ATYPICAL DEVELOPMENT OF SPATIAL WORKING MEMORY BRAIN ACTIVATION IN BINGE-DRINKING ADOLESCENTS

By

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A THESIS

Presented to the Department of Behavioral Neuroscience

and the Oregon Health & Science University

School of Medicine

in partial fulfillment of

the requirements for the degree of

Master of Science

March 2018

School of Medicine

Oregon Health & Science University

CERTIFICATE OF APPROVAL

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TABLE OF CONTENTS

Acknowledgements

Thank you to Hannah Stein, Sarah Alberti, and members of the Developmental Brain Imaging for their assistance with participant scheduling and data collection. This research was supported by the National Institute on Alcohol Abuse and Alcoholism (T32AA007468-30, Ryabinin; R01AA017664, Nagel).

Abstract

Adolescence is a period of neurodevelopment, which renders the brain vulnerable to the neurotoxic effects of alcohol. Preclinical and human studies suggest that frontal and parietal cortices – regions critical for intact working memory (WM) – may be impacted by binge drinking during this time. While cross-sectional studies have shed light on differences in working memory brain activation between binge-drinking adolescents and non-using peers, few have used longitudinal data to investigate the development of working memory in the brain. The current study used functional magnetic resonance imaging (fMRI) to examine the developmental trajectories of brain response during spatial WM in 55 adolescents. At baseline, all participants were alcohol-naïve or had minimal drinking experience (< 10 drinks and zero binges). By revisit, half of the participants emerged into binge drinking (*n*=28) and half continued to not use alcohol (*n*=27), but groups did not differ statistically on age, gender, puberty, and time between scans. Linear mixed-effects analyses revealed that binge-drinking adolescents showed a significant increase in activation with age in superior parietal (b = 0.11, p < 0.01) and inferior parietal (b = 0.10, p < 0.01) lobules during spatial WM. At baseline, prior to alcohol use, adolescents who later emerged into binge drinking showed premorbid lower brain activation in parietal, temporal, and occipital regions during spatial WM. Across all adolescents, there was an increase in spatial WM activation with age in bilateral medial frontal / precentral gyri, primarily due to a significant decrease in activation during the simpler vigilance control condition of the task. These findings provide evidence of altered neurodevelopmental trajectories and premorbid differences in binge-drinking adolescents, which may aid future education, prevention, and intervention efforts.

Key words

Adolescence, Binge Drinking, Development, fMRI, Working Memory

1. Introduction

Binge drinking is the most commonly reported alcohol use pattern among adolescents. 13% of underage people (12-20 years old) reported binge drinking – ≥5 drinks for men and ≥4 drinks for women within two hours [1] – in the past 30 days [2]. Rates of underage binge drinking rise during adolescence, with 5% and 17% of 8thand 12th graders reporting binge alcohol use in the past two weeks [3]. Alcohol use, and binge drinking in particular, has been associated with lower school performance, drunk driving, unprotected sex, externalizing behaviors, and other substance use [4, 5]. Furthermore, an increased risk of developing an alcohol use disorder (AUD) has been associated with adolescent onset of alcohol use [6]. Because binge drinking is prevalent among adolescents and has been associated with other adverse outcomes, it has spurred interest in understanding the impact this behavior has on the developing adolescent brain.

Normatively occurring structural and cognitive neurodevelopment parallels this time of increasing alcohol use. The adolescent brain typically undergoes cortical thinning and increased myelination to refine synaptic connections and promote efficient neural communication [7-10]. Fronto-parietal circuitry, particularly regions of the prefrontal cortex, continues to mature into late adolescence and early adulthood [7, 8, 10, 11]. This circuitry underlies executive functions, such as response inhibition, attention, and working memory, functions which also continue to behaviorally develop late into adolescence [For review: 12, 13, 14]. The ongoing development occurring during this period renders the adolescent brain vulnerable to exogenous influences and neural insults, such as binge alcohol use.

Indeed, rodent models suggest adolescence is a period during which the brain and behavior are particularly vulnerable to the effects of binge ethanol consumption [15-18]. In humans, longitudinal studies have shown that binge-drinking during the adolescent years is associated with thinner overall cortices, as well as thinner frontal, temporal, and cingulate

cortices compared to non-using controls [19], and binge-drinking adolescents have reduced white matter volumes [19-21]. Moreover, a recent cross-sectional study reported that reduced frontal and parietal cortical thickness is negatively correlated with the largest number of binge-drinking episodes [22], suggesting some potential of an alcohol dose response on the brain. In two retrospective studies by Bava and colleagues, binge-drinking adolescents had lower fraction anisotropy (FA), a measure of white matter microstructure, in fronto-parietal circuitry [23], and lower FA in the inferior longitudinal fasciculus, a white matter pathway connecting temporal and occipital regions of the brain, correlated with poorer working memory (WM) and attention in binge drinkers [24]. In addition to structural brain differences, deficits in neurocognitive functioning have also been associated with binge-drinking behavior [For review: 25].

One neurocognitive deficit that has been previously linked to binge-drinking in adolescence is WM, or the active maintenance and manipulation of information [26]. As noted above, WM continues to normatively develop late into adolescence [27-29]. Cross-sectional neuropsychological studies have revealed that binge-drinking adolescents exhibit poorer overall executive functioning and WM ability compared to non-using peers [24, 30]. Further, longitudinal studies have shown that poorer, premorbid WM abilities predicted frequency of alcohol use [31] and onset of first drink and first binge-drinking episode [32]. These studies demonstrate the potential for poor WM ability to be a risk factor for later alcohol use, as well as the need for additional longitudinal studies to discover the temporal relationship between alcohol use and poor WM skills.

The neural substrates of WM include the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex, frontal poles, inferior and posterior parietal cortex, premotor cortex, and cerebellum [For review: 33]. In typically developing adolescents, cortical volume reduction, thought to be associated with normative synaptic pruning [34], in fronto-parietal circuitry has been associated with improved working memory ability [35]. Developmental

functional magnetic resonance imaging (fMRI) cross-sectional studies have shown that WM blood oxygen-level dependent (BOLD) response in frontal and inferior parietal cortices is greater in older adolescents and adults compared to children [36-39]; however, older adolescents also showed lower WM BOLD response in the superior parietal cortex [36]. Mimicking cross-sectional findings, a meta-analysis of WM development in healthy adolescents revealed that older ages were associated with greater WM BOLD response in bilateral middle frontal gyri (MFG), left precuneus, and left inferior parietal lobule (IPL) and lower WM BOLD response in right superior frontal gyrus (SFG), left postcentral gyrus (PoCG), and left IPL [For review: 40]. More recent longitudinal studies of WM development have shown that WM activation in subcortical structures, such as the basal ganglia, predicts WM performance, while fronto-parietal activation correlated with subjects' current WM performance [41, 42]. Another longitudinal study of development showed that brain activation during WM in IPL, DLPFC, anterior cingulate, anterior insula, pallidum, and putamen decreased with age throughout adolescence [43].

