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Reduced Left Executive Network Functional Connectivity Is Associated With Alcohol Use Disorders

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Abstract

Background—Altered functional connectivity in critical networks has been associated with chronic alcohol abuse. In turn, changes in connectivity in executive control networks may undermine the ability to control alcohol consumption. It was hypothesized that network connectivity would be reduced in individuals with problematic alcohol use (ALC) compared to controls and that diminished network connectivity would be associated with greater failure to control drinking.

Methods—Resting state functional magnetic resonance imaging was analyzed to identify fourteen previously identified intrinsic connectivity networks (ICNs) using a priori regions of interest in cases ranging from binge drinkers to those with severe alcohol use disorder, as well as control subjects. Analyses tested for differences in network connectivity strength between 255 ALC cases and 87 age- and gender-matched controls. Further, structural equation analysis, using 383 ALC cases, tested whether functional connectivity strength mediated the relationship between years of regular drinking and alcohol problems.

Results—The age- and gender-matched analysis showed that ALC had significantly lower network connectivity strength than controls in the left executive control (LECN), basal ganglia (BG) and primary visual (PV) networks. For all ALC, LECN connectivity strength in negatively correlated with failed control and alcohol disorder severity. Edges connecting parietal regions with dorsolateral prefrontal, middle frontal and temporal regions within the LECN drove these

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relationships. A positive association between years of drinking and severity of alcohol problems was mediated by reduced executive control network connectivity.

Conclusions—This study reports relationships between network strength and problematic alcohol use, suggesting that chronic drinking negatively impacts brain connectivity, specifically in the left executive control network. Altered functional connectivity, related to chronic alcohol abuse, may contribute to the etiology of alcohol dependence and relapse.

Keywords

alcohol dependence; executive control; functional connectivity; functional network; resting state

INTRODUCTION

The consequences of heavy alcohol use on brain structure have been studied extensively using imaging modalities to repeatedly demonstrate negative impacts from chronic use. For example, overall decreases in brain volume have been found to covary with alcohol intake (Harding et al., 1996), theorized to result from the neurotoxic effects of alcohol (Lishman, 1990). The frontal lobe and limbic systems, basal forebrain, and cerebellum have been shown to be particularly vulnerable to alcoholism-related damage (Sullivan et al., 2000, Dirksen et al., 2006, Oscar-Berman et al., 1997, Kril et al., 1997, Pfefferbaum et al., 1997). These regions play key roles in cognitive processes including executive functioning (Sullivan and Pfefferbaum, 2005), as well as mediating and reinforcing appetitive drive hypothesized to influence the inability to control alcohol consumption (Everitt and Robbins, 2005).

Further, functional connectivity analyses, which quantify the connections between brain regions based on temporal correlation (Wig et al., 2011), have shown that chronic alcohol use affects relationships among these important regions. For example, compared to healthy controls (HC), recently abstinent alcoholic patients showed reduced fronto-cerebellar functional connectivity derived from a motor task (Rogers et al., 2012) and reduced fronto-striatal connectivity during response inhibition (Courtney et al., 2013). Long-term abstinent alcoholic subjects show reduced resting state synchrony between the nucleus accumbens (NAcc) and thalamus, caudate, postcentral, and parietal regions, yet increases between the NAcc and frontal regions. The authors suggested that reduced connectivity between decision-making regions with appetitive drive regions yet increased connectivity with inhibitory control regions may represent an adaptive mechanism which helps sustain abstinence (Camchong et al., 2013). Further, functional connectivity measured within multiple networks was lower in relapsing alcoholics compared to those who sustained abstinence (Camchong et al., 2012, Beck et al., 2012). These studies converge to support dysfunctional connectivity, associated with sustained alcohol use, as an underlying mechanism contributing to poor inhibitory control.

Understanding the effects of alcohol abuse on functional connectivity has important implications for the etiology and treatment of alcohol dependence. Given that only a few studies have examined these effects, we sought to examine the association between problem alcohol use and functional connectivity in individuals ranging from binge drinkers to those

with severe alcohol use disorder (ALC). As the studies above demonstrated changes in multiple brain networks, we chose to utilize the functionally defined intrinsic connectivity networks (ICNs) defined by Shirer et al. (2012). These fourteen ICNs are comprised of 90 distinct regions of interest (ROIs), or network nodes, that encompass the majority of the cortical and subcortical gray matter (Shirer et al., 2012) and can be mapped to canonical functions: auditory; primary and higher visual; language; sensorimotor; anterior and posterior salience; basal ganglia; dorsal, ventral and precuneus default mode; and bilateral executive control systems (Chakravarthy et al., 2010, Seeley et al., 2007, Damoiseaux et al., 2006, Greicius et al., 2003, Hampson et al., 2006, Smith et al., 2009, Beckmann et al., 2005, Kiviniemi et al., 2009). As long-term heavy drinking has been shown to have detrimental effects on cognition and executive function (Goldstein et al., 2004, Parsons and Nixon, 1993, Pitel et al., 2007, Sullivan et al., 2000), we were particularly interested in networks involved in these functions, specifically the Right and Left Executive Control (R/L ECN). We hypothesized that ALC subjects would have reduced connectivity strength in the both ECNs and that lower ECN connectivity strength would be correlated with disease severity.

