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RESEARCH REPORT

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Brain structural covariance network differences in adults with alcohol dependence and heavy-drinking adolescents

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Abstract

Background and aims: Graph theoretic analysis of structural covariance networks (SCN) provides an assessment of brain organization that has not yet been applied to alcohol dependence (AD). We estimated whether SCN differences are present in adults with AD and heavy-drinking adolescents at age 19 and age 14, prior to substantial exposure to alcohol.

Design: Cross-sectional sample of adults and a cohort of adolescents. Correlation matrices for cortical thicknesses across 68 regions were summarized with graph theoretic metrics.

Setting and participants: A total of 745 adults with AD and 979 non-dependent controls from 24 sites curated by the Enhancing NeuroImaging Genetics through Meta Analysis (ENIGMA)–Addiction consortium, and 297 hazardous drinking adolescents and 594 controls at ages 19 and 14 from the IMAGEN study, all from Europe.

Measurements: Metrics of network segregation (modularity, clustering coefficient and local efficiency) and integration (average shortest path length and global efficiency).

Findings: The younger AD adults had lower network segregation and higher integration relative to non-dependent controls. Compared with controls, the hazardous drinkers at age 19 showed lower modularity [area-under-the-curve (AUC) difference = −0.0142, 95% confidence interval (CI) = −0.1333, 0.0092; *P*-value = 0.017], clustering coefficient (AUC difference = −0.0164, 95% CI = −0.1456, 0.0043; *P*-value = 0.008) and local efficiency (AUC difference = −0.0141, 95% CI = −0.0097, 0.0034; *P*-value = 0.010), as well as lower average shortest path length (AUC difference = −0.0405, 95% CI = −0.0392, 0.0096; *P*-value = 0.021) and higher global efficiency (AUC difference = 0.0044, 95% CI = −0.0011, 0.0043; *P*-value = 0.023). The same pattern was present at age 14 with lower clustering coefficient (AUC difference = −0.0131, 95% CI = −0.1304, 0.0033; *P*-value = 0.024), lower average shortest path length (AUC difference = −0.0362, 95% CI = −0.0334, 0.0118; *P*-value = 0.019) and higher global efficiency (AUC difference = 0.0035, 95% CI = −0.0011, 0.0038; *P*-value = 0.048).

Conclusions: Cross-sectional analyses indicate that a specific structural covariance network profile is an early marker of alcohol dependence in adults. Similar effects in a cohort of heavy-drinking adolescents, observed at age 19 and prior to substantial alcohol exposure at age 14, suggest that this pattern may be a pre-existing risk factor for problematic drinking.

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KEYWORDS
Alcohol, cortical thickness, graph theory, neurodevelopment, structural covariance networks

INTRODUCTION

Alcohol dependence (AD) is characterized by persistent and compulsive alcohol use despite negative health consequences [1]. Alcohol use entails an enormous burden for society and is a leading cause of preventable mortality world-wide [2]. AD has been associated with lower gray matter volume across widespread regions of the brain and especially within prefrontal cortex and brain areas related to reward processing [3–5]. The extent to which these effects arise from exposure or reflect pre-existing differences which contribute to the development of AD remains unclear. Alcohol use initiates during adolescence [6], and early onset increases the risk for later problematic patterns of consumption including dependence [7]. There is some evidence that alcohol use may disrupt brain maturation [8,9]. While some studies have found regional gray matter differences in alcohol-naive adolescents at risk for AD [10,11] others have found changes following exposure [12]. The specifics regarding interactions between alcohol use and the brain in terms of pre-existing risk factors, age and duration/quantity of use still require substantial clarification.

The study of structural covariance networks (SCN) provides an assessment of brain organization. Similar to functional connectivity, SCN are defined by regional covariance of distinct brain features. In SCN these features are structural, such as gray matter volume or cortical thickness. This method detects networks that are partially consistent with those identified by functional and diffusion-based MRI [13]. The presence of correlated brain features may indicate synchronized maturation due to shared plastic or trophic influences. Evidence from neurodegenerative studies suggests that network disturbances precede global gray matter decline, for example, in frontotemporal dementia [14], Parkinson's disease [15] and mild cognitive impairment [16]. Network differences have also been reported in dependence upon alcohol and other substances [17–19]. Remarkably, network alterations were found in alcohol-naive adolescents at greater risk for AD [20], suggesting that these effects predate exposure and may represent a risk factor. However, such evidence comes from resting state functional magnetic resonance imaging (fMRI) studies and no work has reported such effects using SCN to date.

To summarize SCN features we use graph theory analysis, which offers powerful yet simple metrics to describe the relations within a network that is represented as a collection of nodes (e.g. brain regions) and edges (e.g. correlations). We explored group-level differences in cortical thickness and graph theory metrics derived from SCN in two large samples, comprising a cross-sectional data set of adults with AD and non-dependent adult controls curated by the Enhancing NeuroImaging Genetics through Meta Analysis (ENIGMA)–Addiction consortium (https://www.enigmaaddiction.com) and a longitudinal adolescent cohort collected at ages 14 and 19 by the IMAGEN project (https://imagen-europe.com). We first examined whether the relationship between AD and cortical thickness in the adult sample was age-dependent. Next, we explored the same adult sample for group differences in SCN metrics, assessing if these were also related to age. Then, turning to the adolescent sample, we tested whether cortical thickness and SCN properties were related to hazardous drinking patterns at age 19. Finally we examined, retrospectively, if similar findings were present in the same sample at age 14 before substantial alcohol use.

