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# Spatial Working Memory Performance and fMRI Activation Interactions in Abstinent Adolescent Marijuana Users

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# Abstract

Previous studies have suggested neural disruption and reorganization in adult marijuana (MJ) users. However, it remains unclear if these effects persist in adolescents after 28 days of abstinence, and if they do, what performance by brain response interactions occur. MJ users (*n*=17) and controls (*n*=17) adolescents aged 16 to 18 were recruited from local schools. Functional magnetic resonance imaging data were collected after 28 days' monitored abstinence as participants performed a spatial working memory task. MJ users showed performance by brain response interactions in the bilateral temporal lobes, left anterior cingulate, left parahippocampal gyrus and right thalamus (clusters $\geq$ 1358μl; $p < 0.05$), although groups did not differ on behavioral measures of task performance. MJ users show differences in brain response to a spatial working memory task despite adequate performance, suggesting a different approach to the task via altered neural pathways.

# Spatial Working Memory Performance and fMRI Activation Interactions in Abstinent Adolescent Marijuana Users

Marijuana is consistently the most widely used illicit drug among adolescents (SAMHSA, 2006). Fourty-four percent of twelfth-graders have used marijuana in their lifetime, 20% used in the past month, and 5% use daily (Johnston, O'Malley, Bachman & Schulenberg, 2006), representing a large increase from the 16% of 8th graders who have tried marijuana. Furthermore, 40% of high school students who used marijuana in the past year met criteria for marijuana abuse or dependence (Chen, Sheth, Elliot, & Eagerm, 2004). Marijuana use in adolescence causes significant concern since marijuana use may impact the brain, which is still developing throughout adolescence. Though overall brain size stabilizes around age five (Durston, Hulshoff Pol, Casey, Giedd, Buitelaar, & van Engeland, 2001), important progressive and regressive developmental processes continue throughout adolescence, including myelination (Jernigan & Gamst, 2005; Giedd, Blumenthal, Jeffries, Castellanos, Liu, Zijdenbos, Paus, Evans, & Rapoport, 1999), synaptic refinement (Huttenlocher, & Dabholkar, 1997), reductions of grey matter volumes (Sowell, Trauner, Gamst, & Jernigan, 2002; Gogtay, Giedd, Lusk, Hayashi, Greenstein, Vaituzis, Nugent, Herman, Clasen, Toga, Rapoport, & Thompson, 2004; Giedd et al., 1999) and improved cognitive and functional efficiency (Casey, Giedd, & Thomas, 2000; Durston, Davidson, Tottenham, Galvan, Spicer, Fossella, & Casey, 2006). It is unclear how heavy marijuana use at this time could influence neural development. The long-term effects of marijuana have not yet been determined, but could potentially have major implications on social, academic, and occupational functioning.

Although a good deal of research has been done on the effects of marijuana in chronic adult users, very little is known about adolescent users. Studies have shown that chronic marijuana has an influence on the neuropsychological performance of adults within a week of use. Specifically differences have been found in attention and executive functioning (Pope, & Yurgelun-Todd, 1996; Bolla, Brown, Eldreth, Tate, & Cadet, 2002), memory (Pope, Jacobs, Mialet, & Yurgelun-Todd, 1997; Solowij, Stephens, Roffman, Babor, Kadden, Miller, Christiansen, McRee, & Vendetti, 2002), psychomotor speed and manual dexterity (Croft, Mackay, Mills, & Gruzelier, 2001). One study demonstrated verbal learning deficits among marijuana users compared to controls 0, 1, and 7 days following use, but that these impairments subsided after a 28-day abstinence period (Pope et al. 2001). However, others have identified impairments in memory, executive functioning, psychomotor speed, and manual dexterity after 28 days of verified abstinence compared to published norms (Bolla et al. 2002). Furthermore, adults who began use early in adolescence (before age 17) demonstrated greater decrements on verbal IQ after a 28-day abstinence period those who began late in adolescence (after age 17) and non-using controls, suggesting an adolescent vulnerability (Pope, Gruber, Hudson, Cohane, Huestis, & Yurgelun-Todd, 2003).

Due to its high safety profile and good spatial resolution, functional magnetic resonance imaging (fMRI) has become a powerful method for visualizing neural activation. Research on adult marijuana users has shown alterations in brain response via fMRI scanning. More specifically, these studies have demonstrated an increase in spatial working memory (SWM) brain response in marijuana users compared to normal age-matched controls in the pre-frontal cortex, anterior cingulate, and the basal ganglia (Kanayama, Rogowska, Pope, Gruber, & Yurgelun-Todd, 2004). This suggests a compensatory neural response as well as recruitment of additional brain areas to achieve necessary task requirements, as seen in a recent study of task performance and brain functioning in marijuana users (Quickfall & Crockford, 2006). However, because this study was done on adults who were abstinent for only 6-36 hours prior to the scan, it may be that these effects reflect recent use and not persisting effects (Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2001). Others have characterized visuospatial attention among 12 recent marijuana users who had used 2 – 24 hours earlier, 12 abstinent users who not used for an average of 38 months, and 19 non-using controls (Chang, Yakupov, Cloak & Ernst 2006). Both active and abstinent users showed decreased brain response in prefrontal, parietal, and cerebellar regions that normally subserve visual attention, and increased activation in alternate regions, suggesting brain response alterations even after extended abstinence. These adult fMRI studies point to altered neural functioning among marijuana using adults during visuospatial tasks, particularly in frontal and parietal regions.

Less is known about neurocognitive functioning in adolescent marijuana users. A longitudinal study of ten adolescent marijuana users showed incomplete recovery of learning and memory impairments even after six weeks of abstinence (Schwartz, Gruenewald, Klitzner, & Fedio, 1989). Recent fMRI studies of SWM involving alcohol-abusing adolescents and marijuana and alcohol-abusing adolescents have found that marijuana and alcohol were associated with greater changes than alcohol alone. Specifically, after an average of 8 days of abstinence, adolescent marijuana users showed an increase in dorsolateral prefrontal activation and reduced inferior frontal response compared to alcohol users and non-using controls, suggesting compensatory working memory and attention activity associated with heavy marijuana use during youth (Schweinsburg, Schweinsburg, Cheung, Brown, Brown, & Tapert, 2005). Adolescent marijuana users demonstrated increased right hippocampal activity and poorer attention and verbal working memory performance compared to demographically similar tobacco smokers and non-using controls, suggesting compensatory neural recruitment, even after a month of abstinence (Jacobsen, Mencl, Westerveld, & Pugh, 2004). In a follow-up study, marijuana-using youths who were abstinent at least two weeks performed similarly as non-users on verbal working memory during *ad libitum* smoking and again during nicotine withdrawal, but exhibited increased parietal activation and poorer verbal delayed recall during nicotine withdrawal compared to non-marijuana users (Jacobsen, Pugh, Constable, Westerveld, & Mencl, 2006). Together, these studies suggest altered working memory functioning among adolescent marijuana users that may persist after a month of abstinence. Yet it is unclear how variability in task performance might contribute to brain activation patterns.

