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Cortical Thickness, Surface Area and Volume of the Brain Reward System in Alcohol Dependence: Relationships to Relapse and Extended Abstinence

Timothy C. Durazzo[a,b], **Duygu Tosun**[b], **Shannon Buckley**[b], **Stefan Gazdzinski**[b], **Anderson Mon**[a,b], **Susanna L. Fryer**[a,b], and **Dieter J. Meyerhoff**[a,b]

[a] Department of Radiology and Biomedical Imaging, University of California, San Francisco

[b] Center for Imaging of Neurodegenerative Diseases, San Francisco VA Medical Center

Abstract

BACKGROUND—At least 60% of those treated for an alcohol use disorder will relapse. Empirical study of the integrity of the brain reward system (BRS) is critical to understanding the mechanisms of relapse as this collection of circuits is implicated in the development and maintenance of all forms of addictive disorders. This study compared thickness, surface area and volume in neocortical components of the BRS among non-smoking light drinking controls (Controls), individuals who remained abstinent and those who relapsed after treatment.

METHODS—Seventy-five treatment-seeking alcohol dependent individuals (abstinent for 7 ± 3 days) and 43 Controls completed 1.5T proton magnetic resonance imaging studies. Parcellated morphological data was obtained for following bilateral components of the BRS: rostral and caudal anterior cingulate cortex, insula, medial and lateral orbitofrontal cortex, rostral and caudal middle and superior frontal gyri, amygdala and hippocampus as well as for 26 other bilateral neocortical regions. Alcohol dependent participants were followed over 12-months after baseline study and were classified as Abstainers (no alcohol consumption; n=24) and Relapsers (any alcohol consumption; n=51) at follow-up.

RESULTS—Relapsers and Abstainers demonstrated lower cortical thickness in the vast majority of BRS regions as well as lower global thickness compared to Controls. Relapsers had lower total BRS surface area than both Controls and Abstainers, but Abstainers were not significantly different from Controls on any surface area measure. Relapsers demonstrated lower volumes than Controls in the majority of regions, while Abstainers showed lower volumes than Controls in the superior frontal gyrus, insula, amygdala and hippocampus, bilaterally. Relapsers exhibited smaller volumes than Abstainers in the right rostral middle and caudal middle frontal gyri and the lateral orbitofrontal cortex, bilaterally. In Relapsers, lower baseline volumes and surface areas in multiple regions were associated with a greater magnitude of post-treatment alcohol consumption.

CONCLUSIONS—Results suggest Relapsers demonstrated morphological abnormalities in regions involved in the “top down” regulation/modulation of internal drive states, emotions, reward processing and behavior, which may impart increased risk for the relapse/remit cycle that afflicts many with an AUD. Results also highlight the importance of examining both cortical thickness and surface area to better understand the nature of regional volume loss frequently observed in AUD. Results from this report are consistent with previous research implicating plastic neurobiological changes the brain reward system in the maintenance of addictive disorders.

Address correspondence to: Timothy C. Durazzo, Ph.D., Center for Imaging of Neurodegenerative Disease (114M), San Francisco Veterans Administration Medical Center, 4150 Clement St. (114M), San Francisco, CA 94121, (415) 221-4810 x4157, (415) 750-2152 (fax), timothy.durazzo@ucsf.edu.

Keywords

alcohol dependence; neuroimaging; brain volume; cortical thickness; surface area; relapse

INTRODUCTION

It is estimated that at least 60% of individuals who seek treatment for an alcohol use disorder (i.e., alcohol dependence or abuse) will resume hazardous levels of alcohol consumption (Krampe et al., 2007; McKay et al., 2006; Miller et al., 2001), typically within 6 months following treatment (Maisto et al., 2007; Maisto et al., 2006; Udo et al., 2009). However, a significant portion of those with alcohol use disorders do not return to a chronically relapsing/remitting course after treatment (Delucchi and Weisner, 2010; Miller et al., 2001; Moos and Moos, 2006; Moos et al., 2006). Sustained abstinence and the chronic relapsing/remitting cycle in alcohol use disorders appear to result from a complex interplay among multiple biopsychosocial factors (Baler and Volkow, 2006; Bradizza et al., 2006; Donovan, 1996; Kalivas and Volkow, 2005; Moos and Moos, 2006; Walter et al., 2006; Witkiewitz and Marlatt, 2007). A considerable amount of research has addressed the potential neuropsychological, psychiatric, sociodemographic and behavioral factors associated with relapse in alcohol use disorders [e.g., (Bottlender and Soyka, 2005; Bradizza et al., 2006; Driessen et al., 2001; Glenn and Parsons, 1991; Kodl et al., 2008; McKay, 1999; Moos and Moos, 2006; Ritvo and Park, 2007; Rosenbloom et al., 2004; Vengeliene et al., 2008; Zywiak et al., 2006)]. However, the latent neurobiological factors that contribute to sustained abstinence and/or increased risk for relapse after treatment for alcohol use disorders are not well understood. A greater understanding of these neurobiological factors is necessary to identify the mechanisms associated with both sustained long-term abstinence and the relapse/remit cycle that afflicts so many with an alcohol use disorders.

Human in-vivo neuroimaging methods have facilitated study of the neurobiological correlates of relapse in alcohol use disorders (Fowler et al., 2007; Volkow et al., 2003; Volkow et al., 2004; Volkow et al., 2008) and encompass studies of brain blood flow, morphology and metabolites. In individuals studied at approximately 18 days of abstinence from alcohol, lower frontal cerebral blood flow was observed in those who relapsed relative to those who remained abstinent for approximately 2 months following treatment (Noel et al., 2002). Higher brain activation in the putamen, anterior cingulate, and medial prefrontal cortex was related to level of alcohol consumption in those who relapsed two months after treatment (Grusser et al., 2004). Higher BOLD response in the thalamus and striatum in response to affectively positive cues were inversely related to drinking days and overall alcohol intake in those who relapsed after treatment (Heinz et al., 2007). In our studies of treatment-seeking individuals with alcohol use disorders, assessed after one week and again after five weeks of abstinence (Durazzo et al., 2010a), we observed that those who relapsed within 12 months of treatment demonstrated lower frontal gray matter (GM) perfusion at both 1 and 5 weeks of abstinence compared to controls and participants that remained abstinent for at least 12 months. Controls and abstainers were equivalent on frontal GM perfusion at both assessment points. In treatment seeking alcoholics initially studied between one and 12 week of abstinence (Wrase et al., 2008), those who relapsed within 6 months following treatment demonstrated significantly lower amygdala volume compared to individuals who maintained sobriety over the same interval. In addition, relapsers demonstrated smaller hippocampal and ventral striatal volumes than controls, but were equivalent to abstainers on volumes in these regions. Abstainers exhibited a smaller ventral striatum than controls. In the treatment group, as a whole, smaller amygdala volume was correlated with greater alcohol craving, which appeared to be driven by the relapsers. In treatment-seeking alcoholics abstinent for 3–5 days, those who relapsed within 3 weeks of

study demonstrated lower concentrations of cerebellar N-acetylaspartate [NAA; a surrogate indicator of neuronal integrity (Moffett et al., 2007)] and choline-containing compounds [Cho; marker of cell membrane turnover and/or synthesis (Ross and Bluml, 2001)] at 3–5 days of abstinence relative to controls. No differences in cerebellar metabolite levels at 3–5 days of abstinence were observed between individuals who relapsed between 3 weeks and 3 months and controls. No group differences between were found for frontal white matter (WM) metabolite levels (Parks et al., 2002).

