

# The Role of Aging, Drug Dependence, and Hepatitis C Comorbidity in Alcoholism Cortical Compromise

Edith V. Sullivan, PhD; Natalie M. Zahr, PhD; Stephanie A. Sassoon, PhD; Wesley K. Thompson, PhD; Dongjin Kwon, PhD; Kilian M. Pohl, PhD; Adolf Pfefferbaum, MD

**IMPORTANCE** The prevalence of alcohol misuse increased substantially over a decade in adults, particularly in those aged 65 years or older. Ramifications for brain structural integrity are significant, especially in older adults.

**OBJECTIVES** To combine cross-sectional, longitudinal data to test age-alcoholism interactions and examine the association between prevalent comorbidities (drug dependence and hepatitis C virus [HCV] infection) and cortical volume deficits in alcohol dependence.

**DESIGN, SETTING, AND PARTICIPANTS** During 14 years, 826 structural magnetic resonance images were acquired in 222 individuals with alcohol dependence and 199 age-matched control participants (aged 25-75 years at initial study), parcellated with a common atlas, and adjusted for brain volume. Longitudinal data were available on 116 participants with alcoholism and 96 control participants. *DSM-IV* criteria determined alcohol and drug diagnoses; serology testing determined HCV status. The study was conducted at SRI International and Stanford University School of Medicine from April 11, 2003, to March 3, 2017.

**MAIN OUTCOMES AND MEASURES** Magnetic resonance imaging–derived regional cortical volumes corrected for supratentorial volume and sex.

**RESULTS** Of the 222 participants with alcoholism, 156 (70.3%) were men; mean (SD) age was 48.0 (10.0) years; the mean age for the 199 control participants was 47.6 (14.0) years. Participants with alcohol dependence had volume deficits in frontal ( $t = -5.732$ ,  $P < .001$ ), temporal ( $t = -3.151$ ,  $P = .002$ ), parietal ( $t = -5.063$ ,  $P < .001$ ), cingulate ( $t = -3.170$ ,  $P = .002$ ), and insular ( $t = -4.920$ ,  $P < .001$ ) cortices; deficits were prominent in frontal subregions and were not sex dependent. Accelerated aging occurred in frontal cortex ( $t = -3.019$ ,  $P < .02$ ) and precentral ( $t = -2.691$ ,  $P < .05$ ) and superior gyri ( $t = -2.763$ ,  $P < .05$ ) and could not be attributed to the amount of alcohol consumed, which was greater in younger-onset than older-onset participants with alcoholism ( $t = 6.1191$ ,  $P < .001$ ). Given the high drug-dependence incidence (54.5%) in the alcoholism group, analysis examined drug subgroups (cocaine, cannabis, amphetamines, opiates) compared with drug-dependence-free alcoholism and control groups. Although the alcohol plus cocaine ( $t = -2.310$ ,  $P = .04$ ) and alcohol plus opiate ( $t = -2.424$ ,  $P = .04$ ) groups had smaller frontal volumes than the drug-dependence-free alcoholism group, deficits in precentral ( $t = -2.575$ ,  $P = .01$ ), supplementary motor ( $t = -2.532$ ,  $P = .01$ ), and medial ( $t = -2.800$ ,  $P = .01$ ) volumes endured in drug-dependence-free participants with alcoholism compared with control participants. Those with HCV infection had greater deficits than those without HCV infection in frontal ( $t = 3.468$ ,  $P = .01$ ), precentral ( $t = 2.513$ ,  $P = .03$ ), superior ( $t = 2.533$ ,  $P = .03$ ), and orbital ( $t = 2.506$ ,  $P = .03$ ) volumes, yet total frontal ( $t = 2.660$ ,  $P = .02$ ), insular ( $t = 3.526$ ,  $P = .003$ ), parietal ( $t = 2.414$ ,  $P = .03$ ), temporal ( $t = 3.221$ ,  $P = .005$ ), and precentral ( $t = 3.180$ ,  $P = .01$ ) volume deficits persisted in the uninfected participants with alcoholism compared with control participants with known HCV status.

**CONCLUSIONS AND RELEVANCE** Drug dependence and HCV infection compounded deleterious effects of alcohol dependence on frontal cortical volumes but could not account for the frontally distributed volume deficits in the drug-free participants with alcoholism. We speculate that age-alcohol interactions notable in frontal cortex put older adults at heightened risk for age-associated neurocompromise even if alcohol misuse is initiated later in life.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2018.0021  
Published online March 14, 2018.

← Editorial

+ Supplemental content

**Author Affiliations:** Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California (Sullivan, Zahr, Kwon, Pfefferbaum); Center for Health Sciences, SRI International, Menlo Park, California (Zahr, Sassoon, Kwon, Pohl, Pfefferbaum); Department of Family Medicine and Public Health, University of California, San Diego (Thompson).

**Corresponding Author:** Edith V. Sullivan, PhD, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine (MC5723), 401 Quarry Rd, Stanford, CA 94305 (edie@stanford.edu).

It is well established through in vivo neuroimaging<sup>1-3</sup> and postmortem<sup>4,5</sup> studies that chronic, excessive alcohol consumption can result in regional brain shrinkage. This assertion is supported by longitudinal evidence indicating that at least partial reversal of tissue volume deficits and ventricular dilatation occur early in abstinence—over days to weeks<sup>6,7</sup>—and that further cortical tissue shrinkage ensues with resumption of drinking.<sup>1,8,9</sup> The most commonly reported regions affected in vivo are frontally distributed, notably superior and middle lateral, orbital, and medial frontal gyri in individuals with treated<sup>10-12</sup> and never-treated<sup>13</sup> alcoholism. Prefrontal cortex is also a target of normal aging, showing pronounced volume decline from approximately age 50 years onward.<sup>14-16</sup> The potential interaction of normal aging and alcoholism has been borne out in several cross-sectional studies in which accelerated volume declines appear by approximately age 45 years in alcohol-dependent groups.<sup>17,18</sup> Assessing the association between age-alcoholism interactions and brain structure has new urgency considering current epidemiologic data indicating a major increase, measured throughout a decade, of 106.7% (from 1.5% to 3.1% of the US population) in the prevalence of alcohol use disorder (AUD) in individuals aged 65 years or older. This increasing prevalence of AUD is also occurring in younger adults, ranging from a 44.4% increase in individuals aged 18 to 29 years to 47.7% in those aged 30 to 44 years and 81.5% in adults aged 45 to 64 years.<sup>19</sup> To date, the locus and extent of enduring regional cortical volume deficits, however, have not been examined longitudinally across the adult age range in large samples of participants with alcohol dependence.

Factors that contribute to persistent or accelerated brain volume abnormalities are still being identified but likely include alcohol consumption variables of frequency and amount drunk, age at onset of alcohol misuse, and conditions resulting from years of abusive drinking, such as withdrawal signs and symptoms<sup>20</sup> and alcoholism-related nutritional deficiencies.<sup>21,22</sup> Perhaps the most salient factor is age, which may render the older brain especially vulnerable to insult from other factors, including excessive alcohol consumption and attendant events. Among these events are accruing detoxification experiences; comorbid licit and illicit drug dependence, which is a frequent concomitant factor of alcohol misuse<sup>23</sup>; and acquired medical conditions, such as hepatitis C virus (HCV) infection, which is prevalent in individuals who misuse alcohol.<sup>24,25</sup>

Alcohol use disorder and drug use comorbidity rates are high, highlighting the relevance of potentially compounding effects of substance dependence on brain structural integrity. Estimates indicate that 4 of 5 adults with a substance use disorder also have AUD<sup>26</sup> and that 15% of adults with AUD also have a substance use disorder.<sup>27</sup> Commonly abused substances in the United States include cocaine, opiates, amphetamines, and cannabis. Several studies report enhancement of activation in reward networks of the striatum or enlargement in striatal structures compared with control participants with drug dependence meta-analyses,<sup>28,29</sup> whereas studies of alcoholism report striatal volume deficits involving caudate nucleus, nucleus accumbens, or globus pallidus.<sup>10</sup> Overall, evi-

## Key Points

**Question** What is the pattern of alcoholism-associated cortical volume deficits, and are they accelerated with aging or augmented by drug dependence or hepatitis C virus infection comorbidity in alcohol-dependent men and women spanning adulthood?

