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The Influence of Recency of Use on fMRI Response During Spatial Working Memory in Adolescent Marijuana Users

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Abstract

Some neurocognitive recovery occurs within a month of abstinence from heavy marijuana use, yet functional magnetic resonance imaging (fMRI) has revealed altered activation among recent and abstinent adult users. Here, we compared fMRI response during a spatial working memory (SWM) task between adolescent marijuana users with brief and sustained durations of abstinence.

Participants were 13 recent users (2 – 7 days abstinent), 13 abstinent users (27 – 60 days abstinent), and 18 non-using controls, all ages 15 – 18. Groups were similar on demographics, had no psychiatric or medical disorders, and user groups were similar on substance histories. Teens performed a 2-back SWM task during fMRI.

Groups performed similarly on the task, but recent users showed greater fMRI response in medial and left superior prefrontal cortices, as well as bilateral insula. Abstinent users had increased response in the right precentral gyrus (clusters $\geq 1328 \mu\text{l}$, $p < .05$).

This cross-sectional study did not examine changes in brain response among the same participants over time. Yet results suggests that adolescents who recently used marijuana show increased brain activity in regions associated with working memory updating and inhibition, compared to users with weeks to months of abstinence. This study preliminarily suggests that (1) recent marijuana use may disrupt neural connections associated with SWM and result in compensatory brain response, and (2) sustained abstinence from marijuana may be associated with improvements in SWM response among adolescents.

Regular marijuana use is prevalent among teenagers (Johnston et al. 2006). However, it remains unclear whether potential neural disruption associated with adolescent marijuana use is permanent, or whether alterations improve with abstinence, raising the possibility of neurocognitive recovery. Functional neuroimaging may help differentiate the neurocognitive

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effects of recent use from the potentially persisting impact of heavy marijuana use in adolescence.

The adult literature indicates impairments in learning and memory, attention, visuospatial skills, processing speed, and executive functioning among heavy marijuana users within a few days of use (Bolla et al. 2002; Croft et al. 2001; Lyons et al. 2004; Pope et al. 1997; Pope & Yurgelun-Todd 1996; Solowij et al. 2002; Varma et al. 1988). Longitudinal evidence suggests that marijuana-related verbal learning deficits, observed following recent use, disappear after 28 days of abstinence in a sample of adults (Pope et al. 2001). In contrast, compared to published test norms, 28-day abstinent adults demonstrated memory, executive functioning, and motor impairments that correlated with lifetime use (Bolla et al. 2002). A functional magnetic resonance imaging (fMRI) study examined visuospatial attention among 12 recent marijuana users who had used 2 – 24 hours before scanning, 12 abstinent users who had been abstinent an average of 38 months, and 19 non-using controls (Chang et al. 2006). Active users demonstrated greater levels of functional abnormalities than abstinent users in prefrontal and cerebellar regions, and a longer duration of abstinence was associated with normalization of function.

The question of whether cognitive abilities change with abstinence in adolescents has begun to be explored. Marijuana-dependent youths showed poorer memory performance relative to control youths at treatment intake, and failed to show improvements in short term memory following 6 weeks of abstinence (Schwartz et al. 1989). In a cross-sectional study of youths, current heavy users showed deficits in immediate and delayed memory, processing speed, and overall IQ, yet 3-month abstinent users performed similarly as controls (Fried, Watkinson & Gray 2005). Others have found fMRI evidence of altered working memory activation among abstinent adolescent marijuana users (Jacobsen et al. 2004; Jacobsen et al. 2007; Schweinsburg et al. 2008). However, as participants were not assessed soon after marijuana discontinuation, it is unclear whether observed abnormalities represented changes in functioning during early abstinence. We previously identified altered fMRI response to a spatial working memory (SWM) task among adolescents with comorbid marijuana and alcohol use disorders after an average of eight days of marijuana abstinence (Schweinsburg et al. 2005). Thus, altered functioning has been described in both recent and abstinent adolescent marijuana users, particularly on working memory tasks. However, it remains unclear whether neural activation patterns might change during the first month of abstinence, as recent and abstinent users have not yet been compared with fMRI.

