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# Disturbed Cerebellar Growth Trajectories in Adolescents Who Initiate Alcohol Drinking

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## ABSTRACT

**BACKGROUND:** The cerebellum is a target of alcoholism-related brain damage in adults, yet no study has prospectively tracked deviations from normal cerebellar growth trajectories in adolescents before and after initiating drinking.

**METHODS:** Magnetic resonance imaging tracked developmental volume trajectories of 10 cerebellar lobule and vermis tissue constituents in 548 no/low drinking youths age 12 to 21 years at induction into this 5-site, NCANDA (National Consortium on Alcohol and NeuroDevelopment in Adolescence) study. Over the 3- to 4-year longitudinal examination yielding 2043 magnetic resonance imaging scans, 328 youths remained no/low drinkers, whereas 220 initiated substantial drinking after initial neuroimaging.

**RESULTS:** Normal growth trajectories derived from no/low drinkers indicated that gray matter volumes of lobules V and VI, crus II, lobule VIIB, and lobule X declined faster with age in male youths than in female youths, whereas white matter volumes in crus I and crus II and lobules VIIIA and VIIIB expanded faster in female youths than in male youths; cerebrospinal fluid volume expanded faster in most cerebellar regions of male youths than female youths. Drinkers exhibited accelerated gray matter decline in anterior lobules and vermis, accelerated vermian white matter expansion, and accelerated cerebrospinal fluid volumes expansion of anterior lobules relative to youths who remained no/low drinkers. Analyses including both alcohol and marijuana did not support an independent role for marijuana in alcohol effects on cerebellar gray matter trajectories.

**CONCLUSIONS:** Alcohol use–related cerebellar growth trajectory differences from normal involved anterior lobules and vermis of youths who initiated substantial drinking. These regions are commonly affected in alcohol-dependent adults, raising the possibility that cerebellar structures affected by youthful drinking may be vulnerable to age–alcohol interactions in later adulthood.

*Keywords:* Adolescence, Alcohol, Brain, Cerebellum, Development, Marijuana

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For nearly a century, clinical and neuropathological studies have observed vulnerability of the cerebellum to excessive alcohol consumption (1,2). Initial findings on cell macrostructure and cellular dysmorphology were guided by detection of ataxia of gait notable in older dependent drinkers, with neuropathological examination revealing a selectivity of damage to the anterior lobules (2–4). Magnetic resonance imaging (MRI) studies later confirmed cerebellar volume shrinkage in alcohol use disorder (AUD) in vivo with selective effect on anterosuperior lobules (5–8) and regions of the corpus medullare (9). Despite this legacy of AUD-related cerebellar dysmorphology, little attention has been given to its potential insult in adolescents who initiate substantial drinking, which is now known to alter the trajectory of normal cortical development (10,11).

Only a few in vivo neuroimaging studies have measured cerebellar volume in high-drinking compared with low-drinking adolescents, and all have been cross-sectional, making it difficult to rule out the role of pre-exposure factors causing group differences (12). Youths who engaged in binge drinking exhibited volume deficits of the cerebellar hemispheres that were significant for gray matter but marginal for white matter and without sex differences; volume deficit severity was related to binge-drinking intensity measured as peak number of drinks in the 3 months before MRI acquisition (13). A cross-sectional study of adolescents and young adults with adolescent-onset AUD identified volume deficits in the total cerebella of male ($n$ = 8), but not female ($n$ = 6), youths relative to their sex-matched control groups (14). A role for family history of alcoholism was identified in late adolescents and young adults, where high-risk offspring ($n$ = 72) had larger volumes of the corpus medullare than low-risk offspring ($n$ = 59) and had a cerebellar region inferior to the horizontal fissure (lobules VIIA to X and tonsil). Although history of alcohol use

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was accounted for statistically for the 22 high-risk participants who met diagnostic criteria for alcohol or drug abuse or dependence before MRI, a follow-up analysis of this subgroup was not reported (15).

The recognized influence of alcohol on the cerebellum in adult AUD, together with a few small-scale studies supporting cerebellar vulnerability during growth years of adolescence, provides justification for conducting longitudinal investigation using refined measurement approaches to track potential trajectory deviations from normal regional cerebellar development (16). The first step in this endeavor requires establishment of normal growth trajectories and consideration of sexual dimorphism in maturing adolescents, with adolescence age range now hypothesized to extend into the early 20s (17). Cross-sectional MRI studies (18–20) confirmed with longitudinal examination (10,11,21) describe cortical growth patterns by tissue type and region, indicating gray matter volume decline complemented by white matter and cerebrospinal fluid (CSF) volume increase during adolescence into young adulthood. This systematic neurorestructuring may be a reflection of gray matter pruning to accommodate environmental experience and genetic influence, and white matter growth to expand connectivity for increasing potential for complex cognition. To date, the few studies of cerebellar development in adolescence (22–25) have focused on volume of the total structure and indicate nonspecific declines with age.

An initial longitudinal study measured volumetric changes in regions of the cerebellar vermis and hemispheres of 25 male and 25 female participants, age 5 to 24 years at baseline, selected quasi-randomly from the National Institute of Mental Health longitudinal study of normal brain development to have had at least 3 MRI scans at 2-year intervals (26). Adjustment for total brain volume attenuated, but did not fully remove, the ubiquitous sex differences of greater cerebellar volumes in males than in females, notable in the superoposterior region. Sex differences in developmental trajectories of other regions may have been blurred because volumes were not analyzed by tissue type, i.e., gray matter, white matter, and CSF, each of which follows different growth trajectories in the cerebral cortex (19,21,27–29) and may also do so in the cerebella (30). Furthermore, sexual dimorphism in cerebellar volume change over intervals of 1.5 to 5.6 years indicated that boys followed a quadratic function with a peak in volume at age 15.6 years, whereas girls showed steady decline over the 7- to 24.3-year age range in the 53 youths examined 2 or more times (31). Despite the strength of longitudinal studies, none to date have tracked developmental changes in the separate tissue types or in parcellated lobules of this complex structure (32,33), which may develop differentially by age and sex (34) and be differentially vulnerable to environmental insult from alcohol use (35).

In this article, we report a novel longitudinal analysis of structural MRI data collected at 3 or 4 annual visits in 548 youths of the NCANDA (National Consortium on Alcohol and NeuroDevelopment in Adolescence) study (36). All participants had met study entry criteria for no/low drinking and drug consumption at initial MRI. By the fourth MRI, 220 had initiated drinking beyond levels permitted at study entry, and 328 remained no/low drinkers, thus providing the basis for a prospective study on the effects of drinking on the adolescent cerebellum. Accordingly, this study had 3 aims: 1) to characterize normal developmental trajectories and potential sexual dimorphism of gray matter, white matter, and CSF volumes of the total cerebellum in youths who remained no/low drinkers for all MRI examinations; 2) to determine normal growth patterns by sex of cerebellar volumes by lobule; and 3) to localize patterns of deviations from normal by region and tissue type in youths who initiated moderate to heavy alcohol use. Additional analyses explored whether the magnitudes of cerebellar volume trajectory deviations were related to quantity or frequency of drinking, co-use of alcohol and marijuana, or motor performance.

