Title

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Journal

Alcohol Clinical and Experimental Research, 43(5)

ISSN

0145-6008

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Publication Date

2019-05-01

DOI

10.1111/acer.13998

Peer reviewed

The Relationship Between Regional Cerebral Blood Flow Estimates and Alcohol Problems at 5-Year Follow-Up: The Role of Level of Response

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Background: Acute alcohol consumption is associated with temporarily increased regional cerebral blood flow (CBF). The extent of this increase appears to be moderated by individual differences in the level of response (LR) to alcohol's subjective effects. The low LR phenotype is a known risk factor for the development of alcohol problems. This study investigates how the low LR phenotype relates to the relationship between alcohol-related changes in CBF and alcohol problems 5 years later.

Methods: Young adults (ages 18 to 25) were selected based on their LR to alcohol and underwent a neuroimaging protocol including arterial spin labeling and functional scans. These participants were recontacted ~5 years later and assessed on alcohol outcomes. A final sample of 107 subjects (54 low and 53 high LR subjects) was included in the analyses. Whole-brain analysis revealed 5 clusters of significant alcohol-induced, versus placebo-induced, CBF changes that were consistent with a previous report. Peak alcohol–placebo CBF response was extracted from these regions and, along with the LR group, submitted to a hierarchical linear regression predicting alcohol problems. Analyses controlled for age, sex, and baseline alcohol problems.

Results: In the regression analysis, greater alcohol–placebo CBF difference in the right middle/superior/inferior frontal gyri and bilateral anterior cingulate gyri clusters predicted greater future alcohol problems for the low LR group, whereas this relationship was not found to be significant in the high LR group.

Conclusions: This study demonstrates a clinically important relationship between CBF and future alcohol problems, particularly in individuals with a low LR phenotype. These initial results help to elucidate the neurobiological pathways involved in the development of alcohol use disorders for individuals with low LR.

Key Words: Cerebral Blood Flow, Level of Response, Alcohol Problems, Arterial Spin Labeling, Young Adults.

ALCOHOL USE DISORDERS (AUDs) remain a highly prevalent and burdensome condition for the affected individuals and society. According to the recent National Survey on Drug Use and Health results, approximately 6% of individuals ages 12 or older, or 11% of young adults (ages 18 to 25 years old), met criteria for an AUD in 2016 (Substance Abuse and Mental Health Services Administration, 2017). The excessive use of alcohol is associated with a number of negative physical and psychosocial consequences (Gmel and Rehm, 2003; Piano et al., 2017; Squeglia et al., 2014), together resulting in approximately $249 billion in costs to the United States in 2010 (Sacks et al., 2015). These substantial estimates underscore the need for additional research on the origins of AUDs to facilitate targeted prevention and intervention strategies.

The development of an AUD is likely to involve a number of genetic and environmental influences. Further, the traditional conceptualization of AUD includes a diverse set of individual phenotypes, leading to significant heterogeneity in disorder development and presentation (Hyman, 1999). To gain traction in AUD research, many researchers have turned to the study of more narrowly defined intermediate phenotypes related to AUDs (Claus et al., 2011; Hines et al., 2005). The use of an intermediate/endophenotype approach has led to enhanced power in genetic (Dick et al., 2006) and neurobiological studies (Ray et al., 2010), and has provided greater opportunity for the discovery of early points of intervention in those at high risk for disorder development (Savage et al., 2015; Schuckit et al., 2016).

Intermediate phenotypes that capture how an individual responds to alcohol have proven to be clinically important and reliable risk factors for AUD development (King et al.,

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Received for publication November 15, 2018; accepted February 28, 2019.

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DOI: 10.1111/acer.13998

2014; Schuckit et al., 2007). In particular, the low level of response (LR) phenotype has been shown to be a genetically influenced characteristic (Schuckit, 2009) that predicts future heavy drinking and risk for developing AUDs (Chung and Martin, 2009). This model suggests that individuals with a low LR profile, meaning they need higher blood alcohol concentrations (BACs) to experience alcohol effects, are at greater risk for heavy drinking and alcohol problems than individuals who exhibit a high LR profile (Schuckit et al., 2007, 2008; Zhang et al., 2015). The low LR profile has been associated with a general dampening of physiological markers in these individuals following alcohol administration, including reduced alcohol-related effects on adrenocorticotropic hormone and prolactin release and less intense changes to cortical electroencephalograms and event-related potentials, as compared to their high LR counterparts (Ehlers and Schuckit, 1988; Schuckit et al., 1987, 1988a,b).

An individual's LR also appears to have measurable neural correlates. Functional magnetic resonance imaging (fMRI) studies using cognitive and emotional-based tasks to probe the low LR phenotype suggest 2 primary findings despite similar task-related behavioral performance: (i) low LR individuals, as compared to high LR individuals, tend to have greater regional blood oxygen level–dependent (BOLD) response under baseline or placebo conditions (Schuckit et al., 2012; Tapert et al., 2004; Trim et al., 2010), potentially reflecting the need for greater cognitive effort during task performance (Schuckit et al., 2016); and (ii) low LR individuals show a general tendency for dampened or attenuated BOLD response following acute alcohol administration, as compared to high LR individuals who often show the opposite response postalcohol (Paulus et al., 2012; Schuckit et al., 2012). Importantly, LR-related BOLD response in the right middle frontal gyrus and the left anterior insula during an emotion processing task was found to predict future alcohol consumption and alcohol-related problems at 5-year follow-up (Schuckit et al., 2016), suggesting the presence of clinically relevant variation in the neural profile of the LR phenotype.

