Sex differences in the interacting roles of impulsivity and positive alcohol expectancy in problem drinking: A structural brain imaging study

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ABSTRACT

Alcohol expectancy and impulsivity are implicated in alcohol misuse. However, how these two risk factors interact to determine problem drinking and whether men and women differ in these risk processes remain unclear. In 158 social drinkers (86 women) assessed for Alcohol Use Disorder Identification Test (AUDIT), positive alcohol expectancy, and Barratt impulsivity, we examined sex differences in these risk processes. Further, with structural brain imaging, we examined the neural bases underlying the relationship between these risk factors and problem drinking. The results of general linear modeling showed that alcohol expectancy best predicted problem drinking in women, whereas in men as well as in the combined group alcohol expectancy and impulsivity interacted to best predict problem drinking. Alcohol expectancy was associated with decreased gray matter volume (GMV) of the right posterior insula in women and the interaction of alcohol expectancy and impulsivity was associated with decreased GMV of the left thalamus in women and men combined and in men alone, albeit less significantly. These risk factors mediated the correlation between GMV and problem drinking. Conversely, models where GMV resulted from problem drinking were not supported. These new findings reveal distinct psychological factors that dispose men and women to problem drinking. Although mediation analyses did not determine a causal link, GMV reduction in the insula and thalamus may represent neural phenotype of these risk processes rather than the consequence of alcohol consumption in non-dependent social drinkers. The results add to the alcohol imaging literature which has largely focused on dependent individuals and help elucidate alterations in brain structures that may contribute to the transition from social to habitual drinking.

1. Introduction

Studies of risk mechanisms for alcohol use disorders may provide insights that would inform the development of more effective preventive and therapeutic interventions. One important risk mechanism, heightened behavioral impulsivity, has received particularly intensive study (Coskunpinar et al., 2013; Klein et al., 2016; Sanchez-Roige et al., 2016; Stephan et al., 2016; Wardell et al., 2016). Impulsivity can be characterized by questionnaire assessment or laboratory test. For instance, positive urgency (tendency to lose control when one feels exhilarated) as assessed by Urgency, Premeditation, Perseverance, Sensation seeking, and Positive urgency or UPPS-P scale (Whiteside and Lynam, 2001) was bidirectionally related to higher levels of alcohol use in college students (Kaiser et al., 2016). Adolescents with a family

history of alcohol or substance use disorders initiated early alcohol and drug use in part due to increased impulsivity and sensation seeking, as assessed by the Barratt Impulsiveness Scale and Sensation Seeking Scale for Children (Acheson et al., 2016). In an alcohol self-administration paradigm, high-responders showed higher measures of impulsivity on a delayed discounting task, compared to low-responders (Stangl et al., 2016). However, laboratory studies suggested that impulsivity, when assessed in several different ways, does not directly predispose individuals to problem drinking (Mullen et al., 2016; Stevens et al., 2017). In community dwelling problem drinkers, a money-based "Alcohol-Savings Discretionary Expenditure" index but not analogous measures of behavioral impulsivity predicted stable moderation drinking (i.e., longer-term behavior regulation) compared to stable abstinence or relapse (Tucker et al., 2016).

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Alcohol use may be further enhanced by prior positive experiences with alcohol and the expectation of future positive effects with alcohol consumption (Brown et al., 1985). Alcohol expectancy can be measured by the Alcohol Expectancy Questionnaire (AEQ, (Brown et al., 1980). Alcohol expectancy also mediated attentional bias to alcohol-related cues in social drinkers (Field et al., 2011; Townshend and Duka, 2001) and predicted alcohol use in adolescents (Cranford et al., 2010; Shell et al., 2010; Urban et al., 2008) as well as alcohol consumption and hazardous drinking in young adults (Grotmol et al., 2010; Lee et al., 1999; Palfai and Wood, 2001; Pastor and Evans, 2003; Wardell et al., 2012; Young et al., 2006; Zamboanga, 2005; Zhang et al., 2002). Individuals who experience positive effects of alcohol in the laboratory reported heavier drinking patterns and lower negative alcohol expectancies (Stangl et al., 2016). Problem drinkers demonstrated significantly higher positive alcohol expectancies than non-problem drinkers on all AEQ subscales (Vilenne and Quertemont, 2015). Further, delivery of messages that challenge positive alcohol expectancy reduced alcohol consumptions (Dunn et al., 2000; Wiers and Kummeling, 2004) and changes in alcohol expectancy predicted treatment outcome in dependent individuals undergoing cognitive behavioral therapy (Young et al., 2011). These studies support alcohol expectancy as a psychological risk factor and predictor of alcohol misuse.

Impulsivity and drinking motives, such as positive alcohol expectancy, may interact to influence drinking behavior (Jones et al., 2014; Stevens et al., 2017). Although individuals higher in impulsivity were not significantly more likely to engage in unplanned drinking, those who reported higher levels of impulsivity demonstrated stronger intention to drink and, in turn, consumed more alcohol (Stevens et al., 2017). In young adults, alcohol expectancy mediated the association between reward sensitivity and hazardous alcohol use (Gullo et al., 2010) and predicted or interacted with impulsivity, social anxiety, or mood state to predict alcohol use and alcohol-related problems (Fu et al., 2007; McCarthy et al., 2001; Meade Eggleston et al., 2004; Stein et al., 2000; Zamboanga, 2006). Alcohol expectancy and disinhibition both moderated alcohol use related risky sexual behavior (Kiene et al., 2016). Characterizing the interactive effects of alcohol expectancy and impulsivity may help to better identify factors promoting the development of problem drinking.

