The American Journal on Addictions, 14:64–72, 2005
ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1080/10550490590899862

Lack of Hippocampal Volume Change in Long-term Heavy Cannabis Users

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The effects of cannabis smoking on the morphology of the hippocampus are still unclear, especially because previous human studies have examined primarily younger, shorter-term users. We used magnetic resonance imaging to investigate these effects in a group of 22 older, long-term cannabis users (reporting a mean [SD] of 20,100 [13,900] lifetime episodes of smoking) and 26 comparison subjects with no history of cannabis abuse or dependence. When compared to control subjects, smokers displayed no significant adjusted differences in volumes of gray matter, white matter, cerebrospinal fluid, or left and right hippocampus. Moreover, hippocampal volume in cannabis users was not associated with age of onset of use nor total lifetime episodes of use. These findings are consistent with recent literature suggesting that cannabis use is not associated with structural changes within the brain as a whole or the hippocampus in particular. (Am J Addict 2005;14:64–72)

Many studies in recent decades have examined the effects of chronic cannabis use on human cognition and behavior. Regular cannabis use has been linked to deficits in memory, learning, and attention.[1–3] Researchers have also used various methods to determine whether cannabis use results in brain atrophy or morphometric changes. These latter studies have thus far yielded equivocal data. One of the first studies in this area, used pneumoencephalographic techniques to measure the physical changes found in young cannabis users.[4] These investigators found evidence of cerebral atrophy, although subsequent studies applying more advanced technologies did not reproduce these findings.[5,6] More recently, magnetic

Received December 20, 2002; revised March 25, 2003; accepted May 30, 2003.
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resonance imaging (MRI) has been used to measure the regional brain volume of young adult cannabis users. Block and colleagues measured tissue volumes in heavy users, including gray and white matter and ventricular cerebrospinal fluid (CSF), and found no detectable effect found on hippocampal volume.[7] Somewhat similar findings were reported in a subsequent study of 57 moderate to heavy cannabis users with a mean age of 31.3 years.[8] These investigators found a significantly decreased ratio of gray matter to whole brain volume in users who began smoking at age 16 or less as compared to later-onset users but found no differences between the age-of-onset groups in the amygdala or hippocampus.

However, the above studies have examined primarily younger, shorter-term cannabis users, rather than smokers with a history of heavy use over decades. This limitation may be important, since animal studies provide suggestive evidence that morphological change may occur with prolonged heavy cannabis exposure.[7] Specifically, animal studies of binding affinity have demonstrated that delta 9-tetrahydrocannabinol (THC), the active ingredient in cannabis, accumulates preferentially in the hippocampus in comparison to other structures.[9–11] Studies of rats, using both light and electron microscopy techniques, have found significant THC-induced changes in the rat hippocampus following chronic exposure. These studies were designed to administer doses of THC comparable to very heavy daily use in humans.[12] For example, Scallet and colleagues[13] dosed rats for ninety days with daily high levels of THC (10–60 mg/kg) and found significant decreases in the mean volume of neurons of the hippocampal CA3 region. Similar results were attained in a study by Landfield et al.,[14] in which rats were treated with THC for an eight month period (up to 8 mg/kg, five times weekly). Using synthetic cannabinoids with potency comparable to THC, Lawston and colleagues dosed rats twice daily (2.0 mg/kg) for 21 days, and found a significant morphological change within the hippocampal CA1 region.[15] These tissue decreases identified in the rat hippocampus after heavy cannabis exposure may be linked to hippocampal dysfunction demonstrated previously in studies on both rats and humans.[12,16,17]

These animal studies, taken together with the previous observations of memory deficits in human cannabis users, and the fact that the hippocampus has a high density of cannabinoid receptors, combine to suggest that chronic heavy cannabis usage might be associated with decreased hippocampal volume in humans. Admittedly, as noted above, previous MRI studies of frequent smokers have failed to find these morphological changes. However, we hypothesized that older, more long-term heavy cannabis users, with much greater lifetime cannabis exposure than those assessed in previous studies, might demonstrate such changes on high-resolution magnetic resonance imaging. Therefore, we examined the association of chronic heavy cannabis use with the volume of the hippocampus and of whole brain tissue.

MATERIALS AND METHODS

Sample

We examined 22 chronic heavy cannabis users, recruited in the course of an earlier neuropsychological study previously presented in detail.[18] Briefly, subjects were individuals aged 30–55 years who had smoked marijuana on at least 5,000 separate occasions. Lifetime episodes of cannabis use were calculated by establishing a year-by-year estimate of frequency of use in initial interviews with subjects.[18] Subjects were excluded if they reported:

1. the use of any other class of drugs of abuse more than 100 times in their lives

2. a history of alcohol abuse or dependence by DSM-IV criteria,[19] as determined by the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996)
3. a current DSM-IV Axis I disorder other than simple phobia or social phobia, as determined by the SCID
4. a history of suffering from head injury with a loss of consciousness requiring hospitalization
5. current use of any psychoactive medication
6. a medical, psychiatric, or neurological condition that might affect cognitive function.

