**Associations between drinking and cortical thickness in young adult drinkers: Findings
from the Human Connectome Project**

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Abstract

Background. Previous neuroimaging studies examining relations between alcohol misuse and cortical thickness have revealed that increased drinking quantity and alcohol use disorder severity are associated with thinner cortex. Although conflicting regional effects are often observed, associations are generally localized to frontal regions (e.g., dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), and anterior cingulate cortex), with parietal and temporal cortex also implicated in some studies. Inconsistent findings may be attributed to methodological differences, modest sample sizes, and limited consideration of sex differences.

Method. This study examined neuroanatomical correlates of drinking quantity and heavy episodic drinking in a large sample of young adults ($N=706$; M age = 28.8; 51% female) using magnetic resonance imaging data from the Human Connectome Project (HCP). **Results.**

Hierarchical linear regression models (controlling for age, sex, education, income, smoking, drug use, twin status, and intracranial volume) revealed significant inverse associations between drinks/week and frequency of heavy drinking and cortical thickness in a majority of regions examined. The largest effect sizes were found for frontal regions (i.e., DLPFC, IFG, and the precentral gyrus). Follow-up regression models revealed that the left DLPFC was uniquely associated with both drinking variables. Sex differences were also observed, with significant effects largely specific to men. **Conclusions.** This study adds to the understanding of brain correlates of alcohol use in a large, gender-balanced sample of young adults who exhibit a range of drinking levels. Although the cross-sectional methodology used in the present study preclude causal inferences, these findings provide a foundation for rigorous hypothesis testing in future longitudinal investigations.

Key Words: Alcohol; cortical thickness; dorsolateral prefrontal cortex; heavy drinking; human connectome project; neuroanatomy

Introduction

Detrimental effects of alcohol on brain structure have been widely reported in the literature (Gazdzinski et al. 2005; Moselhy et al. 2001; Pfefferbaum et al. 2001; Oscar-Berman & Marinković 2007). These morphological effects include reductions in grey matter volume of cortical and subcortical structures (e.g., Fein et al., 2002; Grodin, Lin, Durkee, Hommer, & Momenan, 2013) and various abnormalities in brain activation patterns revealed via functional neuroimaging (e.g., Chanraud, Pitel, Pfefferbaum, & Sullivan, 2011; Shokri-Kojori, Tomasi, Wiers, Wang, & Volkow, 2017; Zheng, Kong, Chen, Zhang, & Zheng, 2015). In particular, abnormalities in areas of the frontal lobes, including the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC), have been emphasized as a neuroanatomical hallmarks of alcohol use disorder (AUD) (Mechtcheriakov et al. 2007; Moselhy et al. 2001). Functional consequences of alcohol-related decreases in DLPFC volume include impairments in executive functions, behavioral control, and decision-making, among other higher-level neurocognitive processes (Crews & Boettiger 2009).

Previous research has also shown that alcohol misuse correlates with lower levels of cortical thickness, most prominently in the frontal regions of the brain, however these findings have not been consistent across all studies. A magnetic resonance imaging (MRI) by Durazzo et al., (2011) compared individuals with AUD (N = 75) to healthy controls (N = 43) and found that the predominately male (96%) AUD group exhibited significantly thinner frontal cortices, including the DLPFC, ACC, anterior insula, and medial and lateral OFC (see also Durazzo, Mon, Gazdzinski & Meyerhoff 2013). Fortier et al., (2011) compared abstinent AUD participants to controls using a more sex balanced sample (38% female). The AUD group exhibited thinner

cortex in a variety of frontal regions largely corresponding to the DLPFC, but there were no significant differences in the additional frontal regions reported by Durazzo et al. (2011; 2013). Momenan et al. (2012) compared cortical gray matter thickness in a large sample of individuals with AUD ($N = 130$) and controls ($N = 69$). The AUD group exhibited significantly thinner cortex in the bilateral DLPFC, right insula, precentral gyrus, and precuneus. Significant sex differences were also found with the AUD women exhibiting differences from control women in precentral and postcentral gyri, but none of the classic prefrontal regions. Men with AUD, however, exhibited differences from control men in frontal regions (anterior insula, DLPFC). Pennington et al. (2015) reported that male participants with AUD exhibited less bilateral ACC thickness compared to male control participants. Most recently, the Addiction Working Group of the Enhancing Neuro-Imaging Genetics through Meta-Analysis (ENIGMA) project conducted a ‘mega-analysis’ of structural MRI data pooled from 23 research laboratories in 14 countries (Mackey et al. 2018). The participants included people with polysubstance use disorders and controls ($N = 3,240$, of which 292 had an AUD). Compared to the control group, the AUD group had lower levels of cortical thickness in many of the same regions identified in prior studies, including DLPFC, ACC, insula, OFC, precentral gyrus, precuneus, and posterior cingulate, among others. Sex differences were not reported in this study.

Studies have also investigated sub-clinical samples of drinkers. For example, Mashhoon et al., (2014) examined cortical thickness in a sample of 23 (48% female) emerging adult binge drinkers vs. 31 (48% female) emerging adult light drinkers. In *a priori* region of interest analyses, they found that the rostral ACC and left dorsal posterior cingulate cortex were significantly thinner in the binge drinking group than the light drinking group. Within the binge drinking group, thickness of the rostral ACC and was negatively correlated with alcohol

consumption over the last three months, the average number of drinks consumed per drinking period, and the number of drinks consumed per day.

