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Neural Correlates of Verbal Learning in Adolescent Alcohol and Marijuana Users

Alecia Dager Schweinsburg, Ph.D.^c, Brian C. Schweinsburg, Ph.D.^{c,d}, Bonnie J. Nagel, Ph.D.^e, Lisa T. Eyler, Ph.D.^{a,b}, and Susan F. Tapert, Ph.D.^{a,b}

^aVA San Diego Healthcare System

^bUniversity of California, San Diego, Department of Psychiatry

^cYale University, Department of Psychiatry

^dVA Connecticut Healthcare System

^eOregon Health & Science University

Abstract

Aims—Alcohol and marijuana are the most widely used intoxicants among adolescents, yet their potential unique and interactive influences on the developing brain are not well established. Brain regions subserving learning and memory undergo continued maturation during adolescence, and may be particularly susceptible to substance-related neurotoxic damage. Here, we characterize brain response during verbal learning among adolescent users of alcohol and marijuana.

Design—Participants performed a verbal paired associates encoding task during fMRI scanning.

Setting—Adolescent subjects were recruited from local public schools and imaged at a University-based fMRI Center.

Participants—Participants were 74 16- to 18-year-olds, divided into four groups: (1) 22 controls with limited alcohol and marijuana experience, (2) 16 binge drinkers, (3) 8 marijuana users, and (4) 28 binge drinking marijuana users.

Measurements—Diagnostic interview assured that all teens were free from neurologic or psychiatric disorders; urine toxicology and breathalyzer verified abstinence for 22–28 days before scanning; a verbal paired associates task was administered during fMRI.

Findings—Groups demonstrated no differences in performance on the verbal encoding task, yet exhibited different brain response patterns. A main effect of drinking pointed to decreased inferior frontal but increased dorsal frontal and parietal fMRI response among binge drinkers (corrected $p < .05$). There was no main effect of marijuana use. Binge drinking $\times$ marijuana interactions were found in bilateral frontal regions (corrected $p < .05$), where users of either alcohol or marijuana showed greater response than non-users, but users of both substances resembled non-users.

Conclusions—Adolescent substance users demonstrated altered fMRI response relative to nonusing controls, yet binge drinking appeared associated with more differences in activation than marijuana use. Alcohol and marijuana may have interactive effects that alter these differences, particularly in prefrontal brain regions.

Corresponding Author: Susan F. Tapert, Ph.D., VA San Diego Healthcare System (151B), 3350 La Jolla Village Drive, San Diego, CA 92161, (858)552-8585 x2599, stapert@ucsd.edu.

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Keywords

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Introduction

Alcohol is the most used intoxicant among adolescents, with 25% of 12th graders having drunk 5+ drinks during the previous 2 weeks, indicating high rates of heavy episodic, or binge, drinking [1]. Marijuana is the most widely used illicit drug among teenagers [1]. Among 12th graders, 19% report past-month and 5% daily use, reflecting substantial regular intake [1]. Little is known about the differential influence of binge drinking and marijuana use on the developing brain. Regions maturing throughout adolescence include the hippocampus and prefrontal cortex [2–4], implicated in learning and memory [5, 6] and potentially susceptible to damage from chronic alcohol and marijuana exposure. Understanding the influence of adolescent alcohol and marijuana use on learning and memory is important, as education and future opportunities could be impacted.

Alcohol and marijuana use in adolescence are each associated with altered learning and memory. Heavy alcohol use in adolescence has been associated with poorer verbal and object recall [7]. Adults who began chronic marijuana use as young adolescents performed worse on verbal recall than late-onset users, even after 28 days of abstinence [8]. Several studies have characterized verbal learning decrements among adolescent marijuana users [9–12], which appear to be greater among adolescent than adult users, persisting up to six weeks following discontinuation [13].