The study of cerebral blood flow (CBF) could provide additional neurobiological information regarding the heightened risk for heavier drinking, alcohol problems, and AUDs associated with the low LR profile. CBF is tightly coupled with glucose metabolism (Jueptner and Weiller, 1995) and brain function (Raichle et al., 1976), and reductions in regional CBF and glucose metabolism in the sober state, particularly in frontal brain regions, have been observed with the misuse of multiple substances (Murray et al., 2015), including alcohol (Hamdi et al., 2003; Moselhy et al., 2001). These regional CBF reductions have been associated with severity of AUD (Hamdi et al., 2003) and important functional outcomes, such as relapse to drinking after treatment (Durazzo et al., 2010) and neurocognitive functioning (Goldstein et al., 2004).

Although there is general agreement that acute alcohol consumption at low to moderate levels is associated with temporarily increased regional CBF (Gundersen et al., 2013; Khalili-Mahani et al., 2011; Tiihonen et al., 1994), the intensity of this increase appears to be moderated, in part, by individual differences in LR (Strang et al., 2015; Tolentino et al., 2011). Consistent with a general dampening of alcohol-induced physiological effects, nondependent young adult alcohol drinkers with a low LR profile demonstrate less increase in CBF after acute alcohol consumption as compared to those with a high LR, particularly in frontal and cingulate brain regions.

Taken together, the literature suggests a notable relationship between frontal CBF, alcohol-related outcomes, and LR. However, it remains unknown whether the increase in CBF following acute alcohol administration is clinically meaningful as a potential biologically based marker of future alcohol problems and whether the known differences in LR-related CBF increases following alcohol affect this potentially predictive relationship. The current paper attempts to address these research questions by testing whether alcohol- versus placebo-related CBF estimates can predict alcohol problem outcomes 5 years later in a longitudinal sample of young adults who differ in their LR to alcohol. Analyses focused on 5 frontal clusters associated with alcohol-related CBF changes first identified in a data-driven, whole-brain, voxel-wise analysis by Tolentino and colleagues (2011) that included a subset of the present study data. We hypothesized that the magnitude of change in these regional CBF estimates during alcohol–placebo challenge at baseline would predict alcohol problems at 5-year follow-up (i.e., less CBF change to alcohol will predict more alcohol problems later). Given the increased risk associated with the low LR phenotype, we further hypothesized that the predictive relationship of the magnitude of CBF change will be stronger in low LR than high LR. Due to the novelty of the study aims, no cluster-specific hypotheses were made.

MATERIALS AND METHODS

Participants and Study Design

The data for the analyses were taken from a recently completed study (for a more thorough description of methods, see Schuckit et al., 2016). Briefly, potential participants were initially identified through mailings to students at a local university, using procedures approved by the UCSD Human Research Protections Program. The mailings included questions about demography and the Self-Report of the Effects of alcohol (SRE) questionnaire, which includes 4 questions pertaining to the number of standard alcoholic drinks (~10 g ethanol [EtOH]) needed to experience a range of effects (i.e., feeling effects, slurred speech, unsteady gait, and unwanted falling asleep) the first 5 times of drinking (before chronic tolerance was likely to have developed; Schuckit et al., 1997).

Consistent with all our prior studies of LR and most additional studies of this phenotype, young adults with more limited drinking histories (e.g., no histories of AUDs) were targeted to minimize the chances that we are measuring the results of consistent heavy drinking and to determine whether these early responses to alcohol can serve as predictors of future alcohol use behaviors. Thus, inclusion criteria for the study were as follows: (i) ages 18 to 25; and (ii) having consumed at least 1 full standard alcoholic drink in the past (due

to the requirement of some previous exposure to alcohol for completion of the SRE and alcohol challenge procedures). Exclusionary criteria were as follows: (i) a lifetime or current diagnosis of alcohol or other drug dependence, bipolar, or schizophrenia (American Psychiatric Association, 1994); (ii) a current medical condition or use of a medication that might interfere with an alcohol challenge or brain blood flow; (iii) previous head trauma with loss of consciousness >3 minutes; (iv) current pregnancy; (v) left handedness; and (vi) MRI contraindications (e.g., claustrophobia, irremovable metal).

Participants were preselected based on their SRE scores (~upper and lower SRE thirds) and scheduled for a face-to-face interview which included the full Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview (Bucholz et al., 1994; Schuckit et al., 2012). The SSAGA was designed to assess psychological, physical, and social manifestations of alcohol abuse/dependence and other psychiatric disorders and includes questions on recent alcohol consumption (quantity and frequency of current alcohol use) and alcohol-related problems. If deemed eligible, participants were then invited to the laboratory to complete an acute alcohol challenge procedure to verify their LR profile. The alcohol challenge procedure included the consumption of 0.70 ml/kg for women and 0.75 ml/kg for men of laboratory-grade EtOH consumed over ~10 minutes (resulting peak BACs of ~60 mg/dl). Participants then completed the 7-item version of the Subjective High Assessment Scale (SHAS), an analogue self-report measure of positive and negative subjective feelings of alcohol intoxication (Eng et al., 2005), every 15 to 30 minutes for ~3 hours. Approximately 80% of the preselected participants displayed consistent LR profiles on the SHAS and SRE (for more detailed methods, see Trim et al., 2010).

