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# Gender dimorphism of brain reward system volumes in alcoholism

Kayle S. Sawyer[a,b,*], Marlene Oscar-Berman[a,b,c], Olivier J. Barthelemy[d], George M. Papadimitriou[e], Gordon J. Harris[f], Nikos Makris[e]

[a] Department of Anatomy & Neurobiology, Boston University School of Medicine, Boston, MA 02118, USA
[b] VA Boston Healthcare System, Boston, MA 02130, USA
[c] Departments of Neurology and Psychiatry, Boston University School of Medicine, Boston, MA 02118, USA
[d] Department of Psychological and Brain Sciences, Boston University, Boston, MA 02215, USA
[e] Center for Morphometric Analysis, and Athinoula A. Martinos Center, Departments of Neurology, Psychiatry, and Radiology, Massachusetts General Hospital, Boston, MA 02114, USA
[f] Radiology Computer Aided Diagnostics Laboratory, and Center for Morphometric Analysis, Massachusetts General Hospital, Boston, MA 02114, USA

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ABSTRACT

The brain's reward network has been reported to be smaller in alcoholic men compared to nonalcoholic men, but little is known about the volumes of reward regions in alcoholic women. Morphometric analyses were performed on magnetic resonance brain scans of 60 long-term chronic alcoholics (ALC; 30 men) and 60 nonalcoholic controls (NC; 29 men). We derived volumes of total brain, and cortical and subcortical reward-related structures including the dorsolateral prefrontal (DLPFC), orbitofrontal, and cingulate cortices, and the temporal pole, insula, amygdala, hippocampus, nucleus accumbens septi (NAc), and ventral diencephalon (VDC). We examined the relationships of the volumetric findings to drinking history. Analyses revealed a significant gender interaction for the association between alcoholism and total reward network volumes, with ALC men having smaller reward volumes than NC men and ALC women having larger reward volumes than NC women. Analyses of a priori subregions revealed a similar pattern of reward volume differences with significant gender interactions for DLPFC and VDC. Overall, the volume of the cerebral ventricles in ALC participants was negatively associated with duration of abstinence, suggesting decline in atrophy with greater length of sobriety.

## 1. Introduction

Identification of gender differences in association with Alcohol Use Disorder (referred to hereafter as "alcoholism") has sparked controversy regarding the extent of cerebral and neuropsychological pathology (Lancaster, 1994; Mann et al., 2005; Oscar-Berman and Marinković, 2007; Ruiz and Oscar-Berman, 2013; Pfefferbaum and Sullivan, 2002; Sullivan et al., 2004; US Department of Health and Human Services, 1997), but little research exists to inform this debate. Independent neuropathological processes may distinguish the residual effects of alcoholism on women from those on men, and neuroimaging provides insight into how brain structures are differentially affected with abstinence. Importantly, care should be taken not to confound the long-term neuropsychological sequelae of alcoholism with the responses to acute intoxication, or other health consequences associated with ongoing heavy alcohol consumption. These confounding factors can be mitigated by comparing men and women after long periods of abstinence. The few studies examining the relationship between gender and long-term alcoholism pathology have produced conflicting results, especially in terms of specific effects on the brains of women. Using structural magnetic resonance imaging (MRI), Pfefferbaum and colleagues (Pfefferbaum et al., 2001) found less brain shrinkage among alcoholic women than among alcoholic men. Kroft and colleagues (Kroft et al., 1991) found that the average ventricular volume in alcoholic women was within the typical range found in MRI studies of nonalcoholic women of similar ages. However, Hommer and colleagues (Hommer et al., 1996) found that the corpus callosum was smaller in alcoholic women than in alcoholic men and nonalcoholic control women; alcoholic men did not differ from nonalcoholic control men. Using computerized tomography scans to measure atrophy, Jacobson (Jacobson, 1986) reported that alcoholic women presented with greater ventricular enlargement and widening of cortical sulci than nonalcoholic women, and Mann and colleagues (Mann et al., 2005) found comparable degrees of brain atrophy in men and women despite shorter drinking histories in the women. Therefore, to clarify these conflicting results, we sought to examine how different lengths of abstinence are related to brain morphometry, from relatively short- (four weeks) through long periods (many years).

* Correspondence to: Boston University School of Medicine, 72 E Concord St, Berman Lab, AnatNeuro L-10, Boston, MA 02118, USA.
*E-mail address:* kslays@bu.edu (K.S. Sawyer).

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In other studies, Pfefferbaum and colleagues measured white matter brain microstructure in alcoholic women by using diffusion tensor imaging (DTI) (Pfefferbaum and Sullivan, 2002; Pfefferbaum et al., 2010, 2009). They noted cerebral white matter abnormalities in women alcoholics that were not observed with conventional MRI, suggesting that alcohol use by women is associated with white matter microstructural disruption that may antedate detection with the use of grosser measures of white matter volumetric loss (Pfefferbaum and Sullivan, 2002). They also found that fractional anisotropy changes showed gender differences, being more pronounced in the corpus callosum in men and more pronounced in the centrum semiovale in women (Pfefferbaum and Sullivan, 2002). Additionally, Pfefferbaum and colleagues (Pfefferbaum et al., 2009) reported that, when matched for alcohol exposure, alcoholic women showed more DTI signs of white matter degradation than alcoholic men in several fiber bundles, and that alcoholic women with longer abstinence from alcohol had larger cortical white matter volumes (Pfefferbaum et al., 2002, 2001). However, in a later study, Pfefferbaum et al. did not identify alcoholism-related differences in diffusion measures (Pfefferbaum et al., 2010). Ruiz and colleagues (Ruiz et al., 2013) found widespread white matter degradation in alcoholic women (in frontal, temporal, ventricular, and callosal regions) but only callosal degradation in men; women experienced faster callosal white matter recovery during abstinence. However, another study using magnetic resonance spectroscopy (MRS) to compare alcoholic men and women (Schweinsburg et al., 2003) found that in frontal lobe gray matter, but not frontal lobe white matter, alcoholic women had a significantly greater deficit in concentrations of N-acetylaspartate (a marker for neuronal integrity) than alcoholic men. The MRS findings are consistent with the suggestion by Hommer and colleagues (Hommer, 2003) that gray matter damage distinguishes alcoholic women and men to a greater extent than white matter damage. These discrepant findings necessitate non-directional hypotheses when considering differences between alcoholic men and women not only in total gray matter, white matter, and ventricular volumes, but also in the total “extended reward and oversight system” (Makris et al., 2008) and its component subregions.

