# A structural MRI study of differential neuromorphometric characteristics of binge and heavy drinking

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ABSTRACT

Background: Alcohol misuse often manifests in two different patterns of drinking; Binge Drinking (BD; $\geq 4$ (women) or $\geq 5$ (men) drinks/day, $\leq 12$ days/month) or Heavy Drinking (HD; $\geq 3$ (women) or $\geq 4$ (men) drinks/day, $\geq 16$ days/month). Although direct comparisons have not been made, structural MRI studies indicate that the two types of drinking behaviors might be associated with different neuromorphometric characteristics.

Methods: This study used a cross-sectional design to compare brain structure (using MRI derived subcortical volume and cortical thickness measures) between participants with histories of BD ($N = 16$), HD ($N = 15$), and Healthy Controls (HC; $N = 21$). Whole-brain analyses were used to quantify group differences in subcortical volume and cortical thickness. Resulting cortical thickness clusters were quantified for their areas of overlap with resting-state network parcellations.

Results: BD was associated with decreased volumes of the bilateral global pallidus and decreased cortical thickness within the left superior-parietal cluster ($p < .05$). This cortical cluster overlapped in surface area with the dorsal-attention (50.86%) and the fronto-parietal network parcellations (49.14%). HD was associated with increased cortical thickness in the left medial occipito-parietal cluster ($p < .05$). This cluster primarily overlapped with the visual network parcellation (89%) and, to a lesser extent, with a widespread number of network parcellations (dorsal-attention: 3.8%; fronto-parietal: 3.5%; default-mode: 3.2%).

Conclusions: These data indicate that histories of BD and HD patterns are associated with distinct neuromorphometric characteristics. BD was associated with changes within the executive control networks and the globus pallidus. HD was associated with widespread changes, that are primarily localized within the visual network.

## 1. Introduction

Research on alcohol misuse has identified two common patterns of pathological drinking behavior: (1) the consumption of high amounts of alcohol over short periods of time, referred to as Binge Drinking (BD[1]; $\geq 4$ (women) or $\geq 5$ (men) drinks/day, $\leq 12$ days/month (N.I.A.A.A., 2017) and (2) the consumption of alcohol at more frequent occasions, referred to as Heavy Drinking (HD; $\geq 3$ (women) or $\geq 4$ (men) drinks/day, $\geq 16$ days/month (N.I.A.A.A., 2016). An accumulating body of evidence suggests that the two types of drinking patterns are associated with different neurological, cognitive, and motivational profiles (Litten et al., 2015). These profiles might emerge during adolescence, and

often last through adulthood (Casey & Jones, 2010; Donovan, 2004). To date, the two patterns have only been studied in separate samples with inconsistent definitions and widely varying results (see (Cservenka & Brumback, 2017) for a review).

Studies which compared BDs and HDs to control samples (lacking direct BDs to HDs contrasts), suggest that the two drinking patterns might be associated with different cognitive and neurobiological features. BD is associated with heightened impulsive characteristics (Scaife & Duka, 2009) and alcohol related motivational deregulation involving positive reinforcement (thus, primarily drinking for the pleasurable effects; (G. F. Koob & Le Moal, 2005). Additionally, individuals who engaged in BD, were shown to have regional executive control

alterations (Banca et al., 2016; Correas et al., 2016; Watson, Newton-Mora, & Pirkle, 2016) as well as disrupted functional connectivity between areas that are involved in volitional control of attention (Herman, Critchley, & Duka, 2018). Comparatively, individuals with histories of more frequent drinking episodes (thus more akin to HD behavior), appear to possess compulsive characteristics involving negative reinforcement of alcohol consumption (thus, consuming alcohol to alleviate discomfort; (George. F. Koob & Le Moal, 2005; George F. Koob & Volkow, 2016)), neurocognitive disruptions in automatic processing of information (George F. Koob & Volkow, 2010), and reduced functional connectivity within the default mode network (Shokri-Kojori, Tomasi, Wiers, Wang, & Volkow, 2017). Structural MRI (sMRI) derived neural property comparisons (volume and thickness of brain tissue) between individuals who engaged BD and HD patterns as compared to the Healthy Control (HC) group, suggest that the two drinking patterns are associated with different structural changes. BD was associated with volumetric and cortical thickness changes within frontal and parietal regions (Banca et al., 2016; Lisdahl, Thayer, Squeglia, McQueeny, & Tapert, 2013; Lindsay M. Squeglia et al., 2012). Studies which examined alcohol misuse, that was more akin to HD, reported widespread neuromorphometric changes which included frontal, temporal, occipital (Fortier et al., 2011), subcortical, cerebellar (Mechtcheriakov et al., 2007), and brain-stem regions (L. M. Squeglia et al., 2014) (for a detailed review of BD and HD studies, see (Cservenka & Brumback, 2017)). Studies that focused on samples that are akin to more severe HDs, reported morphometric alterations within the precuneus (chronic AUD: (Durazzo et al., 2014)) and the posterior cingulate cortex (PCC) (abstinent alcohol dependent patients: (Rando et al., 2011)). Interestingly, larger PCC volume was associated with a genetic variant (within GRIN2B) in an adolescent AUD population, suggesting a potential genetic risk component of its neuromorphometric properties (Dalvie et al., 2017).

Given that a broad range of comorbid conditions frequently co-occur with binge and heavy types of alcohol consumption (see (Maksimovskiy et al., 2014) and (Petersen & Zettle, 2009), for examples), and that the two types of drinking patterns were often studied in different demographic samples (see (Cohen-Gilbert et al., 2017) and (Mayhugh et al., 2016), for examples), conclusive comparisons between BD and HD links to structural neural changes cannot be made. Nevertheless, such comparisons have the potential to provide evidence with regards to whether the two types of drinking behaviors are associated with distinct neural signatures.

To date, no studies have directly compared sMRI measures of participants with BD histories to sMRI measures of participants with HD histories, relative to HC participants. The current study addresses this gap by comparing sMRI derived neuromorphometric measures (using cortical thickness and subcortical volume) between the aforementioned groups using a cross-sectional design. Cortical thickness was used in order to quantify the extent to which neuromorphometric differences between BD and HD groups might impact cortical networks, the cortex was parcellated using a Yeo 7-Network atlas (Yeo et al., 2011). This approach allowed for a more robust interpretation of regional differences in the context of prior work. This atlas has been selected because of well-developed quantification of human brain networks, that is based on 1000 subjects (Yeo et al., 2011). Exact quantification was accomplished by applying the Yeo 7-Network solution cortical parcellations to the cortical surface, superimposing the BD and HD ROI clusters, and calculating the area of overlap between clusters and the respective Yeo networks.

We hypothesized that participants with BD histories would have reduced cortical thickness within brain regions that were associated with the executive control networks (frontal and parietal regions), as compared to participants with HD histories and HCs (Müller-Oehring et al., 2013; Weiland et al., 2014). Participants with HD histories were predicted to have reduced cortical thickness within brain regions localized to the posterior cingulate cortex and the precuneus regions, as

compared to all other participants (Chanraud, Pitel, Pfefferbaum, & Sullivan, 2011; Gonçalves et al., 2016). These hypotheses were tested by first comparing whole-brain cortical thickness measures between BDs, HDs, and HCs and then by measuring the extent to which any significant clusters overlapped with major resting state network parcellations (Yeo et al., 2011). For subcortical volume, we predicted that both groups of participants with BD and HD histories, would have altered ventral striatal volume, in comparison to HCs. This prediction is based on prior studies which showed that ventral striatum was affected in individuals with an AUD (Howell et al., 2013; Sullivan, Deshmukh, De Rosa, Rosenbloom, & Pfefferbaum, 2005). We examined this hypothesis by comparing whole-brain subcortical volumetric measures between participants with BD histories, participants with HD histories, and HC.

## 2. Materials and methods

Analyses were conducted using the Data Repository of the VA RR&D Translational Research Center for TBI and Stress Disorders (TRACTS) (McGlinchey, Milberg, Fonda, & Fortier, 2017). The TRACTS longitudinal cohort study recruited OEF/OIF/OND Veterans between the ages of 18 and 65, and collected an extensive battery of neuropsychological, clinical, physiological, and imaging measures.

