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Non-linear volume recovery

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Serial longitudinal magnetic resonance imaging data indicate non-linear regional gray matter volume recovery in abstinent alcohol-dependent individuals

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ABSTRACT

The trajectory of regional volume changes during the first year of sustained abstinence in those recovering from an alcohol use disorder is unclear because previous research typically employed only two assessment points. To better understand the trajectory of regional brain volume recovery in treatment-seeking alcohol-dependent individuals (ALC), regional brain volumes were measured after 1 week, 1 month and 7.5 months of sustained abstinence via magnetic resonance imaging at 1.5 T. ALC showed significant volume increases in frontal, parietal and occipital gray matter (GM) and white matter (WM), total cortical GM and total lobar WM, thalamus and cerebellum, and decreased ventricular volume over 7.5 months of abstinence. Volume increases in regional GM were significantly greater over 1 week to 1 month than from 1 month to 7.5 months of abstinence, indicating a non-linear rate of change in regional GM over 7.5 months. Overall, regional lobar WM showed linear volume increases over 7.5 months. With increasing age, smoking ALC showed lower frontal and total cortical GM volume recovery than non-smoking ALC. Despite significant volume increases, ALC showed smaller GM volumes in all regions, except the frontal cortex, than controls after 7.5 months of abstinence. ALC and controls showed no regional WM volume differences at any assessment point. In non-smoking ALC only, increasing regional GM and WM volumes were related to improving processing speed. Findings may indicate a differential rate of recovery of cell types/cellular components contributing to GM and WM volume during early abstinence, and that GM volume deficits persist after 7.5 months of sustained sobriety in this ALC cohort.

Keywords Alcohol use disorders, brain volume, cigarette smoking, cognition, recovery.

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INTRODUCTION

Magnetic resonance (MR)-based neuro-imaging studies of treatment-seeking alcohol-dependent individuals (ALC), during early abstinence from alcohol (i.e. from 1 week to 1 month of abstinence), have consistently shown regional gray matter (GM) volume loss that is most prominent in the anterior frontal lobe, posterior parietal lobe, cingulate gyrus, insula, hippocampus and cerebellum (Buhler & Mann 2011; Demirakca *et al.* 2011; van Eijk *et al.* 2013; Durazzo *et al.* 2014b). White matter (WM) volume loss in early abstinent ALC is reported in all four lobes, particularly in the frontal WM (Buhler & Mann 2011; Monnig *et al.* 2013). Longitudinal studies indicate that treatment-seeking ALC demonstrate variable levels of regional GM and WM volume recovery during the first year of sustained abstinence (Buhler & Mann 2011; van Eijk *et al.* 2013; Monnig *et al.* 2013). Although treatment-seeking ALC show regional volume recovery with sustained sobriety, most ALC continue to demonstrate significantly smaller volumes in multiple brain regions after 6–12 months of abstinence compared with controls (Buhler & Mann 2011; Monnig *et al.* 2013).

Investigations of brain volume recovery with sobriety have typically employed two assessment points—a

baseline study after approximately 1 month of abstinence and a follow-up study after 6–12 months of abstinence, where only linear rates of volume changes could be assessed (Buhler & Mann 2011). Consequently, little is known about the actual trajectory of regional volume changes during the first year of abstinence. Some studies suggest that treatment-seeking ALC experience more rapid brain volume increases over the first month of sobriety than during later months of sustained abstinence (Pfefferbaum *et al.* 1995; Agartz *et al.* 2003; Gazdzinski, Durazzo & Meyerhoff 2005; Yeh *et al.* 2007; Mon *et al.* 2011), which indicates that volume change is not necessarily linear over the first year of sobriety. Additionally, few studies have examined associations between changes in brain volume and neurocognition during early abstinence; therefore, the functional relevance of volume changes during this period is unclear. Differential rates of change in brain morphology over the first year of abstinence may be clinically relevant because ALC with the smallest regional cortical GM volume, particularly in the anterior frontal regions, at approximately 1 week (Cardenas *et al.* 2011; Durazzo *et al.* 2011b) and 1 month (Rando *et al.* 2010) of abstinence had an increased relapse risk within the year after treatment. Furthermore, ALC with the lowest processing speed at 1 month of abstinence showed a significantly increased risk for relapse after treatment (Durazzo *et al.* 2008).

The rate and extent of brain volume recovery in abstinent ALC may be influenced by age, sex, diet/nutrition, genetic factors, and co-morbid medical, psychiatric and substance use disorders, and chronic cigarette smoking (Durazzo, Gazdzinski & Meyerhoff 2007b; Oscar-Berman & Marinkovic 2007; Mon *et al.* 2013). It is well established that medical, psychiatric and substance use disorders and cigarette smoking are highly prevalent in alcohol use disorders (Mertens *et al.* 2005; Durazzo & Meyerhoff 2007; Hasin *et al.* 2007; Moss, Chen & Yi 2010). Cigarette smoking in non-clinical samples (Durazzo, Meyerhoff & Nixon 2010, 2012, 2013) and in alcohol use disorders (Durazzo *et al.* 2007a, 2011a, 2014b; Gazdzinski *et al.* 2008, 2010; Luhar *et al.* 2013) is associated with significant morphological abnormalities, primarily in the anterior frontal, posterior parietal and mesial temporal regions. Serial assessment of the influence of the above variables on brain morphological changes during abstinence will assist in clarifying the factors promoting the considerable heterogeneity in the rate and extent of brain volume recovery demonstrated by ALC during abstinence.

The goal of this longitudinal study was to investigate regional changes of the lobar and subcortical brain volumes in treatment-seeking ALC over approximately 7.5 months of sustained abstinence. Assessment points after approximately 1 week, 1 month and 7.5 months of abstinence enabled a comparison of the rates of change of regional brain volumes during early abstinence (i.e. from 1 week to 1 month) to changes occurring over an intermediate period of abstinence (i.e. 1–7.5 months). We specifically examined the effects of co-morbid cigarette smoking, medical conditions, and psychiatric and substance use disorders on longitudinal volume changes in ALC, as well as the associations between changes of regional brain volumes and neurocognition. We predicted that:

1 The rate of regional volume changes in ALC is greater from 1 week to 1 month than from 1 to 7.5 months.
2 Smoking ALC (sALC) demonstrate less recovery than non-smoking ALC (nsALC) in frontal GM and WM volumes over 7.5 months; age interacts with smoking status (sALC versus nsALC), where, with increasing age, sALC show less GM and WM recovery in the frontal and parietal lobes than nsALC.
3 Over 7.5 months of abstinence, increasing frontal and parietal GM and WM in ALC is associated with improving learning and memory, and working memory; increasing lobar GM and WM across the brain relate to improving processing speed.
4 After 7.5 months of abstinence, both nsALC and sALC continue to demonstrate significantly smaller regional brain volumes than never-smoking controls (CON).

