

REGULAR RESEARCH ARTICLE

The Neural Processes Interlinking Social Isolation, Social Support, and Problem Alcohol Use

Thang M. Le[○], Wuyi Wang, Simon Zhornitsky, Isha Dhingra, Yu Chen, Sheng Zhang, Chiang-Shan R. Li[○]

Department of Psychiatry (Drs Le, Wang, Zhornitsky, Dhingra, Chen, Zhang, and Li), Department of Neuroscience (Dr Li), and Interdepartmental Neuroscience Program (Dr Li), Yale University School of Medicine, New Haven, Connecticut, USA.

Correspondence: Thang M. Le, PhD, Connecticut Mental Health Center, S105, 34 Park Street, New Haven, CT 06519-1109, USA (thang.le@yale.edu).

Abstract

Background: Subjective feeling of social isolation, as can be measured by perceived burdensomeness (PB), is a major risk factor for alcohol misuse. Heightened PB is associated with elevated stress response and diminished cognitive control, both of which contribute to problem drinking. Here, we sought to identify the neural substrates underlying the relationship between PB and alcohol misuse.

Methods: We employed resting-state functional magnetic resonance imaging data collected from 61 problem drinkers to characterize the functional connectivity of the hypothalamus and ventral striatum (VS) in relation to PB. We specifically examined whether the connectivities of the hypothalamus and VS were differentially influenced by PB to produce contrasting effects on alcohol use. Finally, we evaluated how individual differences in social support modulate the inter-relationships of social isolation, neural connectivity, and the severity of problem drinking.

Results: Whole-brain multiple regressions show a positive relationship between PB and hypothalamic connectivity with the hippocampus and an inverse pattern for VS connectivity with the middle frontal gyrus. Difference in strength between the 2 connectivities predicted the severity of problem drinking, suggesting an imbalance involving elevated hypothalamic and diminished prefrontal cortical modulation in socially isolated problem drinkers. A path analysis further revealed that the lack of social support was associated with a bias toward low prefrontal connectivity, which in turn increased PB and facilitated problem drinking.

Conclusions: Altered hypothalamus and VS connectivity may underlie problem drinking induced by social isolation. The current findings also highlight the important role of social support as a potential protective factor against alcohol misuse.

Key Words: Perceived burdensomeness, problem drinking, hypothalamus, ventral striatum, social support

Introduction

Social isolation due to perceived burdensomeness (PB), defined as the belief that one is a burden or liability to others (Van Orden et al., 2006), represents a major risk factor of alcohol use disorders (Gauthier et al., 2017). Alcohol can serve to alleviate stress and negative mood resulting from social isolation, perpetuating drinking through negative reinforcement

(Gonzalez and Skewes, 2013). Specifically, individuals with high PB frequently withdraw from social interactions (Van Orden et al., 2012), lack in social support (Hollingsworth et al., 2018), and exhibit heightened stress response (Buitron et al., 2016), all of which can promote drinking as a maladaptive coping strategy. PB is also associated with reduced cognitive

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Significance Statement

Social isolation represents a major risk factor for alcohol misuse. Yet, the neural processes linking social isolation to problem drinking remain poorly understood. Here, by characterizing resting-state functional connectivity of the hypothalamus and ventral striatum (VS) in relation to perceived burdensomeness (PB), we found evidence of elevated hypothalamic hippocampal and diminished prefrontal cortical-VS connectivities in problem drinkers. The net strength of the 2 circuit connectivities predicted drinking severity, thus suggesting deficient control of drinking motivation. Further, the lack of social support was associated with a bias toward lower prefrontal cortical-VS connectivity, which in turn increased PB and facilitated problem drinking. The findings support a mechanism of isolation-induced drinking and highlight the importance of social support as a potential protective factor against alcohol misuse.

control (Silva et al., 2015), which plays a role in the enhanced reward response to alcohol in problem drinkers (Fleming and Bartholow, 2014). Heavy drinking alienates family and friends, resulting in further deterioration of social support and worsening sense of isolation, driving individuals to even heavier alcohol use (Peirce et al., 2000). In contrast, social support has been shown to predict lower risk of alcohol misuse in nondependent drinkers (Wills and Ainette, 2012) as well as sustained abstinence in alcoholics following treatment (Marlatt and Witkiewitz, 2004). Despite PB's significant role in problem drinking, the neural processes inter-relating PB and alcohol misuse remain poorly understood.

