Binge drinking is associated with higher cortisol and lower hippocampal and prefrontal gray matter volume: Prospective association with future alcohol intake

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ABSTRACT

Background: Cortisol is a significant driver of the biological stress response that is potently activated by acute alcohol intake and increased with binge drinking. Binge drinking is associated with negative social and health consequences and risk of developing alcohol use disorder (AUD). Both cortisol levels and AUD are also associated with changes in hippocampal and prefrontal regions. However, no previous research has assessed structural gray matter volume (GMV) and cortisol concurrently to examine BD effects on hippocampal and prefrontal GMV and cortisol, and their prospective relationship to future alcohol intake.

Methods: Individuals who reported binge drinking (BD: N = 55) and demographically matched non-binge moderate drinkers (MD: N = 58) were enrolled and scanned using high-resolution structural MRI. Whole brain voxel-based morphometry was used to quantify regional GMV. In a second phase, 65% of the sample volunteered to participate in prospective daily assessment of alcohol intake for 30 days post-scanning.

Results: Relative to MD, BD showed significantly higher cortisol and smaller GMV in regions including hippocampus, dorsal lateral prefrontal cortex (dlPFC), prefrontal and supplementary motor, primary sensory and posterior parietal cortex (FWE, p < 0.05). GMV in bilateral dlPFC and motor cortices were negatively associated with cortisol levels, and smaller GMV in multiple PFC regions was associated with more subsequent drinking days in BD.

Conclusion: These findings indicate neuroendocrine and structural dysregulation associated with BD relative to MD. Notably, BD-associated lower GMV regions were those involved in stress, memory and cognitive control, with lower GMV in cognitive control and motor regions also predicting higher levels of future alcohol intake in BD.

1. Introduction

Binge drinking is hazardous to health (Grant et al., 2017) and responsible for almost half (46%) of alcohol-related deaths (NIAAA. Drinking, 2021). The National Institute of Alcohol Use and Alcohol Addiction (NIAAA) defines binge drinking as a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to 0.08 percent - or 0.08 g of alcohol per deciliter - or higher, which corresponds to consuming 5 or more drinks in men, or 4 or more drinks in women over a 2-h period. In addition, drinking 15 or more drinks/week for men and 8 or more per week in women is also associated with serious health problems such as cancers (NIAAA. Drinking, 2021; Okoro et al., 2004; Siqueira et al., 2015), risk of developing alcohol use disorder (AUD) (Siqueira et al., 2015; Chassin et al., 2002) and cognitive deficits in attention and working memory (Crego et al., 2009). This risky pattern of alcohol consumption has a bidirectional relationship with stress: stress, trauma and socioeconomic hardships are associated with higher levels of binge drinking (Kanny et al., 2020; Grzywacz and Almeida, 2008), and drinking itself triggers the body's stress response. Specifically, acute alcohol intake stimulates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in cortisol release (Blaine and Sinha, 2017). Regular binge levels of alcohol consumption results in dysregulation of this

neuroendocrine circuit, including neuroendocrine tolerance and blunted cortisol responses to stress (Blaine et al., 2019; Lee and Rivier, 1997; Richardson et al., 2008). These findings underscore the need to understand the neuropathology underlying cortisol and alcohol misuse.

Past work has highlighted common neural mechanisms sensitive to both alcohol and cortisol. For example, reduced hippocampal gray matter volume (GMV) is associated with elevated basal cortisol levels (Lupien et al., 1998), and lower GMV in the hippocampus has been reported in adolescent and young binge drinkers (Meda et al., 2018; Scaife and Duka, 2009). Other regions with a high density of cortisol receptors, such as the amygdala, as well as key regulatory and behavioral control regions of prefrontal cortex (Gropper et al., 2016; Hermens et al., 2013) have also been shown to have lower GMV in AUD adults (Grace et al., 2021; Mackey et al., 2019). Consistent with the bidirectional interactions between stress and drinking, these regions also play key roles in regulating the stress cortisol response (Herman et al., 2016; Sinha et al., 2016). Nevertheless, the link between whole brain GMV and concurrent cortisol levels in binge vs non-binge drinkers, or the potential for these alterations to predict subsequent real-world alcohol intake, remains unclear.

Thus, the current study systematically compared individuals who binge drink (BD) to those who are non-binge moderate drinkers (MD) to evaluate potential differences in brain morphology and morning cortisol levels. Participants were carefully assessed for recent alcohol consumption and categorized into BD and MD groups utilizing the NIH-NIAAA definition (NIAAA. Drinking, 2021) of binge versus non-binge drinking levels, and also participated in a structural magnetic resonance imaging (sMRI) scan to measure whole brain GMV along with concurrent fasting morning cortisol sampling. Additionally, a large subset of participants enrolled in a follow-up phase post scanning to prospectively report their daily alcohol intake for 30 days after the MRI scan.

Using this approach, the following specific hypotheses were tested. First, consistent with past findings, we hypothesized that BD would have higher fasting morning cortisol levels than MD (Blaine et al., 2019). Second, we hypothesized that BD would have lower GMV in the hippocampus and medial, lateral and motor prefrontal cortices. Integrating these findings, our third hypothesis was that higher cortisol levels will be predictive of lower GMV in these regions for BD. Finally, utilizing the follow-up phase, we hypothesized that lower GMV in our *a priori* regions of interest (namely, hippocampus and medial, lateral and motor prefrontal cortices) would have functional significance for BD, such that they would be prospectively associated with future higher alcohol intake for these individuals.

2. Materials and methods

2.1. Participants

Participants were healthy community adults recruited from the greater New Haven, Connecticut area via flyers, radio and social media advertisements calling for individuals who 'liked beer'. Participants were healthy, non-substance using (except for alcohol), beer drinking men and women (N = 113, 56 males/57 females) aged 18–57 years and categorized into the binge drinking (BD) and moderate non-binge drinking (MD) groups using NIAAA specified criteria (NIAAA. Drinking, 2021) and with evidence of binge drinking episodes (five or more drinks in men; four or more drinks in women; per drinking episode) for the BD and no episodes of binge drinking for the MD group. Young to middle aged individuals aged 18–57 years old were included as recent estimates show significant growth in prevalence of binge drinking in this age range (Binge, 2019). Six of the BD and 3 of the MD group reported using cigarettes recreationally, but none were daily users. In addition, 15 out of 57 women were taking oral contraceptives. Participants were excluded if they had a history of psychotic disorders, current pregnancy, any nonremovable metal in their bodies, a history of loss of consciousness for longer than 30 min and any current other medical, psychiatric, or substance use disorder including alcohol use disorder (AUD) and taking medications for such illnesses. The BD and MD groups were not significantly different on sex, race, IQ, education, nicotine use and handedness, however, they differed in age, with MD older than BD (Table 1) and thus age was a covariate in all analyses. The follow-up real-world drinking assessment phase included 43 BD and 26 MD from the original sample (61%; N = 69, 34 males/35 females) (see Table 1). All participants provided written informed consent to participate in the study, and all procedures approved by the Human Investigation Committee of the Yale University School of Medicine.

