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Aerobic Exercise Moderates the Effect of Heavy Alcohol Consumption on White Matter Damage

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Abstract

Background—Chronic alcohol abuse is related to numerous deleterious neurobiological consequences, including loss of gray matter, damage to white matter, and impairment of cognitive and motor functions. Aerobic exercise has been demonstrated to slow cognitive decline and decrease the negative neural changes resulting from normal aging and from several diseases. It is possible that exercise may also prevent or repair alcohol-related neurological damage. The present study tested the hypothesis that aerobic exercise protects white matter in anterior and dorsal areas of the brain from damage related to heavy alcohol use.

Methods—60 individuals underwent a diffusion tensor imaging session and completed measures of alcohol consumption, loss of control over drinking and aerobic exercise participation. Analyses examined the relationship of exercise, alcohol and their interaction to fractional anisotropy (FA) in the superior longitudinal fasciculus (SLF), external capsule (EC), superior and anterior corona radiata and fornix. The relationship of aerobic exercise and alcohol consumption to self-reported loss of control over drinking were also examined.

Results—A significant interaction was observed between alcohol consumption and aerobic exercise participation on FA in the SLF and EC. In the models examining loss of control over drinking, a significant interaction between aerobic exercise and alcohol consumption was observed, such that alcohol consumption was associated with loss of control more strongly for low exercisers than high exercisers.

Conclusions—These results indicate that the association between heavy alcohol consumption and white matter damage in the EC and SLF, and the association between alcohol consumption and loss of control over drinking, are greater among individuals who do not exercise regularly. These results are consistent with the notion that exercise may protect white matter integrity from alcohol-related damage.

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Conflicts of Interest

No conflicts of interest exist.

Keywords

White Matter; Aerobic Exercise; Alcohol; Neuroimaging

Introduction

Heavy alcohol consumption is associated with a number of deleterious health outcomes, such as cancer, liver disease, and widespread damage to the brain, including gray and white matter (WM) loss (Gutjahr et al., 2001; O'Keefe et al., 2007; Pfefferbaum and Sullivan, 2005; Pfefferbaum et al., 2000a; Rosenbloom et al., 2003). Specifically, heavy alcohol exposure is significantly associated with decreased WM fiber quality, which is a particularly harmful outcome given that WM tracts provide the structural connectivity necessary for communication across brain regions. Among alcohol dependent individuals, decreases in WM integrity have been observed in superior and anterior regions (i.e., external capsule (EC), internal capsule, frontal forceps, fornix, superior cingulate and longitudinal fasciculi) compared to controls (Pfefferbaum et al., 2009). Recent work suggests that alcohol may be associated with lower fractional anisotropy (FA; the most widely used measure of WM diffusivity) in the corona radiata and EC (Monnig et al., 2012). Consistent with research on adult binge drinkers, adolescent binge drinkers show lower WM integrity than controls in superior and anterior areas including the EC, superior longitudinal fasciculus (SLF) and corona radiata (McQueeney et al., 2009). These results emphasize consistency in terms of regional differences (e.g., EC, SLF, etc) and highlight the possibility that infrequent episodes of heavy drinking may significantly compromise WM. In sum, research has demonstrated considerable convergence across both adolescent and adult samples regarding the relationship between alcohol consumption and damage to WM tracts such as the SLF and EC.

Conversely, aerobic exercise appears to be associated with improvements in WM integrity among both healthy and clinical populations, and may reduce age and disease-related WM damage. For instance, aerobic fitness was associated with greater WM volume and integrity among older, healthy adults (Colcombe et al., 2006; Marks et al., 2007). Further, findings from a one-year aerobic exercise intervention among healthy older adults found that greater aerobic fitness derived from the intervention was associated with greater change in WM integrity in the frontal and temporal lobes (Voss et al., 2012). Aerobic exercise may also be associated with higher FA among individuals with particular neurological disorders. In the early-stages of Alzheimer's Disease, cardiorespiratory fitness has been shown to be associated with regional brain volumes in the medial temporal and parietal cortices (Honea et al., 2009) as well as with reduced brain atrophy (Burns et al., 2008). Among individuals with multiple sclerosis, better cardiovascular fitness is associated with higher WM integrity in the anterior corona radiata (ACR) (Prakash et al., 2010). Thus, exercise appears to exert protective effects against normal aging-related WM loss, as well as against the effects of neurological disease states on WM.

