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Structural brain differences in alcohol-dependent individuals with and without comorbid substance dependence

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ABSTRACT

Background: Over 50% of individuals with alcohol use disorders (AUD) also use other substances; brain structural abnormalities observed in alcohol dependent individuals may not be entirely related to alcohol consumption. This MRI study assessed differences in brain regional tissue volumes between short-term abstinent alcohol dependent individuals without (ALC) and with current substance use dependence (polysubstance users, PSU).

Methods: Nineteen, one-month-abstinent PSU and 40 ALC as well as 27 light-drinkers (LD) were studied on a 1.5 T MR system. Whole brain T1-weighted images were segmented automatically into regional gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) volumes. MANOVA assessed group differences of intracranial volume-normalized tissue volumes of the frontal, parietal, occipital, and temporal lobes and regional subcortical GM volumes. The volumetric measures were correlated with neurocognitive measures to assess their functional relevance.

Results: Despite similar lifetime drinking and smoking histories, PSU had significantly larger normalized WM volumes than ALC in all lobes. PSU also had larger frontal and parietal WM volumes than LD, but smaller temporal GM volumes and smaller lenticular and thalamic nuclei than LD. ALC had smaller frontal, parietal, and temporal GM, thalamic GM and cerebellar volumes than LD. ALC had more sulcal CSF volumes than both PSU and LD.

Conclusion: One-month-abstinent ALC and PSU exhibited different patterns of gross brain structural abnormalities. The larger lobar WM volumes in PSU in the absence of widespread GM volume loss contrast with widespread GM atrophy in ALC. These structural differences may demand different treatment approaches to mitigate specific functionally relevant brain abnormalities.

1. Introduction

Brain tissue volume losses in the frontal, temporal and select subcortical regions of individuals with alcohol use disorders (AUD) have consistently been reported with volumetric magnetic resonance imaging (for review see Buhler and Mann, 2011), and so have deficiencies in executive skills, learning and memory, processing speed, visuospatial skills and working memory (Durazzo and Meyerhoff, 2007; Oscar-Berman, 2000; Stavro et al., 2012). Today, more than half of individuals with AUD who present for treatment also chronically abuse illicit substances (e.g., Medina et al., 2004). Substance use disorders have adverse effects on brain biology and function separate from those of AUD (see Barros-Loscertales et al., 2011; Ersche et al., 2011; Fein et al., 2002; Lim et al., 2008; O'Neill et al., 2001; Cousijn et al., 2012; Matochik et al., 2005; Yucel et al., 2008; Berman et al., 2008; Chang et al., 2007; Thompson et al., 2004; Tobias et al., 2010).

Comorbid alcohol and substance use disorders (i.e., polysubstance use disorder: PSUD) have also been associated with brain morphological abnormalities. Liu et al. (1998) reported smaller normalized gray matter (GM) and white matter (WM) volumes of the

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prefrontal lobe in polysubstance abusers (cocaine, alcohol, heroin, marijuana) abstinent from substance use for more than 2 weeks compared to controls. Tanabe et al. (2009) also reported smaller GM volumes of the bilateral medial orbitofrontal cortex in long-term (over 2 years) abstinent individuals dependent on two or more substances (most often cocaine, amphetamine, and alcohol) compared to controls. As in AUD, the neurobiological abnormalities in individuals with PSUD are accompanied by cognitive deficiencies, particularly in visual and verbal memory, attention, psychomotor speed, visuomotor skills, problem solving and abstraction abilities (Block et al., 2002; Medina et al., 2004).

Thus, brain morphological abnormalities appear to occur in somewhat similar brain regions with similar neurocognitive deficits in AUD with and without comorbid substance abuse. To determine potential unique group differences, there is the need to directly contrast the magnitude and spatial distribution of structural brain abnormalities and their associated neurocognitive abnormalities in AUD with and without comorbid substance abuse. Directly contrasting structural brain abnormalities and their neurocognitive correlates in AUD with and without substance abuse will help design more efficacious treatment strategies tailored to individuals with PSUD or AUD. In this context, we showed recently that one-month-abstinent treatment-seeking PSUD individuals have prefrontal metabolite concentrations that were uniquely different from those of alcohol dependent individuals at similar abstinence duration, reflecting neuronal and glial dysfunction partly related to neurocognition (Abé et al., 2013).

This quantitative volumetric magnetic resonance imaging (MRI) study, contrasted differences in total and regional GM, WM and subcortical tissue volumes as well as ventricular and sulcal cerebrospinal fluid (CSF) between abstinent alcohol dependent individuals without current illicit substance dependence (ALC) and those with current psychostimulant dependence (PSU). ALC and PSU groups were abstinent from alcohol and/or psychostimulants for about one month. The functional relevance of our MRI measures was assessed by correlating them with neurocognitive measures. Since ALC recover brain tissue volume significantly but not completely within their first month of sobriety (Zipursky et al., 1989; Durazzo et al., 2014; Gazdzinski et al., 2005a,b; Pfefferbaum et al., 1995; Trabert et al., 1995; Van Eijk et al., 2013), while individuals with PSUD show regional GM tissue volume deficits even after many weeks and years of abstinence (Liu et al., 1998; Tanabe et al., 2009), we tested the following hypotheses in treatment-seeking individuals after one month of abstinence from alcohol and other substances: (1) PSU have smaller lobar GM, WM and subcortical tissue volumes as well as larger CSF volumes than light-drinking controls (LD) and ALC and (2) in PSU and in ALC, smaller lobar GM and WM volumes correlate with worse measures of working memory, processing speed, visual-spatial learning and memory and auditory-verbal learning and general intelligence.