This study was designed to investigate the differences in neural activation between recent and abstinent adolescent marijuana users. Evidence in adults suggests that substantial neuropsychological recovery appears to occur after the first week of abstinence, and full normalization is observed following one month of abstinence (Pope et al. 2001). Therefore, in order to best characterize the persisting vs. residual effects of marijuana, we examined fMRI response during a SWM task among: (1) recent marijuana using teens that had used within one week of testing, (2) abstinent marijuana using teens that had not used for 27 days, and (3) demographically similar non-using controls. Blood oxygen level-dependent (BOLD) fMRI was collected during a SWM task that activates bilateral dorsolateral prefrontal and posterior parietal networks in adolescents (Schweinsburg, Nagel & Tapert 2005), and has been associated with neural dysfunction among youths with alcohol use disorders (Tapert et al. 2004) as well as marijuana abuse (Schweinsburg et al. 2008; Schweinsburg et al. 2005). Based on our previous findings, we predicted that recent users would show increased levels of frontal lobe fMRI activation than abstinent users, indicating compensatory neural recruitment.

Method

Participants

Participants were selected from adolescent brain imaging studies of 15- to 18-year-olds recruited from local high schools (Tapert et al. 2003; Tapert et al. 2004; Tapert et al. 2007). Teens and their parents were individually screened with telephone interviews; informed consent and assent (for minors), approved by the University of California Human Research Protections Program, were obtained from all participants and their parents. Exclusion criteria included left-handedness; history of neurological disorder or head injury with loss of consciousness > 2 minutes; history of an Axis I psychiatric disorder (including attention-deficit hyperactivity disorder) other than alcohol or marijuana use disorders or conduct disorder; current psychotropic medication use; family history of bipolar I or psychotic disorders; prenatal alcohol or other drug exposure; learning disabilities; and MRI contraindications. Teens with alcohol use disorders or conduct disorder (one control, three recent users, and two abstinent users) were not excluded due to high comorbidity with heavy marijuana use (Agosti, Nunes & Levin 2002; Brown et al. 1996).

Previous studies in adults have suggested considerable neurocognitive recovery following a week of abstinence, and complete normalization after 28 days (Pope et al. 2001). Therefore, the current study examined marijuana users in two groups: 13 recent users who had used within one week of scanning (abstinent 2 – 7 days), and 13 abstinent users who had been abstinent between 27 and 60 days. Non-using control adolescents ($n=18$) were included to aid interpretation of fMRI differences between the marijuana using groups by identifying brain regions typically activated by this SWM task among demographically similar healthy youths (see Figure 1 for a graphic of the study design). We previously characterized fMRI response to SWM among nonusing controls and abstinent marijuana users (Schweinsburg et al. 2008). Some of those participants were also included in the current study, but the recent and abstinent marijuana users here have not yet been directly compared. All three groups herein were similar in gender and ethnic composition, estimated premorbid IQ, socioeconomic status, mood, and behavioral indices (see Table 1). Importantly, recent and abstinent marijuana users were comparable on all substance use characteristics (including alcohol use) other than recency of marijuana use. As expected, marijuana groups demonstrated greater involvement with alcohol and marijuana than controls. Abstinent marijuana users reported more lifetime uses of other drugs than controls, but average lifetime use was relatively limited in all groups.

Measures

Behavioral Characteristics—Lifetime and recent substance use were characterized with the Customary Drinking and Drug Use Record (CDDR)(Brown et al. 1998). 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 imaging. Parents completed the Child Behavior Checklist, which provided indices of externalizing and internalizing behavior (Achenbach & Rescorla 2001) (see Table 1).

Neuropsychological functioning—Visuospatial skills (Block Design), working memory (Digit Span), and estimated premorbid IQ (Vocabulary) were ascertained with age-appropriate subtests from the Wechsler Intelligence Scale for Children-Third Edition (WISC-III)(Wechsler 1993), Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler 1997), or Wechsler Abbreviated Scale of Intelligence (WASI)(Wechsler 1999).

