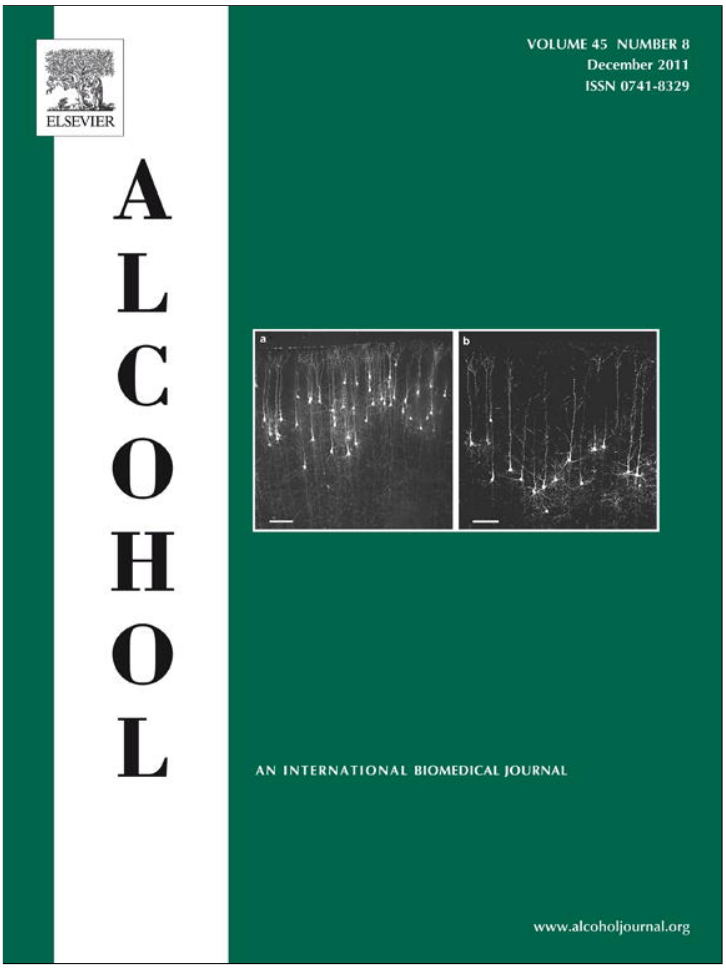

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Effects of alcohol intoxication and gender on cerebral perfusion: an arterial spin labeling study

Elizabeth Rickenbacher[a], Douglas N. Greve[b], Sheeva Azma[c], Josef Pfeuffer[d], Ksenija Marinkovic[e,*]

[a]*Champalimaud Neuroscience Programme, Instituto Gulbenkian de Ciência, Oeiras P-2781-90, Portugal*
[b]*Martinos Center, MGH-Harvard Medical School, Charlestown, MA 02129, USA*
[c]*Interdisciplinary Program in Neuroscience, Georgetown University, Medical Center, Washington, DC 2000, USA*
[d]*Siemens Healthcare, MR Application Development, Erlangen D-91052, Germany*
[e]*Department of Radiology, University of California, San Diego, CA 92093-0841, USA*

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Abstract

An increasing number of studies use functional MRI (fMRI) and blood oxygen level-dependent (BOLD) signal to investigate the neurofunctional basis of acute alcohol effects on the brain. However, the BOLD signal reflects neural activity only indirectly as it depends on regional hemodynamic changes and is therefore sensitive to vasoactive substances, such as alcohol. We used MRI-based pulsed arterial spin labeling (ASL) method to quantify effects of acute intoxication on resting cerebral perfusion. Gender effects have not been previously examined and yet they are of particular interest given the differences in hormonal dynamics, alcohol metabolism, and hemodynamic regulation. Nineteen young, healthy individuals (nine women) with no personal or familial alcohol- or drug-related problems served as their own controls by participating in both alcohol (0.6 g/kg ethanol for men, 0.55 g/kg for women) and placebo scanning sessions in a counterbalanced manner. Regionally specific effects of the moderate alcohol dose on gray matter perfusion were examined with voxel-wise and region-of-interest analyses suggesting an interaction between gender and alcohol beverage. Acute intoxication increased perfusion in bilateral frontal regions in men but not in women. Under placebo, stronger cortical perfusion was observed in women compared with men primarily in the left hemisphere in frontal, parietal, and temporal areas. These results emphasize gender differences and regional specificity of alcohol's effects of cerebral perfusion possibly because of interactive influences on hormonal, metabolic, and hemodynamic autoregulatory systems. Alcohol-induced perfusion increase correlated positively with impulsivity/antisocial tendencies, consistent with dopaminergic mediation of reward, and its effects on cortical perfusion. Additional ASL studies are needed to investigate dose- and time-dependent effects of alcohol intoxication and gender on the hemodynamic factors that conjointly influence BOLD signal to disambiguate the vascular/metabolic mechanisms from the neurally based changes.

Keywords: Cerebral blood flow; CBF; Perfusion; MRI; ASL; Alcohol; Gender; Impulsivity

Introduction

Despite its widespread use and vast costs resulting from its abuse, alcohol's effects on the functional neuroanatomy are still poorly understood. Better understanding of the neural basis of alcohol's effects on cognition and behavioral regulatory functions could provide crucial insight into alcohol-induced cognitive impairments as well as dysregulation of self-control and inability to desist drinking. Studies of acute alcohol challenge are important as they can reveal the neural circuits underlying behavioral impairments caused by intoxication and can inform and guide pharmacological research on possible agents aiming to diminish or reverse alcohol's effects. In concert with studies on chronic alcoholics and populations at risk, they help to parse out the effects of alcohol neurotoxicity, genetic susceptibility, and environmental factors, offering insight into neural systems that may be most susceptible to chronic alcohol abuse.

The most common method of choice in studies investigating functional neuroanatomy is T2*-weighted blood oxygen level-dependent (BOLD) signal because of its high sensitivity and excellent spatial resolution. Consequently, the prominence of BOLD functional MRI studies examining effects of acute intoxication on cognitive functions

* Corresponding author. Department of Radiology, University of California, San Diego, 9500 Gilman Dr. MC 0841, La Jolla, CA 92093-0841, USA. Tel.: +858-246-0575; fax: +858-534-1078.
E-mail address: xenia@ucsd.edu (K. Marinkovic).

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has been rising with increased reliance on neuroimaging methods in the field of alcohol use and alcoholism. Working memory tasks resulted in BOLD signal changes in frontal and parietal areas when the average blood–alcohol concentration (BAC) levels reached ~0.08% (Gundersen et al., 2008; Paulus et al., 2006). Similar intoxication levels affected activity primarily in frontal circuitry during simulated driving (Calhoun et al., 2004; Meda et al., 2009). Intoxication levels at ~0.08% also affected limbic activation to emotional faces (Gilman et al., 2008) and to alcoholic drink odors at ~0.05% (Bragulat et al., 2008).

