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Effects of abstinence and chronic cigarette smoking on white matter microstructure in alcohol dependence: Diffusion tensor imaging at 4 T

Yukai Zou[a,b,*], Donna E. Murray[c,d], Timothy C. Durazzo[e,f], Thomas P. Schmidt[d], Troy A. Murray[d], 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] Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA 94143, United States
[d] Center for Imaging of Neurodegenerative Diseases (CIND), San Francisco VA Medical Center, San Francisco, CA 94121, 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

Background: We previously reported widespread microstructural deficits of brain white matter in alcohol-dependent individuals (ALC) compared to light drinkers in a small 1.5 T diffusion tensor imaging study employing tract-based spatial statistics. Using a larger dataset acquired at 4 T, the present study is an extension that investigated the effects of alcohol consumption, abstinence from alcohol, and comorbid cigarette smoking on white matter microstructure.
Methods: Tract-based spatial statistics were performed on 20 1-week-abstinent ALC, 52 1-month-abstinent ALC, and 30 controls. Regional measures of fractional anisotropy (FA) and mean diffusivity (MD) in the significant clusters were compared by Analysis of Covariance. The metrics were correlated with substance use history and behavioral measures.
Results: 1-week-abstinent ALC showed lower FA than controls in the corpus callosum, right cingulum, external capsule, and hippocampus. At 1 month of abstinence, only the FA in the body of the corpus callosum of ALC remained significantly different from controls. Some regional FA deficits correlated with more severe measures of drinking and smoking histories but only weakly with mood and impulsivity measures.
Conclusion: White matter microstructure is abnormal during early abstinence in alcohol dependent treatment seekers and recovers into the normal range within about four weeks. The compromised white matter was related to substance use severity, mood, and impulsivity. Our findings suggest that ALC may benefit from interventions that facilitate normalization of DTI metrics to maintain abstinence, via smoking cessation, cognitive-based therapy, and perhaps pharmacology to support remyelination.

1. Introduction

Alcohol dependence is associated with significant brain injury, negative health consequences (Sullivan, 2000; Oscar-Berman and Marinkovic, 2003; Zahr, 2014), and nearly 88,000 annual deaths in the United States (NIAAA, 2015). Around 80% of the alcohol-dependent individuals in North America also smoke cigarettes (Romberger and Grant, 2004; Durazzo and Meyerhoff, 2007). Cigarette smoking by itself has detrimental effects on neurobiology and cognition (Bolego et al., 2002; Hawkins et al., 2002; Garey et al., 2004; Durazzo et al., 2014a,b). In the United States, approximately 400,000 people die from cigarette smoking every year (Giovino, 2002), making it one of the largest preventable causes of death (Danaei et al., 2009).

Magnetic Resonance Imaging (MRI) can assess non-invasively the morphometry of brain tissue in alcohol use disorders (AUD) (Zahr, 2014). Macrostructural MRI studies of AUD described loss of gray matter (GM) and white matter (WM) volume (Pfefferbaum et al., 1992; Rohlfing et al., 2006; Bühler and Mann, 2011; Demirakca et al., 2011). A meta-analysis reported smaller GM volumes in alcohol-dependent individuals compared to controls in

* Corresponding author at: Weldon School of Biomedical Engineering, Purdue University, 206 S. Martin Jischke Drive, West Lafayette, IN 47907-2032, United States.
E-mail address: yukaizou2012@gmail.com (Y. Zou).

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the prefrontal cortex, posterior cingulate cortex, and dorsal striatum (Xiao et al., 2015). Longitudinal MRI studies showed partially reversible brain tissue loss with abstinence from alcohol, and the underlying mechanisms likely involve remyelination and glial cell proliferation (Sullivan and Pfefferbaum, 2005; Crews and Nixon, 2009). Recently, we reported WM volume recovery in alcohol-dependent individuals over 7.5 months of abstinence, and frontal WM showed the greatest change during the change over the first month of abstinence (Durazzo et al., 2015).

Magnetic resonance-based diffusion tensor imaging (DTI) can assess damage to the microstructure of WM tissue, potentially reflecting fiber organization and myelin changes in the brain (Basser et al., 1994; Mori and Zhang, 2006). Fractional anisotropy (FA), a common DTI metric, is sensitive to neuronal characteristics such as the axonal size, density, and myelination, while mean diffusivity (MD) reflects the magnitude of water diffusion (Beaulieu, 2002; Mori and Zhang, 2006; Wozniak and Lim, 2006; Wheeler-Kingshott and Cercignani, 2009; Jbabdi et al., 2010; Jeurissen et al., 2013). WM fibers without pathology or injury typically show relatively high FA, as the intact myelin layers restrict the directions of water diffusion; lower FA (and the typically associated higher MD) indicates less directed water diffusion and may suggest fiber demyelination in pathological states (Pfefferbaum and Sullivan, 2005; Zahr, 2014). Widespread age-dependent microstructural abnormalities have been reported in AUD via DTI and interpreted to potentially reflect damage to myelin and axons (Pfefferbaum et al., 2006; Yeh et al., 2009; Zahr, 2014; Sorg et al., 2015).

