Psychological Medicine (2017), **47**, 655–668. © Cambridge University Press 2016
doi:10.1017/S0033291716002920

ORIGINAL ARTICLE

Alcohol use is associated with thinner cerebral cortex and larger ventricles in schizophrenia, bipolar disorder and healthy controls

E. H. Lange[1,2]*, S. Nerland[1], K. N. Jørgensen[1,2], L. Mørch-Johnsen[1,2], R. Nesvåg[1,3], C. B. Hartberg[2], U. K. Haukvik[1,2], K. Osnes[1], I. Melle[2,4], O. A. Andreassen[2,4] and I. Agartz[1,2]

[1] *Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway*
[2] *NORMENT and K. G. Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway*
[3] *Norwegian Institute of Public Health, Oslo, Norway*
[4] *Division of Mental Health and Addiciton, Oslo University Hospital, Oslo, Norway*

Background. Excessive alcohol use is associated with brain damage but less is known about brain effects from moderate alcohol use. Previous findings indicate that patients with severe mental illness, particularly schizophrenia, are vulnerable to alcohol-related brain damage. We investigated the association between levels of alcohol consumption and cortical and subcortical brain structures in schizophrenia and bipolar disorder patients and healthy controls, and investigated for group differences for this association.

Method. 1.5 T structural magnetic resonance images were acquired of 609 alcohol-using participants (165 schizophrenia patients, 172 bipolar disorder patients, 272 healthy controls), mean (S.D.) age 34.2 (9.9) years, 52% men. Past year alcohol use was assessed with the Alcohol Use Disorder Identification Test – Consumption part (AUDIT-C). General linear models were used to investigate associations between AUDIT-C score and cortical thickness, surface area, and total brain and subcortical volumes.

Results. Increasing AUDIT-C score was linearly associated with thinner cortex in medial and dorsolateral frontal and parieto-occipital regions, and with larger left lateral ventricle volume. There was no significant interaction between AUDIT-C score and diagnostic group. The findings remained significant after controlling for substance use disorders, antipsychotic medication and illness severity.

Conclusion. The results show a dose-dependent relationship between alcohol use and thinner cortex and ventricular expansion. The findings are present also at lower levels of alcohol consumption and do not differ between schizophrenia or bipolar disorder patients compared to healthy controls. Our results do not support previous findings of increased vulnerability for alcohol-related brain damage in severe mental illness.

Received 27 April 2016; Revised 5 October 2016; Accepted 14 October 2016; First published online 10 November 2016

Key words: Alcohol consumption, alcohol-related disorders, brain, gray matter, magnetic resonance imaging, psychotic disorders.

Introduction

Excessive alcohol use is associated with structural brain changes (Harper, 2009), and may contribute to the structural brain changes found in schizophrenia and bipolar disorder (Schiffer *et al.* 2010; Nery *et al.* 2011). There are indications of increased vulnerability to alcohol-related brain injury in schizophrenia (Sullivan *et al.* 2000*b*; Mathalon *et al.* 2003), although results are conflicting (Nesvag *et al.* 2007). Investigating the effects of alcohol use at different consumption levels on brain structure in severe mental illness might yield new insights.

* Address for correspondence: E. H. Lange, MD, Department of Psychiatric Research, Diakonhjemmet Hospital, PO Box 85 Vinderen, 0319 Oslo, Norway.
(Email: elisabeth.lange@medisin.uio.no)

Patients suffering from *severe mental illnesses* (schizophrenia or bipolar disorder) are at increased risk for misuse of alcohol and other substances (Regier *et al.* 1990). Prevalence of alcohol use disorders (AUDs; i.e. alcohol abuse or dependence) is higher in bipolar disorder than in schizophrenia (Nesvag *et al.* 2015), with lifetime prevalence estimates of 35% and 20%, respectively (Koskinen *et al.* 2009; Di Florio *et al.* 2014). Co-morbid AUD, or even levels of alcohol use below threshold for AUD, negatively impact course and outcome of schizophrenia (Mueser *et al.* 1998; Large *et al.* 2014) and bipolar disorder (Levin & Hennessy, 2004; Goldstein *et al.* 2006).

Widespread gray- and white-matter deficits in both cortical and subcortical structures are found in *alcohol-dependent patients* (Sullivan & Pfefferbaum, 2005; Buhler & Mann, 2011; Monnig *et al.* 2013). Gray-matter

reductions were shown in adolescents and young adults with AUD (Welch *et al.* 2013) and in heavy drinkers (Kubota *et al.* 2001; Cardenas *et al.* 2005; Thayer *et al.* 2016). Regarding moderate alcohol consumption, there is some evidence of a negative relationship with brain structural measures (Mukamal *et al.* 2001; Ding *et al.* 2004; Taki *et al.* 2004; Paul *et al.* 2008; Kapogiannis *et al.* 2012), whereas others have found no association (Sasaki *et al.* 2009; Davis *et al.* 2014; Preti *et al.* 2014) or positive associations (den Heijer *et al.* 2004; Sachdev *et al.* 2008; Gu *et al.* 2014; Downer *et al.* 2015). Longitudinal studies have demonstrated that both gray-matter (Pfefferbaum *et al.* 1995; Gazdzinski *et al.* 2005; Cardenas *et al.* 2007) and white-matter (Agartz *et al.* 2003; Cardenas *et al.* 2007) volume loss, ventricular enlargement (Wobrock *et al.* 2009) and reduced white-matter integrity (Pfefferbaum *et al.* 2014) can show partial reversibility with abstinence in alcohol-dependent patients.

Studies of *alcohol-related brain damage in patients with severe mental illness* have yielded mixed results. Schizophrenia and bipolar disorder both demonstrate cortical (Bora *et al.* 2010; Haijma *et al.* 2013) and subcortical (van Erp *et al.* 2015; Hibar *et al.* 2016) changes with greater subcortical alterations and more widespread cortical deficits in schizophrenia (Arnone *et al.* 2009; Ellison-Wright & Bullmore, 2010). Scientific evidence indicates more pronounced findings in schizophrenia (Sullivan *et al.* 2000*b*; Mathalon *et al.* 2003; Schiffer *et al.* 2010; Smith *et al.* 2011) and bipolar disorder (Nery *et al.* 2011) patients with co-morbid AUD than without AUD. Nery *et al.* (2011) reported structural brain changes only in bipolar disorder patients with AUD, while patients without AUD did not differ from healthy controls (Nery *et al.* 2011). Mathalon *et al.* (2003) found reduced prefrontal cortex volumes in patients with schizophrenia and alcohol dependence compared to patients with schizophrenia or alcohol dependence alone with lower lifetime alcohol consumption in the co-morbid group than in the alcohol-dependent group, suggesting an increased vulnerability for alcohol-related brain damage in schizophrenia (Mathalon *et al.* 2003). In contrast, Nesvåg *et al.* (2007) reported heavy alcohol use to be related to equally reduced frontal white-matter volumes in both schizophrenia patients and healthy controls (Nesvåg *et al.* 2007).

Three previous *cortical thickness* studies reported widespread thinner cortices in alcohol-dependent patients compared to healthy controls (Durazzo *et al.* 2011; Fortier *et al.* 2011; Momenan *et al.* 2012). Durazzo *et al.* (2011) found regional area reductions in abstinent alcohol-dependent patients that later relapsed (Durazzo *et al.* 2011). To our knowledge, there are no previous studies on how different levels of alcohol consumption are related to measures of cortical thickness, surface area or subcortical volumes in severe mental illness.

In the present study, we investigated associations between quantitative estimates of alcohol consumption and measured cortical thickness, surface area, total brain, white-matter and subcortical volumes in a cross-sectional sample ($n = 609$) of patients with severe mental illness and healthy controls. We used the Alcohol Use Disorders Identification Test, Consumption part (AUDIT-C) to obtain dimensional data on alcohol consumption. Composed of the three first items of the AUDIT that cover quantity and frequency of drinking and frequency of binge drinking, AUDIT-C is a self-report instrument validated for detecting heavy drinking and AUD (Reinert & Allen, 2007).

We expected alcohol use to be associated with thinner cortex, particularly in frontal regions (Durazzo *et al.* 2011; Fortier *et al.* 2011; Momenan *et al.* 2012), ventricular expansion (Hayakawa *et al.* 1992; Ding *et al.* 2004), hippocampal (Agartz *et al.* 1999) and subcortical volume reductions (Sullivan *et al.* 2000*a*). We hypothesized stronger associations in patients than in healthy controls (Mathalon *et al.* 2003; Nery *et al.* 2011).