Taken together these studies generally suggest that alcohol misuse, possibly even at levels below clinical threshold for AUD, is associated with less cortical thickness than is typical; however, the specific regions implicated differ widely across studies (see summary of significant findings in Table 1). Methodological limitations of previous studies may explain these inconsistent results. Most notably, sample sizes in previous studies have been relatively small, with a few notable exceptions (e.g., Momenan et al., 2012). Second, a majority of prior studies were not balanced in regards to sex, with some studies recruiting very few or no women. Finally, prior studies often examined a limited number of composite brain regions or individual anatomical regions, and the selection of these regions varied widely across studies.

As a result of inconsistent findings and limitations in the current literature, the aim of the current study was two-fold. First, to clarify the inconsistency across studies, we sought to examine cortical thickness in a comprehensive list of ROIs to determine which regions were associated with drinking quantity and heavy drinking. Second, we sought to explore these variables within a sample that was significantly larger, and more sex balanced than samples in previously published work. The current study examined T1-weighted structural MRI data from active drinkers (i.e., at least one standard drink weekly) in the open-source Human Connectome Project (HCP) dataset. The HCP is a multi-site neuroimaging research study that is systematically mapping the structure and function of the human brain. In addition to high-quality MRI scans, the HCP study collected a wide array of clinical and neurocognitive assessments including measures of alcohol use. We capitalized on this unique resource to examine associations between cortical thickness and two indices of alcohol use—weekly drinking

quantity and frequency of heavy episodic drinking—in the largest sample of participants to date. We also examined sex differences in the patterns of association between cortical thickness and the alcohol variables. Based on the general trends in previous studies, we hypothesized that alcohol consumption and frequency of heavy drinking would be negatively associated with cortical thickness, particularly in frontal regions (e.g., DLPFC, OFC, ACC, and anterior insula).

Materials and Methods

Participants

Structural MRI brain scans were drawn from the 1200 Subjects HCP dataset (released March 1, 2017; available at <http://www.humanconnectome.org/>). The primary HCP participant pool consisted of community adults between the ages of 22-35. Participants were excluded from the HCP study if they had a history of neurodevelopmental, neuropsychiatric, or neurological disorders, as well as significant medical conditions such as diabetes or high blood pressure. The use of drugs or tobacco were not exclusionary and these variables were included as covariates in all analyses (see below). The current study sample consisted of HCP participants who reported consuming at least one alcoholic drink per week over the last year (details below), resulting in a sample of 711 participants. An additional 5 participants were excluded due to incomplete data (3 did not complete the drinking assessments, and 2 did not provide full demographic information). The final sample consisted of 706 participants.

Assessments

Participants completed the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA, Bucholz et al., 1994). The SSAGA assesses physical, psychological, and social symptoms of alcohol abuse and dependence as well as other psychiatric disorders using DSM-III-R and DSM-IV criteria. The SSAGA also covers general demographic information, medical

history, information about tobacco and drug use, and other mental health variables. Participants also completed a seven-day retrospective report of alcohol and tobacco use. Participants provided a commercially available urine drug screen for biochemical testing of recent drug use. Access to restricted participant demographic and clinical data was granted via written permission from the HCP study.

Alcohol Variables

Two alcohol variables from the HCP dataset were examined in the current study. The first, “Total drinks in past 7 days”, was taken from the retrospective alcohol use assessment. The second, “Frequency of drinking 5+ drinks in past 12 months”, was taken from the SSAGA assessment. This variable was coded categorically in the HCP dataset, but the coding for the highest frequency differed for males and females (i.e., the maximum response of 3+ days/week was coded as 1 for males, but 2 for females). The next lowest value (1-2 days/week) was coded as 2 for both males and females. Therefore, no distinction could be made between 1-2 vs. 3+ days/week for females. To standardize the maximum response, the data were recoded as follows (and reverse-scored such that higher values reflect greater frequency): 1 = never; 1-11 days/year = 2; 1-3 days/month = 3; weekly or greater = 4. Inclusion of both weekly drinking and heavy drinking was based on prior research that focused specifically on structural brain correlates of binge drinking as a unique predictor of cortical thickness differences (e.g., Mashnoon et al. 2014).

MRI Data Acquisition and Data Quality Control

High-resolution T1-weighted structural images were collected on a 3T Siemens Skyra scanner (Siemens AG, Erlanger, Germany) with a 32-channel head coil (for full acquisition protocol, see Van Essen et al. 2013). Briefly, images were acquired with a 0.7 mm³ isotropic

resolution (FOV = 224 x 240, matrix = 320 x 320, 256 sagittal slices; TR = 2400 ms and TE = 2.14 ms). Following MRI, each structural scan was examined by a trained rater to assess the overall quality of the scan's contrast, blurring, ringing, and other possible artifacts. Only the scans rated as excellent were released as part of the HCP dataset. For full explanation of HCP quality control procedures, see Marcus et al., 2013.

FreeSurfer Processing Pipelines

Cortical thickness data were generated using the HCP minimal preprocessing pipeline described in Glasser et al., 2013. In the first part of the pipeline, PreFreeSurfer is used to produce a clear structural volume space for each subject, align the images, perform a B₁ correction, and register the subject's structural volume space to the MNI space. The second part of the pipeline is based on FreeSurfer version 5.2 (<http://surfer.nmr.mgh.harvard.edu>) (Fischl 2012). This pipeline ensures that the volume is segmented into predefined structures, that the white and pial surfaces are reconstructed, and that FreeSurfer's folding based surface registration (to the surface atlas fsaverage) is performed. Structural data analyzed for the current study came from this second step. This pipeline generates 34 anatomical regions of interest (ROIs) per cortical hemisphere. The mean cortical thickness in each of the 68 ROIs was provided per person in the HCP public dataset.