Among normal adolescents, spatial working memory task performance is associated with activation in bilateral prefrontal and posterior parietal brain regions (Schweinsburg, Nagel, & Tapert, 2005; Thomas King, Franzen, Welsh, Berkowitz, Noll, Birmaher, & Casey, 1999; Klingberg, Forssberg, & Westerberg, 2002). Adult studies have suggested increased frontal and parietal activity associated with greater spatial working memory task difficulty (Diwadkar, Carpenter, & Just, 2000; Jansma, Ramsey, Coppola, & Kahn, 2000; Leung, Seelig, & Gore, 2004). FMRI studies of adolescent and adult marijuana users have suggested that increased neural responding associated with marijuana use may be evidence of compensatory neural recruitment to maintain task performance (Schweinsburg, Schweinsburg et al., 2005; Schweinsburg et al., submitted; Jacobsen et al., 2004; Jacobsen et al., 2006; Kanayama et al., 2004; Chang et al., 2006; Quickfall et al., 2006). Therefore, the relationship between task performance and neural response may differ between marijuana users and controls, with a stronger positive relationship among marijuana users. The interaction between task performance and fMRI response to SWM has not yet been studied in adolescent marijuana users.

The goal of the present study was to understand how task performance patterns contribute to neural activation in abstinent adolescent marijuana users. We studied blood oxygen level dependent (BOLD) fMRI neural activation during a SWM task which typically activates bilateral prefrontal and posterior parietal networks in adolescents and adults (Thomas et al., 1999; Schweinsburg, Nagel, & Tapert, 2005; Wager & Smith, 2003; Tapert et al., 2001; Tapert et al., 2004). This SWM task has been shown to be sensitive to brain response abnormalities in adolescent alcohol (Tapert, Schweinsburg, Barlett, Brown, Frank, Brown, & Meloy, 2004) and marijuana (Schweinsburg, Schweinsburg, et al., 2005; Schweinsburg et al., submitted) users. In this study, both adolescent users and controls were required to abstain from all drugs and alcohol for 28 days prior to their fMRI scan, and all were free from psychiatric disorders and learning disabilities.

Based on our previous work (Schweinsburg, 2005) we predicted that after 28 days of abstinence, marijuana users as a group would perform as well as controls; however, the task performance would vary within each group resulting in a group by task performance interaction that would be associated with brain response. Specifically, we hypothesized that there would be interactions between task performance and fMRI response in the bilateral dorsolateral prefrontal and posterior parietal cortices, such that marijuana users show a stronger positive association between performance and brain response than controls in these regions.

## Methods

### *Participants*

Flyers were distributed at local high schools, community colleges and universities to recruit 16- to 18-year-old adolescents (Tapert et al., 2003). Adolescent participants provided written informed assent (if age 16 or 17) or consent (if age 18) for their participation, and guardians (usually a parent) provided consent for youths under age 18, we well as consent for their own participation. This included an interview about their adolescent's health and development history. The University of California San Diego Human Research Protections Program approved this study. Participants were initially screened for eligibility and then were given a 45-minute phone interview to collect information about general health, psychiatric disorders, and lifetime substance use. Participant parents gave consent for their own participation and were interviewed for detailed information about family health history and prenatal conditions. The computerized NIMH Diagnostic Interview Schedule for Children Predictive Scale (DISC-PS-4.32b) (Lucas, Zhang, Fisher, Shaffer, Regier, Narrow, Bourdon, Dulcan, Canino, Rubio-Stipec, Lahey, & Friman P, 2001; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) was conducted separately with the youth and a parent to exclude adolescents with a potential psychiatric disorder (including conduct disorder, attention deficit-hyperactivity disorder, and substance use disorders). Other exclusion criteria included prenatal substance exposure, birth complications, psychotropic medication use, physical health problems, neurological dysfunction, head injury, family history of bipolar I or psychotic disorder (collected with the Family History Assessment Module screener; Rice et al., 1995), left-handedness, learning disability, or MRI incompatibility. Teens found to meet diagnostic criteria for alcohol use disorder were not excluded due to high comorbidity with marijuana use (Agosti, Nunes, & Levin, 2002). Two subjects, both in the marijuana group, met criteria for alcohol abuse.

Groups consisted of 17 heavy marijuana users and 17 non-using demographically similar controls. Users reported 477 episodes of lifetime marijuana use, on average, and control participants reported no more than five lifetime uses of marijuana. Groups were comparable in age, gender, ethnicity, family history of substance use disorders, and depressed and anxious mood (see Table 1). Marijuana users and control teens showed similar levels of IQ, as prorated by the Wechsler Abbreviated Scale of Intelligence Vocabulary and Block Design subtests (Wechsler, 1999; Ryan, Carruthers, Miller, Souheaver, Gontkovsky, & Zehr, 2005), and socioeconomic status (Hollingshead, 1965). Even though marijuana users reported more use of other drugs than controls, lifetime use of other drugs was less than 27 times across all substance types besides nicotine, alcohol, and marijuana. MJ users reported higher rates of alcohol than controls, and both groups had low rates of tobacco use (see Table 1).

### *Measures*

*Substance Use.* Substance intake was assessed using the Customary Drinking and Drug Use Record (Brown et al., 1998). Self-reported information was collected about lifetime and past three-month use of marijuana, alcohol, nicotine, and other drugs. Strong internal consistency, test-retest and inter-rater reliability have been shown with adolescent Customary Drinking and Drug Use Record assessments (Stewart, & Brown, 1995; Brown et al., 1998). The Timeline Followback was used to assess drug and alcohol use for the previous 28 days. Participants were asked to point out for each day whether they used or drank. If they disclosed use, they were to indicate how many hits of marijuana or drinks of alcohol they consumed (Sobell, & Sobell, 1992). “Drinks” were defined as one can of beer, one glass of wine or one shot of hard liquor to clarify amount of alcohol consumed. If asked, a “hit” of marijuana was defined as a puff from a pipe, bong, joint or vaporizer since smoking is the most common method of use.

