Title

Associations between alcohol use and sex-specific maturation of subcortical gray matter morphometry from adolescence to adulthood: Replication across two longitudinal samples

Authors

Jones, Scott A

Morales, Angelica M

Harman, Gareth

et al.

Publication Date

2023-10-01

DOI

10.1016/j.dcn.2023.101294

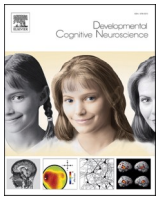
Peer reviewed

Developmental Cognitive Neuroscience 63 (2023) 101294

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: www.elsevier.com/locate/dcn



Associations between alcohol use and sex-specific maturation of subcortical gray matter morphometry from adolescence to adulthood: Replication across two longitudinal samples

Scott A. Jones [a], Angelica M. Morales [a], Gareth Harman [a,b], Kalene A. Dominguez-Savage [a], Sydney Gilbert [a], Fiona C. Baker [c], Massimiliano de Zambotti [c], David B. Goldston [d], Kate B. Nooner [e], Duncan B. Clark [f], Beatriz Luna [f], Wesley K. Thompson [g], Sandra A. Brown [h], Susan F. Tapert [i], Bonnie J. Nagel [a,*]

[a] Department of Psychiatry, Oregon Health & Science University, Portland, OR, USA
[b] Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, OR, USA
[c] Center for Health Sciences, SRI International, Menlo Park, CA, USA
[d] Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC, USA
[e] Department of Psychology, University of North Carolina Wilmington, Wilmington, NC, USA
[f] Departments of Psychiatry, Psychology and Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, PA, USA
[g] Population Neuroscience and Genetics Lab, University of California, San Diego, CA, USA
[h] Department of Psychology and Psychiatry, University of California, San Diego, La Jolla, CA, USA
[i] Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA

ARTICLE INFO

Keywords:
MRI
Sex differences
Adolescence
Alcohol
Longitudinal
Replication

ABSTRACT

Subcortical brain morphometry matures across adolescence and young adulthood, a time when many youth engage in escalating levels of alcohol use. Initial cross-sectional studies have shown alcohol use is associated with altered subcortical morphometry. However, longitudinal evidence of sex-specific neuromaturation and associations with alcohol use remains limited. This project used generalized additive mixed models to examine sex-specific development of subcortical volumes and associations with recent alcohol use, using 7 longitudinal waves (n = 804, 51% female, ages 12–21 at baseline) from the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA). A second, independent, longitudinal dataset, with up to four waves of data (n = 467, 43% female, ages 10–18 at baseline), was used to assess replicability. Significant, replicable non-linear normative volumetric changes with age were evident in the caudate, putamen, thalamus, pallidum, amygdala and hippocampus. Significant, replicable negative associations between subcortical volume and alcohol use were found in the hippocampus in all youth, and the caudate and thalamus in female but not male youth, with significant interactions present in the caudate, thalamus and putamen. Findings suggest a structural vulnerability to alcohol use, or a predisposition to drink alcohol based on brain structure, with female youth potentially showing heightened risk, compared to male youth.

1. Introduction

Adolescence is a critical period of development, during which several biopsychosocial changes ensue (for review, see Galvan, 2021). For the past few decades, scientists have dedicated concerted effort toward understanding adolescent brain development and associated behavioral phenomena. An understanding of the evolving structure of the adolescent brain began with a hallmark longitudinal imaging study demonstrating non-linear decreases in cortical gray matter volume and linear increases in white matter volume from childhood through adolescence (Giedd et al., 1999). Since then, several longitudinal investigations have confirmed these findings (e.g., Mills et al., 2016) and have also shown overall stable and/or declining global subcortical volume across adolescence, with considerable individual variability noted (Mills et al., 2021).

Both global and regional patterns of brain structural development

* Correspondence to: Oregon Health & Science University, 3181 SW Sam Jackson Park Road UHN-80R1, Portland, OR 97239, USA.
E-mail address: nagelb@ohsu.edu (B.J. Nagel).

https://doi.org/10.1016/j.dcn.2023.101294
Received 4 May 2023; Received in revised form 28 August 2023; Accepted 1 September 2023
Available online 3 September 2023

are well documented to show differences between male and female adolescents and young adults. Decades of cross-sectional findings support several sex-specific differences in brain structure in childhood and adulthood (Ruigrok et al., 2014; Sowell et al., 2007). More recent longitudinal investigations have corroborated these findings, with male adolescents and young adults showing overall larger cortical and subcortical volumes than female adolescents and young adults (Backhausen et al., 2021; Herting et al., 2018; Wierenga et al., 2014; Wierenga et al., 2018a). These same studies also provide evidence of sex-specific non-linear developmental trajectories for major subcortical regions, including limbic, striatal, and basal ganglia brain structures across adolescence. While some trajectories replicate across developmental samples, others diverge (Herting et al., 2018; Mills et al., 2021), suggesting that additional investigations are necessary to establish consistency.

During this developmental period, the majority of adolescents initiate alcohol use. Recent Monitoring the Future data suggest that by the 12th grade, over 60% of youth have tried alcohol in their lifetime, and over 30% have drunk in the past month; by young adulthood, 32% of individuals report binge-level (5 + drinks in a row) alcohol drinking (Miech et al., 2023). Our prior work, in the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) sample, examining longitudinal trajectories of cortical maturation in adolescence and into young adulthood suggests that binge drinking is associated with more rapid volumetric decline in nearly all cortical regions, with the greatest effects observed in the frontal lobe (Infante et al., 2022; Pfefferbaum et al., 2018). Similar effects of accelerated cortical volume decline as a function of alcohol use have been demonstrated previously in smaller longitudinal adolescent samples (Heikkinen et al., 2017; Infante et al., 2018; Squeglia et al., 2014), highlighting the robustness of this alcohol-related effect on neurodevelopment.

While fewer studies have examined alcohol use in association with subcortical volumes, greater decreases in caudate volume over time have been found in association with alcohol consumption (Squeglia et al., 2014). Moreover, a recent analysis of multiple longitudinal adolescent samples confirmed accelerated decreases in caudate volume (as well as accelerated decreases in amygdala and hippocampus volumes) in those with a lifetime history of alcohol use compared to those who never have drank alcohol (El Marroun et al., 2021); however, no dose-dependent associations were observed in this analysis, limiting interpretability. Understanding subcortical volumetric development and associations with alcohol use early in life is important, in large part due to the critical role these structures play in addiction-relevant emotion, reward, and cognitive functions (for review, see Volkow et al., 2019). In addition, smaller brain volumes in many of these regions have been associated with alcohol use disorders (AUD), and other comorbidities, in adults (Shim et al., 2019; Zahr and Pfefferbaum, 2017), are evident in early-onset adolescent AUD (De Bellis et al., 2000) and may be predictive of a higher likelihood of relapse following treatment (Segobin et al., 2014).