METHODS

Adult sample

A total of 1724 participants (745 with AD and 979 non-dependent controls) ranging from 18 to 56 years were included from 24 studies contributing to the ENIGMA–Addiction consortium. All procedures were in accordance with the Declaration of Helsinki. A variety of instruments were used to diagnose AD based on the DSM-IV criteria (see Supporting information, Table SM1).

Participants with a history of neurological disease or contraindications for MRI were excluded. Additionally, individuals with AD were excluded for any other Axis I disorder (i.e. including dependence upon other substances) other than mood or anxiety.

Structural T1-weighted images were prepared using FreeSurfer (version 5.3) [21,22] through CBRAIN (www.computecanada.ca), a network of high-performance computing facilities in Canada [23]. ENIGMA quality control protocols were followed (http://enigma.ini.usc.edu/protocols/imaging-protocols). Additional visual inspection was performed at the University of Vermont on random subsamples to confirm consistent quality across sites. Details regarding the scanner vendor and image acquisition protocols are presented in Supporting information, Table SM1. Average cortical thickness was extracted from 68 regions of interest (ROIs) parcellated according to the Desikan–Killiany atlas [24]. Inter-site scanner effects were removed with *ComBat* [25]. This method allows elimination of unwanted non-biological sources of variation in the data (i.e. scanner effects) while preserving relevant information such as age, sex and group within a Bayesian framework. For a more detailed explanation, see Fortin *et al.* [25].

Age windows

SCN exploits inter-individual variance in thickness to derive estimates of covariance at the group level (see below). Consequently, in order to

generate groups of AD and control participants for comparisons across different ages, the data set was analyzed using a moving window approach. The 6-year-wide age windows started at age 18 and increased in 1-year steps (i.e. 18–24, 19–25, 20–26… 50–56). The cut-off was set at age 56 due to limited numbers of individuals above this age. A 6-year window was selected as it maximized the numbers of individuals per window (100 on average) while being reasonably narrow to detect age-related differences. We attempted to match AD and non-dependent groups for age and sex (ratio 1:1) at all windows using a nearest-neighbor algorithm from the *MatchIt* package [26].

Adolescent sample

A sample of 1068 adolescents was drawn from the IMAGEN project, a multi-site study which acquired longitudinal data at ages 14 (baseline) and 19 (follow-up) at eight European imaging centers. Non-siblings with MRI data available at baseline and follow-up were included. Missing age at follow-up from 112 participants was imputed with the average difference in years between baseline and follow-up (i.e. 4.64 years). The Alcohol Use Disorders Identification Test (AUDIT) was used to assess problematic alcohol use. AUDIT total scores equal to or greater than 8 indicate hazardous drinking [27]. Participants surpassing this threshold at follow-up were classified as hazardous drinkers. Those who did not meet this cut-off (i.e. seven or fewer) at baseline and follow-up were considered controls. Groups were matched for age and sex with a ratio of two controls for each hazardous drinker (2:1). The final groups were composed of 594 controls and 297 hazardous drinkers.

Structural T1-weighted scans were collected at each site following Alzheimer's Disease Neuroimaging Initiative (ADNI) protocols to minimize site effects [28] (https://github.com/imagen2/imagen_mri/tree/master/protocols). Preparation of images and site-effect adjustments were the same as described for the adult sample.

Network construction

With this approach, a single network is derived from a correlation matrix exploiting inter-individual variation generated by pooling subjects from a predetermined group. The thickness of each ROI represents a node, and the correlation between ROIs describes an edge. The strength of an edge illustrates within-group correlations in thickness across pairs of nodes. Edges are thresholded and binarized and, finally, graph theory metrics are derived at the group level. In both the adult and adolescent samples, ROIs were residualized for mean global thickness using linear regressions. Age and sex were residualized in the adult sample where balancing groups for these features was not possible. Adjacency matrices were generated with Pearson's correlations among the residualized ROIs for each group and age window in the adult sample and for each group and time-point (i.e. follow-up and baseline) in the adolescent sample. This step returned group-specific (i.e. two groups, two matrices) correlation matrices of 68 by 68 nodes with a maximum possible density of 2278 edges. Matrices were proportionally thresholded along a wide range of densities to prevent differences arising from unequal-sized networks or arbitrary thresholds. Matrices spanned from D_{min} to 0.3 in increasing steps of 0.01. Here, D_{min} equaled the minimum density at which groups displayed at least one edge per node: this ensured that comparisons were conducted on fully connected networks. Network construction and graph theory metrics were derived with the *brainGraph* package [29].

Graph theory metrics

Global SCN properties were summarized with a variety of graph theory metrics assessing network segregation and integration across all densities.

Metrics of segregation

Metrics of segregation rely upon short-range edges and capture how correlated adjacent nodes are in terms of cortical thickness, with higher scores reflecting higher correlations. Three metrics of segregation were used: clustering coefficient (*Cp*), modularity and local efficiency (E_{local}). *Cp* reflects the extent to which the neighbors of a node are each other's neighbors [30]. That is, it represents whether nodes that are related to a certain node are also correlated with each other. Modularity exposes the degree to which same-module nodes are correlated with each other but not with other modules [31]. E_{local} expresses the ability of a cluster to remain connected (correlated) after a node is removed [32]. If low, it may suggest that the relationships within a cluster are reliant upon too few nodes.