Previous imaging studies have characterized how brain structures and functions are altered in association with problem drinking, with the great majority of studies conducted in dependent drinkers. In morphometric studies, alcohol use is correlated with gray matter shrinkage in the cortical striatal limbic circuits, suggesting chronic, neurotoxic effects of alcohol on cerebral structures (Yang et al., 2016). On the other hand, evidence accumulates that cerebral gray matter volumes may represent neural markers of psychological traits that dispose individuals to problem drinking (Charpentier et al., 2016; Holmes et al., 2016; Luciana et al., 2013; Schilling et al., 2013). Thus, whether changes in cerebral morphometry reflect primarliy the effects of alcohol or may represent a trait marker of individual vulnerability to problem drinking remains to be investigated. This issue is particularly salient in nondependent social drinkers, who may not have suffered as extensively from prolonged drinking as is typical of dependent drinkers.

The current study explored relationships between alcohol consumption, brain structure, alcohol expectancies, and impulsivity in male and female social drinkers. Brain structure was characterized with MRI, impulsivity was characterized with the Barratt Impulsivity Scale (BIS), alcohol expectancy was characterized using the AEQ, and problem drinking was measured using the Alcohol Use Disorder Identification Test (AUDIT) score. We used general linear models to evaluate expectancy and impulsivity as predictors of problem drinking. We then conducted voxel-based morphometry analysis to identify the structural brain correlates of these risk variables. Subsequently, we performed mediation analyses to examine the relationship between the risk variables, gray matter volume (GMV) correlates of problem drinking, and AUDIT score. In particular, because alcohol use is known to affect cerebral structures, we aimed to distinguish two specific hypotheses 1) that risk variables cause problem drinking, which in turn leads to changes in GMV, and 2) that GMV, as a neural phenotype of individual vulnerability, causes higher alcohol expectancy and impulsivity which in turn leads to problem drinking. Because men and women show important differences in their drug and alcohol using behaviors and clinical profiles of substance/alcohol use disorders (Beck et al., 1995; Brady and Randall, 1999; Derringer et al., 2010; Greenfield et al., 2010; Hensing and Spak, 2009; Kampov-Polevoy et al., 2004; McGue et al., 1997; Schulte et al., 2009), these analyses were conducted in a sample combining men and women as well as separately for men and women.

2. Materials and methods

1. Subjects and assessment

Study participants were recruited by advertisements in local newspapers and radio stations and by flyers posted in the greater New Haven area. All participants were screened to be free of major medical illness, past or present neurological (e.g., epilepsy, learning impairments, head trauma) and axis I psychiatric illnesses including substance use disorders (SCID-I for DSM-IV), denied current use of illicit substances, and showed negative urine toxicology tests for stimulants, opioids, marijuana, and benzodiazepines at the time of initial screening and fMRI. Candidates currently using any psychotropic medications were excluded. Pregnant or lactating women also were not included. Participants were further required to be free of MRI-contraindications based on the Yale Magnetic Resonance Research Center's safety guidelines. All subjects signed a written informed consent, in accordance to a protocol approved by the Yale Human Investigation Committee.

One hundred and fifty-eight social drinkers (86 women; age 29.8 ± 10.6 years) participated in the study. All participants completed questionnaires regarding their alcohol use over the past year, including average number of days of alcohol use and the average number of drinks consumed per occasion, framed on a monthly basis, and were evaluated with the Alcohol Use Disorders Identification Test (AUDIT, (Babor et al., 2001). AUDIT scores are calculated from the sum of ten self-report questions regarding level of alcohol use, alcohol-related problems, and concern expressed by others for one's drinking behavior. Each question is scored from 0 to 4, with higher numbers indicating a greater level of risk for having or developing an alcohol use disorder. The mean (± SD) AUDIT scores were 4.1 (± 3.4) for women, 6.5 (± 4.7) for men, and 5.2 (± 4.2) for women and men combined. These AUDIT scores appeared to be typical of non-dependent drinkers and were significantly lower than those reported for alcohol dependent individuals (Rubinsky et al., 2010). A summary of demographic and clinical data is presented in Table 1A.

Participants were assessed with the Alcohol Expectancy Questionnaire (AEQ-3; (George et al., 1995)) and the Barratt Impulsivity Scale (BIS-11, (Patton et al., 1995)). The AEQ underwent several revisions since its introduction by Brown et al. (1980), and AEQ-3 consisted of 40 items to address both positive (6 subscales) and negative (2 subscales) alcohol expectancy (George et al., 1995). Each subscale contains 4 to 6 statements that can be endorsed on a six-point scale, from "disagree strongly (1)" to "agree strongly (6)". The global positive subscale contains five items and thus ranges from 5 to 30 in total score, with a greater score indicating higher global positive alcohol expectancy. Although the expectancy subcomponents are statistically discernible, the high subscale inter-correlations (ranging from $r = 0.42$ to 0.92, mean = 0.78) suggest that the degree of distinctiveness among the subscales is at best modest (George et al., 1995). Thus, in the current study, we focused on the "global positive" as a variable to identify the influence of alcohol expectancy on inter-subject variations in AUDIT score. Used to evaluate an impulsive personality trait, the BIS-11 is a 30-item self-report questionnaire designed to measure impulsivity. All items are scored on a 4-point scale (1 = rarely/never; 2 = oc-

Table 1
Demographics of participants and correlations between AUDIT and drinking variables.

(A) Demographics of participants.

Groups	all (n = 158)	women (n = 86)	men (n = 72)	p value*
Age (years)	29.8 ± 10.6	30.2 ± 11.8	29.4 ± 9.1	0.6384
AUDIT	5.2 ± 4.2	4.1 ± 3.4	6.5 ± 4.7	0.0002
Years of drinking	12.0 ± 10.1	12.1 ± 11.3	11.9 ± 8.5	0.8917
Total drinks per month	17.8 ± 19.8	13.2 ± 14.6	23.3 ± 23.5	0.0012
Frequency of binge drinking	11.4%	4.7%	19.4%	0.0036ˆ
GP	10.8 ± 4.1	10.6 ± 4.1	11.0 ± 4.1	0.5368
BIS	60.3 ± 9.1	59.2 ± 9.2	61.7 ± 8.8	0.0926

*two-tailed two-sample t-test and ˆchi-square test for sex difference.

