

Association of Gray Matter and Personality Development With Increased Drunkenness Frequency During Adolescence

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IMPORTANCE Alcohol abuse correlates with gray matter development in adolescents, but the directionality of this association remains unknown.

OBJECTIVE To investigate the directionality of the association between gray matter development and increase in frequency of drunkenness among adolescents.

DESIGN, SETTING, AND PARTICIPANTS This cohort study analyzed participants of IMAGEN, a multicenter brain imaging study of healthy adolescents in 8 European sites in Germany (Mannheim, Dresden, Berlin, and Hamburg), the United Kingdom (London and Nottingham), Ireland (Dublin), and France (Paris). Data from the second follow-up used in the present study were acquired from January 1, 2013, to December 31, 2016, and these data were analyzed from January 1, 2016, to March 31, 2018. Analyses were controlled for sex, site, socioeconomic status, family history of alcohol dependency, puberty score, negative life events, personality, cognition, and polygenic risk scores. Personality and frequency of drunkenness were assessed at age 14 years (baseline), 16 years (first follow-up), and 19 years (second follow-up). Structural brain imaging scans were acquired at baseline and second follow-up time points.

MAIN OUTCOMES AND MEASURES Increases in drunkenness frequency were measured by latent growth modeling, a voxelwise hierarchical linear model was used to observe gray matter volume, and tensor-based morphometry was used for gray matter development. The hypotheses were formulated before the data analyses.

RESULTS A total of 726 adolescents (mean [SD] age at baseline, 14.4 [0.38] years; 418 [58%] female) were included. The increase in drunkenness frequency was associated with accelerated gray matter atrophy in the left posterior temporal cortex (peak: $t_{1,710} = -5.8$; familywise error (FWE)-corrected $P = 7.2 \times 10^{-5}$; cluster: 6297 voxels; $P = 2.7 \times 10^{-5}$), right posterior temporal cortex (cluster: 2070 voxels; FWE-corrected $P = .01$), and left prefrontal cortex (peak: $t_{1,710} = -5.2$; FWE-corrected $P = 2 \times 10^{-3}$; cluster: 10 624 voxels; $P = 1.9 \times 10^{-7}$). According to causal bayesian network analyses, 73% of the networks showed directionality from gray matter development to drunkenness increase as confirmed by accelerated gray matter atrophy in late bingers compared with sober controls ($n = 20$ vs 60 ; $\beta = 1.25$; 95% CI, -2.15 to -0.46 ; $t_{1,70} = 0.3$; $P = .004$), the association of drunkenness increase with gray matter volume at age 14 years ($\beta = 0.23$; 95% CI, 0.01 - 0.46 ; $t_{1,584} = 2$; $P = .04$), the association between gray matter atrophy and alcohol drinking units ($\beta = -0.0033$; 95% CI, -6×10^{-3} to -5×10^{-4} ; $t_{1,509} = -2.4$; $P = .02$) and drunkenness frequency at age 23 years ($\beta = -0.16$; 95% CI, -0.28 to -0.03 ; $t_{1,533} = -2.5$; $P = .01$), and the linear exposure-response curve stratified by gray matter atrophy and not by increase in frequency of drunkenness.

CONCLUSIONS AND RELEVANCE This study found that gray matter development and impulsivity were associated with increased frequency of drunkenness by sex. These results suggest that neurotoxicity-related gray matter atrophy should be interpreted with caution.

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Alcohol intoxication (ie, drunkenness) is frequent among adolescents and conveys greater risk for alcohol abuse.¹ Although alcohol addiction has been associated with brain atrophy,² heavy drinking in adolescents is also associated with reduced volume and thickness of frontal and temporal gray matter.³ Longitudinal structural brain studies found greater frontocortical and temporal cortex thinning in adolescents who did not drink alcohol at baseline but transitioned into alcohol abuse during follow-up^{4,5} compared with adolescents who drank no or low amounts of alcohol. However, this difference was absent when the groups were matched for age and when adolescents with no or low drinking were compared with those who transitioned into moderate drinking.⁶

During adolescence, the development of reward processing has been suggested to precede the development of cognitive control,^{7,8} thus promoting risky decision-making, including alcohol abuse.⁹ Moreover, the regions that are most sensitive to alcohol-related atrophy are also involved in brain networks engaged in response inhibition,¹⁰ decision-making,^{11,12} and alcohol-triggered emotions.¹³ Atrophy in anterior cingulate and in superior frontal and middle temporal gyri is a factor in alcohol abuse.¹⁴⁻¹⁷ Together, these observations suggest a role for brain developmental mechanisms in the onset of alcohol abuse.

Suggestions by previous studies that heavy drinking was associated with brain damage in adolescents were based on nonsignificant group difference at baseline and significant group difference after the onset of drinking.³⁻⁶ This exclusive reliance on time precedence ignores the dynamic nature of brain development that begins even before birth¹⁸ and might be associated with alcohol-related developmental trajectories that are established before the onset of drinking. Instead, causality may be inferred from observational studies using corroborative evidence, including but not restricted to temporality.¹⁹ Furthermore, studies did not report behavioral changes, such as in personality during adolescence, which are known to be factors in alcohol abuse.²⁰

Thus, the directionality of the association between brain development and frequency of drunkenness remains unknown to date. Specifically, is alcohol abuse associated with changes in brain structure in adolescents and young adults, or is there a trajectory of brain development that is a contributing factor in behavior, which may put certain adolescents at greater risk of alcohol abuse?