Using seven longitudinal waves of data from NCANDA, we investigated subcortical structural development across adolescence and young adulthood and examined whether the developmental trajectories differed by sex. Further, we tested how quantity of recent alcohol use may be dose-dependently associated with these developmental trajectories and whether sex-specific effects of alcohol use were present. Based on prior literature, we expected to observe a main effect of sex in our developmental trajectories, such that male adolescents would have larger subcortical volumes than female adolescents over time, and that there would be sex-specific differences in these developmental trajectories. Further, we expected a greater quantity of recent alcohol use to be negatively associated with subcortical volumes. Finally, to add confidence to our results, a second, independent longitudinal dataset was utilized to assess the replicability of all findings.

2. Methods

2.1. Participants

This study used data from two independently collected datasets. First, seven waves of longitudinal data were included from NCANDA. This study recruited youth between 12 and 21 years of age from five sites across the United States: Duke University, Oregon Health & Science University (OHSU), University of Pittsburgh, SRI International, and University of California San Diego (UCSD). Using an accelerated longitudinal design, participants underwent yearly visits (baseline and 6 follow-up visits are included here) to complete a comprehensive neuropsychological assessment (Sullivan et al., 2016), self-reports of behavior, psychiatric symptoms, and substance use (Brown et al., 2015), and a multimodal neuroimaging session (Pfefferbaum et al., 2016; Pohl et al., 2016). Further recruitment, demographic and procedural details have been published elsewhere (Brown et al., 2015). Following exclusions for brain abnormalities (Pfefferbaum et al., 2016), and discrepancies or missingness in substance use self-reports (see Section 2.2), 3923 cases across 804 subjects were utilized from this dataset.

The second dataset used for replication was a recently completed 10-year longitudinal study of adolescent neurodevelopment, conducted at OHSU, which included a high preponderance of youth “at-risk” (AR) for alcohol use, determined from familial history of alcoholism and other psychopathology (hereafter referred to as the AR study) (Jones et al., 2019). This study recruited youth between 10 and 18 years of age. All youth were followed until age 21 years via phone screens, and a subset of youth reporting recent alcohol use, along with age- and sex-matched youth without a drinking history (~37% of the sample) were brought into the laboratory for at least one (and up to 4) follow-up visits at various intervals (see, Jones et al., 2021a). At all visits, participants completed a neuropsychological assessment, self-reported behavior, psychiatric symptoms, and substance use, and completed a multimodal neuroimaging session. Following exclusions for discrepancies or missingness in substance use self-reports (see Section 2.2), 744 cases across 467 subjects were utilized from this dataset.

For both the NCANDA and AR studies, adults provided informed consent, while adolescents and their parents provided informed assent and consent, respectively. The respective institutional review board approved all procedures for each site. Exclusionary criteria at baseline for both studies included major Axis I psychiatric disorders, serious major medical conditions (including head trauma), learning or developmental disorders, current use of psychoactive medication, and MRI contraindications. For the AR study, at baseline, all participants were largely alcohol and drug naïve ($\leq$ 10 lifetime alcohol drinks, $<$ 3 drinks on any one occasion, $\leq$ 10 uses of marijuana, no daily cigarette use, or any other drug use). For the NCANDA study, while a majority of participants had limited drug and alcohol exposure at enrollment (Table S1), a small proportion (n = 133) were recruited who exceeded these age-specific alcohol and marijuana low-use thresholds (Brown et al., 2000). Sensitivity analyses (see Section 3.4) examined all final models in the NCANDA sample while excluding those who exceeded baseline substance use thresholds during recruitment.

The NCANDA data in this manuscript are based on the following data releases: Pohl KM, Sullivan EV, Podhajsky S, Baker FC, Brown SA, Clark DB, Colrain IM, DeBellis M, Goldston D, Nagel BJ, Nooner KB, Tapert SF, Pfefferbaum A: The `NCANDA_PUBLIC_6Y_REDCAP_V02` Data Release of the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA), Sage Bionetworks Synapse. https://dx.doi.org/10.7303/syn26133773 (Cummins et al., 2021); Pohl KM, Sullivan EV, Baker FC, Brown SA, Clark DB, Colrain IM, DeBellis M, Goldston D, Nagel BJ, Nooner KB, Tapert SF, Pfefferbaum A: The `NCANDA_PUBLIC_6Y_STRUCTURAL_V01` Data Release of the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA), Sage Bionetworks Synapse. https://doi.org/10.7303/syn32773308 (Ouyang et al., 2022). The AR data in this manuscript may be provided upon

request (including a formal project outline) to the corresponding author.

2.2. Self-reported substance use

For both studies, adolescents completed the Customary Drinking and Drug Use Record (CDDR) to estimate recent alcohol use (Brown et al., 1998) at every visit. Recent alcohol use questions of interest for the NCANDA study included a measure of frequency ("During the last 30 days, how many days did you drink alcohol") and quantity ("Over the last month, in the average 24-hour period you were drinking, how many alcoholic drinks did you have?"). The AR study used slight variations of these questions to measure frequency ("During the last 3 months, how many days per month did you drink alcohol?") and quantity ("Over the last 3 months, in the average 24-hour period you were drinking, how many alcoholic drinks did you have?") of recent alcohol use. For both studies, frequency and quantity measures were multiplied together to create a single measure of recent alcohol use, which approximated the total number of alcohol containing drinks per month. This "total drinks" variable was log-transformed prior to analyses due to extreme values in the distributions (Fig. S1).

For quality control purposes in both datasets, the following discrepant reporting in participants' self-reported alcohol use on the CDDR resulted in case-wise exclusion: reporting more days of drinking in the past 30 days (or past 3 months) than days drinking in the past year or reporting a non-zero frequency or quantity measure of alcohol use, but not both (NCANDA n = 24; AR n = 1). Further, cases where substance use data were missing were not included in the current analysis (NCANDA n = 37, AR n = 7).

2.3. Image acquisition

For the NCANDA study, T1-weighted images were collected in the sagittal plane using a 3 T General Electric (GE) Discovery MR750 with an 8-channel head coil (TR = 5.904 ms, TI = 400 ms, TE = 1.932 ms, flip angle = 11°, voxel size = 1.2 × 0.9375 × 0.9375 mm, 146 slices), a 3 T Siemens TIM TRIO with a 12-channel head coil, or 3 T Siemens PRISMA FIT with a 20-channel head and neck coil (TR = 1900 ms, TI = 900 ms, TE = 2.92 ms, flip angle = 9°, voxel size = 1.2 × 0.9375 × 0.9375 mm, 160 slices).

For the AR study, T1-weighted images were collected in the sagittal plane using a 3 T Siemens TIM TRIO with a 12-channel head coil or PRISMA FIT with a 20-channel head and neck coil (TR = 2300 ms, TI = 900 ms, TE = 3.58–3.61 ms, flip angle = 10°, voxel size = 1.1 × 1 × 1 mm, 160 slices).

2.4. Image analyses

To extract subcortical volume estimates, T1-weighted images from both studies were processed with a standardized longitudinal segmentation pipeline using FreeSurfer v6.0 (Reuter et al., 2012). This processing included a cross-sectional segmentation step, along with generation of an unbiased within-subject template used to guide longitudinal segmentation. From this pipeline, the current study examined 7 subcortical gray matter regions-of-interest (ROIs): accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus. Additional preprocessing steps applied as part of the NCANDA protocol (e.g., ad-hoc skull-stripping and intensity normalization beyond that carried out by FreeSurfer) have been outlined previously (Pfefferbaum et al., 2018; Pfefferbaum et al., 2016).