As studies have shown that aging has an impact on functional connectivity (Andrews-Hanna et al., 2007, Damoiseaux et al., 2008, Tomasi and Volkow, 2012, Allen et al., 2011), we first compared an age-matched subset of ALC subjects with a group of HC to examine connectivity differences associated with problematic alcohol use. We expected that the ALC cases would have reduced resting state synchrony within ECNs implicated in addiction, but also tested whether differences compared to controls might be found globally within all ICNs. We also posited that reduced within-network functional connectivity in the ECNs, may be the neurobiological link between the neurotoxic effects of chronic alcohol exposure and problem alcohol use, having a mediating role on this relationship. To test this hypothesis, we used a structural equation model to test the indirect effect of alcohol exposure on problem alcohol use via network connectivity strength.

MATERIALS AND METHODS

Participants

Four hundred and twenty-two individuals with ALC and 97 controls were recruited from the greater Albuquerque metropolitan region through advertisements in local print, online media, and radio advertisements. Subjects were paid $120 for participation in both the questionnaire and neuroimaging sessions. ALC participants had to report binge drinking (5 or more drinks per drinking occasion for men, 4 or more for women) at least 5 times in the past month with exclusionary criteria of previous brain injury or loss of consciousness for more than 5 minutes, a history of severe alcohol withdrawal, or a positive pregnancy test. Additional exclusionary criteria for the HC subjects included a history of neurological disorder, mental retardation, lifetime history of dependence or use within the last 12 months of PCP, amphetamines or cocaine, current or past psychiatric disorder (with the exception of one lifetime depressive episode), antidepressant use within the last six months and lifetime antidepressant use of more than one year. Subjects were required to stop drinking 24 hours prior and pass a breathalyzer prior to participation. Individuals with excessive motion (>2 mm translational or 0.035 radians rotational movement, n=39 ALC, n=10 HC) or technical

problems (wrong acquisition plane, n=1 ALC) were excluded. The final full ALC sample included 383 subjects with the following comorbid substance use within the past 60 days (No/Yes/Unknown): Cigarettes, 105/278; Marijuana, 213/146/24; Other Substances, 326/33/24 (cocaine – 11; methamphetamine – 3; hallucinogens – 5; opiates – 3; two or more of these substances – 11). Written informed consent, approved by the University of New Mexico Human Research Committee, was obtained from all participants.

To select the age- and gender-matched subsample of ALC subjects, all ALC subjects less than the mean age (25.6 years) of the HC group were included. The remainder of the ALC subjects who were younger than the maximum age (53.3 years) of the HC group were assigned random numbers and sequentially added to the ALC subsample until the two groups, (ALC, n=255; HC, n=87) did not differ by age or gender.

Measures

ALC participants were assessed with the Alcohol Use Disorders Identification Test (AUDIT; scores >8 are indicative of hazardous drinking/ dependence, (Saunders et al., 1993), the Failed Control subscale of the Impaired Control Scale (ICS-FC; evaluating failure of attempts to control drinking in the last 6 months, (Heather et al., 1998), and a questionnaire on drinking which including the question, “For how many years have you been drinking regularly?” to determine years of regular drinking (YRD).

Image Acquisition

Whole brain resting state fMRI was performed on a 3-T Siemens Trio scanner with a 12-channel radio frequency coil. In the scanner, tape was placed across the participants’ forehead to serve as feedback for movement reduction. T_2*-weighted functional images were acquired using a gradient-echo echo-planer imaging (EPI) sequence: TE = 29 ms, TR = 2 s, flip angle = 75°, slice thickness = 3.5 mm, slice gap = 1.05 mm, field of view = 240 mm, 64 × 64 matrix, voxel size = 3.75 mm × 3.75 mm × 3.5 mm. Resting-state scans were 5 minutes in duration. Subjects were instructed to keep their eyes open and fixate on a cross. High-resolution T_1-weighted structural image were acquired with a 5-echo multi-echo MPRAGE sequence: TE = 1.64, 3.5, 5.36, 7.22, and 9.08 ms, TR = 2.53 s, TI = 1.2 s, flip angle = 7°, excitations = 1, slice thickness = 1 mm, field of view = 256 mm, resolution = 256 × 256 ×176, voxel size 1 × 1 × 1 mm, pixel bandwidth =650 Hz.

Image Pre-Processing

Functional images were preprocessed using an automated pipeline based around SPM 5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5) including realignment, slice-timing correction, spatial normalization to Montreal Neurological Institute (MNI) space, reslicing, and smoothing with a 10 mm full-width half-max Gaussian kernel (Scott et al., 2011). Time-series of cerebrospinal fluid and white-matter fluctuations, motion parameters and first derivative of motion parameters were progressively regressed from the time-series data followed by band-pass filtering (0.01-0.1Hz) using in house scripts (Welsh et al., 2010). For additional exploration of data processing, including motion exclusion and despiking, see Supplemental Methods.