In this cohort study, we adopted 3 complementary approaches to investigate the directionality of the association between gray matter development and the increase in drunkenness frequency. The first approach was causal bayesian network (CBN), which belongs to probabilistic reasoning and provides graphic representations of network conditional dependencies.²¹ Causal bayesian network addresses the questions of directionality, uncertainty, and complexity in a set of random, interrelated variables²² and is used in various fields.²³⁻²⁵ Reliable application of CBN requires a multidimensional assessment of interrelated features that possibly mediate the association between the brain and frequency of drunkenness, including sociodemographic status, genetics, cognition, behaviors, and personality. The second approach

Key Points

Question What is the directionality of the association between the increased frequency of drunkenness and gray matter development during adolescence?

Findings In this cohort study of 726 adolescents enrolled in the IMAGEN European cohort, the 3 complementary approaches used (causal bayesian networks, temporality analyses, and exploration of exposure-response curves) suggested that accelerated gray matter atrophy in the frontal and posterior temporal cortices was associated with an increased risk for drunkenness.

Meaning Findings from this study suggest that the neurotoxicity interpretation of the drinking-related acceleration of gray matter atrophy should be applied with caution.

was temporality analyses in 3 different samples of alcohol consumers. The third approach was exploration of the exposure-response curves. The full procedure is detailed in the eMethods and eAppendix in the [Supplement](#). The analyses workflow and participant flowchart are shown in eFigures 1 and 2 in the [Supplement](#).

Methods

Participants

The present cohort study analyzed participants enrolled in IMAGEN, a prospective, multicenter brain imaging study.²⁶ Healthy adolescents were recruited at age 14 years from schools around 8 sites in Germany (Mannheim, Dresden, Berlin, and Hamburg), the United Kingdom (London and Nottingham), Ireland (Dublin), and France (Paris). Data from the second follow-up used in the present study were acquired from January 1, 2013, to December 31, 2016, and were analyzed from January 1, 2016, to March 31, 2018. Exclusion criteria are detailed in the eMethods in the [Supplement](#). Participants' alcohol, cannabis, and tobacco consumption and personality features were assessed at ages 14 years (baseline), 16 years (first follow-up), 19 years (second follow-up), and 23 years (third follow-up), thereby reducing the confounding factor of age. Structural brain imaging and cognitive measures were acquired at baseline and second follow-up. Written informed consent was obtained from all participants. This study was approved by the institutional ethics committee of King's College London, University of Nottingham, Trinity College Dublin, University of Heidelberg, Technische Universität Dresden, Commissariat à l'Énergie Atomique et aux Énergies Alternatives, and University Medical Center at the University of Hamburg in accordance with the Declaration of Helsinki.²⁷ The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Main Outcomes and Measures

Frequency of drunkenness was measured with the following question on the European School Survey Project on Alcohol and Other Drugs: How many times did you get drunk in the

last 12 months (intoxicated from drinking alcoholic beverages, for example staggering when walking, not being able to speak properly, throwing up, or not remembering what happened)? The mean value of each response category was used for analyses (eg, a value of 3 on the European School Survey Project on Alcohol and Other Drugs referred to 3 to 5 episodes of drunkenness, yielding a score of 4). The increase in drunkenness frequency estimated by latent growth modeling was quantitative and normally distributed.

After the quality control procedure, 1938 (969 × 2) scans were preprocessed using the SPM-12b longitudinal pairwise tool (Functional Imaging Laboratory Methods Group). The mid-point within-participant templates were segmented with the VBM-8 toolbox (Christian Gaser, University of Jena) to avoid using adult tissue probability maps.²⁸ A between-participant template was generated with the diffeomorphic anatomical registration through exponentiated lie (DARTEL) algebra.²⁹ SPM-12b and SPM8-5236 (VBM8) were run on MATLAB, version 7.14.0 (The MathWorks Inc).

Confounding factors (socioeconomic status, puberty score, negative life events, and family history of alcohol dependency) were controlled for (eFigure 1 and eMethods in the Supplement). A polygenic risk score (PRS) for alcohol consumption³⁰ was required to meet the CBN assumptions to reduce the risk of identifying a spurious direct link. Cognition (working memory, decision-making, and response inhibition) and behavior (delay discounting, passive avoidance learning, and personality) variables are detailed in the eMethods in the Supplement. Alcohol drinking units (at age 23 years) were acquired using the timeline follow-back method. Body mass index was not controlled for (eMethods in the Supplement). Missing values were imputed using multiple imputation.³¹

Statistical Analysis

Associations between quantitative variables were tested using hierarchical linear models, a 1-level random intercept for site and sex with lmerTest, version 3.1-0 (Per Bruun Brockhoff). All *P* values were Bonferroni corrected (eTable 1 in the Supplement). Two-sided *P* < .05 was considered statistically significant.

Increases in drunkenness frequency and in personality changes were estimated with latent growth modeling. Mplus (Muthén & Muthén) provided the slope (ie, the increase) and the intercept (ie, drunkenness frequency at age 14 years, given the frequency at each time point) for each participant. Missing values were estimated using maximum likelihood from all of the data available³² under the missing-completely-at-random assumption (Little MCAR test: $\chi^2_{1,290} = 286$; *P* = .60).