### 2.1. Sample characteristics

A sample of 52 participants was selected from a larger TRACTS sample ($n = 433$) based on (1) meeting the criteria for a history of mutually exclusive BD, HD, or HCs (no alcohol misuse), (2) not having a history of a neurological impairments, psychotic conditions, moderate or severe Traumatic Brain Injury (TBI), or non-alcohol and non-nicotine substance abuse/dependence, and (3) having a complete dataset of all relevant variables.

Definitions for BD and HD groups were based on modified NIAAA criteria consistent with the following rationale. NIAAA defines BD as consuming at least 4 drinks for women and 5 for men within the course of 2 h (N.I.A.A.A., 2016). HD is defined as engaging in the BD pattern for 5 or more days in a month (N.I.A.A.A., 2016). Further modification was made based on our previous work, in order to avoid overlap and accommodate the lack of hour-by-hour accuracy, which was not available on the Lifetime Drinking History (LDH; (Skinner & Sheu, 1982)). According to LDH, all BD and HD participants started drinking at approximately the same age (mean age: 17.59 years) and continued to drink in their respective and mutually exclusive patterns until their assessment in the TRACTS longitudinal cohort study.

### 2.1.1. BD (N = 16)

Operationally defined as an individual who (1) reported a pattern of consuming ≥4 (women) or ≥ 5 (men) drinks per day on 12 or fewer occasions per month, without a history of HD, and (2) started drinking between the ages of 12–25.

### 2.1.2. HD (N = 15)

Operationally defined as an individual who reported a pattern of consuming ≥3 (women) or ≥ 4 (men) drinks per day on 16 or more occasions per month, without a history of BD, and (2) started drinking between the ages of 12–25.

### 2.1.3. HC (N = 21)

Operationally defined as individuals who do not consume alcohol at pathological levels (thus, without any history of BD, HD, or Alcohol Use Disorder (AUD); as measured by SCID DSM-IV (First & Gibbon, 2004)). Seventeen individuals within this group reported a history of social drinking (below pathological levels) and 4 participants have not reported any alcohol consumption.

Psychiatric characteristics were measured using the posttraumatic

**Table 1**

Psychiatric and combat information.

All standard deviation measures are noted in parentheses. Significance levels, marked by "*", have been set at $p < .05$, and group differences are indicated within the corresponding cells. Significant differences have been found in DASS scores (sub-scores as well as total scores; HD > BD/HC (with the exception of DASS anxiety; HD > BD)) and mean CAPS scores (HD > BD/HC). Abbreviations: Standard Deviation (S.D.); Depression and Anxiety Stress Scales (DASS); Clinician Administered PTSD Scale (CAPS); Deployment Risk and Resiliency Inventory II (DRRI).

| Drinking pattern | | Psychiatric variables | | | | Combat information | |
|---|---|---|---|---|---|---|---|
| | | DASS anxiety total score | DASS depression total score | DASS stress total score | CAPS total score | DRRI combat | DRRI other |
| Binge drinking (BD) | Mean: | 1.5 | 3.37 | 6.5 | 29.25 | 14.56 | 7 |
| N = 16 | S.D.: | (2.68) | (3.56) | (6.67) | (20.06) | (10.65) | (5.1) |
| | Range: | 0–8 | 0–10 | 0–22 | 2–66 | 2–38 | 0–15 |
| Heavy drinking (HD) | Mean: | 8.00* | 11.47* | 14.00* | 61.87* | 21.14 | 9.14 |
| N = 15 | S.D.: | (11.56) | (10.86) | (11.46) | (27.66) | (13.54) | (4.88) |
| | Range: | 0–40 | 0–40 | 0–42 | 4–99 | 3–51 | 1–15 |
| | | HD > BD | HD > BD/HC | HD > BD/HC | HD > BD/HC | | |
| Healthy controls (HC) | Mean: | 3.37 | 3.56 | 5.68 | 33.19 | 13.11 | 5.94 |
| *N* = 21 | S.D.: | (5.12) | (4.88) | (6.74) | (25.14) | (11.41) | (4.45) |
| | Range: | 0–20 | 0–16 | 0–24 | 0–75 | 0–37 | 0–14 |

**Table 2**

Demographic and health information.

All standard deviation measures are noted in parentheses. Significance levels, marked by "*", have been set at $p < .05$, and group differences are indicated within the corresponding cells. Significant differences have been found in mean years of education (HD < HC), number of women, (HC > HD), number of smokers (HD > BD/HC). Abbreviations: Standard Deviation (S.D.); Estimated (Est.); Education (Edu.); Mild Traumatic Brain Injury (mTBI); Clinician-administered PTSD Scale (CAPS); Medications (Meds.).

| Drinking pattern | | Demographic characteristics | | | | Health information | | |
|---|---|---|---|---|---|---|---|---|
| | | Est. IQ | Age | Years of Edu. | Gender: number of women | Number of smokers | Number of military mTBI | Number of meds. (Median) |
| Binge drinking (BD) | Mean: | 99.875 | 34 | 14.13 | | 3 | 0.375 | 0 |
| N = 16 | S.D.: | (12.53) | 8.35 | 2.16 | 1 | | (0.72) | (0.89) |
| | Range: | 75–119 | 23–46 | 12–18 | | | 0–2 | 0–3 |
| Heavy drinking (HD) | Mean: | 99.93 (8.12) | 30.08 (7.17) | 13.2 (1.23)* | | 6* | 1.9 | 1 |
| N = 15 | S.D.: | 83–111 | 23–49 | 12–16 | 0 | HD > BD/HC | (3.95) | (1.55) |
| | Range: | | | | | | 0–16 | 0–5 |
| Healthy controls (HC) | Mean: | 99.99 | 34.74 (10.19) | 14.86 (2.22) | | 1 | 0.24 | 0 |
| N = 21 | S.D.: | (9.33) 73–123 | 20–53 | 12–19 | 6* | | (0.54) | (0.29) |
| | Range: | | | | HC > HD | | 0–2 | 0–5 |

**Table 3**

Alcohol consumption information.

All standard deviation measures are noted in parentheses. Significance levels, marked by "*", have been set at $p < .05$, and group differences are indicated within the corresponding cells. As expected, significant differences have been found between HD/BD groups and HC group in weight-adjusted LDH levels; HC < BD/HD. Although drinking onset age falls within the adolescent period (12–25), mean age of HD and BD onset was found to be significantly different; BD < HD. Abbreviations: Standard Deviation (S.D.); Lifetime Drinking Total (LDH), Structured Clinical Interview for DSM-IV (SCID). The "Age of First Drink" variable indicates the mean age at which participants engaged in alcohol consumption for the first time, independent of pathological drinking patterns.

| Drinking pattern | | Alcohol consumption information | | | | |
|---|---|---|---|---|---|---|
| | | LDH total (weight corrected) | Mean length of total drinking time (in years) | SCID alcohol abuse | SCID alcohol dependence | Age of first drink |
| Binge drinking (BD) | Mean: | 1519.08 | 17.09 | | | 17.25 |
| | S.D.: | (582.13) | (6.89) | Current: 1 | Current: 0 | (2.35) |
| | Range: | 902.11–3189 | 7.4–30.6 | Lifetime: 6 | Lifetime: 4 | 13–21 |
| Heavy drinking (HD) | Mean: | 2437.42 (2608.52) | 12.53 | | | 17.93 |
| | S.D.: | 254.5–9391.4 | (9.12) | Current: 1 | Current: 3 | (4.33) |
| | Range: | | 3–32.9 | Lifetime: 2 | Lifetime: 11 | 7–22 |
| Healthy controls (HC) | Mean: | *122.75 | N/A | | | 17.48 |
| | S.D.: | (239.68) | | Current: 0 | Current: 0 | (6.23) |
| | Range: | 0–843.23 | | Lifetime: 0 | Lifetime: 0 | 0–24 |
| | | HC < BD/HD | | | | |

stress disorder (PTSD) symptom severity scores (obtained from the Clinician Administered PTSD Scale for DSM-IV (CAPS) (Blake et al., 1995; Gray, Litz, Hsu, & Lombardo, 2004; Weathers, Keane, & Davidson, 2001; Weathers, Ruscio, & Keane, 1999)), depression, anxiety, and stress scales (DASS) (Crawford & Henry, 2003), as well as the DSM-IV SCID diagnoses. Demographic characteristics included estimated premorbid IQ (as measured by Weschler Test of Adult Reading (Wechsler, 2001)), age at the time of testing, years of education, and gender. Relevant health information included the number of mild TBIs throughout the participant's lifetime, number of medications taken (total, psychotropic, and non-psychotropic), and participants' cigarette smoking status. Combat exposure was measured using the

Combat subscale of the Deployment Risk and Resiliency Inventory (DRRI) (King, King, & Vogt, 2003). Alcohol consumption factors, derived from the LDH, include: total weight-adjusted amount of alcohol consumed during the course of the participants' lifetime, age of drinking onset, and the total amount of time spent drinking. This information is presented in Tables 1, 2, and 3. Participants were also equated on their dominant handedness, as well as the number of medications that they were taking at the time of testing.