For the baseline imaging protocol, 120 participants were identified (60 low LR and 60 high LR) to take part in 2 neuroimaging sessions administered in random order, 1 after consuming the 0.70 to 0.75 ml/kg dose of EtOH as described above and 1 after a no-alcohol placebo beverage, each consumed over 10 minutes. Participants were also assessed again on indices of recent alcohol consumption and alcohol problems/AUD symptoms using selected questions from the SSAGA interview (Bucholz et al., 1994; Schuckit et al., 2012). Possible alcohol problems included the 11 DSM-IV abuse and dependence items plus blackouts, morning drinking, efforts to stop drinking, self-help group attendance, and receiving professional help for alcohol-related difficulties (total possible problem count of 16). The major focus for the baseline results of the original papers was on the relationship of the LR status of the subject to the BOLD response contrast patterns in relevant regions of interest, with arterial spin labeling (ASL) measures of CBF used as a covariate (Paulus et al., 2012; Schuckit et al., 2012; Trim et al., 2010).

Participants were then recontacted by telephone approximately 5 years later and assessed again on indices of recent alcohol consumption (quantity and frequency of alcohol use during follow-up) and alcohol problems/AUD symptoms using the selected SSAGA questions. Complete CBF and follow-up data are available for 109 subjects (55 low and 54 high LR participants).

Neuroimaging Protocol

Imaging data were collected at the UCSD fMRI Center with a 3-Tesla General Electric (Milwaukee, WI) Signa Excite HD scanner using an 8-channel head array coil. Scanning began 22 minutes after the start of beverage administration and included a number of functional scans (see Paulus et al., 2012; Schuckit et al., 2012; Trim et al., 2010) prior to the resting ASL scan. Collection of resting-state ASL data began approximately 60 minutes after the start of beverage consumption, thus occurring at peak or the initial phase of the descending BAC limb. Each scan session included a sagittally acquired high-resolution spoiled gradient-recalled anatomical sequence (25 cm field of view; 256 × 256 matrix; 124 slices each 1.0 mm thick covering the whole brain; 4.8 ms echo time; and 20 ms repetition time). Three sequences were acquired to obtain absolute CBF measurements during each session. Resting brain blood perfusion was measured with pulsed ASL using a modified flow-sensitive alternating inversion recovery sequence with both presaturation pulses and PICORE QUIPSS 2 postinversion saturation pulses and a spiral readout with 4 interleaves to reduce signal dropout (22 × 22 cm field of view, a 64 × 64 matrix, 3.2 ms echo time, 2,500 ms repetition time, postsaturation and inversion times of TI1 = 600 ms and TI2 = 1,600 ms, tag thickness 10 cm, tag to proximal slice gap 1 cm, twenty 5 mm axial slices, and 40 volumes for 20 tag + control image pairs) (Wong, 2005). In addition, a scan without inversion pulses was acquired to obtain an estimate of the equilibrium magnetization of cerebral spinal fluid (CSF), and a minimum contrast image was acquired to adjust for coil inhomogeneities (Restom et al., 2007).

Data Processing

Imaging data were processed using Analysis of Functional NeuroImages (AFNI; afni.nimh.nih.gov; Cox, 1996), FMRIB Software Library (FSL; Oxford, UK) (Smith et al., 2004), and locally created MATLAB scripts. As in the original study (Tolentino et al., 2011), each ASL data set was first reconstructed using the SENSE algorithm (Pruessmann et al., 1999; Weiger et al., 2002) to reduce sensitivity to the modulations that occur between shots caused by physiological fluctuations or motion. Second, an automated MATLAB script including AFNI and FSL tools processed the ASL data. Third, the ASL time series were coregistered to the middle time point to minimize the effects of participant motion. Fourth, surround subtraction of the tag–control time series was performed to create an uncorrected perfusion time series and slice timing delays were accounted for, making the inversion time (TI2) slice specific.

Each participant's session-specific high-resolution T1-weighted image was skull stripped using AFNI's 3dSkullStrip. A mask from the same session average A3 or ASL image was then calculated using 3dAutomask and applied to the CBF data. The high-resolution anatomicals were then aligned to these masked CBF images using AFNI's align_epi_anat script and segmented using FSL's FAST algorithm to define CSF, gray matter, and white matter regions. The aligned high-resolution and full-field CBF images were warped to Talairach space using AFNI's auto_tlrc function and resampled to a 4 × 4 × 4 mm resolution grid with AFNI's adwarp. Voxels with negative intensities were replaced with zero (Brown et al., 2003). Data from both the alcohol and placebo sessions were visually screened for data quality and alignment.

