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Decreased Perfusion in Young Alcohol-Dependent Women as Compared With Age-Matched Controls

Camellia P. Clark, Gregory G. Brown, Lisa T. Eyler, Sean P. A. Drummond, Deborah R. Braun, and Susan F. Tapert

VA San Diego Healthcare System, Department of Psychiatry, University of California at San Diego, San Diego, California, USA

Abstract

Aim—To use the superior spatial resolution of magnetic resonance imaging (MRI) to examine differences in cerebral perfusion between young alcohol dependent and normal women.

Methods—Eight alcohol dependent women and 8 controls (all ages 18–25) received single-slice resting perfusion-weighted MRI (directly proportional to brain blood flow), with slices located above the corpus callosum.

Results—Alcohol-dependent women had decreased perfusion in prefrontal and left parietal regions.

Conclusions—Reduced perfusion has not previously been reported in young, physically healthy alcohol dependent females, yet is consistent with previously reported decreased cerebral activity in alcohol dependence.

Keywords

Alcohol abuse; alcoholism; perfusion magnetic resonance imaging

INTRODUCTION

Alcohol dependence is relatively common from adolescence onwards. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies of alcohol dependent adults have shown decreased cerebral blood flow (CBF) (1) and glucose metabolic rate (2). However, most previous studies excluded females, who may be somewhat more vulnerable to the effects of chronic drinking on the brain (3). Because baseline CBF can influence the magnitude of the blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) signal (4), understanding resting perfusion differences is important for the interpretation of fMRI studies. fMRI perfusion offers finer spatial resolution than PET and SPECT methods. We hypothesized that resting fMRI perfusion would be reduced in frontal regions among young women with histories of alcohol dependence.

METHODS

Participants

Eight alcohol dependent women (18–25 years) were recruited from a study of adolescent substance abuse, and 8 control women were recruited from the community. All participants were right-handed, age 18–25, and had no history of any DSM-IV disorder except alcohol-

Address correspondence to Camellia P. Clark, Department of Psychiatry 9151B, University of California at San Diego, 9500 Gilman Dr., La Jolla, CA 92093. E-mail: cclark@vapop.ucsd.edu.

induced syndromes, neurological illness or significant head injury, or current use of a medication which might affect cerebral circulation.

At the time of scanning, 4 women with histories of alcohol dependence engaged in heavy weekend binge drinking; one had not used alcohol in one year; 2 had not used alcohol in 6 months; and one had not used alcohol in one month. No control had any history of substance use disorder. Groups were matched for ethnicity, age, education, family history, smoking, and menstrual cycle phase. Participants voluntarily signed consent forms approved by the UCSD Institutional Review Board.

Measures

The Customary Drinking and Drug Use Record (CDDR) (5) obtained detailed alcohol, drug, and nicotine use history, including symptoms of abuse and dependence criteria and withdrawal symptoms. Participants were excluded for metallic implants or claustrophobia. General health data were obtained, along with a brief neuropsychological battery. Participants completed mood and sleepiness scales at the time of scanning (6).

Procedures

Participants were asked to abstain from alcohol (2) and other drugs (7) for at least 48 hours prior to imaging. The minimum time since last drink was 3 days. Breathalyzer (AlcoSensor IV, St. Louis, MO) and urine toxicology screens were negative for all participants. Portions of the CDDR were repeated just prior to scanning to verify absence of acute alcohol withdrawal (8).

Participants were scanned on a 1.5-Tesla Siemens scanner using a standard head coil. A high-resolution MRI image (MPRAGE, voxels $1 \times 1 \times 1$) was obtained. Perfusion-weighted images were obtained during resting conditions (eyes open) using a pulsed arterial spin labeling sequence (9). For this sequence, the difference between tagged and control images is directly proportional to brain blood flow in ml blood/ml tissue/minute (9). A single axial slice 8 mm thick (voxels $2.81 \text{ mm} \times 2.81 \text{ mm}$) was obtained (TR: 3000 ms; TE: 15 ms; flip angle: 90° ; FOV: 360 mm; 90 repetitions; total time: 4 minutes and 30 seconds). For each participant, the slice was prescribed by obtaining the first slice consisting grossly of gray matter above the corpus callosum.