Cross-sectional fMRI studies have also shown that WM brain activation is altered in adolescent heavy alcohol users. Adolescents with AUDs have greater BOLD response in bilateral parietal cortices [44], bilateral SFG, left inferior frontal gyrus, right MFG, IPL, precuneus, and middle temporal gyrus (MTG) [45], as well as lower BOLD response in the left precentral gyrus (PreCG) and bilateral precuneus and cerebellum [44, 45]. At binge-drinking levels, adolescents exhibit lower BOLD response in the right SFG and IFG [46] and middle occipital gyrus (MOG) [47], as well as greater BOLD response in the right SFG, right MFG/SFG gyrus, left medial frontal gyrus (meFG), and right IPL [47] compared to non-using controls. A single longitudinal study, using a traditional repeated-measures ANOVA to analyze brain activation, revealed that adolescents who transitioned into binge drinking showed less activation at baseline in the right IPL and left meFG, prior to alcohol use, than adolescents who remained non-drinkers [47]. After transitioning to alcohol use, binge-drinking adolescents showed

increased BOLD response compared non-drinkers in the same two regions [47]. Adolescent studies using WM tasks revealed a pattern of lower brain activation in heavy alcohol users prior to alcohol use and greater activation after initiating heavy drinking. Taken together, these findings suggest that premorbid differences in WM brain activity may be a risk factor for future binge drinking, as well as the idea that WM-related brain response is altered in association with binge-drinking behavior. However, due to the paucity of longitudinal studies on spatial WM brain response in adolescent binge drinkers and the need to appropriately model age, or time, as a non-categorical, continuous variable, the relationship between WM activation and binge drinking in adolescents is still unclear.

The current study replicates and extends the findings of previous studies of binge-drinking adolescents and WM brain activation by using linear mixed-effects analyses to appropriately model the developmental trajectories of spatial WM activation in alcohol-naïve adolescents who go on to binge drink and those who remain non-users. This study was designed to investigate premorbid differences in spatial WM activation at baseline, prior to drinking, as well as the developmental trajectory of this activation both normatively and following emergence into binge drinking. I hypothesized that i) adolescent binge drinkers would show less spatial WM activation in fronto-parietal circuitry, prior to alcohol use, compared to non-drinking controls and ii) adolescent binge drinkers would show an increase with age in fronto-parietal spatial WM activation, while controls would not show an increase. Because altered neurocognitive brain response is linked to adolescent binge alcohol use, it is necessary to unravel the neurobiological premorbid risk factors for and consequences of binge drinking. A better understanding of how alcohol impacts the development of WM brain activation will benefit psychoeducational efforts that seek to reduce adolescent alcohol use through education, prevention, and intervention.

2. Methods

2.1 Participants

Fifty-six healthy adolescents (aged 12 to 17 at baseline) were recruited from the local community as part of a larger, ongoing study on adolescent neurodevelopment in at-risk youth. Following written assent from the adolescents and consent from their parents, all participants underwent comprehensive structured interviews administered by a trained research assistant, including the Diagnostic Interview Schedule for Children Predictive Scales (DISC-PS-4.32b) [48], the Brief Lifetime version of the Customary Drinking and Drug Use Record (CDDR) [49], and the Family History Assessment Module (FHAM) [50]. Family history density (FHD) was calculated based on the number of relatives with an AUD and how closely related an adolescence was to those relatives. Higher scores indicated greater prevalence of familial AUDs, with parents contributing 0.5, grandparents 0.25, and aunts and uncles a weighted ratio of 0.25, divided by the number of their siblings. Adolescents were excluded from initial enrollment based on significant alcohol or drug use (>10 lifetime alcoholic drinks or >2 drinks/occasion, >5 uses of marijuana, >4 cigarettes/day, or any other drug use), inability of a biological parent to provide family history information, probable DSM-IV psychiatric disorder diagnosis, left-handedness (Edinburgh Handedness Inventory [51], serious medical problems, neurological illness, significant head trauma (loss of consciousness >2 minutes), history of psychotic disorders in biological parents, prenatal exposure to drugs or alcohol, learning disability, pregnancy, and MRI contraindications. All procedures were approved by the Oregon Health & Science University (OHSU) Institutional Review Board.

The Hollingshead Index of Social Position [52], which is based on the current occupation and highest education level of each parent, is still commonly used as a measure of socioeconomic status (SES) [47, 53]. To obtain an estimate of intellectual functioning, adolescents were administered the Wechsler Abbreviated Scale of Intelligence [54]. Pubertal maturation was assessed using the self-rated Pubertal Development Scale (PDS) [55], which

has been shown to be highly correlated to the self-ratings on the Tanner's Sexual Maturation Scale [56].

2.1.1 Final sample

Of the initial 56 participants, 38 had two usable scan time points (baseline and revisit), 17 could only contribute one time point to the model, and one control participant was missing both scan time points, resulting in that participant being unable to contribute to the model. From the total number of time points collected (n=112), 19 time points were missing for the following reasons: no scan data (10 time points), spatial WM and/or vigilance task accuracy was below a 70% threshold (2 time points), and excessive head motion (>30% of frames censored; 7 time points). This resulted in a total of 93 time points included in the LME model, with a remaining sample of 28 binge-drinking adolescents and 27 non-using controls. Missing data were estimated using REML in AFNI and R.

2.2 Binge-drinking criterion

To assess alcohol and substance use following initial collection of baseline neuroimaging and neuropsychological data, adolescents were administered the CDDR and 90-day Timeline Followback (TLFB) [57] during follow-up phone interviews conducted approximately every 90 days. The majority of participants were alcohol-naïve at baseline with a small subsample of binge-drinking adolescents (*n*=4) having reported minimal drinking experience (See **Table 1**). Adolescents who initiated binge drinking and met binge-drinking criterion (≥3 episodes of drinking ≥4 alcoholic drinks within the past 3 months) were brought in and re-assessed using the same baseline neuroimaging and neuropsychological measures. Non-using controls, developmentally matched (based on sex, age, pubertal stage, and time since baseline) to binge-drinking adolescents, were also brought in for re-assessment. All participants were administered the same reassessment protocol. 28 binge-drinking adolescents met the above criterion and were carefully matched to 28 non-using controls. 72 hours prior to

their revisit, adolescent were asked to refrain from drug and alcohol use, and absence of acute alcohol intoxication was confirmed using a breathalyzer (AlcoHAWK ABI). Urinary analysis, using the iCup A.D. 12-panel (Alere; Part# 01 102 2027), was conducted to check for cannabis and other substance use.

2.3 Imaging procedures

2.3.1 Acquisition

Adolescents were scanned on a 3.0 Tesla Siemens Magnetom Tim Trio system (Siemens Medical Solutions, Erlangen, Germany) at OHSU's Advanced Imaging Research Center. A T_1-weighted MPRAGE scanning sequence (TR = 2300 ms, TE = 3.58 ms, TI = 900 ms, acquisition matrix = 256 x 240 mm, flip angle = 10^0, resolution = 1 mm x 1 mm x 1 mm, 160 slices) was used to acquire whole-brain, high-resolution anatomical images in the sagittal plane. Functional images were collected in the axial plane parallel to the anterior-posterior commissure using a T_2-weighted gradient echo-planar BOLD sequence (TR = 2000 ms, TE = 30 ms, field of view = 240 mm, flip angle = 90^0, resolution = 3.75 mm x 3.75 mm x 3.8 mm, 33 slices).