Statistical Analyses

Whole-brain, voxel-level analysis was conducted using a paired *t*-test (AFNI 3dttest++) to contrast perfusion values between the placebo and alcohol sessions (alcohol–placebo and placebo–alcohol contrasts computed). To control for type I error, the Clustsim nonparametric randomization/permutation option of 3dttest++ was used with a conservative voxel-wise alpha of 0.001 and cluster-wise alpha of 0.05, which estimated a cluster size threshold of 7 contiguous voxels. The AFNI version used for all analyses included the bug-correction in 3dClustSim. The randomization step of the clustering process randomizes the signs of the model residuals, whereas the permutation step permutes the imaging volume assignment across the 2 image sets in order to determine a 0.05 cluster size threshold. As discussed by Eklund and colleagues (2016), nonparametric permutation tests offer precise control of false positives. Furthermore, AFNI's 3dtest++ randomization step alone has been shown to produce false positive rates (FPR) compatible with the nominal 95% confidence interval (FPR: 3.65 to 6.35%; Cox et al., 2017). To be consistent with the original manuscript (Tolentino

et al., 2011), an averaged gray matter mask was created from the individual FAST gray matter volumes using AFNI's 3dcalc function, which was then used to restrict the results of the *t*-test. Two subjects (1 high LR and 1 low LR) exhibited extreme alcohol–placebo CBF estimates across all clusters of interest (>50 ml/100 g/min difference between conditions) and were excluded from the analyses, leaving a final sample of 107 subjects (54 low and 53 high LR subjects).

Five clusters of interest corresponding to the original article results (Tolentino et al., 2011) were then identified from the significant clusters of whole-brain alcohol–placebo contrast activation. CBF estimates from each of these clusters were extracted from each subject. Independent samples *t*-tests were conducted to compare high and low LR groups on these 5 alcohol–placebo CBF cluster estimates.

To test the predictive utility of the CBF estimates, the mean alcohol–placebo activation for these 5 clusters were entered into a hierarchical linear regression model predicting alcohol problem count at follow-up. Participant sex was controlled for given that females tend to exhibit greater increases in global perfusion following acute alcohol administration (Marxen et al., 2014). Thus, sex, age, and baseline level of alcohol problems were entered in Step 1 of the model as they represented theoretically important a priori covariates. LR group membership and the 5 main effect cluster CBF estimates were entered in Step 2, followed by the interaction between the cluster CBF estimates and the LR group entered in Step 3. All values were entered in their original metric (uncentered) given the meaningfulness of 0 in the CBF cluster estimates (0 representing no difference between alcohol and placebo) and the LR group variable (low LR coded as 0 and high LR coded as 1) (Shieh, 2011). An exploratory whole-brain correlation with follow-up alcohol problems count including LR group as a between-subjects factor was also conducted on alcohol–placebo CBF difference maps using AFNI 3dttest++ ($p < 0.01$, uncorrected). In addition, an exploratory hierarchical linear regression model consistent with the model above was run with average alcohol use frequency per month serving as the baseline covariate and outcome of interest.

RESULTS

Participants

The sample demography and alcohol use characteristics relevant to the key analyses are presented in Table 1. As shown in this table, participants were approximately 20 and 25 years old at baseline and follow-up, respectively. There were roughly equal numbers of males and females in the sample. As expected, the low LR group generally reported greater maximum drinks and alcohol problems than the high LR group both at the baseline and follow-up time points; yet, only the baseline differences met statistical threshold (*p*-values < 0.05). Both the LR groups exhibited significantly greater maximum drinks and alcohol problems at follow-up as compared to baseline (*p*-values <0.001). No differences were observed between baseline and follow-up time points with respect to usual drinks in either group (*p*-values >0.28).

Neuroimaging

Whole Brain. Given our expanded sample from 88 subjects in the prior paper (Tolentino et al., 2011) to 107 in the current paper, a whole-brain alcohol–placebo CBF contrast analysis was conducted in order to replicate and extend upon the original findings by Tolentino and colleagues (2011). The alcohol–placebo contrast revealed significant alcohol-related CBF response in 23 clusters (see Table 2). These results are largely consistent with the original analysis despite the inclusion of 19 additional subjects and more stringent statistical thresholding practices. Also consistent with the original analysis, no significant results were obtained for the reverse contrast, placebo–alcohol.

Cluster Identification. Of the whole-brain results, 5 clusters largely consistent with the original analysis by Tolentino and colleagues (2011) were selected for further analysis (presented in bold in Table 2). As depicted in Fig. 1, these clusters included the (i) right middle/superior/inferior frontal gyri (red), (ii) left middle/superior frontal gyri (purple), (iii) bilateral medial/superior frontal and cingulate gyri (green), (iv) bilateral anterior cingulate gyri (yellow), and (v) right precentral gyrus (blue).

LR Differences in Alcohol-Related CBF. In an effort to replicate the original study findings and to determine whether the LR groups differed in alcohol-related CBF response within the selected clusters, mean CBF responses to alcohol–placebo were extracted from the 5 clusters identified and statistically compared across groups. Consistent with the original paper, the low LR group generally exhibited a smaller CBF change in response to alcohol–placebo administration across the extracted clusters as compared to the high LR group; however, only the bilateral medial/superior frontal and cingulate gyri cluster reached statistical significance, $t\,(1,105) = -2.398$, $p = 0.018$ (see Fig. 2).

