Published in final edited form as:
Alcohol. 2008 March ; 42(2): 67–76. doi:10.1016/j.alcohol.2008.01.002.

Are Treated Alcoholics Representative Of The Entire Population With Alcohol Use Disorders? - A Magnetic Resonance Study of Brain Injury

Stefan Gazdzinski[a], **Timothy C. Durazzo**[a,b], **Michael W. Weiner**[a,b,c,d], and **Dieter J. Meyerhoff**[a,b]

a*Center for Imaging of Neurodegenerative Diseases (CIND), San Francisco, CA, USA*

b*Department of Radiology and Biomedical Imaging University of California, San Francisco, CA, USA*

c*Department of Psychiatry University of California, San Francisco, CA, USA*

d*Department of Medicine University of California, San Francisco, CA, USA*

Abstract

Almost all we know about neurobiological brain injury in alcohol use disorders has been derived from convenience samples of treated alcoholics. Recent research has demonstrated more comorbid conditions, poorer psychosocial functioning, and higher dependence levels in treated alcoholics than in their treatment-naïve counterparts. Thus, it is not clear whether neuroimaging results from convenience samples of treated alcoholics can be generalized to the entire population with alcohol use disorders. We compared 35 treated alcoholics at one week of abstinence (ALC) and 32 treatment-naïve heavy drinkers (HD) on regional brain volumes and metabolite concentrations obtained by in-vivo magnetic resonance at 1.5 Tesla to evaluate for potential group differences. Then, we evaluated whether comorbid cigarette smoking and common demographic and clinical variables mediated any existing neurobiological group differences. ALC demonstrated smaller lobar gray matter volumes and thalami than HD, exacerbated by chronic smoking. Furthermore, concentrations of N-acetyl-aspartate (NAA, an accepted marker of neuronal viability), choline-containing metabolites (involved in membrane turnover), and myo-Inositol (a putative marker of glial cells and osmolyte) were lower in multiple brain regions of ALC compared to HD. The lower NAA concentrations in white matter of ALC vs. HD were explained by average number of drinks per month over the year preceding study. However, the other group differences were not explained by common drinking, demographic, and clinical variables (used as covariates at the same time) or by excluding participants with comorbid mood disorders. Taken together, this suggests that the degree of brain atrophy, as well as neuronal and membrane injury in clinical samples of alcoholics cannot be generalized to the much larger population with alcohol use disorders that does not seek treatment.

Keywords

alcohol use disorder; treatment; structural MRI; MR spectroscopy; brain

Corresponding Author: Stefan Gazdzinski, Ph.D., Center for Imaging of Neurodegenerative Diseases (CIND), 4150 Clement Street (114M), San Francisco, CA 94121, USA, Phone: (415) 221-4810 ext 2553, FAX (415) 668-2864, Email: stefan.gazdzinski@ucsf.edu.

Introduction

Most neuroimaging research investigating the neurobiological consequences of alcohol use disorders (AUD - alcohol abuse or alcohol dependence) have studied convenience samples of individuals in their forties and fifties who were treated for AUD. From the estimated 27 million Americans exhibiting an AUD at some time during their lives only about 15% ever received any treatment (Cohen et al., 2007) and recent epidemiological studies provide views of AUD-related consequences in the general population that are very different from those in clinical samples (e.g., NESARC, USDHHS, Alcohol Research & Health, Volume 29, Number 2, 2006). In fact, mean age of onset of AUD in the U.S. population is about 22 years; 72% of this population had only one 2-5 years long episode of alcohol abuse or dependence followed by spontaneous remission (Hasin et al., 2007). Although help-seeking for alcohol related problems is often associated with negative life-events (Tucker et al., 2004), individuals with AUD who seek/receive treatment have greater dysfunction in intimate relationship and vocational functioning (Tucker et al., 2004), higher prevalence of psychiatric comorbidities, such as major depressive disorder, post-traumatic stress disorder (PTSD), schizophrenia spectrum disorders, or antisocial personality disorder than their treatment-naïve counterparts (Fein et al., 2002; Moss et al., 2007), they report more emotional problems and less engagement in everyday activities (work, family, entertainment) and more severe dependence (Kaskutas et al., 1997; Lloyd et al., 2004; Lukassen and Beaudet, 2005; Tucker et al., 2004). Finally, Fein and colleagues (Fein and Landman, 2005) demonstrated that treated alcoholics drink significantly more and have more periods of abstinence than their treatment-naïve counterparts, despite similar drinking patterns earlier in life before they met criteria for heavy drinking (women, 80 drinks per month; men, 100 drinks per month).

The foregoing suggests that treated and treatment naïve alcoholics may not simply represent a continuum of AUD. Thus, it is not clear whether the neurobiological abnormalities observed in treated individuals with AUD can be generalized to the much larger treatment-naïve population with AUD.

Magnetic resonance imaging (MRI) studies with treated cohorts consistently demonstrated widespread morphological abnormalities involving sulcal widening, and volume loss in neocortical gray matter (GM), white matter (WM), thalami, and cerebellar vermis (see (Sullivan, 2000 for review). Proton magnetic resonance spectroscopy studies of treated alcoholics demonstrated lower concentrations of N-acetyl-aspartate (NAA; a marker of neuronal viability) and of choline-containing compounds (Cho; involved in cell membrane breakdown and synthesis) relative to healthy controls, primarily in the frontal lobes and cerebellar vermis (Bendszus et al., 2001; Fein et al., 1994; Jagannathan et al., 1996; Parks et al., 2002; Seitz et al., 1999), as well as higher concentrations of thalamic myo-inositol (m-Ino; a putative marker of glial cells and osmolyte)(Schweinsburg et al., 2000).

Additionally, recent research indicates that cigarette smoking, which is highly prevalent among individuals with AUD (e.g., Daeppen et al., 2000; John et al., 2003; Romberger and Grant, 2004), is associated with regionally specific biological brain injury. Smokers show regional gray matter volume reductions (Brody et al., 2004; Gallinat et al., 2006), reduced NAA in medial temporal lobe (Gallinat et al., 2007), greater generalized atrophy with older age (e.g., Hayee et al., 2003) as well as global cerebral blood flow deficits (e.g., Rourke et al., 1997). We demonstrated in treated alcohol dependent individuals that chronic cigarette smoking had detrimental effects on regional neocortical gray matter (GM) volumes, regional concentrations of NAA and Cho in multiple brain regions, and frontal and parietal cerebral blood flow (reviewed in Durazzo et al., 2007b). Chronic cigarette smoking was also found to compound regional neocortical GM volume loss in treatment-naïve heavy drinkers (HD)(Durazzo et al., 2007a). Lastly, neurocognition was found to be adversely affected by chronic smoking in both

alcoholic and non-alcoholic samples (Durazzo et al., 2006b; Friend et al., 2005; Glass et al., 2005).