**Findings** This combined cross-sectional/longitudinal study evaluated magnetic resonance imaging data collected during 14 years in 199 control and 222 alcohol-dependent participants. Findings revealed frontally distributed cortical volume deficits in individuals with alcohol dependence, accelerated age-dependent decline, and compounded deficits with drug dependence or hepatitis C virus infection comorbidity.

**Meaning** These findings raise concern for heightened risk of accelerated cortical aging with alcohol dependence even when alcohol misuse develops later in life.

dence indicates that various constellations of drug and alcohol misuse confer some selective and other overlapping effects on brain structure.

Hepatitis C virus infection also occurs with high prevalence in individuals with AUD<sup>25</sup> and is the most common blood-borne infection in the United States. Hepatitis C virus can infiltrate the brain<sup>30</sup> with presence in the frontal but not occipital cortex.<sup>31</sup> The prevalence of HCV is highest (approximately 75%) in those born between 1945 and 1965 who are now approximately aged 50 to 70 years, which is the time of notable senescent brain structural declines in unaffected persons<sup>14-16</sup> and accelerates in individuals with alcoholism.<sup>17</sup> Alcoholism and HCV infection comorbidity also increases the risk of chronic liver disease morbidity and mortality.<sup>25</sup> Although intravenous drug use is the most recognized vehicle of infection, other non-drug-related causes exist and include male-to-male sex and body tattoos.<sup>32</sup>

Given the known independent contributions of age, alcoholism, drug, and HCV infection to frontal volume insult, we tested the hypotheses that alcohol-dependent adults (1) would exhibit significant cortical volume deficits and show accelerated aging selective to frontal cortical loci; (2) would have greater volume deficits, especially affecting frontal sites, than those without drug dependence; (3) would show compounded alcoholism-related volume deficits in frontal cortex when infected with HCV; and (4) who were drug-free and HCV-infection-free would have enduring volume deficits.

## Methods

### Participants

The participants were drawn from our ongoing longitudinal studies of brain magnetic resonance imaging (MRI) (control participants<sup>15</sup> and those with alcoholism<sup>33</sup>). Clinical psychologists (including S.A.S.) or research nurses administered the Structured Clinical Interview for *DSM-IV*<sup>34</sup> to all study participants.<sup>33</sup> Only participants meeting *DSM-IV* criteria for alcohol dependence were included in the patient group. Prospective control participants did not meet *DSM-IV* criteria for

any Axis I disorder. Quantity of lifetime alcohol consumption and date of last drink were obtained from all participants by interview.<sup>35-37</sup> The study was conducted from April 11, 2003, to March 3, 2017. All study participants provided written informed consent, and the study was approved by the institutional review boards of Stanford University School of Medicine and SRI International. Participants received financial compensation.

Of the 222 participants with alcoholism, 123 (55.4%) also met historical *DSM-IV* criteria for substance dependence. Substances most commonly used to dependence were cocaine, cannabis, amphetamines, and opiates: 86 participants with alcoholism (38.7%) had a lifetime history of cocaine dependence, 50 (22.5%) had a history of cannabis dependence, 44 (19.8%) had a history of amphetamine dependence, and 30 (13.5%) had a history of opiate dependence. Approximate mean remission time for the most recent nonalcohol substance of abuse/dependence was 495.8 weeks (median, 294 weeks). One control participant developed cannabis dependence at a later MRI scan but had no drug diagnosis at her initial visit. Of the 222 participants with alcoholism, 107 (48.2%) had current nicotine dependence, 35 (15.8%) had a history of nicotine dependence, 60 (27.0%) never had nicotine dependence, and the status of 20 (9.0%) was unknown. Of the 199 control participants, 14 (7.0%) had current nicotine dependence, 6 (3.0%) had a history of nicotine dependence, 117 (58.8%) never had nicotine dependence, and the status of 62 (31.2%) was unknown.

## MRI Acquisition and Analysis

### Image Acquisition

Data obtained with MRI were acquired between April 11, 2003, and March 3, 2017 (3-T GE whole-body MR systems; General Electric Healthcare). An 8-channel phased-array head coil and the same axial acquisition protocol were used throughout (eAppendix 1 in the [Supplement](#)).

### Statistical Analysis

All statistical analyses (eAppendix 2 in the [Supplement](#)) were performed with the R statistical language software.<sup>38</sup> The magnitude of cortical gray matter volume is correlated with supratentorial volume (svol). To examine each gray matter volume region independent of svol, the regression of regional volume on svol was computed for control participants with a general linear model (*lm* in R); this function was then applied to the data of all participants at each scan. Only control participants were used in the fitting function to ensure that the estimate of association was not influenced by disease.<sup>35,39</sup> This procedure also minimized sex effects given that women, in general, have smaller heads and svol than men (mean svol for control women, 1199.3 mL vs control men, 1360.5 mL;  $t = 11.397$ ;  $P < 10^{-16}$  in the present sample).

## Results

A control group was selected to match the 25- to 75-year age range of the alcoholism group at study entry. Mean (SD) age of the 222 alcohol-dependent participants was 48.0 (10.0)

years; the mean age for the 199 control participants was 47.6 (14.0) years. A total of 826 MRIs were analyzed: 417 acquired in 199 control and 409 acquired in 222 alcohol-dependent participants. Of the 199 control and 222 alcohol-dependent participants scanned at entry, 96 control (48.2%) and 116 alcohol-dependent participants (52.3%) had 2 or more MRIs. Of these, 47 control (5.0%) and 71 alcohol-dependent participants (61.2%) had 2 MRIs, 21 control (2.1%) and 31 alcohol-dependent participants (26.7%) had 3 MRIs, 11 control (11.5%) and 9 alcohol-dependent participants (7.8%) had 4 MRIs, and 17 control (17.7%) and 5 alcohol-dependent participants (4.3%) had 5 or more MRIs (eFigure 1 in the [Supplement](#)). Consistent with epidemiologic studies of alcoholism,<sup>19</sup> the groups comprised more men than women, but the control and alcoholism groups had similar sex representation and were of similar ages ([Table](#); eTable 1 in the [Supplement](#)). All analyses were based on regional brain volumes adjusted for total brain volume (svol), which minimized differences attributable to sex.