The 26 control subjects were individuals recruited from newspaper advertisements who reported:

1. no lifetime history of any DSM-IV Axis I disorder, including no lifetime history of cannabis abuse or dependence, and alcohol or other substance abuse or dependence as determined by the SCID
2. no history of a head injury with loss of consciousness requiring hospitalization
3. no current use of any psychoactive medication
4. no medical, psychiatric, or neurological condition that might affect cognitive function or brain morphology.

Subjects in both study groups were excluded if they had metal implants or dental braces (due to the MRI procedure indications) or if they were uncooperative with the study protocol. All subjects in both groups signed informed consent for the study after the procedures were fully explained. Image acquisition was completed within 24 hours of study enrollment.

Imaging Procedure

Structural neuroimaging was performed on each subject using a 1.5 Tesla GE Signa whole-body scanner. Sagittal localizing images were acquired, followed by T1-weighted coronal images of the whole brain (3 mm spoiled gradient-recalled acquisition; SPGR). Images were acquired using the following parameters: TR = 35 ms, TE = 5 ms, flip angle = 45°, 256 × 256 matrix, and voxel dimensions = 0.976 × 0.976 mm. Image analysis was conducted offline on a microcomputer using a semi-automated segmentation software package (MRX). A single trained operator made all measurements blind to the group status of the subjects. This individual had previously established interrater reliability ($r > 0.87$) with another trainer and also completed intrarater reliability studies. Structural boundaries were placed for the hippocampus, as well as for the whole brain, aided by use of an anatomical atlas.[20]

Morphometric Analysis of Images. Images were segmented into gray and white matter using MRX, a semi-automated algorithm.[20] The full series of coronal images was transferred from the MR scanner to a Sun workstation and filtered to reduce noise. Seed points were chosen to define a range of pixel intensities for gray and white matter, and the components of the image were divided into tissue types using a fully automated algorithm. Measurements of the hippocampal complex included the hippocampus and the parahippocampal gyrus. The anterior portion was defined as the first slice where the mamillary bodies appeared and the optic chiasm split into the optic tracts; the posterior portion was defined as the last slice in which the cerebral aqueduct was distinguishable.[20]

Statistical Analysis

Differences between the groups on baseline demographic variables were assessed using Fisher's exact test for binary variables and the t test for continuous variables. Differences between groups on brain

volumetric measurements were assessed using linear regression adjusting for age, ethnicity (white vs. non-white), and sex. Group was entered as a dummy variable, and age was entered as chronological age. All significance levels are two-tailed, with the alpha set at $p = .05$. An intrarater reliability coefficient was calculated for various brain regions as $r = .90$.

RESULTS

Demographics

The 22 chronic heavy cannabis users were similar in ethnic and sex distribution to the 26 controls but older in mean age (see Table 1). Cannabis users reported a mean (SD) of 20,140 (13,866) episodes of smoking (range 5,000–54,300 episodes). They had begun smoking at a mean age of 16.0 (4.1) years (range 12–28). All subjects were smoking at least once per day at entry into the study. They had been smoking cannabis for a mean (SD) of 22.6 (5.7) years (range 12–33 years) at the time of study entry; they reported smoking at least once per day for a mean of 18.9 (7.5) years (range 1–33 years). Typically, they had smoked on two to four separate occasions each day during their years of daily smoking. All of the 22 subjects met DSM-IV criteria for cannabis dependence during their years of daily smoking. Further details on the attributes of the entire sample of cannabis users, from which these 22 subjects were drawn, have been presented previously.[21] The 22 long-term cannabis users had smoked a mean of 2,727.4 (2,980.8) packs of tobacco cigarettes in their lives (range 0–9,360), and they had consumed a lifetime mean of 6,524.1 (5,933.8) alcoholic drinks (range 0–20,280), where a "drink" was defined as twelve ounces of beer, four ounces of wine, or 1.5 ounces of distilled liquor. Although we did not possess specific information on episodes of cannabis use (if any) by the controls or their lifetime levels of tobacco, alcohol, or other substance use, these subjects had been screened to exclude any history of substance abuse or dependence, as mentioned above.