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

*Psychopathological Syndromes.* Parents were interviewed about the child's internalizing and externalizing behaviors via the Child Behavior Checklist (Achenbach & Rescorla, 2001).

*Spatial Working Memory (SWM) Task.* This task (Tapert et al., 2001; Kindermann, Brown, Zorrilla, Olsen, & Jeste, 2004) consisted of 18 21-second blocks that alternated between resting fixation, vigilance, and working memory conditions (see Figure 1). Each block began by showing a one-second word cue that prompted the upcoming block. The resting fixation block began with the cue "LOOK" and subjects were asked to look at the fixation cross. Each vigilance block was prompted by the cue "DOTS" and subjects were asked to respond with a button press to figures that had a dot above them (30% of the figures). Before each working memory block, the cue "WHERE" appeared on the screen. During these blocks, abstract figures were individually shown in one of eight spatial locations, and subjects were instructed to respond with a button press every time a figure appeared in the same location as a previous figure had been within that block. Unknown to the subject, repeat location stimuli were 2-back, and composed 30% of stimuli. For both the vigilance and working memory conditions, stimuli were presented for 1000 ms, with an interstimulus interval of 1000 ms (21 seconds per block; total task time=7 minutes, 48 seconds; see Figure 1). All subjects were given practice with the task prior to entering the scanner and were monitored to ensure they understood the task instructions. Performance data were collected for accuracy and reaction time with a fiber optic response box.

### *Procedures*

*Toxicology.* The toxicology procedure was designed to ensure that participants would not use substances in the 28 days prior to the fMRI scan. Cannabis metabolites can reliably remain detectible in urine for at least four days (Fraser, Coffin, & Worth, 2002). Subjects were required to give a urine sample every three to four days each week during the 28 days prior to the fMRI session to make sure there was no recent use of cannabis, amphetamines, methamphetamines, benzodiazepines, cocaine, barbiturates, codeine, morphine, phencyclidine, and ethanol. Samples were collected and analyzed at the VA Medical Center using CEDIA DAU assays. Collections were observed to minimize the risk of participant tampering. Quantitative indices were tracked to determine if tetrahydrocannabinol (THC) metabolite levels decreased during the 28-day period. Participants who initially screened positive for cannabis were accepted and retained, as long as THC metabolite indices decreased continually throughout the 28 days. If participant's levels increased or if a positive screen was obtained after a negative screen, the participant was given the option to restart the 28-day abstinence period or was dropped from the study. All participants produced negative urine toxicology screens at the time of scanning. Breathalyzers checked for recent alcohol use prior to the fMRI scan.

*Imaging.* Anatomical and functional imaging data were acquired with a 1.5 Tesla General Electric Signa LX scanner (Milwaukee, WI). The high-resolution structural scan was collected in the sagittal plane using an inversion recovery prepared T1-weighted 3D spiral fast spin echo sequence (TR=2000 ms, TE=16 ms, FOV=240 mm, 256 x 256, resolution=0.94 x 0.94 mm x 1.33 mm, 128 continuous slices, acquisition time=8:36) (Wong, Luh, Buxton, & Frank, 2000). The functional scan was acquired in the axial plane using T2*-weighted spiral gradient recall echo imaging (TR=3000 ms, TE=40 ms, flip angle=90°, FOV=240 mm, 64 x 64, 19-21 slices covering the whole brain, slice thickness=7 mm, reconstructed in-plane resolution=1.88 × 1.88 mm, 156 repetitions).

### *Data Analyses*

*Task Performance.* SWM task reaction time and accuracy data were collected during scanning and composite scores were calculated to provide a single, comprehensive measure of performance and use fewer degrees of freedom in analyses, providing more statistical power (Rympa, Berger, & D'Esposito, 2002). Reaction-time data and accuracy measures were converted into z-scores, and reaction-time z-scores were subtracted from accuracy z-scores to compute the performance composite score. Using this approach, high accuracy would result in a high positive z-score, while low reaction time, which is better, would result in a high negative z-score. Therefore subtraction of the negative reaction time z-score from the positive accuracy z-score would yield a positive index indicating high overall performance

*Imaging Data.* Imaging data from each teen were processed as in our prior studies (e.g., Tapert et al, 2003, 2004; Schweinsburg et al, 2005) using Analysis of Functional NeuroImages (AFNI; http://afni.nimh.nih.gov/afni/; Cox,1996). Time series data were corrected for motion. Number of removed repetitions and average movement in each direction throughout the task were examined in relation to group, task, and interactions using correlational analyses. The average percent of repetitions removed for excessive motion during the task was 8%, resulting in 92% retained for analyses. There were no significant differences between groups in bulk motion in any of the six movement directions (roll, pitch, and yaw rotations; superior, left, and posterior displacements). The average rotational movement throughout the task for MJ users was 0.04, 0.14, and 0.05 degrees for roll, pitch, and yaw, respectively. In controls the average rotational movement throughout the task was 0.07, 0.13, and 0.06 degrees for roll, pitch, and yaw, respectively. Among MJ users, the average translational movement was 0.11, 0.05, and 0.08 mm for superior, left, and posterior, respectively; the average translational movement of controls was 0.14, 0.06, and 0.07 mm for superior, left, and posterior, respectively. There was a significant group difference in the roll direction ($t(32) = 2.35$, $p = 0.03$), although such movements were quite small.

Next, fMRI data were deconvolved with a reference function that coded the hypothesized BOLD signal for each task condition (see Figure 1; Ward, 2002; Cox & Jesmanowicz, 1999). Controlling for linear trends, spin history effects, and delays in hemodynamic response, we computed for each brain voxel a fit coefficient that represented the relationship between the observed and hypothesized signal change for contrasts between SWM and vigilance conditions (Friston, Williams, Howard, Frackowiak, & Turner, 1996). These functional datasets were warped into standard space (Talairach & Tournoux, 1988), resampled into 3 $mm^3$ voxels and smoothed with a 5 mm Gaussian filter.

*Statistical Analyses.* Regression analyses determined the variability in brain response accounted for by group, task performance, and their interaction. These group level analyses were performed in each voxel of the brain and examined the BOLD response contrast between SWM and vigilance. To control for Type I error, we only interpreted significant effects in clusters of 50 contiguous significant voxels ($p < .05$; 1358μl in volume), yielding an overall clusterwise $\alpha = .05$, determined by Monte Carlo simulations (Ward, 2000). Exploratory follow-up regression analyses were performed to determine the nature of the group by performance interaction.