Spatial working memory task—The SWM task (Kindermann et al. 2004; Tapert et al. 2001) was administered in a blocked design, with 18–21-second blocks that alternated

between working memory, baseline vigilance, and fixation. In the SWM condition, participants viewed abstract line drawings that were sequentially presented in one of eight locations on a screen, and were instructed to press a button every time a figure appeared in the same location as a previous design within that block. Repeat location stimuli were 2-back, and 3 of 10 trials in each block were target items. The baseline vigilance condition presented the same abstract stimuli shown in the same possible spatial locations as in the SWM condition, and subjects were to press a button every time a figure appeared with a dot above it (30% of trials). Resting blocks displayed a fixation cross in the center of the screen. For working memory and vigilance conditions, stimuli were presented for 1000 ms with an interstimulus interval of 1000 ms (21 seconds/block; total task time=7 minutes, 48 seconds).

Procedures

Toxicology screening—Most teens in the abstinent group were selected from an ongoing study involving a biweekly toxicology screening procedure to ensure abstinence from substances for at least 28 days prior to scanning (Tapert et al. 2007). Three teens who did not undergo the 28-day toxicology screening procedure reported that last use was 27 days or more prior to scanning and provided urine screens negative for cannabinoids and other drugs at the scan session. Since these teens were not required to be abstinent and had not received monetary incentive to maintain abstinence for a month before the scan, it is unlikely that information regarding their date of last use would be falsified (Martin et al. 1996); these participants were thus included in the abstinent group. Based on available toxicology data at the time of scanning, all teens in the abstinent group produced toxicology screens negative for cannabinoids. Teens in the recent use group were asked to be abstinent for at least 48 hours before scanning. Urine toxicology screens were obtained the time of scanning for 8 participants in the recent use group. Five recent users had positive screens, and three recent users produced negative screens despite self-reported use during the week of the scan. Negative screens can be observed as soon as four days following use (Huestis & Cone 1998); therefore, self-reported use is not inconsistent with urine toxicology results among the three recent users with negative screens.

Imaging protocol—Anatomical and functional imaging data were acquired using a 1.5 Tesla General Electric Signa LX scanner. A high-resolution, sagittally acquired structural scan was collected with an inversion recovery prepared T1-weighted 3D spiral fast spin echo sequence (Wong et al. 2000) (TR=2000 ms, TE=16 ms, FOV=240 mm, resolution= $0.9375 \times 0.9375 \times 1.328$ mm, 128 continuous slices, acquisition time=8:36). The functional scan was acquired axially with T2*-weighted spiral gradient recall echo imaging (TR=3000 ms, TE=40 ms, flip angle=90°, FOV=240 mm, 19–21 slices covering the whole brain, slice thickness=7 mm, reconstructed in-plane resolution= 1.875×1.875 mm, 156 repetitions).

Data Analyses

Demographic, mood, behavioral, and drug use characteristics were compared between groups with ANOVA or chi-square tests as appropriate, and significant differences were followed-up with Tukey all pairwise comparisons. Standardized scores for neuropsychological tests were obtained from published norms, and compared between groups with ANOVA. Significant differences were followed-up with Tukey all pairwise comparisons. SWM task performance was examined with repeated measures ANOVA to characterize the main effects of task condition (vigilance vs. SWM), group, and their interaction, both for accuracy and reaction time. Significant interactions were followed up with simple effects *t*-tests.

Imaging data were processed and analyzed using Analysis of Functional NeuroImages (AFNI) (Cox 1996). Processing began with motion correction of the time series data (Cox &

Jesmanowicz 1999). This created an output file for each participant containing the adjustments made for three rotational and three displacement parameters. Two independent raters inspected the time series data to remove any repetitions on which the algorithm did not adequately adjust for motion or other artifacts. Valid datasets were required to have at least 85% of repetitions retained (on average 97% of repetitions were retained for the 44 participants described here). Using a deconvolution procedure (Ward 2002), the time series data were then correlated with a reference function that represented the hypothesized BOLD signal across the time course of the task and modeled expected delays in hemodynamic response (Cohen 1997). This multiple linear regression approach yielded a fit coefficient that represented the fit between the observed and hypothesized signal for SWM relative to vigilance, while controlling for linear trends and degree of motion correction. Anatomical and functional datasets were warped into standard space (Talairach & Tournoux 1988), and functional data were resampled into 3.0 mm³ voxels and smoothed with a 5.0 mm full-width half-maximum Gaussian filter.