In addition to influencing white matter integrity, chronic heavy alcohol intake may be related to impairments in executive functions (Ratti et al., 2002) including impaired inhibitory control (Lawrence et al., 2009). Aerobic exercise may be related to improvements in self-regulation that would theoretically be associated with increased inhibitory control. For example, a 2-month long exercise program produced significant gains in self-regulatory capacity (Oaten and Cheng, 2006). The possibility that exercise might improve inhibitory control generally led to the idea that exercise might specifically be associated with improved inhibitory control over drinking. Thus, in addition to examining the interaction of exercise and alcohol on white matter integrity, the present study will also explore the relationship

between alcohol and exercise with failed control over drinking. Although the potential for exercise to produce positive outcomes for individuals with alcohol use disorders has been suggested (Read and Brown, 2003), little is known about the potentially protective and/or reparative neurobiological effects of aerobic exercise among individuals at risk for WM damage resulting from alcohol abuse. Given the benefits of aerobic exercise on WM integrity among aging and clinical populations, the potential application of exercise for the prevention or reversal of alcohol-related neural damage should be explored. The first step is to show an association between self-reported exercise and greater WM fiber coherence among alcohol-abusing individuals.

The purpose of this study was to determine whether there is cross-sectional evidence in support of the proposition that aerobic exercise is associated with less damage on specific WM tracts among heavy drinkers. To that end, this preliminary study examined the relationship between aerobic exercise and FA in the anterior corona radiata (ACR), superior corona radiata (SCR), SLF, EC, and fornix. These tracts were selected because previous studies have demonstrated that heavy alcohol consumption is associated with WM damage in these regions (McQueeney et al., 2009; Monnig et al., 2012; Pfefferbaum et al., 2009). Given that FA changes over the course of normal aging (Meier-Ruge et al., 1992; Pfefferbaum et al., 2000b; Salat et al., 2005), participant age was included as a covariate in all WM analyses. We hypothesized that, controlling for age, individuals who exercise less will exhibit a stronger negative relationship between alcohol consumption and FA in the ACR, SCR, SLF, EC, and fornix and a stronger relationship between alcohol consumption and loss of control over drinking.

Materials and Methods

Participants

Participants were drawn from a large database designed to share common brain and clinical data collected across studies on alcohol and nicotine use (Scott, 2011). Subjects were recruited using flyers posted around a college campus and surrounding areas, newspaper advertisements and online postings. To be included, each subject needed to have a diffusion tensor imaging (DTI) scan, measures of alcohol use (the AUDIT and TLFB, described below), and a measure of aerobic exercise (the VAEQ, described below). Data from 37 men and 23 women with these common measures were available for analysis (see Table 1). Participants were between the ages of 21–55 ($M = 32$, $SD = 9.8$, range: 21–53 years) and varied on total number of alcoholic drinks consumed over the past 60 days ($M = 101.22$, $SD = 125.12$, range: 0–303 drinks) and total number of cigarettes smoked over the past 60 days ($M = 436.06$, $SD = 497.19$, range: 0–2000 cigarettes). Participants also varied in minutes of aerobic exercise per week over the past three months ($M = 96.01$ minutes, $SD = 90.61$ minutes, range: 0–420 minutes). Twenty individuals included in these analyses reported using cannabis at least once in the past 60 days ($M = 6.82$ days, $SD = 15.21$ days, range: 0–60 days). Individuals included in the present analyses did not have to be current smokers, and 21 individuals did not report any cigarette smoking over the previous 60 days. There was no minimum drinking criteria, and 8 participants reported no drinking over the past 60 days. 15% of our sample (9 individuals) had total scores of 16 or greater on the AUDIT, which is suggestive of high levels of problem drinking (Miller et al., 1992). Finally, there was no minimum requirement for aerobic exercise participation, and 7 individuals reported no aerobic exercise over the past three months.