However, the BOLD signal reflects neural activity only indirectly as a result of neurovascular coupling and it depends on regional changes in cerebral blood flow (CBF), cerebral blood volume, and cerebral metabolic rate of oxygen use ($CMRO_2$) (Buxton, 2002). Therefore, it is possible that these observed effects are partly caused by alcohol's effects on factors other than the neural activation (Iannetti and Wise, 2007). Because of its complex dependence on hemodynamic regulation, the BOLD signal is sensitive to anything that can alter hemodynamics and the neurovascular coupling, including pharmacological agents, disease, and so on. Under such circumstances, the neural activation is confounded with vascular changes and the BOLD signal cannot be interpreted unambiguously in isolation (Brown et al., 2007; Buxton et al., 2004; Liu and Brown, 2007). Alcohol is a vasoactive pharmacological agent, which modulates regional cerebral perfusion in a dose-dependent manner (Mathew and Wilson, 1991). It may affect the baseline perfusion reflected in a change in BOLD signal, which would in turn affect task-induced BOLD changes (Brown et al., 2003). Indeed, studies using positron emission tomography (PET) or related single-photon emission tomography (SPECT) methods have reported regionally specific changes in CBF during rest that were alcohol dose dependent. Alcohol increased CBF in prefrontal and temporal areas (Mathew and Wilson, 1986; Sano et al., 1993; Tiihonen et al., 1994; Volkow et al., 1988), as well as the anterior cingulate (AC) cortex and brainstem (Ingvar et al., 1998). Alcohol-induced cerebral vasodilation and consequently increased CBF were confirmed with transcranial Doppler (Blaha et al., 2003; Stendel et al., 2006).

Arterial spin labeling (ASL) is a noninvasive MRI-based technique that uses magnetically labeled arterial blood as an endogenous tracer to measure regional CBF (Buxton et al., 1998a; Detre et al., 2009; Golay et al., 2004; Wong et al., 1999). Diffusion of labeled blood into tissue alters the local magnetization revealing a component of the MRI signal that is dependent on the local rate of blood flow (Calamante et al., 1999; Detre and Alsop, 1999). It permits quantification of cerebral perfusion in physiological units expressed in milliliter of blood per 100 g of tissue per minute. The ASL method has been used to examine CBF in abstinent alcohol-dependent individuals and showed decreased frontoparietal perfusion (Clark et al., 2007; Mon et al., 2009). In a study investigating relapse, a group of treatment-seeking alcohol-dependent individuals were scanned at baseline and after ~35 days of abstinence and followed for 1 year. Individuals who resumed drinking had lower frontal CBF both at baseline and after ~35 days of abstinence in comparison with those who remained abstinent during the follow up period (Durazzo et al., 2010). ASL-measured cortical perfusion was also found to be reduced by cocaine infusion (Gollub et al., 1998) and chronic cigarette smoking in alcohol-dependent individuals (Gazdzinski et al., 2006; Mon et al., 2009).

In the present study, we used the ASL technique to measure resting gray matter perfusion in a group of healthy individuals who served as their own controls by participating in both placebo and moderate (0.6 g/kg ethanol for men, 0.55 g/kg for women) alcohol conditions in a counterbalanced manner. Previous studies confirmed that the ASL CBF measurements are highly stable across sessions (Hermes et al., 2007; Parkes et al., 2004; Pfefferbaum et al., 2010; Wang et al., 2011), making it appropriate for intersession comparisons. Furthermore, the anatomical MR images were acquired in the same session with the ASL scans, facilitating precise coregistration (Brown et al., 2007; Tracey, 2001). Despite previous evidence of the gender differences in CBF (Hermes et al., 2007; Parkes et al., 2004), hormonal balance (Baxter et al., 1987), alcohol metabolism (Kwo et al., 1998), and autonomic vascular regulation (Hart et al., 2009), gender differences in CBF under alcohol challenge have not been investigated. The goal of our study was to use ASL to examine regional effects of alcohol intoxication on gray matter perfusion in men and women and provide a preliminary insight into the hemodynamic changes underlying the BOLD signal effects in acute intoxication studies with moderate alcohol dose.

Methods

Participants

Nineteen individuals (nine women, age [mean ± standard deviation] = 24.9 ± 2.6 years, range = 22–33 years) served as their own controls as they participated in both alcohol and placebo sessions in a counterbalanced manner. Answers on the adapted Alcohol Use Questionnaire (Cahalan et al., 1969) indicated that the study participants were light-moderate drinkers who reported drinking occasionally (1.8 ± 0.9 times per week on average) and in low to moderate amounts (2.2 ± 0.7 drinks per occasion). All participants reported drinking in social settings on a regular basis. No gender differences were observed in the amount or frequency of drinking. All participants were young, healthy, right-handed, and nonsmokers with no alcohol or drug-related problems. They reported experiencing no health issues, never suffered from seizures or concussions, and were not taking any medications at the time of the

study. None of the subjects were ever arrested or treated for alcohol or drug problems. Short Michigan Alcohol Screening Test questionnaire (Selzer et al., 1975) detected no alcoholism-related symptoms and the participants reported no family history of alcoholism or drug abuse for the first- or second-degree relatives. The participants' reported drinking habits were quite a bit lighter than the nationwide average of 3.7 drinks per occasion for young adults (Chen et al., 2004), indicating that it is unlikely that they had acquired high levels of tolerance to alcohol or that they suffered from the long-term CNS effects observed in heavy social drinkers (Nichols and Martin, 1996; Parsons and Nixon, 1998). Data were collected from two other individuals but because of technical problems with one of their scans, they were not included in the analyses.

Experimental procedure

The participants were requested to abstain from food for at least 3 h and from alcohol at least 48 h before each experimental session and were asked about their compliance on their arrival to the laboratory. Participants were screened with an electronic breathalyzer (Alcotest 7410, Draeger Safety, Inc.) for the presence of alcohol. They were also tested for other substances, including marijuana, cocaine, methamphetamine, nicotine, opiates, and phencyclidine with a FDA approved multidrug screen test kit (Medimpex Inc.). Female subjects were tested for pregnancy before each scanning session to ascertain that they were not pregnant. All participants tested negative on all tests. In addition to self-report of the phase of their menstrual cycle, we obtained quick screen measures of luteinizing hormone (Medimpex, Inc.). For seven women, both scans took place during low hormonal levels; two were in the early follicular phase (menstruation) for both sessions and five women were using birth control, providing a constant hormonal status. For one woman, both scans fell during her luteal phase and for another one session took place in the early follicular and the other during the luteal phase. Caffeine intake was not quantified. However, participants were encouraged to refrain from drinking coffee for at least three hours before the beginning of each session. In addition, all scanning sessions took place in the early evening when caffeine intake is lowest (Smith, 2002).