Method

Subject sample

The participants were recruited from 2003 to 2011 as part of an ongoing multi-center study of psychotic disorders [Thematically Organized Psychosis (TOP) study] conducted by the Norwegian Centre for Mental Disorders Research (NORMENT). Patients with schizophrenia spectrum or bipolar spectrum disorders were recruited from major public psychiatric hospitals and outpatient clinics in the Oslo region in Norway. Healthy control subjects were randomly selected from the population register of the same catchment area as the patients, and invited to participate. Inclusion criteria for all participants were age 18–65 years, no history of head injury leading to loss of consciousness, and absence of previous or current somatic illness that might affect brain morphology. Further, controls were excluded if they or first-degree relatives had a history of severe psychiatric disorder (schizophrenia, bipolar disorder or major depression), or if they had a lifetime alcohol or other substance use disorder.

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Protection Authority and performed in accordance with the Helsinki Declaration of ethics in medical research. All subjects gave written consent to participate after the study procedures had been explained to them.

https://doi.org/10.1017/S0033291716002920 Published online by Cambridge University Press

Clinical assessment

All patients underwent thorough clinical investigation by trained psychologists and physicians. DSM-IV diagnoses were determined using semi-structured interviews (Structured Clinical Interview for DSM-IV, patient version, modules A–E; First *et al.* 2002) and reviewing clinical records. All interviewers underwent structured training, supervision and reliability testing, with an overall agreement for diagnostic categories of 82%, kappa = 0.77 [95% confidence interval (CI) 0.60–0.94] (Ringen *et al.* 2008). Psychosocial functioning was rated using the split version of the Global Assessment of Functioning Scale (GAF; Pedersen *et al.* 2007). Current psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987), and affective symptoms were assessed with the Inventory of Depressive Symptoms – Clinician Rating (IDS; Rush *et al.* 1996) and the Young Mania Rating Scale (YMRS; Young *et al.* 1978). Information on use of psychotropic medication was obtained from interviewing the patient and reviewing medical records. Dose of antipsychotic medication at the day of magnetic resonance imaging (MRI) scan was converted into chlorpromazine equivalents (Jørgensen *et al.* 2015). The healthy controls were evaluated with the Primary Care Evaluation of Mental Disorders (Prime-MD; Spitzer *et al.* 1994).

Assessment of alcohol and other substance use

Both patients and controls completed the Alcohol Use Disorders Identification Test (AUDIT; Saunders *et al.* 1993), a self-report instrument reviewing amount and pattern of alcohol use during the last 12 months. The AUDIT-Consumption part (AUDIT-C) comprises the first three items of the AUDIT covering amount and frequency of alcohol consumption, and frequency of binge drinking ($\geqslant$6 alcohol units on the same occasion). Each item is scored from 0 to 4 with a maximum total score of 12. This spans a wide range of consumption levels with a score of 1 corresponding to consumption of $\leqslant$2 units per month, while a score of 12 corresponds to a weekly consumption of $\geqslant$40 units. In a factor analysis of multiple samples, the three items of AUDIT-C loaded on a single factor, indicating that it represents a scale which is separate from alcohol-related consequences (Doyle *et al.* 2007). AUDIT-C was validated as an independent screening tool for detecting heavy drinking and AUD in a variety of settings (Bush *et al.* 1998; Gual *et al.* 2002; Rumpf *et al.* 2002; Bradley *et al.* 2007; Kaarne *et al.* 2010) (for further discussion on the use of AUDIT-C see Supplementary material). AUDIT-C score was available for 671 participants. AUDIT-C was administered on the day of MRI acquisition for all participants except 24 patients. For the 24 patients AUDIT-C score was obtained during the clinical assessment performed at a median of 37 days (range 1–480 days) before MRI. We included participants who reported alcohol use during the last year (i.e. AUDIT-C $\geqslant$ 1), resulting in 609 participants, comprising 165 schizophrenia spectrum disorder patients (schizophrenia n = 130, schizophreniform disorder n = 15, schizoaffective disorder n = 20; hereafter referred to as schizophrenia patients), 172 bipolar spectrum disorder patients (bipolar disorder type I n = 104, bipolar disorder type II n = 60, bipolar disorder NOS n = 8; hereafter referred to as bipolar disorder patients) and 272 healthy controls. Since reasons for abstinence were unknown, and could potentially confer selection bias (de Bruin *et al.* 2005*b*), we excluded 62 participants (schizophrenia n = 41, bipolar disorder n = 11, healthy controls n = 10) who reported abstinence from alcohol.

All participants were administered The Drug Use Disorders Identification Test (DUDIT; Berman *et al.* 2005), reviewing the use of illicit substances and misuse of legal prescription drugs over the last year. For the patients, information about lifetime and current substance use was recorded in addition to assessment of DSM-IV diagnoses of alcohol and other substance use disorders.

MRI acquisition

All participants underwent MRI scanning on the same 1.5 T Siemens Sonata scanner (Siemens Medical Solutions, Germany) equipped with a standard head coil. After a conventional three-plane localizer, two sagittal T1-weighted magnetization-prepared rapid-gradient echo volumes were acquired with the Siemens tfl3d1_ns pulse sequence (echo time = 3.93 ms, repetition time = 2730 ms, inversion time = 1000 ms, flip angle = 7°, field of view = 24 cm, voxel size = 1.33 × 0.94 × 1 mm, number of partitions = 160) and subsequently averaged together, after rigid-body registration, to increase the signal-to noise ratio. Patients and controls were scanned interchangeably. No major scanner upgrade was performed during the study period. All scans were evaluated by a neuroradiologist. Scans showing brain pathology were excluded.

MRI post-processing

FreeSurfer software (version 5.3.0) (http://surfer.nmr.mgh.harvard.edu/) was used to automatically compute measurements of cortical thickness and area across the cortical surface, and subcortical structure volumes. Briefly, this process consists of within-subject motion correction and averaging, intensity corrections, skull stripping and tissue classification. The pial and gray-white surfaces were then reconstructed and used to obtain measures of cortical thickness and area at

https://doi.org/10.1017/S0033291716002920 Published online by Cambridge University Press

approximately 1 60 000 vertices in each hemisphere across the cortical surface. The volumes of subcortical structures were estimated by counting number of voxels in the tissue classified volumes (Dale *et al.* 1999; Fischl *et al.* 1999, 2002). For the present study the cortical thickness maps were smoothed with a 20 mm full-width half maximum Gaussian kernel constrained to lie on the cortical surface. To investigate the effect of kernel size, additional analyses using a smoothing kernel of 10 mm were performed (see Supplementary material).

Statistical analyses

Analyses were performed using SPSS v. 22.0 (IBM Corp., USA), and R v. 3.1.2 (R Foundation for Statistical Computing, Austria). The vertex-wise statistical maps of cortical thickness were created in FreeSurfer.

Demographic and clinical data

Group differences in demographic and symptom variables were examined with χ^2 tests (categorical variables), one-way ANOVA or Student's *t* tests (continuous variables). Non-parametric tests (Kruskal–Wallis *H* test, Mann–Whitney *U* test) were used for non-normally distributed variables (duration of illness, YMRS, AUDIT and DUDIT total scores).

Cortical thickness and surface area analyses

For the surface based analyses, a general linear model was fit at each vertex with cortical thickness or cortical area as dependent variables and AUDIT-C score as variable of interest, covarying for age, gender and diagnostic group (schizophrenia, bipolar disorder or healthy control). To test the hypothesis of differential effect of alcohol in patients and controls, interaction terms between AUDIT-C score and diagnostic groups were tested and included if significant. Since previous studies reported gender (Hommer *et al.* 2001; Pfefferbaum *et al.* 2001) as well as age (Pfefferbaum *et al.* 1992) differences in the effect of alcohol on brain structure, we tested interaction terms between AUDIT-C score and age and gender, one at a time, and included them if they demonstrated significant effect. A 5% false discovery rate (FDR; Genovese *et al.* 2002) was applied to adjust for multiple comparisons.

Subcortical volume analyses

For total brain volume and subcortical volumes, linear regression models were fitted with age, gender, estimated total intracranial volume (eTIV) and diagnostic group entered as independent variables in addition to the AUDIT-C score. Interaction terms between AUDIT-C score and age, gender and diagnostic group were tested one at a time and included if significant. The Bonferroni–Holm method (Holm, 1979) was used to correct for multiple testing (33 subcortical volumes tested resulting in a significance threshold for the lowest *p* value of $p = 0.05/33 = 0.0015$).

Post-hoc *analyses*

Based on significance maps from surface-based analyses of the effect of AUDIT-C score, we used FreeSurfer to create clusters of regions remaining significant after FDR correction. Mean cortical thickness or area was extracted for clusters larger than 15 cm^2. These clusters were used for *post-hoc* analyses of the relative importance of each independent variable (AUDIT-C, age, gender, group) by linear regression models with mean cortical thickness or area for each cluster as dependent variable. The clusters were also used to test higher-order interactions between age, group and AUDIT-C score for each gender.

