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White matter microstructural correlates of relapse in alcohol dependence

Yukai Zou[a,b], Donna E. Murray[c,d], Timothy C. Durazzo[e,f], Thomas P. Schmidt[c], Troy A. Murray[c], Dieter J. Meyerhoff[c,d,*]

[a] Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN 47906, United States
[b] College of Veterinary Medicine, Purdue University, West Lafayette, IN 47906, United States
[c] Center for Imaging of Neurodegenerative Diseases (CIND), San Francisco VA Medical Center, San Francisco, CA 94121, United States
[d] Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA 94143, United States
[e] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, United States
[f] Mental Illness Research Mental Illness Research and Education Clinical Centers, Sierra-Pacific War Related Illness and Injury Study Center, VA Palo Alto Health Care System, Palo Alto, CA 94304, United States

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ABSTRACT

Identification of neural correlates of relapse to alcohol after treatment is clinically important as it may inform better substance abuse treatment. Few studies have specifically analyzed the white matter microstructure in treatment seekers as it might relate to relapse risk versus long-term abstinence. Using 4 Tesla diffusion tensor imaging, we compared two groups of one-month-abstinent treatment-seekers, who were classified based on their drinking status between six and nine months after treatment initiation. We hypothesized that subsequent relapsers had greater white matter microstructural deficits in specific brain regions than long-term abstainers. At one month of abstinence, 37 future relapsers versus 25 future abstainers had lower fractional anisotropy (a measure of axonal organization and membrane integrity) in the corpus callosum and right stria terminalis/fornix, higher diffusivity in the genu of the corpus callosum, left and right stria terminalis/fornix, and lower diffusivity in left anterior corona radiata. These differences existed despite similar lifetime and recent drinking and smoking histories in the groups. Longer smoking duration in relapsers was associated with lower fractional anisotropy in right stria terminalis/fornix. The study identified specific microstructural biomarkers of alcohol relapse risk in adults, contributing to the definition of a neurobiological relapse risk profile in alcohol use disorder.

1. Introduction

Alcohol use disorder (AUD) is associated with a chronically relapsing-remitting course over lifetime (Witkiewitz and Marlatt, 2007). Most individuals treated for AUD will relapse to hazardous alcohol consumption within just six months of treatment (Kirshenbaum et al., 2009; Meyerhoff and Durazzo, 2010; Witkiewitz, 2011). Resumption to hazardous drinking for long periods relates to clinically significant impairments of psychosocial functioning (e.g., unemployment, relationship/marital discord, legal entanglements) and maintains cognitive dysfunction in AUD (Durazzo et al., 2008; Maisto et al., 2006, 2007). On the other hand, sustained abstinence following treatment relates to significant improvements in neurocognitive and adaptive psychosocial functioning (e.g., Pennington et al., 2013 and references cited therein) and to at least partial recovery from prefrontal neurobiological injury thought to be related to previous chronic heavy alcohol use (for reviews see Buhler and Mann, 2011; Xiao et al., 2015; Zahr, 2014).

Various neuroimaging modalities have been employed to characterize brain changes with chronic alcohol consumption and to identify potential imaging biomarkers of increased relapse risk after AUD treatment (e.g., Meyerhoff and Durazzo, 2010; Meyerhoff et al., 2013; Seo and Sinha, 2014, 2015; for review see Moeller and Paulus, 2018). Brain biomarkers measured either alone or together with other markers often provide better predictions of treatment outcomes than measures of for example education, neurocognition, craving, stress or psychiatric symptomatology (e.g., Volkow and Baler, 2013; Gabrieli et al., 2015). Identification of specific neural correlates of relapse are therefore clinically important as it may inform better substance abuse treatment and predict long-term clinical outcomes. For example, structural

* Corresponding author at: Center for Imaging of Neurodegenerative Diseases (CIND), San Francisco VA Medical Center, 4150 Clement Street (114M), San Francisco, CA 94121, United States.
E-mail address: dieter.meyerhoff@ucsf.edu (D.J. Meyerhoff).

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magnetic resonance imaging (MRI) performed at treatment entry showed that alcohol dependent individuals who relapsed after treatment have less cortical gray matter than those who sustained several months of abstinence, in particular in prefrontal regions including the orbitofrontal, anterior cingulate, and dorsolateral prefrontal cortices (Beck et al., 2012; Cardenas et al., 2011; Durazzo et al., 2011; Rando et al., 2011; Seo et al., 2015). An early study also reported reduced amygdala volume in future relapsers versus abstainers and generally smaller hippocampi compared to healthy controls (Wrase et al., 2008). The structural integrity of these brain regions and the neural networks they are embedded in are critically important for impulse/inhibitory control, emotional regulation, craving, and evaluation/anticipation of stimulus salience and hedonics, concepts important for the development and persistence of addictive disorders including relapse (Koob and Volkow, 2016; Volkow and Baler, 2013; Volkow et al., 2012).

Diffusion tensor imaging (DTI) is another modality to probe in-vivo brain morphology in AUD. It is based on the differential diffusivity of water molecules along or perpendicular to white matter tracts and provides measures of local white matter microstructural integrity that complement macrostructural measurements of cortical and white matter volumes. One DTI metric commonly computed is fractional anisotropy (FA), a sensitive marker of white matter organization or fiber coherence at the microstructural level, reflecting axonal organization and membrane integrity. White matter FA has been generally found to be lower in corpus callosum, major frontocortico-striatal tracts and limbic pathways of individuals with AUD compared to healthy controls (Yeh et al., 2008; Gazdzinski et al., 2010; Kuceyeski et al., 2013; Monnig et al., 2015; Sorg et al., 2015; Zou et al., 2017). Lower FA in AUD is interpreted to reflect primarily axonal dystrophy or loss and demyelination or myelin loss (Beaulieu, 2002; Zahr, 2014), which is also associated with natural processes of white matter aging (Peters, 2002). Although FA deficits have been described in long-term alcohol abstinent individuals (Fortier et al., 2014), lower regional FA also has been shown to be at least partly reversible over short (Gazdzinski et al., 2010; Zou et al., 2017) and longer periods of abstinence from alcohol (Pfefferbaum et al., 2014).