Hypothalamic dysfunction may contribute to alcohol misuse elicited by social isolation. The hypothalamus is connected with a network of cortical and subcortical structures, including the hippocampus, amygdala, and prefrontal cortex (PFC) (Jacobson and Sapolsky, 1991; Dedovic et al., 2009a). As a neural hub of motivated behavior, the hypothalamus is integral to the psychophysiological responses to social isolation (Cacioppo et al., 2015). Indeed, social exclusion in humans elicited activation in the hypothalamus (Karremans et al., 2011) along with decreases in oxytocin (Pournajafi-Nazarloo et al., 2013) and increases in cortisol (Cacioppo et al., 2015) levels. Social isolation also raised the hypothalamic neuropeptide Y level (Thorsell et al., 2006) and activated the central preproenkephalin opioid system (Iglesias et al., 1992), likely as a response to reduce social stress (Morales-Medina et al., 2010). These cellular and molecular changes have been found to facilitate ethanol intake as a stress-coping mechanism in animal models (Ehlers et al., 1998; Valdez and Koob, 2004). Additionally, the hypothalamus is thought to modulate alcohol craving through the involvement of both orexigenic and anorexigenic peptides (Leggio, 2009). Stimulation of the lateral hypothalamus elicited craving and reinforced alcohol seeking in rodents (Wayner, 2002; Marchant et al., 2009). Emerging evidence associates alcohol use with reduced levels of oxytocin, a hypothalamic hormone central to social behaviors, in both the hypothalamus and hippocampus (King et al., 2020). It is plausible that deficits in social rewards facilitate alcohol misuse. Indeed, the administration of oxytocin reduced alcohol consumption in rodents (Stevenson et al., 2017) and attenuated activations to alcohol cues in the insula, occipital cortex, and hippocampus in humans (Hansson et al., 2018). Together, both clinical and preclinical studies have suggested that social isolation may enhance hypothalamic stress response and facilitate alcohol consumption.

As a component of the frontostriatal system that regulates motivated behaviors, the ventral striatum (VS) represents another brain region that may support isolation-related substance and alcohol misuse. Alcohol consumption induces VS dopamine release in both social (Boileau et al., 2003) and dependent human drinkers (Boileau et al., 2003). In mice following

social defeat, ethanol administration elevated VS dopamine release, enhancing the reinforcing properties of alcohol (Yavich and Tiihonen, 2000). Furthermore, socially deprived rats exhibited reduction in VS norepinephrine, increases in anxiety-like symptoms (Brenes et al., 2008), and greater vulnerability to heavy alcohol consumption (Butler et al., 2016). These pre-clinical findings implicate the VS in motivating drinking via alcohol's rewarding and anxiolytic properties. Human studies have also revealed the role of the VS circuits in alcohol craving and consumption (Nikolova et al., 2016; Zhang and Li, 2018). In particular, the VS receives top-down regulatory signals from the PFC (Cohen et al., 2012), and the PFC-VS connectivity may play a role in restraining drinking (Forbes et al., 2014). Disruption of the PFC-VS circuit along with deficits in cognitive control, especially during emotional stress, is widely reported of alcohol and drug users (Li and Sinha, 2008). Thus, the PFC may limit the extent to which the VS facilitates alcohol use in response to social isolation.

In the current study, we sought to identify the neural substrates that support the relationships between social isolation, social support, and problem alcohol use. Using resting-state functional magnetic resonance imaging (fMRI) data in problem drinkers, we examined the patterns of hypothalamus and VS connectivity in relation to PB and drinking severity. We specifically tested the hypothesis that problem drinking increases with social isolation via enhanced hypothalamic connectivity with regions of the stress circuit, including the insula, amygdala, and hippocampus. In contrast, social isolation and alcohol use were expected to be negatively associated with VS connectivity with the PFC, reflecting the reduced cognitive control in drinking to cope with emotional distress. Finally, we employed path analysis to examine the role of social support in moderating the inter-relationships between PB, brain connectivity, and alcohol misuse.

Methods

Participants and Assessments

Sixty-one problem drinkers (24 females; 17 smokers; age = 34.4 ± 11.9 years; education = 14.9 ± 2.71 years) participated in the study. Participants underwent clinical screening and received urine toxicology tests at intake and prior to imaging. All participants were current drinkers with an Alcohol Use Disorder Identification Test (AUDIT) (Saunders et al., 1993) score >6 (see below). All were required to be otherwise physically healthy with no major medical illnesses, current use of prescription medications, history of head injury or neurological illness, current or history of axis I disorders as defined by the DSM-IV, or positive urine test results for illicit substance use. Participants provided written informed consent after details of the study

were explained in accordance with institute guidelines and a research protocol approved by the Yale Human Investigation Committee.

To assess the degree of social isolation, participants completed the 15-item version of the Interpersonal Need Questionnaire (Van Orden et al., 2008, 2012). The questionnaire assesses perceived burdensomeness (PB; 6 items) and thwarted belongingness (9 items). We focused on the subscale PB, which refers to the belief that “others would be better off without me.” Individual items were rated on a 7-point scale ranging from 1 (not at all true) to 7 (very true), with some items reversely coded and higher scores indicating greater severity. The current sample showed an average PB score of 10.9 ± 7.3 (mean \pm SD), suggesting a relatively higher degree of loneliness compared with healthy adults as reported in previous work (Vanyukov et al., 2017; Chu et al., 2018). To assess the level of social support the participants received, we administered the Multidimensional Scale of Perceived Social Support (MSPSS), which quantifies perceived social support from family, friends, and significant others (Zimet et al., 1988). The 12 items were rated on a 7-point scale ranging from 1 (very strongly disagree) to 7 (very strongly agree), with higher scores indicating greater perceived support. The current sample showed an average MSPSS score of 59.8 ± 18.6 .