Network functional connectivity analysis

The fourteen ICNs were identified using publicly available, functionally defined ROIs (Shirer et al., 2012, Figure 1). Functional connections between nodes, defined as edges, were calculated, creating a correlation matrix between the time-series of all nodes within each network for each subject, again using in house scripts (Welsh et al., 2010). A Fisher r-to-z transformation was applied to yield z-scores for use in subsequent analyses. Connectivity strength is a global measure of connectivity calculated as the mean of all pairwise correlations between nodes within each network (Lynall et al., 2010). As motion has been shown to influence functional connectivity (Van Dijk et al., 2012), the framewise displacement (FD, (Power et al., 2012), for each subject was calculated across the entire resting state run from the image motion parameters for use as a covariate. For additional seed-based analyses, validating these networks for the ALC sample, see Supplemental Methods.

Data Analyses

SPSS Statistical Software version 18 (Chicago, IL) was used to perform multivariate analysis of variance including FD as a covariate (MANCOVA) to determine if the matched HC and ALC groups differed on connectivity strength including all fourteen networks.

For networks identified as significant in the univariate analysis of the MANCOVA, relationships between network strength with AUDIT and ICS-FC scores were assessed for all ALC subjects.

Models to Test of the Indirect Effect of Alcohol Exposure on Alcohol Problems through Network Connectivity Strength

To test the indirect effect of alcohol exposure on alcohol problems via ECN connectivity strength, we tested the model in Figure 2 for the entire ALC sample in EQS Version 6.1 (Bentler and Wu, 2003). The dependent measure is a latent variable defined as alcohol problems with AUDIT and ICS-FC serving as indicators. As age and YRD were highly correlated in the ALC sample ($r = 0.727$, $p < 0.001$) we chose to use YRD as the sole exogenous variable in the model.

RESULTS

Demographic and psychometric measures

Table 1 shows sample characteristics for all groups. The HC and ALC subset were well matched on age ($t = 1.60$, $p = 0.110$) and gender (Chi-Square = 0.088, $p = 0.766$).

Group network connectivity analysis

The MANCOVA revealed a significant effect of group on network connectivity strength ($F(14,326)=2.910$, $p<0.001$, partial $\eta 2 = 0.111$); univariate tests showed that the HC and age- and gender-matched ALC groups differed on connectivity strength for four networks (LECN: $F = 5.348$, $p = 0.021$; sensorimotor (SM): $F = 5.177$, $p = 0.024$; basal ganglia (BG): $F = 14.234$, $p < 0.001$; primary visual (V1): $F = 5.171$, $p= 0.024$) indicating that chronic alcohol use, not age was driving these network differences (Table 2, Figures 3-4).

For all ALC, LECN network strength was negatively correlated with both ICS-FC and AUDIT scores (Table 3) remaining significant when controlling for FD, gender and age ($r = -0.125$, $p = 0.015$ and $r = -0.158$, $p=0.002$ respectively), which suggests that motion, gender nor age were driving the results. To further insure that age was not driving these effects, the sample was split at 40 years, finding the same negative relationships between LECN connectivity and ICS-FC and AUDIT within both groups: Young ALC (n = 307, Age = 27.2(5.1)): $r = -0.161$, $p = 0.005$ and $r = -0.177$, $p=0.002$ respectively; Old ALC (n = 76, Age = 46.7(4.5)): $r = -0.299$, $p=0.009$ and $r = -0.264$, $p = 0.021$ respectively. Connectivity strength of the other networks identified in the MANCOVA was not related to either ICS-FC or AUDIT.

Further exploration within the LECN was done by evaluating relationships between the behavioral measures and each edge z-score again controlling for motion. The significance threshold for edge correlations was set as $p = 0.05/n$ where n = number of edges within a network; for the LECN, which has 30 edges, the significance threshold was $p = 0.0017$. For all ALC, within the LECN, negative correlations with ICS-FC and/or AUDIT were found with edges between the dorsal lateral prefrontal cortex (DLPFC) and parietal lobe (PAR), middle frontal gyrus (MFG) and temporal gyrus (TL), and between TL and both MFG and PAR (Figure 5 and Table 4).

Mediation Model

In the mediation model, which included the entire ALC sample, robust estimation with maximum likelihood estimation of missing data was utilized. Thus we present the robust fit statistics and significance of the parameters evaluated with robust standard errors. The mediation model produced an excellent fit to the data (Figure 2). There were significant paths from YRD to LECN connectivity strength ($B = -0.43$, $p<0.001$) indicating that more years of regular drinking were associated with weaker connectivity. There was also a significant path from LECN connectivity strength to alcohol problems ($B = -0.24$, $p<0.001$), indicating higher connectivity strength was associated with less problematic drinking. The indirect effect of years drinking on alcohol problems was significant ($z = -2.86$, $p<0.01$), indicating a significant mediated effect. However, mediation was not complete, as there was a remaining significant direct effect of years drinking on problematic drinking ($B=0.31$, $p<0.001$).

