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BOLD Response and Spatial Working Memory in Adolescents with Alcohol Use Disorders

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Abstract

Background: Previous studies have suggested neural disruption and reorganization in young and older adults with alcohol use disorders (AUD). However, it remains unclear at what age and when in the progression of AUD changes in brain functioning might occur.
Methods: Alcohol use disordered (n=15) and nonabusing (n=19) males and females ages 15-17 were recruited from local high schools. Functional magnetic resonance imaging (fMRI) data were collected after a minimum of 5 days' abstinence as participants performed spatial working memory and simple motor tasks.
Results: Adolescents with AUD showed greater brain response to the spatial working memory task in bilateral parietal cortices, and diminished response in other regions including the left precentral gyrus and bilateral cerebellar areas (clusters ≥ 943 μl, $p < .05$), although groups did not differ on behavioral measures of task performance. No brain response differences were observed during a simple finger tapping task. The degree of abnormality was greater for teens who reported experiencing more withdrawal or hangover symptoms, and who consumed more alcohol.
Conclusions: Adolescents with AUD show abnormalities in brain response to a spatial working memory task, despite adequate performance, suggesting that subtle neuronal reorganization may occur early in the course of AUD.

KEY WORDS: alcohol use disorders; fMRI; adolescence; spatial working memory; withdrawal
RUNNING HEAD: fMRI in Adolescents with Alcohol Use Disorders

BOLD Response and Spatial Working Memory in Adolescents with Alcohol Use Disorders

Alcohol use and related disorders are common and significant problems during adolescence. Nearly a third of U.S. 12th graders report having gotten drunk in the past month (Johnston, O'Malley, & Bachman, 2003), and approximately 9% of high school students meet diagnostic criteria for alcohol abuse or dependence (Rohde, Lewinsohn, Kahler, Seeley, & Brown, 2001). Adolescents often drink until high blood alcohol concentrations are achieved, and hangover and mild withdrawal symptoms are relatively common (Stewart & Brown, 1995).

Youths who have consumed alcohol chronically and heavily often demonstrate subtle neurocognitive abnormalities. Chronic heavy drinking during the teenage years is associated with poorer performance on tasks of learning and memory, attention, and visuospatial functioning in mid-adolescence (Brown, Tapert, Granholm, & Delis, 2000), late adolescence (Tapert & Brown, 1999), and young adulthood (Tapert, Granholm, Leedy, & Brown, 2002). Cognitive performance appears particularly affected in youths who report experiencing hangover and/or withdrawal symptoms after drinking episodes (Tapert et al., 2002). Furthermore, abnormalities in brain functioning have been observed in alcohol dependent young women who had drank heavily during adolescence (Tapert et al., 2001). However, it is unclear when in the progression of alcohol use disorders (AUD) and at what neuromaturational stage these changes occur, particularly given the myelination and synaptic refinement that continue throughout adolescence (Huttenlocher, 1990; Paus et al., 1999).

Animal studies have suggested that alcohol differentially affects adolescents compared to adults, possibly due to continuing neuromaturation. Compared to adult rodents, adolescents are more susceptible to hippocampal injury (Slawecki, Betancourt, Cole, & Ehlers, 2001) and the motor (White et al., 2002) and memory (White, Ghia, Levin, & Swartzwelder, 2000) impairing effects of alcohol, but are less likely to evidence its sedating effects (Silveri & Spear, 2002). The neuronal damage caused by drinking in adolescent humans is less clear, although a structural magnetic resonance imaging (MRI) study suggested smaller hippocampal volumes in youths with AUD (De Bellis et al., 2000).

We previously showed reduced parietal and frontal blood oxygen level dependent (BOLD) response and enhanced response in the right inferior occipital gyrus during a spatial working memory task in alcohol dependent young women (Tapert et al., 2001) using functional MRI (fMRI). These women also demonstrated modestly poorer performance on the spatial working memory task. Based on evidence of the neurocognitive impact of alcohol during adolescence, neuroimaging findings with young women, and animal models of adolescent alcohol effects, we hypothesized that adolescents with AUD would show subtle fMRI response abnormalities to the same spatial working memory task relative to demographically similar controls with minimal drinking histories.

Method

Participants

Recruitment and screening procedures are detailed elsewhere (Tapert et al., 2003). Briefly, recruitment flyers were distributed at San Diego area high schools. After teens telephoned in response, preliminary interviews ascertained eligibility, and then legal guardians were asked further exclusionary questions. After a description of the study, written informed consent and assent, approved by the University of California San Diego Institutional Review Board, were obtained from parents and adolescents. Eligible teens were administered a 90-

minute detailed screening interview covering family history of substance use and psychiatric disorders using the Family History Assessment Module screener (Rice et al., 1995), substance use and abuse/dependence criteria using the Customary Drinking and Drug Use Record (CDDR; (Brown et al., 1998), and adolescent psychiatric diagnoses using the Computerized Diagnostic Interview Schedule for Children 4.0 (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The FHAM and C-DISC were also administered to parents by different interviewers to corroborate adolescent reports. C-DISC diagnoses were calculated in standard composite fashion. In cases of FHAM discrepancies, additional data were obtained or data were coded to represent the lower level of functioning.

Exclusionary criteria for the present study were: current use of psychoactive medications; significant maternal drinking (≥4 drinks/occasion or ≥7 drinks/week) or illicit drug use during pregnancy; family history of bipolar I or psychotic disorders; inadequate English skills; sensory problems; left handedness; irremovable metal in the body; smoking >4 cigarettes/day; lifetime use of marijuana >40 times; lifetime use of other drugs >8 times; or history of neurological illness, head trauma with loss of consciousness >2 minutes, serious medical problems, learning disability, or DSM-IV psychiatric or substance disorder other than AUD. Because of high comorbidity with substance use disorders (Brown, Gleghorn, Schuckit, Myers, & Mott, 1996; Myers, Stewart, & Brown, 1998), teens meeting criteria for conduct disorder (n=2) were not excluded. Overall, 9% of the 729 youths who responded to the flyer met eligibility criteria for the study, and most ineligibilities were due to psychiatric symptomatology, other drug involvement, or braces.