Volume Measurements

After adjusting for age, ethnicity, and sex, we found no differences even approaching significance between the heavy cannabis users and controls on mean gray matter, white matter, cerebrospinal fluid, or total brain volume (see Table 2). The groups also showed no significant adjusted differences in either the absolute volumes of the left or right hippocampus or in the ratio of these absolute volumes to total brain volume. In an exploratory analysis, we also repeated all of the comparisons in Table 2 without adjusting for age, and we again repeated these comparisons using a reduced age-matched sample of the sixteen oldest controls (mean age 33.9 years) and the sixteen youngest cannabis users (mean age 35.1 years). In both of these exercises, we found

TABLE 1. **Demographic Features of Cannabis Users vs. Control Subjects**

Demographic feature	Cannabis users (n = 22)	Control subjects (n = 26)	t	*p*
Age, years, mean (SD)	38.1 (6.2)	29.5 (8.5)	3.9	<0.001
Sex, female, n (%)	6 (27.2)	7 (26.9)		1.0
Education, years, mean (SD)	14.2 (2.5)	16.2 (1.8)	−3.1	0.004
Ethnicity, non-white, n (%)	5 (22.3)	2 (7.7)		0.22

TABLE 2. **Brain Morphological Measurements in Cannabis Users and Control Subjects**

Measurement [Mean (SD)]	Cannabis users (n = 22)	Control subjects (n = 26)	Estimated differences between groups*		
			Mean (SE)	t	*p*
Total gray matter	780 (115)	817 (85)	−46.5 (33.8)	−1.38	0.18
Total white matter	525 (78)	533 (97)	3.3 (28.6)	0.12	0.91
Cerebrospinal fluid	35.1 (14.9)	38.6 (21.1)	−3.4 (6.5)	−0.52	0.61
Total brain volume (TBV)	1305 (148)	1350 (140)	−43.2 (44.4)	−0.97	0.33
Left hippocampus	7.1 (0.8)	7.9 (1.2)	−0.3 (0.4)	−0.84	0.41
Right hippocampus	7.2 (0.9)	7.6 (1.1)	0.1 (0.3)	0.39	0.7
Total hippocampal volume	14.3 (1.6)	15.5 (2.2)	−0.2 (0.6)	−0.27	0.79
Left hippocampus/TBV†	0.55 (0.07)	0.59 (0.09)	−0.008 (0.03)	−0.26	0.80
Right hippocampus/TBV†	0.55 (0.07)	0.56 (0.08)	0.02 (0.03)	0.97	0.34
Total hippocampal volume/TBV†	1.10 (0.13)	1.15 (0.15)	0.01 (0.05)	0.33	0.75

*By linear regression, adjusted for age, sex, and ethnicity.
†Expressed as percent of total brain volume (TBV).

no major changes in the levels of significance, with all of the comparisons in the table remaining non-significant ($p > 0.1$ in all cases). In a further exploratory analysis, we also compared the twelve heavy cannabis users who first began smoking at age fifteen or less with the ten users who first began smoking at age sixteen or above on all of the volumetric measurements shown in Table 2. We again found no significant differences between these age-of-onset subgroups, or between either of these subgroups and the control subjects. We also specifically examined gray matter as percent of total brain volume in the fifteen subjects who began smoking at age sixteen or earlier. We chose this age as the dividing mark for "early-onset" use because three studies have reported differences on neuroimaging measures and neuropsychological measures between subjects who began smoking prior to age sixteen and those who began at seventeen or later.[8,22,23] However, the younger-onset users did not differ from the seven older-onset users ($p = 0.47$) or the 26 control subjects ($p = 0.15$) on this comparison. Next, among the 22 heavy users, we assessed the association between log-transformed lifetime episodes of smoking and all of the volumetric measurements. Again, none of these associations approached significance. Finally, among the twenty heavy users who received neuropsychological testing, we assessed the associations between hippocampal volume (as a ratio of total brain volume) and scores on various cognitive tests, including Buschke's Selective Reminding Test, the Wechsler Memory Scale, and the Benton Visual Retention Test using linear regression adjusting for age and gender. None of these associations approached statistical significance.

