



## Full length article

## Peripheral immune factors are elevated in women with current or recent alcohol dependence and associated with altered mood and memory

Clare J. Wilhelm<sup>a,c</sup>, Bret E. Fuller<sup>a,b,c</sup>, Marilyn Huckans<sup>a,b,c,d</sup>, Jennifer M. Loftis<sup>a,c,d,\*</sup><sup>a</sup> Research and Development Service, VA Portland Health Care System, Portland, OR, USA<sup>b</sup> Mental Health and Clinical Neurosciences Division, VA Portland Health Care System, Portland, OR, USA<sup>c</sup> Department of Psychiatry, Oregon Health & Science University, Portland, OR, USA<sup>d</sup> Methamphetamine Abuse Research Center, Oregon Health & Science University, Portland, OR, USA

## ARTICLE INFO

## Keywords:

Alcohol use disorder  
Sex differences  
Anxiety  
Depression  
Cognitive impairment  
Inflammation

## ABSTRACT

**Background:** The adverse effects of alcohol on brain function result, in part, from inflammatory processes. The sex-specific neuropsychiatric consequences and inflammatory status of active alcohol dependence and early remission from dependence have not been investigated.

**Methods:** Neuropsychiatric symptoms, inflammatory factors, and liver enzymes were compared in a prospective cohort study of adults with (n = 51) or without (n = 31) a current or recent history of alcohol dependence.

**Results:** Neuropsychiatric profiles were similar in adults with current or recent alcohol dependence regardless of sex. In male and female participants measures of depression (female p < 0.05, male p < 0.001), anxiety (female p < 0.001, male p < 0.001), and memory complaints (female p < 0.001, male p < 0.05) were elevated, relative to non-dependent controls. Significant sex × alcohol dependence history interactions were observed for plasma levels of tissue inhibitor of metalloproteinase 1 (TIMP-1) and brain derived neurotrophic factor (BDNF), with women in the alcohol dependent group exhibiting increased levels of both analytes (p < 0.05) relative to controls. Positive correlations between TIMP-1 levels and measures of depression (r<sup>2</sup> = 0.35, p < 0.01), anxiety (r<sup>2</sup> = 0.24, p < 0.05) and memory complaints (r<sup>2</sup> = 0.44, p < 0.01) were found in female, but not male, participants.

**Conclusions:** Though neuropsychiatric profiles were similar for men and women with current or recent alcohol dependence, plasma factors associated with increases in depression, anxiety, and memory impairment differed and support the need to tailor treatments based on sex.

## 1. Introduction

Sexual dimorphism is observed in many pathological processes including brain diseases and responses to a variety of drugs, including alcohol. For instance, women are more vulnerable to alcohol-induced organ damage in the periphery, with higher rates or greater severity of cardiomyopathy, peripheral neuropathy, some types of cancer and liver cirrhosis (Ammendola et al., 2000; Fernandez-Sola and Nicolas-Arfelis, 2002; Kovacs and Messingham, 2002; Praud et al., 2016). Due to differences in body mass composition, as well as other still unknown factors, women are more susceptible to the harmful effects of alcohol than men, as reflected by the lower alcohol consumption recommendations for women vs. men provided by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Sex differences in alcohol-induced brain damage and cognitive impairment have rarely been addressed in clinical studies, and a consensus of whether increased damage or

dysfunction is observed in women is lacking (reviewed in Nixon et al., 2014). In general, studies suggest that women exhibit brain damage with less total alcohol consumption, or more damage with similar levels of intake than men, though not all studies have observed this phenomenon (Hommer, 2003). Women may recover from alcohol-induced white matter damage more quickly than men (Ruiz et al., 2013). Sex differences have also been observed in the relationship between circulating inflammatory factors such as C-reactive protein and the quantity of alcohol consumed (Oliveira et al., 2010). Mortality, the most devastating consequence of alcohol abuse, is higher in women who have a greater-than two-fold increased risk of premature death than men with alcohol dependence (John et al., 2013), a finding that has been confirmed by systematic meta-analysis of mortality risks in alcohol use disorders (Roerecke and Rehm, 2013). Despite accumulating evidence, little effort has been extended to identify the mechanisms underlying sex-differences in alcohol responses.

\* Corresponding author at: VA Portland Health Care System (R & D16), 3710 SW US Veterans Hospital Rd Portland, OR 97239, USA.  
E-mail addresses: [loftisj@ohsu.edu](mailto:loftisj@ohsu.edu), [jennifer.loftis2@va.gov](mailto:jennifer.loftis2@va.gov) (J.M. Loftis).

About half of the nearly 20 million people with an alcohol use disorder in the United States develop neuropsychiatric symptoms that adversely impact addiction treatment outcomes. The course of alcohol use disorders appears to vary between the sexes, with women showing higher levels of alcohol craving associated with nicotine use (Hitschfeld et al., 2015) and increased vulnerability to alcohol relapse (Abulseoud et al., 2013). Further, women exhibit stronger associations between alcohol abuse and depression or anxiety than men (King et al., 2003), and women with depression report engaging in heavy episodic alcohol drinking more frequently than women without depression (Pedrelli et al., 2016).

A strong link between depression and inflammatory signaling has been established, and mounting evidence suggests that inflammation may play a similar role in anxiety and memory dysfunction (Huckans et al., 2015b; Vogelzangs et al., 2013). Women experience higher rates of depression than men (reviewed in Albert, 2015), and inflammation appears to be a key contributor to depression in women (reviewed in Derry et al., 2015). Chronic alcohol consumption also induces inflammatory responses that contribute to the drug's adverse neuropsychiatric effects. For example, neuroinflammation is evident in the brains of adults with a history of alcohol abuse, with increased activation of microglia and elevated expression of central and peripheral inflammatory factors (Achur et al., 2010; He and Crews, 2008). Studies using animal models of alcohol abuse observe greater inflammation following alcohol exposure in females than males both in the brain (Alfonso-Loeches et al., 2013; Wilhelm et al., 2014) and in the periphery (Fulham and Mandrekar, 2016). Thus, we hypothesize that men and women with alcohol dependence may exhibit differences in the symptom severity or inflammatory factors associated with neuropsychiatric impairments.