Participants showed an average of 17.1 ± 12.2 years of drinking and consumed an average of 1.7 ± 1.2 drinks per occasion over the prior month. Participants also completed the AUDIT, with higher scores suggesting greater risk for having or developing an alcohol use disorder. Problem drinking is defined by an AUDIT score of 7 or higher (Donovan et al., 2006). The group's average AUDIT score was 15.0 ± 8.8 . Participants further completed a self-assessment of out-of-control drinking on a scale from 0 to 10 (0 = completely in control, 10 = completely out of control), reporting an average score of 2.8 ± 2.7 . Additionally, a subsample of participants ($n=27$) was evaluated with the State-Trait Anxiety Inventory and Beck Depression Inventory-II, which yielded an average score of 87.2 ± 24.9 and 14.8 ± 13.6 , respectively.

Imaging Protocol and Data Processing

All participants completed one 10-minute run of resting-state fMRI. Conventional T1-weighted spin echo sagittal anatomical images were acquired for slice localization using a 3T scanner (Siemens Trio, Erlangen, Germany). Anatomical 3D MPRAGE images were obtained with spin echo imaging in the axial plane parallel to the anterior commissure–posterior commissure line with repetition time (TR) = 1900 ms, echo time (TE) = 2.52 ms, bandwidth = 170 Hz/pixel, FOV = 250×250 mm, matrix = 256×256 , 176 slices with slice thickness = 1 mm, and no gap. Functional blood oxygenation level-dependent (BOLD) signals were acquired using multiband imaging (multiband acceleration factor = 3) with a single-shot gradient echo-planar imaging sequence. Fifty-one axial slices parallel to the anterior commissure–posterior commissure line covering the whole brain were acquired with TR = 1000 ms, TE = 30 ms, bandwidth = 2290 Hz/pixel, flip angle = 62° , FOV = 210×210 mm, matrix = 84×84 , voxel size = 2.5 mm isotropic, and no gap.

Imaging data were preprocessed using SPM12 (Wellcome Trust Centre for Neuroimaging). Images from the first 5 TRs at the beginning of the run were discarded to ensure only BOLD signals at steady-state equilibrium between RF pulsing and relaxation were included in analyses. Images of individual participants were first realigned (motion corrected) and corrected for slice timing. A mean functional image volume was

constructed for each participant per run from the realigned image volumes. These mean images were co-registered with the high-resolution structural image and then segmented for normalization with affine registration followed by nonlinear transformation. The normalization parameters determined for the structure volume were then applied to the corresponding functional image volumes for each participant. Voxel size after normalization was 2.5 mm isotropic. Finally, the images were smoothed with a Gaussian kernel of 4-mm full width half maximum.

Analysis of Resting-State Functional Connectivity (rsFC)

In the analysis of rsFC, we reduced spurious BOLD variances with additional preprocessing. Signals from the ventricles, white matter, and whole brain were removed through a linear regression in addition to the 6 parameters obtained by rigid body head-motion correction. As BOLD fluctuations below a frequency of 0.1 Hz may contribute to regionally specific BOLD correlations, we applied a temporal band-pass filter ($0.009 \text{ Hz} < f < 0.08 \text{ Hz}$) to the time course to obtain low-frequency fluctuations.

To minimize the effects of micro head motion (>0.1 mm), which represents a significant source of spurious correlations in rsFC analysis, we implemented the “scrubbing” method (Power et al., 2012) to remove time points affected by head motions. Briefly, for every time point t , we computed the framewise displacement given by $FD(t) = |\Delta d_x(t)| + |\Delta d_y(t)| + |\Delta d_z(t)| + |\Delta \alpha(t)| + |\Delta \beta(t)| + |\Delta \gamma(t)|$, where $\Delta d_x(t) = d_x(1-t) - d_x(t)$, and similarly for the 3 translational parameters (d_x, d_y, d_z) and the 3 rotational parameters (α, β, γ). The 3 rotational parameters were computed as the displacement of millimeters, which were transformed from degrees by calculating displacement on the surface of a sphere with a radius from the cortex to the center of the head of 50 mm. The second head movement metric was the root mean square variance (DVARs) of the differences in % BOLD intensity $I(t)$ between consecutive time points across voxels, computed as follows: $DVARs(t) = \sqrt{\langle |I(t) - I(t-1)|^2 \rangle}$, where the brackets indicate the mean across voxels. Finally, to compute each participant's correlation map, we removed time points that exceeded the head motion limit $FD(t) > 0.5$ mm or $DVARs(t) > 0.5\%$ (Power et al., 2012). On average, 1% of the time points were removed across participants.