2.2. Screening and intake procedures

All participants completed interviews and questionnaires assessing medical, demographic, and substance use characteristics as well as to determine psychiatric diagnoses (using the Structured Clinical Interview for the Diagnostic and Statistical Manual IV-TR (First et al., 1995)). Participant's drinking history was assessed using the Cahalan Quantity Frequency Variability Index (QFVI) (Cahalan et al., 1969; Babor et al., 2011) which assesses alcohol intake patterns, including typical and maximum frequency and amounts of alcohol intake, types of alcohol usually consumed and time period of specific recent pattern of intake. At all appointments including the MRI scan day, alcohol and carbon

Table 1
Participants.

Characteristics	Phase 1		Phase 2	
	Binge Drinkers (BD)	Moderate Drinkers (MD)	BD	MD
	(N = 55)	(N = 58)	(N = 43)	(N = 26)
	Mean [SD]	Mean [SD]	Mean [SD]	Mean [SD]
Age (years)[a]	26.45 [8.27]	31.4 [10.45]	24.98 [5.78]	29.27 [9.46]
Education (years)	15.4 [1.94]	16.1 [2.3]	15.30 [1.95]	15.94 [2.18]
Shipley IQ estimate	115.45 [5.58]	114.05 [6.87]	115.72 [5.07]	115.4 [5.84]
Years of alcohol use	11.05 [35.39]	6.15 [8.35]	11.5 [40.11]	5.24 [8.5]
Days of alcohol use/ month[b]	10.04 [6.14]	5.79 [5.79]	10.63 [6.39]	6.7 [5.93]
Amount of drinks/ occasion[b]	4.04 [4.9]	2.72 [2.91]	4.44 [5.44]	2.88 [2.88]
Days since last drink (Prescan)[c]	5.15 [3.75]	31.85 [76.55]	4.68 [2.02]	34 [72.05]
	N [%]	N [%]	N [%]	N [%]
Sex (Male)	26 [47.24]	30 [51.72]	21 [38.18]	13 [50]
Race (Caucasian)	35 [63.64]	32 [55.17]	30 [69.77]	18 [69.23]
Smoking status (Smoker)	6 [10.91]	3 [5.17]	5 [10.82]	3 [5.2]
Lifetime mood disorder	9 [16.36]	9 [15.52]	8 [18.6]	1 [3.85]
Lifetime anxiety disorder	5 [9.1]	10 17.24]	3 [8.98]	4 [15.38]
Alcohol use (smartphone monitoring period)				
			Mean [SD]	Mean [SD]
Heavy drinking days[d]			4.91 [4.05]	1.16 [2.45]
Total number of drinking days[d]			10.69 [5.86]	5.82 [6.78]

[a] Binge drinkers < Moderate drinkers, Phase 1: *p* = 0.006; Phase 2: *p* = 0.022.
[b] Binge drinkers > Moderate drinkers, Phase 1: *p* < 0.001; Phase 2: *p* = 0.018.
[c] Binge drinkers < Moderate drinkers, Phase 1: *p* = 0.006; Phase 2: *p* = 0.012.
[d] Binge drinkers > Moderate drinkers, Phase 2: p < 0.001.

monoxide breathalyzers and urine toxicology screens confirmed that participants were in an alcohol, nicotine and drug-free state. Participants were also asked to refrain from alcohol use prior to the MRI scan day for 24–48 h. MRI scan days for women was not scheduled during ovulation days, assessed via self-report and based on 28–30 day cycles.

2.3. Cortisol measurement

All participants arrived at the Yale Magnetic Resonance Research Center at 7:00 a.m. after overnight fasting to control for diurnal cortisol dynamics (Hansen et al., 2008). An intravenous line was inserted in the nondominant forearm for blood draws to obtain repeated plasma sampling at four timepoints, at pre-scan after IV insertion (7:15 a.m.), during the scan at 8:30 and 9:30 a.m. and at end of scan at 10:00 a.m. during the 2-h MRI scan period. Blood (4 ml per timepoint) was collected in EDTA-coated tubes (BD Biosciences, Franklin Lakes, N.J.). Blood samples were immediately stored on ice, and plasma was separated by centrifugation at 4 °C for 10 min at $1000 \times g$. Aliquots of plasma were stored in polypropylene tubes at −80 °C until assayed. Cortisol levels were assessed via radioimmunoassay at the Yale Center for Clinical Investigation Core Laboratory (Blaine et al., 2020).

2.4. MRI data acquisition and preprocessing

Structural magnetic resonance imaging (sMRI) data were acquired using a high-resolution T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence (voxel size = 1 mm^3, field of view = 256 × 256, TR = 300 msec, TE = 2.46 msec, flip angle = 7°) using two 3-T Siemens Prisma scanners (Siemens, Erlangen, Germany; BD: 53% Prisma A, 47% Prisma B; MD: 56% Prisma A, 44% Prisma B). There were no significant differences in the proportion of subjects from each group for whom data was acquired on different scanners.

Image segmentation (into gray matter, white matter, and cerebrospinal fluid) and registration were conducted using segmentation and the DARTEL registration algorithms (SPM12). By using the segmentation procedure, improvements were given to the registration model as well as including additional tissue probability maps to better model cerebrospinal fluid (CSF) and other nonbrain voxels. DARTEL (Ashburner, 2007) is a high-dimensional and diffeomorphic registration algorithm which has shown excellent performance among registration algorithms (Klein et al., 2009). To provide better initial estimates for segmentation, each image was manually set for space origin to the anterior commissure and aligned with the plane of the anterior and posterior commissures (SPM12 Display). Default settings were used for segmentation and for bias correction, spatial normalization, and segmentation of the original structural images in the same model. A modulation step was used in normalization to ensure the overall tissue amount was not altered. Resulting segmentations of GM were validated visually (Cerasa et al., 2009; Davies et al., 2009) as manual segmentation is considered the gold standard for evaluation of the quality of automated tissue classification (Anbeek et al., 2004; Bouix et al., 2007). In particular, cortical thickness relative to each subject's native space image and to a published report of cortical thickness (Fischl and Dale, 2000) was evaluated. Appropriate face validity was demonstrated by gray matter (GM) segmentation in all images. The first author (SF) performed all the preprocessing steps including image registration and segmentations of gray matter volume described above and manual visualization for quality control while blind to study group. After completing these steps, Dr. Fan was unblinded in order to perform second-level analyses. Additionally, no statistical outliers were identified in the extracted values representing segmented GM, white matter (WM) and CSF tissues.