As done in previous studies examining global (Pfefferbaum et al., 2016) and regional (e.g., Backhausen et al., 2021; Herting et al., 2018) volumetric subcortical development, right and left hemispheric volumes were averaged, and all results are presented for bilateral regions-of-interest. Similar to previous work by our group (Infante et al., 2022), sensitivity analyses were carried out to examine all final models in the left and right hemispheres separately (see Section 3.4). Further, as the type of statistical model and inclusion of covariates have been shown to influence the study of sex differences and structural development, findings using absolute volumes, without covarying or adjusting for intracranial volume (ICV), are presented to align with recent studies of subcortical development (Backhausen et al., 2021; Herting et al., 2018; Wierenga et al., 2018a). As noted previously (Herting et al., 2018), the inclusion of allometric covariates, such as ICV, may largely be redundant when examining longitudinal development, as between-subject differences due to differences in head size are captured at the individual level using random intercepts via mixed effects modeling (described in Section 2.6). However, for completeness, sensitivity analyses examined all final models controlling for baseline ICV (see Section 3.4).

2.5. Outlier detection

For both studies, case-wise outlier detection excluded ROIs with a volume of more than 2.69 standard deviations from the sample mean across time points. This statistical outlier cutoff has been used previously by the NCANDA consortium (e.g., Phillips et al., 2021) and is part of a standardized protocol intended to harmonize analyses across multiple sites and datasets (http://enigma.ini.usc.edu/protocols/imaging-protocols/), particularly when visual inspection of ROI boundaries is impractical due to large sample sizes. This outlier detection was estimated across all timepoints, separately for male and female participants due to overall main effects of sex on subcortical volume and sex differences in the variability of anatomical volumes (Wierenga et al., 2018b). Outlier counts for both samples were $\leq$ 1% and ranged from 17 to 39 cases (NCANDA) and 4–8 cases (AR), depending on ROI.

2.6. Development, sex differences, and alcohol effects in the NCANDA sample

To assess the effects of age and sex on subcortical development, we fit a series of Generalized Additive Mixed Models (GAMMs) using the 'mgcv' package (Wood, 2017) in R v4.1.1 (R Core Team, 2020), independently for each ROI in the NCANDA sample. All models included nested random intercepts per participant, family, and data collection site and were fit with Maximum Likelihood (ML) estimation to allow for direct statistical comparison of nested models using likelihood ratio tests (LRT). Three successive models assessed the pattern of age-related subcortical development across the whole sample (Model 1), a main effect of sex (Model 2), and differences in the age-related developmental trajectories by sex (Model 3).

$$\text{volume} \sim \text{s(age)}, \text{random} = \text{list(site} = \sim 1, \text{family} = \sim 1, \text{subject} = \sim 1) \quad (1)$$

$$\text{volume} \sim \text{s(age)} + \text{sex}, \text{random} = \text{list(site} = \sim 1, \text{family} = \sim 1, \text{subject} = \sim 1) \quad (2)$$

$$\text{volume} \sim \text{s(age, by} = \text{sex)} + \text{sex}, \text{random} = \text{list(site} = \sim 1, \text{family} = \sim 1, \text{subject} = \sim 1) \quad (3)$$

The best model fit for the overall developmental effect was determined via a two-step method described previously (Jones et al., 2021b). First, we compared the overall fit of all three models using LRTs. Then, if Model 3 was determined to be the best-fitting model, we refit Model 3 with sex included as an ordered factor. Instead of generating separate trajectories for male and female youth, this method creates a difference trajectory between male and female youth, akin to a traditional interaction term. A significant model improvement via LRTs and a significant difference term between trajectories were deemed necessary to retain Model 3. The difference between Model 3 (with sex as a factor) and our re-fit of the model (with sex as an *ordered* factor) is largely cosmetic, and allows us to test the significance of both the individual smoothed trajectories for male and female participants, as well as the difference between those two smoothed trajectories.

Next, to assess the association between recent alcohol use and subcortical volumes, we added a main effect of alcohol use (i.e. a

constant effect of alcohol use across age) and an alcohol use-by-age interaction (i.e. an effect of alcohol use that increases or decreases across age), as well as interaction terms between alcohol use and sex. In these models, recent alcohol use was treated as a time-varying predictor (i.e. a unique measurement was included for each MRI session - see Section 2.2). These predictors were added to and compared to the best-fitting developmental GAMM using LRTs. Of note, though we tested 7 different ROIs, no correction for multiple comparisons was carried out, as the model building strategy results in a different final model for each ROI and ensures that fixed effects are only interpreted in models that best describe the underlying data structure for each ROI independently. This is also in line with similar studies using GAMMs, and a model building strategy like that outlined above, to assess development in these 7 subcortical ROIs (Backhausen et al., 2021; Herting et al., 2018; Wierenga et al., 2018a).

2.7. Assessing replication in the AR sample

To examine replication in a secondary dataset, the final best-fitting NCANDA model was fit in the AR dataset. All parameters were identical, except for the random intercept of site, which is missing from the AR dataset, as all scans were collected at the same location. Then, three replication criteria, which were identified in the Open Science Collaboration (Open Science Collaboration, 2015) and utilized previously (e.g., Owens et al., 2022), were used as replicability metrics:

1) Direction criterion: percentage of significant tests in the NCANDA sample that were in the same direction in the AR sample.

2) Significance criterion: percentage of significant tests in the NCANDA sample that were significant in the same direction in the AR sample.

3) Confidence interval criterion: percentage of significant tests in the NCANDA sample that had effect sizes in the AR sample within the 95% confidence interval of the NCANDA sample effect size.

All three criteria were applied to significant main effects of sex, alcohol use, and sex-by-alcohol use interactions in the NCANDA sample. However, given that fitting smoothed age-related effects in GAMMs does not produce discrete directional estimates (an inherent limitation of the modeling strategy), the direction and confidence interval criteria could not be directly applied to developmental effects. Therefore, only the significance criterion was applied to all significant smoothed age effects (separately for male and female participants, where appropriate).

Additionally, an exploratory step-wise modeling strategy, like that carried out for the NCANDA sample (described in Section 2.6), was repeated for the AR sample to identify regions where unique developmental, sex-specific, or alcohol-related effects were present in the AR sample but not in the NCANDA sample (see supplement).

3. Results

3.1. Sample characteristics

A full demographic breakdown of the NCANDA sample has been reported previously (Brown et al., 2015). Additionally, for comparative purposes, sample demographics are presented by study and sex in Table 1.

Table 1
Sample demographics.