Data Processing and Analysis

Image data were processed with Analysis of Functional NeuroImages (AFNI) 2.56g (10). Perfusion images were coregistered to the middle repetition to minimize movement artifact. For each repetition, images of the running difference between tagged and nontagged images were calculated. The first three repetitions and outlier repetitions were omitted, and the remaining repetitions were averaged. Perfusion data for individual scans were spatially smoothed (11,12) then transformed into Talairach coordinates. Because we considered our analyses exploratory, we used 2-tailed tests and did not correct for multiple comparisons in region of interest (ROI) analyses.

Talairach Daemon-based templates (13) were created bilaterally for the cuneus and all frontal Brodmann areas (BA) expected to intersect the perfusion slice (BA 6, 7, 8, 9, 10, 24, 32, and 46). For each participant and each ROI, voxels outside the participant's perfusion slice were omitted. Participants whose perfusion slice did not include a given ROI were excluded from analysis of that ROI. Nonparametric statistics were used where appropriate based on non-normal distributions or decreased participant numbers.

Voxelwise analyses used an independent samples between-groups *t*-test (14). We used a cluster threshold to protect against Type I error, requiring a minimum volume of 5 adjacent voxels (based on Monte Carlo simulations), yielding an overall α of $p = .025$ (15). Clusters of significant between-group differences were used as masks, with individual values examined for each participant. As with the a priori ROIs, participants whose perfusion slice did not include the cluster were excluded.

RESULTS

The alcohol-dependent group reported more drinks per month consumed (143.6 ± 212.9 vs. 8.5 ± 7.1 , $p < .05$), more alcohol withdrawal symptoms during the previous 2 years (2.9 ± 2.7 vs. $.3 \pm .8$, $p < .05$), and fewer days since last episode of drinking ≥ 4 drinks (106.4 ± 141.7 vs. 880.8 ± 331.6 , $p < .05$) than controls.

Whole slice perfusion did not differ between groups ($p = .44$). One predefined ROI differed significantly between groups: the right middle frontal gyrus (BA 9), where alcohol dependent participants' perfusion was less than that of controls (Mann-Whitney U, $p = .004$, $\eta^2 = .60$). Although right BA 46 did not significantly differ between groups (based on 3 controls and 2 alcohol-dependent participants), its η^2 of .75 suggests that a difference may have been apparent with adequate participant numbers. There were no ROIs or clusters in which perfusion was greater for alcohol dependent participants than for healthy controls.

Voxelwise analyses revealed 6 clusters in which perfusion was significantly less in alcohol dependent participants than in nondrinkers (see Table 1): bilateral middle frontal gyri, left precuneus, right cingulate, and bilateral inferior parietal lobules. Using each of these clusters as ROIs, we tested participants' individual perfusion values for between-group differences. The left precuneus and bilateral inferior parietal lobule clusters remained significantly different between the groups ($p < .30$, Mann-Whitney U); the bilateral middle frontal gyrus clusters were marginally significant (e.g., $p < .10$, Mann-Whitney U). However, effect sizes (η^2) for all 6 clusters ranged from .47 to .83, in the predicted direction, and were greatest for clusters in right- and left-middle frontal gyri (BA 9), particularly on the right (see Figure 1).

To control for any influence of recent heavy drinking, perfusion values for all a priori ROIs, cluster-derived ROIs, and whole slice means were reanalyzed using ANOVA within days since last heavy drinking episode (≥ 4 drinks) as a covariate. Days since last heavy drinking did not significantly predict perfusion in any cluster, and perfusion remained significantly reduced in the alcohol dependent group compared to controls for right BA 46, right BA 32, and left BA 40 (all $p < .05$), with a trend toward significance for right BA 9 ($p = .08$).

DISCUSSION

Our findings of decreased resting perfusion in alcohol dependent participants compared with nondrinkers are consistent with previous PET and SPECT reports, particularly for frontal areas (7). Careful study execution ruled out intoxication or withdrawal as confounds. Like previous BOLD findings (6), these results document abnormal brain activity in relatively young alcohol dependent participants. However, most previous imaging studies excluded females and studied considerably older alcohol dependent participants. These studies suggest that chronic heavy drinking, even in physically healthy young adults, might be associated with altered CBF regulation.