## Regional Volume Deficits in Participants With Alcoholism

Examination of the 6 major cortical volumes identified 5 regions showing volume deficits in the alcoholism compared with control groups: frontal ( $t = -5.732$ ,  $P < .001$ ), temporal ( $t = -3.151$ ,  $P = .002$ ), parietal ( $t = -5.063$ ,  $P < .001$ ), cingulate ( $t = -3.170$ ,  $P = .002$ ), and insular ( $t = -4.920$ ,  $P < .001$ ) cortices ([Figure 1](#); eTable 2A in the [Supplement](#)); the exception was the occipital lobe. Analysis of the 23 cortical subregions (eFigure 2 for frontal subregions in the [Supplement](#)) revealed gray matter volume deficits in the alcoholism compared with the control group in 16 regions (false discovery rate corrected; eTable 2B in the [Supplement](#)): precentral ( $t = -5.428$ ,  $P < .001$ ), superior ( $t = -3.131$ ,  $P = .005$ ), middle ( $t = -2.763$ ,  $P = .01$ ), inferior ( $t = -2.318$ ,  $P = .03$ ), supplementary motor ( $t = -3.891$ ,  $P < .001$ ), medial ( $t = -4.481$ ,  $P < .001$ ) frontal; insula ( $t = -4.920$ ,  $P < .001$ ); anterior ( $t = -2.681$ ,  $P = .01$ ) and midposterior ( $t = -2.156$ ,  $P = .05$ ) cingulate; postcentral ( $t = -3.946$ ,  $P < .001$ ), superior ( $t = -3.492$ ,  $P = .002$ ), inferior ( $t = -4.002$ ,  $P < .001$ ), precuneus ( $t = -3.148$ ,  $P = .005$ ), paracentral ( $t = -3.051$ ,  $P = .006$ ) parietal; and superior ( $t = -2.865$ ,  $P = .01$ ) and middle ( $t = -2.914$ ,  $P = .01$ ) temporal. Volume deficits were prominent in frontal, parietal, and insular cortices and were less so but still significant in temporal and cingulate regions ([Figure 2](#)). Testing for diagnosis-by-sex interactions yielded no significant effects in either the 6- or the 23-regional volume analyses.

## Age-Alcoholism Interactions

The effect of age was examined independently for the control and alcoholism groups. The control group showed significant aging effects in 5 of the 6 cortical regions: frontal  $t = -11.672$ ,  $P < .001$ ; cingulate  $t = -4.471$ ,  $P < .001$ ; occipital  $t = -2.983$ ,  $P < .001$ ; parietal  $t = 11.660$ ,  $P < .001$ ; temporal  $t = -13.210$ ,  $P < .001$  (not insula). The alcoholism group showed aging effects in 5 of the 6 cortical regions: frontal  $t = -10.998$ ,  $P < .001$ ; insula  $t = -2.511$ ,  $P = .01$ ; cingulate  $t = -2.374$ ,  $P = .02$ ; parietal  $t = -6.195$ ,  $P < .001$ ; temporal  $t = -5.535$ ,  $P < .0001$  (not occipital). Age-alcohol interactions occurred in the alcoholism group over and above those measured in the control group for the frontal cortex only ( $t = -3.019$ ,  $P = .02$ ) (eTable 3A in the [Supplement](#)).

Table. Demographic Data for the Control and Alcoholism Groups

Demographic Variable <sup>a</sup>	Control	Alcoholism
Sex, No. (%)		
Men	107 (53.8)	156 (70.3)
Women	92 (46.2)	66 (29.7)
Self-defined race/ethnicity, No. (%)		
Asian	28 (14.1)	3 (1.4)
African American	28 (14.1)	69 (31.1)
White	106 (53.2)	98 (44.1)
Other/unknown	37 (18.6)	52 (23.4)
Detoxifications or treatment, No. (%)	NA	
Yes		83 (46.6)
No		95 (53.4)
Drank to stop symptoms, No. (%)	NA	
Yes		96 (48.7)
No		101 (51.3)
Reported seizures	NA	
Yes		14 (7.0)
No		186 (93.0)
Age, y, mean (SD)		
Men	47.7 (13.7)	48.5 (10.2)
Women	45.9 (14.3)	48.2 (9.4)
Education, mean (SD), y	16.0 (2.4)	13.3 (2.4)
Socioeconomic status, mean (SD) <sup>b</sup>	25.4 (11.3)	41.8 (14.4)
WTAR FSIQ estimate, mean (SD) <sup>c</sup>	105.6 (9.3)	98.3 (11.5)
Alcoholism onset age, mean (SD), y	NA	25.5 (9.6)
Lifetime alcohol consumed at final MRI, mean (SD), kg	34.0 (57.0)	1202.0 (885.8)
Alcohol consumed in year before MRI, mean (SD), kg	NA	35.3 (46.1)
Days since last drink, mean (SD)	NA	290.5 (689.3)
Alcohol consumed in year before MRI, median, kg	NA	20.2
Days since last drink, median	NA	92

Abbreviations: FSIQ, full-scale intelligence quotient; MRI, magnetic resonance imaging; NA, not applicable; WTAR, Wechsler Test of Adult Reading.

<sup>a</sup> Data on some variables were not obtained for all patients.

<sup>b</sup> Lower score indicates higher status.

<sup>c</sup> Participants had either the National Adult Reading Test or the WTAR for IQ; 10 points were added to the National Adult Reading Test IQ to make it comparable to the WTAR Full Scale IQ.

Age-associated declines were detected in all 7 frontal subregions of the alcoholism and control groups (eTable 3B in the Supplement). Furthermore, the alcoholism group showed age-alcoholism interactions in the precentral ( $t = -2.691$ ,  $P = .04$ ) and superior frontal ( $t = -2.763$ ,  $P = .04$ ) cortices that exceeded the age declines identified in the control participants (Figure 3; eFigure 3 in the Supplement).

To identify factors that contributed to the age-alcoholism interactions, we examined drinking variables commonly associated with age. Total alcohol ingested in a lifetime correlated with mean age of alcohol-dependent individuals ( $r = 0.263$ ;  $P < .001$ ), and older age of alcoholism onset correlated with older age at examination ( $r = 0.367$ ;  $P < .001$ ) (eFigure 4 in the Supplement). Smaller, age-adjusted frontal cortical volumes showed a correlational trend

with total lifetime alcohol consumption ( $r = -0.122$ ;  $P = .07$ ). Many participants had a relatively late onset of alcohol dependence. To test for regional volume differences in older participants (age  $\geq 40$  years), we divided that alcoholism group into those with early onset (by age 30 years,  $n = 117$ ) and those with late-onset (age  $\geq 40$  years,  $n = 24$ ). This comparison revealed smaller age-adjusted frontal cortical volumes in the late-onset relative to the early-onset group ( $t = -2.271$ ;  $P = .03$ ) even having controlled for normal aging effects. The late-onset group had lower lifetime alcohol consumption than the early-onset group (early mean, 1480.8 kg; late mean, 759.9 kg;  $t = 6.1191$ ;  $P < .001$ ), but these groups did not differ significantly in days since last drink ( $t = 1.4525$ ;  $P = .15$ ).