	NCANDA		AR	
	Female	Male	Female	Male
N (%)	410 (51%)	394 (49%)	202 (43%)	265 (57%)
Age: Mean (SD)	16.31 (2.57)	16.09 (2.48)	14.10 (1.62)	14.37 (1.71)
Parental Education: Median (years)	16	17	17	16
Household Income: Median (thousands)	$100-$200	$100-$200	$75-$100	$75-$100
Race/Ethnicity: N (%)				
Asian	31 (8%)	32 (8%)	1 (<1%)	7 (3%)
African-American/Black	63 (15%)	36 (9%)	5 (3%)	5 (2%)
Hispanic	38 (9%)	43 (11%)	13 (7%)	10 (4%)
Multiracial	17 (4%)	16 (4%)	17 (8%)	15 (6%)
Native America/American Indian	0 (0%)	3 (1%)	1 (<1%)	2 (1%)
Pacific Islander	3 (1%)	1 (<1%)	0 (0%)	1 (<1%)
Caucasian/White	258 (63%)	263 (67%)	163 (82%)	218 (85%)

3.2. Subcortical development and associations with alcohol use in the NCANDA sample

Model comparisons for all regions in the NCANDA sample are presented in Table S2, and the final best fitting model for each region can be found in Table 2. Developmental model comparisons found both a significant main effect of sex (all $\beta s > 0.516$, $ps < 0.001$), and significant sex-specific developmental trajectories in the accumbens, caudate, hippocampus, and pallidum (from order factor models, all interaction $Fs > 15.84$, $ps < 0.001$). Qualitatively describing the GAMMs, volumes appear to increase with age in the pallidum and decrease with age in the accumbens and caudate in all youth; meanwhile, female youth showed decreases, while male youth showed increases in hippocampal volume over age (Fig. 1). Further, there was a significant main effect of sex (but no interaction with age) in the amygdala, putamen and thalamus (all $\beta s > 0.862$, $ps < 0.001$). Qualitatively, volumes appear to increase in the amygdala and decrease in the putamen and thalamus with age in all youth (Fig. 1). In all regions, male youth had significantly greater volumes than female youth.

Model comparisons and examination of fixed effects also revealed that recent alcohol use was significantly associated ($\beta = -0.015$, $p < 0.001$) with smaller hippocampal volumes in both male and female youth (Table S2 & Table 2). Alcohol use-by-sex interactions were observed in the caudate, putamen, and thalamus (all $\beta s > 0.016$, $ps < 0.05$). In female youth, there was a significant negative association between alcohol use and volume in the caudate ($\beta = -0.021$, $p < 0.001$) and thalamus ($\beta = -0.032$, $p < 0.001$), and a trend-level association in the putamen ($\beta = -0.015$, $p = 0.053$). In male youth, there was no association between alcohol use and volume in any of these three regions (all $p's > 0.05$). There was no association between alcohol use and accumbens, amygdala, or pallidum volumes. There were no significant time-varying effects of recent alcohol use in any region.

3.3. Replication in the AR sample

The results of fitting all final NCANDA models to the AR data can be found in Table S3. The results of all replication criteria are presented in Table 3. Each of the seven regions with a significant main effect of sex in the NCANDA sample met the direction and significance replication criteria in the AR sample. Further, the confidence interval criterion was met for four of the seven regions. That is, of the seven significant main effects of sex in the NCANDA sample, 57% met all three replication criteria, while 100% met at least two replication criteria.

In the hippocampus, where there was a significant main effect of alcohol use, all three significance criteria were met. Meanwhile, for the three regions demonstrating sex-by-alcohol use interactions (caudate, putamen, and thalamus), the direction criterion was met in all three regions, the significance criterion was met in the caudate, and the confidence interval criterion was met in the putamen and thalamus. Overall, of the four regions demonstrating either a main effect of alcohol use or a sex-by-alcohol use interaction in the NCANDA sample, 25% met at all three replication criteria, while 100% met at least two replication criteria.

Finally, of the 11 developmental effects present in the NCANDA

Table 2
Final best-fitting generalized additive mixed-effects model for the NCANDA sample.

	Parametric coefficients							Smooth terms		
	Estimate	Std Error	95% CI		t-value	p-value		edf	F-stat	p-value
Accumbens ~ s(age, by = sex) + sex										
Intercept	-0.3599	0.2290			-1.57	0.1160	s(age): female	1.00	60.58	< 0.0001
Sex (male)	0.5309	0.0553	0.4224	0.6393	9.59	< 0.0001	s(age): male	2.80	5.29	0.0069
Amygdala ~ s(age,) + sex										
Intercept	-0.5303	0.0549			-9.66	< 0.0001	s(age)	4.24	23.80	< 0.0001
Sex (male)	1.0382	0.0566	0.9273	1.1491	18.35	< 0.0001				
Caudate ~ s(age, by = sex) + sex + alcohol + alcohol:sex										
Intercept	-0.3086	0.0967			-3.19	0.0014	s(age): female	5.13	310.90	< 0.0001
Sex (male)	0.6329	0.0628	0.5098	0.7559	10.08	< 0.0001	s(age): male	2.90	356.60	< 0.0001
Alcohol	-0.0208	0.0043	-0.0292	-0.0124	-4.84	< 0.0001				
Alcohol: Sex (male)	0.0163	0.0056	0.0053	0.0273	2.89	0.0038				
Hippocampus ~ s(age, by = sex) + sex + alcohol										
Intercept	-0.4360	0.0642			-6.79	< 0.0001	s(age): female	3.39	32.84	< 0.0001
Sex (male)	0.9278	0.0561	0.8179	1.0377	16.55	< 0.0001	s(age): male	4.54	8.93	< 0.0001
Alcohol	-0.0152	0.0036	-0.0223	-0.0082	-4.23	< 0.0001				
Pallidum ~ s(age, by = sex) + sex										
Intercept	-0.2896	0.1647			-1.76	0.0787	s(age): female	3.70	5.00	0.0006
Sex (male)	0.5157	0.0627	0.3929	0.6385	8.23	< 0.0001	s(age): male	1.00	57.53	< 0.0001
Putamen ~ s(age) + sex + alcohol + alcohol:sex										
Intercept	-0.4749	0.0698			-6.81	< 0.0001	s(age)	4.96	275.50	< 0.0001
Sex (male)	0.8929	0.0596	0.7761	1.0097	14.98	< 0.0001				
Alcohol	-0.0165	0.0085	-0.0331	0.0002	-1.94	0.0526				
Alcohol: Sex (male)	0.0265	0.0100	0.0070	0.0460	2.66	0.0078				
Thalamus ~ s(age) + sex + alcohol + alcohol:sex										
Intercept	-0.4341	0.0450			-9.64	< 0.0001	s(age)	4.41	46.36	< 0.0001
Sex (male)	0.8615	0.0603	0.7433	0.9797	14.29	< 0.0001				
Alcohol	-0.0317	0.0074	-0.0462	-0.0172	-4.28	< 0.0001				
Alcohol: Sex (male)	0.0222	0.0087	0.0052	0.0393	2.55	0.0107				

sample (age effects in the amygdala, putamen and thalamus, and sex-specific age effects in the accumbens, caudate, hippocampus, and pallidum), the significance criterion was met for 9/11 (82%) of these effects. Replication was not found for significant accumbens development in male or female youth.