MATERIALS AND METHODS

Participants

ALC were recruited from the VA Medical Center (SFVAMC) Substance Abuse Day Hospital and the Kaiser Permanente Chemical Dependence Recovery Program outpatient clinics in San Francisco, CA, and never-smoking CON were recruited from the local community. Participants provided written consent before engaging in study procedures, which conformed to the Declaration of Helsinki, and was approved by the University of California and SFVAMC. A total of 111 unique ALC (44 nsALC and 67 sALC) participants were enrolled. Thirty-six nsALC and 46 sALC were first studied after 7 ± 4 days of abstinence (assessment point 1 = AP1) and 82 abstinent ALC were re-assessed after approximately 1 month of abstinence (AP2). An additional 29 ALC presented for treatment at our site after 2–3 weeks of sobriety because they underwent detoxification at other facilities; these 29 participants completed their first assessment after approximately 1 month of abstinence at AP2. Of the 111 total ALC participants studied at AP2, 66 (59 percent) relapsed between AP2 and AP3, 3 sALC were

excluded after AP2 because they stopped smoking, and 6 participants were lost to follow-up (e.g. moved out-of-state or no longer interested in participating). Of the 111 ALC studied at AP2, 36 (18 nsALC and 18 sALC) maintained continuous sobriety from alcohol (and consistent smoking levels) for at least 6 months following AP2 and were studied again after 226 ± 60 days of abstinence (AP3). Demographic and alcohol consumption variables between ALC groups studied at AP1, AP2 or AP3 were not significantly different, and ALC groups did not differ in length of abstinence at any AP. Thirty-two CON completed a baseline study, and 15 were assessed again after 278 ± 104 days. Table 1 provides demographic and clinical information for the 82 ALC participants studied at AP1 and 32 CON studied at baseline.

Primary inclusion criteria for ALC were a current DSM-IV (American Psychiatric Association 1994) diagnosis of alcohol dependence, fluency in English, consumption of > 150 alcohol-containing drinks/month (1 alcoholic drink equivalent = 13.6 g pure ethanol) for at least 8 years before enrollment for men, and consumption of > 80 drinks per month for at least 6 years before enrollment for women. Primary exclusion criteria for ALC and CON are fully detailed elsewhere (Durazzo *et al.* 2004). In brief, all participants were free of psychiatric, neurological, physical and medical conditions known or suspected to influence brain morphology and neurocognition, with the exceptions of mood disorders, hepatitis C, hypertension and type 2 diabetes for ALC; these medical conditions are highly prevalent in ALC (Mertens *et al.* 2005; Moss *et al.* 2010). For ALC, current/past unipolar mood disorders (e.g. major depression) were not exclusionary given the high co-morbidity with both alcohol dependence (Mertens *et al.* 2003) and cigarette smoking (Durazzo *et al.* 2010). In ALC, dependence on any substance (other than alcohol or nicotine) within 5 years prior to enrollment was exclusionary. Participants were screened for recent alcohol and illicit substances at each AP.

Clinical assessment

At their first assessment, participants completed the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition, Version 2.0, and standardized questionnaires assessing depressive [Beck Depression Inventory (BDI)] and anxiety [State-Trait Anxiety Inventory, for Y-2 (STAI)] symptomatology, lifetime alcohol consumption [Lifetime Drinking History (LDH)], lifetime substance use consumption (questionnaire assessing substance type, and quantity and frequency of use based on the Addiction Severity Index and NIDA Addictive Drug Survey) and level of nicotine dependence via the Fagerström Tolerance Test for Nicotine Dependence. From the LDH, average number of drinks/month over 1 year prior to enrollment and average number of drinks/month over lifetime were calculated. Family history of

Table 1 Group demographics and clinical measures for alcohol-dependent individuals (ALC) at assessment point 1 and controls (CON) at baseline.

Measure	*CON* (n = *32*)	*nsALC* (n = *36*)	*sALC* (n = *46*)
Days abstinent	NA		
AP1		7 (4)	7 (3)
AP2		34 (9)	32 (9)
AP3		225 (57)	227 (65)
Age[a]	47 (9)	52 (11)	49 (9)
Education[b]	17 (3)	14 (2)	14 (2)
Male (percent)	91	88	93
Percent Caucasian	72	75	74
Positive family history for alcoholism[c]	43	84	80
1-year average drinks/month[d]	16 (17)	328 (182)	446 (209)
Lifetime average drinks/month[d]	16 (14)	163 (107)	277 (147)
History of co-morbid substance abuse/dependence (percent)	NA	22	19
History of co-morbid psychiatric disorder (percent)	NA	42	40
History of co-morbid medical disorder (percent)	NA	50	52
Beck Depression Inventory[c]	4 (2)	14 (2)	15 (2)
State-Trait Anxiety Inventory—Trait[c]	32 (8)	47 (10)	50 (13)
Fagerström Test of Nicotine Dependence	NA	NA	5 (2)
Pack-years	NA	NA	25 (18)
Lifetime years of smoking	NA	NA	25 (12)

Note: Values are presented as mean (standard deviation). [a]nsALC > CON. [b]CON > nsALC = sALC. [c]CON < nsALC = sALC. [d]sALC > nsALC > CON. $P < 0.05$ for all group differences. NA = not applicable; Positive family history for alcoholism = mother, father, maternal grandparent and/or paternal grandparent indicated by participant to have a history of an alcohol use disorder.

alcoholism [Family History of Alcoholism Questionnaire (FHA)] was obtained via questionnaire by asking participants to classify all first- and second-degree blood relatives who experienced an alcohol use disorder during their lifetime. Participants were considered FHA-positive if they reported their mother, father and/or grandparent (maternal or paternal) had any lifetime history of 'problematic' alcohol consumption. At all APs, the total number of cigarettes smoked per day and lifetime years of smoking were recorded for sALC. At AP3, the Timeline Follow-Back Interview was used in ALC to assess any alcohol consumption and the quantity/frequency of any other substance use. For ALC, review of electronic medical records and/or telephone interview of collateral sources (i.e. family or friends) were used to verify their abstinence/relapse status [see Durazzo *et al.* (2011b) for details and corresponding references for the above measures].