2.3.2 Working memory task

While in the scanner, adolescents performed a modified blocked design fMRI spatial and verbal working memory task. Task details can be found elsewhere [58]. Briefly, the task alternated between six blocks of a spatial WM 2-back condition, a verbal WM 2-back condition, and a vigilance condition. The spatial WM stimuli consisted of white, capitalized, phonemically similar letters presented in various spatial locations on a black screen. Participants were instructed to respond via a button press when a stimulus appeared in "the same LOCATION as two screens before," while ignoring the stimulus content. For the verbal WM condition, participants were instructed to respond when a stimulus was "the same LETTER as two screens before," while ignoring the spatial location. During the vigilance condition, participants were presented with gray and white dots and were instructed to respond whenever a gray dot

appeared. In addition to BOLD response, task accuracy and reaction times for correct trials were collected for all block conditions. It should be noted that verbal WM data were modeled, but were not included in the current analysis.

2.3.3 Image pre-processing

Data processing and analysis were conducted using Analysis of Functional NeuroImages (AFNI) [59]. Preprocessing included anatomical masking and removal of non-brain skull and tissue, slice timing correction, motion correction, co-registration of functional images to anatomical images, and spatial smoothing using a 6 mm full-width half-max Gaussian kernel. Motion was assessed using frame-wise displacement (FD). This method calculates frame-to-frame motion by summing "the absolute values of volume-by-volume changes in the six rigid body parameters" (three rotational and three displacement) [60, 61]. Due to excessive head motion contributing to signal artifact, frames were censored if FD > 0.7 mm [62]. Time points (baseline or revisit scan) with >30% of their frames removed, per block condition, were treated as missing data in the LME models.

Time series data were normalized in order to compare contrasts and extract percent signal change. A vector representing the task design for the WM (both spatial and verbal) and vigilance blocks was used to correlate the time series data, while covarying for motion and linear trends and modeling delays in the hemodynamic response [63]. The BOLD response is represented by the fit coefficients derived from fitting the times series data to the model. For each individual voxel in the brain, the BOLD response was contrasted between spatial WM and vigilance, spatial WM and baseline, as well as vigilance and baseline. AFNI's intrinsic baseline functioned as the estimated baseline, which included the mean BOLD signal from the entire time course of the task, linear drift, unmodeled fixation periods between trials, and regressors of no interest (e.g. motion parameters) [59]. Lastly, functional data were resampled into $3mm^3$ voxels and transformed into standard Talairach coordinates [64] prior to group-level analysis.

2.4 Group-level analysis

2.4.1 Demographic data

Demographic data were analyzed using SPSS Statistics 24 (Armonk, NY: IBM Corp). Variables were assessed for normal distribution using Shapiro-Wilk tests and examined for outliers >2.5 SD from the mean. Baseline and revisit variables were compared between binge-drinking adolescents and non-using controls using independent-samples *t*-tests or Mann-Whitney U tests for non-normal or ordinal data (i.e. pubertal status). Gender composition was examined between groups at baseline using a chi-squared test.

2.4.2 Behavioral and imaging data

Behavioral and imaging data were analyzed using AFNI and R (version 3.3.2). To appropriately model the longitudinal nature of the data (i.e. continuous variables, within subject variability, missing data), linear mixed-effects (LME) models tested the effects and interaction of binge-drinking status and age on spatial WM task accuracy, reaction times, and BOLD response. To obtain an unbiased estimation of variance components (subject-specific, or random, effects), missing data were handled using restricted maximum likelihood (REML). For all LME models, group at the intercept (binge-drinking adolescent or non-using control), age (centered at the intercept, or average baseline age), and a group-by-age interaction term were entered into the model as fixed effects, and random intercepts were estimated for each subject. For the behavioral data, LME models were used to test the effects and interaction of binge-drinking status and age on task accuracy and reaction times.

For the imaging data, spatial WM-specific activation was determined separately for each group at each time point by conducting four separate one-sample *t*-tests for the spatial WM vs vigilance contrast. AFNI's 3dLME [65], which utilizes the R package *nlme* [66], was used to analyze a group effect at baseline, an age effect, and an interaction of group and age on spatial WM vs vigilance BOLD response at the whole-brain level. To best represent task-related BOLD

response for the entire sample and constrain analyses to regions of task-related activation, a voxel threshold of $p < 0.05$ was applied to individual group activation maps for each time point, which were then combined to create a single task-related activation map (**Supplementary Fig. 1**). Then, the task-specific activation map was used to threshold the whole-brain 3dLME findings. To correct for multiple comparisons, AFNI's 3dClustSim [67], including the autocorrelation function parameters estimated from 3dLME's residuals output, was used to determine a cluster-size threshold ($\alpha < 0.01$, ≥27 voxels) for the given voxel-wise threshold ($p < 0.01$). For all significant clusters, AFNI's 3dROIstats was used to extract percent signal change values for the spatial WM vs vigilance, spatial WM vs baseline, and vigilance vs baseline contrasts.

To obtain coefficients for significant clusters and simple effects, post-hoc ROI analyses were performed using R and *nlme*. To examine the simple effects of spatial WM vs baseline and vigilance vs baseline, an additional four fixed effects (block type (spatial WM or vigilance), block-by-group, block-by-age, and block-by-group-by-age) and random intercept estimates for block type nested in each subject were included in the LME models for BOLD response. Again, missing data were handled using REML.

2.4.3 Drinking measures

To explore alcohol and substance use characteristics in relation to spatial WM BOLD response, additional LME models were fit for binge-drinking adolescents only. Alcohol and marijuana use variables from the CDDR and TLFB, including lifetime drinks, lifetime binges, and episodes of marijuana use were examined individually as time-varying predictors of spatial WM BOLD response. Alcohol or marijuana use, age, and use-by-age interaction were included as fixed effects. Random intercepts were estimated for each subject.

3. Results

3.1 Demographic and spatial working memory behavioral data

Participants were not significantly different at baseline on any demographic variables (**Table 1**). LME modeling did not reveal a significant group effect at baseline, age effect, or group-by-age interaction on task accuracy or reaction times (**Table 2**).

[Insert Table 1 and 2 here]

3.2 Spatial working memory fMRI data

As has been previously demonstrated [36, 58, 68], adolescents, across groups, showed the typical spatial WM BOLD response pattern, with activation in fronto-parietal circuitry and deactivation in default mode network brain regions. LME analyses were restricted to spatial WM-related (2-back vs. vigilance) areas of activation and deactivation. Results from AFNI's 3dLME investigating spatial WM vs. vigilance BOLD response revealed differences in activation throughout fronto-parietal circuitry, with a statistically significant group effect at baseline, age effect, and group-by-age interaction (See **Table 3**). To determine if a subsample of adolescents with minimal alcohol use at baseline (n=4) were driving the baseline effect, the analyses were rerun, removing these four participants. The same baseline effects remained; thus, the participants were not excluded from the analyses.

