Effects of frequent marijuana use on brain tissue volume and composition

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Received 10 November 1999; accepted 3 December 1999

Acknowledgements: This research was supported by grants DA10554, NIDA, NIH, and RR00059, General Clinical Research Centers Program, NCRR, NIH. Thanks to William Yuh, M.D. for providing clinical interpretations of each MRI; Linda Smith and Michael Daugherty for assisting in data collection; Karen Cretsinger and Helen Keefe for trimming the traces of the hippocampus; and C.K. Brown for statistical analyses.

To investigate CNS effects of frequent marijuana use, brain tissue volume and composition were measured using magnetic resonance imaging (MRI) in 18 current, frequent, young adult marijuana users and 13 comparable, non-using controls. Automated image analysis techniques were used to measure global and regional brain volumes, including, for most regions, separate measures of gray and white matter. The marijuana users showed no evidence of cerebral atrophy or global or regional changes in tissue volumes. Volumes of ventricular CSF were not higher in marijuana users than controls, but were, in fact, lower. There were no clinically significant abnormalities in any subject's MRI. Sex differences were detected in several global volume measures. *NeuroReport* 11:491–496 © 2000 Lippincott Williams & Wilkins.

Key words: Brain; Cerebral atrophy; Cerebrospinal fluid; Gray matter; Magnetic resonance imaging; Marijuana; Sex; Ventricles; White matter

INTRODUCTION

Considering that marijuana is the most widely used illicit drug, the question of whether frequent marijuana use produces structural changes in the human brain has received remarkably little attention for many years. In 1971, a study by Campbell and colleagues using air encephalography detected cerebral atrophy in young individuals (mean age 22 years) with histories of consistent marijuana smoking, based on measurements of the lateral and third ventricles [1]. The results were widely publicized, but could not be replicated in three studies reported between 1977 and 1983 using computed tomography (CT), which observed no abnormalities [2–4]. These studies involved relatively low-resolution images and imprecise methods of image analysis, relative to current methodology. This is also true of a fifth, incomplete report from this era, which indicated that echoencephalography did not show enlargement of the third venticle in chronic hashish users [5].

As a result of the vast improvements in neuroimaging technologies and methods of image analysis in recent years, further examination of possible structural brain changes in marijuana users seems overdue. We studied marijuana users and comparable controls using multimodality, high resolution, thin slice MRI. Automated image analysis software provided accurately measured volumes of ventricular CSF and brain tissue partitioned into major brain regions (e.g. frontal lobe). For most of these regions, separate volume measurements for gray and white matter were made [6–8]. These imaging techniques provided increased sensitivity for detecting atrophy that was mild, regionally specific, or specific to gray or white matter – atrophy that could easily have been missed in the CT studies conducted years ago. There is no evidence of such specificity in marijuana's effects, but the possibility merits investigation considering findings with other drugs of abuse: alcohol-induced atrophy is predominantly due to a reduction in white matter volume, and the gray matter damage appears to be regionally specific [9].

The hippocampus is of particular interest with respect to marijuana because it has one of the highest densities of cannabinoid receptors in the brain [10] and appears to play a major role in mediating some of the drug's effects [11]. Possible effects of frequent marijuana use on the volume of the human hippocampus have not as yet been studied. We therefore measured hippocampal volume using an auto-

mated tracing technique based on artificial neural network methodology [12].

Use of illicit drugs other than marijuana may produce brain pathology that can be seen on MRI by a clinician, but would not be detected with our automated analysis techniques [13]. To check for individual abnormalities that might be missed by our automated techniques, a clinical interpretation of each MRI was provided by a neuroradiologist.

MATERIALS AND METHODS

Subjects: Subjects were 18 current, frequent, young adult marijuana users and 13 comparable, non-using control subjects who were participating in a study of effects of frequent marijuana use on brain structure, regional cerebral blood flow (rCBF), and cognition. Results concerning rCBF and cognition will be reported separately. All subjects were required to be right ear dominant according to a dichotic screening test and right-handed. Exclusion criteria included a history of schizophrenia; history of bipolar disorder, or current depression, according to the Quick Diagnostic Interview Schedule [14]; histories of mental retardation or brain disease unrelated to drug use; severe obesity (body mass index $\geqslant 40\,kg/m^2$, corresponding to World Health Organization grade III overweight); and current use of prescribed psychotropic drugs or drugs that might affect the rCBF results. There were additional exclusion criteria relevant to cognitive tests administered to subjects, but not to the topic of this report (e.g. criteria concerning impaired auditory and visual functioning). Both marijuana users and controls were recruited by advertisements in campus and community newspapers and paid for participation. The research was conducted with the understanding and written consent of each subject (and the approval of the responsible University of Iowa ethical committee).

