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ORIGINAL INVESTIGATION

Effects of marijuana on visuospatial working memory: an fMRI study in young adults

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Abstract
Objectives The effects of marijuana use on visuospatial working memory were investigated in 19–21-year-olds using functional magnetic resonance imaging (fMRI).
Methods Participants were members of the Ottawa Prenatal Prospective Study, a longitudinal study that collected a unique body of information on participants from infancy to young adulthood including: prenatal drug history, detailed cognitive/behavioral performance, and current and past drug usage. This information allowed for the measurement of an unprecedented number of potentially confounding drug exposure variables including: prenatal marijuana, nicotine, alcohol, and caffeine exposure and offspring alcohol, marijuana, and nicotine use. Ten marijuana users and 14 nonusing controls performed a visuospatial 2-back task while fMRI blood oxygen level-dependent response was examined.
Results Despite similar task performance, marijuana users had significantly greater activation in the inferior and middle frontal gyri, regions of the brain normally associated with visuospatial working memory. Marijuana users also had greater activation in the right superior temporal gyrus, a region of the brain not typically associated with visuospatial working memory tasks.
Conclusions These results suggest that marijuana use leads to altered neural functioning during visuospatial working memory after controlling for other prenatal and current drug use. This alteration appears to be compensated for by the recruitment of blood flow in additional brain regions. It is possible that this compensation may not be sufficient in more real-life situations where this type of processing is required and thus deficits may be observed. Awareness of these neural physiological effects of marijuana in youth is critical.

Keywords Visuospatial working memory · Marijuana · Executive functioning · Functional magnetic resonance imaging

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Introduction

Marijuana continues to be the most commonly used illegal drug in the world, with almost 160 million people, aged 15–64, reporting having used marijuana in the last year (World Drug Report 2007). Although the marijuana plant contains several hundred compounds, its most psychoactive ingredient is THC or delta-9-tetrahydrocannabinol (Mechoulam and Gaoni 1967). Research has found that THC binds to CB1 receptors, which are located in various concentrations throughout the brain, with high densities found in the frontal regions of the cerebral cortex and in the hippocampus (Devane et al. 1988; Herkenham et al. 1990). The frontal cortex is responsible for executive functioning processes such as decision making, planning, problem solving, focused attention, response inhibition, cognitive

flexibility, and working memory (Denkla 1993; Fuster 1997). The hippocampus is also involved in several types of memory, including spatial memory (Glikmann-Johnston et al. 2008). Of particular importance, due to its utility in much of daily living, is visuospatial working memory. This refers to the processes involved in the storage and manipulation of visuospatial information for a short amount of time, followed by its retrieval (Baddeley 1999). It is important to determine if marijuana use affects this type of executive functioning, especially during such a significant developmental window of prefrontal cortex growth as the teenage/young adult years. Visuospatial working memory is not only subserved by the frontal cortex and the hippocampus but also the parahippocampal gyrus, posterior parietal cortex, precuneus, and fusiform gyrus (Maguire et al. 1998, 2000; Aguirre et al. 1996; Ploner et al. 2000; Shipman and Astur 2008). Due to the high concentration of CB1 receptors in regions of the brain responsible for visuospatial working memory, it is not surprising that a considerable body of neurocognitive research has found that both acute and nonacute marijuana users show visuospatial working memory deficits compared to controls (Harvey et al. 2007; Ilan et al. 2004; Pope et al. 2001; Schwartz et al. 1989). However, the neural-cognitive effects of marijuana use are not consistent or well established in the literature and thus controversy still exists with respect to its effects on the neural underpinnings of cognitive processing ability.

Most recently, functional magnetic resonance imaging (fMRI) has been used to shed light on the neural mechanisms that underlie visuospatial working memory deficits among marijuana users (Kanayama et al. 2004; Chang et al. 2006; Schweinsburg et al. 2008). Evidence from fMRI research conducted on healthy controls has found that visuospatial working memory depends upon prefrontal and parietal cortical integrity, specifically, the inferior and middle frontal gyri, the inferior and superior parietal cortex, and the precuneus (Pfefferbaum et al. 2001). Other areas involved include the cingulate gyrus, the premotor cortex, and the occipital gyrus (Pfefferbaum et al. 2001).