Potentially confounding variables were tested for subcortical volumes where AUDIT-C score had a significant effect and for the cortical clusters. First, linear regression models investigating effect of AUDIT-C score on structural brain measures (covaried for age, gender and diagnoses, and eTIV, for subcortical volumes) were rerun excluding participants with a current AUD ($n = 34$) or reporting intake of alcohol in the 24 h prior to MR scanning ($n = 112$). Next, potentially confounding effects of tobacco use (Jørgensen *et al.* 2015), illicit substance use (Berman *et al.* 2008; Lorenzetti *et al.* 2010; Ide *et al.* 2014), illness severity, duration of illness and antipsychotic medication (Ho *et al.* 2011; Andreasen *et al.* 2013) and years of education were tested by entering all variables in the model, one at a time (see Supplementary material for details).

Results

Demographic and clinical data

There were more women among bipolar disorder patients than among schizophrenia patients or healthy controls (Table 1). The schizophrenia patients were significantly younger, and the schizophrenia and bipolar patients had fewer years of education than the healthy controls. Mean AUDIT-C score did not differ between groups. Distribution of AUDIT-C score by group is shown in Supplementary Fig. S2. AUDIT-C score was significantly higher in men than in women in healthy controls and bipolar patients, and inversely related to age in healthy controls and schizophrenia patients (see Supplementary Table S1 and Fig. S3). The schizophrenia patients had shorter duration of illness, more severe symptoms and worse psychosocial functioning than the bipolar disorder patients (Table 1). Eight percent of the schizophrenia patients

https://doi.org/10.1017/S0033291716002920 Published online by Cambridge University Press

Table 1. *Demographic and clinical characteristics of the study sample, n = 609* [*mean ± S.D. or number (%) unless otherwise specified*]

Characteristic[a]	Schizophrenia (*n* = 165)	Bipolar disorder (*n* = 172)	Healthy controls (*n* = 272)	Statistics		
				Test	*p* value	*Post-hoc*
Age, years	31.8 ± 9.2	35.0 ± 11.1	35.1 ± 9.4	$F = 6.5$	0.002	BD, HC > SCZ
Gender, men	92 (56)	74 (43)	149 (55)	$\chi^2 = 7.3$	0.03	SCZ, HC > BD
Education, years	12.9 ± 2.5	13.5 ± 2.3	14.3 ± 2.4	$F = 18.7$	<0.001	HC > SCZ, BD
Smoking	83 (53)	90 (56)	45 (22)	$\chi^2 = 53.4$	<0.001	SCZ, BD > HC
AUDIT-C score	4.3 ± 2.4	4.5 ± 2.4	4.4 ± 1.8		n.s.	
AUD current	13 (8)	21 (12)	–		n.s.	
AUD past	13 (8)	15 (9)	–		n.s.	
Illicit SUD, lifetime	32 (19)	31 (18)	–		n.s.	
Illness duration, years[b]	6.6 [0.4–41.6]	10.6 [0.6–43.5]	–	$Z = -5.0$	<0.001	
GAF – functioning	43.4 ± 9.7	53.6 ± 12.2	–	$t = 8.4$	<0.001	
GAF – symptoms	42.2 ± 10.3	56.3 ± 11.3	–	$t = 12.0$	<0.001	
PANSS positive	15.0 ± 5.4	10.0 ± 3.6	–	$t = 9.7$	<0.001	
PANSS negative	15.3 ± 6.1	10.0 ± 3.4	–	$t = 9.6$	<0.001	
PANSS general	31. ± 8.3	25.6 ± 5.6	–	$t = 7.9$	<0.001	
PANSS total	61.9 ± 16.5	45.4 ± 9.5	–	$t = 11.1$	<0.001	
IDS	17.1 ± 12.6	16.6 ± 11.9	–		n.s.	
YMRS[b]	2.0 [0–23]	2.0 [0–28]	–		n.s.	
Current medication						
Antipsychotics	135 (82)	62 (36)	–			
CPZ equivalent dose (mg)	387.5 ± 343.9	228.4 ± 198.8	–			
Lithium	1(1)	31 (18)	–			
Other mood stabilizer	21 (13)	73 (42)	–			
Antidepressant	42 (25)	43 (25)	1[c]			

AUDIT-C, Alcohol Use Disorder Identification Test – Consumption part; AUD, alcohol use disorder; SUD, substance use disorder; GAF, Global Assessment of Functioning scale; PANSS, Positive And Negative Syndrome Scale; IDS, Inventory of Depressive Symptomatology; YMRS, Young Mania Rating Scale; CPZ, chlorpromazine equivalents; BD, bipolar spectrum disorder; HC, healthy controls; SCZ, schizophrenia spectrum disorder; n.s., not significant.

[a] Information on smoking was missing for 88 subjects (69 controls), duration of illness was missing for three patients, PANSS was missing for five patients, IDS was missing for 78 patients, YMRS was missing for 29 patients.

[b] Median (range).

[c] One control reported using citalopram 30 mg daily but was not diagnosed with current or previous psychiatric disorder.

and 12% of the bipolar patients had a current AUD, mainly alcohol dependence (77% and 67%, respectively). Supplementary Table S2 presents AUDIT and DUDIT total scores and data on use of illicit drugs.

Association between AUDIT-C score and cortical thickness and surface area

Increasing AUDIT-C score was related to thinner cortex in frontal and occipital brain regions bilaterally (Fig. 1*a, b*; with corresponding effect-size maps in Fig. 2*a, b*). There were no significant interaction effects between AUDIT-C score and age, gender or diagnostic group in the vertex-wise analyses. We extracted mean cortical thickness for eight cortical clusters (>15 cm^2) that reached FDR-adjusted statistical significance. The eight clusters included the left superior frontal gyrus and medial parts of right superior frontal gyrus, regions of right insula, right caudal middle frontal and bilateral rostral middle frontal and parieto-occipital regions (depicted in Supplementary Fig. S4*a, b*, see Supplementary Table S3 for coordinates and detailed description of the clusters). Main effect of AUDIT-C for each cluster is given in Table 2.

There were no significant associations between AUDIT-C score and surface area and no significant interactions between AUDIT-C score and age, gender or diagnoses for the surface area analyses.

Association between AUDIT-C score and subcortical volumes

There was a statistically significant positive association between AUDIT-C score and left lateral ventricle

https://doi.org/10.1017/S0033291716002920 Published online by Cambridge University Press

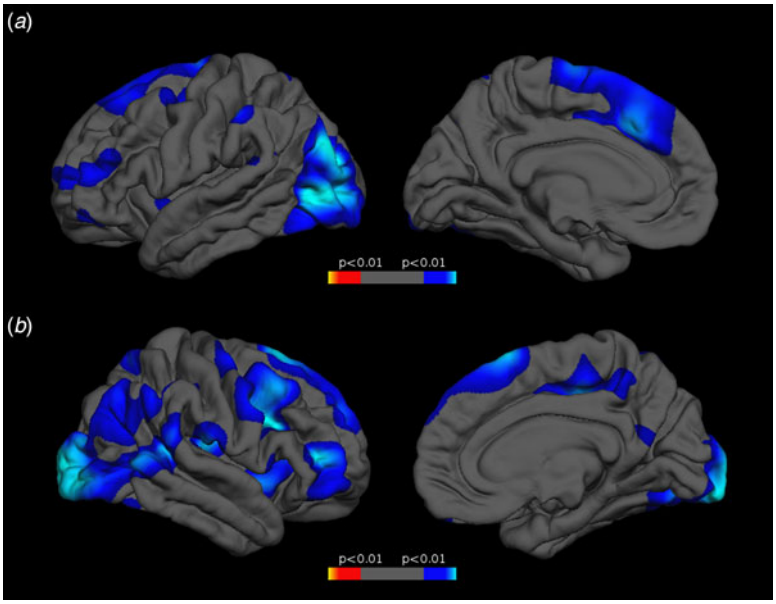

Fig. 1. (*a, b*) FDR-corrected statistical p-maps demonstrating negative association between AUDIT-C score and cortical thickness in (*a*) left and (*b*) right hemisphere, lateral and medial view, in 609 participants. FDR, False discovery rate; AUDIT-C, Alcohol Use Disorder Identification Test – Consumption part.