Following segmentation, single-level GM and WM segments were warped to the space of the mean image averaged from all the study participants and normalized to the Montreal Neurological Institute (MNI) template space using default settings (DARTEL), which include resampling to 1.5 mm^3 voxels (reducing memory demands for the large number of parameters estimated by the registration algorithm). Final outputs were modulated GM segments (1.5 mm^3 voxels) smoothed using an 8-mm Gaussian filter (Rando et al., 2011, 2013a, 2013b). Gaussian smoothing reduces the effects of residual misregistration on potential group differences and reduces departures from normality that may occur at some voxels (Ashburner and Friston, 2000).

2.5. Follow-up phase: post-scan daily diary assessment of alcohol intake over 30 days

A large subgroup of BD (N = 43) and MD (N = 26) (61% of the original sample) participated in a follow-up phase added after study initiation. In this phase, participants reported their daily alcohol intake up to 36 days (50 participants reported drinking data for 30 days while 19 provided daily data for up to 36 days) using a smartphone application (MetricWire, https://metricwire.com/). They were asked to complete the prompt at 5 pm each day. Typically, the participants were asked these questions: 1) "Did you drink alcohol since the last prompt?", 2) "How much did you drink in total? (If they answered "yes" on question 1)", 3) "Did you drink anything yesterday after your last survey; how much did you drink in total?". The amount of alcohol intake per day was calculated as the sum of the amount since the last prompt the day before (Q3) plus total alcohol intake on that day (Q1-2). We used these questions to derive three metrics of real-world drinking behavior reported daily for the 30-day monitoring period. First, to calculate the *average number of alcoholic drinks per day*, which was the sum of alcohol drinks was divided by the number of monitoring days. Second, *number of drinking days* was the total days when alcohol was consumed during the assessment period, and third, *number of heavy drinking days* was the number of days on which binge drinking occurred (5 or more drinks/ occasion in men and 4 or more drinks/occasion in women).

2.6. Data analysis

Between-group differences on demographic, clinical characteristics, baseline and prospective drinking measures as well as basal cortisol levels were examined using IBM SPSS Statistics version 26 (64-bit edition).

All structural MRI images were preprocessed in SPM 12 (see above) and second-level statistical between-group comparisons were conducted using AFNI (version 16.0.09). To test our hypothesis that GMV would differ between BD and MD, a linear mixed-effect (3dLME) model (Chen et al., 2013) was created in AFNI, with whole brain GMV analyzed as a function of Group (BD vs MD) with covariates for age, sex, educational level, and global brain size (i.e., estimated total intracranial volume (TICV), calculated by summing voxel-wise native space GM, WM and CSF segments per subject). To correct for multiple comparisons, we used family-wise error correction determined by Monte Carlo simulation using AFNI's 3dClustSim (bi-sided first-nearest neighbor). A threshold p value of 0.005 was considered statistically significant for whole-brain GMV analysis and an additional family-wise cluster correction of $p = 0.05$ was used.

For post-hoc analyses examining the directionality of associations between cortisol, GMV and future drinking, Bioimage Suite version 35 (Joshi et al., 2011) was utilized with a whole brain significance threshold of $p < 0.005$ and an additional cluster correction $p = 0.05$. Similarly, to test the third and final hypothesis exploring whether high cortisol levels were associated with changes in GMV in BD, and whether cortisol and GMV were associated with future alcohol intake in BD, Bioimage Suite version 35 was used to conduct whole-brain correlation analysis in the BD group at the whole brain significance threshold of $p < 0.005$ and an additional cluster correction of $p = 0.05$ was used.

3. Results

3.1. Participants

Binge and moderate drinkers were not significantly different on sex, race, IQ, education, handedness, and smoking status, as well as lifetime incidence of mood and anxiety disorders. On average, binge drinkers were younger than moderate drinkers, (t(111) = -2.78, $p = 0.003$) (Table 1); accordingly, age and also sex and education were included as covariates in all group differences analyses. As expected, baseline assessment of drinking revealed participants in the BD group had significantly more alcohol drinking days ($p < 0.001$) and consumed more per drinking day ($p < 0.001$). However, the groups did not differ in the number of years of alcohol use (Table 1).

3.2. Participants in the post-scan prospective daily alcohol intake follow-up phase

The subgroup of participants who completed the follow-up phase did not differ significantly from the main cohort in age, sex, years of education, IQ, race, alcohol use variables, proportion of smokers, or lifetime diagnoses of mood disorders. Consistent with baseline group data, BD relative to MD participants who completed the follow up phase also consumed significantly more drinks per day (t(74) = 4.45, $p < 0.001$) and had significantly more drinking days (t(88) = 3.64, $p < 0.001$) and heavy drinking days (t(88) = 5.32, $p < 0.001$) during the 30-day follow-up (Table 1).

3.3. Differences in whole brain GMV by drinking group

Consistent with our hypothesis, we found that individuals in the BD group had significantly lower GMV than MD in regions including bilateral hippocampus, right dlPFC, bilateral motor areas (pre-motor, pre-SMA, SMA), left primary sensory cortex, right angular gyrus, right dorsal parietal central cortex, and bilateral visual cortex (Table 2, and Fig. 1a). No GMV clusters were identified that were significantly higher in BD compared to MD. To ensure that these differences were not driven by other stress-related psychopathology, we ran post-hoc analyses excluding individuals with lifetime mood (N = 18) and anxiety disorders (N = 15) and found that the GMV differences between BD and MD groups remained significant. Sex was included as a factor and there were no sex main effects or interactions in the whole-brain gray matter volume when comparing binge drinkers to moderate drinkers after controlling for sex as one of the confounding variables in our brain imaging model. Furthermore, post-hoc secondary LME analyses assessed whether age differences between drinking groups moderated GMV differences between drinking groups, and we found no significant interactions between age and drinking groups on whole brain GMV (see the Supplemental Methods).

An additional post-hoc exploratory analysis was also conducted to specifically assess sex differences in the GMV differences between BD and MD groups. Drinking Group effects were different in males and females in the regions of bilateral amygdala and hippocampus and left SMA. The significant interactions were driven by lower GMV in the right hippocampus and left SMA in BD males relative to MD males, and lower GMV in the left hippocampus and right hippocampus extended to the amygdala area in BD females relative to MD females (see the Supplemental Methods, Results, Table S1 and Fig. S1).

3.4. Higher fasting morning cortisol in binge drinking group

Cortisol levels dropped significantly during the 7:00am-10:00am scan window (main effect Time: F(3) = 37.39, $p < 0.001$), as expected based on morning drop in cortisol known to occur in the 24-h diurnal variation of cortisol levels (Blaine et al., 2019) (Fig. 1b). Notably, cortisol levels differed significantly between BD and MD (main effect Drinking Group: F(1) = 5.79, $p = 0.018$; Drinking Group x Time: F(7) = 17.47, $p < 0.001$). Post-hoc independent samples t-tests revealed that BD had significantly elevated cortisol levels at 8:30 a.m. (t = 2.70, $p = 0.011$) and 9:30 a.m. (t = 2.43, $p = 0.023$), but not at the 7:15 a.m. and 10:00 a.m. timepoints (Fig. 1b). These higher cortisol levels in BD were not significantly associated with recent past alcohol use. Also, there were no sex differences in the cortisol elevations seen in the BD vs. MD at the 8:30 and 9:30 a.m. timepoints, however female BD were significantly higher than the male BD group at the first 7:15 a.m. timepoint (p < 0.05), and no significant sex differences were seen in the MD group.