Recent neuroimaging studies have reported effects of adolescent alcohol and marijuana use. Adolescents with alcohol use disorders demonstrate smaller hippocampi [14–16] and prefrontal volumes [17, 18] than non-users. Adolescent binge drinkers show poorer white matter integrity than non-drinkers, including projections from hippocampal and frontal regions [19], and increased frontal and parietal activation and lack of hippocampal response during verbal learning [20]. In contrast, corpus callosum microstructure appears normal among individuals with adolescent-onset alcohol use disorders [21]. Functional magnetic resonance imaging (fMRI) studies of adolescent marijuana users have characterized increased prefrontal and parietal activation among users during spatial working memory [22, 23] and inhibitory processing [24]. During verbal working memory, adolescent nicotine and marijuana users failed to deactivate the hippocampus [25], but demonstrated increased frontal, parietal, and hippocampal activation with greater task difficulty during nicotine withdrawal [12].

The interactive effects of concomitant alcohol and marijuana use are less clear. Adolescent users of both substances actually demonstrate normal hippocampal volumes and asymmetry as compared to controls, but abnormal relationships between verbal learning and hippocampal volume asymmetry [16]. Although adolescents with alcohol use disorders show smaller prefrontal cortex volumes than controls [17], heavy marijuana using teens show only subtle volume abnormalities [26]. Similarly, binge drinking heavy marijuana users demonstrate fewer microstructural white matter abnormalities than those who binge drank alone [27]. In contrast, adolescents with comorbid alcohol and marijuana use disorders have greater activation aberrations during spatial working memory than adolescents with alcohol use disorders alone, suggesting a unique effect of marijuana use on frontoparietal networks [23]. However, none of these studies included a marijuana-only group.

The current study was designed to understand the influence of adolescent binge drinking and heavy marijuana use on blood oxygen level dependent (BOLD) response measured by fMRI during a verbal paired associates encoding task. Previous studies in adults and adolescents suggested that neurocognitive effects of heavy marijuana use might persist following at least three weeks of abstinence [11, 28–30]. Therefore, participants were required to remain abstinent from marijuana for at least three weeks before scanning to ensure that any differences were not due to residual effects of recent use. Based on previous studies, we predicted that both binge drinking and marijuana use would be associated with increased prefrontal and reduced hippocampal fMRI response during verbal encoding. Based on our previous work comparing users of alcohol alone or combined with marijuana [16, 27], we predicted that heavy episodic drinking would be associated with greater deviations than heavy marijuana use.

Method

Participants

Participants were 74 16- to 18-year-olds recruited from local schools. Written informed assent and consent, approved by the University of California San Diego Human Research Protections Program, were obtained from each teen and parent. Exclusions were teen history of medical or neurological disorders, DSM-IV psychiatric diagnoses other than alcohol or marijuana use disorder, head injury with loss of consciousness ≥ 2 minutes, learning disabilities, left handedness, and MRI contraindications; and maternal substance use during pregnancy. Parents and youth completed the Diagnostic Interview Schedule for Children Predictive Scales [31] to rule out psychiatric disorders, and the Family History Assessment Module [32]. Parents provided socioeconomic status information [33] to facilitate group matching. Teens provided biweekly urine toxicology and breathalyzer samples for 22–28 days before scanning.

Four groups of adolescents were evaluated: (1) controls (CON; $n = 22$) with very limited alcohol or marijuana experience (< 5 lifetime uses of marijuana, < 5 lifetime uses of alcohol); (2) binge drinkers (BD; $n = 16$) who typically drank ≥ 4 drinks/occasion for females or ≥ 5 drinks/occasion for males [19, 34, 35] in the previous 3 months, but had used marijuana < 10 times; (3) marijuana users (MJ; $n = 8$) who had used marijuana ≥ 180 times, but had no binge drinking episode in the previous 3 months; and (4) binge drinking marijuana users (BD+MJ; $n = 28$) who typically binge drank (≥ 4 drinks/occasion for females or ≥ 5 drinks/occasion for males) in the previous 3 months and had used marijuana ≥ 180 times in their lives. Approximately half the BD and CON participants were in our study examining encoding in binge drinkers [20].