DISCUSSION

Using a large sample with a range of alcohol problems, this study investigated the relationship between chronic alcohol abuse and resting state functional connectivity of brain networks critically involved in regulation and control. The age- and gender-matched subset of ALC subjects had significantly lower network strength in the LECN, SM, BG and PV than controls. Further, for the entire sample of ALC subjects, LECN connectivity strength was negatively associated with measures of hazardous drinking and loss of control over alcohol consumption. Within the LECN, we identified key nodes significantly associated with disease severity. We then tested a model to show that LECN connectivity strength mediates the relationship between chronic alcohol exposure and problematic alcohol use.

Given our sample size was an order of magnitude greater than previous studies, the current study highlights the importance the LECN in the addiction cycle. Our results suggest that detrimental degradation of pathways within the left executive system may be a critical neurobiological mechanism through which chronic alcohol use impairs individuals' ability to control or discontinue use.

Neuroimaging research supports the existence of multiple large-scale connected networks with distinct functional and behavioral domains (Laird et al., 2011, Fair et al., 2007) including complex cognitive systems involved in multi-level functions including decision-making, inhibition, and response control. Of particular interest, poor cognitive control has been suggested to be involved in the addiction cycle, particularly with respect to maintaining abstinence. These dysfunctions in control are thought to be further negatively impaired with chronic alcohol use (see reviews including (Moselhy et al., 2001, Lyvers, 2000)). While these 'executive functions' have historically been associated with the 'frontal lobe' (Baddeley et al., 1997, Miyake et al., 2000), a network, or systems, approach posits that the coordinated interaction of multiple brain regions is a critical component of executive function. Using a functional approach, bilateral executive control networks have been identified that include regions in the parietal lobe, DLPFC, the MFG and contralateral cerebellar areas (Shirer et al., 2012), which we queried for this study.

As hypothesized, we found that network strength, in LECN, though not in the RECN, was lower in ALC than HC and negatively correlated with disorder severity. Within the LECN, we examined the edges, or the pairwise temporal correlations between ROIs to identify the nodes that seemed to drive this relationship. We found negative associations between both failed control and AUDIT scores and the connectivity between the parietal, DLPFC, MFG and caudate nodes suggesting poor function of this control network. This is consistent with studies that have reported negative associations between white matter integrity in tracts connecting frontal and parietal regions and substance use (Pfefferbaum et al., 2009, Schulte et al., 2010), validating the important relationship between these structures and impaired control in ALC. Of interest, a recent study of stimulant dependent individuals (SDI), a majority of whom was also dependent on alcohol, found a lateralized differentiation of the ECNs. As resting state amplitude in the left DLPFC correlated with approach behaviors, the authors suggested that the LECN may be involved in maintaining a bias toward seeking and taking drugs, rather than representing a failure of executive control (Krmpotich et al., 2013). Our results, however, would suggest that poor communication between critical nodes within the LECN might, in fact, represent such a failure.

Failed control over alcohol consumption, which has been correlated with measures of alcohol dependence and negatively predictive of treatment outcome (Heather et al., 1998), was found here to negatively relate to LECN connectivity strength, suggesting an underlying mechanism for control dysfunction. Specifically, deficits in the connectivity integrity between key structures may be involved in loss of control over drinking. A primary structure that showed reduced edge connectivity was the DLPFC, a region associated with top-down attentional focus thought to be involved in cognitive control over memory representations. This control is hypothesized to be influenced by emotional information and impacts including that from the MFG, which is implicated in mood awareness and regulation; the

MFG was another primary node with poor edge connectivity. We also identified poor connectivity with the parietal lobe node which is suggested to be involved in the complementary roles of sustaining attention and responding to salient stimuli (Singh-Curry and Husain, 2009). Thus reduced connectivity between these critical regions, across our large ALC sample, suggests inefficient in-network communication of goals and priorities, potentially contributing to poor behavioral control.

Our results, finding differences between ALC and controls in multiple networks, are in agreement with work showing resting state connectivity altered with other substance use from cocaine (Krmpotich et al., 2013, Gu et al., 2010), heroin (Upadhyay et al., 2010), and prescription opioids (Upadhyay et al., 2010) to alcohol (Camchong et al., 2013, Chanraud et al., 2011). The lower resting state connectivity we report in the SM network also agrees with task-related results finding reduced connectivity between premotor and cerebellar regions in alcoholics and is consistent with neuropatholocial deficits associated with alcoholism (Rogers et al., 2012). However, Chanraud et al (2011) reported that controls (n=15) had more positive resting state connectivity within the default mode network that ALC subjects (n=15) which we did not find. Further Camchong et al. (2012) found than relapsing alcoholics (n=29) had lower connectivity within not only the ECNs, but also within reward, visual and salience networks than abstainers (n=40), networks where we did not find significant effects, possibly attributable to our large sample of subjects with varying degrees of disorder. Our study also did not include follow up data for evaluation of relapse, however, given the finding that measures of severity were associated with degradation of network integrity only within the LECN across 383 ALC subjects, the negative impact of chronic alcohol use on this control system may be critically important in the addiction cycle. As task-related fronto-striatal connectivity reductions in abstinent alcoholics have been related to impairments in learning, as well as magnitude of alcohol craving (Park et al., 2010), perhaps deficits in resting state LECN functional connectivity, representing reduced communication and cooperation between control system nodes, would also be predictive of cognitive decline. This should be studied in future work, particularly in light of a recent report finding no cognitive deficits in treatment naïve alcoholics in contrast with consistently reported deficits in chronic, in-treatment alcoholics (Smith and Fein, 2010).

