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Relationships between drinking quantity and frequency and behavioral and hippocampal BOLD responses during working memory performance involving allocentric spatial navigation in college students

Barbara C. Banz[a,b,*], Patrick D. Worhunsky[b], Brian P. Pittman[b], Robert S. Astur[c], Howard A. Tennen[d], Sarah A. Raskin[e], Carol S. Austad[f], Rebecca M. Wood[f], Carolyn R. Fallahi[f], Marc N. Potenza[b,g,h,i,j,1], Godfrey D. Pearlson[b,g,k,1]

[a] Developmental Neurocognitive Driving Simulation Research Center (DrivSim Lab), Department of Emergency Medicine, Yale University School of Medicine, 464 Congress Avenue, Suite 272, New Haven, CT, 06519, USA
[b] Department of Psychiatry, Yale University School of Medicine, 1 Church Street, 7thFloor, New Haven, CT, 06511, USA
[c] Department of Psychological Sciences, University of Connecticut, Bousfield Psychology Building, 406 Babbidge Road, Unit 1020, Storrs, CT, 06269, USA
[d] Department of Community Medicine and Healthcare, University of Connecticut School of Medicine, 195 Farmington Avenue, Suite 210, Farmington, CT, 06032, USA
[e] Department of Psychology, Trinity College, Life Sciences Center, Hartford, CT, 06106, USA
[f] Department of Psychological Science, Central Connecticut State University, Marcus White 228, 1615 Stanley Street, New Britain, CT, 06050, USA
[g] Department of Neuroscience, Yale University School of Medicine, 200 South Frontage Road, New Haven, CT, 06519, USA
[h] Child Study Center, Yale University School of Medicine, 230 South Frontage Road, New Haven, CT, 06519, USA
[i] The National Center on Addiction and Substance Abuse, Yale University School of Medicine, New Haven, CT, 06519, USA
[j] The Connecticut Mental Health Center, 34 Park Street, New Haven, CT, 06519, USA
[k] Olin Neuropsychiatry Research Center, Hartford Hospital/Institute of Living, 200 Retreat Avenue, Hartford, CT, 06114, USA

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ABSTRACT

Background: Quantity and frequency of drinking may be used to effectively quantify the severity of alcohol-use. Drinking-severity has been related to neurocognitive impairments in such domains as spatial working memory (SWM). Youth drinking has been associated with altered neurofunctional underpinnings of SWM. The current study examined the relationship between drinking-severity and SWM processing.

Methods: One-hundred-and-seventy college drinkers reported the maximum number of drinks in a 24 -h period in the last six-months (quantity) and average number of drinking weeks in the last six-months (frequency). All participants performed a virtual Morris Water Task during fMRI which included trials where the target platform was visible or hidden.

Results: Greater quantity was associated with reduced SWM-related activity in the dorsolateral prefrontal cortex ($F(1, 167) = 4.15$, $p = .04$). Greater frequency was associated with reduced SWM-related activity in the hippocampus ($F(1, 167) = 4.34$, $p = 0.039$). Greater quantity was associated with longer search times ($r = 0.21$, $p = .005$) and greater platforms found ($r = 0.19$, $p = .01$) in VISIBLE trials. We did not find a relationship between drinking quantity or frequency and gender on SWM-related activity, although men found more platforms in both HIDDEN ($F(1, 168) = 11.7$, $p = 0.0008$) and VISIBLE ($F(1, 168) = 23.0$, $p < .0001$) trials compared to women.

Conclusions: Altered SWM-related hippocampal function relating to alcohol use in young adults raises questions regarding the impact on young adult health and the nature of the findings. Future studies should examine whether these differences may lead to cognitive deficits later in life.

* Corresponding author at: 464 Congress Avenue, Suite 272, New Haven, CT, 06519, USA.
E-mail addresses: barbara.banz@yale.edu (B.C. Banz), patrick.worhunsky@yale.edu (P.D. Worhunsky), brian.pittman@yale.edu (B.P. Pittman), robert.astur@uconn.edu (R.S. Astur), tennen@uchc.edu (H.A. Tennen), sarah.raskin@trincoll.edu (S.A. Raskin), austad@ccsu.edu (C.S. Austad), woodre@ccsu.edu (R.M. Wood), fallahic@ccsu.edu (C.R. Fallahi), marc.potenza@yale.edu (M.N. Potenza), godfrey.pearlson@yale.edu (G.D. Pearlson).
[1] Authors contributed equally to the generation of the manuscript

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1. Introduction

High-risk alcohol-use is prevalent during youth (Naimi et al., 2003), especially college students (O'Malley and Johnston, 2002). Early-life alcohol-use has been related to subsequent alcohol-use disorders (AUDs) (Chassin et al., 2002; DeWit et al., 2000) and alcohol-related deaths (Rehm et al., 2009). Whereas many correlates/consequences of early-life alcohol-use have been investigated, less is known regarding alcohol-use and brain function in college students (Worhunsky et al., 2016; Dager et al., 2014). The present study evaluated two drinking-severity components and neuroimaging and behavioral performance related to a virtual Morris Water Task (vMWT), a spatial working memory (SWM) test.