## METHODS AND MATERIALS

### Participants

This longitudinal analysis included 548 participants who were no/low drinkers at baseline and had 2 or 3 additional (annual) follow-up MRI scans: 80 participants had 3 MRI scans, and 468 had 4 MRI scans, totaling 2043 scans. The institutional review boards of the 5 NCANDA sites approved this study: University of California at San Diego, SRI International, Duke University Medical Center, University of Pittsburgh, and Oregon Health & Science University (36).

**Subject Demographics.** As described previously (11), participants were characterized by age, sex, self-identified ethnicity, and socioeconomic status as determined as the highest level of education achieved by either parent (Table 1) (37). All participants submitted samples to a 14-panel urine toxicology screen for data exclusion if positive on the study day (11,36).

**Criteria for Alcohol Grouping.** All 548 participants at study entry met 2 sets of drinking criteria determined with the Customary Drinking and Drug Use Record (38) described previously (11,36) and herein. First, the initial NCANDA inclusion criteria for no/low drinking were as follows: maximum lifetime drinking days for male and female participants was ≤5 for age 12 to 15.9 years, ≤11 for age 16 to 16.9 years, ≤23 for age 17 to 17.9 years, and ≤51 for age 18 years old and older. The maximum allowable drinks per occasion was ≤3 for female participants at any age but varied by age for male participants: ≤3 for age 12 to 13.9 years, ≤4 for age 14 to 19.9 years, and ≤5 for age 20 years old and older. Second, heavy, moderate, and no/low drinkers were categorized using the modified Cahalan *et al.* (39) inventory, comprising quantity (average and maximum consumption) and frequency combinations to classify drinking levels based on past year patterns. The final data set comprised 328 youths who remained in the no/low double criterion group and 220 youths who transitioned from no/low drinkers to either moderate drinkers ($n$ = 120) or heavy drinkers ($n$ = 100) (Table 1). Also determined was lifetime marijuana use (in days) at the time of the final MRI scan.

### MRI Acquisition and Analysis

MRI scans were acquired on 3T systems from 2 manufacturers: 3T Discovery MR750 scanners (GE Healthcare, Waukesha, WI) at 3 sites (University of California at San Diego, SRI

**Table 1. NCANDA Demographics for 548 Youths at Baseline and Final MRI Visit of Subgroups Defined by Interim Drinking**

| | Baseline | Longitudinal (Values at Final MRI) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Transitioned to Drinking | | | | | | |
| | Full Group No/Low | Maintained No/Low | Moderate | Heavy | All | Statistic | No/Low vs. Moderate | No/Low vs. Heavy | No/Low vs. All |
| Age at Baseline, Years | | | | | | | | | |
| Male | | | | | | | | | |
| Mean | 15.61 | 17.82 | 19.18 | 19.60 | 19.42 | *t* | −3.808 | −6.049 | −6.126 |
| SD | 2.27 | 2.26 | 2.20 | 1.86 | 2.02 | *p* | .0003 | .000 | .000 |
| *n* | 272 | 159 | 50 | 63 | 113 | | | | |
| Female | | | | | | | | | |
| Mean | 15.65 | 17.83 | 19.69 | 19.77 | 19.72 | *t* | −6.088 | −5.107 | −7.110 |
| SD | 2.33 | 2.26 | 2.10 | 2.06 | 2.08 | *p* | .000 | .000 | .000 |
| *n* | 276 | 169 | 70 | 37 | 107 | | | | |
| Male and female | | | | | | | | | |
| Mean | 15.63 | 17.82 | 19.48 | 19.66 | 19.56 | *t* | −7.159 | −8.023 | −9.353 |
| SD | 2.30 | 2.26 | 2.15 | 1.92 | 2.05 | *p* | .000 | .000 | .000 |
| *n* | 548 | 328 | 120 | 100 | 220 | | | | |
| Socioeconomic Status[a] | | | | | | | | | |
| Mean | 16.74 | 16.66 | 16.85 | 16.91 | 16.88 | *t* | −0.710 | −0.951 | −1.03 |
| SD | 2.49 | 2.52 | 2.58 | 2.28 | 2.45 | *p* | .000 | .343 | .305 |
| *n* | 548 | 328 | 120 | 100 | 220 | | | | |
| BMI Percentile | | | | | | | | | |
| Mean | 58.59 | 59.52 | 59.20 | 51.25 | 55.86 | *t* | 0.109 | 2.447 | 1.571 |
| SD | 28.45 | 29.22 | 26.84 | 29.70 | 28.39 | *p* | .913 | .0155 | .117 |
| *n* | 548 | 326 | 120 | 100 | 220 | | | | |
| Internalizing Symptoms T Score | | | | | | | | | |
| Mean | 47.58 | 47.43 | 46.58 | 46.05 | 46.35 | *t* | 0.704 | 1.134 | 1.147 |
| SD | 8.23 | 10.08 | 11.71 | 10.52 | 11.17 | *p* | .482 | .2585 | .252 |
| *n* | 548 | 324 | 119 | 95 | 214 | | | | |
| Externalizing Symptoms T Score | | | | | | | | | |
| Mean | 47.35 | 46.89 | 46.38 | 44.65 | 45.62 | *t* | 0.456 | 2.115 | 1.480 |
| SD | 8.08 | 9.34 | 10.91 | 8.99 | 10.12 | *p* | .649 | .036 | .14 |
| *n* | 548 | 324 | 119 | 95 | 214 | | | | |
| Lifetime Drinking Days | | | | | | | | | |
| Mean | 0.39 | 0.96 | 18.98 | 67.18 | 40.89 | *t* | −10.079 | −10.226 | −11.429 |
| SD | 1.42 | 2.65 | 19.52 | 64.72 | 51.77 | *p* | .000 | .000 | .000 |
| *n* | 548 | 325 | 120 | 100 | 220 | | | | |
| Lifetime Drinks | | | | | | | | | |
| Mean | 0.01 | 1.18 | 42.39 | 249.07 | 140.24 | *t* | −9.694 | −11.777 | −10.97 |
| SD | 0.14 | 3.98 | 42.23 | 198.57 | 173.77 | *p* | .000 | .000 | .000 |
| *n* | 474 | 283 | 99 | 89 | 188 | | | | |