We performed single-sample *t*-tests for recent users, abstinent users, and controls to determine regions that showed significantly increased or decreased response to SWM relative to vigilance within each group. To control for multiple comparisons in whole-brain data, we used a combination of cluster volume and voxel thresholding (Forman et al. 1995). Clusters from each single-sample *t*-test were considered significant if they consisted of 49 contiguous voxels ($p < .05$) that exceeded 1328 μ l in volume, yielding an overall cluster-wise $\alpha = .05$ for the whole brain within each group.

BOLD response to SWM relative to vigilance was evaluated between abstinent and recent marijuana use groups in a whole-brain independent samples. Again, we controlled for Type I error using the same thresholding technique as described for the single sample *t*-tests. Clusters were considered significant if they encompassed at least 49 contiguous voxels ($t(24) > 2.06$, $p < .05$), yielding significant clusters $\geq 1328 \mu$ l at an overall cluster-wise $\alpha = .05$. In each region demonstrating a group difference, we examined the relationship between BOLD response and marijuana use characteristics as well as potentially confounding factors (e.g., other substance use and conduct disorder) with exploratory regression analyses among the 26 users.

Results

Neuropsychological Functioning

As shown in Table 2, abstinent and recent users did not significantly differ in Vocabulary [$F(2,40)=1.51$, $p < .24$], Block Design [$F(2,39)=0.25$, $p < .78$], or Digit Span [$F(2,41)=2.50$, $p < .10$] scores. Both marijuana use groups performed similarly as controls on these tests.

SWM Task Performance

Button box logging failed for one recent user, one abstinent user, and one control. Available data revealed a main effect for greater accuracy on vigilance than SWM trials [$F(1,38)=7.33$, $p=.01$; see Table 2] and no main effect for group or a group $\times$ condition interaction for accuracy. For reaction time, a main effect showed teens were faster on SWM than the vigilance condition [$F(1,38)=30.76$, $p < .001$]. A trend for a group $\times$ condition interaction for reaction time [$F(2,38)=2.87$, $p=.07$] indicated that recent users had slightly faster reaction times for vigilance than abstinent users and controls, and abstinent users showed slightly faster responding than recent users and controls on SWM trials.

Data Quality

Distributions of fMRI response were examined for outliers (Tabachnick & Fidell 2007) in each significant cluster (see Table 3), and none were found. Overall motion was quite minimal, ranging from 0.03 to 0.10 mm for superior-inferior displacement, 0.01 to 0.13 mm for left-right displacement, 0.01 to 0.25 mm for posterior-anterior displacement, 0.01 to 0.23° for roll rotation, 0.02 to 0.57° for pitch rotation, and 0.02 to 0.17° for yaw rotation. Groups did not differ with regard to discarded repetitions or motion correction applied in any of the six motion parameters, except that abstinent users had more head motion in the left-right direction than recent users [$t(24) = 2.49$; $p < .025$]. However, such movement did not account for group differences in BOLD response in any region reported below.

fMRI Response

Single sample t -tests showed that the overall pattern of BOLD response was similar in all three groups, with greater SWM activation relative to vigilance in bilateral prefrontal, premotor, cingulate, and posterior parietal areas ($p < .05$), and reduced SWM response relative to vigilance in medial prefrontal cortex, medial posterior cingulate and cuneus, and several temporal regions ($p < .05$; see Figure 2).

The independent samples t -test revealed that recent users had greater SWM response than abstinent users in the following regions: a large cluster spanning medial bilateral cingulate, medial frontal gyrus, and left superior and middle frontal gyri (Brodmann's area [BA] 8); medial bilateral superior frontal gyrus (BA 6/8); left insula and precentral gyrus (BA 13); and right insula and inferior frontal gyrus (BA 13; see Table 3 and Figure 3). As revealed by single sample t -tests, in frontal and insular regions, recent users demonstrated greater response to SWM than to vigilance, while abstinent users showed reduced response to SWM relative to vigilance, and controls did not show significantly increased or decreased response to SWM relative to vigilance. Abstinent users showed greater BOLD response than recent users only in the right precentral gyrus (BA 4). In this region, recent users demonstrated reduced SWM response relative to vigilance, but controls and abstinent users showed no significant response.