The groups were not statistically different on demographics, estimated verbal IQ (Vocabulary T -score), or mood (see Table 1). BD and BD+MJ were not statistically different on recency of use, drinking days per month, or age of first drink, and showed more alcohol use than non-binge drinking groups. However, BD+MJ teens reported more lifetime drinking episodes and drinks per occasion than BD teens. MJ and BD+MJ showed no statistical differences in degree of marijuana involvement, but had more extensive marijuana use than non-marijuana users. Marijuana users reported more lifetime use of other drugs than non-marijuana users. No participant was a regular smoker, and all had low Fagerstrom Nicotine Dependence scores [36].

Measures

Substance Involvement—The Customary Drinking and Drug Use Record (CDDR) [37] assessed lifetime and current use of alcohol, marijuana, tobacco, and other drugs,

withdrawal symptomatology, and DSM-IV substance use disorder criteria. The Timeline Followback [38] assessed substance use patterns covering the 22 days prior to scanning and the month preceding being asking to stop.

Verbal Paired Associates Task [20, 39–41]—Subjects were instructed to memorize highly associated pairs of monosyllabic nouns (presented for 5 seconds each) before and during fMRI scanning. Before scanning, participants memorized a list of 16 word pairs. Recall was immediately tested by presenting the first member of a pair and asking subjects to verbalize the second member of that pair. Learning and recall trials were repeated until the participant correctly recalled 10 of 16 pairs. During scanning, participants viewed 32 pairs of associated words in a block design, including 16 previously learned pairs and 16 novel pairs. Participants were to learn all the word pairs. The task included blocks of fixation trials with variable durations of 8, 12, and 16 seconds. The order of conditions was pseudo-random and fixed across subjects. After scanning, recall was assessed as in the pre-scan session.

Procedures

Toxicology screening—To ensure abstinence from marijuana and other drugs before scanning, all teens underwent biweekly urine toxicology screening for 22–28 days [22, 24]. Urine samples were tested for evidence of recent use of cannabis, amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, codeine, morphine, phencyclidine, and ethanol. THCCOOH, the main secondary metabolite of THC, can be detected in urine several weeks after last use [42, 43], so participants were determined abstinent from marijuana if values decreased with each sample [44]. Two participants in the MJ+BD group reported drug use during the toxicology screening period: one used dextroamphetamine 15 days before scanning, and one used cocaine 21 days before scanning. One MJ+BD participant used prescription codeine per medical guidelines on the day of scanning.

Image Acquisition—Images were collected on a 3-Tesla GE scanner with a sagittally acquired structural image collected with an inversion recovery prepared T1-weighted SPGR sequence (repetition time = 8 ms, echo time = 3 ms, field of view = 240 mm, resolution = 1 mm³, 176 continuous slices, acquisition time = 7:19). During the verbal encoding task, T2*-weighted echo planar imaging was acquired (repetition time = 4000 ms, echo time = 30 ms, flip angle = 90°, field of view = 240 mm, 32 axial slices covering the whole brain, slice thickness = 3.8 mm, in-plane resolution = 3.75 × 3.75 mm, 69 repetitions, acquisition time = 4:36). We have detected hippocampal signal contrast using a similar protocol [20, 39, 41].

Data Analysis—An automated motion correction algorithm was applied to time series datasets [45]. Two trained raters removed repetitions containing residual visible head motions; all datasets retained >85% of repetitions. Next, datasets were deconvolved with a reference function representing the task design while accounting for hemodynamic delays [46] and covarying for motion and linear trends. This yielded fit coefficients representing BOLD response contrast during encoding for each voxel. Our previous work with this task suggested little BOLD response contrast difference between novel and previously learned word pairs and the most robust contrast was for encoding novel word pairs [41]. To best examine brain regions involved in novel verbal learning, we focused on response contrast to novel word pairs. Data were transformed into standard coordinates [47, 48] and functional data were resampled into 3 mm isotropic voxels and spatially smoothed with a Gaussian filter (5 mm full width half maximum).