**Table 1. Continued**

| | Baseline | Longitudinal (Values at Final MRI) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Transitioned to Drinking | | | | | | |
| | Full Group No/Low | Maintained No/Low | Moderate | Heavy | All | Statistic | No/Low vs. Moderate | No/Low vs. Heavy | No/Low vs. All |
| Lifetime Binges | | | | | | | | | |
| Mean | 0.00 | 0.003 | 2.27 | 26.07 | 13.09 | *t* | −7.129 | −8.551 | −8.144 |
| SD | 0.00 | 0.055 | 3.48 | 30.49 | 23.83 | *p* | .000 | .000 | .000 |
| *n* | 548 | 325 | 120 | 100 | 220 | | | | |
| Lifetime Marijuana Days | | | | | | | | | |
| Mean | 28.22 | 3.66 | 29.36 | 107.17 | 64.73 | *t* | −2.859 | −5.202 | −5.723 |
| SD | 102.88 | 24.65 | 90.34 | 195.90 | 152.62 | *p* | .005 | .000 | .000 |
| *n* | 548 | 328 | 120 | 100 | 220 | | | | |
| Cigarette Smokers[b] | | | | | | | | | |
| No/yes | 520/27 | 304/24 | 87/33 | 47/53 | 134/86 | $\chi^2$ | 32.229 | 108.400 | 82.861 |
| | | | | | | *p* | .00001 | .00001 | .00001 |
| Family History of Alcoholism | | | | | | | | | |
| Negative/positive | 502/46 | 302/26 | 111/9 | 89/11 | 200/20 | $\chi^2$ | 0.0220 | 0.917 | 0.232 |
| | | | | | | *p* | .881 | .338 | .63 |
| Self-Declared Ethnicity | | | | | | | | | |
| Caucasian, *n* | 407 | 227 | 95 | 85 | 180 | $\chi^2$ | 9.3210 | 9.731 | 14.352 |
| African American, *n* | 74 | 58 | 8 | 8 | 16 | *p* | .025 | .021 | .002 |
| Asian, *n* | 59 | 37 | 16 | 6 | 22 | | | | |
| Other, *n* | 8 | 6 | 1 | 1 | 2 | | | | |
| Site (Scanner Manufacturer) | | | | | | | | | |
| UPitt (Siemens Healthcare), *n* | 72 | 46 | 15 | 11 | 26 | $\chi^2$ | 4.361 | 6.630 | 8.618 |
| SRI (GE Healthcare), *n* | 96 | 52 | 24 | 20 | 44 | *p* | .359 | .157 | .071 |
| Duke (GE Healthcare), *n* | 112 | 79 | 19 | 14 | 33 | | | | |
| OHSU (Siemens Healthcare), *n* | 118 | 68 | 28 | 22 | 50 | | | | |
| UCSD (GE Healthcare), *n* | 150 | 83 | 34 | 33 | 67 | | | | |

BMI, body mass index; Duke, Duke University Medical Center; MRI, magnetic resonance imaging; NCANDA, National Consortium on Alcohol and NeuroDevelopment in Adolescence; OHSU, Oregon Health & Science University; SRI, SRI International; UCSD, University of California at San Diego; UPitt, University of Pittsburgh.

[a]Highest education of a parent.

[b]Yes = ever smoked a cigarette.

International, and Duke University Medical Center), and 3T TIM Trio scanners (Siemens Healthcare, Erlangen, Germany) at 2 sites (University of Pittsburgh and Oregon Health & Science University). Cerebellar tissue was segmented into gray matter, white matter, and CSF (Figure 1); lobular quantification was accomplished with the spatially unbiased infratentorial (SUIT) atlas (Figure 2) (40). Further details appear in the Supplement and have been described previously (11).

## Statistical Analysis

The final unit of measure for each tissue type was its probability times the voxel volume. Dependent measures were segmented volumes of gray matter, white matter, and CSF for the whole cerebellum and for volumes of the SUIT lobular and vermis parcellations. Covariate variables were self-identified ethnicity (Asian, African American, Caucasian, other), collection site, scanner manufacturer (GE Healthcare, Siemens Healthcare), and intracranial volume (ICV).

**Developmental Patterns Derived From the No/Low Drinking Group.** Analysis of the cerebellum as a whole and as segmented by tissue type was multilayered, starting with a salient sex difference that all native volumes were significantly greater for male participants than for female participants as groups. These differences were markedly attenuated, but not completely eliminated, when controlling for ICV, manufacturer, site, and ethnicity using stepwise Akaike information criterion (stepAIC in R; R Foundation for Statistical Computing, Vienna, Austria [http://www.r-project.org/]) to select variables to include in the final general linear model. Linear mixed effects modeling (lmer in R) was performed on the residual values (with the mean of all subjects added to preserve relative magnitudes) to examine the volumetric change over age.