Alcohol consumption during youth may have neurotoxic effects (Peeters et al., 2014; Jacobus and Tapert, 2013), possibly due to neuronal fragility during neuromaturation (Spear, 2015). Greater neurocognitive impairment has been related to greater drinking quantity and frequency. Greater quantity of drinks during a single occasion has been related to diminished fronto-parietal-circuitry engagement during response inhibition (Worhunsky et al., 2016). Differential activation of memory-related and default-mode regions has been related to greater quantity and/or frequency of drinking (Dager et al., 2014; Squeglia et al., 2011; Tapert et al., 2004). Data suggest important relationships between drinking-severity (both quantity and frequency) and impaired neurocognition (Squeglia et al., 2014; Ewing et al., 2014). Due to differences in relationships with drinking frequency and quantity, separate evaluation of these measures is warranted.

Impairment in SWM has been reported in alcohol-consuming youth, possibly reflecting differences in neural activation during tasks probing egocentric SWM (i.e., self-to-object positioning) in youth with AUDs (Tapert et al., 2004). Gender-related differences suggest unique vulnerabilities. Men with AUDs perform better than either gender controls, and women with AUDs perform worse than all groups; neural activation in men with AUDs deviates less from the activation of controls than do those of women with AUDs (Caldwell et al., 2005). This pattern is also evident in binge-drinking adolescents (Squeglia et al., 2011), suggesting gender and youth drinking may influence SWM processing.

Although previous studies have investigated alcohol and gender effects on egocentric SWM, their influences on allocentric SWM (i.e., object-to-object positioning) are less well understood. Tasks such as the vMWT rely on allocentric spatial navigation (Astur et al., 2002) and learning and memory (Folley et al., 2010). The vMWT was developed as a human analogue of the rodent Morris Water Task employed to investigate hippocampal function via allocentric spatial navigation (Astur et al., 1998). The vMWT, in which individuals navigate within a virtual pool of water to find a goal platform, differs from prior SWM tasks. The vMWT requires subjects to attend to, organize, update and rehearse task-relevant information, and thus the task draws heavily on working memory (Folley et al., 2010). The hidden condition measures both working and allocentric memory and relies on widespread functional networks involving frontal and temporal regions, insula, inferior parietal cortex and caudate (Folley et al., 2010). During control trials (platform-visible condition), individuals rely on explicit navigation and must learn spatial relationships between spatial cues and platform locations. Visible trials are also linked to frontal and mesial temporal regions invoked by hidden trials but uniquely involve anterior cingulate cortex (ACC; Folley et al., 2010). Allocentric tasks (i.e., vMWT) may provide translational insight into spatial learning and memory and longer-term neurocognitive deficits.

vMWT performance relies on multiple neural regions. The hippocampus, parahippocampal gyrus (PHG), fusiform gyrus, ACC, putamen, visual cortex, dorsolateral prefrontal cortex (DLPFC) and other frontal regions have been implicated (Folley et al., 2010; Antonova et al., 2009; Shipman and Astur, 2007; Spiers and Maguire, 2007; Warburton et al., 1998). The vMWT may rely on hippocampal functioning due to allocentric spatial navigation and learning and memory components. Differential activation of these regions has been associated with youth drinking (Squeglia et al., 2014; Ewing et al., 2014; Squeglia et al., 2011) and with adult AUDs (Vollstädt-Klein et al., 2010; Charlet et al., 2014) during egocentric SWM task performance. The current study may help delineate similarities in deficits among young-adult drinking and clinical populations. Non-human-primate and rat models suggest the adolescent hippocampus may be highly vulnerable to alcohol damage (Taffe et al., 2010; Crews et al., 2007; Markweise et al., 1998). However, findings relating drinking-severity to hippocampal volume in humans appear inconsistent (Nagel et al., 2005; DeBellis et al., 2000), although Meda et al. (2018) demonstrated alcohol dose-related longitudinal volume documents in the same college sample studied here. Therefore, using a task that engages these regions may help clarify seemingly inconsistent findings.

Neurocognitive deficits related to youth drinking are widespread (Squeglia et al., 2014; Ewing et al., 2014; Pascual et al., 2007). Our study sought to evaluate the relationships between drinking-severity measures (quantity, frequency) and behavioral and brain measures of SWM. We hypothesized that differences in SWM-related activations and poorer task performance would relate to drinking-severity (larger quantities, higher frequencies). We also hypothesized gender-related differences in the relationships of drinking-severity to SWM, with men performing better than women, particularly among individuals with more severe drinking patterns.

2. Materials and methods

2.1. Participants

Two-hundred-and-sixty first-year undergraduate students (141 female) were recruited from two colleges/universities in northeastern United States as part of the NIAAA-funded Brain and Alcohol Research in College Students (BARCS) program which recruited mainly freshman (> 95%) through school emails, flyers, and classroom visits (Meda et al., 2017; Worhunsky et al., 2016; Dager et al., 2014). Study procedures were approved by institutional review boards at Trinity College, Central Connecticut State University, Hartford Hospital, and Yale University. Each participant provided written informed consent. Individuals were excluded from fMRI procedures due to history of seizures or traumatic brain injuries, positive urine screens for drugs of abuse, positive alcohol breathalyzer screens, current pregnancies, or diagnoses of schizophrenia or bipolar disorder (assessed through the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998)). Four participants were excluded based on Structured Clinical Interview for the DSM-IV (SCID; First et al., 2001) report of alcohol or drug abuse. Participants with incomplete task data (N = 7), those reporting no lifetime drinking (N = 40), or those exhibiting excessive motion (N = 39; criteria below) were excluded from all analyses. The number of participants excluded due to in-scanner movement is rather high, but given multiple recent publications emphasizing confounding effects of fMRI movement artifacts (Goto et al., 2016), we believe erring on the side of caution is advisable. Demographic and drinking information for excluded individuals is listed in Table S1.