Metrics of integration

Metrics of integration reveal between-community correlations and depend on shortcuts or long-distance paths to bring distant nodes together. We used the average shortest path length (*Lp*) and global efficiency (E_{global}). *Lp* denotes the average of the shortest number of edges passed through to reach other nodes in the network. This shortest path length is first calculated for all pairs of nodes sequentially (i.e. the average shortest path from A to B, from A to C,… from X to Z) and then averaged across all nodes. E_{global} is comparable to the inverse of *Lp* (i.e. 1/*Lp*) with the exception that it incorporates all paths among two nodes (i.e. not just the shortest path but the full set of paths between A and B). By capturing these parallel or redundant paths, E_{global} is often preferred for networks that contain disconnected nodes [30]. Note that these edges are in the graph space and reflect correlations in cortical thicknesses between brain regions so do not represent anatomical connectivity. Lower *Lp* and higher E_{global} imply a

greater presence of shorter paths and better integrated networks [30] and indicate that distant nodes are more correlated. See Methods in Supporting information, SM3, for more details on these metrics.

Statistical analyses

None of the analyses conducted in the current work were pre-registered and should be therefore considered exploratory.

Cortical thickness comparisons

First, we examined if the difference in cortical thickness between AD and non-dependent groups was age-dependent. For this purpose, we conducted linear regression models in the full adult sample (n = 1724) to predict global (mean) cortical thickness by including group, sex and age and their interactions. Next, we adopted the moving age window approach to map group age-related differences in both global and regional cortical thickness. Age and sex balance was assessed at every window with parametric tests (i.e. t-test, χ^2 test). If groups were different, age and sex were entered as covariates. Models included global or regional cortical thickness as the dependent variable and group as its main predictor. A false-discovery rate (FDR) correction was adopted to minimize type I errors in regional cortical thickness analyses (i.e. 68 ROI = 68 tests per age window, 33 age windows).

In the adolescent sample, linear regressions for global and regional cortical thickness were performed separately for follow-up and baseline with group as the main predictor and also FDR-adjusted (i.e. 68 tests, two time-points). All analyses were done in R version 4.1.0 [30].

Graph theory metrics comparisons

For both the adult and adolescent samples, between-group differences in graph theory metrics (i.e. *Cp*, modularity, E_{local}, *Lp*, E_{global}) were addressed with two-sided permutation tests at each density. Non-parametric permutation testing was required as metrics were calculated on the group level (i.e. one value per group). Area under the curve (AUC) analyses were used to prevent results from depending upon a single threshold. Individuals were randomly shuffled among groups 1000 times and two-sided AUC tests performed. The observed AUC differences were compared with critical values based on the 95th percentile of the distribution of permuted AUC differences. The level of significance was set at P-value < 0.05 uncorrected. These analyses were performed at every age window (n = 33) in the adult sample and for follow-up and baseline visits in the adolescent sample. Supplementary tests involved a subset of hazardous drinkers (n = 110) and controls (n = 220) with no alcohol use at baseline (AUDIT = 0) to investigate if any observed effect could be disentangled from exposure.

Behavioral and cognitive tests

To more clearly characterize the phenotype of each group in the adolescent sample, we examined group differences on the development and well-being assessment (DAWBA) externalizing problems scale, the impulsivity scale from the temperament and character inventory (TCI) and the risk-taking score from the Cambridge gambling task (CGT). Groups were compared in a series of cross-sectional linear mixed models adjusting for fixed (i.e. age and sex) and random effects (i.e. site). Because of their exploratory nature, the significance level for these tests was Bonferroni-adjusted and set at P-value < 0.008 (three tests per two time-points: 0.05/6 = 0.008).

RESULTS

A summary of socio-demographic characteristics of the adult and adolescent samples is available in Table 1.

Cortical thickness results

In the adult sample, the AD group exhibited lower global cortical thickness compared to the non-dependent group (t_{1716} = −4.42, P-value < 0.001). The group × age interaction was significant (t_{1716} = −3.20, P-value = 0.001), whereas the group × sex interaction was not (t_{1716} = −0.52, P-value = 0.606). The AD group had a steeper age-related slope (r = −0.32) than non-dependent controls (r = −0.24) (see Figure 1). The main effect of sex (t_{1716} = −0.60, P-value = 0.547) and its interaction with age (t_{1716} = 0.75, P-value = 0.454) were not significant.

Contrasts performed at each age window showed groups differed on global cortical thickness at age window 25–31 and in each subsequent age window (see Figure 2). Also, ROI-level contrasts revealed

TABLE 1 Demographics of the adult and adolescent samples (mean ± standard deviation or frequency)

		n	Age (years)	Females	AUDIT total
Adults	Alcohol-dependent	745	33.9 ± 10.3	239	–
	Non-dependent controls	979	28.9 ± 9.58	406	–
Follow-up Adolescents	Hazardous drinkers	297	19.1 ± 0.74	126	11.6 ± 3.87
	Controls	594	19.1 ± 0.72	255	3.63 ± 2.12
Baseline Adolescents	Hazardous drinkers	297	14.4 ± 0.36	126	1.95 ± 2.58
	Controls	594	14.4 ± 0.41	255	0.84 ± 1.41

Abbreviation: AUDIT, Alcohol Use Disorders Identification Test.