AUD participants (n=15) met current DSM-IV criteria for alcohol abuse (n=7) or dependence (n=8), and normal controls (n=19) had limited or no experience with alcohol or other drugs (see Table 1). Participants in both groups were typically from upper-middle to upper class families and above average intellectually, although AUD teens' families had higher annual household incomes and were more likely to be white than control teens. AUD youths typically drank 5-6 drinks on weekend nights and had met criteria for AUD for approximately 1-2 years. All but two AUD participants, who disclosed recent marijuana use (12 and 20 days prior to scanning), were free from substances other than alcohol for 30 days prior to scanning. AUD youths reported higher levels of nervousness prior to scanning than controls, although well within the normal range (see Table 1).

Measures

Structured Clinical Interviews. Adolescent participants and parents were separately administered confidential structured clinical interviews (Brown, Vik, & Creamer, 1989) by bachelor's level psychometrists of the same gender to ascertain demographic characteristics, medical and developmental history, and social and academic functioning. Parents were asked about the teen's developmental history and familial socioeconomic status (Hollingshead, 1965), and given the Child Behavior Checklist (Achenbach, 1991).

Substance Use History. Substance involvement and abuse/dependence diagnoses were assessed with the CDDR (Brown et al., 1998), which collects lifetime and past 3-month information on alcohol, nicotine, and other drug use, and assesses DSM-IV abuse and dependence criteria (American Psychiatric Association, 1994), withdrawal symptomatology, and other negative consequences associated with substance use. Good internal consistency, test-retest, and inter-rater reliability have been demonstrated with adolescents (Brown et al., 1998; Stewart & Brown, 1995). The Timeline Followback (Linda C. Sobell & Sobell, 1992; L. C. Sobell, Sobell, Leo, & Cancilla, 1988) was administered to depict substance use patterns for the

30 days prior to scanning. On the day of scanning, all participants submitted samples for Breathalyzer (Intoximeter, St. Louis) and urine drug toxicology analyses.

Neuropsychological Testing. On the day of scanning, a 90-minute neuropsychological test battery was administered covering attention, working memory, learning and memory, executive, visuospatial, and language functioning. The battery consisted of: Wechsler Intelligence Scale for Children-III (Wechsler, 1993) subtests for participants ≤16 years old, and Wechsler Adult Intelligence Scale-III (Wechsler, 1997) subtests for 17-year-olds (Vocabulary, Block Design, Digit Span, Coding/Digit Symbol, and Arithmetic); Wide Range Achievement Test-3 (Wilkinson, 1993) Reading and Arithmetic subtests; California Verbal Learning Test-Children's Version (Delis, Kramer, Kaplan, & Ober, 1994); Rey-Osterrieth Complex Figures Test (Osterrieth, 1944) copy and 30-minute delay, Trail Making Test Parts A & B (Reitan & Wolfson, 1985); and Stroop Color and Word Test (Golden, 1978). Right-handedness was confirmed with the Edinburgh Handedness Inventory (Oldfield, 1971).

State measures. The Beck Depression Inventory (Beck, 1978) and state scale of the Spielberger State Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970) assessed mood at the time of scanning. The Stanford Sleepiness Scale (Glenville & Broughton, 1978) measured alertness immediately before and after scanning with self-report ratings of 1 for alert to 7 for almost asleep.

Procedures

Participants were asked to abstain from alcohol and other drugs for at least 48 hours before scanning. Imaging sessions were held Thursday evenings between 20:00-22:00 to maximize recovery from weekend drinking and to maintain consistent circadian influence across subjects. The most recent drinking reported was 5 days prior to scanning. No withdrawal symptoms were disclosed or evident in any participant on the day of scanning. Upon arrival for the imaging session, all participants submitted samples for Breathalyzer and urine drug toxicology analyses. No participant had a positive breath alcohol concentration or toxicology screen, other than two positive for THC, described previously. A subset of participants (n = 9 for each group) provided blood samples to permit evaluation of blood density (see Table 1), as hematocrit was related to BOLD response in one study (Levin et al., 2001). Participants were administered neuropsychological tests and interviews, trained on the fMRI tasks, then given affective and sleepiness self-report measures. Parent interviews were conducted by a separate interviewer to corroborate adolescent reports.

Once supine in the scanner, the participant's head was stabilized to minimize motion. The MRI technologist localized the head position, ensured that the subject could fully view the display screen, and asked the teen to test the 4-button opto-isolated response box in the right hand. Task stimuli were presented from a laptop computer through a data projector to a screen in the MRI room near the foot of the scanner bed. The participant viewed stimuli through a mirror mounted on the head coil.

Images were acquired with spiral pulse sequences, which can help reduce the effects of motion on time series acquisitions (Meyer, Hu, Nishimura, & Macovski, 1992; Noll, Cohen, Meyer, & Schneider, 1995). The imaging protocol included a high-resolution structural image collected in the sagittal plane using an inversion recovery prepared T1-weighted 3D spiral fast spin echo sequence optimized for maximum contrast between gray and white matter (Wong, Luh, Buxton, & Frank, 2000) (TR=2000 ms, TE=16 ms, FOV=240 mm, slab thickness=170 mm, matrix size 256 x 256 in-plane and 128 in the sagittal direction, resolution=0.9375 × 0.9375 mm × 1.328 mm, 128 continuous slices, acquisition time=8:36). BOLD-weighted functional imaging

was performed using a spiral acquisition. Images were acquired in the axial plane using T2*-weighted spiral gradient recall echo imaging sequence (TE=40 ms, flip angle=90°, FOV=240 mm, 19-21 slices covering the whole brain, slice thickness=7 mm, in-plane resolution=1.875 × 1.875 mm).

The spatial working memory task was chosen to explore the neural substrates of spatial working memory functioning and to probe the integrity of these brain regions in adolescents with AUD. The task (Kindermann, Brown, Zorrilla, Olsen, & Jeste, 2004; Tapert et al., 2001) was adapted from McCarthy (McCarthy et al., 1994); see Figure 1 for task description. In addition, a finger tapping task was administered to 13 of the AUD and 13 of the control adolescents to assess BOLD response to simple motor activity. This task alternated between 10 tap blocks and 10 rest blocks. During the tap blocks, the screen read, "TAP" and subjects were instructed to touch the thumb to each finger one by one, bimanually. During rest blocks, the screen read, "REST" and subjects were instructed to relax their hands (10s/block, TR=3000, 60 repetitions, total task time=3:20). Practice trials were administered prior to scanning.

