Published in final edited form as:

Alcohol Clin Exp Res. 2011 October ; 35(10): 1831–1841. doi:10.1111/j.1530-0277.2011.01527.x.

Adolescent Binge Drinking Linked to Abnormal Spatial Working Memory Brain Activation: Differential Gender Effects

Lindsay M. Squeglia², Alecia Dager Schweinsburg³, Carmen Pulido⁴, and Susan F. Tapert^{1,2,4,*}

¹ VA San Diego Healthcare System

² San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology

³ Yale University, Department of Psychiatry

⁴ University of California San Diego, Department of Psychiatry

Abstract

Background—Binge drinking is prevalent during adolescence, and its effect on neurocognitive development is of concern. In adult and adolescent populations, heavy substance use has been associated with decrements in cognitive functioning, particularly on tasks of spatial working memory (SWM). Characterizing the gender-specific influences of heavy episodic drinking on SWM may help elucidate the early functional consequences of drinking on adolescent brain functioning.

Methods—40 binge drinkers (13 females, 27 males) and 55 controls (24 females, 31 males) ages 16 to 19, completed neuropsychological testing, substance use interviews, and a spatial working memory task (SWM) during functional magnetic resonance imaging (fMRI).

Results—Significant binge drinking status x gender interactions were found ($p < .05$) in 8 brain regions spanning bilateral frontal, anterior cingulate, temporal, and cerebellar cortices. In all regions, female binge drinkers showed *less* SWM activation than female controls, while male bingers exhibited *greater* SWM response than male controls. For female binge drinkers, less activation was associated with poorer sustained attention and working memory performances ($ps < .025$). For male binge drinkers, greater activation was linked to better spatial performance ($p < .025$).

Conclusion—Binge drinking during adolescence is associated with gender-specific differences in frontal, temporal, and cerebellar brain activation during a SWM task, which in turn relate to cognitive performance. Activation correlates with neuropsychological performance, strengthening the argument that BOLD activation is both affected by alcohol use and is an important indicator of behavioral functioning. Females may be more vulnerable to the neurotoxic effects of heavy alcohol use during adolescence, while males may be more resilient to the deleterious effects of binge drinking. Future longitudinal research will examine the significance of SWM brain activation as an early neurocognitive marker of alcohol impact to the brain on future behaviors such as driving safety, academic performance, and neuropsychological performance.

* Corresponding author: Susan F. Tapert, Ph.D., 3350 La Jolla Village Drive (151B), San Diego, CA 92161, US; telephone: 858-552-8585, fax: 858-642-6474; stapert@ucsd.edu..

Financial Disclosures

The authors report no conflicts of interest or financial disclosures.

Keywords

adolescence; alcohol; binge; gender; fMRI

1. INTRODUCTION

Heavy episodic or “binge” drinking is the most prevalent pattern of alcohol consumption among adolescents. Typically defined as ≥ 4 drinks/occasion for females or ≥ 5 drinks/occasion for males (Wechsler, 1992), 28% of 12th graders report binge drinking in the past month (Wechsler, 1995). Even in the absence of an alcohol use disorder (AUD) diagnosis, binge drinking in adolescence presents a public health concern due to reduced judgment and increased risky behaviors. Crucial neuromaturational processes (e.g., cortical thinning, neurochemical changes (Luna, 2009; Spear, 2009) may be interrupted by repeated binge alcohol consumption, yet the potential neural affect of alcohol use during this developmental period is still not fully understood.

Neurocognitive impairments have been characterized in adult alcoholism, particularly in the domains of spatial skills, learning and memory, and executive functioning (Chanraud, Pitel, Rohlfing, Pfefferbaum, & Sullivan, 2010; Grant, 1987). Neuroimaging studies have identified structural, chemical, and functional abnormalities that parallel cognitive decrements (Pfefferbaum et al., 2001; Pfefferbaum, Rosenbloom, Rohlfing, & Sullivan, 2009; Pfefferbaum et al., 2000; Sullivan & Pfefferbaum, 2005). Consistent with neuropsychological findings of working memory and spatial functioning, functional magnetic resonance imaging (fMRI) has revealed aberrant activation patterns during spatial working memory tasks, particularly in frontal regions (Pfefferbaum, Desmond, et al., 2001). While the majority of the adult literature suggests females are more susceptible to alcohol-related brain damage (Hommer, Momenan, Kaiser, & Rawlings, 2001; Hommer et al., 1996; Jacobson, 1986), some research suggests men may be more vulnerable (Pfefferbaum, Rosenbloom, Deshmukh, & Sullivan, 2001).

Adolescents with AUD have also shown declines in spatial functioning (Tapert & Brown, 1999) and differences in brain response during tasks of spatial working memory (SWM) with continued heavy drinking following treatment (Wechsler, Dowdall, Davenport, & Rimm, 1995). Alcohol dependent young adult women who continued drinking heavily after treatment demonstrated reduced brain response and poorer task performance (Tapert et al., 2001).

The possible influence of sub-diagnostic binge drinking is less clear. A longitudinal study characterizing substance-naïve adolescents using neuropsychological testing found decreased spatial functioning in females who initiated heavy drinking by the 3-year follow-up compared to adolescents who remained continuous non-users, while males who initiated heavy drinking showed reductions in attention over the follow-up period (Squeglia, Spadoni, Infante, Myers, & Tapert, 2009). These findings suggest that some areas of relative cognitive weakness may be more vulnerable to effects of alcohol and hangover, as females tend to outperform males on tasks of psychomotor speed and accuracy, while males perform better on visuospatial tests (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). The potential underlying mechanism could be disruption of myelination, as widespread white matter microstructural abnormalities have been observed among adolescent binge drinkers, despite relatively short and benign drinking histories (McQueeney et al., 2009).

Neurodevelopmental trajectories show gender-specific patterns. During childhood and adolescence, females show earlier peaks in cortical gray matter volume (Giedd et al., 1999),

as well as earlier improvements on SWM performance (Vuontela et al., 2003). Healthy adolescents also exhibit an age-related shift in brain response during SWM, with girls and boys showing different patterns indicating gender-specific strategies (Schweinsburg, Nagel, & Tapert, 2005). Likewise, adolescents with AUD have demonstrated gender discrepancies in prefrontal volumes (Medina et al., 2008), and preliminary evidence has suggested greater functional aberrations during SWM among adolescent girls when compared to boys (Caldwell et al., 2005). Taken together, these studies indicate that there may be differential neural effects of alcohol by gender throughout development.

In summary, the existing literature suggests a frontoparietal network implicated in working memory (Wager & Smith, 2003) that develops earlier in females (Giedd, et al., 1999). These regions may also be particularly susceptible to alcohol-related damage, with females showing greater adverse effects than males. To better characterize the influence of gender and alcohol use on frontoparietal functioning, we examined fMRI response during SWM among male and female adolescent binge drinkers. Based on areas subserving SWM and previous literature examining brain activation among adolescent drinkers (Caldwell, et al., 2005; Tapert et al., 2004), we hypothesized that differences in blood oxygen level dependent (BOLD) activation between adolescent binge drinkers and controls would be found in bilateral superior frontal gyri, right inferior frontal gyrus, bilateral anterior cingulate, and right superior parietal lobule, and that these differences would be more pronounced for female than male drinkers (Caldwell, et al., 2005; Squeglia, et al., 2009).