To examine seed-based rsFC, we obtained the hypothalamus mask ($k=10$ voxels) from the WFU PickAtlas (Maldjian et al., 2003) and the VS mask ($k=276$ voxels) as defined from our previous work using both cytoarchitectonic and topographical criteria (Li et al., 2014). The correlation coefficient between the averaged time course of the seed region and that of every other voxel of the brain was computed then Fisher's z transformed for each participant. The Z maps were used in group, random-effect analyses in which we conducted a whole-brain multiple regression for each seed (i.e., hypothalamus and VS) against the PB scores with age and sex as the covariates. All imaging results were examined with the threshold of voxel-level $P < .001$ (uncorrected) in combination with cluster-level $P < .05$ (corrected for family-wise error of multiple comparisons) according to current reporting standards (Poldrack et al., 2008; Woo et al., 2014).

Path Analysis

We evaluated the differential effects of social support (MSPSS score) on the rsFC of the hippocampus and hypothalamus (Hipp/

Hypo) as well as the middle frontal gyrus and VS (MFG/VS), both modulating problem drinking (AUDIT score) via social isolation (PB score) (see Results). Path analysis involves a set of exogenous variables with variance not accounted for by the model and endogenous variables with variance explained in part by other variables in the model (Wuensch, 2016; Le et al., 2020). Path analysis is conducted with regression analysis, which predicts the effects of all other variables on the endogenous variables. The beta weights (β) from these multiple regressions are the path coefficients. Standardized path coefficients convey assumptions about the directionality of interactions between variables. Model fit is typically assessed with fit indices that include the root mean square estimation of approximation (≤ 0.08 for an acceptable fit), chi-square ($\chi^2/df, \leq 3$), comparative fit index ($\geq .9$), and standardized root mean square residual ($\leq .08$) (Hu and Bentler, 1995; Chen et al., 2008).

Specifically, we included the MSPSS score as the exogenous variable, whereas the Hipp/Hypo rsFC, MFG/VS rsFC, PB, and AUDIT scores served as the endogenous variables. In this model, MSPSS score impacted Hipp/Hypo and MFG/VS connectivities, which in turn indirectly influenced AUDIT scores via their effects on PB. Bootstrapping was employed to evaluate both direct and indirect effects statistically.

Results

Drinking Behavior and Social Isolation Assessments

Across participants, greater severity of problem drinking was associated with greater social isolation and less social support. Table 1 details the linear relationships across drinking and social isolation variables.

Perceived Burdensomeness and Resting-State Functional Connectivity

First, we examined the relationship between resting-state connectivity of the hypothalamic seed and PB. A whole-brain multiple regression showed that greater PB was associated with increased hypothalamic connectivity with the right hippocampus and right middle temporal gyrus (Fig. 1A; Table 2). In contrast, lower PB was associated with increased hypothalamic connectivity with the bilateral precentral gyri, paracentral lobule, and right superior parietal lobule.

Similarly, we assessed the VS connectivity in relation to PB, which was positively correlated with VS connectivity with bilateral middle temporal gyri and right posterior putamen (Fig. 1B; Table 2). PB scores were also negatively correlated with VS connectivity with the right MFG.

Differential Role of Hipp/Hypo and MFG/VS rsFC in Drinking

As the hippocampus and MFG have both been demonstrated to be involved in the regulation of social stress and drinking behavior (George et al., 2001; Dager et al., 2013; Vaisvaser et al., 2013), we focused on these regions to better characterize the rsFC of the hypothalamus and VS in relation to PB. We extracted the parameter estimates of the Hipp/Hypo as well as the MFG/VS rsFC. Controlling for age and sex, AUDIT scores showed a positive relationship with the Hipp/Hypo rsFC ($r = .39, P = .002$; Fig. 2A) and a negative relationship with the MFG/VS rsFC ($r = -.35, P = .006$; Fig. 2B). In contrast, MSPSS scores were negatively correlated with the Hipp/Hypo rsFC ($r = -.30, P = .019$; Fig. 2C) and positively correlated with the MFG/VS rsFC ($r = .36, P = .005$; Fig. 2D). All correlations remained significant with FDR correction for multiple comparisons. To rule out the effects of head motion in these findings, we also included FD (mean \pm SD = $.15 \pm .11$ mm) as a covariate in the correlations. The results were virtually unchanged, suggesting that head motion did not represent a confound.

To determine the differential effects of the 2 connectivities in relation to PB and AUDIT scores, we conducted a path analysis, controlling for age, sex, and smoking status. We tested the scenario in which the level of social support (i.e., MSPSS score) influenced the rsFC of Hipp/Hypo as well as MFG/VS, which in turn differentially modulated problem drinking via social isolation, as measured by AUDIT and PB scores, respectively (Fig. 3A). The model showed a good fit (fit indices: root mean square estimation of approximation = $.08$ [90% CI: 0.00 – 0.226], $\chi^2/df = 1.45$, standardized root mean square residual = $.067$, and comparative fit index = $.975$). Specifically, MSPSS showed significant negative modulation on Hipp/Hypo connectivity ($\beta = -.29, P = .02$), which elevated PB ($\beta = .37, P < .001$). PB then facilitated problem drinking ($\beta = .41, P = .001$). In contrast, MSPSS increased MFG/VS connectivity ($\beta = .35, P = .004$), which suppressed PB ($\beta = -.30, P = .001$). Taken together, social support exerted opposing effects on the rsFC of Hipp/Hypo and MFG/VS, and the 2 connectivities in turn influenced PB in opposite directions to regulate alcohol use.