Data Analysis

Data were processed and analyzed using Analysis of Functional NeuroImages (AFNI) (Cox, 1996). First, a motion correction algorithm corrected small movements by aligning each volume in the time series with a selected base volume (Cox & Jesmanowicz, 1999), estimating three rotation and three displacement parameters for each participant. Next, time series data were correlated with a set of seven task reference vectors consisting of one seed reference function representing the alternating conditions over the course of the task (see Figure 1) and the same reference vector shifted forward in six 1-second increments to account for delays in hemodynamic response (Bandettini, Jesmanowicz, Wong, & Hyde, 1993). Only the reference vector producing the highest correlation with the time series data was used. Simultaneously, the estimated degree of motion (i.e., parameters resulting from motion correction) and linear trends were covaried. This yielded fit coefficients for every subject in each voxel reflecting the degree of BOLD response to spatial working memory blocks relative to vigilance blocks (a "spatial working memory response"), or to tap blocks relative to rest blocks. Next, imaging data were transformed to standard coordinates (Talairach & Tournoux, 1988) for structural localization. Functional data were resampled into $3.5mm^3$ isotropic voxels. A spatial smoothing Gaussian filter (full-width half maximum = 3.5mm) managed anatomic variability. BOLD response contrast between groups was compared in independent samples *t*-tests. In addition, BOLD response contrast was predicted by alcohol involvement variables in regressions. For all analyses, type I error risk was controlled by requiring that voxels surpass a voxel-wise $\alpha = .05$, and only activations that consisted of at least 22 contiguous significantly activated voxels (943 μl) were interpreted. Neuropsychological and task data were compared between groups in one-way analyses of variance.

To see if motion during the spatial working memory task differed between groups, each subject's absolute mean for each of the six motion parameters across the time series data was compared in oneway ANOVAs. The estimated degree of motion was similar between groups for all six parameters (all p's > .24). To estimate task-correlated motion, the six parameters were correlated with the task reference vector across the time series for each subject. The median correlation values for roll, pitch, and yaw rotations and superior, left, and posterior displacements, respectively, were -.020, .009, -.013, -.037, -.017, and -.019 for controls and -.016, .006, .005, -.016, -.022, and -.023 for AUD teens. These values were compared between groups with a nonparametric Kruskal-Wallis test, and no significant differences were found.

Results

AUD and control groups performed similarly on all neuropsychological tests (see Table 2). However, after controlling for parent income, AUD teens performed worse than controls on Block Design ($p<.05$). No significant group differences were found for accuracy on the spatial working memory task (90% for AUD group and 87% for control group), vigilance accuracy, or reaction time for either condition. A trend suggested that AUD youths reacted more quickly during the spatial working memory condition ($p = .07$).

An independent samples t-test compared BOLD spatial working memory response between groups. Teens with AUD showed significantly more spatial working memory response (i.e., more activation during spatial working memory blocks relative to vigilance blocks) in large regions consisting of both the right and left precunei and both superior parietal lobules. AUD teens showed significantly less spatial working memory response than controls in several brain regions: left precentral gyrus; left inferior temporal and fusiform gyri; right mesial inferior precuneus; right cuneus extending into the middle occipital gyrus; left superior occipital gyrus; an area comprising the left middle occipital, lingual, and fusiform gyri and cerebellar declive; bilateral cerebellum including bilateral semi-lunar lobules, right nodule, right tonsil, and right uvula; and right cerebellar culmen and declive (see Table 3 and Figure 2). The same pattern of results was found after excluding the two participants with conduct disorder.

To better understand the main effects of condition and group for the clusters listed in Table 3, each group was evaluated separately in single-sample t-tests (see Figure 3), and BOLD response was contrasted between spatial working memory and fixation conditions as well as between vigilance and fixation conditions. For the two large regions where AUD teens showed greater spatial working memory response than controls, AUD teens consistently showed more intense response during spatial working memory blocks relative to vigilance and to fixation, while controls showed a smaller degree of enhanced response to spatial working memory blocks relative to the other conditions. A variety of relationships explained the group differences where AUD teens showed diminished spatial working memory response. In the left precentral gyrus, right precuneus, and left middle occipital/cerebellar declive regions, AUD teens showed less spatial working memory response (relative to fixation and to vigilance) than controls. However, in the left inferior temporal and fusiform gyri, AUD teens showed more vigilance response than controls, while groups were equivalent on spatial working memory response. In the right cuneus and middle occipital gyrus, both groups showed more response during vigilance than spatial working memory blocks, but AUD youths showed less spatial working memory response than controls. Similarly, in the right cerebellar culmen and declive, both groups showed more vigilance than spatial working memory response, but the degree of difference was greater among AUD teens than controls. In the left superior occipital gyrus, AUD teens demonstrated a greater degree of deactivation to the spatial working memory blocks relative to fixation and to vigilance conditions than controls. In the bilateral cerebellum area, both groups showed deactivation during spatial working memory blocks (relative to fixation) and a mixture of enhanced and diminished vigilance response throughout the region, but the controls showed more deactivation during vigilance than did AUD teens.

To assess the continuous relationship between BOLD response and alcohol involvement, regression analyses were conducted among teens with AUD to see if lifetime and recent (past 3 month) drinks consumed and alcohol withdrawal symptoms predict spatial working memory response, relative to vigilance. Lifetime indices of alcohol involvement predicted less spatial working memory response. Specifically, lifetime drinks consumed predicted less spatial working

memory response in: a region including the left cingulate, left paracentral gyrus, and bilateral medial frontal gyri; an area comprising the right cingulate, paracentral, and medial frontal gyri; the right insula extending into the putamen; and the left anterior cerebellum including the tonsil, dentate, and tuber. Similarly, lifetime alcohol withdrawal symptoms predicted less spatial working memory response in: the left middle frontal and precentral gyri; an area including the right cuneus, superior occipital, and middle temporal gyri; the right cerebellar declive and lingual gyrus; and the right cerebellar culmen (see Table 4 and Figure 4). However, recent (past 3-month) drinks consumed predicted more spatial working memory response in the left inferior frontal gyrus; right medial to superior frontal gyri; right caudate nucleus and head; left middle temporal gyrus; and left cerebellar tonsil. Similarly, past 3-month alcohol withdrawal symptoms predicted more spatial working memory response in a region consisting of bilateral anterior cingulate and left medial frontal gyrus; and right superior temporal gyrus (see Table 5 and Figure 4). Lifetime drinks consumed correlated with more CVLT-C perseverations ($p<.05$), but no other performance correlations with these four alcohol involvement variables were found.