Using fMRI, Kanayama et al. (2004) compared neural activity among long-term heavy marijuana users and controls, during a spatial working memory task. Despite no significant differences between the two groups on task performance, the marijuana group showed greater activation than controls in the inferior, superior, and middle frontal gyri, precentral gyrus, and anterior cingulate, regions of the brain typically associated with tasks requiring spatial working memory. Marijuana users also showed hyperactivity in regions of the caudate, putamen, and superior temporal gyri, areas of the brain not commonly linked with spatial working memory tasks. Using a visual spatial attention task and fMRI, Chang et al. (2006) compared brain activity among active marijuana users, abstinent marijuana users, and nonusing controls. They found that although task performance was similar, both active and abstinent marijuana users showed less activation in the right prefrontal region, the dorsal and medial parietal regions, and the medial cerebellum compared to controls. However, both marijuana groups showed greater activation than controls in various alternate regions. Similarly, Schweinsburg et al. (2008) found that during a spatial working memory task, abstinent marijuana-using teens showed less activity in the middle frontal gyrus but greater activity in the superior parietal lobule compared to nonusing adolescents despite similar task performance. Taken together, these studies show that marijuana use and exposure leads to altered patterns of brain activity during visuospatial working memory, frequently in the absence of observed performance differences compared to control participants. However, a consistent pattern of activation has yet to be determined and thus a full understanding of the effects of marijuana on neural processing during visuospatial working memory has yet to be attained.

There are several limitations in these studies that may explain why the results are not consistent. First, Kanayama et al. (2004) failed to measure lifetime consumption of alcohol and nicotine use in the control group although this information was available for the marijuana group. Second, despite measuring for alcohol and nicotine use, Chang et al. (2006) did not test for between group differences in these substances, introducing the possibility that these drugs, with known influences on brain activity, may be confounding the results (Jacobsen et al. 2007; Tapert et al. 2004).

These limitations have been addressed in the present paper by the use of participants from the Ottawa Prenatal Prospective Study (OPPS) for whom extensive background information was available. The OPPS is an ongoing longitudinal investigation initiated in 1978, with the primary objective of examining the effects of "soft" prenatal drug exposure on offspring. Children were followed from infancy to young adulthood and detailed information has been collected on their prenatal drug exposure, current and past drug use, cognitive/behavioral performance, and over 4,000 lifestyle variables. Full details on the recruitment of women early in their pregnancies, the determination of their drug use (Fried et al. 1980), and findings for the children from birth to adolescence have been published elsewhere (Fried 2002a, b; Fried et al. 1998, 2003).

The objective of the present study was to examine fMRI blood oxygen level-dependent (BOLD) response among current marijuana users and nonusing controls during a visuospatial 2-back task, using OPPS participants. This information allowed for the measurement of an unprece-

dented number of potentially confounding drug exposure variables including: prenatal marijuana, nicotine, alcohol, and caffeine exposure and offspring alcohol and nicotine use. It was hypothesized that despite similar task performance, marijuana users would require greater activation than controls in regions that typically subserve visuospatial working memory to successfully perform the task, including the prefrontal cortex.

Method

Participants

Participants were recruited from the OPPS and signed an informed consent prior to inclusion in the study. This study was approved by The Ottawa Hospital ethics board in agreement with the ethical standards laid down in the 1964 Declaration of Helsinki. Ten marijuana users (six males, four females, mean age 20, range of ages 19–21) and 14 nonusing controls (nine males, five females, mean age of 20, range of ages 19–21) were imaged. Current marijuana use was defined as regular use of marijuana cigarettes per week (>1 joint/week). The current marijuana group reported using an average of 11.48 marijuana joints per week (range of 2–37.5 joints/week) on a regular basis and had been smoking marijuana for an average of 4.55 years. This would approximate the lifetime use for this group of an average of 2,697 joints smoked. Previous publications have considered 180–1,844 lifetime occurrences of marijuana as heavy exposure (Bava et al. 2009). Alternatively, the nonusing control group reported never using marijuana regularly. Sporadic marijuana use was reported by three of the 14 controls but on no more than one to four occasions in the past year. No participants, from either group, had used other illicit drugs on a regular basis or within the month prior to testing. The illicit drug categories included were amphetamines, crack, cocaine, heroin, mushrooms, hashish, lysergic acid, steroids, solvents, and tranquilizers. Seven of the ten marijuana users smoked nicotine cigarettes on a regular basis while no participants from the nonusing control group smoked cigarettes on a regular basis. This has been controlled for in the statistical analysis.

Participants from both groups were right handed, had English as his/her first language, and were between the ages of 19 and 21. All participants were from middle-class homes, and no parents of the participants were reported to have an Axis I diagnosis from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association 1994). Participants previously completed a comprehensive psychological battery including, the Wechsler Adult Intelligence Scale-III (Wechsler 1997), the NEO Personality Inventory (Costa and McCrae 1989), and the Computerized Diagnostic Interview Schedule for Children (Bacon 1997), which assessed current psychiatric illness based on DSM-IV criteria. Parents also previously completed the Conners' Parent Rating Scale (Goyette et al. 1978) and provided information on socioeconomic status. No significant differences were found between current marijuana users and nonusers on these scales; therefore, they were not included in the fMRI analyses (see Table 1).