2. Materials and methods

2.1. Participants

Treatment-seeking PSU ($n = 19$) and ALC ($n = 117$) were recruited from the San Francisco VA Medical Center and Kaiser Permanente. For statistical reasons, we reduced our large ALC cohort to 40 individuals by matching them on age, education, smoking status and drinking variables to the smaller PSU group. Both ALC and PSU participants completed the structured clinical interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Axis I Disorder Patient Edition, Version 2.0 (First et al., 1998). Prior to enrollment, male participants consumed more than 150 alcoholic drinks (one drink contains 13.6 g of ethanol) per month for at least 8 years; females consumed more than 80 drinks per month for at least 6 years. PSU individuals were diagnosed with both alcohol dependence and dependence on at least one psychostimulant, with or without nicotine dependence and cannabis use disorder. All PSU met DSM-IV dependence criteria for at least one illicit substance and 10.5% met criteria for cannabis use disorder. Specifically, 12 PSU met criteria for cocaine dependence (63%) and 2 of these were either abusing or dependent on cannabis; 2 other PSU met criteria for both cocaine and methamphetamine dependence (10.5%); and yet 2 others were dependent on both cocaine and opiates (10.5%); 2 other PSU met criteria for methamphetamine dependence only (10.5%) and 1 for opiate dependence only (5.5%). In the PSU group, 32% were non-smokers, including 2 ex-smokers. All ALC participants met DSM-IV criteria for alcohol dependence with or without nicotine dependence. 15 ALC participants (37%) were non-smokers, including 6 ex-smokers; the proportion of smokers did not differ among ALC and PSU. All ex-smokers among ALC and PSU individuals had stopped smoking for at least 5 years before the study. Within the ALC group, 2 individuals were currently abusing cannabis, while 3 had past cannabis abuse, currently in full remission. In addition, one ALC participant each showed past dependence on cocaine, amphetamines, or opioids, but all were currently in full remission. Thus, while the ALC participants were "clean" alcohol dependent individuals, the PSU participants were all dependent on alcohol and 84% on cocaine; only about 11% in both groups had a current or past cannabis use disorder diagnosis. Other non-substance-related inclusion and exclusion criteria were described previously (Durazzo et al., 2004). All ALC and PSU participants were tested daily with breathalyzers for alcohol consumption and randomly for substance use during outpatient treatment to ensure sobriety during the one-month-abstinence period. Twenty-seven non-substance-using LD, without histories of medical or psychiatric conditions known or suspected to influence brain structural outcome measures were recruited from the local community. Twenty-one of the LD individuals (77%) were never-smokers, and the proportion of non-smokers in the LD group was not significantly different from that in ALC or PSU ($p \geq 0.07$) (see Table 1).

2.2. Clinical assessment

Within one day of the MR study, participants completed standardized questionnaires for alcohol withdrawal (CIWA-Ar; Addiction Research Foundation Clinical Institute of Withdrawal Assessment for Alcohol; Sullivan et al., 1989), depression (Beck Depression Inventory; Beck, 1978) and anxiety symptomatology (State-Trait Anxiety Inventory, Y-2, STAI; Spielberger et al., 1977). Alcohol consumption over lifetime was assessed with the lifetime drinking history (LDH; Skinner and Sheu, 1982; Sobell and Sobell, 1990; Sobell et al., 1988). From the LDH, age of onset of heavy drinking [defined as consuming >100 alcoholic drinks per month (male) or >80 drinks per month (female)] was derived and the average number of alcoholic drinks consumed per month over 1 year, 8 years before enrollment and over lifetime estimated. For PSU, substance use history (other than alcohol) was assessed with an in-house questionnaire based on the Addiction Severity Index (McLellan et al., 1992), NIDA Addictive Drug Survey (Smith, 1991), drinking history, and Axis I disorders Patient Edition, Version 2.0 (SCID-I/P; First et al., 1998). The questionnaire probed for information on phases of drug use for each substance that a participant had a current or past disorder diagnosis on. The variables recorded included age of first and last use, number of total lifetime phases, duration of individual and total lifetime phases (including phases of abstinence), frequency and quantity of use during each phase, and route of administration. Another variable recorded was money spent per day on a substance, which was then converted to one metric, using catchment area-specific conversion norms. Thus, monthly averages for grams of the substances over 1 year prior to enrolment and over lifetime were estimated.

To evaluate the nutritional status and alcohol-related or other hepatocellular injury, laboratory tests for serum, pre-albumin, alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltransferase were obtained within three days of each MR scan. The values of these variables in the liver and the white blood cell counts were not significantly different between the groups. Table 1 shows demographics, alcohol consumption and select blood variables for LD, ALC and PSU.

