The Effects of Alcohol and Cannabis Use on the Cortical Thickness of Cognitive Control and salience Brain Networks in Emerging Adulthood: A Cotwin Control Study

Supplement 1

Table of Contents

Supplemental Methods and Materials

Section S1. Sample demographics

The racial composition of the sample was as follows: 92.2% White/Caucasian, 2.8% Black/African American; 2.5% Hispanic; 1.4% mixed/other; 0.7% Native American; 0.5% Asian/Pacific Islander.

Table S1. Quantification of measures used in the composite drink and cannabis index measures.

	Alcohol			Cannabis	Alcohol/Cannabis
Score	Quantity	Intoxications	Max Drinks	Uses	Frequency
0	0	0	0	0	None
1	1 to 3	1 to 5	1 to 3	1 to 4	Less than once per year to less than once a month
2	4 to 6	6 to 10	4 to 6	5 to 30	1-3 times per month
3	7 to 10	11 to 20	7 to 10	31 to 100	1-4 times per week
4	11 to 20	21 to 50	11 to 20	101 to 400	Nearly every day to once a day
5	21 to 29	51 to 149	21 to 29	≥ 401	Two or more times a day
6	≥ 30	≥ 150	≥ 30	N/A	N/A

Note: Uses and frequency are on a 0 to 5 scale, and the remaining three measures are on a 0 to 6 scale.

Section S2. MRI acquisition and processing

Structural MRI data were collected on 3T Siemens Trio (n = 100) and Prisma (n = 336) MRI scanners (32-channel array head coil) at the Center for Magnetic Resonance Research, University of Minnesota. A software upgrade occurred during the study (n: pre-upgrade = 306, post-upgrade = 130). Three-dimensional T_1-weighted sagittal plane anatomical images were acquired using the following magnetization prepared rapid gradient echo sequence: TR = 2530 ms;

TE = 3.65 ms; flip angle = 7°; matrix size = 256 × 256; FOV = 256 mm; GRAPPA = 2; 240 coronal slices with 1-mm isotropic voxels; single shot; interleaved acquisition.

Supplemental Results

Section S3. Alcohol and cannabis use: descriptives, heritability, and twin differences

Average alcohol use across emerging adulthood for individuals in the lowest quartile of drink index scores corresponded to drinking 1–3 times per month, 1–3 drinks each occasion, as many as 4–6 at one time, and having been intoxicated 1–5 times. For those in the highest quartile, their average use corresponded to drinking 1–4 times per week, 4–6 drinks each occasion, as many as 11–20 at one time, and having been intoxicated ≥ 150 times. For cannabis use, those in the lowest quartile reported no use in emerging adulthood (150 individuals had cannabis index scores of 0). For those in the highest quartile, average use corresponded to using cannabis two or more times per day and a total of ≥ 401 uses. The correlation between drink and cannabis index scores was 0.561. Four reported no alcohol or cannabis use, 146 individuals reported using only alcohol, and no individuals used only cannabis in the last seven years.

To characterize the relative influence of genetic and environmental influences on alcohol and cannabis use, we calculated twin correlations, conducted standard biometric analyses, and evaluated within-pair concordance/discordance for drink and cannabis index scores.

Biometric models (1), which treat the twin pair as the unit of analysis, were fit to determine the relative influence of genes and environment on drink and cannabis index scores. These models decompose the phenotypic variance into that accounted for by latent variables representing three contributing sources: additive genetic factors (A), common environmental factors shared by members of a twin pair that contribute to twin similarity (C; shared rearing environment), and nonshared environmental factors unique to each twin that contribute to twin differences (E; e.g.,

differences in drinking). Note that estimates of E also capture measurement error. Biometric models were fit using the *OpenMx* package (2) in R using the raw data and full information maximum likelihood estimation to obtain unbiased parameter estimates in the presence of missing data. To test the relative effect of the two sources of familial influences, a base model estimating all ACE parameters was fit and then compared to more parsimonious nested models which set either A or C parameters to zero. The best-fitting models were selected on the basis of the lowest value for the Bayesian information criterion (BIC; parameters penalty), a fit statistic that jointly expresses best relative goodness of fit and parsimony (3).