We selectively recruited marijuana users whose use of illicit drugs other than marijuana was limited, and less extensive than their use of marijuana. Subjects with a history of dependence on alcohol or any illicit drugs other than marijuana were excluded. Diagnoses of dependence were based on the Quick Diagnostic Interview Schedule, supplemented in doubtful cases with interviewing by a psychiatrist specializing in addictions.

Imaging: T1-weighted images using a spoiled GRASS sequence, and PD and T2-weighted images, were obtained for the automated image analyses with a 1.5 T GE Signa Scanner. The T1-weighted parameters were 1.5 mm coronal slices, 40° flip angle, 24 ms TR, 5 ms TE, 2 NEX, 26 cm FOV, and 256×192 matrix. The PD and T2-weighted parameters were: 3.0 or 4.0 mm coronal slices, 32 ms TE (for PD) or 96 ms TE (for T2), 3000 ms TR, 1 NEX, 26 cm FOV, 256×192 matrix, and echo train length 8. Additional routine axial FLAIR and axial FSE T2 series were obtained for clinical interpretation by a neuroradiologist, who was unaware of whether individuals were marijuana users or controls.

Image analysis: The technical quality of each MRI was verified in an initial review. Several components of a locally developed collection of software, BRAINS, were used for image processing and analysis [6–8,12,15,16]. Details of the methods, as well as evidence of their reliability and validity, are given elsewhere. In essence, a three-dimensional data set was created and the images were realigned and resampled. Following a linear transformation into Talairach atlas space [17], which defines a three-dimensional grid of boxes (extended by us to include the cerebellum), regional volumes (frontal, parietal, temporal, and occipital lobes; subcortical region; and cerebellum) were derived [6,8]. A box that included more than one region was assigned to whichever region occupied the majority of the box. An additional, overlapping set of boxes was used for measuring ventricular CSF (including the lateral and third ventricles, but not the fourth ventricle). A multispectral discriminant analysis method with automated training class selection was used to classify each voxel as gray matter, white matter, or CSF [7]. The volumes of ventricular CSF and total (including surface) CSF were obtained. Separate volume measurements for gray matter and white matter were obtained for each region except the occipital lobe and cerebellum. In the latter two regions, the measurements did not achieve adequate validity, for technical reasons related to partial volume artifacts.

Tracing of the hippocampus (the gray matter, i.e. excluding most of the efferent pathway of the hippocampus) was done by an artificial neural network [12], 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 0.74 to 0.83) [15].

Statistical analyses: Volume data were analyzed by analyses of covariance including group (marijuana versus placebo) and sex as between-subjects factors. Height was used as the covariate for 'global' volumes, i.e. total intracranial tissue (the sum of all gray and white matter, including part of the brain stem); total CSF (including surface CSF); total intracranial volume (the sum of total intracranial tissue and total CSF); combined cerebral gray matter and combined cerebral white matter (summed over the frontal, temporal, and parietal lobes and the subcortical region, but excluding the occipital lobe and the cerebellum, as discussed above); and ventricular CSF. Total intracranial volume was used as the covariate for the regional volumes. Left and right sides were analyzed separately, as well as combined, for all regions except the subcortical region. Adequacy of matching of marijuana users and controls was examined using *t*-tests for quantitative characteristics (e.g. age) and Fisher's exact tests for categorical characteristics (e.g. sex). A significance level of $p < 0.05$ was used for all tests.

RESULTS

Matching of groups: The groups did not differ significantly in sex distribution (50% and 46% men among the marijuana users and controls, respectively) or mean ($\pm$ s.e.) age (22.3 ± 0.5 and 22.6 ± 0.5 years), height (172.3 ± 1.7 and 171.0 ± 2.9 cm), or weight (75.0 ± 3.0 and 77.5 ± 3.9 kg).

Marijuana users had slightly less education than controls (14.8 ± 0.3 and 15.9 ± 0.4 years, $t(29) = 2.1$, $p = 0.04$), 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 [18], achievement tests administered when the subjects attended the fourth grade of grammar school (5.3 ± 0.2 and 5.5 ± 0.3). Most subjects were currently students, so the difference between groups in education cannot be interpreted as a difference in terminal educational levels.