Our magnetic resonance (MR) studies of treatment-naïve HD, who were about a decade younger than samples of treated alcoholics generally reported in the literature, suggest lower magnitudes of brain structural and metabolite abnormalities than those reported in treated alcoholics. Compared to light-drinking controls, HD had smaller GM volumes, but no significant WM volume deficits (Cardenas et al., 2005; Fein et al., 2002), lower NAA concentrations in frontal WM and higher Cho, Cr, and m-Ino concentrations in parietal GM (Meyerhoff et al., 2004). These findings suggest frontal axonal injury and possibly gliosis or a chronically altered osmolytic state in HD.

This report focuses on a retrospective comparison of regional brain volumes and metabolite concentrations between two convenience samples of treated alcohol dependent individuals abstinent from alcohol for one week (ALC)(Durazzo et al., 2004; Gazdzinski et al., 2005b) and actively drinking HD (Cardenas et al., 2005; Meyerhoff et al., 2004). To the best of our knowledge, no direct comparisons of these neuroimaging measures between HD and ALC have been reported. Both groups were compared to non-smoking light drinking controls (nsLD) derived from the control groups of the cited studies to facilitate interpretation of the results. We hypothesized that ALC demonstrate smaller volumes of lobar GM, WM, and thalami than HD, ALC manifest lower lobar NAA and Cho concentrations than HD, and that concurrent chronic cigarette smoking in both ALC and HD exacerbates regional GM volume losses and metabolite abnormalities. In follow-up analyses, we evaluated whether these differences were mediated by a combination of demographic and clinical variables.

Materials and Methods

Participants

We used a cohort of community dwelling, HIV-seronegative HD from a study of the effects of HIV and AUD on the central nervous system (Cardenas et al., 2005; Meyerhoff et al., 2004), and a cohort of treated abstinent alcoholics (ALC) from an ongoing study assessing the effects of alcohol dependence and abstinence on brain structure, metabolite concentrations, and function (Durazzo et al., 2004; Durazzo et al., 2006a; Durazzo et al., 2006b; Gazdzinski et al., 2005a; Gazdzinski et al., 2005b). ALC had been recruited from the San Francisco VA Medical Center Substance Abuse Day Hospital (SADH) and the San Francisco Kaiser Permanente Chemical Dependence Recovery Programs serving San Francisco Bay Area community, whereas HD and nsLD had been recruited from the same community via advertisements.

Given the older age of the entire ALC cohort vs. the entire HD cohort, to minimize the effects of accelerated brain injury in alcoholics with aging on our analyses (Pfefferbaum et al., 1992), and to minimize potential gender effects on differences in alcohol induced brain injury (e.g., Hommer et al., 2001), we equated our ALC and HD groups on age and gender. From both larger cohorts described above, we included 35 ALC, 45.9±8.3 years of age [20 smokers (sALC) and 15 non-smokers (nsALC)], 32 HD, 42.4±8.9 years of age [14 smokers (sHD) and 18 non-smokers (nsHD)] and 38 age-matched non-smoking light drinkers (nsLD, 45.4±8.1). Nine ALC did not contribute to previous reports, whereas all HD were used in previous manuscripts. At the time of MR study, HD generally reported abstaining from drinking alcohol for at least 12 hours and did not manifest any gross signs of withdrawal (Meyerhoff et al., 2004). ALC were studied 6±3 days after their last alcoholic drink; they were screened daily for alcohol and drug use in their treatment programs and screened again prior to study procedures (via Breathalyzer and urine drug test).

The inclusion and exclusion criteria for ALC are fully described in Durazzo et al. (2004) and for HD in Cardenas et al. (2005). In short, ALC met DSM-IV criteria for alcohol dependence ALC consumed more than 150 standard alcoholic drinks per month (80 for women) for at least 8 years prior to enrollment into the study. A standard drink contains 13.6 grams of pure ethanol, equivalent of 12 oz. beer, 5 oz. wine, or 1.5 oz. liquor. Classification as a HD required average consumption of at least 100 (80 for women) standard alcoholic drinks per month for a minimum of 3 years prior to enrollment and active alcohol consumption at time of study. Twenty-two HD participants were alcohol dependent; ten HD met DSM-IV criteria for alcohol abuse - they were included because some research (Li et al., 2007; Saha et al., 2006) suggests that abuse and dependence form a continuum of alcoholism severity rather than two distinct conditions and because our own analyses showed no differences in metabolite concentrations between these two subgroups (Meyerhoff et al., 2004). Also the HD group measures did not change significantly when these ten alcohol abusing HD were removed from analyses. nsLD consumed less than 45 drinks per month over lifetime and had no history of alcohol abuse or dependence and not more than two successive months of alcohol consumption greater than 100 drinks/month. Alcohol consumption over lifetime in all groups was assessed via the Lifetime Drinking History (Skinner and Sheu, 1982; Sobell and Sobell, 1992; Sobell et al., 1988).

For sALC, nicotine dependence and smoking behavior were assessed with the Fagerstom Tolerance Test for Nicotine Dependence (FTND, Fagerstrom et al., 1991). All sALC were active, daily smokers. Ten nsALC never smoked, whereas five nsALC quit smoking more than three years prior to enrollment. For HD, smoking frequency was obtained with an in-house self-report questionnaire that covered six months prior to enrollment. HD were considered smokers if they reported smoking daily or nearly everyday. Sixteen nsHD reported no consumption of any tobacco product, whereas two nsHD reported smoking about once a month.

All participants were free of general medical, neurological, and psychiatric conditions, except unipolar mood disorders, hypertension, and hepatitis C in ALC and HD. In particular, none of the participants suffered from PTSD. Unipolar mood disorders and anxiety disorders were not exclusionary due to their high reported incidence among individuals with AUD (e.g., Gilman and Abraham, 2001; Grant et al., 2004; Huang et al., 2006) and chronic cigarette smokers (e.g., Fergusson et al., 2003; Paperwalla et al., 2004).

Participants completed structured clinical interviews as previously described (Durazzo et al., 2004) and their medical records were reviewed. Five sALC and three nsALC met DSM-IV criteria for substance-induced (alcohol) mood disorder with depressive features. Two sALC and one nsALC were diagnosed with recurrent major depression, one nsALC with major depression in partial remission and another sALC with recurrent major depression in early full remission; two nsALC and five sALC took antidepressants at the time of study. One sHD and one nsHD had single depressive episodes in full remission, whereas another sHD had recurrent major depression in full remission.