In this study, self-report measures of depression, anxiety, and memory complaints were used to explore associations among neuropsychiatric symptoms and a panel of immune factors to identify potential sex-specific effects of alcohol dependence in adults. We focused on cytokines and chemokines commonly associated with inflammation-related depression including interferon- $\gamma$  (IFN- $\gamma$ ) and interleukin-6 (IL-6) (Dahl et al., 2016; Huckans et al., 2015a), and emerging factors that we and others have recently found to contribute to mood and cognitive impairments including matrix metalloproteinase-3 (MMP-3), tissue inhibitor of metalloproteinases-1 (TIMP-1), and brain derived neurotrophic factor (BDNF) (Hoyo-Becerra et al., 2013; Hoyo-Becerra et al., 2015; Huckans et al., 2015b; Rybakowski et al., 2013; Zhang et al., 2016). A hypothesis of this study was that relationships between inflammatory markers and neuropsychiatric symptoms may be sex-specific, thus associations were examined within each sex and not across the entire sample population. Our results identify distinct plasma profiles linked with alcohol dependence and neuropsychiatric impairment in men and women. These findings emphasize the need to develop sex-specific treatments for alcohol and other substance use disorders, particularly interventions (e.g., immunotherapies) targeting neuropsychiatric symptoms that hinder early recovery efforts.

## 2. Material and methods

### 2.1. Participants

Participants were categorized into the following study groups: 1) control group ( $n = 31$ ;  $n = 10$  female;  $n = 21$  male): adults with no lifetime history of dependence on any substance other than nicotine or caffeine and 2) alcohol dependent group ( $n = 51$ ): adults actively using alcohol and currently meeting criteria for alcohol dependence ( $n = 21$ ;  $n = 5$  female;  $n = 16$  male) and adults in early remission from alcohol dependence (defined as  $\geq 1$  month and  $\leq 9$  months) ( $n = 30$ ;  $n = 6$  female;  $n = 24$  male). Research participants in the early remission group were recruited from Portland, Oregon area addiction treatment centers. Participants who were active users or controls were recruited

from the Portland, Oregon community through word of mouth and via study advertisements posted in clinics, websites, and newspapers.

General exclusion criteria included history of a major medical illness or current use of medications that are likely to be associated with serious neurological or immune dysfunction [e.g., stroke, traumatic brain injury, human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) infection, primary psychotic disorder, immunosuppressants, antivirals, or anti-tumor necrosis factor (TNF) agents]. Additional exclusion criteria for the control group included: 1) meets criteria for lifetime history of dependence on any substance (other than nicotine or caffeine dependence) based on Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) (American Psychiatric Association, 2000) and confirmed by the Mini International Neuropsychiatric Interview questionnaire (MINI) (Sheehan et al., 1998), 2) for men, average recent alcohol use  $> 6$  standard drinks/day for  $\geq 1$  year, and 3) for women, average recent alcohol use  $> 4$  standard drinks/day for  $\geq 1$  year, and 4) a positive test on a urine drug analysis for any drug of abuse on the day of the study. The urine drug analysis tested for the following drugs: amphetamine, tetrahydrocannabinol/cannabis, opiates, cocaine, and methamphetamine. Additional inclusion criteria for the alcohol dependent groups included: 1) meets DSM-IV (American Psychiatric Association, 2000) criteria for current or recent dependence on alcohol, confirmed by the MINI (Sheehan et al., 1998), 2) for men, average use  $> 6$  standard drinks/day for  $\geq 1$  year during active dependence, and 3) for women, average use  $> 4$  standard drinks/day for  $\geq 1$  year during active dependence. Participants in the alcohol dependent group did not test positive on a urine drug analysis for any drug of abuse on the day of the study. Other reported drug usage by control and alcohol groups is reported in Supplemental Table S1 and indicates that use of other drugs (with the exception of nicotine and alcohol) was not recent.

### 2.2. Ethical approval

The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) and was approved by the Institutional Review Boards at the VA Portland Health Care System and Oregon Health & Science University. Research participants gave informed consent after the procedures of the study were explained in full.

### 2.3. Procedures

Participants were compensated with grocery store vouchers (\$50) to complete the following procedures: clinical interview, urine drug analysis, HCV and HIV antibody screening, blood sample collection for immune factor analysis and liver function measurements, and questionnaires to assess depression, anxiety, and memory. All procedures were carried out by a certified phlebotomist/retired licensed practical nurse that was trained and supervised by a licensed psychologist and clinical neuropsychologist (MH). All measures were entered into a database and double-checked by separate study personnel prior to analysis.

#### 2.3.1. Questionnaires

1) Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001), a nine-item measure of depression severity. 2) Generalized Anxiety Disorder-7 Scale (GAD-7) (Spitzer et al., 2006), a seven-item measure of anxiety. 3) Prospective-Retrospective Memory Questionnaire (PRMQ) (Smith et al., 2000), a 16-item measure of self-reported memory complaints.

#### 2.4. Multiplex assessment of inflammatory factors

Following all other study procedures, blood was drawn in the afternoon (mean time was 1:28 PM, SD = 2:35 h) by one-time venipuncture into cell preparation tubes (BD Vacutainer Systems, Franklin

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