ALC participants with a current/past history of a non-exclusionary medical condition that may have influenced brain morphology and/or neurocognition were considered to be positive for the medical co-morbidity factor; the most common medical co-morbidities were current hypertension and hepatitis C seropositivity. ALC were considered positive for the substance use disorder co-morbidity factor if they met the criteria DSM-IV for past dependence (> 5 years prior to enrollment), or current/past substance abuse; most met the criteria for cocaine or methamphetamine abuse/dependence. ALC were considered to be positive for a psychiatric co-morbidity if they met the current or lifetime DSM-IV criteria for a unipolar mood or anxiety disorder; the majority met the criteria for a major depressive disorder or substance (alcohol)-induced mood disorder, with depressive features.

Neurocognitive assessment

Participants completed a battery of measures that assessed working memory, processing speed, and auditory-verbal and visuospatial learning and memory within 48 hours of their MR scan. Alternate forms were used, where available, at follow-up assessments. The following measures were administered: Wechsler Adult Intelligence Scale, 3rd ed. (WAIS-III)—Digit Span (working memory), Symbol Search and Digit Symbol (processing speed); California Verbal Learning Test-II (CVLT-II)—Immediate Recall trials 1–5 (auditory-verbal learning), Short-and-Long Delay Free Recall (auditory-verbal memory); Brief Visual Memory Test (BVMT) Revised-Total Recall (visuospatial learning) and Delayed Recall (visuospatial memory). See Pennington *et al.* (2013) for corresponding references for the above measures.

MR data acquisition and processing

Structural images were acquired on a 1.5 T MR system (Vision, Siemens Medical Systems, Iselin, NJ, USA) with a T1-weighted magnetization prepared rapid acquisition gradient echo sequence (1×1 mm^2 in-plane resolution, 1.5-mm slabs) oriented orthogonal to the long axis of the hippocampus. Tissue intensity-based segmentation of cortical and subcortical GM, WM and cerebrospinal fluid (CSF) from T1-weighted images was conducted with the semi-automated expectation-maximization segmentation method (Van Leemput *et al.* 1999). This method employs a probabilistic segmentation of GM, WM and CSF to each magnetic resonance imaging voxel based on T1-weighted tissue intensity [see Mon *et al.* (2013) for method details and reliability]. Absolute volumes (in cc) for GM and WM of the four major lobes and subcortical regions [cerebellum, thalamus, caudate, lenticular nucleus (sum of putamen and globus pallidus)] and ventricles were obtained by non-linear co-registration of tissue maps to a reference atlas [see Studholme *et al.* (2003) for method details and reliability]. Groups showed no significant differences in magnitudes of change for the left and right hemisphere regions in all longitudinal analyses (data not shown), so results for summed left and right hemisphere volumes are presented. Total cortical GM and WM volumes were calculated by summing the respective GM and WM volumes from the frontal, parietal, temporal and occipital lobes. Intracranial volume (ICV) was calculated as the sum of total GM, WM, ventricular and sulcal CSF volumes. Due to high within-group variability, caudate volume was excluded from all analyses.

Data analyses

Cross-sectional analyses

Comparisons between groups on demographic and clinical variables were completed with multivariate analysis of variance or Fisher's exact test where appropriate. Volume comparisons between nsALC, sALC and CON at each AP were conducted with generalized linear modeling with group (nsALC, sALC, CON), age and ICV as predictors. Significant main effects for group ($P < 0.05$) were followed-up with pairwise *t*-tests. In comparisons between nsALC and sALC, lifetime average number of drinks/month and 1-year average drinks/month were separately employed as covariates because of the significantly greater alcohol consumption in sALC (see Table 1). Standard Bonferroni correction was applied to pairwise comparisons for each region (adjusted $P \leq 0.017$). Effect sizes for pairwise comparisons (see Table 6) were calculated with Cohen's *d* (Cohen 1988).

Longitudinal analyses (see Supporting Information Appendix S1 for details)

ALC. Regional volume change over 7.5 months (i.e. over AP1, AP2 and AP3) for ALC was evaluated with linear mixed modeling. Main effects and interactions for all analyses were considered significant at $P < 0.05$. In all longitudinal analyses described below, medical, psychiatric and substance abuse co-morbidities (binary factors) were separately added to models as secondary predictors, following examination for the effects of smoking status, age, ICV and months abstinent.

Analysis 1. Tested for a non-linear trajectory of regional volume changes in ALC over AP1, AP2 and AP3. For each region, a base model with smoking status (nsALC versus sALC), age, ICV, lifetime average drinks/month (or 1-year average drinks/month), months abstinent (linear), smoking status × months abstinent (or smoking status × age) was statistically compared with a second model containing the foregoing predictors plus a quadratic term for months abstinent (i.e. months abstinent^2).

Analysis 2. Examined rates of change (i.e. slopes) in ALC for regional volumes between AP1-AP2 and AP2-AP3. This analysis also tested for differences in slopes for AP1-AP2 versus AP2-AP3 for each region.

Analysis 3. Tested associations between change in regional brain volumes and change in neurocognitive measures across all assessment points, separately for nsALC and sALC. Neurocognitive and regional volumes were standardized to CON to form *z*-scores. The neurocognitive measure (e.g. BVMT Delayed Recall) was the dependent measure, with age, education, months abstinent (linear), lifetime average drinks/month and regional brain volume (e.g. frontal GM) as predictors. False discovery rate (FDR) (Benjamini & Hochberg 1995) was used to control for multiplicity of associations across models. Due to highly similar findings for Digit Span and Digit Symbol (see Supporting Information Table S1), these tests were combined into a single 'Processing Speed' measure by calculating the arithmetic mean of *z*-scores for each measure.