Participants were excluded if they met DSM-IV criteria for dependence on any other substance than alcohol or nicotine in the six months prior to enrollment for HD and within five years for ALC. None of the nsLD reported abuse or dependence on any substance. Standard liver and blood panels were completed within one day of the MR study to assesse hepatocellular injury and red blood cell status. Serum prealbumin assessed the nutritional status in ALC (Weinrebe et al., 2002) but was not obtained for HD. ALC participants' prealbumin levels were within normal limits. A contiguous family history density score (FHD) was calculated for each participant; FHD weights the alcoholism status of parents and grandparents by their genetic relatedness to the participant (Miranda et al., 2003; Stoltenberg et al., 1998) and predicts alcohol related problems (Grant, 1998). The American National Adult Reading Test (Grober and Sliwinski, 1991) estimated premorbid verbal intelligence and Beck Depression Inventory

(BDI; Beck, 1978) assessed current depressive symptomatology. BDI for ALC was obtained at one month of sobriety (not at the time of MRI study) to minimize the effects of acute withdrawal on this measure. Anxiety symptomatology in ALC was assessed with State-Trait Anxiety Inventory, Y-2 (STAI Y-2; Spielberger et al., 1977) and with modified STAI Y-2 in HD. One sALC had anxiety disorder and one nsHD had panic disorder. The Institutional Review Boards of the University of California San Francisco and the San Francisco VA Medical Center approved all procedures, and written informed consent was obtained from all participants prior to study.

Data Acquisition and Processing

All MR data were obtained on a standard 1.5T MR system (Siemens Vision, Iselin, NJ). Structural MRI data were acquired with standard sequences: 1) a double-spin echo sequence with $TR/TE_1/TE_2$ = 5000/20/80 ms, 1×1 mm^2 in-plane resolution and 3 mm slice thickness, no slice gap, oriented along the orbito-meatal angle +5 °, yielded proton density and T_2-weighted MR images and 2) magnetization-prepared rapid gradient echo images acquired with ms, 15° flip angle, 1×1mm^2 in-plane resolution, and 1.5-mm-thick coronal partitions oriented orthogonal to the long axes of hippocampi as seen on a sagittal scout MR image, yielded T_1-w images. MRI was followed by automated head shimming and multislice short-TE MRSI (TR/TE/TI = 1800/25/165 ms) (Schuff et al., 1999). Spectra were acquired in three parallel planes, each 15 mm thick, and 6 mm apart, angulated parallel to the double-spin echo slices. They covered the major cerebral lobes, thalamus, subortical nuclei, midbrain, and cerebellar vermis.

For structural analyses, probability maps of GM, WM, and CSF within major lobes, subcortical nuclei, brainstem, and cerebellum were obtained from T_1-w images by combining three-tissue probabilistic segmentation and masks of major lobes, subcortical nuclei, brainstem, and cerebellum, as previously described (Cardenas et al., 2005). To account for individual variation in head size, absolute volumes of labeled structures were divided by intracranial volume. Processing details for spectroscopic data were described in (Meyerhoff et al., 2004; Schuff et al., 2001). The final outcome measures were tissue-specific, atrophy corrected, absolute mean metabolite concentrations expressed in institutional units; they were not reported in molar units to avoid possibly inaccurate assumptions about relaxation times.

Experienced neuroradiologists examined all images for evidence of any cerebrovascular disease or structural abnormalities. All participants with early confluent or confluent areas of white matter signal hyperintensities were excluded from the analyses. The volumes of white matter signal hyperintensities in remaining participants were estimated to be less than 1% of the individual's total-lobar WM volume (Gazdzinski et al., 2005b).

Study Design and Statistical Analyses

We performed three analyses implemented with SPSS-12.0 for Windows (SPSS; Chicago, IL) and SPLUS 6.0 (Insightful Corp., 2001). Validity of all models was verified graphically and analytically. In particular, we assured that there were no thresholds in associations of MR measures with demographic and clinical variables within the combined ALC and HD group.

Analysis 1—This analysis assessed for differences between ALC, HD, and nsLD in regional brain volumes as well as atrophy corrected concentrations of NAA, Cho, Cr, and m-Ino with one-way multivariate analyses of variance (MANOVA; Wilks' Lambda), separately for GM and WM tissues. The use of MANOVA accounted for the inter-correlations between outcome measures and controlled for family-wise error rates across assessed regions. Age was not used as a covariate, because groups were matched on this parameter and age did not generally predict metabolite concentrations in nsLD (unpublished results). Follow-up t-tests comparing ALC,

HD and nsLD for a given region (e.g., frontal GM) were corrected for multiple comparisons using the conservative Bonferroni method. The volumes of thalami, caudate, lenticular nuclei,, brainstem, and cerebellum as well as metabolite concentrations in these regions were evaluated separately with univariate analysis of variance (ANOVA), as some individuals' data from these regions were excluded for quality reasons. Excluded data were roughly equally distributed across the groups. To control for family-wise error rate, the individual ANOVA significance levels were adjusted for the five structures of interest (adjusted alpha = 0.01). Significant ANOVA's were further evaluated with follow-up pairwise t-tests and corrected for multiple comparisons using the Bonferroni method.

Analysis 2—used 2×2 MANOVAs in families of regions described above to assess simultaneously the effects of smoking and treatment status (i.e., ALC or HD) as well as their interactions on regional brain volumes and metabolites.

Analysis 3—This analysis assessed whether any differences in volumetric and metabolite measures between ALC and HD, observed in Analyses 1 and 2, were mediated by measures of drinking severity and demographic and clinical variables. They utilized one-way multivariate analyses of covariance (MANCOVA) for metabolites, and (smoking status) × (treatment status) MANCOVA for regional brain volumes. For clarity, we only report the contrasts between ALC and HD as percent difference and significance levels (p).

As over-fitted models are likely to produce spurious results and because the recommended number of observations per predictor (factor or covariate) should be more than ten (Babyak, 2004), we did not include all possible covariates and their interactions in the models. Instead, we limited the set of covariates in our analyses to factors that correlated with the MR outcome at $p<0.20$ and were different in ALC vs. HD at $p<0.20$. Additionally, to reduce the number of covariates, among highly intercorrelated predictors, such as different measures of drinking severity, we selected only one predictor that showed the strongest association with our outcome measures.. Based on these criteria, we simultaneously entered age, education, average number of drinks per month in the year preceding the study, and alanine aminotransferase (ALT, marker of liver injury) as factors and used them simultaneously in our main analyses. No interactions between covariates were included in the model. FHD and number of months of drinking at levels exceeding 100 drinks per month were not included in the models as the former correlated with average number of drinks per month in the year preceding the study ($r=0.53$, $p=0.001$), but not with our outcome MR measures ($r>-0.13$, $p>0.29$), whereas the latter correlated with age ($r=0.52$, $p=0.001$).

In additional analyses, we expanded the set of covariates to include BDI, FHD, hematocrit, white blood cells count (wbc), months of drinking at levels exceeding 100 drinks per month, and total lifetime alcohol consumption (a cumulative measure of alcohol consumption). Given the higher number of predictors in these additional models, they were susceptible to overfitting (and thus more likely to produce spurious results), so their results were used only to explore if additional covariates affected the patterns of findings. We did not correct for multiple comparisons in order to minimize the chance of failing to identify potential variables that mediate differences between ALC and HD.

Results

Demographics

Table 1 lists alcohol measures and other demographic and clinical variables. ALC, HD, and nsLD were matched on age ($p=0.19$), and all groups were equivalent on years of formal education ($p=0.43$), AMNART ($p=0.12$), and intracranial volume ($p=0.22$).