Several limitations of this study should be noted. The connectivity analysis here reveals interregional correlations but not information regarding causal or directional relationships between nodes, or whether other brain regions may drive these relationships. To identify ICNs, we used a publicly available atlas of functional ROIs (Shirer et al., 2012). This approach defined networks of interest based on an independent sample to allow for unbiased evaluation of differences between our cases and controls. Network definition is an ongoing question in the field, and the use of another atlas, or of data driven ROIs, may be evaluated as a focus of future work. In addition, this study is cross-sectional and observational, thus we are unable to assess causation, and it is possible that other models would be an equally good fit to the data (c.f., (MacCallum et al., 1993)). Further, given the high correlation between the length of chronic alcohol use and age, we are unable to determine the independent effects of these variables in this study. And despite the correlation we report between LECN and disorder severity, the effect size is moderate. Other factors, likely genetic and environmental, are undoubtedly contributing to subjects' alcohol problems.

Finally, it is possible that the ALC subjects in our study may have had preexisting differences in functional connectivity that contributed to vulnerability to their disorder rather than the lower network strengths being the consequences of chronic use. Longitudinal imaging studies, as well as studies of at-risk populations, are needed to further investigate this possibility.

The current study reports negative relationships between on functional connectivity strength in the left executive control network, duration of chronic alcohol use, and disorder severity that may represent how such alcohol use negatively impacts brain function. Deterioration in functional connectivity strength in the LECN involved in cognitive control, decision–making and regulatory processes, may represent less efficient communication and function within this important network. These results suggest that altered functional connectivity related to problematic alcohol use may contribute to the underlying pathology of addiction, particularly with increasing longevity of disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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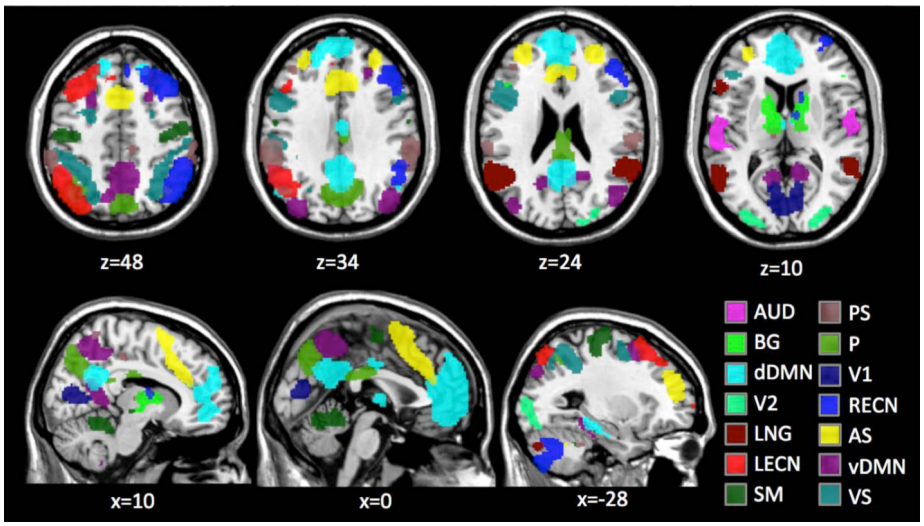

Figure 1. Fourteen Intrinsic Connectivity Networks

The ICNs are comprised of 90 distinct ROIs or nodes encompassing the majority of the cortical and subcortical gray matter that were downloaded from Stanford's FIND Lab (Shirer 2012) and include: auditory; primary and higher visual; language; sensorimotor; anterior and posterior salience; basal ganglia; dorsal, ventral and precuneus default mode; and bilateral executive control systems.