2.3. Assessment of neurocognitive function

The neurocognitive domains and constituent measures evaluated were as follows (for details, see Durazzo et al., 2010): Executive skills: Short Categories Test, color-word portion of the Stroop Test, Trail Making Test part B, Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) Similarities, Wisconsin Card Sorting Test-64: Computer Version 2-Research Edition non-perseverative errors, perseverative errors, and perseverative responses. Fine Motor Skills: Grooved Pegboard Test. General Intelligence: Ward-7 Full Scale IQ; based on WAIS-III Arithmetic, Block Design, Digit Span, Digit Symbol, Information, Picture Completion, and Similarities subtests. Learning and memory: Auditory-verbal: California Verbal Learning Test-II Immediate Recall trials 1–5 (learning), Short and Long Delay Free Recall (memory). Visuospatial: Brief Visuospatial Memory Test-Revised, Total Recall (learning) and Delayed Recall (memory). Processing speed: WAIS-III Digit Symbol, Stroop Color & Word, WAIS-III Symbol Search Trail Making Test-A. Visuospatial skills: WAIS-III Block Design; Luria-Nebraska Item 99. Working memory: WAIS-III Arithmetic, WAIS-III Digit Span. The raw scores for all neurocognitive measures (except Luria-Nebraska Item 99 ratio) were converted to age-adjusted (e.g., Short Categories Test, Stroop Color-Word Test, WAIS-III subtests) or age-and-education-adjusted (e.g., Trails A and B via Heaton Compendium Norms; Heaton et al., 1991) standardized scores. The standardized scores were then converted to z-scores for all measures. For the Luria-Nebraska Item 99 ratio, raw scores were converted to z-scores based

Table 1
Demographics, substance use and blood variables for LD, ALC, and PSU (mean ± standard deviation).

Variable	LD	ALC	PSU	Pair-wise comparisons
N (females)	27 (3)	40 (3)	19 (0)	–
Age (years)	48.0 ± 8.0	50.2 ± 5.4	46.7 ± 7.1	LD = ALC = PSU (NS)
Education (years)	15.4 ± 2.2	13.5 ± 1.7	12.4 ± 1.1	LD > ALC ($p < 0.001$)
				LD > PSU ($p < 0.001$)
				ALC = PSU (NS)
Body mass index (kg/m^2)	26.5 ± 0.9	26.3 ± 0.7	28.3 ± 1.2	LD = ALC = PSU (NS)
AMNART	118.0 ± 6.9	114.4 ± 9.0	105.9 ± 8.3	LD > ALC ($p < 0.001$)
				LD > PSU ($p < 0.001$)
				ALC > PSU ($p = 0.018$)
1-yr average drinks (month)	19 ± 21	402 ± 224	286 ± 273	ALC = PSU (NS)
				LD < ALC ($p < 0.001$)
				LD < PSU ($p < 0.001$)
8-yr average drinks (month)	19 ± 18	325 ± 166	258 ± 231	ALC = PSU (NS)
				LD < ALC ($p < 0.001$)
				LD < PSU ($p < 0.001$)
Lifetime average drinks per month	19 ± 15	233 ± 120	246 ± 241	ALC = PSU (NS)
				LD < ALC ($p < 0.001$)
				LD < PSU ($p < 0.001$)
Age of onset of heavy drinking	–	23 ± 7	20 ± 5	ALC = PSU (NS)
Months of heavy drinking	–	240 ± 97	239 ± 114	ALC = PSU (NS)
Duration of abstinence (days)	–	32 ± 8	28 ± 11	ALC = PSU (NS)
Smokers, *n* (%)	6 (22)	25 (63)	13 (68)	ALC = PSU (NS)
				LD < ALC ($\chi^2 = 0.07$)
				LD < PSU ($\chi^2 = 0.09$)
Medical comorbidities, *n* (%)	–	18 (45)	11 (58)	ALC = PSU (NS)
Psychiatric comorbidities, *n* (%)	–	17 (43)	12 (63)	ALC = PSU (NS)
Pre-albumin (g/dL)	29.7 ± 6.3	25.1 ± 6.4	30.8 ± 7.4	LD > ALC ($p = 0.027$)
				ALC < PSU ($p = 0.009$)
				LD = PSU (NS)
White blood cell counts (K/cm)	7.0 ± 1.7	7.7 ± 2.3	5.5 ± 1.2	LD < PSU ($p = 0.022$)
				ALC < PSU ($p = 0.001$)
				LD = ALC (NS)
Hematocrit (%)	43.8 ± 3.0	41.6 ± 4.1	43.2 ± 3.0	LD > ALC ($p = 0.038$)
				LD = PSU (NS)
				ALC = PSU (NS)
Beck depression inventory	4.6 ± 4.3	10.9 ± 7.8	11.7 ± 8.5	LD < ALC ($p < 0.001$)
				LD < PSU ($p < 0.001$)
				ALC = PSU (NS)
State-trait anxiety inventory – state	33.0 ± 7.5	44.0 ± 11.1	42.8 ± 11.4	LD < ALC ($p < 0.001$)
				LD < PSU ($p < 0.001$)
				ALC = PSU (NS)
CIWA	1.4 ± 2.2	2.0 ± 2.8	1.9 ± 2.9	LD = ALC = PSU (NS)

1-yr average: number of alcoholic drinks per month over 1 year prior to study; 8 yr average: number of alcoholic drinks per month over 8 years prior to study; months heavy drinking: number of months of greater than 100 alcoholic drinks per month; lifetime average: number of alcoholic drinks per month over lifetime; AMNART: American National Adult Reading Test; CIWA: clinical institute of withdrawal assessment; NS: groups are not significantly different on the measure.

on the performance of 27 non-smoking light drinking controls (Durazzo et al., 2012), since there are no published procedures available for this measure.