3.5. Relationship between altered GMV and concurrent high cortisol levels in BD

We next tested whether the elevated cortisol levels in BD were associated with differences in whole-brain GMV within this cohort. Lower GMV in bilateral dlPFC, premotor and SMA were significantly associated with higher cortisol levels at the 8:30 a.m. (whole brain corrected, FWE p < 0.05) (Fig. 1c). Post-hoc secondary analyses were performed to examine the role of sex in the association between brain GMV and cortisol levels and no significant sex-specific associations were observed. Notably, the cortisol associated SMA GMV was at a different location to the SMA clusters observed in the sex X drinking groups interaction effect (see the Supplemental Methods, Table S1 and Fig. S1). Additionally, we observed no significant association between hippocampal GMV and cortisol in the BD group.

3.6. Associations between lower GMV and higher future alcohol intake in BD

Finally, we tested the predictive validity of GMV changes in BD by assessing its impact on levels of future alcohol intake. Using the
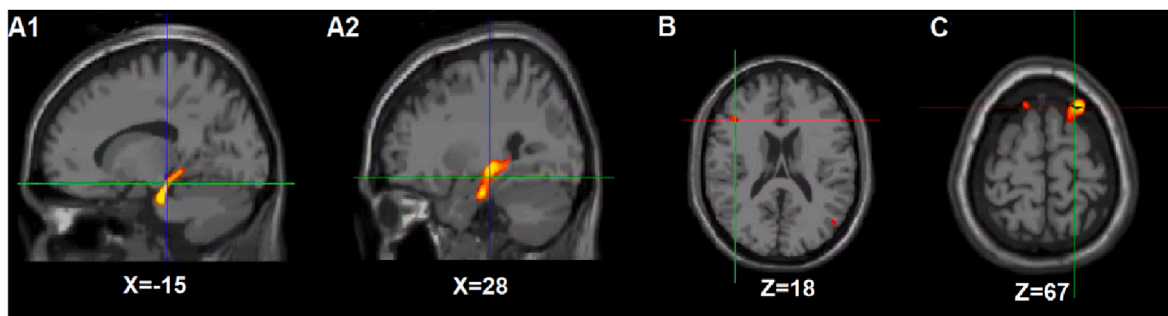
Table 2
Group differences in GMV (Binge drinkers < Moderate drinkers)[a,b].

Cluster[b]	Lateralization	Broadman Area	Cluster Size	MNI Coordinates		
				x	y	z
Dorsal Lateral Prefrontal Cortex	Right	46	62	42	−27	19.5
Hippocampus Extended Parahippocampal Gyrus	Left	36	936	−28.5	13.5	−30
	Right	36	1416	31.5	22.5	−15
Pre-Motor, Pre and Supplementary Motor Area	Left	6	445	−16.5	−15	61.5
	Right	6	90	15	−25	72
Primary Sensory Cortex	Left	1	185	−39	42	58
Angular Gyrus	Right	40	201	33	49.5	43.5
Dorsal Parietal Central Cortex	Right	31	289	4.5	58.5	45
Visual Cortex	Left	19	68	−43.5	67.5	19.5
	Right	19	189	46.5	72	0

[b] Family-wise error rate cluster p value of 0.05 (whole brain p < 0.005 threshold).
[a] Using the Nonlinear Yale MNI to Talairach Conversion Algorithm (Talairach, 1988).

Fig. 1a. Whole brain GMV analyses showing clusters with lower gray matter volume in binge vs moderate drinkers in the hippocampal and prefrontal areas.
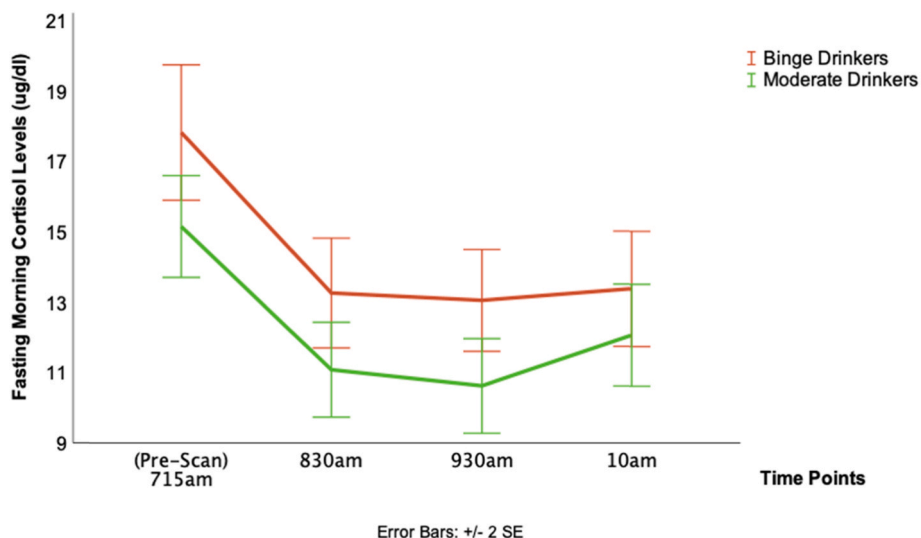

Fig. 1b. Differences between binge and moderate drinkers in fasting morning cortisol levels.
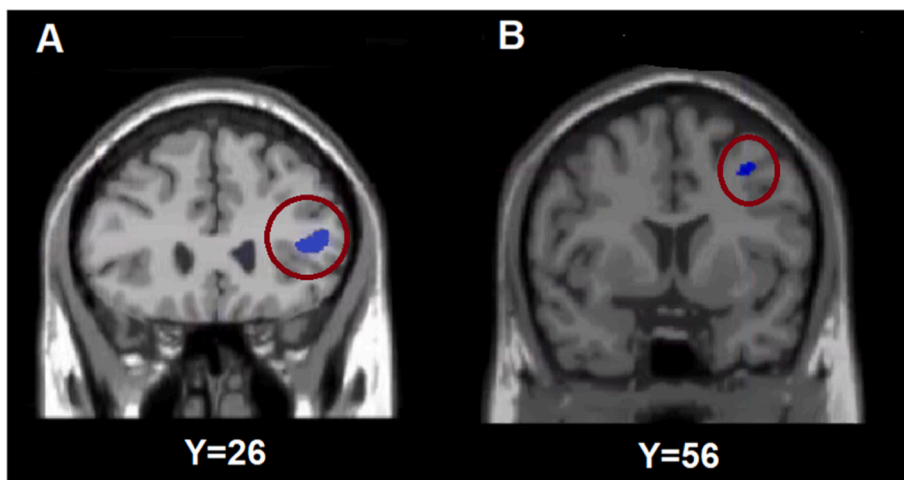