Participants completed a self-report drug questionnaire, which requested information on current and past marijuana use, as well as other drug use. Participants were not asked to abstain from drug use on the day of testing. Detailed information about participant's prenatal drug exposure was previously gathered (see Fried et al. 1980). Details of drugs used and prenatal exposure for each group are provided in Table 2. Significant differences were found between groups for current nicotine and alcohol use and again, have been addressed in the statistical analyses below. MRI compatibility was fulfilled by each participant whereby no participant had a pacemaker, metal implants, accidents leaving metal in eyes, recent surgery, metal dental work (aside from fillings), or insufficient vision for viewing the task. Participants were excluded if (a) they met DSM-IV criteria for an Axis I disorder using the C-DISC, (b) if they tested positive for cocaine, opiates, or amphetamines in their urine or self-reported regular use of any of these drugs (defined as once/month or more), (c) there was a contraindication to MRI, or (d) if there were any abnormalities in their structural MRI scans.

Measures

The task was presented to the participants on a back projection screen, located at the foot of the patient table, via a mirror attached to the head coil. All lighting in the scanning room was turned off. Button-press responses were recorded via a MRI-compatible fiber optic device (Lightwave Medical, Vancouver, British Columbia, Canada).

Visuospatial 2-back task

The visuospatial 2-back task was adapted from the standard n-back task (Cohen et al. 1997). The paradigm (see Fig. 1) consisted of the letter "O" presented in white on a black background at one of nine different positions on the screen. The "O" was displayed in this position for 75 ms before being relocated to one of the other nine positions. The task was a block design and included two conditions: a control condition (match to center) and a visuospatial working memory condition (2-back). The control condition began with the instruction "Match to Centre" on the screen for 4 s at the start of each control condition block. Each time the "O" was presented in the middle of the screen a button

Table 1 Environmental and IQ variables for current marijuana users and nonusing controls

Variable	Current marijuana users (n=10, mean (SE))	Nonusing controls (n=14, mean (SE))	Results (ANOVA)
Family income	31,610 (5367.65)	31,611 (4707.74)	$F(1,21)=0.00$ ($p<0.99$)
WAIS verbal IQ	106.10 (4.10)	116.53 (3.60)	$F(1,21)=3.66$ ($p<0.07$)
NEO neuroticism	44.50 (15.87)	46.00 (8.00)	$F(1,18)=0.08$ ($p<0.79$)
NEO extraversion	49.50 (17.85)	59.33 (7.44)	$F(1,18)=2.94$ ($p<0.10$)
NEO openness	49.88 (10.90)	57.33 (11.50)	$F(1,18)=2.10$ ($p<0.16$)
NEO agreeableness	45.88 (11.40)	54.75 (12.60)	$F(1,18)=2.55$ ($p<0.13$)
NEO conscientiousness	46.75 (13.97)	54.92 (13.79)	$F(1,18)=1.67$ ($p<0.21$)
Connors (learning problems)	0.17 (2.91)	−0.50 (2.42)	$F(1,20)=0.36$ ($p<0.55$)
Connors (impulsivity–hyperactivity)	0.21 (0.92)	−0.17 (1.07)	$F(1,20)=0.77$ ($p<0.39$)
Connors (anxiety)	−0.26 (0.34)	0.30 (1.13)	$F(1,20)=1.87$ ($p<0.19$)

No significant differences were observed between the groups for any variable

response with the right index finger was required (Fig. 1b). The visuospatial working memory condition began with the instruction "2-Back" on the screen for 4 s at the start of each visuospatial working memory condition block. Each time the "O" was presented in the same position that it was in two presentations before, a button response with the right index finger was required (Fig. 1c). There were also rest periods of 30 s at the beginning, middle, and end of the task. A white box was presented on the screen during these rest periods and no response was required.

Both the control (match to center) and visuospatial working memory condition (2-back) were comprised of 16 stimuli, presented every 2 s. The task allows for manipulation of the memory load by changing the instructions while maintaining all other features of the task including number of stimuli, number, and type of response of the same (Braver et al. 1997; Carlson et al. 1998; Pfefferbaum et al. 2001). This ensures that following the subtraction of the neural activity during the control condition (match to center) from that during the visuospatial working memory condition (2-back) only the neural activity involved in processing the visuospatial working memory information is observed in the statistical parametric maps. The order of blocks were counterbalanced with the control condition (match to center) followed by the visuospatial working memory condition (2-back) for three alternations, the middle rest period, and then three alternations with the visual spatial working memory condition (2-back) followed by the control condition (match to center) blocks (Fig. 1d).

Procedures

The marijuana using group was not required to abstain from smoking marijuana prior to scanning. All participants provided a urine sample upon arrival at the MRI unit. The urine sample was tested for cannabis, amphetamines, opiates, cocaine, creatinine, and cotinine. All metabolite concentrations were adjusted for creatinine to control for urine dilution. Participants completed a self-report drug questionnaire following the fMRI session to ensure the blindness of the fMRI researcher. The drug questionnaire and urine sample results were compared for validity of self-report current drug use.