## 2.2. Neuroimaging data acquisition and preprocessing

MRI structural data were acquired in the Neuroimaging Research for Veterans Center (NeRVe) at VA Boston Healthcare System using a Siemens 3 T TIM Trio system with a 12-radiofrequency channel head coil. For each subject, two T1-weighted MPRAGE scans were collected [3D sequence, flip angle 7°, acquisition matrix = 256 × 256, echo time = 3.32 ms, repetition time = 2530 ms, slice thickness = 1 mm, TE = 3.32, in-plane resolution = 1.0 mm$^2$, 176 sagittal slices] and then averaged to increase the signal to noise ratio. Data were stored and processed at the NeRVe Image Processing Cluster.

Volumetric neuroimaging data were preprocessed using the standard FreeSurfer 5.3 processing stream (Fischl & Dale, 2000). The pre-processing pipeline generated 31 raw volumetric measurements (in mm$^3$) for grey matter subcortical segmentations (Fischl, Salat, Busa, Albert, Dieterich, Haselgrove, et al., 2002; Hommer, Momenan, Kaiser, & Rawlings, 2001). Neuroimaging data was visually inspected by a trained technician, at the time of acquisition, and scans with excessive motion artifacts were re-acquired. Following acquisition, during the pre-processing stage, all images were processed using the same machine to avoid discrepant findings (Gronenschild et al., 2012), and a trained research assistant reviewed the quality of the surface segmentations. Screening for outliers was performed during pre-processing, as well as during statistical analyses of the preprocessed data. Measurements were calculated using the Desikan 2006 and Salat 2009 atlases (Desikan et al., 2006; Salat et al., 2009). Prior to measuring the volumetric regions of interest, the data was affine registered using the Montreal Neurological Institute atlas (MNI305) space and B1 bias field corrected. The total volume was labeled using the subject-specific measurements as well as a probability atlas for greatest accuracy Fischl et al., 2002). Subcortical structures were corrected for the estimated total intracranial volume (eTIV), in order to account for between-subject head size differences (Buckner et al., 2004). The following subcortical structures have been examined on the right and left hemisphere: ventral diencephalon, amygdala, hippocampus, pallidum, putamen, caudate, and thalamus.

## 2.3. Statistical analyses

Freesurfer version 5.3 (Fischl & Dale, 2000; Fischl et al., 2002; Fischl et al., 2004a; Han & Fischl, 2007; Ségonne et al., 2004) was used for cortical thickness and surface area analyses and JMP Pro 12 software (JMP®, 1989–2007.) was used for all other analyses.

### 2.3.1. Covariates

Differences between HD, BD, and HC groups in potentially confounding variables were examined using ANOVA, t-tests, and chi-square tests (as appropriate). In cases when group differences were found to be significant ($p < .05$), the respective variable(s) were classified as covariates in the statistical models. This included 8 variables: (1) gender (number of women; HC > HD), (2) number of smokers (HD > BD/HC), (3) CAPS severity score (HD > BD/HC), (4) DASS anxiety sub-scores (HD > BD), (5) DASS Depression sub-score (HD > BD/HC), (6) DASS Stress sub-score (HD > BD/HC), (7) number of current (at the time of testing) depression episodes (HD > BD/HC), (8) Number of lifetime recurrent depression episodes (BD < HD/HC).

### 2.3.2. Volumetric analyses

ANOVA tests were conducted using the BD, HD, and HC groups as independent variables, and each volumetric ROI as a dependent measure (independently) without any covariates. Volumetric ROIs with alpha levels below 0.05 were corrected for multiple comparisons using the FDR adjustment. The FDR correction for multiple comparisons has been selected in order to control for the rate of false positive errors, while maximizing power (Benjamini & Hochberg, 1995). Additionally, the utilization of this method is consistent with prior studies of brain volume (see (Durazzo, Mon, Gazdzinski, & Meyerhoff, 2017) and (Sawyer et al., 2017) for examples). Stepwise regression, using backward elimination, was run in order to identify which of the covariates had a significant effect on the dependent measure. Variables with significant effects were included as covariates in the linear models, which were then rerun.

Age was added as a covariate to all analyses due to previous findings which reported its effect on brain tissue (Gennatas et al., 2017). Post-hoc tests were run on the resulting dependent measures that remain significant.

### 2.3.3. Cortical thickness analyses

The FreeSurfer 5.3 software (Desikan et al., 2006) pipeline was used for these analyses. This method computes grey matter thickness measures in millimeters squared (mm$^2$) for regions that can be identified via customizable and standardized atlases (Fischl, Liu, & Dale, 2001; Fischl, Sereno, Tootell, & Dale, 1999; Ségonne, Pacheco, & Fischl, 2007). Two T1-weighted MPRAGE scans were averaged together for each subject, using a combination of FreeSurfer and FSL tools (Desikan et al., 2006; Fischl et al., 2004b; Smith et al., 2004; Woolrich et al., 2009). Each subject's data was resampled into common space (using FreeSurfer's fsaverage subject) and concatenated into a single file. The data were smoothed at 15 full-width/half-max (FWHD) for each hemisphere.

Whole-brain ANCOVAs were run with "age" as a covariate using the following comparisons: (1) BD vs. HC, (2) HD vs. HC, and (3) BD vs. HD (to confirm unique signature of each drinking pattern). Vertex and cluster-wise corrections for multiple comparisons were applied using the $p < .05$ as a threshold. In addition to "age", 8 variables that were significantly different between the BD, HD, and HC, were included as covariates in separate models. The models were thus run for a total of 9 times. This approach was selected in order to avoid overfitting the model in our analyses.

Resulting clusters were taken into account if, and only if, they satisfied the following three conditions: (1) significantly differed between each pathological group (BD ≠ HD), as well as the control group (BD | HD ≠ HC); (2) survived the voxel and cluster-wise correction for multiple comparisons; (3) remained significant in each of the models, controlling for covariates.

Given that each model (BD vs. HD, BD vs. HC, as well as separate models for each of the covariates) generated overlapping but slightly different clusters, the resulting clusters were reduced in area, in order to isolate the main effect of each drinking pattern. This was done by taking a surface area intersection of all resulting clusters (CLUSTER$_1$ ∩ CLUSTER$_2$ ∩ CLUSTER$_n$) and generating a final ROI for each group (BD ROI and HD ROI), which consisted of cortical surface area which all results had in common.

In order to localize and better identify the effect of drinking patterns on cortical tissue, the BD and HD ROIs were quantified according to their respective impact on brain networks, using the Yeo 7-Network solution cortical atlas (Yeo et al., 2011). This was accomplished by applying the Yeo 7-Network solution cortical parcellations to the cortical surface, superimposing the BD and HD ROI clusters, and calculating the area of overlap between clusters and the respective Yeo networks.