Group-level analyses were performed on whole brain fMRI data in a two-factor ANOVA, coding for binge drinking status (BD and BD+MJ vs. CON and MJ) and marijuana use status (MJ and BD+MJ vs. CON and BD). We interpreted only clusters comprised of contiguous activated ($\alpha < .05$) voxels $> 1512 \mu\text{l}$ in volume, yielding a 5% brain-wise probability of false positive. Tukey pairwise comparisons (family-wise $\alpha = .05$), compared average BOLD response within each cluster showing a $\text{BD} \times \text{MJ}$ interaction among groups. Data distributions were examined for normality and outliers within each group. A single sample t -test was performed among CON for interpreting group differences in relation to typical activation to this task. Given the effect sizes previously observed [20,22], $\alpha = .05$, and cell sizes > 8 , power to detect hypothesized effects was $> .89$.

Due to the importance of hippocampal functioning in learning and memory, we examined BOLD response specifically within the left and right hippocampi. As in [20], we defined left and right hippocampal regions of interest (ROIs) using the Talairach atlas within AFNI. Hippocampal ROIs were resampled to the same grid as functional datasets; left and right hippocampal ROIs were 3.3 cm^3 each. BOLD response during novel encoding was averaged across the hippocampal ROIs for each subject, then examined in a two-factor ANOVA.

Exploratory regressions examined whether other substance use characteristics were associated with verbal encoding BOLD response. Average fit coefficients for novel encoding were calculated for each participant within each region exhibiting a significant main effect or interaction. ANCOVA determined whether lifetime uses of other drugs contributed to BOLD response above and beyond the effects of binge drinking, marijuana use, and their interaction.

Results

Behavioral Performance

Neither binge drinking nor marijuana use was associated with verbal encoding task performance (see Table 1). During scanning, participants recalled $82 \pm 12\%$ of word pairs, on average. Fourteen adolescents (19%) did not perform to criterion (10/16 correct pairs) on the first learning trial, requiring a second learning trial (evenly distributed across groups).

fMRI Response

BOLD Response in Nonusing Controls—CON demonstrated significant activation during verbal encoding in left middle/inferior frontal gyri, bilateral superior/inferior parietal lobule, bilateral middle/inferior occipital gyri, medial frontal gyrus, and bilateral hippocampi.

Main Effect for Binge Drinking—Collapsing across marijuana use group, binge drinkers ($n = 44$) showed more BOLD response during novel encoding than nondrinkers ($n = 30$) in two clusters: (1) right superior frontal gyrus (Brodmann's Area [BA] 10); and (2) right postcentral gyrus and inferior parietal lobule (BA 40; see Table 2 and Figure 1; all clusters $> 1512 \mu\text{l}$, corrected $p < .05$). Binge drinkers demonstrated less BOLD response than nondrinkers in five clusters: (1) left fusiform gyrus (BA 37); (2) left precentral gyrus (BA 6); (3) right middle and inferior frontal gyri (BA 46, 9); (4) left medial frontal gyrus and cingulate (BA 6, 24); and (5) left inferior parietal lobule and precuneus (BA 19, 39, 40).

Main Effect for Marijuana Use—Collapsing across drinking group, marijuana users ($n = 36$) did not differ significantly from nonusers ($n = 38$) in any brain region on BOLD response during novel encoding.