Prior to commencing imaging, participants were required to view the visuospatial 2-back task outside the scanner and perform one block of the control condition (match to

Table 2 Drug exposure for marijuana users and nonusing controls

Drug exposure	Current marijuana users (n=10, mean (SE))	Nonusing controls (n=14, mean (SE))	Results (MANOVA)
Prenatal marijuana (joints/week)	8.82 (3.4)	1.12 (2.87)	$F(1,22)=2.99$ ($p<0.10$)
Prenatal nicotine (cigarettes/day)	10.41 (3.15)	3.09 (2.66)	$F(1,22)=3.14$ ($p<0.09$)
Current nicotine (cigarettes/day)	7.75 (1.29)	0.00 (1.09)	$F(1,22)=20.91$ ($p<0.001$)
Prenatal alcohol (AA/day)[a]	0.13 (0.10)	0.28 (0.08)	$F(1,22)=1.41$ ($p<0.25$)
Current alcohol (drinks/week)	4.77 (1.02)	2.00 (0.86)	$F(1,22)=4.48$ ($p<0.05$)
Prenatal caffeine (mg/day)	85.10 (29.96)	66.36 (25.31)	$F(1,22)=0.23$ ($p<0.64$)

[a] Ounces of absolute alcohol per day

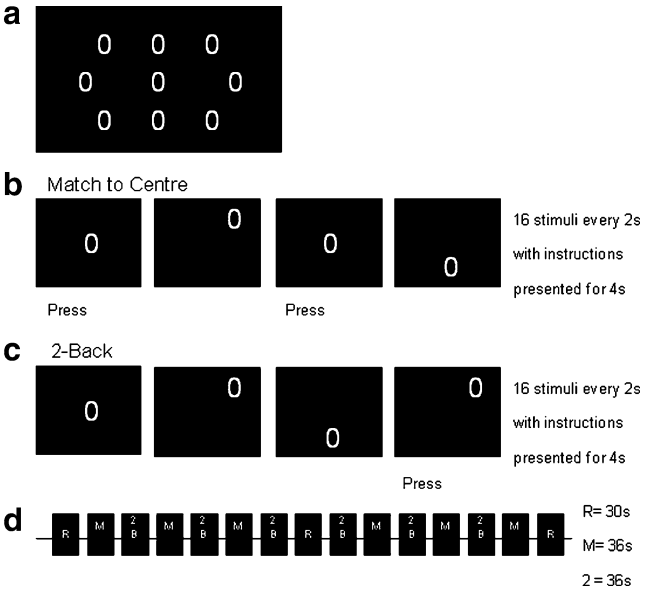

Fig. 1 **a** The nine positions where the zero stimulus was presented, one at a time. **b** An example of four stimulus presentations for the match to center condition with "Press" indicating where an appropriate response should occur. **c** An example of four stimulus presentations for the 2-back condition with "Press" indicating where an appropriate response should occur. **d** A time line for each of the blocks performed with *R* as the rest condition, *M* as the match to center condition and *2* as the 2-back condition. The *space between blocks* does not represent time, just a separation of blocks for ease of demonstration

center) and one block of the visuospatial working memory condition (2-back). This ensured that all participants were able to perform the task accurately. Participants were also instructed to press the button on the response device as quickly and as accurately as possible and, if they made a mistake, to continue without thinking about the mistake.

Imaging parameters

All imaging was performed using a 1.5 Tesla Siemens Magnetom Symphony MR scanner with the quantum gradient set (maximum amplitude=30 mT/m and slew rate=125 T/m/s). Subjects lay supine with their head secured in a standard MRI head holder. A conventional T1-weighted spin echo localizer was acquired and used to align the slice orientation for the fMRI scans such that the anterior commissure–posterior commissure line in the sagittal view was at right angles to the slice selection gradient. This localizer was also used to prescribe a subsequent three-dimensional FLASH (TR/TE 11.2/21 ms, flip angle 60°, field of view (FOV) 26 × 26 cm^2, 256 × 256 matrix, slice thickness 1.5 mm) volume acquisition used for further structural analyses. Whole brain fMRI was performed using a T2*-weighted echo planar pulse sequence (TR/TE 3,000/40 ms, flip angle 90°, FOV 24 × 24 cm^2, 64 × 64 matrix, slice thickness 5 mm, 27 axial slices, bandwidth 62.5 kHz).

Image postprocessing

Prior to statistical analyses, functional images from the first 9 s of the initial rest block were discarded to ensure that longitudinal magnetic relaxation (T1 effects) had stabilized. The remaining functional images were realigned to correct for motion by employing the procedures of Friston et al. (1995), using Statistical Parametric Mapping (SPM5) software. The motion correction did not exceed 1 mm for any subject. Images were spatially normalized to match the echo planar imaging template provided in SPM5. Following spatial normalization, images were smoothed with an 8-mm full-width at half-maximum Gaussian filter.