All procedures were in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent approved by the Human Research Committee at Massachusetts General Hospital and the Partners Healthcare Network was obtained from all participants before participation. Before the first experimental session, the participants were familiarized with the setup and the scanner. No beverages were administered at that time but the participants filled out questionnaires probing their handedness (Oldfield, 1971), quantity and frequency of alcohol use (Cahalan et al., 1969), severity of alcoholism-related symptoms (Selzer et al., 1975), level of response to alcohol (Schuckit et al., 1997), and personality (Eysenck and Eysenck, 1975; Zuckerman, 1971), in addition to providing information about their medical history and family history of alcoholism. Subsequently, the subjects participated in placebo and alcohol sessions that were counterbalanced in order of presentation. The two sessions took place 31.6 ± 24.0 days apart on average.

Subjects were given a beverage that consisted of 0.6 g/kg ethanol for men and 0.55 g/kg for women to adjust for the body mass index difference (Friel et al., 1999). Alcohol (vodka Gray Goose) was mixed with orange juice (20% vol/vol). In the placebo condition, orange juice of the same volume was administered (Marinkovic et al., 2001). The beverage was served in two glasses, which the subjects were asked to consume in a 10-min period. The entire session, including preparations, beverage consumption, and task lasted approximately for 2 h.

The BAC of each participant was checked on arrival to the laboratory at the start of each session and was estimated with the electronic breathalyzer during the times when the subject was outside the scanning chamber, approximately every 5 min, starting 15 min after drinking. Because no electronic devices could be used inside the scanner room, a saliva alcohol test (Q.E.D., STC Technologies, Inc.) was used to estimate the BAC during scans. Participants performed an antisaccade task (results reported in a separate manuscript) before resting ASL scan, which was administered at the end of the scanning session, on a descending limb of BAC. The average BAC measured immediately after the ASL scan was $0.043 \pm 0.01\%$, at 98 min after the start of drinking. Although female participants tended to have a lower average BAC than males (0.038% vs. 0.047%), the difference was not significant ($F[1, 17] = 2.1$, $P > .17$).

Image acquisition and analysis

Imaging data were acquired at the Martinos Center in Boston, Massachusetts with a 3T Siemens Trio Tim whole-body scanner system (Siemens Healthcare, Erlangen, Germany) fitted with the standard vendor's 12-channel head coil. Special care was taken to minimize head motion with the use of a special pillow, foam padding, and head ''clamps'' that allowed participants to maintain a comfortable but stable position during scanning. Exposure to scanner noise was reduced with 29 db earplugs and pillow padding.

The resting-state scans were acquired with pulsed ASL (Kim, 1995; Kwong et al., 1995) for perfusion-weighted imaging using an echo planar imaging (EPI) readout. The protocol combined quantitative imaging of perfusion using a single subtraction-second version (QUIPSS-II) with the flow-sensitive alternating inversion recovery, slice- and nonslice-selective hyperbolic secant inversion pulse labeling scheme (Wong et al., 1998). The ASL sequence lasted 7 min and comprised axial-oblique anterior-posterior commissure oriented images of 24 slices with 5-mm thickness that were acquired using identical sequence parameters in

ascending slice order (inferior–superior): repetition time (TR) = 4,000 ms, echo time (TE) = 13 ms, tagging duration inversion time 1 (TI1) = 600 ms after which QUIPSS-II saturation was done; starting time of echo planar imaging (EPI) read-out of TI2 = 1,600 ms (first slice); voxel size 3.1 × 3.1 × 5.0 mm^3; matrix size = 64 × 64, field of view (FOV) = 200 mm; flip angle (FA) = 90°, EPI readout bandwidth = 2298 Hz/Px. To minimize the impact of static tissue, two presaturation pulses were applied in the imaging planes immediately before the inversion pulse. QUIPSS-II was done with an inferior as well as a superior saturation slab outside the slices.

Structural data were acquired with two high-resolution, three-dimensional, Fourier-transformed magnetization-prepared rapid acquisition gradient echo (MPRAGE) T1-weighted sequences that optimize contrast for a range of tissue properties (TR = 2,530 ms, TE = 3.25 ms, FA = 7°, FOV = 256, 128 sagittal slices, 1.33 mm thickness, in-plane resolution 1 mm × 1 mm). The FreeSurfer (surfer.nmr.mgh.harvard.edu) analysis package was used to analyze structural images and ASL data from each subject (Dale et al., 1999; Fischl et al., 1999a). Each participant's cortical surface was reconstructed using an automatic gray/white segmentation, tessellation, and inflation of the folded surface tessellation patterns. These surfaces were registered with a canonical brain surface created from an average of 40 brains (Fischl et al., 1999b) allowing for high-resolution group averaging based on surface alignment. The affine transform that mapped the anatomical for each individual to the MNI305 average brain was also computed (Collins et al., 1995).

ASL data were motion corrected with AFNI software (Cox, 1996). The amount of head motion did not differ between genders or sessions and did not exceed the maximum of 2 mm in any subject. The Siemens ASL sequence automatically computed a perfusion-weighted map and a relative CBF map with the formula described by Wang et al. (2003) using a fully relaxed M0 volume acquired at the beginning of each series (γ = 0.9 mL/g, α = 95%, T1a_blood = 1,500 ms). Each individual's map was aligned with the anatomical images using boundary-based registration (Greve and Fischl, 2009). The CBF maps were then resampled to the MNI305 space by concatenating the CBF-anatomical and anatomical-MNI305 transforms. Voxel-wise general linear model analysis was performed with random effects model using the FreeSurfer mri_glmfit program. Images of the overall group average ASL-CBF for each gender and beverage condition are shown in Fig. 1. Beverage differences were computed as two-sample *t*-tests for males and females separately. Similarly, gender differences were computed for alcohol and placebo separately. These are shown in Fig. 2 and Fig. 3, respectively in the form of the statistical parametric maps in cortical surface space.