[Insert Table 3 here]

3.2.1 Group effect at baseline

As seen in **Table 3** and **Figure 1**, a significant group effect at the average baseline age in spatial WM vs vigilance BOLD response was found in six clusters. Compared to non-using controls, adolescents who went on to binge drink exhibited lower BOLD response, at baseline (prior to drinking), in the PoCG/IPL (b = -0.38, p < 0.01), middle temporal gyrus (MTG) (b = -0.18, p < 0.01), precuneus (b = -0.63, p < 0.01), angular gyrus (AG) (b = -0.39, p < 0.01), MOG (b = -0.21, p < 0.01), and superior parietal lobule (SPL) (b = -0.44, p < 0.01).

To better understand whether the group effect at baseline on the contrast of spatial WM vs vigilance BOLD response was driven by spatial WM or vigilance, the contrast was separated into BOLD response during spatial WM vs baseline and vigilance vs baseline. Post-hoc ROI analysis revealed that the group effect at baseline was confirmed by a significant group-by-block interaction in all six clusters (b = 0.20 – .65, p < 0.01). A group-by-block interaction may most likely manifest as 1) a group effect only on baseline spatial WM BOLD response or only on baseline vigilance BOLD response or 2) a block effect only in binge-drinking adolescents or only in non-using controls at baseline. Consistent with a group effect at baseline, binge-drinking adolescents showed significantly lower BOLD response than controls for the spatial WM condition, but not the vigilance condition, in the PoCG/IPL (b = -0.33, p < 0.01), MTG (b = -0.22, p < 0.01) and precuneus (b = -0.48, p < 0.01). In the AG, there was a significant block effect at baseline in controls, with greater spatial WM BOLD response compared to vigilance BOLD response (b = 0.46, p < 0.01). In the MOG, there was a significant block effect at baseline in binge-drinking adolescents, with greater vigilance BOLD response compared to spatial WM BOLD response (b = -0.14, p < 0.01). Finally, in the SPL, there was a significant block effect at baseline in both binge-drinking adolescents (b = 0.28, p < 0.01) and controls (b = 0.72, p < 0.01), with greater spatial WM BOLD response compared to vigilance BOLD response; however, the difference between conditions was smaller in binge-drinking adolescents than in controls. Graphs for all simple contrasts may be found in **Supplementary Figure 2**.

[Insert Figure 1 here]

3.2.2 Age effect

A significant age effect on spatial WM vs vigilance BOLD response was found in the meFG (**Table 3; Fig. 2**). Across groups, adolescents showed an increase with age in spatial WM vs vigilance BOLD response (b = 0.04, p < 0.01). To further investigate the influence of spatial WM and vigilance BOLD response on this effect, the spatial WM vs vigilance contrast was

separated, as previously mentioned. In the meFG, the age effect was confirmed by a block-by-age interaction trending towards significance at the $p < 0.01$ level ($b = 0.034$, $p = 0.0154$), with a significant decrease with age in BOLD response during the simpler vigilance condition ($b = -0.033$, $p < 0.01$), but not during the spatial WM condition.

[Insert Figure 2 here]

3.2.3 Group-by-age interaction

A significant group-by-age interaction was found in two parietal clusters, including the precuneus/SPL ($b = 0.11$, $p < 0.01$) and IPL/PoCG ($b = 0.10$, $p < 0.01$) (**Table 3; Fig. 3)**. Binge-drinking adolescents showed a significant increase with age in spatial WM vs vigilance BOLD response in both clusters (precuneus/SPL: $b = 0.07$, $p < 0.01$; IPL/PoCG: $b = 0.07$, $p < 0.01$). Controls showed a decrease with age, but the change did not reach statistical significance (precuneus/SPL: $b = -0.05$, $p = 0.016$; IPL/PoCG: $b = -0.03$, $p = 0.073$).

As with the group effect at baseline and age effect, the spatial WM vs vigilance contrast was separated to further examine the group-by-age interaction on spatial WM and vigilance BOLD response. The group-by-age interaction was driven by a significant block-by-age interaction in binge-drinking adolescents in the precuneus/SPL ($b = 0.06$, $p < 0.01$) and IPL/PoCG ($b = 0.08$, $p < 0.01$), which revealed a significant increase with age in BOLD response during the spatial WM condition, but not the vigilance condition. Non-using controls did not show a significant block-by-age interaction in either region.

[Insert Figure 3 here]

3.2.4 Dose-related response

In the two regions where a significant group-by-age interaction was found, post-hoc analyses in binge-drinking adolescents did not reveal any association between spatial WM vs vigilance BOLD response and substance use variables, including lifetime drinks (SPL: b=-0.013, p=0.62;

IPL: *b*=-0.05, *p*=0.60), lifetime binges (SPL: *b*=-0.04, *p*=0.49; IPL: *b*=-0.06, *p*=0.41), or episodes of marijuana use (SPL: *b*=- -0.004, *p*=0.84; IPL: *b*=0.003, *p*=0.91).

4. Discussion

The goal of the current study was to investigate the developmental trajectories of spatial WM brain response among adolescents who emerge into binge drinking compared to continuously non-using controls. Consistent with my hypotheses, a significant group-by-age interaction was found in two key parietal areas that are part of the fronto-parietal and dorsal attention networks. This result was driven by significant increase with age in spatial WM activation in binge-drinking adolescents, while controls showed a non-significant decrease. Furthermore, binge drinking adolescents, compared to controls, also exhibited pre-drinking activation differences in multiple areas of the parietal cortex.

As noted, spatial WM brain activation in binge-drinking adolescents followed an altered developmental trajectory from controls in spatial WM-related parietal circuitry. In the superior and inferior parietal lobules, binge-drinking adolescents showed an increase with age in spatial WM activation, consistent with previous longitudinal findings in binge-drinking adolescents [47]. However, this trajectory is contrary to typical functional neurodevelopment. In parietal areas, developing adolescents process information more efficiently during many cognitive tasks, including spatial WM [36, 69]. Age-related increases in brain activity tend to reflect inefficiency in WM abilities [27, 37, 70]. Therefore, the increasing activity in binge-drinking adolescents suggests immature and less efficient WM brain activity compared to non-using peers.

In addition, baseline differences in spatial WM activation were observed between binge-drinking adolescents and non-using peers. At baseline, prior to alcohol use, binge-drinking adolescents exhibited significantly lower spatial WM activation in the superior and inferior parietal lobules, similar to areas found for the interaction. Binge-drinking adolescents also showed lower spatial WM activation in the MTG and MOG, areas involved in visuospatial

processing. Despite the pre-drinking differences in BOLD response, adolescents who emerged into binge drinking still showed intact task performance at baseline, which is in agreement with previous findings [47]. However, previous studies have shown that less premorbid activation in frontal and parietal areas during an inhibition task predicted future heavy alcohol use in adolescents, despite intact performance [71]. Given the essential role fronto-parietal circuitry plays in functions such as WM, response inhibition, visuospatial processing, and decision making, lower brain activation in fronto-parietal regions during spatial WM may indicate a risk for future binge alcohol use in adolescents.

