taking or other social processes rather than the result of mere alcohol exposure. It is well known that during adolescence, profound morphological and functional changes occur in the human (Arain et al., 2013). In particular, the prefrontal cortex (implicated in cognitive processes) and limbic system change significantly impacting self-control, decision making, emotions and risk-taking behaviour (Arain et al., 2013).

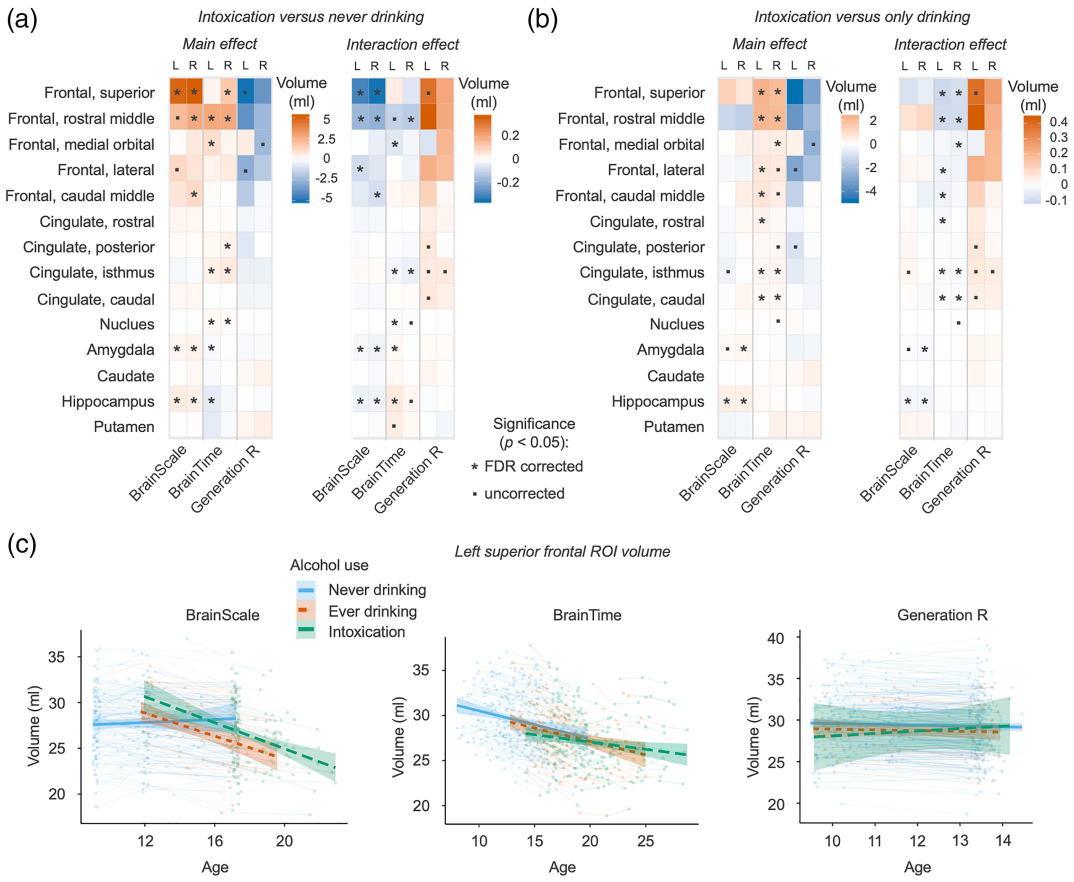

FIGURE 3 The association of adolescent alcohol intoxication and change in subcortical brain volumes (main and interaction effects) in the BrainScale, BrainTime and the Generation R Study. All volumes were converted from mm^3 to ml. Panel (a) shows the direction of the associations of adolescent intoxication versus never drinking and cortical brain volumes found in the three cohorts in two correlograms (one for the main effects and one for the interaction effects). Panel (b) shows the direction of the associations of adolescent intoxication versus alcohol drinking (without intoxication) and cortical brain volumes found in the three cohorts in two correlograms (one for the main effects and one for the interaction effects). Panel (c) shows the individual subject data for the left superior frontal volume in each cohort (never drinking vs. ever drinking vs. intoxication). FDR, false discovery rate