Participants were excluded if they reported a serious medical illness in the past 6 months, were currently taking insulin, reported use of illegal substances other than cannabis, or met *DSM-IV* criteria for a psychotic spectrum disorder, bipolar spectrum disorder, or current major depressive episode. Because the risk to fetuses associated with MRI is unknown,

females were excluded if they were pregnant (as indicated by a urine pregnancy screen) or were trying to become pregnant. Participants were recruited from the Albuquerque Metropolitan area and were required to provide informed consent prior to beginning study procedures. All study procedures were approved by the University of New Mexico's Human Research Protections Office.

Self-Report Measures

60-day Time Line Follow Back (TLFB)—The TLFB (Sobell et al., 1979) is an interviewer-administered assessment used to obtain estimates of daily alcohol, cigarette, and other drug use. The TLFB has demonstrated good psychometric characteristics within a variety of drinker groups (Sobell et al., 1979).

Alcohol Use Disorders Identification Test (AUDIT)—The AUDIT (Saunders et al., 1993) is a measure used to assess both current problems (occurring within the last 3 months) and lifetime problems associated with drinking behavior. The AUDIT consists of 10 questions covering alcohol consumption, drinking behavior, adverse psychological reactions, and alcohol-related problems. The sum of the first three AUDIT items focus on quantity and frequency of drinking and comprise the AUDIT alcohol consumption subscore (AUDIT-c). These items are (1) “How often do you have a drink containing alcohol?” (2) “How many drinks do you have on a typical day when you are drinking?” and (3) “How often do you have 6 or more drinks on one occasion?” The maximum score is 12. In the present study, the AUDIT-c had good reliability, $\alpha = .81$. The AUDIT-c was used in the present analyses rather than the AUDIT total because our hypothesis aims to elucidate the relationship between FA and *quantity* of alcohol consumption rather than problems associated with excessive drinking more globally. The AUDIT-c was included as an alcohol consumption measure in addition to the TLFB-TD in the present analyses given that the AUDIT-c is a simpler measure of alcohol intake, and less vulnerable to self-report errors. TLFB assessments covering long intervals have shown reduced accuracy on a fine-grained scale (Hoepfner et al., 2010), so the present study's inclusion of the AUDIT-c served to corroborate TLFB findings.

Voluntary Aerobic Exercise Questionnaire (VAEQ)—The VAEQ assesses levels of voluntary exercise (Bryan and Rocheleau, 2002). Participants indicated how frequently they engaged in exercise activities in the past three months and past week. The exercise composite score used in these analyses was composed of four items: (1) “In the past three months, what is the average number of days per week that you engaged in aerobic exercise?” (2) “In the past three months, what is the average number of total minutes per week that you engaged in aerobic exercise?” (3) “In the past week, how many days did you engage in aerobic exercise?” and (4) “In the past week, what is the total number of minutes that you engaged in aerobic exercise?” These variables were standardized and averaged to form the VAEQ composite score ($\alpha = .83$).

Impaired Control Scale (ICS)—The ICS (Heather et al., 1993) is a 25 item scale measuring (1) the degree to which a participant has attempted to exert control over his or her drinking in the past month, (2) the degree of success in controlling drinking in the last three months, and (3) the participant's belief in his or her ability to control drinking. The ICS failed control subscale (ICSfc) relates to difficulties in limiting alcohol consumption and exerting control over drinking behavior over the past 3 months, and significantly predicts treatment outcome (Heather et al., 1993). Some participants did not complete the ICS questionnaire, and therefore, these individuals were excluded in the ICSfc analysis. ICS data were only collected for 36 of the subjects tested in the WM analyses. Reliability for the ICSfc subscale in this sample was adequate, $\alpha = .77$.