Selection of Regions of Interest

We examined cortical thickness in a series of *a priori* regions that were chosen based on previous studies on cortical morphology in alcohol use samples (Bae et al. 2016; Durazzo et al. 2013; Durazzo et al. 2011; Fortier et al. 2011; Mashhoon et al. 2014; Momenan et al. 2012; Pennington et al. 2015). Specifically, we identified 18 bilateral ROIs that have shown significant differences in at least one of these prior studies. Following conventions used in prior studies

(e.g., Durazzo et al., 2013, 2011; Pennington et al., 2015), a subset of these regions were combined into composite regions corresponding to the ACC, OFC, IFG, and DLPFC, reducing the number of regions from 18 to 12. The ACC composite region was created by combining the caudal and rostral ACC segments. The DLPFC composite was created by combining the caudal MFG, rostral MFG, and the SFG segments. Lastly, the OFC composite was created by combining the lateral and medial OFC segments. The only previous study to observe significant results for the IFG (Momenan et al. 2012) did not indicate a specific sub-component of the IFG (*pars opercularis*, *pars orbitalis*, *pars triangularis*), so these three regions were combined into a single IFG composite region. The final list of 12 *a priori* ROIs and the studies reporting differences in these areas is provided in Table 1. The anatomical locations of individual ROIs and composite regions are depicted in Figure 1. These ROIs were examined separately for the left and right hemispheres using the average cortical thickness values for each region provided in the HCP dataset.

Data Analytic Plan

Hierarchical multiple linear regression models were conducted to examine associations between cortical thickness indices and alcohol variables. Separate regression models were calculated for each of the ROIs. Step one of the models included age, sex, education, income, twin status, total intracranial volume, tobacco use, cannabis use, and other drug use as covariates. On the SSGA, tobacco use was defined as total tobacco use in the past 7 days, cannabis use was defined as the total times participants used marijuana; and other drug use was defined as the total times participants reporting using illicit drugs on the SSAGA. In addition to the self-report drug use variables, a binary variable was calculated based on any positive screen on the urine drug test (1 = any positive; 0 = all negative). Selection of these covariates was based on previous work

that has shown that age (e.g., Peters, 2006), sex (e.g., Taki et al., 2011), socioeconomic status (e.g., Piccolo, Merz, He, Sowell, & Noble, 2016), education (e.g., Boller, Mellah, Ducharme-Laliberté, & Belleville, 2017), use of cigarettes (e.g., Durazzo et al., 2013) and cannabis and other drug use (e.g., Li et al., 2014; Lopez-Larson et al., 2011) are significantly associated with variation in cortical thickness. Twin status (i.e., monozygotic or not; dizygotic or not) was included given the twin enrichment of the HCP dataset. Estimated total intracranial volume was included to control for differences in overall head size. Each cortical thickness ROI was added in the second step of the model and change in R^2 was examined. Separate regression models were calculated for drinks/week and frequency of heavy drinking. Given the relatively large number of ROIs, we applied a two-tailed False Discovery Rate (FDR; Benjamini & Hochberg, 1995) correction of $q < .05$ to reduce inflation of type I error rate in the individual regression analyses.

We then conducted an iterative regression analysis to determine the unique contributions of the ROIs that were significantly associated with the drinking variables in the individual regression models, after correcting for multiple comparisons (similar to the approach used in (Owens et al. 2018)). In these models, individual ROIs that were found to be associated with alcohol use at FDR $q < .05$ in the previous step were entered sequentially starting with the largest effect size and proceeding to the smallest effect size. At each iteration, ROIs that significantly increased the variance explained by the model (i.e., had a significant ΔR^2) were retained in the model. The iterative regression analysis used a conventional significance level of $p < .05$ and 95% confidence intervals are reported for regression coefficients.

Finally, we explored potential sex difference associations between cortical thickness and the alcohol variables by repeating the primary analyses including an interaction term that was calculated by standardizing each region and sex, then multiplying each region by sex. To

minimize type-1 error, only ROIs with significant main effects in the primary analyses (following FDR correction) were included in the follow-up analyses of sex effects. A conservative significance level of $p < .005$ was used for these analyses.

Results

Preliminary Analyses

Complete sample characteristics are provided in Table 2. Participants consumed an average of 7.2 drinks per week, and 44.5% engaged in heavy drinking (5+ drinks on an occasion) on a monthly or greater basis. Compared to women, men consumed significantly more drinks per week, $F(1,705) = 86.11, p < .0001, \eta^2 = .11$, and reported significantly higher frequency of heavy drinking, $F(1, 705) = 92.60, p < .0001, \eta^2 = .12$.

We examined bivariate correlations among mean cortical thickness values for the 24 ROIs included in the primary analyses. The complete correlation matrix is provided in Supplementary Table 2. The magnitude of the associations between ROIs within the same hemisphere varied widely, with slightly smaller magnitude correlations in the right ($r_s = .15 - .79$) compared to left ($r_s = .30 - .79$) hemisphere. Magnitude of correlations between the hemispheric homologues of bilateral ROIs also varied ($r_s = .37 - .85$), with the largest magnitude associations between left and right DLPFC ($r = .85$), IFG ($r = .73$), precentral gyrus ($r = .77$), postcentral gyrus ($r = .77$), precuneus ($r = .75$), and superior temporal gyrus ($r = .75$).