Taken together, baseline differences in spatial WM activation, an increase in activation with age, and intact WM performance suggests that binge-drinking adolescents may employ an alternative neural strategy to achieve a similar level of executive functioning for spatial WM. This alternative neural strategy could be a form of neural compensation, meaning binge-drinking adolescents' brains may need to work harder to achieve the same level of executive functioning. It is important to note that a spatial WM 2-back task is a relatively easy neurocognitive task and not nearly as demanding as a real-life situation. Over taxing WM load or poorer WM performance have been associated with greater impulsive choice on delay discounting tasks [72-74]. Therefore, when a task becomes more demanding, such as in real-world situations, altered spatial WM brain activity may lead to a break-down in executive functioning and poorer decision-making. Further, when WM cognitive abilities are diminished, the risk for future alcohol use and developing an AUD rises [For review: 31, 32, 75].

In addition to investigating differences in developmental trajectories and baseline activation between binge-drinking and non-using adolescents, the longitudinal design of this study allowed for examination of typical neurodevelopment related to spatial WM. Findings suggest that, regardless of binge-drinking status, adolescents showed an increase with age in the meFG during the spatial WM vs vigilance condition, which was driven mainly by a significant decrease with age in activation during the simpler control vigilance condition. This suggests

that, as adolescents age, the level of meFG activity for spatial WM does not change, but that attention-specific activation to simple tasks decreases with age. An increasing developmental trajectory in meFG activity during spatial WM is consistent with previous findings that reported increased frontal activity in older adolescents [36, 37, 69]. However, the specific observation that the “increase” in spatial WM activation was driven by a decrease in the simpler vigilance condition is not present in these other studies. This is because the other studies used different tasks, did not explore contrasts between the task and control conditions, and, therefore, were not able to look at condition-specific activation.

Possible limitations of the current study should be considered. First, multi-level modeling, such as LME, allows one to model individual (within-subject) growth, but a minimum of three time-points per subject are needed to appropriately model variation in an individual’s change (or slope) with time. By having two time-points per subject, I was only able to model trajectories at the group level. Second, with only nine females per group, the current study did not have enough statistical power to adequately examine sex differences in the development of spatial WM brain activation. Previous studies have shown that brain activation may differ by sex in the context of binge drinking [for example:46]. Additional longitudinal data collection, still ongoing, will be necessary to answer questions regarding individual and sex differences. Third, neuroimaging findings did not have a dose-related association to any of the substance use variables, preventing a more concrete link between spatial WM brain activation and alcohol use. Due to the relatively short duration of alcohol use in binge-drinking adolescents, it is possible I was unable to detect an alcohol dose effect, which may only become apparent after prolonged alcohol use. Fourth, binge-drinking adolescents did not show a difference in spatial WM task performance, compared to non-using controls, despite showing differences in brain activation. This may be because of the simplicity of the 2-back task, and a more difficult task that increases the demand on WM ability may reveal performance differences. Fifth, missing data, estimated using REML, were not missing completely at random. Some data were missing due to

systematic criteria, such as excess head motion or poor WM task performance. It is entirely possible that head motion and poor performance may be linked to binge drinking and may bias results. However, it is notable that the data were missing variably at baseline and revisit, as well as in binge drinkers and controls, suggesting that this may not have impacted the results. Finally, it should be noted that it is entirely possible that the current non-using adolescents may initiate binge drinking at a later time. Therefore, caution should be employed when considering pre-existing differences in spatial WM brain activation as risk factors for future binge drinking.

5. Conclusions

The current study replicates and expands upon previous cross-section and longitudinal findings on WM brain activation in binge-drinking adolescents. Results suggest that adolescents who emerge into binge drinking show an increase with age in parietal spatial WM BOLD response with age, and that pre-existing hypoactivity in parietal circuitry may reflect a potential risk factor for future binge drinking. Given the important role of WM in many day-to-day functions [76], altered WM brain response may contribute to later deleterious outcomes, such as less efficient decision-making and future alcohol use. Future directions along this line of research will primarily focus on collecting additional longitudinal data from the current sample of adolescents to i) characterize individual differences in developmental trajectories of spatial WM brain activation, ii) examine whether prolonged binge-drinking behavior will lead to performance differences on a relatively simple spatial WM 2-back task, and iii) confirm whether or not pre-existing brain activation differences act as reliable risk factors for binge drinking by monitoring if currently non-using controls emerge into binge drinking.

6. References

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Table 1. Baseline demographics

	Bingers	Controls	Statistic
	(*n* = 28)	(*n* = 27)	
Age	14.59 (1.33)	14.97 (1.24)	t_{53} =1.11, p = 0.27
Gender (male/female)	19 (9)	18 (9)	$x^2_{1,55}$ =0.01, p = 0.93
Pubertal stage	3.71 (0.98)	3.63 (0.79)	U_{53} = 3.73, Z = -0.86, p = 0.93
Hollingshead SES	28.36 (14.75)	29.63 (10.42)	t_{53} = 0.37, p = 0.71
IQ	112.57 (10.11)	110.78 (10.51)	t_{53} = 0.65, p = 0.52
Family history density	0.35 (0.30)	.35 (0.30)	t_{53} = 0.06, p = 0.95
Lifetime drinks	0.38 (1.24)	0 (0)*	t_{52} = 1.59, p = 0.12
Lifetime marijuana use	0 (0)	0 (0)*	na

Values presented as Mean (SD).
*At revisit, one control participant reported having one alcoholic drink and one episode of marijuana use.

Table 2. Spatial working memory task performance

	Bingers	Controls	Statistic
	(*n* = 28)	(*n* = 27)	
Spatial WM accuracy (%)[a]	93.97 (0.97)	93.15 (1.03)	b = 0.80, p = 0.57
Spatial WM RT (ms)[b]	543.26 (22.49)	533.79 (23.06)	b = 9.50, p = 0.77
Per year increase in accuracy[c]	0.09 (0.37)	1.03 (0.42)	b = 0.93, p = 0.10
Per year decrease in RT[d]	-11.62 (6.20)	-9.49 (7.08)	b = -2.14, p = 0.82

Values presented as Mean (SEM).
95% confidence interval (CI): [a]93.37 to 93.75; [b]534.29 to 542.69; [c]0.50 to 0.64; [d]-11.74 to -9.34

Table 3. 3dLME analysis of spatial WM vs vigilance BOLD response in binge-drinking and non-using adolescents

Anatomical location	Side	x	y	z	Volume (voxels)	*F*-value
Group effect at baseline						
Cluster 1: PoCG, IPL	R	-52.5	25.5	47.5	138	25.13
Cluster 2: MTG, ITG, MOG	R	-40.5	61.5	5.5	53	19.65
Cluster 3: Precuneus, SPL	L	22.5	73.5	50.5	42	17.14
Cluster 4: AG, Precuneus	R	-40.5	70.5	32.5	36	14.21
Cluster 5: MOG	L	40.5	73.5	5.5	28	13.34
Cluster 6: SPL, Precuneus	R	-10.5	61.5	56.5	28	14.6
Age effect						
Cluster 1: meFG	R/L	7.5	13.5	65.5	39	22.91
Group-by-age interaction						
Cluster 1: Precuneus, SPL	L	22.5	58.5	41.5	84	18.45
Cluster 2: IPL, PoCG	R	-52.5	28.5	44.5	56	19.72

Clusters with significant effects or interactions in analysis of spatial working memory vs vigilance BOLD response. Presented for each cluster is the anatomical location of each significant cluster, the peak voxel coordinates in standard Talairach space, the size of the cluster, and corresponding *F*-value.