## Results

### *Behavioral Performance*

SWM task performance data were available for all 34 subjects. The vigilance condition revealed an average accuracy of 97±1.84% for users and 96± 2.39% (mean±SD) for controls. Reaction times for vigilance were 623±42ms for users and 637±66ms for controls. The SWM condition demonstrated an average accuracy percentage of 94±5.26 in users and 93±6.11 for controls, and reaction times were 540±84.93 in users and 548±85.48 in controls. Independent samples t-tests to compare means showed no differences between the groups for both accuracy and reaction times in the vigilance and SWM conditions. The vigilance composite score was 0.51 ± 1.03 for users and -0.02 ± 1.74 for controls. For SWM, the MJ users scored 0.01 ± 1.29 and controls scored 0.27 ± 1.29. Within subjects analyses revealed that there was no significant difference in composite scores between vigilance and SWM conditions ($F(1,32) = 0.09$, $p < 0.76$), and no group by task condition (SWM vs. vigilance) interaction ($F(1,32) = 1.20$, $p < 0.28$). Between subjects analyses demonstrated no group differences ($F(1,32) = 0.21$, $p < 0.65$).

### *FMRI Response*

A main effect of group revealed that marijuana users showed significantly ($p < 0.05$) greater activation than controls in a cluster encompassing the right basal ganglia, as well as in a second cluster encompassing the right precuneus, postcentral gyrus, and superior parietal lobule (Brodmann's Area (BA) 7) and in the left precuneus and superior parietal lobule (BA 7). There was no region in which marijuana users demonstrated reduced activation compared to controls (Table 2).

Across all subjects, both users and controls, behavioral performance data positively predicted activation in seven clusters (see Table 2): (1) right middle temporal gyrus, parahippocampal gyrus, and inferior temporal gyrus; (2) right cerebellar tonsil; (3) right inferior parietal lobule, supramarginal gyrus, angular gyrus, and middle temporal gyrus; (4) left middle temporal gyrus and superior temporal gyrus; (5) left middle occipital gyrus, middle temporal gyrus, and inferior temporal gyrus; (6) right middle frontal gyrus; and (7) left middle frontal gyrus and inferior frontal gyrus. There were no regions in which performance was negatively associated with brain response (see Table 2).

A group by performance interaction was found in five clusters (see Table 2): (1) left superior temporal lobule, left superior temporal gyrus and left middle temporal gyrus; (2) right temporal gyrus and right uncus; (3) left anterior cingulate; (4) left uncus and left parahippocampal gyrus; and (5) right thalamus and right pulvinar. We observed positive associations between SWM response and task performance in users and negative associations for controls in the first ($F(3,30) = 7.92$, $p < 0.0001$; $R^2 = 36\%$; see Figure 2) and third ($F(3,30) = 6.33$, $p < 0.002$; $R^2 = 31\%$; see Figure 4) clusters. A negative association among users and positive association in controls was revealed in the second ($F(3,30) = 4.97$, $p < 0.006$; $R^2 = 27\%$; see Figure 3), fourth ($F(3,30) = 5.5$, $p < 0.004$; $R^2 = 35\%$; see Figure 5), and fifth ($F(3,30) = 4.39$, $p < 0.011$; $R^2 = 29\%$; see Figure 6) clusters.

There was a group difference in movement found in the right basal ganglia in the roll direction ($t(32) = 2.35$, $p = 0.03$). However, findings were re-examined using movement as a covariate, and all findings remained unchanged (*p*'s < .025). Performance and BOLD response data were checked for outliers, and none were found. Cases appearing as possible outliers on scatterplots were removed and analyses were redone; results remained unchanged. Both groups were checked for outliers on mood measures; although neither group contained an outlier on the BDI, the marijuana group contained one outlier on the Hamilton Anxiety Rating Scale. Analyses were re-run excluding this subject and results remained unchanged.

## Discussion

This study examined the association between behavioral performance and brain response during a SWM task among 16- to 18-year-old marijuana users and controls after 28 days of abstinence. Results suggest that, in general, marijuana-using teens performed similarly on SWM than controls, perhaps due to the low difficulty level of the task (only 8 spatial locations and 2-back working memory load), which approached ceiling effects. This has been observed in fMRI studies of SWM in adult marijuana users (Kanayama et al., 2004). However, specific localization and intensity of response varied between the MJ users and controls, with MJ users showing more performance-related activation in certain regions and less in others. These differential patterns emerged despite similar overall task performance across groups, suggesting an alternate relationship between task performance and brain activity among marijuana users.

MJ users showed significantly more activation than controls in the right basal ganglia, an area associated with skill learning (Halsband & Lange, 2006). Since the subjects were only allowed to practice the task once before entering the scanner, it is possible that the MJ users were still in the skill learning process during imaging. The other two clusters, which were significantly more activated in marijuana users than controls, were the right and left parietal lobes. Bilateral parietal regions have been implicated in attention, spatial perception, imagery, working memory, special encoding, episodic retrieval, skill learning monitoring, organization, and planning during working memory (Cabez & Nyberg, 2000; Wager & Smith, 2003). It is possible that there is compensatory neural effort in these areas, as observed in SWM studies of adult marijuana users (Kanayama et al., 2004).

The performance data positively related to activation in several areas, and did not negatively associate with brain response in any region. Performance was positively associated with activation in the left and right temporal regions, which are associated with verbal mechanisms and episodic, nonverbal working memory and retrieval, respectively (Cabeza et al., 2000). This suggests that good task performance may be related to using multiple memory modalities. High-scorers showed more activation in the bilateral prefrontal and bilateral parietal regions that have been shown to activate during SWM tasks in youths (Thomas et al., 1999; Schweinsburg at al., 2005).

The performance by group interactions were the focus of this study and yielded the most interesting results. In particular, an interaction in the left superior temporal gyrus suggested a positive association in the users and a negative association in the controls. This may imply that the MJ users used more of a verbal strategy to achieve high task performance scores than the controls. This is interesting when considering the previous findings of deficits in verbal learning and IQ in marijuana using adolescents compared to controls (Fried, Watkinson, & Gray, 2005).

Furthermore, the right superior temporal gyrus showed an interaction where users had a negative association and controls had a positive association. Previous studies have shown this area to be involved in poorer recognition of previously seen words (de Zubicaray, McMahon, Eastburn, Finnigan, & Humphreys, 2005). This would support the notion that users are relying on a verbal strategy so that better performance linked to a *decrease* in activation in the right superior temporal gyrus. Moreover, an interaction in the right thalamus and pulvinar showed a negative association in the users and a positive association in the controls. These subcortical structures have shown an association with spatial neglect when damaged (Karnath, Himmelbach, & Rorden, 2002). It is interesting that these areas have a negative association in users and a positive association in controls, and may suggest that marijuana users utilize less spatial strategies than controls.