ALC versus CON. CON had two assessment points (baseline and follow-up). Therefore, comparisons of regional volume changes between nsALC, sALC and CON involved assessment of volume changes over AP1-3 interval for nsALC and sALC versus change over the baseline follow-up interval for CON. Linear mixed modeling was used and predictors included group (nsALC, sALC, CON), age, ICV, time (months abstinent for ALC and inter-scan interval for CON) and group × time interaction.

RESULTS

Participant demographics and clinical measures

There were no differences between nsALC, sALC and CON on the percentage of males and Caucasians. CON were younger than nsALC and had more years of education than nsALC and sALC (all $P < 0.05$). Both nsALC and sALC had a higher percentage of relatives (i.e. mother, father and/or grandparents) who had a history of an alcohol use disorder. Lifetime and 1-year average drinks/month were higher in sALC than nsALC (both $P < 0.05$). No differences were apparent between nsALC and sALC on the BDI, STAI and frequency of co-morbid substance use, psychiatric or medical conditions (see Table 1).

Regional volume changes for ALC over 7.5 months

Analysis 1—ALC rates of change in regional volumes over all APs (AP1-AP2-AP3; see Table 2 and Supporting Information Fig. S1)

Cortical GM and subcortical regions. Models containing both the linear (all $P \leq 0.004$) and the quadratic (all $P \leq 0.004$) terms for months abstinent were significant for frontal, parietal, occipital and total cortical GM, as well as for the cerebellum, thalamus and ventricular CSF volume. There were no main effects for smoking status, and the smoking status × linear/quadratic months abstinent interaction was not significant (all $P > 0.20$). A smoking status × age interaction was observed for the frontal and total cortical GM (both $P < 0.03$); with increasing age, sALC showed significantly less volume recovery than nsALC over 7.5 months. Compared to nsALC, the adverse effect of increasing age on volume recovery for sALC was four times greater in the frontal GM and three times greater in total cortical GM (magnitude differences in age-related slopes not shown). Temporal GM and lenticular nucleus showed no significant changes with abstinence. Given there were no significant effects for smoking status or smoking status × months abstinent interactions, the positive slopes for the linear term for months abstinent indicated that the ALC group, as a whole, showed significant volume increases in frontal, parietal, occipital and total cortical GM, cerebellum and thalamus over 7.5 months of abstinence. The significant negative slope (i.e. 'frowning' parabola) of the quadratic term for months abstinent in the above GM regions indicated that ALC showed different rates of regional volume change between AP1-AP2 than between AP2-AP3.

Lobar WM. For frontal, parietal, temporal WM and total lobar WM, only the linear term for months abstinent was significant. There was no main effect for smoking status or interactions among smoking status, age and months abstinent. The positive linear slope for each region

Table 2 Linear and quadratic rates of change for alcohol-dependent individuals in regional volumes over 7.5 months of abstinence.

	Linear			*Quadratic*		
Region	*β months abstinent*	*SE*	P-*value*	*β months abstinent*	*SE*	P-*value*
Frontal GM	1.68	0.28	< 0.001	–0.0048	0.0011	< 0.001
Parietal GM	0.95	0.17	< 0.001	–0.0030	0.0006	< 0.001
Temporal GM	0.49	0.26	0.07	–0.0018	0.0010	0.09
Occipital GM	0.30	0.10	0.004	–0.0015	0.0004	0.004
Total cortical GM	3.93	0.57	< 0.001	–0.0120	0.00007	< 0.001
Frontal WM	0.40	0.08	< 0.001	–0.0003	0.0011	0.82
Parietal WM	0.20	0.04	< 0.001	0.0003	0.0003	0.79
Temporal WM	0.13	0.03	< 0.001	–0.0006	0.0004	0.17
Occipital WM	0.13	0.09	0.13	–0.0006	0.0003	0.06
Total lobar WM	0.75	0.14	< 0.001	0.0000	0.0017	0.95
Cerebellum	0.93	0.13	< 0.001	–0.0027	0.0005	< 0.001
Thalamus	0.12	0.03	< 0.001	–0.00033	0.00010	< 0.001
Lenticular nucleus	–0.01	0.31	0.15	0.00003	0.00010	0.91
Ventricular CSF	–1.05	0.20	< 0.001	0.00282	0.00070	< 0.001

Note. β = slope. CSF = cerebrospinal fluid; GM = gray matter; SE = standard error of the estimate; WM = white matter.

Table 3 Linear rates of change in regional volumes for alcohol-dependent individuals over AP1-AP2 and AP2-AP3 intervals.

	AP1-AP2			*AP2-AP3*			*Difference in β AP1-AP2 versus AP2-AP3*
Region	*β months abstinent*	*SE*	P-*value*	*β months abstinent*	*SE*	P-*value*	P-*value**
Frontal GM	2.21	0.49	< 0.001	0.39	0.10	0.001	< 0.001
Parietal GM	0.90	0.25	< 0.001	0.07	0.05	0.21	0.002
Temporal GM	0.27	0.55	0.62	0.02	0.05	0.67	0.49
Occipital GM	0.16	0.11	0.15	0.05	0.05	0.23	0.13
Total cortical GM	3.94	0.77	< 0.001	0.35	0.22	0.13	< 0.001
Frontal WM	1.27	0.75	0.09	0.38	0.09	0.002	< 0.01
Parietal WM	0.14	0.27	0.61	0.30	0.05	< 0.001	0.45
Temporal WM	0.31	0.16	0.06	0.15	0.03	< 0.001	0.34
Occipital WM	0.04	0.13	0.75	0.06	0.03	0.039	0.74
Total lobar WM	1.43	0.83	0.09	0.92	0.19	< 0.001	0.55
Cerebellum	0.86	0.15	< 0.001	0.21	0.05	0.001	0.02
Thalamus	0.18	0.05	0.001	0.02	0.01	0.001	0.002
Lenticular nuclei	–0.01	0.05	0.88	–0.01	0.01	0.62	0.99
Ventricular CSF	–1.83	0.28	< 0.001	–0.22	0.06	< 0.001	< 0.001

Note: *Significant *P*-value ($P < 0.05$) indicates that rate of volume change over AP1-AP2 is statistically greater than volume change over AP2-AP3. β = slope. CSF = cerebrospinal fluid; GM = gray matter; SE = standard error of the estimate; WM = white matter.

indicated that ALC, as a group, demonstrated a significant linear increase in frontal, parietal, temporal and total lobar WM over 7.5 months.