2.2. Drinking assessment

Current and past alcohol-use was assessed through an in-house interview using items from the Semi-Structured Assessment for the Genetics of Alcoholism (Bucholz et al., 1994), SCID (First et al., 2001), and MINI (Sheehan et al., 1998). The Fagerström Test of Nicotine Dependence (FTND; Heatherton et al., 1991), Family History Assessment Module for family history of alcohol dependence (Rice et al., 1995), and a handedness questionnaire were administered. Comorbid alcohol and substance use is relatively low in BARCS participants (Meda et al., 2017; Table S2). Drinking quantity was defined by participant response to the following question: "What is the largest number of drinks you

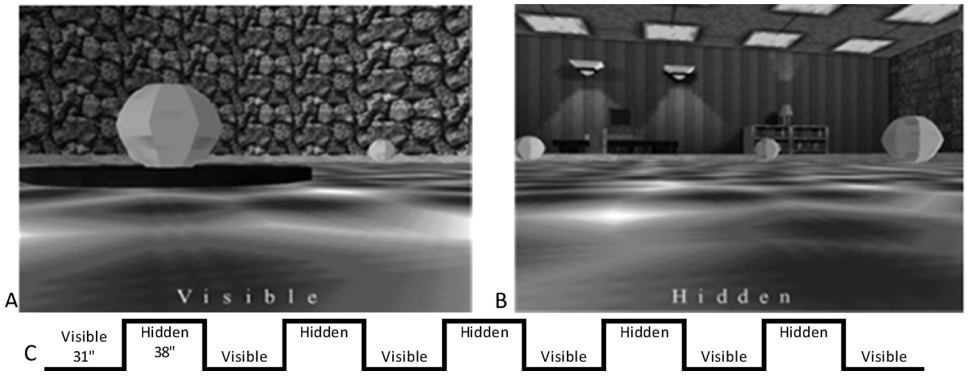

Fig. 1. The Virtual Water Maze Task. Grayscale examples of a VISIBLE trial search with platform and masked walls (A) and a HIDDEN trial with no platforms and unmasked walls (B). Diagram C depicts the presentation timeline of one run. (Folley et al., 2010). Fig. S1 is the color version of the task.

have had in a 24 -h period in the past 6-months?" (Fig. S1). Frequency was defined by participant response to the following question: "How many weeks did you drink in the last 6-months?" (Fig. S1). These two measures were chosen *a priori* for defining drinking-severity in the last 6-months as they are identical to those successfully used in previous work from our group (Meda et al., 2017; Worhunsky et al., 2016; Dager et al., 2014, 2013).

2.3. vMWT

This study used a block design with VISIBLE and HIDDEN conditions (Folley et al., 2010). Participants joystick-navigated through a pool within a room to find platforms. During HIDDEN trials, cues (e.g., furniture) were at set locations. During VISIBLE trials, a brick wall kept participants from using cues to remember platform locations. Four identical yellow balls hovered in the centers of each quadrant as possible references for the platform, which was below one of the balls, in both condition-types. During VISIBLE trials, the platform was visible directly underneath the yellow ball and the water (grayscale version Fig. 1A; color version Fig. S2A). However, during HIDDEN trials, the platform was not visible below the water's surface (grayscale version Fig. 1B; color version Fig. S2B). The platform was in the same location for both VISIBLE and HIDDEN trials throughout the experiment. Each trial began by participants being randomly "dropped" in one of four quadrants (north, south, east, or west). When a platform was found, "Congratulations!" would appear on the screen. The trial length was fixed. Once a platform was found, the participant would reenter the pool to search for the platform as many times as possible. Therefore, the total number of events was dependent on how quickly participants found the platform; the number of platforms found in the VISIBLE trials across all three blocks ranged from 13 to 35 (SD = 4.1) and in the HIDDEN trials across all three blocks ranged from 8 to 25 (SD = 3.3). Trial errors occurred if a participant navigated to an incorrect cue. A buzzer would sound until the participant navigated away from the incorrect cue. Unsuccessful trials would occur if the individual moved throughout the pool without finding the platform during the trial time. When time expired, participants were moved to the next block condition.