As the rsFC of Hipp/Hypo and VS/MFG showed opposite effects on drinking severity, we next examined how their net impact may determine PB-induced problem drinking. We computed the difference in strength of the 2 connectivities (i.e., Hipp/Hypo rsFC minus VS/MFG rsFC). This connectivity strength difference was negatively correlated with MSPSS ($r = -.42, P < .001$; Fig. 3B) but positively correlated with PB ($r = .69, P < .001$; Fig. 3C) and AUDIT ($r = .46, P < .001$; Fig. 3D) scores. Thus, greater Hippo/Hypo connectivity relative to the MFG/VS connectivity was associated

Table 1. Relationships Across Drinking and Social Isolation Characteristics

	PB	MSPSS	AUDIT	Years of drinking	OOC drinking	No. drinks/occasion
PB	1	-.59***	.46***	0.25	.40**	0.06
MSPSS		1	-.40**	-.29*	-.34*	-.35**
AUDIT			1	0.22	.78***	.56***
Years of drinking				1	.36*	.36**
OOC drinking					1	.52***
No. drinks/occasion						1

Abbreviations: AUDIT, Alcohol Use Disorder Identification Test; MSPSS, Multidimensional Scale of Perceived Social Support; OOC, out-of-control; PB, perceived burdensomeness.

* $P < .05$, ** $P < .01$, *** $P < .001$. No. drinks refers to the average number of drinks per drinking occasion in the past months. All correlations controlled for age and sex.

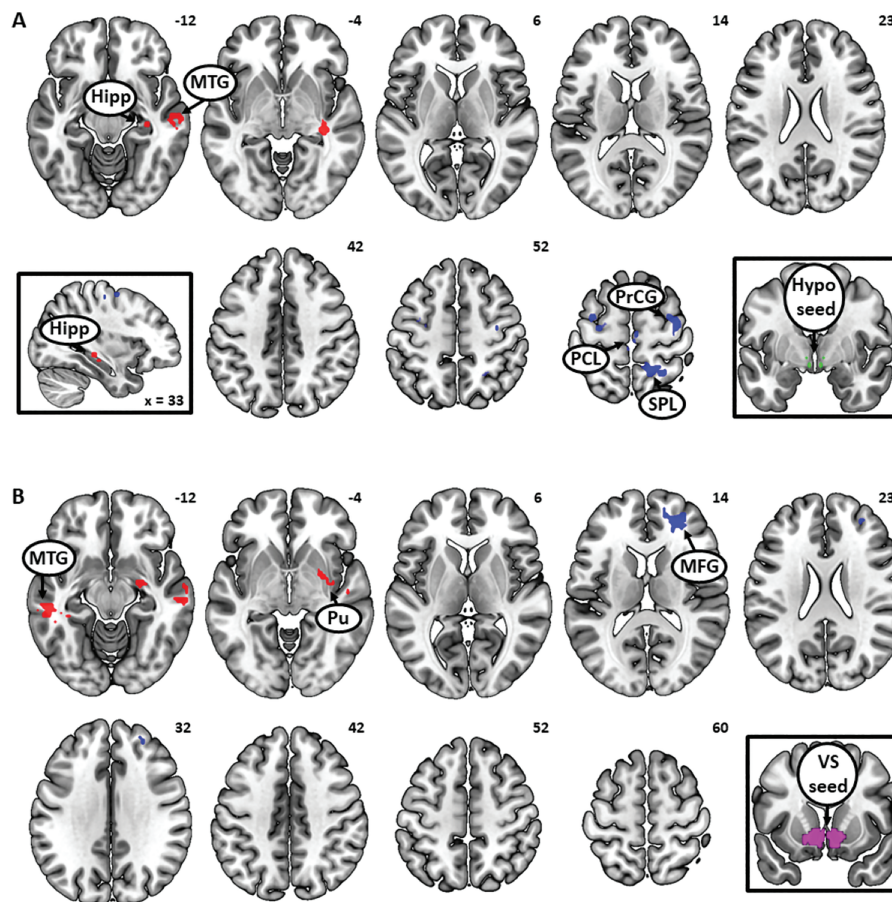


Figure 1. Whole-brain multiple regressions of resting-state functional connectivity against perceived burdensomeness (PB) scores. (A) PB showed a significant positive correlation with hypothalamic connectivity (hypo; right inset, in green) with the right hippocampus (Hipp; left inset) and middle temporal gyrus (MTG) and a negative correlation with hypothalamic connectivity with bilateral precentral gyri (PrCG), paracentral lobule (PCL), and right superior parietal lobule (SPL). (B) PB showed a significant positive correlation with ventral striatum (VS) connectivity (right inset, in purple) with bilateral MTG and right putamen (Pu) and a negative correlation with VS connectivity with the right middle frontal gyrus (MFG).

with lower social support, higher sense of isolation, and more severe drinking.