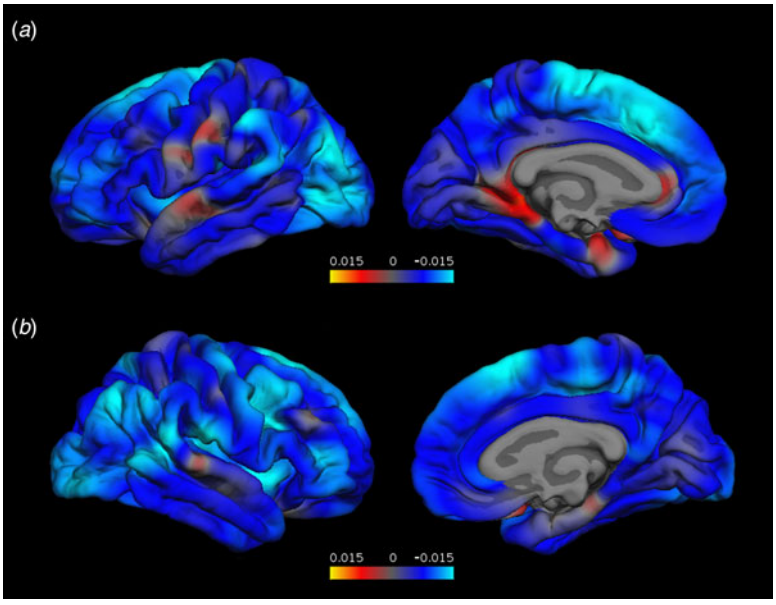

Fig. 2. (*a, b*) Effect-size maps (in millimeters) of the association between AUDIT-C score and cortical thickness in (*a*) left and (*b*) right hemisphere, lateral and medial view, in 609 participants. AUDIT-C, Alcohol Use Disorder Identification Test – Consumption part.

volumes ($\beta = 0.124$, $p = 0.001$) (Table 3). There was a nominally significant positive association between AUDIT-C and right lateral ventricular volumes ($\beta = 0.086$, $p = 0.022$), and negative associations between AUDIT-C and total brain volume ($\beta = -0.043$, $p = 0.003$), left hippocampus ($\beta = -0.075$, $p = 0.027$) and right putamen ($\beta = -0.068$, $p = 0.023$) volumes, but these were not significant after adjusting for multiple testing.

Post-hoc *analyses*

Supplementary Fig. S4*a, b* depicts with bar graphs the relative contribution of all independent variables (AUDIT-C, age, gender and diagnostic group) in each cluster. As expected, age explained the most variance in all clusters, but we also noted a substantial contribution of group. In the higher-order interaction analyses,

https://doi.org/10.1017/S0033291716002920 Published online by Cambridge University Press

Table 2. *Effect of AUDIT-C score on mean cortical thickness in the cortical clusters. Linear regression models covaried for age, gender and diagnostic group (n = 609)*

Cluster label		Thickness (mm)		Main effect of AUDIT-C score					
		Mean	S.D.	*B*	S.E.	*β*	*t*	*p* value	R^2 change (%)
L1	Parieto-occipital	2.12	0.13	−0.014	0.002	−0.225	−5.67	2.2×10^{-8}	4.6
R1	Parieto-occipital	1.94	0.12	−0.012	0.002	−0.209	−5.14	3.8×10^{-7}	4.0
L2	Superior frontal	2.65	0.19	−0.014	0.003	−0.158	−4.41	0.00001	2.3
R2	Superior frontal	2.92	0.29	−0.021	0.005	−0.155	−3.95	0.00009	2.2
L3	Rostral middle frontal	2.18	0.19	−0.015	0.003	−0.167	−4.40	0.00001	2.5
R3	Rostral middle frontal	1.99	0.24	−0.015	0.005	−0.132	−3.25	0.001	1.6
R4	Caudal middle frontal	2.20	0.13	−0.015	0.003	−0.158	−4.21	0.00003	2.3
R5	Insula	2.47	0.23	−0.014	0.004	−0.135	−3.52	0.0005	1.7

AUDIT-C, Alcohol Use Disorder Identification Test – Consumption part.

no results survived correction for multiple tests (see Supplementary material for details).

The association between AUDIT-C and mean cortical thickness in the cortical clusters and left lateral ventricular volume remained significant when the 34 patients with a current AUD were removed from the sample and after removing the 112 participants with alcohol intake in the 24 h prior to MR scanning. The main effect of AUDIT-C score remained significant when potential confounders (detailed in the Supplementary material) were added to the model.

Discussion

The main finding was the dose-dependent relationship between increasing levels of alcohol use and ventricular enlargement and thinner cortex in widespread brain regions in participants reporting past year alcohol consumption. The association between alcohol use and structural changes was not significantly different in schizophrenia or bipolar disorder patients compared to healthy controls. The effects remained significant after controlling for substance use disorders, including AUDs, illicit substance use, antipsychotic medication and disease severity.

The cortical regions associated with alcohol use (parts of superior and middle frontal gyri bilaterally, right insula and bilateral parieto-occipital regions) are in accordance with gray-matter deficits found in studies of alcohol-dependent patients in treatment (Jernigan *et al.* 1991; Fein *et al.* 2009; Durazzo *et al.* 2011; Fortier *et al.* 2011; Rando *et al.* 2011; Momenan *et al.* 2012), treatment-naive alcohol-dependent individuals (Fein *et al.* 2002; Cardenas *et al.* 2005) and in moderate alcohol consumption (Taki *et al.* 2004). Interestingly, the temporal gray-matter reductions often reported in alcohol dependence (Jernigan *et al.* 1991; Pfefferbaum *et al.* 1997; Cardenas *et al.* 2007; Fortier *et al.* 2011), also found in studies of heavy drinkers (Cardenas *et al.* 2005; Thayer *et al.* 2016) were not found in our study.

We found substantial effects in the frontal cortex bilaterally, including parts of middle frontal gyri and medial aspects of superior frontal gyri, although the strongest association with alcohol use was found in the parieto-occipital clusters. Neuroimaging of alcohol-dependent individuals have found the frontal lobes to be the region most affected by alcohol (Sullivan & Pfefferbaum, 2005). *Post-mortem* findings of selective neuronal loss in the superior frontal association cortex in alcohol dependence (compared with lack of neuronal loss in motor cortex) (Kril *et al.* 1997) supports a particular vulnerability to alcohol toxicity in this region. Of functional relevance, the medial frontal cortex is involved in cognitive control over habitual actions (Isoda & Hikosaka, 2007) and atrophy in these regions in alcoholics has been suggested to lead to reduced ability to override habitual responses to environmental cues, stress and other factors leading to alcohol relapse (Rando *et al.* 2011). The dorsolateral prefrontal cortex (DLPFC), located in the middle frontal gyri, is part of the mesocorticolimbic circuit, a 'reward network' involved in behavioral reinforcement (Bowirrat & Oscar-Berman, 2005) considered central to the neurobiology of alcohol dependence (Koob, 1999). Structural alterations in the DLPFC could disrupt the network (Makris *et al.* 2008*b*) and increase the risk for drug-seeking behavior (Bowirrat & Oscar-Berman, 2005).

Ventricular enlargement is an established finding in studies of alcohol dependence (Jernigan *et al.* 1991; Hayakawa *et al.* 1992; Wobrock *et al.* 2009) and of

https://doi.org/10.1017/S0033291716002920 Published online by Cambridge University Press

Table 3. *Main effect of AUDIT-C score on subcortical volumes, n = 609. Linear regression models, covaried for age, gender, group and estimated total intracranial volume. Uncorrected p values*