We previously combined measures from multimodality proton magnetic resonance (MR) studies, neurocognitive, psychiatric, and sociodemographic assessment to predict outcome following treatment for alcohol use disorders. Unipolar mood disorders and neurocognitive measures of processing speed, decreased levels of NAA in temporal GM and frontal WM as well as lower levels of frontal GM Cho were independent predictors of resumption of hazardous levels of alcohol consumption within 12-months following treatment (Durazzo et al., 2008). In a follow-up study (Durazzo et al., 2010b), we specifically assessed brain metabolite levels in multiple regions of the brain reward system (BRS), including the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), insula, superior corona radiata (SCR) and cerebellar vermis, in treatment-seeking alcohol dependent individuals at approximately 1-week-of-abstinence (baseline) and in non-smoking controls. Participants who resumed hazardous levels of alcohol consumption within 12 months of treatment demonstrated significantly lower baseline NAA concentrations than controls and abstainers in all regions. Relapsers also exhibited lower concentrations of creatine-containing compounds than abstainers in the DLPFC, SCR and cerebellar vermis. Abstainers did not differ from controls on metabolite concentrations in any region.

Taken together, the available neuroimaging literature suggests biochemical, metabolic and/or morphologic abnormalities in multiple components of the BRS in early recovery are associated with relapse after treatment for alcohol use disorders. Neurobiological abnormalities in the BRS are implicated as major contributors to the development and maintenance of all forms of substance use disorders (Bowirrat and Oscar-Berman, 2005; Kalivas and O'Brien, 2008; Kalivas and Volkow, 2005; Koob, 2003; Lubman et al., 2004; Makris et al., 2008b; Pierce and Kumaresan, 2006; Volkow et al., 2004; Volkow et al., 2008; Wrase et al., 2008). Major components of the BRS include, but are not limited to, the DLPFC, orbitofrontal cortex (OFC), insula, ACC, amygdala, hippocampus, thalamus, nucleus accumbens, ventral tegmental area, and other regions/nuclei in the ventral pallidum and basal forebrain (Kalivas and Volkow, 2005; Makris et al., 2008b; Volkow et al., 2008).

To our knowledge, there are no published reports concurrently examining neocortical surface area, thickness and volume in treatment-seeking alcohol dependent individuals. It is well established the layered neocortical cellular architecture demonstrates a modular/columnar organization that is oriented perpendicular to the cortical surface (Innocenti and Vercelli, 2010). Neocortical surface area is suggested to reflect the number and/or width of columns, while cortical thickness is related to the number or density of cells in a column (Rakic, 1988). Cortical thickness is associated with neurocognitive function in healthy controls (Choi et al., 2008; Dickerson et al., 2008; Walhovd et al., 2006) and cocaine users (Makris et al., 2008a). As cortical volume is the product of cortical surface area and thickness, examination of both metrics may provide more specific information on the consequences of alcohol use disorders on the cellular architecture of regional neocortical tissue (Hutton et al., 2009; Makris et al., 2008a; Panizzon et al., 2009).

The primary purpose of this study was to examine brain morphology in multiple components of the BRS in alcohol dependent individuals near the inception of outpatient treatment for alcohol use disorders (i.e., baseline) to determine if these measures distinguish those who

relapsed after treatment from those who remained abstinent over a 12-month period. Morphological assessment focused on measurements of regional neocortical surface area, thickness and volume. We predicted the alcohol dependent cohort, as a whole, would demonstrate lower baseline cortical thickness, smaller surface areas and volumes than non-smoking, light-drinking controls in the following neocortical components of the brain BRS: rostral and caudal ACC, insula, medial and lateral OFC, rostral and caudal middle frontal gyri and superior frontal gyri (the rostral and caudal middle frontal and superior frontal gyri comprise the bulk of the DLPFC). Based on our previous spectroscopic imaging findings in this cohort (Durazzo et al., 2010b), we predicted that those who resumed hazardous alcohol consumption following treatment demonstrate lower baseline cortical thickness, smaller surface areas and volumes than individuals who remained abstinent and controls in the above listed components of the BRS. We also predicted that lower cortical thickness surface areas and volumes in these BRS components are related to greater levels of alcohol consumption in those who relapsed after outpatient treatment.

METHODS

Participants

Seventy-five outpatient participants (4 females) were recruited from the VA Medical Center Substance Abuse Day Hospital and the Kaiser Permanente Chemical Dependence Recovery Program in San Francisco. Primary inclusion criteria for the alcohol dependent participants were fluency in English, DSM-IV diagnosis of alcohol dependence or alcohol abuse at the time of enrollment, consumption of greater than 150 standard alcohol-containing drinks (i.e., 13.6 grams of ethanol) per month for at least 8 years prior to enrollment for men, or consumption of greater than 80 drinks per month for at least 6 years prior to enrollment for women. Controls (n = 43; 4 females) were recruited from the local community. Participants were between 28 and 66 years of age. See Table 1 for group demographic data. All participants provided written informed consent prior to study according to the Declaration of Helsinki and the informed consent document and procedures were approved by the University of California San Francisco and the San Francisco VA Medical Center. Approximately 70% of participants in the current report were included in our earlier work (Durazzo et al., 2010a, and Durazzo et al., 2010b).

Medical exclusion criteria for all participants were history of any the following: dependence on any substance other than alcohol or nicotine in the 5 years immediately prior to enrollment, intravenous drug use in the 5 years immediately prior to enrollment in the study, current opioid agonist therapy, intrinsic cerebral masses, HIV/AIDS, cerebrovascular accident, brain aneurysm, arteriovenous malformations, peripheral vascular disease, myocardial infarction, uncontrolled chronic hypertension (systolic > 180 mmHg and/or diastolic > 120 mmHg), type I diabetes, moderate or severe chronic obstructive pulmonary disease, non-alcohol related seizures, significant exposure to known neurotoxins (e.g., toluene, carbon tetrachloride), demyelinating and neurodegenerative diseases, clinically documented Wernicke-Korsakoff syndrome, alcohol-induced persisting dementia, penetrating head trauma, and closed head injury resulting in loss of consciousness for more than 10 minutes. Psychiatric exclusion criteria were history of schizophrenia-spectrum disorders, bipolar disorder, dissociative disorders, post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, and major depression with mood-incongruent psychotic symptoms. Hepatitis C, type-2 diabetes, hypertension, unipolar mood disorder (major depression and/or substance-induced mood disorder) were permitted in the alcohol dependent cohort given their high prevalence in AUD (Hasin et al., 2007; Mertens et al., 2003; Mertens et al., 2005; Parekh and Klag, 2001; Stinson et al., 2005). Controls had no history of any DSM-IV Axis I Disorder. Participants were urine-tested for illicit substances

immediately before all assessments (i.e., cannabinoids, opiates, phencyclidine, cocaine, and amphetamines) and did not test positive for these substances at any assessment.

Baseline Assessment

Baseline clinical and MR procedures for the alcohol dependent participants were conducted 7 ± 3 days after last drink. All alcohol dependent individuals were actively involved in stabilization/early recovery outpatient treatment at the time of the baseline assessment, and duration of programs typically ranged from 14–28 days.

Clinical Measures—At the baseline assessment participants completed the Clinical Interview for DSM-IV Axis I Disorders, Version 2.0 (SCID-I/P (First *et al.*, 1998) and semi-structured interviews for lifetime alcohol consumption [Lifetime Drinking History; (Sobell and Sobell, 1992; Sobell et al., 1988)] and substance use (in-house questionnaire assessing substance type, and quantity and frequency of use)]. From the Lifetime Drinking History, average number of alcoholic drinks per month over 1 year prior to enrollment, average number of drinks per month over lifetime, lifetime years of regular drinking (i.e., years in which the participant consumed at least one alcoholic drink per month), age of onset and duration of heavy drinking (defined as drinking more than 100 drinks per month in males and 80 drinks per month in females) were calculated. Premorbid verbal intelligence was estimated with the American National Adult Reading Test (Grober and Sliwinski, 1991). Participants also completed standardized questionnaires assessing depressive [Beck Depression Inventory, BDI (Beck, 1978)], and anxiety symptomatology [(State-Trait Anxiety Inventory, form Y-2, STAI (Spielberger et al., 1977)], and nicotine dependence via the Fagerstrom Tolerance Test for Nicotine Dependence (FTND) (Fagerstrom et al., 1991). These measures were typically completed within one day of the magnetic resonance study described below.