(B) Correlations between AUDIT and age, AEQ Global Positive (GP) score, BIS total score, and GP × BIS score. With correction for multiple comparisons ($0.05/12 = 4.2 \times 10^{-3}$), significant p values are bolded.

Groups	all (n = 158)		women (n = 86)		men (n = 72)	
	r	p	r	p	r	p
Age	− 0.2672	**6.9×10^{-4}**	− 0.2882	7.1×10^{-3}	− 0.2695	2.2×10^{-2}
GP	0.5179	**3.2×10^{-12}**	0.5727	**8.3×10^{-9}**	0.4989	**8.2×10^{-6}**
BIS	0.2657	**7.4×10^{-4}**	0.1230	2.6×10^{-1}	0.3509	**2.5×10^{-3}**
GP × BIS	0.5515	**5.9×10^{-14}**	0.5611	**1.9×10^{-8}**	0.5413	**9.1×10^{-7}**

casionally; 3 = often; 4 = almost always/always). The total score thus ranges from 30 to 120, with a higher score indicating increased impulsivity. Eleven of the 30 items are reverse scored to avoid response bias. The BIS-11 has been translated into many different languages with good internal consistency and test–retest reliability (Fossati et al., 2001; Li and Chen, 2007; Someya et al., 2001).

2. Clinical data analysis

We performed linear regressions of AUDIT score against alcohol expectancy-global positive score (GP), Barratt Impulsivity Scale total score (BI), and the interaction of BI and GP or BI × GP, each for men, women and the combined sample, to assess the association of problem drinking with these risk variables. Further, in general linear models (GLM), we considered AUDIT score as the dependent variable and GP, BI, and/or the interaction term BI × GP, as an independent (risk) variable, all with age as a covariate:

Model 1: $AUDIT = \beta_0 + \beta_1 \times GP + \beta_2 \times BI + \varepsilon$.
Model 2: $AUDIT = \beta_0 + \beta_1 \times GP + \beta_2 \times BI + \beta_3 \times BI \times GP + \varepsilon$
Model 3: $AUDIT = \beta_0 + \beta_1 \times GP + \varepsilon$
Model 4: $AUDIT = \beta_0 + \beta_1 \times BI + \varepsilon$
Model 5: $AUDIT = \beta_0 + \beta_1 \times BI \times GP + \varepsilon$
Model 6: $AUDIT = \beta_0 + \beta_1 \times GP + \beta_2 \times BI \times GP + \varepsilon$
Model 7: $AUDIT = \beta_0 + \beta_1 \times BI + \beta_2 \times BI \times GP + \varepsilon$

where β's represented the coefficients and ε's the error terms. The models were ranked using the Bayesian information criterion (BIC) as well as the Akaike information criterion (AIC). The GLM's were performed in Matlab R2015b using Econometric and Statistics toolboxes for women and men combined, as well as for women and men separately.

3. Imaging protocol

All participants were scanned on a Siemens 3-Tesla scanner (Trio; Siemens AG, Erlangen, Germany). Data for each participant consisted of a single high-resolution T1-weighted gradient-echo scan: 176 slices; 1 mm^3 isotropic voxels; field of view = 256 × 256 mm; data acquisition matrix = 256 × 256; TR = 2530 ms; TE = 3.66 ms,

bandwidth = 181 Hz/pixel; flip angle = 7°.

4. Voxel-based morphometry (VBM)

The aim of VBM is to identify differences in the local composition of brain tissue and its association with behavioral and cognitive measures, while discounting large scale differences in gross anatomy and position. This can be achieved by spatially normalizing individuals' structural images to the same stereotactic space, segmenting the normalized images into distinct brain tissues, smoothing the gray-matter images, and performing a statistical test to localize significant associations between anatomical and behavioral measures (Ashburner and Friston, 2000).

VBM was performed using the Computational Anatomy Toolbox (CAT 12 r933, http://dbm.neuro.uni-jena.de/cat/) packaged in Statistical Parametric Mapping 12 (Wellcome Department of Imaging Neuroscience, University College London, U.K.). CAT12 provides several components optimized for morphometry, including internal interpolation, affine preprocessing (affine registration of bias-corrected images), partial volume segmentation, denoising, DARTEL normalization, local adaptive segmentation, skull-stripping, adaptive maximum a posteriori segmentation, and a final "clean-up". In short, T1 images were first co-registered to the Montreal Neurological Institute or MNI template space (1.5 mm^3 isotropic voxels) using a multiple stage affine transformation, during which the 12 parameters were estimated. Co-registration started with a coarse affine registration using mean square differences, followed by affine registration using mutual information. In this step, coefficients of the basis functions that minimize the residual square difference between individual image and the template were estimated. Tissue probability maps constructed from 452 healthy subjects were used in affine transformation, and affine regularization was performed with ICBM space template – European brains. Affine preprocessing was performed with default parameter 'light'. After affine transformation, a spatial-adaptive non-local means denoising filter (Manjon et al., 2010) with default parameter 0.5 was applied, to account for intensity variations (inhomogeneity) and noise caused by different positions of cranial structures within the MRI coil; and, finally, they were segmented into cerebrospinal fluid, gray matter and white