Practice vMWT trials were completed in a mock scanner to allow participants to become comfortable with the task and scanner environment. Practice trials included 16 HIDDEN trials, 4 VISIBLE trials, and one probe trial in which the target platform was not included. During HIDDEN and VISIBLE practice trials, the platform was in the same environment as that which was used in the scanner. However, as there is a high wall occluding the room and any room or geometric cues within the VISIBLE condition, participants were unable to learn the placement of the platforms. Once practice trials were successfully completed, participants performed the fMRI task. During scanning, each participant completed three blocks of trials, composed of six VISIBLE and five HIDDEN conditions. Each trial began with a 3s-instruction cue indicating condition-type ("VISIBLE" or "HIDDEN") as the participant was being "dropped" into the pool and before the individual could navigate the pool. Each VISIBLE trial was 31 s and each HIDDEN trial was 38 s, inter-trial intervals between blocks were 2.4 s, and each block of trials lasted 7 m 13 s (Fig. 1C).

In both HIDDEN and VISIBLE trials, four factors assessed performance. Performance measures included average number of successfully found platforms, time (minutes), distance travelled to find platforms (arbitrary units) and searching-related errors. As condition blocks were fixed times, search times was calculated from time being dropped into the pool to finding the platform. Therefore, search times varied between participants.

2.4. Neuroimaging

Functional neuroimaging data were acquired using a Siemens Allegra 3 T scanner at the Olin Neuropsychiatry Research Center. Images were collected using an echoplanar image gradient-echo pulse sequence (TR = 1.86 s, TE = 27 ms, Flip = 70°, 64 × 64, 3.4 x 3.4 mm in-plane resolution, 3 mm slice thickness, 1 mm gap, 36 slices) that covered the brain from the frontal pole to the parieto-occipital fissure. Runs consisted of 230 timepoints. A T1 weighted axial MPRAGE structural image was acquired (TR = 2500, TE = 2.74, Flip = 8°, 1 mm, 0 gap, 176 slices).

2.5. Image processing and analysis

Functional images were preprocessed with SPM12 (Wellcome Functional Imaging Laboratory, London, UK). Data were realigned and normalized into Montreal-Neurological-Institute space with 3 × 3 x 3 mm voxels, smoothed with a 6-mm FWHM Gaussian kernel. Participants (N = 39) with excessive motion during scanning (> 1 voxel displacement) resulting in < 2 runs without excessive motion were removed from analyses.

Individual data were modeled using a block design (i.e., HRF-convolved 30 s boxcar design) for HIDDEN and VISIBLE conditions (Shipman and Astur, 2007). As the majority of each block consisted of searching, this design was selected to model loading on SWM-related regional activity relative to more phasic activity that might be expected from instances of finding individual platforms. Individual data were modeled using a block design for HIDDEN and VISIBLE conditions (Shipman and Astur, 2007). Effects of HIDDEN and VISIBLE conditions were estimated through a General Linear Model for each voxel with motion-correction parameters included as regressors.

2.6. Regions of interest

Individual differences in drinking behavior related to SWM-related

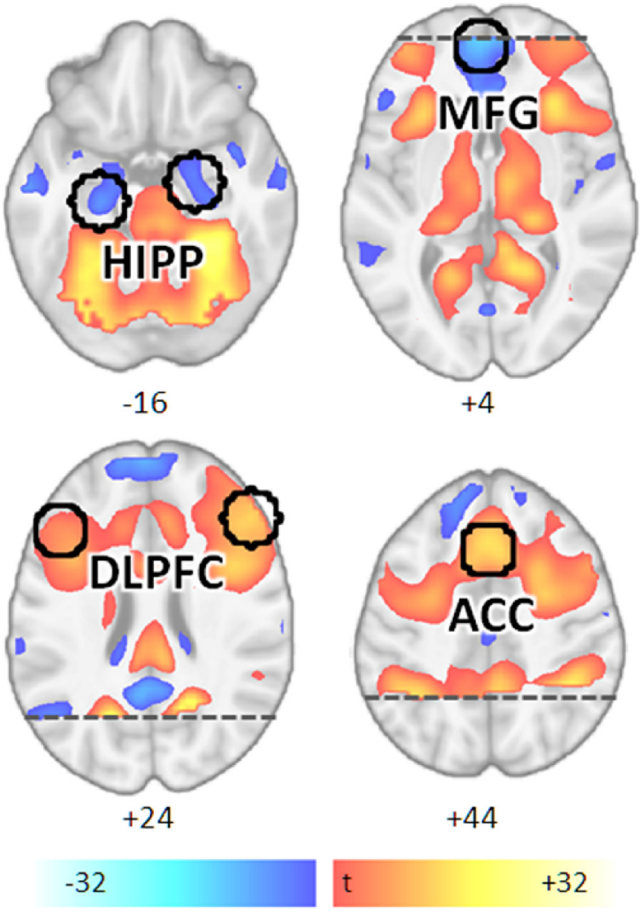

Fig. 2. Regions of interest for spatial working memory processing during vMWT task focusing on HIDDEN-VISIBLE condition contrasts. The circles represent the regions of interest. Positive activation (yellow-red) represents regions having greater activation during HIDDEN trials, negative activation (blue coloring) represents regions having greater activation during VISIBLE trials. Frontal pole to parieto-occipital fissure scanning cutoffs are represented by dotted lines (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

activity were examined using a region-of-interest-based (ROI-based) analysis. Regions were selected from previous SWM research employing the current task or functionally similar ones: DLPFC, middle frontal gyrus (MFG), ACC, and hippocampus (Folley et al., 2010; Antonova et al., 2009; Shipman and Astur, 2007; Spiers and Maguire, 2007; Warburton et al., 1998). To identify SWM-related activity within those regions in the current study, the within-subject contrast of HIDDEN-VISIBLE conditions (HID-VIS) across all participants was performed at a voxel-level family-wise-error-corrected (FWE) threshold of pFWE < 0.00001 (Fig. 2). Spherical volumes (radius = 12 mm) around peak activity were then used to examine activity within ROIs. Bilateral spheres were generated for the DLPFC and hippocampus ROIs.