Behavioral performance parameters and analyses

Reaction time for each response, errors of commission, and omission were recorded. Errors of commission included any response following the presentation of a nontarget stimulus within 900 ms of stimulus presentation. Omission errors were defined as a failure to respond to a target stimulus within 900 ms. Mean reaction times were calculated for both the control condition (match to center) and the visuospatial working memory condition (2-back) for all accurate responses occurring within 900 ms of stimulus presentation. These data were analyzed with SPSS 15 using a MANCOVA with nicotine and alcohol as covariates.

Imaging whole brain analysis

All imaging analyses were performed using SPM5. Individual participant fixed effects analyses were performed for the comparison of the visuospatial working memory condition (2-back) minus the control condition (match to center). One contrast image was created per person, and these images were then used for second-level random effects analyses. Random effects analyses eliminate highly discrepant variances between and within individuals in constructing an appropriate error term for hypothesis testing and generalizability to the population. Due to the availability of information on each participant's drug use history and exposure, comparisons between the marijuana users and nonusers were performed using several two sample *t* tests. Prenatal marijuana has been shown to play a role in visuospatial working memory (Smith et al. 2006), and even though there was not a significant difference between groups for prenatal drug effects, it was deemed important to determine if in fact these exposures were impacting on the results of current marijuana use on neural functioning. Thus, two sample *t* tests were performed with nicotine and alcohol used as covariates, another was performed with only nicotine used as a covariate, and finally nicotine, as

well as prenatal marijuana and prenatal nicotine were used as covariates. In subsequent analyses, in an attempt to control for acute marijuana effects, each analysis was performed with only those participants who had not smoked on the day of testing and then again with all participants. Also, analyses were performed with and without the one nonuser who had smoked marijuana 3 days prior to testing.

Results

Drug questionnaire and urine sample data

All marijuana users had smoked marijuana within 1 week of fMRI testing, with four of the ten participants smoking marijuana on the day of testing (two participants smoked one joint in the morning while two smoked throughout the day as was typical for their regular use). The average urine cannabis at the time of testing for the group of ten using participants was 460 μg/L, with a range from 16 to 1,325 μg/L. One of the nonusers had smoked one joint 3 days prior to testing and had 45 μg/L in his urine; no other exposure was reported for the months prior to testing. No other nonuser showed cannabis in their urine. The average number of joints smoked by the using group for the 7 days prior to testing, for the using group, was 4.2, 4.55, 3.15, 2.75, 2.9, 4.6, and 4.35, and on the day of testing, the average use was 2.5 joints. The cotinine values for urine samples revealed an average value of 888 μg/L for the marijuana using group (seven of ten were cigarette smokers) while only 9.8 μg/L for the nonusing group (values may be present due to secondhand smoke exposure). The significant difference between groups for nicotine use was addressed in the statistical analysis and amount of nicotine use was used as a covariate for each analysis. No participant from either group reported alcohol consumption on the day of imaging. One of the marijuana using participants reported drinking 15 alcoholic drinks on the day prior to testing but no other participant reported more than seven drinks for the 2 days prior to testing. This eliminates the possibility that the results were related to the acute effects of alcohol consumption.

The Pearson correlation between the drug questionnaire results and the urine samples for levels of marijuana use was 0.97 ($p<0.001$) while that for nicotine (cotinine/creatinine) was 0.91 ($p<0.001$). This high concordance validated the use of the self-report drug questionnaire results for current use and drug history.

Behavioral performance data

There were no significant performance differences between marijuana users and nonusing controls on reaction time, errors of omission, and errors of commission while controlling for nicotine and alcohol use (Table 3).

Whole brain analysis

Fixed effects group analyses revealed a similar pattern of activation during the visuospatial n-back task for each group of participants. This demonstrates that the task was activating the expected brain regions, including inferior and superior parietal lobe, inferior and middle frontal gyri, premotor cortex, and cingulate gyrus. This analysis for the nonusing group is presented in Fig. 2. However, when comparing the groups in the random effects analysis, there were significant differences between them. Analyses for each of the performed two sample t tests yielded a similar pattern of activation difference between the groups. The results from the analyses with the additional covariates suggest that alcohol, prenatal marijuana, and prenatal nicotine exposure did not contribute to the differences between groups. Despite the poor power and uneven group sizes for the analyses that were performed to control for acute marijuana exposure (e.g., removing those participants who smoked marijuana on the day of testing and the one nonuser who smoked marijuana 3 days prior to testing), the results suggest that acute marijuana effects were not the contributing factor to the group differences. Thus, to increase the power of the study, only the results from the analysis with nicotine as a covariate and with all participants included are reported.

