ELSEVIER

Pharmacology, Biochemistry and Behavior 72 (2002) 237–250

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Effects of frequent marijuana use on memory-related regional cerebral blood flow

Robert I. Block[a,*], Daniel S. O'Leary[b], Richard D. Hichwa[c], Jean C. Augustinack[d,1], Laura L. Boles Ponto[c], M.M. Ghoneim[a], Stephan Arndt[b], Richard R. Hurtig[e], G. Leonard Watkins[c], James A. Hall[f], Peter E. Nathan[g], Nancy C. Andreasen[b]

[a]*Department of Anesthesia, University of Iowa, Room 5140, Westlawn Building, Iowa City, IA 52242, USA*
[b]*Department of Psychiatry, University of Iowa, Iowa City, IA 52242, USA*
[c]*Department of Radiology, University of Iowa, Iowa City, IA 52242, USA*
[d]*Department of Anatomy and Cell Biology, University of Iowa, Iowa City, IA 52242, USA*
[e]*Department of Speech Pathology and Audiology, University of Iowa, Iowa City, IA 52242, USA*
[f]*School of Social Work, University of Iowa, Iowa City, IA 52242 USA*
[g]*Department of Psychology, University of Iowa, Iowa City, IA 52242 USA*

Received 26 March 2001; received in revised form 8 November 2001; accepted 16 November 2001

Abstract

It is uncertain whether frequent marijuana use adversely affects human brain function. Using positron emission tomography (PET), memory-related regional cerebral blood flow was compared in frequent marijuana users and nonusing control subjects after 26+ h of monitored abstention. Memory-related blood flow in marijuana users, relative to control subjects, showed decreases in prefrontal cortex, increases in memory-relevant regions of cerebellum, and altered lateralization in hippocampus. Marijuana users differed most in brain activity related to episodic memory encoding. In learning a word list to criterion over multiple trials, marijuana users, relative to control subjects, required means of 2.7 more presentations during initial learning and 3.1 more presentations during subsequent relearning. In single-trial recall, marijuana users appeared to rely more on short-term memory, recalling 23% more than control subjects from the end of a list, but 19% less from the middle. These findings indicate altered memory-related brain function in marijuana users.

Keywords: Brain; Cerebellum; Chronic use; Hippocampus; Human; Marijuana; Memory; Positron emission tomography; Prefrontal cortex; Regional cerebral blood flow

1. Introduction

Marijuana has remained the most widely used illicit drug for decades. Adverse effects of frequent marijuana use on human brain function and cognition are of serious concern. Remarkably few studies have examined effects of frequent marijuana use on human brain function (Solowij, 1998), and many were conducted years ago with less sophisticated techniques.

In a previous study, we found that long-term, frequent (7+ times weekly) users of marijuana, relative to nonusing control subjects, showed impairments in some aspects of memory, as well as impairments on achievement tests assessing verbal expression and mathematics (Block and Ghoneim, 1993). This study, in contrast to virtually all other studies of mental abilities of drug users, controlled for the possibility that the marijuana users were poorer intellectually before they started using marijuana by matching marijuana users and nonusers on their scores during the fourth grade on the Iowa Tests of Basic Skills (Hieronymus et al., 1982), achievement tests that have been administered in almost all Iowa communities for decades.

In the present study, we expanded this line of research by having frequent marijuana users perform memory tests

* Corresponding author. Tel.: +1-319-335-8975; fax: +1-319-335-8996.

E-mail address: robert-block@uiowa.edu (R.I. Block).

[1] Present address: Alzheimer's Research Unit, Harvard Medical School, Massachusetts General Hospital, Charlestown, MA 02129, USA.

0091-3057/02/$ – see front matter
PII: S0091-3057(01)00771-7

while we used positron emission tomography (PET) with [^{15}O]water to measure normalized regional brain blood flow (subsequently abbreviated rCBF — an abbreviation that is used here to include the normalization process described below). The memory tests differed in their relative demands on encoding into episodic memory and retrieval from episodic memory. Episodic memory is a form of memory that enables people to remember personally experienced events (in contrast to impersonal general knowledge). Encoding processes that occur during the event initiate memory storage. Later, retrieval processes operate on the stored information and lead to conscious remembering (Tulving et al., 1994a). Prefrontal rCBF changes were of special interest in the present study because a prominent memory model, Endel Tulving's "hemispheric encoding/retrieval asymmetry" model (Nyberg et al., 1996; Tulving et al., 1994a), postulates differential prefrontal lateralization of episodic memory encoding and retrieval. Tulving et al. (1994b) observed activation of right dorsolateral prefrontal cortex during episodic memory retrieval. Reviewing other studies (Nyberg et al., 1996; Tulving et al., 1994a), he observed that left prefrontal regions are differentially more involved in episodic memory encoding, whereas right prefrontal regions are differentially more involved in episodic memory retrieval.

Hippocampal rCBF changes were also of special interest because the hippocampus has one of the highest densities of cannabinoid receptors (Herkenham et al., 1990) and may play a major role in mediating some cannabinoid effects on memory in animals (Hampson and Deadwyler, 1998; Solowij, 1998). Effects of marijuana use on hippocampal rCBF have not been studied.

2. Method

2.1. Subjects

Subjects were 18 frequent marijuana users and 13 nonusing control subjects. The marijuana users were using marijuana 7+ times weekly on average (mean ± S.E., 18 ± 2 times), and had been using at about this rate for the last 2+ years (mean, 3.9 ± 0.4 years). Control subjects had never used marijuana ($N = 10$), or only once or twice in their lives ($N = 3$), and had never used any other illegal drugs. All subjects were right ear-dominant according to a dichotic screening test and right-handed, had adequate hearing, as assessed by pure tone thresholds in both ears, without pronounced differences between ears, and were native English speakers. Exclusion criteria included serious uncorrected visual problems; history of dependence on alcohol or any illicit drugs other than marijuana according to the Quick Diagnostic Interview Schedule (Marcus et al., 1991), supplemented in doubtful cases with interviewing by a psychiatrist; history of schizophrenia, history of bipolar disorder, or current depression (Marcus et al., 1991); histories of mental retardation or brain disease unrelated to drug use; severe obesity; and current use of prescribed psychotropic drugs or drugs that might affect the PET results. We selectively recruited marijuana users whose use of illicit drugs other than marijuana was as limited as feasible. Drug use history was obtained using the Addiction Severity Index (McLellan et al., 1992) and locally developed instruments. Subjects were recruited by advertisements. The experiment was conducted with the understanding and consent of each subject, following approval of the experimental protocol by the University of Iowa institutional review committee for the use of human subjects.

2.2. Sessions and supervised abstinence

All subjects were admitted twice to an inpatient research ward for overnight hospitalizations. PET was done during the second hospitalization and was preceded by at least 26 h (mean, 27.8 ± 0.3 h) of monitored abstinence, to eliminate the short-term effects of recent marijuana use. Subjects' presence on the ward was monitored by staff every 15 min. Subjects were instructed to abstain from marijuana and other drugs for at least 7 h before their hospital admission at 7:00 a.m. All marijuana users reported abstaining from marijuana for at least 7.5 h before admission (mean, 15.7 ± 3.5 h). A cognitive test session, including memory testing, was done during the first hospitalization, which followed similar procedures (e.g., subjects instructed to abstain for 7+ h before admission; testing preceded by 24+ h of monitored abstinence). Urine screens of all subjects were negative for all illegal drugs, except for marijuana in the marijuana users, at a preliminary screening session, and on the mornings of the cognitive test session and the PET session. Nonuse of alcohol during the hospitalizations was verified by this urine screening, together with breath tests about every 4 h. Subjects abstained from caffeine on the day of the PET session until its completion, and from tobacco from at least 1 h before the PET session until its completion; they also abstained during the cognitive testing in the first hospitalization.

2.3. Memory tests

During the cognitive test session in the first hospitalization, the subject learned a list of 15 common words, such as "drum," "curtain," "bell," etc., to a criterion of two consecutive perfect recalls, using Buschke's (1973) "selective reminding technique.". First, the list was read by the tester and the subject tried to recall as many words as he could. The subject tried to recall the whole list on each subsequent test trial, but on learning trials after the first, he was reminded only of the words that he had missed on the immediately preceding test trial. During the second hospitalization, on the day before PET, the subject relearned the same list, again to a criterion of two consecutive perfect recalls. (The relearning data were lost for one control subject

due to tester error.) Next, the subject was played a recording of the list and recalled it according to the procedures to be used in the PET session, and again relearned it; this was done to reduce the possibility that the changed procedures in the PET session, e.g., computerized presentation of a digitized recording of the list rather than presentation by the tester, would disrupt memory.

The PET session included memory tests that were derived from modifications of previous PET work by our group (Andreasen et al., 1995). Subjects were lying quietly, with eyes closed, during all tests. During one data acquisition period, the subject tried to orally recall the list relearned on the previous day, without any prompting. During another period, the subject heard the computerized presentation of this list again and immediately tried to recall it. During a third period, the subject heard a list of 15 different common words and immediately tried to recall them. These tests are referred to below as the OLD LIST W/O P (''old list without presentation''), OLD LIST W P (''old list with presentation''), and NEW LIST. The three tests differed in their relative demands on episodic memory encoding and retrieval, with OLD LIST W/O P expected to place the greatest demands on retrieval and NEW LIST to place the greatest demands on encoding. During each test, the subject recalled the words for 40 s, and was asked to repeat them if he could not think of any more. The two lists were from the Rey Auditory Verbal Learning Test (Rey, 1964), and their use as old and new lists was counterbalanced as closely as possible over subjects within each group.