		Volume (ml)		Main effect of AUDIT-C score					
Brain structure volume		Mean	S.D.	*B*	S.E.	*β*	*t*	*p* value	R^2 change (%)
Total brain		1148.582	122.400	−2.461	0.819	−0.043	−3.005	**0.003**	0.2
Cerebral white matter	L	253.396	32.969	−0.283	0.288	−0.018	−0.981	0.327	0.0
	R	254.552	32.951	−0.311	0.287	−0.020	−1.083	0.279	0.0
Lateral ventricle	L	8.801	4.886	0.281	0.085	0.124	3.303	**0.001***	1.4
	R	8.122	4.623	0.186	0.081	0.086	2.294	**0.022**	0.7
Inferior lateral ventricle	L	0.429	0.227	0.006	0.004	0.059	1.487	0.138	0.3
	R	0.401	0.216	0.002	0.004	0.024	0.593	0.553	0.1
3rd ventricle		1.037	0.396	0.009	0.007	0.046	1.304	0.193	0.2
4th ventricle		1.761	0.618	0.014	0.012	0.047	1.116	0.247	0.2
Cerebellum white matter	L	14.335	1.983	−0.019	0.030	−0.021	−0.635	0.525	0.0
	R	14.881	2.085	−0.021	0.032	−0.021	−0.642	0.521	0.0
Cerebellum cortex	L	51.822	5.650	−0.069	0.084	−0.026	−0.819	0.413	0.1
	R	53.357	5.951	−0.124	0.087	−0.045	−1.424	0.155	0.2
Thalamus	L	7.646	0.917	−0.005	0.013	−0.012	−0.409	0.683	0.0
	R	7.076	0.786	0.011	0.010	0.030	1.100	0.272	0.1
Caudate	L	3.634	0.452	−0.008	0.007	−0.037	−1.113	0.266	0.1
	R	3.900	0.491	−0.006	0.007	−0.024	−0.766	0.444	0.1
Putamen	L	5.845	0.732	−0.011	0.011	−0.034	−1.032	0.302	0.1
	R[a]	5.646	0.693	−0.022	0.010	−0.068	−2.283	**0.023**	0.3
Pallidum	L	1.543	0.270	−0.003	0.005	−0.022	−0.594	0.552	0.0
	R	1.579	0.197	−0.003	0.003	−0.035	−1.067	0.287	0.1
Hippocampus	L	3.461	0.397	−0.014	0.006	−0.075	−2.215	**0.027**	0.5
	R	3.545	0.406	−0.009	0.006	−0.049	−1.442	0.150	0.2
Amygdala	L	1.587	0.237	−0.003	0.004	−0.028	−0.813	0.416	0.1
	R	1.633	0.240	−0.003	0.004	−0.030	−0.904	0.366	0.1
Accumbens	L	0.697	0.130	0.0002	0.002	0.005	0.137	0.891	0.0
	R	0.658	0.112	−0.001	0.002	−0.027	−0.729	0.466	0.1
Brainstem		21.901	2.668	0.004	0.034	0.003	0.113	0.910	0.0
Corpus callosum		0.951	0.162	−0.0001	0.003	−0.001	−0.037	0.971	0.0
Posterior									
Mid-posterior		0.430	0.096	−0.003	0.002	−0.073	−1.797	0.073	0.5
Central		0.442	0.088	−0.003	0.002	−0.069	−1.702	0.089	0.4
Mid-anterior		0.456	0.098	−0.003	0.002	−0.068	−1.715	0.087	0.4
Anterior		0.891	0.155	0.001	0.003	0.008	0.204	0.839	0.0

AUDIT-C, Alcohol Use Disorder Identification Test – Consumption part.

*Significant after correction for multiple comparisons with Bonferroni–Holm for 33 tests.

[a] Right putamen: there was significant interaction between AUDIT-C and age, main effect displayed is with interaction term included in the model.

moderate alcohol consumption (Mukamal *et al.* 2001; Ding *et al.* 2004) and has been associated with cerebral atrophy (Jernigan *et al.* 1991; Hayakawa *et al.* 1992; Ding *et al.* 2004). The positive association between alcohol use and left ventricular volume found in our sample is thus in accordance with the scientific literature.

We did not observe a differential brain effect of alcohol between patients with severe mental illness and controls. Hence, our findings do not support the hypothesis that patients with severe mental illness have increased vulnerability to alcohol-induced brain damage. Previous studies showing increased vulnerability for alcohol in schizophrenia or bipolar disorder differ from ours in design as they have compared patients with and without co-morbid AUD and healthy controls (Nery *et al.* 2011; Smith *et al.* 2011), often with an additional group of alcohol-dependent subjects without severe mental illness (Sullivan *et al.* 2000*b*; Mathalon *et al.* 2003). There were comparably few patients with co-morbid AUD in our sample.

https://doi.org/10.1017/S0033291716002920 Published online by Cambridge University Press

Therefore, if the increased vulnerability to alcohol-induced brain injury in severe mental illness is linked to alcohol dependence, this could help to explain the discrepant results between previous studies and ours. Further, our results are in line with an earlier study from our group on a separate sample (Nesvåg *et al.* 2007). Using a similar design as the present study, schizophrenia patients and healthy controls showed similar relationship between alcohol use and smaller frontal white-matter volumes (Nesvåg *et al.* 2007).

We found no significant gender differences in the effect of alcohol consumption on structural brain measures. Results of previous studies appear contradictory, with some findings indicating greater vulnerability to alcohol's effects on brain structure in women (Agartz *et al.* 1999; Hommer *et al.* 2001; Paul *et al.* 2008) while others have found more pronounced effects in men (Pfefferbaum *et al.* 2001; Taki *et al.* 2004; de Bruin *et al.* 2005*a*; Fein *et al.* 2009) or no gender differences (Cardenas *et al.* 2005; Momenan *et al.* 2012). Variations in sampling, image analysis, and gender differences in alcohol consumption might contribute to the heterogeneity of these results; e.g. the Cardenas *et al.* (2005) study included only nine alcohol-dependent women and nine healthy control women, and in the study by Taki *et al.* (2004) lifetime consumption in women was 12% of that in men, whereas consumption levels were comparable across genders in the study by Hommer *et al.* (2001).

Cortical thickness and area are thought to represent distinct biological entities, arising independently during neurodevelopment (Rakic, 1988). In the present study, we found alcohol use to be associated with cortical thickness but not cortical surface area. Our finding is in agreement with a recent study by Thayer *et al.* (2016) that found AUDIT score to be associated with cortical volume and thickness but not surface area in heavy drinkers (Thayer *et al.* 2016). It supports the understanding that cortical thickness is more sensitive to environmental influences (Goldman *et al.* 2009; Habets *et al.* 2011), whereas surface area is thought to be more resistant to change after developmental completion (Rakic, 1988).

The similar levels of AUDIT-C scores between patients and healthy controls were unexpected considering that the AUD prevalence generally is higher in patients with severe mental illness than in the general population (Regier *et al.* 1990; Grant *et al.* 2015). Mean AUDIT-C scores and AUDIT total scores in the healthy controls in our study corresponded well to those found in corresponding age groups in a recent population-based survey in Norway (Mathiesen *et al.* 2012). Also similar to Mathiesen *et al.* AUDIT-C scores were higher among men than women and inversely related to age in the healthy control group, altogether indicating that alcohol use in our control sample was representative of the Norwegian general population. Patients with problematic substance use might be underrepresented in our sample as they might be less likely to participate in research projects. Yet, the rates of 8% current AUD in schizophrenia and 12% in bipolar disorder in our sample correspond well with findings in a Norwegian registry-based population study reporting a 5-year AUD prevalence (with or without co-morbid drug use disorders) of 9.5% in schizophrenia and 12.5% in bipolar disorder (table 2 in Nesvåg *et al.* 2015), indicating that our patient sample is representative of the Norwegian patient population. In analogy, a meta-analysis showed a 9.4% prevalence of current AUD in schizophrenia (Koskinen *et al.* 2009) and co-morbid current AUD was found in 12% of Swedish bipolar disorder patients (van der Werf-Eldering *et al.* 2010), whereas rates were higher in other Western countries (e.g. The Netherlands and the United States, table 1 in Hunt *et al.* 2016). *Per capita* alcohol consumption correlated positively with co-morbidity rates in a meta-analysis of AUD in bipolar disorder (Di Florio *et al.* 2014). *Per capita* alcohol consumption in Norway is among the lowest in Europe (6.6 litres per year in 2010; WHO Global Information System on Alcohol and Health, 2010). Moreover, gender ratio may influence co-morbidity rates of AUD in severe mental illness studies, with generally higher rates in men than in women (Koskinen *et al.* 2009; Di Florio *et al.* 2014). The gender distribution in our study was fairly equal whereas men are overrepresented in many studies of severe mental illness. Both factors can partly explain the relatively low prevalence of AUD in our study.

The present study is naturalistic and cross-sectional and the following limitations apply: First, we could not make assumptions about causality, only investigate the statistical association between alcohol use and structural brain measures. Second, a large part of the patient group used illicit substances in addition to alcohol (Table 1 and Supplementary Table S2). Both cocaine (Makris *et al.* 2008*a*; Ide *et al.* 2014) and amphetamine (Berman *et al.* 2008) dependencies have been associated with cortical gray-matter reductions (in the frontal lobe and other regions) although alcohol has been shown to be an important factor also in brain changes in amphetamine dependency (Lawyer *et al.* 2010). This opens up for the possibility that our findings could in part be related to other substance use than alcohol, but since the alcohol effect remained significant after controlling for tobacco and other substance use, we have indications that this was not the case. Further, excluding all patients with illicit substance use would have made our sample less representative.

https://doi.org/10.1017/S0033291716002920 Published online by Cambridge University Press

The strengths of the study include the large and thoroughly characterized subject sample. Moreover, all MR images were acquired on the same scanner and there were no major software or hardware upgrades during the study period.