The most robust effect of this study was that marijuana users demonstrated significantly greater activation than nonusers, during the visuospatial working memory condition (2-back) minus the control condition (match to center), at a p value corrected for cluster level at 0.05 in a large cluster of 1,173 voxels, in the right inferior frontal gyrus (x,y,z=33, 36, −10; z=3.75), the left middle frontal gyrus (x,y,z=−27, 45, −15, Brodmann area 11, z=3.35), and the right superior temporal gyrus (x,y,z=36, 18, −40, Brodmann area 38, temporal pole, z=3.31; Fig. 3). Results also showed a trend toward greater activation for the marijuana group compared to nonusing controls for this contrast in the cingulate gyrus (x,y,z=12, −33, 25, z=3.42, uncorrected at 0.05; cluster size of 306 voxels).

Discussion

The present study examined fMRI BOLD response among current marijuana users and nonusing controls, from the OPPS, during a visuospatial working memory task. Despite similar task performance, significant group differences emerged in the BOLD response, with current marijuana

Table 3 Performance data for the two conditions of the visuospatial 2-back task for marijuana users and nonusing controls

Performance measure	Marijuana users (n=10, mean (SE))	Nonusing controls (n=14, mean (SE))	Results (MANCOVA)
Errors of omission (match to center)	0.00 (0.09)	0.09 (0.08)	$F(3,17)=0.41$ ($p<0.75$)
Errors of omission (2-Back)	6.77 (3.36)	3.57 (3.16)	$F(3,17)=2.23$ ($p<0.12$)
Errors of commission (match to center)	0.14 (0.39)	0.78 (0.37)	$F(3,17)=0.51$ ($p<0.68$)
Errors of commission (2-back)	0.68 (0.55)	1.02 (0.52)	$F(3,17)=0.19$ ($p<0.90$)
Reaction time (s, match to center)	0.47 (0.04)	0.50 (0.03)	$F(3,17)=0.58$ ($p<0.64$)
Reaction time (s, 2-back)	0.52 (0.06)	0.55 (0.05)	$F(3,17)=0.22$ ($p<0.88$)

users displaying significantly greater and more extensive activation than nonusers.

The most substantial effect of the study was that marijuana users demonstrated significantly greater activation during visuospatial working memory in the inferior and middle frontal gyri, compared to nonusing controls. These regions of the brain have been typically implicated in visuospatial working memory tasks along with other tests of executive functioning (D'Esposito et al. 1998; Ricciardi et al. 2006; Pfefferbaum et al. 2001). Our results are also consistent with those of Kanayama et al. (2004) who found that during a spatial working memory task, heavy marijuana users showed greater activation of brain regions normally used for this type of processing. In contrast, using a visual attention task, Chang et al. (2006) found that compared to controls, active and abstinent marijuana users had decreased activation in these regions. Schweinsburg et al. (2008) also found that during a spatial working memory task, adolescent marijuana users showed less activity in the middle frontal gyrus but more activity in the superior parietal lobule, compared to controls. However, the marijuana users in the Schweinsburg et al. (2008) study were abstinent for 1 month prior to testing, which could account for some of the inconsistencies with our study.

Taken together, our results have provided further evidence, with more control than previous studies, that regular marijuana use affects the brain by requiring increased effort to perform visuospatial working memory. This is also suggested by Kanayama et al. (2004) and Schweinsburg et al. (2008) who consider that marijuana users work harder than commonly required to perform visuospatial working memory tasks, evidenced by this greater activation in brain regions typically used to complete such tasks. Recently, Nagel et al. (2005) found that spatial working memory task performance negatively predicted fMRI BOLD response; participants with greater accuracy and faster reaction times required less neural resources to adequately perform the task. Although in the