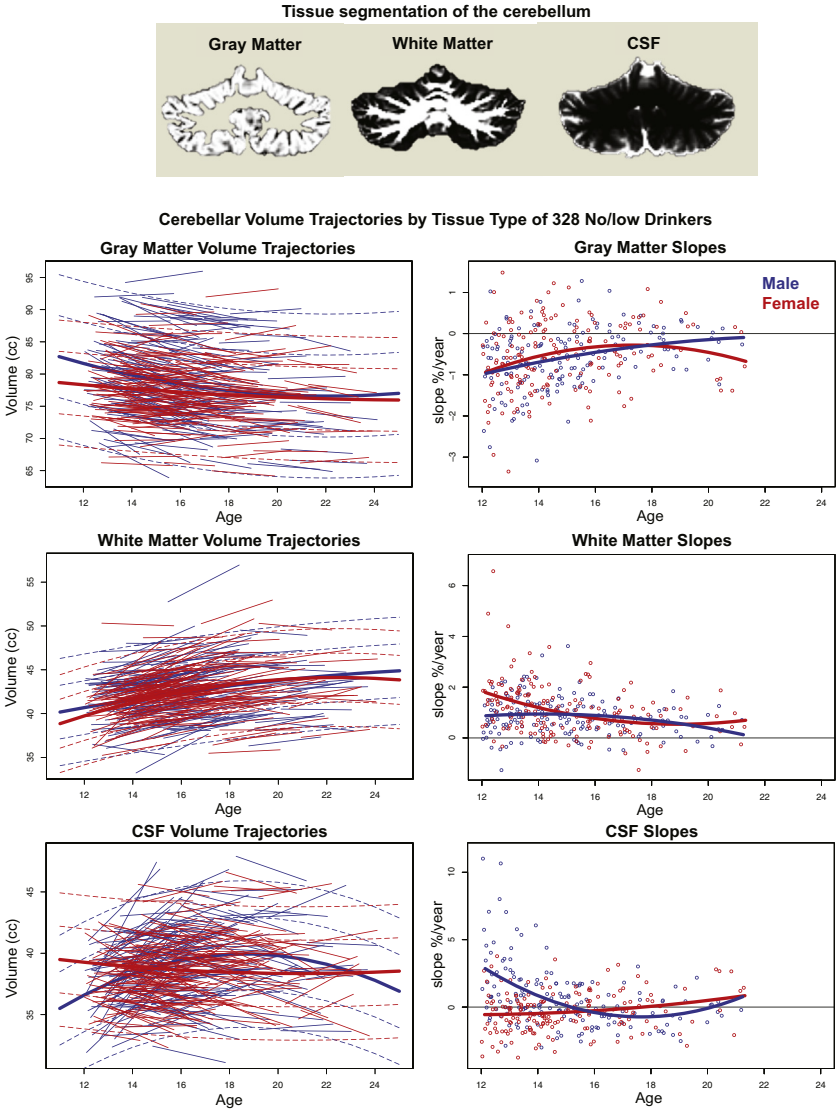


**Figure 1.** (Top panel) Example of tissue segmentation of a coronal slice through the cerebellum. (Bottom left panel) Data plots show cerebellum volume trajectories by tissue type of the 328 no/low drinkers plotted over age at magnetic resonance imaging. The lmer fits with ±1 and 2 SD separately computed for boys (blue) and girls (red) are also plotted. (Bottom right panel) Data plots show slope (expressed as % change per year) of each participant plotted over age at initial magnetic resonance imaging. Although the regression fits by sex are different, overall the rate of gray matter volume loss diminishes with age, whereas white matter growth slows in older adolescence in both sexes. Trajectories of the cerebrospinal fluid (CSF) volumes followed quadratic function in boys and a linear function in girls; the suggestion of increasing slopes in early adulthood might herald the normal aging effect of CSF volume accrual with age-related tissue shrinkage.

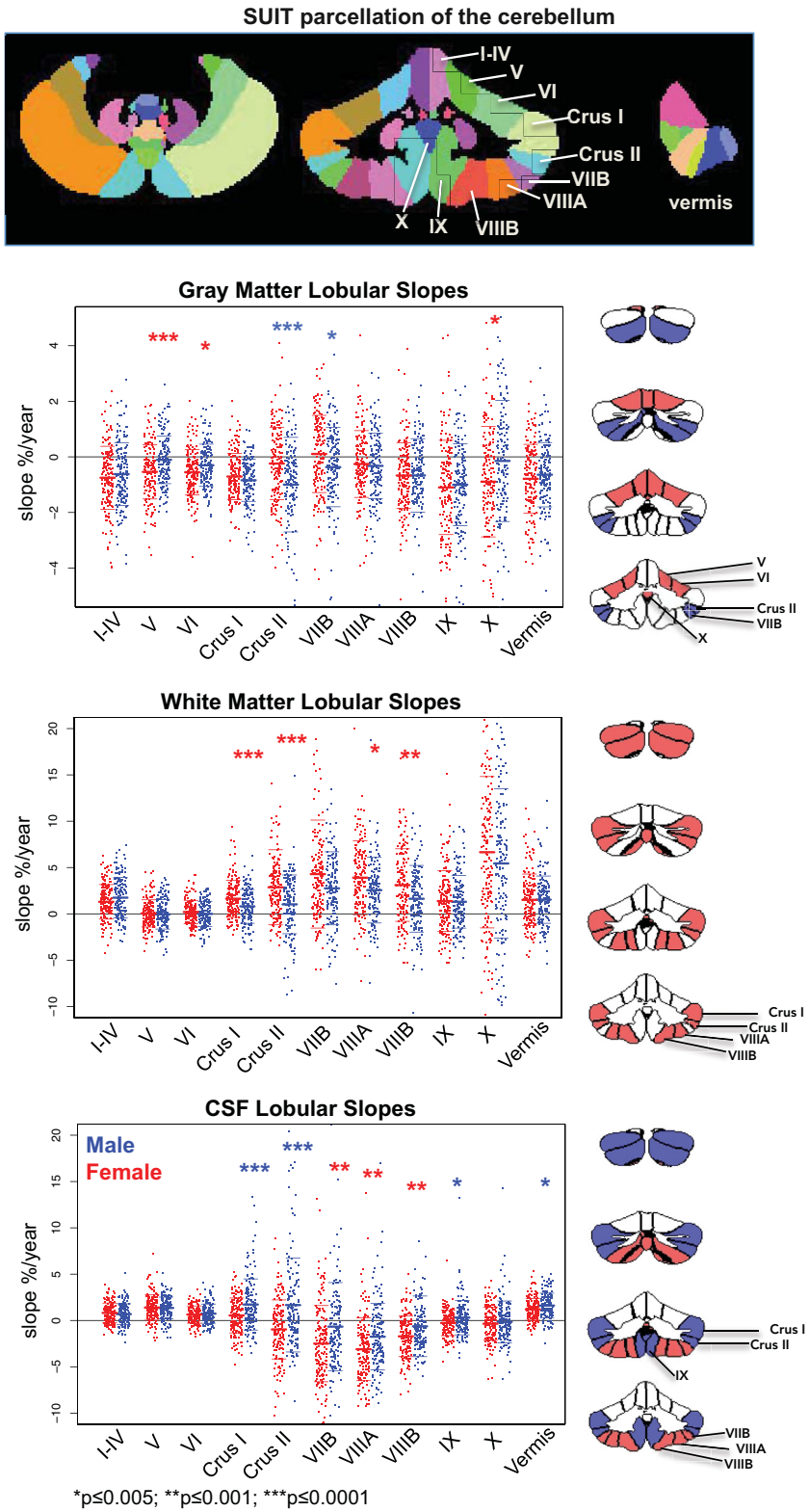


**Figure 2.** (Top panel) Color-coded labels of the quantified lobules and vermis of the cerebellum. (Bottom left panel) Jitterplots of slopes (expressed as % change per year) by tissue type for each male (blue) and female (red) participant who remained as the 328 no/low drinkers. Asterisks mark sex differences in slopes meeting correction for multiple comparisons. (Bottom right panel) Coronal cerebellar slices indicate lobules showing sex differences. For gray matter, the slopes were steeper (that is, showed faster volume declines) in female participants than in male participants (lobules V, VI, and X) (marked in red), whereas the slopes were steeper in male participants than in female participants (crus II and lobule VIIB) (marked in blue). For white matter, slopes indicated faster increases in crus I, crus II, lobule VIIIA, and lobule VIIIB of female participants than male participants (marked in red). The pattern of sexual dimorphism was complex for cerebrospinal fluid (CSF) volume changes. The slopes were steeper in crus I, crus II, and lobule X (marked in blue) indicating faster rates of CSF volume increases in male participants than in female participants. By contrast, the slopes were steeper in lobules VIIB, VIIIA, and VIIIB (marked in red) indicating faster rates of CSF volume decreases in female participants than in male participants. SUIT, spatially unbiased infratentorial.

Analysis of age-dependent trajectories of parcellated lobules by tissue type was based on slopes, which represented change in cerebellar volumes over time and comprised a series of linear changes per individual. Accordingly, for each subject, the slope of 3 or 4 annual data points was computed as a function of the subject's centered age (each subject's age − mean age) and then expressed as a percent of the first (baseline) observation. Thus, slopes were expressed as percent change per year from baseline and were computed for volumes of the total cerebellum and SUIT lobules and each tissue type. Slopes were regressed against (age + age$^2$ + ICV + manufacturer + site + ethnicity) using stepAIC to select variables to include in the final general linear model. To preserve directional information, the average slope for the whole group was added to the residuals to form the final slope metric for each subject for each SUIT lobule (also done below). Sex differences were tested with *t* tests.