To examine the extent to which marijuana use characteristics and potential confounds (e.g., other substance use) might influence observed group differences, we conducted exploratory regression analyses. Of the substance use characteristics listed in Table 1, no index of marijuana, alcohol, cigarette, or other drug use, except for recency of marijuana use, was related to BOLD response in any region demonstrating a difference between recent and abstinent user groups, and group differences remained significant after controlling for alcohol, nicotine, or other drug use. State anxiety score was positively associated with BOLD response in the left insula/precentral gyrus [$F(1,25) = 4.55$, $p < .05$, $R^2 = 0.16$, $b = 0.40$]. When anxiety and group (recent vs. abstinent users) were simultaneously entered, group remained a significant predictor of left insula response ($p < .005$), while anxiety became a predictor at the trend level ($p = .051$). Group differences in BOLD response between recent and abstinent users remained significant after excluding participants with conduct disorder.

Discussion

This study provides a cross-sectional indication of changes in neural response patterns during early abstinence from marijuana among adolescents. Heavy marijuana using teenagers with 2 – 7 days of abstinence demonstrated greater brain response during spatial working memory than teens that had been abstinent for at least 27 days in medial and left superior prefrontal cortex, and bilateral anterior insula. However, controls did not show

significant BOLD response in these frontal and insula regions, suggesting the areas are not normally employed during this SWM task, and may be ancillary regions recruited by recent users to maintain performance levels.

Recent users demonstrated enhanced SWM response in medial and left superior prefrontal cortex compared to abstinent users. This region shows strong functional links to posterior parietal cortices (for review, see Wise et al. 1997), and activation here has been associated with continuous updating and sequencing during spatial working memory (Leung et al. 2007; Owen et al. 2005; Wager & Smith 2003; Zurowski et al. 2002). In support of this perspective, lesions of left superior frontal cortex lead to deficits in performance of n-back working memory tasks as executive demands increase, particularly in the spatial domain (du Boisgueheneuc et al. 2006). This region is also activated during uncertainty in decision making (Volz, Schubotz & von Cramon 2005) and appears to have a general role in cognitive control across a variety of tasks (Derrfuss, Brass & von Cramon 2004). Similar to the current study, Chang and colleagues (Chang et al. 2006) observed increased visual attention activation in medial frontal regions among adult recent marijuana users relative to users abstinent at least 2 weeks. Given these prior studies, more effortful cognitive control and working memory updating may correspond with greater superior frontal activation among recent users, particularly if recent users are more uncertain in their responding or if executive demands are high. In contrast, abstinent users may display strategy shifts, requiring less demand on sequencing abilities and general executive control, and task processing may become more efficient with greater lengths of abstinence, eliciting less uncertainty in responding.

Bilateral anterior insula/inferior frontal activation was greater in recent users compared to abstinent users. The insula maintains interconnections with both prefrontal and posterior parietal cortices (Selemon & Goldman-Rakic 1988), and is involved in cognitive control and inhibition (Derrfuss, Brass & von Cramon 2004; Wager et al. 2005). Bilateral insula response has been observed across different inhibitory tasks, particularly in relation to task difficulty (Wager et al. 2005). For instance, when performing a response inhibition task, insula activation increases during sleep deprivation, but not after normal sleep, indicating a compensatory role when more effort is required (Chuah et al. 2006). In the context of spatial working memory, the anterior insula has been suggested to assist in selecting appropriate responses and inhibiting irrelevant information (Lepsien et al. 2005). Adult alcoholics performing a SWM task activated a right inferior frontal region that was more ventral and posterior than activation among controls (Pfefferbaum et al. 2001), and overlapping with the anterior insula region activated by recent users in the current study. The authors suggested that this shift in activation may indicate reorganization of cognitive networks associated with alcoholism, particularly in relation to inhibitory control during SWM. Thus, increased insula response among recent marijuana users may reflect greater inhibitory effort during periods of active marijuana use, whereas abstinent users may no longer require the same degree of inhibitory control. Importantly, the insula may be involved in maintaining protracted substance use patterns. Increased insula activation predicts relapse to substance use among individuals with stimulant dependence (Paulus, Tapert & Schuckit 2005), and cigarette smokers with insular lesions were more likely to maintain abstinence compared to smokers without brain damage (Naqvi et al. 2007). Thus, it could be that the abstinent users in the current study demonstrated reduced insula response because they were able to maintain abstinence for four weeks prior to scanning; it is unclear whether the recent marijuana users, with their heightened insula activation, would have also been able to remain abstinent for the study. Longitudinal investigations of marijuana users who do and do not relapse within the first month will help clarify this issue.