Cortical thickness and drinking quantity

Multiple regression analyses examining drinking quantity (drinks/week) are presented in Table 3 (the covariate-only model is presented in Supplementary Table 2). After applying FDR correction, these analyses revealed statistically significant effects for 18 out of 24 ROIs. In each case, lower cortical thickness was associated with greater drinking quantity. Among the

significant ROIs, effect sizes were generally small in magnitude, with the largest found for left DLPFC, the left precentral gyrus, and the right superior temporal gyrus. The iterative regression to determine incremental associations of each ROI with alcohol use began with the ROI that had the largest effect size (left DLPFC). Subsequently, we added the remaining significant ROIs individually in order of effect size to determine which ROIs would account for significant variance in drinking quantity. This analysis revealed that after including left DLPFC, no additional ROIs were associated with a statistically significant change in R^2 ($ps > .05$).

Cortical thickness and heavy drinking frequency

Regression results for the heavy drinking frequency variable are presented in Table 4. Compared to the drinking quantity results above, these analyses generally revealed smaller magnitude effects in fewer ROIs following FDR correction (14 out of 24 ROIs). In each case, higher frequency of heavy drinking was associated with lower cortical thickness. The largest effect sizes were found for the left DLPFC and the left precentral gyrus. Results of the iterative regression analysis were similar to drinking quantity. Beyond left DLPFC, no other ROIs accounted for a significant change in R^2 ($ps > .05$).

Exploratory Analyses of Sex Effects

We explored potential sex differences in the relationship between cortical thickness and alcohol variables for the regions that exhibited significant main effects in the primary analyses above. In the case of drinks per week, we found significant region $\times$ sex interactions in 4 of 18 ROIs examined (Table 5), including left insula, left OFC, left IFG, and left STG. In each case, male participants showed a significant negative association between cortical thickness and drinks/week which was not observed in female participants. None of region $\times$ sex interactions were significant for heavy drinking frequency (Supplementary Table 3).

Discussion

The current study examined neuroanatomical correlates of alcohol use and heavy episodic drinking in one of the largest sex-balanced samples to date. Consistent with previous studies, we found that thinner cortex in a number of regions was associated with greater alcohol consumption and more frequent heavy drinking. Furthermore, these findings make three important contributions to the literature: 1) they empirically demonstrate the unique association of the left DLPFC with alcohol use compared to other regions, 2) they demonstrate sex differences in associations of cortical thickness with alcohol use, and 3) they indicate significant associations between cortical morphometry and drinking in a relatively young and typical sample of drinkers. These contributions are discussed below.

The first main contribution of these findings is the robust association between the left DLPFC and drinking quantity and frequency of heavy drinking. This finding is consistent with several prior cortical thickness studies showing significantly thinner cortex in DLPFC among individuals with AUD or binge drinking (Durazzo et al. 2013; Durazzo et al. 2011; Fortier et al. 2011; Pennington et al. 2015; Bae et al. 2016; Mackey et al. 2018). The DLPFC findings are particularly important given the role of this region in cognitive control and other executive functions that contribute to drinking decisions (Niendam et al. 2012). The DLPFC is also commonly targeted via neuromodulation interventions using non-invasive brain stimulation techniques (e.g., Boggio et al., 2008; Coles, Kozak, & George, 2018; Lupi et al., 2017; Mishra, Nizamie, Das, & Praharaj, 2010) and cognitive interventions such as executive function or working memory training (Duda and Sweet, *In Press*; Olesen, Westerberg and Klingberg, 2004; Takeuchi *et al.*, 2011). Furthermore, by demonstrating that no regions are associated with alcohol use beyond their shared associations with the DLPFC, the current study highlights the

importance of DLPFC in understanding how alcohol use is linked with the brain. There are several possible interpretations of this finding. One interpretation is that reduced DLPFC thickness is causing more problematic alcohol use (perhaps through impaired executive control or other DLPFC-mediated cognitive mechanisms) and all other regional cortical thickness associations with alcohol are solely the result of their association with DLPFC thickness. This would suggest cortical thickness in the DLPFC is a key driver of alcohol use. Another interpretation is that alcohol use is causing cortical thinning across the whole brain through a single mechanism, with the most severe atrophy occurring in the DLPFC. This would suggest that the hierarchical regression results are indicative only of the high magnitude of the correlations between the DLPFC and alcohol. However, the cross-sectional nature of the HCP data does not permit conclusions about causality, and future longitudinal research is needed to tease apart such interpretations.

The significant sex differences are also notable. Studies examining differences in the influence of alcohol on the brain between men and women are sparse and discrepant (Hommer 2003). Some studies of alcohol use disorder samples have reported greater brain shrinkage in women compared to men (e.g., Hommer, Momenan, Kaiser, & Rawlings, 2001), others have reported effects in the reverse direction (Pfefferbaum et al. 2001) or no sex differences (Gescuk, Woods, Mello, Weiss & Mendelson; Pfefferbaum & Sullivan 2002). Although several previous studies examined cortical thickness in relation to alcohol misuse, only one study by Momenan et al. (2012) reported gender effects. The large sample size and relatively equal sex distribution of the HCP dataset provided us the opportunity to test sex effects sufficient statistical power. Our results suggest that the associations between reduced cortical thickness and drinking in this sample of younger adult drinkers may be driven by effects in the men. The regions implicated

were predominately localized in the DLPFC and other frontal regions (e.g, OFC, IFG, ACC), supporting the important role of frontal regions in drinking behavior.