2. MATERIALS AND METHODS

2.1 Participants

Participants ($N=95$) were 40 binge drinking (13 females, 27 males) and 55 control (24 females, 31 males) adolescents age 16 to 19 recruited from San Diego area public schools as part of ongoing longitudinal neuroimaging studies on adolescent substance use (Bava et al., 2009; McQueeney, et al., 2009; Squeglia, et al., 2009; Tapert et al., 2007). Consent and assent (for participants under age 18) were obtained, and participants and parents were screened for eligibility. Exclusionary criteria were: no parent or guardian available to provide corroborating information; parental history of bipolar, psychotic, or antisocial personality disorder; prenatal exposure to alcohol (>2 drinks on an occasion or >4 drinks in a week) or any illicit drugs; premature birth (<36 weeks gestation); history of any neurological problem (e.g., migraine, traumatic brain injury with loss of consciousness >2 minutes) or serious medical illness; lifetime use of psychotropic medications; current or past probable DSM-IV Axis I diagnosis (APA, 1994) other than conduct disorder, oppositional defiant disorder, simple phobia, or alcohol abuse, assessed by the Diagnostic Interview Schedule for Children Predictive Scales (Lucas et al., 2001) administered to youth and parent; MRI contraindications (e.g., braces); left-handedness; colorblindness or non-correctable vision or hearing problem; marijuana use >3x/month in past three months; >25 lifetime uses of other illicit substances; and substance use in the 72 hours before scanning (confirmed with breathalyzer and urine toxicology). Participants were compensated \$200 for completing the comprehensive interview, scan, and neuropsychological testing.

Approximately 12% of respondents to flyer distributions at local schools met eligibility criteria. Binge drinkers were participants who had ≥ 4 (for females) or ≥ 5 (for males) drinks on at least one occasion (NIAAA, 2004; Wechsler, Davenport, Dowdall, Moeykens, & Castillo, 1994) in the 3 months prior to scanning, while controls (matched on age at the group level) had <3 drinks in the past 3 months (see Table 1). The study protocol was executed in accordance with the University of California, San Diego Human Research Protections Program.

2.2 Measures

2.2.1 Substance use—The Customary Drinking and Drug Use Record (Brown et al., 1998) was administered to obtain self-reported quantity and frequency of lifetime, past year, and past 3 month alcohol, tobacco, marijuana, and other drug use. Estimates of blood alcohol concentration (BAC) were calculated using peak number of drinks, duration of consumption, gender, and body mass index (Fitzgerald, 1995; Widmark, 1922). The Timeline Followback (Sobell & Sobell, 1992) assessed substance use frequency and quantity for the 30 days prior to scanning, with temporal cues to aid recall. To maximize accuracy, corroborating information from a parent and one other biological relative, breathalyzer, and urine toxicology were collected.

2.2.2 Neuropsychological measures—Within one week of imaging, participants were administered a neuropsychological battery assessing cognitive domains previously associated with alcohol-related deficits, including spatial, attention, working memory, learning and memory, and executive functioning. Measures of spatial functioning and working memory hypothesized to be correlated with activation to the SWM task included: Complex Figure copy and 30-minute delay accuracy (Loring & Meador, 2003; Meador et al., 1993; Rey & Osterrieth, 1993; Taylor, 1969); Wechsler Abbreviated Scale of Intelligence (WASI) Block Design (Wechsler, 1999); and Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Span (Wechsler, 1997). Because attention and processing speed underlie working memory, Digit Vigilance Test (DVT) (Lewis, 1995) and WAIS-III Digit-Symbol Coding (Wechsler, 1997) were also examined. Wide Range Achievement Test-3 Reading scores (WRAT-3) (Wilkinson, 1993) were obtained as a measure of premorbid functioning and intellectual capacity.

2.2.3 Family background—The Family History Assessment Module (FHAM) (Rice et al., 1995), administered to youth and parents, ascertained familial density of AUD and other substance use disorder (SUD) by adding 0.5 for each biological parent and 0.25 per biological grandparent (Zucker, Ellis, & Fitzgerald, 1994), endorsed by either youth or parent as having an AUD or SUD. Socioeconomic background information (i.e., educational attainment, occupation, and salary of each parent) was obtained from parents, and converted to a Hollingshead Index of Social Position score (SES) (Hollingshead, 1965).

2.2.4 Development—Pubertal Development Scale (PDS) (Petersen, Crockett, Richards, & Boxer, 1988) was obtained to assess pubertal staging, and was calculated separately by gender.

2.2.5 Psychopathology and mood—Parents of participants ages 16 to 18 completed the Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001), while youth ages 18 to 19 living independently from parents completed the Adult Self Report (ASR) (Achenbach & Rescorla, 2001) to obtain an age- and gender-normed continuous measure of internalizing and externalizing psychopathology. The Beck Depression Inventory (BDI) (Beck, Steer, & Brown, 1996) and Spielberger State Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970) assessed mood state at the time of scanning, and the Karolinska Sleepiness Scale (KSS) (Åkerstedt & Gillberg, 1990) assessed alertness (1=extremely alert to 9=extremely sleepy) before and after scanning. While no participant exceeded the cutoff suggestive of depression, BDI scores were higher for female binge drinkers than all controls ($p < .05$). Pre- and post-KSS scores were higher for males than females (regardless of drinking, $p < .05$). No other covariate measure differed between groups.

2.3 Procedures

2.3.1 Imaging—Participants completed a 1-hour brain imaging session. Immediately before scanning, participants received instructions and practiced the task on a laptop to ensure comprehension of directions. Participants were placed comfortably on the scanner table and the head was stabilized within the head coil using foam cushions (NoMoCo Pillow, La Jolla, CA). Task stimuli were projected onto a screen at the foot of the scanner bed, viewed from a mirror attached to the head coil. A fiber-optic button box (Current Designs, Pittsburgh, PA) recorded responses and reaction times; button responses were tested and participants were reminded of task instructions prior to scanning.

Imaging data were collected at the UCSD Keck fMRI Center from a 3-Tesla CXX4 short bore Excite-2 MR system (General Electric, Milwaukee, WI) with an 8-channel phase-array head coil. Scan sessions involved a 10-second scout scan to assure good head placement and slice selection covering the whole brain; a sagittally acquired high-resolution 3*d* T1-weighted anatomical (FOV 24 cm, 256 × 256 × 192 matrix, 0.94 × 0.94 × 1 mm voxels, 176 slices, TR=20 ms, TE=4.8 ms; flip angle 12°, 7:26); field maps using 2 different echo times to assess field inhomogeneities and signal distortions under the same parameters as echo-planar images, applied to all fMRI acquisitions to minimize warping and signal dropouts; and a T2*-weighted axially acquired echo-planar imaging sequence to measure BOLD signal (FOV=24 cm, 64 × 64 matrix, 3.75 × 3.75 × 3.8 mm voxels, 32 slices, TE=30 ms, flip angle 90°, ramped bandwidth 250 KHz, TR=3000 ms, 156 slices).