3.4. Sensitivity analyses

When excluding individuals who exceeded baseline substance use criteria, all primary findings described in Section 3.2 remained significant, except the following: the developmental effect in the accumbens in male youth ($F = 3.084$, $p = 0.051$) and the sex-by-alcohol interactions in the putamen ($\beta = 0.019$, $p = 0.076$) and thalamus ($\beta = 0.019$, $p = 0.051$) were all reduced to trend-level. Importantly, when looking at these effects in *only* those subjects who exceeded baseline substance use criteria, we see significant accumbens development in male youth ($F = 3.354$, $p = 0.027$), a significant sex-by-alcohol interaction in the putamen ($\beta = 0.048$, $p = 0.047$) and a trend-level sex-by-alcohol effect in the thalamus ($\beta = 0.038$, $p = 0.071$). This suggests these two groups do not differ substantially in subcortical volume development, or its association with recent alcohol use. Instead, the exclusion of those exceeding baseline substance use criteria likely results in a loss of power, particularly for detecting significant sex-by-alcohol interaction effects, as those exceeding baseline substance use criteria help add variability to the recent alcohol use variable, particularly on the higher end of this distribution.

When including ICV at baseline as a covariate, all developmental, sex-by-age, and alcohol-related effects remained significant. However, the main effects of sex in the accumbens ($\beta = 0.097$, $p = 0.135$) and caudate ($\beta = -0.011$, $p = 0.877$) were no longer significant when controlling for baseline ICV.

When refitting all final models (outlined in Section 3.2) separately in the left and right hemispheres, most findings remained unchanged, with a few exceptions. Significant accumbens development in male youth appeared to be driven by the left ($F = 5.087$, $p = 0.008$) but not right hemisphere ($F = 0.713$, $p = 0.399$), and the sex-specific interaction of alcohol use on brain volume in the putamen and thalamus appeared stronger in the left (putamen: $\beta = 0.031$, $p = 0.004$; thalamus: $\beta = 0.022$, $p = 0.020$), than right (putamen: $\beta = 0.019$, $p = 0.079$; thalamus: $\beta = 0.019$, $p = 0.085$) hemisphere.

4. Discussion

This study analyzed the large, longitudinal NCANDA dataset to examine patterns of subcortical structural maturation in the adolescent and young adult brain and to determine the extent to which alcohol use is associated with subcortical brain volume during this developmental period. To provide further confidence in our observed effects, we sought to replicate the findings in a separate, independent, longitudinal adolescent sample. In support of our hypotheses, we demonstrated both sex specificity and alcohol-related associations in subcortical developmental trajectories. Establishment of sex-specific developmental trajectories of subcortical structures may be relevant for identifying subcortical substrates of learning, habit formation, and reward processing (Burton et al., 2015; Lipton et al., 2019) with implications for addictive behaviors (Volkow et al., 2019).

Developmentally, we found significant, replicable decreases in caudate, putamen, and thalamus volumes and increases in pallidum and amygdala volumes in all youth. These effects are all consistent with one or more previous longitudinal reports (Backhausen et al., 2021; Dennison et al., 2013; Herting et al., 2018; Wierenga et al., 2014; Wierenga et al., 2018a). Herein, the pallidum, caudate, hippocampus, and accumbens developmental trajectories differed significantly by sex (with all but the accumbens effect replicated in a second dataset). Sex-specific developmental effects in all of these regions have been noted previously, using a comparable developmental age range and modeling strategy (i.e., GAMMSs) (Backhausen et al., 2021; Herting et al., 2018). Qualitatively, in our study, this difference appeared to be driven by greater overall increases in pallidum volumes with age in male than female youth, earlier declines in caudate volumes in female than male youth, greater overall declines in accumbens volumes in female than male youth, and directionally different effects in the hippocampus, with male

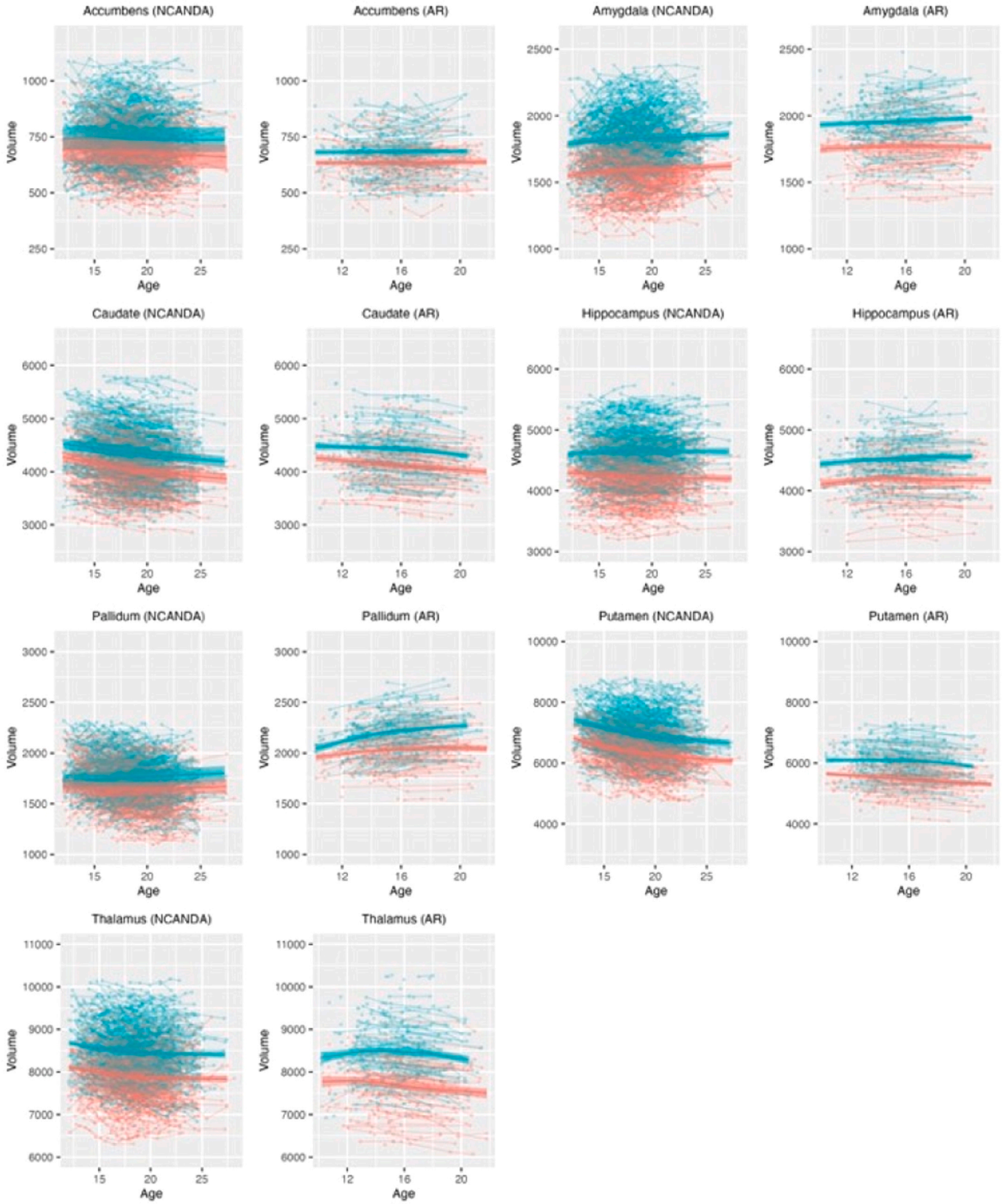


Fig. 1. Smoothed age-related developmental trajectories and 95% confidence intervals for male (blue) and female (red) participants based off the final best fitting generalized additive mixed model (GAMM) for each region of interest in NCANDA and AR samples.