Degrees of freedom = 1,53 for group; 1,36 for age and group-by-age interaction.

R, right; L, left; AG, angular gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; meFG, medial frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; PoCG, postcentral gyrus; SPL, superior parietal lobule.

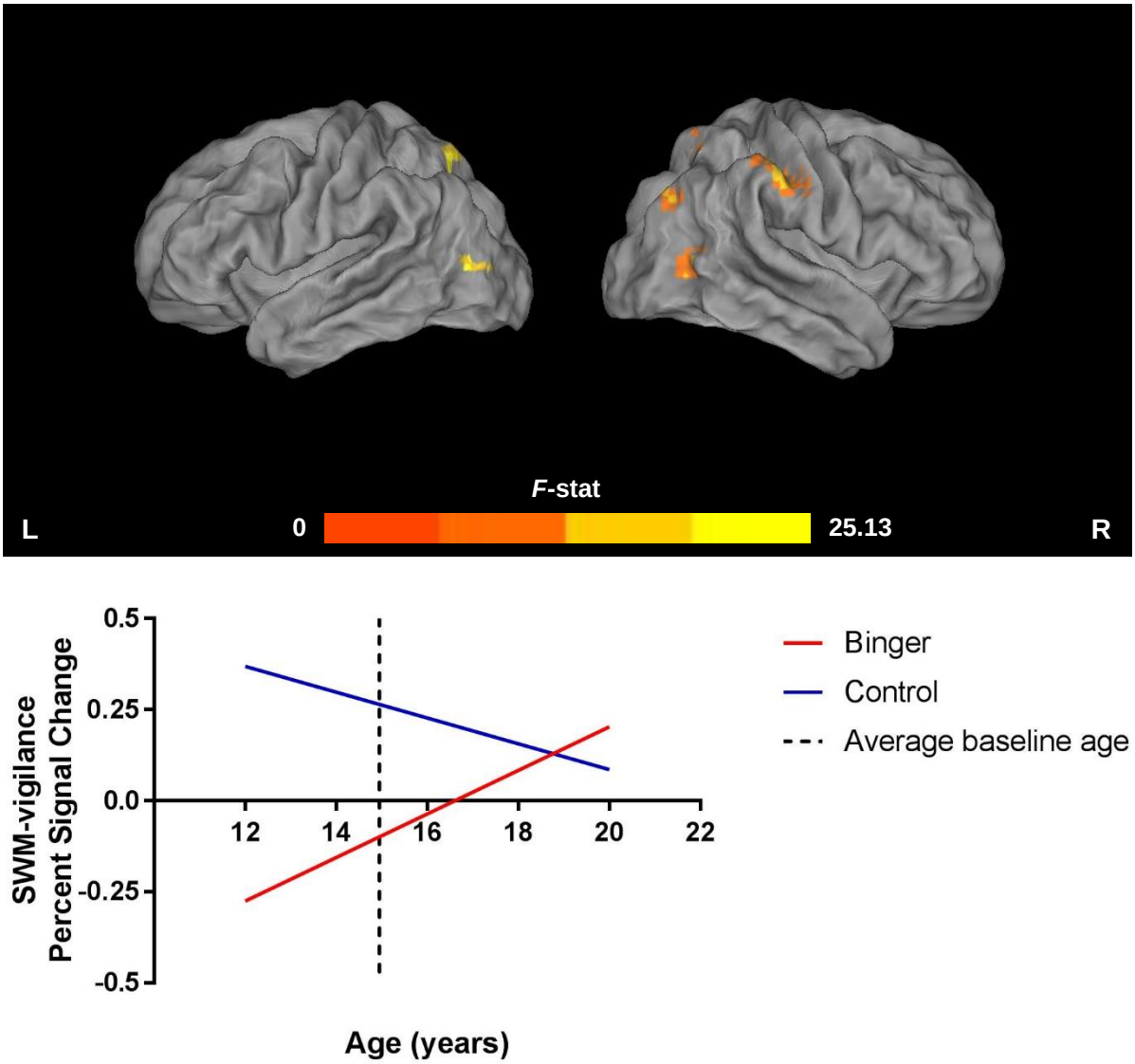


Fig. 1. Group effect at average baseline age. Significant group effect at baseline in spatial WM vs vigilance brain activation in the left precuneus and middle occipital gyrus and right postcentral gyrus/inferior parietal lobule, middle temporal gyrus, angular gyrus, and superior parietal lobule. Representative trajectories of percent signal change with age during spatial WM vs vigilance are plotted for binge-drinking adolescents (red) and non-using controls (blue). Average age at baseline (dotted black line).

