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Supplemental Material

Altered Brain Developmental Trajectories in Adolescents after Initiating Drinking

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INTRODUCTION

Here we present initial evidence of altered adolescent brain growth trajectory associated with moderate and heavy alcohol use from a national, multi-site, prospective study of hundreds of participants studied before and after they initiated harmful levels of alcohol use.

Cortical shrinkage in normal development is typically interpreted as normal pruning of neuropil constituents in response to absence of environmental or interoceptive input (e.g.,1, 2) (for review, 3). Support for this hypothesis derives from studies based on sleep physiology and on positron emission tomography (PET). Specifically, pubertal maturational changes in sleep electrophysiology measured longitudinally in adolescents revealed a steep decline in delta power density, which paralleled thinning in cortical layers known to evidence synaptic pruning (4, 5). Glucose metabolism measured cross-sectionally with PET characterized a rise in regional cortical metabolism from 5 weeks of age, peaking at about 9 years (5), and declining thereafter (6, 7), paralleling the sleep markers of maturation, the temporal course of the rise and fall of cortical volumes (8), and synaptic remodeling through pruning (9). In contrast to cortical thinning, growth of white matter determines ultimate intracranial volume (8) and is thought to underlie maturating connectivity with experience (10).

METHODS

Informed consent. The Institutional Review Boards (IRB) of each site approved this study. All participants underwent IRB-approved informed consent processes at each visit. Adult participants or the parents of minor participants provided written informed consent before participation at each annual visit; minor participants provided assent.

Alcohol history determination. Participants completed the Customary Drinking and Drug use Record (CDDR) (11) to characterize past and current alcohol and substance use. Historical variables regarding substance use obtained with the CDDR included 9 temporally-linked measures: cumulative days consuming alcohol over a lifetime; maximum drinks per session, total number of drinks, binges, and hangovers in the past year; and days drinking, total drinks, maximum drinks per occasion, and hangover symptoms in the last month quantified with the Hangover Symptoms Scale (12). Lifetime and past month marijuana use data were also collected.

Demographics

In light of the substantial differences in salaries, incomes, and occupational categories across the five geographically-distributed data collection sites, we expressed SES with reference to parental education level, which is less subject to geographical differences in the U.S. Most subjects reported a single self-identified ethnicity (Caucasian, African-American, Asian, Pacific Islander, and Native American) with some reporting mixed heritage. There were adequate numbers of the first three types to assign categorical ethnicity, with dual-heritage identifications assigned to the minority ethnicity group (e.g., Asian-Caucasian was categorized as Asian). Male youth were disproportionately represented in the heavy relative to the moderate drinking group (χ^2=6.5821, p=.0103) (reviewed in 13).

Internalizing and externalizing symptoms, considered high risk for alcohol use and problems (14), were quantified using the Achenbach System of Empirically Based Assessment (15, 16). Participants under age 18 years completed the Youth Self-Report; participants over age 18 completed the Adult Self-Report. Each scale yielded age- and sex-normed continuous measures, where T-scores >60 from the externalizing and internalizing scales were in the subclinical psychopathology range.

Cahalan et al. alcohol consumption criteria

Heavy drinkers ranged from moderate frequency (e.g., 2x/month) with high quantity consumption (e.g., with 3-4 drinks on average and > 4 drinks maximum) to higher frequency (e.g., 1x/week or more) with moderate quantity consumption (e.g., with 2-3 drinks on average and >4 drinks maximum). Moderate drinkers ranged from low drinking frequency (e.g., <1x/month) with moderate quantity consumption (e.g., with 2-3 drinks on average and 4-5 drinks maximum) to moderate frequency (e.g., 1x/week) and low quantity consumption (e.g., with 2 drinks on average and <4 drinks maximum). No/low drinkers reported no or low quantity and frequency consumption (e.g., <1x/month, <2 drinks on average, and <4 drinks maximum).