Greater lifetime and 1-year average drinks/month were associated with less recovery of frontal GM volume in ALC (both $P < 0.03$). In sALC, greater lifetime years of smoking was related to lower frontal WM recovery ($P = 0.03$). Medical, psychiatric and substance abuse co-morbidities were not significant predictors of volume change in any region (all $P > 0.30$).

Analysis 2—ALC rates of change for regional volumes between AP1-AP2 and AP2-AP3 (see Table 3)

Cortical GM and subcortical regions. There were no significant main effects for smoking status or smoking status × months abstinent interactions between AP1-AP2 and AP2-AP3, so nsALC and sALC were combined into a single ALC group. Over the AP1-AP2 interval, ALC showed increased frontal, parietal and total cortical GM, increases in the cerebellar and thalamic volumes, and

decreases in ventricular CSF (all $P < 0.05$). Over the AP2-AP3 interval, ALC demonstrated a significant increase in frontal GM. The rate of volume change over AP1-AP2 was significantly greater than over AP2-AP3 in the frontal, parietal and total cortical GM, cerebellum, thalamus and ventricular CSF (all $P < 0.05$). This indicates that the significant quadratic term for months abstinent in these regions was driven by steep volume increases over AP1-AP2 and a flatter positive trajectory over AP2-AP3. For example, the frontal GM increased approximately 2.2 cc/month over AP1-AP2 but only 0.39 cc/month over AP2-AP3.

Lobar WM. ALC showed no statistically significant changes in lobar WM over the AP1-AP2 interval, but significant increases in all lobes and total lobar WM over the AP2-AP3 interval. Except for the frontal WM, there were no differences in regional volume change rates between the AP1-AP2 and AP2-AP3 intervals. This supports the findings from Analyses 1 and 2, which demonstrated significant linear volume changes across WM regions over approximately 7.5 months of abstinence.

Greater lifetime and 1-year average drinks/month were associated with less recovery of frontal GM volume (both $P < 0.03$) over the AP1-AP2 and AP2-AP3 intervals. In smokers, greater lifetime years of smoking was related to less frontal WM recovery over both AP1-AP2 and AP2-AP3 (both $P \leq 0.03$). Medical, psychiatric and substance abuse co-morbidities were not significant predictors of volume change in any region across either interval (all $P > 0.30$).

Analysis 3—Associations between regional brain volume and neurocognitive changes in ALC (see Table 4)

For nsALC, improving processing speed was associated with increasing volumes in all GM and WM regions over 7.5 months of abstinence, except the thalamus. In nsALC, there were also multiple associations between changes in working memory and auditory-verbal/visuospatial learning and memory and regional volumes ($P = 0.03$–0.04), but these did not survive correction for multiple comparisons. There were no significant associations between changes in neurocognitive measures and regional volumes in sALC *before* FDR correction (all $P > 0.07$). nsALC and sALC showed statistically equivalent rates of change and variances in both regional brain volumes and processing speed over 7.5 months (data not shown), so the lack of association between changes in volumes and processing speed in sALC was not attributable to a restriction of range in sALC.

Table 4. Linear rates of change in regional volumes as predictors of change in processing speed over 7.5 months for non-smoking alcohol-dependent individuals.

	Processing speed		
Region	β	*SE*	P-*value* *(FDR corrected)*
Frontal GM	0.16	0.03	< 0.001
Parietal GM	0.18	0.04	< 0.001
Temporal GM	0.11	0.03	< 0.001
Occipital GM	0.18	0.05	< 0.001
Total cortical GM	0.11	0.03	< 0.001
Frontal WM	0.15	0.04	< 0.001
Parietal WM	0.16	0.04	< 0.01
Temporal WM	0.19	0.04	< 0.001
Occipital WM	0.17	0.05	< 0.01
Total lobar WM	0.15	0.04	< 0.001
Cerebellum	0.21	0.07	< 0.01
Thalamus	0.08	0.07	0.28
Lenticular nucleus	0.19	0.07	< 0.01
Ventricular CSF	–0.07	0.06	0.28

Note: β = slope. CSF = cerebrospinal fluid; FDR = false discovery rate; GM = gray matter; SE = standard error of the estimate; WM = white matter.

Comparisons of ALC and CON on regional volume changes (see Table 5)

There were no main effects for smoking status or smoking status × months abstinent interactions for regional volumes in ALC, so nsALC and sALC were combined into a single group. A group (ALC versus CON) × time interaction was observed for all regions (all $P < 0.05$), except the temporal GM and WM and the lenticular nucleus. ALC showed significant volume increases in all regions (all $P < 0.05$), except the temporal GM and lenticular nucleus, which is consistent with findings from Analyses 1 and 2. CON showed no changes between baseline and follow-up in any region.

Cross-sectional comparisons between ALC and CON on regional volumes at AP1, AP2 and AP3 (see Table 6)

Because no significant volume changes were observed in CON, the larger baseline sample ($n = 32$) was used in all cross-sectional comparisons to ALC. At both AP1 and AP2, both nsALC and sALC showed smaller frontal, parietal and total cortical GM, thalamus and lenticular nucleus volumes than CON (all $P \leq 0.017$), with moderate-to-large effect sizes for the observed differences. At AP1, sALC showed smaller occipital GM volume than nsALC, and a trend ($P = 0.03$) for smaller occipital GM volume. There were no group differences for the cerebellum, ventricular CSF volume and WM in any region at AP1, AP2 or AP3. At AP3, groups were not different in

Table 5 Comparisons of controls (CON) and alcohol-dependent individuals (ALC) on regional volumes over study interval.