The MZ twin correlations were larger than DZ correlations for drink index (MZ [95% CI] = 0.57 [0.45, 0.67]; DZ = 0.31 [0.14, 0.50]) and cannabis index (MZ = 0.66 [0.56, 0.75]; DZ = 0.41 [0.23, 0.56]) scores, and both were well below unity.

For both alcohol and cannabis, setting the shared environmental parameter (C) to zero resulted in a more parsimonious and better fitting model relative to both the full ACE model and the model setting the additive genetic (A) parameter to zero. BIC values for each model were as follows: for alcohol, ACE = 1178.70, CE = 1175.82, AE = 1173.89; for cannabis, ACE = 1674.54, CE = 1676.21, AE = 1669.45. We report parameter estimates from the best-fitting AE (i.e., setting C to zero) models. For alcohol, the standardized biometric variance component estimates indicated a moderate influence of additive genetic (A [95% CI] = 0.55 [0.43, 0.65]) and nonshared environmental (E = 0.45 [0.35, 0.57]) factors on individual differences in drink index scores. A similar pattern emerged for cannabis index scores, with significant additive genetic (A = 0.66 [0.56, 0.74]) and nonshared environmental (E = 0.34 [0.26, 0.44]) influence.

To investigate the degree of similarity/dissimilarity in alcohol and cannabis exposure, absolute twin difference scores (|TwinA – TwinB|) for the drink and cannabis index measures were

categorized into approximately equal sized quartile groups and descriptive statistics were computed on these twin difference scores for the lowest (most concordant) and highest (most discordant) quartile groups. For alcohol, the most concordant quartile (n = 59 pairs) had minimal twin differences in drink index scores (mean [SD] = 0.18 [0.11], range = 0.00–0.25), with the heavier-drinking twins scoring only 0.11 SD higher than their lesser-drinking cotwins. In contrast, the most discordant quartile (n = 41 pairs) had large twin differences in drinking (mean [SD] = 1.73 [0.55], range = 1.25–4.00), with the heavier-drinking twin scoring roughly half a standard deviation higher on the drink index. Turning to cannabis, for the most concordant quartile (n = 71 pairs), there were no twin differences in cannabis index scores (mean [SD] = 0.00 [0.00], range = 0.00–0.00); that is, cotwins from these pairs had identical scores. However, cannabis twin differences among the most discordant quartile (n = 40 pairs) were sizable (mean [SD] = 3.08 [0.94], range = 2.00–5.00), with the heavier-using twins scoring nearly 1 SD higher than their lesser-using cotwins on the cannabis index. These results indicate that in the context of the moderately sized genetic influence on both alcohol and cannabis use, there were still appreciable within-pair differences in exposure, supporting the use of the cotwin control analysis (CTC) in this sample.

Section S4. Robustness of the alcohol use-cortical thickness individual-level phenotypic associations to the influence of potentially relevant covariates

Additional models were computed to test whether the observed significant associations between alcohol use and cortical thickness remained significant after adjusting for a collection of covariates that may potentially confound the associations, namely internalizing and externalizing psychopathology and traumatic life events. Internalizing was assessed with a shortened version of the Inventory for Depression and Anxiety Symptoms-II (IDAS-II; (4)) self-report questionnaire

that yielded scores on dysphoria, suicidality, panic, social anxiety, and traumatic avoidance and traumatic intrusions associated with posttraumatic stress disorder. Measures of externalizing were Diagnostic and Statistical Manual of Mental Disorders IV symptom counts of conduct disorder and antisocial personality disorder assessed by trained clinical interviewers. Trauma exposure was assessed with an interviewer-administered version of the Trauma Assessment for Adults (5), which assesses lifetime exposure to a variety of stressful/disturbing events (e.g., natural disasters, military combat experience, serious illness or injury, etc.); a trauma exposure index was calculated by totaling the number of exposures across the events. The reader is referred to Keyes et al. (6) and Wilson et al. (7) for further details regarding these measures.