Several possible mechanisms may subserve the observed results. First, fronto-parietal networks continue structural and functional development throughout adolescence, supporting maturation of working memory abilities (Klingberg 2006; Klingberg, Forssberg & Westerberg 2002; Schweinsburg, Nagel & Tapert 2005; Thomas et al. 1999), and may be particularly vulnerable to insult during youth. Cannabinoid receptors are densely located in frontal cortex (Eggan & Lewis 2006; Glass, Dragunow & Faull 1997; Herkenham et al. 1990). Further, the cannabinoid receptor system develops relatively late (Biegon & Kerman 2001), and receptor densities peak during adolescence among rats (Rodriguez de Fonseca et al. 1993), potentially increasing sensitivity to cannabinoid effects in adolescents. Although the neurobiological consequences of chronic cannabinoid exposure are still unclear, alterations of these developing receptor systems may underlie spatial working memory changes among adolescent marijuana users. For instance, chronic marijuana use leads to cannabinoid receptor down-regulation in human basal ganglia structures (Villares 2007), which form a frontostriatal network critical to working memory processing (e.g., Chudasama & Robbins 2006). In addition, substantial increases or decreases in dopamine activity lead to impaired working memory performance (for review, see Robbins 2000). Chronic cannabinoid administration is associated with reduced dopamine functioning in rat prefrontal cortex that lasts at least 2 weeks following exposure, but begins to normalize with abstinence (Jentsch et al. 1998; Verrico, Jentsch & Roth 2003). Thus, neurochemical changes that subserve working memory could normalize with sustained abstinence, contributing to the different fMRI activation patterns between recent and abstinent marijuana users.

As BOLD response is influenced by cerebral blood flow, it is possible that perfusion data would mediate results reported here. Altered resting frontal and cerebellar blood flow have been observed among recently-using adult chronic marijuana users (Block et al. 2000; Loeber & Yurgelun-Todd 1999; Lundqvist, Jonsson & Warkentin 2001; Sneider et al. 2006). After a month of abstinence, blood flow velocity and cerebrovascular resistance remained elevated among adult marijuana users, yet those using marijuana at levels consistent with our sample (i.e., 15.9 days per month) demonstrated some improvement in vascular resistance (Herning et al. 2005). The BOLD signal arises from dynamic shifts in cerebral blood flow during activation paradigms (Cohen, Ugurbil & Kim 2002; Hoge et al. 1999; Uludag et al. 2004). Thus, altered BOLD response in adolescent marijuana users could reflect compromised cerebrovasculature. Partial recovery of cerebrovascular perfusion after a month of abstinence (Herning et al. 2005) may contribute to fMRI activation differences between abstinent and recent marijuana users in the current study.

Abstinent users only demonstrated greater response than recent users in the right precentral gyrus, yet the mechanism behind this group difference is unclear. All participants were right handed and responded with their right index finger during the SWM task, so greater right precentral activation among abstinent users cannot be explained by manual response differences. This increased right precentral response among abstinent users may relate to motor circuitry underlying their faster reaction times, or could be indicative of greater inter-hemispheric motor overflow.

Indices of marijuana use, alcohol use, and other drug use characteristics (including quantity, duration, and frequency of use) were not related to brain response in any region demonstrating a group difference. This indicates that, of the variables examined, only recency of use was related to neural response patterns. This supports the suggestion that recent use may influence brain functioning more than cumulative lifetime exposure (Pope et al. 2001), and points to the possibility that neural functioning may normalize with longer durations of abstinence.