Region	*Baseline* *CON* (n = *32*)	*AP1* *ALC* (n = *82*)	*Follow-up* *CON* (n = *15*)	*AP3* *ALC* (n = *36*)	*CON change baseline to follow-up (percent)*	*ALC change AP1 to AP3 (percent)*	*Group × time interaction P-value*
Frontal GM	221.3 (8.0)	212.6 (10.4)	221.1 (7.9)	218.3 (8.6)	0.1	2.7	0.001
Parietal GM	123.8 (6.0)	117.3 (6.5)	123.1 6.0)	119.9 (6.0)	0.6	2.2	0.01
Temporal GM	151.2 (7.7)	146.8 (6.1)	150.4 (7.6)	147.5 (7.1)	–0.5	0.5	0.17
Occipital GM	57.3 (4.4)	54.3 (5.0)	57.4 (4.4)	55.1 (4.8)	0.2	1.5	0.01
Total cortical GM	553.7 (17.2)	531.8 (19.9)	552.0 (16.8)	540.1 (16.0)	0.3	1.6	0.01
Frontal WM	205.4 (12.3)	207.4 (13.0)	207.1 (12.6)	210.7 (11.9)	0.8	1.6	0.001
Parietal WM	94.2 (5.9)	94.8 (6.4)	95.1 (6.8)	97.6 (6.9)	1.0	3.0	0.02
Temporal WM	57.5 (3.1)	56.7 (3.5)	57.1 (3.0)	57.2 (3.3)	–0.7	1.0	0.08
Occipital WM	35.3 (3.3)	34.1 (3.2)	34.9 (3.3)	35.2 (3.5)	1.3	3.1	0.001
Total lobar WM	394.7 (20.6)	391.2 (20.5)	395.5 (20.8)	399.6 (20.9)	0.2	2.1	0.004
Cerebellum	124.2 (10.3)	119.6 (9.6)	124.3 (10.1)	123.0 (10.1)	0.03	2.8	0.02
Thalamus	6.8 (1.2)	5.8 (1.1)	6.9 (1.3)	6.1 (1.1)	1.4	5.2	0.02
Lenticular nucleus	7.0 (1.3)	6.6 (1.0)	6.9 (1.3)	6.4 (1.0)	–1.4	–2.3	0.23
Ventricular CSF	25.5 (5.5)	28.9 (8.8)	26.4 (5.6)	27.4 (9.4)	1.9	–5.5	< 0.001

Note: Values are presented as mean (standard deviation). Reported values are estimated means from longitudinal models comparing volume change in CON and ALC. A significant group × time interaction ($P < 0.05$) indicates that volume change over time was greater in ALC than for CON. CSF = cerebrospinal fluid; GM = gray matter; WM = white matter.

frontal GM volume, and nsALC was equivalent to CON on thalamic volume. Otherwise, the group differences in GM, WM and subcortical structures demonstrated at AP1 was still apparent after 7.5 months of abstinence at AP3.

DISCUSSION

The primary findings from this study are as follows: (1) ALC (both nsALC and sALC) showed significant volume increases in all GM and WM regions over approximately 7.5 months of abstinence, except the temporal GM and the lenticular nucleus, as well as decreased ventricular volume over 7.5 months; medical, psychiatric and substance misuse co-morbidities were not significant predictors of regional volume change; (2) rates of volume change for ALC for the cortical and subcortical GM were significantly greater over 1 week to 1 month of abstinence than over 1–7.5 months of abstinence; linear WM volume changes were observed in ALC over 7.5 months of abstinence; (3) sALC showed significantly less recovery with increasing age than nsALC in the frontal GM and total cortical GM over 7.5 months; (4) over 7.5 months of abstinence, improving processing speed was associated with increasing volumes in multiple regions in nsALC, but not in sALC; and (5) after 7.5 months of abstinence, nsALC and sALC were statistically equivalent to the never-smoking CON on frontal GM volume, but continued to demonstrate significantly lower parietal, temporal and total cortical GM, and thalamic volumes than CON. Neither nsALC nor sALC differed significantly from CON on regional WM volumes at AP1, AP2 or AP3.

The divergent rates of volume increases for regional GM and WM demonstrated by ALC suggest that the neuronal components (e.g. dendrites/dendritic spines, cell bodies) and glial cells (e.g. protoplasmic astrocytes) that primarily constitute the tissue mass of cortical and subcortical GM may recover at a different rate than the components contributing to WM (e.g. myelin, oligodendrocytes, neuronal axons, fibrous astrocytes). In ALC, 58 percent of total cortical GM volume recovery (i.e. 5.3 of 9.1 cc) occurred over the first month of abstinence and was driven by frontal GM increases. For lobar WM, the majority of volume recovery in ALC occurred over the AP2-AP3 interval (approximately 6.5 months), with the exception of the frontal WM, where the rate of change was greater over the first month of abstinence. Previously, we found ALC demonstrated significant increases in frontal and parietal GM *N*-acetylaspartate (NAA; marker of neuronal integrity) and choline-containing compounds (Cho, marker of cell membrane turn-over/synthesis) over 1 month of abstinence (Durazzo *et al.* 2006). Additionally, higher frontal GM NAA level was associated with greater frontal GM thickness (Durazzo *et al.* 2011a) in 1-week abstinent ALC, and increasing frontal Cho was related to increasing global brain volume in ALC over 7 weeks of sobriety (Bartsch *et al.* 2007). Finally, data from humans and animal models suggest that the morphological recovery in ALC during early and extended abstinence may be related to increases in neuronal dendritic arbor, soma/cell volume, synaptic density, glial proliferation (particularly microglia) and remyelination (Dlugos & Pentney 1997; Sullivan &

Table 6 Regional volumes and effect sizes for group differences for all assessment points.