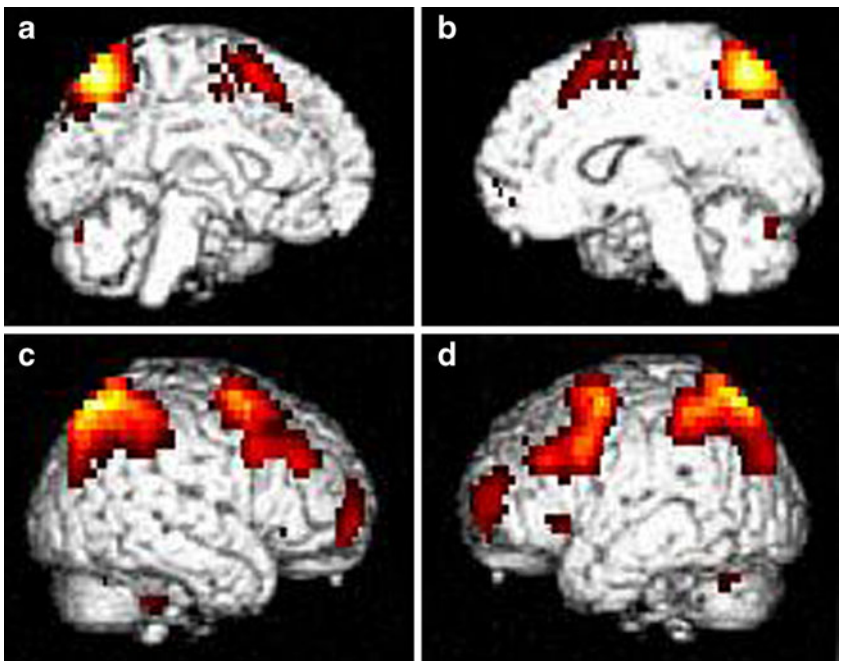

Fig. 2 Significant brain activation patterns for the first level analysis of the nonusing participants for the comparison of the 2-back condition minus the match to center condition (n=14). **a** and **b** represent *left* and *right medial sagittal views*, respectively. **c** and **d** represent *right and left lateral views*, respectively. Results are reported using a stringent FWE correction at p=0.001

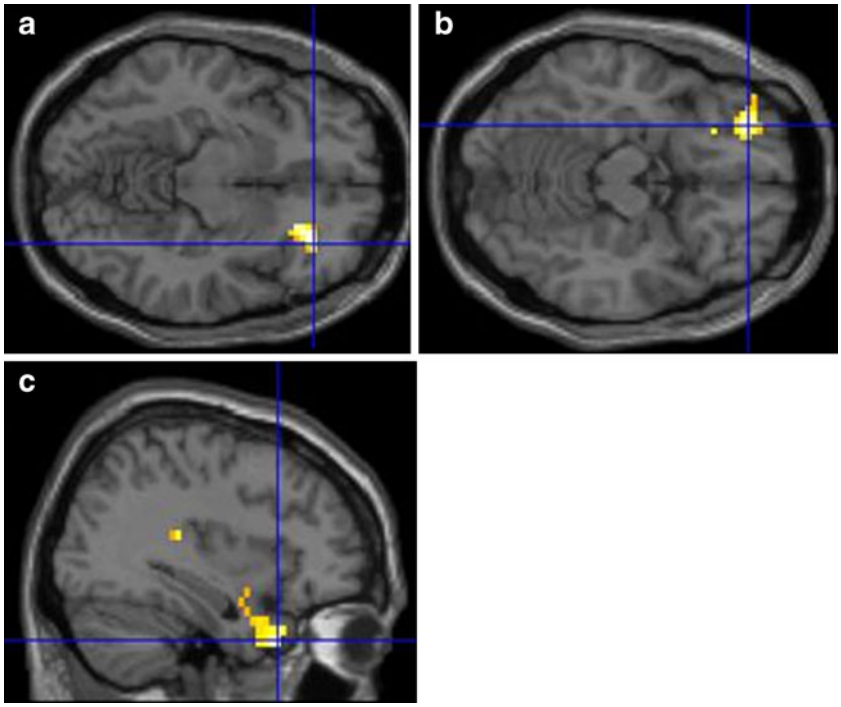

Fig. 3 *Blue cross hairs* indicate where marijuana users demonstrated significantly greater activation than nonusers during the visuospatial working memory condition (2-back) minus the control condition (match to center). **a** Right inferior frontal gyrus. **b** Left middle frontal gyrus. **c** Right superior temporal gyrus (right temporal pole)

present study there were no performance differences, most likely due to the relative simplicity of the task, greater activation among marijuana users in brain regions that generally subserve visuospatial working memory suggests deficits, as greater neural resources were required to adequately perform the task. Challenged with a harder task, current marijuana users may not be able to compensate and performance may suffer. Support for this can be derived from several neurocognitive studies which using more difficult tasks have found performance deficits among marijuana users compared to controls (Harvey et al. 2007; Ilan et al. 2004; Pope et al. 2001; Schwartz et al. 1989).