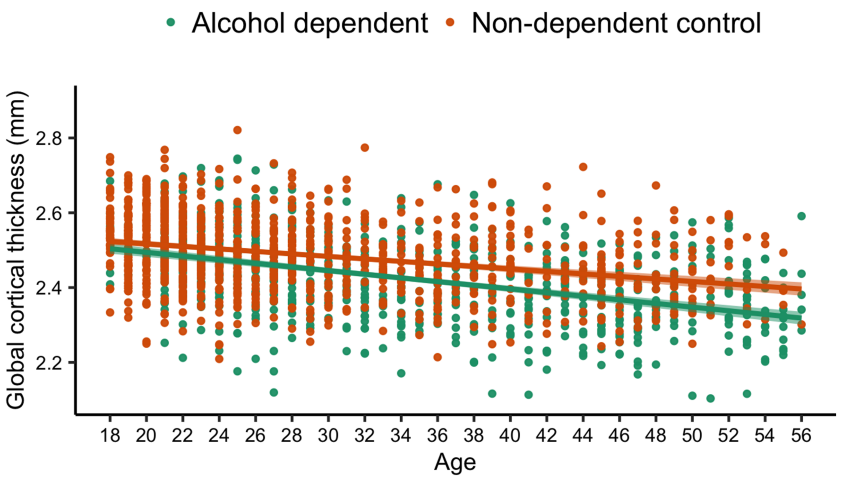

FIGURE 1 Global cortical thickness and age interaction between groups

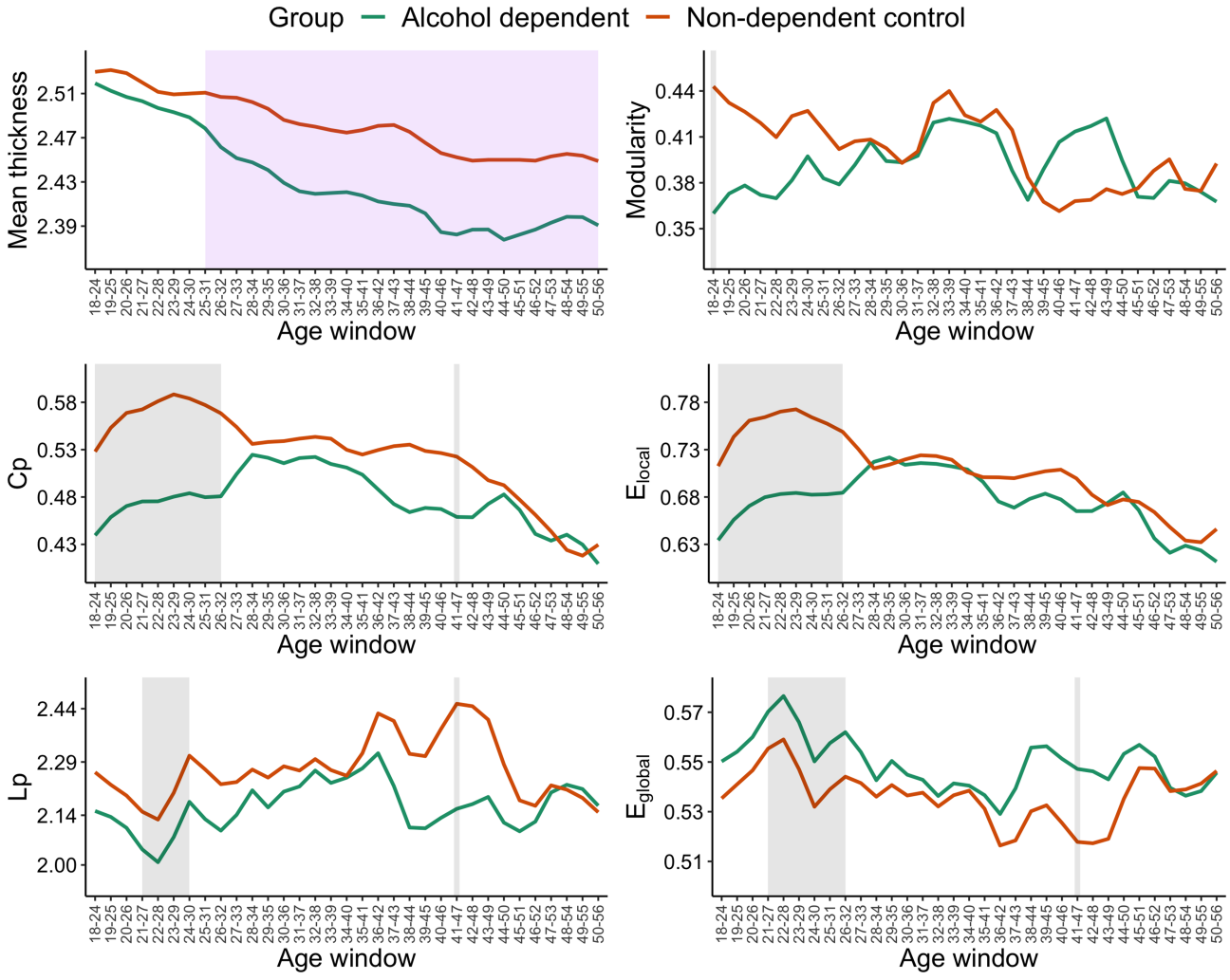

FIGURE 2 Global cortical thickness and graph theory metrics plotted as a function of age using age windows for the adult Enhancing NeuroImaging Genetics through Meta Analysis (ENIGMA)–Addiction consortium data set. Shaded areas represent statistically significant differences ($P < 0.05$) between groups

that the number of regions with a significant difference in thickness increased in the older age windows (e.g. from four ROIs at age window 18–24 to 54 ROIs at age window 41–47). Further ROI results are provided in the Supporting information, Figure SM2 (plots performed with the *ggseg* package [31]). Table 2 presents demographic summaries at each age window.