A final important contribution of the current study relates to the nature of the HCP sample, which was notable in its relatively younger age and lack of neurodevelopmental disorders, neuropsychiatric disorders, and neurologic disorders (Van Essen et al. 2013) which may negatively impact cortical thickness. Significant negative associations between reduced cortical thickness and alcohol variables in a sample of young adults without a lifelong history of alcohol misuse suggests that low levels of cortical thickness may be a risk factor for engagement in alcohol misuse. However, we emphasize that suggesting causation is outside the scope of a cross-sectional study. Future longitudinal studies will be informative in unpacking the causal relationship between cortical thickness and alcohol misuse.

These findings should be considered within the context of several potential limitations. One notable limitation concerns the alcohol measures, which were based on retrospective self-report and, as such, may have been subject to recall bias or demand characteristics. Of note, the HCP was not designed to specifically investigate alcohol use in relation to brain structure and function, so the measurement resolution for alcohol variables was somewhat coarse. Another consideration is that the sample was comprised of young adults between the ages of 22–35. Although the younger age range allowed us to infer relationships with brain structure that are presumably independent of extensive neurotoxicity from chronic alcohol misuse, these findings may not generalize to other age groups or individuals with psychiatric or other health conditions. Additionally, it is possible that effect sizes were smaller in the current results than would be the case if a clinical sample were used with more severe alcohol use disorder (e.g., Mackey et al., 2018).

In summary, this study further clarifies the structural brain correlates of alcohol use in a large sample of drinkers. The large HCP cohort provided high statistical power and we observed significant effects in a majority of regions reported in prior studies. When considered together, however, the DLPFC was the region most robustly and uniquely associated with the alcohol variables. Our findings are also consistent with the recent ‘mega-analysis’ of cortical thickness deficits in people with AUD compared to healthy controls (Mackey et al. 2018), but also provide an important extension by demonstrating significant associations in a comparatively younger and less severe sample of drinkers. The consistency between our results and prior studies is an important finding in the context of prominent concerns about reproducibility in psychology (Maxwell et al. 2015; Lindsay 2015), including recent discussions in the fields of addictions (Munafò 2017) and neuroimaging (Gorgolewski & Poldrack 2016). Although the current study cannot speak to disentangling cause from consequence, these findings provide a foundation for rigorous hypothesis testing in future longitudinal investigations.

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Figure Captions

Figure 1. Anatomical locations of FreeSurfer regions of interest

Lateral (top) and medial (bottom) views of inflated brain surface showing locations of regions of interest produced by cortical segmentation in FreeSurfer. The four composite regions are depicted in color: DLPFC is shown in red (consisting of superior frontal gyrus, and caudal and rostral middle frontal gyrus); ACC is shown in blue (consisting of caudal and rostral anterior cingulate); OFC is shown in green (comprised of lateral and medial OFC); IFG is shown in purple (comprised on *pars opercularis*, *pars orbitalis*, and *pars triangularis* sub-regions) .

Table 1 Region of Interest Selection Based on Previous Findings

Region	Durazzo (2011a)	Durazzo (2013)	Fortier (2011)	Mashnoon (2014)	Momenan (2012)	Pennington (2015)	Bae (2016)
DLPFC	X	X	X		X	X	X
ACC	X	X		X		X	
Anterior insula	X	X			X	X	
OFC	X	X					
IFG					X		
Precentral gyrus			X		X		
Postcentral gyrus			X		X		
Precuneus					X		
Posterior Cingulate				X			
Middle Temporal			X				
Superior Temporal			X				
Lateral Occipital			X				

Note. DLPFC = Dorsolateral prefrontal cortex; ACC = Anterior cingulate cortex; OFC = Orbitofrontal cortex; IFG = Inferior frontal gyrus; Regions marked with X indicate statistically significant findings in the respective papers

Table 2. Sample Characteristics

Variable	Mean(SD); N %; Median
Sex	49% Male; 51% Female
Age	28.77 (3.60)
Education	15.08 (1.74)
Income	\$50,000-74,999
Drinks Per Week	7.22 (6.63)
Heavy Drinking Frequency	
Never	165 (23.4%)
1-11 days/year	227 (32.2%)
1-3 days/month	141 (20.0%)
Weekly or greater	173 (24.5%)
Any Tobacco Use	165 (23.4%)
Any Cannabis Use	454 (64.3%)
Any Illicit Use	188 (26.6%)
Urine Screen Positive	100 (14.2%)
Twin Status	24.8% MZ; 14.8% DZ

Note: *N* = 706; MZ = monozygotic twin; DZ = dizygotic twin

Table 3. Cortical Thickness in Individual Regions of Interest Predicting Drinks per Week