Compared to HD, ALC consumed 56% and 48% more monthly drinks over one year and three years prior to enrollment, respectively, and consumed 27% more alcohol over lifetime (all $p<0.001$). The HD and ALC groups did not differ on age of onset of heavy drinking ($p=0.93$), defined as consuming more than 100 drinks/month; however, ALC drank at these levels significantly longer than HD ($p=0.03$). ALC with mood disorders did not differ on age or measures of drinking and smoking severity from the ALC without mood disorders. ALC had significantly higher FHD of alcoholism than both HD and nsLD (both $p<0.001$), with no significant differences between smokers and non-smokers within ALC and HD groups. sALC were daily smokers with medium to high level of nicotine dependence (FTND=5.1±2.1), who smoked 18.2±8.2 cigarettes per day for 17.6±12.9 years, resulting in 18.3±16.3 pack-years. Ten sHD reported smoking daily, four nearly every day, which suggested generally lower smoking severity in sHD as a group than in sALC. Aspartate aminotransferase (AST, a marker of liver injury) was elevated among both ALC and HD; alanine aminotransferase (ALT), albumin and blood panel measures in both groups were in the normal range.

Analysis 1 - Effects of group membership on neuroimaging measures

This analysis tests the hypothesis that ALC had smaller volumes of lobar GM, WM and thalami than HD, and that their lobar NAA and Cho concentrations were lower than in HD. Comparisons were also made with corresponding measures in nsLD.

Regional volumes—MANOVAs comparing ALC, HD, and nsLD were significant for neocortical GM ([$F(8,198)=3.6$, $p=0.003$] and CSF [$F(10, 196)=3.07$, $p=0.001$], and ANOVAs were significant for GM and CSF in frontal, parietal, temporal, and occipital lobes [all $F(2,102)>6.19$, $p<0.003$], but not for ventricular CSF [$F(2,102)=1.24$, $p=0.29$]. The follow-up analyses revealed ALC demonstrated 4-9% smaller GM volumes in frontal, parietal, temporal, and occipital lobes than HD (all $p<0.03$) and 6-11% smaller GM volumes than nsLD (all $p<0.001$), consistent with our primary hypotheses. The 2-4% smaller GM volumes in HD relative to nsLD were not statistically significant ($p>0.30$), but they were numerically equivalent to our previous reports that demonstrated significantly smaller GM volumes in a larger (Cardenas et al., 2005) or different sample of HD (Fein et al., 2002). Frontal and temporal sulcal CSF volumes in ALC were 15-17% larger than in HD (both $p<0.002$) and sulcal CSF in all major lobes were 20-25% larger compared to nsLD ($p<0.001$). Although ventricular CSF was 6% larger in ALC compared to HD and 18% larger than in nsLD, these differences were not statistically significant. The MANOVA for WM regions was not significant [$F(8,198)=0.92$, $p=0.39$]. The numerically smaller frontal WM volume in ALC vs. nsLD (-4%) was consistent with our preliminary report (Gazdzinski et al., 2005b). Finally, the ANOVA for thalamic volumes was significant [$F(2,88)=5.66$, $p=0.005$], with thalamic volumes in ALC 8% smaller than in HD and nsLD (both $p<0.04$).

Regional NAA—MANOVA comparing NAA concentrations between ALC, HD, and nsLD was significant for GM regions [$F(8,198)=2.74$, $p=0.014$], with follow-up ANOVAs significant for parietal and temporal GM NAA [$F(2,102)>3.47$, $p<0.04$]. ALC had 7% lower NAA in parietal GM than in HD ($p=0.03$); NAA in temporal GM was 11% lower in ALC than HD ($p=0.001$) and 9% lower than nsLD ($p=0.01$).

MANOVA comparing NAA concentrations in WM regions approached statistical significance [$F(8,198)=1.93$, $p=0.057$] and the follow-up ANOVAs were significant for frontal and parietal WM [$F(2,102)>3.77$, $p<0.03$]. Among WM regions, only parietal WM NAA was 14% lower in ALC than HD ($p=0.03$). Frontal WM NAA (7%, $p=0.01$) and parietal WM NAA (19%, $p=0.002$) were lower in ALC than nsLD. HD did not differ significantly from nsLD on regional NAA. However, frontal WM NAA in HD was numerically lower than in nsLD, consistent with

a 5% statistically significant difference reported in a larger group of HD comprising individuals of this study (Meyerhoff et al., 2004).

Regional Cho—MANOVAs comparing concentrations of Cho-containing compounds between ALC, HD, and nsLD were significant for GM [$F(8,198)=3.65$, $p=0.002$] and WM [$F(8,198)=2.57$, $p=0.011$]. Follow-up ANOVAs were significant for parietal and temporal GM Cho [$F(2,102)>3.08$, $p<0.05$] and for frontal and parietal WM Cho [$F(2,102)>6.07$, $p<0.002$]. Cho in ALC versus HD was 11% lower in parietal GM ($p=0.002$), 9% lower in temporal GM ($p=0.05$), and 13% lower in parietal WM ($p=0.007$). Compared to nsLD, ALC had lower Cho in frontal and parietal WM (13%, $p=0.001$, and 15%, $p=0.001$, respectively). ANOVA for lenticular nucleus Cho was significant [$F(2,98)=5.86$, $p=0.004$], with ALC exhibiting 10% lower Cho than nsLD ($p=0.02$). Parietal GM Cho in HD was numerically lower than in nsLD (-4%), consistent with our previous significant findings in a larger sample (Meyerhoff et al., 2004).

Regional m-Ino—MANOVAs comparing concentrations of m-Ino between ALC, HD, and nsLD were significant for GM [$F(8,198)=3.34$, $p=0.004$] and WM [$F(8,198)=2.50$, $p=0.02$]. ANOVAs were significant for parietal GM and parietal WM [$F(2,102)>6.32$, $p<0.003$]. ALC showed 10% lower parietal GM ($p=0.005$) and 11% lower parietal WM m-Ino concentrations relative to HD ($p=0.002$). HD had 9% higher m-Ino in parietal GM compared to nsLD ($p=0.01$).

Regional Cr—MANOVAs comparing concentrations of Cr between ALC, HD, and nsLD were significant in GM [$F(8,198)=4.04$, $p=0.001$], but not in WM. Follow-up ANOVAs were significant for temporal and parietal GM [$F(2,102)>4.00$, $p<0.02$]. Temporal GM Cr in ALC was 11% lower than HD ($p=0.02$) and parietal GM Cr was 7% lower than nsLD ($p=0.02$).

Analysis 2 -Effects of chronic cigarette smoking on regional brain measures

This analysis evaluated our hypothesis that concurrent chronic cigarette smoking in both ALC and HD exacerbates regional GM volume losses and regional metabolite abnormalities.