2.3.2 Spatial Working Memory (SWM) task—The SWM fMRI task (see Figure 1) was created to assess brain regions subserving SWM (Kindermann, Brown, Zorrilla, Olsen, & Jeste, 2004; Tapert, et al., 2001); adapted from (McCarthy et al., 1994). This task consists of 18 blocks of alternating experimental (i.e., SWM) and baseline (i.e., simple vigilance) conditions (20s each), in addition to three rest blocks interspersed throughout the task where the participant was instructed to stare at a fixation cross in the center of the screen. In the SWM condition, abstract Kimura line drawings (Kimura, 1963) appeared in one of eight locations, and participants were told to press a button when a design reappeared in a previously occupied location during that block. On average, 3 of the 10 stimuli presented during a block were repeat locations of stimuli presented two prior (i.e., 2-back). In the baseline vigilance condition, the same stimuli were presented in identical locations, but participants were instructed only to press the button when a dot appeared above the stimulus (i.e., 3 out of the 10 stimuli from that block). Therefore, the baseline vigilance condition provided a control for simple motor and visual attention processes involved in the experimental condition. Both conditions were presented for 1000 ms and had a 1000 ms interstimulus interval, with a total task time of 7 minutes and 48 seconds (see Tapert et al., 2004 for block presentation order). Participants were reminded before each block with a prompt on the screen indicating “LOOK” for the fixation periods, “DOTS” for the vigilance condition, and “WHERE” for the SWM condition (8 seconds total). It is assumed that all individuals included in analyses were actively engaged in the task, as all participants performed well above chance level (vigilance accuracy = 96.40% ± 4.18; SWM accuracy = 93.65% ± 5.03). BOLD response contrast during the SWM (“WHERE”) relative to vigilance (“DOTS”) condition (i.e., the differential activation between conditions) was used as the dependent variable in analyses. Vigilance rather than fixation has been shown to be a valid active baseline measure, better localizing regions specifically involved in SWM (Tapert, et al., 2004).

2.4 Data Analyses

Data were processed and analyzed using Analysis of Functional NeuroImages (AFNI) (Cox, 1996). Artifact and aberrant signal levels were examined in each repetition of each slice

using an automated locally-created algorithm. Motion in time series data were corrected by registering each acquisition to the maximally stable base volume with an iterated least squares algorithm (Cox & Jesmanowicz, 1999). Motion correction applied for 3 displacement and 3 rotational parameters were output for each repetition per participant. After automated motion correction, two trained raters visually inspected each time series dataset *en cine* to omit any remaining repetitions with visually discernible movement. A dataset was not used if more than 15% of repetitions were discarded ($n=3$, not described in this paper).

No significant main effects or interactions were found on bulk motion, or task-correlated motion determined by correlating the task reference function with each of the 6 motion parameters.

Deconvolution was conducted on time series data with a reference function that convolved the behavioral stimuli with a hemodynamic response model (Cohen et al., 1997) while covarying for linear trends and motion correction applied (Bandettini, Jesmanowicz, Wong, & Hyde, 1993) and ignoring the first 3 repetitions, resulting in a functional image in which every voxel contained a fit coefficient representing the change in signal across behavioral conditions and a threshold t -statistic. Standardization transformations were made for each anatomical image (Talairach & Tournoux, 1988), and functional datasets were warped in accordance to manage individual anatomical heterogeneity. Functional data were resampled into isotropic voxels (3 mm^3), and a spatial smoothing Gaussian filter (full-width half maximum 5 mm) was applied. Co-registration of structural images to functional images was performed with a mutual information registration program (Cox & Jesmanowicz, 1999) that robustly handles images with different signal characteristics and spatial resolutions. Masks were created to demarcate each hypothesized region of interest (ROI; i.e., bilateral superior frontal gyri, right inferior frontal gyrus, bilateral anterior cingulate, and right superior parietal lobule) using the atlas available in AFNI (Talairach & Tournoux). AFNI *3dRegAna* examined within each ROI the influence of gender, binge drinking, and their interaction on SWM response. To control for Type I error, *AlphaSim* (Ward, 2000) determined the threshold cluster size needed to surpass a volume-wise 0.05 two-tailed alpha value, given a per-voxel alpha threshold of 0.05. Minimal volumes of contiguous voxels with effect p -values >0.05 for each ROI to be considered significant were: 756 μL for left and right superior frontal gyri, 810 μL for right inferior frontal gyrus, 702 μL for bilateral anterior cingulate, and 378 μL for right superior parietal lobule. Next, a whole brain exploratory analysis was conducted, with a volume threshold of 2538 μL .

SWM response coefficient values, averaged across each significant ROI, were imported from AFNI to SPSS using *3dROIstats* for each participant. Because of the unequal number of male and female drinkers and controls, homogeneity of BOLD response variance was tested using Levene's test of equality of error variances, and variance of BOLD responses between groups were shown to be homogenous. SWM response, neuropsychological, and substance use data were screened for outliers, and results were confirmed using SPSS. Correlations between BOLD signal and neuropsychological data were completed in SPSS. One female binge drinker had an outlying (>3.5 standard deviations from the mean) SWM response value in the anterior cingulate, and another female binge drinker had an outlying SWM response value in the right anterior superior frontal gyrus. Three binge drinking males each had one outlying value for SWM response (one each for anterior cingulate, left medial frontal gyrus, and left declive). There were no outliers for neuropsychological measures, peak drinks, or days since last alcohol use. When outlying datasets were removed, results remained unchanged, except for neuropsychological follow-up correlation analyses; therefore outliers were removed for these analyses. For exploratory follow-up analyses

between SWM response and neuropsychological tests, Type I error correction was set at $p < 0.05$.

3. RESULTS

3.1 Task Performance

Task performance data were available for 36/37 females and 57/58 males. There were no significant main effects for drinking status or gender, or an interaction ($p < .05$), for task accuracy or reaction time (see Table 1). Average accuracy for females was 96.78% (range: 93-100%) on vigilance and 94.35% (range: 79-99%) on SWM trials, and average reaction time was 612.40 (range: 509.20-765.70) for vigilance and 547.12 (range: 375.70-685.20) for SWM. For males, average accuracy was 96.16% (range: 59-99%) on vigilance and 93.21 (range: 80-100%) on SWM trials, and average reaction time was 604.22 (range: 477.50-790.80) for vigilance condition and 533.62 (range: 343.30-755.20) for SWM condition (see Table 1).

3.2 Region of Interest Findings

No main effect of gender was found for any of the five regions of interest. However, main effects for binge drinking group were found in right superior frontal gyrus (BA 6, 10; cluster size: 864 μ L, $p = .02$) and right inferior frontal gyrus (BA 47; cluster size: 864 μ L, $p = .03$), with binge drinkers showing less activation than controls (i.e., SWM relative to vigilance BOLD response). Significant binge $\times$ gender interactions were found in three of the five hypothesized regions of interest, including anterior cingulate, right inferior frontal gyrus, and 2 separate clusters within the superior frontal region of interest (right dorsal and right anterior superior frontal gyri). For all interactions, female binge drinkers exhibited significantly less SWM response than control females, while male binge drinkers showed significantly more activation than male controls (see Table 2; Figures 2 & 3).