CBF Cluster Prediction of Alcohol Problems at Follow-Up

Next, a hierarchical linear regression model was conducted to determine the predictive utility of the CBF response, and the possible moderating role of the LR group, on alcohol problems at 5-year follow-up. The results of this analysis are depicted in Table 3. Step 1 evaluates how 3 baseline characteristics used as covariates relate to the number of alcohol problems during the follow-up period, with results indicating significant contribution for only baseline alcohol problems and the 3 items explaining 8% of the variance (the R^2), $F(3, 103) = 2.86$, $p = 0.04$.

Step 2 evaluated whether there were significant main effects in the regression analysis when it was expanded to include LR group and the relevant CBF clusters. This step revealed no significant main effects for the key variables entered into these analyses, and the 5% increase in R^2 from Step 1 to Step 2 did not account for a significant increase in variance over Step 1, F change $(6, 97) = 1.01$, $p = 0.42$.

Step 3 extends Steps 1 and 2 by adding all interactions between LR group and CBF cluster estimates. This step increased the R^2 to 0.24, with a significant R^2 change of 0.11, $F(5, 92) = 2.716$, $p < 0.03$, and a total of 24% variance in

Table 1. Sample Demographics

Variable	% Frequency or mean (SD)				Baseline LR group difference (*p*-values)	Follow-up LR group difference (*p*-values)
	Low LR (n = 54)		High LR (n = 53)			
	Baseline	Follow-up	Baseline	Follow-up		
Age	19.72 (1.42)	25.02 (1.71)	19.92 (1.49)	25.09 (1.76)	0.47	0.82
% male	50.0		45.3		0.62	0.62
Ethnicity (%)					0.22	0.22
Hispanic	20.4		32.1			
Non-Hispanic	77.8		66.0			
Unknown/other	1.8		1.9			
Usual drinks per drinking day	3.92 (1.70)	3.56 (1.77)	3.16 (1.78)	3.19 (1.44)	**0.03**	0.24
Max drinks per drinking day	7.94 (3.89)	11.09*** (4.50)	5.89 (3.30)	9.57*** (4.03)	**<0.01**	0.07
Average drinking days per month	7.18 (4.56)	11.98*** (6.68)	6.04 (4.87)	10.23*** (7.16)	0.25	0.22
Alcohol problems count	0.80 (0.92)	2.96*** (2.63)	0.38 (0.60)	2.09*** (2.18)	**<0.01**	0.07

***Significant change from baseline to follow-up (p-values <0.001). The bolded numbers are the actual p-values of significance.

Table 2. Clusters of Significant CBF Response from the Whole-Brain Alcohol–Placebo Contrast Across All Subjects (Thresholded at a Voxel-Wise Alpha of 0.001 and Cluster-Wise Alpha of 0.05; ≥7 Contiguous Voxels)

Cluster	Location	Voxels	X	Y	Z
1	**R middle/superior/inferior frontal gyri**	**106**	**46**	**43**	**8**
2	**L middle/superior frontal gyri**	**70**	**−34**	**39**	**40**
3	**Bil medial/superior frontal and cingulate gyri**	**40**	**−6**	**−9**	**64**
4	Bil thalamus	39	−6	−21	8
5	**Bil anterior cingulate gyri**	**35**	**2**	**39**	**0**
6	R inferior temporal gyrus/fusiform gyrus	28	62	−17	−24
7	**R precentral gyrus**	**21**	**50**	**−5**	**48**
8	R superior/medial frontal gyri	19	2	−9	64
9	R inferior frontal gyrus/precentral gyrus	16	50	15	8
10	R inferior parietal lobule/insula	15	58	−33	20
11	L inferior temporal gyrus/fusiform gyrus/culmen	14	−58	−49	−12
12	L inferior/middle temporal gyrus	13	−62	−25	−16
13	Bil cingulate/precuneus	10	2	−61	28
14	L supramarginal gyrus/inferior parietal lobule	10	−58	−49	32
15	L inferior temporal gyrus/fusiform gyrus	9	−58	−9	−24
16	L middle temporal gyrus	9	−62	−49	0
17	R middle/superior frontal gyrus	9	42	15	52
18	L precentral gyrus/middle frontal gyrus	9	−42	−1	48
19	R middle/superior temporal gyrus	8	66	−21	−12
20	R middle temporal gyrus	8	62	−37	0
21	L parahippocampal gyrus	7	−26	−37	4
22	L middle frontal gyrus	7	−30	51	−4
23	R supramarginal gyrus/inferior parietal lobule	7	58	−53	36

Bolded clusters represent clusters consistent with the previous report (Tolentino et al., 2011) and were extracted for follow-up analyses.
X, Y, and Z Talairach coordinates indicate the location of peak voxel activation within each cluster. L = left, R = right, Bil = bilateral.

predicting follow-up alcohol problems explained. Within this third step, controlling for sex, age, and baseline alcohol problems, a significant interaction was observed between LR group and alcohol–placebo CBF response in the right middle/superior/inferior frontal gyri cluster (Cluster 1; $B = -0.16$, $p = 0.04$). Examination of each group's conditional effects (i.e., the effect of each group separately, controlling for the other model variables) of the alcohol–placebo CBF response in the right middle/superior/inferior frontal gyri cluster revealed that greater CBF response in this cluster predicted greater alcohol problems for the low LR group at a trend level ($B = 0.09$, $p = 0.09$), while greater alcohol–placebo CBF response in this cluster was nonsignificantly associated with less alcohol problems for the high LR group (model reran with the high LR group recoded as 0: $B = -0.07$, $p = 0.13$).