Causal bayesian networks, following the Bayes theorem, modeled the posterior conditional probability of a consequence after observation of the distribution of the probability of new previous evidences in an iterative process. This approach is suited to modeling the directionality between variables acquired at the same time and to providing probabilistic dependencies in a directed acyclic graph.²¹ In addition, given a set of variables, CBN can be estimated in a data-driven approach. Each network corresponds to a goodness of

fit to the observed data score (bayesian gaussian equivalent). The procedure of “hill climbing” adds, deletes, and reverses arcs in the current directed acyclic graph at a time until the bayesian gaussian equivalent no longer improves.^{33(p19-20)}

We reported only the edges replicated in more than 90% of the 10 000 bootstrapped CBNs,³³ and their directionality was the dominant direction (>50% of the bootstrapped CBNs^{24,33}). Increases in drunkenness frequency between ages 14 and 19 years, drunkenness frequency at age 14 years, gray matter development between ages 14 and 19 years (first principal component), gray matter volume at age 14 years (first principal component of the same clusters), and PRS were considered. All CBN analyses used bnlearn.³³

We considered individuals with minimal experiences with alcohol, tobacco, and cannabis use until they were 16 years of age (117 had a maximum of 2 occasions of drinking alcohol in their lifetime¹⁶ from the initial sample of 726 participants). We compared gray matter development (first principal component) among the late drinkers (ie, for 20 participants, episodes of drunkenness occurred during mainly the last month before the scans at 19 years of age; for 60 participants in the sober control group, 0 lifetime drunkenness episodes occurred).

We tested whether gray matter volume among the 3 clusters (first principal component) at age 14 years was associated with increased drunkenness frequency after age 14 to 19 years in a selected subsample of participants without any episode of drunkenness the year before age 14 years (*n* = 604).

We tested whether gray matter atrophy (first principal component) was associated with frequency of drunkenness (*n* = 594) and alcohol drinking units at age 23 years (*n* = 532). We used the increase in binge drinking (ie, 5 drinks in a row) to control for previous alcohol intoxication.

We stratified effect sizes according to site by sex. We explored the exposure-response curves¹⁹ (*n* = 726) by ranking the strata according to increasing gray matter atrophy and increasing drunkenness frequency.

Results

In total, 2216 healthy adolescents were recruited into the IMA-GEN cohort. The present study included 726 (33%) of these participants with good-quality data (Table 1; eFigure 2 in the Supplement). Among the 726 participants, the mean (SD) age at baseline was 14.4 (0.38) years, 418 (58%) were female, and all were white. One hundred and two individuals (14%) had at least 1 drunkenness episode.

Association With Site, Sex, Impulsivity, and Accelerated Gray Matter Atrophy

Drunkenness significantly increased over time (estimated SE = 8.1; *P* < .001) (eFigure 3 in the Supplement). Significant differences were found between sites (analysis of variance $F_{7,718} = 12.4$; *P* = 4.8×10^{-15}), with higher increases in drunkenness frequency in England and Ireland (London, Nottingham, and Dublin) compared with the continental sites. The mean increase in drunkenness frequency was greater in male

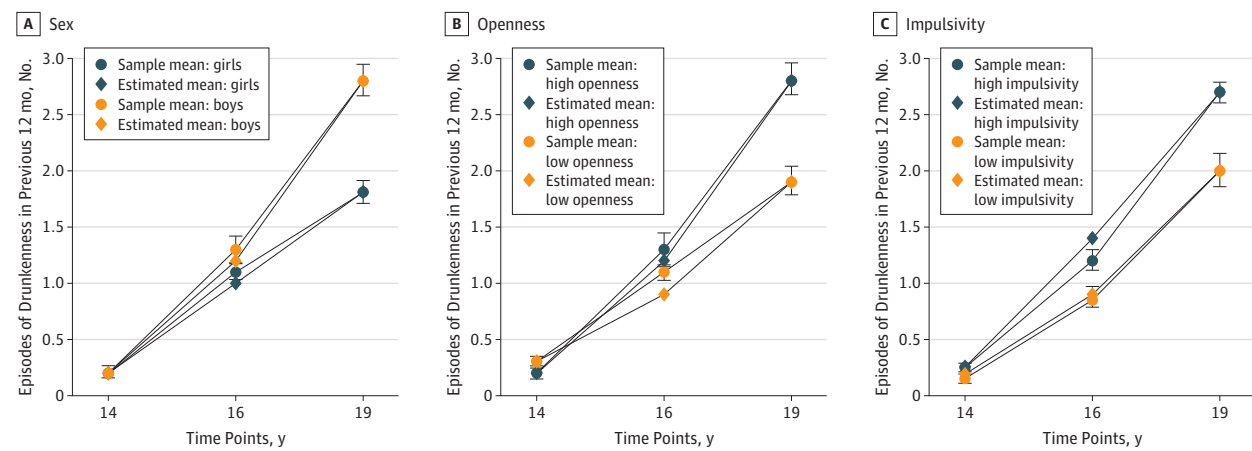
Table 1. Variables Description Within the Sample^a