The nature of the interaction revealed a positive association in marijuana users and a negative association in controls in the left anterior cingulate. This region has been linked to attention, decision-making, cue response, and response monitoring (Ansari, Fugelsang, Dhital, & Venkatraman, 2006; Dosenbach, Visscher, Palmer, Miezin, Wenger, Kang, Burgund, Grimes, Schlaggar, & Petersen, 2006). It may be that good performing marijuana users are making a more conscious decision to react to task cues than controls, who may be reacting more automatically. The left parahippocampal gyrus demonstrated an interaction of negative association in marijuana users and positive association for controls. This region is involved in working memory and is recruited when the temporal lobe is not in use (Yetkin, Rosenberg, Weiner, Purdy, & Cullum, 2006). Since marijuana users are using more energy in the left temporal lobe as their performance increases, higher scoring subjects may rely less on the parahippocampal gyrus.

The distinct interactions viewed in these different areas of the brain can mean that different systems are at work, and as one part of a system decreases in action, the other area of the system increases in activation. Previous studies suggest that subjects who do not use traditional strategies for specific tasks showed an increased extent of activation and recruitment of additional areas, specifically verbal areas, to accomplish the task (Yetkin et al., 2006; Kindermann et al., 2004). More specifically, the pattern of results suggests that marijuana users may apply a verbal strategy to the task when achieving higher scores. It is possible that this alternative way of using the brain may be less efficient; this would explain the greater overall activation in users versus controls and recruitment of other brain regions as a compensation method. A recent review also found that multiple neuroimaging studies of marijuana users pointed toward recruitment of compensatory regions as well as task-related regions to achieve task demands (Quickfall et al., 2006).

A possible limitation to this study is the interpretation of a difference in fMRI activation between experimental groups. It is possible that alternative neural pathway use is more dynamic and versatile. It is unclear whether the results are an adverse effect of the marijuana use or merely a benign difference. Further studies that more carefully describe the relationships between task performance and brain response will clarify this question. Another limitation of the current study is that most marijuana users were also moderately heavy alcohol drinkers. While these participants are representative of the population of adolescent marijuana users, most of whom also consume alcohol (Agosti et al., 2002), it is nonetheless difficult to disentangle the effects that may be related to alcohol use. Alcohol use correlated with brain response in the right thalamus and pulvinar in the current study, but results remained significant even when accounting for alcohol use, and alcohol use did not correlate to activation in any other significant regions. Our previous research identified brain response abnormalities among marijuana users above and beyond those demonstrated by users of alcohol alone (Schweinsburg, Schweinsburg et al., 2005), supporting the hypothesis of marijuana-specific differences in brain response, even among teens who are heavy drinkers. Future studies should attempt to clarify the differential and interactive impact of concomitant alcohol and marijuana use on brain functioning on adolescents. Furthermore, lifetime marijuana use episodes were associated with activation in the right uncus and superior temporal gyrus. Future analyses could further investigate the associations of other brain regions, as well as neuropsychological performance, with lifetime use episodes. These subtle differenced among users may provide additional insight into the mechanisms involved with prolonged abstinence from marijuana.

Future studies should also focus on investigating the nature of interactions in other domains of cognition to test if other types of tasks show these patterns. A more complex task should be an aim for future studies because it may elicit a difference in task performance. If a user's neural differences are actually a compensatory tool, then a more difficult task may overcome their compensation abilities, therefore resulting in performance deficits. In addition, a parametric manipulation of working memory load could help specify degree of compensatory activation in marijuana users compared to controls, as marijuana users may reach a limit earlier than controls. Further studies could also explore which mechanisms and strategies subjects utilize during the tasks through qualitative data investigation.

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*Tab1e 1.* Characteristics of Adolescent Participants

| | MJ<br>(*n*=17)<br>M (SD) or % | Controls<br>(*n*=17)<br>M (SD) or % |
|---|---|---|
| Age (range 16 – 18) | 18.06 (0.75) | 17.9 (1.12) |
| % Female | 18% | 29% |
| % Caucasian | 77% | 71% |
| % Family history negative [a] | 53% | 77% |
| CBCL Externalizing T-score | 47.31 (5.73) | 44.48 (7.05) |
| CBCL Internalizing T-score | 46.74 (7.57) | 46.89 (8.83) |
| Beck Depression Inventory | 4.41 (7.07) | 1.76 (2.59) |
| Spielberger State Anxiety T-score | 38.04 (8.39) | 40.74 (10.20) |
| Parent annual salary (thousands) | 116.35 (84.03) | 121.00 (73.50) |
| WASI Vocabulary T-score | 55.53 (8.74) | 55.53 (7.93) |
| WASI Block Design T-score | 59.82 (5.67) | 54.35 (11.19) |
| Lifetime alcohol use episodes* | 147.35 (125.26)* | 9.94 (30.71)* |
| Average cigarettes per day | 1.59 (1.67) | 0.35 (7.21) |
| Lifetime marijuana use episodes* | 477.06 (260.07)* | 0.53 (1.33)* |

MJ: marijuana using teens with 28 days of abstinence; CBCL: Child Behavior Checklist; WASI: Wechsler Abbreviated Scale of Intelligence.

*$p<0.0001$

*Table 2*. BOLD Response Differences to the Spatial Working Memory Task Between Abstinent Marijuana Users and Control Adolescents