TABLE 2 Demographics of the adult sample across age windows (mean ± standard deviation or frequency)

Age window (years)		Alcohol-dependent	Non-dependent controls	Statistic (t/χ^2)
18–24	*n*	182	182	–
	Age	22.3 ± 1.43	22.3 ± 1.43	0
	Female	75	79	0.10
19–25	*n*	209	209	–
	Age	22.9 ± 1.44	22.9 ± 1.44	0
	Female	84	88	0.09
20–26	*n*	243	243	–
	Age	23.4 ± 1.69	23.4 ± 1.70	−0.13
	Female	94	98	0.08
21–27	*n*	269	269	–
	Age	23.7 ± 1.94	23.7 ± 1.91	0.18
	Female	103	103	0
22–28	*n*	258	258	–
	Age	24.7 ± 1.98	24.7 ± 1.99	0.18
	Female	100	99	0
23–29	*n*	232	232	–
	Age	25.6 ± 1.92	25.6 ± 1.92	−0.16
	Female	90	90	0
24–30	*n*	217	217	–
	Age	26.5 ± 2.01	26.6 ± 2.00	−0.17
	Female	81	81	0
25–31	*n*	188	188	–
	Age	27.6 ± 1.96	27.6 ± 1.95	0
	Female	65	65	0
26–32	*n*	178	178	–
	Age	28.6 ± 2.05	28.5 ± 1.92	0.53
	Female	62	63	0
27–33	*n*	151	151	–
	Age	29.5 ± 1.90	29.5 ± 1.93	−0.03
	Female	52	52	0
28–34	*n*	147	147	–
	Age	30.7 ± 2.08	30.6 ± 2.00	0.31
	Female	50	57	0.53
29–35	*n*	132	132	–
	Age	31.9 ± 2.00	31.5 ± 2.03	1.47
	Female	37	37	0
30–36	*n*	130	130	–
	Age	32.8 ± 2.05	32.7 ± 2.17	0.23
	Female	39	44	0.28
31–37	*n*	121	121	–
	Age	33.9 ± 2.01	33.9 ± 1.99	−0.06
	Female	36	46	1.49
32–38	*n*	122	122	–
	Age	35.0 ± 2.07	35.0 ± 1.94	−0.22
	Female	36	44	0.91

(Continues)

TABLE 2 (Continued)

Age window (years)		Alcohol-dependent	Non-dependent controls	Statistic (t/χ^2)
33–39	*n*	113	113	–
	Age	36.1 ± 1.91	36.1 ± 1.91	0.03
	Female	31	34	0.09
34–40	*n*	120	120	–
	Age	36.8 ± 2.05	36.8 ± 1.95	−0.10
	Female	32	42	1.58
35–41	*n*	115	115	–
	Age	38.0 ± 2.02	37.8 ± 1.89	0.98
	Female	28	39	2.11
36–42	*n*	111	111	–
	Age	38.9 ± 1.96	38.6 ± 1.94	1.24
	Female	32	42	1.64
37–43	*n*	95	95	–
	Age	39.4 ± 1.75	39.6 ± 1.82	−0.65
	Female	30	34	0.21
38–44	*n*	93	93	–
	Age	40.3 ± 1.70	40.5 ± 1.99	−0.59
	Female	26	38	2.88
39–45	*n*	96	96	–
	Age	41.5 ± 1.67	41.9 ± 2.26	−1.96
	Female	22	44	10.18*
40–46	*n*	94	94	–
	Age	43.7 ± 1.71	43.2 ± 2.21	1.66
	Female	27	38	2.35
41–47	*n*	84	84	–
	Age	45.2 ± 1.70	44.3 ± 1.85	3.17*
	Female	32	35	0.10
42–48	*n*	85	85	–
	Age	44.4 ± 1.89	45.0 ± 1.81	−2.36
	Female	36	36	0
43–49	*n*	88	88	–
	Age	46.7 ± 1.52	46.0 ± 1.88	2.43*
	Female	31	35	0.22
44–50	*n*	92	92	–
	Age	47.2 ± 1.57	46.8 ± 2.01	1.52
	Female	27	36	1.54
45–51	*n*	88	88	–
	Age	47.8 ± 1.64	47.5 ± 2.03	1.10
	Female	28	28	0
46–52	*n*	74	74	–
	Age	48.9 ± 2.12	48.5 ± 1.95	1.17
	Female	9	20	4.29*
47–53	*n*	62	62	–
	Age	49.4 ± 2.05	49.6 ± 1.80	−0.51
	Female	0	16	16.15*

(Continues)

TABLE 2 (Continued)

Age window (years)		Alcohol-dependent	Non-dependent controls	Statistic (t/χ^2)
48–54	*n*	56	56	–
	Age	50.0 ± 1.73	50.2 ± 1.76	−0.81
	Female	10	14	0.48
49–55	*n*	52	52	–
	Age	51.0 ± 1.43	51.1 ± 1.98	−0.23
	Female	13	13	0
50–56	*n*	39	39	–
	Age	51.5 ± 1.07	52.0 ± 1.87	−1.41
	Female	11	8	0.28

*$P < 0.05$.