Magnetic Resonance Acquisition and Analyses

Image Acquisition: At baseline, a volumetric magnetization-prepared rapid gradient echo (MPRAGE) was acquired with TR/TE/TI = 9.7/4/300 ms, 15° flip angle, 1×1 mm^2 in-plane resolution, and 1.5-mm-thick coronal partitions oriented perpendicular to the main long axes of bilateral hippocampi as seen on sagittal scout MRI. See Gazdzinski and colleagues (Gazdzinski et al., 2005) for detailed information on MR acquisition methods.

Image Processing: The publically available Freesurfer (v4.5) volumetric segmentation and cortical surface reconstruction methods (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2004; Fischl et al., 1999) were used to obtain regional measures of neocortical volumes (mm^3), surface area (mm^2), and thickness (mm). A normalized intensity image was created after correction for field inhomogeneities and the skull and other extrinsic, non-parenchymal tissue had been removed. The intensity normalized, skull-stripped image was then further processed by a segmentation procedure based on the geometric structure of the gray/white interface. The resulting volume was covered with a triangular tessellation and deformed to produce an accurate and smooth representation of the gray/white interface as well as the pial surface. Vertex-based cortical thickness measurements (see Figure 1) were obtained as the distance between the reconstructed surface representations of the gray-white interface and pial surfaces. The reconstructed cortical surface models for each participant were manually inspected to ensure segmentation accuracy. Each cortical surface was spatially normalized to a template cortical surface using a non-rigid high-dimensional spherical averaging method to align cortical folding patterns. Spatial normalization to the template cortical surface allowed to automatically parcellate the neocortical surfaces into 34 anatomical regions of interest (ROI; see Figure 2) per cortical hemisphere (Fischl et al., 2004). Average cortical thickness, surface area, and volume were obtained for all 34 bilateral neocortical ROIs. Volumes were

also obtained for the amygdala and hippocampus. Total BRS [i.e., rostral and caudal ACC, insula, medial and lateral OFC, rostral and caudal middle frontal gyri and superior frontal gyri cortical thickness, surface area, and volume (plus amygdala and hippocampus for volumes)] were calculated by summing the values for the respective morphological measures across the individual BRS ROIs for both hemispheres. Global cortical thickness, surface area, and volume regions were calculated by summing the values for the respective morphological measures across all 34 parcellated ROIs for both hemispheres.

Follow-up Assessment for Alcohol Dependent Cohort

Primary follow-up for the alcohol dependent participants occurred between 1 – 12 months after baseline studies. Forty-seven of 75 alcohol dependent participants were revaluated 237 ± 84 days after baseline assessment with all MR, psychiatric and behavioral measures administered at the baseline assessment. The Timeline Follow-Back Interview (Sobell and Sobell, 1992) was used to assess post treatment alcohol consumption, and the quantity/frequency of any other substance use was recorded. For the remaining 28 participants, follow-up assessment involved face-to-face and/or telephone contact with participants (n = 14), review of available medical records (confined to entries from mental health professionals providing outpatient substance abuse treatment for the participant; n = 11), and/or telephone interview of collateral sources (i.e., family or friends; n = 3).

Participants were designated as Abstainers (n = 24) if they met all the following criteria: a) self-reported no alcohol consumption between the baseline assessment and follow-up; b) there was no report of alcohol consumption between the baseline and follow-up in available medical records; and c) available laboratory indicators of alcohol consumption (e.g., gamma glutamyltransferase; GGT) were within normal limits at follow-up. Participants were designated as Relapsers (n = 51) if they met any of the following criteria: a) any self-reported alcohol consumption between the baseline assessment and follow up via telephone or in-person interview; b) alcohol consumption was indicated in medical records; c) report of alcohol use by a relative or close friend of the participant via telephone or in-person interview. To assist in characterizing the severity of the drinking episode(s) for Relapsers, we identified the number of participants who met Project MATCH criteria for an alcohol relapse (i.e., males: ≥ 3 consecutive days of consumption of ≥ 6 drinks per day; females: ≥ 3 consecutive days of consumption of ≥ 4 drinks per day). These criteria were applied only to those Relapsers who provided specific quantity/frequency information regarding their drinking episodes after the baseline assessment (see Table 2).

The 24 Abstainers were initially reassessed 223 ± 78 days and the 51 Relapsers 251 ± 97 days after the baseline assessment; the assessment interval was not statistically significant between groups. All 24 Abstainers were again successfully re-contacted in person or via telephone after the initial follow-up assessment, at different intervals, to obtain self-reports on their drinking status. At the longest follow-up interval, Abstainers self-reported 1028 ± 679 days (min = 365, max = 2508) of continuous sobriety following their baseline assessment. This information was verified by medical records and/or collateral sources when possible.

Data Analyses

Alcohol Dependent Cohort (ALC) and Controls—In this analysis, we compared Controls and the combined ALC cohort (i.e., Abstainers + Relapsers) to test our prediction that alcohol use disorders are associated with abnormalities of thickness, surface area and volume in neocortical components of the BRS. Group comparisons among Controls and ALC were conducted with multivariate analysis of covariance (MANCOVA), with intracranial volume and age as covariates. There was a trend (p = .10) for younger age in

Controls than ALC and age shows robust associations with regional neocortical volume (Pfefferbaum et al., 1998; Sullivan et al., 2004), surface area and thickness (Hutton et al., 2009; Im et al., 2008; Kochunov et al., 2010; Kochunov et al., 2007). Significant univariate tests ($p < .05$) for each ROI were followed-up with pairwise t-tests. For regional BRS thickness, surface area and volumes, alpha levels for pairwise t-tests were corrected for multiple comparisons according to the number of BRS ROIs [16 ROIs for regional neocortical thickness and surface area and 20 ROIs for regional volumes (i.e., 16 neocortical regions plus bilateral hippocampus and amygdala)] and the average intercorrelations among the BRS ROIs for all groups combined for each morphological measure (see Sankoh et al., 1997). Average intercorrelations among individual BRS regions and the corresponding adjusted alpha levels for pairwise t-tests were as follows: ($r = 0.49$, $p \leq .011$) for volumes, ($r = 0.45$, $p \leq .011$) for surface area and ($r = 0.40$, $p \leq .009$) for cortical thickness. Total BRS and global cortical thickness, surface area and volume for Controls and ALC were compared with a MANCOVA, with intracranial volume and age as covariates. BRS and global measures alpha levels for pairwise t-tests were corrected for multiplicity according to the number of total measures (i.e., 6) and the average intercorrelations among these measures ($r = 0.52$), yielding an adjusted $p \leq .022$. Effect sizes for pairwise comparisons were calculated via Cohen's *d* (Cohen, 1988).

Abstainers, Relapsers and Controls—Group comparisons between Abstainers, Relapsers and Controls on BRS neocortical thickness, surface area and volume were conducted with multivariate analysis of covariance (MANCOVA), with intracranial volume and age as covariates to test our hypothesis that the alcohol dependent participants differed in baseline BRS morphological measures as a function of relapse status. For each neocortical morphological measure, significant univariate tests ($p < .05$) for ROIs were followed-up with pairwise t-tests; alpha levels for these t-tests used the same corrected p-values for pairwise t-tests as described above in Controls vs. ALC. Alpha levels for pairwise t-tests were corrected for multiplicity as described for Controls vs. ALC ($p \leq .011$ for BRS volumes, $p \leq .011$ for BRS surface area and $p \leq .009$, BRS cortical thickness, $p \leq .022$ for total BRS and global neocortical measures). Effect sizes for pairwise comparisons were calculated via Cohen's *d* (Cohen, 1988).