In an effort to further quantify and examine potential regional differences because of alcohol intoxication and gender, a region-of-interest (ROI) analysis was conducted on the perfusion measured in the cortical ribbon. Each subject's cortical surface was parcellated into neuroanatomical areas based on a probabilistic atlas (Desikan et al., 2006; Fischl et al., 2004). Within these anatomical boundaries, measures of perfusion (mL/100 g/min) were calculated for each ROI, for each participant, and for each session. Because the slice prescription did not cover the entire brain reliably across all subjects, the areas in the

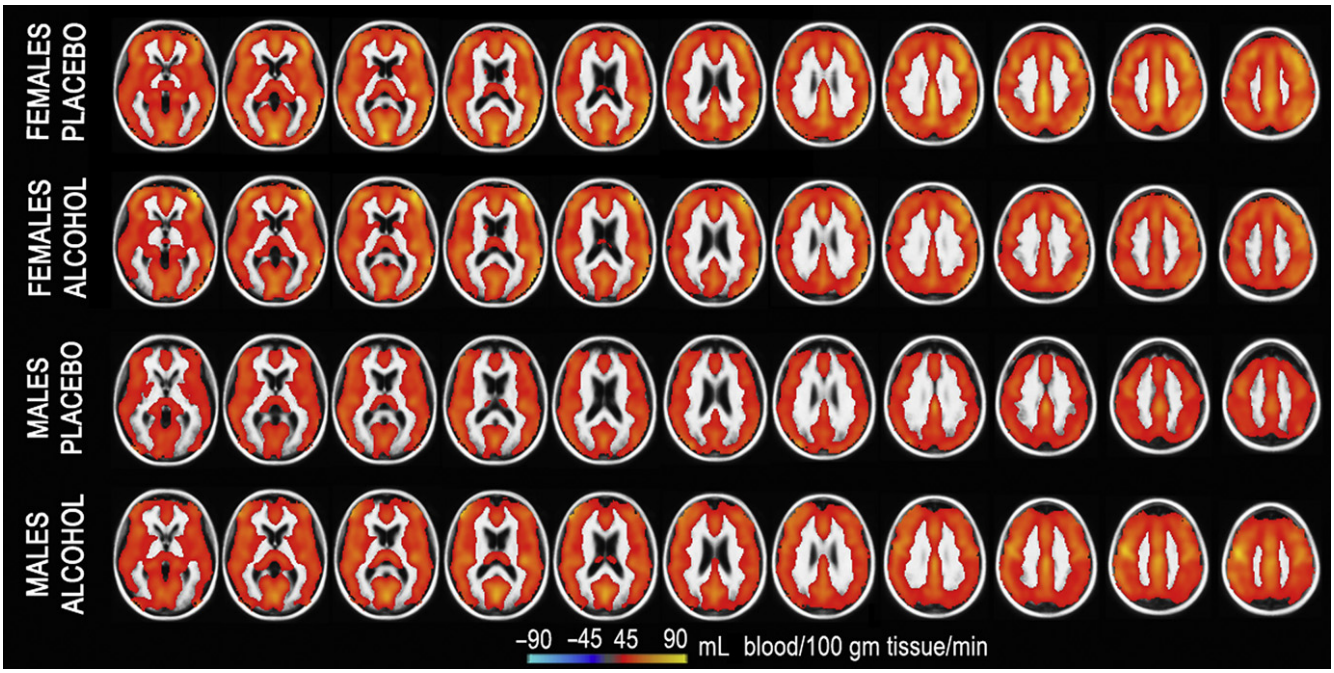

Fig. 1. Group average CBF for each gender and beverage condition. Interslice distance is 5 mm and the CBF is quantified in milliliter of blood per 100 g of tissue per minute. *Abbreviation*: CBF, cerebral blood flow.

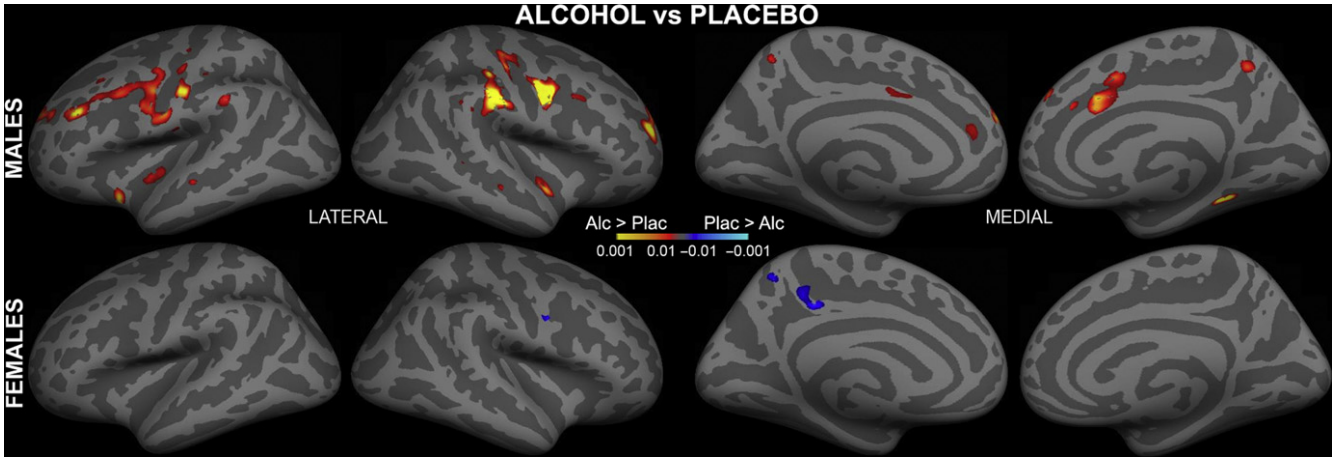

Fig. 2. Voxel-wise analysis of beverage differences for each gender displayed on the inflated cortical surface of both hemispheres, with *P*-values displayed as a color scale. Acute intoxication increased CBF in men but not in women. *Abbreviations*: CBF, cerebral blood flow; Alc, alcohol; Plac, placebo.

inferoventral temporal (i.e., fusiform, parahippocampal, and entorhinal cortices), orbitofrontal, and frontopolar regions were excluded from the ROI analyses. Forty ROIs were analyzed in this manner and they included the following cortical areas in both hemispheres: (1) superior frontal gyrus, (2) rostral middle frontal gyrus, (3) pars triangularis of the inferior frontal gyrus, (4) pars opercularis of the inferior frontal gyrus, (5) caudal middle frontal gyrus, (6) rostral AC cortex, (7) caudal AC cortex, (8) precentral gyrus, (9) superior temporal gyrus, (10) middle temporal gyrus, (11) banks of the superior temporal sulcus (i.e., the posterior aspect of the superior temporal sulcus), (12) postcentral gyrus, (13) superior parietal cortex, (14) supramarginal gyrus, (15) inferior parietal cortex, (16) precuneus cortex, (17) lateral occipital cortex, (18) lingual gyrus, (19) cuneus cortex, and (20) pericalcarine cortex. Detailed description of the anatomical ROI delineation can be found in (Desikan et al., 2006).