Regional volumes—The 2 (smoking status) × 2 (treatment status) MANOVA comparing GM volumes between ALC and HD yielded a significant smoking effect [$F(3,60)=3.06$, $p=0.023$]. Smoking ALC and HD demonstrated 5-6% smaller parietal, temporal, and occipital GM volumes relative to their corresponding non-smoking counterparts (all $p<0.04$). In WM regions, no main effects or interactions were apparent (all $p>0.29$). This is generally consistent with our smoking-related results reported in a smaller sample of ALC (Gazdzinski et al., 2005b), a larger sample of HD (Durazzo et al., 2007a), and with the results of Analysis 1 reported above.

Regional metabolites—Smoking effects were not significant for any region [$F(3,61)<1.14$, $p>0.35$]. However, interactions between smoking status and treatment status were significant for NAA, Cr, and m-Ino concentrations in WM [all $F(4,60)>3.78$, $p<0.008$]. These interactions reflected generally larger WM metabolite differences between sALC and nsALC than between sHD and nsHD. In follow-up analyses, sALC typically demonstrated non-significantly lower regional NAA and Cho concentrations compared to both nsALC and nsLD, generally consistent with our earlier results from a smaller cohort comprising the individuals of this study Durazzo et al., 2004). Thus, the lack of regional metabolite differences between sHD and nsHD may reflect the lesser smoking severity in sHD compared to sALC.

Analysis 3 -Effects of demographic and clinical variables and comorbid conditions on the observed differences between ALC and HD

When age, education, average number of drinks per months in the year preceding the study, and ALT were simultaneously used as covariates, treatment status effect for lobar GM volumes was associated with 4% smaller parietal GM volumes in ALC than in HD ($p=0.05$), whereas smoking was associated with 4-6% smaller volumes of parietal, temporal, and occipital GM volumes than non-smoking ($p<0.05$). The differences of metabolite concentrations between ALC and HD remained significant in the presence of the foregoing covariates. In particular, ALC compared to HD demonstrated 8% lower parietal GM NAA ($p=0.02$), 8-15% lower Cho in parietal and temporal GM and in frontal, parietal, and temporal WM (all $p<0.03$), 6-13% lower m-Ino in GM and WM of frontal, temporal, and parietal lobes ($p<0.05$), and 6-10% lower Cr in parietal GM, temporal GM, and frontal WM ($p<0.04$). However, the higher one-year average number of drinks per month in ALC accounted for the differences between ALC and HD in regional WM NAA. Use of the larger set of covariates that also included BDI, FHD, hematocrit, wbc, months of drinking at levels exceeding 100 drinks per month, and total lifetime alcohol consumption, or exclusion of all participants with comorbid unipolar mood disorders, past drug abuse/dependence, or hepatitis C did not significantly affect the reported neurobiological differences between ALC and HD.

Discussion

This study describes differences in markers of neurobiological brain injury between treated (ALC) and treatment-naïve individuals (HD) with AUD. ALC demonstrated greater abnormalities than HD in the form of smaller neocortical GM and thalamic volumes, as well as lower NAA in parietal lobe and temporal GM, consistent with greater regional neuronal injury in ALC versus HD. ALC also demonstrated lower Cho, Cr, and m-Ino concentrations in parietal and temporal lobes than HD, which suggests differences in cell membrane synthesis/turnover and glial function between these groups, an osmotic abnormality in HD due to current alcohol consumption (Ende et al., 2006; Meyerhoff et al., 2004), or some acute effects of non-overt alcohol withdrawal. Smoking exacerbated GM volume losses in both ALC and HD and metabolite abnormalities within the ALC cohort, which confirms previous reports on smaller samples included in these analyses (Durazzo et al., 2007a; Durazzo et al., 2004; Gazdzinski et al., 2005b).

While the one-year average number of drinks per month explained the greater axonal injury in WM in ALC compared to HD, the smaller GM volumes in ALC, the greater neuronal dysfunction, and the differences in cell membrane synthesis/turnover and glial function in ALC relative to HD could not be explained by group differences in age, education, average number of drinks per months in the year preceding the study, and ALT, or by other measures of drinking severity, FHD of alcohol-related problems, and other clinical variables. The observed group differences were also not significantly affected by the presence of common comorbid neuropsychiatric and medical conditions alone (unipolar mood disorders, past drug abuse/dependence, or hepatitis C) in the respective groups. Taken together, this suggests that the greater neurobiologic abnormalities in ALC compared to HD is mediated by other factors not considered in this study. Such factors may include repeated withdrawals in ALC (Crews et al., 2004), subclinical thiamine deficiency (Harper, 1998), subclinical levels of anxiety and antisocial personality characteristics (Fein et al., 2006; Grant et al., 2004; Pridmore et al., 2005), levels of cigarette consumption (Durazzo and Meyerhoff, 2007), and drinking patterns [binge vs. continuous; drinking period interruptions etc.(Fein and Landman, 2005)], as well as distinct genetic predispositions and gene- environment interactions (e.g. Whitfield et al., 2004). These factors could render ALC more susceptible to alcohol induced brain injury than HD. Finally, the brain volumetric and metabolite differences could have been influenced by

potential unrecorded group differences in nutrition, exercise, overall physical health, and previous exposure to environmental cigarette smoke. Our data do not seem to support the possibility that maternal alcohol consumption during pregnancy and associated prenatal brain injury significantly contributed to observed differences between ALC and HD, as the intracranial volume (a measure potentially sensitive to maternal alcohol consumption during pregnancy (e.g., Fein and Di Sclafani, 2004) as well as education and premorbid intelligence [generally accepted measures of cognitive reserve in aging studies (Valenzuela and Sachdev, 2006)] did not differ between ALC and HD.

The limitations of this study include a moderate sample size and lack of important parameters such as severity of chronic cigarette smoking in the HD group. They precluded comprehensive assessment of the relationships of demographic and clinical variables and their interactions with our neuroimaging measures. Additionally, as cigarette smoking is associated with more alcohol consumption, we cannot exclude the possibility that potentially more tobacco consumption in ALC vs. HD explains the observed differences in brain injury. Furthermore, the small proportion of female participants did not allow assessment of sex effects. As HD recruitment used more relaxed inclusion criteria regarding the use of illicit substances than ALC recruitment, the differences in the degree of brain injury from substance use between these groups could be underestimated. Additionally, ALC were examined after one week of alcohol abstinence, during which some recovery from brain injury may have occurred and lead to an underestimation of volume and/or metabolite differences between ALC and HD. Finally, ALC participants were predominantly veterans of the U.S. Armed Forces, just as many participants of previous neuroimaging reports, and thus were possibly not representative of the entire population receiving alcoholism treatment. However, despite these limitations, the study adds unique information on neurobiological injuries in different cohorts with AUD.

Conclusions

This study demonstrated more brain injury in treated alcoholics than in their age-matched treatment naïve counterparts that could not be explained by the differences in drinking severity and other demographic and clinical variables commonly recorded in clinical samples, as well as FHD of alcohol related problems. All this puts into question the common practice of extrapolating information on the neurobiological injury in clinical samples of treated alcoholics to the entire population with AUD.