2.4. MRI data acquisitions and processing

Whole brain three-dimensional T1-weighted coronal images and two-dimensional T2-weighted oblique-axial images were acquired on a 1.5 Tesla magnet (Vision, Siemens Medical Systems, Iselin, NJ), using Magnetization Prepared Rapid Acquisition Gradient Echo imaging sequence (TR/TI/TE = 9/300/4 ms, 1 mm × 1 mm in-plane resolution, 1.5 mm slabs) and spin-echo imaging sequence (TR/TE$_2$ = 2500/80 ms, 1 mm × 1 mm in-plane resolution, 3 mm slice thickness), respectively.

After re-alignment of each subject's T1- and T2-weighted images, the expectation maximization segmentation method (Van Leemput et al., 1999) was applied to the T1-weighted images to segment the brain into WM, GM, and CSF after co-registration and correction for bias field intensity variation of the T1-weighted images. The major lobes and subcortical regions were then parcellated by overlaying the tissue maps on a reference atlas containing landmarks of 36 brain regions (see Studholme et al., 2001), including the regions reported here. The volumes of total cortical GM and total lobar WM were calculated by summing the respective GM and WM values from the major lobes. The intracranial volume (ICV) was estimated by summing all regional tissue and CSF volumes.

2.5. Statistics

Multivariate analysis of variance (MANOVA) assessed group differences on age and education, differences between ALC and PSU on drinking and smoking severities, days of abstinence, anxiety and depression symptoms, as well as basic clinical laboratory measures (see Table 1). Multivariate analyses of covariance (MANCOVAs) examined group differences on ICV-normalized volumes of 4 GM regions (i.e., fGM, pGM, oGM, tGM), 4 WM regions (fWM, pWM, oWM, tWM), 5 subcortical regions (i.e., lenticular GM, caudate GM, thalamus GM, total brainstem and total cerebellum) and 5 CSF regions (i.e., fCSF, pCSF, oCSF, tCSF and ventricular CSF) separately (f, p, o and t stand for frontal, parietal, occipital and temporal, respectively). For total and regional cortical GM volumes and CSF, only age was a significant predictor of group variances and was therefore used as a covariate. For total and regional lobar WM volumes, only the body mass index (BMI) contributed significantly to the variances and therefore was the only used covariate. Neither age nor BMI was a significant predictor of subcortical tissue volume variance. Participants' cigarette smoking status was not a significant predictor of any tissue volume; however, this exploration has to be treated with caution, as the proportion of smokers in the LD sample tended to be smaller than in the patient groups. Given our *a priori* hypotheses, all MANCOVAs of tissue volumes were followed-up with post hoc analyses (to assess group differences for GM, WM, or CSF volumes) as well as pairwise and univariate *t*-tests (comparing LD, ALC and PSU). Also because of our *a priori* hypothesis, we did not correct for multiple comparisons. The reported *p*-values for GM are 1-tail, but those for WM and CSF volumes are 2-tail, because PSU unexpectedly had greater WM and smaller CSF volumes than LD and ALC. Although ALC and PSU did not differ significantly on the frequency of medical and psychiatric co-morbidities, these comorbidities were controlled for in all group comparisons. Effect sizes for pairwise comparisons were calculated using Cohen's *d* (Cohen, 1988). Associations of the MRI outcome measures with measures of neurocognitive test performance used Pearson's correlations.

3. Results

3.1. Participant characterization

As shown in Table 1, LD, ALC, and PSU groups were not significantly different on age and BMI, but LD had significantly more years of education than ALC and PSU. ALC participants had significantly lower pre-albumin levels than LD and PSU, whereas PSU had significantly lower white blood cell counts than LD and ALC; however, pre-albumin levels and white blood cell counts in all groups were within the normal range. Covarying for these variables did not change the results of our main analyses. No other clinical laboratory measures differed significantly among groups.

Regarding medical comorbidities, 9 ALC and 2 PSU tested positive for hepatitis C and 8 ALC and 4 PSU had medically controlled hypertension. Inclusion/exclusion of individuals with these common medical comorbidities from the statistical analyses did not substantially change the results.

3.2. MRI outcome measures

Table 2 shows ICV, ICV-normalized GM, WM, and subcortical tissue volumes for all examined regions, and Table 3 shows the ventricular and lobar ICV-normalized CSF volumes for all groups, with effect sizes and *p*-values for group comparisons. All groups were statistically similar on ICV.

3.2.1. ICV-normalized GM volumes. MANCOVA with age as covariate revealed a significant main effect of age [$F(2, 80) = 4.74$, $p = 0.002$] and group [$F(2, 80) = 2.1$, $p = 0.041$] for GM volumes. Significant group effects were observed for total cortical GM [$F(2, 82) = 6.4$, $p = 0.003$), fGM [$F(2, 82) = 5.22$, $p = 0.008$], pGM [$F(2, 82) = 3.98$, $p = 0.023$], and a trend for tGM [$F(2, 82) = 2.80$, $p = 0.067$]. Pairwise comparisons showed that ALC compared to LD had less total cortical GM and smaller volumes of all but the occipital lobe. PSU had less GM than LD in the temporal lobe only, and PSU had larger frontal GM volume than ALC.