2.4. Control test

To determine memory-related rCBF changes, rCBF during a control test was subtracted from rCBF during each memory test. The control test, which controlled for speech activity, consisted of repeatedly counting ''1, 2, 3,...'' for 40 s at a rate of about one word per second. Subjects practiced this counting on the day before PET. This repetitious rehearsal of a vastly overlearned, automatized sequence was intended to minimize episodic memory retrieval and encoding.

2.5. Imaging and image processing

PET data were acquired using the [^{15}O]water bolus injection method with a GE4096PLUS Scanner. Fifteen slices (6.5 mm center-to-center) were acquired with an intrinsic in-plane resolution of 8-mm FWHM and a 10-cm axial field of view (Hurtig et al., 1994). The subject received an intravenous injection of 50 mCi of [^{15}O]water. The period of recall in the memory tests or counting in the control test started 10 s before the estimated arrival of the [^{15}O]water bolus in the brain. Following a preliminary scout injection that provided an initial estimate of bolus arrival time, eight paradigms were administered during the PET session; the four paradigms related to memory are reported here. rCBF while lying quietly, without any specific instructions concerning mental activities, has been described elsewhere (Block et al., 2000b). Anxiety was evaluated three times — after the scout injection and the third and seventh paradigms — using the Beck Anxiety Inventory (Beck et al., 1988), a 21-item questionnaire with possible scores ranging from 0 (*least anxiety*) to 63 (*most anxiety*).

For subjects in whom an arterial line could be placed, arterial blood was sampled to allow calculation of tissue perfusion; but because arterial lines could not be placed in four marijuana users and four control subjects, the analyses reported are based on relative flow measurements, i.e., normalized radioactivity data (''count data''), which were available for everyone, rather than absolute flow measurements. Most other groups using the [^{15}O]water method have performed the majority of their studies with relative flow measurements based on radioactivity data only. We have found that image analysis strategies such as the one used here, which involved normalization of voxel or regional values by dividing by global, whole brain values, show a very high correlation between count data and flows (Arndt et al., 1996b). For example, analyses using count data vs. flow data of the present subjects while lying quietly without any specific instructions concerning mental activities showed little difference (Block et al., 2000b).

In the present analyses, radioactivity (i.e., count) images were filtered (18-mm Hanning filter) and normalized as described above. Due to technical problems, data were unavailable for one marijuana user for the NEW LIST, and for one control for the OLD LIST W P. Magnetic resonance images (contiguous 1.5-mm slices acquired coronally with an SPGR sequence) (Block et al., 2000a), which were obtained during the first hospitalization or on an outpatient basis, and PET images were coregistered and landmarks identified on the former images were used to place each brain into a standardized coordinate space (Talairach and Tournoux, 1988).

2.6. Statistical analyses

2.6.1. Images

Subtractions of the control test from each memory test were performed on normalized count data for each individual voxel for each subject. Differences between marijuana users and control subjects in the subtraction results for each voxel were tested using distribution-free, randomization analyses (Arndt et al., 1996a). A t statistic for each voxel indicated the likelihood of finding a difference as large as that actually observed. Contiguous voxels showing significant differences at an uncorrected significance level of $P < .005$ were then clustered together. Because differences in one or a handful of voxels would likely have little practical significance, we consider between-group ''activation differences'' meaningful and report them only if they involve at least 50 contiguous voxels (roughly 0.1 cc). Such activation differences

indicated differences between marijuana users and control subjects in memory-related rCBF changes.

Supplementary randomization analyses also compared marijuana users and control subjects for each memory test and the control test individually (rather than comparing subtractions of the control test from each memory test). The subtraction results for marijuana users and control subjects were also examined separately by Worsley analyses (Worsley et al., 1992), again focusing on differences involving 50+ contiguous voxels that were each individually significant.

rCBF was automatically measured within tracings of the hippocampus (the gray matter, i.e., excluding most of the efferent pathway of the hippocampus). The tracing was done on the magnetic resonance images using an automated tracing technique based on artificial neural network methodology (Magnotta et al., 1999), which had previously been trained with traces provided by an expert human tracer working from detailed tracing guidelines. Although achieving good reliability, the neural network is routinely overly conservative, so the traces produced by the neural network were trimmed by two research assistants who had contributed to development of the tracing guidelines and achieved good reliability in tracing (intraclass R^2 for left and right hippocampus for the two tracers ranging from .74 to .83) (Pantel et al., 1999).

To analyze the hippocampal rCBF data, difference scores for each subject and side (left vs. right hippocampus) were calculated by subtracting the control test rCBF value from each of the three memory test rCBF values. These difference scores were submitted to an analysis of variance (ANOVA) involving memory test (the three tests) and side as within-subjects factors, and group (marijuana users vs. control subjects) as a between-subjects factor.

2.6.2. Memory tests

To analyze learning of the old list, the $\log_e$-transformed numbers of presentations of the list required to reach the criterion of two consecutive perfect recalls in the two sessions (initial learning during the first hospitalization and relearning on the day before PET) were submitted to an ANOVA (the numbers of presentations during the first hospitalization were not normally distributed before transformation according to the Shapiro–Wilk test, but were after transformation). The ANOVA involved session as a within-subjects factor and group and list (the two different lists) as between-subjects factors.

To analyze memory of the NEW LIST in the PET session, for each part (i.e., the beginning, middle, and final five words in the order of presentation), the proportion of words that were recalled was determined. These data were submitted to an ANOVA involving the part of the list as a within-subjects factor and group and list as between-subjects factors. In this kind of test, subjects typically show primacy and recency effects, i.e., better recall at the beginning and end of a list than in the middle (Capitani et al., 1992). The primacy and recency effects were examined by contrasts of the first and last parts of the list, respectively, with the middle part; and the interactions of these contrasts with group were also examined. Corresponding ANOVAs were done for recall of the OLD LIST W/O P and the OLD LIST W P in the PET session.

2.6.3. Comparability of marijuana users and control subjects

The comparability of the groups was assessed using *t* tests for quantitative characteristics (e.g., age) and Fisher's Exact Tests for categorical characteristics (e.g., gender). A significance level of $P < .05$ was used.

3. Results

3.1. Comparability of the groups

The groups did not differ in gender distribution or mean age, height, weight, total intracranial volume, volumes of major brain regions, or hippocampal volume. Marijuana users had slightly (1.1 years) less education than control subjects, but the groups did not differ in mental abilities prior to the onset of marijuana use, estimated by grade equivalent composite scores on the Iowa Tests of Basic Skills (Hieronymus et al., 1982) achievement tests administered when the subjects attended the fourth grade of elementary school. Details are described elsewhere (Block et al., 2000a). The groups also did not differ in the interval between the original learning of the old list and its relearning on the day before PET (23.6 ± 5.1 and 24.0 ± 5.0 days).

Mean anxiety ratings after the scout injection were 0.1 ± 0.1 and 1.3 ± 0.4 for the marijuana users and control subjects, respectively. Corresponding ratings were 0.1 ± 0.1 and 0.1 ± 0.1 after the third paradigm and 0.1 ± 0.1 and 0.2 ± 0.1 after the seventh paradigm. Although both groups reported very little or no anxiety throughout the session, the marijuana users were slightly less anxious than the control subjects after the scout injection ($P < .05$). The groups did not differ later in the session.

3.2. Drug use

Unlike the control subjects, who had never used any illegal drugs other than marijuana, the marijuana users had experience with such drugs. However, this experience was reasonably limited. The marijuana users were not heavy alcohol drinkers; they exceeded the control subjects in days of alcohol use in the 2 years preceding the screening session, but not in the preceding 30 days. Details are described elsewhere (Block et al., 2000a). The marijuana users reported a significantly higher frequency than the control subjects of tobacco use per day, averaged over the previous year; but the groups did not differ significantly in use during the 8 h preceding the PET session, or (for those

who used during this period) the number of minutes since the last use. The final 45% of subjects were also asked corresponding questions about the 8 h preceding the magnetic resonance imaging, as well as questions about average tobacco and caffeine use during a 1-week period; and the groups did not differ significantly.

3.3. Learning

Marijuana users performed more poorly than control subjects, i.e., they required more presentations, in learning and relearning the old list to criterion during the two initial sessions preceding PET [$F(1,27) = 4.3$, $P = .048$]. The means are shown in Fig. 1. Not surprisingly, far fewer presentations were necessary to relearn the list on the day before PET than to learn it initially during the cognitive test session in the first hospitalization [$F(1,26) = 17.1$, $P = .0003$]. Despite this, the impairment in the marijuana users did not vary between sessions, i.e., the number of extra presentations required by marijuana users, relative to control subjects, was similar for initial learning (2.7) and relearning (3.1) [$F(1,26) = 0.4$, $P = .54$, for the Group × Session interaction].

This highly overlearned list then functioned as the old list during PET and was, not surprisingly, recalled almost perfectly during PET by both marijuana users and control subjects. The groups did not differ in numbers of words recalled during PET, either for OLD LIST W P (14.8 ± 0.1 and 14.7 ± 0.2) or OLD LIST W/O P (14.0 ± 0.2 and 14.0 ± 0.3).