Drug use

All participants also submitted samples to a 14-panel urine toxicology screen for tetrahydrocannabinol, amphetamine, methamphetamine, methylenedioxy-methamphetamine, cocaine, phencyclidine, benzodiazepines, barbiturates, morphine, oxycodone, methadone, buprenorphone, propoxyphene, and tricyclic antidepressants, and a breathalyzer for alcohol to

confirm absence of evidence for recent use of drugs of abuse. Participants were asked to abstain from substance use for 72 hours prior to testing and scanning. Participants with clinical or biological evidence of recent use were excluded from that day, rescheduled, and tested again for recent use of substances on the return visit.

MRI Acquisition

The longitudinal data for the current analysis comprised MR images collected on 483 of the initial 674 no-to-low baseline participants (17) who had 2-year (and in most cases, 1 year) follow-up MRI and CDDR data, met the double alcohol inclusion criteria, met FreeSurfer SNR criteria, and had adequate quality imaging data.

MRIs were acquired in the sagittal plane on systems from two manufacturers: 3T General Electric (GE) Discovery MR750 at three sites (UCSD, SRI, and Duke) and 3T Siemens TIM TRIO scanners at two sites (University of Pittsburgh and OHSU). MRI acquisition and analysis details appear in supplemental material. The GE sites used an Array Spatial Sensitivity Encoding Technique (ASSET) for parallel and accelerated imaging with an 8-channel head coil and acquired an Inversion Recovery-SPoiled Gradient Recalled (IR-SPGR) echo sequence (TR=5.904ms, TI=400ms, TE=1.932ms, flip angle=11˚, NEX=1, matrix=256x256, FOV=24cm, slice dimensions=1.2 x 0.9375 x 0.9375mm, 146 slices). The Siemens sites used a 12-channel head coil and parallel imaging and temporal acceleration with iPAT and acquired an MPRAGE sequence (TR=1900ms, TI=900ms, TE=2.92 ms, flip angle=9˚, NEX=1, matrix=256x256, FOV=24cm, slice dimensions=1.2 x 0.9375 x 0.9375mm, 160 slices). All sites also collected sagittal T2-weighted images with the same geometric prescription as the T1-weighted acquisitions for use in skull stripping.

Scalable Informatics for Biomedical Imaging Studies (SIBIS)

The data were based on a formal, locked data release (NCANDA_PUBLIC_2Y_STRUCTURAL_MEASUREMENTS_V01) provided by the software platform Scalable Informatics for Biomedical Imaging Studies (SIBIS; https://github.com/sibis-platform). SIBIS consists of IT infrastructure for collecting behavioral and imaging data at the NCANDA sites, Internet, and application programming interfaces for uploading the acquired data to a central biomedical data repository, a validated workflow to perform quality control, a multi-modal image processing pipeline for structural scores, and a release mechanism for disseminating the data to be used for publications. Below is a brief review the structural MR imaging pipeline; the non-imaging component of SIBIS is described elsewhere (18-20).

MRI Analysis

Preprocessing of the T1-weighted (T1w) and T2-weighted (T2w) MRI data involved noise removal (21), correcting field inhomogeneity via N4ITK (22), aligning T2w to T1w MRIs using CMTK (23), repeating image inhomogeneity correction of both modalities confined to the brain mask defined by aligning SRI24 atlas (24) to T1w MRI using the symmetric, diffeomorphic non-rigid registration called ANTS (25). The brain mask was refined by majority voting (26) accomplished across maps extracted by FSL BET (27), AFNI 3dSkullStrip (28), FreeSurfer mri_gcut (29), and the Robust Brain Extraction (ROBEX) method (30), which were applied on combinations of bias and non-bias corrected T1w and T2w images. Using the refined masked, we repeated the image inhomogeneity correction.

