

The Residual Cognitive Effects of Heavy Marijuana Use in College Students

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Objective.—To assess whether frequent marijuana use is associated with residual neuropsychological effects.

Design.—Single-blind comparison of regular users vs infrequent users of marijuana.

Participants.—Two samples of college undergraduates: 65 heavy users, who had smoked marijuana a median of 29 days in the past 30 days (range, 22 to 30 days) and who also displayed cannabinoids in their urine, and 64 light users, who had smoked a median of 1 day in the last 30 days (range, 0 to 9 days) and who displayed no urinary cannabinoids.

Intervention.—Subjects arrived at 2 PM on day 1 of their study visit, then remained at our center overnight under supervision. Neuropsychological tests were administered to all subjects starting at 9 AM on day 2. Thus, all subjects were abstinent from marijuana and other drugs for a minimum of 19 hours before testing.

Main Outcome Measures.—Subjects received a battery of standard neuropsychological tests to assess general intellectual functioning, abstraction ability, sustained attention, verbal fluency, and ability to learn and recall new verbal and visuospatial information.

Results.—Heavy users displayed significantly greater impairment than light users on attentional/executive functions, as evidenced particularly by greater perseverations on card sorting and reduced learning of word lists. These differences remained after controlling for potential confounding variables, such as estimated levels of premorbid cognitive functioning, and for use of alcohol and other substances in the two groups.

Conclusions.—Heavy marijuana use is associated with residual neuropsychological effects even after a day of supervised abstinence from the drug. However, the question remains open as to whether this impairment is due to a residue of drug in the brain, a withdrawal effect from the drug, or a frank neurotoxic effect of the drug.

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DURING the last 30 years, more than 40 studies have examined the residual effects of cannabis on neuropsychological performance. We have reviewed these studies in detail previously.¹ Most of the studies produced positive results, but many failed to find residual impairment in cannabis users. These inconsistent findings may reflect several methodological difficulties. First, the term *residual effect* is ambiguous. It may refer to impairment simply due to a drug residue of cannabinoids lingering in the central nervous system (CNS) after acute intoxication has subsided, or it may refer to actual CNS damage that persists even after the drug

residue has vanished. Most studies do not distinguish between the concepts of drug residue and CNS alteration effects in their analyses.¹

Second, it is difficult to quantify the total amount of cannabis ingested by the subjects under study. This problem is minimized in laboratory studies, in which a known amount of cannabis or its active principle, tetrahydrocannabinol, is administered to subjects, followed by testing at various time points after ingestion.^{1,2-5} However, this design cannot assess the residual effects (in both senses of the term) of months or years of daily cannabis use. Naturalistic studies of actual users avoid this limitation,^{1,6-11} but some of these studies have examined users without a strictly supervised period of abstinence before testing.^{8,11} Lacking such supervision, it is possible that some users arrived for testing only a few hours after last using the drug; therefore, some test results may

have reflected the effects of acute intoxication rather than residual effects.

Third, comparisons of cannabis users with nonusers may be influenced by confounding variables. Of particular importance is the possibility that users might have been more impaired than nonusers on neuropsychological functioning even before they began to use cannabis. Only one previous, recent study has thoroughly controlled for such premorbid differences.¹¹ Other potential sources of confounding include the possibility that heavy cannabis users might display greater rates of premorbid psychopathology or more frequent use of other drugs than controls. Also, evidence suggests that heavy users of cannabis are disproportionately male,¹ yet we are aware of only one study that has matched users and nonusers on sex¹¹ and of no study that has analyzed the residual effects of marijuana in men and women separately.¹

For editorial comment see p 560.

One way to reduce the influence of confounding variables, at least to some extent, is to compare heavy cannabis users against a control group of light cannabis users rather than a control group of nonusers. Infrequent users might be expected to differ less from heavy users on some possible confounding variables than would control subjects who had never used cannabis at all, while still differing sharply from heavy users on the specific variable chosen for study, namely extent of recent cannabis use. We used this design, together with additional methodological strategies to address the problems discussed above, to test the hypothesis that frequent marijuana use might produce residual neuropsychological effects in college students.

METHODS

Subjects

From mid 1991 to late 1993, we advertised in student newspapers at colleges in the Boston, Mass, area for students who had smoked marijuana for at least 2 years and who were willing to

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participate in a 24-hour study for \$150 compensation. This study was approved by the McLean Hospital Institutional Review Board. Our advertisement indicated that students were eligible whether they smoked marijuana frequently or only occasionally. All respondents were then screened on the telephone by the principal investigator, who assured them of the confidentiality of their responses and then asked a series of 15 questions about marijuana and other drug use. In fact, only one of these questions, the number of days of marijuana smoking in the past month, was used to select subjects; all other questions were designed simply to mask the actual selection criterion of the study. By this method, we reduced the risk that students might guess the selection criterion and then misrepresent their extent of marijuana use to gain entrance to the study.