Drug use: Urine screens of all subjects were negative for all illegal drugs, except for marijuana in the marijuana users, at a preliminary screening session. The marijuana users were using marijuana seven or more times weekly on average (mean 18 ± 2 times), and had been using about this often for the last 2 or more years (mean 3.9 ± 0.4 years). Controls had never used marijuana ($n = 10$), or only once or twice in their lives ($n = 3$); and had never used any other illegal drugs.

No marijuana user reported using any of nine classes of illegal drugs other than marijuana specified by the Addiction Severity Index [19] as often as once per month on average during the 2 years preceding the screening session. No marijuana user used any such class more than 99 times in his or her life, and 61% never used any class more than nine times; lifetime use of 9–99 times was reported for one class by 28% and for more than one class by 11%. In the preceding 30 days, 67% used no illegal drugs other than marijuana; 22% used one class on one day; 6% used one class on two days; and 6% used two classes, each on one day.

The marijuana users were not heavy alcohol drinkers. They used alcohol 5.8 ± 0.7 days per month on average in the preceding 2 years and 6.0 ± 1.0 days on average in the preceding 30 days. Controls used alcohol on fewer days in the preceding 2 years (3.4 ± 0.6, $t(29) = -2.4$, $p = 0.02$), but not in the preceding 30 days (4.2 ± 0.8; difference not significant). The number of 'standard' alcoholic drinks consumed by the marijuana users on an average day recently was none for 22%; some, but not more than one, for 50%; and two for 28%. Corresponding percentages for controls did not differ significantly (23%, 69%, and 8%, respectively).

Global volumes: Analyses of global brain tissue and CSF volumes for marijuana users and controls, with height covaried, provided no evidence of cerebral atrophy (Table 1). Volumes of ventricular CSF were not higher in marijuana users than controls but were, in fact, lower. This difference remained significant when total intracranial volume was covaried, either by itself or in addition to height ($F(1,26) = 7.26$ and $F(1,25) = 7.09$, respectively, $p < 0.05$). This difference was not accompanied by any differences between marijuana users and controls in total intracranial volume, total intracranial tissue, total CSF, combined cerebral gray matter, or combined cerebral white matter.

Differences between marijuana users and controls did not vary for men and women, i.e. group (marijuana users vs. controls) and sex did not interact. However, means pooled over group were higher for men than women for total intracranial volume, total intracranial tissue, combined cerebral gray matter, and ventricular CSF (Table 1).

Regional volumes: Analyses of regional volumes, with total intracranial volume co-varied, indicated no significant differences between marijuana users and controls for the frontal, temporal, parietal and occipital lobes; the cerebellum; the subcortical region; or the hippocampus (Table 2). This was the case, wherever examined (Table 2), for left and right sides; and for gray matter, white matter, and both combined. There were no significant sex differences; nor did the differences between marijuana users and controls vary for men and women. Additional analyses combining the left and right side values that are listed separately in Table 2 also showed no effects of group, sex, or their interaction.

Clinical interpretations: Examination of the MRI scans of the marijuana users and controls by a neuroradiologist revealed no clinically significant abnormalities in any subject.

DISCUSSION

This MRI study detected no evidence of cerebral atrophy or other brain pathology in frequent marijuana users, through either automated global and regional volume measurement or clinical interpretation by a neuroradiologist. Contrary to the Campbell *et al.* air encephalography study that reported cerebral atrophy in marijuana users [1], volumes of ventricular CSF were lower in marijuana users than controls in the present study.

It is uncertain why the Campbell *et al.* study [1] found apparent cerebral atrophy in marijuana users, in contrast to

Table 1. Global volumes (cm^3).

Measurement	Marijuana users	Controls	Men	Women
Total intracranial volume	1430 ± 28	1436 ± 33	1507 ± 36†	1359 ± 34
Total intracranial tissue	1352 ± 26	1351 ± 31	1418 ± 33†	1285 ± 32
Total CSF	79 ± 7	85 ± 8	89 ± 9	74 ± 8
Combined cerebral gray matter excluding occipital lobe	644 ± 12	641 ± 14	676 ± 15††	609 ± 15
Combined cerebral white matter excluding occipital lobe	409 ± 9	412 ± 10	428 ± 11	393 ± 11
Ventricular CSF	11 ± 1*	16 ± 1	16 ± 1†	10 ± 1

Least squares means ($\pm$ s.e.) are shown. All are adjusted for height; those by group (marijuana users *vs* controls) are also adjusted for sex, and *vice versa*. Total intracranial tissue is the sum of all gray and white matter. Total intracranial volume is the sum of total intracranial tissue and total CSF, which includes surface CSF. Combined cerebral gray matter and combined cerebral white matter are summed over the frontal, temporal, and parietal lobes, and the subcortical region, but exclude the occipital lobe and cerebellum, for which gray and white matter were not distinguished (see text).