For baseline visits only, the skull-stripped T1w image was registered to the SRI24 atlas (24) via ANTS (25). To ensure the longitudinal consistency of the structural measures, ANTS also

registered the baseline to the follow-up T1w MRIs (with skull) to align the brain mask of the baseline to each visit. Using the aligned brain mask, the skull-stripping and image inhomogeneity correction of the follow-up scans was repeated. Afterwards, the inter-visit alignment was refined by ANTS registering the processed T1w MRIs (without skull) of baseline to the ones of the follow-up visits. The corresponding transformation was then used to align the SRI24 atlas to each visit. Furthermore, the intensity profile of the registered follow-up scan was matched to the baseline by smoothing both images (Gaussian Filter with 3mm kernel), computing the ratio between the smoothed intensities of the two time points at each image location, and then applying that ratio to the follow-up scan.

We extracted longitudinal image scores using two different atlases. To produce volume scores based on the SRI24 atlas, longitudinal brain tissue segmentation (gray matter, white matter, and cerebrospinal fluid) was performed via Atropos (31). The resulting label maps of each time point was parcellated by the SRI24 atlas, which identified supratentorial volume (svol), pons, corpus callosum, and a large central white matter sample including the centrum semiovale and internal capsule. To compute structural scores based on the FreeSurfer software (32) [http://www.sciencedirect.com/science/article/pii/S1053811912000389], we applied its cross-sectional approach to the skull-stripped MRI of each time point, which, in part, refined the brain masks removing voxels having low T2-weighted intensities near the brain surface. Based on the refined brain masks, longitudinal FreeSurfer (32, 33) applied to the aligned baseline and follow-up T1-weighted MRIs resulted in bilateral surface area, volume, and thickness measures. Initial testing collapsed the Desikan-Killiany regions-of-interest (ROI) (34) [surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation] into bilateral frontal, temporal, parietal, occipital, cingulate, and insular cortices. Secondary analyses used all 34 individual Desikan-Killiany bilateral cortical ROIs. For this report, only volume (a function of surface area and thickness) was considered.

Statistical Analysis

For display (Figure 1, left panel), Linear Mixed-Effects Models (lme4, R Version 3.2.4 [http://www.r-project.org/]) of native values, before and after svol was removed by regression, demonstrate svol as a major contribution to apparent sex differences.

The group matching procedure used "MatchIt" in R with exact sex and ethnicity and nearest age (35).

DISCUSSION

As would be expected from epidemiological (for review,13) and laboratory studies (e.g.,36, 37, 38), the heavy drinking group had proportionately greater male (60%) than female (40%) representation than the even sex distribution in the full baseline group and a higher percentage of family history positive youth (14.5%) than the moderate (7.7%) or no/low (7.6%) drinking groups. In addition, the female moderate drinkers tended to have the highest internalizing scores (mean T=46.2, $F(1,123)=2.654$, $p=.106$), whereas the male heavy drinkers had the highest externalizing scores (mean T=46.8, $F(1,123)=4.318$, $p=.04$). Other studies have identified these variables as predictors of alcohol use in youth (e.g.,39).

Examination of marijuana co-use with alcohol on trajectories revealed no additional effect of marijuana, thus providing further support for the conclusion that regionally accelerated tissue decline in the alcohol transitioners could be attributable to alcohol

consumption itself. Of note, the marijuana co-use group comprised 67% male youth, whereas the non-marijuana drinkers comprised only 43% male youth (χ^2=4.585, p=.0323). Another characteristic difference between these groups was the higher level of externalizing symptomatology in marijuana users regardless of drinking level (F(1,122)=6.102, p=.0149).