In recalling the NEW LIST (the one that subjects had never heard before) during PET, marijuana users showed an increased recency effect, i.e., better recall for the words at the end of the list than those in the middle, relative to control subjects [$F(1,26) = 4.5$, $P = .04$]; marijuana users recalled 23% more than control subjects from the end, but 19% less from the middle. This is shown in Fig. 2. The groups did not differ in the primacy effect, i.e., better recall for the words at the beginning of the list than those in the middle ($P = .54$); mean recall at the beginning was equal for marijuana users and control subjects. Nor did the groups differ in recall for the list as a whole, because their contrasting levels of recall at the end and middle balanced each other out in the averaging process; mean recall for beginning, middle, and end combined was 7.7 ± 0.4 words for marijuana users, compared to 7.5 ± 0.5 words for control subjects. Over all subjects in both groups combined, the primacy and recency effects were highly significant [$F(1,26) = 18.3$, $P = .0002$, and $F(1,26) = 22.0$, $P = .0001$, respectively, for the overall contrasts of beginning vs. middle and end vs. middle].

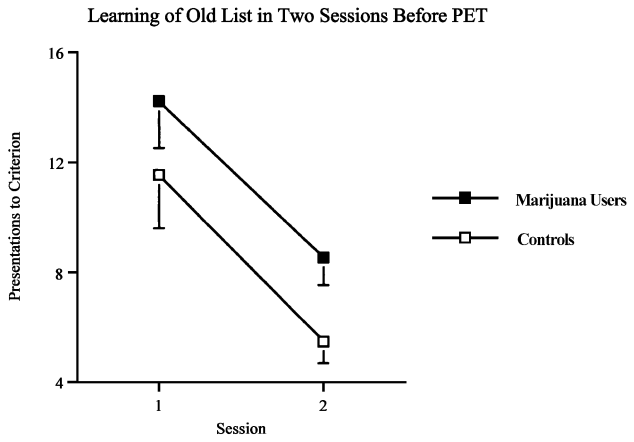

Fig. 1. Learning during the two initial sessions of the list that functioned as the OLD LIST W P and OLD LIST W/O P for PET. Numbers of presentations of the list required to reach the criterion of two consecutive perfect recalls are shown. 1 = Initial learning during the cognitive test session in the first hospitalization; 2 = relearning on the day before PET. Marijuana users were impaired relative to control subjects, and relearning required fewer presentations than initial learning, but these two effects did not interact (see text).

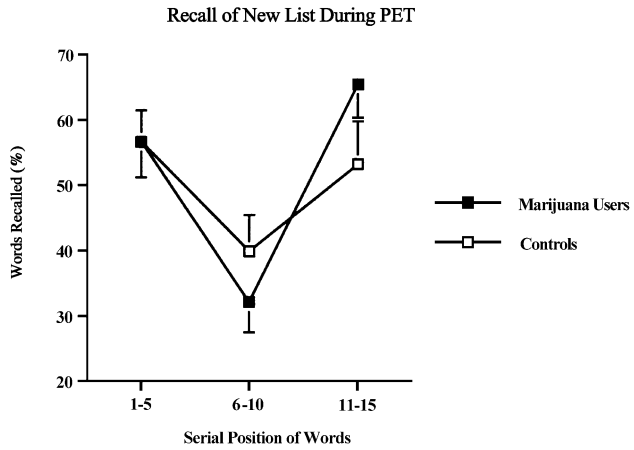

Fig. 2. Memory for the NEW LIST in the PET session. For each third of the list (words 1–5, 6–10, and 11–15 in the order of presentation), the proportion of words that were recalled is shown. Primacy and recency effects occurred; marijuana users showed an increased recency effect relative to control subjects, but the groups did not differ in overall recall (see text).

3.4. Hippocampal rCBF

The ANOVA of rCBF changes in the hippocampus showed a difference in memory-related lateralization between marijuana users and control subjects [$F(1,29) = 5.10$, $P = .03$ for the Group × Side interaction]. This is illustrated in Fig. 3. The three memory tests did not differ in these hippocampal effects; and the ANOVA showed no other significant effects. Follow-up analyses indicated that, in control subjects, the left, language-dominant hippocampus was more active than the right hippocampus in the memory tests, relative to the control test [$F(1,12) = 7.45$, $P = .02$]. Marijuana users showed no such laterality effect [$F(1,17) = 0.27$, $P = .61$]. The left hippocampus showed increased memory-related activity, i.e., a value above zero in Fig. 3, for control subjects, but not marijuana users; the right hippocampus did not show increased memory-related activity for either group.

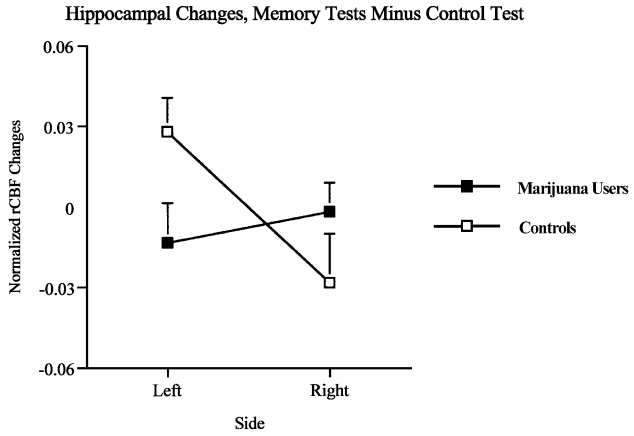

Fig. 3. Hippocampal rCBF difference scores, calculated by subtracting the control test rCBF value from each of the three memory test rCBF values. Results are pooled over the three memory tests, because they did not differ in these hippocampal effects. Positive change scores indicate greater hippocampal activity in the memory tests than the control test, and negative change scores indicate the opposite. All scores were normalized relative to whole brain activity before calculating changes; therefore, no units are specified for the *y*-axis. Control subjects showed greater left than right hippocampal activity in the memory tests, relative to the control test, whereas marijuana users did not (see text).

3.5. Randomization analyses

The randomization analyses identified regions in which activations in the memory tests, relative to the control test, differed between marijuana users and control subjects. Prefrontal and cerebellar differences were most prominent.

3.5.1. Prefrontal differences between groups

The randomization analyses showed that prefrontal activations in the memory tests, relative to the control test — which normally occur (Tulving et al., 1994a) — were less apparent in marijuana users than control subjects. Table 1 lists the 10 prefrontal regions in which marijuana users and control subjects differed significantly. The control subjects showed increased rCBF in the memory test, in contrast to the control test, in these regions. The marijuana users showed decreased rCBF or smaller increases.

The prefrontal differences between groups were more common in recall of the NEW LIST than the OLD LIST W P or OLD LIST W/O P (Table 1). The rCBF changes in marijuana users were most common in the left hemisphere for recall of the NEW LIST. However, there were also rCBF changes in the right hemisphere in marijuana users. These were most frequent in Brodmann's area (BA) 8.

rCBF differences in marijuana users relative to control subjects in prefrontal areas that may be related to working memory (Fiez et al., 1996; Owen et al., 1999), e.g., BA 46, were consistent with differences in other parts of prefrontal cortex (Table 1). During recall of the NEW LIST, which would be expected to place the most demands on working memory, rCBF differences in Broca's area (data not shown in Table 1, as it is not prefrontal), which may be related to verbal working memory (Awh et al., 1995; Fiez et al., 1996; Grafton, 1995), were consistent with differences in prefrontal cortex: There was a region in BA 44 in which marijuana users showed a smaller rCBF increase than control subjects in the memory test, relative to the control test (3% and 10%, respectively; $t = 3.0$, 53 voxels). The coordinates from the atlas of Talairach and Tournoux (1988) of the most statistically significant difference within the region, i.e., the voxel with the largest t value, were $x = -40$, $y = 13$, $z = 24$, where x = mm to right (+) or left (−) of interhemispheric fissure, y = mm anterior (+) or posterior (−) to anterior commissure, and z = mm superior (+) or inferior (−) to a plane

Table 1
Prefrontal rCBF decreases in marijuana users relative to control subjects, in memory tests relative to control test

Test	Location	BA #	Voxels (#)	Talairach *x*, *y*, *z*	Side	Marijuana users, change (%)	Control subjects, change (%)	*t*	Fig. 4
OLD LIST W/O P	DL	8	73	42, 14, 46	R	−2	5	3.1	–
OLD LIST W P	DL	8	137	42, 14, 46	R	−3	5	3.0	–
	M	10	157	−1, 59, 19	L	−6	2	3.2	–
	DL[a]	45/46	378	36, 33, 12	R	−5	5	3.9	–
NEW LIST	DL	9	65	−16, 34, 41	L	1	8	3.0	–
	DL	46	83	−29, 40, 21	L	1	8	3.0	B9
	DL	8	171	−28, 11, 35	L	−2	6	3.4	B10
	V	11	249	11, 63, −15	R	−6	2	3.3	–
	DL	8	339	42, 13, 46	R	−2	7	3.7	–
	DL/V	10/11/46	1205	−34, 44, −8	L	−5	4	3.9	A1, B12

Changes involving at least 50 contiguous voxels (roughly 0.1 cc) are listed (see text). The marijuana users showed decreased rCBF, relative to control subjects, in the memory tests, relative to the control test, in all these regions. The fifth column from the left gives coordinates of the voxel with the largest *t* value from the atlas of Talairach and Tournoux (1988) (see text). The seventh and eighth columns from the left show the percentage changes in rCBF in the memory tests, relative to the control test, for marijuana users and control subjects, respectively. The control subjects showed increased rCBF in the memory test, relative to the control test, in all these regions. The marijuana users showed decreased rCBF in eight regions and smaller increases than the control subjects in the other two regions. The rightmost column gives the panels (A–C) and landmark point numbers for those changes that are visible in Fig. 4. OLD LIST W/O P = old list without presentation; OLD LIST W P = old list with presentation; BA = Brodmann's area; DL = dorsolateral prefrontal; M = medial prefrontal; V = ventral prefrontal; L = left; R = right; – = none.