Tract-Based Spatial Statistics (TBSS) is a DTI analysis method that creates a mean FA skeleton representing the major fiber bundles connecting different cortical brain regions. It minimizes the effects of geometric distortion from data acquisition, reduces partial volume effects, and therefore improves the power of detecting regional FA differences at group level (Smith et al., 2006; Bach et al., 2014). We applied TBSS for determining microstructural differences between treatment-seeking alcohol-dependent individuals and light drinkers: FA was lower in fibers within frontal WM, limbic pathways, and between cortico-striatal regions; in the small group of patients, associations between drinking severity and regional FA were insignificant (Yeh et al., 2009). Other TBSS studies in alcohol dependence reported FA deficits specifically within cingulum, corpus callosum, fornix (Durkee et al., 2013; Trivedi et al., 2013; Pfefferbaum et al., 2014; Smith et al., 2015; Sorg et al., 2015), and superior longitudinal fasciculus (Pfefferbaum et al., 2014; Segobin et al., 2015). Microstructural abnormalities were most pronounced in major tracts within frontal WM (Fortier et al., 2014; Pfefferbaum et al., 2014; Sorg et al., 2015) and related to higher lifetime alcohol consumption (Sorg et al., 2015).

Contrary to the rather consistent findings of lower FA in AUD, both higher and lower regional FA was shown in chronic cigarette smokers. FA was *lower* in smokers than non-smokers within prefrontal WM and fronto-striatal fibers (Zhang et al., 2011), corpus callosum, anterior internal capsule, and the projection fibers connecting frontal cortices (Lin et al., 2013; Savjani et al., 2014). Others reported *higher* FA in smokers than non-smokers within right prefrontal WM, cingulum, and corpus callosum (Paul et al., 2008; Hudkins et al., 2012), fronto-parietal tracts and superior longitudinal fasciculus (Liao et al., 2011), internal and external capsules, and superior corona radiata (Yu et al., 2015).

To date, few DTI studies have addressed the influence of comorbid tobacco use on brain microstructure in AUD. In a large study of heavy drinkers, cigarette smoking did not affect WM microstructure significantly (Monnig et al., 2015). In a small longitudinal study of alcohol-dependent individuals between one and four weeks of abstinence, we detected trends to FA increases within frontal and temporal WM in non-smokers but not in smokers (Gazdzinski et al., 2010). These analyses suggest that smoking adversely affects WM microstructure and hinders its recovery during abstinence from alcohol. Correspondingly, using MR spectroscopy, we detected lower concentrations of *N*-acetylaspartate (NAA), a marker of neuron health and viability (Miller, 1991; Schuff et al., 2001; Meyerhoff, 2014), within frontal WM of smoking versus non-smoking alcohol-dependent individuals (Wang et al., 2009; Durazzo et al., 2013); longitudinal recovery of NAA during alcohol abstinence was greater in the non-smoking than smoking individuals (for review see Meyerhoff, 2014). These findings suggest axonal injury related to cigarette smoking that affects neurobiological injury in AUD and hampers neurobiological recovery during abstinence (Durazzo et al., 2004; Wang et al., 2009).

Here, we used TBSS to extend our original DTI study at 1.5 T (T) (Yeh et al., 2009) by analyzing 4T DTI data obtained from smoking and non-smoking treatment seeking alcohol-dependent individuals at 1 week and 1 month of abstinence and from controls. We tested for effects of alcohol consumption, smoking and duration of abstinence from alcohol on WM microstructural measures. Based on the cited previous work, we defined a priori regions of interest (ROIs) (cingulum, corpus callosum, fornix, hippocampus, internal and external capsules, and superior longitudinal fasciculus) and expected regional WM microstructural abnormalities to be related to drinking and smoking severities. We specifically hypothesized that:

1 1-week-abstinent, treatment-seeking alcohol dependent individuals (ALC) have microstructural WM abnormalities compared with controls that correlate with measures of lifetime substance use history.
2 1-week-abstinent ALC have greater microstructural WM abnormalities than 1-month-abstinent ALC.
3 Among ALC at 1-month of abstinence and CON, cigarette smokers show greater microstructural WM abnormalities than non-smokers.

2. Methods

2.1. Participants

Structural MRI and DTI datasets were analyzed from ALC at approximately 1 week (1wkALC, n = 20) and 1 month (1moALC, n = 52) of abstinence, including both current cigarette smokers (sALC) and non-smokers (nsALC). Of these, 12 ALC had data sets at both time points, whereas 40 ALC had their first assessment at approximately 1 month of abstinence. Thirty control participants (CON, both smokers and non-smokers) were chosen from a larger group of community recruits and were matched to the ALC participants on age, gender, and smoking status. Participants were excluded for all neurological or psychiatric disorders known to affect neurobiology or cognition, except cigarette smoking. In addition, ALC were excluded for a history of illicit drug dependence in the past 5 years. Further inclusion and exclusion criteria were described (Durazzo et al., 2004). The male ALC participants were required to consume >150 alcoholic drinks per month for at least 8 years before treatment, whereas female ALC participants consumed >80 drinks per month for at least 6 years before treatment. A lifetime history of alcohol consumption was obtained (Skinner and Sheu, 1982; Sobell and Sobell, 1990; Sobell et al., 1988), self-reported impulsivity was measured using the Barratt Impulsivity Scale (BIS-11) (Patton et al., 1995), and participants completed standardized questionnaires assessing depressive [Beck Depression Inventory, BDI; (Beck, 1978)] and anxiety symptomatologies [State-Trait Anxiety Inventory, STAI; (Spielberger et al., 1977)], as well as nicotine dependence [Fagerstrom Tolerance Test for Nicotine Dependence, FTND; (Heatherton et al., 1991)]. Basic