Fig. 1c. Associations between cortisol and gray matter volume in binge drinkers only.

prospective follow-up phase drinking data, we examined relationships between whole brain GMV and future daily drinking across a subsequent 30-day period. Lower GMV in the left orbito-frontal cortex (OFC)/amygdala, left ventral anterior cingulate cortex, bilateral dlPFC, left dorsal ACC, medial PFC, left insular, right premotor/supplementary motor area, bilateral angular gyrus, right primary visual cortex, and right visual motor cortex were significantly associated with greater number of future any drinking days in BD (Table 3, Fig. 2a). Also, lower

GMV in bilateral OFC, left dorsal ACC, bilateral dlPFC, left anterior PFC, premotor and bilateral supplementary motor area, right primary motor area, bilateral insular, right temporal pole and bilateral visual cortex was also associated with higher number of future heavy drinking days in BD (Table 3, Fig. 2b-2c). There were no significant associations with amounts of alcohol intake that met the corrected whole brain threshold. Post-hoc secondary analyses also revealed no significant associations between GMV and future drinking days in the MD group.

Table 3

Associations between GMV and future drinking behavior (Binge drinkers only) [a].

Cluster[b]	Lateralization	Broadman Area	Cluster Size	MNI Coordinates		
				x	y	z
Clusters Associated With Number of Drinking Days						
Orbito Frontal Cortex/Amygdala	Left	11	678	−11	27	−18
Ventral Anterior Cingulate Cortex	Left	24	68	−11	46	0
Dorsal Lateral Prefrontal Cortex	Left	9	64	−22	47	32
Dorsal Lateral Prefrontal Cortex	Left	9	89	−45	33	32
Dorsal Lateral Prefrontal Cortex	Right	9	85	48	28	32
Dorsal Lateral Prefrontal Cortex	Right	46	1453	44	44	14
Dorsal Anterior Cingulate Cortex	Left	32	1861	−11	28	23
Medial Prefrontal Cortex	Right	32	469	2	−16	53
Insular	Left	13	343	−33	15	−15
Premotor/Supplementary Motor	Right	6	89	24	2	63
Angular Gyrus	Left	39	765	−34	−64	39
Angular Gyrus	Right	39	879	40	−44	35
Primary Visual Cortex	Right	17	1556	2	−78	5
Visual Motor Cortex	Right	7	1895	33	−44	54
Clusters Associated With Heavy Drinking Days						
Orbtio Frontal Cortex	Left	11	699	−9	35	−17
Orbito Frontal Cortex	Right	11	987	25	35	−17
Orbito Frontal Cortex	Right	11	78	30	59	−17
Dorsal Anterior Cingulate	Left	32	2342	−9	35	19
Dorsal Lateral Prefrontal Cortex	Left	9	925	−34	41	46
Dorsal Lateral Prefrontal Cortex	Right	9	762	9	50	46
Anterior Prefrontal Cortex	Left	10	599	−2	59	−5
Premotor/Supplementary Motor	Left	6	790	−10	−24	79
Premotor/Supplementary Motor	Left	6	1892	−3	8	69
Premotor/Supplementary Motor	Right	6	574	5	−24	51
Primary Motor Area	Right	4	823	40	−23	68
Insular	Left	13	1987	−42	11	−17
Insular	Right	13	622	40	17	−9
Temporal Pole	Right	38	2376	25	10	−40
Visual Cortex	Left	18	102	−17	−85	−8
Visual Cortex	Right	18	87	20	−78	−8

[b]Family-wise error rate cluster p value of 0.05 (whole brain threshold of $p < 0.005$).

[a] Using the Nonlinear Yale MNI to Talairach Conversion Algorithm (Talairach, 1988).
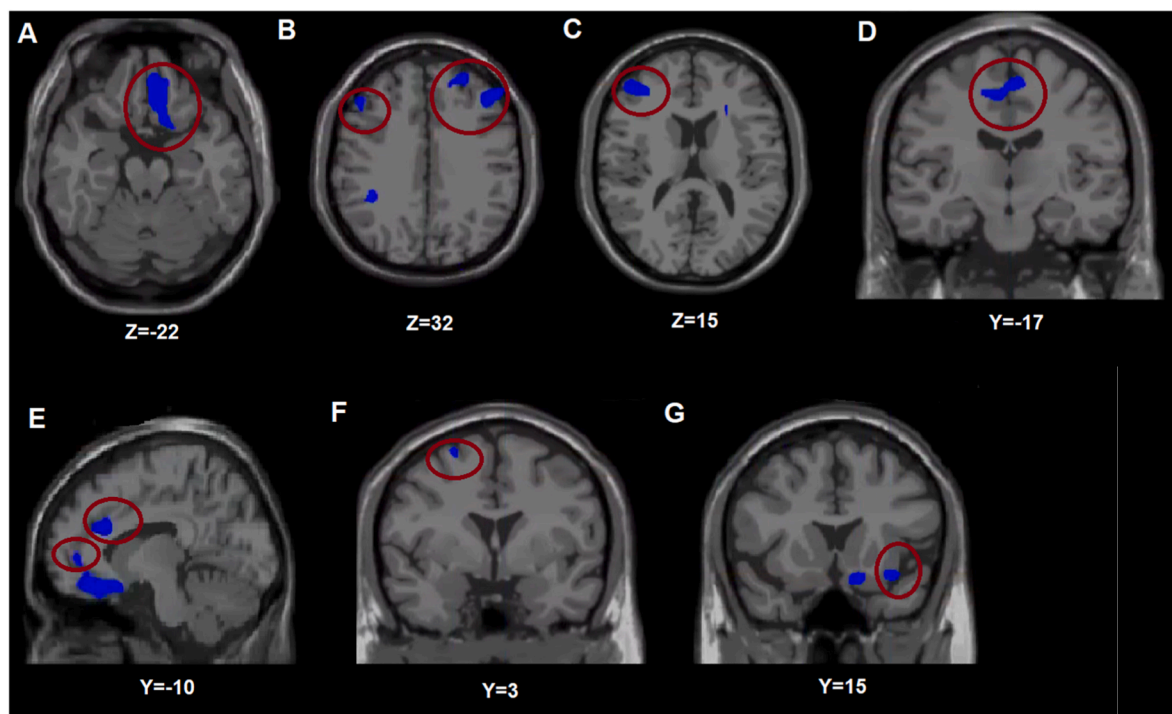
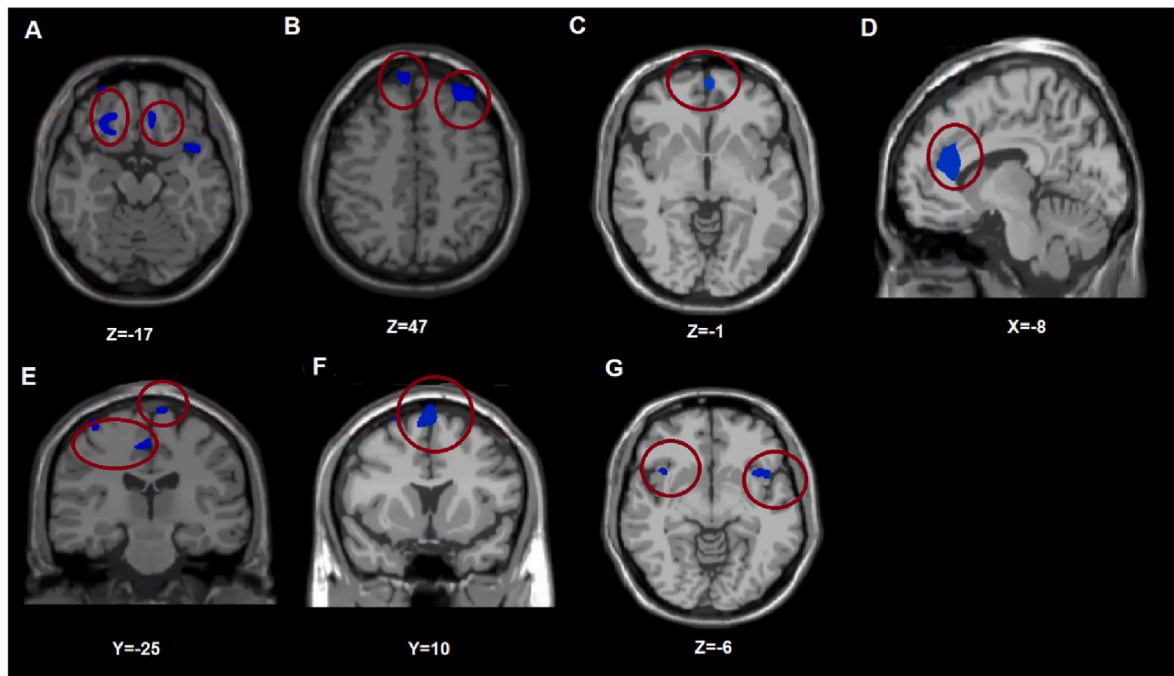**Fig. 2a.** Lower GMV Predicts Future Number of Drinking days in BD.