In addition to the areas typically activated during spatial working memory, marijuana users also showed greater activation during visuospatial working memory in the right superior temporal gyrus. The specific location of this difference was in the most anterior portion of the superior temporal gyrus, the temporal pole. This is not a brain region typically associated with visuospatial working memory (D'Esposito et al. 1998; Pfefferbaum et al. 2001; Ricciardi et al. 2006). These results are consistent with those of Kanayama et al. (2004), however, who found that compared to controls, marijuana users recruited several additional brain regions not characteristically used to perform spatial working memory tasks, including the superior temporal gyrus, caudate, and the putamen. Chang et al. (2006) also found that both marijuana groups had greater activation in several ancillary regions, including the superior temporal gyrus, when completing a visuo-attention task, compared to controls. The superior temporal gyrus results in the present study are considerably more anterior to the Kanayama and the Chang results, and include the temporal pole. This result has yet to be observed in an fMRI study of marijuana use in young adults. Typically, the temporal pole is considered a multimodal perceptual analysis area with multiple connections with the prefrontal cortex (Bava et al. 2009). Interestingly, using diffusion tensor imaging, studies have found altered white matter tracts in adolescent substance users in this area (Ashtari et al. 2009; Bava et al. 2009). These studies included both marijuana and alcohol users and thus are limited in their ability to focus on the effect of marijuana alone. However, these studies support the present result of a significant impact of regular marijuana use on the neural functioning of the temporal pole, and perhaps the connections between this area and the prefrontal cortex. Together, these results suggest that marijuana users require more neural resources to compensate for visuospatial working memory deficits and to perform the task successfully.

There was also a trend for marijuana users to show greater activity in the cingulate gyrus. The cingulate gyrus has important influences on attentional monitoring and has been shown to be involved in spatial working memory tasks (Luks et al. 2002; Pfefferbaum et al. 2001). These results are consistent with the findings of Kanayama et al. (2004) who also found that marijuana users showed greater activity in the anterior cingulate compared to controls, suggesting that marijuana users need to work harder to perform the task in order to compensate for neurophysiological deficits.

This study provides support for previous findings of the effects of early regular use of marijuana on neural processing

during visuospatial working memory. The strength of the paper is the use of the OPPS sample and thus the ability to control for such an unparalleled number of lifestyle variables, including drug use over the lifespan. This unique methodology strengthens the validity of the results and provides outcomes that are able to shed light on more exclusive contributions of marijuana on neural processing than previous studies. The finding of increased activity in the temporal pole of marijuana users also requires further investigation with the OPPS sample as it may provide further insight into the effects of marijuana on brain functioning.

Possible limitations of the study should be considered. First, the results cannot be generalized to other ethnic or socioeconomic status populations as the OPPS is primarily a Caucasian, middle-class population. Second, the present study used a block design rather than an event related design. A block design does not permit the separation of working memory from visuospatial processing or other cognitive processes. However, the design of the task, including the same motor output and sensory input for both conditions, ensured as much as possible that the only difference between the two cognitive tasks was visuospatial working memory. Third, there was no abstinence period for the participants of either group. This may have ensured that the results were indicative of the regular use of the drug rather than just the acute effect of marijuana on neural processing. However, rigorous statistical analyses were performed including and not including those participants who smoked marijuana on the day of testing. These subsequent analyses, despite having less power and more uneven number of participants per group than the reported results, did show similar group differences. This suggests that the reported results are not indicative of the acute marijuana effects but rather of the regular marijuana use of these participants. This accentuates the fourth limitation of sample size and the need for increased power in future studies that are currently underway to replicate these results with more OPPS participants.

Visuospatial working memory is but one aspect of executive functioning that has been shown to be impacted by marijuana use. fMRI studies examining additional facets of executive functioning have also found altered patterns of brain activity among marijuana users (for review see Chang and Chronicle 2007) during response inhibition, interference, monitoring, and verbal working memory tasks. Again, the ability to control for other drug effects is limited in these studies. Thus, future results from the OPPS participants, who performed three other tasks of executive functioning while in the scanner, will provide invaluable information on the effects of marijuana, controlling for other psychoactive drug use and exposures. These results will also be important to determine the risks that youth are taking when using marijuana on a regular basis during such a critical time in neural growth.

Comparing the results from the current paper with the Smith et al. (2006) study of the long-term effect of prenatal marijuana exposure on executive functioning provides interesting information on the effects of marijuana at different developmental stages. Smith et al. (2006) found that prenatal marijuana exposure was significantly related to greater activation in the left inferior and middle frontal gyri, left parahippocampal gyrus, left middle occipital gyrus, and the left cerebellum during the same visuospatial working memory task as was reported in the present paper. There was also significantly less activity in the right inferior and middle frontal gyri. The reported lateralization of effects was opposite for the prenatal versus the current use studies and different areas of the brain were affected in each study. This is of interest because it provides neuroimaging evidence that marijuana has a different effect on executive functioning dependent on the developmental stage when the exposure occurs. This was highlighted by using prenatal marijuana as a covariate in one of the analyses with the outcome suggestive that the prenatal exposure to marijuana was not impacting the effects of regular current use of marijuana in these participants. This will be addressed further in future articles using these OPPS participants.

In conclusion, using fMRI and a unique sample of participants, neural compensation in the prefrontal cortex and temporal pole was observed in young adults who use marijuana on a regular basis. This significant impact of marijuana on brain functioning at such a young age is important for future neural development and should be widely acknowledged and discussed in an attempt to reduce the possible long-term detrimental effects that early use may have on the brain.

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