2.7. Statistical analysis

Outcome and predictor variables were assessed for normality using normal probability plots, Kolmogorov test statistics, and subsequently, model residual plots. All variables were sufficiently normally distributed. Activation levels were compared using a linear mixed model that included region (4 ROIs) and condition (VISIBLE, HIDDEN) as within-subject factors, difference in distance travelled between conditions (HID-VIS distance) as a covariate, and random-subject effects. Least-square means were compared post-hoc to determine the nature of significant effects. The best-fitting variance-covariance structure was determined by information criteria. Gender effects (between-subjects) were tested in the above model.

A separate mixed model was used for each ROI to evaluate the effects of drinking on ROI activation. Due to correlations between quantity and frequency of drinking (r = 0.69), each was tested separately. Models included condition as a within-subject factor, drinking quantity/frequency as a continuous predictor, HID-VIS distance as a covariate, and random-subject effects. Gender was tested as a between-subjects effect. Levels of association between drinking and activations were tested by estimating slopes for each condition and/or gender. Both unadjusted and Bonferroni-adjusted (for 4 ROIs) *p*-values are presented.

Each performance outcome was evaluated in a mixed model with condition included as a within-subjects effect. Effects of drinking and gender were tested in the model. All analyses were conducted using SAS, version 9.4 (Cary, NC).

3. Results

3.1. Participant demographics

Participants (N = 170; 85 women) had a mean age of 18.42 (SD = .7) years; 75% were Caucasian, 10% black/African-American, 6.5% Asian, 0.4% Native American, 5% Latino, and 9.2% Hispanic. Participants were university freshman at one of two local colleges/universities with a mean IQ score in the Wechsler Adult Intelligence Scale of 109.4 (SD = 11.3; Wechsler, 2008), a mean Hollingshead socioeconomic score of 12.65 (SD = 5.6), and performed adequately on measures of visuospatial and executive functioning (CogState Groton Maze Learning Task (mean number of total errors was 10.3 (SD = 5.97; Pietrzak et al., 2008), Two-back Memory (mean accuracy was 1.06 (SD = .39)). Twenty-nine participants reported very low nicotine dependence (mean FTND score = .72); none self-reported high levels of nicotine dependence. Participants reported a mean maximum of 9.09 (SD = 7.02) drinks per 24 -hs in the last six-months, and drank a mean of 10.39 (SD = 8.96) weeks in the past six-months. There was a significant correlation between drinking quantity and frequency (r = .69, $p < .01$; Fig. S2). Performance data by gender are presented (Table 1).

Table 1
Participant Demographic Information, Drinking Behaviors, and vMWT Performance.

Variable	Men	Women	Total
Age, years (SD)	18.83 (.73)	18.80 (.82)	18.81 (.78)
Drinking Behavior (SD)			
Frequency*	12.35 (9.65)	8.48 (7.76)	10.42 (8.94)
Quantity*	11.57 (7.56)	6.62 (5.44)	9.09 (7.02)
HIDDEN-VISIBLE (SD)			
Distance	−35.12 (27.27)	−31.11 (29.71)	−33.11 (28.50)
Time	−0.79 (0.54)	−0.65 (0.52)	−0.72 (0.53)
Errors	−0.36 (1.99)	−0.07 (1.78)	−0.22 (1.89)
Platforms	−6.29 (4.55)	−5.06 (3.94)	−5.68 (4.29)
HIDDEN (SD)			
Distance*	106.74 (15.49)	112.78 (16.48)	109.76 (16.23)
Time*	2.27 (0.35)	2.10 (0.36)	2.19 (0.36)
Errors*	0.65 (1.08)	1.07 (1.59)	0.86 (1.37)
Platforms*	18.8 (3.21)	17.14 (3.11)	17.97 (3.26)
VISIBLE (SD)			
Distance	141.84 (14.52)	143.88 (16.58)	142.86 (15.57)
Time*	3.06 (0.44)	2.75 (0.40)	2.91 (0.45)
Errors	1.04 (2.56)	1.16 (2.12)	1.10 (2.34)
Platforms*	25.08 (4.07)	22.25 (3.63)	23.66 (4.10)

Performance measures for distance in arbitrary virtual distance units, average time per condition block in minutes, average number of errors per condition block, and average number of platforms successfully found per condition block.
* Denotes significant gender difference, p < .05.