Descriptive statistics and zero-order correlations among these measures are presented in Table S4 (see separate Excel file). Alcohol and cannabis use were both positively correlated with internalizing, externalizing, and trauma exposure measures. Turning to whether these potential covariates accounted for the observed alcohol-cortical thickness associations, as shown in Table S5 (see separate Excel file), in the overwhelming majority of cases these covariates were not significantly associated with cortical thickness and had no meaningful effect on the significance of the alcohol-cortical thickness associations. There were only a small number of exceptions to this, including cortical thickness of the salience network opercular/insula areas for which the drink index effects became non-significant when adjusting for externalizing symptoms or comorbid cannabis use. One possible interpretation for these findings is that that deviations in these particular regions may index variance related to behavioral disinhibition/externalizing psychopathology more broadly instead of variance specific to alcohol use. Nevertheless, taken together these results suggest that the inclusion of potentially relevant covariates had, by and large, very little effect on the alcohol effects observed in this report.

Section S5. Associations between cortical thickness and behavioral disinhibition

We investigated whether cortical thickness deviations in areas showing significant alcohol use effects related to personality and psychopathological measures of behavioral disinhibition/externalizing via post-hoc exploratory analyses, which if true, would provide potential evidence of a link between cortical thickness deviations, alcohol use, and disinhibitory behaviors. We used a brief version of the Multidimensional Personality Questionnaire (8) to assess variation in normative personality traits; of interest were scales related to impulsivity/behavioral disinhibition, namely the control scale (reverse-coded so higher scores reflect impulsive tendencies, carelessness, lack of planning, etc.) and the harm avoidance scale (reverse-coded so higher scores reflect enjoyment of risky and dangerous experiences/activities). The Personality Inventory for DSM-5 (PID-5; (9)) was used to assess variation in maladaptive personality traits; of interest were scores on three measures of the externalizing superordinate factor: 1) the disinhibition factor, composed of distractibility, impulsivity, and irresponsibility facets; 2) the antagonism factor, composed of manipulativeness, deceitfulness, and grandiosity facets; and 3) the risk-taking facet. Measures of externalizing psychopathology were Diagnostic and Statistical Manual of Mental Disorders-IV symptom counts of conduct disorder and antisocial personality disorder assessed by trained clinical interviewers (for details, see (6,7)). A principal component analysis was conducted on the seven measures to calculate a general composite of behavioral disinhibition (and reduce the number of statistical tests). Cronbach's α for the seven measures equaled 0.82 and zero-order correlations ranged from 0.22 to 0.66. The scree test, Kaiser rule, and parallel analysis all supported extracting a single principal component (variance accounted for: 48%; component loadings range: 0.57–0.82) from which component scores were calculated. The behavioral disinhibition composite was moderately correlated with alcohol use ($r = 0.46$).

Results of the linear mixed models of cortical thickness (dependent variable) and behavioral disinhibition composite scores (independent variable) are presented in Table S6.

Table S6. Associations between cortical thickness and behavioral disinhibition composite scores.

Area	Beta (SE)	t (df)	p-value
Control A			
PFCl	-0.025 (0.017)	-1.458 (422)	0.1455
IPS	-0.021 (0.015)	-1.429 (408)	0.1538
Control B			
PFCld	-0.020 (0.022)	-0.929 (426)	0.3534
PFClv	-0.019 (0.024)	-0.809 (428)	0.4187
PFCmp	-0.021 (0.012)	-1.761 (426)	0.0789
Temp	-0.036 (0.021)	-1.680 (382)	0.0937
Control C			
pCun	-0.012 (0.017)	-0.690 (417)	0.4903
Salience A			
FrMed	**-0.095 (0.036)**	**-2.635 (428)**	**0.0087**
FrOper	**-0.020 (0.008)**	**-2.327 (424)**	**0.0205**
Ins	**-0.025 (0.011)**	**-2.242 (415)**	**0.0255**
ParMed	**-0.036 (0.018)**	**-2.058 (424)**	**0.0402**
ParOper	-0.010 (0.010)	-1.004 (400)	0.3162
Salience B			
PFCl	-0.002 (0.014)	-0.166 (420)	0.8679
PFClv	-0.001 (0.009)	-0.116 (399)	0.9077
PFCmp	-0.011 (0.009)	-1.272 (423)	0.2039