Table 3
Replication criteria in the AR sample.

	Accumbens	Amygdala	Caudate	Hippocampus	Pallidum	Putamen	Thalamus
Main effect of Sex							
Direction	YES	YES	YES	YES	YES	YES	YES
Significance	YES	YES	YES	YES	YES	YES	YES
Confidence Interval	YES	NO	YES	YES	NO	YES	NO
Main effect of Alcohol							
Direction				YES			
Significance				YES			
Confidence Interval				YES			
Sex-by-Alcohol Interaction							
Direction			YES			YES	YES
Significance			YES			NO	NO
Confidence Interval			NO			YES	YES
Combined Age							
Significance		YES				YES	YES
Female Age							
Significance	NO		YES	YES	YES		
Male Age							
Significance	NO		YES	YES	YES		

youth showing increases in volume with age and female youth decreases. In addition to these developmental effects, as hypothesized, we also noted overall main effects of sex, with male youth having significantly larger volumes than female youth across the entire developmental age range (without adjustment for ICV). In addition to replicating previous reports (Backhausen et al., 2021; Herting et al., 2018; Wierenga et al., 2014; Wierenga et al., 2018a), we provide evidence that these effects also persist in the amygdala, putamen, pallidum, hippocampus, and thalamus, even after controlling for differences in baseline ICV.

This is the first study to our knowledge to demonstrate longitudinal, replicable associations between subcortical volumes and recent alcohol use. Here, we show significant sex-by-alcohol use interactions in the caudate, putamen, and thalamus (driven by significant negative associations between alcohol use and brain volumes in the caudate and thalamus in female but not male youth), and a significant negative association between alcohol use and hippocampal volume in all youth; all of these results are at least partially replicated across the NCANDA and AR samples. These findings are also consistent with previous longitudinal reports, which found a negative relationship between alcohol use and caudate and hippocampal volume, but did not report sex differences (El Marroun et al., 2021; Squeglia et al., 2014). They are also consistent with previous cross-sectional reports, which noted stronger negative associations between alcohol use and cortical and subcortical volumes in female than male youth (Medina et al., 2008; Pfefferbaum et al., 2016; Seo et al., 2019). These sex-specific alcohol-related effects, in the caudate for example, could be due to differences in maturational timing, such that earlier maturation in female youth may make this region more vulnerable to effects of alcohol (compared to male youth) or may predispose female youth to drink more alcohol. Meanwhile, in the hippocampus, though male and female youth demonstrate divergent developmental trajectories (particularly early in adolescence), alcohol use is associated with smaller volumes in all youth. While we cannot disentangle cause and effect in human studies, this observation may well reflect a neurotoxic effect of alcohol use. Rodent models have shown the hippocampus to be particularly sensitive to alcohol's effects (for review, see Walker et al., 2021), and have indicated that adolescent alcohol use inhibits neurogenesis in the hippocampus during adulthood (Wooden et al., 2021). In our study, alcohol's association with hippocampal volume appears impervious to an individual's neurodevelopmental time course.

This study has several strengths. First, it is the largest study to our knowledge to model longitudinal, sex-specific, non-linear development of subcortical brain volumes alongside sex-specific associations with alcohol, with our results providing a high degree of congruence with several previous reports. Second, many of our findings, including negative associations between recent alcohol use and subcortical volumes, were partially replicated in a second independent dataset. Importantly, this successful replication occurred despite minor differences in scanner sequence and processing pipelines between the two datasets, further suggesting robustness of the effects. While recent reports shed light on the limitations of smaller datasets (e.g. the AR dataset used herein) for finding replicable effects using brain-wide association analyses (Marek et al., 2022), we demonstrate the utility of these studies as replication datasets for larger, better powered consortium-based analyses.

Despite these strengths, several limitations should also be noted. First, while we demonstrated replicable sex differences across all subcortical brain regions, the functional relevance of sex differences in brain structure, both in healthy and diseased states, has been highly debated (Becker et al., 2017) and warrants additional exploration. In addition, our measurement of "sex" (as assigned at birth) does not incorporate the host of biological, social, and environmental influences that attach to such a construct. Future research, better considering nuanced differences between male and female brain development, including measuring more precise explanatory variables (including puberty and sex hormones) at a more granular level, is encouraged. Second, while this study used dose-dependent measures of recent alcohol use (incorporating frequency and quantity of use), improving on the binary variables utilized previously (e.g., El Marroun et al., 2021), there remains a need for improvements in our assessment and modeling of the complexity in the timing and pattern of alcohol use in adolescents and young adults (e.g. weekly episodic heavy drinking vs. low levels of daily use). In addition, our structural measurements did not include subregional specificity, which has been additionally shown to vary by sex (Fish et al., 2020; Mu et al., 2020) and in alcohol using populations (Grace et al., 2021; Phillips et al., 2021). Further, to overcome methodological differences and match analytic models between samples, we chose not to adjust for other potential confounds, including known risk factors for adolescent substance use (such as family history of alcohol use disorder), as well as the potential for biased attrition (e.g. the NCANDA study had approximately 81% retention over the 7 years of data collection included here). As such, it's unclear whether differences in sample composition or lack of control for confounding factors have limited replicability in certain regions and not others. While future studies will be necessary to explore other known risk factors, a relative strength of the current analysis is its ability to find such a high degree of replicability despite differences in sample composition and without controlling for additional confounds. Finally, while GAMMs are flexible for fitting developmental trajectories and are commonly used to study brain development (e.g., Backhausen et al., 2021; Herting et al., 2018), they remain limited in their ability to detect temporal causality and are

largely associative in nature. Alternative statistical techniques with more rigid developmental constraints, but predictive modeling (e.g. cross-lagged models), may be a beneficial follow-up to these findings. Nonetheless, we believe these analyses establish a reliable foundation regarding development effects which may inform future modeling strategies geared towards assessing the timing or nuance of alcohol-related effects on brain development.

5. Conclusions

Our study demonstrates significant, replicable volumetric longitudinal changes in adolescents and young adults over time that include decreases in caudate, putamen, and thalamus volumes and increases in pallidum volumes in all youth, regardless of sex or recent alcohol use. Further, replicable sex-specific developmental effects suggest a greater increase in pallidum volumes with age in male youth compared to female youth and greater declines in caudate volume in female youth compared to male youth. While the functional significance of these sex-specific developmental effects remains unclear, they should be considered in future studies modeling developmental changes in subcortical structure. Finally, we demonstrate partially replicable negative associations between recent alcohol use and caudate, hippocampus, and thalamus volumes, with effects in the caudate and thalamus driven largely by female youth. Future work will be necessary to elucidate the mechanism, functional relevance and long-term behavioral implications of these alcohol-related effect on subcortical volumes during development, which may provide a window into improving prevention and intervention efforts.