3.3 Exploratory Whole Brain Findings

Whole-brain analyses examined if additional regions differed between binge drinking and control females and males ($>2538 \mu$ L, corrected $p < .05$). No main effects of binge drinking or gender were found, but significant binge $\times$ gender interactions were observed in left medial frontal, right middle temporal, and left superior temporal gyri, and the left cerebellar declive (see Table 2 and Figures 2 & 3). In all regions, female binge drinkers had significantly less BOLD response during SWM vs. vigilance trials relative to female controls, and male binge drinkers had greater BOLD activation than male controls, which was consistent with ROI analyses.

3.4 Simple Effects

In SPSS, t-tests followed-up on the 8 clusters (from ROI and whole brain results) with significant binge $\times$ gender interactions. Female binge drinkers showed *less* ($p < .01$) SWM response than female controls in all eight clusters: right dorsal superior frontal (Cohen's $d = -1.27$), right anterior superior frontal ($d = -1.26$), right inferior frontal ($d = -1.27$), anterior cingulate ($d = -0.77$), left medial frontal ($d = -1.23$), right middle temporal ($d = -1.31$), left superior temporal ($d = -1.05$), and left declive ($d = -1.45$) regions. Male binge drinkers showed significantly *greater* BOLD response than male controls in 4 of the 8 clusters: left medial frontal ($d = 0.52$), right middle temporal ($d = 0.60$), left superior temporal ($d = 0.75$), and left declive ($d = 0.68$) regions (see Figures 2 & 3).

3.5 Examination of Covariates

Demographic and emotional factors were examined to disentangle the contribution of alcohol use on cognitive functioning from pre-existing, developmental, or state variables. Age, family history of alcoholism, socioeconomic status, internalizing, externalizing, pubertal development stage, depression, state anxiety, and pre- and post-scan sleepiness scores were used as covariates if they correlated ($p < .05$) with SWM response in brain regions found to have a significant interaction (in ROI or whole brain analyses). Age correlated with right middle temporal gyrus SWM response ($r = .25, p = .02$). Familial alcoholism density and externalizing scores negatively correlated with right inferior frontal gyrus activation ($r = -.24, p = .02$; $r = -.25, p = .02$, respectively). Depressed mood correlated with right dorsal superior frontal gyrus ($r = -.33, p = .001$), right anterior superior frontal gyrus ($r = -.24, p = .02$), and left declive ($r = -.21, p = .05$) SWM response. State anxiety scores correlated with right middle temporal ($r = -.23, p = .03$) and left declive ($r = -.23, p = .02$) activation. After controlling for these covariates, the pattern of results remained unchanged, suggesting that the binge drinking by gender interaction findings were robust to the potential influence of these developmental, mental health, and state factors.

3.6 Individual Differences in Alcohol and Other Substance Use

To further examine if level of substance involvement was linked to activation, Pearson correlations were run between substance use variables and SWM BOLD response contrast in regions exhibiting a binge x gender interaction for female and male binge drinkers. Alcohol, marijuana, and other substance use and recency did not correlate with BOLD response for female or male binge drinkers ($p > .05$).

3.7 Neuropsychological Correlates

For binge drinkers, correlations between SWM response in areas with significant interactions and neuropsychological tests of spatial functioning, attention, and processing speed were examined to determine if brain activation was linked to behavioral deficits. In terms of attention, for female binge drinkers ($n = 13$), less SWM response in the right dorsal superior frontal gyrus correlated with slower DVT completion ($r = -.69, p = .02$), and less activation in left declive was related to worse WAIS-III Digits backwards performance ($r = -.64, p = .02$) (see Figure 4). In terms of spatial functioning, for male binge drinkers ($n = 27$), greater right inferior frontal gyrus activation correlated with better Complex Figure copy accuracy ($r = .49, p = .02$) and Block Design scores ($r = .44, p = .02$) (see Figure 5). No other neuropsychological task (see Table 1 for specific neuropsychological measures) correlated with SWM response, and for control males and females, neuropsychological measures did not correlate with SWM response.

4. DISCUSSION

This study characterized brain response during SWM in male and female adolescents with and without recent histories of binge drinking. Although groups performed similarly on the task, different patterns of BOLD response were observed. As expected, teens who engaged in at least one binge drinking episode in the 3 months prior to scanning demonstrated different activation in frontal regions, and alcohol use was differentially associated with BOLD response between males and females in frontal, temporal, and cerebellar regions. The results are significant as these adolescents are relatively healthy, high functioning young people with minimal, if any, current other substance use or mental health problem.

Both the region of interest and whole-brain analyses revealed divergent activation between males and females, in several frontal regions, temporal cortex, and the cerebellum. In all clusters showing a gender by alcohol use interaction, female drinkers exhibited less BOLD

response than female controls, whereas male drinkers demonstrated greater BOLD response than male controls. Notably, the brain activation differences between bingers and non-bingers showed quite large effect sizes (i.e., the overall Cohen's d for the eight regions where females bingers had greater SWM response than female controls was 1.2, while the overall effect size was 0.6 for the four regions where male bingers exhibited less SWM response than male controls). These results parallel and extend our previous findings among adolescents with AUD, in which SWM response in the right superior frontal gyrus and anterior cingulate was low in girls with AUD, but high in boys with AUD compared to gender-matched controls (Caldwell, et al., 2005). Similarly, our previous work identified less SWM response in middle and superior frontal gyri among alcohol dependent young women than female controls (Tapert, et al., 2001). Taken together with the current findings, these studies suggest reduced SWM-related activation in young female drinkers, yet increased activation among young male drinkers. Female binge drinker's hypoactivation could indicate a greater degree of influence on the frontal brain systems, a finding that is supported by the correlations of lower SWM response with poorer attention and working memory performance, and is consistent with longitudinal neuropsychological findings (Squeglia, et al., 2009). This reduced frontal activation among female adolescent drinkers could have important implications, as diminished working memory and other executive functions may contribute to further substance involvement (Casey, Getz, & Galvan, 2008). In contrast to females, males' activation may be less adversely influenced by heavy substance use. Male binge drinkers exhibited equal or greater activation in frontal areas to the SWM task (yet less baseline vigilance response), which was associated with better cognitive performance on spatial tasks. This is consistent with previous findings that females who begin heavy drinking during adolescence exhibit greater decrements on visuospatial tasks over time than males, despite having comparable pre-drinking spatial abilities (Squeglia et al., 2009). While the current findings are cross-sectional, there is suggestion that these deficits are a result of drinking rather than premorbid differences in cognition.