The relationship between task performance and BOLD response was explored in regression analyses in which accuracy on the spatial working memory task, group, and their interaction predicted to BOLD response to spatial working memory trials relative to vigilance. Significant clusters were followed up with regression analyses for each group. BOLD response in the cuneus and in the lingual gyrus was significantly predicted by the interaction between performance and group. Follow-up analyses revealed that AUD participants showed a negative relationship between task accuracy and BOLD response (i.e., those who were most accurate had less activation) in these regions.

To see if the BOLD response differences observed for the spatial working memory task might be due to alcohol-related hemodynamic functioning abnormalities, BOLD response to a simple finger tapping task was compared between groups. The task alternated between tap and rest conditions, and fMRI data were correlated with a reference vector that coded the task conditions over the time series, using AFNI's 3dFIM+ program. No group differences were observed in BOLD response to the finger tapping task in any brain region.

Discussion

This preliminary study of brain functioning in adolescents at the earliest stages of AUD suggested abnormal BOLD response to a spatial working memory task relative to that of controls, despite intact task and neuropsychological performance and normal BOLD response to a simple motor task. Adolescents with AUD showed less response during a spatial working memory condition than controls in some brain regions, including bilateral cerebellar areas, left precentral gyrus (Brodmann Area (BA) 44), and bilateral middle occipital regions (BA 18/19), but greater response in large bilateral parietal regions (BA 7) (see Figure 2). The overall pattern of spatial working memory response (see Figure 3) was consistent with previous fMRI studies, showing pronounced bilateral dorsolateral prefrontal and superior posterior parietal activation (Cabeza & Nyberg, 2000; Kwon, Reiss, & Menon, 2002; Nelson et al., 2000; Thomas et al., 1999).

The few fMRI studies of cognitive functioning among individuals with AUD have shown both overactivation and underactivation of AUD participants as compared to demographically similar controls without drinking problems. Using region of interest analyses, Desmond and colleagues (Desmond et al., 2003) found increased BOLD response among alcohol dependent men (mean age = 50) to a verbal working memory task in left frontal (BA 44/45) and right superior cerebellar regions, compared to matched controls. The alcohol dependent men

performed adequately on the task, suggesting that alternate neural systems compensated for disrupted or damaged regions. In another study by the same group, alcohol dependent men showed diminished response in bilateral dorsolateral prefrontal regions to a 2-back spatial working memory task compared to controls in the context of intact performance (Pfefferbaum et al., 2001). The authors suggested that the alcohol dependent men relied on the ventral ("What?") stream in contrast to the more appropriate dorsal ("Where?") stream used by the controls. Across these studies, it appears that chronic heavy drinking is associated with interference within neural systems typically used for certain tasks, but that neural compensation can produce intact performance levels through the utilization of alternate, albeit potentially less suitable, systems (Price & Friston, 1999). However, if task demands or alcohol-induced disruption increase, performance problems may emerge.

In the present study, indices of relatively recent alcohol involvement (i.e., drinks consumed and alcohol withdrawal/hangover in the past 3 months) predicted enhanced BOLD response to a spatial working memory task relative to an active baseline, but not performance abnormalities. This pattern of results could suggest compensatory mechanisms relying upon prefrontal and temporal regions. In contrast, cumulative indices of lifetime alcohol consumption and post-drinking effects predicted diminished BOLD response, possibly suggesting a reduced capacity to respond in some areas to certain task demands, including regions that were recruited by the spatial working memory task in healthy control youths (e.g., middle frontal and cerebellar areas). It is possible that this pattern could result from alcohol slowing the progress of adolescent neuromaturational processes. These relationships do not appear to be due to very recent alcohol involvement, as brain response in these regions did not correlate with days since last drink for either group. The group differences observed are less likely due to cerebrovasculature abnormalities or problems in regions subserving motor functioning, as the adolescents with AUD showed normal BOLD response to the finger tapping task. This finding contrasts with that of Parks and colleagues (Parks et al., 2003) who found somewhat abnormal BOLD response during a simple motor task in alcohol dependent adults, suggesting that early in the course of AUD, the neural substrates of motor functions may remain intact, while those of more difficult or complex functions such as working memory could be affected.

BOLD response to the same spatial working memory task appeared somewhat more abnormal and consistently diminished in 18-25 year old alcohol dependent females, among whom performance decrements were detected (Tapert et al., 2001). The contrast between the adolescents and young adults with AUD suggests that adverse alcohol-related brain effects may progress and change as heavy drinking continues across adolescent neurodevelopment, and BOLD response abnormalities may herald future performance problems if heavy drinking continues. However, longitudinal studies of adolescent males and females will be required to verify this impression.

Several limitations of this study warrant consideration. First, as in many fMRI studies, participant motion is a source of error. We have attempted to minimize motion artifact in our fMRI studies by taping participants comfortably but securely to the head coil structure, and by correcting for motion in our analyses. Furthermore, significant stimulus-correlated movement was not observed in either group (max $r = .04$). Second, our sample size is relatively small and limits the investigation of moderator effects (e.g., gender or family history). Third, although groups were reasonably well matched, factors other than a history of alcohol involvement could have influenced the findings, such as history of other drug or nicotine use, health or sleep differences, and recency of alcohol use. Fourth, it is possible that behavioral processes not

specific to working memory, such as poor motivation or general inattentiveness, might have altered response to the working memory task. However, as all participants performed well above chance, it appears that they understood the instructions and were not guessing. It is difficult to interpret regions in which deactivations to the active conditions were found, which are likely due to uncontrolled brain activity during the rest condition. The present design targets the evaluation of working memory by controlling for motor, sensory, and attention functions. However, as some brain areas show more BOLD response during vigilance than working memory, spatial attention may not be an ideal baseline condition because it produces neuronal activation in several specific brain regions (LaBar, Gitelman, Parrish, & Mesulam, 1999). Finally, the current study is cross-sectional, and in order to infer that alcohol causes compensatory neural reorganization, longitudinal studies are required.