### Drug and Alcohol Dependence Comorbidity

The first test of drug comorbidity examined volumes of the 5 alcoholism subgroups (101 alcohol only, 86 alcohol-cocaine, 30 alcohol-opiates, 44 alcohol-amphetamines, 50 alcohol-cannabis) against control volumes of the 6 lobar regions. Each of these 5 subgroups had volume deficits in frontal, insula, and parietal cortices relative to control participants ( $P < .004$ ; eTable 4). Furthermore, alcohol-dependent participants without a drug history ( $t = -2.86$ ,  $P = .02$ ) and those with a cocaine history ( $t = -2.586$ ,  $P = .03$ ) also showed volume deficits in temporal cortices; in addition, the cocaine group had deficits in cingulate cortex ( $t = -2.717$ ,  $P = .03$ ). Those with alcohol dependence with amphetamine ( $t = 2.448$ ,  $P = .04$ ) or cannabis ( $t = 2.596$ ,  $P = .04$ ) histories had larger occipital volumes than control participants (eTable 4 in the Supplement). The second test examined volumes of the 4 alcoholism subgroups with histories of drug dependence against the alcoholism subgroup with no history of drug dependence. The alcohol-cocaine ( $t = -2.310$ ,  $P = .04$ ) and alcohol-opiate ( $t = -2.424$ ,  $P = .04$ ) groups had smaller frontal volumes than the alcoholism group without drug histories (eTable 4 and eFigure 5 in the Supplement), whereas the alcoholism subgroup with amphetamine ( $t = 2.591$ ,  $P = .02$ ) or cannabis ( $t = 2.722$ ,  $P = .02$ ) histories had larger occipital volumes than the non-drug-dependent alcoholism subgroup.

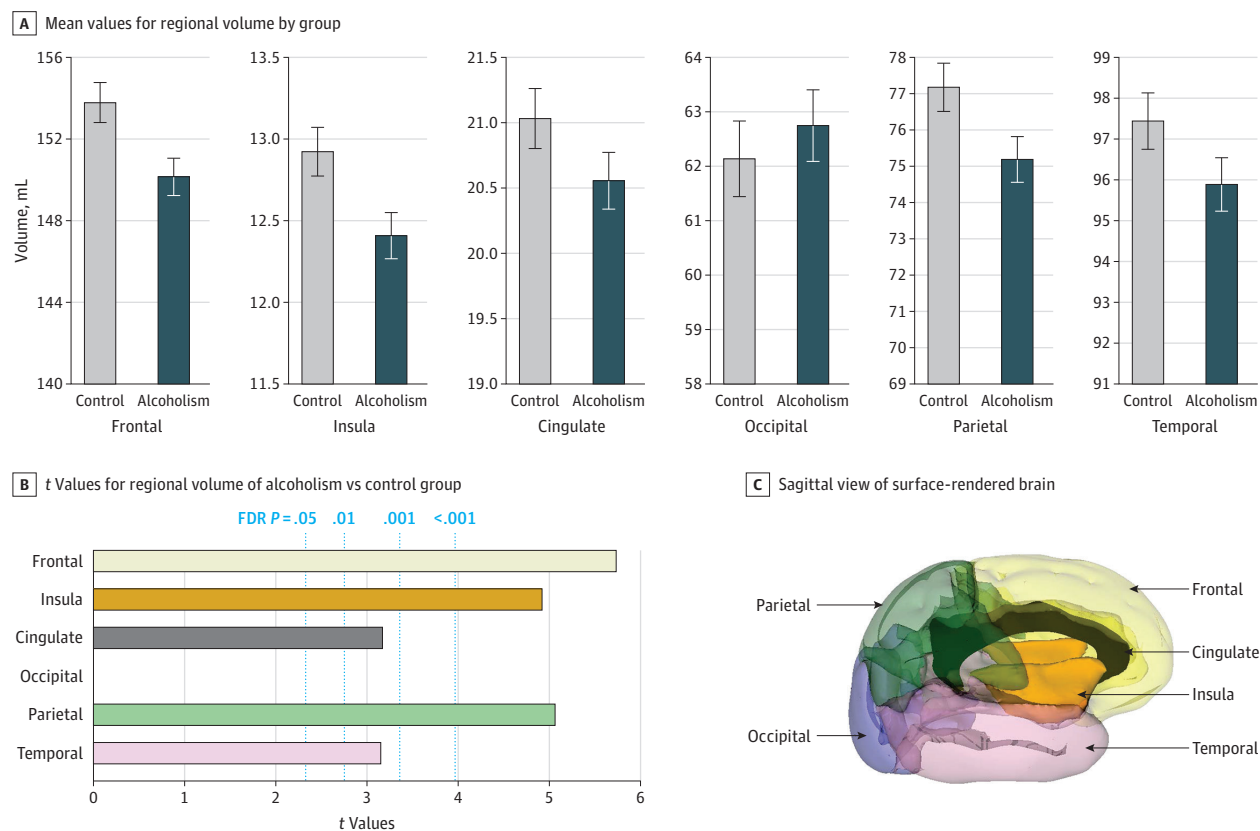
Given the observed frontal deficits, we tested for group differences in the 7 frontal volumes. Three regions showed significant volume deficits in the alcoholism group with no history of drug dependence and each of the 4 alcohol-drug groups relative to control participants: precentral ( $t = -2.575$ ,  $P = .01$ ), supplementary motor ( $t = -2.532$ ,  $P = .01$ ), and medial ( $t = -2.800$ ,  $P = .01$ ) cortices. Comparisons of the alcohol-drug groups with the nondrug alcoholism group did not yield significant differences for any of the 7 frontal subregions (eTable 4 in the Supplement).

### HCV-Alcoholism Comorbidity

We compared the volumes of 6 lobar regions in alcohol-dependent participants with and without HCV infection comorbidity (eTable 1 in the Supplement). Results indicated smaller volumes in those with HCV infection than without HCV infection in the frontal volumes only ( $t = 3.468$ ,  $P = .01$ ) (Figure 4; eTable 5 in the Supplement). Analysis of the 7 frontal subregions revealed larger volumes for alcohol-



Figure 1. Regional Cortical Volumes Showing Volume Deficits in 222 Alcohol-Dependent Participants



A, Mean values for each volume by group; error bars indicate 95% CI. B, Values from *t* tests for regional volumes indicating group differences and false discovery rate (FDR)-corrected *P* values. In 5 of the 6 regions, the alcoholism group had smaller volumes than the control group. The *t* value for the occipital comparison indicated a nonsignificant higher value for the alcoholic than control group. C, Sagittal view of a surface-rendered brain indicating the 6 global cortical regions used for volumetric analysis.

dependent participants without HCV infection in the precentral ( $t = 2.513$ ,  $P = .03$ ), superior ( $t = 2.533$ ,  $P = .03$ ), and orbital ( $t = 2.506$ ,  $P = .03$ ) cortices (eTable 5A in the Supplement). Compared with the 89 control participants with known HCV status, the 115 alcohol-dependent participants free of HCV infection had significant volume deficits in frontal ( $t = 2.660$ ,  $P = .02$ ), insular ( $t = 3.526$ ,  $P = .003$ ), parietal ( $t = 2.414$ ,  $P = .03$ ), temporal ( $t = 3.221$ ,  $P = .005$ ), and precentral ( $t = 3.180$ ,  $P = .01$ ) cortical volumes (eTable 5B in the Supplement).