3.2.2. ICV-normalized WM volumes. MANCOVA with BMI as covariate revealed a significant main effect of BMI [$F(2, 80) = 3.1$, $p = 0.020$] and group [$F(2, 80) = 3.58$, $p = 0.001$] for WM volumes. Significant group effects were observed for total WM and all lobar WM volumes except oWM: total WM [$F(2, 82) = 9.93$, $p < 0.001$], fWM [$F(2, 82) = 7.38$, $p = 0.001$], pWM [$F(2, 82) = 9.99$, $p < 0.001$], and tWM [$F(2, 82) = 6.19$, $p = 0.003$]. Pairwise comparisons showed PSU with significantly larger WM volumes than ALC for all four lobes and with significantly larger fWM and pWM than LD. ALC showed WM volumes similar to LD in all lobes except the temporal lobe, where ALC had less WM than LD. Of all lobar WM volumes, pWM volume in PSU correlated positively with average amount of cocaine used over the year prior to the study ($r = 0.55$, $p = 0.044$, uncorrected).

3.2.3. ICV-normalized subcortical volumes. MANOVA revealed a significant main effect of group for subcortical tissues [$F(2, 80) = 2.65$, $p = 0.005$]. Significant group effects were observed for thalamic GM [$F(2, 80) = 5.95$, $p = 0.004$] and total cerebellar volume [$F(2, 80) = 3.25$, $p = 0.044$]. Pairwise comparisons showed PSU had smaller lenticular and thalamic GM volumes than LD, and ALC had smaller thalamic GM and total cerebellar volumes than LD. ALC and PSU had statistically similar volumes of all the subcortical regions examined.

3.2.4. ICV-normalized CSF volumes. MANCOVA using age as covariate revealed a significant main effect of age [$F(2, 79) = 2.6$, $p = 0.043$] and group [$F(2, 79) = 6.95$, $p < 0.001$] for CSF volumes. Significant group effects were observed for total sulcal CSF [$F(2, 79) = 7.33$, $p = 0.001$], fCSF [$F(2, 79) = 10.90$, $p < 0.001$) and tCSF [$F(2, 79) = 18.52$, $p < 0.001$]. Pairwise comparisons showed that ALC had more total sulcal CSF in these regions than both LD and PSU (see Table 3). PSU had similar sulcal CSF volumes than LD, except for the temporal lobe, where PSU had less CSF than LD. Ventricular CSF volumes were comparable among all three groups. Lobar CSF volumes did not correlate significantly with the corresponding lobar WM volumes.

When the larger sample of 117 ALC was analyzed, the results were consistent with those reported here in the smaller ALC sample: effect sizes were essentially the same while the significant *p*-values reported here became even smaller. Thus, our findings in the smaller ALC sample were representative of the larger sample and not obtained by chance. Furthermore, excluding the six females in the ALC and LD groups from analyses did not significantly change the group means or any of the statistical analyses (e.g., tGM in LD changed from 101.7 ± 4.7 with inclusion of women to 101.8 ± 4.9 without women, while the tGM means for ALC changed from 98.2 ± 5.0 with to 98.5 ± 4.8 without women; the corresponding *p*-values of the *t*-tests changed from 0.008 to 0.011, respectively).

3.3. Correlations of MRI outcome measures with neurocognitive domains

Correlations were obtained between ICV-normalized regional tissue volumes that were not age-corrected and age-corrected neurocognitive measures. In PSU, smaller pGM volume, although not significantly different from ALC and LD, related to worse visuospatial learning and memory (both $r \geq 0.50$, $p < 0.05$); no lobar WM volume in PSU correlated significantly with any of the neurocognitive measures. In ALC, worse visuospatial learning correlated with less total cortical GM and worse visuospatial skills with smaller fGM volume (both $r = 0.39$, $p \leq 0.014$); lower fine motor skills related to smaller oGM volume ($r = 0.43$, $p = 0.008$). Also in ALC, lobar WM volume did not correlate significantly with neurocognitive measures, except intelligence, which correlated negatively with oWM ($r = -0.36$, $p = 0.022$). Finally, in the smaller group of LD, several correlations between neurocognitive measures and mostly occipital lobe volumes were observed, but these were all in the unexpected direction.

4. Discussion

In this cross-sectional volumetric MRI study, one-month-abstinent alcohol dependent individuals without current psychostimulant dependence (ALC), ALC individuals with current dependence on at least one psychostimulant (PSU),and drug-free LD differed significantly on regional GM and WM volumes normalized to ICV: PSU had significantly *larger* lobar WM volumes than LD and ALC, whereas ALC showed no regional WM volume differences compared to LD. GM volumes in PSU were lower only in the temporal lobe, thalami and lenticular nuclei compared to LD. In ALC however, most lobar cortical GM volumes, thalamic GM, and total cerebellar volume were significantly smaller than in LD. Consistent with these tissue volume differences, sulcal CSF volumes of the frontal and temporal lobes in PSU were smaller than in both ALC and LD. All effect sizes for the significant WM differences between PSU and LD or ALC were greater than 0.50, indicating moderate-to-large magnitude group differences. Parietal WM volume in PSU correlated positively with prior year cocaine use, suggesting a substance-related parietal WM volume expansion. Frontal, parietal, and total cortical GM volumes were associated with some critical neurocognitive domain measures in both PSU and ALC, but not in LD. These neuroimaging abnormalities may serve as polysubstance abuse biomarkers and as potential targets for pharmacological and

Table 2
ICV-normalized GM, WM, and subcortical volumes (1000×) (mean ± standard deviation) for LD, ALC and PSU, together with effect sizes and *p*-values of pairwise follow-up *t*-tests.