In summary, this study suggests that alcohol-related abnormalities in brain functioning may be detected as early as mid-adolescence, even in physically healthy males and females with relatively brief problematic drinking histories, particularly in parietal, cerebellar, and frontal regions. Future longitudinal studies can help address how drinking heavily during adolescence might interfere with the neuromaturational processes of this developmental stage, such as myelination and synaptic refinement, and the extent to which youth who have achieved abstinence can recover. Perfusion and diffusion imaging in conjunction with fMRI studies can address possible blood flow abnormalities and test connectivity models to more closely examine neural network reorganization. Finally, it will be important to closely characterize gender differences in brain response to chronic heavy drinking in youth, especially as girls develop earlier than boys, yet boys tend to start drinking sooner than girls. The results of this study may be useful feedback for young people who drink heavily.

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Table 1
Characteristics of Adolescent Participants

	Alcohol Use Disordered (n = 15) % or M (SD)	Normal Controls (n = 19) % or M (SD)
% Female	33%	42%
Age (range 15-17)	16.77 (0.66)	16.50 (0.83)
Grades completed	10.07 (0.80)	9.47 (2.20)
Parent annual salary (thousands)	103.67(60.72)	68.11(28.38)
% Caucasian *	100%	74%
% Family history negative [a]	42%	38%
Child Behavior Checklist Externalizing T-score	42.76 (4.88)	43.74 (6.85)
Child Behavior Checklist Internalizing T-score	42.89 (5.98)	42.53 (4.41)
Beck Depression Inventory total	5.21 (4.98)	2.68 (3.70)
Spielberger State Anxiety T-score [b] **	43.10 (8.40)	36.84 (4.65)
Sleepiness before scanning	3.20 (1.47)	2.58 (1.30)
Sleepiness after scanning	4.20 (1.66)	3.42 (1.30)
Blood hematocrit level [c]	42.33 (4.00)	43.89 (3.89)
Drinks consumed, lifetime **	128.93 (142.89)	5.11 (10.88)
Drinks per month, past 3 months ***	41.47 (31.26)	2.00 (4.51)
Alcohol withdrawal symptoms, lifetime	2.57 (1.91)	0.72 (0.82)
Alcohol withdrawal symptoms, past 3 months ***	2.27 (2.05)	0.05 (0.23)
Alcohol abuse/dependence criteria, past 3 months ***	2.47 (1.81)	0.11 (0.32)
Days since last alcohol (minimum = 5) *	16.73 (14.91)	67.90 (60.46)
Nicotine use days in past month	2.20 (3.19)	0.37 (1.61)
Lifetime marijuana use times *	11.33 (12.93)	1.47 (4.65)
Lifetime other drug use times	0.73 (2.58)	0.00 (0.00)

[a] No first- or second-degree biological relative with alcohol or drug abuse or dependence
[b] Normed to high school sample for each gender
[c] n = 9 for each group
* $p < .05$ ** $p < .01$ *** $p < .001$

Table 2
Neuropsychological and Task Scores of Adolescent Participants

	Alcohol Use Disordered (n = 15) M (SD)	Normal Controls (n = 19) M (SD)	p-value
Vocabulary scaled score	12.53 (1.77)	12.21 (2.80)	.70
Block Design scaled score	11.60 (3.04)	11.42 (2.14)	.84
Digit Span scaled score	11.20 (2.57)	10.47 (2.99)	.46
Coding/Digit Symbol scaled score	10.47 (3.16)	10.32 (2.63)	.88
Arithmetic scaled score	12.07 (1.62)	11.26 (3.94)	.43
WRAT3 Reading standard score	106.73 (8.00)	105.84 (7.49)	.74
WRAT3 Arithmetic standard score	109.40(10.89)	101.79(13.42)	.08
CVLT-C List A total T-score	47.47 (6.14)	49.92 (10.13)	.52
CVLT-C Long delay free recall z-score	-0.10 (0.57)	-0.16 (1.05)	.84
CVLT-C Discriminability z-score	-0.20 (0.59)	-0.29 (0.79)	.71
ROCF copy accuracy (max. = 36)	27.60 (2.77)	26.39 (3.77)	.31
ROCF 30-minute delay accuracy (max. = 36)	14.77 (4.85)	14.82 (3.54)	.97
Trails Making Test part A time (seconds)	22.93 (5.20)	22.32 (6.57)	.77
Trail Making Test part B time (seconds)	56.27 (10.68)	53.74 (13.49)	.56
Stroop Interference	0.92 (5.50)	-0.26 (6.62)	.58
Spatial working memory accuracy	0.90 (0.05)	0.87 (0.09)	.11
Spatial working memory reaction time [a]	565.04(42.00)	597.13(64.55)	.07
Vigilance accuracy	0.96 (0.01)	0.95 (0.03)	.25
Vigilance reaction time [a]	576.23(34.22)	616.97(82.86)	.10

[a] For correct trials on which a response was made

Table 3

Regions of Significant Differences between Teens with Alcohol Use Disorders and Controls in BOLD Response on Spatial Working Memory Relative to Simple Vigilance (N = 34, $p < .05$)

Anatomic Region	Brodmann Area	Volume (μl)	Talairach Coordinates [a] x	y	z	Effect Size Cohen's d
AUD < Controls						
R mesial inferior precuneus	7	1072	5R	75P	42S	7.81
R cuneus & middle occipital g	18/19	986	9R	92P	14S	7.59
L cerebellar declive, middle occipital, lingual, & fusiform	18/19	1415	37L	78P	8I	6.00
L superior occipital g	19	1115	33L	75P	24S	4.52
B cerebellar semi-lunar lobule, nodule, tonsil, & uvula	-	1158	2L	64P	39I	4.25
R cerebellar culmen & declive	-	1243	23R	50P	11I	4.14
L inferior temporal & fusiform g	20	1372	54L	29P	15I	3.46
L precentral g	44	1286	61L	6A	10S	.86
AUD > controls						
R precuneus & superior parietal lobule	7	3859	9R	71P	52S	9.29
L precuneus & superior parietal lobule	7	1586	16L	64P	49S	7.22

[a] Talairach coordinates refer to the maximum signal intensity group difference within the cluster.
Abbreviations: AUD alcohol use disorder; G gyrus; B bilateral; R right; L left; A anterior; P posterior; S superior; I inferior.