matter, using an adaptive maximum a posteriori method (Rajapakse et al., 1997) with k-means initializations. In segmentation, partial volume estimation was performed with a simplified mixed model of at most two tissue types (Tohka et al., 2004), and a local adaptive segmentation was executed with default parameter 0.5 to account for GM inhomogeneity prior to the final adaptive maximum a posteriori estimation. Segmented and the initially registered tissue class maps were normalized using DARTEL (Ashburner, 2007), a fast diffeo-morphic image registration algorithm of SPM. As a high-dimensional non-linear spatial normalization method, DARTEL generates mathematically consistent inverse spatial transformations. We used the standard DARTEL template in MNI space, constructed from 555 healthy subjects of the IXI-database (http://www.brain-development.org/), to drive the DARTEL normalization. Skull-stripping and final clean up (to remove remaining meninges and correct for volume effects in some regions) were performed with default parameters of 0.5′s. Normalized GM maps were modulated to obtain the absolute volume of GM tissue corrected for individual brain sizes. Finally, the GM maps were smoothed by convolving with an isotropic Gaussian kernel. Smoothing helps in compensating for the inexact nature of spatial normalization and reduces the number of statistical comparisons; however, it reduces the accuracy of localization. Most VBM studies used a kernel size of FWHM = 12 mm. We used a smaller kernel size of FWHM = 8 mm to enhance localization accuracy.

In group analyses, we employed multiple regressions as informed by the best GLMs of the clinical data. The rationale was to identify the neural correlates of variables that best predicted AUDIT within each group; that is, GP for women, and BI × GP for men and for women and men combined (please see Results). Therefore, we regressed the GM volumes of the whole brain against GP score for women; and GM volumes against BI × GP score for men and for men and women combined, all with age as a covariate, as with GLM analysis of the clinical data.

5. Mediation analysis

We examined whether GMV variation of the regions of interest mediates the correlation between alcohol expectancy (GP) or the interaction between impulsivity and alcohol expectancy (BI × GP) and problem drinking (as indexed by AUDIT score), with age as covariate. We performed mediation analyses (MacKinnon et al., 2007), using the toolbox M3, developed by Tor Wager and Martin A. Lindquist (http://wagerlab.colorado.edu/tools). Regions of interest (ROI) were derived from group results and the GMV of these ROIs of individual participants were obtained by averaging the voxel GM volume densities within each individual region.

In a mediation analysis, the relation between the independent variable X and dependent variable Y, i.e. X➔Y, is tested to see if it is significantly mediated by a variable M. The mediation test is performed by employing three regression equations (MacKinnon et al., 2007):

$$Y = i_1 + cX + e_1$$
$$Y = i_2 + c'X + bM + e_2$$
$$M = i_3 + aX + e_3$$

where a represents X➔M, b represents M➔Y (controlling for X), c' represents X➔Y (controlling for M), and c represents X➔Y. The constants i_1, i_2, i_3 are the intercepts, and e_1, e_2, e_3 are the residual errors. In the literature, a, b, c and c' were referred as path coefficients or simply paths (MacKinnon et al., 2007; Wager et al., 2008), and we followed this notation. Variable M is said to be a mediator of the correlation X➔Y if ($c − c'$), which is mathematically equivalent to the product of the paths $a × b$, is significantly different from zero (MacKinnon et al., 2007). If the product $a × b$ and the paths a and b are significant, one concludes that X➔Y is mediated by M. In addition, if path c' is not significant, there is no direct connection from X to Y and that X➔Y is completely mediated by M. Note that path b is the relation between Y and M, controlling for X, and should not be confused with

the correlation coefficient between Y and M.

3. Results

1. Alcohol expectancy and drinking variables

Global positive alcohol expectancy (GP) averaged across participants at 10.8 ± 4.1 (mean ± standard deviation), similar to the mean of 9.7 reported earlier for a cohort of 1260 social drinkers (George et al., 1995), with no differences between men and women. Barratt Impulsivity Scale (BIS) score averaged across participants at 60.3 ± 9.1, with men showing marginally higher score than women. AUDIT score across participants was 5.2 ± 4.2, indicating a moderate level of problem drinking in this cohort of social drinkers (Babor et al., 2001), with men showing higher level of problem drinking. Table 1A summarizes these results.

Using Pearson coefficients, we correlated the AUDIT score with age, GP score, BIS score, and GP × BIS score in women, men and the combined group. The results showed that AUDIT was negatively correlated with age in men and women as well as for the combined group. AUDIT was positively correlated with GP in men and women as well as for the combined group. AUDIT was positively correlated with BIS for men as well as for men and women combined but not for women alone (Table 1B). We further examined whether these correlations with AUDIT varied between men and women by comparing the regression slopes (Zar, 1999). The results showed that the correlation between AUDIT and BIS scores is significantly reduced in women as compared to men (slope test, $t = 2.018$, $p = 0.045$), but no sex differences were observed for the correlations between AUDIT and GP, between AUDIT and GP × BIS, or between AUDIT and age ($p = 0.51$, $p = 0.57$, and 0.37, respectively) (Fig. 1).

In the GLM with age as covariate, the best predictor for problem drinking, as indexed by AUDIT, was GP (model 3, BIC = 430.5), followed by BI × GP (model 5, BIC = 431.0), for women. For men as well as men and women combined, the best predictor of AUDIT was BI × GP (model 5, BIC = 413.1 and 856.1, respectively), followed by GP (model 3, BIC = 416.7 and 861.5, respectively). Lower BIC values indicated better models, and use of the Akaike Information Criterion (AIC) led to the same conclusions. Thus, alcohol expectancy alone best predicted problem drinking in women whereas alcohol expectancy and impulsivity interacted to determine problem drinking in men and the entire cohort.