Hubert M-estimation robust fit outlier tests have been performed on all significant measures (using the default setting in JMP software).
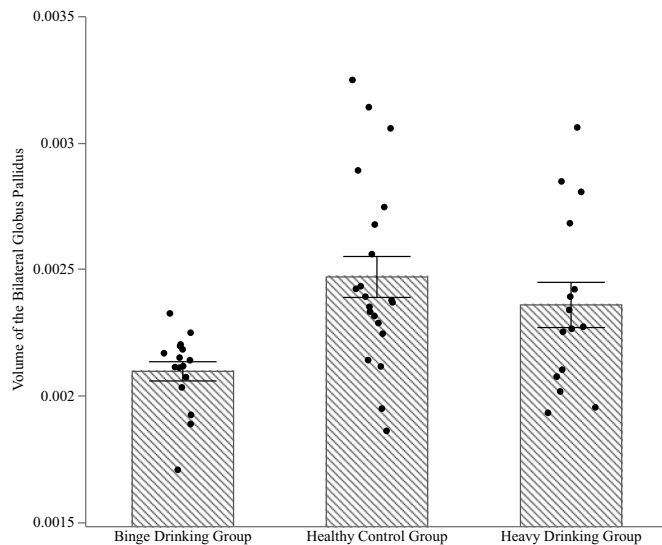
**Fig. 1.** Bilateral globus pallidus volume.

This figure depicts subject-specific as well as group mean values for the volume of the bilateral globus pallidus (in mm$^3$), adjusted for head size. Group mean values are as follow: Binge Drinkers: 0.0021 mm$^3$, Heavy Drinkers: 0.0024 mm$^3$, Healthy Controls: 0.0025 mm$^3$. The Binge Drinking group's mean globus pallidus volume is significantly smaller in comparison to Healthy Controls' ($p < .023$) and Heavy Drinkers' ($p < .0007$). The image inside the graph is an example of a one-slice segmented FreeSurfer volume with the globus pallidus indicated by the arrows.

## 3. Results

### 3.1. Volumetric results

ANOVA revealed a significant group effect for the bilateral globus pallidus ($F(2, 49) = 6.65$, $p < .05$, $f = 0.51$). Post-hoc *t*-tests showed that the globus pallidi are smaller within the BD group, as compared to HD group ($t(48) = 2.14$, $p < .05$, $d = -2.14$), as well as within the BD group, as compared to HC group ($t(48) = 3.63$, $p < .05$, $d = -3.62$). Fig. 1 displays the individual and group means for the bilateral globus pallidus. No significant outliers have been detected (Huber N Outliers = 0).

### 3.2. Cortical thickness results

Cortical thickness analyses revealed a significantly thinner cluster within the left superior parietal region in BD participants, as compared to HD and HC groups (BD < HD: $F(1, 29) = 12.73$, $p < .05$, $f = -3.53$; BD < HC: $F(1, 35) = 22.69$, $p < .05$, $f = -3.19$). Results for the HD group showed a thicker cluster within the left medial occipital lobe in comparison to the BD and HC groups (HD > BD: $F(1, 29) = 14.14$, $p < .05$, $f = 2.97$; HD > HC: $F(1, 34) = 12.73$, $p < .05$, $f = 2.49$). Results from these comparisons are presented in Fig. 2. Cohen's f values were calculated for maximum vertices. No significant outliers have been detected (Huber N Outliers = 0).

Yeo-network overlap analyses indicate that BD ROI mostly overlaps with the executive control networks. Specifically, it overlaps with the posterior region of the dorsal attention network by 615.794 mm$^2$ and with the fronto-parietal network by 594.938 mm$^2$. Overlap with the ventral attention and default mode networks are comparatively small, at 1.313 mm$^2$ and 0.676 mm$^2$, respectively. Fig. 3 displays the visual overlap of the BD ROI with Yeo networks and a quantifiable metric is presented in Fig. 4.

The HD cluster mostly overlaps with the dorsal attention network (50.508 mm$^2$ overlap), as well as the visual network (1201.023 mm$^2$ overlap). The HD cluster also has a small widespread overlap with other

networks. The overlaps include the frontoparietal network's lateral superior region (0.149 mm$^2$ overlap), frontoparietal network's medial superior region (46.357 mm$^2$ overlap), ventral attention network's lateral region (0.297 mm$^2$ overlap), ventral attention network's medial region (0.483 mm$^2$ overlap), the default mode network's lateral region (0.361 mm$^2$ overlap), and the default mode network's medial region (43.806 mm$^2$ overlap). These results are displayed in Fig. 4.

## 4. Discussion

sMRI data from the current study are the first to show that individuals with histories of BD and HD have morphologically distinct neurological profiles. These differences were found within subcortical volume, cortical thickness, and surface area measures. Specifically, participants with histories of BD have smaller volume of the bilateral globus pallidus in comparison to participants with histories of HD and HC. Cortical thickness measures indicate that participants with histories of BD have reduced cortical thickness within the superior parietal region, in comparison to participants with histories of HD and HC. This region overlaps in area with fronto-parietal and dorsal attention network parcellations (49.14% and 50.86% of the full effect, respectively). Participants with HD histories have increased cortical thickness in the medial occipito-parietal region, in comparison to participants with histories of BD and HC. This region mostly overlaps in area with the visual network parcellation (89.49% of the full effect) and, to a smaller extent, has a widespread overlap with other networks parcellations: the default-mode network (3.29% of the full effect), fronto-parietal network (3.45% of the full effect), and the dorsal attention network (3.76% of the full effect).

Contrary to our hypothesis, only participants with histories of BD presented with decreased bilateral volume of the globus pallidus, in comparison to participants with histories of HD and HC. This is an intriguing finding as it offers a potential way to differentiate individuals who engaged in BD and HD patterns based on sMRI brain morphometry. Previous structural neuroimaging studies have shown that volumetric and tissue intensity measures within the globus pallidus were affected in alcoholism and alcohol related disorders (Binesh et al., 2006; Córdoba, Sanpedro, Alonso, & Rovira, 2002; Juhás et al., 2017; Nardelli, Lebel, Rasmussen, Andrew, & Beaulieu, 2011; Zahr & Pfefferbaum, 2017). The current findings indicate that the global pallidus is uniquely affected in participants with histories of BD, in comparison to participants with histories of HD. This finding offers additional support for the previously theorized claims regarding differential characteristics of binge and heavy types of alcohol consumption (Gilpin & Koob, 2008; Heilig & Koob, 2007). Further investigation should be conducted on the domains of cognitive function that is associated with the globus pallidus in the context of alcohol misuse. The globus pallidus has been shown to be involved in addiction maintenance (Harris & Koob, 2017; Moussawi, Kalivas, & Lee, 2016), which likely occurs via reward sensitivity (Adam et al., 2013; Hong & Hikosaka, 2008). Given that this structure is differentially affected, an examination of reward sensitivity differences between individuals with histories of BD and HD patterns might offer insight about the nature of reward processing domains that differentiate the two drinking profiles (Gilpin & Koob, 2008; Heilig & Koob, 2007).