Table 4

Greater Lifetime Alcohol Involvement Predicts Diminished BOLD Response to Spatial Working Memory Relative to Simple Vigilance in Adolescents with Alcohol Use Disorders (n = 15)

Anatomic Region	Brodmann Area	Volume (μl)	Talairach Coordinates [a] x	y	z	Coefficient (β)
Lifetime drinks:						
L cingulate, L paracentral g						
B medial frontal g	6/24/31	2401	5L	8P	38S	-0.04
R cingulate, paracentral,						
medial frontal g	24/31	943	2R	8P	42S	-0.04
R insula & putamen	13	1029	33R	6A	10S	-0.04
L anterior cerebellum						
(tonsil, dentate, & tuber)	-	1158	30L	54P	29I	-0.04
Lifetime withdrawal symptoms:						
R cerebellar declive & lingual g	18	1072	9R	85P	18I	-8.04
R cerebellar culmen	-	1029	40R	40P	25I	-4.10
R cuneus, superior occipital,						
& middle temporal g	19	1286	30R	82P	28S	-3.83
L middle frontal & precentral g	6	1243	23L	15P	56S	-3.29

[a] Talairach coordinates refer to the maximum signal intensity group difference within the cluster. Abbreviations: G gyrus; B bilateral; R right; L left; A anterior; P posterior; S superior; I inferior.

Table 5

Greater Recent Alcohol Involvement Predicts More BOLD Response to Spatial Working Memory Relative to Simple Vigilance in Adolescents with Alcohol Use Disorders (n = 15) [a]

Anatomic Region	Brodmann Area	Volume (μl)	Talairach Coordinates x	y	z	Coefficient (β)
Past 3 month drinks per month:						
L inferior frontal g	44/45	1586	54L	17A	17S	0.28
R caudate nucleus & head	-	1286	2R	3A	7S	0.26
R medial to superior frontal g	10	1372	2R	48A	10S	0.25
L middle temporal g	21	1415	61L	19P	8I	0.21
L cerebellar tonsil	-	1115	23L	57P	36I	0.19
Past 3 month withdrawal symptoms:						
B anterior cingulate &						
L medial frontal g	9/10/32	1115	2L	45A	21S	3.57
R superior temporal g	22	943	61R	43P	10S	3.50

[a] Talairach coordinates refer to the maximum signal intensity group difference within the cluster. Abbreviations: G gyrus; B bilateral; R right; L left; A anterior; P posterior; S superior; I inferior.

Figure 1: The spatial working memory task consisted of 18 20-second blocks alternating between experimental (spatial working memory) and baseline (vigilance) conditions. Blocks of rest were in the beginning, middle, and end of the task, during which a fixation cross appeared in the center of the screen. In the spatial working memory condition, figures appeared one at a time in one of eight locations. Stimuli and locations were chosen to minimize verbal labeling (e.g., stimuli were abstract line drawings and were not presented in the four compass positions). Participants were to press a button when a design appeared in a location already occupied in that block. On average, three of the 10 stimuli in each block were repeat locations, and repeats were 2-back. In the vigilance condition, the same stimuli were presented in the same locations, but a dot appeared above figures on 30% of trials. Participants were to press a button when a dot appeared. The purpose of the baseline was to control for simple motor and attention processes involved in the experimental condition. In both conditions, stimuli were presented for 1000 ms, and each interstimulus interval was 1000 ms (20 s/block, TR=3000ms, 156 repetitions).