Variable	Baseline	Follow-up 1	Follow-up 2
Age, y	14.4 (0.38) [12.9 to 15.7]	16.5 (0.56) [15 to 18.8]	18.8 (0.6) [17.1 to 21.1]
Sex, No. (%)			
Female	418 (58)	ND	ND
Male	308 (42)	ND	ND
Site proportion, No. (%)			
London	120 (17)	ND	ND
Nottingham	138 (19)	ND	ND
Dublin	48 (7)	ND	ND
Berlin	72 (10)	ND	ND
Hamburg	82 (11)	ND	ND
Mannheim	92 (13)	ND	ND
Paris	66 (9)	ND	ND
Dresden	108 (15)	ND	ND
ESPAD			
Frequency of drunkenness	0.5 (1.8) [0 to 29.5]	4.2 (8.7) [0 to 41]	9.7 (12.5) [0 to 41]
Tobacco	0.16 (1.4) [0 to 21]	0.8 (2.7) [0 to 21]	1.6 (4) [0 to 21]
Cannabis	0.26 (2.4) [0 to 41]	2.6 (8.3) [0 to 41]	5.1 (11.7) [0 to 41]
LEQ			
Negative life events	6.4 (2.8) [0 to 16]	5.9 (2.7) [0 to 17]	3.6 (2.2) [0 to 14]
SURPS			
Impulsivity	2.4 (0.4) [1.4 to 4]	2.2 (0.4) [1 to 3.4]	2.1 (0.4) [1 to 3.4]
Sensation	2.6 (0.5) [1 to 4]	2.7 (0.5) [1.2 to 4]	2.7 (0.5) [1 to 4]
Anxiety sensitivity	2.3 (0.4) [1 to 3.8]	2.3 (0.5) [1 to 4]	2.4 (0.5) [1 to 4]
Negative thinking	1.9 (0.4) [1 to 3.4]	1.8 (0.4) [1 to 3.6]	1.9 (0.4) [1 to 4]
NEO PI			
Neuroticism	23.13 (7.5) [4 to 45]	22.57 (5.9) [1 to 44]	20.8 (8.2) [1 to 47]
Extraversion	29.7 (5.9) [10 to 45]	29.2 (5.9) [10 to 45]	29.4 (5.9) [11 to 45]
Openness	26.7 (5.7) [11 to 45]	27.7 (5.9) [8 to 48]	28.9 (6.4) [12 to 45]
Agreeableness	29.6 (5.1) [6 to 44]	30.2 (5.3) [11 to 45]	32.3 (5.5) [9 to 46]
Conscientiousness	27.9 (6.6) [8 to 48]	28.6 (7) [9 to 47]	30.2 (7.2) [4 to 48]
CGT			
Deliberation time, ms	2245.55 (7194.52) [736.51 to 181363.1]	ND	1626.21 (699.30) [734.5 to 12682.45]
Risk taking	0.52 (0.14) [0.05 to 0.89]	ND	0.52 (0.12) [0.13 to 0.86]
Delay aversion	0.23 (0.14) [-0.7 to 0.77]	ND	0.20 (0.15) [-0.13 to 0.83]
Quality of decision-making	0.94 (0.08) [0.45 to 1]	ND	0.96 (0.06) [0.55 to 1]
Overall bet	0.48 (0.13) [0.05 to 0.83]	ND	0.48 (0.11) [0.14 to 0.83]
Risk adjustment	1.65 (0.96) [-0.6 to 4.6]	ND	1.98 (0.95) [-0.3 to 4.78]
Pattern recognition memory, No. of correct trials	95.3 (7.6) [41.7 to 100]	ND	95.9 (7.1) [54 to 100]
Rapid visual processing	0.9 (0.05) [0.7 to 1]	ND	0.93 (0.04) [0 to 1]
Spatial working memory			
Between errors	18.6 (13) [0 to 63]	ND	11.1 (12.2) [0 to 74]
Strategy	31 (5.4) [18 to 43]	ND	27.7 (6.2) [18 to 44]
Affective go or no-go mean correct latency, ms			
Negative	490 (111.8) [222 to 888]	ND	513.3 (89.5) [215 to 964]
Positive	473.5 (107.8) [196.9 to 828.9]	ND	497.5 (87.8) [239 to 903]
Affective go or no-go total omissions, No.			
Negative	11.4 (7.9) [0 to 36]	ND	6.2 (5.5) [0 to 36]
Positive	13.3 (7.3) [0 to 36]	ND	8 (5.4) [0 to 36]
Delay discounting κ value	0.023 (0.03) [0 to 0.25]	ND	0.024 (0.03) [0 to 0.24]

Abbreviations: CGT, Cambridge Guessing Task (modified version of the Cambridge Gambling Task; CGT variables detailed in the eMethods in the Supplement); ESPAD, European School Survey Project on Alcohol and Other Drugs; LEQ, Life Events Questionnaire; ND, no data acquired at the corresponding time point; NEO PI, Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness Personality Inventory; SURPS, Substance Use Risk Profile Scale (this scale measured sensation seeking, impulsivity, anxiety sensitivity, and negative thinking).

^a All values given as mean (SD) [range] unless otherwise indicated.

Figure 1. Increase in Drunkenness Among 726 Participants



Error bars are the SEM from the sample at each time point.

compared with female participants (0.52 vs 0.34; 95% CI, 12%-24%; $t_{1,724} = 5.9$; $P = 3.6 \times 10^{-9}$) (Figure 1A). Among possible personality,²⁰ cognition,³⁴ and behavioral³⁵ confounding factors, only the increases in openness ($\beta = 0.10$; 95% CI, 0.05-0.16; $t_{1,690} = 4$; $P = 2.4 \times 10^{-3}$) and in impulsivity ($\beta = 1.06$; 95% CI, 0.57-1.9; $t_{1,707} = 3.6$; Bonferroni-corrected [25 models] $P = 6.7 \times 10^{-3}$) were associated with an increase in drunkenness frequency (Figure 1B and C; eTable 2 in the Supplement). Polygenic risk score was not associated with an increase in drunkenness frequency ($\beta = 3209$; 95% CI, -2769 to 9187; $t_{1,699} = 1$; $P = .30$).