Drinking × Marijuana Interaction—Four clusters showed a significant drinking × marijuana interaction for BOLD response during novel encoding: (1) left superior frontal and middle frontal gyri (BA 6, 8); (2) right superior and middle frontal gyri (BA 6,8); (3) right inferior and middle frontal gyri (BA 10, 45); and (4) medial bilateral cuneus and lingual gyrus (BA 18; see Table 3 and Figure 2). Pairwise comparisons characterized the nature of these interactions. In the left superior/middle frontal cluster, MJ demonstrated significantly greater response than CON and BD+MJ. In the right superior/middle frontal cluster, both MJ and BD groups showed significantly more response than CON. In the right middle/inferior frontal cluster, MJ showed greater response than CON and BD+MJ, and BD showed more activation than CON. In the bilateral cuneus and lingual gyrus cluster, both MJ and BD groups showed significantly less activation than CON, and BD also showed less response than BD+MJ. In no region did CON significantly differ from BD+MJ, or BD differ from MJ.

Within both left and right hippocampal ROIs, significant BOLD response contrast during verbal encoding was observed in BD, BD+MJ, and CON, but not in the MJ group (see Table 3). No main effects or interactions of alcohol or marijuana use on right or left hippocampal BOLD response were seen. Hippocampal response was not related to task performance.

We examined the possible influence of other drug use on BOLD response in regions that differed between groups. BOLD response was not associated with other drug use in any cluster except for the left precentral gyrus, where BD had shown less response than non-drinkers. Here, ANCOVA revealed that total lifetime other drug use was positively associated with BOLD response above and beyond the effects of binge drinking, marijuana use, and their interaction ($F(1,69) = 9.25, p < .005$). After including lifetime other drug use in the model, binge drinking remained a significant predictor of BOLD response in this region.

Given previous findings of gender differences in neurocognitive function related to alcohol [49] and marijuana [50], we explored the potential influence of gender on group differences. For all clusters, gender was not a contributor to the model, and all results remained when gender was included. Boys and girls did not perform significantly differently on the task.

Discussion

This study examined the neural underpinnings of verbal encoding among adolescent binge drinkers and marijuana users after >3 weeks of monitored marijuana abstinence. Results indicated a main effect of binge drinking and an interaction between binge drinking and marijuana use, but no main effect of marijuana use, on activation.

Binge drinking was associated with less encoding-related activation than non-bingers, independent of marijuana use, in medial cuneus and left posterior parietal cortices, yet greater activation in lateral right parietal and anterior right superior frontal areas, overlapping with our previous findings among non-marijuana using adolescent drinkers [20]. Binge drinkers in the current study showed diminished BOLD response in bilateral dorsolateral prefrontal regions typically involved in verbal rehearsal [for review, see 51]. Others have observed diminished bilateral dorsolateral prefrontal response among adult alcoholics during spatial working memory [52]. This altered frontoparietal functioning could indicate different use of strategies, or reorganization of networks for verbal rehearsal and encoding. For instance, left prefrontal activation has been associated with elaborative learning during novel encoding [53], which could suggest that binge drinkers utilize less sophisticated rehearsal strategies than controls. Recent developmental work has observed increasing dorsolateral prefrontal activation with age during working memory, as youth

become more dependent on working memory networks [54]. Thus, reduced dorsolateral prefrontal response may indicate less mature responding among binge drinkers.

Results revealed interactions between binge drinking and marijuana use, particularly in frontal regions. Interestingly, within these areas, both marijuana- and binge-drinking-only groups evinced similar degrees of increased BOLD response than controls, while teens who binge drank plus used marijuana had control-like levels. This could indicate compensatory recruitment among users of alcohol or marijuana alone in regions involving working memory, selecting and monitoring information, and processing subgoals [e.g., 55].

Counter-intuitively, in clusters with interactions, users of both substances showed intermediate response patterns between controls and single substance use groups. This is consistent with fewer neurocognitive differences among users of both marijuana and alcohol than those who use alcohol alone [16, 17, 26, 27, 56]. The mechanism is unclear, but it is possible that cannabinoids may yield some neuroprotective anti-inflammatory properties that counteract effects of heavy alcohol exposure [57–59]. Alternatively, the differential effect of concomitant use may relate to the recency of intoxication for each substance. Adolescents in the current study had been abstinent from marijuana for >22 days, but may have used alcohol more recently. We previously identified unique brain response patterns during spatial working memory among recent heavy users of both substances in comparison to heavy drinkers [23]. Thus, it is important to consider the time course of normalization following cessation [20]. Another alternative is that simultaneous but opposing processes may exist in proximal regions. For example, if the frontal areas showing interactions contained small neural beds of impaired neurons as well as overactive neurons compensating for insults, the net result would be similar overall activation as in controls.