A group difference in cortical thickness was not observed in the adolescent sample at either baseline or follow-up.

Structural covariance results

In the adult sample, the AD group exhibited significantly lower modularity, *Cp* and E_{local} relative to the non-dependent group in the younger age windows, consistent with lower segregation. Whereas modularity effects were present at the 18–24 age window only, *Cp* and E_{local} effects were significant in all windows starting at 18–24 until age window 26–32 (see Figure 2). A single effect emerged at age window 41–47 but only for *Cp*. The AD group had significantly higher E_{global} in age window 19–25. This group showed lower *Lp* and higher E_{global} from age windows 21–27 to 24–30, suggesting greater integration. The AD group additionally showed higher E_{global} from age windows 25–31 to 26–32. At age window 41–47, this group had lower *Lp* and greater E_{global} [note: all analyses were repeated using different age window solutions (e.g. 5-, 7-, 8-, 9- and 10-year-wide windows) and results remained significant in the younger AD; results not shown]. The observed differences and confidence intervals (CI) are available in the Supporting information, SM4.

In the adolescent sample, significant effects were found at follow-up for all graph theory metrics. Similar to the early age windows in the adult AD group, the adolescent hazardous drinking group exhibited lower modularity (AUC difference = −0.0142, 95% CI = −0.1333, 0.0092; *P*-value = 0.017), *Cp* (AUC = −0.0164, 95% CI = −0.1456, 0.0043; *P*-value = 0.008) and E_{local} (AUC difference = −0.0141, 95% CI = −0.0097, 0.0034; *P*-value = 0.010) compared to controls (see Figure 3). Similarly, adolescent hazardous drinkers also presented lower *Lp* (AUC difference = −0.0405, 95% CI = −0.0392, 0.0096; *P*-value = 0.021) and greater E_{global} (AUC difference = 0.0044, 95% CI = −0.0011, 0.0043; *P*-value = 0.023). A number of effects were observed at baseline mimicking those observed at follow-up and at the early age windows in the adult sample. At baseline (i.e. age 14), and prior to substantial alcohol exposure, the future hazardous drinking group had lower *Cp* (AUC difference = −0.0131, 95% CI = −0.1304, 0.0033; *P*-value = 0.024), lower *Lp* (AUC difference = −0.0362, 95% CI = −0.0334, 0.0118; *P*-value = 0.019) and higher E_{global} (AUC difference = 0.0035, 95% CI = −0.0011, 0.0038); *P*-value = 0.048). A subset of the hazardous drinking adolescents who were alcohol-naive at baseline (i.e. AUDIT = 0) showed a similar pattern to the larger group at follow-up, although the effects were not significant at baseline (see Figure 3).

Behavioral and cognitive results

At follow-up, the hazardous drinking group exhibited higher externalizing symptoms ($t_{747.58} = 3.94$, *P*-value < 0.001), impulsivity ($t_{631.87} = 4.83$, *P*-value < 0.001) and risk-taking scores ($t_{868.93} = 3.61$, *P*-value < 0.001) compared to the control group. Similarly, at baseline, the (future) hazardous drinking group scored higher on externalizing symptoms ($t_{825.09} = 2.87$, *P*-value = 0.004) and impulsivity ($t_{756} = 2.71$, *P*-value = 0.007). Risk-taking results did not survive Bonferroni-adjustments ($t_{605.12} = 2.12$, *P*-value = 0.035).

DISCUSSION

In a large adult cross-sectional sample, we found that the difference in global cortical thickness between AD and non-dependent groups was influenced by age, being greater in older individuals. The moving age window analysis identified an initial significant group difference in global cortical thickness in the 25–31 age window and in all the older age windows. With regard to SCN, the AD group consistently presented lower segregation and higher integration of SCN compared to non-dependent controls in the younger but not the older age windows, an opposite pattern to what was observed with the average cortical thickness. We found similar SCN effects in an independent sample of adolescents with no cortical thickness differences in hazardous drinkers at age 19. Most notably, SCN differences were observed in the same adolescents 5 years earlier who, at age 14, had little to no life-time alcohol exposure. Taken together, results indicate that SCN effects are related to alcohol drinking (i.e. alcohol dependence or hazardous drinking) in the absence of cortical thickness differences.