Fig. 2b. Lower GMV Predicts Future Number of Heavy Drinking days in BD.
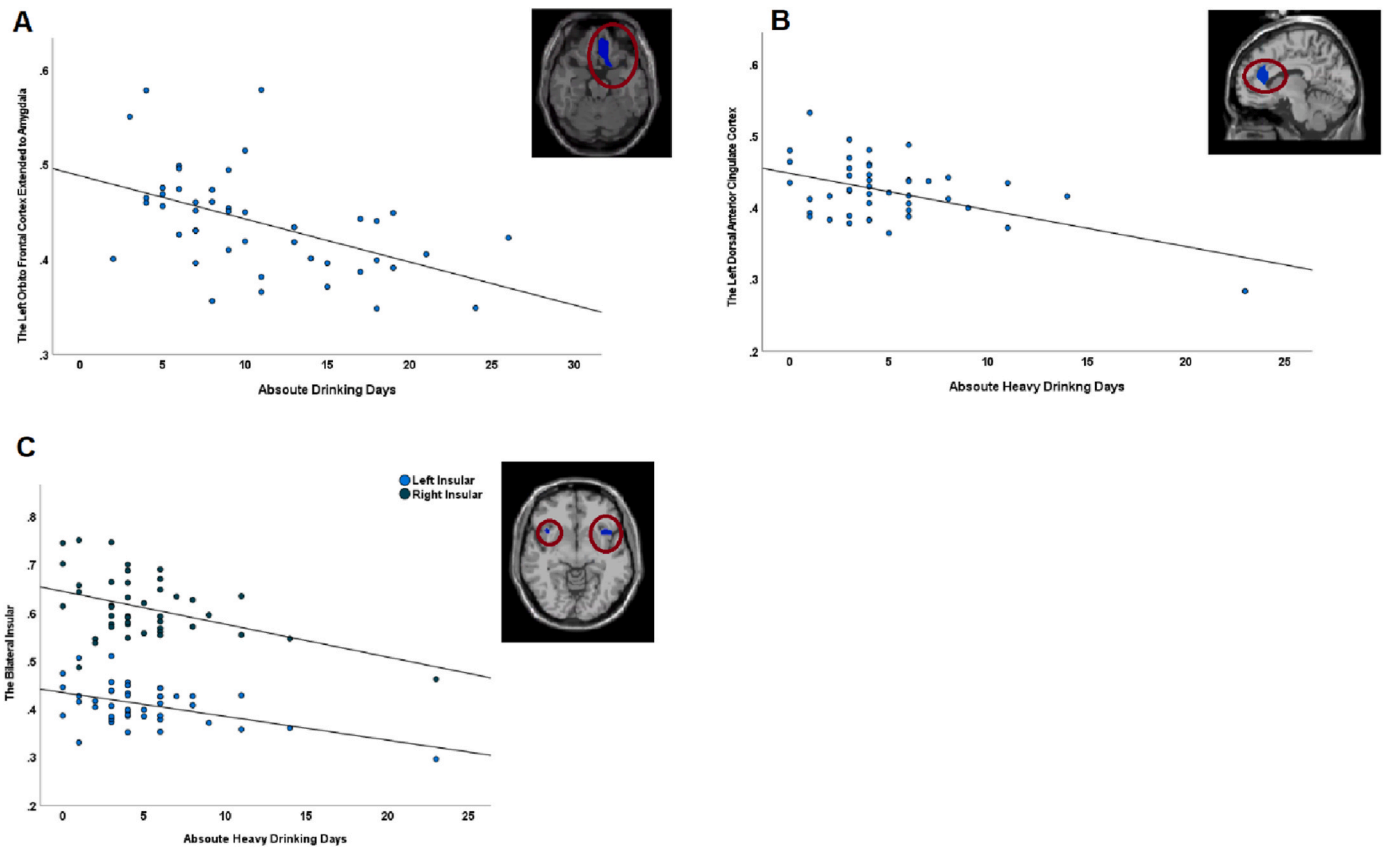

Fig. 2c. Scatterplots of select regions from Fig. 2b showing associations between lower GMV in the orbito frontal cortex extended to the amygdala, dorsal anterior cingulate cortex, bilateral insular and higher future drinking behavior in BD.