2. Voxel-based morphometry (VBM)

On the basis of these results, we employed voxelwise multiple regression with GP and age as regressors for women and BI × GP and age as regressors for men and for men and women combined. At a threshold of voxel $p < 0.0001$, uncorrected, combined with cluster $p < 0.05$ FWE corrected (k > 100 voxels), regions that correlated negatively with alcohol expectancy were localized to the right posterior insula (1295 mm³, peak voxel MNI coordinate [41 −4 −16], $T = 4.54$) in women (Fig. 2, red cluster). A cluster that correlated negatively with the interaction term BI × GP was identified in the left thalamus (803 mm³, peak voxel [−6 −18 12], $T = 4.50$; Fig. 2, green cluster) in men and women combined. In men alone, the same left thalamus cluster was significant but only at $p < 0.005$, uncorrected.

3. Mediation analysis

In regressions with age as a covariate, we computed and confirmed pairwise partial correlations of the average GMV with AUDIT, and GP or BI × GP. For women, the GMV of the right posterior insula was correlated with AUDIT and GP ($r = −0.29$, $p = 6.2 × 10^{-3}$ and $r = −0.45$, $p = 1.6 × 10^{-5}$, respectively). For women and men combined, the GMV of the left thalamus was correlated with AUDIT
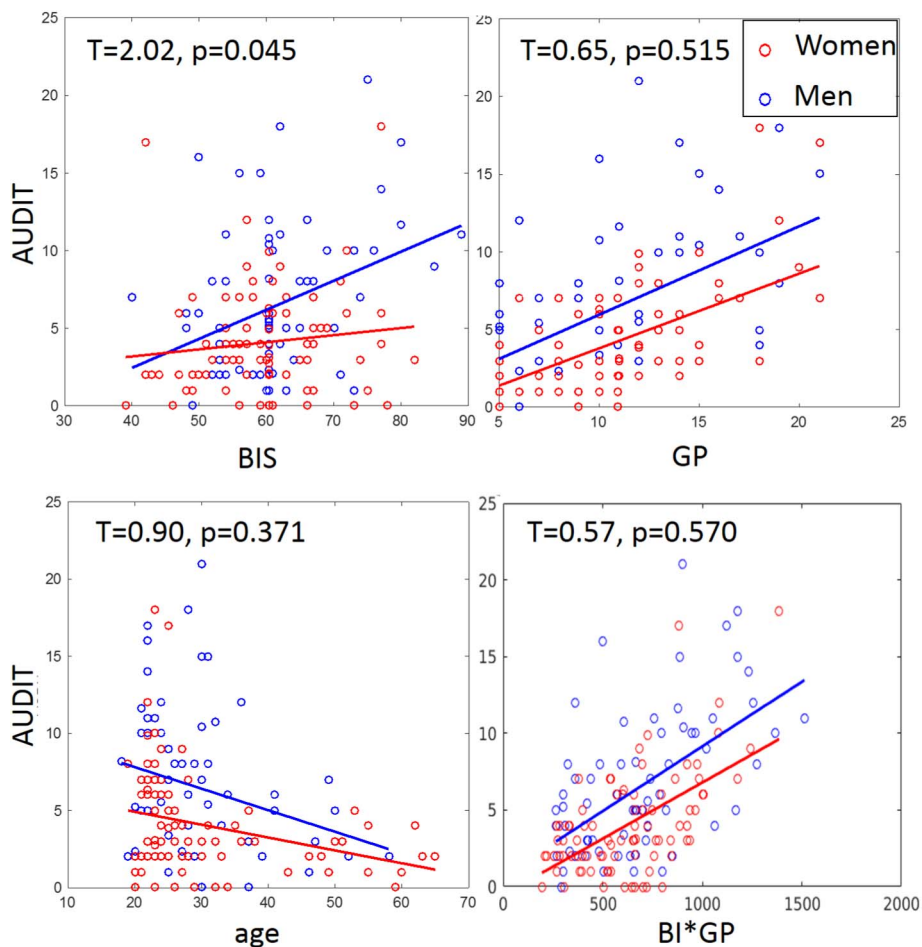
Fig. 1. Comparison of regression slopes between men and women. Significant slope differences are observed in the regression between AUDIT and BIS ($t = 2.018$, $p = 0.045$) but not GP, GP $\times$ BIS, or age.
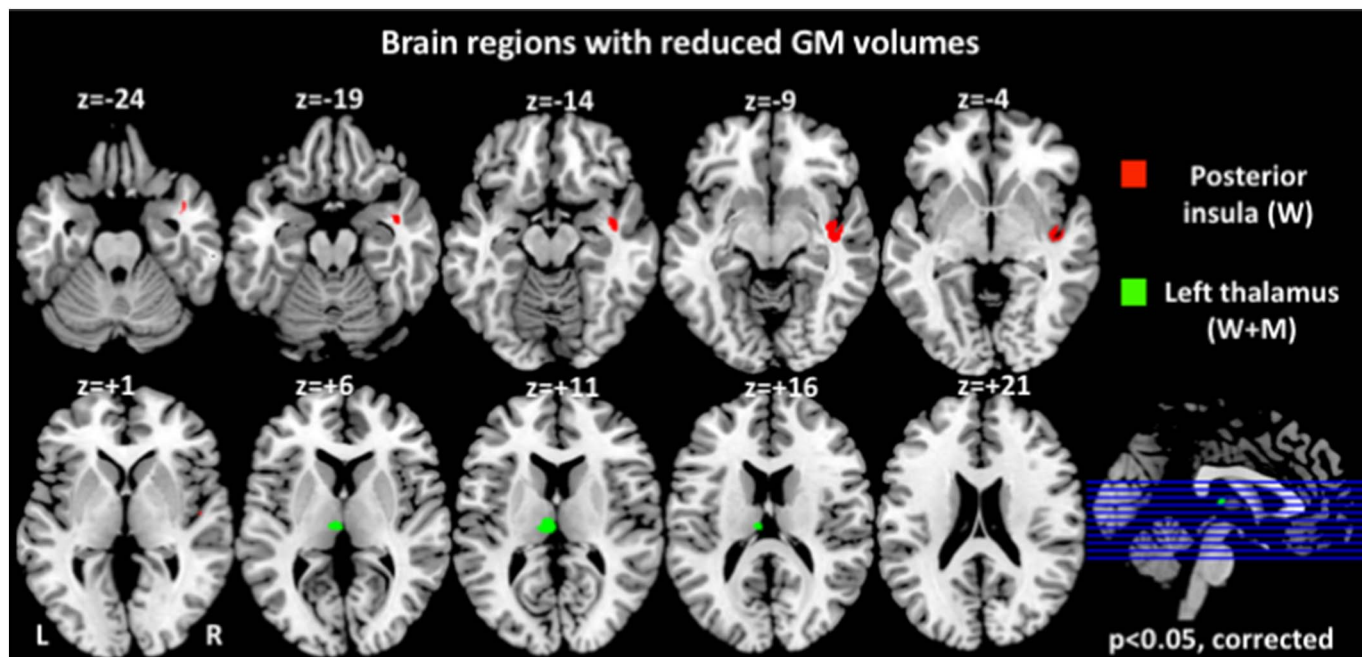