[a] Also right hemisphere homologue of Broca's area.

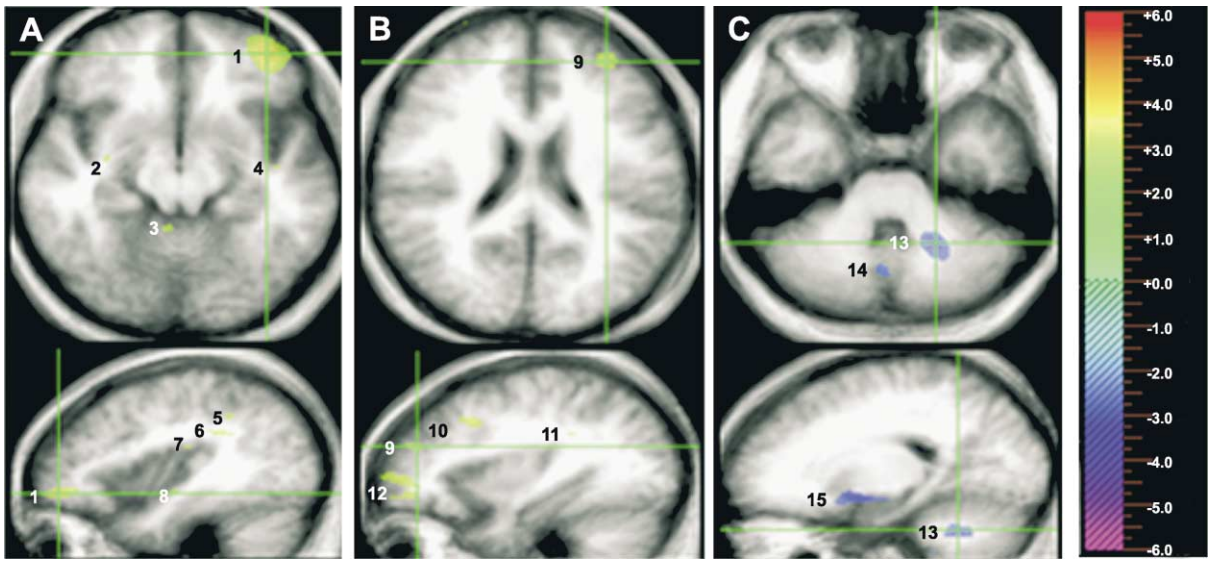

Fig. 4. rCBF changes observed in the randomization analyses. Panels A–B illustrate rCBF decreases found in the randomization analyses in left dorsolateral prefrontal cortex in the marijuana users (relative to the control subjects) during recall of the NEW LIST (relative to the control test). Panel C illustrates an rCBF increase in the cerebellum in the marijuana users during recall of the NEW LIST. The difference that each panel was selected to illustrate is indicated by the crosshairs. The specific locations in panels A–C were BA 10/11/46, BA 46, and dentate nucleus, respectively (landmark points 1, 9, and 13, respectively). In each panel, the other differences that occurred in the selected planes and that were in the same direction (i.e., rCBF increases or decreases) as the one indicated by the crosshairs are also shown. Each panel shows axial and sagittal sections. In each panel, the activation differences are superimposed on the computer-averaged magnetic resonance image of the brains of all the subjects. Colors indicate the magnitudes of the *t* values testing the statistical significance of the activation differences. The pallet at the right indicates the color coding. All images follow radiological convention, with left and right reversed. The activation differences are identified by numbers (referred to in the text as "landmark points"). Those that met the size criterion ($\geq$50 voxels), in addition to the ones indicated by the crosshairs, were (using the abbreviations DL = dorsolateral, M = medial, and V = ventral): 3 = cerebellum (anterior vermis); 4 = superior temporal gyrus (BA 22); 6 = Wernicke's area (BA 40); 8 = superior temporal gyrus (BA 22); 10 = DL prefrontal cortex (BA 8); 11 = Wernicke's area (BA 40); 12 = DL/V prefrontal cortex (BA 10/11/46); 14 = cerebellum (posterior vermis); 15 = globus pallidus/putamen. Those that did not meet the size criterion (<50 voxels) were: 2 = claustrum/putamen; 5 = posterior cingulate/precuneus (BA 31); 7 = motor cortex (BA 4).

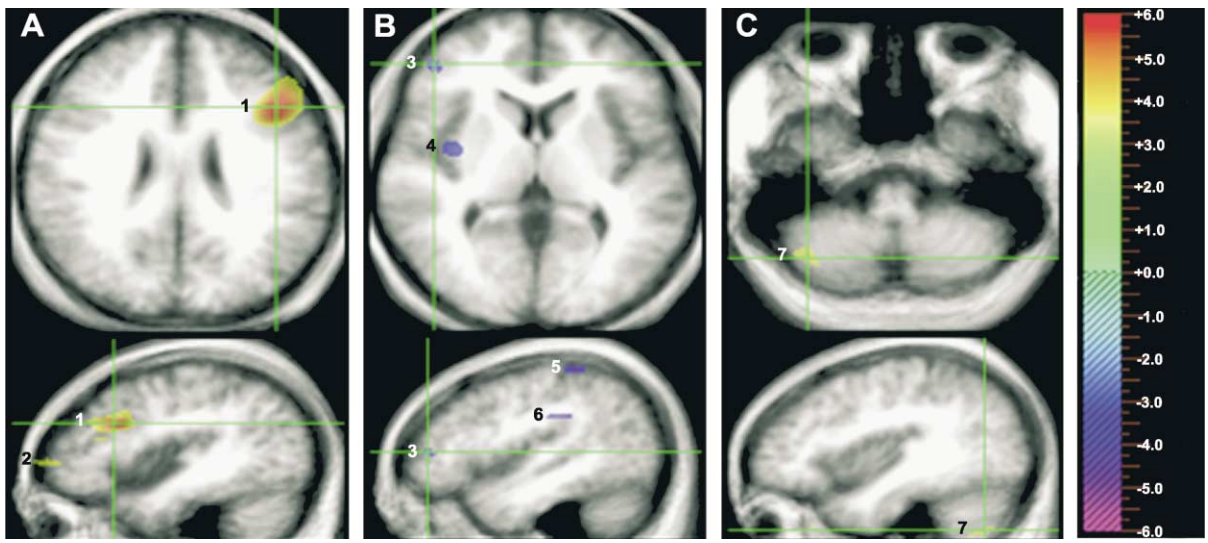

Fig. 5. rCBF changes observed in the Worsley analyses, which were done separately for marijuana users and control subjects. Positive *t* values in the color pallet at the right indicate increased rCBF in the memory test, relative to the control test. See Fig. 4 for other conventions that were followed. The differences that the figures were selected to illustrate (indicated by the crosshairs) were in dorsolateral prefrontal cortex for panels A–B and the cerebellum for panel C. Panel A shows increased rCBF during recall of the NEW LIST (relative to the control test) in control subjects in left BA 9 (and also in Broca's area, BA 44) (landmark point 1). Panel B shows decreased rCBF during recall of the OLD LIST W P in marijuana users in right BA 46 (landmark point 3). Panel C shows increased rCBF during recall of the NEW LIST in marijuana users in right inferior, posterior cerebellum (landmark point 7). The activation differences, in addition to the ones indicated by the crosshairs, were (using the abbreviation DL = dorsolateral): 2 = DL prefrontal (BA 10); 4 = insula; 5 = Wernicke's homologue (BA 40); 6 = Wernicke's homologue (BA 40). All met the size criterion ($\geq$50 voxels).

passing through the anterior and posterior commissures. During recall of the OLD LIST W/O P and the OLD LIST W P, however, a contrasting pattern occurred in Broca's area, i.e., the marijuana users showed increased rCBF in the memory tests, relative to the control test, whereas the control subjects showed decreased rCBF (4% and −4%, respectively; $t=-3.4$, 169 voxels; $x=-41$, $y=18$, $z=6$ for OLD LIST W/O P; and 4% and −3%, respectively; $t=-2.9$, 59 voxels; $x=-35$, $y=15$, $z=6$ for OLD LIST W P).

Panels A–B of Fig. 4 illustrate rCBF decreases in left dorsolateral prefrontal cortex in the marijuana users (relative to the control subjects) during recall of the NEW LIST (relative to the control test). The crosshairs in panels A–B indicate differences in BA 10/11/46 and BA 46, respectively (landmark points 1 and 9, respectively). Some other prefrontal rCBF differences for the NEW LIST shown in Table 1 are also visible in panel B; the landmark point numbers are specified in Table 1.