Our inability to identify factors explaining the differences in brain injury between ALC and HD might suggest that individual susceptibility to alcohol induced brain damage, in interaction with drinking severity, may explain our findings. Greater brain injury in treated alcoholics may underlie poorer psychosocial functioning of these individuals that in turn may render them more likely to continue drinking.

Finally, our results also call for more studies on neurobiology and function in treatment-naïve individuals dwelling in the community as they represent the vast majority of individuals with AUD.

Acknowledgements

Supported by AA10788 (DJM) and AA11493 (MWW) and the Veterans Affairs Research Service.

References

Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. Psychosom. Med 2004;66:411–421. [PubMed: 15184705]

Beck, AT. Depression Inventory. Center for Cognitive Therapy; Philadelphia: 1978.

Bendszus M, Weijers HG, Wiesbeck G, Warmuth-Metz M, Bartsch AJ, Engels S, Boning J, Solymosi L. Sequential MR imaging and proton MR spectroscopy in patients who underwent recent detoxification for chronic alcoholism: correlation with clinical and neuropsychological data. AJNR Am. J. Neuroradiol 2001;22:1926–1932. [PubMed: 11733327]

Brody AL, Mandelkern MA, Jarvik ME, Lee GS, Smith EC, Huang JC, Bota RG, Bartzokis G, London ED. Differences between smokers and nonsmokers in regional gray matter volumes and densities. Biol. Psychiatry 2004;55:77–84. [PubMed: 14706428]

Cardenas VA, Studholme C, Meyerhoff DJ, Song E, Weiner MW. Chronic active heavy drinking and family history of problem drinking modulate regional brain tissue volumes. Psychiatry Res 2005;138:115–130. [PubMed: 15766635]

Cohen E, Feinn R, Arias A, Kranzler HR. Alcohol treatment utilization: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend 2007;86:214–221. [PubMed: 16919401]

Crews FT, Collins MA, Dlugos C, Littleton J, Wilkins L, Neafsey EJ, Pentney R, Snell LD, Tabakoff B, Zou J, Noronha A. Alcohol-induced neurodegeneration: when, where and why? Alcohol. Clin. Exp. Res 2004;28:350–364. [PubMed: 15112943]

Daeppen JB, Smith TL, Danko GP, Gordon L, Landi NA, Nurnberger JI Jr. Bucholz KK, Raimo E, Schuckit MA, The Collaborative Study Group on the Genetics of Alcoholism. Clinical correlates of cigarette smoking and nicotine dependence in alcohol-dependent men and women. Alcohol Alcohol 2000;35:171–175. [PubMed: 10787393]

Durazzo TC, Cardenas VA, Studholme C, Weiner MW, Meyerhoff DJ. Non-treatment-seeking heavy drinkers: Effects of chronic cigarette smoking on brain structure. Drug Alcohol Depend 2007a;87:76–82. [PubMed: 16950573]

Durazzo TC, Gazdzinski S, Banys P, Meyerhoff DJ. Cigarette smoking exacerbates chronic alcohol-induced brain damage: a preliminary metabolite imaging study. Alcohol. Clin. Exp. Res 2004;28:1849–1860. [PubMed: 15608601]

Durazzo TC, Gazdzinski S, Banys P, Meyerhoff DJ. Brain metabolite concentrations and neurocognition during short-term recovery from alcohol dependence: Preliminary evidence of the effects of concurrent chronic cigarette smoking. Alc. Clin. Exp. Res 2006a;30:539–551.

Durazzo TC, Gazdzinski S, Meyerhoff DJ. The neurobiological and neurocognitive consequences of chronic cigarette smoking in alcohol use disorders. Alcohol Alcohol 2007b;42:174–185. [PubMed: 17526627]

Durazzo TC, Meyerhoff DJ. Neurobiological and neurocognitive effects of chronic cigarette smoking and alcoholism. Front. Biosci 2007;12:4079–4100. [PubMed: 17485360]

Durazzo TC, Rothlind JC, Gazdzinski S, Banys P, Meyerhoff DJ. A comparison of neurocognitive function in nonsmoking and chronically smoking short-term abstinent alcoholics. Alcohol 2006b; 39:1–11. [PubMed: 16938624]

Ende G, Walter S, Welzel H, Demirakca T, Wokrina T, Ruf M, Ulrich M, Diehl A, Henn FA, Mann K. Alcohol consumption significantly influences the MR signal of frontal choline-containing compounds. Neuroimage 2006;32(2):740–6. [PubMed: 16759881]

Fagerstrom KO, Heatherton TF, Kozlowski LT. Nicotine addiction and its assessment. Ear Nose Throat J 1991;69:763–765. [PubMed: 2276350]

Fein G, Di Sclafani V, Cardenas VA, Goldmann H, Tolou-Shams M, Meyerhoff DJ. Cortical gray matter loss in treatment--naive alcohol dependent individuals. Alcohol. Clin. Exp. Res 2002;26:558–564. [PubMed: 11981133]

Fein G, Di Sclafani V, Finn P, Scheiner DL. Sub-diagnostic psychiatric comorbidity in alcoholics. Drug Alcohol Depend. 2006

Fein G, Landman B. Treated and treatment-naive alcoholics come from different populations. Alcohol 2005;35:19–26. [PubMed: 15922134]

Fein G, Meyerhoff DJ, Di Sclafani V, Ezekiel F, Poole N, MacKay S, Dillon WP, Constans J-M, Weiner MW. 1H magnetic resonance spectroscopic imaging separates neuronal from Glial changes in alcohol-related brain atrophy. Chapter in NIAAA Research Monograph No 27/Alcohol and Glial Cells 1994:227–241.

Fein G, Di Sclafani V. Cerebral reserve capacity: implications for alcohol and drug abuse. Alcohol 2004;32:63–67. [PubMed: 15066705]

Fergusson DM, Goodwin RD, Horwood LJ. Major depression and cigarette smoking: results of a 21-year longitudinal study. Psychol. Med 2003;33:1357–1367. [PubMed: 14672244]

Friend KB, Malloy PF, Sindelar HA. The effects of chronic nicotine and alcohol use on neurocognitive function. Addict. Behav 2005;30:193–202. [PubMed: 15561461]

Gallinat J, Lang UE, Jacobsen LK, Bajbouj M, Kalus P, von Haebler D, Seifert F, Schubert F. Abnormal hippocampal neurochemistry in smokers: evidence from proton magnetic resonance spectroscopy at 3 T. J. Clin. Psychopharmacol 2007;27:80–84. [PubMed: 17224719]

Gallinat J, Meisenzahl E, Jacobsen LK, Kalus P, Bierbrauer J, Kienast T, Witthaus H, Leopold K, Seifert F, Schubert F, Staedtgen M. Smoking and structural brain deficits: a volumetric MR investigation. Eur. J. Neurosci 2006;24:1744–1750. [PubMed: 17004938]