**Testing Differences Between Drinking Groups.** Slopes of individual participants were computed for all adolescents, participants who remained no/low drinkers, and participants who had moved from no/low consumption to the category of moderate or heavy drinking criteria based on Cahalan *et al.* (39). To determine the effect of drinking, a general linear model predicted slope as a function of drinking (no/low vs. drinker) + age + age$^2$ + sex + ICV + manufacturer + site + ethnicity, using stepAIC to select variables to include in the final model. No/low versus combined moderate plus heavy drinker slope differences were tested with *t* tests. This procedure was also performed with separate drinker categories (moderate and heavy).

## RESULTS

### Trajectories of Normal Cerebellar Structural Growth by Sex

**Total Volumes by Tissue Type.** On average, the total cerebellum comprising all gray matter, white matter, and CSF volumes was significantly larger in male participants than in female participants (169 cc vs. 151 cc: $t_{1158.7}$ = 24.023, $p$ = .00001) with little evidence for growth beyond midteen years (Supplemental Figure S1, top). Adjustment for ICV markedly attenuated the sex difference in cerebellar total volume (Supplemental Figure S1, bottom).

Segmenting the ICV-corrected total volume by tissue type revealed age-related sex differences in growth patterns. Gray matter volume declined faster in male youths than in female youths with age (lmer age-by-sex $z$ = −5.874, $p$ = .0001). By contrast, white matter volume enlarged faster in female youths than in male youths (age-by-sex $z$ = −3.104, $p$ = .0019), whereas CSF volume expanded faster in male youths than in female youths over age (age-by-sex $z$ = 8.150, $p$ = .0000) (Figure 1 and Supplemental Figure S2). The developmental trajectories were quadratic for boys for all 3 tissue types but followed linear trends for gray matter and CSF in girls (Table 2).

**Slopes of Lobular Volumes by Tissue Type.** Gray matter volumes declined with age in all 11 regions in male youths and in 10 regions in female youths, whose sole positive slope was for lobule VIIB (Figure 2, Supplemental Table S1). Significantly faster gray matter volume declines occurred in lobules V, VI, and X of girls relative to boys, whereas boys showed faster volume declines than girls in crus II. Lobule VIIB trajectories were positive for girls, but negative for boys. White matter slopes indicated positive volumetric acceleration that

**Table 2. Fits of Regressions of Total Volumes by Tissue Type Over Age in the No/Low Group**

| | Linear Age *z* | Age *p* | Quadratic Age *z* | Age *p* | Age$^2$ *z* | Age$^2$ *p* |
|---|---|---|---|---|---|---|
| Male and Female | | | | | | |
| Gray matter | −13.600 | .000000 | −6.530 | .000000 | 4.738 | .000002 |
| White matter | 24.370 | .138000 | 10.189 | .000000 | −6.952 | .000000 |
| CSF | 4.058 | .000050 | 5.642 | .000000 | −5.160 | .000000 |
| Total | 8.932 | .000000 | 7.769 | .000000 | −6.598 | .000000 |
| Male | | | | | | |
| Gray matter | −13.420 | .000000 | −7.370 | .000000 | 5.550 | .000000 |
| White matter | 15.910 | .000000 | 4.584 | .000005 | −2.468 | .013600 |
| CSF | 7.753 | .000000 | 9.710 | .000000 | −8.697 | .000000 |
| Total | 6.611 | .000000 | 7.241 | .000000 | −6.362 | .000000 |
| Female | | | | | | |
| Gray matter | −6.143 | .000000 | – | – | – | – |
| White matter | 18.570 | .000000 | 9.663 | .000000 | −7.172 | .000000 |
| CSF | −3.331 | .000865 | – | – | – | – |
| Total | 6.056 | .000000 | 3.608 | .000309 | −2.818 | .004829 |
| Age-by-Sex Interaction | | | | | | |
| Gray matter | −5.874 | .000000 | | | | |
| White matter | −3.104 | .001910 | | | | |
| CSF | 8.150 | .000000 | | | | |
| Total | 1.483 | .138000 | | | | |

CSF, cerebrospinal fluid.

**Table 3. Group Differences in Slopes of Volumes of Cerebellar Tissue Type**

| | No/Low Youth ($n$ = 328) | | Moderate Drinkers ($n$ = 120) | | No/Low vs. Moderate | | |
|---|---|---|---|---|---|---|---|
| Slope[a] | Mean | SD | Mean | SD | $t$ | $df$ | $p^b$ |
| Gray Matter Overall | −0.501 | 0.746 | −0.673 | 0.934 | 1.811 | 177.513 | .0718 |
| White Matter Overall | 0.895 | 0.863 | 0.990 | 0.876 | −1.021 | 208.942 | .3082 |
| CSF Overall | 0.039 | 1.842 | 0.537 | 1.644 | −2.746 | 235.296 | .0065 |
| | No/Low Youth ($n$ = 328) | | Heavy Drinkers ($n$ = 100) | | No/Low vs. Heavy | | |
| | Mean | SD | Mean | SD | $t$ | $df$ | $p^b$ |
| Gray Matter Overall | −0.501 | 0.746 | −0.803 | 1.133 | 2.501 | 126.235 | .0137 |
| White Matter Overall | 0.895 | 0.863 | 1.158 | 0.952 | −2.473 | 152.008 | .0145 |
| CSF Overall | 0.039 | 1.842 | 0.217 | 1.565 | −0.955 | 189.998 | .3407 |
| | No/Low Youth ($n$ = 328) | | All Drinkers ($n$ = 220) | | No/Low vs. All | | |
| | Mean | SD | Mean | SD | $t$ | $df$ | $p^b$ |
| Gray Matter Overall | −0.501 | 0.746 | −0.732 | 1.029 | 2.858 | 369.893 | .0045 |
| White Matter Overall | 0.895 | 0.863 | 1.067 | 0.913 | −2.203 | 451.626 | .0281 |
| CSF Overall | 0.039 | 1.842 | 0.391 | 1.613 | −2.368 | 508.888 | .0183 |

CSF, cerebrospinal fluid.
[a]Slopes are adjusted for intracranial volume, age, socioeconomic status, site, and manufacturer.
[b]Bonferroni correction ($\alpha$ = .05, 2-tailed) for 3 tissue comparisons $p \leq .017$.

was significantly greater in girls than in boys in crus I, crus II, lobule VIIIA, and lobule VIIIB. CSF volume slopes of crus I and the vermis were positive for both sexes but indicated faster increases for male youths than for female youths. The opposite occurred for lobules VIIB, VIIIA, and VIIIB. The CSF expansion patterns indicated positive slopes for male youths and negative slopes for female youths in crus II and lobule IX.