We found significant atrophy in the inferior frontal and temporal cortices independent of drunkenness ($n = 907$) (Figure 2A and B; eTables 7, 8, and 9 in the Supplement). An increase in drunkenness frequency was associated with accelerated gray matter atrophy in the left posterior temporal cortex (peak: $t_{1,710} = -5.8$; familywise error (FWE)-corrected $P = 7.2 \times 10^{-5}$; cluster: 6297 voxels; $P = 2.7 \times 10^{-5}$), in the right posterior temporal cortex (cluster: 2070 voxels; FWE-corrected $P = .01$), and in the left prefrontal cortex (peak: $t_{1,710} = -5.2$; FWE-corrected $P = 2 \times 10^{-3}$; cluster: 10 624 voxels; $P = 1.9 \times 10^{-7}$), extending to the left anterior insula and the anterior cingulate (Figure 2C and Table 2). These 3 clusters were also observed using a voxelwise hierarchical linear model (eFigure 4 and eTable 3 in the Supplement) and were confirmed with the increase of binge drinking (5 drinks in a row) and the first principal component of the 3 clusters ($\beta = -0.76$; 95% CI = -0.97 to -0.55; $t_{1,701} = -7.1$; $P = 3.5 \times 10^{-12}$) (eResults and eFigure 4 in the Supplement).

Directionality Analyses

Bootstrapping revealed that 100% of the CBNs showed an association between gray matter atrophy and an increase in drunkenness frequency, of which 73% showed a direction from gray matter development to increased drunkenness frequency (Figure 3A). We found increased gray matter atrophy (between ages 14 and 19 years) in the late bingers compared with sober controls ($n = 20$ vs 60; $\beta = 1.25$; 95% CI, -2.15 to

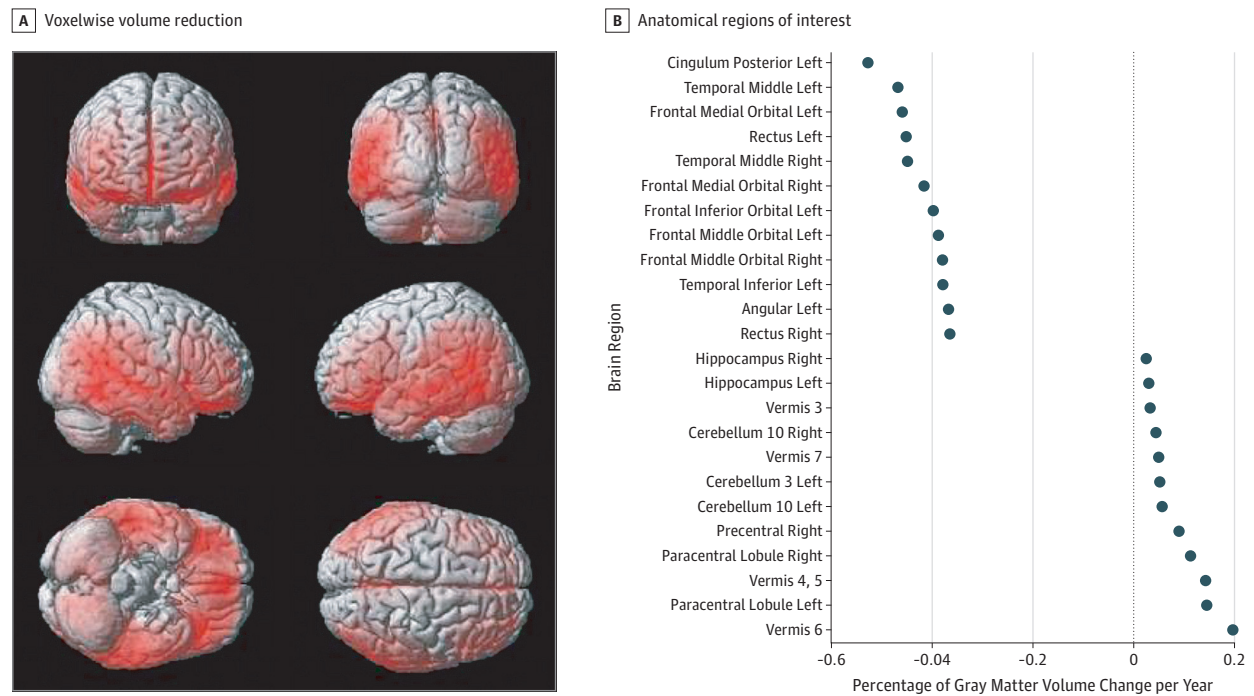
-0.46; $t_{1,70} = 0.3$; $P = .004$). Gray matter volume at age 14 years among nondrinkers was associated with a future increase in drunkenness frequency between ages 14 and 19 years ($n = 604$; $\beta = 0.23$; 95% CI, 0.01-0.46; $t_{1,584} = 2$; $P = .04$). Conversely, drunkenness frequency at age 14 years was not associated with gray matter development between ages 14 and 19 years in the whole sample ($n = 726$; $\beta = 0.03$; 95% CI, -0.09 to 0.14; $t_{1,700} = 0.4$; $P = .60$) or in the sample of alcohol drinkers at age 14 years ($n = 122$; $\beta = -1 \times 10^{-3}$; 95% CI, -0.22 to 0.22; $t_{1,106} = -0.01$; $P > .99$). Gray matter development was negatively associated with frequency of drunkenness ($n = 594$; $\beta = -0.16$; 95% CI, -0.28 to -0.03; $t_{1,533} = -2.5$; $P = .01$) and alcohol drinking units at age 23 years ($n = 532$; $\beta = -0.0033$; 95% CI, -6×10^{-3} to -5×10^{-4} ; $t_{1,509} = -2.4$; $P = .02$).