Gazdzinski S, Durazzo TC, Meyerhoff DJ. Temporal dynamics and determinants of whole brain tissue volume changes during recovery from alcohol dependence. Drug Alcohol Depend 2005a;78:263–273. [PubMed: 15893157]

Gazdzinski S, Durazzo TC, Studholme C, Song E, Banys P, Meyerhoff DJ. Quantitative brain MRI in alcohol dependence: preliminary evidence for effects of concurrent chronic cigarette smoking on regional brain volumes. Alcohol. Clin. Exp. Res 2005b;29:1484–1495. [PubMed: 16131857]

Gilman SE, Abraham HD. A longitudinal study of the order of onset of alcohol dependence and major depression. Drug Alcohol Depend 2001;63:277–286. [PubMed: 11418232]

Glass JM, Adams KM, Nigg JT, Wong MM, Puttler LI, Buu A, Jester JM, Fitzgerald HE, Zucker RA. Smoking is associated with neurocognitive deficits in alcoholism. Drug Alcohol Depend 2006;82(2): 119–26. [PubMed: 16169161]

Grant B, Stinson F, Dawson D, P C, Dufour M, Compton W, Pickering RP, Kaplan K. Prevalence and co-occurance of substance use disorders and independent mood and anxiety disorders. Arch. Gen. Psychiatry 2004;61:807–816. [PubMed: 15289279]

Grant BF. The impact of a family history of alcoholism on the relationship between age at onset of alcohol use and DSM-IV alcohol dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. Alcohol Health Res. World 1998;22:144–147. [PubMed: 15706789]

Grober E, Sliwinski M. Development and validation of a model for estimating premorbid verbal intelligence in the elderly. Journal of Clinical and Experimental Neuropsychology 1991;13:933–949. [PubMed: 1779032]

Harper C. The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? J. Neuropath. Exp. Neurol 1998;57:101–110. [PubMed: 9600202]

Hasin DS, Stinson FS, Ogburn E, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch. Gen. Psychiatry 2007;64:830–842. [PubMed: 17606817]

Hayee A, Haque A, Anwarullah A, Rabbani M. Smoking enhances age related brain atrophy-a quantitative study with computed tomography. Bangladesh Med. Res. Counc. Bull 2003;29:118–124. [PubMed: 15053274]

Hommer D, Momenan R, Kaiser E, Rawlings R. Evidence for a gender-related effect of alcoholism on brain volumes. Am. J. Psychiatry 2001;158:198–204. [PubMed: 11156801]

Huang B, Grant BF, Dawson DA, Stinson FS, Chou SP, Saha TD, Goldstein RB, Smith SM, Ruan WJ, Pickering RP. Race-ethnicity and the prevalence and co-occurrence of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, alcohol and drug use disorders and Axis I and II disorders: United States, 2001 to 2002. Compr. Psychiatry 2006;47:252–257. [PubMed: 16769298]

Jagannathan NR, Desai NG, Raghunathan P. Brain metabolite changes in alcoholism: An in vivo proton magnetic resonance spectroscopy (MRS) study. Magnetic Resonance Imaging 1996;14:553–557. [PubMed: 8843367]

John U, Meyer C, Rumpf HJ, Hapke U. Probabilities of alcohol high-risk drinking, abuse or dependence estimated on grounds of tobacco smoking and nicotine dependence. Addiction 2003;98:805–814. [PubMed: 12780369]

Kaskutas LA, Weisner C, Caetano R. Predictors of help seeking among a longitudinal sample of the general population, 1984-1992. J. Stud. Alcohol 1997;58:155–161. [PubMed: 9065893]

Li TK, Hewitt BG, Grant BF. The Alcohol Dependence Syndrome, 30 years later: a commentary. the 2006 H. David Archibald lecture. Addiction 2007;102:1522–1530. [PubMed: 17680851]

Lloyd JJ, Chen CY, Storr CL, Anthony JC. Clinical features associated with receipt of alcohol treatment. J. Stud. Alcohol 2004;65:750–757. [PubMed: 15700513]

Lukassen J, Beaudet MP. Alcohol dependence and depression among heavy drinkers in Canada. Soc. Sci. Med 2005;61:1658–1667. [PubMed: 15869834]

Meyerhoff D, Blumenfeld R, Truran D, Lindgren J, Flenniken D, Cardenas V, Chao LL, Rothlind J, Studholme C, Weiner H. Effects of heavy drinking, binge drinking, and family history of alcoholism on regional brain metabolites. Alcohol. Clin. Exp. Res 2004;28:650–661. [PubMed: 15100618]

Miranda R Jr. Meyerson LA, Myers RR, Lovallo WR. Altered affective modulation of the startle reflex in alcoholics with antisocial personality disorder. Alcohol. Clin. Exp. Res 2003;27:1901–1911. [PubMed: 14691377]

Moss HB, Chen CM, Yi HY. Subtypes of alcohol dependence in a nationally representative sample. Drug Alcohol Depend 2007;91:149–158. [PubMed: 17597309]

Paperwalla KN, Levin TT, Weiner J, Saravay SM. Smoking and depression. Med. Clin. North Am 2004;88:1483–1494. x–xi. [PubMed: 15464109]

Parks MH, Dawant BM, Riddle WR, Hartmann SL, Dietrich MS, Nickel MK, Price RR, Martin PR. Longitudinal brain metabolic characterization of chronic alcoholics with proton magnetic resonance spectroscopy. Alcohol. Clin. Exp. Res 2002;26:1368–1380. [PubMed: 12351932]

Pfefferbaum A, Lim KO, Zipursky RB, Mathalon DH, Rosenbloom MJ, Lane B, Ha CN, Sullivan EV. Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: a quantitative MRI study. Alcohol. Clin. Exp. Res 1992;16:1078–1089. [PubMed: 1471762]

Pridmore S, Chambers A, McArthur M. Neuroimaging in psychopathy. Aust. N. Z. J. Psychiatry 2005;39:856–865. [PubMed: 16168013]

Romberger DJ, Grant K. Alcohol consumption and smoking status: the role of smoking cessation. Biomed. Pharmacother 2004;58:77–83. [PubMed: 14992787]

Rourke SB, Dupont RM, Grant I, Lehr PP, Lamoureux G, Halpern S, Yeung DW, San Diego HIV Neurobehavioral Research Center. Reduction in cortical IMP-SPET tracer uptake with recent cigarette consumption in a young group of healthy males. Eur. J. Nucl. Med 1997;24:422–427. [PubMed: 9096094]

Saha TD, Chou SP, Grant BF. Toward an alcohol use disorder continuum using item response theory: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychol. Med 2006;36:931–941. [PubMed: 16563205]

Schuff N, Amend D, Knowlton R, Tanabe J, Norman D, Fein G, Weiner MW. Age-related metabolite changes and volume loss in hippocampus by proton MR spectroscopic imaging and MRI neurobiology of aging. Neurobiol. Aging 1999;20:279–285. [PubMed: 10588575]

Schuff N, Ezekiel F, Gamst A, Amend D, Capizzano A, Maudsley AA, Weiner MW. Region and tissue differences of metabolites in normally aged brain using 1H magnetic resonance spectroscopic imaging. Magnetic Resonance in Medicine 2001;45:899–907. [PubMed: 11323817]

Schweinsburg BC, Taylor MJ, Videen JS, Alhassoon OM, Patterson TL, Grant I. Elevated myo-inositol in gray matter of recently detoxified but not long-term alcoholics: A preliminary MR spectroscopy study. Alc. Clin. Exp. Res 2000;24:699–770.