4. Discussion

Stress both promotes and is modulated by risky drinking behavior (Blaine and Sinha, 2017), underscoring a need to understand common neural mechanisms supporting these processes. Here we investigated alterations in brain structure (whole brain gray matter volume, GMV) and stress hormone levels (cortisol) associated with binge drinking. We found that binge levels of alcohol intake were associated with lower

GMV in stress regulatory regions and higher cortisol levels, and that these GMV differences prospectively predicted higher future alcohol intake among binge drinkers.

Consistent with past results (Blaine and Sinha, 2017; Blaine et al., 2019), we found that binge drinkers (BD) had higher cortisol levels than moderate drinkers (MD). Active drinking is known to increase cortisol levels (Blaine et al., 2019; Wand and Dobs, 1991), and higher basal cortisol levels have been associated with blunted stress responses among patients with alcohol use disorder (AUD) (Sinha et al., 2009). The current results provide further support that HPA axis changes may play a role in increasing AUD risk among binge alcohol users who do not yet meet diagnostic criteria for AUD, and also may influence their continued use and alcohol relapse risk (Sinha et al., 2011). Among BD, higher cortisol levels showed non-sex specific associations with lower GMV in dorsolateral prefrontal cortex (dlPFC) and supplementary motor area (SMA). The dlPFC is known to be sensitive to stress hormones (Arnsten, 2009) and plays a key role in emotion regulation (Ochsner et al., 2012), while the SMA is involved in impulse control and response inhibition (Li et al., 2006). Consistent with this role of the dlPFC and SMA, we have also previously shown that higher cortisol is associated lower PFC function, suggestive of lower stress coping that is associated with higher binge levels of alcohol intake (Sinha et al., 2016).

In addition to cortisol-related differences in brain structure, we also observed significant group-level differences in GMV between BD and MD. Specifically, BD had lower GMV in SMA, dlPFC and hippocampus. This is consistent with and extends past research in adolescent BD and adult AUD (Grace et al., 2021; Yang et al., 2016; Hermens and Lagopoulos, 2013, 2018; Wilson et al., 2017). For example, white matter structural deficits were reported in sensory and motor cortices among binge drinking young adults (Smith et al., 2017), and disrupted structural/functional connectivity between these sensory and motor areas and fronto-limbic regions has been reported in adult drinkers (Crespi et al., 2019; Zhornitsky et al., 2018). Similarly, smaller GMV in dlPFC has been consistently reported in adolescents and young adults engaging in binge drinking behaviors as well as adults with AUD (Gropper et al., 2016; Yang et al., 2016; Hermens and Lagopoulos, 2013, 2018; Squeglia et al., 2015). Chronic alcohol consumption in AUD is also significantly associated with impaired hippocampal structure and function (Grace et al., 2021; Schweinsburg et al., 2010). Meda et al. (2018) conducted a 2-year longitudinal assessment of MD and BD young adults and reported progressive reductions in GMV in several PFC regions such as the anterior cingulate and dlPFC as in our study that was associated with binge drinking. Critically, the clinical significance of the current findings are that these structural hippocampal and PFC changes may be apparent prior to the development of AUD and are associated with binge drinking.

The areas of the brain identified as having smaller GMV in the BD group also support cognitive and affective operations known to be compromised in binge drinkers. For example, functional alterations in premotor areas have been linked to deficits in decision making, inhibitory control and working memory in young adult binge drinkers and adults with AUD (Campanella et al., 2013; Cservenka and Brumback, 2017; Hu et al., 2015). Hippocampus and dlPFC also play important functional roles in stress reactivity, suggesting a common mechanism underlying both chronic alcohol intake and stress dysregulation. While we did not find a direct association between hippocampal GMV and fasting cortisol, the hippocampus is known to provide negative feedback to the HPA axis (Zhu et al., 2014), and, as mentioned earlier, dlPFC plays an important role in emotion regulation (Ochsner et al., 2012). Notably, there were no differences in lifetime prevalence of mood and anxiety disorders or stress levels between the BD and MD groups and removal of those with previous mood and anxiety disorders from the sample, did not change the GMV results described above. Nonetheless, premorbid differences in stress regulation may influence both GMV and drinking levels in the sample. Recent work showed that connectivity between these regions predicts emotional stress responses in healthy individuals (Goldfarb et al., 2020), but not in those who engage in risky drinking

behavior (Goldfarb et al., 2022). This previous work is consistent with current findings of both higher cortisol in BD group as well as an association of higher cortisol with lower dlPFC supporting lower stress responses in BD group.

Finally, we directly tested the clinical relevance of lower GMV in the BD group by assessing the prospective significance of lower GMV and their association with future drinking behavior in the BD group. We found *lower* corticolimbic GMV was associated with *greater* subsequent real-world number of days of drinking and heavy drinking behavior only in the BD and no such associations were found in the MD group. Specifically, regions in which lower GMV were associated with higher alcohol intake in BD included anterior PFC, dorsal ACC, medial PFC, motor and premotor areas that are shown to have altered reactivity to alcohol cues in AUD (De Ridder et al., 2011; Huang et al., 2018) and to play important roles in reward-related decision making (Bush et al., 2002). Lower GMV in the amygdala and insula also predicted higher drinking in BD, consistent with past work showing lower gray matter volume and higher functional impairment in these regions in AUD (Grace et al., 2021; Mackey et al., 2019; Wetherill et al., 2013), and thus potentially extending their influence also in the risk of AUD (Grace et al., 2021; Koob and Volkow, 2016).

5. Conclusions

In summary, the current study identified widespread GMV reductions alongside altered stress physiology across individuals engaging in binge drinking. While this group comparison does not demonstrate a causal role of binge alcohol intake on cortisol and GMV, current findings included prospective longitudinal assessment of real-world daily drinking to assess the clinical and practical relevance of the GMV findings and found an association between lower specific structural brain volumes and higher future drinking behaviors. These findings need to be placed in the context of the study limitations. First, although we found no association between past alcohol intake and GMV, we cannot rule out that the observed lower GMV in BD may have been partly driven by a sub-group of individuals with longer years of alcohol intake and heavy alcohol intake during mid adolescence, but the findings are consistent with prior work in AUD and in adolescent BD. Second, while lower GMV were observed in regions that have been associated with altered stress networks and impaired cognitive functions in BD, further cognitive phenotyping and a larger cohort will be necessary to directly link these morphological differences to altered cognitive function. Third, the current findings did not have the power to fully assess the direct biological and clinical significance of the lower GMV in BD by identifying specific volume thresholds associated with the relative risk of future risky drinking behavior and future studies with large samples will be needed to fully assess the biological significance of these findings. Finally, the study was limited by small numbers of women on oral contraceptives and lack of adequate numbers tested at different phases of the menstrual cycle. This may have limited our ability to find overall sex differences in GMV and explore fully sex influences on GMV within drinking groups. In post-hoc exploratory analyses, sex differences in GMV in the BD groups for the bilateral amygdala, hippocampus and SMA were observed. These were driven by lower GMV in the hippocampus and SMA in the BD males relative to MD males and lower bilateral hippocampus and amygdala GMV in BD females relative to MD females, consistent with previous research reporting sex differences in GMV in BD and AUD samples (Grace et al., 2021; Wilsnack et al., 2018). As cortisol levels are sensitive to sex steroid hormone fluctuations that may vary by phase of the menstrual cycle, its effect on cortisol and GMV might differentially influence male and female binge drinkers, and this requires further study. Despite these limitations, the current study identified concurrent brain structural and cortisol adaptations in a heterogenous sample of adult binge drinkers relative to non-binge moderate drinkers and also showed the importance of these differences in predicting future risky drinking behavior amongst binge drinkers.