### Group Differences in Alcohol-Dependent Participants Scanned Once vs Multiple Times

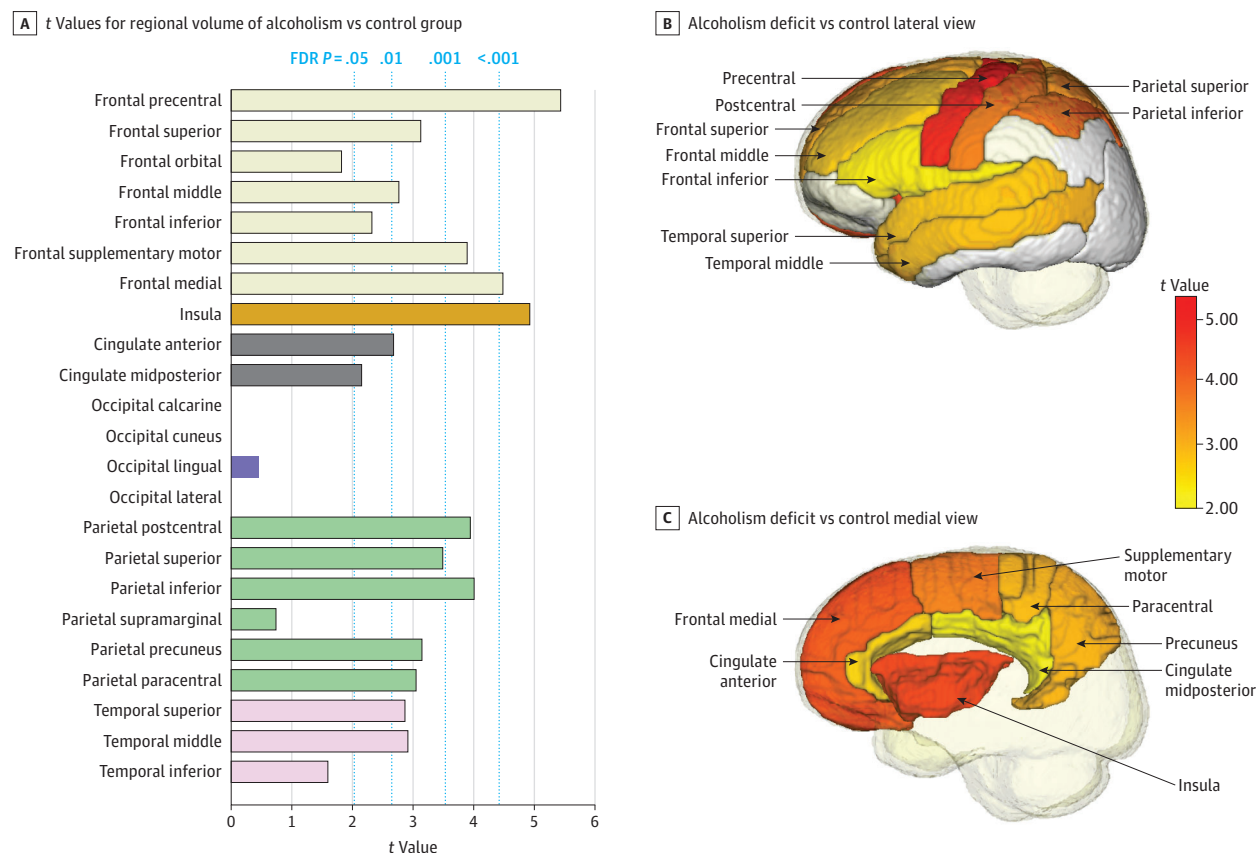
Questioning whether alcohol-dependent participants who received 1 MRI differed in demographic or volume data from those who returned for multiple examinations revealed significant differences in alcohol consumption variables between these subgroups (eTable 6 in the Supplement). The subgroup scanned once had drunk more alcohol in the year before scanning ( $t = 2.076$ ,  $P = .04$ ) and had a shorter interval between the last drink and the scan ( $t = -2.030$ ,  $P = .04$ ). Even greater differences were identified for the number of detoxifications ( $\chi^2 = 106.69$ ,  $P < .001$ ), history of drinking to stop symptoms ( $\chi^2 = 72.04$ ,  $P < .001$ ), and seizures ( $\chi^2 = 12.432$ ,  $P < .001$ ), all of which occurred with greater

frequency in the single- than multiple-scan subgroup. Our reanalysis of the MRI data with respect to these subgroups revealed a similar pattern of regional volume deficits and frontal age interactions in both subgroups (single group  $t = -3.339$ ;  $P < .001$ ; multiple group  $t = -2.510$ ;  $P = .01$ ) (eFigure 6 in the Supplement), with the single MRI group having even greater volume deficits than the multiple MRI group in frontal, temporal, parietal, and occipital regions.

### Discussion

Examination of cortical brain structure using atlas-based, quantitative MRI revealed regionally selective volume deficits in the 222 alcohol-dependent participants relative to a control group spanning the same 50-year adult age range. Regional volumes most extensively affected included lateral and medial frontal, parietal, and insular cortices with additional deficits in temporal and cingulate regions. These effects endured when examining alcohol-dependent participants without comorbidity of drug dependence or HCV infection, and there was evidence for compounded untoward effects of drug dependence and HCV infection with alcoholism. Although our cohort of nearly 200

Figure 2. Gray Matter Regions Showing Volume Deficits in 222 Alcohol-Dependent Participants



Values from t tests for regional volumes indicating group differences and false discovery rate (FDR)-corrected P values. The t values for 3 occipital regional comparisons indicated a nonsignificant higher value for the alcoholic than

control group. (A). In general, the alcohol-dependent group had smaller volumes than the control group. Lateral (B) and medial (C) sagittal views of the gray matter regions show volume deficits in alcohol-dependent participants.

control participants showed an expected age-related cortical volume decline salient in precentral and superior frontal regions, longitudinal analysis of the alcoholism group data identified age-alcoholism interactions beyond those observed in control participants. These findings in alcohol-dependent and control participants, examined 1 to 8 times or more during intervals of 1 week to 12.5 years, representing, to our knowledge, the largest and longest-studied group to date, support our study hypotheses regarding alcoholism-associated accelerated aging and cortical volume deficits independent of drug dependence or HCV infection comorbidity.