Several factors may contribute to the observed gender differences. When compared to male binge drinkers, female bingers exhibited greater lifetime alcohol and other substance use. While female binge drinkers had more marijuana and substance use days, illicit substance use was not associated with decreased BOLD activation in any of the eight regions. Female's greater alcohol use days could be contributing to the differences in activation; however, males actually had higher peak drinks and greater drinks per occasion (twice that of females) and males and females were achieving equivalent BAC levels. For female binge drinkers, poorer attention and processing speed was associated with less frontal BOLD response, which supports the interpretation that, among girls, the reduced BOLD response may indicate subtle neuronal insults in circuits required for these functions. Moreover, previous work has indicated that females may be more vulnerable to alcohol-related neurotoxicity and resulting cognitive decrements than males (Caldwell, et al., 2005; Hommer, et al., 2001; Hommer, et al., 1996; Jacobson, 1986; Mann, Batra, Gunthner, & Schroth, 1992; Squeglia, et al., 2009).

In contrast, greater frontal BOLD response was associated with better spatial performance among male drinkers. Thus, male drinkers may be able to engage more compensatory systems to achieve SWM task demands. Early in the course of drinking, males may be more resilient and able to recruit additional neural resources to maintain performance. This gender difference may not be as apparent on a task where females show a general advantage, such as a more verbally focused or sequential task (Lezak et al., 2004).

The gender-specific patterns may relate to differences in neuromaturation, hormonal fluctuations, and alcohol metabolism differences. Adolescent females show a 1-2 year earlier development of cortical gray matter (Giedd, et al., 1999; Lenroot & Giedd, 2010).

Alcohol use at a given chronological age may occur during different stages of neuromaturation for boys and girls, resulting in different outcomes. Specifically, earlier female pubertal development as compared to males may place females at a more neuromaturationally vulnerable stage (e.g., prefrontal synaptic pruning) at the time binge drinking begins. Hormonal level variability and menstrual cycle phase has been shown to differentially affect performance on spatially related tasks by gender (Hampson, 1995; Williams & Meck, 1991), and alcohol-induced fluctuations in hormone levels could explain the dissimilar effects of alcohol on brain activation between genders (Emanuele, LaPaglia, Steiner, L., & Emanuele, 2001; Kim et al., 2003). Females' slower rates of gastric metabolism, higher ratio of body fat, and lower body weight may contribute to the observed differences in how alcohol affects physiology (Frezza et al., 1990; Wechsler, et al., 1995).

Limitations of this study include the cross-sectional design and relatively small sample of binge drinking females. Abnormalities in brain activation and cognition might have preceded alcohol use (Tapert, Baratta, Abrantes, & Brown, 2002). Given the relatively low level of alcohol consumption and bingeing episodes over lifetime, it is possible that the activation pattern observed may serve as a phenotypic marker for other risk factors related to the development of hazardous drinking patterns in adolescence. Future longitudinal research with larger sample sizes, already in progress, will help clarify the temporal sequence of alcohol involvement and neurocognitive performance. Correlations between BOLD response and neuropsychological measures do not surpass strict Bonferroni corrections; however, these exploratory analyses help elucidate the clinical importance of activation differences. Additionally, differences in BOLD activation could be driven by insults to white matter (McQueeney, et al., 2009), differences in underlying gray matter, or differences in blood flow and connectivity (Clark et al., 2007), neither of which were examined in this study. Future research employing neuroimaging indices like diffusion tensor imaging and arterial spin labeling will help elucidate the relationships between adolescent alcohol use and brain functioning.

These findings have clinical and public health implications, especially given the participants' relatively limited experience with alcohol, lack of diagnosable drinking problem, limited other substance use, and absence of psychopathology. If confirmed with longitudinal data, binge drinking during this transitional period could have lasting academic, occupational, and social implications extending into adulthood. Less efficient brain activation, particularly for females, could contribute to future risky behaviors and greater substance use.

Acknowledgments

This research was supported by grants from the National Institute on Alcohol Abuse and Alcoholism (R01 AA13419, PI: Tapert; F31 AA018940, PI: Squeglia, F32 AA018597, PI: Pulido) and the National Institute on Drug Abuse (R01 DA021182, P20 DA024194, P20 DA027834).

The authors thank Veronique Boucquey, Norma Castro, Sonja Ebersson, Diane Goldenberg, Alejandra Infante, Joanna Jacobus, Sonia Lentz, Anthony Scarlett, Scott Sorg, Rachel Thayer, Drs. Sunita Bava, Sandra Brown, Karen Hanson, M.J. Meloy, Reagan Wetherill, and the participating families and schools.

References

- Achenbach, T.M.; Rescorla, L.A. Manual for the ASEBA School-Age Forms & Profiles. University of Vermont, Research Center for Children, Youth, & Families; Burlington, VT: 2001.
- Åkerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. *International Journal of Neuroscience*. 1990; 52:29–37. [PubMed: 2265922]
- APA. Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). American Psychiatric Association; Washington, DC: 1994.

- Bandettini PA, Jesmanowicz A, Wong EC, Hyde JS. Processing strategies for time-course data sets in functional MRI of the human brain. *Magnetic Resonance in Medicine*. 1993; 30:161–173. [PubMed: 8366797]
- Bava S, Frank LR, McQueeney T, Schweinsburg BC, Schweinsburg AD, Tapert SF. Altered white matter microstructure in adolescent substance users. *Psychiatry Research: Neuroimaging*. 2009; 173:228–237.
- Beck, AT.; Steer, RA.; Brown, GK. Manual for the Beck Depression Inventory-2. Psychological Corporation; San Antonio, TX: 1996.
- Brown SA, Myers MG, Lippke L, Tapert SF, Stewart DG, Vik PW. Psychometric evaluation of the Customary Drinking and Drug Use Record (CDDR): A measure of adolescent alcohol and drug involvement. *Journal of Studies on Alcohol*. 1998; 59(4):427–438. [PubMed: 9647425]
- Caldwell LC, Schweinsburg AD, Nagel BJ, Barlett VC, Brown SA, Tapert SF. Gender and adolescent alcohol use disorders on BOLD (blood oxygen level dependent) response to spatial working memory. *Alcohol & Alcoholism*. 2005; 40(3):194–200. [PubMed: 15668210]
- Casey BJ, Getz S, Galvan A. The adolescent brain. *Developmental Review*. 2008; 28(1):62–77. [PubMed: 18688292]
- Chanraud S, Pitel AL, Rohlfing T, Pfefferbaum A, Sullivan EV. Dual tasking and working memory in alcoholism: relation to frontocerebellar circuitry. *Neuropsychopharmacology*. 2010; 35(9):1868–1878. [PubMed: 20410871]
- Clark CP, Brown GG, Eyler LT, Drummond SP, Braun DR, Tapert SF. Decreased perfusion in young alcohol-dependent women as compared with age-matched controls. *American Journal of Drug and Alcohol Abuse*. 2007; 33(1):13–19. [PubMed: 17366242]
- Cohen JD, Perlstein WM, Braver TS, Nystrom LE, Noll DC, Jonides J, et al. Temporal dynamics of brain activation during a working memory task. *Nature*. 1997; 386(6625):604–608. [PubMed: 9121583]
- Cox RW. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*. 1996; 29:162–173. [PubMed: 8812068]
- Cox RW, Jesmanowicz A. Real-time 3D image registration for functional MRI. *Magnetic Resonance in Medicine*. 1999; 42(6):1014–1018. [PubMed: 10571921]
- Emanuele NV, LaPaglia N, Steiner J, L. K, Emanuele MA. Effect of chronic ethanol exposure on female rat reproductive cyclicity and hormone secretion. *Alcoholism: Clinical & Experimental Research*. 2001; 25:1025–1029.
- Fitzgerald, EF. Intoxication Test Evidence. 2nd Ed. Clark Boardman Callaghan; Deerfield, IL: 1995.
- Frezza M, diPadova C, Pozzato G, Terpin M, Baraona E, Lieber CS. High blood alcohol levels in women: the role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. *New England Journal of Medicine*. 1990; 322:95–99. [PubMed: 2248624]
- Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, et al. Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neuroscience*. 1999; 2(861-863)
- Grant I. Alcohol and the brain: neuropsychological correlates. *Journal of Consulting and Clinical Psychology*. 1987; 55(3):310–324. [PubMed: 3597943]
- Hampson E. Spatial cognition in humans: possible modulation by androgens and estrogens. *Journal of Psychiatry & Neuroscience*. 1995; 20(5):397–404. [PubMed: 8527425]
- Hollingshead, AB. Two-factor index of social position. Yale University Press; New Haven, CT: 1965.
- Hommer DW, Momenan R, Kaiser E, Rawlings RR. Evidence for a gender-related effect of alcoholism on brain volumes. *American Journal of Psychiatry*. 2001; 158:198–204. [PubMed: 11156801]
- Hommer DW, Momenan R, Rawlings R, Ragan P, Williams W, Rio D, et al. Decreased corpus callosum size among alcoholic women. *Archives of Neurology*. 1996; 53:359–363. [PubMed: 8929159]
- Jacobson R. The contributions of sex and drinking history to the CT brain scan changes in alcoholics. *Psychological Medicine*. 1986; 16:547–549. [PubMed: 3763773]