Notes: Nominally significant effects ($p < 0.05$) are in bold. No test was significant after false discovery rate adjustment (all q-values ≥ 0.1275). All models adjust for sex, age, zygosity, scanner, and acquisition software covariates.
Abbreviations: PFC, prefrontal cortex; IPS, intraparietal sulcus; Temp, temporal; pCun; precuneus; FrMed, frontal medial; FrOper, frontal operculum; Ins, insula; ParMed, parietal medial; ParOper, parietal operculum; l, lateral; d, dorsal; v, ventral; mp, medial posterior.

We observed nominally significant negative associations ($p < 0.05$) between behavioral disinhibition and cortical thickness of four salience network areas, namely the frontal medial, parietal medial, insula, and frontal operculum cortex. This provides preliminary suggestive evidence that impulsivity and disinhibitory behaviors may be a link between cortical thickness

deviations in the salience network and risk for alcohol use. However, we note that these analyses were exploratory, and no tests survive false discovery rate adjustment (all q-values ≥ 0.1275). Nonetheless, the behavioral disinhibition-cortical thickness associations are in the expected direction across all tests, but as small effect sizes may preclude significance, the null results after adjusting for multiple comparisons may reflect type II errors that might be detected in larger samples. Further work is needed to better understand the complex relationship between cortical thickness variations, alcohol use, and disinhibited behaviors that contribute to substance misuse risk.

Section S6. The cotwin control within-pair effects are robust to unshared confounders

The cotwin control analysis accounts for all confounding influence shared by twins but does not control for unshared factors that differ between cotwins which may relate to the exposure (alcohol) and outcome (cortical thickness) and potentially confound the within-pair exposure effect. To address this, we examined whether cotwins who were most discordant on the drink index (i.e., twins from pairs in the highest quartile of absolute twin differences in drink index scores; n = 41 pairs) significantly differed on a collection of covariates that may potentially confound the associations, namely internalizing (IDAS-II scores), externalizing (conduct disorder, antisocial personality disorder), and traumatic life events (i.e., the same covariate phenotypes used above). The heavier- and lesser-drinking twins did not statistically differ in conduct disorder symptoms (p = 0.2444), antisocial personality disorder symptoms (p = 0.2094), dysphoria (p = 0.4990), suicidality (p = 0.4458), panic (p = 0.5592), social anxiety (p = 0.4412), PTSD-related traumatic intrusions (p = 0.2466), PTSD-related traumatic avoidance (p = 0.6031), or trauma exposure index scores (p = 0.4211). As expected, heavier-drinking twins did have greater cannabis index scores

relative to their lesser-drinking cotwins ($p < 0.0001$), but as noted above, cannabis use did not account for the alcohol-cortical thickness associations.

We recomputed the cotwin control analyses for the four areas that exhibited significant within-pair effects (control lateral PFC, and salience frontal medial, frontal operculum, and parietal medial areas) to test whether the drink index within-pair effects remained significant after adjusting for each of these covariates (separate models were computed for each area-covariate pair). The within-pair effects remained significant for the lateral PFC (p-values ≤ 0.0030), frontal medial (p-values ≤ 0.0383), and parietal medial (p-values ≤ 0.0146) areas; the within-pair effect for the frontal operculum was no longer significant when adjusting for cannabis use ($p = 0.0894$) but was robust to all other covariates (p-values ≤ 0.0411). Taken together, these findings suggest that these potentially confounding unshared factors have little impact on the observed within-pair alcohol exposure effects.