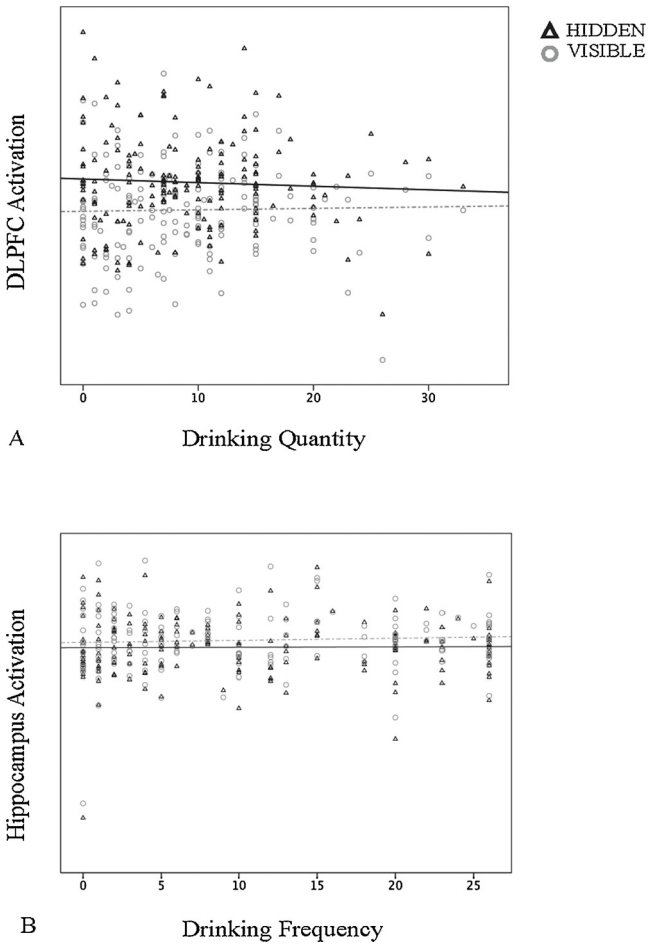

Fig. 3. Comparing activation during HIDDEN and VISIBLE search conditions by drinking-severity measure. A. The relationship between DLPFC activation and drinking; B. the relationship between hippocampus activation and drinking frequency.

3.2. ROI activation

Mixed model analyses revealed a condition-by-region interaction (F (31,183) = 315, $p < .0001$) explained by greater MFG ($p < .0001$) and bilateral hippocampal ($p < .0001$) activation during VISIBLE versus HIDDEN trials, and greater ACC ($p < .0001$) and bilateral DLPFC ($p < .0001$) activation during HIDDEN versus VISIBLE trials.

3.3. ROI activation and drinking

An interaction between condition and the maximum number of drinks in 24-hs in the last six-months implicated the DLPFC (F (1167) = 4.15, $p = .04$ ($p_{Bonferroni} = .16$)). Differences in activation between trials were greatest at lower observed quantities of drinking, with differences diminishing as drinking quantities increased (Fig. 3A). An interaction between condition and drinking frequency implicated the hippocampus (F(1167) = 4.34, $p = 0.039$ ($p_{Bonferroni} = .16$)). Differences in activation between trials were greatest at higher observed frequencies of drinking (Fig. 3B). No association between quantity or frequency of drinking and activation was observed in the ACC and MFG.

3.4. Task performance

Participants found fewer platforms (F(1169) = 294, $p < .0001$, $p_{Bonferroni} < .0001$), spent less time searching (F(1169) = 308, $p < .0001$, $p_{Bonferroni} < .0001$), and travelled shorter distances (F (1169) = 229, $p < .0001$, $p_{Bonferroni} < .0001$) during HIDDEN compared to VISIBLE conditions. Although fewer errors were committed during hidden trials, the difference was not statistically significant (F (1169) = 2.83, p = 0.09, $p_{Bonferroni} = .36$). Participants with higher quantities of drinking spent more time searching ($r = 0.21$, $p = .005$, $p_{Bonferroni} = .02$) and found more platforms ($r = 0.19$, $p = .01$, $p_{Bonferroni} = .04$) during VISIBLE trials.

3.5. Gender-Related effects on activation, drinking behavior, task performance

Men reported more severe drinking with greater quantity (F (1168) = 24.04, $p < .0001$, $p_{Bonferroni} < .0001$) and frequency (F (1168) = 8.30, $p = .004$, $p_{Bonferroni} = .016$) of recent drinking.

No gender effects were observed in regional activation during either condition. Associations between drinking behavior and activation did not differ by gender. Compared to women, men travelled shorter distances during HIDDEN (F(1168) = 6.21, $p = .014$, $p_{Bonferroni} = .056$) but not VISIBLE ($p = .40$, $p_{Bonferroni} = 1$) trials, searched for longer during both HIDDEN (F(1168) = 10.4, $p = 0.002$, $p_{Bonferroni} = .008$) and VISIBLE (F(1168) = 23.2, $p < .0001$, $p_{Bonferroni} < .0001$) trials, and found more platforms during both HIDDEN (F(1168) = 11.7, $p = 0.0008$, $p_{Bonferroni} = .003$) and VISIBLE (F(1168) = 23.0, $p < .0001$, $p_{Bonferroni} < .0001$) trials.

Nonsignificant findings are detailed in Table S3.