Author contributions

All authors have made substantial contributions to the paper. SF: conceptualized and designed the manuscript and analyses, conducted all analyses and wrote the initial draft of the manuscript. RS: conceptualized and designed the manuscript and analyses, planned the overall project and study design, oversaw data collection of all phases, contributed to conceptualizing the manuscript and in rewriting and revisions of the manuscript. DS: oversaw data collection of all phases. CL: contributed substantially to the data management. NF: contributed substantially to the data management. EG: quality control and analyses.

Role of the funding source

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2023.100540.

Fig. 1a: Panel A1 shows the shows the left hippocampus extended to the parahippocampal gyrus with crosshairs at Montreal Neurological Institute (MNI) coordinates x = −28.5, y = 13.5, z = −30 (Brodmann's area 36). Panel A2 shows right hippocampus extended to the parahippocampal gyrus at MNI coordinates x = 31.5, y = 22.5, z = −15 (Brodmann's area 36). Panel B shows the right dorsal lateral prefrontal cortex at MNI coordinates x = 42, y = −27, z = 19.5 (Brodmann's area 46). Panel C shows the bilateral motor areas with crosshair indicating the left motor area at MNI coordinates x = −16.5, y = −15, z = 61.5; the right motor areas at MNI coordinates right: x = 15, y = −25, z = 72 (Brodmann's area 6).

Fig. 1b: BD showed higher fasting morning cortisol levels (ug/dl) during the MRI session (Main Effect: BD > MD, p < 0.02). Post-hoc independent samples t-tests revealed that BD had significantly elevated cortisol levels at the 8:30 a.m. (p < 0.01) and the 9:30 a.m. (p < 0.023) timepoints.

Fig. 1c: Whole brain correlation analysis show significant clusters of gray matter volume associated with cortisol levels only in BD (Panel A-B). Panel A shows lower left dorsal lateral prefrontal cortex at MNI coordinates X = −41, Y = 36, Z = 4 (Brodmann's area 46) associated with higher cortisol levels (negative association shown in blue). Panel B shows the left premotor and supplementary motor area at MNI coordinates X = −36, Y = 8, Z = 45 (Brodmann's area 6) associated with higher cortisol levels in BD (shown in blue).

Fig. 2a: Whole brain correlation analysis in Panel A-G show significant clusters of lower gray matter volume associated with higher future number of drinking days in BD (specific regions of negative association shown in blue). Panel A shows the left orbito frontal cortex/amygdala at MNI coordinates X = −11, Y = 27, Z = −18 (Brodmann's area 11). Panel B red circled from the left to the right show the dorsal lateral prefrontal cortex at MNI coordinates (right dorsal lateral prefrontal cortex: X = 48, Y = 28, Z = 32 (Brodmann's area 9); left dorsal lateral prefrontal cortex: X = −22, Y = 47, Z = 32 (Brodmann's area 9); left dorsal lateral

prefrontal cortex: X = −45, Y = 33, Z = 32 (Brodmann's area 9)). Panel C red circle shows the right dorsal lateral prefrontal cortex at MNI coordinates X = 44, Y = 44, Z = 14 (Brodmann's area 46). Panel D shows the medial prefrontal cortex at MNI coordinates X = 2, Y = −16, Z = 53 (Brodmann's area 32). Panel E red circled from the bottom to the top show the left ventral anterior cingulate at MNI coordinates: X = −11, Y = 46, Z = 0 (Brodmann's area 24), the left dorsal anterior cingulate cortex at MNI coordinates: X = −11, Y = 28, Z = 23 (Brodmann's area 32). Panel F shows the right premotor/supplementary motor area at MNI coordinates: X = 24, Y = 2, Z = 63 (Brodmann's area 6). Panel G red circled the left insular cortex at MNI coordinates: X = −33, Y = 15, Z = 35 (Brodmann's area 13).

Fig. 2b: Whole brain correlation analysis in Panel A-G show significant clusters of lower gray matter volume associated with high future number of heavy drinking days in BD (shown in blue). Panel A red circled from the left to the right show the orbito frontal cortex at MNI coordinates (the right orbito frontal cortex: X = 25, Y = 35, Z = −17 (Brodmann's area 11); the right oribto frontal cortex: X = 30, Y = 59, Z = −17 (Brodmann's area 11); the left orbito frontal cortex: X = −9, Y = 35, Z = −17 (Brodmann's area 11)). Panel B red circled from the left to the right show the dorsal lateral prefrontal cortex (the right dorsal lateral prefrontal cortex: X = 9, Y = 5-, Z = 46 (Brodmann's area 9), the left dorsal lateral prefrontal cortex: X = −34, Y = 41, Z = 46 (Brodmann's area 9)). Panel C shows the left anterior prefrontal cortex at MNI coordinates X = −2, Y = 59, Z = −5 (Brodmann's area 10). Panel D shows the left dorsal anterior cingulate cortex at MNI coordinates X = −9, X = 35, Z = 19 (Brodmann's area 32). Panel E red circled from the left to the right show the premotor/supplementary motor areas (the right premotor/supplementary motor area: X = 5, Y = −24, Z = 51 (Brodmann's area 6); the left premotor/supplementary motor area: X = −10, Y = −24, Z = 79 (Brodmann's area 6); the left premotor/supplementary motor area: X = −3, Y = 8, Z = 69 (Brodmann's area 6)). Panel F shows the right motor area at MNI coordinates X = 30, Y = −23, Z = 68 (Brodmann's area 4). Panel G red circled from the left to the right show the insular (the right insular: X = 40, Y = 17, Z = −9 (Brodmann's area 13); the left insular: X = −42, Y = 11, Z = −17 (Brodmann's area 13)).

Panel A-C show significant negative associations between gray matter volume in the orbito frontal cortex extended to the amygdala (r = −0.475, p < 0.001), the dorsal anterior cingulate cortex (r = −0.49, p < 0.001) and the bilateral insular (left insular r = −0.474, p < 0.001; right insular: r = −0.434, p = 0.003) associated with future drinking behavior.

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