Cortical thickness results offer sMRI evidence for the presence of differential characteristics between BD and HD. The left lateral superior parietal region, which is affected in participants with histories of BD, overlaps with networks that are involved in executive control: such as volitional attention processes (Majerus, Péters, Bouffier, Cowan, & Phillips, 2017) and planning goal directed actions (Dixon, Girn, & Christoff, 2017). This finding builds on prior studies, which reported similar neuromorphometric changes in AUD (Dager et al., 2015; Kim, Im, Lee, & Lee, 2017), by showing that these regions are selectively affected in individuals with histories of BD, and might not be generalizable to other types of alcohol misuse.
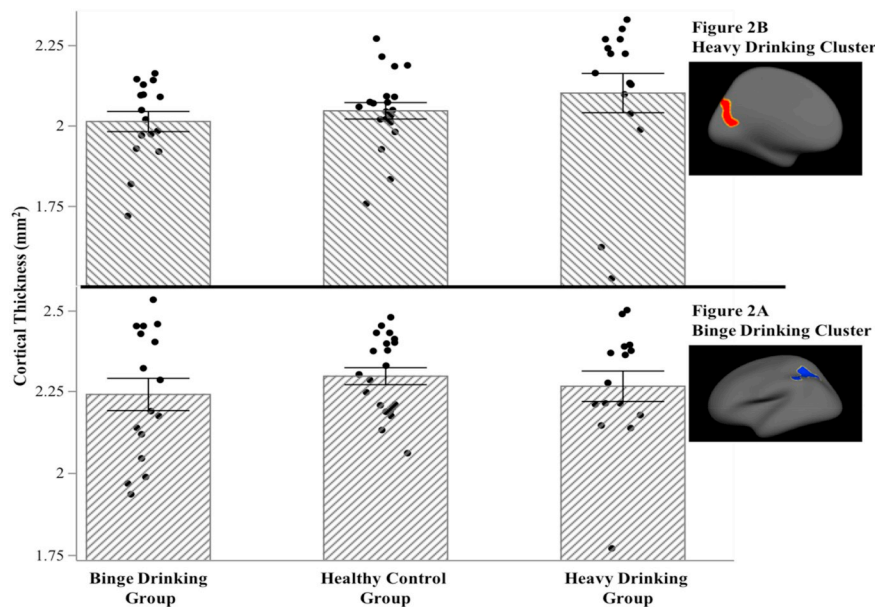
**Fig. 2.** Binge and heavy drinking clusters.
This figure presents the mean values for the Binge Drinking cluster (Fig. 2A) divided by the following groups: Binge Drinkers (Mean: 2.24 mm², Standard Deviation: 0.2), Heavy Drinkers (Mean: 2.27 mm², Standard Deviation: 0.18), and Healthy Controls (Mean: 2.3 mm², Standard Deviation: 0.12). Fig. 2B presents the mean values for the Heavy Drinking cluster divided by the following groups: Heavy Drinkers (Mean: 2.1 mm², Standard Deviation: 0.24), Binge Drinkers (Mean: 2.01 mm², Standard Deviation: 0.12), and Healthy Controls (Mean: 2.05 mm², Standard Deviation: 0.12). The mean values have been extracted from the Heavy Drinking cluster displayed on the right-hand side of the image (Heavy Drinking > Binge Drinking/Healthy Controls; $p < .05$; FWHD = 15).

The left medial occipital-parietal cluster, which is affected in participants with the HD patterns, overlaps with networks that were shown to support visual information processing (De Schotten et al., 2011). This finding builds on prior studies, which presented numerous reports of the effects of alcohol misuse on the occipital lobe (Bagga et al., 2014; Volkow et al., 2008; G. J. Wang et al., 2000). Regional specificity of these findings, within the occipital cortex, might be explained by a selectively large concentration of γ-aminobutyric acid (GABA) receptors within the occipital regions (Hill & Toffolon, 1990; Nicholson, Andre, Tyrrell, Wang, & Leibowitz, 1995; Pearson & Timney, 1998; Watten, Magnussen, & Greenlee, 1998), which alcohol is known to target (Volkow et al., 2008). Furthermore, the small, but widespread, overlap of HD participants' cluster with several network parcellations, which extends beyond the visual network, is consistent with previously reported effects of problem drinking on a broad range of cortical regions and networks (Fortier et al., 2011; Müller-Oehring, Jung, Pfefferbaum, Sullivan, & Schulte, 2014; Shokri-Kojori et al., 2017). Current data suggest that these effects might be linked to the HD type of alcohol consumption, rather than be generalizable to all types of alcohol misuse.

Given that the implication of directionality differences in cortical thickness are difficult to interpret using only neuromorphometric information, we speculate that these findings are consistent with impulsive characteristics of BD and compulsive (involving higher frequency) characteristics of HD (Koob, 2009). Thinner clusters in BDs, within the left parietal area, might relate to deregulations in impulsive BD behavior. The thicker left medial occipital-parietal region, in HD participants, might be associated with changes within a selectively large concentration of GABA) receptors within the occipital regions (Hill & Toffolon, 1990; Nicholson et al., 1995; Pearson & Timney, 1998; Watten et al., 1998). Pre-clinical studies are necessary for conclusive interpretations to empirically link neuromorphometry, tissue changes, neurochemical alterations, and drinking behavior, as such relationships have not yet been established.

### 4.1. Limitations

A number of limitations should be considered. Importantly, the nature of the cross-sectional design prevents causal interpretations of these data. A longitudinal analysis needs to be conducted in order to
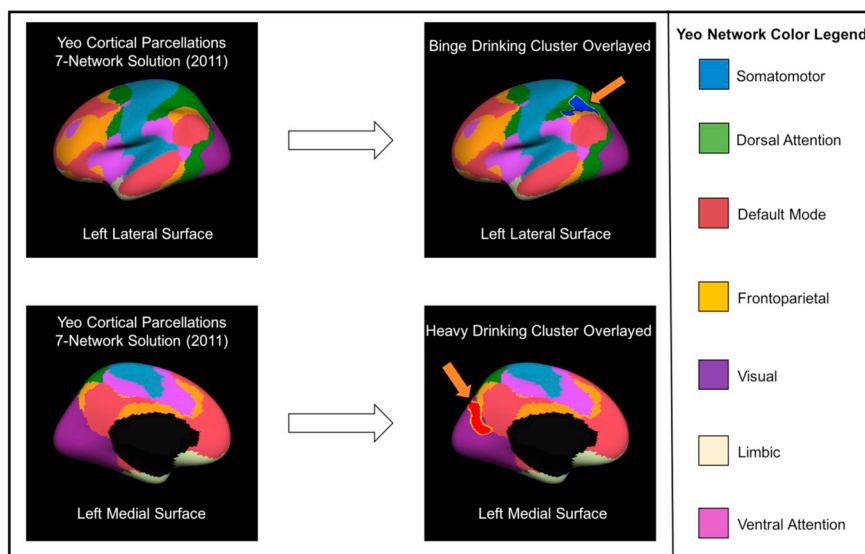


**Fig. 3.** Intersections of significant clusters with Yeo networks.
Images on the left column indicate the Yeo 7-Network solution cortical parcellation overlay. The two images in the right column show the superimposed Binge (top, in blue) and Heavy Drinking groups' (bottom, in red) clusters on top of the Yeo 7-Network atlas. This superimposition has allowed for a quantification of the degree and extent to which each of the networks is affected by the clusters. Upper right image contains a legend for the 7 major networks; Heavy Drinking group's overlap is in red and Binge Drinking group's overlap is in blue. As shown, the Heavy Drinking group's cluster primarily intersects with the visual network at 1201.023 mm² and to a much lesser extent with the default mode network (44.367 mm²), dorsal attention network (50.508 mm²), and the frontoparietal network (46.357 mm²). The Binge Drinking group's cluster intersects with the dorsal attention network (615.794 mm²) as well as the frontoparietal network (594.938 mm²). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
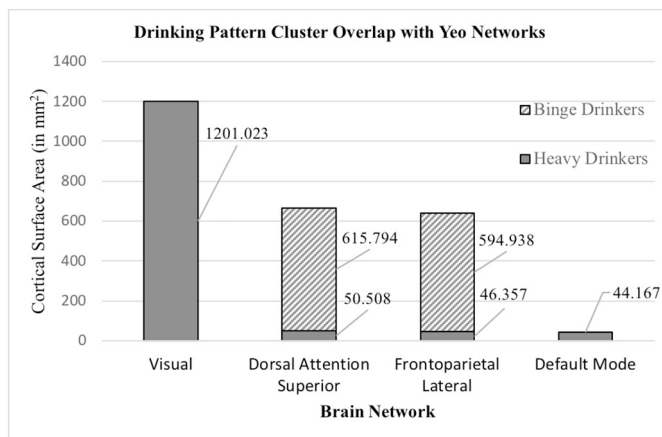
**Fig. 4.** Quantified intersections of significant clusters with Yeo networks. This graph is a quantified representation of each group's cluster overlap with the Yeo 7-Network solution cortical parcellation atlas. The Binge Drinking group's networks are impacted by the Bing Drinking group's cluster in the following way: dorsal attention superior component network is impacted at 50.86% of the entire effect, and the frontoparietal network's lateral component is impacted at 49.14% of the full effect. The impact of Heavy Drinking group's cluster is mostly localized to the visual network, at ~89%, but also impacts other networks in a widespread but comparatively smaller way; the dorsal attention network's superior component is impacted at 3.8% of the full effect, the frontoparietal network's lateral component is impacted at 3.5% of the full effect, and the default mode network is impacted at 3.2%, of the full effect. Relatively negligible intersection measures (below $1.5\,mm^2$) have not been included as they account for less than ~0.35% of the average size of presented intersections.

identify the causes and consequences of neurological changes and the respective drinking patterns. Additionally, a large number of untested premorbid conditions, preceding the onset of drinking, may have impacted participants' neuromorphometry in ways that overlap with, or account for, the current findings. These factors may include in-utero exposure to alcohol, environmental effects (e.g., parental style, early childhood relationships), as well as familial histories of substance abuse. Furthermore, the full effects of comorbid conditions could not be fully controlled, due to a limited sample size. A replication with larger samples will be necessary to confirm the reported effects.