Section S7. Bivariate biometric modeling

While the main interest of this paper was the use of the CTC to test for evidence that the observed cortical thickness deviations were consistent with the deleterious environmental consequences of substance exposure on the young adult brain (i.e., the within-pair effect in the cotwin control models), we also fit a series of etiologically-informative bivariate biometric models to complement the CTC analyses and investigate the sources of the significant familial between-pair effects. The CTC models presented in the main text are based on a counterfactual model designed to test the degree to which observed phenotypic associations are consistent with confounding factors or the consequences of an environmental exposure (10,11). However, the CTC is not particularly designed to isolate specific confounding familial factors (genetic or shared environment) that reflect a significant between-pair effect. In contrast, biometric models use

structural equation modeling to describe genetic (A), shared environmental (C), and nonshared environmental (E) influences, modeled as latent variables, on a phenotype and the covariance between phenotypes (12). The bivariate models can be used to test the relative significance of A or C, both of which reflect sources of familial influence, on the covariation between two phenotypes to test the question of whether a familial association is likely due to genetic or shared environmental factors. We fit bivariate biometric models to estimate the magnitude of the correlations between the A, C, and E influences on drink index scores and the same respective influences on the cortical thickness measures that demonstrated significant alcohol effects (i.e., those areas used in the cotwin control analyses) to estimate the degree to which such factors are shared across both phenotypes. In the bivariate models, the nonshared environmental correlation (rE) can be interpreted as an analog to the within-pair CTC effect, while the genetic (rA) and shared environmental (rC) correlations reflect sources of familial influences shared across the two phenotypes in the absence of a significant rE (both rA and rC are captured in the CTC between-pair effect). The effects of sex, age, zygosity, scanner, and acquisition software (i.e., those covariates used in the linear mixed models) were regressed out of each cortical thickness measure, and the residuals were used in biometric analyses.

Bivariate biometric models were fit using the *OpenMx* package (2) in R using the raw data and full information maximum likelihood estimation to obtain unbiased parameter estimates in the presence of missing data. To test the significance of the two sources of familial influences, for all bivariate models a base model estimating all ACE parameters was initially fit and then compared to models in which the A or C parameters are set to zero. The best-fitting models were selected on the basis of the lowest values for the Bayesian information criterion (BIC) and the Akaike information criterion (AIC), which are penalized-likelihood criteria that are different yet

complementary approaches to quantifying the best relative goodness of fit and parsimony between a set of candidate models (e.g., AIC penalizes model complexity less than BIC). In addition to the lowest BIC and AIC, the best fitting model was expected to have the largest BIC and AIC weights, which are normalized transformations of the BIC or AIC that sum to 1 and, for a set of candidate models, can be interpreted as the posterior model probability that a particular model generated the observed data, and the strength of evidence that a model is the best fitting model in the set, respectively (13).

Results from the bivariate biometric models are presented in Table S7. Across all models, the BIC and AIC fit statistics jointly supported AE models (setting C parameters to zero) as the best fitting models relative to the CE or full ACE models. AE models had the lowest BIC and AIC values, indicating better fit, and the largest BIC and ACI weights, indicating greater evidence that the AE model generated the observed data. This agrees with the results from the univariate biometric modeling presented above that provide evidence in favor of an AE model for the drink index. These results support the interpretation that additive genetic influences, and not shared environmental influences, underlie the familial associations observed between alcohol use and cortical thickness of control and salience areas. All phenotypes showed modest to moderate heritability.

While the CTC models can offer evidence for or against familial or exposure effects, these biometric models allowed us to calculate the relative contribution of genetic and nonshared environmental influence to the model-implied phenotypic correlation between drink index scores and cortical thickness. This is of particular interest for those areas that showed evidence for both between- and within-pair effects in the CTC (i.e., control lateral prefrontal cortex [PFCl], salience frontal medial, and salience parietal medial thickness). As shown in Table S7 and visually in Figure

4 (in the main manuscript), the largest contribution to the phenotypic correlation was additive genetic influence across a majority of the cortical areas examined, which is consistent with the CTC results of a strong between-pair effect for most areas. In contrast, the salience frontal opercular area had a larger nonshared environmental contribution to its phenotypic correlation, consistent with its significant CTC within-pair but nonsignificant between-pair effects. Turning to those areas that showed both CTC between-pair and within-pair effects, the phenotypic correlation for control PFCl thickness was primarily driven by nonshared environmental influences, while salience frontal and parietal medial effects were largely driven by additive genetic contribution (in the context of a significant nonshared environmental influence).