Mixed factorial design ANOVA with gender as a between-group factor and beverage and hemisphere as within-subject factors was carried out on the average perfusion values for each gender, beverage, and left and right hemisphere (Woodward et al., 1990). To examine potential regional sensitivity of cerebral perfusion to the effects of alcohol, gender, and hemispheric laterality, the ROIs were grouped into frontal, temporal, parietal, and occipital regions for each hemisphere and submitted to a mixed design ANOVA with gender as a between-group factor and beverage, hemispheric laterality, and cortical regions as within-subject factors. Finally, to examine these effects

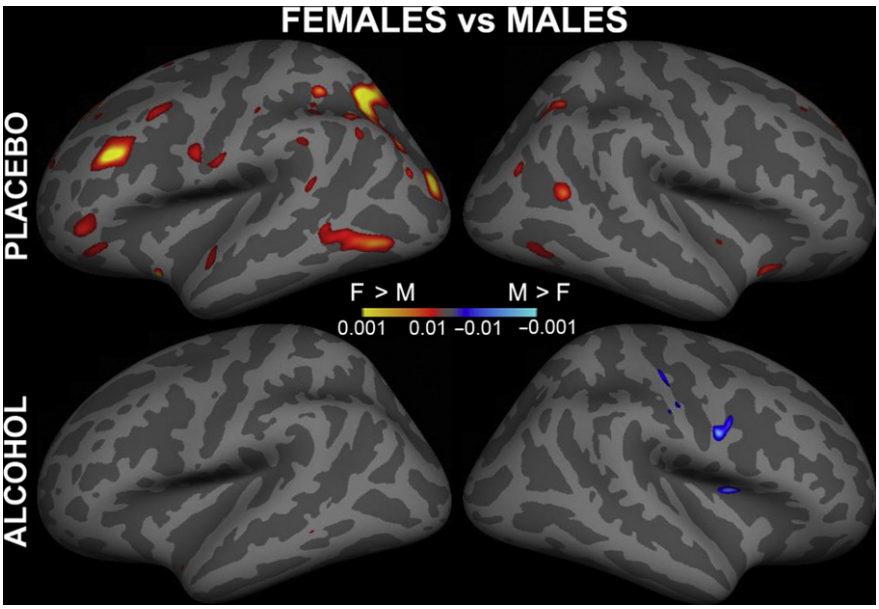

Fig. 3. Voxel-wise analysis of gender differences for each beverage displayed on the inflated lateral cortical surface of both hemispheres. Under placebo, stronger CBF was observed in women compared with men primarily in the left hemisphere. *Abbreviation*: CBF, cerebral blood flow.

across all ROIs simultaneously while controlling for their mutual dependence, we used a multivariate analysis of variance (MANOVA). With the goal of exploring potential trends in the data, a series of univariate ANOVAs were additionally carried out across the ROIs. With the overall alpha level maintained at $P < .05$, the Sidak's correction of the Bonferroni method for protection against inflated type I error adjusted alpha level for each ROI to $P < .001$.

Results

Images of the overall group average CBF for both genders and beverage conditions are shown in Fig. 1. Voxel-wise analyses were performed using random-effects analysis model of the group data for each gender in surface space. Differential images contrasting alcohol and placebo for each gender separately showed significantly stronger perfusion under alcohol in men, but not women, in fronto-parietal regions (Fig. 2), suggesting an interaction between gender and beverage. Figure 3 presents voxel-wise statistical parametric maps of gender differences for each beverage displayed on the inflated cortical surfaces of both hemispheres. Women had stronger perfusion than men under placebo especially in the left hemisphere in the frontal, parietal, and temporal areas.

ROI analysis of the cortical CBF with respect to gender, intoxication, and regional specificity confirmed these observations as described here below. This analysis was performed with graded degrees of anatomical precision comprising the overall hemispheric (Fig. 4), lobar (Fig. 5), and anatomically parcellated CBF measures (Fig. 6). Effects of gender, alcohol intoxication, and hemispheric laterality on the overall cerebral perfusion were analyzed with a $2 \times 2 \times 2$ mixed-design ANOVA (Woodward et al., 1990). The dependent variable was CBF averaged across all the ROIs for each hemisphere. The analysis indicated a significant gender and beverage interaction ($F[1, 17] = 5.1$, $P < .05$) and a significant gender × hemisphere interaction ($F[1, 17] = 5.6$, $P < .05$). These interactions were because of alcohol-induced CBF increase in men, ($F[1, 17] = 5.1$, $P < .05$), but not in women, ($F[1, 17] = 1.0$, $P > .30$). Perfusion was stronger in women than in men under placebo only, ($F[1, 17] = 6.0$, $P < .05$), with no gender differences observed under alcohol, ($F[1, 17] = 0.0$, $P > .5$) (Fig. 4). Gender differences tended to be stronger in the left hemisphere overall, ($F[1, 17] = 4.1$, $P < .06$), and were not significant on the right, ($F[1, 17] = 0.7$, $P > .4$), (Fig. 3).

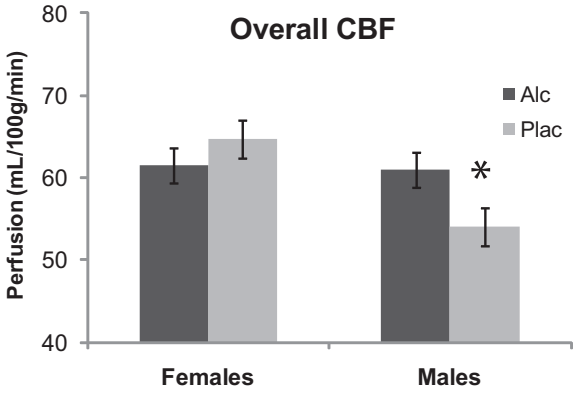

Fig. 4. Effects of gender and alcohol intoxication on the gray matter perfusion. Alcohol-induced CBF increase was observed in men only. Women show stronger CBF than men under placebo. *Abbreviations*: CBF, cerebral blood flow; Alc, alcohol; Plac, placebo.

Regional CBF sensitivity to the effects of gender, alcohol intoxication, and hemispheric laterality was analyzed with ROIs grouped into frontal, temporal, parietal, and occipital regions for each hemisphere in a $2 \times 2 \times 2 \times 4$ mixed-design ANOVA (Fig. 5), (Hermes et al., 2007). Significant interaction was observed for the factors of gender × beverage, ($F[1, 17] = 4.5$, $P < .05$), with stronger CBF observed in women than in men under placebo in the left hemisphere in the frontal, ($F[1, 17] = 7.9$, $P < .01$), temporal, ($F[1, 17] = 8.2$, $P < .01$), and parietal areas, ($F[1, 17] = 8.4$, $P < .01$). There were no gender differences under alcohol. Alcohol increased perfusion in men particularly in frontal regions both on the left, ($F[1, 17] = 5.9$, $P < .05$), and on the right, ($F[1, 17] = 6.2$, $P < .05$) (Figs. 2 and 5). Gender × hemisphere interaction, ($F[1, 17] = 5.6$, $P < .05$), was because of stronger gender differences in the left hemisphere (Fig. 3). Main effect of region, ($F[3, 51] = 7.5$, $P < .001$), indicated that, when summed across the factors of beverage and gender, the overall perfusion was strongest in prefrontal, compared with all other areas, ($F[1, 17] = 11.2$, $P < .01$), and weakest in temporal cortical areas, ($F[1, 17] = 18.8$, $P < .001$).