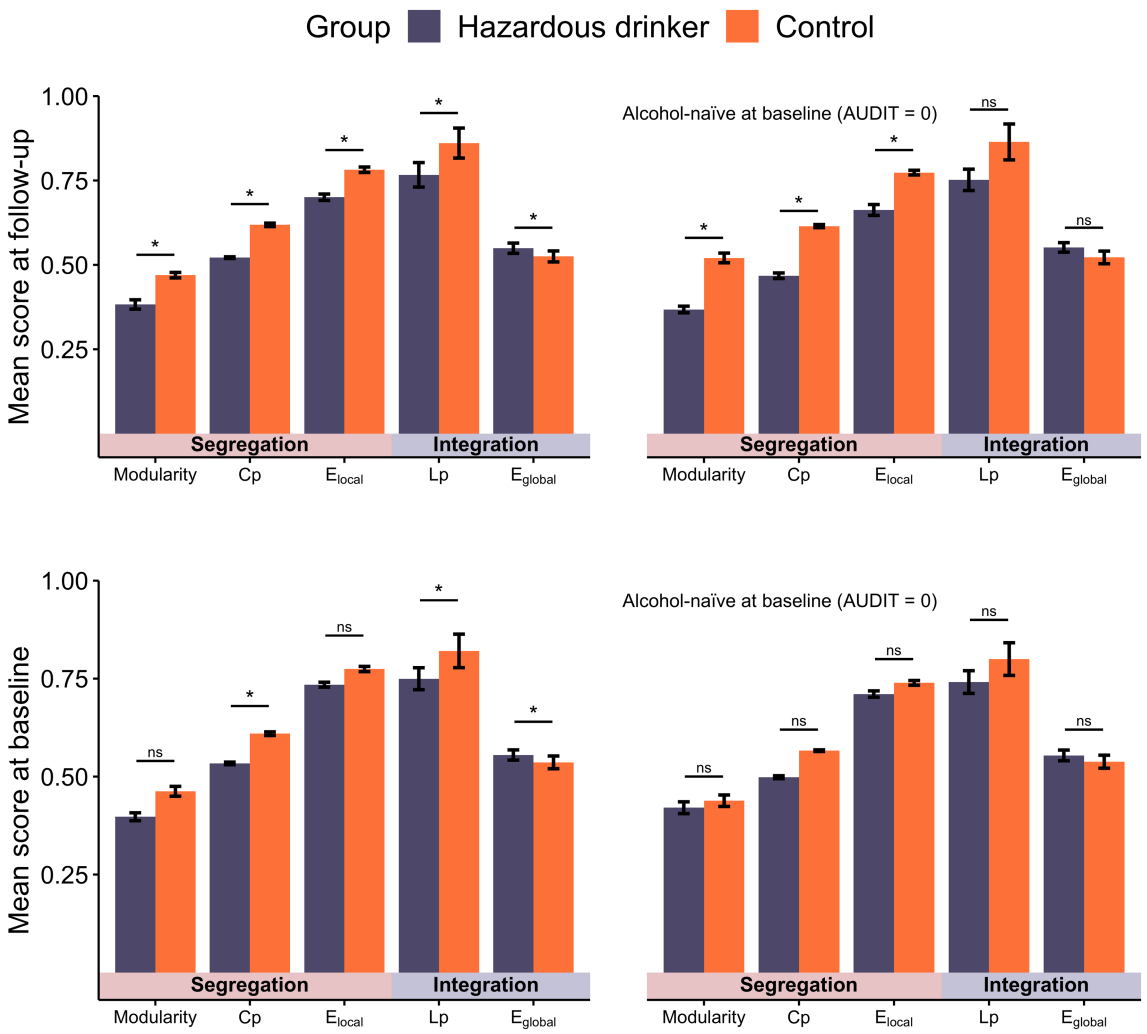

FIGURE 3 Average score of graph theory metrics across densities at follow-up (first row) and baseline (second row). Right-column barplots represent analyses performed in a subset of participants that were alcohol-naive at baseline. Error bars depict the standard error for each measure across densities. *Lp* values were log-scaled to fit the rest of the variables. *$P < 0.05$; NS = non-significant

Alcohol and brain volume

Initiation of alcohol use typically occurs during adolescence [6], and early onset increases the risk for later problematic patterns of use including dependence [7]. Youths initiating alcohol use by age 14 or earlier are five times more likely to be diagnosed as AD later in life than those who started at age 21 or later. From age 14 onwards, each year by which onset of drinking is delayed is followed by a 14% drop in the risk for life-time dependence [32]. Onset of AD peaks in the early 20s [33], with most cases (94.1%) being diagnosed before age 25 [34]. With regard to the brain, older individuals with AD show more regional differences in cortical volume compared to non-dependent controls and to younger individuals with AD [35–37]. The effects of age and chronic alcohol use on the brain have been confirmed in animal models [38]. Sustained alcohol exposure reduces brain-derived neurotrophic factor and nerve-growth factor release, triggers oxidative stress and glutamate excitotoxicity and disturbs mitochondrial function due to the accumulation of toxic metabolites [12]. Some of these factors are related to the etiology of neurodegenerative disease [39]. While the cross-sectional nature of the adult sample results warrants caution, differences in cortical thickness as a function of age quite plausibly reflect the cumulative effect of exposure. However, it is equally possible that older brains are more susceptible to the alcohol neurotoxicity or that the AD duration is influenced by pre-existing gray matter differences.

Alcohol use and structural covariance

Consistent with the present findings, resting-state fMRI studies have reported lower network segregation in alcohol-naive adolescents at risk of AD [18] and AD severity in adults [20]. Lower segregation has also been found in cocaine and heroin dependence [17,19] and internet-gaming disorder [40]. In contrast, the literature is less consistent regarding differences in network integration in both AD and other addictions [17–20,40]. In the present findings, segregation and

integration effects appeared at age windows 18–24 and 21–27 and were not observed in age window 26–32 or older. Although we cannot confirm with cross-sectional data that SCN differences predict gray matter decay as in neurodegenerative work, we speculate that the absence of SCN differences at later windows could be related to the onset of cortical thickness disturbances that obscure SCN effects.