Discussion

The current study examined the neural substrates underlying the relationship between social isolation, social support, and alcohol use in problem drinkers. We found that lack of social support may have induced PB, which in turn facilitated problem drinking via enhanced rsFC between the hypothalamus and hippocampus and reduced rsFC between the MFG and VS. The difference in strength between the 2 connectivities predicted the degree of problem drinking, suggesting enhanced hypothalamic stress response and poor prefrontal cortical control in drinking to cope with social isolation. Taken together, the current study highlighted the neural processes underlying alcohol misuse induced by low social support and heightened sense of burdensomeness.

Hypothalamic Connectivity With the Hippocampus and PB-Induced Drinking

The involvement of the hippocampus in social isolation has been supported with reports of enhanced hippocampal

activation during ostracism (Bolling et al., 2011), negative social evaluation (Dedovic et al., 2009b), and social stress (Vaisvaser et al., 2013). Activity of the hippocampus during social exclusion was also positively related to subjective rating of social pain (Bach et al., 2019). The hippocampus shows abundant corticosteroid receptors (Joëls, 2008), which are likely critical for stress-related learning and memory (Lupien and Lepage, 2001). It is thus highly plausible that the hippocampus influences drinking behavior through its functional connectivity with the hypothalamus in reactivity to stress. Indeed, alcohol administration in rodents reduced stress-induced c-Fos expression in the hippocampus (Ryabinin et al., 1995). Alcohol consumption following stress exposure upregulated hippocampal gamma-aminobutyric acid $\alpha 4$ receptors and reduced stress-elicited anxiety (Gomez et al., 2013). Thus, individuals may seek alcohol to relieve isolation-related stress via hippocampal processes.

Social isolation appears to produce similar biochemical changes in the Hipp/Hypo, suggesting that they may be part of the same stress reactivity pathway. For instance, previous rodent work reported elevated corticotropin-releasing hormone (CRH) mRNA (Pournajafi-Nazarloo et al., 2009), reduced serotonin (Brenes and Fornaguera, 2009), and increased pain signal-related nitric oxide (Zlatković et al., 2014) levels in the hippocampus

Table 2. Perceived Burdensomeness and Resting-State Functional Connectivity

Seed region	Region	MNI coordinates (mm)			Voxel T	Cluster k
		x	y	z		
Hypothalamus	Hippocampus	35	-26	-4	5.59	37
		55	-16	-12	4.52	36
	Precentral gyrus	62	-18	-14	4.05	53
		-35	-4	58	-4.95	
		-25	-11	58	-4.43	
		35	-4	60	-4.78	
		40	-11	60	-3.75	
	Superior parietal lobule	20	-51	58	-4.59	66
	Paracentral lobule	0	-28	63	-4.31	43
5	-18	58	-4.25			
Ventral striatum	Middle temporal gyrus	55	-21	-10	5.02	88
		50	-16	-4	4.68	
		-50	-34	-10	4.90	83
		-62	-24	-14	4.18	
	Putamen	32	-11	-7	4.20	69
		28	-1	-4	4.00	
	Middle frontal gyrus	25	44	13	-5.27	100
		30	46	23	-3.77	
		28	44	30	-4.21	42
		20	46	28	-4.14	

Positive and negative T values indicate positive and negative correlations, respectively. MNI, Montreal Imaging Institute.

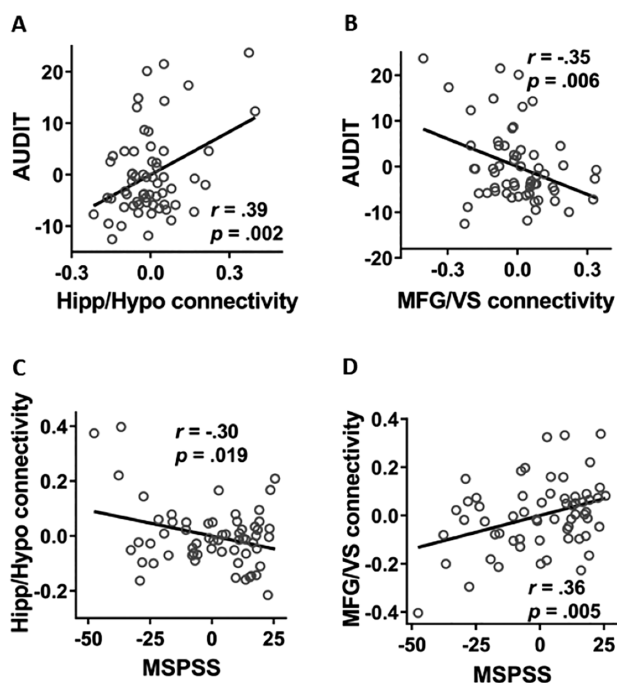


Figure 2. AUDIT scores showed (A) a positive relationship with Hipp/Hypo rsFC and (B) a negative relationship with MFG/VS rsFC. MSPSS scores showed (C) a negative relationship with Hipp/Hypo rsFC and (D) a positive relationship with MFG/VS rsFC. Note that the scatterplots showed results of partial correlations after the effects of sex and age were removed (i.e., residuals were shown for each variable).