Associations of Baseline Morphology with Pre-Treatment Alcohol and Cigarette Consumption in ALC and Post-Treatment Alcohol Consumption in Relapsers—Relationships between BRS ROI volume, surface area, cortical thickness and pre-treatment alcohol and cigarette consumption were examined in the ALC group with Spearman's rho. Post-treatment relapse severity variables for Relapsers (e.g., duration of relapse, number of drinks consumed during relapse) were examined with Spearman's rho. In order to identify any consistent patterns in these analyses, alpha levels ($p \leq .05$) for these correlations were not adjusted for multiplicity of tests. Analyses relating brain morphology to post-treatment alcohol consumption in Relapsers were confined to only those participants who provided detailed information regarding their post-treatment alcohol consumption ($n = 24$). All analyses were conducted with SPSS v17.

RESULTS

Demographic, Alcohol, and Cigarette Consumption Variables

Seventy-nine percent of the Controls and 74% of the alcohol dependent cohort were Caucasian. Of the 75 alcohol dependent participants, 24 (32%) were Abstainers and 51 (68%) were Relapsers. All treatment-seeking participants met DSM-IV criteria for alcohol dependence (with physiological dependence) at study enrollment. Ninety-six percent of Relapsers met Project MATCH criteria for an alcohol relapse. Abstainers and Relapsers

were not different on age, education, predicted premorbid verbal intelligence and the frequency of previous treatment for AUD (see Table 1). Abstainers and Relapsers were also equivalent on number of months of heavy drinking and years of regular drinking. Relapsers showed weak trends to consume more drinks per month over one year prior to enrollment ($p = 0.11$) and over lifetime than Abstainers ($p = 0.17$). The frequency of smokers was equivalent between Relapsers and Abstainers and they were not different cigarette consumption variables (see Table 1). Table 2 provides alcohol use characteristics for Relapsers between the baseline assessment and follow-up.

Comorbid Psychiatric, Medical, and Substance Use Disorders in ALC

Relapsers and Abstainers were equivalent on BDI and STAI scores and on the frequency of medical conditions (primarily hypertension and hepatitis C) and substance use disorders (see Table 1). Relapsers demonstrated a significantly higher frequency ($p < .001$) of comorbid psychiatric conditions (primarily major depression and substance-induced mood disorder with depressive features). Approximately 30% of participants diagnosed with a unipolar mood disorder were on antidepressant medication and approximately 60% percent of hypertensive participants took antihypertensive medications; there were no differences between Relapsers and Abstainers in frequency of use of these medications.

Baseline Morphology in the BRS

Neocortical Thickness

ALC and Controls: The MANCOVA indicated ALC and Controls were significantly different across individual BRS ROIs [$F (16, 99) = 3.04$, $p < .001$]. MANCOVA for total BRS and global thickness, surface area and volumes indicated significant differences between ALC and Controls [$F (6, 109) = 3.04$, $p < .001$]. Univariate tests were significant (all $p \leq .01$) for the following ROIs: Left rostral and right caudal ACC, left and right rostral middle frontal gyri, left caudal middle frontal gyrus, left and right superior frontal gyri, left and right insula, left and right medial OFC, left lateral OFC and global neocortical thickness. Age was a significant predictor ($p < .01$) for all regions except for the right and left caudal ACC, right insula and total BRS neocortical thickness. ICV was a significant predictor ($p < .05$) for the bilateral rostral ACC, right superior frontal gyrus, bilateral lateral OFC and for total BRS and global neocortical thickness. Pairwise comparisons indicated that the ALC demonstrated significantly lower volumes than Controls in all of the above regions and in total BRS and global neocortical thickness (see Table 3).

Abstainers, Relapsers and Controls: The MANCOVA indicated groups were significantly different across individual BRS ROIs [$F (28, 202) = 2.32$, $p < .001$]. MANOVA for total BRS and global thickness, surface area and volumes indicated significant differences among Abstainers, Relapsers and Controls [$F (6, 109) = 3.04$, $p < .001$]. Univariate tests indicated significant group differences (all $p \leq .02$) for the following ROIs: Right rostral ACC, left and right rostral middle frontal gyri, left and right caudal middle frontal gyri, left and right superior frontal gyri, left and right insula, right medial OFC, left and right lateral OFC as well as for total BRS and global neocortical thickness. Results from pairwise group comparisons are given in Table 3. In summary, compared to Controls, Relapsers demonstrated lower cortical thickness in 12 of 16 BRS ROIs and Abstainers showed lower thickness than Controls in 11 of 16 regions. Both Abstainers and Relapsers had significantly lower total BRS and global neocortical thickness than Controls. No significant differences in neocortical thickness were observed between Abstainers and Relapsers across individual BRS ROIs, but Relapsers showed trends ($p = .02$) for lower thickness in the left and right superior frontal gyrus and right lateral OFC than Abstainers. The above findings for comparisons between Abstainers and Relapsers remained unchanged after including alcohol

consumption variables, smoking status, psychiatric, substance abuse and medical comorbidities as covariates.

Neocortical Surface Area

ALC and Controls: MANCOVA indicated no significant group difference across individual BRS ROIs [F (16, 99) = 1.27, p = .23] and the univariate test for total BRS (p = .11) and global (p = .07) surface area were not significant. Age was a significant predictor for the left caudal ACC (p = .008). ICV was a significant predictor of all individual BRS regions, total BRS and global neocortical surface area (p < .001).

Abstainers, Relapsers and Controls: MANCOVA for group was significant for neocortical BRS surface area [F (32, 198) = 1.91, p = .019]; however, univariate tests were only significant (p < .05) for the right caudal ACC, right lateral OFC cortex and total BRS surface area. The univariate test for global surface area was not significant (p = .08). Results from pairwise comparisons indicated Relapsers demonstrated significantly lower surface area than Controls in the right caudal ACC and lower total BRS surface area than Controls and Abstainers (see Table 4). There were no significant differences between Abstainers and Controls in regional and total BRS surface area, and, in several regions, Abstainers had numerically higher values than Controls. The lower global neocortical surface area in Relapsers compared to Abstainers remained significant after including alcohol consumption variables, smoking status, psychiatric, substance abuse and medical comorbidities as covariates. No alcohol consumption variable or comorbid condition was a significant predictor of surface area in the BRS ROIs assessed.

Neocortical, Amygdala and Hippocampal Volumes

ALC and Controls: The omnibus MANCOVA for group was significant [F (16, 99) = 3.04, p < .001]. Univariate tests were significant (p < .05) in the following ROIs: Left rostral and right caudal ACC, left and right rostral middle frontal gyri, left caudal middle frontal gyrus, left and right superior frontal gyri, left and right insula, left and right medial OFC, left and right lateral OFC, left and right amygdala, left and right hippocampus and total BRS and global neocortical volume. Age was a significant predictor (p < .01) for total BRS volume, global volume and all individual BRS regions except ACC subregions, the insula, amygdala and hippocampus, bilaterally. ICV was a significant predictor (p < .001) of all individual BRS regions and total BRS and global volume. Pairwise comparisons indicated ALC showed lower volumes than Controls in all of the foregoing BRS components as well as for total BRS and global volume (see Table 5).