Region	Group	Volume	Contrast	Effect size	*p* value
ICV (in mL)	LD	1478.9 ± 125.9	LD = ALC	0.07	NS
	ALC	1488.0 ± 125.8	LD = PSU	0.06	NS
	PSU	1486.4 ± 139.3	ALC = PSU	0.01	NS
Total GM	LD	371.4 ± 13.3	LD > ALC	0.93	<0.001
	ALC	357.8 ± 15.7	LD = PSU	0.44	NS
	PSU	365.2 ± 14.7	ALC = PSU	0.47	NS
Frontal	LD	148.5 ± 6.6	LD > ALC	0.65	0.003
	ALC	143.6 ± 8.4	LD = PSU	0.24	NS
	PSU	147.0 ± 5.9	ALC < PSU	0.47	0.038
Parietal	LD	82.7 ± 4.6	LD > ALC	0.67	0.006
	ALC	79.4 ± 5.3	LD = PSU	0.41	NS
	PSU	80.8 ± 4.6	ALC = PSU	0.28	NS
Occipital	LD	38.4 ± 3.6	LD = ALC	0.22	NS
	ALC	36.6 ± 3.7	LD = PSU	0.03	NS
	PSU	37.2 ± 3.1	ALC = PSU	0.18	NS
Temporal	LD	101.4 ± 4.7	LD > ALC	0.58	0.042
	ALC	98.6 ± 5.0	LD > PSU	0.50	0.045
	PSU	98.3 ± 7.5	ALC = PSU	0.05	NS
Total WM	LD	267.3 ± 18.2	LD = ALC	0.33	NS
	ALC	262.3 ± 11.6	LD < PSU	0.89	0.003
	PSU	282.3 ± 15.2	ALC < PSU	1.48	<0.001
Frontal	LD	140.2 ± 11.2	LD = ALC	0.18	NS
	ALC	138.5 ± 7.6	LD < PSU	0.86	0.004
	PSU	148.7 ± 8.3	ALC < PSU	1.28	<0.001
Parietal	LD	64.4 ± 4.4	LD = ALC	0.29	NS
	ALC	63.2 ± 3.6	LD < PSU	0.97	0.002
	PSU	68.9 ± 4.9	ALC < PSU	1.33	<0.001
Occipital	LD	23.5 ± 2.5	LD = ALC	0.22	NS
	ALC	23.0 ± 2.0	LD < PSU	0.37	NS
	PSU	24.5 ± 2.9	ALC < PSU	0.60	0.047
Temporal	LD	39.2 ± 2.8	LD > ALC	0.65	0.013
	ALC	37.5 ± 2.4	LD < PSU	0.37	NS
	PSU	40.2 ± 2.6	ALC < PSU	1.08	0.002
Lenticular GM	LD	4.8 ± 0.6	LD = ALC	0.42	NS
	ALC	4.5 ± 0.8	LD > PSU	0.57	0.038
	PSU	4.4 ± 0.8	ALC = PSU	0.12	NS
Caudate GM	LD	4.8 ± 0.4	LD = ALC	0.00	NS
	ALC	4.8 ± 0.5	LD = PSU	0.25	NS
	PSU	4.9 ± 0.4	ALC = PSU	0.22	NS
Thalamic GM	LD	4.6 ± 1.0	LD > ALC	0.77	0.002
	ALC	3.9 ± 0.8	LD > PSU	0.81	0.005
	PSU	3.9 ± 0.7	ALC = PSU	0.00	NS
Total brainstem	LD	18.6 ± 1.4	LD = ALC	0.00	NS
	ALC	18.6 ± 1.3	LD = PSU	0.40	NS
	PSU	19.2 ± 1.6	ALC = PSU	0.41	NS
Total cerebellum	LD	84.3 ± 6.6	LD > ALC	0.80	0.023
	ALC	78.7 ± 7.3	LD = PSU	0.09	NS
	PSU	83.7 ± 6.7	ALC = PSU	0.71	NS

Note: ICV-normalized tissue volume is defined here as [tissue volume/ICV] × 1000. Volumes are estimated means from a group model comparing all three groups. Reported *p*-values are 1-tailed for GM and 2-tailed for all other volumes.

behavioral PSU-specific treatment aimed at decreasing the high relapse rates in PSU.

MR-based structural neuroimaging of individuals with different substance use disorders have yielded mixed findings regarding brain tissue volume alterations. Smaller WM volumes (or density), particularly of the frontal, temporal and cerebellar regions relative to drug-free controls were reported in middle-aged active and abstinent users of cocaine and cannabis (Lim et al., 2008; Matochik et al., 2005; Sim et al., 2007; Solowij et al., 2011). A few reports showed similar WM volumes (or density) in active or abstinent users of these substances compared to controls (Franklin et al., 2002; Hanlon et al., 2011; Liu et al., 1998). However, enlarged volumes or density of frontal, temporal, and subcortical WM were reported in active amphetamine users (Bartzokis et al., 2000; Thompson et al., 2004) and in amphetamine users in both early and long-term abstinence (Jernigan et al., 2005; Tobias et al., 2010). Here, we found larger WM volumes in one-month abstinent PSU compared to both LD and one-month abstinent ALC. Our PSU cohort was dependent on alcohol (100%), cocaine (84%), and methamphetamine (21%). When the four PSU individuals with

Table 3
ICV-normalized ventricular and lobar CSF volumes (1000×) (mean ± standard deviation) for LD, ALC and PSU, together with effect sizes and *p*-values of follow-up *t*-tests.