A similar significant LR group interaction with alcohol–placebo CBF response was observed for the bilateral anterior cingulate gyri cluster (Cluster 4; $B = -0.10$, $p = 0.03$). Examination of the conditional effects revealed that greater alcohol–placebo CBF response in this cluster significantly predicted greater alcohol problems for the low LR group ($B = 0.09$, $p = 0.02$), while greater alcohol–placebo CBF response in this cluster was nonsignificantly associated with less alcohol problems for the high LR group (model reran with the high LR group recoded as 0: $B = -0.01$, $p = 0.74$).

These data are also presented in Figs 3 and 4. Figure 3 depicts the interaction between LR group and alcohol–placebo CBF response from the right middle/superior/inferior frontal gyri cluster (Cluster 1), whereas Fig. 4 depicts the interaction between LR group and alcohol–placebo CBF

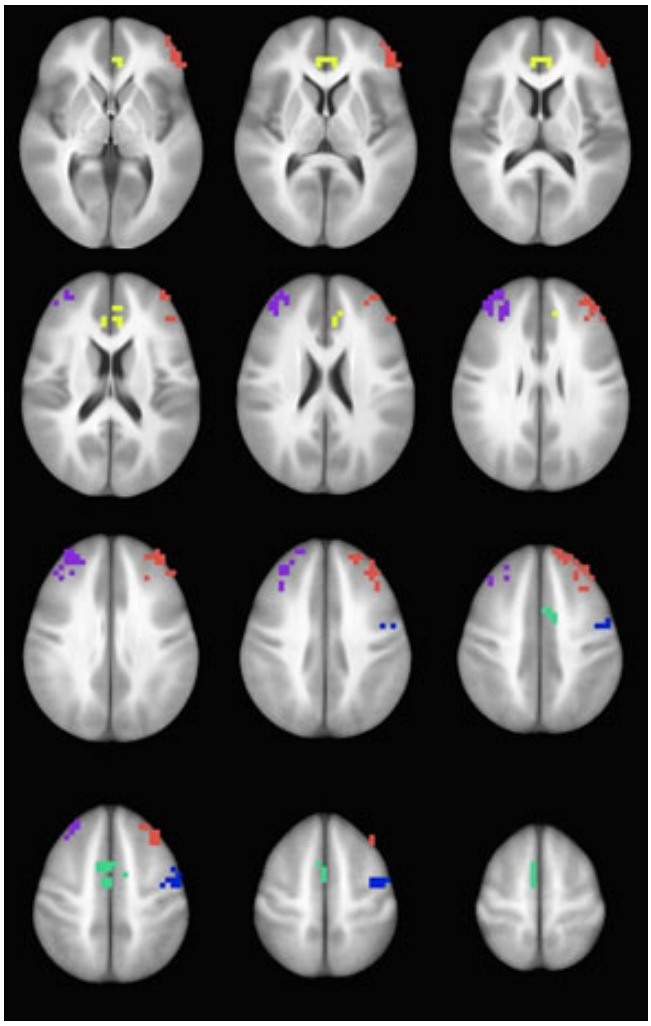

Fig. 1. Clusters of significant alcohol–placebo CBF response extracted for prediction analyses.

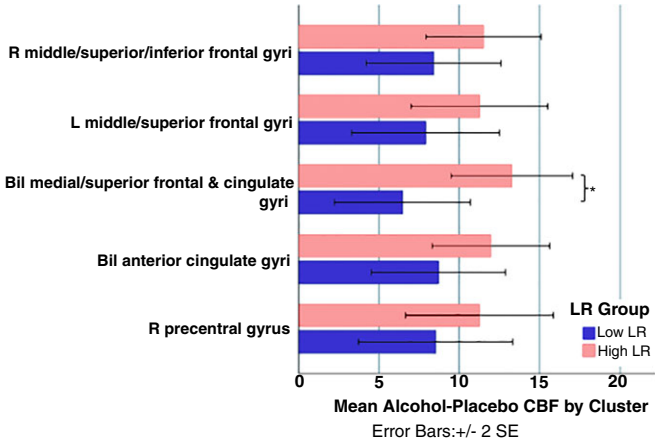

Fig. 2. Mean CBF values by LR group for each cluster extracted.

response from the bilateral anterior cingulate gyri cluster (Cluster 4). As shown in both figures, LR moderated the predictive relationship between CBF response to alcohol and alcohol problems at follow-up such that greater alcohol-related CBF response (plotted on the *x*-axes) generally predicted greater alcohol problems (plotted on the *y*-axes) for the low LR group (shown in blue), yet CBF response and alcohol problems were not significantly related in the high LR group (shown in red).

Exploratory whole-brain correlations (voxel $p < 0.01$, no cluster correction) revealed activation largely constrained within the clusters of interest and were consistent with the results of the regression analysis. The hierarchical model predicting average alcohol use frequency during follow-up did not reveal any significant main or interaction effects pertaining to the variables of interest.