5.1 | Strengths and limitations

In the current study, we used three different cohorts with neuroimaging data at different age ranges and were able to use the same processing pipeline. This makes this unique study the largest of its kind. A strength of this study was the consistency of results across the two older cohorts in particular (BrainScale and BrainTime), especially in the context of the need for cross-sample replications (Poldrack et al., 2017). Nonetheless, our findings must be interpreted in the context of relevant limitations. First, the three cohorts had different designs. The BrainScale cohort examined twins at the same age and their siblings in a family design, BrainTime used an accelerated design (and thus participants of a wide age range) and the Generation R Study used an approach were all the children are assessed at more or less the same age over a long period of time (i.e. one assessment wave may take up to 3 years), and only had two data points. Inclusion and exclusion criteria were different across cohorts, and this could potentially influence findings. Further, all cohorts assessed alcohol use in different ways; therefore, we were limited in further specification of the exposure variables. Also, this difference in assessment could potentially explain the different prevalence rates across cohorts. For example, at the 13–14 years assessment, in BrainTime and BrainScale cohorts about half the participants used alcohol (with an age of initiation at 14 years), whereas in the Generation R cohort, this was about 15% with an average age of initiation at 11.6 years. It could be that alcohol use in the Generation R cohort is lower, because the cohort is younger. However, it is also possible that this is a time trend (e.g. children of the Generation R Study were born in 2002–2005 and BrainScale in 1995–1996), as many countries have seen a decline in alcohol use and an increase in adolescent abstinence,

potentially due to implementation of restrictions on purchase of alcohol, greater understanding of consequences of adolescent alcohol use or changing social norms (Looze et al., 2015; Pennay et al., 2018).

Also, in the Brain Scale study, almost all participants were alcohol users at the last assessment. Moreover, all cohorts collected alcohol use through self-reports, which may be subject to recall bias. We were not able to use cognitive outcomes in the current study, as it was too difficult to harmonize the different assessments across the cohorts. In addition, residual confounding (e.g. socioeconomic indicators, psychopathology or other factors) could have influenced our results as we have not adjusted for these variables in our analyses, but it was important to use similar models in the three cohorts to compare the results.

Thus, these results should be interpreted with caution, and future studies should focus on the association of adolescent alcohol use, cortical thickness, surface area and gyrification and use large longitudinal studies with repeated standardized and validated assessments of alcohol use, consider potential confounding variables and use harmonized processing pipelines for neuroimaging quality control and processing. In addition, using a multicohort design in which pooling data are valid and performing meta-analytic approaches would be informative.

6 | CONCLUSION

In summary, the results of this longitudinal study in three different cohorts suggest that adolescent alcohol use was associated with accelerated decrease in global and regional grey matter volumes, and a decelerated increase of white matter volume. The findings were most prominent and consistent in the older cohorts (BrainScale and BrainTime), whereas in the youngest cohort (the Generation R cohort), we did not find any associations. These findings very cautiously suggest that alcohol use may lead to accelerated maturation of the brain in older adolescents. However, the current study does not allow causal inference due to the observational nature of the study. Therefore, further research is needed using large cohort data with multiple assessments to (a) examine whether these associations persist (and later develop in the younger cohort) in which timing of exposure should be studied in detail, (b) study whether these altered trajectories result in functional impairments (c) identify potential mechanisms underlying these associations, and (d) to determine the causal nature of these relations.

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CONFLICT OF INTEREST

All authors declare no competing financial interests.

ETHICS APPROVAL STATEMENT

All studies were approved by the local Medical Ethics Committee or Central Committee on Research Involving Human Subjects of the Netherlands (CCMO), and all studies were performed in accordance with the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

Written informed consent and assent was obtained from all participants (i.e. adolescents and their parents in case of minors).

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.15411.

DATA AVAILABILITY STATEMENT

- Data from the Generation R study are available upon request to the director (generationr@erasmusmc.nl), subject to local rules and regulations.
- Data from the Brain Scale study are available upon request to the PIs: Prof Hilleke Hulshoff Pol (h.e.hulshoff@umcutrecht.nl) and Prof Dorret Boomsma (d.i.boomsma@vu.nl); subject to local rules and regulations.
- Data from the BrainTime study are available upon request to Eveline Crone (crone@essb.eur.nl); subject to local rules and regulations. We are currently also planning to make these data available via https://brainanddevelopment.nl/projects/braintime/.

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SUPPORTING INFORMATION

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