Emotional, memory, and motivational abnormalities in Alcohol Use Disorder are associated with changes in the mesocorticolimbic system (Bowirrat and Oscar-Berman, 2005; Oscar-Berman and Bowirrat, 2005), a complex multi-functional network responsive to positive and negative reinforcement. Principal components of the mesocorticolimbic reward circuit include the amygdala, hippocampus, nucleus accumbens septi (NAc; part of the ventral striatum), and ventral diencephalon (VDC; including basal forebrain, hypothalamus, sublenticular extended amygdala, mammillary bodies, and a large portion of the ventral tegmentum area), and cortical areas with modulating and oversight functions, such as the dorsolateral prefronatal cortex (DLPFC), orbitofrontal, temporal pole, subcallosal, and cingulate cortices, parahippocampal gyri, and the insula (Alheid and Heimer, 1988; Barbas, 2000; Fuster, 1997; Heimer and Van Hoesen, 2006; LeDoux et al., 1991, 1988; Ochsner and Gross, 2005; Oscar-Berman and Bowirrat, 2005). Collectively, this cortical/subcortical circuitry is referred to as the extended reward and oversight system (Makris et al., 2008) or the reward network.

The brain's reward system is a critical component of the brain disease model of addiction (Volkow et al., 2016). Moreover, Alcohol Use Disorder has been associated with abnormalities in the reward system, but alcoholic women were not included in the research (Makris et al., 2008). Since there are known differences in the ways in which alcoholism affects men and women (Ruiz and Oscar-Berman, 2013), it is essential to disclose these differences, especially with regard to damage in brain systems involved in addiction. The present study directly addresses that concern, with the hopes of customizing individualized treatment and prevention strategies required by precision medicine. Furthermore, abnormalities in this network not only have implications for clarifying the underlying etiology of addictions such as alcoholism, but also could differentially alter the course of treatment and recovery, by affecting sensitivity to feedback, evaluation of the consequences of one's behavior, and the ability to make economic, social, and health-related decisions.

In alcoholics, mesocorticolimbic reward circuit regions previously studied with MRI have demonstrated structural changes with both atrophy and white matter damage (Agartz et al., 1999; Laakso et al., 2000; Pfefferbaum et al., 2005; Schneider et al., 2001; Sullivan et al., 2000, 1995; Szabo et al., 2004). The affected regions include not only the reward network as an interconnected system in its entirety, but also its specific component subregions (Harris et al., 2008; Makris et al., 2008). However, most studies have included only men.

We previously reported morphometric abnormalities in alcoholic men in the reward network (Harris et al., 2008; Makris et al., 2008). Using MRI in the present study, we analyzed brains of abstinent long-term chronic alcoholic (ALC) men and women and healthy nonalcoholic control (NC) men and women to test the hypothesis that there are gender differences with respect to the relationship of alcoholism to volumetric measures of the reward network. We also explored relationships between volumetric alterations of the reward network and drinking history.

## 2. Methods

### 2.1. Subjects

Participants were right-handed (handedness as assessed in (Briggs and Nebes, 1975)) men and women from the Boston area. The study included 60 abstinent long-term chronic alcoholics (ALC; 30 men) and 60 nonalcoholic controls (NC; 29 men) (Table 1). Nine of the ALC men and eight of the NC men were added to the sample of men who had participated in our prior research (Makris et al., 2008). The ALC men and women were selected to have similar drinking history profiles. Participation was solicited from newspaper and web-based advertisements and from Boston University Medical Center, Boston Veterans Affairs (VA) Healthcare System, and VA after-care programs. The Institutional Review Boards of the participating institutions approved this study. Informed consent was obtained prior to neuropsychological testing and scanning. Participants were reimbursed for time and travel expenses. Neurobehavioral and psychiatric evaluations typically required from six to nine hours over two or more days. Participants had frequent breaks as needed.

### 2.2. Clinical evaluation and neuropsychological assessment

Participants underwent a medical history interview and vision testing, plus a series of questionnaires (e.g., handedness, medical history, alcohol and drug use) to ensure they met inclusion criteria. Participants performed a computer assisted, shortened version of the Diagnostic Interview Schedule (Robins et al., 2000) that provides lifetime psychiatric diagnoses according to DSM-IV (American Psychiatric Association, 1994) criteria. Participants were excluded from further participation if any source (DIS scores, hospital records, referrals, or personal interviews) indicated that English was not one of their first languages, or if they had any of the following: corrected visual acuity worse than 20/50 in both eyes; Korsakoff's syndrome; HIV; cirrhosis; major head injury with loss of consciousness greater than 30 min unrelated to alcoholism; stroke; epilepsy or seizures unrelated to alcoholism; schizophrenia; Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) score over 16; electroconvulsive therapy; history of drug use once per week or more within the past four years (except for one ALC woman who had not smoked marijuana within the past six months, and one ALC man who had not used cocaine within the past eight months).

A number of participants were taking medications for a variety of conditions, had used drugs earlier than four years before enrollment, or

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