- Johnston, LD.; O'Malley, PM.; Bachman, JG.; Schulenberg, JE. Monitoring the Future national results on adolescent drug use: Overview of key findings, 2008 (NIH Publication No. 09-7401). National Institute on Drug Abuse; Bethesda, MD: 2009.
- Kim JH, Kim HJ, Noh HS, Roh GS, Kang SS, Cho GJ, et al. Suppression by ethanol of male reproductive activity. *Brain Research*. 2003; 989:91–98. [PubMed: 14519515]
- Kimura, D. Recurring Figures Test. D. K. Consultants; University of Western Ontario: 1963. 1963
- Kindermann SS, Brown GG, Zorrilla LE, Olsen RK, Jeste DV. Spatial working memory among middle-aged and older patients with schizophrenia and volunteers using fMRI. *Schizophrenia Research*. 2004; 68:203–216. [PubMed: 15099603]
- Lenroot RK, Giedd JN. Sex differences in the adolescent brain. *Brain and Cognition*. 2010; 72(1):46–55. [PubMed: 19913969]
- Lewis, RF. Digit Vigilance Test. Psychological Assessment Resources; Odessa, FL: 1995.
- Lezak, MD.; Howieson, DB.; Loring, DW.; Hannay, HJ.; Fischer, JS. Neuropsychological Assessment. 4th ed.. Oxford University Press; New York: 2004.
- Loring, DW.; Meador, KJ. The Medical College of Georgia (MCG) Complex Figures: Four forms for follow-up.. In: Knight, J.; Kaplan, E., editors. Rey-Osterrieth handbook. Psychological Assessment Resources; Odessa, FL: 2003.
- Lucas CP, Zhang H, Fisher PW, Shaffer D, Regier DA, Narrow WE, et al. The DISC Predictive Scales (DPS): Efficiently screening for diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2001; 40(4):443–449. [PubMed: 11314570]
- Luna B. Developmental changes in cognitive control through adolescence. *Advances in Child Development and Behavior*. 2009; 37(233-78)
- Mann K, Batra A, Gunthner A, Schroth G. Do women develop alcoholic brain damage more readily than men? . *Alcoholism: Clinical & Experimental Research*. 1992; 16:1052–1056.
- McCarthy G, Blamire AM, Puce A, Nobre AC, Bloch G, Hyder F, et al. Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. *Proceedings of the National Academy of Sciences USA*. 1994; 91:8690–8694.
- McQueeney T, Schweinsburg BC, Schweinsburg AD, Jacobus J, Bava S, Frank LR, et al. Altered white matter integrity in adolescent binge drinkers. *Alcoholism: Clinical & Experimental Research*. 2009; 33(7):1278–1285.
- Meador KJ, Moore EE, Nichols ME, Abney OL, Taylor HS, Zamrini EY, et al. The role of cholinergic systems in visuospatial processing and memory. *Journal of Clinical & Experimental Neuropsychology*. 1993; 15(5):832–842. [PubMed: 8276939]
- Medina KL, McQueeney T, Nagel BJ, Hanson KL, Schweinsburg AD, Tapert SF. Prefrontal cortex volumes in adolescents with alcohol use disorders: unique gender effects. *Alcoholism: Clinical & Experimental Research*. 2008; 32(3):386–394.
- NIAAA. NIAAA Council approves definition of binge drinking, in NIAAA Newsletter. Vol. 3. Bethesda, MD: 2004.
- Petersen AC, Crockett L, Richards M, Boxer A. A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of Youth and Adolescence*. 1988; 17(2)
- Pfefferbaum A, Desmond JE, Galloway C, Menon V, Glover GH, Sullivan EV. Reorganization of frontal systems used by alcoholics for spatial working memory: an fMRI study. *NeuroImage*. 2001; 14(1 Pt 1):7–20. [PubMed: 11525339]
- Pfefferbaum A, Rosenbloom M, Deshmukh A, Sullivan EV. Sex differences in the effects of alcohol on brain structure. *American Journal of Psychiatry*. 2001; 158(2):188–197. [PubMed: 11156800]
- Pfefferbaum A, Rosenbloom M, Rohlfing T, Sullivan EV. Degradation of association and projection white matter systems in alcoholism detected with quantitative fiber tracking. *Biological Psychiatry*. 2009; 65(8):680–690. [PubMed: 19103436]
- Pfefferbaum A, Sullivan EV, Hedehus M, Adalsteinsson E, Lim KO, Moseley M. In vivo detection and functional correlates of white matter microstructural disruption in chronic alcoholism. *Alcoholism: Clinical & Experimental Research*. 2000; 24(8):1214–1221.
- Rey A, Osterrieth PA, Corwin J, Bylsma FW. Translations of excerpts from Andre Rey's "Psychological examination of traumatic encephalopathy" and P.A. Osterrieth's "The complex figure copy test". *The Clinical Neuropsychologist*. 1993; 7:3–21.