## Deviations From Normal Cerebellar Development in Drinkers

All analyses seeking group differences or correlations controlled for age, sex, manufacturer, site, ethnicity, and ICV. Change in volumes (i.e., trajectory) is expressed as slope, that is, percent change per year from baseline.

**Slopes of Volumes by Tissue Type.** The trend across all lobules and the vermis was for the drinkers to have faster declining gray matter volumes with age than the no/low group (Table 3; Figures 3–5). The gray matter slope differences were strongest in the anterosuperior lobules (lobules I to IV, lobule V, lobule VI, crus I, crus II, and lobule VIIB with $p \leq .05$) with crus I meeting the most stringent correction for multiple comparisons (Supplemental Table S2). Both the white matter and the CSF slope differences indicated that the drinkers had faster

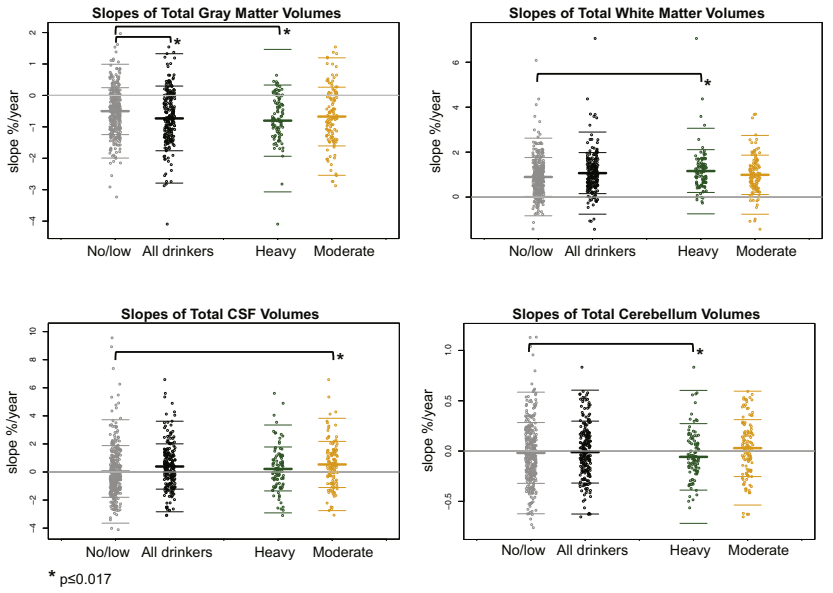


**Figure 3.** Jitterplots of total cerebellar slopes (expressed as % change per year) by each tissue type for the 328 no/low drinkers (gray), all 220 youths who initiated moderate or heavy drinking (black), and the drinkers divided by amount drunk: 100 heavy drinkers (green) and 120 moderate drinkers (gold). Asterisks mark differences from the no/low drinking group in slopes meeting correction for multiple comparisons. CSF, cerebrospinal fluid.

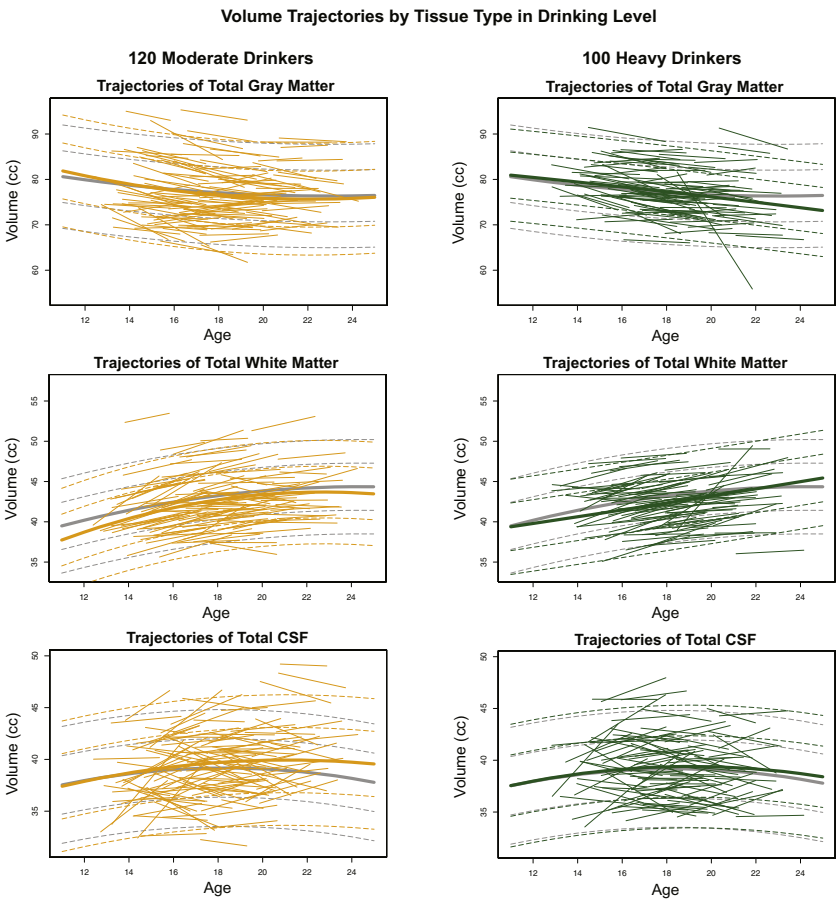


**Figure 4.** Trajectories (i.e., regression lines) of individual moderate drinkers (gold) and heavy drinkers (green). The lmer fits with ±1 and 2 SD separately computed for no/low drinkers (gray), moderate drinkers (gold), and heavy drinkers (green) are also plotted. CSF, cerebrospinal fluid.

increasing volumes than the no/low group. Significant accelerations in the drinkers were present in white matter volumes of vermis and CSF volumes of lobules I to IV, lobule V, and crus I (Figure 5). In no case was the group-by-sex interaction significant.

**Exploratory Correlations Among and With Lobular Trajectories.** Examination of the degree to which cerebellar lobules had similar or dissimilar age-related developmental trajectories was examined by construction of correlational matrices for the gray matter volume slopes of the 10 cerebellar lobules and the vermis (55 pairs of correlations) separately for the no/low and drinking groups. The average within-cerebellum correlations were $r = .372$ for the no/low group and $r = .525$ for the drinking group. Although no individual pair of correlational differences between drinkers and the no/low group met statistical significance criteria for comparison between 2 correlations, of the 55 possible pairs of correlations, 53 were higher for drinkers than for no/low drinkers (Supplemental Figure S3). The 55 correlations for the no/low group and the 55 correlations for drinkers (after *r*-to-*z* transformation) were entered as separate values into a 2-group *t* test and revealed that overall the correlations of the drinkers were significantly higher than those of the no/low group ($t_{107.59} = 3.736$, $p = .0003$).