### Pattern of Cortical Volume Deficits Associated With Alcohol Dependence and Aging

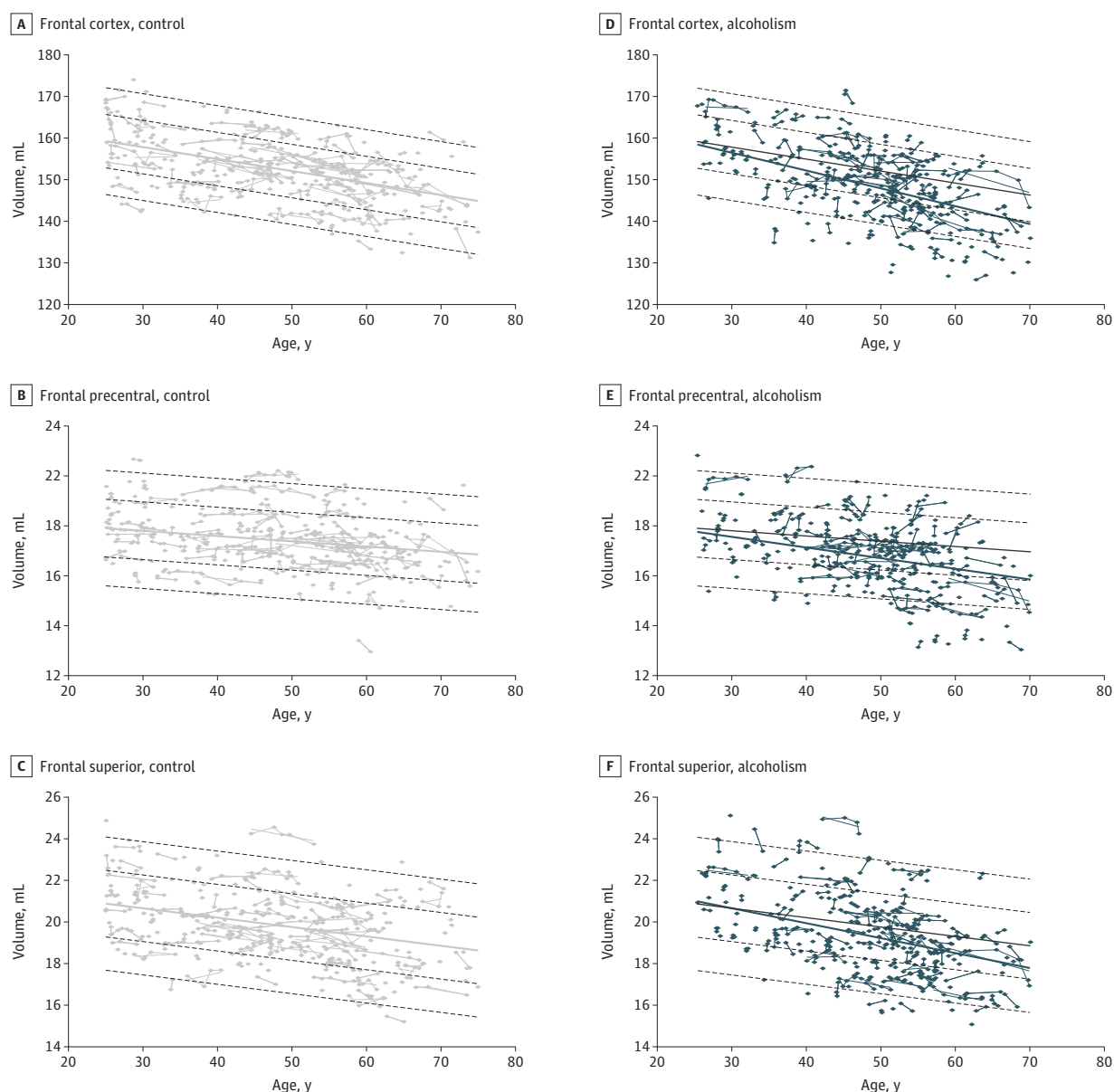
Courville's<sup>40</sup> early claim of focal neuronal loss in alcoholism cases on postmortem study included the superior dorsal surfaces of the frontal cortex in addition to the precentral, postcentral, and superior parietal regions with sparing of temporal, inferior parietal, and occipital regions. This postmortem pattern of regional effects of alcoholism on cortex reflects the in vivo pattern observed herein and consistent with other in vivo studies<sup>2,10</sup> of abstinent alcohol-dependent participants and reviews.<sup>12,13</sup>

A central aim of this longitudinal analysis was to test for age-alcoholism interactions. Accordingly, we observed a selectivity of frontal cortex to age-alcoholism interaction beyond normal aging effects and independent of deficits related to drug dependence. This interaction is consistent with that of a cross-sectional study, which reported an age-alcoholism interaction on nonspecific, total gray matter/white matter volume ratios in alcohol-dependent participants without drug dependence history, but not in those with a comorbid lifetime cocaine use disorder.<sup>41</sup> Our age-alcoholism interaction identified longitudinally supports earlier cross-sectional findings showing that older alcohol-dependent participants had greater cortical volume deficits selective to prefrontal and frontal regions beyond those observed in normal aging.<sup>17,35</sup> The accelerated volume deficits in the older alcohol-dependent participants could not readily be attributed to more years of heavy drinking, given that many had a late onset of their disorder and lower lifetime alcohol consumption estimates than their early-onset counterparts.

### Alcohol and Drug Dependence Comorbidity

Given the high incidence (54.5%) of drug dependence in these alcohol-dependent participants, additional analysis exam-

**Figure 3. Age-Alcoholism Interactions Shown at Each Magnetic Resonance Imaging (MRI) of the 199 Individual Control Participants vs 222 Alcohol-Dependent Participants**



A-C, Frontal regional volumes by age at each MRI in the control participants plotted on their mean (solid gray regression)  $\pm$  1 and 2 SDs (dashed gray lines). D-F, Frontal regional volumes by age at each MRI of the alcohol-dependent

participants plotted on their mean regression (blue line) and overplotted on the control mean (solid gray regression)  $\pm$  1 and 2 SDs (dashed gray lines).

ined subgroups according to the drugs most misused (ie, cocaine, cannabis, amphetamines, opiates) compared with participants with alcoholism free of drug dependence and control participants. Each of these 4 drugs is associated with cortical volume abnormalities, some unique and many overlapping with each other, notably in frontal regions.<sup>23,42</sup>

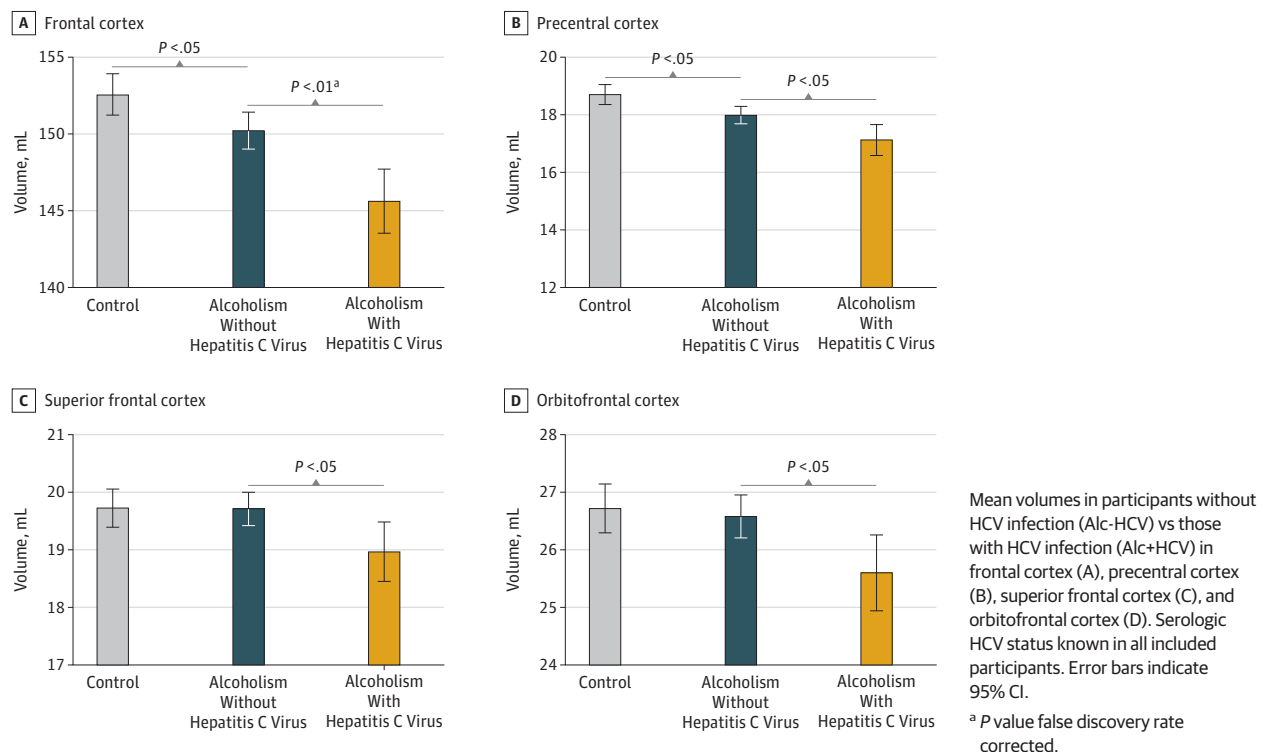
A few studies have considered alcohol-drug comorbidities. One study reported a similar level of prefrontal volume deficits in 6-week abstinent crack-cocaine dependents with or without alcohol dependence.<sup>43</sup> Yet, a larger study failed to detect independent influence of comorbid cocaine dependence

on gray matter volume deficits in alcohol-dependent men.<sup>41</sup> Herein, although the alcohol-cocaine and alcohol-opiate groups had smaller frontal volumes than the drug-dependence-free alcohol-dependent participants, deficits in precentral, supplementary motor, and medial volumes endured when the analysis was limited to drug-dependence-free alcohol-dependent participants.