Abstainers, Relapsers and Controls: The MANCOVA for group was significant [F (28, 202) = 2.37, p < .001]. Univariate tests indicated significant group differences (p < .05) in the following ROIs: Left rostral and right caudal ACC, left and right rostral middle frontal gyri, left and right caudal middle frontal gyri, left and right superior frontal gyri, left and right insula, left and right medial OFC, left and right lateral OFC, left and right amygdala, left and right hippocampus and total BRS and global volume. No significant group differences were observed for total intracranial volume. Results from pairwise comparisons are given in Table 5. Compared to Controls, Relapsers demonstrated lower volumes in 17 of 20 reward system regions, while Abstainers showed lower volumes than Controls in the bilateral superior frontal cortex, insula, amygdalae and hippocampi. Both Relapsers and Abstainers showed lower total BRS and global volume than Controls. Relapsers exhibited significantly smaller volumes than Abstainers in the right rostral middle and right caudal middle frontal gyri, the left and right lateral orbitofrontal cortex and Relapsers showed trends (p < .05) for lower volumes than Abstainers in the left and right superior frontal gyri. Relapsers had lower total BRS volume than Abstainers, but Relapsers and Abstainers were

not significantly different on global neocortical volumes. The observed regional volume differences between Relapsers and Abstainers remained significant after including alcohol consumption variables, smoking status, psychiatric, substance abuse and medical comorbidities as covariates. No alcohol consumption variable or comorbid condition was a significant predictor of volume in any region.

The above results for BRS thickness, surface area and volume were virtually identical if the neocortical measures were scaled to the individual's ICV rather than entering ICV as a covariate in the models.

Associations of Baseline Morphology, Pre-Treatment Alcohol and Cigarette Use in Alcohol Dependent Participants—There were no significant bivariate associations between regional and global measures for volumes, surface area, thickness and pre-treatment alcohol and cigarette use duration and consumption levels after controlling for age.

Associations of Baseline Morphology with Post-Treatment Alcohol Consumption in Relapsers—The most consistent patterns observed were associations between lower volumes and surface areas in multiple BRS ROIs and lower total BRS volume and global neocortical volume with a greater total number of drinks consumed post-treatment in Relapsers. The magnitudes of significant correlations were moderate to strong (rho = |0.41–0.64|; see Table 6). Global neocortical surface area was not significantly associated with any post-treatment alcohol consumption variable. No significant relationships were observed between regional BRS, total BRS and global neocortical thickness and post-treatment alcohol consumption in Relapsers.

DISCUSSION

In this sample of predominately Caucasian male, treatment seeking, alcohol dependent individuals, the primary findings were as follows: 1) The ALC cohort (i.e., Relapsers + Abstainers) demonstrated significantly lower neocortical thickness in 12 of 16 individual BRS regions than Controls as well as lower total BRS and global thickness. The same pattern of lower thickness was evident in both Abstainers and Relapsers relative to Controls. There were no statistically significant differences between Relapsers and Abstainers on neocortical thickness in any ROI. 2) There were no significant differences in surface area measures between the ALC cohort and Controls; however, Relapsers exhibited significantly lower total BRS surface area than Controls and Abstainers. Relapsers and Abstainers were not significantly different on global surface area. Abstainers and Controls were not significantly different on any surface area in any ROI or global measure. 3) ALC showed significantly lower volumes than Controls in most BRS regions as well as total BRS and global volumes. Relapsers demonstrated smaller volumes than Controls in neocortical 17 of 20 ROIs as well as total BRS and global volume, while Abstainers showed smaller volumes than Controls in the bilateral superior frontal cortex, insula, amygdalae and hippocampi and total BRS and global volume. Relapsers had significantly smaller total BRS volume and smaller volumes than Abstainers in the bilateral OFC and the right rostral and right caudal middle frontal gyri, but Relapsers and Abstainers were not significantly different on global volume. 4) After controlling for age, there were no significant relationships in the alcohol dependent cohort between regional measures of brain morphology and *pre*-treatment measures of alcohol and cigarette consumption. 5) In Relapsers, several measures of regional baseline surface area and volume showed moderate-to-strong relationships with *post*-treatment alcohol consumption variables.

The alcohol dependent participants in this study demonstrated distinct patterns for regional and total volume, surface area, and thickness in the BRS. The volume differences between Controls, the alcohol dependent group, as a whole, and in terms of relapse status, were primarily driven by markedly lower global cortical thickness across ROIs in the alcohol dependent participants. The alcohol dependent group, as a whole, was not significantly different than Controls on regional, total and global BRS surface area; this finding was driven by the Abstainers who were not significantly different than Controls on any surface area measure, while Relapsers had lower total BRS surface area than Abstainers and lower total BRS and global surface area than both Controls and Abstainers.

Neocortical thickness is decreased in neurodegenerative diseases (Tosun et al., 2010) and cocaine dependence (Makris et al., 2008a), but there are no previous reports on neocortical thickness and surface area in alcohol use disorders. In a MRI-based study, Makris and colleagues (Makris et al., 2008b) observed smaller global BRS volume in long-term abstinent alcoholics (5.9 ± 10.4 years of sobriety) relative to controls, with the most pronounced volume reductions in alcoholics apparent in the left amygdala, right DLPFC, insula and nucleus accumbens. Wrase and colleagues (Wrase et al., 2008) observed lower volumes in alcohol dependent individuals abstinent for 16 ± 23 days in the amygdala, ventral striatum and hippocampus than controls. The authors reported relapsers showed lower baseline volumes than controls in all three regions, but abstainers demonstrated lower volumes than controls only in the ventral striatum. Relapsers also showed lower amygdala volumes than abstainers. Alcohol and cigarette consumption variables were not related to amygdala, hippocampal or ventral striatum volume in the alcohol dependent group. In the present study, the ALC group and both Abstainers and Relapsers showed significantly lower amygdala and hippocampal volumes than Controls and there were no significant differences between Abstainers and Relapsers in these regions. Similar to Wrase et al., 2008, pre-enrollment alcohol and cigarette consumption were not related to volumes, thickness and surface area of the regions assessed. However, baseline amygdala and hippocampal volumes in Relapsers were robustly related to post-treatment alcohol consumption. In our previous spectroscopic imaging (Durazzo et al., 2010b) and perfusion (Durazzo et al., 2010a) studies, we observed that Relapsers demonstrated lower baseline NAA in the DLPFC and lower frontal GM perfusion than both Controls and Abstainers. Abstainers did not differ from Controls on baseline metabolite or perfusion levels in any ROI, which is generally congruent with the pattern of findings for regional surface area and volumes in this report.

AUD-associated changes in neocortical neuronal and/or glial morphology may result in alterations of GM surface area and/or thickness. Correspondingly, GM volume would be influenced if surface area and/or thickness were altered. Several post mortem neuropathological studies in AUD report neuronal loss in superior frontal neocortical regions [see (Harper, 2009) for review], reduced glial cell density and size in the DLPFC (Miguel-Hidalgo et al., 2002), and lower neuronal and glial cell density in the OFC (Miguel-Hidalgo et al., 2006). Other neuropathological studies of AUD, however, found no abnormalities in neocortical neuronal cell volumes, neuronal and glial cell numbers or lobar and global neocortical surface area, thickness and volume (Fabricius et al., 2007; Jensen and Pakkenberg, 1993). In this alcohol dependent cohort, pre-treatment medical and psychiatric comorbidities, alcohol and cigarette consumption were not associated with any of the MR-based morphologic measures in BRS components or global measures. Therefore, the potential mechanisms contributing to the variability in regional surface areas, thickness and corresponding volumes observed in the alcohol dependent participants are unclear and likely involve genetic, comorbid and/or environmental factors not evaluated in this research.

Although Relapsers demonstrated significantly lower total BRS volumes and surface area than Abstainers, these groups were not significantly different on global neocortical volume

or surface area. This suggests measures of volume and surface area in the BRS may better distinguish Abstainers and Relapsers compared to global neocortical measures. Within the BRS, the greatest morphological differences between Abstainers and Relapsers were apparent in left and right lateral OFC, where Relapsers demonstrated significantly smaller surface area and volume. Intact OFC functions are critical for adaptive and flexible inhibitory decision-making processes. Neurobiological abnormalities in the OFC have been linked to emotional and behavior disturbances that may confer risk for the relapse/remit cycle commonly observed in all substance use disorders (Baler and Volkow, 2006; Kalivas and O'Brien, 2008; Kalivas and Volkow, 2005). Specifically, the OFC is involved in emotion-related learning and regulation of internal affective and drive states (Dom et al., 2005 14230; Rolls, 2004). The OFC is proposed to be principally involved in the representation of the reinforcing, affective and goal values of a stimulus (Rolls and Grabenhorst, 2008), which is critical for self-modification of behavior in accordance with changes in reinforcement contingencies (Dom et al., 2005; Rolls and Grabenhorst, 2008; Spinella, 2002). Behavioral manifestations of OFC injury/dysfunction include impulsivity/disinhibition, inaccurate interpretation of social and emotional cues from others and inappropriate expression of emotional and internal drive states in complex social contexts. Some distinctions have been made between the functions subserved by the medial and lateral regions of the OFC (Rolls and Grabenhorst, 2008), but it is unclear if there is any regional functional specificity within the OFC in alcohol use disorders.