Simple correlations between motor performance on the Grooved Pegboard test (dominant hand) [see Supplement for test description (41)], and each cerebellar gray matter slope revealed small negative correlations with slopes of lobules I to IV and the vermis that were numerically great in the total group of drinkers (IV, $r = -.208$, $p = .0022$; vermis, $r = -.167$, $p = .0144$) than in the controls (IV, $r = -.044$, $p = .4484$; vermis, $r = -.031$, $p = .5861$). The differences between correlations, however, were not significant (I to IV, $z = -1.869$, $p = .0617$; vermis, $z = -1.532$, $p = .1255$).

Exploration of group differences in regional gray matter slopes in relation to family history of alcoholism identified a few modest differences, none of which would sustain correction for multiple comparisons ($\alpha = .05$ for 12 comparisons, $p \leq .004$, 2-tailed). The largest difference was observed in the drinkers, where the family history–positive group had a steeper slope of lobules I to IV (i.e., faster volume decline; mean = −0.913) than the family history–negative group (mean = −0.207; $t = -2.749$, $p = .0127$).

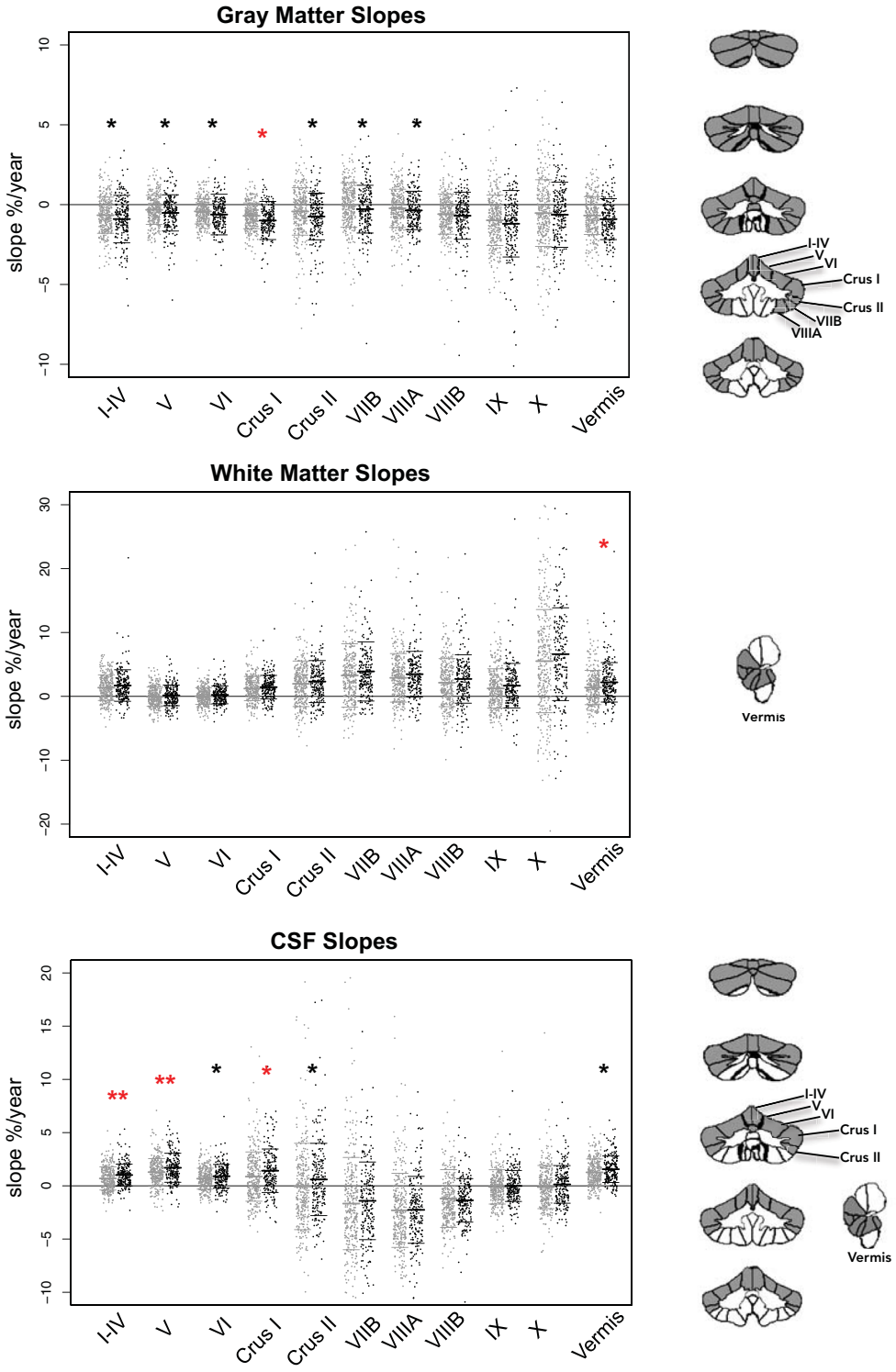


**Figure 5.** Jitterplots of slopes (expressed as % change per year) by tissue type for the 328 no/low drinkers (gray) and all 220 youths who initiated moderate or heavy drinking (black). Red asterisks mark differences from the no/low drinking group in slopes meeting correction for multiple comparisons. Black asterisks note differences with $p \leq .05$ (also see Table 3). The cerebellar images to the right of the jitterplots display in gray the lobules showing group differences ($p \leq .05$) in slopes. CSF, cerebrospinal fluid.

**Differences by Drinking Level.** Exploratory analyses tested for differences between the no/low drinking group and separately for the moderate and heavy drinking subgroups (Table 3). For the total cerebellum, the heavy drinkers had faster rates of gray matter decline and white matter increase than the no/low group ($p < .015$). The moderate drinkers had faster rates of CSF increase than the no/low group ($p = .0065$).

Modest nonparametric correlations emerged between the log-transformed lifetime drinking days across all participants and slopes of each tissue volume. A negative correlation with gray matter slopes ($\rho = -.098$, $p = .0211$) indicated steeper trajectory declines with more alcohol exposure. Positive correlations with white matter ($\rho = .111$, $p = .0093$) and CSF ($\rho = .116$, $p = .0068$) slopes indicated faster increases with greater alcohol exposure.

### Marijuana and Alcohol Co-use

Among all participants who endorsed using alcohol or marijuana ($n = 321$), 127 (40%) youths consumed alcohol but not marijuana, 171 (53%) were co-users, and 23 (7%) used marijuana but not alcohol. To explore the contribution of marijuana use, we used 2 approaches to examine the effects and interactions of lifetime marijuana use on slopes of total cerebellum volume and tissue types (Supplemental Table S3).

First, to the full linear models (no/low vs. drinker and no/low vs. moderate plus heavy drinker), controlling for age, sex, manufacturer, site, ethnicity, and ICV, we added log lifetime days of marijuana use. This analysis failed to yield any significant marijuana use effects or interactions for slopes of any total cerebellum tissue type.