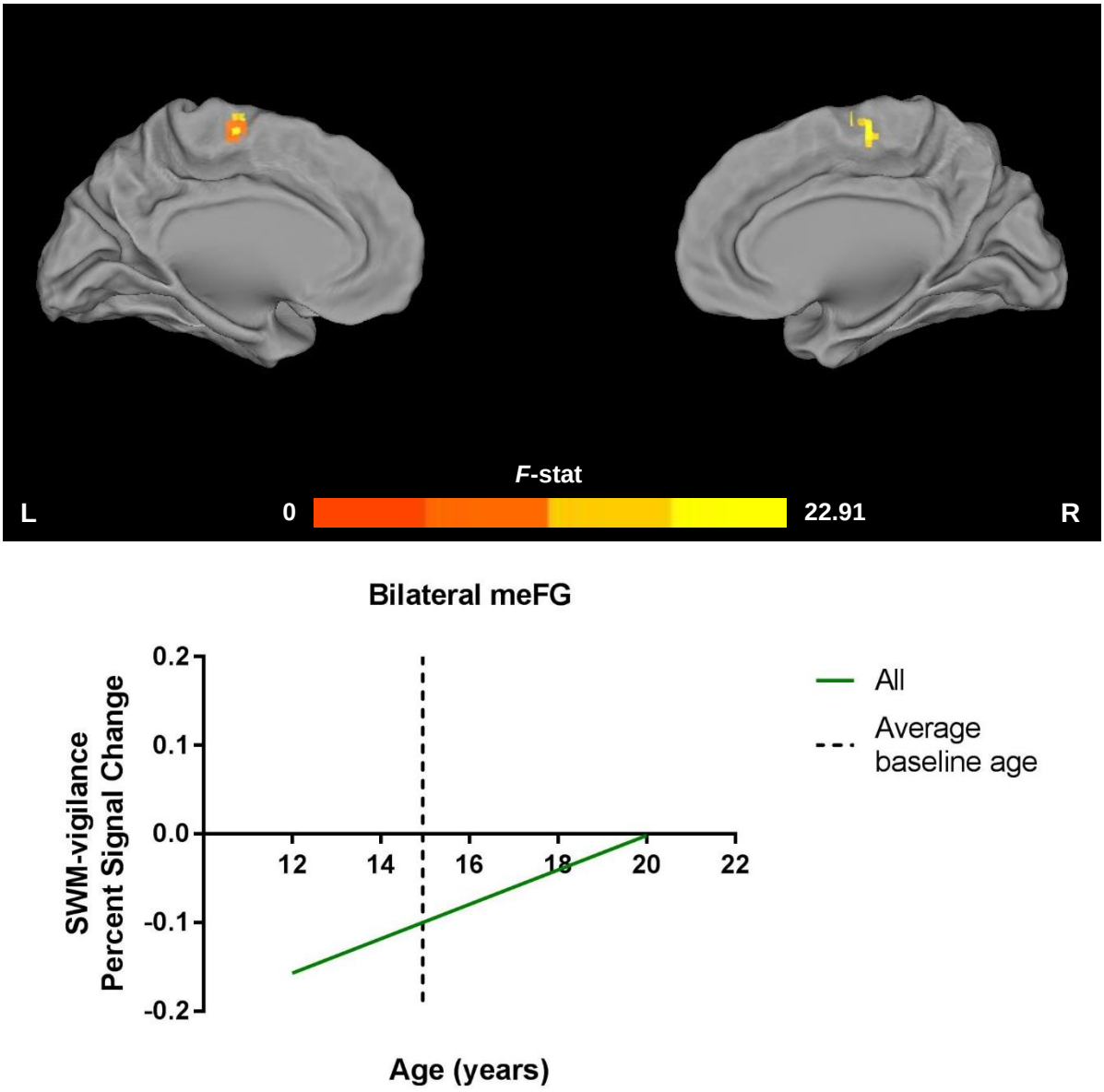


Fig. 2. Age effect. Significant age effect in spatial WM vs vigilance brain activation bilateral medial frontal gyrus. Trajectory of percent signal change with age during spatial WM vs vigilance are plotted for entire sample of adolescents. Average age at baseline (dotted black line).