following social deprivation. Similarly in the hypothalamus, CRH increases with stress and likely helps drive the hypothalamic-pituitary-adrenal axis reactivity to chronic stress (Makino et al., 1995). Hypothalamic serotonin immunoreactivity was found

to decrease in social isolation, potentially inducing aggression and depression-like behaviors in rats (Veenema et al., 2006). Hypothalamic nitric oxide is generated following stress exposure and thought to facilitate stress response, stress-related learning, and depressive symptoms (Gadek-Michalska et al., 2013). Importantly, CRH, serotonin, and nitric oxide have all been implicated in alcohol seeking and consumption. Drinking severity was associated with genetic polymorphisms of the CRH-receptor 1 (Treutlein et al., 2006). Moreover, pharmacological blockade of CRH-receptor 1 reduced alcohol drinking in rats (Cippitelli et al., 2012). Serotonin deficits have long been linked to alcohol abuse (LeMarquand et al., 1994) and were recently confirmed in a postmortem study of alcoholics (Underwood et al., 2018). Chronic alcohol use was also found to be linked with increased nitric oxide in the brain (Lancaster, 1992). As the Hipp/Hypo have direct anatomical connections (Mesulam et al., 1983), it is likely that social isolation modulates hippocampal activity and hypothalamic stress response, leading to drinking as a coping strategy.

MFG Connectivity With the VS and PB-Induced Drinking

The negative correlation between MFG/VS connectivity strength with PB and with AUDIT scores suggests a role of weakened prefrontal cortical control of striatal response in isolation-induced drinking. Past studies have suggested that stress, including that from social isolation, compromised prefrontal cortical functions (Pibiri et al., 2008; Eiland et al., 2012), including altered connectivity between the MFG and VS (Tottenham and Galván, 2016). In human drinkers, prefrontal cortical deficits have been associated with loss of self-control and compulsive alcohol seeking (Pahng et al., 2017). In rodents, glutamate receptors in the medial PFC were upregulated following social isolation (Zhao et al., 2009). Importantly, increases in medial prefrontal cortical

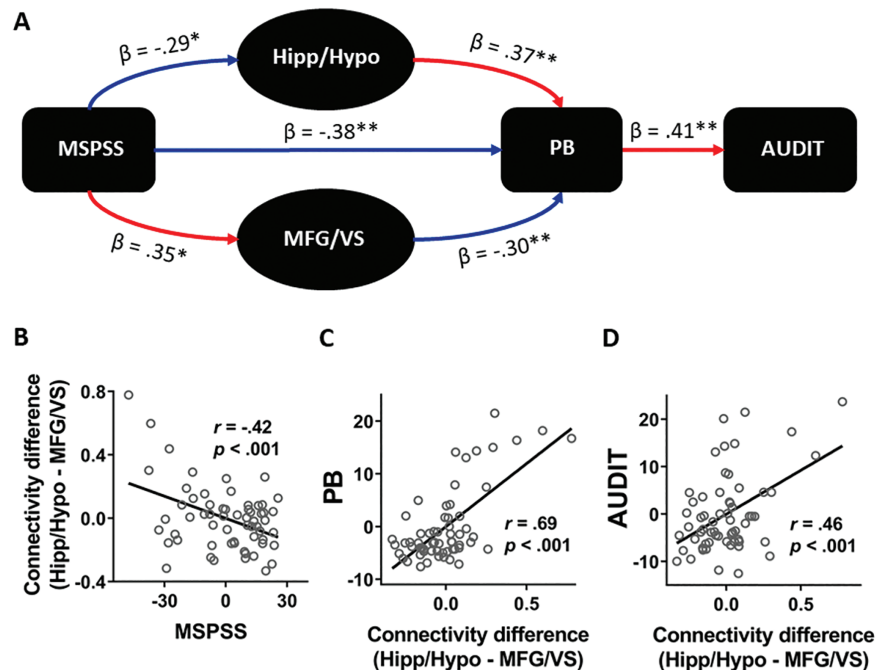


Figure 3. Relationships between social support, social isolation, problem drinking, and the rsFC of the Hipp/Hypo and MFG/VS. (A) Path analysis showed that social support (MSPSS) decreased Hipp/Hypo connectivity and increased MFG/VS connectivity. Hippo/Hypo connectivity was associated with heightened PB and drinking severity, whereas MFG/VS connectivity exhibited the opposite effects. Red and blue arrows indicate positive and negative relationships, respectively. Solid and dotted lines indicate significant and near-significant path coefficients, respectively. (B–D) Greater strength of Hipp/Hypo relative to MFG/VS connectivity was associated with lower social support, higher sense of isolation, and greater degree of problem drinking. * $P < .01$, ** $P < .001$.

glutamatergic inputs to the VS were subsequently reported to be necessary to overcome aversion to foot shocks and bitter taste paired with alcohol consumption (Seif et al., 2013). These findings demonstrate the importance of prefrontal cortical modulation of VS activity in controlling drinking behavior. Corroborating evidence in dependent human drinkers also shows attenuated MFG/VS connectivity during reward processing, suggesting increased impulsivity (Forbes et al., 2014). Additionally, alcoholics exhibited reduced alcohol cue-elicited prefrontal cortical connectivity with the VS in relation to greater reward sensitivity and attenuated cognitive control (Ray et al., 2014). Such investigations, along with the current work, point to a relationship between social isolation, reduced prefrontal cortical connectivity with the VS, and problem drinking.