Ranking the strata according to gray matter atrophy revealed a linear exposure-relation curve, whereas using the frequency of drunkenness to rank the groups did not (eFigures 5 and 6 in the Supplement). Individuals with the fastest gray matter atrophy (female participants from London) had a greater increase in drunkenness frequency compared with individuals with the slowest atrophy (male participants from Paris) ($\beta = 0.28$; 95% CI, 0.11-0.45; $t_{1,98} = 3.3$; $P = .001$). Stratifying the sample by site and sex confirmed greater effect sizes in female participants and in Dresden (continent) (eTables 4 and 5 and eFigures 7 and 8 in the Supplement).

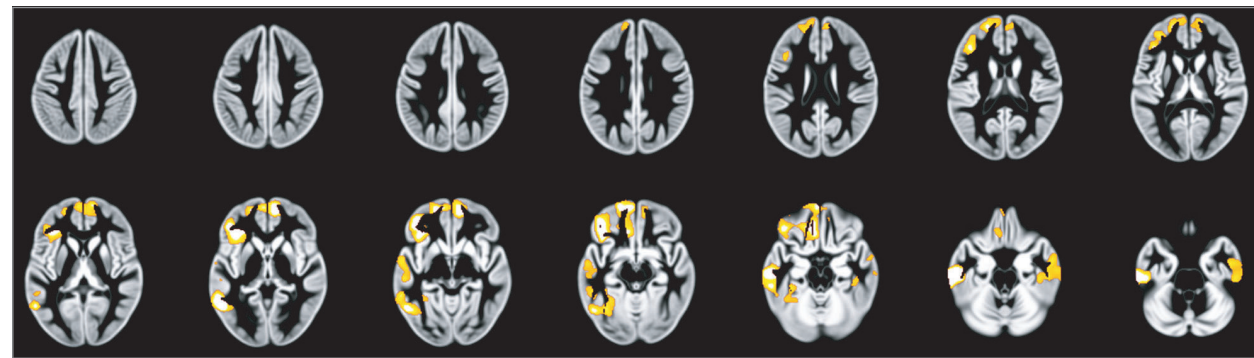
Impulsivity and Gray Matter Development as Independent Sex-Specific Pathways

We found no significant association between gray matter atrophy and increase in impulsivity ($\beta = 0.7$; 95% CI, -1.3 to 2.8; $t_{1,707} = 0.7$; $P = .50$). However, impulsivity at age 14 years correlated strongly with drunkenness frequency at age 14 years ($\beta = 0.6$; 95% CI, 0.3-0.9; $t_{1,712} = 4.1$; $P = 3.9 \times 10^{-5}$) and increase in drunkenness frequency between ages 14 and 19 years ($\beta = 0.3$; 95% CI, 0.2-0.5; $t_{1,708} = 5$; $P = 6.7 \times 10^{-7}$), particularly among male participants ($\beta = 0.6$; 95% CI, 0.4-0.9; $t_{1,293} = 5.4$; $P = 1 \times 10^{-7}$) but not female participants ($\beta = 0.1$; 95% CI, -0.03 to 0.3; $t_{1,405} = 1.5$; $P = .10$). An increase in open-

Figure 2. Gray Matter Development Among Participants



C Volume reduction in frontal and temporal cortices



A, Cerebral regions show the voxelwise volume reduction. B, Percentage of gray matter volume change per year (from gray matter volume at age 14 years). The first 12 regions (on the left of the graph) show the most significant volume reduction (negative values), whereas the remaining 12 regions (on the right of the graph) show the most significant volume increase (positive values). C, The increase in frequency of drunkenness episodes between ages 14 and 19 years

was the variable of interest. Confounding factors were site, sex, latent baseline drinking intercept factor, tobacco use, cannabis use,³⁶ negative score on the Life Events Questionnaire,³⁷ total intracranial volume difference, socioeconomic status, family history, and sex-centered puberty development score. Mass univariate voxelwise analyses were used.

ness between ages 14 and 19 years was not associated with gray matter atrophy ($\beta = -0.1$; 95% CI, -0.3 to 0.06 ; $t_{1,695} = -1.3$; $P = .20$). Openness at age 14 years was not associated with drunkenness at this age ($\beta = -0.005$; 95% CI, -0.02 to 0.01 ; $t_{1,613} = -0.7$; $P = .40$) or with an increase in drunkenness between ages 14 and 19 years ($\beta = 0.008$; 95% CI, 0.001 - 0.01 ; $t_{1,709} = 2.4$; Bonferroni-corrected $P = .07$).

Post hoc CBN analyses tested for the directionality of the association between impulsivity and the increase in drunkenness frequency and PRS (5 variables). Impulsivity at age 14 years and increase in drunkenness frequency were associated with 92% of the networks, suggesting that impulsive be-

havior that was already established at age 14 years was associated with increased drunkenness frequency. Impulsivity and frequency of drunkenness at age 14 years were associated in 91% of the networks, but only 50% of the networks found directionality from impulsivity to drunkenness frequency at this age (Figure 3B).