Seitz D, Widmann U, Seeger U, Nagele T, Klose U, Mann K, Grodd W. Localized proton magnetic resonance spectroscopy of the cerebellum in detoxifing alcoholics. Alcohol. Clin. Exp. Res 1999;23:158–163. [PubMed: 10029218]

Skinner HA, Sheu WJ, The Lifetime Drinking History and the MAST. Reliability of alcohol use indices. J. Stud. Alcohol 1982;43:1157–1170. [PubMed: 7182675]

Sobell, LC.; Sobell, MB. Timeline Follow-Back: A Technique for Assessing Self-Reported Alcohol Consumption. In: Litten, R.; Allen, J., editors. Measuring Alcohol Consumption. Press Inc.; The Humana: 1992. p. 41-72.

Sobell LC, Sobell MB, Riley DM, Schuller R, Pavan DS, Cancilla A, Klajner F, Leo GI. The reliability of alcohol abusers' self-reports of drinking and life events that occurred in the distant past. J. Stud.

Alcohol 1988;49:225–232. [PubMed: 3374136]published erratum appears in J. Stud. Alcohol 1989 Jan;50(1):92

Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Self-Evaluation Questionaire. 1977

Stoltenberg SF, Mudd SA, Blow FC, Hill EM. Evaluating measures of family history of alcoholism: density versus dichotomy. Addiction 1998;93:1511–1520. [PubMed: 9926555]

Sullivan, EV. NIAAA Research Monograph No. 34: Human brain vulnerability to alcoholism: Evidence from neuroimaging studies. In: Noronha, A.; Eckardt, M.; Warren, K., editors. Review of NIAAA's neuroscience and behavioral research portfolio. National Institute on Alcohol Abuse and Alcoholism; Bethesda, MD: 2000. p. 473-508.

Tucker JA, Vuchinich RE, Rippens PD. Different variables are associated with help-seeking patterns and long-term outcomes among problem drinkers. Addict. Behav 2004;29:433–439. [PubMed: 14732433]

Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. Psychol. Med 2006;36:441–454. [PubMed: 16207391]

Weinrebe W, Graf-Gruss R, Schwabe R, Stippler D, Fusgen I. The two-factor method--a new approach to categorizing the clinical stages of malnutrition in geriatric patients. J. Am. Geriatr. Soc 2002;50:2105–2107. [PubMed: 12473037]

Whitfield JB, Zhu G, Madden PA, Neale MC, Heath AC, Martin NG. The genetics of alcohol intake and of alcohol dependence. Alcohol. Clin. Exp. Res 2004;28:1153–1160. [PubMed: 15318113]

Table 1

Demographics and clinical variables

Parameter	nsLD	ALC	HD	nsALC	sALC	nsHD	sHD
Number of participants (females)	38 (8)	35 (2)	32 (5)	15 (0)	20 (2)	18 (4)	14 (1)
Age [years]	45.4 ± 8.1	45.9 ± 8.3	42.4 ± 8.9	47.9 ± 8.1	44.4 ± 8.4	42.7 ± 9.9	42.0 ± 7.8
Education [years]	15.8 ± 2.2**$$	14.0 ± 2.1**	14.4 ± 2.1$$	13.9 ± 2.3	14.1 ± 2.0	15.1 ± 2.1	13.6 ± 1.7
AMNART	119.9 ± 8.4	110.8 ± 9.2	114.0 ± 8.4	109.5 ± 10.3	111.8 ± 8.5	117.1 ± 6.1	110.5 ± 9.4
Family History Density	0.24 ± 0.31**	0.83 ± 0.49**##	0.38 ± 0.41##	0.81 ± 0.40	0.85 ± 0.56	0.35 ± 0.35	0.42 ± 0.48
Beck Depression Inventory	6.0 ± 5.7	7.9 ± 7.7	9.1 ± 8.4	5.1 ± 5.5	10.1 ± 8.5	8.1 ± 7.3	10.3 ± 9.7
1-yr average [drinks/month]	12 ± 17	385 ± 191##	217 ± 135##	403 ± 207	372 ± 183	205 ± 130	233 ± 144
3-yr average [dri/month]	12 ± 17	369 ± 171##	226 ± 121##	385 ± 180	357 ± 168	213 ± 123	242 ± 121
Lifetime average [dri/month]	15 ± 14	218 ± 109	186 ± 146	193 ± 119	236 ± 100	147 ± 87	236 ± 191
Lifetime years	28.2 ± 5.7	29.3 ± 9.3##	25.5 ± 9.5##	31.6 ± 9.3	27.6 ± 9.2	25.5 ± 10.8	25.6 ± 7.9
Total lifetime consumption [kg]	65 ± 63	1035 ± 664##	792 ± 837##	989 ± 751	1069 ± 609	566 ± 417	1081 ± 302
Onset of heavy drinking [years]	-	23.6 ± 9.0	23.4 ± 8.4	26.1 ± 10.3	21.8 ± 7.6	25.7 ± 9.3	20.5 ± 6.2
Months of heavy drinking	-	231 ± 107#	174 ± 110#	222 ± 102	238 ± 113	143 ± 116	213 ± 91
Age at first drink [years]	18.2 ± 3.6	16.6 ± 3.2	16.6 ± 3.4	16.3 ± 3.3	16.8 ± 3.2	16.9 ± 2.6	16.4 ± 4.3
Intracranial Volume [cc]	1498 ± 137	1513 ± 124	1472 ± 150	1501 ± 104	1522 ± 139	1468 ± 171	1478 ± 124
Hep-C [n]	0	4	0	2	2	0	0
Hypertension [n]	0	7	0	2	5	0	0
Unipolar mood disorders	0	13	3	5	8	1	2

AMNART = American National Adult Reading Test; 1-yr average = number of drinks per month over 1-year prior to study; 3 yr average = number of drinks per month over 3- years prior to study; Lifetime average = number of drinks per month over lifetime; Lifetime years = number of years of regular alcohol consumption over lifetime. Total lifetime consumption = total amount of pure EtOH (kg) consumed over lifetime. Onset of heavy drinking = age when alcohol consumption exceeded 100 drinks per month

contrast between ALC and HD;

* contrast between ALC and nsLD;

$ contrast between HD and nsLD; for all contrasts: one symbol $p < 0.05$; two symbols $p < 0.01$.