DISCUSSION

The goal of the present analyses was to investigate the ability of regional alcohol-related CBF response to predict alcohol problems 5 years later within a longitudinal sample of young adults who differ in their LR to alcohol. The primary finding was that greater alcohol–placebo CBF contrast extracted from the right middle/superior/inferior frontal gyri and bilateral anterior cingulate gyri clusters predicted greater future alcohol problems for the low LR group, whereas alcohol-related CBF response in these clusters and future alcohol problems were not significantly related in the high LR group. These findings were observed even after controlling for the impact of sex, age, and the number of alcohol problems at baseline. Importantly, the addition of LR group and alcohol-related CBF response interactions to the statistical model accounted for a significant amount of variance in later alcohol problems (24%) such that prediction of outcomes by CBF was only seen in the low LR group, suggesting the potential importance of considering the combination of both alcohol-related CBF and LR in predicting future alcohol problem development.

With respect to our first hypothesis, less alcohol-related CBF change in bilateral medial/superior frontal and cingulate gyri was associated with more alcohol problems at follow-up, regardless of LR; however, this effect did not exceed the statistical threshold. Instead, consistent with our second hypothesis, the relationship between alcohol-related CBF response and later alcohol problems was only statistically significant within individuals with low LR to alcohol. In line with an overall dampening of alcohol-induced physiological effects (Ehlers and Schuckit, 1988; Schuckit et al., 1987, 1988a,b) and previous CBF analyses on LR (Strang et al., 2015; Tolentino et al., 2011), the low LR group in the present study also generally exhibited a smaller alcohol-related CBF response across the brain as compared to the high LR group. In other words, despite a general tendency for lower alcohol–placebo CBF response in the low LR versus high LR groups, within the low LR group, individuals with greater alcohol-related CBF responses evinced greater alcohol problems at follow-up. Taken together, these results suggest that the combination of a low LR profile and increased

Table 3. Summary of the Hierarchical Regression Analysis Results Predicting Follow-up Alcohol Problems

Model variables	Step 1 *B* (SE)	Step 2 *B* (SE)	Step 3 *B* (SE)
Step 1—Demographic covariates			
Sex	0.61 (0.47)	0.44 (0.48)	−0.08 (0.49)
Age	−0.13 (0.16)	−0.05 (0.17)	−0.02 (0.17)
Baseline alcohol problems	0.82** (0.29)	0.55† (0.32)	0.40 (0.32)
Step 2—Main/conditional effects			
LR group		−0.43 (0.50)	0.93 (0.64)
Cluster 1: R middle/superior/inferior frontal gyri		0.01 (0.04)	0.09† (0.05)
Cluster 2: L middle/superior frontal gyri		0.02 (0.04)	−0.04 (0.05)
Cluster 3: Bil medial/superior frontal and cingulate gyri		−0.06† (0.03)	−0.08† (0.04)
Cluster 4: Bil anterior cingulate gyri		0.03 (0.02)	0.09* (0.04)
Cluster 5: R precentral gyrus		0.01 (0.03)	−0.01 (0.03)
Step 3—Interactions			
Cluster 1 × group			−0.16* (0.07)
Cluster 2 × group			0.10 (0.07)
Cluster 3 × group			−0.01 (0.06)
Cluster 4 × group			−0.10* (0.05)
Cluster 5 × group			0.04 (0.05)
R^2	0.08	0.13	0.24
R^2 change	0.08	0.05	0.11
F for change in R^2	2.86*	1.01	2.72*

**$p < 0.01$, *$p < 0.05$, †$p < 0.10$.

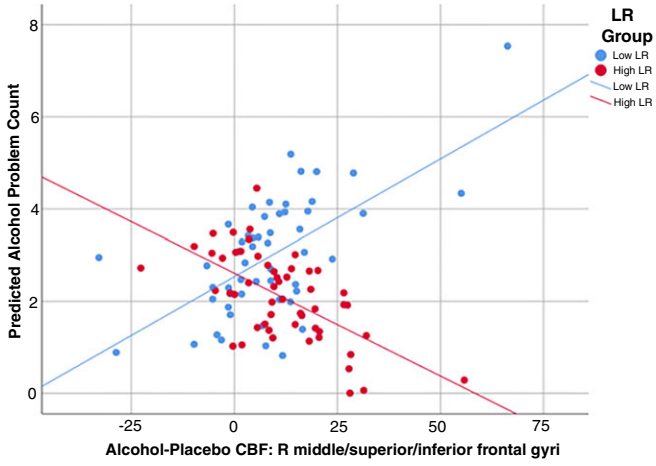

Fig. 3. Scatterplot depicting the interactive effects between alcohol–placebo cerebral blood flow (CBF) values extracted from the right middle/superior/inferior frontal gyri cluster (*x*-axis) and level of response (LR) group on the predicted alcohol problem count scores estimated from the hierarchical analysis (*y*-axis).