Region	Group	Volume	Contrast	Effect size	*p* value
Ventricular CSF	LD	16.6 ± 5.2	LD = ALC	0.26	NS
	ALC	18.1 ± 6.2	LD = PSU	0.04	NS
	PSU	16.3 ± 8.5	ALC = PSU	0.24	NS
Total sulcal CSF	LD	190.5 ± 23.5	LD < ALC	0.84	0.001
	ALC	208.7 ± 20.0	LD = PSU	0.03	NS
	PSU	189.9 ± 15.5	ALC > PSU	1.05	0.003
Frontal	LD	99.8 ± 11.6	LD < ALC	1.04	<0.001
	ALC	112.5 ± 12.7	LD = PSU	0.01	NS
	PSU	99.7 ± 9.5	ALC > PSU	1.14,	<0.001
Parietal	LD	47.7 ± 8.8	LD = ALC	0.23	NS
	ALC	49.6 ± 7.6	LD = PSU	0.05	NS
	PSU	51.6 ± 8.1	ALC = PSU	0.13	NS
Occipital	LD	9.2 ± 2.1	LD = ALC	0.05	NS
	ALC	9.0 ± 1.8	LD = PSU	0.36	NS
	PSU	10.0 ± 2.3	ALC = PSU	0.14	NS
Temporal	LD	33.8 ± 5.5	LD < ALC	0.66	0.007
	ALC	37.2 ± 4.8	LD > PSU	1.22	0.001
	PSU	28.5 ± 2.7	ALC > PSU	2.23	<0.001

Note: ICV-normalized CSF volume is defined here as [CSF volume/ICV] × 1000. Volumes are estimated means from a group model comparing all three groups. Reported *p*-values are 2-tailed.

methamphetamine dependence were removed from the entire PSU sample, all WM volumes remained significantly larger compared to LD or ALC. This observation, together with the positive correlation of parietal WM volume with cocaine use quantities in the PSU suggests that, the larger WM volumes in our PSU cohort were not driven simply by methamphetamine dependence in the PSU group.

Larger WM volumes in recently abstinent methamphetamine users were postulated to be a result of tissue inflammation and/or reactive astrogliosis as a response to tissue injury sustained from the chronic substance abuse (Chang et al., 2007; Thompson et al., 2004). A dose-related enhancement of neurological and histological signs of acute encephalomyelitis (brain inflammation) following *in vivo* administration of amphetamine or cocaine in rats was described (Nunez et al., 2007). Also, in rats administered with cocaine daily for 7 days, increases in glial fibrillary acidic protein and vimentin expressions, the hallmarks of reactive astrocytes and reactive gliosis (Pekny and Nilsson, 2005), were observed in the prefrontal cortex and nucleus accumbens at 3 weeks after substance administration (Bowers and Kalivas, 2003). These findings support the theory of brain tissue enlargement due to reactive astrogliosis. Therefore, it is not out of context to interpret the observed larger lobar WM volumes in our PSU cohort as inflammation and/or glial scarring associated with reactive astrogliosis observed at one month after withdrawal from chronic consumption of both alcohol and illicit substances.

Results of quantitative MRI-based regional GM volume/density in individuals, who purportedly depended on or abused primarily a single drug, have been inconsistent. Some cross-sectional studies reported smaller regional GM volumes/densities (predominantly in the frontal and temporal lobes, but also in thalamus) in both active and abstinent users of cocaine (Fein et al., 2002; Franklin et al., 2002; Lim et al., 2008; Sim et al., 2007), cannabis (Matochik et al., 2005; Yucel et al., 2008), methamphetamine (Berman et al., 2008; Thompson et al., 2004) and heroin (Yucel et al., 2008) compared to controls. Others reported larger GM volumes/densities in cocaine dependent individuals (Hanlon et al., 2011), cannabis abusers (Cousijn et al., 2012) and methamphetamine abusers (Jernigan et al., 2005) compared to controls; and yet others found no effects of chronic cannabis misuse on brain morphology (Block et al., 2000; Medina et al., 2009; Tzilos et al., 2005). On the other hand, while previous reports on the effects of PSUD on brain GM volumes are sparse, they are at least consistent: GM volumes were reduced compared to age-matched drug-free controls in prefrontal and temporo-parietal cortices of active cocaine dependent individuals, many of whom were dependent also on other drugs (Ersche et al., 2011, 2012), in the orbitofrontal cortex of polysubstance abusers abstinent for at least 15 days (Liu et al., 1998), and in prefrontal cortex of polysubstance dependent individuals abstinent for more than 2 years (Tanabe et al., 2009). This suggests GM atrophy in active, short-term and long-term abstinent polysubstance users. We found appreciable GM volume loss in our one-month-abstinent PSU only in the temporal cortex, lenticular and thalamic GM. The apparent "normal" frontal and parietal cortical GM volume in our PSU sample could be the result of reactive astrogliosis described above (where actual cortical GM loss in the PSU may be masked by a comparable amount of volume gain from inflamed astrocytes), or where GM loss is offset by a neuroadaptive response to the need for greater cognitive control over substance use (e.g., Koehler et al., 2013). The discrepancies between regional GM volume findings from our PSU participants and those of the previous studies could relate to the differences in age (our participants were on average 12–15 years older), the duration and type of drugs used, and/or the duration of abstinence: i.e., the younger cohorts in the previous studies could have been less prone to brain inflammation from chronic substance use, brain inflammation may not be present in active users (as in Ersche et al., 2011) or in polysubstance abusers abstinent for a few weeks (as in Liu et al., 1998), or brain inflammation could have subsided after 2 years of abstinence (as in Tanabe et al., 2009). However, this is speculative and can only be tested in longitudinal studies of abstinent polysubstance users: if our speculation/interpretation were correct, the observed GM differences – and particularly the larger WM volumes – should diminish with duration of abstinence as the substance withdrawal-related inflammation subsides over time. Such a dynamic change has been suggested in abstinent methamphetamine users (Chang et al., 2007). Methodological issues in studying brain effects of polysubstance dependence with relevance to the above discussion were recently reviewed (Mackey and Paulus, 2013).