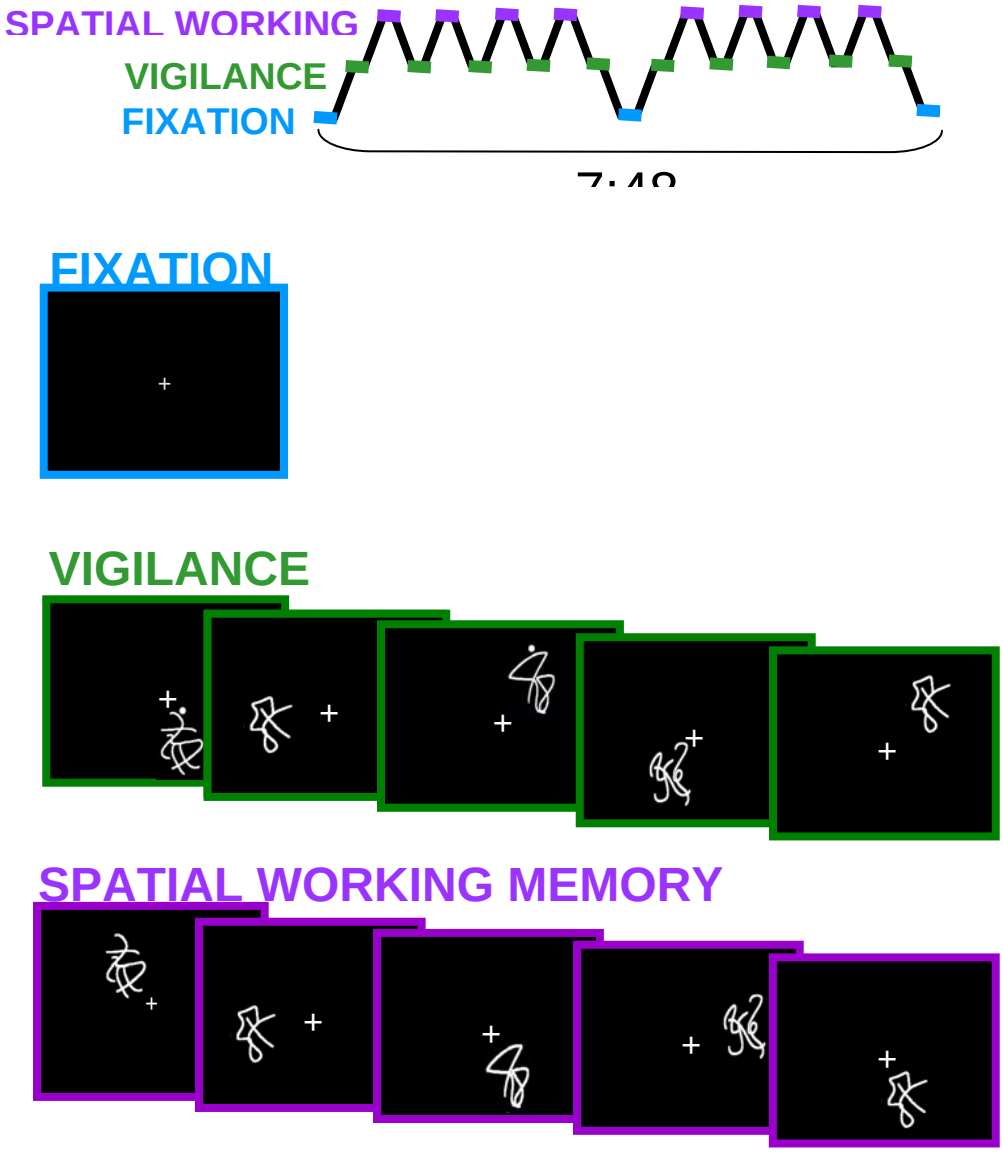


Figure 2. Between-group BOLD response differences during spatial working memory blocks relative to vigilance blocks; yellow/orange colors indicate where teens with alcohol use disorders had less spatial working memory response than controls; blue indicates where teens with alcohol use disorders had more spatial working memory response than controls ($p < .05$; clusters > 943 microliters). Numbers refer to sagittal (x) slice positions. fMRI results are displayed on averaged anatomical brain maps. Abbreviations: Occip, Occipital; Sup Par, Superior Parietal; Mes, Mesial; CBL, Cerebellum.

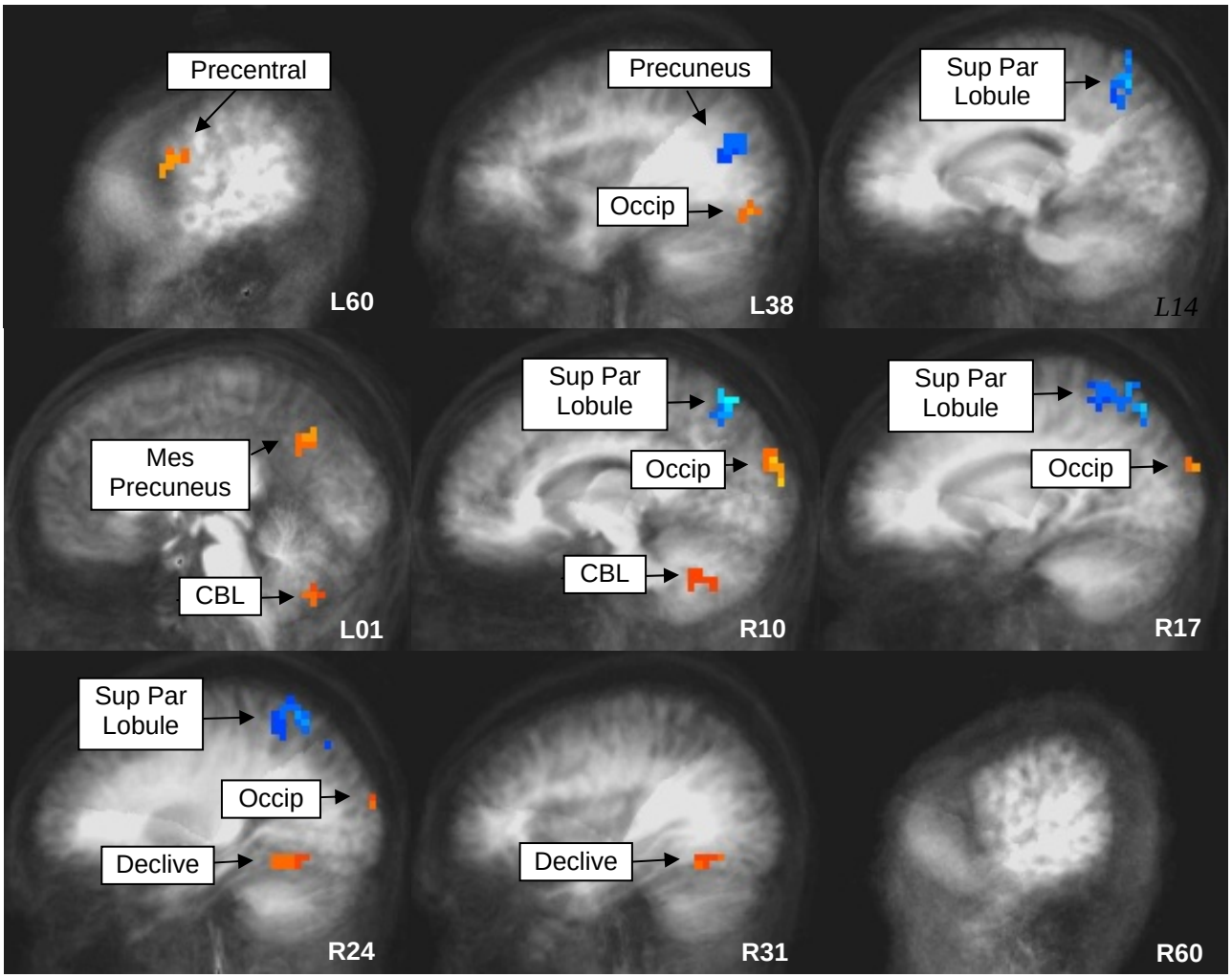


Figure 3. Unthresholded single sample t-test BOLD response differences during spatial working memory blocks relative to vigilance blocks for normal controls (n=19, left) and adolescents with alcohol use disorders (n=15, right); yellow/orange colors indicate regions with greater response during spatial working memory, and blue colors show greater response during vigilance trials.