Although no main effect for marijuana use was seen, interactions pointed to altered BOLD response patterns among marijuana users who did not drink, particularly in lack of hippocampal response contrast during novel encoding. This is consistent with observed hippocampal hypoactivity during associative learning among adult marijuana users following a week of abstinence [60]. We also identified increased frontal response among users of marijuana alone. In contrast, previous reports have characterized reduced prefrontal activation during learning among adult recent marijuana users [60–62]. The differences in the current study were observed following >22 days of confirmed cannabinoid abstinence. Thus, the pattern of compensation or using alternate strategies may change in early abstinence [28], such that recent users reduce brain response, while more abstinent users exhibit hyperactivity.

Our previous fMRI studies of abstinent adolescent marijuana users identified alterations after statistically controlling for alcohol use, but were unable to examine brain response among marijuana using nondrinkers [e.g., 22, 24]. Similarly, an fMRI study of verbal working memory characterized disrupted frontoparietal connectivity among abstinent adolescent marijuana users during nicotine withdrawal [12], but it is unclear what patterns would be observed among nonsmoking marijuana users. The current investigation provides preliminary evidence of subtle differences during verbal learning among abstinent users of marijuana alone, which could suggest persisting differences associated with heavy marijuana use independent of drinking.

These differences in activation were observed despite similar task performance. Because groups performed the task at the same level, comparison of the underlying activation pattern is less likely confounded by differential achievement or motivation. Our previous studies found adolescent heavy drinkers and marijuana users to perform poorly on more sensitive behavioral tasks of verbal memory [7, 11]. Because these populations show deficits on

related tests with a broader range of difficulty, the activation patterns in the current study can be interpreted as possibly inefficient.

Several limitations warrant consideration. To our knowledge, this is the first fMRI study to disentangle the possible effects of alcohol and marijuana use using a full factorial design. However, the sample of marijuana-only subjects was small, since few adolescents only use this substance [63]. The finding of intermediate brain response among users of both substances remains counterintuitive and the underlying mechanism deserves further exploration. Other drug use, although relatively limited, may have contributed to results, although only one region with effects showed a relationship to other drug use, and the effect remained after controlling for other drug use. Longitudinal studies, currently underway, will clarify whether participants differed in neural functioning prior to the onset of substance use. Finally, this study had limited power to detect gender differences, yet this represents an important question for future studies.

In general, each substance-using group displayed deviations in BOLD response relative to non-using controls. In addition, binge drinking and marijuana use appear to have independent as well as interactive effects on brain functioning. Overall, results indicate more brain regions associated with binge drinking than with marijuana use. Results may have implications for public health and prevention strategies. Altered memory functioning associated with adolescent substance use may impact school performance and development. Although alcohol use is legal in most countries, its possible harmful effects should be recognized, particularly at doses exceeding 4 or 5 drinks in an episode.

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Figure 1.

Clusters showing significant main effects for binge drinking (clusters $> 1512 \mu\text{l}$, corrected $p < .05$). Orange indicates regions where CON and MJ (non-drinkers; $n = 30$) showed greater BOLD response during novel encoding than BD and BD+MJ (binge drinkers; $n = 44$); blue clusters represent regions where BD and BD+MJ showed greater BOLD response during novel encoding than CON and MJ.

Figure 2. Clusters showing significant interactions between binge drinking and marijuana use ($N=74$; clusters $>1512 \mu\text{l}$, corrected $p < .05$).