The retrospective nature of clinical and drinking assessments, that was obtained via interview and self-report methods, is prone to biases and recollection error. Although steps were taken to increase the accuracy of these methods, the methodological limitations of self-report should be taken into account. It is also important to note that as part of a sMRI study, we used a cortical parcellation atlas of resting state networks rather than individualized resting state maps. Although the utilized atlas was validated and implemented with a robust surface-based alignment algorithm (based on 1000 participants; (Yeo et al., 2011)), this study would benefit from a replication using each respective subjects' individualized resting state activation. Further, clinical implications of these analyses would be strengthened by a follow-up examination of their associations with carefully selected behavioral measures. Finally, it is important to consider that the analyzed sample consists of previously deployed U.S. Veterans. Although extensive measures were taken to equate the examined groups and minimize the effect of comorbid conditions, mere combat exposure might differentiate this sample from civilian participants. This study would thus benefit from a replication within a civilian sample.

### 4.2. Conclusion

Current data show distinct sMRI-based neuromorphometric signatures of two common types of alcohol misuse (BD and HD).

Individuals with histories of BD present volumetric changes within the globus pallidus as well as cortical thickness changes within the left superior parietal cluster. These regions were previously shown to be involved in reward sensitivity and volitional control of attention. Individuals with histories of HD present with cortical thickness changes within the left medial occipito-parietal cluster. This region has a widespread overlap with cortical network parcellations but is mostly concentrated within the visual network parcellation. The dissociated neuromorphometric findings suggest that different neural mechanisms might be affected in individuals with uncomplicated histories of BD and HD types of alcohol misuse. The AUD population is commonly characterized by a heterogeneous nature of neurological and cognitive changes (Litten et al., 2015). Symptom variability has been attributed to numerous factors, including comorbid conditions (Grant et al., 2015), differing levels of prenatal alcohol exposure (Sulik, 2018), hepatic processing capacity (Wang et al., 2016), and varying age of drinking onset (Barry et al., 2016). Current findings suggest that ways in which individuals consume alcohol (thus, individuals' drinking behavior), constitute an additional factor which might account for some of the heterogeneity in the AUD population. Future studies should focus on disentangling the causes and consequences of neural changes as well as onset of BD and HD types alcohol consumption in order to inform a more targeted characterization and treatment of AUDs.

### References

Adam, R., Leff, A., Sinha, N., Turner, C., Bays, P., Draganski, B., & Husain, M. (2013). Dopamine reverses reward insensitivity in apathy following globus pallidus lesions. *Cerebral Cortex, 49*(5), 1292–1303.

Bagga, D., Khushu, S., Modi, S., Kaur, P., Bhattacharya, D., Garg, M., & Singh, N. (2014). Impaired visual information processing in alcohol-dependent subjects: A proton magnetic resonance spectroscopy study of the primary visual cortex. *Journal of Studies on Alcohol and Drugs, 75*(5), 817–826.

Banca, P., Lange, I., Worbe, Y., Howell, N. A., Irvine, M., Harrison, N. A., ... Voon, V.

(2016). Reflection impulsivity in binge drinking: Behavioural and volumetric correlates. *Addiction Biology, 21*(2), 504–515.

Barry, A. E., King, J., Sears, C., Harville, C., Bondoc, I., & Joseph, K. (2016). Prioritizing alcohol prevention: Establishing alcohol as the gateway drug and linking age of first drink with illicit drug use. *Journal of School Health, 86*(1), 31–38.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society: Series B: Methodological,* 289–300.

Binesh, N., Huda, A., Thomas, M. A., Wyckoff, N., Bugbee, M., Han, S., & Martin, P. (2006). Hepatic encephalopathy: A neurochemical, neuroanatomical, and neuropsychological study. *Journal of Applied Clinical Medical Physics, 7*(1), 86–96.

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., & Keane, T. M. (1995). The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress, 8*(1), 75–90.

Buckner, R. L., Head, D., Parker, J., Fotenos, A. F., Marcus, D., Morris, J. C., & Snyder, A. Z. (2004). A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: Reliability and validation against manual measurement of total intracranial volume. *Neuroimage, 23*(2), 724–738.

Casey, B. J., & Jones, R. M. (2010). Neurobiology of the adolescent brain and behavior: Implications for substance use disorders. *Journal of the American Academy of Child & Adolescent Psychiatry, 49*(12), 1189–1201. https://doi.org/10.1016/j.jaac.2010.08.017.

Chanraud, S., Pitel, A.-L., Pfefferbaum, A., & Sullivan, E. V. (2011). Disruption of functional connectivity of the default-mode network in alcoholism. *Cerebral Cortex, 21*(10), 2272–2281.

Cohen-Gilbert, J. E., Nickerson, L. D., Sneider, J. T., Oot, E. N., Seraikas, A. M., Rohan, M. L., & Silveri, M. (2017). College binge drinking associated with decreased frontal activation to negative emotional distractors during inhibitory control. *Frontiers in Psychology, 8,* 1650.

Córdoba, J., Sanpedro, F., Alonso, J., & Rovira, A. (2002). 1 H magnetic resonance in the study of hepatic encephalopathy in humans. *Metabolic Brain Disease, 17*(4), 415–429.

Correas, A., Cuesta, P., Lopez-Caneda, E., Rodriguez Holguin, S., Garcia-Moreno, L. M., Pineda-Pardo, J. A., ... Maestu, F. (2016). Functional and structural brain connectivity of young binge drinkers: A follow-up study. *Scientific Reports, 6,* 31293. https://doi.org/10.1038/srep31293.

Crawford, J. R., & Henry, J. D. (2003). The Depression Anxiety Stress Scales (DASS): Normative data and latent structure in a large non-clinical sample. *British Journal of Clinical Psychology, 42*(2), 111–131.

Cservenka, A., & Brumback, T. (2017). The burden of binge and heavy drinking on the brain: Effects on adolescent and young adult neural structure and function. *Frontiers in Psychology, 8,* 1111.

Dager, A. D., Austad, C. S., Fallahi, C. R., Pearlson, G. D., Tennen, H., Potenza, M. N., ... Raskin, S. A. (2015). A preliminary prospective study of an escalation in 'maximum daily drinks', fronto-parietal circuitry and impulsivity-related domains in young adult drinkers. *Neuropsychopharmacology, 41*(6), 1637.

Dalvie, S., Brooks, S. J., Cardenas, V., Fein, G., Ramesar, R., & Stein, D. J. (2017). Genetic variation within GRIN2B in adolescents with alcohol use disorder may be associated with larger left posterior cingulate cortex volume. *Acta Neuropsychiatr, 29*(4), 252–258. https://doi.org/10.1017/neu.2016.41.

De Schotten, M. T., Dell'Acqua, F., Forkel, S. J., Simmons, A., Vergani, F., Murphy, D. G., & Catani, M. (2011). A lateralized brain network for visuospatial attention. *Nature Neuroscience, 14*(10).

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., ... Hyman, B. T. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage, 31*(3), 968–980.

Dixon, M. L., Girn, M., & Christoff, K. (2017). Hierarchical organization of frontoparietal control networks underlying goal-directed behavior. *The Prefrontal Cortex as an Executive, Emotional, and Social Brain* (pp. 133–148). .

Donovan, J. E. (2004). Adolescent alcohol initiation: A review of psychosocial risk factors. *Journal of Adolescent Health, 35*(6), e527–e529 529. (e518).

Durazzo, T. C., Mon, A., Pennington, D., Abe, C., Gazdzinski, S., & Meyerhoff, D. J. (2014). Interactive effects of chronic cigarette smoking and age on brain volumes in controls and alcohol-dependent individuals in early abstinence. *Addiction Biology, 19*(1), 132–143. https://doi.org/10.1111/j.1369-1600.2012.00492.x.