All in all, these results on the contributions to the phenotypic correlations are largely consistent with the relative magnitude of the between-pair (familial) and within-pair (exposure) effects from the cotwin control analyses. The biometric modeling results converge with the CTC approach and support the main interpretations regarding evidence for the causal basis of the drinking-cortical thickness associations presented in the main text.

We do note that as discussed in a recent article (14), the power to detect effects in bivariate biometric modeling is highly dependent on sample size. While this sample is relatively large for a clinical neuroimaging cotwin control study, it is modest for a biometric modeling study, and so these results of the biometric modeling should be considered preliminary.

Table S7. Bivariate biometric models between alcohol use (drink index) and cortical thickness.

	Fit statistics				AE biometric model estimates								
					Drink Index		Cortical thickness		Model-implied correlations			Contribution of A and E to rP	
Area	BIC	*w*BIC	AIC	*w*AIC	A	E	A	E	rP	rG	rE	rP-G	rP-R
Control A													
PFCl													
ACE	1414.39	0.00	1375.65	0.07									
CE	1404.66	0.05	1376.49	0.05									
AE	**1398.87**	**0.95**	**1370.70**	**0.88**	0.55 (0.06)	0.45 (0.06)	0.44 (0.07)	0.56 (0.07)	-0.15[c] (0.05)	-0.08 (0.12)	-0.23[b] (0.08)	-0.04	-0.12
IPS													
ACE	1279.05	0.00	1240.31	0.06									
CE	1266.41	0.20	1238.24	0.18									
AE	**1263.59**	**0.80**	**1235.42**	**0.75**	0.55 (0.06)	0.45 (0.06)	0.30 (0.08)	0.70 (0.08)	-0.14[b] (0.05)	-0.22 (0.14)	-0.09 (0.08)	-0.09	-0.05
Control B													
PFCld													
ACE	1607.65	0.00	1568.91	0.08									
CE	1593.86	0.46	1565.69	0.42									
AE	**1593.56**	**0.54**	**1565.39**	**0.49**	0.55 (0.06)	0.45 (0.06)	0.44 (0.07)	0.56 (0.07)	-0.19[c] (0.05)	-0.29[b] (0.11)	-0.10 (0.08)	-0.14	-0.05
PFClv													
ACE	1684.65	0.00	1645.92	0.08									
CE	1683.90	0.00	1655.72	0.00									
AE	**1669.27**	**1.00**	**1641.09**	**0.92**	0.55 (0.06)	0.45 (0.06)	0.64 (0.05)	0.36 (0.05)	-0.16[c] (0.05)	-0.21[a] (0.10)	-0.09 (0.09)	-0.13	-0.03
PFCmp													

ACE	1115.76	0.00	1077.02	0.09									
CE	1102.16	0.46	1073.99	0.42									
AE	**1101.84**	**0.54**	**1073.67**	**0.49**	0.55 (0.06)	0.45 (0.06)	0.45 (0.07)	0.55 (0.07)	-0.13[b] (0.05)	-0.17 (0.12)	-0.09 (0.09)	-0.08	-0.05
Temp													
ACE	1622.69	0.00	1583.96	0.06									
CE	1610.10	0.18	1581.92	0.17									
AE	**1607.02**	**0.82**	**1578.85**	**0.77**	0.55 (0.06)	0.45 (0.06)	0.17 (0.09)	0.83 (0.09)	-0.17[c] (0.05)	-0.37[a] (0.20)	-0.09 (0.08)	-0.11	-0.05
Control C													
pCun													
ACE	1397.52	0.00	1358.79	0.06									
CE	1384.29	0.26	1356.12	0.25									
AE	**1382.22**	**0.74**	**1354.05**	**0.69**	0.55 (0.06)	0.45 (0.06)	0.35 (0.07)	0.65 (0.07)	-0.18[c] (0.05)	-0.30[b] (0.13)	-0.09 (0.08)	-0.13	-0.05
Salience A													
FrMed													
ACE	2028.52	0.00	1989.78	0.07									
CE	2032.44	0.00	2004.27	0.00									
AE	**2012.71**	**1.00**	**1984.54**	**0.93**	0.55 (0.06)	0.45 (0.06)	0.69 (0.05)	0.31 (0.05)	-0.25[c] (0.05)	-0.31[c] (0.09)	-0.17[a] (0.09)	-0.19	-0.06
FrOper													
ACE	796.02	0.00	757.29	0.08									
CE	783.30	0.27	755.13	0.25									
AE	**781.31**	**0.73**	**753.13**	**0.67**	0.55 (0.06)	0.45 (0.06)	0.42 (0.07)	0.58 (0.07)	-0.11[a] (0.05)	-0.05 (0.12)	-0.16[a] (0.08)	-0.03	-0.08
Ins													
ACE	1042.27	0.00	1003.54	0.11									
CE	1029.42	0.39	1001.25	0.35									