Conclusion

The results of the present study show a dose-dependent relationship between increasing levels of alcohol use and widespread cortical thinning and ventricular expansion in drinkers across a continuum of alcohol consumption levels. This association was found in schizophrenia and bipolar disorder patients as well as in healthy control subjects, and did not support previous findings of increased vulnerability to alcohol's brain effects in patients with severe mental illness. Importantly, the statistical effect of alcohol use remained after controlling for AUDs, implicating that alcohol use has a negative effect on brain structure even in the absence of behavioral or social adverse consequences of alcohol. The results emphasize the importance of addressing alcohol use in patients with schizophrenia and bipolar disorder in the clinic as well as in non-mental illness populations. Alcohol should be taken into account as a potential confounder in neuroimaging studies.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S0033291716002920.

Acknowledgements

We thank the study participants and clinicians involved in recruitment and assessment at the Norwegian Research Centre for Mental Disorders (NORMENT). We also thank Thomas Bjella, Marin Furan and Linn Norbom for technical assistance. The study was supported by grants from the Research Council of Norway (grant nos. 190311/V50, 167153/V50, 223273), the South-Eastern Norway Regional Health Authority (grant nos. 2012100, 2011092, 2009037) and the K. G. Jebsen Foundation.

Declaration of Interests

O.A.A. has received speaker's honorarium from pharmaceutical companies Osaka, GSK and Lundbeck. The remaining authors report no conflict of interests.

References

Agartz I, Brag S, Franck J, Hammarberg A, Okugawa G, Svinhufvud K, Bergman H (2003). MR volumetry during acute alcohol withdrawal and abstinence: a descriptive study. *Alcohol and Alcoholism* **38**, 71–78.

Agartz I, Momenan R, Rawlings RR, Kerich MJ, Hommer DW (1999). Hippocampal volume in patients with alcohol dependence. *Archives of General Psychiatry* **56**, 356–363.

Andreasen NC, Liu D, Ziebell S, Vora A, Ho BC (2013). Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: a prospective longitudinal MRI study. *American Journal of Psychiatry* **170**, 609–615.

Arnone D, Cavanagh J, Gerber D, Lawrie SM, Ebmeier KP, McIntosh AM (2009). Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. *British Journal of Psychiatry* **195**, 194–201.

Berman AH, Bergman H, Palmstierna T, Schlyter F (2005). Evaluation of the drug use disorders identification test (DUDIT) in criminal justice and detoxification settings and in a Swedish population sample. *European Addiction Research* **11**, 22–31.

Berman S, O'Neill J, Fears S, Bartzokis G, London ED (2008). Abuse of amphetamines and structural abnormalities in the brain. *Annals of the New York Academy of Sciences* **1141**, 195–220.

Bora E, Fornito A, Yucel M, Pantelis C (2010). Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. *Biological Psychiatry* **67**, 1097–1105.

Bowirrat A, Oscar-Berman M (2005). Relationship between dopaminergic neurotransmission, alcoholism, and Reward Deficiency syndrome. *American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics* **132b**, 29–37.

Bradley KA, DeBenedetti AF, Volk RJ, Williams EC, Frank D, Kivlahan DR (2007). AUDIT-C as a brief screen for alcohol misuse in primary care. *Alcoholism, Clinical and Experimental Research* **31**, 1208–1217.

Buhler M, Mann K (2011). Alcohol and the human brain: a systematic review of different neuroimaging methods. *Alcoholism, Clinical and Experimental Research* **35**, 1771–1793.

Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA (1998). The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Archives of Internal Medicine* **158**, 1789–1795.

Cardenas VA, Studholme C, Gazdzinski S, Durazzo TC, Meyerhoff DJ (2007). Deformation-based morphometry of brain changes in alcohol dependence and abstinence. *Neuroimage* **34**, 879–887.

Cardenas VA, Studholme C, Meyerhoff DJ, Song E, Weiner MW (2005). Chronic active heavy drinking and family history of problem drinking modulate regional brain tissue volumes. *Psychiatry Research* **138**, 115–130.

Dale AM, Fischl B, Sereno MI (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* **9**, 179–194.

Davis BJ, Vidal JS, Garcia M, Aspelund T, van Buchem MA, Jonsdottir MK, Sigurdsson S, Harris TB, Gudnason V, Launer LJ (2014). The alcohol paradox: light-to-moderate

alcohol consumption, cognitive function, and brain volume. *Journals of Gerontology. Series A: Biological Sciences and Medical Sciences* **69**, 1528–1535.

de Bruin EA, Hulshoff Pol HE, Bijl S, Schnack HG, Fluitman S, Böcker KBE, Kenemans JL, Kahn RS, Verbaten MN (2005*a*). Associations between alcohol intake and brain volumes in male and female moderate drinkers. *Alcoholism: Clinical and Experimental Research* **29**, 656–663.

de Bruin EA, Hulshoff Pol HE, Schnack HG, Janssen J, Bijl S, Evans AC, Kenemans JL, Kahn RS, Verbaten MN (2005*b*). Focal brain matter differences associated with lifetime alcohol intake and visual attention in male but not in female non-alcohol-dependent drinkers. *Neuroimage* **26**, 536–545.

den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, van Duijn CM, Hofman A, Breteler MM (2004). Alcohol intake in relation to brain magnetic resonance imaging findings in older persons without dementia. *American Journal of Clinical Nutrition* **80**, 992–997.

Di Florio A, Craddock N, van den Bree M (2014). Alcohol misuse in bipolar disorder. A systematic review and meta-analysis of comorbidity rates. *European Psychiatry* **29**, 117–124.

Ding J, Eigenbrodt ML, Mosley Jr TH, Hutchinson RG, Folsom AR, Harris TB, Nieto FJ (2004). Alcohol intake and cerebral abnormalities on magnetic resonance imaging in a community-based population of middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke* **35**, 16–21.

Downer B, Jiang Y, Zanjani F, Fardo D (2015). Effects of alcohol consumption on cognition and regional brain volumes among older adults. *American Journal of Alzheimers Disease and Other Dementias* **30**, 364–374.

Doyle SR, Donovan DM, Kivlahan DR (2007). The factor structure of the alcohol use disorders 14 identification test (AUDIT). *Journal of Studies on Alcohol and Drugs* **68**, 474–479.

Durazzo TC, Tosun D, Buckley S, Gazdzinski S, Mon A, Fryer SL, Meyerhoff DJ (2011). Cortical thickness, surface area, and volume of the brain reward system in alcohol dependence: relationships to relapse and extended abstinence. *Alcoholism, Clinical and Experimental Research* **35**, 1187–1200.

Ellison-Wright I, Bullmore E (2010). Anatomy of bipolar disorder and schizophrenia: a meta-analysis. *Schizophrenia Research* **117**, 1–12.

Fein G, Di Sclafani V, Cardenas VA, Goldmann H, Tolou-Shams M, Meyerhoff DJ (2002). Cortical gray matter loss in treatment-naive alcohol dependent individuals. *Alcoholism, Clinical and Experimental Research* **26**, 558–564.

Fein G, Shimotsu R, Chu R, Barakos J (2009). Parietal gray matter volume loss is related to spatial processing deficits in long-term abstinent alcoholic men. *Alcoholism, Clinical and Experimental Research* **33**, 1806–1814.

First MB, Spitzer RL, Gibbon M, Williams JB (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version – Patient Edition* (SCID-I/P, Version 2.0). Biometrics Research, New York State Psychiatric Institute: New York, US.

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der KA, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* **33**, 341–355.

Fischl B, Sereno MI, Dale AM (1999). Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. *Neuroimage* **9**, 195–207.

Fortier CB, Leritz EC, Salat DH, Venne JR, Maksimovskiy AL, Williams V, Milberg WP, McGlinchey RE (2011). Reduced cortical thickness in abstinent alcoholics and association with alcoholic behavior. *Alcoholism, Clinical and Experimental Research* **35**, 2193–2201.

Gazdzinski S, Durazzo TC, Meyerhoff DJ (2005). Temporal dynamics and determinants of whole brain tissue volume changes during recovery from alcohol dependence. *Drug and Alcohol Dependence* **78**, 263–273.

Genovese CR, Lazar NA, Nichols T (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* **15**, 870–878.

Goldman AL, Pezawas L, Mattay VS, Fischl B, Verchinski BA, Chen Q, Weinberger DR, Meyer-Lindenberg A (2009). Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. *Archives of General Psychiatry* **66**, 467–477.

Goldstein BI, Velyvis VP, Parikh SV (2006). The association between moderate alcohol use and illness severity in bipolar disorder: a preliminary report. *Journal of Clinical Psychiatry* **67**, 102–106.

Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, Pickering RP, Ruan WJ, Smith SM, Huang B, Hasin DS (2015). Epidemiology of DSM-5 alcohol use disorder: results from the national epidemiologic survey on alcohol and related conditions III. *JAMA Psychiatry* **72**, 757–766.