Region / Composite	L/R	B	SE	β	t	p	95% CI	ΔR^2	FDR
DLPFC	L	-6.66	1.97	-0.12	-3.37	<.001	-10.53, -2.78	.011	sig.
	R	-5.71	2.09	-0.10	-2.73	.006	-9.81, -1.61	.007	sig.
ACC	L	-4.26	1.54	-0.09	-2.76	.006	-7.29, -1.24	.007	sig.
	R	-1.63	1.27	-0.04	-1.29	.199	-4.13, 0.86	.000	n.s.
Insula	L	-4.53	1.57	-0.10	-2.88	.004	-7.61, -1.44	.007	sig.
	R	-2.70	1.72	-0.06	-1.57	.117	-6.09, 0.68	.001	n.s.
OFC	L	-4.27	1.85	-0.08	-2.30	.022	-7.90, -0.63	.004	sig.
	R	-4.04	2.01	-0.07	-2.01	.045	-7.99, -0.09	.003	n.s.
IFG	L	-5.83	1.91	-0.11	-3.06	.002	-9.57, -2.09	.009	sig.
	R	-6.41	1.97	-0.11	-3.25	.001	-10.28, -2.54	.010	sig.
Precentral gyrus	L	-6.45	1.88	-0.12	-3.42	<.001	-10.15, -2.75	.011	sig.
	R	-6.25	2.06	-0.11	-3.03	.003	-10.30, -2.20	.008	sig.
Postcentral gyrus	L	-5.83	2.25	-0.09	-2.59	.010	-10.24, -1.41	.006	sig.
	R	-5.58	2.27	-0.09	-2.45	.014	-10.04, -1.11	.005	sig.

Precuneus	L	-4.84	1.95	-0.09	-2.49	.013	-8.66, -1.02	.005	sig.
	R	-3.63	2.03	-0.06	-1.79	.074	-7.62, 0.35	.002	n.s.
Posterior Cingulate	L	-4.46	1.65	-0.09	-2.70	.007	-7.70, -1.22	.006	sig.
	R	-2.22	1.48	-0.05	-1.50	.134	-5.13, 0.69	.001	n.s.
Middle Temporal	L	-4.65	1.73	-0.09	-2.68	.007	-8.05, -1.25	.006	sig.
	R	-4.68	1.81	-0.09	-2.58	.010	-8.25, -1.12	.006	sig.
Superior Temporal	L	-4.74	1.73	-0.10	-2.74	.006	-8.14, -1.34	.007	sig.
	R	-6.73	1.81	-0.13	-3.71	<.001	-10.29, -3.17	.014	sig.
Lateral Occipital	L	-4.83	2.10	-0.08	-2.30	.021	-8.95, -0.72	.004	sig.
	R	-2.22	2.17	-0.04	-1.02	.307	-6.48, 2.04	.001	n.s.

Note: L=left; R=Right; FDR=False discovery rate (sig. indicates $q < .05$); DLPFC = Dorsolateral prefrontal cortex; ACC = Anterior cingulate cortex; OFC = Orbitofrontal cortex; IFG = Inferior frontal gyrus; ΔR^2 = change in R^2 from covariate model ($R^2=.207$), comprising [list covariates and reference supp mats]

Table 4. Cortical Thickness in Individual Regions of Interest Predicting Heavy Drinking Frequency

Region / Composite	L/R	B	SE	β	t	p	95% CI	ΔR^2	FDR
DLPFC	L	-1.08	0.33	-0.12	-3.28	.001	-1.73, -0.43	.010	sig.
	R	-1.08	0.35	-0.11	-3.11	.002	-1.77, -0.40	.009	sig.
ACC	L	-0.79	0.26	-0.11	-3.07	.002	-1.29, -0.28	.009	sig.
	R	-0.27	0.21	-0.04	-1.25	.210	-0.68, 0.15	.000	n.s.
Insula	L	-0.65	0.26	-0.09	-2.48	.014	-1.17, -0.13	.005	sig.
	R	-0.35	0.29	-0.04	-1.20	.230	-0.91, 0.22	.000	n.s.
OFC	L	-0.30	0.31	-0.03	-0.96	.339	-0.91, 0.31	-.001	n.s.
	R	-0.50	0.34	-0.05	-1.49	.137	-1.16, 0.16	.001	n.s.
IFG	L	-0.92	0.32	-0.10	-2.90	.004	-1.55, -0.30	.008	sig.
	R	-0.70	0.33	-0.07	-2.13	.034	-1.35, -0.05	.003	n.s.
Precentral gyrus	L	-1.03	0.31	-0.11	-3.27	.001	-1.65, -0.41	.010	sig.
	R	-1.04	0.34	-0.11	-3.01	.003	-1.71, -0.36	.009	sig.
Postcentral gyrus	L	-1.00	0.38	-0.09	-2.67	.008	-1.74, -0.27	.006	sig.
	R	-1.07	0.38	-0.10	-2.82	.005	-1.81, -0.32	.007	sig.

Precuneus	L	-0.60	0.33	-0.06	-1.84	.066	-1.24, 0.04	.002	n.s.
	R	-0.60	0.34	-0.06	-1.78	.075	-1.27, 0.06	.002	n.s.
Posterior Cingulate	L	-0.66	0.28	-0.08	-2.40	.016	-1.20, -0.12	.005	sig.
	R	-0.70	0.25	-0.10	-2.86	.004	-1.19, -0.22	.008	sig.
Middle Temporal	L	-0.69	0.29	-0.08	-2.37	.018	-1.26, -0.12	.005	sig.
	R	-0.70	0.30	-0.08	-2.32	.021	-1.30, -0.11	.004	sig.
Superior Temporal	L	-0.33	0.29	-0.04	-1.15	.252	-0.90, 0.24	.000	n.s.
	R	-0.89	0.30	-0.10	-2.92	.004	-1.49, -0.29	.008	sig.
Lateral Occipital	L	-0.66	0.35	-0.07	-1.87	.061	-1.34, 0.03	.002	n.s.
	R	-0.29	0.36	-0.03	-0.80	.423	-1.00, 0.42	-.001	n.s.