Fig. 2. Voxel based morphometry: multiple regressions against global positive alcohol expectancy (GP) and the interaction of GP and Barratt impulsivity (BI) or BI $\times$ GP. Posterior insula GMV was reduced in women with increased GP (upper panel), and left thalamus GMV was reduced with increased BI $\times$ GP in the combined group (lower panel). (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)
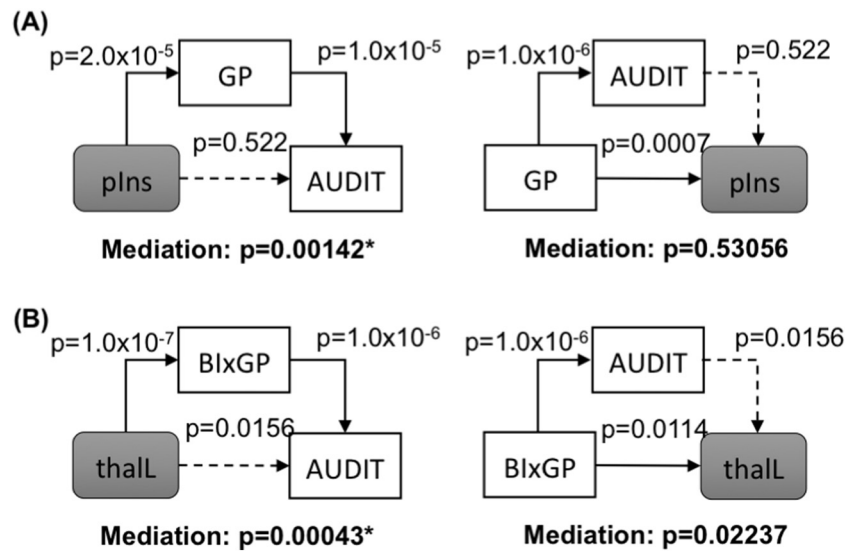
Fig. 3. Single-level mediation analysis of (A) global positive alcohol expectancy (GP), right posterior insula (pIns) gray matter volume (GMV) and AUDIT score in women, and (B) the interaction of GP and Barratt impulsivity (BI × GP), left thalamus (thalL) GMV and AUDIT score in men and women combined. Dashed arrows indicate the lack of a significant connectivity at Bonferroni corrected $p = 0.05/4 = 0.0125$. The asterisk "*" indicates significant mediation.

and BI × GP ($r = -0.33$, $p = 2.6 \times 10^{-5}$ and $r = -0.33$, $p = 2.0 \times 10^{-5}$, respectively). Thus, we performed mediation analysis to test the relationship between the risk factors, AUDIT and GMV. We tested two specific hypotheses. In the first hypothesis, insula/thalamus GMV represents the outcome of problem drinking. That is, we tested GP and BI × GP as risk variables that might cause problem drinking, and which in turn could lead to changes in GMV. According to this hypothesis, AUDIT score would mediate the correlation between GP and insula GMV in women and the correlation between BI × GP and thalamus GMV in women and men combined. In the alternative hypothesis, insula/thalamus GMV represents the neural phenotypes that dispose individuals to higher alcohol expectancy and impulsivity, which in turn leads to problem drinking. According to this hypothesis, GP/BI × GP would mediate the correlation between insula/thalamus GMV and AUDIT score.

We derived for individual subjects the average GMV each for the right posterior insula and left thalamus, and performed a single-level mediation analysis. Because there were a total of four models, we examined the results with an alpha of $0.05/4 = 0.0125$ to guard against false positive for each path coefficient. Fig. 3 summarizes the results. In women, GP fully mediated the correlation between the GMV of right posterior insula and AUDIT score ($p = 0.00142$, path $a \times b$). In contrast, AUDIT score did not mediate the correlation between GP and insula GMV ($p = 0.53056$, path $a \times b$). That is, in confirmation of the second hypothesis, insula GMV may represent a neural correlate that dispose individuals to higher alcohol expectancy and, consequently, problem drinking. In women and men combined, BI × GP fully mediated the correlation between the GMV of left thalamus and AUDIT score ($p = 0.00043$, path $a \times b$). In contrast, AUDIT score only marginally mediated the correlation between BI × GP and thalamus GMV ($p = 0.02237$, path $a \times b$). Again, in confirmation of the second hypothesis, thalamus GMV may represent a neural correlate that dispose individuals to the interacting effects of higher impulsivity and alcohol expectancy and problem drinking as a consequence.