A third CBN analysis evaluated whether the 2 pathways (ie, related to gray matter or impulsivity) were independent from each other (7 variables). We found stable directionality from gray matter development (76%) predominantly among female participants (93%) and from impulsivity at age 14 years to increase in drunkenness (94%) predominantly

Table 2. Clusters and Corresponding Features Associating Gray Matter Development and Increase in Frequency of Drunkenness (N = 726 Participants)

Cluster	Cluster Size (Voxels)	AAL Structures	Peak Location MNI Coordinates	P Value for Cluster Level (FWE Corrected) ^{a,b}	t Value	Brodmann Area	P Value for Peak Level (FWE Corrected) ^a
Left prefrontal	10 624	Lateral frontal gyrus (L)	-42, 34, -12	1.9 × 10 ⁻⁷	5.2	L BA 47	2 × 10 ⁻³
		Middle frontal gyrus (L)	-44, 36, 0		4.96	L BA 45	5 × 10 ⁻³
		Inferior frontal gyrus (L)	-10, 34, -15		4.5	L BA 11	4 × 10 ⁻²
Left temporal	6297	Inferior temporal gyrus (L) + middle temporal gyrus (L)	-62, -21, -24	2.7 × 10 ⁻⁵	5.85	BA 20 + BA 21	7.2 × 10 ⁻⁵
		Fusiform gyrus (L)	-52, -56, 0		5.26	BA 37	1 × 10 ⁻³
Right temporal	2070	Middle temporal gyrus (R)	68, -26, -22	1 × 10 ⁻²	NA	No voxels survived the FWE correction	NA

Abbreviations: AAL, automatic anatomic label; BA, Brodmann area; FWE, familywise error; L, left; MNI, Montreal Neurological Institute; NA, not applicable; R, right.

^a All P values were FWE corrected.

^b P value at the peak level set at P = .001 uncorrected.

among male participants (99%) (Figure 3C-E). Constraining the directionality from the increase of drunkenness toward gray matter development yielded worse model fit indices (eTable 6 in the Supplement). These results remained when the imputed PRS missing values were used (eFigure 9 in the Supplement).

Discussion

Using complementary approaches to determine probable directionality, we found that the accelerated gray matter atrophy in frontal and temporal regions was associated with increased frequency of alcohol intoxication in adolescents. Although this brain development pathway was found in both sexes, it was more prominent in female participants. In male participants, we found a second and independent pathway in which increased impulsivity was associated with increased drunkenness frequency.

The finding that accelerated frontal atrophy was associated with frequency of drunkenness corroborates previous findings.^{4,6} However, Pfefferbaum et al⁶ did not find accelerated temporal atrophy, possibly owing to the cortex parcellation, which might have calculated a different pattern of temporal cortex development.³⁵ Moreover, age had a limited confounding effect in our sample (eResults in the Supplement).

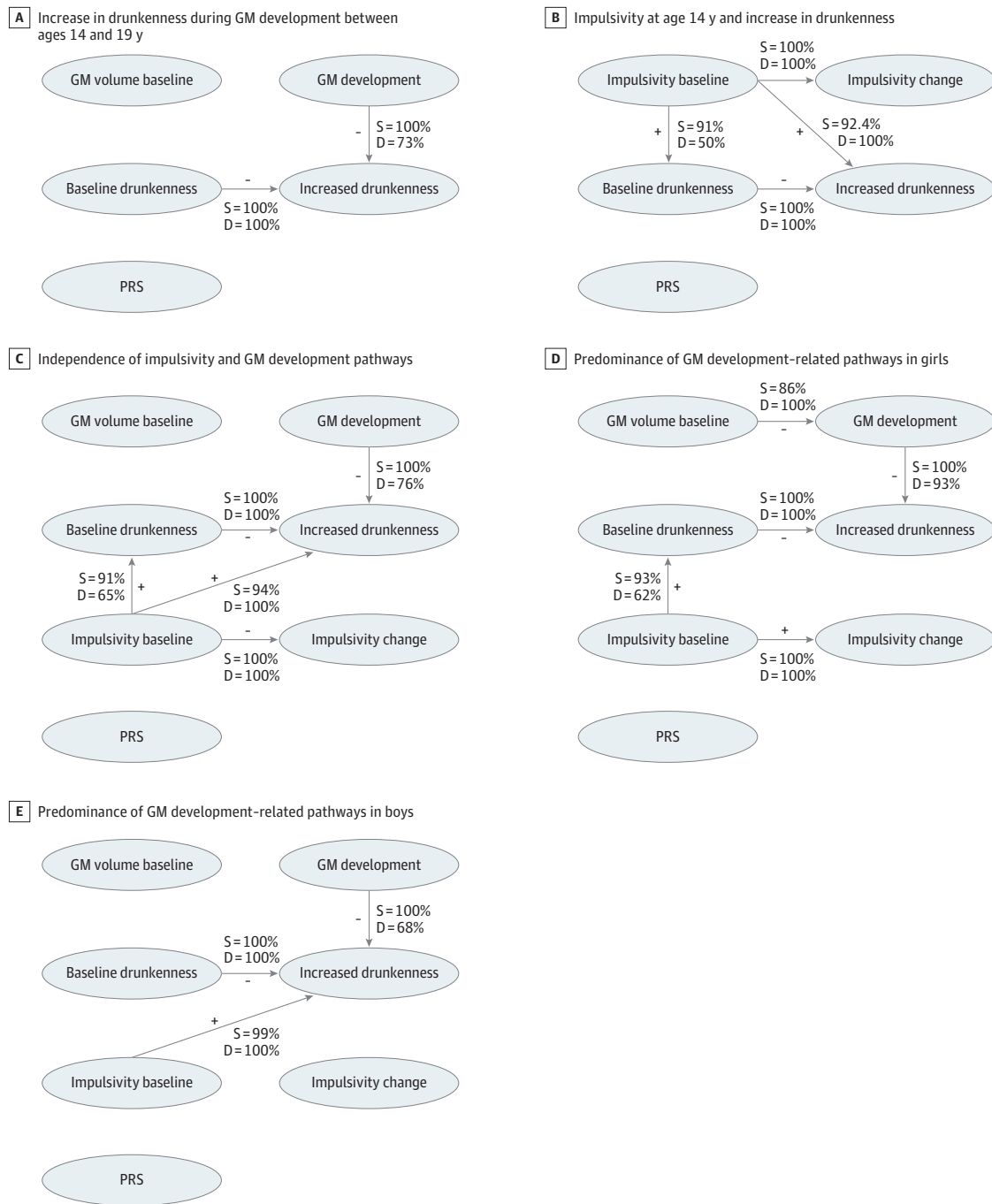
Temporal atrophy was greater during ages 14 to 19 years, whereas the age range of 12 to 21 years⁶ might have influenced temporal atrophy variance. For example, Squeglia et al³⁴ found alcohol abuse-related accelerated atrophy in the temporal cortex using a similar approach as in the present study but with a younger sample at baseline. Results of the present study are consistent with those of a recent meta-analysis in substance dependency, which identified the shared pattern of gray matter atrophy (within the bilateral middle temporal gyrus, the left fusiform gyrus, and the right medial orbitofrontal cortex) across various substance use, suggesting that atrophy may underlie substance dependency in general rather than specific neurotoxicity.³⁸