While the mechanisms contributing to the regional and global morphology exhibited by Abstainers and Relapsers are unclear, there are distinct functional implications for baseline surface area, thickness and volume measured in the BRS for these alcohol dependent cohorts. Overall, the morphological findings in Abstainers and Relapsers suggest that the clinical syndrome of alcohol dependence in this cohort is primarily associated with significantly thinner neocortex in components of the BRS as well as for the global neocortex; this may represent a premorbid condition and serve as a proxy measure for increased risk for the development of AUD. These assertions are supported by the significantly lower neocortical thickness across the majority of BRS ROIs, the lower total BRS and global thickness in both Abstainers and Relapsers relative to Controls and the lack of associations of regional and global morphologic measures with comorbid psychiatric, substance use, medical conditions and pre-treatment alcohol and cigarette consumption in the alcohol dependent cohort. Additionally, Abstainers reported an average of 3 years (1028 ± 679 days) of continuous sobriety following outpatient treatment at long-term follow-up despite demonstrating significantly lower baseline neocortical thickness in 11 of 16 ROIs and lower total BRS and global thickness than Controls. With respect to surface area measures, results suggest that the surface areas of components of the BRS in this cohort may not be exclusively mediated by the clinical syndrome of alcohol dependence. Specifically, Relapsers exhibited lower total BRS surfaces area than Abstainers and Controls, whereas Abstainers and Controls were not significantly different on any surface area measure. With respect to volumes, the differences between Abstainers and Controls were driven by lower cortical thickness in Abstainers. Additionally, BRS volume and surface area measures in Relapsers demonstrated moderate to strong relationships with the magnitude of their post-treatment alcohol consumption, while no associations between baseline cortical thickness measures and severity of relapse were observed. Taken together, this suggests that both neocortical surface area and volume in the BRS ROIs investigated may serve as proxy markers for risk of relapse and/or predict the level of severity of an episode of relapse in this cohort. However, it must be noted that approximately 60% of the alcohol dependent participants had at least one previous treatment and it is unknown if the Abstainers and Relapsers evidenced the same regional morphological pattern observed in this report at the times of their previous treatments.

Limitations of this study include the reliance on self-report and/or medical records for the determination of drinking status at follow-up for some participants, the inability to examine for sex effects due to the small number of female participants, and the modest number of participants in the Abstainer group. We did not examine the influence of coping skills, stress response, self-esteem/self-efficacy, social support, neurocognition and personality disorders, neurocognitive variables, or gene polymorphisms reported to predict relapse after treatment for AUD [e.g., (Bradizza et al., 2006; Krampe et al., 2006; Miller et al., 1996; Sinha and Li, 2007; Teichner et al., 2001; Walter et al., 2006; Wojnar et al., 2009)]. It is highly likely that the magnitude and chronicity of alcohol consumption before and after treatment in our alcohol dependent cohort was influenced not only by the integrity of their brain morphology, but also by genetic or other premorbid and environmental factors not assessed in this phase of our research.

The results from this morphological study, combined with our previous neuroimaging findings in this cohort, suggest Relapsers demonstrate significant adverse neurobiological changes in multiple nodes of the BRS. Taken together, our MR studies with this cohort suggest Relapsers experience dysfunction in regions involved in the “top down” regulation/modulation of internal drive states, emotions, reward processing and reward-related behavior (Baler and Volkow, 2006; Kalivas and Volkow, 2005; Paulus, 2007; Redish et al., 2008; Rolls and Grabenhorst, 2008; Sinha and Li, 2007), which may impart increased risk for the relapse/remit cycle that afflicts many with AUD. The clinical relevance of the morphological abnormalities is suggested by the associations of baseline surface areas and volumes in multiple components of the BRS with measures of *post*-treatment alcohol consumption in Relapsers. Results also highlight the importance of examining both cortical thickness and surface area to better understand the nature of regional volume loss frequently observed in AUD. It is well documented that sustained abstinence from alcohol is associated with neocortical volume increases in those with AUD. Longitudinal studies examining both surface area and cortical thickness may clarify the nature of abstinence related volume changes. Additionally, longitudinal assessment over periods of sustained abstinence, combined with potential genetic markers of vulnerability [e.g., (Wojnar et al., 2009)] will further assist in identifying premorbid factors that may influence the risk of relapse in AUD.

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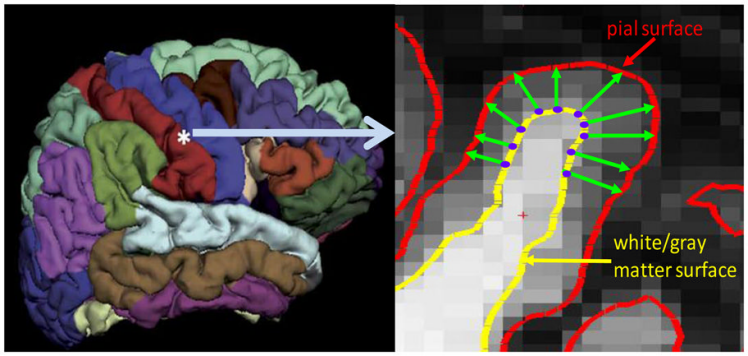

Figure 1.
Freesurfer parcellation of neocortical regions of interest.

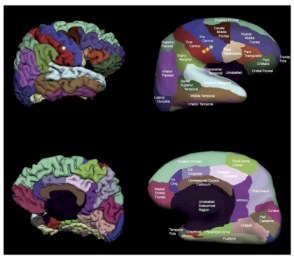

Figure 2.
Cross-sectional representation of neocortical thickness from a Freesurfer anatomical parcel. Pial surface represent outer boundary of neocortical gray matter.

Table 1

Baseline group demographic, alcohol and cigarette consumption, mood and anxiety self-report measures

Variable	Controls (n = 43)	Abstainers (n= 24)	Relapsers (n = 51)
Age	47.3 (7.9)	51.0 (12.1)	49.6 (7.7)
Education	16.3 (2.5)	14.6 (2.3)	13.7 (2.0)
Caucasian (%)	79	71	77
AMNART	118 (7)	115 (9)	114 (9)
1-year ave drinks/month	13 (14)	333 (162)	399 (167)
Lifetime ave drinks/month	17 (15)	198 (120)	247 (152)
Months of heavy drinking	NA	236 (110)	270 (114)
Lifetime years of regular drinking	29 (8)	36 (10)	35 (9)
Smokers (%)	0	50	59
FTND total	NA	5.6 (1.2)	5.0 (2.3)
Smoking duration	NA	23 (13)	23 (11)
Cigarette pack years	NA	25 (18)	26 (20)
Beck Depression Inventory	4 (4)	12 (9)	16 (10)
STAI-trait	38 (7)	45 (11)	49 (12)
Comorbid psychiatric disorder (%)	NA	24	50
Comorbid medical condition (%)	NA	56	54
Comorbid substance abuse disorder (%)	NA	16	21
Body mass index	25.9 (3.1)	27.5 (5.5)	27.1 (6.5)
History of previous treatment for AUD (%)	NA	63	55
Number of previous treatment attempts	NA	1.4 (1.7)	1.8 (1.8)

Note. AMNART: American National Adult Reading Test. FTND: Fagerstrom Test for Nicotine Dependence. NA: not applicable. STAI: State-Trait Anxiety Inventory. Mean (standard deviation).