3.5.2. Cerebellar differences between groups

Table 2 lists the six cerebellar regions in which marijuana users and control subjects differed significantly. The marijuana users showed increased rCBF (relative to control subjects) when recalling the NEW LIST (relative to the control test) in four regions in posterior cerebellar hemisphere and vermis, and dentate nucleus. The region in the dentate nucleus that showed this pattern is indicated by the crosshairs in panel C of Fig. 4 (landmark point 13); one other region that showed this pattern (posterior vermis) is also visible in this panel (landmark point 14). The marijuana users showed the opposite pattern relative to control subjects in two cerebellar regions, both in anterior vermis, during the memory tests (Table 2). One of these regions is visible in panel A of Fig. 4 (landmark point 3). As indicated by the classification in the ninth column from the left in Table 2, the regions in which the marijuana users showed increased rCBF (relative to control subjects) in the memory tests (relative to the control test) were ones that are likely to be potentially related to attention, memory, and other cognitive processes, whereas the regions in which the marijuana users showed the opposite pattern were not. The basis for this classification and its implications are considered in the Discussion. As with the prefrontal differences, the cerebellar differences between groups were more evident in recall of the NEW LIST than the OLD LIST W P or OLD LIST W/O P.

3.5.3. Other differences between groups

In addition to the rCBF differences between groups in prefrontal cortex, cerebellum, hippocampus, and Broca's area discussed above, some differences also occurred in other brain regions. In one or more memory tests (relative to the control test), the marijuana users (relative to the control subjects) showed regions of decreased rCBF in BA 1, 2, 3, 21, 24, 40, 41, and 42, and in the right hemisphere homologue of Broca's area (BA 45); increased rCBF in BA 18, 19, 28, 29, and 30, and in the insula, putamen, and tectum; and both increased and decreased rCBF in BA 6, 7, 22, 23, 31, and 36, and in the globus pallidus. Differences occurred both in locations likely to be involved in memory processes, e.g., BA 28, and in locations unlikely to be so involved, e.g., BA 19. However, these differences were less prominent and consistent than those that were observed in prefrontal cortex and cerebellum. Some of these differences that occurred in the marijuana users (relative to the control subjects) in recall of the NEW LIST (relative to the control test) are illustrated in Fig. 4.

3.5.4. Analyses of each test individually

The analyses described above subtracted the control test rCBF data from the memory test rCBF data. Supplementary randomization analyses compared the marijuana users and control subjects for each individual test. As we recently described (Block et al., 2000b), when the subjects were lying quietly, with eyes closed, without specific instructions as to mental activities, such an analysis indicated that marijuana users, relative to control subjects, showed substantially lower rCBF in a large region of bilateral posterior cerebellar hemispheres and vermis (posterior cerebellar "hypoactivity"). Similarly, in the present study, marijuana users showed lower rCBF than control subjects in posterior cerebellum in each of the memory tests and the control test. This posterior cerebellar hypoactivity, although somewhat smaller than while subjects were lying quietly without specific instructions as to mental activities, was the largest difference of the marijuana users from the control subjects

Table 2
Cerebellar rCBF changes in marijuana users relative to control subjects, in memory tests relative to control test

Test	Location	Voxels (#)	Talairach x, y, z	Side	Marijuana users, change (%)	Control subjects, change (%)	t	Potentially cognitive location?	Fig. 4
OLD LIST W/O P	A vermis	449	3, −56, −10	R	−4	4	3.5	No	–
NEW LIST	S P cerebellum	105	9, −83, −13	R	6	−1	−3.1	Yes	–
	A vermis	123	3, −50, −10	R	−3	5	3.2	No	A3
	P vermis	181	5, −75, −32	R	5	−3	−3.2	Yes	C14
	I P cerebellum	196	31, −48, −38	R	3	−5	−3.4	Yes	–
	Dentate nucleus	402	−17, −54, −27	L	2	−6	−3.3	Yes	C13

The marijuana users and control subjects showed opposite changes in rCBF in the memory tests, relative to the control test, in all these regions. Marijuana users showed decreased rCBF in two regions and increased rCBF in the other four regions. The ninth column from the left indicates whether the location is likely to be potentially related to cognition (see Discussion). A = anterior; P = posterior; I = inferior; S = superior. For other abbreviations and explanations, see Table 1.

for every test: The volumes were 5269, 2662, 4185, 6447, and 8854 voxels for OLD LIST W/O P, OLD LIST W P, NEW LIST, control test, and lying quietly without specific instructions as to mental activities, respectively. The corresponding largest t values and Talairach and Tournoux's (1988) atlas coordinates were $t=4.9$, $x=18$, $y=-81$, $z=-21$; $t=4.1$, $x=26$, $y=-78$, $z=-31$; $t=4.9$, $x=-21$, $y=-73$, $z=-40$; $t=4.4$, $x=-22$, $y=-71$, $z=-38$; and $t=4.7$, $x=28$, $y=-71$, $z=-38$, respectively. At these points of largest t values, marijuana users showed 15%, 15%, 19%, 15%, and 18% lower normalized blood flow than control subjects, respectively.

3.6. Worsley analyses

The Worsley analyses examined marijuana users and control subjects separately and, for each memory test, identified regions in which rCBF was higher or lower than for the control test. The results generally agreed with those of the randomization analyses, but also provided important clarification, as described below.

Panels A–C of Fig. 5 show rCBF changes observed in the Worsley analyses. Generally, for control subjects, episodic memory encoding was associated with left prefrontal activity more strongly than episodic memory retrieval was associated with right hemisphere activity. For example, the crosshairs in panel A in Fig. 5 (landmark point 1) indicate a substantial region of increased rCBF during recall of the NEW LIST (relative to the control test) in control subjects in left BA 9 (and also in Broca's area, BA 44); $t=6.3$; 2197 voxels; $x=-38$, $y=15$, $z=25$.

Consistent with the results of the randomization analyses, the greatest prefrontal differences between marijuana users and control subjects in amounts of activation (which reflected greater activation in the control subjects) were in the left hemisphere during recall of the NEW LIST. Also consistent with results of the randomization analyses, activations in prefrontal regions (e.g., BA 46) and Broca's area that may be related to working memory were smaller during recall of the NEW LIST for marijuana users than control subjects.

The randomization analyses were most sensitive to prefrontal regions in which marijuana users, in contrast to control subjects, showed decreased memory-related activity. However, the Worsley analyses indicated that the marijuana users showed a mixed pattern of both increases and decreases in memory-related prefrontal activity. For example, the crosshairs in panel B in Fig. 5 show decreased rCBF during recall of the OLD LIST W P in marijuana users in right BA 46 (landmark point 3; $t=-4.0$, 52 voxels; $x=45$, $y=39$, $z=7$). In contrast, marijuana users showed increased rCBF during recall of this list in left BA 9 ($t=5.2$, 530 voxels; $x=-37$, $y=20$, $z=28$).

Consistent with the cerebellar differences between groups shown by the randomization analyses, memory-related increases in cerebellar activity were more prominent in the marijuana users than the control subjects. The crosshairs in panel C in Fig. 5 (landmark point 7) indicate a region of increased rCBF during recall of the NEW LIST in right inferior, posterior cerebellum in marijuana users ($t=3.9$, 109 voxels; $x=38$, $y=-66$, $z=-39$).

In addition to the rCBF changes in prefrontal cortex, Broca's area, and cerebellum discussed above, some differences in the memory tests (relative to the control test) also occurred in other brain regions. Some of these are illustrated in Fig. 5.

4. Discussion

Marijuana users, relative to control subjects, showed decreased memory-related prefrontal activations and an absence of memory-related lateralization of hippocampal activity, as well as differences in cerebellum and other brain regions. Important prefrontal (Nyberg et al., 1996; Tulving et al., 1994a) and hippocampal (Lepage et al., 1998) roles in some aspects of episodic memory storage and retrieval have been demonstrated.

4.1. Prefrontal cortex

The randomization analyses indicated that memory-related prefrontal activations were consistently less apparent in marijuana users than control subjects. However, marijuana users did not show a uniform pattern of memory-related decreases in prefrontal activity. The Worsley analyses of the marijuana users separately indicated that they showed a mixed pattern of both decreases and increases in memory-related prefrontal activity. The randomization analyses, directly comparing the two groups, tended to highlight prefrontal regions of memory-related decreases in the marijuana users, which contrasted most sharply with the memory-related increases in activity shown by the control subjects.

In the randomization analyses, the more numerous prefrontal differences between groups in recall of the NEW LIST than the OLD LIST W P or OLD LIST W/O P suggested that the rCBF changes in marijuana users (relative to control subjects) were more related to episodic memory encoding than retrieval. The finding that rCBF changes in marijuana users were most common in the left hemisphere for recall of the NEW LIST is consistent with the association of left prefrontal activity with episodic memory encoding proposed by the hemispheric encoding/asymmetry model (Tulving et al., 1994a). The marijuana users also showed rCBF changes in the right hemisphere in all three memory tests, which may be related to episodic memory retrieval processes. Generally, in the Worsley analyses for control subjects, the association of episodic memory encoding with left prefrontal activity proposed by the model was supported more strongly than the association of episodic memory retrieval with right hemisphere activity. Consistent with our results, the hemispheric encoding/retrieval asym-

metry model was modified very recently, reducing the hypothesized extent of right lateralization of retrieval, while maintaining the hypothesized left lateralization of encoding (Lepage et al., 2000).