Procedure

After providing informed consent, participants completed a battery of self-report questionnaire measures, including the AUDIT, VAEQ, ICS (if collected), and basic demographic variables. Trained research assistants administered all TLFB assessments. Next, participants took part in a Magnetic Resonance Imaging (MRI) scanning session, which included the DTI sequence used in the present analyses.

DTI Image Acquisition and Processing

All images were collected on a 3 Tesla Siemens Trio (Erlangen, Germany) scanner using a single-shot spin-echo echo planar imaging sequence over the whole brain [TE = 84 ms; TR = 9000 ms; FOV = 256 × 256 mm; matrix size = 128 × 128; slice thickness = 2 mm; gradient directions = 30; b-value = 800 s/mm²]. DTI preprocessing included data quality check, motion eddy current correction, and adjustment of diffusion gradient directions. Data was checked for signal dropout, excessive background noise during phase encoding, and motion in the absence of signal dropout. If motion exceeded 4mm of root mean square displacement, volumes were excluded. All the images were registered to a b = 0 s/mm² image using 12 degrees of freedom and affine transformation with mutual information cost function. Diffusion gradient direction was adjusted with rotation corrections to correspond to the image slice orientation and to account for any image rotation that occurred during previous motion and eddy current corrections. Each gradient direction vector was corrected according to the rotation of the transformation. FSL FLIRT was used for image registration and transformations steps, a program written in IDL (www.itlvis.com) detected outliers and performed data. Dtifit was used to calculate the diffusion tensor and the FA maps.

FSL Tract-Based Spatial Statistics (TBSS) (Smith SM et al., 2006) was used to obtain FA values. Each FA image was aligned to the standard-space FMRIB58_FA image with a nonlinear registration algorithm (FMRIB's Nonlinear Image Registration Tool). Following transformation to the target and affine transformation to MNI152 space, all FA images were merged into a single 4D image file, from which the FA skeleton was calculated using a threshold value of 0.2. The Johns Hopkins University International Consortium for Brain Mapping-DTI-81 labels atlas with highest probability thresholding at 25% and white-matter tractography atlas (Mori et al., 2005; Wakana et al., 2007) were used to define WM tracts. Tracts selected for analysis were: EC, ACR, SCR, SLF and fornix (column and body). FA values were averaged across each tract for each participant.

Results

Exercise, Alcohol Consumption and White Matter Integrity

In the regression models reported below, all slope values are reported as standardized regression coefficients. In the following analyses, significance level was set at $p < .05$. A series of ordinary Least Squares (OLS) multiple regression equations were used to regress WM FA in the EC, SLF, ACR, SCR, and fornix on the exercise measure (VAEQ), the number of drinks consumed in the last 60 days from the TLFB-TD (mean centered), and their interaction, while controlling for age. These five WM tracts were selected based upon their demonstrated association with alcohol consumption in several previous studies (McQueeney et al., 2009; Monnig et al., 2012; Pfefferbaum et al., 2009). Additionally, the five WM tracts tested were all relatively highly correlated with one another (see table 2). Thus, a total of five regression equations were estimated for TLFB-TD (see Table 3). In the regression model with FA in the EC as the criterion, the set of predictors accounted for 13.5% of the variance of FA. Inspection of individual regression slopes revealed a main effect of exercise that approached significance ($b = .237$ $t(57) = 1.888$, $p = .064$), a non-

significant main effect of alcohol and a significant exercise by alcohol consumption interaction ($b=.258$ $t(57) = 2.061$, $p=.044$).