Although cross-sectional in nature, this study provides preliminary evidence of changes in neural functioning during the first month of abstinence from marijuana. Longitudinal studies, including assessments after differing lengths of abstinence, are needed to clarify the relationship between abstinence duration and neural response. These studies could examine marijuana users who have been abstinent longer than a month to determine whether these brain response differences continue to normalize with extended abstinence. However, group differences in activation may be mediated by characteristics of those users who are able to sustain abstinence for at least 28 days, and may not reflect changes related to recovery per se. Only prospective assessments across an extended abstinence period can determine whether and when shifts in processing occur.

Most of the marijuana users in this study were moderate to heavy drinkers. Our previous research characterized neural response differences between adolescent alcohol and marijuana users compared to users of alcohol alone, suggesting that marijuana use may influence neural functioning above and beyond the effects of alcohol, particularly in frontal regions (Schweinsburg et al. 2005). Indices of alcohol use did not appear to account for group differences in BOLD response found here, yet it is difficult to disentangle the potential neural influence of each substance. Future studies including teens who use alcohol or marijuana alone will help clarify the contributions of each substance and their interaction on brain functioning. Anxiety levels were correlated with brain response in the current study, and although groups did not differ on anxiety, this may be an important factor to consider in later research. Future studies will benefit from larger sample sizes with power to detect neuropsychological differences between groups. Finally, task accuracy was high in both groups; parametric manipulations of working memory load may further differentiate neural response patterns, and may elicit performance decrements in user groups.

In summary, heavy marijuana using teenagers who had used within a week of scanning demonstrated greater frontal and insular brain response during SWM than marijuana users who had been abstinent for at least 27 days. Interestingly, such frontal and insular activation was not observed in non-using control youths, suggesting that recent users recruit additional brain regions not normally utilized for this SWM task. These fMRI differences suggest increased working memory updating and inhibitory control among recent users despite similar task performance. Although cross-sectional, these results could indicate a change in neural strategy during the first month of abstinence, with less reliance on compensatory recruitment of frontal and insular regions. Finally, increased cognitive control and spatial working memory effort following recent use may have important implications for teens attempting abstinence, but longitudinal investigations are needed to verify these initial impressions.

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Figure 1.
Study design.

Figure 2.

BOLD response to spatial working memory relative to vigilance in recent marijuana users, abstinent marijuana users, and non-using controls. Activation maps represent regions of significantly greater response to the spatial working memory relative to the vigilance trials (orange colors), and greater response to vigilance relative to spatial working memory trials (blue) as determined by single sample *t*-tests ($p < .05$, corrected for multiple comparisons; clusters > 49 contiguous voxels each activated at $p < .05$). Activations are displayed on top of an averaged anatomical image.

Figure 3.

Activation maps showing significant group differences in spatial working memory BOLD response between adolescent marijuana users with recent use ($n=13$) compared to adolescents with sustained abstinence ($n=13$). Activations are displayed on an averaged anatomical image. Activation maps are thresholded at an overall $p<.05$ for the whole brain, corrected for multiple comparisons ($p<.05$, cluster volume ≥ 1328 microliters). Red indicates clusters in which Recent Users showed more brain response than Abstinent Users during spatial working memory; blue indicates clusters in which Abstinent Users showed more response than Recent Users during the simple vigilance control condition.