#### Alcohol and HCV Infection Comorbidity

Alcohol-dependent participants with HCV infection had greater deficits than those without HCV infection in precentral,

**Figure 4. Alcoholism and Hepatitis C Virus (HCV) Infection in Alcohol-Dependent (Alc) and Control (Con) Participants**



superior, and orbital frontal volumes. Nonetheless, the total frontal, insular, and precentral volume deficits were significant in the uninfected alcoholism group compared with control participants with known HCV status. Thus, HCV infection, while having focal effects on frontal brain systems,<sup>30,31</sup> targeted frontally based systems also vulnerable to chronic and extensive alcohol consumption. Whether the compounded untoward effects of alcoholism and HCV infection on brain structure can be ameliorated with successful treatment of the infection remains to be determined.

### Limitations

One limitation of the study is that alcohol-dependent participants were recruited from community-based treatment centers, which, according to estimates, account for less than 25% of individuals needing treatment.<sup>44</sup> Thus, our results cannot necessarily generalize to all adults with AUD.<sup>18</sup> A further limitation is the absence of non-alcohol-dependent drug or HCV-infected comparison groups, which were unavailable. Although formal testing for diagnosis-by-sex interactions identified no sex effects, we are cautious to conclude that sex differences do not occur in alcohol dependence, especially given some evidence from cross-sectional studies reporting greater volume deficits in women than men,<sup>45</sup> although others do not.<sup>46,47</sup> Finally, although testing of functional correlates was beyond the scope of this analysis, ultimate con-

sideration of neurocompromise in the context of the observed frontal distribution of the aging-alcoholism acceleration of volume shrinkage may identify substrates of cognitive, emotion, or motor compromise potentially ameliorated with adequate re-training efforts.

### Conclusions

Alcoholism's target of prefrontal and frontal cortical tissue has been thematic for nearly a century of quantitative analysis. In vivo neuroimaging findings have continued this theme in demonstrating consistencies in compromise of frontal-fugal systems<sup>12</sup> extending to insular and parietal sites, now associated with behaviors commonly observed in alcoholism, such as problems with inhibitory control, poor insight, visuospatial disabilities,<sup>48-50</sup> and liability for relapse.<sup>11</sup> Alcohol is a critical agent in understanding observed brain structural compromise given that neither drug dependence nor HCV infection comorbidities accounted for the frontally distributed volume deficits in the drug-free alcohol-dependent group. Finally, the presence of age-alcoholism interactions notable in frontal cortex puts older alcohol-dependent individuals at heightened risk for age-associated functional compromise,<sup>19</sup> even if excessive drinking is initiated later in life.

### ARTICLE INFORMATION

Accepted for Publication: January 4, 2018.

Published Online: March 14, 2018.

doi:10.1001/jamapsychiatry.2018.0021

**Author Contributions:** Drs Sullivan and Pfefferbaum had full access to all the data in the



study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Sullivan, Pfefferbaum. **Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Sullivan, Zahr, Sassoon, Kwon, Pohl, Pfefferbaum.

**Critical revision of the manuscript for important intellectual content:** Sullivan, Sassoon, Thompson, Pohl, Pfefferbaum.

**Statistical analysis:** Sullivan, Thompson, Kwon, Pohl, Pfefferbaum.

**Obtained funding:** Sullivan, Pfefferbaum.

**Administrative, technical, or material support:** Sullivan, Zahr, Sassoon, Kwon, Pohl, Pfefferbaum. **Study supervision:** Sullivan, Pohl, Pfefferbaum.

**Conflict of Interest Disclosures:** None reported.

**Funding/Support:** This work was supported by the US National Institute on Alcohol Abuse and Alcoholism (NIAAA) grants R01 AA005965, U01 AA013521, U01 AA017347, R37 AA010723, K05 AA017168, and the Moldow Women's Hope and Healing Fund.

**Role of the Funder/Sponsor:** Officers of the NIAAA and representatives of the Moldow Foundation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Additional Contributions:** Ehsan Adeli, PhD (Stanford University), created Figure 2 (top), which displays cortical regions with volume deficits in the alcohol group compared with the control group. There was no financial compensation.