4.2. Memory changes in marijuana users

Whether marijuana use is associated with cognitive deficits remains controversial, but several recent studies, including our own (Block and Ghoneim, 1993), support an association (Solowij, 1998). In the present study, marijuana users, relative to control subjects, were impaired in learning a word list over multiple trials, despite the matching of the groups on mental abilities prior to the onset of marijuana use. Marijuana users required more presentations than control subjects to learn the list to criterion. This is a standard measure of learning in this kind of test.

In single-trial recall of the NEW LIST during the PET session, marijuana users did not show impairment, but showed an increased recency effect. The recency effect is often attributed largely to short-term memory, although alternative explanations have been proposed (Capitani et al., 1992; Squire et al., 1993). Marijuana users seemed to rely more on this type of memory, as opposed to episodic memory encoding and retrieval. Greater reliance on short-term memory could contribute to poorer learning over multiple trials. Greater reliance on short-term memory does not necessarily imply greater memory-related activation in brain regions associated with such memory — which did not, in fact, occur. It implies an altered distribution of memory processes, which could occur in the presence of relatively less activation in marijuana users than control subjects, both in frontal regions related to episodic memory and to working memory (i.e., prefrontal regions such as BA 46, as well as Broca's area) (Awh et al., 1995; Fiez et al., 1996; Grafton, 1995; Owen et al., 1999). Conceivably, control subjects might have used working memory more actively in the service of elaborative episodic memory encoding, whereas marijuana users might have used the short-term store in a more passive manner.

4.3. Hippocampus

Animal models focusing on the adverse effects of Δ^9-tetrahydrocannabinol (Δ^9-THC), the primary psychoactive component of marijuana, on hippocampal function, and similarities between effects of hippocampal lesions and Δ^9-THC's acute effects, have provided the best current theoretical framework for conceptualizing the drug's effects on memory (Hampson and Deadwyler, 1998; Solowij, 1998). Some structural changes in the hippocampus have also been reported in animal models (Scallet et al., 1987).

We found that the left, language-dominant hippocampus was more active than the right hippocampus in control subjects in the memory tests (relative to the control test), presumably because the memory tests involved verbal stimuli. However, the marijuana users showed no lateralization of memory-related hippocampal activity. This difference between groups was not influenced by the differences among the three memory tests, e.g., the relative importance of episodic memory encoding vs. retrieval. Although functional neuroimaging studies in humans have indicated hippocampal activation in both episodic memory encoding and retrieval, consensus about hippocampal involvement in these functions and their localization within the hippocampus has not yet been achieved. Lepage et al. (1998) have proposed a hippocampal encoding/retrieval model based on meta-analysis of PET studies of episodic memory, according to which activations in the hippocampal region associated with encoding and retrieval are located primarily in the rostral and caudal portions of the region, respectively. However, the validity of this model has been disputed based on review of both fMRI and PET studies and direct, within-subjects comparison during episodic memory encoding and retrieval (Schacter et al., 1999; Schacter and Wagner, 1999).

Hippocampal and prefrontal memory-related activity differed with respect to lateralization and between-group differences in lateralization. This is understandable; lateralization of cognitive functions in the brain along the verbal/nonverbal dimension has been more reliably established in temporal regions, including the hippocampus, than in frontal regions (Stuss and Benson, 1984; Tranel, 1994), whereas the hemispheric encoding/retrieval asymmetry model (Tulving et al., 1994a) postulates prefrontal lateralization along the encoding/retrieval dimension in the type of memory tests that we used.

The more prominent recency effect during recall of the NEW LIST in marijuana users relative to control subjects, together with the marijuana users' absence of the laterality effect in hippocampal rCBF that was shown by the control subjects, are somewhat reminiscent of findings in patients who had hippocampal resection (Hermann et al., 1996). Both this surgical study and the present findings suggest that recall from the end of a list fares relatively better than recall from the beginning or middle in the face of reduced left hippocampal activity, presumably because establishment of long-term memory traces is a key aspect of hippocampal functions (Tranel, 1994). Although hippocampal functions also encompass some aspects of short-term memory or working memory (Curtis et al., 2000; Friedman and Goldman-Rakic, 1988; Hampson and Deadwyler, 1998), they may not include the verbal short-term memory processing that contributes to recency effects in word list learning tasks (Capitani et al., 1992; Hermann et al., 1996; Squire et al., 1993).

4.4. Alternative interpretations of the changes in marijuana users

The rCBF changes in marijuana users, relative to control subjects, that we detected after at least 26 h of monitored abstinence from drugs, may reflect changes in brain function

due to frequent marijuana use. Although this interpretation seems the most plausible to us, there are several other possible interpretations, which we discussed in a previous report concerning rCBF when the subjects were lying quietly, with eyes closed, without specific instructions as to mental activities (Block et al., 2000b). Marijuana users might have shown rCBF differences from control subjects prior to beginning marijuana use; marijuana users might have had other characteristics that caused the rCBF differences, e.g., experience with illegal drugs other than marijuana (even though this was reasonably limited); being a marijuana user might have been associated with differences in mental activities that caused the rCBF differences, but that were not directly due to marijuana's effects on the brain; or the abstinence period that we required might have been associated not only with effects of chronic use, but, to some extent, with putative long-lasting acute effects that might last up to a day or so, theoretical effects associated with accumulation of cannabinoids in fatty tissues following frequent use, or abstinence effects. The reasons that we previously discussed for favoring the interpretation that frequent marijuana use produced changes in brain function (Block et al., 2000b) apply to the present results, as well — although none of the alternative interpretations can be entirely excluded.

The most plausible of these alternative interpretations is probably that our findings were due to abstinence from marijuana. Rigorous evidence of abstinence effects with smoked marijuana was provided by Haney et al. (1999b). Some previous reports of abstinence effects were less convincing or involved around-the-clock oral administration of large doses of Δ^9-THC (Jones et al., 1976). Haney et al. (1999b) found that abstinence affected subjective ratings and food intake. Abstinence did not affect memory testing in this study or in a similar study involving orally administered Δ^9-THC (Haney et al., 1999a). Indeed, of five cognitive or psychomotor tests that were administered, abstinence only affected one with smoked marijuana, and none with orally administered Δ^9-THC. Therefore, the relevance of the observed abstinence effects to memory and rCBF is unclear.

Other alternative interpretations, which we did not consider previously (Block et al., 2000b), are that abstinence from caffeine or nicotine could have affected memory or rCBF. Both drugs produce some acute effects on memory (Rezvani and Levin, 2001; Warburton, 1995) and cerebral blood flow (Cameron et al., 1990; Ghatan et al., 1998), and produce abstinence effects, including some effects on task performance (James, 1998; Sommese and Patterson, 1995), and at least for caffeine, some effects on cerebral blood flow (Mathew and Wilson, 1985). Limited evidence suggests nicotine abstinence may have some effect on memory (Snyder et al., 1989), while caffeine abstinence may not (Comer et al., 1997). We required relatively short abstinence periods from both drugs (Griffiths and Woodson, 1988; Snyder et al., 1989) in a rough effort to minimize both acute effects and abstinence effects. Marijuana users and control subjects were treated the same in this respect. Nevertheless, the possibility that caffeine or nicotine abstinence effects influenced our findings cannot be excluded.

Abstinence, whether from marijuana, caffeine, or nicotine, might be associated with increased anxiety-related symptoms. Anxiety affects rCBF (Fredrikson et al., 1997) and could conceivably affect memory (Reidy and Richards, 1997). The minimal anxiety reported by both marijuana users and control subjects during the PET session weighs against the notion that they were experiencing abstinence effects or changes in rCBF or memory due to anxiety.

We also discussed in our previous report (Block et al., 2000b) the limited available data concerning the extent to which some effects of frequent marijuana use on brain function or cognition persist with prolonged abstinence (Solowij, 1998), and how clarifying the persistence of the rCBF changes that we observed would help clarify whether they are due to frequent marijuana use per se. This approach would also help clarify the present findings. One group reported that there were virtually no impairments of memory or other cognitive functions after 28 days of abstinence from marijuana (Pope et al., 2001), but that there were persisting, albeit diminished, alterations of prefrontal cortex activation in a working memory test (Yurgelun-Todd et al., 1998).

We also discussed previously (Block et al., 2000b) the partial, but incomplete, consistency between the rCBF changes that we observed and the distribution of cannabinoid receptors in the brain, and possible reasons for this. This discussion also applies to the present findings and is relevant to their interpretation.

4.5. Independence of effects in different brain regions

Were the memory-related rCBF differences of marijuana users from control subjects in prefrontal cortex, hippocampus, and cerebellum relatively independent of one another? Or were the differences in one brain region fundamental, leading to secondary effects in the other regions?

Because animal models have demonstrated the major role of the hippocampus in mediating some cannabinoid effects on memory (Hampson and Deadwyler, 1998; Solowij, 1998), it is tempting to speculate that the hippocampal effects were fundamental. Although plausible, this requires a substantial inferential leap, considering the lack of other pertinent information, e.g., sufficient animal data concerning memory-related cannabinoid effects on other brain regions.

Indeed, recent animal data suggest that cannabinoids may exert some independent, memory-impairing effects on prefrontal cortex (Diana et al., 1998; Jentsch et al., 1997). Frontal effects of chronic marijuana use in humans have been demonstrated by studies involving functional magnetic resonance imaging (Yurgelun-Todd et al., 1998), auditory event-related potentials (Solowij, 1998), and quantitative electroencephalography (Struve et al., 1994); and suggested by some studies involving cognitive tests (Pope and Yurgelun-Todd, 1996).