Finally, ROI-based MANOVA was carried out across all forty ROIs as dependent variables with the factors of gender, beverage, and hemisphere in an effort to increase spatial precision of potential gender- or beverage-based regional differences (Fig. 6). The overall multivariate analysis across all subjects did not show any significant effects. Similarly, none of the univariate comparisons carried out for each ROI reached Sidak's correction of Bonferroni critical value of $P < .001$ for multiple comparisons that would maintain the overall $\alpha < 0.05$ (all $P > .005$). However, the observed trends further refined the spatial foci of the regional differences reported previously. Here, presented are *P*-values that were not corrected for the inflated probability of type I error because of multiple comparisons (Woodward et al., 1990) but can be considered to represent trends in the data. Cortical perfusion showed a trend toward higher values in women than men under placebo in the left hemisphere in caudal middle frontal gyrus, ($F[1, 17] = 10.4$, $P < .005$), inferior parietal cortex, ($F[1, 17] = 10.3$, $P < .005$), supramarginal gyrus, ($F[1, 17] = 8.0$, $P < .01$), and superior temporal gyrus, ($F[1, 17] = 9.5$, $P < .01$). Alcohol increased perfusion in men bilaterally in the caudal middle frontal gyrus, ($F[1, 17] = 8.0$, $P < .01$), caudal AC, ($F[1, 17] = 8.0$, $P < .01$), supramarginal gyrus, ($F[1, 17] = 8.6$, $P < .01$), and superior temporal cortex, ($F[1, 17] = 4.6$, $P < .05$).

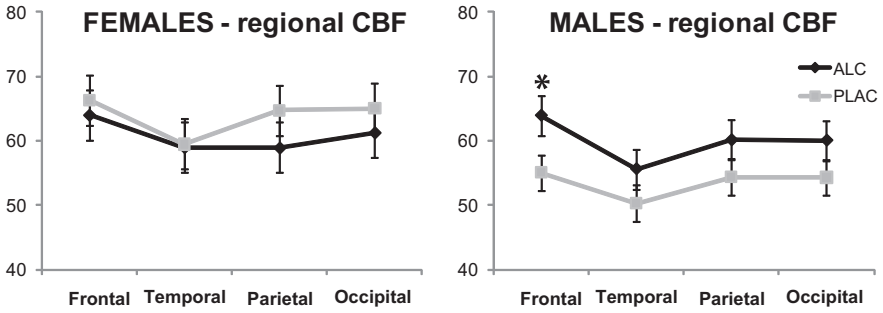

Fig. 5. Regional CBF sensitivity to gender and alcohol intoxication. Alcohol increased perfusion in prefrontal regions bilaterally in men. Furthermore, the statistical analysis indicated that stronger CBF was observed in women as compared with men under placebo in the frontal, temporal, and parietal regions. *Abbreviation*: CBF, cerebral blood flow.

Correlational analysis

Correlations between scores on personality questionnaires and perfusion measures were calculated as a function of beverage, gender, and hemispheric laterality. The Psychoticism/Socialization scale of the Eysenck Personality Questionnaire (EPQ) (Eysenck and Eysenck, 1975) correlated with perfusion under alcohol in the right hemisphere ($r = 0.72$, $P < .001$) and marginally on the left ($r = 0.43$, $P < .1$). This correlation was significant for both genders (females: 0.77, $P < .05$ and males: 0.70, $P < .05$). In contrast, there was no correlation under placebo for either right (0.03, $P > .5$) or left hemisphere (−0.18, $P > .5$).

Discussion

In this experiment, we sought to investigate effects of alcohol intoxication on cortical perfusion in a cohort of young and healthy men and women during rest. CBF was measured from the same participants after ingesting a moderate alcohol dose or placebo in a counterbalanced manner on a descending limb of the BAC curve. The main finding was that acute intoxication increased cortical perfusion in bilateral frontal regions in men, but not in women. Under placebo, stronger perfusion was observed in women as compared with men primarily in the left hemisphere. Results of the ROI-based analyses were consistent across levels of regional specificity and indicated analogous conclusions while adding refinement of spatial precision to the observed effects.

The present results are in overall agreement with previous PET or SPECT studies of resting CBF that used a range of alcohol doses. In most previous studies, no significant CBF changes were observed at the lowest administered alcohol dose (0.5 g/kg) (Mathew and Wilson, 1986; Volkow et al., 1988), although in one study, a bilateral global increase was seen after the measured CBF values were corrected for CO_2 level (Mathew and Wilson, 1986). In a SPECT study, Schwartz et al. (1993) administered 0.6 g/kg to male subjects and observed a 4% CBF increase more than 2 h after drinking. Tiihonen et al. (1994) reported 8% CBF increase in the right prefrontal

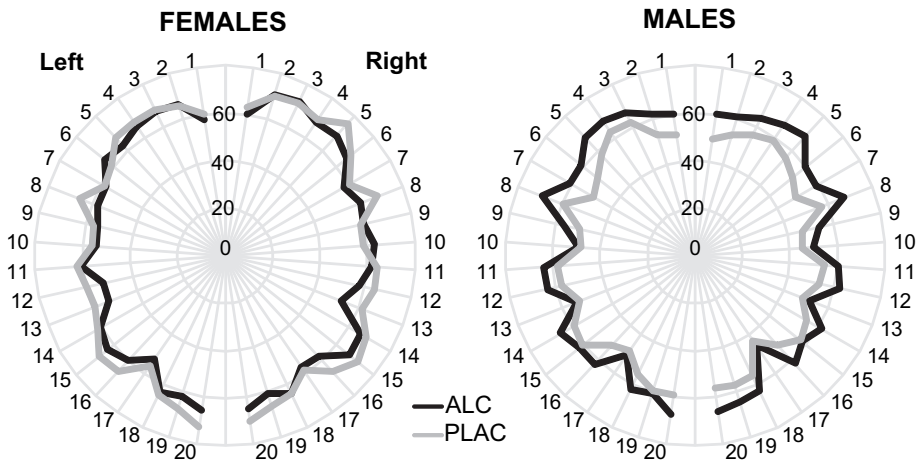

Fig. 6. Group average CBF for 40 ROIs for the left and right hemispheres (Desikan et al., 2006; Fischl et al., 2004). Although the overall MANOVA did not show significant results when corrected for multiple comparisons, alcohol tended to increase perfusion in men in the caudal middle frontal and supramarginal gyri bilaterally. Women tended to show stronger CBF in the left caudal middle frontal, inferior parietal, supramarginal, and superior temporal areas. The list of the ROIs is included in the text. *Abbreviations*: CBF, cerebral blood flow; ROI, region-of-interest; MANOVA, multivariate analysis of variance; Alc, alcohol; Plac, placebo.