## REFERENCES

- Segobin SH, Chételat G, Le Berre AP, et al. Relationship between brain volumetric changes and interim drinking at six months in alcohol-dependent patients. *Alcohol Clin Exp Res*. 2014;38(3):739-748.
- Le Berre AP, Pitel AL, Chanraud S, et al. Chronic alcohol consumption and its effect on nodes of frontocerebellar and limbic circuitry: comparison of effects in France and the United States. *Hum Brain Mapp*. 2014;35(9):4635-4653.
- Bühler M, Mann K. Alcohol and the human brain: a systematic review of different neuroimaging methods. *Alcohol Clin Exp Res*. 2011;35(10):1771-1793.
- Harper CG, Kril JJ, Sheedy D, et al. Neuropathological studies: the relationship between alcohol and aging. In: Gombert ESL, Hegedus AM, Zucker RA, eds. *Alcohol Problems and Aging*. Vol 33. Bethesda: National Institute on Alcohol Abuse and Alcoholism; 1998:117-134.
- Sutherland GT, Sheedy D, Kril JJ. Neuropathology of alcoholism. *Handb Clin Neurol*. 2014;125:603-615.
- van Eijk J, Demirakca T, Frischknecht U, Hermann D, Mann K, Ende G. Rapid partial regeneration of brain volume during the first 14 days of abstinence from alcohol. *Alcohol Clin Exp Res*. 2013;37(1):67-74.
- Wang GY, Demirakca T, van Eijk J, et al. Longitudinal mapping of gyral and sulcal patterns of cortical thickness and brain volume regain during early alcohol abstinence. *Eur Addict Res*. 2016;22(2):80-89.
- Cardenas VA, Studholme C, Gazdzinski S, Durazzo TC, Meyerhoff DJ. Deformation-based morphometry of brain changes in alcohol dependence and abstinence. *Neuroimage*. 2007;34(3):879-887.
- Pfefferbaum A, Sullivan EV, Rosenbloom MJ, Mathalon DH, Lim KO. A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. *Arch Gen Psychiatry*. 1998;55(10):905-912.
- Makris N, Oscar-Berman M, Jaffin SK, et al. Decreased volume of the brain reward system in alcoholism. *Biol Psychiatry*. 2008;64(3):192-202.
- Rando K, Hong KI, Bhagwagar Z, et al. Association of frontal and posterior cortical gray matter volume with time to alcohol relapse: a prospective study. *Am J Psychiatry*. 2011;168(2):183-192.
- Zahr NM, Pfefferbaum A, Sullivan EV. Perspectives on fronto-fugal circuitry from human imaging of alcohol use disorders. *Neuropharmacology*. 2017;122:189-200.
- Fein G, Shimotsu R, Barakos J. Age-related gray matter shrinkage in a treatment naïve actively drinking alcohol-dependent sample. *Alcohol Clin Exp Res*. 2010;34(1):175-182.
- Fjell AM, Westlye LT, Amlien I, et al. High consistency of regional cortical thinning in aging across multiple samples. *Cereb Cortex*. 2009;19(9):2001-2012.
- Pfefferbaum A, Rohlfing T, Rosenbloom MJ, Chu W, Colrain IM, Sullivan EV. Variation in longitudinal trajectories of regional brain volumes of healthy men and women (ages 10 to 85 years) measured with atlas-based parcellation of MRI. *Neuroimage*. 2013;65:176-193.
- Lockhart SN, DeCarli C. Structural imaging measures of brain aging. *Neuropsychol Rev*. 2014;24(3):271-289.
- Pfefferbaum A, Sullivan EV, Mathalon DH, Lim KO. Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcohol Clin Exp Res*. 1997;21(3):521-529.
- Fein G, Di Sclafani V, Cardenas VA, Goldmann H, Tolou-Shams M, Meyerhoff DJ. Cortical gray matter loss in treatment-naïve alcohol dependent individuals. *Alcohol Clin Exp Res*. 2002;26(4):558-564.
- Grant BF, Chou SP, Saha TD, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry*. 2017;74(9):911-923.
- Duka T, Gentry J, Malcolm R, et al. Consequences of multiple withdrawals from alcohol. *Alcohol Clin Exp Res*. 2004;28(2):233-246.
- Pitel AL, Zahr NM, Jackson K, et al. Signs of preclinical Wernicke's encephalopathy and thiamine levels as predictors of neuropsychological deficits in alcoholism without Korsakoff's syndrome. *Neuropsychopharmacology*. 2011;36(3):580-588.
- Thomson AD, Guerrini I, Bell D, et al. Alcohol-related brain damage: report from a Medical Council on Alcohol Symposium, June 2010. *Alcohol Alcohol*. 2012;47(2):84-91.
- Mackey S, Paulus M. Are there volumetric brain differences associated with the use of cocaine and amphetamine-type stimulants? *Neurosci Biobehav Rev*. 2013;37(3):300-316.
- Novo-Veleiro I, Calle CdeL, Domínguez-Quibén S, Pastor I, Marcos M, Laso FJ. Prevalence of hepatitis C virus infection in alcoholic patients: cohort study and systematic review. *Alcohol Alcohol*. 2013;48(5):564-569.
- Fuster D, Sanvisens A, Bolao F, et al. Impact of hepatitis C virus infection on the risk of death of alcohol-dependent patients. *J Viral Hepat*. 2015;22(1):18-24.
- Lipari RN, Van Horn SL. The CBHSQ Report: Trends in Substance Use Disorders Among Adults Aged 18 or Older. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.
- National Institute on Alcohol Abuse and Alcoholism. Other Substance Abuse. <http://www.niaaa.nih.gov/alcohol-health/special-populations-co-occurring-disorders/other-substance-abuse>. Accessed January 29, 2018.
- Luijten M, Schellekens AF, Kühn S, Machielse MW, Sescousse G. Disruption of reward processing in addiction: an image-based meta-analysis of functional magnetic resonance imaging studies. *JAMA Psychiatry*. 2017;74(4):387-398.
- Hall MG, Alhassoon OM, Stern MJ, et al. Gray matter abnormalities in cocaine versus methamphetamine-dependent patients: a neuroimaging meta-analysis. *Am J Drug Alcohol Abuse*. 2015;41(4):290-299.
- Silverstein PS, Kumar S, Kumar A. HIV-1, HCV and alcohol in the CNS: potential interactions and effects on neuroinflammation. *Curr HIV Res*. 2014;12(4):282-292.
- Letendre S, Paulino AD, Rockenstein E, et al; HIV Neurobehavioral Research Center Group. Pathogenesis of hepatitis C virus coinfection in the brains of patients infected with HIV. *J Infect Dis*. 2007;196(3):361-370.
- National Institute on Drug Abuse. Why are cocaine users at risk for contracting HIV/AIDS and hepatitis? <http://www.drugabuse.gov/publications/research-reports/cocaine/are-cocaine-abusers-risk-contracting-hiv-aids-hepatitis-b-c>. Accessed January 29, 2018.
- Pfefferbaum A, Rosenbloom MJ, Chu W, et al. White matter microstructural recovery with abstinence and decline with relapse in alcohol dependence interacts with normal ageing: a controlled longitudinal DTI study. *Lancet Psychiatry*. 2014;1(3):202-212.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 2000.
- Pfefferbaum A, Lim KO, Zipsky RB, et al. Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: a quantitative MRI study. *Alcohol Clin Exp Res*. 1992;16(6):1078-1089.
- Skinner HA. *Development and Validation of a Lifetime Alcohol Consumption Assessment Procedure*. Toronto, Canada: Addiction Research Foundation; 1982.
- Skinner HA, Sheu WJ. Reliability of alcohol use indices: the lifetime drinking history and the MAST. *J Stud Alcohol*. 1982;43(11):1157-1170.

38. R Team. A language and environment for statistical computing. 2017. <https://www.R-project.org/>. Accessed July 4, 2017.
39. Mathalon DH, Sullivan EV, Rawles JM, Pfefferbaum A. Correction for head size in brain-imaging measurements. *Psychiatry Res*. 1993;50(2):121-139.
40. Courville CB. *Effects of Alcohol on the Nervous System of Man*. Los Angeles: San Lucas Press; 1955.
41. Bjork JM, Grant SJ, Hommer DW. Cross-sectional volumetric analysis of brain atrophy in alcohol dependence: effects of drinking history and comorbid substance use disorder. *Am J Psychiatry*. 2003;160(11):2038-2045.
42. Bjork JM, Momenan R, Smith AR, Hommer DW. Reduced posterior mesofrontal cortex activation by risky rewards in substance-dependent patients. *Drug Alcohol Depend*. 2008;95(1-2):115-128.
43. Fein G, Di Sclafani V, Meyerhoff DJ. Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. *Drug Alcohol Depend*. 2002;68(1):87-93.
44. National Institute on Alcohol Abuse and Alcoholism. National Epidemiologic Survey on Alcohol and Related Conditions: Selected Findings. Vol. 29, No. 2, 2006. Washington, DC: National Institute on Alcohol Abuse and Alcoholism; 2006.
45. Hommer D, Momenan R, Kaiser E, Rawlings R. Evidence for a gender-related effect of alcoholism on brain volumes. *Am J Psychiatry*. 2001;158(2):198-204.
46. Pfefferbaum A, Rosenbloom M, Deshmukh A, Sullivan E. Sex differences in the effects of alcohol on brain structure. *Am J Psychiatry*. 2001;158(2):188-197.
47. Pfefferbaum A, Sullivan EV. Microstructural but not macrostructural disruption of white matter in women with chronic alcoholism. *Neuroimage*. 2002;15(3):708-718.
48. Moselhy HF, Georgiou G, Kahn A. Frontal lobe changes in alcoholism: a review of the literature. *Alcohol Alcohol*. 2001;36(5):357-368.
49. Oscar-Berman M, Valmas MM, Sawyer KS, Ruiz SM, Luhar RB, Gravitz ZR. Profiles of impaired, spared, and recovered neuropsychologic processes in alcoholism. *Handb Clin Neurol*. 2014;125:183-210.
50. Le Berre AP, Fama R, Sullivan EV. Executive functions, memory, and social cognitive deficits and recovery in chronic alcoholism: a critical review to inform future research. *Alcohol Clin Exp Res*. 2017;41(8):1432-1443.