Gu Y, Scarmeas N, Short EE, Luchsinger JA, DeCarli C, Stern Y, Manly JJ, Schupf N, Mayeux R, Brickman AM (2014). Alcohol intake and brain structure in a multiethnic elderly cohort. *Clinical Nutrition* **33**, 662–667.

Gual A, Segura L, Contel M, Heather N, Colom J (2002). Audit-3 and audit-4: effectiveness of two short forms of the alcohol use disorders identification test. *Alcohol and Alcoholism* **37**, 591–596.

Habets P, Marcelis M, Gronenschild E, Drukker M, van Os J (2011). Reduced cortical thickness as an outcome of differential sensitivity to environmental risks in schizophrenia. *Biological Psychiatry* **69**, 487–494.

Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS (2013). Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophrenia Bulletin* **39**, 1129–1138.

Harper C (2009). The neuropathology of alcohol-related brain damage. *Alcohol and Alcoholism* **44**, 136–140.

Hayakawa K, Kumagai H, Suzuki Y, Furusawa N, Haga T, Hoshi T, Fujiwara Y, Yamaguchi K (1992). MR imaging of chronic alcoholism. *Acta Radiologica* **33**, 201–206.

Hibar DP, Westlye LT, van Erp TG, Rasmussen J, Leonardo CD, Faskowitz J, Haukvik UK, Hartberg CB, Doan NT, Agartz I, Dale AM, Gruber O, Kramer B, Trost S, Liberg B, Abe C, Ekman CJ, Ingvar M, Landen M, Fears SC, Freimer NB, Bearden CE, Costa Rica/Colombia Consortium for

Genetic Investigation of Bipolar E, Sprooten E, Glahn DC, Pearlson GD, Emsell L, Kenney J, Scanlon C, McDonald C, Cannon DM, Almeida J, Versace A, Caseras X, Lawrence NS, Phillips ML, Dima D, Delvecchio G, Frangou S, Satterthwaite TD, Wolf D, Houenou J, Henry C, Malt UF, Boen E, Elvsashagen T, Young AH, Lloyd AJ, Goodwin GM, Mackay CE, Bourne C, Bilderbeck A, Abramovic L, Boks MP, van Haren NE, Ophoff RA, Kahn RS, Bauer M, Pfennig A, Alda M, Hajek T, Mwangi B, Soares JC, Nickson T, Dimitrova R, Sussmann JE, Hagenaars S, Whalley HC, McIntosh AM, Thompson PM, Andreassen OA (2016). Subcortical volumetric abnormalities in bipolar disorder. *Molecular Psychiatry*. Published online: 9 February 2016. doi:10.1038/mp.2015.227.

Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V (2011). Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Archives of General Psychiatry* **68**, 128–137.

Holm S (1979). A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics* **6**, 65–70.

Hommer D, Momenan R, Kaiser E, Rawlings R (2001). Evidence for a gender-related effect of alcoholism on brain volumes. *American Journal of Psychiatry* **158**, 198–204.

Hunt GE, Malhi GS, Cleary M, Lai HM, Sitharthan T (2016). Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990–2015: systematic review and meta-analysis. *Journal of Affective Disorders*. Published online: 9 July 2016. doi:10.1016/j.jad.2016.07.011.

Ide JS, Zhang S, Hu S, Sinha R, Mazure CM, Li CS (2014). Cerebral gray matter volumes and low-frequency fluctuation of BOLD signals in cocaine dependence: duration of use and gender difference. *Drug and Alcohol Dependence* **134**, 51–62.

Isoda M, Hikosaka O (2007). Switching from automatic to controlled action by monkey medial frontal cortex. *Nature Neuroscience* **10**, 240–248.

Jernigan TL, Butters N, DiTraglia G, Schafer K, Smith T, Irwin M, Grant I, Schuckit M, Cermak LS (1991). Reduced cerebral grey matter observed in alcoholics using magnetic resonance imaging. *Alcoholism, Clinical and Experimental Research* **15**, 418–427.

Jørgensen KN, Skjaervo I, Morch-Johnsen L, Haukvik UK, Lange EH, Melle I, Andreassen OA, Agartz I (2015). Cigarette smoking is associated with thinner cingulate and insular cortices in patients with severe mental illness. *Journal of Psychiatry and Neuroscience* **40**, 241–249.

Kaarne T, Aalto M, Kuokkanen M, Seppa K (2010). AUDIT-C, AUDIT-3 and AUDIT-QF in screening risky drinking among Finnish occupational health-care patients. *Drug and Alcohol Review* **29**, 563–567.

Kapogiannis D, Kisser J, Davatzikos C, Ferrucci L, Metter J, Resnick SM (2012). Alcohol consumption and premotor corpus callosum in older adults. *European Neuropsychopharmacology* **22**, 704–710.

Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261–276.

Koob GF (1999). The role of the striatopallidal and extended amygdala systems in drug addiction. *Annals of the New York Academy of Sciences* **877**, 445–460.

Koskinen J, Lohonen J, Koponen H, Isohanni M, Miettunen J (2009). Prevalence of alcohol use disorders in schizophrenia–a systematic review and meta-analysis. *Acta Psychiatrica Scandinavica* **120**, 85–96.

Kril JJ, Halliday GM, Svoboda MD, Cartwright H (1997). The cerebral cortex is damaged in chronic alcoholics. *Neuroscience* **79**, 983–998.

Kubota M, Nakazaki S, Hirai S, Saeki N, Yamaura A, Kusaka T (2001). Alcohol consumption and frontal lobe shrinkage: study of 1432 non-alcoholic subjects. *Journal of Neurology, Neurosurgery and Psychiatry* **71**, 104–106.

Large M, Mullin K, Gupta P, Harris A, Nielssen O (2014). Systematic meta-analysis of outcomes associated with psychosis and co-morbid substance use. *Australian and New Zealand Journal of Psychiatry* **48**, 418–432.

Lawyer G, Bjerkan PS, Hammarberg A, Jayaram-Lindstrom N, Franck J, Agartz I (2010). Amphetamine dependence and co-morbid alcohol abuse: associations to brain cortical thickness. *BMC Pharmacology* **10**, 5.

Levin FR, Hennessy G (2004). Bipolar disorder and substance abuse. *Biological Psychiatry* **56**, 738–748.

Lorenzetti V, Lubman DI, Whittle S, Solowij N, Yucel M (2010). Structural MRI findings in long-term cannabis users: what do we know? *Substance Use and Misuse* **45**, 1787–1808.

Makris N, Gasic GP, Kennedy DN, Hodge SM, Kaiser JR, Lee MJ, Kim BW, Blood AJ, Evins AE, Seidman LJ, Iosifescu DV, Lee S, Baxter C, Perlis RH, Smoller JW, Fava M, Breiter HC (2008*a*). Cortical thickness abnormalities in cocaine addiction--a reflection of both drug use and a pre-existing disposition to drug abuse? *Neuron* **60**, 174–188.

Makris N, Oscar-Berman M, Jaffin SK, Hodge SM, Kennedy DN, Caviness VS, Marinkovic K, Breiter HC, Gasic GP, Harris GJ (2008*b*). Decreased volume of the brain reward system in alcoholism. *Biological Psychiatry* **64**, 192–202.

Mathalon DH, Pfefferbaum A, Lim KO, Rosenbloom MJ, Sullivan EV (2003). Compounded brain volume deficits in schizophrenia-alcoholism comorbidity. *Archives of General Psychiatry* **60**, 245–252.

Mathiesen EF, Nome S, Richter J, Eisemann M (2012). Alcohol use patterns in a Norwegian general population-based sample with special reference to socio-demographic variables. *Journal of Public Health* **21**, 241–249.

Momenan R, Steckler LE, Saad ZS, van Rafelghem S, Kerich MJ, Hommer DW (2012). Effects of alcohol dependence on cortical thickness as determined by magnetic resonance imaging. *Psychiatry Research* **204**, 101–111.

Monnig MA, Tonigan JS, Yeo RA, Thoma RJ, McCrady BS (2013). White matter volume in alcohol use disorders: a meta-analysis. *Addiction Biology* **18**, 581–592.

Mueser KT, Drake RE, Wallach MA (1998). Dual diagnosis: a review of etiological theories. *Addictive Behaviors* **23**, 717–734.

Mukamal KJ, Longstreth Jr WT, Mittleman MA, Crum RM, Siscovick DS (2001). Alcohol consumption and subclinical findings on magnetic resonance imaging of the brain in older adults: the cardiovascular health study. *Stroke* **32**, 1939–1946.