Table 1

Demographics, Substance Use Characteristics, and Task Performance among Adolescent Participants

	CON (<i>n</i> = 22)	BD (<i>n</i> = 16)	MJ (<i>n</i> = 8)	BD+MJ (<i>n</i> = 28)
	M (SD) or %	M (SD) or %	M (SD) or %	M (SD) or %
Demographics and Mood				
Age (range 16 – 18)	17.6 (0.8)	18.1 (0.7)	18.1 (0.9)	18.0 (1.0)
% Female	27.3	18.8	50.0	17.9
% Caucasian	59.1	56.2	50.0	60.7
% Family history negative [*]	86.4	87.5	62.5	78.6
Parent annual salary (US\$ thousands)	114.5 (88.9)	107.9 (73.4)	86.3 (34.2)	133.0 (134.4)
Vocabulary <i>T</i> -score [†]	58.3 (8.7)	60.6 (9.8)	52.5 (4.7)	59.5 (8.0)
Spielberger State Anxiety <i>T</i> -score	37.6 (8.7)	35.1 (4.1)	39.5 (5.7)	39.2 (7.1)
Beck Depression Inventory Total	2.5 (3.2)	2.2 (2.1)	4.0 (4.2)	3.3 (2.8)
Substance Use Characteristics				
Lifetime drinking episodes ^{c,e}	5.8 (8.2)	50.1 (47.3)	126.5 (119.8)	209.5 (165.8)
Age of first drink ^c	15.7 (1.2)	15.0 (1.8)	13.6 (2.3)	13.5 (2.3)
Drinking days/month, past 3 months ^{a,c,e,f}	0.2 (0.7)	4.1 (2.3)	3.1 (4.9)	9.7 (5.7)
Drinks/occasion, past 3 months ^{a,c,e,f}	0.2 (0.7)	9.4 (4.5)	1.3 (1.6)	12.6 (6.5)
Days since last alcohol use ^{a,c}	206.9 (203.2)	32.4 (11.5)	131.5 (123.4)	25.0 (12.6)
% with alcohol use disorder [§]	0	0	0	35.7
Lifetime marijuana use episodes ^{b,c,d,e}	0.6 (1.2)	2.0 (2.9)	426.5 (280.1)	517.6 (451.3)
Age of first weekly marijuana use	-	-	14.5 (2.5)	14.9 (3.4)
Marijuana days/month, past 3 months ^{b,c,d,e}	0.0 (0.0)	0.3 (0.6)	8.4 (9.3)	11.8 (9.3)
Days since last marijuana use ^{b,c,d,e}	528.0 (257.1)	397.3 (401.0)	117.6 (153.9)	43.4 (37.1)
% with marijuana use disorder [∞]	0	0	50.0	71.4
Fagerstrom Nicotine Dependence [‡]	0.0 (0.0)	0.0 (0.0)	0.1 (0.4)	0.3 (0.8)
Lifetime other drug use episodes ^{b,c,d,e}	0.0	1.1	11.9	9.9
Verbal Paired Associates Task Performance				
% correct recall during scan	81.8 (13.1)	80.7 (11.6)	81.3 (14.5)	83.7 (11.4)
% requiring 2nd pre-scan training	13.6	31.3	37.5	10.7

^{*} No first-degree biological relative with alcohol or drug abuse or dependence

[†] Based on Wechsler Abbreviated Scale of Intelligence [64]

[‡] Max possible score = 10; range 0–3 in this sample [36]

[§] Based on DSM-IV current alcohol abuse or dependence; BD+MJ different from others

[∞] Based on DSM-IV current marijuana abuse or dependence; MJ and BD+MJ different from others

^a CON significantly different from BD (Tukey $\alpha = .05$)

^b CON significantly different from MJ (Tukey $\alpha = .05$)

^cCON significantly different from BD+MJ (Tukey $\alpha = .05$)

^dBD significantly different from MJ (Tukey $\alpha = .05$)