	AP1			*AP1 effect size*			*AP2*			*AP2 effect size*			*AP3*			*AP3 effect size*		
ROI	*CON* (n = *32*)	*nsALC* (n = *36*)	*sALC* (n = *46*)	*nsALC versus CON*	*sALC versus CON*	*sALC versus nsALC*	*CON* (n = *32*)	*nsALC* (n = *44*)	*sALC* (n = *67*)	*nsALC versus CON*	*sALC versus CON*	*sALC versus nsALC*	*CON* (n = *32*)	*nsALC* (n = *18*)	*sALC* (n = *18*)	*nsALC versus CON*	*sALC versus CON*	*nsALC versus sALC*
Frontal GM	221.1 (10.4)	213.1 (10.4)	212.8 (10.3)	0.86[a]	0.90[b]	0.03	222.4 (10.2)	215.9 (10.3)	214.4 (10.1)	0.63[a]	0.78[b]	0.09	222.0 (9.6)	218.6 (9.3)	218.0 (9.2)	0.36	0.43	0.07
Parietal GM	123.2 (6.4)	117.3 (6.5)	117.2 (6.4)	0.90[a]	0.92[b]	0.01	123.1 (6.7)	118.9 (6.7)	118.1 (6.7)	0.62[a]	0.75[b]	0.12	123.8 (6.0)	120.1 (6.1)	119.9 (5.8)	0.83[a]	0.65[b]	0.17
Temporal GM	152.0 (6.1)	147.1 (6.1)	145.8 (6.0)	0.70[a]	1.02[b]	0.12	152.2 (7.0)	147.3 (7.1)	147.1 (6.9)	0.69[a]	0.72[b]	0.03	153.4 (7.0)	147.2 (7.2)	147.8 (6.9)	0.87[a]	0.80[b]	0.09
Occipital GM	56.3 (5.0)	55.4 (5.0)	53.4 (4.9)	0.18	0.59[b]	0.40[c]	56.6 (4.8)	55.9 (4.8)	54.2 (4.7)	0.15	0.52[b]	0.37	56.5 (4.8)	56.4 (4.9)	53.6 (4.7)	0.02	0.63[b]	0.58[c]
Total cortical GM	553.9 (19.6)	533.6 (19.8)	529.2 (19.9)	1.03[a]	1.25[b]	0.07	555.2 (20.0)	538.6 (20.5)	534.8 (19.8)	0.82[a]	1.02[b]	0.19	554.6 (17.9)	542.1 (17.8)	538.9 (17.9)	0.70[a]	0.88[b]	0.18
Frontal WM	206.9 (13.0)	207.4 (13.1)	207.3 (12.8)	0.04	0.3	0.01	206.5 (13.1)	208.5 (13.2)	208.8 (13.1)	0.22	0.23	0.01	206.8 (11.8)	211.0 (12.2)	210.4 (11.6)	0.35	0.30	0.06
Parietal WM	94.5 (6.5)	94.5 (6.4)	95.0 (6.3)	0.01	0.08	0.08	94.6 (6.8)	94.8 (6.8)	94.7 (6.7)	0.02	0.01	0.01	95.0 (6.9)	96.9 (7.1)	97.2 (6.7)	0.28	0.32	0.04
Temporal WM	57.6 (3.5)	56.5 (3.5)	56.8 (3.4)	0.31	0.24	0.06	57.8 (3.8)	56.7 (3.8)	56.7 (3.7)	0.29	0.29	0.00	58.0 (3.3)	56.9 (3.4)	57.5 (3.2)	0.39	0.14	0.18
Occipital WM	35.6 (3.2)	34.1 (3.2)	34.0 (3.2)	0.14	0.07	0.07	34.9 (3.5)	34.6 (3.5)	34.2 (3.4)	0.21	0.09	0.12	34.8 (3.5)	35.4 (3.6)	35.0 (3.4)	0.44	0.34	0.10
Total lobar WM	394.8 (20.5)	391.5 (20.6)	390.8 (20.3)	0.16	0.20	0.04	393.9 (21.6)	392.7 (22.1)	392.8 (21.5)	0.05	0.03	0.01	395.8 (20.8)	399.5 (21.4)	400.3 (20.3)	0.22	0.22	0.04
Cerebellum	123.3 (9.6)	119.9 (9.7)	119.3 (9.5)	0.36	0.42	0.06	123.6 (9.1)	121.8 (9.2)	120.9 (9.0)	0.19	0.29	0.10	124.1 (10.0)	125.3 (10.4)	120.7 (9.8)	0.11	0.34	0.46
Thalamus	6.7 (1.1)	5.7 (1.1)	5.8 (1.0)	0.99[a]	0.93[b]	0.08	6.7 (1.1)	5.8 (1.1)	5.7 (1.1)	0.80[a]	0.88[b]	0.07	6.7 (1.1)	6.3 (1.1)	5.8 (1.0)	0.44	0.91[b]	0.47
Lenticular nucleus	7.0 (1.0)	6.5 (1.0)	6.6 (1.0)	0.59[a]	0.50[b]	0.09	7.0 (1.0)	6.4 (1.0)	6.5 (1.0)	0.57[a]	0.50[b]	0.08	7.0 (0.9)	6.4 (1.0)	6.4 (1.0)	0.57[a]	0.57[b]	0.00
Ventricular CSF	25.7 (8.8)	30.3 (9.0)	27.5 (8.8)	0.52	0.21	0.31	25.8 (9.1)	28.3 (9.1)	27.6 (9.0)	0.27	0.20	0.08	26.2 (9.3)	25.8 (9.8)	28.4 (9.0)	0.04	0.34	0.28

Note: Values are presented as mean (standard deviation). Reported values are estimated means from pairwise comparisons of CON, nsALC and sALC. [a]nsALC mean volume < nsCON mean volume, $P \leq 0.017$. [b]sALC mean volume < nsCON mean volume, $P \leq 0.017$. [c]sALC mean volume < nsALC mean volume, $P \leq 0.017$. CSF = cerebrospinal fluid; GM = gray matter; ROI = region of interest; WM = white matter.

Pfefferbaum 2005; Crews & Nixon 2009). Taken together, the rapid volume increases in cortical GM volumes observed in this ALC cohort during the first month of abstinence may be related to increases of neuronal structural and metabolic integrity, and glial cell proliferation. However, the *in vivo* recovery trajectory of the specific cellular components comprising the cortical and subcortical GM and lobar WM in human ALC is still unclear.