A major hypothesis in a recent review of human neuroimaging studies of acute and chronic marijuana use (Loeber and Yurgelun-Todd, 1999) is that the frontopontocerebellar network is implicated as a site sensitive to cannabinoid-induced alterations in the levels of dopaminergic activity derived through the medial forebrain bundle, which projects from the ventral tegmental area; and that this network influences various types of human behavior that are affected by marijuana. Chronic marijuana use results in changes at the receptor level, which the authors hypothesize lead to alterations in the dopamine system and to reduced blood flow and metabolism, especially in portions of the frontopontocerebellar network. The emphasis in this review on the frontopontocerebellar network is highly consistent in a general sense with the prominent memory-related prefrontal and cerebellar changes in rCBF and overall posterior cerebellar baseline hypoactivity observed in the marijuana users in the present study, but the proposal is not sufficiently detailed to be confirmed or disconfirmed in a more specific sense by the precise pattern of rCBF changes that we observed. This proposal also needs to be integrated with the major role of the hippocampus in mediating some cannabinoid effects on memory (Hampson and Deadwyler, 1998; Solowij, 1998), and with the hippocampal effects observed in the present study.

The present findings cannot answer the question of whether the memory-related rCBF differences of marijuana users from control subjects in different brain regions were independent or causally linked. Understanding of the functioning of brain cannabinoid systems related to memory is too fragmentary to provide a basis for a fully articulated model of our findings.

4.6. Cerebellum

Nevertheless, it is also tempting to speculate that rCBF differences of marijuana users from control subjects in the cerebellum may have been more fundamental than memory-related rCBF differences observed elsewhere in the brain. In contrast to the prefrontal and hippocampal changes, marijuana users showed greater posterior cerebellar memory-related activation than control subjects. However, marijuana users, relative to control subjects, also showed an overall baseline posterior cerebellar hypoactivity, which was revealed by analyses examining each test individually. In our previous report concerning rCBF when the subjects were lying quietly, with eyes closed, without specific instructions as to mental activities (Block et al., 2000b), we noted that this posterior cerebellar hypoactivity contrasted with only a few, much smaller differences elsewhere in the brain. This posterior cerebellar hypoactivity also occurred during all three memory tests and the control test in the present study — and was the largest difference between groups in every analysis. Conceivably, this posterior cerebellar hypoactivity may be related to effects of marijuana use on cerebellar cannabinoid binding sites. Our finding of cerebellar hypoactivity agrees with the only previous PET study of chronic marijuana users, which measured regional cerebral glucose utilization and found decreased relative metabolism in marijuana users in the cerebellum (Volkow et al., 1996). This study did not examine brain activity as a function of test conditions. The primary analyses in the present study subtracted the control test rCBF data from the memory test rCBF data in order to examine memory-related rCBF differences between groups. The results (Table 2) showed memory-related increases in posterior cerebellar activity in the marijuana users (relative to control subjects), but not the posterior cerebellar hypoactivity in the marijuana users, because the latter was present during the control test, as well as each of the memory tests — and was, therefore, "subtracted out" to a large extent.

The cerebellum is among the brain regions that show prominent acute effects of cannabinoids in PET studies in humans, and these cerebellar effects are related to subjective changes, i.e., intoxication and altered sense of time (Mathew et al., 1998; Volkow et al., 1996). Although the cerebellum was traditionally thought to mediate mainly motor functions, more recently a cerebellar contribution to cognition has been hypothesized to result from a role in timing, in sensory information processing, or in attention and prediction of real-time events (Schmahmann, 1997). We have consistently observed cerebellar activations in PET studies involving several types of memory tests (Andreasen et al., 1995). Numerous recent studies indicate that the cerebellum sends output and receives input from multiple cortical regions (Schmahmann, 1997).

The possibility that the baseline hypoactivity and memory-related increases in activity in marijuana users, relative to control subjects, were relevant to memory processing is reinforced by the finding that they were concentrated in posterior, but not anterior, cerebellum. Recently accumulating evidence from neuroimaging studies and studies of patients with cerebellar disease suggests greater potential involvement of posterior than anterior cerebellum in attention, memory, and other higher cognitive functions (Akshoomoff et al., 1997; Allen et al., 1997; Parsons and Fox, 1997; Schmahmann and Sherman, 1997). The memory-related increases in activity in marijuana users in these regions contrasted with the opposite pattern in anterior vermis, which is less likely to be involved in such functions, as well as with the patterns in prefrontal cortex and the hippocampus. As with the prefrontal differences between groups, the cerebellar differences were more common in recall of the NEW LIST than the OLD LIST W P or OLD LIST W/O P, suggesting that they were more related to episodic memory encoding than retrieval.

Conceivably, the posterior cerebellar hypoactivity in the marijuana users, relative to control subjects, might have a direct, adverse effect on some memory functions. The memory-related increases in posterior cerebellar activity in the marijuana users, relative to control subjects, might then, in part, reflect an attempt to bring some portions of this

depressed region up to a serviceable level of activation when confronted with the demands of the memory tests, particularly the recall of the NEW LIST. The posterior cerebellar hypoactivity might also conceivably have indirect effects through a phenomenon analogous to diaschisis, a decrease in brain activity in an area functionally connected to, but distant from, the site of a lesion. Hypoactivity in cerebral cortex may occur due to cerebellar lesions and be responsible for some cognitive dysfunction, e.g., aphasia (Mariën et al., 1996). Analogously, the memory-related rCBF decreases in prefrontal cortex in the marijuana users, relative to control subjects, might be partly due to their posterior cerebellar hypoactivity.

4.7. Conclusion

Marijuana use may be associated with decreased memory-related functioning of some brain regions (e.g., prefrontal cortex and hippocampus) that are critically involved in memory processes, and increased reliance on other regions involved in these processes (e.g., cerebellum), which have themselves been affected by marijuana use — resulting in altered activation patterns, and, in some situations, less efficient information processing. Behavioral consequences of less efficient information processing could be of societal concern considering the widespread use of marijuana.

Acknowledgments

This research was supported by grants DA10554, NIDA, NIH, and RR00059, General Clinical Research Centers Program, NCRR, NIH. We would like to express our appreciation to Linda Smith and Michael Daugherty for assisting in data collection and Karen Cretsinger and Helen Keefe for trimming the traces of the hippocampus. Thanks also to the PET Center nursing and technological staff (Jo Clark, Dean Clermont, Suzanne Kaprich, Julie Koeppel, John Richmond, Robin Thompson, and Christine Ward).

References

Akshoomoff NA, Courchesne E, Townsend J. Attention coordination and anticipatory control. In: Schmahmann JD, editor. The cerebellum and cognition. San Diego (CA): Academic Press, 1997. pp. 575–98.

Allen G, Buxton RB, Wong EC, Courchesne E. Attentional activation of the cerebellum independent of motor involvement. Science 1997;275: 1940–3.

Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Watkins GL, Ponto LL, Hichwa RD. PET studies of memory: novel versus practiced free recall of word lists: II. Neuroimage 1995;2:296–305.

Arndt S, Cizadlo T, Andreasen NC, Heckel D, Gold S, O'Leary DS. Tests for comparing images based on randomization and permutation methods. J Cereb Blood Flow Metab 1996a;16:1271–9.

Arndt S, Cizadlo T, O'Leary D, Gold S, Andreasen NC. Normalizing counts and cerebral blood flow intensity in functional imaging studies of the human brain. Neuroimage 1996b;3:175–84.

Awh E, Smith EE, Jonides J. Human rehearsal processes and the frontal lobes: PET evidence. Ann NY Acad Sci 1995;769:97–117.

Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988; 56:893–7.

Block RI, Ghoneim MM. Effects of chronic marijuana use on human cognition. Psychopharmacology 1993;110:219–28.

Block RI, O'Leary DS, Ehrhardt JC, Augustinack JC, Ghoneim MM, Arndt S, Hall JA. Effects of frequent marijuana use on brain tissue volume and composition. NeuroReport 2000a;11:491–6.

Block RI, O'Leary DS, Hichwa RD, Augustinack JC, Boles Ponto LL, Ghoneim MM, Arndt S, Ehrhardt JC, Hurtig RR, Watkins GL, Hall JA, Nathan PE, Andreasen NC. Cerebellar hypoactivity in frequent marijuana users. NeuroReport 2000b;11:749–53.

Buschke H. Selective reminding for analysis of memory and learning. J Verbal Learn Verbal Behav 1973;12:543–50.

Cameron OG, Modell JG, Hariharan M. Caffeine and human cerebral blood flow: a positron emission tomography study. Life Sci 1990;47:1141–6.

Capitani E, Della Sala S, Logie RH, Spinnler H. Recency, primacy, and memory: reappraising and standardising the serial position curve. Cortex 1992;28:315–42.

Comer SD, Haney M, Foltin RW, Fischman MW. Effects of caffeine withdrawal on humans living in a residential laboratory. Exp Clin Psychopharmacol 1997;5:399–403.

Curtis CE, Zald DH, Lee JT, Pardo JV. Object and spatial alternation tasks with minimal delays activate the right anterior hippocampus proper in humans. NeuroReport 2000;11:2203–7.