DISCUSSION

Using magnetic resonance imaging techniques, we compared 22 chronic heavy cannabis users with 26 healthy controls and found no significant association between cannabis use and hippocampal volume. Among our subjects, all of whom were less than 55 years old, age had little effect on volumetric measurements; all differences between cannabis users and controls were non-significant in age-adjusted, age-matched, and age-unadjusted comparisons. The absence of significant differences between chronic users and controls in whole brain gray matter, white matter, or cerebrospinal fluid suggests that chronic cannabis use may not have a global effect on cerebral tissue volume. These results are consistent with the findings of Block et al.,[7] who utilized imaging techniques to examine global and regional brain volumes in current frequent young adult marijuana smokers vs. non-smoking controls and found no significant differences between the two groups. Our hippocampal volume findings are also consistent with those of Wilson et al.,[8] although we were not able to replicate this group's finding of a decreased ratio of gray matter to total brain volume in younger-onset users. Our study is unique in that it is the first morphological investigation, to our knowledge, to include very long-term heavy cannabis smokers. Previous investigations have generally examined only younger populations of light to moderate smokers.[5–8] For example, the study by Block et al.[7] examined a group of eighteen participants with an average age of 22.3 and fewer than five years of regular cannabis use. Our findings therefore augment earlier investigations by extending their negative findings to subjects with much greater cannabis exposure. Further, the observed absence of volumetric differences between our cannabis users and controls appears consistent with our earlier neuropsychological observations that cognitive deficits in most heavy cannabis users appear to be temporary rather than irreversible.[18,24] On the other hand, it must be remembered that the absence of anatomical changes in brain structures

does not rule out the possibility of functional changes. Moreover, our measure of hippocampal volume does not include measures of specific hippocampal subregions. It is therefore possible that a focal brain change does occur in response to chronic cannabis use, but our current study methods are not able to demonstrate this effect.

It is difficult to compare our results to some of the earlier studies examining the effects of chronic human cannabinoid exposure because these studies used different neuroimaging methods, including pneumoencephalography and computerized axial tomography.[4–6] Findings from these studies had reduced spatial resolution and therefore lacked the precision for reliable measurement of focal brain regions.

Two possible limitations of the current study deserve careful consideration. The first is the possibility that we failed to fully account for possible confounding variables that might have influenced hippocampal volume among the cannabis users. Specifically, the cannabis users were significantly older and less well educated, and had almost certainly used larger amounts of other illicit drugs and alcohol than the control subjects. However, all of these potential confounders would likely be associated with *reduced* hippocampal volume.[25,26] Thus, none of these factors could reasonably account for the *absence* of differences between cannabis users and controls in the present study (barring the unlikely possibility that cannabis is somehow protective of hippocampal volume). Since both cannabis users and controls were recruited by newspaper advertisements in the same metropolitan area, it appears unlikely that there was a serious selection bias that affected one group differently from the other; nevertheless, we cannot exclude the possibility of unrecognized confounders.

Second, we lacked detailed information on the precise lifetime amounts of drug, alcohol, and tobacco use among the control subjects. Although these control subjects were systematically interviewed to exclude any cases of the abuse or dependence of cannabis, alcohol, or any other form of illicit drug, the possibility remains that some control subjects might have used these substances frequently without reaching the threshold of abuse or dependence. However, even allowing for this possibility, it is extremely implausible that any of the controls could have even approached the massive levels of lifetime exposure (more than 20,000 mean episodes of smoking) reported by the long-term heavy cannabis users. It also seems unlikely that the controls would have exceeded the cannabis users on lifetime levels of tobacco or alcohol use; furthermore, nicotine appears to have little effect on hippocampal volume,[27,28] and alcohol does not appear to reduce hippocampal volume as a fraction of total brain volume, even though it may reduce brain volume as a whole.[29] Thus, the possibility of a type II error due to control subjects' drug use seems quite unlikely. The possibility of a type II error due to the modest sample size must also be acknowledged—but the almost identical ratios of hippocampal volume to brain volume in the two groups, after adjustment for age, gender, and ethnicity, argues against a false negative finding due to sample size.

It might also be argued that retrospective assessment of the cannabis users' drug histories might be prone to inaccuracies. However, previous studies have suggested that self-reports of the use of cannabis and other drugs are fairly reliable.[18,30–32]

Although cannabis users with a current Axis I disorder were excluded, one (4.5%) of the users reported a past history of bipolar II disorder—and mood disorders have been shown in some studies to be associated with decreased hippocampal volume.[33] This subject, however, displayed a ratio of hippocampal to brain volume almost exactly at the mean for the cannabis users, so that his inclusion had no effect on the findings. None of the control subjects,

by definition, reported either a current or past Axis I disorder.

Finally, the procedures involved in identifying and measuring the structural boundaries of the hippocampus may have been vulnerable to individual bias and error. Despite the use of anatomical landmarks and proper training and the establishment of high reliability, variations in judgment and resulting data may arise across different studies, making it difficult to compare results. On balance, therefore, our findings appear unlikely to be explained by any of the possible limitations enumerated above; thus, our results add to the current consensus that long-term heavy cannabis use is not associated with prominent morphological changes within the human brain, including the hippocampus.

This research was supported by grants R01 DA12483-1 (Dr. Yurgelun-Todd) and DA-10346 (Dr. Pope) from the National Institute on Drug Abuse, Bethesda, Md.

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