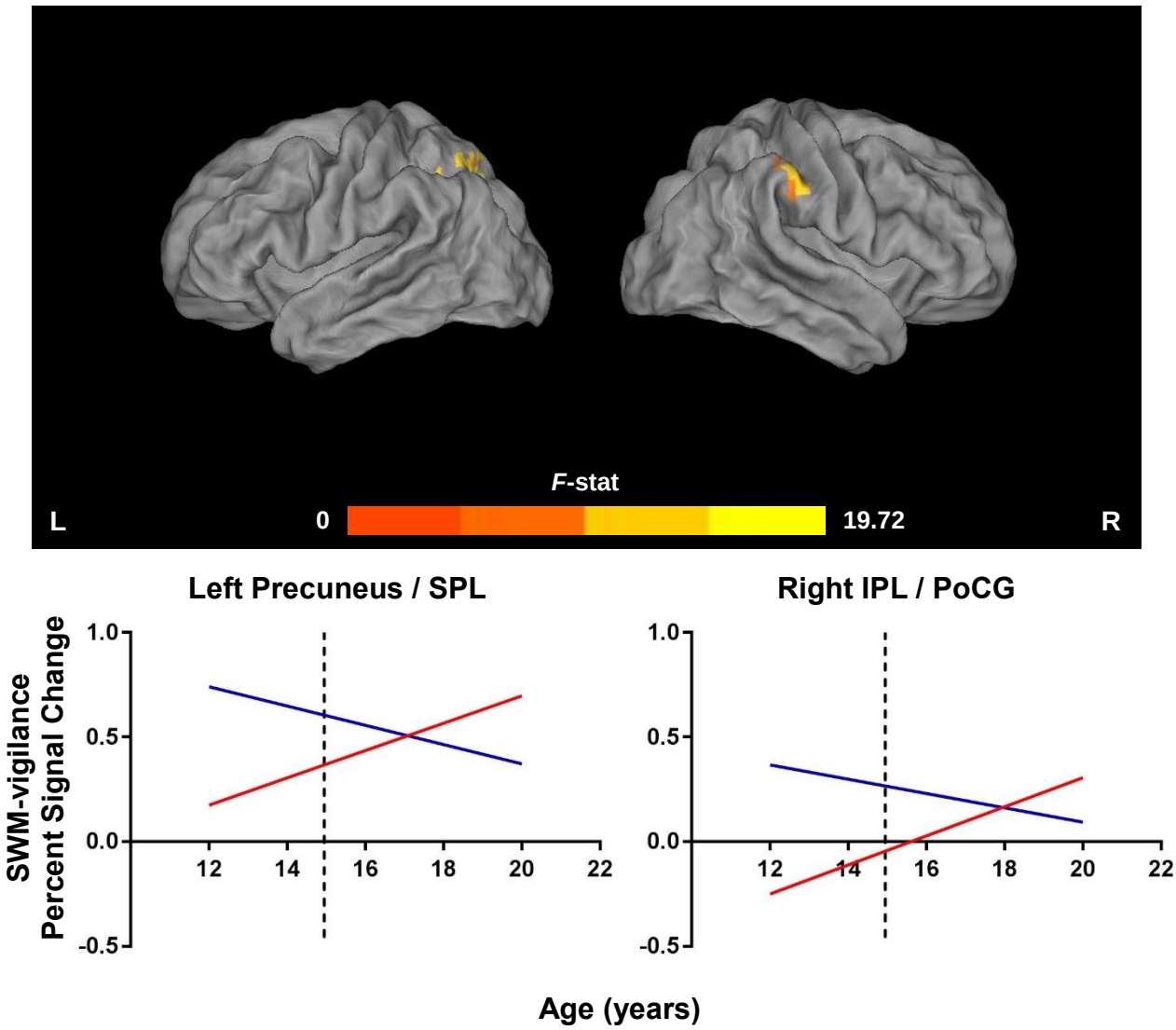
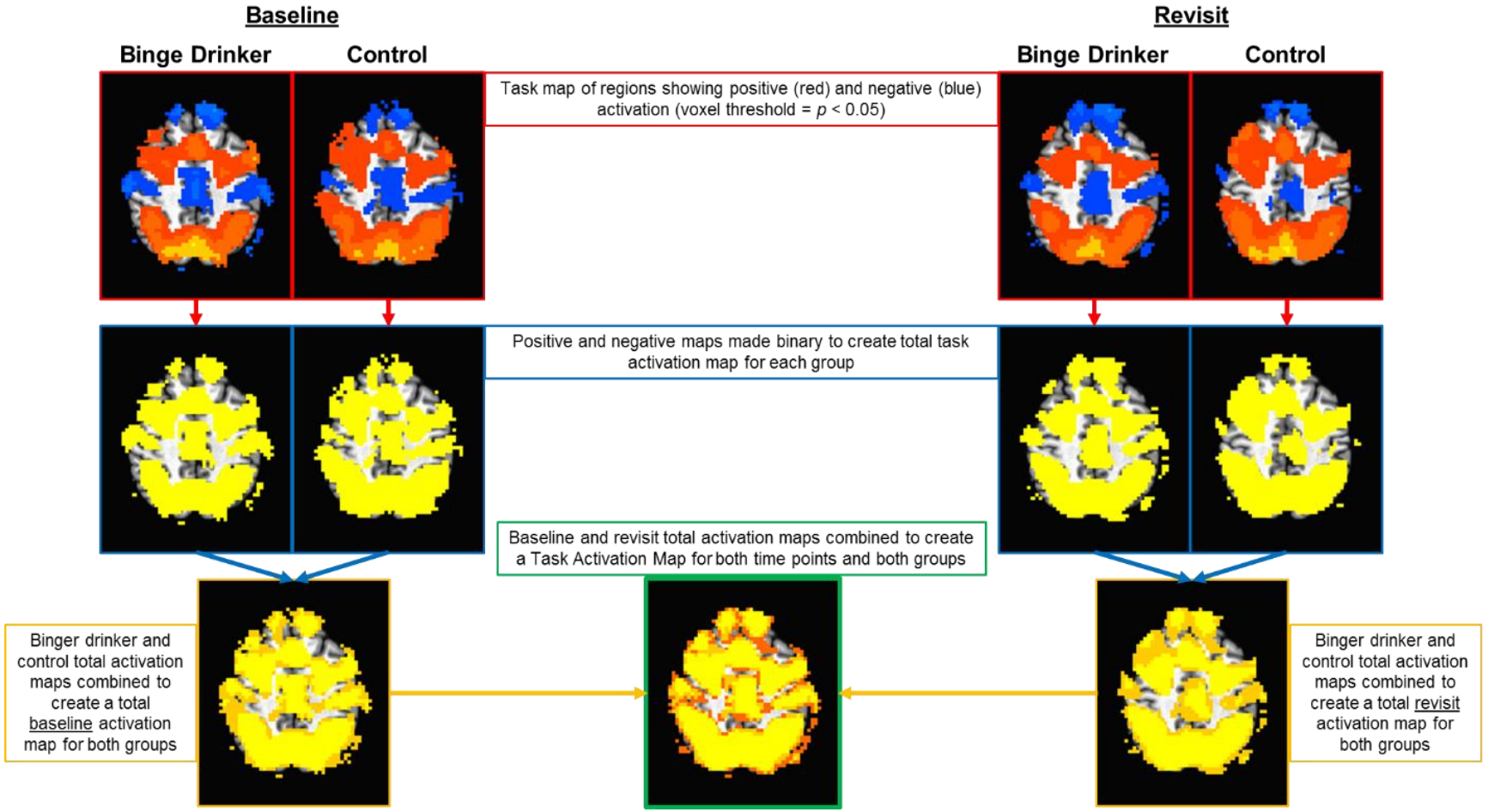
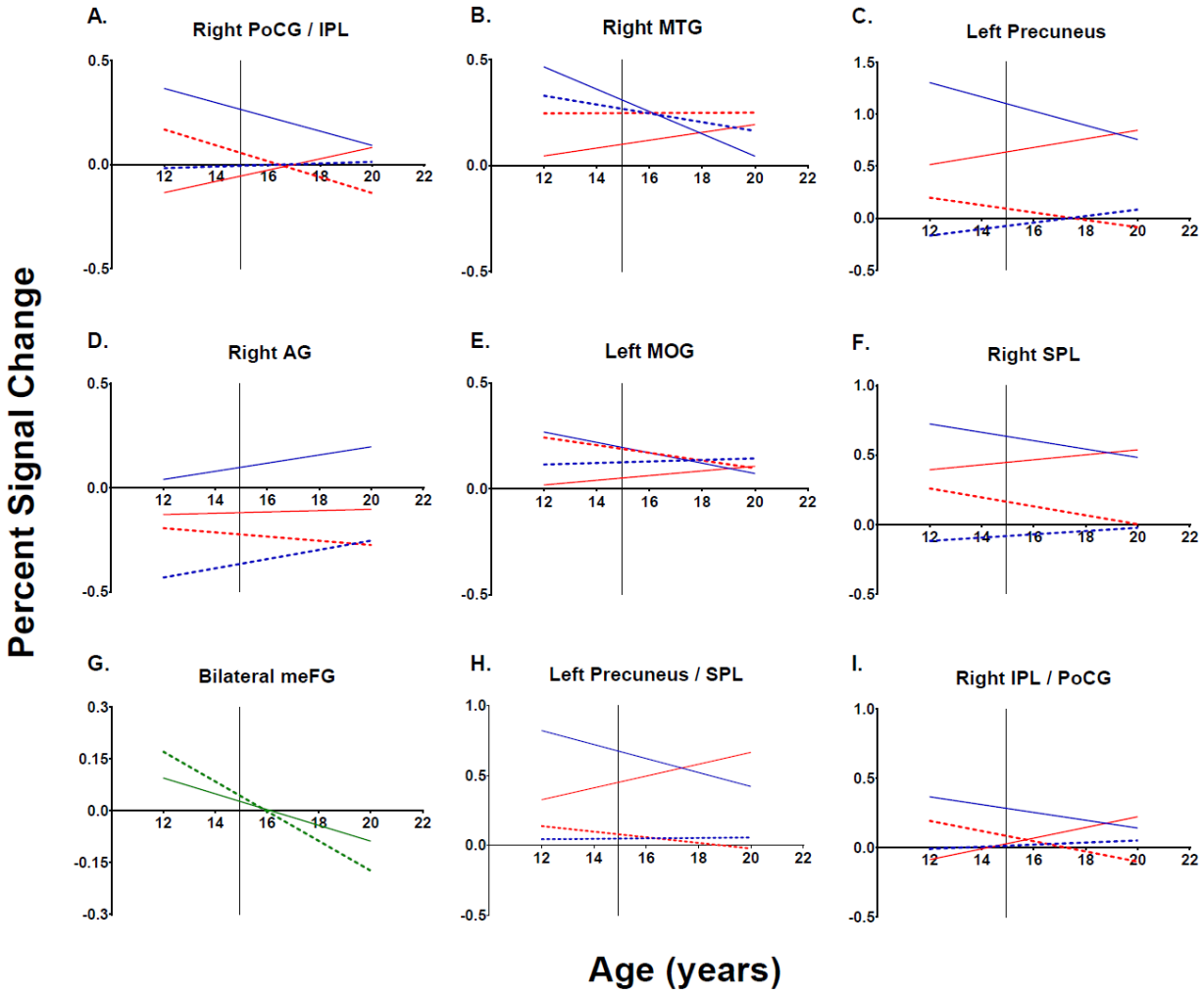


Fig. 3. Group-by-age interaction. Significant group-by-age interaction in spatial WM vs vigilance brain activation in left precuneus/superior parietal lobule and right inferior parietal lobule/postcentral gyrus. Trajectories of percent signal change with age during spatial WM vs vigilance are plotted for binge-drinking adolescents (red) and non-using controls (blue). Average age at baseline (dotted black line).



Supplementary Fig. 1. Spatial working memory task-specific activation map. Red boxes: individual maps of positive (warm colors) and negative (cool colors) activation. Blue boxes: individual binary maps of task activation. Yellow boxes: combined baseline or revisit group activation maps. Green box: combined baseline and revisit actiavtion map for binge drinkers and controls.



Supplementary Fig. 2. Graphs of simple contrasts (spatial WM vs baseline and vigilance vs baseline) between binge-drinking and controls adolescents. **A-F:** Significant group-by-block interaction at baseline in six different brain regions. **G:** Significant block-by-age interaction in one brain region. **H-I:** Binge-drinking adolescents, but not controls, show a significant block-by-age interaction in two brain regions.
Solid lines: spatial WM vs baseline activation; dotted lines: vigilance vs baseline activation; red: binge drinkers; blue: controls; green: all adolescents; vertical black line: average age at baseline.