*Marijuana users and controls differ, $p < 0.05$; †men and women differ, $p < 0.05$; ††men and women differ, $p < 0.01$.

Table 2. Regional volumes (cm^3).

Region	Gray matter		White matter		Gray and white matter combined	
	Marijuana users	Controls	Marijuana users	Controls	Marijuana users	Controls
Frontal						
Left	135 ± 1	135 ± 2	85 ± 1	85 ± 2	220 ± 2	220 ± 3
Right	143 ± 2	142 ± 2	88 ± 1	89 ± 2	231 ± 3	232 ± 3
Temporal						
Left	78 ± 1	78 ± 1	36 ± 1	34 ± 1	114 ± 1	112 ± 1
Right	78 ± 1	77 ± 1	36 ± 1	36 ± 1	113 ± 1	113 ± 1
Parietal						
Left	73 ± 1	72 ± 1	58 ± 1	59 ± 1	131 ± 2	131 ± 2
Right	76 ± 1	75 ± 1	58 ± 1	59 ± 1	134 ± 1	134 ± 2
Occipital						
Left	–	–	–	–	66 ± 2	66 ± 2
Right	–	–	–	–	63 ± 2	62 ± 2
Cerebellum						
Left	–	–	–	–	65 ± 2	67 ± 2
Right	–	–	–	–	66 ± 2	67 ± 2
Subcortical	54 ± 1	52 ± 1	47 ± 1	47 ± 2	101 ± 1	99 ± 1
Hippocampus						
Left	1.9 ± 0.1	1.9 ± 0.1	–	–	–	–
Right	1.9 ± 0.1	1.9 ± 0.1	–	–	–	–

Least squares means (± s.e.), adjusted for total intracranial volume and sex, are shown. No white matter values are given for the hippocampus because the tracing excluded most of its efferent pathway; and gray and white matter were not distinguished for the occipital lobe and cerebellum (see text). There are no significant differences between marijuana users and controls.

the subsequent CT studies [2–4] and the present MRI study. The Campbell *et al.* study differed from the CT studies in several respects, including the possible lesser precision afforded by its neuroimaging methodology and the inclusion of patients referred because of neurological symptoms, whereas subjects in the CT studies did not manifest neurological symptoms or intellectual impairments. The cerebral atrophy observed in the Campbell *et al.* study may have been due to neurological and other problems unrelated to, and confounded with, marijuana use. The present study, which found no evidence of cerebral atrophy in marijuana users, incorporated several improvements in design relative to these past studies. None of them included a concurrently tested control group, as we did. Only age and sex were considered in matching controls with marijuana users in any of these studies, and only in one study were both of these characteristics closely matched [2]. Characteristics that reflect body size and correlate with brain volume, such as height, were not matched.

The marijuana users in the present study were relatively young and most had been using marijuana frequently for < 5 years. The results of the Campbell *et al.* study of young marijuana users notwithstanding, it seems likely that if marijuana caused cerebral atrophy, many more years of use might be required before significant neural death and subsequent replacement of dead tissue by CSF were demonstrable. MRI studies of individuals who have used marijuana for decades are needed.

The finding in the present study that volumes of ventricular CSF were lower in marijuana users than controls was not attributable to confounding by sex, height, or total intracranial volume. Because individuals were not assigned randomly to groups of marijuana users and controls, followed by chronic administration of marijuana to the former, but not the latter, the relationship of this difference in ventricular CSF to marijuana use is correlational rather than causal. Though the groups were balanced on several relevant characteristics, no premorbid MRI data were available, so it is possible that the marijuana users had smaller ventricles than the controls before beginning marijuana use. Nor can we exclude the possibility that other characteristics associated with marijuana use, rather than the drug itself, were responsible for the observed difference. One such characteristic was use of drugs other than marijuana, which was more extensive in the marijuana users than the controls; but there is no basis for expecting use of other drugs to be associated with decreased ventricular CSF. There are some characteristics, such as chronic dehydration, that are related to decreased CSF volume, but there is no basis for expecting marijuana use to be associated with such characteristics.