We extended the investigation to an adolescent longitudinal data set to explore if SCN differences could be observed in those who do not have AD but are showing patterns of hazardous drinking. The adolescent sample replicated the young adult AD group's SCN findings, including the absence of cortical thickness differences relative to controls. At follow-up, the hazardous drinking group had lower segregation (i.e. lower modularity, *Cp* and E_{local}) and higher integration (i.e. lower *Lp* and higher E_{global}) than controls. At baseline, the (future) hazardous drinking group showed lower segregation (i.e. lower *Cp*) and higher integration (i.e. lower *Lp*, higher E_{global}) than controls. Of note, most of the individuals from this group had below-threshold scores (AUDIT < 8), and 37% had reported no alcohol use (AUDIT = 0) at baseline. While supplementary tests on this alcohol-naive subset (i.e. 37%, n = 110) showed similar effects to the larger group at follow-up, null results were found at baseline. Nevertheless, this analysis drastically reduced the sample size and thus chances of Type II error cannot be dismissed.

As graph theory metrics derived from SCN describe the degree of synchronized maturation across nodes [41–43], lower segregation hints at de-synchronization among adjacent nodes in the young AD and the adolescent hazardous drinking groups. By contrast, higher integration means greater synchronization with nodes that belong to other communities. In other words, brain regions are showing atypical similarity in thicknesses to other regions that are distant in the alcohol-drinking groups. Poor segregation and higher integration have previously been related to other psychiatric and neurological conditions [44], including dependence on alcohol and other substances [16–18]. Typically, segregation peaks by late adolescence and young adulthood, probably reflecting functional specialization among cortical regions [44,45]. Therefore, we speculate that our results suggest a protracted cortical maturation in the alcohol-drinking groups [13,42,46]. Asynchronous cortical growth has previously been related to poor decision-making and self-regulation and to elevated reward-seeking behaviors [46,47]. Delayed cortical growth has been associated with inattention [48] and anxious/depression symptoms [49] as well. It has been proposed that disturbed cortical growth renders youth vulnerable to risky behaviors such as early alcohol drinking [47,50]. In Holla *et al*. [18], delayed maturation of functional networks in adolescents at greater risk for AD was associated with more externalizing problems. Externalizing problems suggest failures in self-regulation also resulting as a risk factor for alcohol use [49]. We have found that the hazardous drinking group presented higher externalizing symptom severity scores, were more impulsive and took more risky decisions in a gambling task at ages 14 and 19. Additionally, if the SCN results are an indicator of delayed cortical growth, then the absence of SCN effects after age window 26–32 in AD adults could align with the end of the delayed developmental period. That is, the group differences in SCN may disappear because the relevant maturational processes are complete in both the AD and non-dependent controls. For instance, the *Cp* trajectories in Figure 1 show that the peak in the AD group (age window 28–34) appears delayed as to the peak in the control group (age window 23–29). An alternative possibility is that SCN differences persist but are obscured by the widespread cortical thinning associated with adult AD.

To summarize, the younger AD group exhibited lower segregation and higher integration in the absence of global differences in cortical thickness relative to the control group. Exactly the same pattern was found at age 19 in adolescents with hazardous drinking behavior. This profile was again detected in the same group 5 years earlier prior to substantial alcohol exposure at age 14. Overall, we hypothesize that the SCN profile might reflect the delayed growth of cortico-cortical networks central to the development of functional specializations and related to the successful regulation of reward-related processes. We have also found behavioral signs that suggest delays in cortical maturation. Impaired self-regulation during adolescence (i.e. higher impulsivity and risk-taking) increases the likelihood of engaging in problematic behaviors such as alcohol use [46,47,50]. However, with the current design and approach we cannot confirm whether SCN differences constitute a risk factor for alcohol use or dependence nor if these were independent from exposure; similar but not significant effects were found in a sample of alcohol-naive individuals at age 14, which we attribute to losses in statistical power. However, our analyses provide evidence of a promising brain marker for AD in young adults and for heavy alcohol use at age 19. We offer a retrospective prediction in which a known outcome (i.e. heavy drinking at age 19) is predated by SCN differences at age 14 before any substantial alcohol use. Despite the exploratory nature and methodological limitations, the current study brings intriguing new hypotheses about potential brain markers for future alcohol use.

The current study was limited by several factors. First, alcohol use duration was not measured at many of the ENIGMA–Addiction sites, so it was not possible to disentangle the potential effects of duration and age. Many studies have reported that age and alcohol use duration are highly collinear, especially among heavy drinkers [36]. Despite dependence upon other substances and the presence of other psychiatric disorders being considered reasons for exclusion, we cannot discard other factors such as recreational use of other drugs, anxiety and depression symptoms, or lower education and socio-economic status, partially explaining the results. Age distribution was skewed in the adult sample which required the analyses to go no further than age 56. More notably, the cross-sectional nature of the adult sample restricts the conclusions that we can draw regarding SCN effects preceding, or indeed being causally related to, cortical thickness alterations within an AD individual. Moreover, contrasts for both the adult and adolescent samples were performed at the group level as the SCN approach exploited inter-individual variation so did not provide individual-level metrics. Due to insufficient numbers of female individuals (32% in the AD group), relevant questions on sex differences were left unexplored. Last, and to the best of our knowledge, this is

the first study using SCN metrics and alcohol and hence the current work has a strong exploratory component.

In conclusion, based on two of the largest data sets with neuroimaging data and relevant alcohol phenotypes, young adults with alcohol dependence showed a specific pattern of SCN differences. This SCN profile was replicated in adolescents identified as hazardous drinkers at age 19 and prior to substantial exposure to alcohol at age 14. SCN differences were found in the absence of global differences in cortical thickness. This pattern of lower segregation and higher integration may indicate disruptions in cortico-cortical growth. Further work should address whether such effects represent an early marker for future alcohol use and dependence.

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SUPPORTING INFORMATION

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