AE	**1028.53**	**0.61**	**1000.36**	**0.54**	0.55 (0.06)	0.45 (0.06)	0.31 (0.08)	0.69 (0.08)	-0.10[a] (0.05)	-0.05 (0.14)	-0.14[a] (0.08)	-0.02	-0.08
ParMed													
ACE	1429.11	0.00	1390.37	0.19									
CE	1418.71	0.22	1390.54	0.18									
AE	**1416.17**	**0.78**	**1388.00**	**0.63**	0.55 (0.06)	0.45 (0.06)	0.44 (0.07)	0.56 (0.07)	-0.18[c] (0.05)	-0.22[a] (0.11)	-0.14[a] (0.08)	-0.11	-0.07
ParOper													
ACE	995.93	0.00	957.19	0.06									
CE	983.40	0.16	955.22	0.15									
AE	**980.11**	**0.84**	**951.94**	**0.79**	0.55 (0.06)	0.45 (0.06)	0.27 (0.08)	0.73 (0.08)	-0.12[b] (0.05)	-0.42[b] (0.16)	0.08 (0.09)	-0.16	0.05
Salience B													
PFCl													
ACE	1268.43	0.00	1229.70	0.07									
CE	1255.10	0.31	1226.92	0.29									
AE	**1253.48**	**0.69**	**1225.31**	**0.64**	0.55 (0.06)	0.45 (0.06)	0.38 (0.07)	0.62 (0.07)	-0.14[b] (0.05)	-0.20 (0.13)	-0.09 (0.08)	-0.09	-0.05
PFClv													
ACE	904.53	0.00	865.79	0.09									
CE	891.98	0.28	863.81	0.25									
AE	**890.05**	**0.72**	**861.87**	**0.66**	0.55 (0.06)	0.45 (0.06)	0.23 (0.08)	0.77 (0.08)	-0.12[b] (0.05)	-0.20 (0.16)	-0.09 (0.08)	-0.07	-0.05
PFCmp													
ACE	830.28	0.00	791.54	0.08									
CE	823.33	0.01	795.16	0.01									
AE	**814.73**	**0.99**	**786.56**	**0.91**	0.55 (0.06)	0.45 (0.06)	0.48 (0.07)	0.52 (0.07)	-0.19[c] (0.05)	-0.30[b] (0.11)	-0.07 (0.09)	-0.15	-0.03