4. Discussion

The current study investigated neural correlates of vMWT performance and relationships with drinking behaviors in college students. The study investigated whether SWM-related performance and brain activations were related to specific drinking-severity measures (quantity, frequency) and whether relationships were gender-specific. Hypotheses were partially supported as drinking quantity related to DLPFC activation and drinking frequency to hippocampus activity. Interestingly, activation differences related to drinking quantity and frequency were not found in overlapping regions.

4.1. Task conditions

The data suggest greater MFG and bilateral hippocampus activation during VISIBLE or encoding trials as compared to SWM trials. Previously, the MFG has been associated with cognitive processes (Wang et al., 2016), including SWM (Sneider et al., 2011; Leung et al., 2002). The activation pattern for the hippocampus during VISIBLE trials is consistent with prior data using a version of the vMWT (Sneider et al., 2011). These data suggest the hippocampus is more related to learning locations rather than navigating to maze platforms. Together, MFG and hippocampus activation during VISIBLE trials supports the vMWT as a human analogue to the animal model (Sapiurka et al., 2016).

Our data suggest greater ACC and DLPFC activation during SWM trials. The ACC is related to error detection, conflict monitoring (Orr and Hester, 2012), cognitive control for decision-making (Christopoulos et al., 2009), and risk assessment (Brown and Braver, 2007). Thus, these data suggest greater behavioral monitoring and navigation related to learning during HIDDEN as compared to VISIBLE trials, where navigation may be reliant on cues. DLPFC activation during SWM is consistent with prior studies (Antonova et al., 2009; Spiers and Maguire, 2007). Together, these data suggest that VISIBLE-trial encoded memories may be weaker; thus, top-down processing may be needed to facilitate HIDDEN-trial performance (Spiers and Maguire, 2007).

4.2. Drinking severity

Different relationships between brain activation and drinking quantity and frequency suggest an importance of drinking-severity definition. Specifically, greater drinking quantity during a 24 -h period in the last six-months was related to a decreased difference in DLPFC activation between HIDDEN and VISIBLE conditions. However, greater drinking frequency was related to greater differences in hippocampus activation between HIDDEN and VISIBLE conditions. DLPFC and hippocampus engagement for allocentric SWM and the vMWT change throughout life (Antonova et al., 2009; Moffat and Resnick, 2002). Therefore, the relationship between drinking-severity and DLPFC and hippocampus activity may indicate later-in-life differences in how one navigates complex environments (Moffat and Resnick, 2002), which may vary based on early-life patterns of drinking, although this possibility warrants direct investigation.

The pattern of greater drinking-severity relating to less DLPFC activation during SWM supports previous egocentric task data (Squeglia et al., 2012; Tapert et al., 2004). Decreased DLPFC activation may be interpreted as greater cognitive efficiency and control (Ewing et al., 2014). We conjecture a relationship between drinking, DLPFC activation, and allocentric navigation as similar activations have been found using this task. Differences in DLPFC activation related to drinking-severity but not performance differences suggest SWM performance may not be solely dependent on the DLPFC (Mackey et al., 2016).

Inconsistent associations between DLPFC structure and function and early life alcohol-use have previously been reported. Lateralized DLPFC structural differences may relate to drinking metrics (e.g., decreased right DLPFC volume predictive of drinking frequency (Brumback et al., 2016), greater left DLPFC correlating with drinking quantity and speed in binge-drinking college students (Doallo et al., 2014)). Additionally, response inhibition studies report conflicting DLPFC activation (e.g., decreased left DLPFC activation predictive of non-drinking students transitioning in to heavy alcohol-use (Norman et al., 2011); greater DLPFC activation related to heavy-drinking compared to light-drinking college students (Ames et al., 2014)). These lateralized patterns of structural and functional differences contrast with our current data. DLPFC development is completed during later stages of neuromaturation (Ziegler et al., 2017) and is necessary for successful development of executive functions.

Greater differences in hippocampus activation between HIDDEN and VISIBLE conditions relating to greater drinking frequency support previous data suggesting relationships between hippocampal function and youth drinking (Dager et al., 2014; Nagel et al., 2005; DeBellis et al., 2000) and SWM (Folley et al., 2010; Shipman and Astur, 2007). To our knowledge, this is the first study to relate hippocampal activation during a SWM task to drinking-severity in youth, with greater activation during VISIBLE trials likely relating to increased drinking frequency. Seemingly inconsistent findings suggest lateralized hippocampal structural differences relate to overall drinking-severity, not necessarily frequency, in college drinkers (Dager et al., 2014; Nagel et al., 2005). However, our findings indicate bilateral-hippocampal activation differences are related to drinking frequency. Though seemingly isolated to the VISIBLE trials, this difference related to drinking frequency likely holds implications for SWM navigation. These data suggest a hippocampus-specific vulnerability to chronic alcohol-use in young populations, a vulnerability suggested in both humans and animal models (Taffe et al., 2010; Nagel et al., 2005). The pattern of bilateral-hippocampal activation together with the DLPFC activation supports an argument for inefficient hippocampal activation during SWM navigation and encoding (Folley et al., 2010).