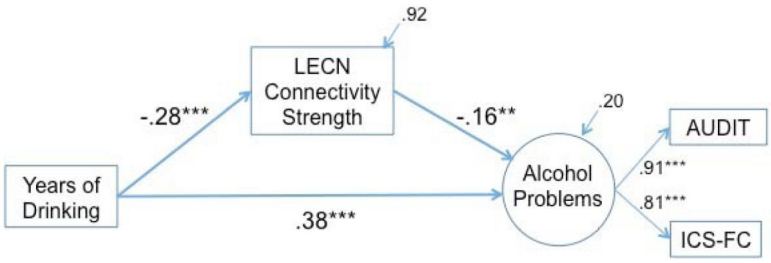

Figure 2. Model of Network Connectivity as a Mediator

A significant mediation of the effect of years drinking on disorder severity through network connectivity was found ($z = -3.07$, $p<0.01$). Notes: LECN=left executive control network, RECN=right executive control network, AS=anterior salience network, AUDIT=Alcohol Use Disorders Identification Test, ICS-FC=Failed Control subscale of Impaired Control Scale. ** $p<0.01$, *** $p<0.001$. Yuan-Bentler χ^2 (1) = 0.869, $p=0.35$, CFI=1.0, RMSEA=0.00.

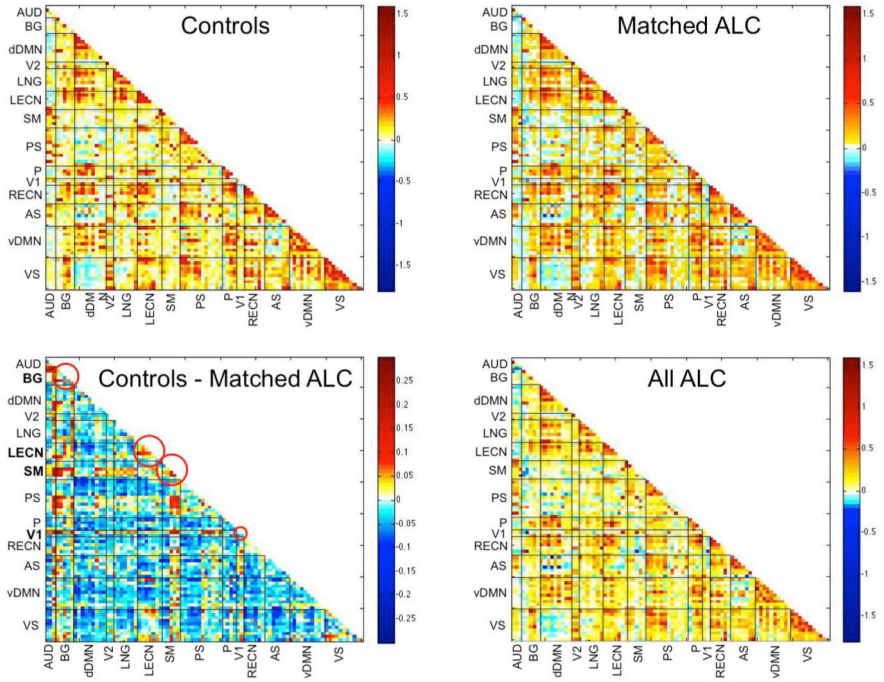

Figure 3. Correlation matrices across all 14 ICNs

Average correlation matrices of functional connectivity for all ICNs by group: HC (n=87); age- and gender-match ALC subset (n=255); and all ALC (n-383). The difference matrix, Controls - Matched ALC, shows the networks that differed between the matched groups with the ALC groups having lower network functional connectivity strength.