Based on expected involvement of right dorsolateral prefrontal cortex (DLPFC) in spatial working memory, altered resting perfusion in right BA 9 and 46 is consistent with altered activation patterns during performance of a spatial working memory task (6). The right DLPFC is in the same vascular territory in which abnormal vascular response to acetazolamide

improved with abstinence (1). Whether right anterior and middle cerebral artery territories are more susceptible to the effects of alcohol dependence on cerebral circulation remains unclear. Sites of decreased perfusion were not limited to DLPFC or to frontal lobe.

One limitation of this study is the use of single slice perfusion imaging, which does not reveal abnormal perfusion elsewhere in the brain. We have recently published whole-brain perfusion data using a faster pulse sequence (11,12). Second, power and reliability are limited by sample size.

Nonetheless, the data reported show multiple sites in which resting perfusion was decreased in young alcohol dependent women. To our knowledge, they represent the first brain imaging of resting activity in females (traditionally under represented in studies of alcohol dependence), specifically in early adulthood. These areas of decreased perfusion were evident independent of days since last heavy drinking episode, suggesting that altered cerebrovascular activity may persist several months into abstinence. Further study may help clarify the relationship between BOLD and perfusion MR signal in alcohol-dependent populations and provide further clues as to the nature and duration of altered cerebral activity.

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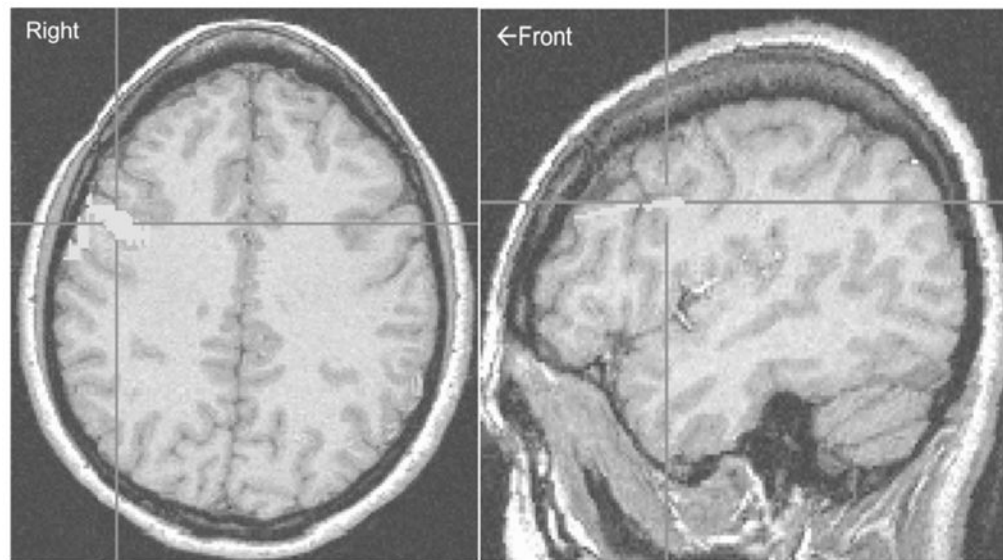


Figure 1. Location of the largest cluster in which alcohol-dependent young women had less perfusion than control women: right middle frontal gyrus (BA 9, Talairach coordinates $x = -43$, $y = -15$, $z = 32$).

Table 1
Clusters in which alcohol dependent participants had less perfusion than controls

Region/Brodmann's Area	(Volume μ l)	Talairach coordinates (mm)			z	Effect size η^2	Mann-Whitney U p	#Participants control/AlcDep
		x	y	z				
Right middle frontal Gyrus	1408	-43	-15	32	.75	.057	4/3	
Left middle frontal Gyrus	1286	37	-25	30	.75	.057	4/3	
Left precuneus	1082	9	51	46	.44	.030	7/4	
Right cingulate	921	-1	-25	30	.69	ns	4/2	
Left inferior parietal lobule	354	56	40	46	.50	.093	8/5	
Right inferior parietal lobule	351	-55	51	45	.55	.059	8/6	

Notes: There were no clusters in which alcohol dependent participants had greater perfusion than nondrinkers; p-values are based only on participants whose perfusion slice included the cluster (n shown in far right column).