area after administering 0.7 g/kg to male subjects. Similarly, the same dose increased CBF by 12% especially in prefrontal areas in a group of male subjects (Sano et al., 1993). Newlin et al. (1982) administered 0.75 g/kg to a group consisting of male and female participants and observed a global gray matter CBF increase of ~20%. Measured 1 h after drinking in males only, a dose of 1 g/kg increased blood flow to the prefrontal and temporal cortices by ~8% but decreased CBF in cerebellum (Volkow et al., 1988). Although most of these studies used male participants only, those with mixed-subject groups (Mathew and Wilson, 1986; Newlin et al., 1982) did not report effects of gender. Our results extend previous findings by indicating that gender modulates effects of alcohol intoxication on cortical perfusion.

Gender exerts powerful effects on resting CBF with greater perfusion observed in women than men under placebo in the left hemisphere, particularly in the frontal (caudal middle frontal gyrus), temporal (superior temporal gyrus), and parietal regions (supramarginal gyrus and inferior parietal cortex). The observed overall gender-based difference replicates previous reports of greater resting cortical perfusion in women compared with men with both MRI-based (Hermes et al., 2007; Parkes et al., 2004; Shin et al., 2007) as well as PET-based methods (Daniel et al., 1989; Mathew et al., 1986; Rodriguez et al., 1988; Shaw et al., 1979). The prevalent supposition for this robust finding rests on hormonal differences between men and women (Baxter et al., 1987; Goldman et al., 1976). This hypothesis is well supported by the evidence of CBF sensitivity to the manipulation of hormonal balance. Pharmacological suppression of gonadal hormones in women results in decreased CBF prefrontally during a cognitive task (Berman et al., 1997). Furthermore, estrogen is correlated with CBF velocity as measured with transcranial Doppler during ovulation induction and after pituitary suppression (Shamma et al., 1992). When measured across a wide age range, the CBF gender difference is the strongest in the decades before the onset of menopause (Shaw et al., 1979).

In the present study, we endeavored to scan our female subjects during the low hormone phase windows as none was scanned during the periovulatory hormonal surge. Nevertheless, it is likely that the differences in the chronic hormonal state between men and women contributed to the greater perfusion in women under placebo (Baxter et al., 1987). However, interaction with alcohol is not as easily explained. If higher estrogen levels in women are primarily responsible for the observed gender differences in CBF, one would expect this difference to be even higher under alcohol given that acute alcohol intoxication increases plasma estradiol in healthy women (Mendelson et al., 1988), which, in turn, increases perfusion (Goldman et al., 1976). Instead, a complex interaction of hormonal balance and alcohol metabolism seems to contribute to CBF differences between men and women. Because of their relatively larger liver volume, women metabolize alcohol faster than men (Kwo et al., 1998). Women's faster elimination rate can explain the slightly, although nonsignificantly, lower BAC in women on the descending BAC limb observed in this study. However, the BAC did not correlate with CBF for either gender, $r = 0.33$ for women and $r = -0.09$ for men. Given that the ASL scan took place on the descending BAC limb, it is possible that metabolic products of alcohol's breakdown, such as acetate, contributed to interindividual and gender differences in blood flow by affecting microcirculatory blood vessels. Acetate causes sedation and decrease in motor activity (Correa et al., 2003) and is present in the bloodstream for much longer time than alcohol (Hannak et al., 1985), suggesting that it may underlie the sedative effects observed on the descending limb of BAC. By causing vasodilation via adenosine receptors, acetate exerts potent effects on CBF. In a SPECT study (Schwartz et al., 1993), a moderate dose of alcohol (0.6 g/kg), equivalent to the dose used in the present experiment, was administered to healthy men. Although the BAC correlated negatively with CBF, which increased by 4%, a significant positive correlation was observed between CBF and blood acetate. In that study, the measurements were taken 134 min after drinks were consumed on the descending BAC limb when the effects of acetate were dominant. As a result of the same alcohol dose, we have also observed a significant perfusion increase in young, healthy men by 12.9% overall (expressed as $[(\text{alc} - \text{plac})/\text{plac}] \times 100$), which was most prevalent in prefrontal areas bilaterally. At the same time, a nonsignificant alcohol-induced CBF decrease of 4.9% was observed in women. No gender differences in CBF were observed under intoxication. Thus, our results confirm previous observations using a different method and extend them by reporting a robust interaction between the factors of alcohol and gender.

Given the complexity of the multifactorially determined hemodynamic mechanisms, some other possible routes of affecting perfusion could be considered as possibly contributing to the observed gender and beverage interactive effects. One such possible influence is through respiratory changes. By altering respiration, alcohol could potentially affect CO_2, which is known to be an effective vasodilator exerting strong effects on CBF (Birn et al., 2006). However, neither high alcohol levels affected arterial CO_2 (Murray et al., 1986) nor the respiratory motor network (Vecchio et al., 2010) as measured in rodents. Because only a moderate alcohol dose was administered in our study, it is unlikely that respiration was affected sufficiently different in men and women to cause changes in CO_2. Another previously suggested factor is the gender-based difference in viscosity of blood (Shaw et al., 1979). Contrary to this hypothesis, however, studies indicate that the CBF is not related to blood viscosity but to arterial oxygen content (Brown and Marshall, 1985). Furthermore, blood viscosity does not appear to be affected even by rather high alcohol dose (1.5 g/kg) (Hillbom et al., 1983). However, changes in cerebral perfusion could derive from

sympathetic effects on the cerebral vasculature (Jordan et al., 2000). Recent studies indicate that autonomic vascular autoregulation differs fundamentally between men and women (Hart et al., 2009), which is again attributed to hormonal differences between genders (Maki and Resnick, 2001). Thus, it is clear that regulatory configuration of the hormonal and vascular systems comprise complicated feedback loops. Consequently, the nature of the alcohol's interactions with gonadal hormones on one hand, and the physiological basis of the gender-based differences in CBF on the other, will need to be disentangled in a series of future studies. Finally, although the CBF was measured during resting, it is possible that different participants engaged in somewhat different types of cognitive or emotional states, increasing the variability in CBF. Esposito et al. (1996) reported that gender differences in PET-measured perfusion depend on the cognitive task as the largest differences were observed during the most challenging tasks probing frontal functions.