^eBD significantly different from BD+MJ (Tukey $\alpha = .05$)

^fMJ significantly different from BD+MJ (Tukey $\alpha = .05$)

Table 2

Regions Showing Significant Main Effects for Binge Drinking on BOLD Response during Novel Verbal Encoding (clusters > 1512 μl , $p < .05$)

Anatomic Region	Brodmann Areas	Volume (μl)	Talairach Coordinates			Effect Size Partial η ²
			x	y	z	
BD and BD+MJ > CON and MJ						
Right postcentral gyrus/inferior parietal lobule	40	2430	-47	47	54	0.20
Right superior frontal gyrus	10	1539	-29	-50	27	0.16
CON and MJ > BD and BD+MJ						
Left fusiform/parahippocampal gyrus/cuneus	17, 30	4050	26	74	-16	0.17
Left precuneus/inferior parietal lobule	19, 39, 40	3888	32	80	39	0.20
Left inferior frontal/precentral gyri	6, 9	2106	47	-5	30	0.14
Right middle/inferior frontal gyri	9, 46	1944	-50	-20	27	0.16
Left medial frontal/cingulate gyrus	6, 24	1890	2	8	54	0.13

Note: Coordinates refer to maximum signal intensity voxel within the cluster. Effect sizes refer to main effect of drinking averaged over the cluster.

Table 3

BOLD Response During Novel Verbal Encoding in Each Group for Regions of Significant Binge $\times$ Marijuana Interactions and the Hippocampal a Priori Region of Interest

Anatomic Region	Brodmann Areas	Volume (μl)	Talairach Coordinates			Activation Mean (SD)			Effect Size Partial η ²	
			x	y	z	CON (n = 22)	BD (n = 16)	MJ (n = 8)		BD+MJ (n = 28)
Significant Interaction Clusters										
Left superior/middle frontal gyri <i>b,c</i>	6, 8	3996	29	-20	51	0.37 (1.37)	5.39 (1.60)	7.96 (2.27)	0.48 (1.21)	0.17
Right inferior/middle frontal gyri <i>a,b,c</i>	10, 45	3645	-44	-41	-1	-1.88 (1.41)	4.41 (1.65)	6.39 (2.33)	-0.76 (1.25)	0.18
Right superior/middle frontal gyri <i>a,b</i>	6, 8	3159	-26	-26	54	-4.79 (1.11)	0.90 (1.31)	2.08 (1.85)	-2.58 (0.99)	0.17
Medial cuneus/lingual gyrus <i>a,b,d</i>	18	2700	2	89	9	7.48(2.25)	-7.20(2.64)	-5.25 (3.74)	1.93(2.00)	0.19
Hippocampal Regions of Interest										
Left hippocampus BOLD Response						2.52(2.60) *	1.67(2.08) *	0.82 (3.09)	2.60(3.23) *	
Left hippocampus Effect Size Cohen's <i>d</i>						1.37	1.14	0.38	1.14	
Right hippocampus BOLD Response						1.57(2.42) *	1.50(2.34) *	1.00 (2.64)	1.56(2.80) *	
Right hippocampus Effect Size Cohen's <i>d</i>						0.92	0.91	0.54	0.79	

Note: Coordinates refer to maximum signal intensity group difference within cluster. Mean activations represent average fit coefficients within each cluster; positive values indicate greater response during encoding than fixation. Partial η^2 refers to effect sizes for interaction within the cluster; Cohen's *d* refers to effect sizes for single sample *t*-tests within hippocampal regions of interest.

^a CON significantly different from BD (Tukey $\alpha = .05$)

^b CON significantly different from MJ (Tukey $\alpha = .05$)

^c MJ significantly different from BD+MJ (Tukey $\alpha = .05$)

^d BD significantly different from BD+MJ (Tukey $\alpha = .05$)

* Novel verbal encoding activation significantly different from zero ($p < .01$)