In order to further explore the nature of this interaction, two additional regression models were calculated, one for the relationship of alcohol consumption to FA in the EC at 1 standard deviation (SD) above the mean on the exercise measure (VAEQ), and one for relationship of alcohol consumption to FA at 1 SD below the exercise mean (see Figure 1). This approach resulted in significance tests for the regression coefficient of the main effect of alcohol consumption at three levels (i.e. 1 SD above, the mean, and 1 SD below the mean on the VAEQ) (Aiken, 1991). Table 1 gives demographic and drinking characteristics for participants in each of these exercise groups. At 1 SD below the exercise mean the main effect of alcohol approached significance, and at 1 SD above the exercise mean, the main effect of alcohol was non-significant (see Figure 1A). The nearly significant, negative slope for alcohol at 1 SD below the exercise mean suggests that for below average exercisers, higher alcohol consumption is associated with lower FA. The non-significant slope for alcohol at the mean and 1 SD above the mean on the VAEQ suggests that for average and above average exercisers, there is no relationship between alcohol consumption and FA in the EC.

In the model with FA in the SLF as the criterion, there was a significant interaction between alcohol and exercise. No significant main effects of exercise or alcohol were observed, and the model accounted for 10.2% of the variance in FA in the SLF. Two additional models were again calculated, testing the relationship of alcohol consumption to FA in the SLF at 1 SD above and 1 SD below the mean VAEQ (see Figure 1B). At 1 SD below the mean, the main effect of alcohol approached significance, and at 1 SD above the mean, the main effect of alcohol was not significant. There was no relationship between alcohol and FA at the mean level of exercise. Thus, the relationship between alcohol consumption and reduced FA was only seen for those who exercised at below average levels. No significant interactions were found in models with FA in the ACR, SCR, or fornix as the criterion.

A second set of regression equations were estimated using our alternate measure of alcohol consumption, the AUDIT-c ($M = 6.00$, $SD = 2.90$). In this analysis, OLS multiple regression was used to regress FA in the EC, ACR, SCR, SLF and fornix on the VAEQ, AUDIT-c (mean centered), and their interaction, while co-varying age. In the equation with FA in the EC as the criterion, the set of predictors accounted for 14.5% of the variance. There was a significant main effect of exercise, a non-significant main effect of alcohol, and a significant exercise by alcohol consumption interaction (see Table 4). We used the same strategy as in the previous regression models to decompose the interaction (see Figure 1C). At 1 SD below the exercise mean, there was a significant main effect of alcohol, and at 1 SD above the exercise mean, the main effect of alcohol was non-significant. The significant negative slope for alcohol at 1 SD below the mean suggests that higher levels of alcohol consumption are associated with lower FA among individuals participating in lower levels of exercise. The non-significant slope for alcohol at 1 SD above the mean suggests that for above average exercisers, there is no relationship between alcohol consumption and FA in the EC. No significant exercise by AUDIT-c interactions were found for FA in the ACR, SCR, SLF or fornix. In the model using FA in the SCR as the criterion, there were significant main effects of exercise, alcohol, and age (see Table 4).

Because alcohol use, cannabis use and cigarette smoking are often comorbid and may confound the significant results described above, the regression analyses that showed a significant exercise by alcohol consumption interaction were repeated including the number of cigarettes smoked and the number of days cannabis was consumed in the past 60 days as covariates. These models were only tested for SLF and EC, because they were the only

tracts for which we observed a differential relationship between alcohol and WM depending on exercise status. Thus, the tests demonstrating a significant exercise by alcohol interaction were repeated controlling for smoking status, in order to confirm that the significant effects could not be better explained by smoking. When the cigarette and cannabis use covariates were included in the model regressing FA in the EC on age, TLFB-TD, exercise, and the TLFB-TD by exercise interaction, the main effect for exercise was significant ($p = .030$) and the interaction no longer reached conventional significance ($p = .080$). Inclusion of these factors in the model regressing FA in the EC on age, exercise, AUDIT-c and the exercise by AUDIT-c interaction did not change the significance of the main effect of exercise ($p = .022$), but the exercise by alcohol interaction in this model no longer reached conventional significance ($p = .131$). Finally, including cigarette smoking and cannabis use as covariates in the model regressing FA in the SLF on age, TLFB-TD, exercise and the exercise by TLFB-TD interaction slightly reduced the effect of the exercise by alcohol interaction ($p = .055$).