- Rice JP, Reich T, Bucholz KK, Neuman RJ, Fishman R, Rochberg N, et al. Comparison of direct interview and family history diagnoses of alcohol dependence. *Alcoholism: Clinical and Experimental Research*. 1995; 19:1018–1023.
- Schweinsburg AD, Nagel BJ, Tapert SF. fMRI reveals alteration of spatial working memory networks across adolescence. *Journal of the International Neuropsychological Society*. 2005; 11(5):631–644. [PubMed: 16212691]
- Sobell, LC.; Sobell, MB. Timeline Follow-back: A technique for assessing self-reported ethanol consumption.. In: Allen, J.; Litten, RZ., editors. *Measuring Alcohol Consumption: Psychosocial and Biological Methods*. Humana Press; Totowa, NJ: 1992. p. 41-72.
- Spear, LP. *The Behavioral Neuroscience of Adolescence*. 1st Edition ed.. W. W. Norton & Co Inc.; New York, NY: 2009.
- Spielberger, CD.; Gorsuch, RL.; Lushene, RE. *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologists Press; Palo Alto, CA: 1970.
- Squeglia LM, Spadoni AD, Infante MA, Myers MG, Tapert SF. Initiating moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys. *Psychology of Addictive Behaviors*. 2009; 23(4):715–722. [PubMed: 20025379]
- Sullivan EV, Pfefferbaum A. Neurocircuitry in alcoholism: a substrate of disruption and repair. *Psychopharmacology*. 2005; 180(4):583–594. [PubMed: 15834536]
- Talairach, J.; Tournoux, P. *Thieme*; New York: 1988. *Coplanar stereotaxic atlas of the human brain. Three-dimensional proportional system: An approach to cerebral imaging.*
- Tapert SF, Baratta MV, Abrantes AM, Brown SA. Attention dysfunction predicts substance involvement in community youth. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2002; 41:680–686. [PubMed: 12049442]
- Tapert SF, Brown GG, Kindermann SS, Cheung EH, Frank LR, Brown SA. fMRI measurement of brain dysfunction in alcohol-dependent young women. *Alcoholism: Clinical & Experimental Research*. 2001; 25(2):236–245.
- Tapert SF, Brown SA. Neuropsychological correlates of adolescent substance abuse: Four-year outcomes. *Journal of the International Neuropsychological Society*. 1999; 5:481–493. [PubMed: 10561928]
- Tapert SF, Schweinsburg AD, Barlett VC, Brown SA, Frank LR, Brown GG, et al. Blood oxygen level dependent response and spatial working memory in adolescents with alcohol use disorders. *Alcoholism: Clinical & Experimental Research*. 2004; 28(10):1577–1586.
- Tapert SF, Schweinsburg AD, Drummond SPA, Paulus MP, Brown SA, Yang TT, et al. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology*. 2007; 194:173–184. [PubMed: 17558500]
- Taylor LB. Localisation of cerebral lesions by psychological testing. *Clinical Neurosurgery*. 1969; 16:269–287. [PubMed: 5811709]
- Vuontela V, Steenari MR, Carlson S, Koivisto J, Fjallberg M, Aronen ET. Audiospatial and visuospatial working memory in 6-13 year old school children. *Learning and Memory*. 2003; 10(1):74–81. [PubMed: 12551966]
- Wager TD, Smith EE. Neuroimaging studies of working memory: A meta-analysis. *Cognitive, Affective, & Behavioral Neuroscience*. 2003; 3(4):255–274.
- Ward, BD. [March 23, 2009] Simultaneous inference for fMRI data.. 2000. from <http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim>
- Wechsler, D. *Wechsler Adult Intelligence Scale*. 3rd ed.. The Psychological Corporation; San Antonio, TX: 1997.
- Wechsler, D. *Manual for the Wechsler abbreviated scale of intelligence*. Psychological Corporation; San Antonio, TX: 1999.
- Wechsler H, Davenport A, Dowdall G, Moeykens B, Castillo S. Health and behavioral consequences of binge drinking in college. A national survey of students at 140 campuses. *Journal of the American Medical Association*. 1994; 272(21):1672–1677. [PubMed: 7966895]
- Wechsler H, Dowdall GW, Davenport A, Rimm EB. A gender-specific measure of binge drinking among college students. *American Journal of Public Health*. 1995; 85(7):982–985. [PubMed: 7604925]

- Wechsler H, Isaac N. 'Binge' drinkers at Massachusetts colleges. Prevalence, drinking style, time trends, and associated problems. *Journal of the American Medical Association*. 1992; 267(21): 2929–2931. [PubMed: 1583763]
- Widmark E. A micromethod for the estimation of alcohol in blood. *Biochemistry*. 1922; 131:473–484.
- Wilkinson, GS. WRAT-3: Wide Range Achievement Test administration manual. 3rd ed.. Western Psychological Services; Wilmington, DE: 1993.
- Williams CL, Meck WH. The organizational effects of gonadal steroids on sexually dimorphic spatial ability. *Psychoneuroendocrinology*. 1991; 16:155–176. [PubMed: 1961837]
- Zucker, RA.; Ellis, DA.; Fitzgerald, HE. Developmental evidence for at least two alcoholisms: I. Biopsychosocial variation among pathways into symptomatic difficulty.. In: Babor, TF.; Hesselbrock, V.; Meyer, RE.; S. W, editors. *Types of Alcoholics: Evidence from Clinical, Experimental and Genetic Research*. The New York Academy of Sciences; New York: 1994. p. 134-146.

LOOK: Just look

DOTS: Press the button with your INDEX finger when you see a figure with a DOT

WHERE: Press the button when any figure appears in the SAME LOCATION as another design

Figure 1.

Spatial Working Memory task (e.g., Tapert et al., 2001; 2004) given to participants. “DOTS” is the simple attention vigilance condition that served as the active baseline; “WHERE” is the spatial working memory condition.

Figure 2.

Graphs with standard error bars depicting the 8 significant ($p < .05$) binge drinking status by gender interactions for spatial working memory BOLD response contrast ($N=95$; female controls=24; male controls=31; female binge drinkers=13; male binge drinkers=27).

R right; L left

Figure 3.

Clusters from region of interest and whole brain analyses showing significant binge drinking status by gender interactions ($p < .05$; $N=95$). Areas in blue indicate where female binge drinkers had significantly *less* BOLD response during SWM vs. vigilance trials relative to female controls, and male binge drinkers had *greater* BOLD activation than male controls.

Figure 4.

For female binge drinkers, lower SWM response was associated with slower performance on a task of sustained attention and poorer working memory.

Figure 5. For male binge drinkers, higher SWM response was associated with better visuospatial performance.