4. Discussion

The current study showed that alcohol expectancy best predicted problem drinking in women, whereas in men as well as in the combined group alcohol expectancy and impulsivity interacted to best predict problem drinking. Alcohol expectancy was associated with decreased gray matter volume (GMV) of the right posterior insula in women and

the interaction of alcohol expectancy and impulsivity was associated with decreased GMV of the left thalamus in women and men combined and in men alone, albeit less significantly. Mediation analyses showed that these risk factors mediated the correlation between GMV and problem drinking and models where GMV resulted from problem drinking were not supported. These new findings reveal distinct psychological factors that dispose men and women to problem drinking.

1. Insula and alcohol misuse

Higher global positive alcohol expectancy (GP) was associated with diminished GMV of the right posterior insula and mediated the correlation between insula GMV and problem drinking, as indexed by the AUDIT score, in women.

The insula is a key structure in the neural circuits that support addictive behavior (Koob and Volkow, 2016). Both natural and drug reward cues evoked activation in the insula (Noori et al., 2016). In rodents inactivation of the caudal insular cortex decreased operant responding for alcohol along with a corresponding decrease in oral alcohol intake (Pushparaj and Le Foll, 2015). In human brain imaging GMVs were significantly smaller among heavy as compared to light drinkers and in individuals with alcohol use disorders as compared to control participants in a number of cortical structures including the posterior insula ($x = 47$, $y = -1$, $z = -14$; $x = -54$, $y = -4$, $z = 10$; and $x = 56$, $y = 0$, $z = 8$) (Heikkinen et al., 2016; Yang et al., 2016). Another study demonstrated significant negative associations between alcohol use disorder severity and GMV throughout temporal, parietal, frontal, and occipital lobes (Thayer et al., 2016). Of relevance to the current findings, a specific age by alcohol use interaction was observed for volume of the right anterior insula ($x = 26$, $y = 20$, $z = -2$), and significant negative associations between heavy alcohol use and GMVs were observed as early as 18–25 years. These findings support the hypothesis that alcohol has deleterious effects on global and regional GM above and beyond age, and that regional associations emerge in early adulthood. However, it was not clear from the latter studies whether the differences in GMV reflect a consequence of chronic alcohol consumption or a neural signature of individual's vulnerability to alcohol misuse. The current findings suggest that in this cohort of light to moderate female social drinkers, insula GMV likely represents a risk neural phenotype rather than an outcome of alcohol consumption. Further, how anterior versus posterior insula contributes to the risk processes of problem drinking

remains to be investigated.

Whereas the bulk of imaging work focuses on characterizing cerebral structural changes as a result of alcohol use, a few studies investigated these differences as a risk factor for alcohol and substance misuse. For instance, a recent work examined the structural brain correlates of sensation seeking and impulsivity and revealed links between sensation seeking and reduced cortical thickness localized to regions implicated in cognitive control (Holmes et al., 2016). Further, the observed associations were evident in participants without a history of alcohol use and predicted heightened alcohol use in an independent cohort, suggesting that cerebral structural variability is potentially associated with risk for alcohol misuse in healthy populations. In another study reduced cortical thickness in the left superior frontal gyrus, in association with trait impulsivity, preceded substance use in adolescents (Schilling et al., 2013). Frontal cortical thinning and blunted white matter development predicted initiation of alcohol use at two years of follow-up in adolescents who had no experience with alcohol at baseline (Luciana et al., 2013). Thus, the current findings add to this literature by identifying the structural brain correlate of alcohol expectancy and alcohol expectancy as a mediator of problem drinking in female social drinkers.

On the other hand, although the mediation analysis did not support changes in insula GMV as a result of alcohol use, the findings did not rule out the influence of prolonged and heavy alcohol use on the structure of insula. In rodents, alcohol exposure leads to changes in the extracellular matrix in the brain, with perineuronal nets (PNs) enclosing subpopulations of neurons in the cortex, and binge alcohol consumption caused a significant increase in PNs in the insula (Chen et al., 2015). The latter along with human studies discussed earlier support the influence of alcohol use on insula structure. It is conceivable that alcohol use may influence the GMV of the insula, increase alcohol expectancy, and perpetuate the etiological processes of alcohol misuse.

2. Thalamus and alcohol misuse

We also showed that GP interacts with Barratt impulsivity (BI) to predict problem drinking in men as well as in men and women combined. Higher interaction of GP and BI (BI × GP) was associated with diminished GMV of the left thalamus and mediated the correlation between thalamus GMV and problem drinking.

Numerous imaging studies reported functional (George et al., 2001; Shokri-Kojori et al., 2016; Wrase et al., 2007) and structural (Kong et al., 2012; Pitel et al., 2015; Sullivan et al., 2003) thalamic changes in alcohol addicts. In our previous fMRI study of social drinkers, higher AUDIT score was correlated with impaired inhibition and diminished responses in the cerebellum, thalamus, frontal and parietal regions, independent of years of alcohol use (Hu et al., 2016). Many other studies specifically support a role of the thalamus in impulsivity related symptomatology in neuropsychiatric illnesses including ADHD and addiction (Bailey and Joyce, 2015; Fassbender et al., 2015; Hu et al., 2015; Hu et al., 2016; Joseph et al., 2015; Kose et al., 2015; Li et al., 2010; Zhang et al., 2016). In particular, changes in thalamic GMVs have been noted in various clinical conditions that implicate impulsivity. For instance, GMVs of brain regions including the thalamus mediated the effects of early life adversities on antisocial behavior (Mackey et al., 2016). Thalamic volume was significantly smaller in marijuana users compared to non-users and associated with greater non-planning and overall impulsivity (Mashhoon et al., 2015). In patients with psychotic disorders suicidal behavior was associated with reduced GMV in cortical and subcortical structures including the left thalamus (Giakoumatos et al., 2013). In magnetic resonance spectroscopic imaging, marijuana users exhibited significantly reduced myo-Inositol levels in the left thalamus, relative to non-using participants, in association with elevated cognitive impulsivity as assessed by BIS-11 (Mashhoon et al., 2013). Reductions in myo-Inositol levels are sugges-

tive of regional glial loss, which can lead to altered regional neurotransmission and GMV reduction (Gispert et al., 2016; Rajkowska and Miguel-Hidalgo, 2007).