Alcohol-related findings from our large sample provide significant support for unique effects on brain activations based on drinking-severity definitions. Based on prior work with this cohort, we chose to evaluate potential differences in neural activation relating to drinking quantity and frequency separately. The current data suggest differing relationships between quantity, frequency and activation patterns, supporting prior work, suggesting comprehensive metrics are needed to capture severe drinking in youth and build our understanding of how different measures of drinking-severity relate to other relevant characteristics (Meda et al., 2017; Brumback et al., 2016; Hingson et al., 2016; Worhunsky et al., 2016; Dager et al., 2014, 2013). Additionally, these data suggest a detrimental relationship between DLPFC, hippocampus, and alcohol that may impact long-term executive functioning and higher-order cognitive processing (Meda et al., 2018). Further investigation is needed to provide a better understanding of DLPFC and hippocampus structural and functional relationships and to understand the extent to which these may be antecedent to or result from alcohol-use during development.

4.3. Task performance

More efficient performance (shorter times, distances, fewer errors) occurred during HIDDEN trials, suggesting better performance is associated with bilateral DLPFC and ACC activation. Relationships between these task-relevant regions and task performance support the vMWT as a relevant adaptation of the rodent MWT to humans. The MWT is a well-established rodent task for studying spatial navigation, learning, and memory. Though both rodent and human tasks are hippocampus-dependent (Shipman and Astur, 2007; Astur et al., 2002), they are not identical (e.g., Astur et al., 2004). However, current data suggest similarities in their neural underpinnings. Thus, findings suggest important translational implications; i.e., animal model data may augment our understanding of human spatial navigation and learning and memory processing.

4.4. Gender-Related findings

We observed gender-related differences in drinking and SWM performance. Men reported more frequent drinking of greater quantities. Gender-related differences in performance support previous vMWT data, with men performing better during HIDDEN trials (Astur et al., 2004, 1998) in which men had shorter search distances. In both conditions, men took longer to find more platforms. This suggests more intentional, learned-search strategies rather than trial-and-error searching. While gender-related differences have previously been reported for HIDDEN trials, gender-related differences during VISIBLE trials have not (Astur et al., 2004, 1998). This may relate to greater power associated with the larger sample size investigated here. Gender-related performance differences suggest that egocentric and allocentric tasks may evaluate different aspects of SWM and cognitive functioning (Folley et al., 2010), particularly as these differences are not found in youth performing egocentric SWM tasks (Schweinsburg et al., 2005; Tapert et al., 2004).

Study limitations exist. As the vMWT is used to understand learning and memory processes typically associated with the hippocampus, functional imaging covered the brain from the frontal pole to the parieto-occipital fissure to ensure total hippocampal acquisition. Thus, functional data related to visual processing were not obtained. While some of our findings did not survive multiple comparisons, the current data do suggest important relationships between neural activation, task performance, and drinking severity particularly in a young population, with behavioral findings appearing more statistically robust than neural findings. Similar to other SWM studies (Squeglia et al., 2011; Caldwell et al., 2005), comparisons to teetotalers were not made, as the current study focused on relationships between drinking-severity and SWM. Our severity measures evaluated past-6-month drinking, which does not permit accounting for potential differences related to very recent or long-term alcohol exposure. Other substances were not included in the analyses as substance-use reports were missing for 70 participants and comorbid substance use within our sample is relatively low (Table S2; Meda et al., 2017). We did include smoking status (Yes/No) in the

models however, results did not differ by smoking status. We did not evaluate possible interactive effects of learning rate or task difficulty. As such, we are unable to determine whether or not drinking histories interact with these factors.

5. Conclusions

The current study offers a novel perspective on the potential consequences of college-aged young-adult drinking employing previously used definitions of drinking-severity. The findings suggest multiple mechanisms by which alcohol may influence allocentric SWM processing: not only via acute intoxication and recent consumption, but also in relation to the quantity or frequency of alcohol-use, or through the cumulative result of long-term consumption. As working memory, the DLPFC, and hippocampus impact several higher-order processes, studies using longitudinal designs will be important in understanding longer-term consequences of youth alcohol-use. Additionally, a mediation analysis on a more diverse population considering factors such as age, socioeconomic status, or other substance use to elucidate potential neural morphology differences related to drinking or task performance would be impactful (Meda et al., 2017). Initiatives such as the ongoing National Consortium on Alcohol and Neurodevelopment in Adolescence and the Adolescent Brain Cognitive Development study will allow larger-scale evaluation of longer-term substance-use throughout development.

Contributors

B.C. Banz conducted statistical analysis, interpreted results, and drafted the original manuscript, tables, and figures. P.D. Worhunsky performed imaging analyses, helped draft the original manuscript, and provided critical feedback on the analyses and the manuscript. B.P. Pittman performed statistical analyses and drafted the statistical analysis and results sections. R.S. Astur was responsible for task design and provided interpretation and feedback on the manuscript. H.A. Tennen, S.A. Raskin, C.S. Austad, R.M. Wood, C.R. Fallahi oversaw the parent study and provided feedback on the manuscript. M.N. Potenza, in conjunction with B.C. Banz and G.D. Pearlson, developed the research questions and approach and was involved in overseeing progress of data analysis and reviewed and revised multiple drafts of the manuscript. G.D. Pearlson was the P.I. for the parent study, provided analytical and writing guidance, and provided critical feedback on the manuscript. All authors approved the final manuscript.

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Appendix A. Supplementary data

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