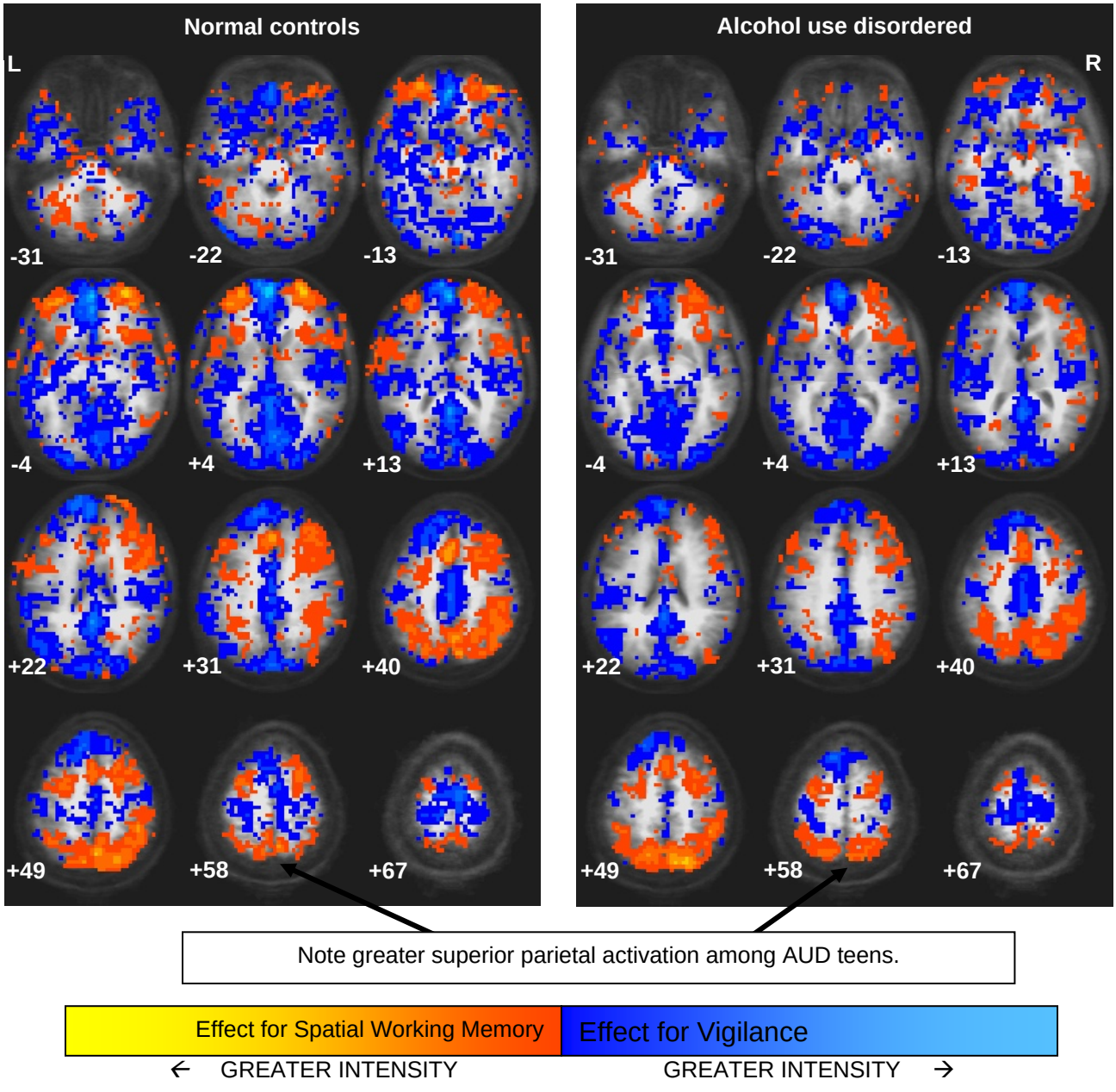
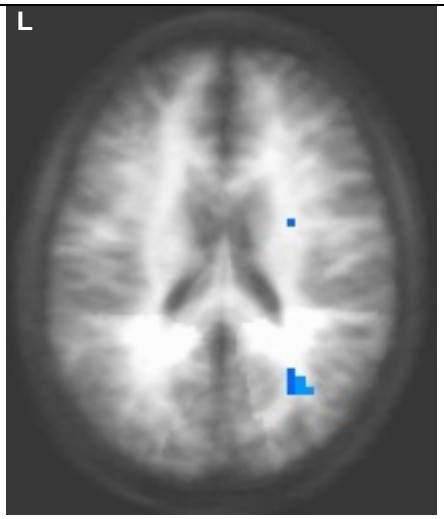
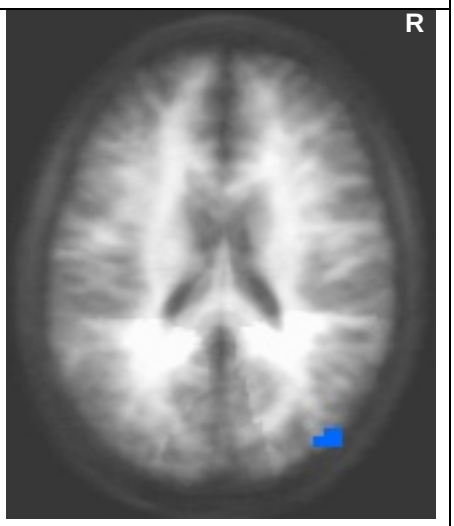


Figure 4. Regression analyses for teens with alcohol use disorders (n=15, p < .05, voxel clusters > 943 microliters); yellow/orange colors indicate regions positively associated with lifetime or recent alcohol consumption or withdrawal, blue colors indicate an inverse relationship between BOLD response and drinking variables (z = +20).

	Alcohol Consumption	Alcohol Withdrawal
Lifetime		
Recent (past 3 months)