The present results extend and augment the existing evidence indicating associations between personality traits and CBF (Ebmeier et al., 1994; O'Gorman et al., 2006). In our study, perfusion under alcohol condition correlated with scores on Psychoticism/Antisocial (P) scale of the EPQ in both genders. The P-scale is taken to represent impulsivity and antisocial tendencies (Hare, 1982). It has been clearly established that personality aspects, such as impulsivity and antisocial behavior, are strongly related to vulnerability to alcohol addiction (Begleiter and Porjesz, 1999; Muller et al., 2008; Schuckit et al., 2004), with P-scale being a strong prospective predictor of a substance use disorder diagnosis (Sher et al., 2000). By the same token, increased mesolimbic dopaminergic activation may underlie vulnerability to drug abuse (Everitt et al., 2008) and is elicited by acute alcohol intoxication (Gessa et al., 1985; Yoder et al., 2009). A recent study in humans demonstrated that impulsive/antisocial tendencies correlated with amphetamine-induced dopamine release in nucleus accumbens, particularly on the right (Buckholtz et al., 2010). Furthermore, administration of a dopamine agonist increased blood flow in prefrontal areas in a right-dominant fashion (Grasby et al., 1993). Thus, our observation that alcohol-induced increase in blood flow correlates with baseline impulsivity is consistent with dopaminergic mediation of the rewarding aspects of alcohol and concomitant with its effects on cerebral perfusion.

Overall, the greatest overall CBF was observed in the frontal regions bilaterally, in agreement with previous reports (Ingvar, 1976; Prohovnik et al., 1980; Rodriguez et al., 1988; Wilkinson et al., 1969) but also refer Hermes et al. (2007) and Pfefferbaum et al. (2010). Studies show that this pattern of regional specificity is maintained under normocapnic anesthesia but is abolished by hypocapnic anesthesia (Wilkinson, 1971). Given the vulnerability of frontal lobes to alcohol effects (Oscar-Berman and Marinkovic, 2007) and their fundamental importance in subserving cognitive functions (Miller and Cohen, 2001), it is important to gain better insight into alcohol's effects on the regional CBF differences during resting and cognitive activity. Regionally specific vascular and metabolic changes exerted by alcohol may be important as markers of cerebral specificity of alcohol-induced vascular changes and could potentially illuminate the physiological basis of strokes and sudden death syndrome in binge drinkers (Altura et al., 1983).

Taken together, evidence suggests that CBF changes may be observed starting at 0.5 g/kg, depending on the time after drinking, gender, type of experimental design, and sample size. This also means that, because of alcohol's vasoactive effects, it may not be possible to interpret results of the fMRI–BOLD studies using higher-level acute alcohol intoxication unambiguously. Although the fMRI–BOLD method is an excellent mapping tool, its relative magnitude difference may not accurately reflect neural changes because of its sensitivity to vasoactive influences. This issue is particularly important given the increasing prominence of fMRI–BOLD studies in alcohol research on one hand, and a limited understanding of alcohol-induced changes in the physiology underlying BOLD on the other (Brown et al., 2003; Iannetti and Wise, 2007; Tracey, 2001). Furthermore, our results indicate that acute intoxication affects resting cortical perfusion in men but not in women on the descending BAC limb. Additional ASL studies with larger samples, different alcohol doses, and measurements at different points after drinking are needed to sort out the effects of alcohol intoxication and gender as they pertain to effects of alcohol and its metabolites, hormonal dynamics, and differences in hemodynamic autoregulation. Future studies will also need to examine whether these results can be generalized across different age groups given significant age-related decrease in cortical perfusion (Bangen et al., 2009; Parkes et al., 2004) as well as age-dependent effects of alcohol on brain function (Oscar-Berman and Marinkovic, 2007).

Furthermore, additional studies are needed to provide a more exact assessment of the relationship between the essential hemodynamic factors and the BOLD signal under intoxication, disambiguating the vascular/metabolic mechanisms underlying the BOLD signal from the neurally based changes. Such studies would mitigate interpretational confounds of nonneural origin and would insure interpretability of the alcohol-induced effects on the BOLD signal (Ances et al., 2008; Hyder, 2004; Liu and Brown, 2007; Perthen et al., 2008). Because of its superior signal-to-noise ratio, higher spatial and temporal resolution and better brain coverage, the BOLD signal has been the method of choice in neuroimaging studies (Brown et al., 2007; Buxton, 2002). Although the BOLD method is an excellent mapping tool, interpreting the magnitude changes as proportionally reflecting neural events is inherently ambiguous (Leontiev et al., 2007). In contrast, the ASL provides quantification of the blood flow and it may be a more faithful index of the functional activity than BOLD because of its sensitivity to changes in capillary bed (Lee et al., 2001). It is sensitive, however, to the factors influencing cerebrovascular

structure, such as aging or disease, (D'Esposito et al., 2003) that result in increased variation in transit times (Buxton et al., 1998a). Using these two complementary methods synergistically provides an opportunity to discern vascular from neurally based changes underlying BOLD. More specifically, dual echo acquisition allows simultaneous measurement of the CBF and BOLD signals (Wong et al., 1997). $CMRO_2$, which is coupled with neural activity (Hyder, 2004), can further be derived with the addition of simultaneous measures of CBF and BOLD during mild hypercapnic (increased arterial CO_2) manipulation. This ''calibrated BOLD'' method (Davis et al., 1998) relies on the observation that ASL reflects changes in CBF, whereas the BOLD is sensitive to changes in both CBF and $CMRO_2$. Mild hypercapnia increases CBF but not $CMRO_2$, effectively providing scaling (calibration) for the BOLD. Estimates of local $CMRO_2$ reflecting neural activity are based on simultaneous measurements of the BOLD and CBF responses within the Davis' model. Consequently, these measures provide excellent insight into the physiological factors underlying BOLD and a way to deconvolve vascular confounds from neural activity (Buxton et al., 1998b, 2004; Liu and Brown, 2007).

In summary, our results indicate that cortical perfusion is affected differently in men compared with women by moderate alcohol intoxication on a descending BAC limb as alcohol-induced CBF increase was observed bilaterally in frontal regions in men only. Under placebo, greater perfusion was observed in women compared with men, confirming previous robust evidence of this effect. These gender-based differences may be because of a complex and possibly interactive set of factors influencing hormonal, metabolic, and hemodynamic autoregulatory systems in the context of alcohol intoxication. Additional ASL studies are needed to investigate the interactive dose-dependent effects of alcohol intoxication and gender and to disambiguate the vascular/metabolic mechanisms underlying the BOLD signal from the neurally based changes. Taken together with previous PET and SPECT studies, our results support the feasibility of fMRI–BOLD at low levels of alcohol intoxication.

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