Table 2

Post-treatment Alcohol consumption characteristics of Relapsers

Variable	mean (SD)	minimum	maximum
Duration of abstinence (days):	126 (77)	2	337
Duration of drinking episode(s) (days)	87 (104)	3	226
Drinks per day during drinking episode(s)	13 (8)	3	24
Total drinks during drinking episode(s)	860 (939)	9	3504
Percent meeting Project MATCH relapse Criteria	96		

Note. Duration of abstinence: number of consecutive abstinent days from Baseline assessment to first drink; Duration of drinking episode(s): total number of days where at least one alcoholic beverage was consumed.

Table 3

Baseline Regional Cortical Thickness[@]

Region	Sub-region	Controls (n = 43)	ALC (n = 75)	Abstainers (n= 24)	Relapsers (n = 51)	Effect Size			
						ALC vs. Controls	Abstainers vs. Controls	Relapsers vs. Controls	Relapsers vs. Abstainers
ACC	L rostral	2.97 (0.21)	2.89 (0.20)	2.87 (0.20)	2.90 (0.22)	0.36	0.48	0.34	0.19
	R rostral	2.96 (0.22)	2.81 (0.20)[a]	2.81 (0.22)[b]	2.82 (0.21)[c]	0.71	0.68	0.68	0.05
	L caudal	2.67 (0.26)	2.61 (0.25)	2.61 (0.28)	2.62 (0.26)	0.24	0.22	0.19	0.03
	R caudal	2.50 (0.20)	2.48 (0.20)	2.45 (0.20)	2.49 (0.21)	0.10	0.25	0.05	0.19
Frontal	L rostral middle	2.39 (0.11)	2.29 (0.11)[a]	2.27 (0.10)[b]	2.29 (0.12)[c]	0.91	1.14	0.87	0.18
	R rostral middle	2.43 (0.11)	2.30 (0.11)[a]	2.30 (0.12)[b]	2.30 (0.11)[c]	1.18	1.13	1.18	0.00
	L caudal middle	2.46 (0.13)	2.38 (0.12)[a]	2.37 (0.13)[b]	2.40 (0.12)[c]	0.64	0.80	0.48	0.24
	R caudal middle	2.47 (0.13)	2.36 (0.12)[a]	2.39 (0.12)	2.35 (0.12)[c]	0.88	0.64	0.96	0.08
	L superior	2.71 (0.12)	2.59 (0.11)[a]	2.62 (0.12)[b]	2.56 (0.12)[c]	1.04	0.75	1.25	0.50
	R superior	2.69 (0.13)	2.56 (0.12)[a]	2.60 (0.12)[b]	2.54 (0.12)[c]	1.04	0.72	1.20	0.50
Insula	L	3.04 (0.16)	2.91 (0.15)[a]	2.89 (0.17)[b]	2.92 (0.16)[c]	0.82	0.90	0.75	0.18
	R	3.11 (0.16)	2.96 (0.15)[a]	2.95 (0.17)[b]	2.96 (0.16)[c]	0.98	0.97	0.93	0.06
OFC	L medial	2.52 (0.18)	2.48 (0.16)	2.49 (0.17)	2.48 (0.15)	0.23	0.18	0.24	0.06
	R medial	2.51 (0.15)	2.40 (0.16)[a]	2.40 (0.16)[b]	2.41 (0.17)[c]	0.71	0.71	0.63	0.06
	L lateral	2.72 (0.13)	2.56 (0.12)[a]	2.56 (0.13)[b]	2.55 (0.13)[c]	1.28	1.23	1.23	0.00
	R lateral	2.69 (0.13)	2.59 (0.12)[a]	2.61 (0.13)[b]	2.54 (0.12)[c]	0.80	0.62	1.20	0.56
Total BRS Cortical Thickness		37.43 (1.28)	35.93 (1.23)[a]	35.74 (1.27)[b]	36.03 (1.26) [c]	1.19	1.32	1.10	0.22
Global Cortical Thickness		171.00 (5.68)	163.92 (5.66)[a]	164.15 (5.68)[b]	163.80 (5.66)[c]	1.25	1.01	1.40	0.16

Note.

[@]mean (standard deviation) adjusted for age and intracranial volume in mm.

[a]ALC < Controls, p ≤ .009.

[b]Abstainers < Controls, p ≤ .009.

[c] Relapsers < Controls, p ≤ .009.

ACC: anterior cingulate cortex. ALC: alcohol dependent cohort (Abstainers + Relapsers). L: left; OFC: orbitofrontal cortex. R: right.

Table 4

Baseline Regional Surface Area[@]

Region	Sub-region	Controls (n = 43)	ALC (n = 75)	Abstainers (n= 24)	Relapsers (n = 51)	Effect Size			
						ALC vs. Controls	Abstainers vs. Controls	Relapsers vs. Controls	Relapsers vs. Abstainers
ACC	L rostral	724 (118)	697 (118)	715 (117)	688 (121)	0.22	0.08	0.30	0.23
	R rostral	552 (116)	552 (114)	553 (116)	551 (115)	0.00	0.01	0.02	0.03
	L caudal	662 (130)	674 (128)	645 (129)	683 (129)	0.10	0.16	0.19	0.29
	R caudal	808 (131)	749 (129)	774 (132)	737 (130)[a]	0.45	0.25	0.54	0.28
Frontal	L rostral middle	5836 (701)	5669 (700)	5864 (700)	5577 (696)	0.24	0.26	0.37	0.41
	R rostral middle	6032 (826)	5917 (821)	6195 (823)	5788 (814)	0.12	0.19	0.30	0.50
	L caudal middle	2507 (459)	2428 (450)	2476 (457)	2405 (456)	0.17	0.07	0.22	0.16
	R caudal middle	2216 (380)	2289 (372)	2369 (377)	2251 (371)	0.19	0.40	0.09	0.32
	L superior	7509 (643)	7257 (675)	7328 (676)	7225 (671)	0.38	0.27	0.43	0.15
	R superior	7371 (643)	7156 (640)	7279 (636)	7098 (635)	0.34	0.14	0.43	0.28
Insula	L	2279 (390)	2140 (389)	2270 (394)	2213 (392)	0.35	0.02	0.17	0.15
	R	2221 (388)	2186 (388)	2202 (391)	2171 (390)	0.09	0.05	0.13	0.08
OFC	L medial	1610 (177)	1577 (175)	1612 (176)	1546 (176)	0.19	0.02	0.36	0.36
	R medial	1778 (196)	1758 (193)	1776 (195)	1749 (192)	0.11	0.01	0.15	0.14
	L lateral	2602 (230)	2623 (233)	2704 (230)	2585 (229)	0.09	0.44	0.07	0.52
	R lateral	2507 (210)	2509 (208)	2646 (205)	2444 (207)	0.01	0.66	0.30	0.98
Total BRS Surface Area		46907 (2793)	46018 (2875)	47156 (2816)	45487 (2699)[a,b]	0.31	0.09	0.52	0.61
Global Cortical Surface Area		1.54×10^5 (6.23^3)	1.52×10^5 (6.21^3)	1.53×10^5 (6.69^3)	1.51×10^5 (6.66^3)[a]	0.36	0.14	0.46	0.32

Note.

[@]mean (standard deviation) adjusted for age and intracranial volume in mm^2.

[a]Relapsers < Controls, $p < .01$.

[b]Relapsers < Abstainers, $p < .01$.

ACC: anterior cingulate cortex. ALC: alcohol dependent cohort (Abstainers + Relapsers). L: left; OFC: orbitofrontal cortex; R: right.