Note: L=left; R=Right; FDR=False discovery rate (sig. indicates $q < .05$); DLPFC = Dorsolateral prefrontal cortex; ACC = Anterior cingulate cortex; OFC = Orbitofrontal cortex; IFG = Inferior frontal gyrus; ΔR^2 = change in R^2 from covariate model ($R^2=.195$), comprising [list covariates and reference supp mats]

Table 5. Sex $\times$ Region of Interest Interactions in Regression Models Predicting Drinks per Week

Region / Composite	L/R	B	SE	β	t	p	95% CI	ΔR^2
DLPFC	L	-1.17	0.45	-0.13	-2.58	.010	-2.06, -0.28	.003
	R	-0.90	0.45	-0.10	-1.99	.047	-1.79, -0.01	.009
ACC	L	-1.16	0.45	-0.13	-2.58	.010	-2.04, -0.28	.016
Insula	L	-1.31	0.46	-0.14	-2.85	.005	-2.22, -0.41	.013
OFC	L	-1.36	0.45	-0.15	-2.99	.003	-2.25, -0.47	.016
IFG	L	-1.35	0.45	-0.15	-3.00	.003	-2.23, -0.47	.020
	R	-1.16	0.45	-0.13	-2.56	.011	-2.04, -0.27	.008
Precentral gyrus	L	-0.87	0.45	-0.10	-1.92	.056	-1.76, 0.02	.019
	R	-0.44	0.46	-0.05	-0.96	.336	-1.33, 0.46	.023
Postcentral gyrus	L	-0.50	0.45	-0.05	-1.10	.273	-1.38, 0.39	.007
	R	-0.57	0.45	-0.06	-1.28	.202	-1.46, 0.31	.009
Precuneus	L	-0.36	0.45	-0.04	-0.78	.435	-1.25, 0.54	.017
Posterior Cingulate	L	-1.08	0.45	-0.12	-2.41	.016	-1.96, -0.2	.021
Middle Temporal	L	-1.09	0.45	-0.12	-2.40	.016	-1.97, -0.2	.005

	R	-0.58	0.46	-0.07	-1.28	.203	-1.48, 0.31	.002
Superior Temporal	L	-1.35	0.45	-0.15	-2.99	.003	-2.23, -0.46	.011
	R	-1.15	0.45	-0.13	-2.54	.011	-2.04, -0.26	.003
Lateral Occipital	L	-0.86	0.45	-0.09	-1.90	.058	-1.74, 0.03	.018

Note: Only regions exhibiting significant main effects in primary analyses were included in follow-up sex-based analyses. Values correspond to ROI x sex predictor, with male = 0; female = 1; L=left; R=Right; DLPFC = Dorsolateral prefrontal cortex; ACC = Anterior cingulate cortex; OFC = Orbitofrontal cortex; IFG = Inferior frontal gyrus; ΔR^2 = change in R^2 from covariate model ($R^2=.176$). Bolded ΔR^2 values reflect significant effects at conservative $p < .005$ level.

Prep

Supplementary Material

Supplementary Table 1.

Correlations between cortical thickness values in the *a priori* regions of interest. Part 1 (below) provides region labels that correspond to column and row numbers in Part 2 (next page).

#	Region	L/R
1	DLPFC	L
2	ACC	L
3	Insula	L
4	OFC	L
5	IFG	L
6	Precentral gyrus	L
7	Postcentral gyrus	L
8	Precuneus	L
9	Posterior Cingulate	L
10	Middle Temporal	L
11	Superior Temporal	L
12	Lateral Occipital	L
13	DLPFC	R
14	ACC	R
15	Insula	R
16	OFC	R
17	IFG	R
18	Precentral gyrus	R
19	Postcentral gyrus	R
20	Precuneus	R
21	Posterior Cingulate	R
22	Middle Temporal	R
23	Superior Temporal	R
24	Lateral Occipital	R

Note: L=left; R=Right; FDR=False discovery rate; DLPFC = Dorsolateral prefrontal cortex; ACC = Anterior cingulate cortex; OFC = Orbitofrontal cortex; IFG = Inferior frontal gyrus

Supplementary Table 1 (continued)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1	--																							
2	.46	--																						
3	.41	.38	--																					
4	.63	.47	.47	--																				
5	.79	.45	.51	.66	--																			
6	.79	.41	.44	.49	.70	--																		
7	.62	.35	.39	.42	.60	.67	--																	
8	.67	.37	.40	.48	.62	.67	.63	--																
9	.48	.44	.30	.36	.43	.43	.34	.45	--															
10	.62	.37	.48	.51	.67	.63	.55	.64	.41	--														
11	.62	.47	.53	.56	.68	.62	.61	.63	.40	.71	--													
12	.54	.37	.45	.48	.58	.59	.64	.69	.37	.65	.63	--												
13	.85	.37	.31	.51	.68	.68	.53	.60	.36	.53	.53	.46	--											
14	.25	.39	.24	.25	.25	.19	.13	.18	.24	.22	.19	.12	.28	--										
15	.29	.24	.44	.38	.32	.26	.25	.24	.13	.33	.35	.28	.36	.22	--									
16	.56	.38	.38	.65	.57	.43	.35	.44	.27	.45	.48	.40	.65	.31	.39	--								
17	.68	.38	.39	.56	.73	.57	.50	.55	.32	.57	.60	.50	.79	.27	.44	.68	--							
18	.66	.32	.34	.36	.57	.77	.55	.58	.30	.51	.51	.50	.75	.22	.35	.49	.65	--						
19	.50	.25	.29	.30	.47	.53	.77	.52	.23	.44	.48	.53	.60	.15	.30	.43	.56	.57	--					
20	.55	.26	.31	.32	.51	.56	.51	.75	.34	.54	.51	.56	.64	.23	.29	.47	.59	.65	.57	--				
21	.33	.25	.20	.23	.30	.26	.21	.29	.37	.28	.23	.23	.35	.55	.19	.29	.31	.30	.24	.35	--			
22	.55	.28	.37	.44	.55	.52	.49	.54	.29	.68	.58	.55	.65	.19	.43	.55	.69	.60	.57	.62	.30	--		
23	.51	.36	.41	.42	.55	.52	.52	.50	.29	.56	.75	.52	.60	.23	.44	.52	.66	.59	.58	.59	.27	.69	--	
24	.40	.25	.32	.33	.45	.45	.53	.55	.23	.52	.48	.71	.51	.15	.35	.46	.55	.56	.60	.62	.28	.63	.57	--

