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

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ABSTRACT

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

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

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

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

1. Introduction

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

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

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

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

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

2. Materials and methods

2.1. Participants

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

2.2. Clinical assessment

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

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

2.3. Assessment of neurocognitive function

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