Although volume recovery in ALC within 1 year of abstinence was observed in multiple studies, many cross-sectional reports indicated that ALC demonstrated significantly smaller regional GM and/or WM volumes after 6 or more months of sobriety than controls (Buhler & Mann 2011; Monnig *et al.* 2013). In the current study, both nsALC and sALC exhibited volume increases in multiple cortical and subcortical GM regions after approximately 7.5 months of sustained abstinence, but both groups continued to manifest lower GM volumes than CON in most regions (i.e. −3.2 percent lower total cortical GM in ALC at AP3). Cerebellar volume also increased significantly in ALC over 7.5 months of abstinence, but it was not significantly different from CON at any AP. Frontal GM was the sole cortical GM region in ALC that was statistically equivalent to CON after 7.5 months of abstinence. Recovery of frontal GM volume is clinically relevant because ALC with lower volumes in frontal subregions (e.g. orbitofrontal and dorsolateral prefrontal cortices) during early abstinence were more likely to relapse within approximately 1 year after treatment (Rando *et al.* 2010; Cardenas *et al.* 2011; Durazzo *et al.* 2011b). For lobar WM, ALC demonstrated significant WM volume increases in all regions except the occipital WM, but cross-sectionally, ALC WM volumes were not significantly different from CON in any region at any AP. This finding is consistent with animal models (Kroenke *et al.* 2014) and several human studies that reported no significant differences in lobar WM volumes between controls and ALC during early and extended abstinence (Monnig *et al.* 2013). Additional longitudinal studies are needed to specifically examine if major subcomponents within the GM and WM regions of interest measured in this study show equivalent rates of change during abstinence.

sALC and nsALC did not differ in regional volume recovery rates, but sALC showed significantly lower frontal and total cortical GM recovery with increasing age than nsALC. The greater magnitude of age-related effects on longitudinal GM volume recovery in sALC were not mediated by their greater level of alcohol consumption, and are consistent with our cross-sectional studies, where 1-week abstinent sALC demonstrated significantly greater age-related frontal GM volume loss than nsALC (Durazzo *et al.* 2014b). Taken together, cigarette smoking in ALC appears to adversely affect the structural integrity

of brain parenchyma comprising the GM of ALC with increasing age [see Durazzo *et al.* (2010, 2014a) for discussion of potential smoking-related mechanisms].

In this study, higher alcohol consumption and cigarette exposure measures were only related to lower recovery of frontal GM and WM volumes, respectively. This supports assertions that the frontal lobe is particularly vulnerable to the effects of hazardous alcohol consumption (Crews & Nixon 2009) and chronic smoking (Durazzo *et al.* 2010). However, alcohol consumption and cigarette exposure measures in ALC showed weak associations ($r \leq -0.25$) with regional volumes in cross-sectional analyses at AP1, AP2 and AP3 (data not shown). Other cross-sectional and longitudinal studies in ALC reported weak or non-significant associations of alcohol consumption variables with regional brain volumes (Buhler & Mann 2011; Monnig *et al.* 2013). Additionally, adolescent offspring of ALC, with minimal alcohol exposure, demonstrated smaller regional brain volumes than offspring of individuals without a history of alcohol use disorders (Tessner & Hill 2010). Given the limited or lack of associations of alcohol consumption, smoking severity, and medical, psychiatric and substance co-morbidities with volume changes and cross-sectional volumes in ALC, we believe that the persistent lower regional cortical and subcortical GM volumes in ALC relative to CON after 7.5 months of abstinence likely reflect the influence of pre-morbid factors (e.g. genetic vulnerability to alcohol use disorders) or co-morbid factors not assessed in this study.

For nsALC only, linear volume increases in lobar GM and WM, cerebellum and lenticular nucleus were robust predictors of improved processing speed over 7.5 months. The measures that formed the processing speed domain require speed and accuracy (i.e. efficiency), which interrogates the integrity of nodes of multiple anterior and posterior circuits and their interconnections (Salthouse 2000; Kolb & Whishaw 2009). The absence of associations between change regional volumes and neurocognition in sALC was not attributable to restriction of range in these measures and may indicate that sALC and nsALC potentially employ different circuits during completion of the processing speed measures. Alternately, sALC may show abnormal functional and/or anatomical connectivity in the multiple cortical–subcortical circuits that subserve processing speed. This may have implications for neuroplasticity-based cognitive remediation approaches for treatment-seeking ALC (e.g. Rupp *et al.* 2012).

This report has limitations that may influence the generalizability of the findings. The level of volume change in ALC in the lobar regions or subcortical structures (e.g. cerebellum) may not be representative of the magnitude of change of all subcomponents (e.g. cerebellar vermis) comprising the larger region of interest. The modest number of observations at TP3 increases the risk of model over-fitting and corresponding Type I error, despite all critical model assumptions having been met in all analyses. The results may have been influenced by factors not assessed in this study, such as personality disorders, diet/nutrition, exercise, subclinical liver dysfunction and genetic predispositions (e.g. Mon *et al.* 2013). Only approximately 10 percent of participants were female, which precluded examination of sex effects.

In conclusion, this cohort of treatment-seeking ALC demonstrated significant recovery of regional GM and WM volumes over 7.5 months of abstinence, the rate of volume change for regional GM was greatest during the first 30 days of abstinence, and volume recovery was not influenced by common medical, psychiatric or substance misuse co-morbidities; however, sALC showed lower frontal and total cortical GM recovery with increasing age than nsALC. Despite significant regional volume recovery, sALC and nsALC continued to demonstrate significantly smaller GM volumes in most regions after 7.5 months of sustained abstinence than CON. Additional longitudinal studies are needed to determine the neuropsychological, psychosocial and treatment implications of these findings.

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Disclosure/Conflict of Interest

The authors have no disclosures and no conflicts of interest to report.

Authors Contribution

TCD and DJM conceptualized and designed the study. TCD recruited and conducted the clinical and neuropsychological assessment of study participants or

directly supervised participant recruitment and assessment. TCD Durazzo was responsible for all statistical analyses, data interpretation and manuscript preparation. AM, SG and P-HY were responsible for magnetic resonance data acquisition. AM completed the quantitative morphological processing and quality control. All authors critically reviewed content and approved the final version for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Volume changes in total cortical gray matter and lobar white matter for the alcohol dependent group (nsALC + sALC) across AP1, AP2, and AP3

Table S1 Linear rates of change in regional volumes as predictors of change in Digit Symbol and Symbol Search over 7.5 months in non-smoking ALC

Appendix S1 Longitudinal analyses