Larger ventricular and lobar CSF volumes have been reported consistently in short-term abstinent and active AUD individuals compared to controls (Buhler and Mann, 2011). However, our findings showed smaller CSF spaces in PSU compared to ALC with similar drinking severities or controls, possibly compensating for

the larger lobar WM volumes within the physical confines of the skull.

Whereas both Ersche papers (Ersche et al., 2011, 2012) showed larger subcortical GM volumes in currently using PSUD individuals (caudate, lenticular nuclei, amygdala and cerebellum, some of which may be premorbid (Ersche et al., 2012)), our abstinent PSU patients had smaller lenticular and thalamic GM as well as normal caudate, cerebellar and brainstem volumes. As the authors speculate that some of these increases may reflect a compensatory response to reduced dopamine neurotransmission, this may have normalized in our abstinent PSU sample.

Our study has limitations: the substance dependent cohort was treatment-seeking and abstinent at time of study, and it included only a few female participants. Our findings may therefore not generalize to female or treatment-naïve substance dependent individuals. The variance of the subcortical volume measures obtained with our automated segmentation method (expectation maximization segmentation) is larger than that shown in manually outlined structures of cocaine dependent individuals (Jacobsen et al., 2001), which might have made it impossible to detect small group differences. The measured tissue volumes comprise of several sub-regions that subserve specific cognitive functions. Thus, our lobar outcome measures lack functional specificity, which likely contributed to the few correlations with neurocognitive measures. Finally, we did not screen participants for DSM-IV Axis II disorders, such as antisocial personality disorders (Fein et al., 2007; Grant et al., 2004; Pridmore et al., 2005), nor did we measure potential group differences in nutrition, exercise and genetic predispositions. All these conditions may also influence brain morphometry and should ideally be considered in future studies of both treatment-naïve and treatment-seeking individuals with well-defined dependence on alcohol and illicit substances. To address the issue of regional specificity of volume changes within the relatively large lobes and to increase the functional relevance of such measures, reliable segmentation and examination of small brain regions or of the cortical ribbon may be needed, such as provided by whole-brain voxel-based morphometry and cortical thickness measures (see e.g., Cardenas et al., 2011; Durazzo et al., 2011; Ersche et al., 2011).

These limitations notwithstanding, our neuroimaging study reveals gross brain structural differences between PSU and ALC that may have implications for different treatment approaches of polysubstance dependence and alcohol dependence. The findings complement previous neuronal and glial differences we detected in the frontal lobe of these substance dependent groups (Abé et al., 2013). Here, we confirmed commonly reported smaller lobar GM and cerebellar volumes and more sulcal CSF in one-month-abstinent middle-aged ALC compared to age-matched LD. However, these volume measures were largely unaffected in one-month-abstinent alcohol dependent PSU. Furthermore, PSU had larger lobar WM volumes than both ALC and LD. The larger WM and the lack of apparent GM volume loss in PSU, despite a very long drinking history similar to that of ALC who showed marked cortical GM volume loss, suggest hypertrophic processes in short-term abstinent PSU, perhaps astrogliosis associated with neuro-inflammation. These processes may mask underlying cortical GM tissue loss associated with chronic polysubstance misuse.

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Contributors

The authors are Anderson Mon, Timothy C. Durazzo, Christoph Abe, Stefan Gazdzinski, David Pennington, Thomas Schmidt and Dieter J. Meyerhoff. Drs. Anderson Mon, Stefan Gazdzinski and Christoph Abe acquired and processed the MRI data. Dr. David Pennington and Mr Thomas Schmidt obtained and processed the neurocognitive data. Drs. Anderson Mon, Timothy Durazzo, Stefan Gazdzinski and Dieter Meyerhoff analyzed all data. Drs. Anderson Mon and Dieter Meyerhoff prepared the first drafts; and thereafter all other authors contributed to the final manuscript submitted here.

Conflict of interest

The authors have no disclosures or conflicts of interest related to this research to report.

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