Table 1

Demographic, substance use characteristics, and fMRI task performance of participants

	Binge Drinkers (n=40)			Controls (n=55)	
	Females (n=13)	Males (n=27)		Females (n=24)	Males (n=31)
Age	17.79 (1.00)	18.12 (0.72)		18.07 (0.92)	17.69 (1.01)
Race (% Caucasian)	69%	67%		79%	65%
Family history of alcoholism density (range 0-2)	0.25 (0.32)	0.31 (0.48)		0.15 (0.29)	0.17 (0.27)
Hollingshead socioeconomic index	24.85 (11.51)	28.78 (16.37)		23.42 (11.98)	28.94 (16.36)
Body mass index ^e	21.70 (2.89)	23.90 (3.20)		21.86 (4.26)	22.49 (3.43)
Pubertal Development Scale total ^d	19.00 (0.74)	17.67 (1.78)		19.17 (0.98)	16.81 (2.41)
Demographic					
Years of education	11.15 (0.99)	11.67 (0.83)		11.63 (1.14)	11.00 (1.03)
Beck Depression Inventory total ^{a e}	5.38 (5.27)	2.22 (2.47)		1.88 (2.49)	2.10 (2.68)
Spielberger State Anxiety total	25.92 (6.44)	25.48 (4.42)		24.92 (4.91)	28.19 (8.12)
CBCL/ASR internalizing T-score	46.36 (9.58)	44.56 (9.90)		41.38 (6.58)	44.00 (6.93)
CBCL/ASR externalizing T-score	48.64 (11.56)	45.52 (9.93)		46.25 (8.88)	44.59 (8.12)
Sleepiness rating before scan ^{d e}	5.15 (1.68)	3.41 (1.37)		4.63 (1.56)	3.58 (1.63)
Sleepiness rating after scan ^d	6.46 (1.85)	5.37 (1.52)		6.38 (1.76)	5.35 (2.14)
Substance Use					
Peak drinks on an occasion, past 3 months ^{abcde}	7.00 (3.03)	10.37 (3.19)		0.17 (0.38)	0.42 (0.92)
Estimated peak BAC, past 3 months ^{abc}	0.27 (0.10)	0.24 (0.08)		0.01 (0.02)	0.01 (0.02)
Lifetime alcohol use occasions ^{abce}	96.00 (82.18)	48.22 (41.39)		2.42 (4.98)	6.10 (10.20)
Average # drinks per drinking day, past month ^{abc}	1.85 (2.61)	3.59 (3.34)		0.00 (0.00)	0.00 (0.00)
Days since last alcohol use ^{abc}	29.62 (20.97)	25.59 (19.13)		253.20 (308.32)	198.94 (352.22)
Tobacco cigarettes per day ^c	0.08 (0.28)	0.07 (0.27)		0.00 (0.00)	0.00 (0.00)
Lifetime marijuana use occasions ^{abce}	17.92 (34.70)	3.37 (3.64)		0.67 (2.10)	0.81 (1.74)
Marijuana use days/month, past 3 months ^c	0.46 (0.88)	0.41 (0.64)		0.17 (0.64)	0.18 (0.03)
Lifetime other drug use occasions ^{abce}	4.69 (7.49)	1.19 (3.03)		0.00 (0.00)	0.00 (0.00)
NP measures					
Complex Figure copy accuracy ^d	29.50 (3.07)	28.86 (3.38)		30.59 (2.76)	28.33 (3.07)
Complex Figure delay accuracy	21.82 (5.14)	20.50 (5.73)		20.22 (5.69)	19.23 (4.79)

	Binge Drinkers (n=40)		Controls (n=55)	
	Females (n=13)	Males (n=27)	Females (n=24)	Males (n=31)
WASI Block Design ^d	56.85 (10.33)	54.00 (12.57)	61.83 (8.23)	55.16 (10.44)
WAIS-III Digits forward	10.77 (2.01)	11.07 (2.66)	10.83 (1.83)	10.83 (1.64)
WAIS-III Digits backward	6.92 (1.61)	8.00 (3.15)	7.25 (2.15)	7.23 (1.99)
DVT completion time (seconds)	164.00 (29.13)	167.27 (36.76)	166.33 (27.97)	173.29 (37.60)
WAIS-III Digit Symbol ^d	89.69 (11.06)	79.81 (14.35)	86.29 (8.85)	78.77 (10.82)
WRAT3 Reading	50.00 (7.29)	52.70 (6.49)	52.42 (6.58)	49.74 (5.29)
Vigilance accuracy (%)	97.31 (1.25)	95.27 (7.54)	96.48 (1.56)	96.90 (1.45)
Spatial working memory accuracy (%)	95.95 (2.35)	92.51 (5.30)	93.46 (5.62)	93.79 (5.04)
fMRI				
Vigilance reaction time (ms)	610.81 (59.31)	615.92 (63.27)	613.30 (63.88)	594.42 (57.98)
Spatial working memory reaction time (ms)	554.23 (78.32)	543.64 (100.43)	543.10 (84.22)	525.22 (72.47)

Note: CBCL: Child Behavior Checklist; ASR: Adult Self Report; NP: neuropsychological; WASI: Wechsler Abbreviated Scale of Intelligence; WAIS-III: Wechsler Adult Intelligence Scale, 3rd edition; DVT: Digit Vigilance Test; WRAT3: Wide Range Achievement Test, 3rd edition. All NP scores are raw values, unless otherwise noted. For the full sample, ethnicity was: 19% Latino; race was: 70% Caucasian, 20% multiracial, 4% African-American, 3% Asian, 2% Native American, and 1% Native Hawaiian.

^aFemale binge drinkers >female controls, $p<.05$
^bMale binge drinkers > male controls, $p<.05$
^cBinge drinkers > controls, $p<.05$
^dFemale > male, $p<.05$
^eFemale binge drinkers ≠ male binge drinkers, $p<.05$

Table 2
Significant binge status by gender interactions for BOLD response to spatial working memory ($N=95$).

			Talairach Coordinates ^a			Peak activation <i>M</i> (SD)				
Anatomical region	Brodmann Area(s)	Volume (μl)	x	y	z	Female Binge	Female Control	Male Binge	Male Control	η ²
Regions of interest analysis:										
R dorsal superior frontal gyrus	6	1323	-16.5	-28.5	53.5	-3.00 (3.27)	1.92 (4.42)	0.65 (4.31)	-0.46 (4.53)	0.10
R anterior superior frontal gyrus	10	1188	-13.5	-61.5	17.5	-5.07 (5.20)	0.52 (3.47)	0.42 (6.94)	-2.34 (4.86)	0.13
R inferior frontal gyrus	47	972	-46.5	-22.5	-9.5	-2.56 (2.28)	1.17 (3.46)	1.09 (3.87)	-0.16 (3.27)	0.11
B anterior cingulate cortex	24	729	-7.5	-37.5	-3.5	-3.45 (5.42)	0.07 (3.57)	0.46 (5.50)	-1.52 (4.32)	0.08
Whole brain analysis:										
L medial frontal gyrus	10, 11	5589	1.5	-52.5	-6.5	-4.32 (4.59)	0.01 (3.58)	0.55 (5.84)	-2.07 (3.98)	0.12
R middle temporal gyrus	21, 22	11340	-58.5	16.5	-6.5	-1.66 (1.85)	0.65 (1.68)	0.41 (1.54)	-0.76 (2.28)	0.17
L superior temporal gyrus	38, 28	3132	25.5	-7.5	-33.5	-1.17 (1.07)	0.24 (1.30)	0.11 (1.05)	-1.02 (1.87)	0.16
L cerebellar declive	-	9666	43.5	64.5	-21.5	-1.11 (1.84)	1.55 (1.84)	1.68 (3.84)	-0.50 (2.44)	0.16

R *right*; L *left*; B *bilateral*

^aCoordinates refer to the location of the peak group difference in SWM response within the cluster