Relationship Between Alcohol Consumption, Exercise, and Impaired Control Over Drinking

In order to better understand the clinical implications of aerobic exercise among heavy drinkers, we conducted ancillary analyses of the ICSfc. OLS regression was used to regress ICSfc on exercise, AUDIT-c and the exercise by AUDIT-c interaction. At the mean level of exercise, there was a significant exercise by alcohol consumption interaction, $b = -.348$, $t(31) = -2.164$, $p = .038$, and a non-significant main effect of alcohol consumption, (see Figure 1D). We used the same strategy as in the previous regression models to decompose the interaction (see Figure 1D). At $1SD$ below the mean exercise level, there was a significant main effect of alcohol consumption, and at $1SD$ above the mean exercise level, the main effect of alcohol consumption was not significant. Thus, level of aerobic exercise moderated the strength of the relationship between alcohol consumption and failed control score, such that the relationship between alcohol consumption and failed control was stronger for individuals below the exercise mean than for those above the mean. This relationship was not observed when the TLFB total drinks variable was used to represent alcohol consumption in the same model.

Discussion

The degree to which aerobic exercise moderates the relationship between alcohol and WM integrity was examined. The association between alcohol consumption and WM integrity in the EC and SLF was significantly greater among individuals who do not exercise regularly, whereas alcohol consumption did not appear to be associated with WM damage among individuals who exercise regularly. When smoking and cannabis use were included as covariates, results were not substantially changed, suggesting that smoking and cannabis use do not explain the differential relationship of alcohol use based on exercise status to FA in the EC and SLF. Further, the association between consumption and loss of control over drinking was greater in individuals exercise less compared to those who exercise more. A possible explanation is that exercise may mitigate the experience of loss of control over drinking. However, the lack of consistency in results when TLFB-TD was used as the alcohol consumption measure in the models of failed control suggest that further research is needed examining the relationship between alcohol and exercise. In summary, these preliminary findings are consistent with the hypothesis that aerobic exercise may mitigate or reverse alcohol-related damage in the EC and SLF, two WM tracts which may have specific relevance for substance use disorders more generally, as well as loss of control over drinking.

There are a number of alternative explanations for the present findings. First, it is possible that regular exercisers have been exercising frequently for many years prior to study participation. The long-term effects of regular exercise participation on the brain may be difficult to disentangle from brain changes that occur in the short-term. Thus, studies relating neural characteristics to exercise behavior should consider lifelong exercise behavior in addition to more recent reports of exercise participation. Another possible explanation for these results involves the association of physical activity with other lifestyle behaviors, including a healthier diet (Mensink et al., 1997), and improved sleep (Youngstedt, 2005). However, a large epidemiological study of over 250,000 respondents found that major health behaviors—alcohol consumption, diet, smoking and exercise—are unrelated to one another (Newsom et al., 2005). Thus, further research illuminating the relationship between physical activity and other health behaviors is necessary before this can be adequately explored as an explanation for these results. Future studies should measure and control for dietary factors, sleep and other health-promoting behaviors in addition to exercise. Additionally, several recent cross-sectional studies have demonstrated a somewhat paradoxical association between drinking and exercise, in which it appears that heavy drinking is associated with more exercise (French et al., 2009; Lisha et al., 2012). The design of these studies is such that no causal conclusions can be drawn, but this represents an interesting question for future work. In our sample, it does appear that the highest exercising group was also the highest drinking group (see Table 1), so our findings are consistent with prior work in that regard.