Table 5

Baseline Regional Volume[@]

Region	Sub-region	Controls (n = 43)	ALC (n = 75)	Abstainers (n= 24)	Relapsers (n = 51)	Effect Size			
						ALC vs. Controls	Abstainers vs. Controls	Relapsers vs. Controls	Relapsers vs. Abstainers
ACC	L rostral	2497 (413)	2282 (412)[a]	2391 (417)	2272 (415)[c]	0.52	0.25	0.54	0.28
	R rostral	1866 (351)	1756 (412)	1872 (357)	1749 (358)	0.28	0.02	0.33	0.34
	L caudal	1888 (422)	1801 (425)	1763 (436)	1805 (429)	0.21	0.29	0.20	0.09
	R caudal	2259 (414)	2008 (415)[a]	2099 (394)	1968 (421)[c]	0.61	0.39	0.70	0.32
Frontal	L rostral middle	15384 (2028)	14167 (2171)[a]	14643 (2047)	13890 (2035)[c]	0.58	0.36	0.74	0.37
	R rostral middle	16205 (2203)	14990 (2210)[a]	15662 (2228)	14409 (2035)[c]	0.55	0.24	0.85	0.59
	L caudal middle	6566 (1205)	5955 (1201)[a]	6096 (1254)	5860 (1206)[c]	0.51	0.38	0.59	0.19
	R caudal middle	5857 (913)	5667 (907)	5964 (921)	5549 (935)[d]	0.21	0.11	0.33	0.45
	L superior	22462 (1925)	20428 (1931)[a]	20994 (1944)[b]	20233 (1935)[c]	1.06	0.76	1.16	0.39
	R superior	21644 (2028)	19730 (2036)[a]	20321 (2047)[b]	19531 (2035)[c]	0.94	0.65	1.04	0.39
Insula	L	6602 (499)	6161 (493)[a]	6221 (509)[b]	6149 (499)[c]	0.88	0.76	0.91	0.14
	R	6572 (479)	6130 (476)[a]	6178 (490)[b]	6107 (542)[c]	0.92	0.81	0.91	0.16
OFC	L medial	4620 (544)	4313 (536)[a]	4352 (544)	4294 (548)[c]	0.57	0.47	0.60	0.10
	R medial	4996 (570)	4682 (563)[a]	4747 (568)	4651 (585)[c]	0.55	0.42	0.60	0.17
	L lateral	7551 (645)	7172[a] (445)	7481 (658)	7027 (642)[c, d]	0.70	0.10	0.81	0.70
	R lateral	7269 (622)	6966 (611)[a]	7246 (612)	6834 (607)[c, d]	0.49	0.04	0.71	0.68
Amyg	L	1604 (130)	1500 (127)[a]	1457 (130)[b]	1520 (129)[c]	0.81	1.13	0.65	0.48
	R	1652 (130)	1556 (131)[a]	1520 (129)[b]	1564 (136)[c]	0.74	1.02	0.66	0.33
Hippo	L	4351 (382)	4099 (375)[a]	4093 (377)[b]	4120 (378)[c]	0.67	0.68	0.61	0.07
	R	4447 (381)	4122 (377)[a]	4068 (377)[b]	4140 (376)[c]	0.86	1.00	0.81	0.19
Total BRS Volume		1.35×10^5 (8.31×10^3)	1.24×10^5 (8.30×10^3)[a]	1.28×10^5 (8.34×10^3)[b]	1.22×10^5 (8.32×10^3)[c, d]	1.32	0.84	1.56	0.64
Global Cortical Volume		4.32×10^5 (2.14×10^4)	4.02×10^5 (2.15×10^4)[a]	4.08×10^5 (2.14×10^4)[b]	3.98×10^5 (2.13×10^4)[c]	1.40	1.10	1.57	0.47

Region	Sub-region	Controls (n = 43)	ALC (n = 75)	Abstainers (n= 24)	Relapsers (n = 51)	Effect Size			
						ALC vs. Controls	Abstainers vs. Controls	Relapsers vs. Controls	Relapsers vs. Abstainers
ICV		1.60×10^6 (1.59×10^5)	1.59×10^6 (1.50×10^5)	1.59×10^6 (1.59×10^5)	1.58×10^6 (1.39×10^5)	<.01	<.01	<.01	<.01

Note.

[@] mean (standard deviation) adjusted for age and intracranial volume in mm^3.

[a] ALC < Controls.

[b] Abstainer < Controls, p ≤ .011.

[c] Relapsers < Controls p ≤ .011.

[d] Relapsers < Abstainer, p ≤ .011.

ACC: anterior cingulate cortex. ALC: alcohol dependent cohort. Amyg: amygdala. Hippo: Hippocampus. ICV: intracranial volume; L: left. OFC: orbitofrontal cortex. R: right

Table 6

Relationships between baseline volumes, surface area and post-treatment measures of alcohol consumption in Relapsers (n = 24)

Region	Sub-region	Total Number of Drinks		Average Number of Drinks/Day		Duration of Relapse		Duration of Abstinence	
		Volume	Surface Area	Volume	Surface Area	Volume	Surface Area	Volume	Surface Area
ACC	L rostral	−0.31	−0.20	−0.29	−0.19	−0.16	−0.09	0.07	0.10
	R rostral	−0.07	−0.14	−0.30	−0.13	0.09	−0.16	0.21	−0.16
	L caudal	−0.28	−0.26	−0.28	−0.19	−0.34	−0.29	0.09	−0.01
	R caudal	−0.01	0.14	−0.43*	−0.13	−0.13	−0.03	0.08	0.11
Frontal	L rostral middle	−0.43*	−0.25	−0.03	−0.11	−0.36	−0.23	0.09	0.01
	R rostral middle	−0.27	−0.06	0.11	−0.01	−0.30	−0.16	0.02	0.01
	L caudal middle	−0.41*	−0.27	−0.18	−0.21	−0.28	−0.23	0.22	0.17
	R caudal middle	−0.39	−0.27	−0.20	−0.28	−0.29	−0.16	0.13	0.17
	L superior	−0.49*	−0.41*	−0.08	−0.20	−0.47*	−0.41*	0.03	0.12
	R superior	−0.61**	−0.44*	0.06	−0.09	−0.55**	−0.44*	0.13	0.09
Insula	L	−0.59**	−0.48*	−0.01	0.11	−0.53**	−0.54**	0.25	0.22
	R	−0.64**	−0.54**	−0.08	−0.01	−0.53**	−0.48*	0.15	0.07
OFC	L medial	−0.35	−0.37	−0.07	−0.05	−0.47*	−0.41*	0.24	0.04
	R medial	−0.48*	−0.37	−0.01	−0.16	−0.40	−0.41*	0.13	−0.02
	L lateral	−0.49*	−0.51*	−0.01	−0.08	−0.47*	−0.43*	0.24	0.21
	R lateral	−0.52**	−0.39	−0.17	−0.07	−0.46*	−0.42*	0.44*	0.17
Amyg	L	−0.58**	NA	−0.01	NA	−0.56**	NA	0.11	NA
	R	−0.34	NA	0.10	NA	−0.41*	NA	0.26	NA
Hippo	L	−0.47*	NA	0.17	NA	−0.56**	NA	0.19	NA
	R	−0.40	NA	0.02	NA	−0.46*	NA	0.13	NA
Total BRS		−0.60**	−0.41*	0.01	−0.12	−0.56**	−0.37	0.18	0.04
Global Cortical		−0.55**	−0.36	−0.01	−0.09	−0.51*	−0.34	0.20	0.08

Note.

* $p < .05$ (2-tailed);

** $p < .01$;

ACC: anterior cingulate cortex; Amyg: Amygdala; Duration of abstinence: number of consecutive days of abstinent from Baseline assessment to first drink; Hippo: hippocampus; L: left; NA = Not available; OFC: orbitofrontal cortex; R: right.