The thalamus is also implicated in psychological processes closely related to alcohol expectancy, such as cue-elicited craving (see (Jasinska et al., 2014) for a review). In individuals with variant frontotemporal dementia, GMV reduction in the basal ganglia, insula, and thalamus was associated with excessive food, drug, and sex seeking behavior (Perry et al., 2014). However, no studies to our knowledge has examined the role of thalamic GVM in these risk processes of problem drinking.

Questions arise whether reduced thalamic volume reflect the effects of chronic alcohol consumption or an individual risk marker for alcohol misuse. One is to note that despite a large number of studies reporting reduction in thalamic GMV in alcohol dependence (Yang et al., 2016), other work, including a meta-analysis of close to 296 cases and 359 controls, failed to reveal these changes (Cardenas et al., 2011; Xiao et al., 2015). It is possible that thalamic volume reduction occurs only in a subpopulations of alcohol dependent individuals but does not reflect a universal outcome in association with chronic alcohol use. These individual differences may be central to our understanding of the cerebral manifestations of problem drinking. In support, a longitudinal study showed that smaller volume of bilateral thalamus at treatment entry is related to relapse to heavy alcohol consumption; the cerebellum, striatum, and cingulate gyrus but not the thalamus recovered in GMV during abstinence (Segobin et al., 2014). Further, compared to controls, at-risk adolescents with a positive family history of alcohol abuse demonstrated significantly smaller volumes of the thalamus and other cortical and subcortical structures in association with externalizing symptoms scores (Benegal et al., 2007). In animal work, VBM showed that reduced GMV in the thalamus, ventral tegmental area, insular and cingulate cortex in alcohol-naïve Marchigian-Sardinian (msP) alcohol-preferring rats, as compared to control rats, establishing a cerebral structural risk factor for excessive alcohol consumption (Gozzi et al., 2013). Together, there is evidence to support thalamus volume as a neural phenotype that disposes individuals to alcohol misuse. The current findings contribute to this thesis by showing that thalamic volume reduction may underlie an interacting role of alcohol expectancy and impulsivity in determining problem drinking.

3. Alcohol misuse and sex differences

Men and women show important differences in the clinical characteristics of drug and alcohol use behaviors. Consistent with previous studies, men showed higher AUDIT score than women, likely reflecting sex differences in the complex interactions between alcohol pharmacokinetics, socio-cultural factors, and a myriad of psychological processes that contribute to problem drinking (Erol and Karpyak, 2015). The current results showed that impulsivity is related to problem drinking in men but not in women (Fig. 1). A direct test of slope difference in the linear regression of AUDIT against BIS score confirmed the sex difference. On the other hand, positive alcohol expectancy is associated with problem drinking in both men and women. Affirming these associations, general linear models showed that alcohol expectancy and the interaction of alcohol expectancy and impulsivity best predicted problem drinking in women and men, respectively. These findings are consistent with sex differences in the role of behavioral impulsivity as a risk factor in binge drinking (Adan et al., 2016) and use of caffeinated alcoholic beverages in college students (Amlung et al., 2013). Notably, in contrast, some studies of dependent individuals showed that women tend to have higher impulsivity compared to men (Lejuez et al., 2007; Perry et al., 2013; Winhusen and Lewis, 2013). It is plausible that, compared to men, women are more susceptible to the effects of chronic alcohol consumption and exhibited impaired frontal functioning and greater impulsivity after prolonged alcohol use (Nederkoorn et al., 2009). These considerations also speak to the

importance of distinguishing early and dependent use in characterizing the clinical and neural profiles of drug and alcohol using populations.

4. Limitations of the study and conclusions

This is cross-sectional study and the conclusion that insula and thalamus GMV disposes individuals to problem drinking needs to be confirmed in a longitudinal setting. Both impulsivity and alcohol expectancy can be further explored with functional imaging and it remains to be seen whether the insula and thalamus are functionally related to these risk factors for alcohol misuse. Although both linear regression and GLM support alcohol expectancy as a primary risk variable in women and the interaction of alcohol expectancy and impulsivity in men and in the combined sample, the BIC and AIC values of the second best models are fairly close. Again, a longitudinal study would help clarify the roles of these risk variables in the development of problem drinking and how these risk processes differ between male and female drinkers. In addition, the role of negative alcohol expectancy in problem drinking needs to be examined in future work, particularly in the context of interaction with avoidance personality traits. Further, impulsivity was assessed with self report, and it remains to be seen how behavioral measures of impulsivity, as such performance outcomes of the stop signal task (Bednarski et al., 2012; Hendrick et al., 2010; Ide and Li, 2011), may by itself or in interaction with alcohol expectancy contribute to problem drinking.

In conclusion, the current findings demonstrate that in women alone alcohol expectancy best predicted problem drinking whereas in men and in men and women combined, the interaction of alcohol expectancy and Barratt impulsivity interacts to determine problem drinking. Reduction in right posterior insula and left thalamus GMV are potential neural phenotypes of these risk factors. The current results of cerebral morphometry add to a growing literature on sex differences in the psychological processes related to alcohol use and in the effects of alcohol use on brain structures.

Authors contribution

Ide and Zhornitsky participated in the design of the study, data analyses and writing of the manuscript. Zhang and Hu participated in the design of the study and data collection. Krystal and Li participated in the design of the study and writing of the manuscript.

Conflicts of interest

We have no financial interests to disclose for the current study.

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