Diana M, Melis M, Gessa GL. Increase in meso-prefrontal dopaminergic activity after stimulation of CB1 receptors by cannabinoids. Eur J Neurosci 1998;10:2825–30.

Fiez JA, Raife EA, Balota DA, Schwarz JP, Raichle ME, Petersen SE. A positron emission tomography study of the short-term maintenance of verbal information. J Neurosci 1996;16:808–22.

Fredrikson M, Fischer H, Wik G. Cerebral blood flow during anxiety provocation. J Clin Psychiatry 1997;58:16–21.

Friedman HR, Goldman-Rakic PS. Activation of the hippocampus and dentate gyrus by working-memory: a 2-deoxyglucose study of behaving rhesus monkeys. J Neurosci 1988;8:4693–706.

Ghatan PH, Ingvar M, Eriksson L, Stone-Elander S, Serrander M, Ekberg K, Wahren J. Cerebral effects of nicotine during cognition in smokers and non-smokers. Psychopharmacology 1998;136:179–89.

Grafton ST. Mapping memory systems in the human brain. Semin Neurosci 1995;7:157–63.

Griffiths RR, Woodson PP. Caffeine physical dependence: a review of human and laboratory animal studies. Psychopharmacology 1988;94: 437–51.

Hampson RE, Deadwyler SA. Role of cannabinoid receptors in memory storage. Neurobiol Dis 1998;5:474–82.

Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. Psychopharmacology 1999a;141:385–94.

Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following smoked marijuana in humans. Psychopharmacology 1999b;141:395–404.

Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, De Costa BR, Rice KC. Cannabinoid receptor localization in brain. Proc Natl Acad Sci USA 1990;87:1932–6.

Hermann BP, Seidenberg M, Wyler A, Davies K, Christeson J, Moran M, Stroup E. The effects of human hippocampal resection on the serial position curve. Cortex 1996;32:323–34.

Hieronymus AN, Lindquist EF, Hoover HD. Manual for school administrators, Iowa Tests of Basic Skills. Chicago (IL): Riverside, 1982.

Hurtig RR, Hichwa RD, O'Leary DS, Ponto LLB, Narayana S, Watkins GL, Andreasen NC. Effects of timing and duration of cognitive activation in [^{15}O] water PET studies. J Cereb Blood Flow Metab 1994;14:423–30.

James JE. Acute and chronic effects of caffeine on performance, mood, headache, and sleep. Neuropsychobiology 1998;38:32–41.

Jentsch JD, Andrusiak E, Tran A, Bowers MB, Roth RH. Δ^9-Tetrahydrocannabinol increases prefrontal cortical catecholaminergic utilization and impairs spatial working memory in the rat: blockade of dopaminergic effects with HA966. Neuropsychopharmacology 1997;16:426–32.

Jones RT, Benowitz N, Bachman J. Clinical studies of cannabis tolerance and dependence. Ann NY Acad Sci 1976;282:221–39.

Lepage M, Habib R, Tulving E. Hippocampal PET activations of memory encoding and retrieval: the HIPER model. Hippocampus 1998;8: 313–22.

Lepage M, Ghaffar O, Nyberg L, Tulving E. Prefrontal cortex and episodic memory retrieval mode. Proc Natl Acad Sci USA 2000;97:506–11.

Loeber RT, Yurgelun-Todd DA. Human neuroimaging of acute and chronic marijuana use: implications for frontocerebellar dysfunction. Hum Psychopharmacol: Clin Exp 1999;14:291–304.

Magnotta VA, Heckel D, Andreasen NC, Cizadlo T, Westmoreland Corson P, Ehrhardt JC, Yuh WTC. Measurement of brain structures with artificial neural networks: two- and three-dimensional applications. Radiology 1999;211:781–90.

Marcus S, Robins LN, Bucholz K. Quick Diagnostic Interview Schedule III-R. St. Louis (MO): Washington University School of Medicine, 1991.

Mariën P, Saerens J, Nanhoe R, Moens E, Nagels G, Pickut BA, Dierckx RA, De Deyn PP. Cerebellar induced aphasia: case report of cerebellar induced prefrontal aphasic language phenomena supported by SPECT findings. J Neurol Sci 1996;144:34–43.

Mathew RJ, Wilson WH. Caffeine consumption, withdrawal and cerebral blood flow. Headache 1985;25:305–9.

Mathew RJ, Wilson WH, Turkington TG, Coleman RE. Cerebellar activity and disturbed time sense after THC. Brain Res 1998;797:183–9.

McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M. The fifth edition of the Addiction Severity Index. J Subst Abuse Treat 1992;9:199–213.

Nyberg L, Cabeza R, Tulving E. PET studies of encoding and retrieval: the HERA model. Psychon Bull Rev 1996;3:135–48.

Owen AM, Herrod NJ, Menon DK, Clark JC, Downey SPMJ, Carpenter TA, Minhas PS, Turkheimer FE, Williams EJ, Robbins TW, Sahakian BJ, Petrides M, Pickard JD. Redefining the functional organization of working memory processes within human lateral prefrontal cortex. Eur J Neurosci 1999;11:567–74.

Pantel J, O'Leary DS, Cretsinger K, Bockholt HJ, Magnotta V, Andreasen NC. A new method for the in vivo volumetric measurement of the human hippocampus with high neuroanatomical accuracy. Neuroimage 1999;9:S164.

Parsons LM, Fox PT. Sensory and cognitive functions. In: Schmahmann JD, editor. The cerebellum and cognition. San Diego (CA): Academic Press, 1997. pp. 255–71.

Pope HG, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. JAMA 1996;275: 521–7.

Pope HG, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry 2001;58:909–15.

Reidy J, Richards A. Anxiety and memory: a recall bias for threatening words in high anxiety. Behav Res Ther 1997;35:531–42.

Rey A. L'examen clinique en psychologie. Paris: Presses Universitaires de France, 1964.

Rezvani AH, Levin ED. Cognitive effects of nicotine. Biol Psychiatry 2001; 49:258–67.

Scallet AC, Uemura E, Andrews A, Ali SF, McMillan DE, Paule MG, Brown RM, Slikker W. Morphometric studies of the rat hippocampus following chronic delta-9-tetrahydrocannabinol (THC). Brain Res 1987;436:193–8.

Schacter DL, Wagner AD. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus 1999;9: 7–24.

Schacter DL, Curran T, Reiman EM, Chen K, Bandy DJ, Frost JT. Medial temporal lobe activation during episodic encoding and retrieval: a PET study. Hippocampus 1999;9:575–81.

Schmahmann JD, editor. The cerebellum and cognition. San Diego (CA): Academic Press, 1997.

Schmahmann JD, Sherman JC. Cerebellar cognitive affective syndrome. In: Schmahmann JD, editor. The cerebellum and cognition. San Diego (CA): Academic Press, 1997. pp. 433–40.

Snyder FR, Davis FC, Henningfield JE. The tobacco withdrawal syndrome: performance decrements assessed on a computerized test battery. Drug Alcohol Depend 1989;23:259–66.

Solowij N. Cannabis and cognitive functioning. Cambridge: Cambridge Univ. Press, 1998.

Sommese T, Patterson JC. Acute effects of cigarette smoking withdrawal: a review of the literature. Aviat Space Environ Med 1995;66: 164–7.

Squire LR, Knowlton B, Musen G. The structure and organization of memory. Annu Rev Psychol 1993;44:453–95.

Struve FA, Straumanis JJ, Patrick G. Persistent topographic quantitative EEG sequelae of chronic marihuana use: a replication study and initial discriminant function analysis. Clin Electroencephalogr 1994; 25:63–75.

Stuss DT, Benson DF. Neuropsychological studies of the frontal lobes. Psychol Bull 1984;95:3–28.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain: 3-D proportional system: an approach to cerebral imaging. New York: Thieme, 1988.

Tranel D. Memory, neural substrates. In: Ramachandran VS, editor. Encyclopedia of human behavior, vol. 3. San Diego (CA): Academic Press, 1994. pp. 149–64.

Tulving E, Kapur S, Craik FIM, Moscovitch M, Houle S. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. Proc Natl Acad Sci USA 1994a;91:2016–20.

Tulving E, Kapur S, Markowitsch HJ, Craik FIM, Habib R, Houle S. Neuroanatomical correlates of retrieval in episodic memory: auditory sentence recognition. Proc Natl Acad Sci USA 1994b;91:2012–5.

Volkow ND, Gillespie H, Mullani N, Tancredi L, Grant C, Valentine A, Hollister L. Brain glucose metabolism in chronic marijuana users at baseline and during marijuana intoxication. Psychiatry Res 1996;67: 29–38.

Warburton DM. Effects of caffeine on cognition and mood without caffeine abstinence. Psychopharmacology 1995;119:66–70.

Worsley KJ, Evans AC, Marrett S, Neelin P. A three dimensional statistical analysis for CBF activation studies in human brain. J Cereb Blood Flow Metab 1992;12:900–18.

Yurgelun-Todd DA, Gruber SA, Hanson RA, Baird AA, Renshaw PF, Pope HG. Residual effects of marijuana use: an fMRI study. In: Harris LS, editor. Problems of drug dependence, 1998: Proceedings of the 60th Annual Scientific Meeting, The College on Problems of Drug Dependence. NIDA Res Monogr 179. Bethesda (MD): National Institute on Drug Abuse, 1998. p. 78.