Prenatal exposure to alcohol has been suggested as a factor in gray matter development.^{39,40} However, we could not find any significant association between amount of alcohol intake during pregnancy and gray matter development (eResults in the Supplement).

Two important conditions for the successful application of CBN are controlling for potential confounding factors and verifying the results using long-term data.^{22,33} Unmeasured factors might confound the association between gray matter development and increase in drunkenness frequency. In the present study, we integrated various confounding factors, including demographic, behavioral, and genetic factors relevant to alcohol use. Thus, the comprehensive and multidomain assessment of possible confounding factors of increased drunkenness¹⁶ meets the assumptions for using CBN. Meanwhile, the longitudinal design of the study supports gray matter atrophy preceding the onset of drunkenness episodes in different temporal patterns of alcohol use. First, baseline gray matter volume was significantly associated with future frequency of drunkenness, corroborating previous results that gray matter development was associated with alcohol abuse.^{14-17,41} Second, late drinkers had accelerated atrophy. Although accelerated atrophy among late drinkers may not be induced by drunkenness within the last month before the assessment, we cannot formally rule out this possibility. Third, the cerebral pattern related to adolescent drunkenness is also associated with alcohol intake and drunkenness frequency at adulthood. This association remains significant, accounting for an increase in binge drinking that may indicate adult alcohol use⁴² and arguing for time precedence from gray matter development during adolescence to adult alcohol intake.

Plotting the effect sizes according to sex-by-site groups ranked by higher rate of gray matter atrophy revealed a linear trend of exposure-response curve, and the group with the fastest rate of gray matter atrophy had a greater increase in drunkenness frequency compared with the group with the slowest rate of gray matter atrophy. Conversely, ranking the groups according to drunkenness frequency did not provide the typical curve, suggesting that alcohol is toxic.⁴³⁻⁴⁷

Figure 3. Causal Bayesian Networks



Bayesian gaussian equivalent scores were -4610.7 (A), -4570.6 (B), -6407.7 (C), -3685.6 (D), and -2738.7 (E). The confounding factors (sex, site, puberty development score, negative life events, family history of alcoholism, and socioeconomic status) were modeled by regressing out their corresponding variance from each variable of interest (ie, node). Minus (-) or plus (+) sign

indicates either negative or positive associations between the nodes; D indicates direction or proportion of networks (10 000 bootstraps) showing a direction from one node to another; GM, gray matter; PRS, polygenic risk score; and S, strength or the proportion of networks (10 000 bootstraps) with a statistically significant association.

Limitations

This study has some limitations. Causality can be proven only in randomized clinical trials, which are not feasible for ethical reasons. Therefore, compelling evidence from large,

longitudinal, and well-characterized observational studies are the best evidence available according to the Hill criteria for inferring causality.¹⁹ The possible limitations of this approach are the unmeasured confounders that obscure true causality

despite controlling for numerous intervening variables. Short of conducting a randomized clinical trial, we cannot rule out the possibility of the simultaneous occurrence of gray matter atrophy and increase in alcohol intoxication without any causation. For example, recent genetic epidemiologic investigations suggested that the presumed protective effect of moderate alcohol intake on stroke might be noncausal.⁴⁸ Moreover, PRS score and the increase in drunkenness were not significantly associated, suggesting that the genetic contribution of drunkenness frequency during adolescence was not fully controlled for.

Although the temporal analyses were performed on 3 different patterns of alcohol consumption with the limited confounding factor of previous alcohol intake, the current design prevented the unambiguous determination that gray matter development occurred before the increase in drunkenness frequency. We believe that cohorts with multiple time points and individuals at high risk for alcohol dependency are needed to increase the proportion of heavy drinkers in future studies. Some CBNs can have equivalent classes, but the

increase in drunkenness frequency is part of a V structure network, which renders their identification more robust (eAppendix in the Supplement).

We used voxel-based morphometry to obtain gray matter volume and tensor-based morphometry to obtain gray matter development. Although widely used, these frameworks provided different cerebral features, and strong conclusions require replication.

Conclusions

This study, which included a large, long-term, and well-characterized cohort of healthy adolescents in Europe, found that gray matter development and impulsivity were associated with increased frequency of drunkenness by sex. These findings add to the evidence suggesting a cerebral predisposition to alcohol abuse. We believe the results of this study call for a more cautious interpretation of neurotoxicity-related gray matter atrophy.

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