The EC has been associated with alcohol use disorders in adults (Monnig et al., 2012; Pfefferbaum et al., 2009) and binge drinking in adolescents (McQueeney et al., 2009). The EC is a group of WM fibers located between the claustrum and the lentiform nucleus, and it separates the claustrum from the putamen. It is also a route for cholinergic fibers projecting from the basal forebrain to the cerebral cortex. There is growing evidence that the EC may be a critical region, especially with respect to the relationship between alcohol and brain development during adolescence and young adulthood (e.g. McQueeney et al., 2009). It's important to note that in our data, in addition to the alcohol consumption by exercise interaction, there was also a significant main effect of exercise on WM integrity in the EC, which remained unchanged when cigarette and cannabis use was considered in the model, suggesting that the EC may also be an important region for further testing the effects of exercise more broadly (i.e. among samples drawn from non-substance using populations), ideally in experimental designs.

The present study also demonstrated a significant alcohol by exercise interaction on WM integrity in the SLF. The SLF consists of a bundle of long association fibers connecting the frontal to occipital lobe and back regions of the temporal and parietal lobes. The SLF runs along the superior margin of the claustrum, and serves as the major frontal-parietal WM connection. Previous research suggests that FA in this area is significantly decreased among binge drinking adolescents (Bava, 2009; Jacobus et al., 2009; McQueeney et al., 2009) and alcohol dependent adults (Pfefferbaum et al., 2009). Our data suggest that further investigation of this area among substance using populations participating in various levels of aerobic exercise participation is warranted.

Limitations and Future Directions

It should be noted that the present study represents an *exploratory* analysis of the interactive relationship between aerobic exercise and alcohol consumption in association with white matter integrity in five intercorrelated white matter tracts, selected on the basis of previously demonstrated associations with alcohol in the literature. Given that exploratory research involves generating a posteriori hypotheses based on study observations (Jaeger and Halliday, 1998), the emphasis in the present study was on reducing Type II error. Thus, we

did not make any corrections to protect against Type I error. Additionally, the 5 white matter tracts tested were relatively highly correlated with one another, and strict correction was not appropriate, given the non-independence of the dependent variables examined.

An inherent limitation of this study was the use of retrospective, self-report data to quantify exercise. Future work will benefit from the inclusion of objective measures of aerobic exercise behavior (i.e., actigraphy, heart rate monitors) or fitness (i.e., maximal aerobic capacity). However, while the use of objective physical activity measures may represent an improvement over self-report (see Levi, 2011) these devices are by no means free of error (Matthews, 2011). Another limitation of the present study is the cross-sectional design, which precludes assumptions of causality. Future efforts will include a longitudinal design and random assignment of heavy drinkers to aerobic exercise versus placebo-controlled conditions.

Given that we did not have control over the duration, intensity, frequency or type of aerobic exercise in which participants engaged, it is difficult to address the “dose” of aerobic exercise that may be necessary to obtain neuro-protective benefits. A goal for future work is to examine duration, intensity and frequency of exercise in order to better understand the nature of the relationship between exercise and damage to WM resulting from alcohol abuse. A dose response study is also important for developing the public health implications of this research, as it will be critical to understand the exercise “dose” that is necessary to achieve neural benefits. Replication in a highly controlled, randomized, longitudinal, dose response study employing objective measurement of aerobic exercise participation represents a logical next step. Additional research is also needed to clarify whether the possibly protective effects of exercise on WM are mechanistically related to the effects of exercise on control over drinking, improved drinking outcomes (i.e., Brown et al., 2009) and reduced urge to drink (i.e., Ussher et al., 2004). Despite the limitations of this exploratory study, these results provide a solid foundation for the exploration of the potential of aerobic exercise to mitigate or reverse the damaging effects of heavy alcohol use on the brain.

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Figure 1.

a) panel A shows FA in the external capsule as a function of TLFB total drinks, represented at the mean on the VAEQ, at 1SD above the mean on the VAEQ, and at 1 SD below the mean on the VAEQ. b) panel B shows FA in the superior longitudinal fasciculus as a function of TLFB total drinks, represented at the mean on the VAEQ, at 1 SD above the mean on the VAEQ, and at 1 SD below the mean on the VAEQ. c) panel C shows FA in the external capsule as a function of AUDIT-c scores, represented at the mean on the VAEQ, at 1 SD above the mean on the VAEQ, and at 1 SD below the mean on the VAEQ. d) panel D shows ICSfc scores as a function of AUDIT-c scores represented at the mean on the VAEQ, at 1 SD above the mean on the VAEQ, and at 1 SD below the mean on the VAEQ.