While two earlier longitudinal studies showed attenuated white matter volume growth in pons and corpus callosum in heavy-drinking youth, the current study found decreased growth only for central white matter volume (p=.0344, uncorrected). The tissue-based trajectory differences suggest that initiating heavy drinking during the growth years of adolescence has potentially differential effects on gray matter and white matter volume development, possibly with respect to mechanisms of gray matter pruning and white matter expansion and myelination. Alternatively, measures of gray matter volume may be more sensitive than those of white matter. Tissue shrinkage in normal development is typically interpreted as normal pruning of neuropil constituents in response to absence of environmental or interoceptive input (e.g.,15, 16). One speculative interpretation of the apparent acceleration of the pruning trend notable in young adolescent drinkers is an over-exuberance of the typical synaptic refinements, suggesting an alteration of progression into the later stages of neurodevelopment.

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Supplemental Table. Mean residualized volumes and t-test differences between the no/low and heavy drinking groups and p-values for the 34 FreeSurfer ROIs

Region of interest (ROI)	Mean	t	uncorrected p	adjusted p
frontalpole	-1.8634838	0.28267049	0.777573493	0.85282254
caudalmiddlefrontal	**-2.2474363**	**-3.20350528**	**0.001464748**	**0.02377815**
lateralorbitofrontal	-1.7027995	-1.40706427	0.16017338	0.32034676
medialorbitofrontal	-1.6641957	-1.1039058	0.270287835	0.43489767
paracentral	*-1.6607567*	*-2.04893725*	*0.041110569*	*0.1164799*
parsopercularis	*-1.4757981*	*-2.328787*	*0.020360429*	*0.0865318*
parsorbitalis	-2.1688183	-1.5904716	0.112506864	0.23907709
parstriangularis	*-2.1404769*	*-2.43113188*	*0.01548368*	*0.0865318*
precentral	*-1.2290262*	*-2.47463877*	*0.013744708*	*0.0865318*
rostralmiddlefrontal	*-2.6154937*	*-2.14102999*	*0.032866508*	*0.1110648*
superiorfrontal	**-1.5783155**	**-3.0959195**	**0.002098072**	**0.02377815**
inferiorparietal	-2.6762046	-1.28074383	0.201014796	0.36169955
postcentral	*-1.7962486*	*-2.10468575*	*0.035932744*	*0.1110648*
precuneus	*-2.007058*	*-2.2048668*	*0.028023508*	*0.1058666*
superiorparietal	-2.4252064	-1.62125987	0.105738236	0.23907709
supramarginal	-2.2596892	-1.66747494	0.0961911	0.23500586
cuneus	*-1.7377284*	*-2.35963883*	*0.018765222*	*0.0865318*
lateraloccipital	-1.9101856	-0.59640048	0.551240099	0.65666749
lingual	-1.1967916	-1.27758391	0.20212622	0.36169955
pericalcarine	0.3092154	-0.92059083	0.357810756	0.52893764
bankssts	-2.7540927	-0.68335118	0.494774738	0.64701312
temporalpole	-0.8573634	-0.29603932	0.767351413	0.85282254
entorhinal	-0.666269	-0.06781642	0.945965154	0.94596515
fusiform	-1.5436273	-0.68575904	0.493256456	0.64701312
inferiortemporal	-2.4838566	-0.19402511	0.846253259	0.87796252
middletemporal	-2.170363	-0.58317581	0.560098741	0.65666749
parahippocampal	-1.1170502	-0.18650732	0.852140091	0.87796252
superiortemporal	-1.3828514	-1.6645848	0.09676712	0.23500586
transversetemporal	-1.0428155	-0.60183123	0.547622408	0.65666749
caudalanteriorcingulate	-0.9365606	-1.0786047	0.281404377	0.43489767
isthmuscingulate	*-1.8069184*	*-2.38640357*	*0.017471324*	*0.0865318*
posteriorcingulate	**-1.6443726**	**-3.12310425**	**0.001917771**	**0.02377815**
rostralanteriorcingulate	-0.8838348	-1.2118194	0.226286304	0.38468672
insula	-0.6734757	-0.78103711	0.435235837	0.6165841

Italic font: unadjusted p≤0.05 and displayed on Figure 5

bold font: FDR-adjusted p-value and displayed in orange in Figure 5