Durazzo, T. C., Mon, A., Gazdzinski, S., & Meyerhoff, D. J. (2017). Regional brain volume changes in alcohol-dependent individuals during early abstinence: Associations with relapse following treatment. *Addiction Biology, 22*(5), 1416–1425.

First, M. B., & Gibbon, M. (2004). *The structured clinical interview for DSM-IV Axis I disorders (SCID-I) and the structured clinical interview for DSM-IV Axis II disorders (SCID-II).*

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences, 97*(20), 11050–11055.

Fischl, B., Sereno, M. I., Tootell, R. B., & Dale, A. M. (1999). High-resolution intersubject averaging and a coordinate system for the cortical surface. *Human Brain Mapping, 8*(4), 272–284.

Fischl, B., Liu, A., & Dale, A. M. (2001). Automated manifold surgery: Constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Transactions on Medical Imaging, 20*(1), 70–80.

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., ... Montillo, A. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron, 33*(3), 341–355.

Fischl, B., Salat, D. H., Van Der Kouwe, A. J., Makris, N., Ségonne, F., Quinn, B. T., & Dale, A. M. (2004a). Sequence-independent segmentation of magnetic resonance images.

*Neuroimage, 23,* S69–S84.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D. H., ... Kennedy, D. (2004b). Automatically parcellating the human cerebral cortex. *Cerebral Cortex, 14*(1), 11–22.

Fortier, C. B., Leritz, E. C., Salat, D. H., Venne, J. R., Maksimovskiy, A. L., Williams, V., & McGlinchey, R. E. (2011). Reduced cortical thickness in abstinent alcoholics and association with alcoholic behavior. *Alcoholism: Clinical and Experimental Research, 35*(12), 2193–2201.

Gennatas, E. D., Avants, B. B., Wolf, D. H., Satterthwaite, T. D., Ruparel, K., Ciric, R., ... Gur, R. C. (2017). Age-related effects and sex differences in gray matter density, volume, mass, and cortical thickness from childhood to young adulthood. *Journal of Neuroscience, 37*(20), 5065–5073.

Gilpin, N. W., & Koob, G. F. (2008). Neurobiology of alcohol dependence: Focus on motivational mechanisms. *Alcohol Research & Health, 31*(3), 185.

Gonçalves, Ó. F., Carvalho, S., Leite, J., Fernandes-Gonçalves, A., Carracedo, A., & Sampaio, A. (2016). Gray matter morphological alteration in obsessive compulsive disorder: Evidence for an inhibitory control and emotional regulation disorder. *Principles and Practice of Clinical Research, 2*(2).

Grant, B. F., Goldstein, R. B., Saha, T. D., Chou, S. P., Jung, J., Zhang, H., ... Huang, B. (2015). Epidemiology of DSM-5 alcohol use disorder: Results from the National Epidemiologic Survey on Alcohol and related conditions III. *JAMA Psychiatry, 72*(8), 757–766.

Gray, M. J., Litz, B. T., Hsu, J. L., & Lombardo, T. W. (2004). Psychometric properties of the life events checklist. *Assessment, 11*(4), 330–341.

Gronenschild, E. H., Habets, P., Jacobs, H. I., Mengelers, R., Rozendaal, N., Van Os, J., & Marcelis, M. (2012). The effects of FreeSurfer version, workstation type, and Macintosh operating system version on anatomical volume and cortical thickness measurements. *PLoS One, 7*(6).

Han, X., & Fischl, B. (2007). Atlas renormalization for improved brain MR image segmentation across scanner platforms. *IEEE Transactions on Medical Imaging, 26*(4), 479–486.

Harris, R. A., & Koob, G. F. (2017). The future is now: A 2020 view of alcoholism research. *Neuropharmacology, 122*(1), 1–2.

Heilig, M., & Koob, G. F. (2007). A key role for corticotropin-releasing factor in alcohol dependence. *Trends in Neurosciences, 30*(8), 399–406.

Herman, A. M., Critchley, H. D., & Duka, T. (2018). Binge drinking is associated with attenuated frontal and parietal activation during successful response inhibition in fearful context. *The European Journal of Neuroscience,* 1–14.

Hill, J. C., & Toffolon, G. (1990). Effect of alcohol on sensory and sensorimotor visual functions. *Journal of Studies on Alcohol, 51*(2), 108–113.

Hommer, D. W., Momenan, R., Kaiser, E., & Rawlings, R. R. (2001). Evidence for a gender-related effect of alcoholism on brain volumes. *American Journal of Psychiatry, 158*(2), 198–204.

Hong, S., & Hikosaka, O. (2008). The globus pallidus sends reward-related signals to the lateral habenula. *Neuron, 60*(4), 720–729.

Howell, N. A., Worbe, Y., Lange, I., Tait, R., Irvine, M., Banca, P., ... Voon, V. (2013). Increased ventral striatal volume in college-aged binge drinkers. *PloS one, 8*(9).

JMP® (1989–2007). *SAS Institute Inc. (Version 12). Cary, NC.*

Juhás, M., Sun, H., Brown, M. R., MacKay, M. B., Mann, K. F., Sommer, W. H., & Greenshaw, A. J. (2017). Deep grey matter iron accumulation in alcohol use disorder. *Neuroimage, 148,* 115–122.

Kim, S., Im, S., Lee, J., & Lee, S. G. (2017). Disrupted control network connectivity in abstinent patients with alcohol dependence. *Psychiatry Investigation, 14*(3), 325–332.

King, D., King, L., & Vogt, D. (2003). *Manual for the Deployment Risk and Resilience Inventory (DRRI): A collection of measures for studying deployment-related experiences of military veterans.* Boston, MA: National Center for PTSD.

Koob, G. F. (2009). Neurobiological substrates for the dark side of compulsivity in addiction. *Neuropharmacology, 56,* 18–31.

Koob, G. F., & Le Moal, M. (2005). Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. *Nature Neuroscience, 8*(11), 1442–1444. https://doi.org/10.1038/nn1105-1442.

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology, 35*(1), 217.

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. *The Lancet Psychiatry, 5*(8), 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8.

Lisdahl, K. M., Thayer, R., Squeglia, L. M., McQueeny, T. M., & Tapert, S. F. (2013). Recent binge drinking predicts smaller cerebellar volumes in adolescents. *Psychiatry Research: Neuroimaging, 211*(1), 17–23. https://doi.org/10.1016/j.pscychresns.2012.07.009.

Litten, R. Z., Ryan, M. L., Falk, D. E., Reilly, M., Fertig, J. B., & Koob, G. F. (2015). Heterogeneity of alcohol use disorder: Understanding mechanisms to advance personalized treatment. *Alcoholism: Clinical and Experimental Research, 39*(4), 579–584.

Majerus, S., Péters, F., Bouffier, M., Cowan, N., & Phillips, C. (2017). The dorsal attention network reflects both encoding load and top–down control during working memory. *Journal of Cognitive Neuroscience,* 1–16 Early Access.

Maksimovskiy, A. L., McGlinchey, R. E., Fortier, C. B., Salat, D. H., Milberg, W. P., & Oscar-Berman, M. (2014). White matter and cognitive changes in veterans diagnosed with alcoholism and PTSD. *Journal of Alcoholism and Drug Dependence, 2*(1).

Mayhugh, R. E., Moussa, M. N., Simpson, S. L., Lyday, R. G., Burdette, J. H., Porrino, L. J., & Laurienti, P. J. (2016). Moderate-heavy alcohol consumption lifestyle in older adults is associated with altered central executive network community structure during cognitive task. *PLoS One, 11*(8).

McGlinchey, R. E., Milberg, W. P., Fonda, J. R., & Fortier, C. B. (2017). A methodology for assessing deployment trauma and its consequences in OEF/OIF/OND veterans: The TRACTS longitudinal prospective cohort study. *International Journal of Methods in*

*Psychiatric Research, 26*(3), e1556.