Note: Model fit statistics and parameter estimates (standard errors in parentheses) from the series of bivariate biometric models between drink index scores and cortical thickness. Only those areas that showed significant associations with alcohol use in the main analyses

were selected for biometric modeling. The best fitting models, as determined by the BIC and AIC criteria, are bolded. All *p*-values for A and E parameter estimates were $p < 0.0032$ except for Control B temporal cortex thickness which was $p = 0.0523$.
The model-implied phenotypic correlation (rP) is the sum (within rounding error) of the genetic and nonshared environmental contributions (rP-G and rP-E). Because the main individual-level and cotwin control analysis results set expectations regarding the anticipated directionality of the phenotypic and genetic/nonshared environmental correlations, a hypothesis-driven one-tailed significance test was used for the rP, rG, and rE correlations, where [a] $p < 0.05$, [b] $p < 0.01$, and [c] $p \leq 0.001$.
Abbreviations: BIC, Bayesian information criterion (parameter penalty); *w*BIC, BIC weight (also known as Schwarz weight); AIC, Akaike information criterion (parameter penalty); *w*AIC, AIC weight (or Akaike weight); A, additive genetic influence (heritability); C, shared environmental influence; E, nonshared environmental influence; rP, model-implied phenotypic correlation; rG, genetic correlation; rE, nonshared environmental correlation; rP-G, genetic contribution to total model-implied phenotypic correlation; rP-E = nonshared environmental contribution to total model-implied phenotypic correlation; PFC, prefrontal cortex; IPS, intraparietal sulcus; Temp, temporal; pCun; precuneus; FrMed, frontal medial; FrOper, frontal operculum; Ins, insula; ParMed, parietal medial; ParOper, parietal operculum; l, lateral; d, dorsal; v, ventral; mp, medial posterior

Supplemental References

1. Neale MC (2009): Biometrical Models in Behavioral Genetics. In: Kim Y-K, editor. *Handbook of Behavior Genetics*. Springer, pp 15–33.
2. Boker S, Neale M, Maes H, Wilde M, Spiegel M, Brick T, *et al.* (2011): OpenMx: An Open Source Extended Structural Equation Modeling Framework. *Psychometrika* 76: 306–317.
3. Raftery AE (1995): Bayesian model selection in social research. *Sociological Methodology 1995, Vol 25* 25: 111–163.
4. Watson D, O'Hara MW, Naragon-Gainey K, Koffel E, Chmielewski M, Kotov R, *et al.* (2012): Development and validation of new anxiety and bipolar symptom scales for an expanded version of the IDAS (the IDAS-II). *Assessment* 19: 399–420.
5. Resnick HS, Best CL, Kilpatrick DG, Freedy JR, Falsetti SA (1993): Trauma assessment for adults. *Charleston, SC: Medical University of South Carolina*.
6. Keyes MA, Malone SM, Elkins IJ, Legrand LN, McGue M, Iacono WG (2009): The Enrichment Study of the Minnesota Twin Family Study: Increasing the Yield of Twin Families at High Risk for Externalizing Psychopathology. *Twin Res Hum Genet* 12: 489–501.
7. Wilson S, Malone SM, Hunt RH, Thomas KM, Iacono WG (2017): Problematic alcohol use and hippocampal volume in a female sample: disentangling cause from consequence using a co-twin control study design. *Psychol Med* 1–12.
8. Tellegen A, Waller NG (2012): Exploring personality through test construction: Development of the multidimensional personality questionnaire. *The SAGE Handbook of Personality Theory and Assessment: Volume 2 — Personality Measurement and Testing*. 1 Oliver's Yard, 55 City Road, London EC1Y 1SP United Kingdom: SAGE Publications Ltd, pp 261–292.
9. Krueger RF, Derringer J, Markon KE, Watson D, Skodol AE (2012): Initial construction of a maladaptive personality trait model and inventory for DSM-5. *Psychol Med* 42: 1879–1890.
10. Thapar A, Rutter M (2019): Do natural experiments have an important future in the study of mental disorders? *Psychol Med* 49: 1079–1088.
11. Rutter M (2007): Proceeding From Observed Correlation to Causal Inference The Use of Natural Experiments. *Perspect Psychol Sci* 2: 377–395.
12. Posthuma D (2009): Multivariate genetic analysis. In: Kim Y-K, editor. *Handbook of Behavior Genetics*. Springer, pp 47–59.
13. Burnham KP, Anderson DR (2004): Multimodel inference. *Sociol Methods Res* 33: 261–304.
14. Verhulst B (2017): A power calculator for the classical twin design. *Behav Genet* 47: 255–261.