Few studies to date, however, have specifically analyzed the white matter microstructure as it might relate to relapse risk versus successful long-term abstinence from chronic heavy drinking: One study (Sorg et al., 2012) showed significantly lower FA in major fiber tracts of the anterior brain including corpus callosum and forceps minor of 16 treatment seeking alcoholics at 3 weeks of abstinence who had resumed heavy drinking within 6 months, compared to 29 matched alcoholics who largely maintained abstinence over that same period. Another smaller study demonstrated only statistically weak regional FA reductions in the corpus callosum and fornix at 1 year of abstinence in 10 individuals who relapsed to heavy drinking within the subsequent years compared to those 27 who managed to abstain over the same time (Pfefferbaum et al., 2014). In treatment-seeking adolescents, who had not been exposed to chronic alcohol consumption for long, lower FA in prefrontal brain and temporal lobe was related to greater alcohol problem severity (drinking frequency) at 6-month follow-up (Chung et al., 2013). Given the dearth of information on these potential microstructural biomarkers of relapse risk in treatment-seeking adults and the relatively small numbers of resumers/relapsers in these studies, we compared treatment-seekers at one month of abstinence, who were classified based on their drinking status (abstinent or relapsed) between 6 and 9 months after treatment initiation. We hypothesized that high-resolution DTI data obtained at about one month of abstinence show that subsequent relapsers (REL) had greater regional white matter microstructural deficits than long-term abstainers (ABST). Our analyses focused on the participants we previously found to have deficits in white matter integrity compared to light/non-drinking controls (Zou et al., 2017), on those white matter tracts that we and others found affected by chronic alcohol consumption and relapse status, and on the potential effects of chronic cigarette smoking on our primary DTI measures. The presented analyses expand a growing body of literature on the definition of a neurobiological relapse risk profile for AUD, which may be employed clinically to focus treatment resources on those most in need.

2. Methods

2.1. Participants

Sixty-two alcohol dependent individuals were recruited from the VA Medical Center Substance Abuse Day Hospital and the Kaiser Permanente Chemical Dependence Recovery outpatient treatment clinics in San Francisco; all were in treatment and verifiably abstinent for approximately 1 month when structural neuroimaging was performed. The predominantly male Veteran participants were between 25 and 70 years of age and all met DSM-IV criteria for alcohol dependence. Forty-three participants from our previous account of this population (Zou et al., 2017) were included in the current study. All participants provided written informed consent prior to study procedures that had been approved by the University of California San Francisco and the VA Medical Center in accordance with the Declaration of Helsinki.

Inclusion/exclusion criteria: Primary inclusion criteria were fluency in English, DSM-IV diagnosis of alcohol dependence or abuse at baseline (all met criteria for alcohol dependence), consumption of > 150 standard alcohol-containing drinks (i.e., 13.6 grams of pure ethanol) per month for > 8 years prior to enrollment for males, and > 80 drinks per month for > 6 years prior to enrollment for females. Exclusion criteria were a history of the following: dependence on any substance other than alcohol or nicotine in the 5 years immediately prior to enrollment, any intravenous drug use in the 5 years prior to baseline study, opioid agonist/replacement therapy, intrinsic cerebral masses, HIV/AIDS, cerebrovascular accident, cerebral aneurysm, arteriovenous malformations, myocardial infarction, medically uncontrolled chronic hypertension, type-I diabetes, chronic obstructive pulmonary disease, non-alcohol related seizures, significant exposure to established neurotoxins, demyelinating and neurodegenerative diseases, Wernicke-Korsakoff syndrome, delirium, penetrating head injury, and closed head injury resulting in loss of consciousness > 10 minutes. Psychiatric exclusion criteria were history of schizophrenia-spectrum disorders, bipolar disorder, cyclothymia, PTSD, obsessive-compulsive disorder and panic disorder. Not exclusionary were hepatitis C (by self-report and medical charts review), type-2 diabetes, hypertension, unipolar mood disorders (i.e., major depression, substance-induced mood disorder), given their high prevalence in those with an AUD (Grant et al., 2015; Mertens et al., 2005). Participants seropositive for hepatitis C did not take interferon or other medications to manage active symptomatology. Participants were breathalyzed and urine-tested for illicit substances before assessment and no participant tested positive for any tested substances at any assessment.

2.2. Clinical Measures

At baseline, participants completed the Clinical Interview for DSM-IV Axis I Disorders, Version 2.0 (SCID-I/P) and semi-structured interviews for lifetime alcohol consumption (Lifetime Drinking History) and substance use (in-house questionnaire assessing substance type, and quantity and frequency of use) (Pennington et al., 2013). From the Lifetime Drinking History, average number of alcoholic drinks/month over 1 year prior to enrollment and average number of drinks/month over lifetime were calculated. All participants also completed standardized questionnaires assessing impulsivity (Barratt Impulsivity Scale, BIS-11) (Patton et al., 1995), depressive (Beck Depression Inventory, BDI) (Beck, 1978) and anxiety symptomatologies (State-Trait Anxiety Inventory, Trait form Y-2, STAI) (Spielberger et al., 1977), as well as nicotine dependence (Fagerström Tolerance Test for Nicotine Dependence, FTND) (Heatherton et al., 1991). As white matter microstructure