Mechtcheriakov, S., Brenneis, C., Egger, K., Koppelstaetter, F., Schocke, M., & Marksteiner, J. (2007). A widespread distinct pattern of cerebral atrophy in patients with alcohol addiction revealed by voxel-based morphometry. *Journal of Neurology, Neurosurgery, and Psychiatry, 78*(6), 610–614. https://doi.org/10.1136/jnnp.2006. 095869.

Moussawi, K., Kalivas, P. W., & Lee, J. W. (2016). Abstinence from drug dependence after bilateral globus pallidus hypoxic-ischemic injury. *Biological Psychiatry, 80*(9), e79–e80.

Müller-Oehring, E., Jung, Y., Sullivan, E., Hawkes, W., Pfefferbaum, A., & Schulte, T. (2013). Midbrain-driven emotion and reward processing in alcoholism. *Neuropsychopharmacology, 38*(10), 1844–1853.

Müller-Oehring, E. M., Jung, Y. C., Pfefferbaum, A., Sullivan, E. V., & Schulte, T. (2014). The resting brain of alcoholics. *Cerebral Cortex, 25*(11), 4155–4168.

N.I.A.A.A (2016). Drinking levels defined. Retrieved from https://www.niaaa.nih.gov/ alcohol-health/overview-alcohol-consumption/moderate-binge-drinking.

N.I.A.A.A (2017). Alcohol facts and statistics. Retrieved from https://www.niaaa.nih. gov/alcohol-health/overview-alcohol-consumption/alcohol-facts-and-statistics.

Nardelli, A., Lebel, C., Rasmussen, C., Andrew, G., & Beaulieu, C. (2011). Extensive deep gray matter volume reductions in children and adolescents with fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research, 35*(8), 1404–1417.

Nicholson, M. E., Andre, J. T., Tyrrell, R. A., Wang, M., & Leibowitz, H. W. (1995). Effects of moderate dose alcohol on visual contrast sensitivity for stationary and moving targets. *Journal of Studies on Alcohol, 56*(3), 261–266.

Pearson, P., & Timney, B. (1998). Effects of moderate blood alcohol concentrations on spatial and temporal contrast sensitivity. *Journal of Studies on Alcohol, 59*(2), 163–173.

Petersen, C. L., & Zettle, R. D. (2009). Treating inpatients with comorbid depression and alcohol use disorders: A comparison of acceptance and commitment therapy versus treatment as usual. *The Psychological Record, 59*(4), 521–536.

Rando, K., Hong, K. I., Bhagwagar, Z., Li, C. S., Bergquist, K., Guarnaccia, J., & Sinha, R. (2011). Association of frontal and posterior cortical gray matter volume with time to alcohol relapse: A prospective study. *The American Journal of Psychiatry, 168*(2), 183–192. https://doi.org/10.1176/appi.ajp.2010.10020233.

Salat, D. H., Lee, S. Y., Van der Kouwe, A., Greve, D. N., Fischl, B., & Rosas, H. D. (2009). Age-associated alterations in cortical gray and white matter signal intensity and gray to white matter contrast. *Neuroimage, 48*(1), 21–28.

Sawyer, K. S., Oscar-Berman, M., Barthelemy, O. J., Papadimitriou, G. M., Harris, G. J., & Makris, N. (2017). Gender dimorphism of brain reward system volumes in alcoholism. *Psychiatry Research: Neuroimaging, 263*, 15–25.

Scaife, J. C., & Duka, T. (2009). Behavioural measures of frontal lobe function in a population of young social drinkers with binge drinking pattern. *Pharmacology Biochemistry and Behavior, 93*(3), 354–362. https://doi.org/10.1016/j.pbb.2009.05. 015.

Ségonne, F., Dale, A. M., Busa, E., Glessner, M., Salat, D., Hahn, H. K., & Fischl, B. (2004). A hybrid approach to the skull stripping problem in MRI. *Neuroimage, 22*(3), 1060–1075.

Ségonne, F., Pacheco, J., & Fischl, B. (2007). Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Transactions on Medical Imaging, 26*(4), 518–529.

Shokri-Kojori, E., Tomasi, D., Wiers, C. E., Wang, G. J., & Volkow, N. D. (2017). Alcohol affects brain functional connectivity and its coupling with behavior: Greater effects in male heavy drinkers. *Molecular Psychiatry, 22*(8), 1185–1195.

Skinner, H., & Sheu, W.-J. (1982). Reliability of alcohol use indices. The lifetime drinking history and the MAST. *Journal of Studies on Alcohol, 43*(11), 1157–1170.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., ... Flitney, D. E. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23*, S208–S219.

Squeglia, L. M., Sorg, S. F., Schweinsburg, A. D., Wetherill, R. R., Pulido, C., & Tapert, S. F. (2012). Binge drinking differentially affects adolescent male and female brain morphometry. *Psychopharmacology, 220*(3), 529–539. https://doi.org/10.1007/ s00213-011-2500-4.

Squeglia, L. M., Rinker, D. A., Bartsch, H., Castro, N., Chung, Y., Dale, A. M., ... Tapert, S. F. (2014). Brain volume reductions in adolescent heavy drinkers. *Developmental Cognitive Neuroscience, 9*, 117–125. https://doi.org/10.1016/j.dcn.2014.02.005.

Sulik, K. K. (2018). Prenatal alcohol exposure and abnormal brain development–findings from basic research. *Ethical and Legal Perspectives in Fetal Alcohol Spectrum Disorders (FASD)* (pp. 37–48). Springer.

Sullivan, E. V., Deshmukh, A., De Rosa, E., Rosenbloom, M. J., & Pfefferbaum, A. (2005). Striatal and forebrain nuclei volumes: contribution to motor function and working memory deficits in alcoholism. *Biological Psychiatry, 57*(7), 768–776.

Volkow, N. D., Ma, Y., Zhu, W., Fowler, J. S., Li, J., Rao, M., ... Wang, G.-J. (2008). Moderate doses of alcohol disrupt the functional organization of the human brain. *Psychiatry Research: Neuroimaging, 162*(3), 205–213.

Wang, G. J., Volkow, N. D., Franceschi, D., Fowler, J. S., Thanos, P. K., Scherbaum, N., ... Felder, C. A. (2000). Regional brain metabolism during alcohol intoxication. *Alcoholism: Clinical and Experimental Research, 24*(6), 822–829.

Wang, F., Li, Y., Zhang, Y.-J., Zhou, Y., Li, S., & Li, H.-B. (2016). Natural products for the prevention and treatment of hangover and alcohol use disorder. *Molecules, 21*(1), 64.

Watson, T. D., Newton-Mora, M., & Pirkle, J. (2016). Event-related potential correlates of processing alcohol-related pictures in young adult binge drinkers. *The American Journal of Drug and Alcohol Abuse, 42*(1), 77–87. https://doi.org/10.3109/00952990. 2015.1099660.

Watten, R. G., Magnussen, S., & Greenlee, M. W. (1998). Spatial-frequency discrimination, brain lateralisation, and acute intake of alcohol. *Perception, 27*(6), 729–736.

Weathers, F. W., Ruscio, A. M., & Keane, T. M. (1999). Psychometric properties of nine scoring rules for the Clinician-administered Posttraumatic Stress Disorder Scale. *Psychological Assessment, 11*(2), 124.

Weathers, F. W., Keane, T. M., & Davidson, J. R. (2001). Clinician-Administered PTSD Scale: A review of the first ten years of research. *Depression and Anxiety, 13*(3), 132–156.

Wechsler, D. (2001). *Wechsler Test of Adult Reading: WTAR.* Psychological Corporation.

Weiland, B. J., Heitzeg, M. M., Zald, D., Cummiford, C., Love, T., Zucker, R. A., & Zubieta, J.-K. (2014). Relationship between impulsivity, prefrontal anticipatory activation, and striatal dopamine release during rewarded task performance. *Psychiatry Research: Neuroimaging, 223*(3), 244–252.

Woolrich, M. W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., ... Smith, S. M. (2009). Bayesian analysis of neuroimaging data in FSL. *Neuroimage, 45*(1), S173–S186.

Yeo, T. B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., ... Fischl, B. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology, 106*(3), 40.

Zahr, N. M., & Pfefferbaum, A. (2017). Alcohol's effects on the brain: Neuroimaging results in humans and animal models. *Alcohol Research: Current Reviews, 38*(2), 183.