| Anatomic Region | Brodmann's Area | Volume (µl) | Talairach Coordinates [a] x | y | z | t statistic [b] |
|---|---|---|---|---|---|---|
| Main Effect for Group | | | | | | |
| MJ > Controls | | | | | | |
| Right claustrum, putamen, caudate, thalamus, globus paladus, insula, globus paladus | -- | 3024 | 32R | -17P | 12S | 2.27 |
| Right precuneus, superior parietal lobule, postcentral gyrus | 7 | 2943 | 8R | -53P | 69S | 4.47 |
| Left superior parietal lobule, precuneus | 7 | 2133 | -11L | -65P | 63S | 4.29 |
| Main Effect for Performance | | | | | | |
| Positive Relationship | | | | | | |
| Right middle and inferior temporal gyrus, parahippocampal gyrus | 20, 21, 36 | 8802 | 62R | -41P | -4I | 3.17 |
| Right cerebellar tonsil | -- | 5184 | 8R | -32P | -46I | 7.07 |
| Right inferior parietal lobule, supramarginal gyrus, angular gyrus, middle temporal gyrus | 39, 40 | 4131 | 41R | -53P | 51S | 2.56 |
| Left middle and superior temporal gyrus | 21, 22 | 3267 | -56L | -41P | -1I | 2.99 |
| Left middle occipital gyrus, middle and inferior temporal gyrus | 37, 39 | 1512 | -50L | -62P | -7I | 2.48 |
| Right middle frontal gyrus | 9 | 1458 | 47R | 14A | 33S | 3.40 |
| Left middle and inferior frontal gyrus | 47 | 1404 | -50L | 35A | -4I | 3.27 |
| Interaction of Group × Performance | | | | | | |
| Left superior temporal lobule, superior and middle temporal gyrus | 13, 41 | 2700 | -59L | -41P | 6S | 2.71 |
| Right superior temporal gyrus, uncus | 38 | 2187 | 32R | 2A | -34I | 3.70 |
| Left anterior cingulate | 32 | 1917 | -2L | 26A | 4S | 5.30 |
| Left uncus, parahippocampal gyrus | 28, 35 | 1593 | -23L | -8P | -28I | 3.62 |
| Right thalamus | -- | 1539 | 23R | -29P | 6S | 1.75 |

MJ: 28-day abstinent marijuana using teens; SWM: spatial working memory

[a] Talairach coordinates refer to maximum signal intensity group difference or relationship within the cluster; R, right; L, left; A, anterior; P, posterior; S superior; I, inferior.

[b] *t*-statistic represents maximum intensity *t*-value of all voxels within the cluster

# Figure Captions

*Figure 1*. The spatial working memory task design.

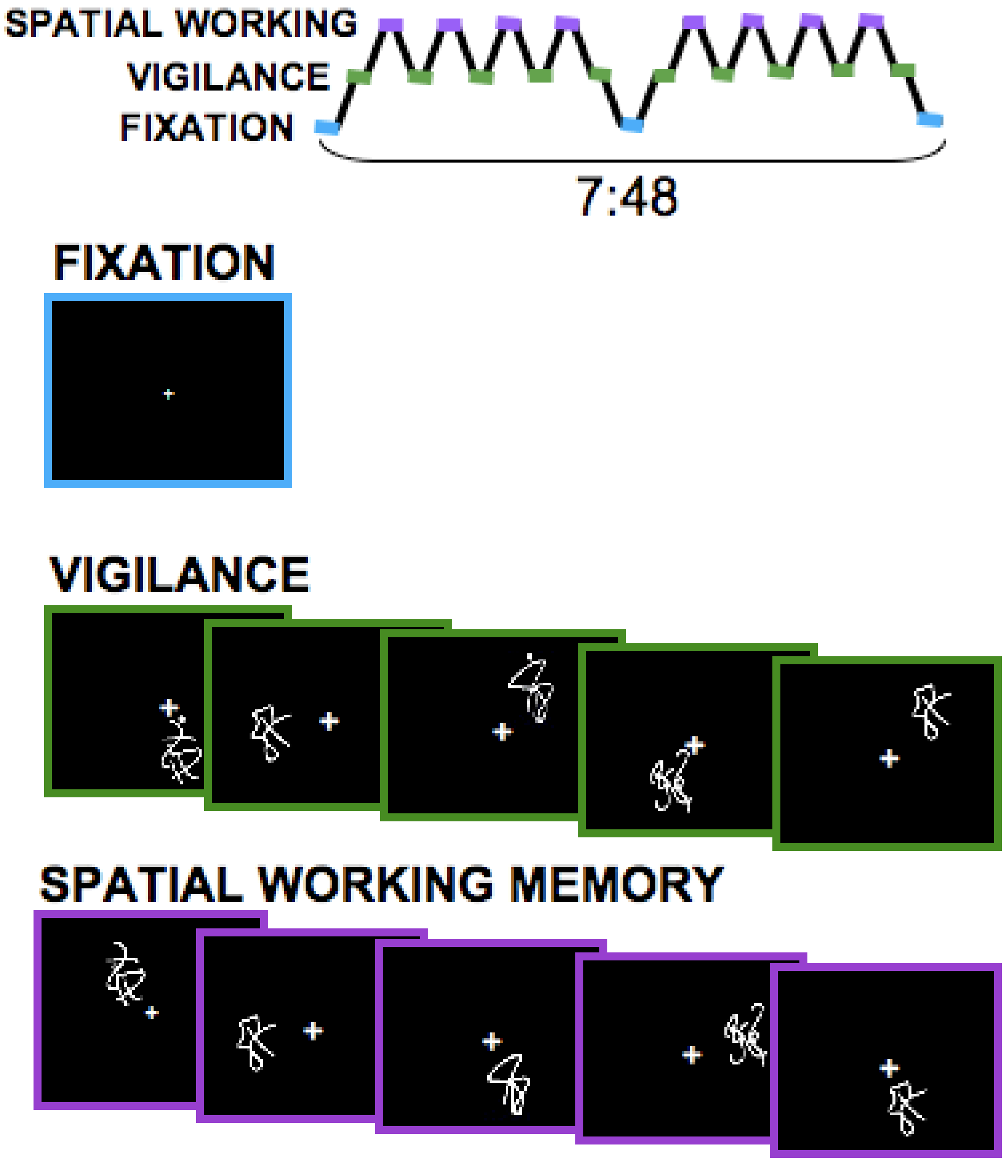

*Figure 2*. BOLD response interactions to the spatial working memory task in the left superior and middle temporal gyrus.