Table 1

Participant Characteristics

	Recent Users (<i>n</i> = 13)	Abstinent Users (<i>n</i> = 13)	Controls (<i>n</i> = 18)
	M (SD) or %	M (SD) or %	M (SD) or %
Age	17.07 (0.53)	17.58 (0.92)	17.34 (0.82)
% Female	31%	31%	39%
% Caucasian	92%	85%	89%
% Family history negative ^a	33%	46%	56%
Parent annual salary (thousands) [*]	82.33 (53.42)	149.09 (76.95)	103.22 (63.82)
Beck Depression Inventory total	5.69 (6.21)	4.83 (7.04)	2.00 (2.68)
Spielberger State Anxiety <i>T</i> -score	43.29 (7.64)	41.06 (8.28)	39.37 (8.87)
Lifetime marijuana use episodes [†]	342.31 (260.49)	515.38 (275.67)	1.50 (4.68)
Years of weekly marijuana use [†]	2.30 (1.21)	2.65 (1.71)	0
Marijuana use/month, past 3 months [†]	14.17 (9.8)	16.85 (10.47)	0.06 (0.24)
Days since last marijuana use ^{*†}	3.33 (1.72)	38.08 (10.28)	671.11 (434.57)
Lifetime alcohol use episodes [†]	140.92 (234.82)	184.85 (164.39)	7.11 (13.85)
Drinks/month, past 3 months [†]	39.00 (47.34)	54.77 (50.96)	1.78 (4.68)
Days since last alcohol use [†]	14.69 (14.14)	20.31 (12.53)	106.18 (97.75)
Tobacco cigarettes per day [†]	1.23 (2.28)	1.62 (2.96)	0
Days since last cigarette use ^{b †}	61.44 (121.07)	120.00 (284.99)	586.60 (637.94)
Fagerstrom Test for Nicotine Dependence total (max = 10)	0.08 (0.28)	0.31 (0.85)	0
Lifetime other drug use episodes [‡]	4.77 (7.90)	9.15 (12.24)	0.78 (3.30)

^aNo first- or second-degree biological relative with alcohol or drug abuse or dependence

^bFigure includes only those who reported lifetime use (9 Recent Users, 12 Abstinent Users, 5 Controls)

^{*}*p* < .05 for recent vs. abstinent users only

[†]*p* < .05 for controls vs. recent users, and controls vs. abstinent users; *n.s.* for recent vs. abstinent users

[‡]*p* < .05 for controls vs. abstinent users only

Table 2

Neuropsychological and Spatial Working Memory Task Performance

	Recent Users (<i>n</i> = 13)	Abstinent Users (<i>n</i> = 13)	Controls (<i>n</i> = 18)
	M (SD) or % [range]	M (SD) or % [range]	M (SD) or % [range]
Vocabulary <i>T</i> -score	56.9 (7.1) [47 – 67]	53.6 (9.8) [37 – 70]	58.7 (6.9) [48 – 77]
Block Design <i>T</i> -score	54.0 (8.7) [40 – 67]	56.6 (7.7) [40 – 64]	55.0 (9.7) [35 – 66]
Digit Span scaled score	12.0 (3.3) [7 – 17]	13.3 (3.0) [8 – 19]	10.9 (2.2) [7 – 15]
Vigilance % correct	95.50 (4.08) [83 – 98]	95.00 (4.77) [81 – 99]	96.00 (2.40) [88 – 98]
SWM % correct	93.25 (4.65) [84 – 98]	91.83 (6.47) [79 – 98]	91.41 (8.88) [60 – 99]
Vigilance reaction time (ms)	609.78 (62.20) [535 – 777]	620.62 (47.01) [558 – 709]	628.60 (78.98) [530 – 828]
SWM reaction time (ms) *	572.95 (71.64) [465 – 679]	513.85 (81.36) [370 – 678]	574.33 (87.41) [380 – 706]

* $p = .07$ for group difference between Recent and Abstinent Users; no other significant pairwise differences were identified

Table 3

BOLD Response Differences to the Spatial Working Memory Task between Recent ($n=13$) and Abstinent ($n=13$) Marijuana Users

Anatomic Region	Brodmann's Area	Volume (μl)	Talairach Coordinates ^a			Effect Size Cohen's <i>d</i> ^b
			x	y	z	
<i>Recent > Abstinent</i>						
Medial cingulate, medial frontal gyrus, left superior & middle frontal gyri	8	6129	2	23	42	2.34
Medial bilateral superior frontal gyrus	6, 8	1539	2	26	57	1.63
Left insula & precentral gyrus	13	4347	-53	14	6	1.49
Right insula & inferior frontal gyrus	13	2484	41	23	-7	1.90
<i>Abstinent > Recent</i>						
Right precentral gyrus	4	1431	56	-17	39	1.62

^aTalairach coordinates refer to maximum signal intensity group difference within the cluster

^bCohen's d calculated from average t -value of all voxels within the cluster