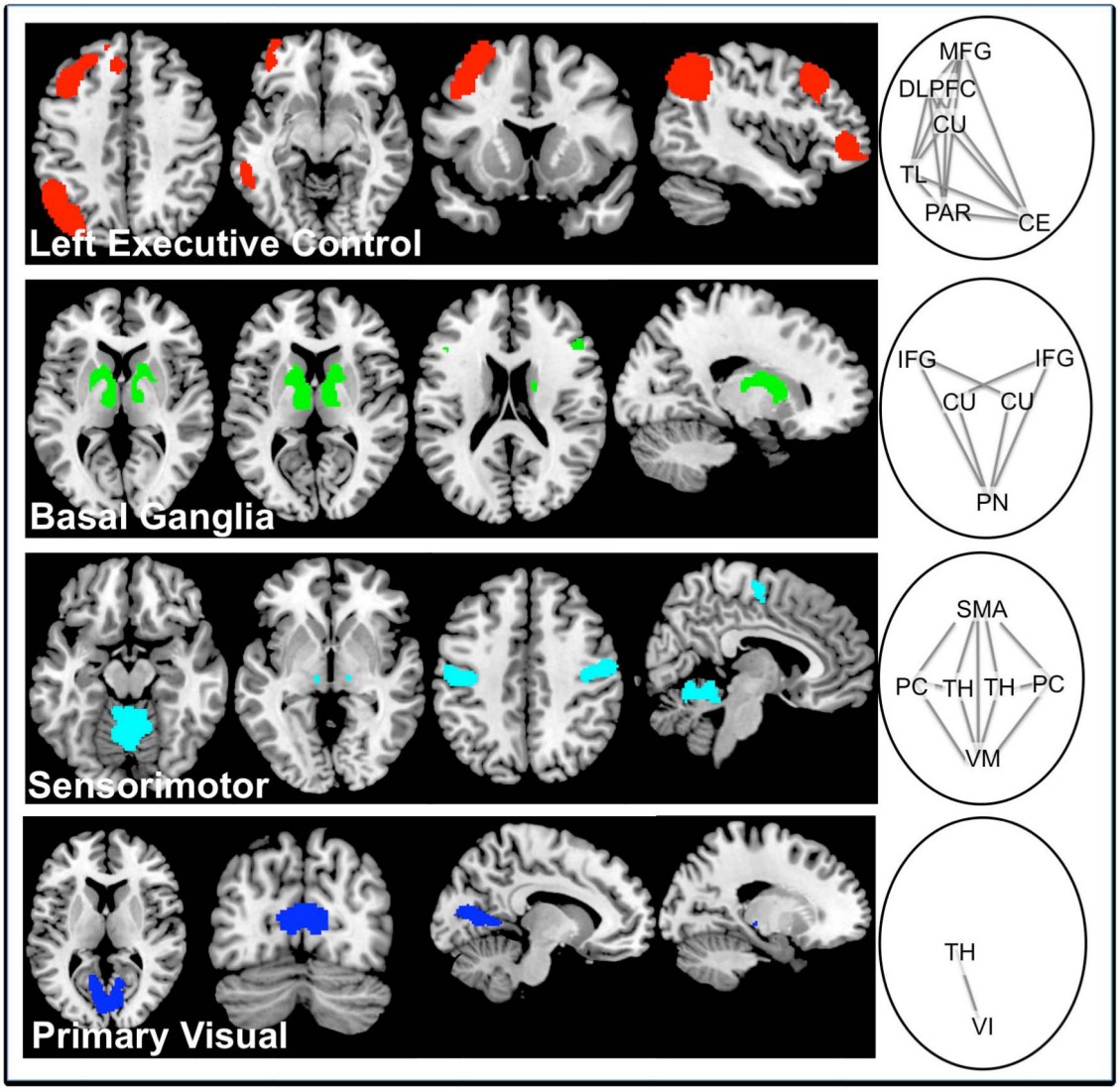

Figure 4. Networks Different between ALC Subjects and Controls

ROIs defining the networks with significantly lower connectivity strength in age- and gender-matched ALC subjects (n=255) and controls (n=87) include the left executive control (LECN), Basal Ganglia (BG), Sensorimotor (SM), and Primary Visual (PV) network's. Table 2 details the acronyms of the network nodes displayed in the right panel.

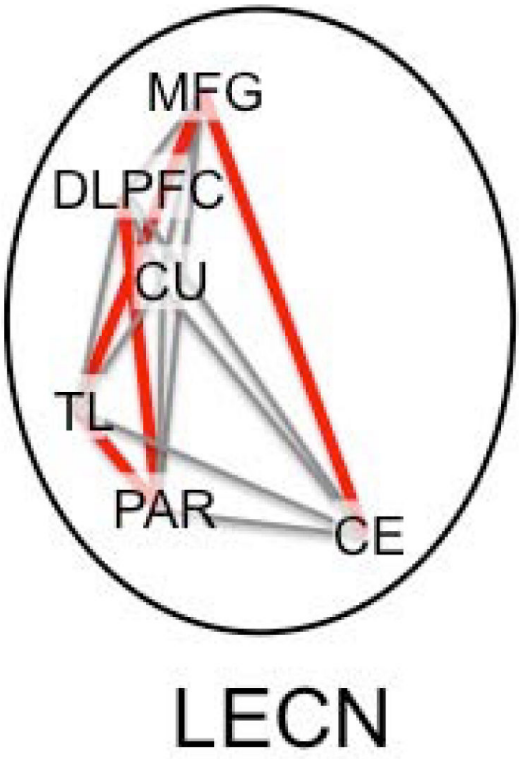

Figure 5. Edges Associated with Alcohol Problems

Depiction of edges within networks significantly correlated with failed control of alcohol consumption and/or alcohol use disorder severity within the left executive control network. Nodes between these edges include the left middle frontal gyrus (MFG), dorsolateral prefrontal cortex (DLPFC), temporal lobe (TL) and right cerebellum (CE).

Table 1

Subject characteristics for control and alcohol use disorder subjects.