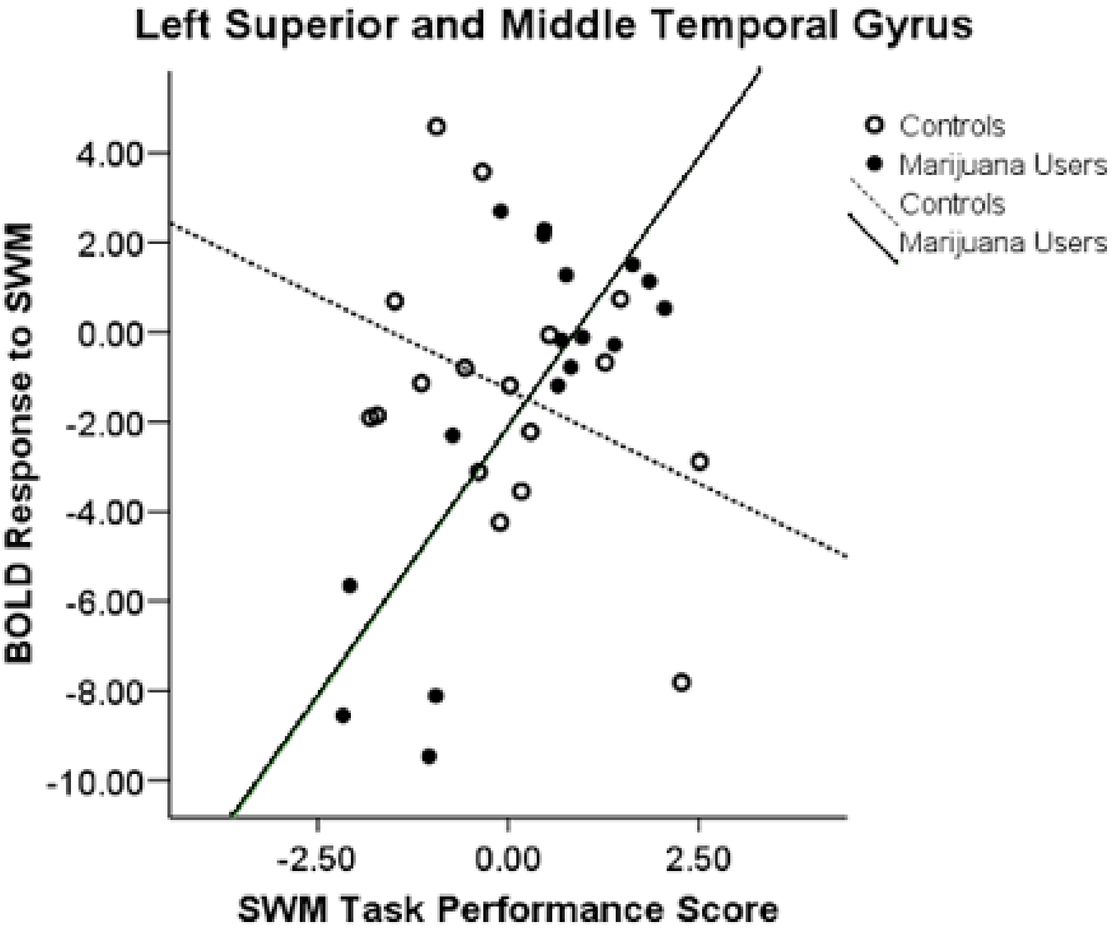

*Figure 3.* BOLD response interactions to the spatial working memory task in the right uncus and superior temporal gyrus.

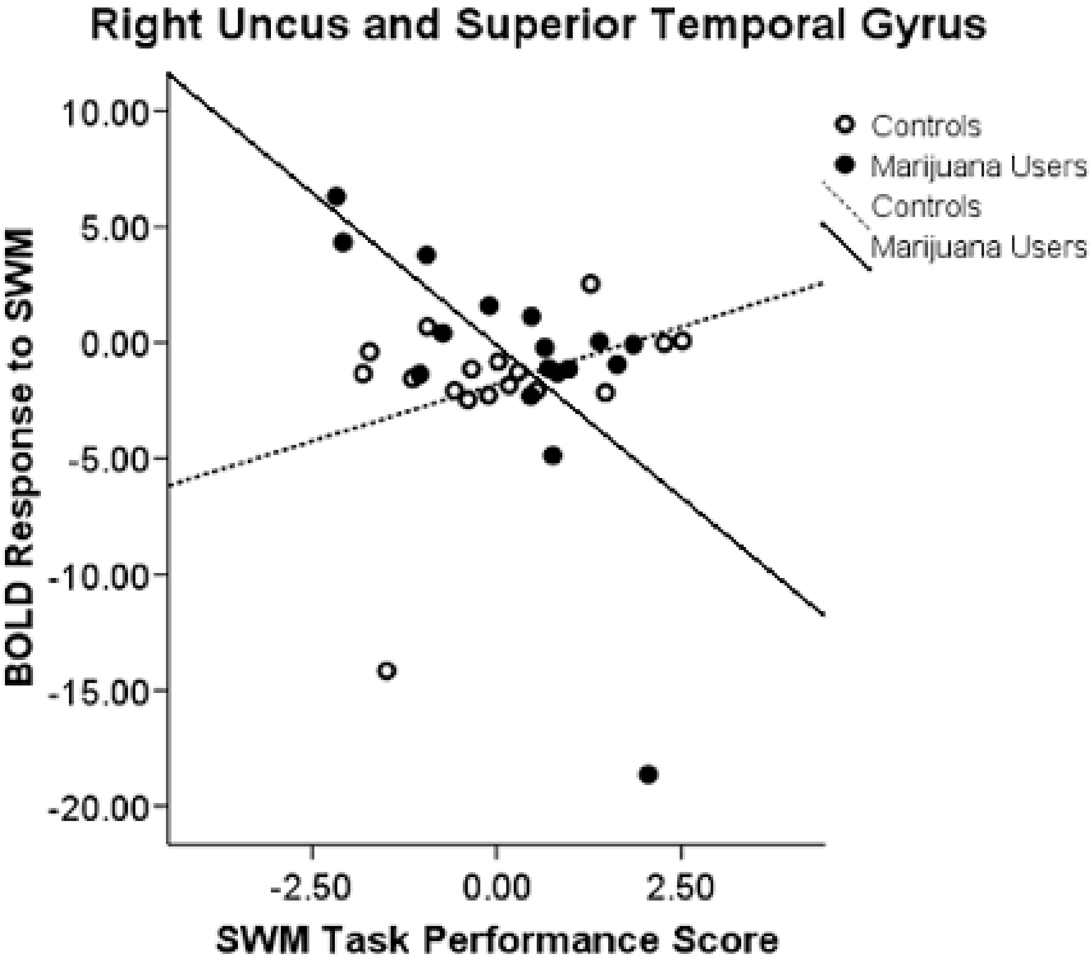

*Figure 4*. BOLD response interactions to the spatial working memory task in the left anterior cingulate.