Table 1

Sample Demographics

Characteristic		<i>Frequencies</i>		
		VAEQ 1SD above	VAEQ centered	VAEQ 1SD below
<i>N</i>		10	41	9
Sex				
	Female	5	16	2
	Male	5	25	7
Age				
	21–25	2	13	4
	26–35	6	14	1
	36–45	2	8	3
	46–55	0	6	1
Race/Ethnicity				
	White	6	29	4
	African American	0	1	0
	Asian or Pacific Islander	0	0	0
	Hispanic/Latino	4	6	5
	American Indian/Native American	0	1	0
	Mixed race/ethnicity	0	4	0
TLFB Total Drinks over 60-days (mean)		103.61	80.38	83.30

Note. *SD* = standard deviation. VAEQ = Voluntary Aerobic Exercise Questionnaire. TLFB = Timeline Follow Back.

Table 2

Correlations between white matter tract integrity, as measured by fractional anisotropy (FA), of the 5 tracts tested in all regression analyses

White Matter Tract	ACR	SCR	EC	Fornix	SLF
Anterior Corona Radiata (ACR)	1	.695**	.482**	.467**	.591**
Superior Corona Radiata (SCR)	.695**	1	.468**	0.215	.663**
External Capsule (EC)	.482**	.468**	1	0.053	.500**
Fornix (column & body)	.467**	0.215	0.053	1	0.132
Superior Longitudinal Fasciculus (SLF)	.591**	.663**	.500**	0.132	1

Note:

* $p < .05$, two-tailed.

** $p < .01$, two-tailed.

*** $p < .001$, two-tailed.

Table values are represented as Pearson Correlations.

Table 3

Standardized regression coefficients from models regressing white matter integrity (measured by fractional anisotropy) on age, TLFB-TD, VAEQ, and the interaction of TLFB-TD and VAEQ .

Predictor Variables	Criterion Variables				
	EC	SCR	ACR	SLF	Fornix
Age	.147	-.270 *	-.460 ***	-.143	-.498 ***
Alcohol Consumption (TLFB-TD)	-.068	-.132	-.075	-.061	.011
Exercise (VAEQ)	.237	.218	.089	.070	-.024
TLFB-TD*VAEQ	.258 *	.238	-.022	.264 *	.042

NOTE: TLFB-TD=timeline follow-back total drinks; VAEQ=voluntary aerobic exercise questionnaire; EC=external capsule; SCR=superior corona radiate; ACR=anterior corona radiate; SLF= superior longitudinal fasciculus

*
p < .05, two-tailed.
**
p < .01, two-tailed.

p < .001, two-tailed.

Table values are represented as standardized coefficients.

Table 4

Standardized regression coefficients from models regressing white matter integrity (measured by fractional anisotropy) on age, AUDIT-c, VAEQ, and the interaction of AUDIT-c and VAEQ.

Predictor Variables	Criterion Variables				
	EC	SCR	ACR	SLF	Fornix
Age	.089	-.351**	-.510***	-.210***	-.517***
Alcohol Consumption (AUDIT-c)	-.170	-.262*	-.208	-.153	-.092
Exercise (VAEQ)	.294*	.271*	.121	.115	.022
AUDIT-c *VAEQ	.267*	.237	.066	.220	.147

NOTE: AUDIT-c=AUDIT consumption subscale; VAEQ=voluntary aerobic exercise questionnaire; EC=external capsule; SCR=superior corona radiate; ACR=anterior corona radiate; SLF= superior longitudinal fasciculus

*
p < .05, two-tailed.
**
p < .01, two-tailed.

p < .001, two-tailed.

Table values are represented as standardized coefficients.