Nery FG, Matsuo K, Nicoletti MA, Monkul ES, Zunta-Soares GB, Hatch JP, Lafer B, Soares JC (2011). Association between prior alcohol use disorders and decreased prefrontal gray matter volumes in bipolar I disorder patients. *Neuroscience Letters* **503**, 136–140.

Nesvåg R, Frigessi A, Jonsson EG, Agartz I (2007). Effects of alcohol consumption and antipsychotic medication on brain morphology in schizophrenia. *Schizophrenia Research* **90**, 52–61.

Nesvåg R, Knudsen GP, Bakken IJ, Hoye A, Ystrom E, Suren P, Reneflot A, Stoltenberg C, Reichborn-Kjennerud T (2015). Substance use disorders in schizophrenia, bipolar disorder, and depressive illness: a registry-based study. *Social Psychiatry and Psychiatric Epidemiology* **50**, 1267–1276.

Paul CA, Au R, Fredman L, Massaro JM, Seshadri S, Decarli C, Wolf PA (2008). Association of alcohol consumption with brain volume in the Framingham study. *Archives of Neurology* **65**, 1363–1367.

Pedersen G, Hagtvet KA, Karterud S (2007). Generalizability studies of the global assessment of functioning-split version. *Comprehensive Psychiatry* **48**, 88–94.

Pfefferbaum A, Lim KO, Zipursky RB, Mathalon DH, Rosenbloom MJ, Lane B, Ha CN, Sullivan EV (1992). Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: a quantitative MRI study. *Alcoholism, Clinical and Experimental Research* **16**, 1078–1089.

Pfefferbaum A, Rosenbloom M, Deshmukh A, Sullivan E (2001). Sex differences in the effects of alcohol on brain structure. *American Journal of Psychiatry* **158**, 188–197.

Pfefferbaum A, Rosenbloom MJ, Chu W, Sassoon SA, Rohlfing T, Pohl KM, Zahr NM, Sullivan EV (2014). White matter microstructural recovery with abstinence and decline with relapse in alcohol dependence interacts with normal ageing: a controlled longitudinal DTI study. *Lancet Psychiatry* **1**, 202–212.

Pfefferbaum A, Sullivan EV, Mathalon DH, Lim KO (1997). Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcoholism, Clinical and Experimental Research* **21**, 521–529.

Pfefferbaum A, Sullivan EV, Mathalon DH, Shear PK, Rosenbloom MJ, Lim KO (1995). Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. *Alcoholism, Clinical and Experimental Research* **19**, 1177–1191.

Preti A, Muscio C, Boccardi M, Lorenzi M, de Girolamo G, Frisoni G (2014). Impact of alcohol consumption in healthy adults: a magnetic resonance imaging investigation. *Psychiatry Research* **224**, 96–103.

Rakic P (1988). Specification of cerebral cortical areas. *Science* **241**, 170–176.

Rando K, Hong KI, Bhagwagar Z, Li CS, Bergquist K, Guarnaccia J, Sinha R (2011). Association of frontal and posterior cortical gray matter volume with time to alcohol relapse: a prospective study. *American Journal of Psychiatry* **168**, 183–192.

Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the epidemiologic catchment area (ECA) study. *JAMA* **264**, 2511–2518.

Reinert DF, Allen JP (2007). The alcohol use disorders identification test: an update of research findings. *Alcoholism: Clinical and Experimental Research* **31**, 185–199.

Ringen PA, Lagerberg TV, Birkenaes AB, Engn J, Faerden A, Jonsdottir H, Nesvåg R, Friis S, Opjordsmoen S, Larsen F, Melle I, Andreassen OA (2008). Differences in prevalence and patterns of substance use in schizophrenia and bipolar disorder. *Psychological Medicine* **38**, 1241–1249.

Rumpf HJ, Hapke U, Meyer C, John U (2002). Screening for alcohol use disorders and at-risk drinking in the general population: psychometric performance of three questionnaires. *Alcohol and Alcoholism* **37**, 261–268.

Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH (1996). The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychological Medicine* **26**, 477–486.

Sachdev PS, Chen X, Wen W, Anstey KJ (2008). Light to moderate alcohol use is associated with increased cortical gray matter in middle-aged men: a voxel-based morphometric study. *Psychiatry Research* **163**, 61–69.

Sasaki H, Abe O, Yamasue H, Fukuda R, Yamada H, Takei K, Suga M, Takao H, Kasai K, Aoki S, Ohtomo K (2009). Structural and diffusional brain abnormality related to relatively low level alcohol consumption. *Neuroimage* **46**, 505–510.

Saunders JB, Aasland OG, Babor TF, de Jr lF, Grant M (1993). Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption–II. *Addiction* **88**, 791–804.

Schiffer B, Muller BW, Scherbaum N, Forsting M, Wiltfang J, Leygraf N, Gizewski ER (2010). Impulsivity-related brain volume deficits in schizophrenia-addiction comorbidity. *Brain* **133**, 3093–3103.

Smith MJ, Wang L, Cronenwett W, Goldman MB, Mamah D, Barch DM, Csernansky JG (2011). Alcohol use disorders contribute to hippocampal and subcortical shape differences in schizophrenia. *Schizophrenia Research* **131**, 174–183.

Spitzer RL, Williams JB, Kroenke K, Linzer M, deGruy III FV, Hahn SR, Brody D, Johnson JG (1994). Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *Journal of the American Medical Association* **272**, 1749–1756.

Sullivan EV, Deshmukh A, Desmond JE, Lim KO, Pfefferbaum A (2000*a*). Cerebellar volume decline in normal aging, alcoholism, and Korsakoff's syndrome: relation to ataxia. *Neuropsychology* **14**, 341–352.

Sullivan EV, Deshmukh A, Desmond JE, Mathalon DH, Rosenbloom MJ, Lim KO, Pfefferbaum A (2000*b*). Contribution of alcohol abuse to cerebellar volume deficits in men with schizophrenia. *Archives of General Psychiatry* **57**, 894–902.

Sullivan EV, Pfefferbaum A (2005). Neurocircuitry in alcoholism: a substrate of disruption and repair. *Psychopharmacology* **180**, 583–594.

Taki Y, Goto R, Evans A, Zijdenbos A, Neelin P, Lerch J, Sato K, Ono S, Kinomura S, Nakagawa M, Sugiura M, Watanabe J, Kawashima R, Fukuda H (2004). Voxel-based morphometry of human brain with age and

cerebrovascular risk factors. *Neurobiology of Aging* **25**, 455–463.

Thayer RE, Hagerty SL, Sabbineni A, Claus ED, Hutchison KE, Weiland BJ (2016). Negative and interactive effects of sex, aging, and alcohol abuse on gray matter morphometry. *Human Brain Mapping* **37**, 2276–2292.

van der Werf-Eldering MJ, Burger H, Holthausen EA, Aleman A, Nolen WA (2010). Cognitive functioning in patients with bipolar disorder: association with depressive symptoms and alcohol use. *PLoS ONE* **5**, e13032.

van Erp TG, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, Agartz I, Westlye LT, Haukvik UK, Dale AM, Melle I, Hartberg CB, Gruber O, Kraemer B, Zilles D, Donohoe G, Kelly S, McDonald C, Morris DW, Cannon DM, Corvin A, Machielsen MW, Koenders L, de Haan L, Veltman DJ, Satterthwaite TD, Wolf DH, Gur RC, Gur RE, Potkin SG, Mathalon DH, Mueller BA, Preda A, Macciardi F, Ehrlich S, Walton E, Hass J, Calhoun VD, Bockholt HJ, Sponheim SR, Shoemaker JM, van Haren NE, Pol HE, Ophoff RA, Kahn RS, Roiz-Santianez R, Crespo-Facorro B, Wang L, Alpert KI, Jonsson EG, Dimitrova R, Bois C, Whalley HC, McIntosh AM, Lawrie SM, Hashimoto R, Thompson PM, Turner JA (2015). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecular Psychiatry* **21**, 547–553.

Welch KA, Carson A, Lawrie SM (2013). Brain structure in adolescents and young adults with alcohol problems: systematic review of imaging studies. *Alcohol and Alcoholism* **48**, 433–444.

Wobrock T, Falkai P, Schneider-Axmann T, Frommann N, Wolwer W, Gaebel W (2009). Effects of abstinence on brain morphology in alcoholism: a MRI study. *European Archives of Psychiatry and Clinical Neuroscience* **259**, 143–150.

WHO Global Information System on Alcohol and Health (2010). (http://gamapserver.who.int/gho/interactive_charts/gisah/consumption_adult/atlas.html). World Health Organization. Accessed 3 October 2016.

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978). A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry* **133**, 429–435.

https://doi.org/10.1017/S0033291716002920 Published online by Cambridge University Press