In short, we cannot offer any obvious, plausible biological interpretation for the difference between marijuana users and controls in ventricular CSF, either by postulating some direct effect of marijuana use on CSF volume or some indirect linkage through other, associated characteristics. Ventricular CSF volume is an indirect measure of neural loss, not a direct one; so the lower volumes in marijuana users than controls should not be interpreted as an indicator of neural health in the marijuana users. In fact, there were no differences between groups in total intracranial tissue or any of the other global and regional volume measures in Table 1 and Table 2. With the significance level of $p < 0.05$ that was used, there was one chance in 20 of a difference between groups occurring by

chance, and the difference in ventricular CSF may have been just such a type I error.

When a study does not find a hypothesized difference, such as cerebral atrophy in marijuana users in the present case, questions of power sometimes arise. Such questions are largely moot in the present study, however, because we found a difference in ventricular CSF in the direction opposite to the hypothesis and also found several effects of sex, demonstrating the sensitivity of the volume measures.

In addition to examining volumes of large brain regions, we focused on one small structure, the 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 the acute effects of Δ^9-THC, have provided the best current theoretical framework for conceptualizing the drug's effects on memory [11]. Some structural changes in the hippocampus have been reported in animal models. For example, rats studied 7 months after discontinuation of chronic, high-dose Δ^9-THC treatment showed reduced mean volume of neurons and their nuclei and decreased synaptic density in the hippocampal CA3 region [20]. The present study found no effect of frequent marijuana use on overall human hippocampal volume. This, of course, does not preclude the possibility that anatomical changes at a microscopic level might be detected in postmortem studies in humans.

Clinical interpretations of each MRI by a neuroradiologist were considered necessary to avoid missing possible brain abnormalities that might not be identified by our automated analysis techniques. These techniques would not detect focal abnormalities that occurred in some marijuana users, but in different locations for different individuals, and might not detect cerebral atrophy that occurred in only a few users. In several users of opiates, cocaine, and other drugs, MRI suggested vascular pathology in varying locations, revealing lesions, mainly in white matter, that could represent areas of demyelination [13]. There have been a few case reports of stroke in young men associated with heavy marijuana smoking in the absence of major risk factors [21], so the possibility of small focal defects in marijuana users without obvious manifestations of cerebrovascular disease deserved examination. In the present study, however, the neuroradiologist observed no clinically significant abnormalities in any marijuana users or controls.

Although differences between male and female brains were not the focus of this study, some interesting sex differences were observed. Even with height controlled, total intracranial volume was higher for men than women, and corresponding differences also occurred for total intracranial tissue, combined cerebral gray matter, and ventricular CSF. With total intracranial volume controlled, there were no sex differences in regional brain tissue volumes. The present findings agree well with those of other MRI studies in most respects. We have generally found greater global brain tissue volumes in men than women with height controlled, and limited sex differences in regional tissue volumes for the structures examined in the present study with intracranial volume controlled; and findings of other groups have been comparable (for review see [22]). However, the present findings diverge from those of some other studies in some respects, e.g. they diverge from findings of one recent study indicating that men, relative to women, had lower percentages of supertentorial gray matter, but higher percentages of white matter and total CSF; and equal percentages of ventricular CSF [23]. Such divergences could be related to differences in the populations studied. For example, most of our subjects would have been excluded from other MRI studies because of their frequent marijuana use.

Ventricular CSF volume is related to age, and the mean age of subjects in the present study (22.3 years for marijuana users and 22.6 years for controls) corresponded closely to that of the marijuana users in the Campbell *et al.* study reporting cerebral atrophy due to marijuana use (22 years) [1]. The higher ventricular CSF volume of men than of women that was detected in the present study may have contributed to the apparent cerebral atrophy due to marijuana use in the Campbell *et al.* study, in which sex was confounded with marijuana use. All the marijuana users were men, whereas most of the controls (54%) were women.

CONCLUSION

The results of the present study indicate that frequent marijuana use does not produce clinically apparent MRI abnormalities or detectable global or regional changes in brain tissue volumes of gray or white matter, or both combined. However, these findings by no means give marijuana a clean bill of health. In fact, anatomical abnormalities might occur at a microscopic level that cannot be detected by MRI, and MRI abnormalities might be observed in individuals who used marijuana for longer periods than our subjects. Frequent marijuana use may produce brain abnormalities that are detectable with other research techniques. The marijuana users and controls in the present study showed some differences in rCBF and cognitive function ([24] manuscript in preparation); we have previously observed some cognitive impairments in marijuana users [25]; and other researchers, using electrophysiological methods, measurement of rCBF and regional cerebral metabolism, and cognitive testing, have reported some, albeit limited, changes in marijuana users [26]. Only by applying, in addition to structural neuroimaging, the full arsenal of other available brain research techniques, will a complete picture of effects of frequent marijuana use on brain structure and function eventually emerge.

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