Note: Color scale denotes effect size (r): Red = < .30; Orange = .30 - .49; Light green = .50 - .69; Dark green = .70 - 1.0

Supplementary Table 2.

Covariate Models Predicting Drinks per Week and Frequency of Heavy Drinking

Covariate	B	SE	β	t	p	95% CI	R²
<i>Drinks per Week</i>							.207
Sex	-3.13	0.60	-0.24	-5.21	<.0001	-4.31, -1.95	
Age	-0.07	0.07	-0.04	-1.07	.283	-0.20, 0.06	
Income	0.04	0.12	0.01	0.35	.729	-0.19, 0.27	
Education	0.25	0.15	0.07	1.75	.081	-0.03, 0.54	
Tobacco Use	0.02	0.01	0.06	1.62	.106	0.00, 0.04	
Cannabis Use	0.68	0.18	0.18	3.74	<.0001	0.32, 1.04	
Other Drug Use	0.80	0.23	0.15	3.51	<.0001	0.35, 1.25	
Urine Screen (Pos/Neg)	0.09	0.77	0.00	0.12	.901	-1.41, 1.06	
MZ Twin Status	-0.74	0.54	-0.05	-1.36	.174	-1.80, 0.33	
DZ Twin Status	0.19	0.66	0.01	0.29	.772	-1.10, 1.48	
Total ICV	0.00	0.00	0.03	0.75	.456	0.00, 0.00	
<i>Heavy Drinking Frequency</i>							.144
Sex	-0.53	0.10	-0.24	-5.26	<.0001	-0.72, -0.33	
Age	-0.04	0.01	-0.14	-3.75	<.0001	-0.06, -0.02	
Income	0.02	0.02	0.04	1.03	0.304	-0.02, 0.06	
Education	0.00	0.02	0.00	0.02	0.981	-0.05, 0.05	
Tobacco Use	0.00	0.00	0.07	1.78	0.076	0.00, 0.01	
Cannabis Use	0.16	0.03	0.25	5.26	<.0001	0.10, 0.22	
Other Drug Use	0.00	0.04	0.00	-0.07	0.941	-0.08, 0.07	
Urine Screen (Pos/Neg)	-0.06	0.13	-0.02	-0.43	0.665	-0.31, 0.20	
MZ Twin Status	-0.10	0.09	-0.04	-1.13	0.259	-0.28, 0.08	
DZ Twin Status	-0.03	0.11	-0.01	-0.27	0.790	-0.24, 0.19	
Total ICV	0.00	0.00	0.04	0.87	0.384	0.00, 0.00	

Note: MZ = monozygotic; DZ = dizygotic; ICV = intracranial volume; Sex (0 = male; 1 = female)

Supplementary Table 4.

Sex x Region of Interest Interactions in Regression Models Predicting Heavy Drinking Frequency

Region / Composite	L/R	B	SE	β	t	p	95% CI	ΔR^2
DLPFC	L	-0.03	0.08	-0.02	-0.36	.722	-0.18, 0.12	.003
	R	0.02	0.08	0.01	0.29	.769	-0.13, 0.17	.004
ACC	L	-0.14	0.08	-0.10	-1.92	.056	-0.29, 0.00	.015
Insula	L	-0.07	0.08	-0.04	-0.89	.374	-0.22, 0.08	.011
IFG	L	-0.01	0.08	0.00	-0.07	.942	-0.15, 0.14	.012
Precentral gyrus	L	0.00	0.08	0.00	0.01	.995	-0.15, 0.15	.012
	R	-0.01	0.08	-0.01	-0.15	.878	-0.16, 0.14	.005
Postcentral gyrus	L	-0.02	0.08	-0.01	-0.24	.811	-0.17, 0.13	.010
	R	0.02	0.08	0.02	0.32	.751	-0.12, 0.17	.001
Posterior Cingulate	L	-0.13	0.08	-0.08	-1.67	.096	-0.27, 0.02	.005
	R	0.03	0.07	0.02	0.34	.734	-0.12, 0.17	.010
Middle Temporal	L	-0.04	0.08	-0.03	-0.53	.595	-0.19, 0.11	.001
	R	0.01	0.08	0.01	0.12	.905	-0.14, 0.16	.007
Superior Temporal	R	-0.02	0.08	-0.01	-0.24	.813	-0.17, 0.13	.002

Note: Only regions exhibiting significant main effects in primary analyses were included in follow-up sex interaction analyses. L=left; R=Right); DLPFC = Dorsolateral prefrontal cortex; ACC = Anterior cingulate cortex; IFG = Inferior frontal gyrus; ΔR^2 = change in R^2 from covariate model ($R^2=.163$).