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.

Acknowledgements

We would like to thank past and present research staff at Duke University, Oregon Health & Science University, University of Pittsburgh, SRI International, and University of California San Diego, for their instrumental role in participant scheduling and data collection. This work was funded by the National Institute on Alcohol Abuse and Alcoholism [AA021697, AA021695, AA021692, AA021696, AA021681, AA021690, AA021691, AA017664], the National Institute of Health [S10OD021701 and S10OD018224] for the 3 T Siemens Prisma MRI instrument and High-Performance Computing Cluster housed in OHSU's Advanced Imaging Research Center, and the Oregon Opportunity Partnership for advancing biomedical research. Additionally, AMM received funding from the National Institute on Drug Abuse (K01DA046649).

Data statement

The NCANDA data in this manuscript are based on the following data releases: Pohl KM, Sullivan EV, Podhajsky S, Baker FC, Brown SA, Clark DB, Colrain IM, DeBellis M, Goldston D, Nagel BJ, Nooner KB, Tapert SF, Pfefferbaum A: The `NCANDA_PUBLIC_6Y_REDCAP_V02` Data Release of the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA), Sage Bionetworks Synapse. https://dx.doi.org/10.7303/syn26133773 (Cummins et al., 2021); Pohl KM, Sullivan EV, Baker FC, Brown SA, Clark DB, Colrain IM, DeBellis M, Goldston D, Nagel BJ, Nooner KB, Tapert SF, Pfefferbaum A: The `NCANDA_PUBLIC_6Y_STRUCTURAL_V01` Data Release of the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA), Sage Bionetworks Synapse. https://doi.org/10.7303/syn32773308 (Ouyang et al., 2022). The AR data in this manuscript may be provided upon request (including a formal project outline) to the corresponding author.

Disclosures

The authors declare no conflicts of interest, financial or otherwise, related to this work.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2023.101294.

References

Backhausen, L.L., Fröhner, J.H., Lemaître, H., Artiges, E., Martinot, M.-L.P., Herting, M. M., Sticca, F., Banaschewski, T., Barker, G.J., Bokde, A.L., 2021. Adolescent to young adult longitudinal development of subcortical volumes in two European sites with four waves. bioRxiv.

Becker, J.B., McClellan, M.L., Reed, B.G., 2017. Sex differences, gender and addiction. J. Neurosci. Res. 95, 136–147.

Brown, S.A., Myers, M.G., Lippke, L., Tapert, S.F., Stewart, D.G., Vik, P.W., 1998. Psychometric evaluation of the customary drinking and drug use record (CDDR): a measure of adolescent alcohol and drug involvement. J. Stud. Alcohol 59, 427–438.

Brown, S.A., Tapert, S.F., Granholm, E., Delis, D.C., 2000. Neurocognitive functioning of adolescents: effects of protracted alcohol use. Alcohol Clin. Exp. Res 24, 164–171.

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., 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, 895–908.

Burton, A.C., Nakamura, K., Roesch, M.R., 2015. From ventral-medial to dorsal-lateral striatum: neural correlates of reward-guided decision-making. Neurobiol. Learn Mem. 117, 51–59.

Cummins, K.M., Brumback, T., Chung, T., Moore, R.C., Henthorn, T., Eberson, S., Lopez, A., Sarkissyan, T., Nooner, K.B., Brown, S.A., 2021. Acceptability, validity, and engagement with a mobile app for frequent, continuous multiyear assessment of youth health behaviors (mNCANDA): mixed methods study. JMIR mHealth uHealth 9, e24472.

De Bellis, M.D., Clark, D.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, 737–744.

Dennison, M., Whittle, S., Yücel, M., Vijayakumar, N., Kline, A., Simmons, J., Allen, N.B., 2013. Mapping subcortical brain maturation during adolescence: evidence of hemisphere-and sex-specific longitudinal changes. Dev. Sci. 16, 772–791.

El Marroun, H., Klapwijk, E.T., Koevoets, M., Brouwer, R.M., Peters, S., Van't Ent, D., Boomsma, D.I., Muetzel, R.L., Crone, E.A., Hulshoff Pol, H.E., 2021. Alcohol use and brain morphology in adolescence: A longitudinal study in three different cohorts. Eur. J. Neurosci. 54, 6012–6026.

Fish, A.M., Nadig, A., Seidlitz, J., Reardon, P.K., Mankiw, C., McDermott, C.L., Blumenthal, J.D., Clasen, L.S., Lalonde, F., Lerch, J.P., Chakravarty, M.M., Shinohara, R.T., Raznahan, A., 2020. Sex-biased trajectories of amygdalo-hippocampal morphology change over human development. Neuroimage 204, 116122.

Galvan, A., 2021. Adolescent brain development and contextual influences: a decade in review. J. Res Adolesc. 31, 843–869.

Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., Paus, T., Evans, A.C., Rapoport, J.L., 1999. Brain development during childhood and adolescence: a longitudinal MRI study. Nat. Neurosci. 2, 861–863.

Grace, S., Rossetti, M.G., Allen, N., Batalla, A., Bellani, M., Brambilla, P., Chye, Y., Cousijn, J., Goudriaan, A.E., Hester, R., Hutchison, K., Labuschagne, I., Momenan, R., Martin-Santos, R., Rendell, P., Solowij, N., Sinha, R., Li, C.R., Schmaal, L., Sjoerds, Z., Suo, C., Terrett, G., van Holst, R.J., Veltman, D.J., Yucel, M., Thompson, P., Conrod, P., Mackey, S., Garavan, H., Lorenzetti, V., 2021. Sex differences in the neuroanatomy of alcohol dependence: hippocampus and amygdala subregions in a sample of 966 people from the ENIGMA Addiction Working Group. Transl. Psychiatry 11, 156.

Heikkinen, N., Niskanen, E., Kononen, M., Tolmunen, T., Kekkonen, V., Kivimaki, P., Tanila, H., Laukkanen, E., Vanninen, R., 2017. Alcohol consumption during adolescence is associated with reduced grey matter volumes. Addiction 112, 604–613.

Herting, M.M., Johnson, C., Mills, K.L., Vijayakumar, N., Dennison, M., Liu, C., Goddings, A.-L., Dahl, R.E., Sowell, E.R., Whittle, S., 2018. Development of subcortical volumes across adolescence in males and females: A multisample study of longitudinal changes. Neuroimage 172, 194–205.

Infante, M.A., Courtney, K.E., Castro, N., Squeglia, L.M., Jacobus, J., 2018. Adolescent brain surface area pre- and post-cannabis and alcohol initiation. J. Stud. Alcohol Drugs 79, 835–843.

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., 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, 2611–2620.