Second, using data from all 548 participants, we entered log lifetime days of marijuana use and log lifetime drinking days instead of the alcohol use categorical grouping variables into the general linear models. Using marijuana days without considering alcohol use revealed a significant effect of lifetime marijuana on the gray matter slope ($z = -1.982$, $p = .0480$); a similar analysis of lifetime drinking days without consideration of marijuana yielded a larger effect ($z = -3.424$, $p = .00062$). When marijuana and alcohol were entered into the same model, only the alcohol effect ($z = -2.462$, $p = .0141$), and not a marijuana effect ($z = -0.958$, $p = .3384$), was significant, and there was no interaction between the 2 use measures ($z = 0.949$, $p = .3432$). A similar pattern of results emerged for cerebellar white matter slopes but produced no significant effects or interactions for marijuana. Furthermore, neither lifetime drinking nor lifetime marijuana use was a significant predictor of CSF volume slopes.

## DISCUSSION

In addressing the 3 study aims, we found that 1) the cerebellar volumes of youths who remained in the no/low group for all MRI examinations exhibited sexual dimorphism, with male youths having larger gray matter, white matter, and CSF volumes, a difference that was attenuated with adjustment for ICV; 2) normal developmental rates of tissue and lobular volumetric change differed by sex; and 3) rates of change, detected most robustly in regional gray matter and CSF volume slopes, were greater in youths who initiated substantial alcohol use than in youths who refrained from such drinking.

### Patterns of Normal Cerebellar Development

In the 348 participants who remained no/low drinkers, the annual rates of change differed by tissue type and sex, effects not detectable when measuring the total, undifferentiated cerebellum. Gray matter volumes declined faster and CSF volumes increased faster in male youths than in female youths, whereas white matter volume expanded at faster rates in female youths than in male youths. Annual rates of gray matter volume declines for male youths were quadratic and on average −0.61%/year and were linear for female youths and on average −0.53%/year. By contrast, rates of white matter volume growth were 1.11%/year for female youths and 0.86%/year for male youths. Although CSF volumes expanded in male youths (0.71%/year), CSF volumes contracted in female youths (−0.34%/year). The gray matter findings are consistent with a previous longitudinal study (31), in which boys followed a quadratic function with a peak in gray matter volume at age 15.6 years, whereas girls showed a steady decline without evidence for an inflection over the age range of 7 to 24 years examined.

Tracking neuromaturational change in tissue constituent by lobular volume and sex is novel and extends the few existing longitudinal studies of adolescent cerebellar development. Gray matter volume declines were faster in lobules V, VI, and X of girls than in boys, whereas the opposite held for crus II and lobule VIIB; these lobules are included in the superoposterior region and are among the last to have developed phylogenetically in evolution and ontogenetically in adolescence (26). Although white matter volume evidenced expansion in both sexes, growth rates were greater in female youths than in male youths in crus I and crus II and lobules VIIIA and VIIIB; these lobules are included in the inferoposterior region, which were among the first to develop phylogenetically (26). Rates of CSF volume changes were variable by lobule and sex, showing greater expansion in crus I and crus II, lobule IX, and the vermis of boys than those of girls, but greater expansion in lobules VIIIA and VIIIB of girls than boys. Division of lobule by tissue type expands depiction of age and sex influences on maturation of the cerebellum, contributing to underlying causes of its regional allometry (26). One resulting speculation suggests that if regions differ in rates of development, it may be that untoward effects of exposure to agents such as alcohol or drugs would be magnified during active development.

### Alcohol Use–Related Deviations From Normal Cerebellar Development

Quantitative structural analysis of the cerebellum revealed accelerated gray matter decline and CSF expansion in the total group of youths who initiated moderate to heavy drinking. The trend across all lobules and the vermis was for the drinkers to have faster declining gray matter volumes with age than the no/low group. These alcohol use–related cerebellar trajectory differences were located primarily in the vermis and anterosuperior lobules, which are regions commonly affected in adults with chronic alcoholism [(in vivo, lobules 5 and 6);

(postmortem, lobules 2, 3, 4)]. Remaining to be tested is whether youths who refrain from excessive alcohol consumption can show structural recovery; furthermore, even if recovery occurs, one might question whether the structures affected with youthful drinking are selectively vulnerable to age–alcohol interactions in later adulthood (42).

Several findings based on correlations were consistent with the possibility that deviations from normal growth trajectories were related to drinking. First, albeit modest, simple correlations between greater percent changes per year of each tissue type and number of drinking days at the final MRI scan suggest an alcohol dose effect. Second, the correlations of gray matter trajectories among the lobules were higher in the moderate to heavy drinkers than in the no/low drinkers, suggesting an emergent homogeneity of interrelationships among trajectories of the cerebellar lobular volumes in the drinkers. We speculate that attenuation of normal allometric heterogeneity (and possible heterochronicity) of developmental trajectories may reflect an alcohol-induced synchrony among structural developmental trajectories of the cerebellum.

### Limitations

Despite the prospective nature of this study, factors in addition to alcohol consumption may have contributed to deviations from the norm. One factor was marijuana use. In our NCANDA cohort, many youths consumed both alcohol and marijuana, but disproportionately more youths only drank alcohol than only consumed marijuana. Including days of marijuana use in the analyses did not independently contribute to the detection of alcohol effects. Although we may not have had the power to detect specific untoward marijuana effects because marijuana use was not the primary focus of this study and so few participants used marijuana without alcohol, our results comport with a longitudinal study of 1000 adolescent boys focused on developing marijuana use trajectories of no-to-high use (43). About a decade after initial questioning, a subset of 181 young men underwent MRI; grouping by marijuana use trajectory yielded no regional volumetric differences, leading to the conclusion that adult brain structure is not associated with adolescent marijuana use.

Furthermore, lack of significant interactions indicating sexual dimorphism in trajectory differences does not necessarily confirm their absence; rather, they may have been below detection in our current sample because of its age range and consumption rates among other factors. In addition, reliance on self-reported alcohol and drug use, although essential without continuous monitoring, is subject to imperfect recall and guarded responses.

### Conclusions

The cerebellum is aptly named the little brain, being only 13% of the total intracranial volume. Despite its size, the cerebellum has 3.6 times the number of neurons in the cerebral cortex (44), has major circuitry relays with cortical systems (32,33), and appears to undergo pruning and remodeling during adolescence analogous to that of the cortex (45). Taken in the context of our previous report on neurodevelopment and the toll initiation of alcohol consumption takes on the cerebral cortex (11), we conclude that adolescents who initiate drinking are vulnerable to trajectory disturbance of normal brain development affecting extensive frontal/cingulate/cerebellar systems. Continued examination of the NCANDA cohort has the potential to detect further divergence from normal trajectories with continued drinking and to localize the extent of recovery with sustained abstinence.

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