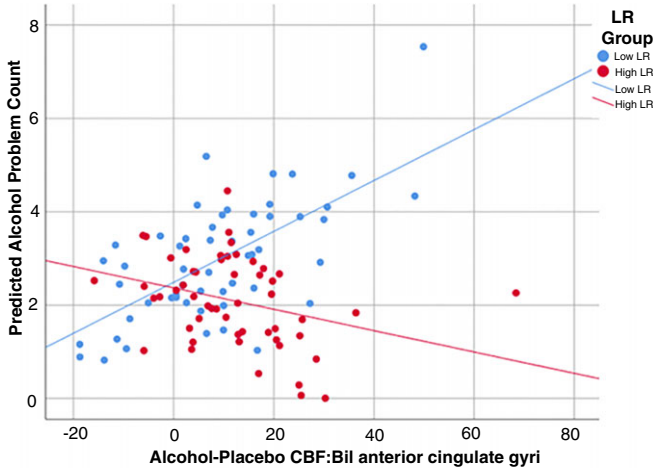

Fig. 4. Scatterplot depicting the interactive effects between alcohol–placebo cerebral blood flow (CBF) values extracted from the bilateral anterior cingulate gyri cluster (*x*-axis) and level of response (LR) group on the predicted alcohol problem count scores estimated from the hierarchical analysis (*y*-axis).

alcohol-related CBF response represents an especially risky phenotype for the development of later alcohol problems.

Consistent with the original baseline analysis on a subset of these subjects (Tolentino et al., 2011), the largest clusters of alcohol–placebo CBF response in the whole-brain analysis were observed in the frontal and anterior cingulate gyri. The frontal systems are known to be affected by acute alcohol administration (Zheng et al., 2015) and BOLD activation in the right middle frontal gyrus during an emotional processing task has been identified as a strong predictor of future alcohol problems (Schuckit et al., 2016). The frontal systems are involved in a host of cognitive and emotional processes including decision making, affect and stress regulation, and problem solving, many of which have been linked with the risk for, or consequences of, AUDs (for a review, see Moselhy et al., 2001). In addition, the anterior cingulate is important for adaptive decision making (Kennerley and Walton, 2011) and is often implicated in the processing of alcohol-related cues (Schacht et al., 2013). Thus, regionally specific alcohol-related CBF response in these frontal and anterior cingulate areas in a nonclinical sample of low LR young adults may represent another neurobiological marker

of a more general cognitive/emotional AUD risk factor, such as the need for greater cognitive effort during task performance (Schuckit et al., 2016). However, the direction of effects in the present resting-state analysis does not seem to fit this model as high LR individuals tended to show enhanced alcohol versus placebo CBF response across the regions of study, suggesting greater resource utilization as compared to low LR individuals. Only within the low LR group do we see a statistically significant relationship between greater CBF response to alcohol and greater alcohol-related problems at follow-up. Further investigation of CBF in the context of other known risk markers, such as externalizing/internalizing profiles and impulsivity, may help to clarify how CBF function in these specific frontal and cingulate regions relates to alcohol-related behavioral outcomes.

Alternatively, given that the majority of studies demonstrating differential LR-related effects on BOLD markers of emotional and cognitive processing statistically controlled for CBF estimates in their analyses (Paulus et al., 2012; Schuckit et al., 2012, 2016), CBF response to alcohol may represent a neurophysiological process likely related to, yet independent from, these emotional and cognitive processes. For example, early rodent models have observed similar regionally specific effects on CBF following acute alcohol intoxication (Goldman et al., 1973), suggesting that tissue metabolism in these regions may increase at lower alcohol concentrations across species (Hoffman et al., 1986). Regionally specific increases in tissue metabolism may reflect the stimulating properties inherent to the consumption of alcohol (Newlin et al., 1982); yet, greater research is needed to fully understand the physiological processes underlying these regional alcohol-induced effects. Additional CBF investigations incorporating measures of the stimulating responses to alcohol in humans (e.g., the brief Biphasic Alcohol Effects Scale; Rueger and King, 2013) may be particularly insightful in this regard.

There are a number of additional factors that must be considered when interpreting these results. The sample size, while relatively large for neuroimaging studies, may be underpowered to detect smaller effects of CBF and LR on alcohol outcomes and may have led to the nonsignificance of the other clusters investigated. Further, assessment of CBF during alternative time points along the blood alcohol curve may produce differential results. Replications of these results across the blood alcohol curve are required to determine whether the pattern of cluster involvement is a stable finding. In addition, this sample is comprised of college students of higher socioeconomic backgrounds who were not experiencing clinical levels of AUD or other psychopathology at the time of CBF assessment. This limits our ability to generalize these results to more socioeconomically disadvantaged and clinically severe populations with AUD development prior to young adulthood. The results obtained in this sample of young adults should also be considered within the context of ongoing neurodevelopment of frontal systems (e.g., Simmonds et al., 2014) and may not generalize to older populations. Advantages of the study include a high follow-up rate (91% of the baseline sample) and thorough characterization of the LR profile.

In conclusion, this study adds to the growing body of the literature supporting the link between CBF and important functional outcomes in AUDs (Durazzo et al., 2010; Goldstein et al., 2004). The results demonstrated a clinically relevant relationship between CBF and future alcohol problems, particularly in individuals with a low LR phenotype. Although the functional mechanisms underlying this relationship remain unclear, these initial results advance CBF as an important neurobiological marker for AUD risk, which may help to elucidate the relationship between the low LR phenotype and the development of later alcohol problems.

ACKNOWLEDGMENTS

Support for this study was provided by NIH/NIAAA grants 1R21 AA021827 and 1R01 AA021162. KEC was supported by training grants from NIAAA (T32 AA013525) and NIMH (T32 MH018399).

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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