Jones, S.A., Van Fossen, R.P., Thompson, W.K., Baker, F.C., Clark, D.B., Nagel, B.J., 2021b. Developmental trajectories of Big Five personality traits among adolescents

and young adults: Differences by sex, alcohol use, and marijuana use. Journal of personality.
Jones, S.A., Morales, A.M., Nagel, B.J., 2019. Resilience to risk for psychopathology: The role of white matter microstructural development in adolescence. Biol. Psychiatry.: Cogn. Neurosci. Neuroimaging 4, 180–189.
Jones, S.A., Kliamovich, D., Nagel, B.J., 2021a. Sex hormones partially explain the sex-dependent effect of lifetime alcohol use on adolescent white matter microstructure. Psychiatry Res.: Neuroimaging 307, 111230.
Lipton, D.M., Gonzales, B.J., Citri, A., 2019. Dorsal striatal circuits for habits, compulsions and addictions. Front Syst. Neurosci. 13, 28.
Marek, S., Tervo-Clemmens, B., Calabro, F.J., Montez, D.F., Kay, B.P., Hatoum, A.S., Donohue, M.R., Foran, W., Miller, R.L., Hendrickson, T.J., 2022. Reproducible brain-wide association studies require thousands of individuals. Nature 1–7.
Medina, K.L., McQueeny, T., Nagel, B.J., Hanson, K.L., Schweinsburg, A.D., Tapert, S.F., 2008. Prefrontal cortex volumes in adolescents with alcohol use disorders: unique gender effects. Alcohol Clin. Exp. Res 32, 386–394.
Miech, R.A., Johnston, L.D., Patrick, M.E., O'Malley, P.M., Bachman, J.G., Schulenberg, J.E., 2023. Monitoring the Future National Survey Results on Drug Use, 1975–2022. Monitoring the Future Monograph Series. The University of Michigan, Ann Arbor: Institute for Social Research.
Mills, K.L., Goddings, A.-L., Herting, M.M., Meuwese, R., Blakemore, S.-J., Crone, E.A., Dahl, R.E., Güroğlu, B., Raznahan, A., Sowell, E.R., Tamnes, C.K., 2016. Structural brain development between childhood and adulthood: convergence across four longitudinal samples. Neuroimage 141, 273–281.
Mills, K.L., Siegmund, K.D., Tamnes, C.K., Ferschmann, L., Wierenga, L.M., Bos, M.G.N., Luna, B., Li, C., Herting, M.M., 2021. Inter-individual variability in structural brain development from late childhood to young adulthood. Neuroimage 242, 118450.
Mu, S.H., Yuan, B.K., Tan, L.H., 2020. Effect of gender on development of hippocampal subregions from childhood to adulthood. Front Hum. Neurosci. 14, 611057.
Open Science Collaboration, 2015. Estimating the reproducibility of psychological science. Science 349, aac4716.
Ouyang, J., Zhao, Q., Adeli, E., Zaharchuk, G., Pohl, K.M., 2022. Self-supervised learning of neighborhood embedding for longitudinal MRI. Med. Image Anal. 82, 102571.
Owens, M.M., Hyatt, C., Xu, H., Thompson, M., Miller, J., Lynam, D., MacKillop, J., Gray, J.C., 2022. Replicability of the neuroanatomical correlates of impulsive personality traits in the ABCD study.
Pfefferbaum, A., Rohlfing, T., Pohl, K.M., Lane, B., Chu, W., Kwon, D., Nolan Nichols, 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.C., Prouty, D., De Bellis, M.D., Voyvodic, J.T., Clark, D.B., Luna, B., Chung, T., Nagel, B.J., 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, 4101–4121.
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., 2018. Altered brain developmental trajectories in adolescents after initiating drinking. Am. J. Psychiatry 175, 370–380.
Phillips, R.D., De Bellis, M.D., Brumback, T., Clausen, A.N., Clarke-Rubright, E.K., Haswell, C.C., Morey, R.A., 2021. Volumetric trajectories of hippocampal subfields and amygdala nuclei influenced by adolescent alcohol use and lifetime trauma. Transl. Psychiatry 11, 1–13.
Pohl, K.M., Sullivan, E.V., Rohlfing, T., Chu, W., Kwon, D., Nichols, B.N., 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., Schirda, C., Nagel, B.J., 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.
R Core Team, 2020. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.
Reuter, M., Schmansky, N.J., Rosas, H.D., Fischl, B., 2012. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage 61, 1402–1418.
Ruigrok, A.N., Salimi-Khorshidi, G., Lai, M.C., Baron-Cohen, S., Lombardo, M.V., Tait, R. J., Suckling, J., 2014. A meta-analysis of sex differences in human brain structure. Neurosci. Biobehav Rev. 39, 34–50.
Segobin, S.H., Chételat, G., Le Berre, A.P., Lannuzel, C., Boudehent, C., Vabret, F., Eustache, F., Beaunieux, H., Pitel, A.L., 2014. Relationship between brain volumetric changes and interim drinking at six months in alcohol-dependent patients. Alcohol.: Clin. Exp. Res. 38, 739–748.
Seo, S., Beck, A., Matthis, C., Genauck, A., Banaschewski, T., Bokde, A.L., Bromberg, U., Büchel, C., Quinlan, E.B., Flor, H., 2019. Risk profiles for heavy drinking in adolescence: differential effects of gender. Addict. Biol. 24, 787–801.
Shim, J.H., Kim, Y.T., Kim, S., Baek, H.M., 2019. Volumetric reductions of subcortical structures and their localizations in alcohol-dependent patients. Front Neurol. 10, 247.
Sowell, E.R., Peterson, B.S., Kan, E., Woods, R.P., Yoshii, 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, 1550–1560.
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, 117–125.
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., 2016. Cognitive, emotion control, and motor performance of adolescents in the NCANDA study: contributions from alcohol consumption, age, sex, ethnicity, and family history of addiction. Neuropsychology 30, 449.
Volkow, N.D., Michaelides, M., Baler, R., 2019. The neuroscience of drug reward and addiction. Physiol. Rev. 99, 2115–2140.
Walker, C.D., Kuhn, C.M., Risher, M.L., 2021. The effects of peri-adolescent alcohol use on the developing hippocampus. Int Rev. Neurobiol. 160, 251–280.
Wierenga, L., Langen, M., Ambrosino, S., van Dijk, S., Oranje, B., Durston, S., 2014. Typical development of basal ganglia, hippocampus, amygdala and cerebellum from age 7 to 24. Neuroimage 96, 67–72.
Wierenga, L.M., Bos, M.G., Schreuders, E., vd Kamp, F., Peper, J.S., Tamnes, C.K., Crone, E.A., 2018a. Unraveling age, puberty and testosterone effects on subcortical brain development across adolescence. Psychoneuroendocrinology 91, 105–114.
Wierenga, L.M., Sexton, J.A., Laake, P., Giedd, J.N., Tamnes, C.K., Pediatric Imaging, N., Study, G., 2018b. A key characteristic of sex differences in the developing brain: greater variability in brain structure of boys than girls. Cereb. Cortex 28, 2741–2751.
Wood, S.N., 2017. Generalized additive models: an introduction with R. CRC press,.
Wooden, J.I., Thompson, K.R., Guerin, S.P., Nawarawong, N.N., Nixon, K., 2021. Consequences of adolescent alcohol use on adult hippocampal neurogenesis and hippocampal integrity. Int Rev. Neurobiol. 160, 281–304.
Zahr, N.M., Pfefferbaum, A., 2017. Alcohol's effects on the brain: neuroimaging results in humans and animal models. Alcohol Res 38, 183–206.