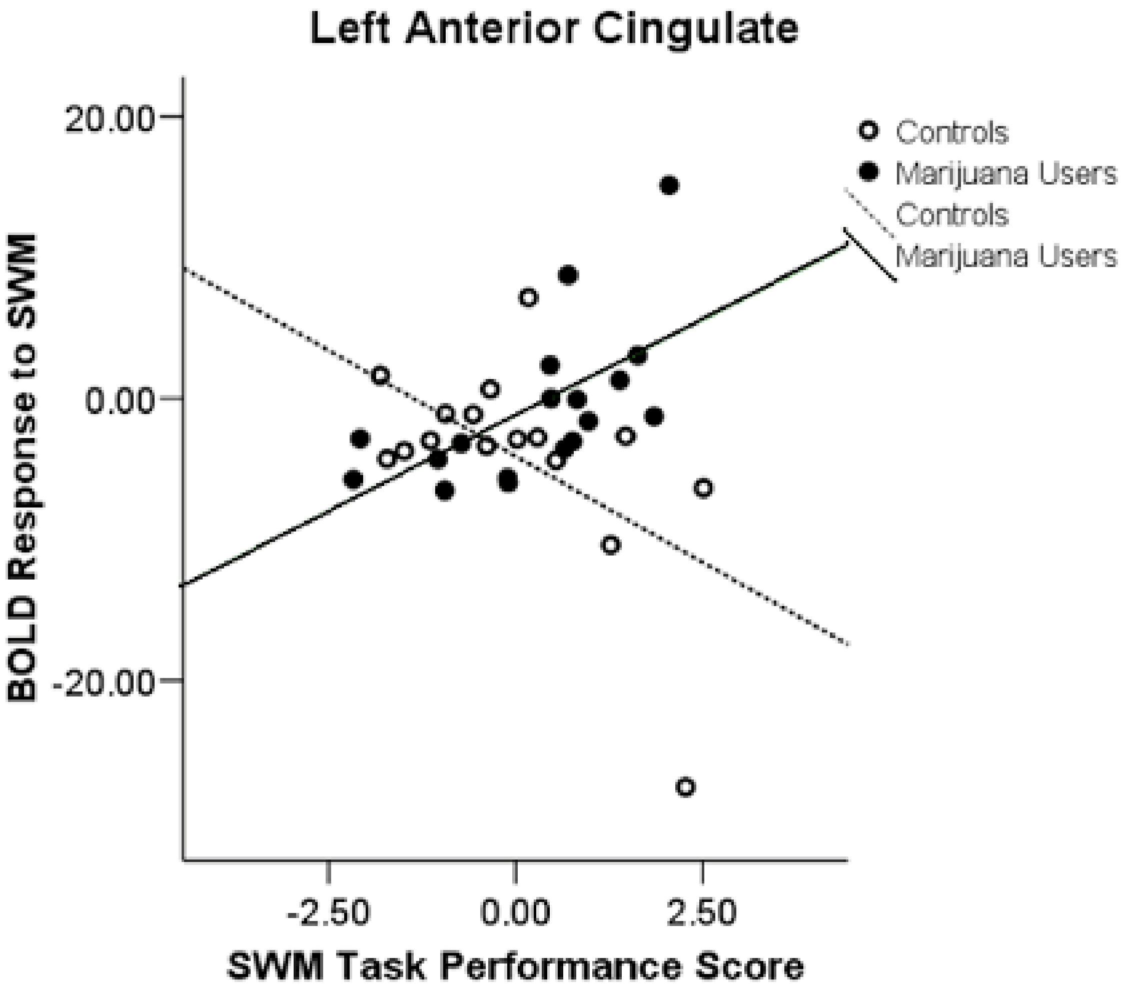

*Figure 5*. BOLD response interactions to the spatial working memory task in the left uncus and parahippocampal gyrus.

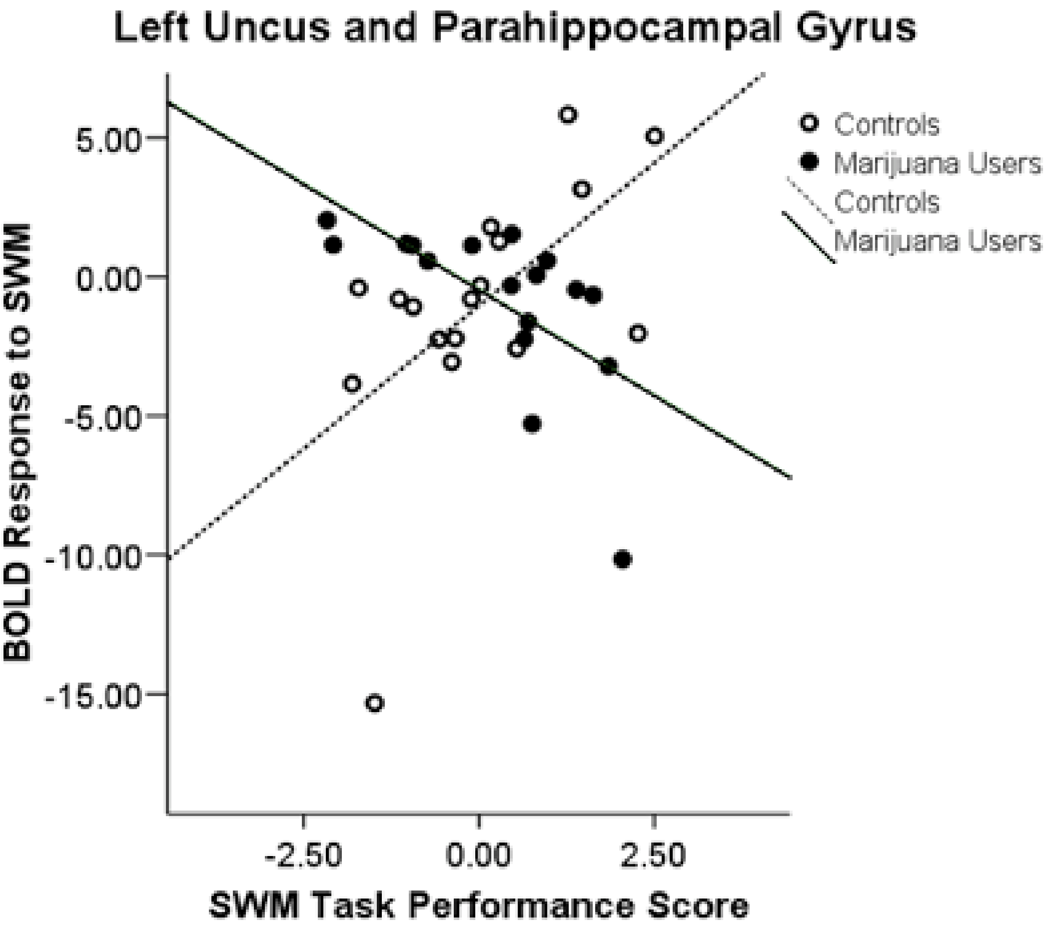

*Figure 6*. BOLD response interactions to the spatial working memory task in the right thalamus.