	Controls	Age Matched ALC	All ALC
N	87	255	383
Males:Females	59:37	162:104	257:150
Age	25.8 (8.3)	26.9 (6.9)	31.1 (9.3)
Range	21.0 – 53.3	21.0 – 53.0	21.0 – 56.0
Years of Regular Drinking	NA	7.8 (6.7)	11.9 (9.3)
ICS-FC	NA	14.8 (9.1)	16.8 (9.6)
AUDIT	NA	14.9 (7.0)	16.3 (7.9)
Ethnicity			
Caucasian	44	115	175
African American	1	5	8
Asian/Native Hawaiian	3	3	4
Latino	18	53	82
Native American	3	26	35
Mixed	10	30	48
Unknown	8	23	31
Network Connectivity			
LECN	0.46 (0.14) *	0.41 (0.14)	0.38 (0.14)
RECN	0.45 (0.12)	0.44 (0.13)	0.42 (0.13)
AS	0.39 (0.10)	0.41 (0.12)	0.40 (0.12)
PS	0.22 (0.07)	0.21 (0.07)	0.21 (0.07)
dDMN	0.38 (0.11)	0.40 (0.11)	0.38 (0.12)
vDM	0.37 (0.09)	0.39 (0.11)	0.38 (0.11)
P	0.48 (0.14)	0.50 (0.14)	0.49 (0.14)
BG	0.21 (0.09) *	0.17 (0.09)	0.17 (0.09)
SM	0.32 (0.12) **	0.29 (0.11)	0.30 (0.12)
AUD	0.48 (0.17)	0.46 (0.15)	0.46 (0.15)
LNG	0.35 (0.11)	0.35 (0.11)	0.34 (0.11)
PV	0.20 (0.18) *	0.14 (0.17)	0.14 (0.18)
HV	1.26 (0.33)	1.29 (0.29)	1.28 (0.29)
VS	0.41 (0.11)	0.40 (0.12)	0.39 (0.12)
Framewise Displacement	0.17 (0.08)	0.19 (0.09)	0.21 (0.10)

ALC, Subjects with alcohol use problems; YRD, Years of regular drinking; NA, Not applicable; ICS-FC, Impaired Control Scale, Failed Control subscale; IT, Alcohol Use Disorder Identification Test; LECN, left executive control; RECN, right executive control; AS, anterior salience; PS, posterior salience; dDMN, dorsal default mode; vDM, ventral default mode; P, precuneus; BG, basal ganglia; SM, sensorimotor; AUD, auditory; LGN, language; PV, primary visual; HV, high visual; VS, visuospatial.

** Significant group difference, p≤0.001.

* Significant group difference, p=0.024.

Dta presented as Mean (Standard Deviation) where applicable.

Table 2

Definition of nodes for networks different between ALC subjects (N=255) and controls (N=87).

NETWORK Area	Abbreviation
LEFT EXECUTIVE CONTROL	
1. Left Middle Frontal Gyrus/Superior Frontal Gyrus	DLPFC
2. Left Inferior Frontal Gyrus/ Orbitofrontal Gyrus	MFG
3. Left Superior Parietal Gyrus/ Inferior Gyrus/Precuneus/Angular Gyrus	PAR
4. Left Inferior Temporal Gyrus/ Middle Temporal Gyrus	TL
5. Right Crus I/Crus II/Lobule VI	CE
6. Left Thalamus/Caudate	CU
BASAL GANGLIA	
1. Left Caudate/Putamen/Pallidum/Thalamus	CU
2. Right Caudate/Putamen/Pallidum/Thalamus	CU
3. Left Inferior Frontal Gyrus	IFG
4. Right Inferior Frontal Gyrus	IFG
5. Pons	PN
SENSORIMOTOR	
1. Left Pre/Postcentral Gyri	PC
2. Right Pre/Postcentral Gyri	PC
3. Supplementary Motor Area	SMA
4. Right Middle Frontal Gyrus	MFG
5. Left Thalamus	TH
6. Right Thalamus	TH
7. Vermis	VM
PRIMARY VISUAL	
1. Primary Visual	V1
2. Left Thalamus	TH

Table 3

Correlations of network connectivity strengths with measures of alcohol disorder severity (n=383).

	ICS-FC		AUDIT	
Network Strength	r	p	r	p
Left Executive Control	−0.250	<0.001	−0.254	<0.001
Basal Ganglia	−0.007	0.893	0.005	0.929
Sensorimotor	0.001	0.988	−0.047	0.355
Primary Visual	−0.003	0.989	0.000	0.996

ICS-FC, Impaired Control Scale, Failed Control subscale; AUDIT, Alcohol Use Disorder Identification Test.

Table 4

Edges with significant relationships with failed control and alcohol use severity measures controlling for motion for n=383 ALC subjects.

NETWORK	ICS-FC		AUDIT	
Edges between Brain Nodes	**r**	**p**	**r**	**p**
LECN				
L DLPFC – L MFG	−0.135	0.00828	−0.186	**0.00026**
L DLPFC – L PAR	−0.213	**0.00003**	−0.215	**0.00002**
L DLPFC – L TL	−0.185	**0.00029**	−0.215	**0.00003**
L MFG – L TL	−0.130	0.01116	−0.163	**0.00142**
L MFG – CE	−0.126	0.01399	−0.140	**0.00623**
L PAR – L TL	−0.176	0.00058	−0.194	**0.00015**

ICS-FC, Impaired Control Scale, Failed Control subscale; AUDIT, Alcohol Use Disorder Identification Test; LECN, left executive control network; L, left; R, right; DLPFC, dorsolateral prefrontal cortex; MFG, middle frontal gyrus; PAR, parietal cortex; TL, temporal lobe; CE, cerebellum.

Bold indicates edge meets corrected significance threshold within the specified network as detailed in text.