Our results suggest that the Hipp/Hypo and MFG/VS resting-state connectivities work in opposite directions in their modulation of PB and problem drinking. Elevated hypothalamic connectivity with the hippocampus was associated with heightened PB and increased drinking severity, whereas the prefrontal cortical connectivity with the VS showed the inverse effects. Furthermore, the difference in their connectivity strength was predictive of the degree of alcohol misuse, suggesting opposing processes in regulating alcohol consumption in response to social isolation. Earlier research has proposed that the hypothalamus, hippocampus, and VS are part of a large system supporting instinctive behaviors in response to both internal needs and motivational stimuli such as reward and threats (Risold et al., 1997). The MFG, in contrast, is an important structure in the PFC commonly implicated in inhibitory control (Munakata et al., 2011). It stands to reason that the balance between these 2 systems determines motivated behaviors. As such, chronic social isolation can create an imbalanced or biased state toward over-reactive stress response and deficiency in inhibitory control, leading to excessive alcohol consumption as a maladaptive behavior.

The Role of Social Support in Alcohol Misuse

As individuals seek alcohol to cope with their negative emotional experiences resulting from social isolation, it is intuitively appealing that social support would serve as a protective factor against alcohol misuse. Indeed, there is ample evidence that those with higher support from family and friends engage less in problem drinking (Piko, 2000; Groh et al., 2007; Hamdan-Mansour et al., 2007). Social support also facilitates recovery from alcohol dependence (Rumpf et al., 2002) and maintains abstinence (Bond et al., 2003) in treatment-seeking individuals. In the treatment of substance and alcohol use disorders, social support has been incorporated as one of the core components of behavioral activation intervention that emphasizes substance-free positive reinforcement (Daughters et al., 2018). Enhancement of social skills, support, and rewards can facilitate cognitive control and reduce avoidance (Hopko et al., 2011), both of which have been found to disengage individuals from drug use (Martínez-Vispo et al., 2018) and sustain abstinence (Daughters et al., 2018). In contrast, lack of social support is associated with increased impulsivity and alcohol consumption in both light (Pauley and Hesse, 2009) and dependent (Jakubczyk et al., 2013) drinkers. In recent months, the COVID-19 pandemic has further highlighted the detrimental effects of reduced social interaction on problem drinking. Studies have reported increased alcohol consumption in those experiencing loneliness and isolation (Wardell et al., 2020). Vulnerable populations such as the elderly (Satre et al., 2020) and individuals with psychiatric disorders (Tso and Park, 2020) who typically receive less social support are particularly at risk. Thus, the current findings are consistent with this body of work showing that social support plays a key role in preventing alcohol misuse. Moreover, by demonstrating the interacting roles of the brain regions implicated in social stress response and inhibitory control, we characterized the neural correlates for this relationship.

Limitations and Conclusions

A number of limitations should be considered. Due to the modest sample size, especially of female drinkers, we did not examine sex differences in the neural processes associating PB to problem alcohol use. As men and women may engage in alcohol misuse via different psychological and neural processes (Ide et al., 2017; Hu et al., 2018), more research is warranted to investigate how social isolation may contribute to problem drinking differently between the sexes. Second, we examined rsFC, which is known to reflect individual differences in functional organization of the brain (Cole et al., 2013). Behavioral paradigms, including those that probe reward processing, cognitive control, and social exclusion, are needed to fully characterize how social isolation contributes to problem alcohol use. Third, while the findings of path analysis suggest causal relationship between clinical variables and neural markers, longitudinal research is required to understand how social isolation and social support may perpetuate and ameliorate problem drinking, respectively. Finally, as we did not have complete data for anxiety and depression, both of which can impact alcohol use, for all participants, we were unable to examine their potential roles in modulating the relationship between social isolation and problem drinking.

In conclusion, by combining functional connectivity analyses and assessments of PB and social support in problem drinkers, we were able to reveal the neural substrates underlying the relationship between social isolation and alcohol misuse. This relationship is characterized by 2 opposing processes, one involving regions implicated in stress response and the other involving prefrontal cortical modulation. Our findings suggest that alcohol misuse in socially isolated drinkers likely involves enhanced stress reactivity and diminished cognitive control. The results also highlight the importance of social support as a protective factor against problem drinking, calling attention to the need to enlist families and friends in the prevention and intervention of alcoholism.

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Statement of Interest

All authors declare no conflicts of interest in the current work.

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