Only subjects reporting regular marijuana use (a minimum of 22 days of the past 30 days) and subjects reporting only occasional use (a maximum of 9 days in the past 30 days) were accepted for the study. During the actual recruitment process, we attempted when possible to obtain subjects at the highest and lowest ends of the frequency range, so that in practice most of the heavy users recruited had smoked at least 27 days in the last 30 days, while most light users had smoked no more than 3 days. We also attempted to keep the groups approximately balanced for sex by temporarily rejecting candidates of one sex if a surplus of that sex developed. Rejected callers were simply told that they were ineligible for unspecified reasons.

Study Procedures

Qualifying subjects were asked to arrive at McLean Hospital by 2 PM on the first day of the study. They were informed that they could smoke marijuana at their usual frequency before this time, but that they would be supervised following their arrival at the hospital to ensure that they did not consume any further marijuana or any other drug (aside from their customary amounts of tobacco and caffeine) during the study period. On the afternoon of the first day, after signing informed consent, subjects completed a demographic questionnaire, including questions regarding their self-reported high school Scholastic Aptitude Test (SAT) scores, questions regarding subjective residual effects of marijuana, and the questions of the RAND Mental Health Inventory.¹² We then asked subjects about their frequency of marijuana use during each year since they first began using the drug and the number of days on which they had smoked mari-

juana during the last 30 days. In addition, we asked the specific days on which subjects had smoked and the number of episodes of smoking per day in each of the last 7 days. Incidents of smoking had to occur at least 1 hour apart to be counted as separate episodes. We also obtained subjects' self-reports of current frequency of alcohol, tobacco, and caffeine use; lifetime use of other types of illicit drugs; and most recent date of use of each other type of illicit drug reported. Finally, we administered the Axis I and Axis II portions of the Structured Clinical Interview for DSM-III-R (SCID)¹³ to determine subjects' lifetime history of psychiatric disorders by the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R)*.¹⁴ Subjects also gave a urine sample, which was tested for cannabinoids, as well as for amphetamines, barbiturates, methaqualone, opiates, phencyclidine, cocaine metabolites, and benzodiazepines.

Subjects then spent the remainder of that day and night under supervision. They had dinner, watched television, studied, or otherwise occupied themselves until bedtime, then slept in a room that could be observed by a monitor through a one-way mirror to ensure that they did not smoke marijuana at night. The following morning they were awakened at about 8:30 AM, permitted to drink their customary amount of coffee and have their customary breakfast, and then were administered a battery of neuropsychological tests between approximately 9 AM and 1 PM. Thus, all subjects had been abstinent from marijuana and other drugs for a minimum of 19 hours, and in practice usually at least 24 hours, before performing their testing.

Test Battery

During the testing session, an investigator blinded to the subject's history administered a neuropsychological test battery. First, the vocabulary subtest of the Wechsler Adult Intelligence Test-Revised (WAIS-R)¹⁵ was administered to obtain an estimate of the subject's Verbal Intelligence Quotient (VIQ). Thereafter, attention and memory were assessed with the Stroop test,¹⁶ the Wisconsin Card Sorting Test (WCST),¹⁷ the Benton Verbal Fluency Test (Benton VFT),¹⁸ the Wechsler Memory Scale (WMS),¹⁹ the California Verbal Learning Test (CVLT),²⁰ and the Rey-Osterich Complex Figure Test (ROCF).²¹ All scores are reported herein as means and SDs unless otherwise specified.

Statistical Analysis

Differences between the heavy and light users and between other dichoto-

mous groups (ie, heavy vs light male users, heavy vs light female users) were initially assessed using Student's *t* test for continuous variables. For R×C contingency tables, we computed significance by the exact test,²² and for ordered categorical data, by the Cochran-Armitage trend test.²³ Subsequently, we performed analyses of covariance (ANCOVA), in which VIQ or SAT scores were entered into the model along with frequency of marijuana use, to assess the relative significance of each of these variables in determining test performance.

RESULTS

We recruited and interviewed 161 students. Two were excluded because they described only intermediate marijuana use on interview (approximately 15 days per month), even though they had reported nearly daily use on prior telephone screening. Of the 159 subjects accepted, six were excluded from analysis because of possible confounding variables: one was suspected of surreptitiously using marijuana despite supervision during the study; one reported a prior head injury with prolonged loss of consciousness; and four displayed current psychiatric disorders likely to affect neuropsychological test performance (two cases of major depression, one case of bipolar disorder, and one case of schizotypal personality disorder).

The remaining 153 subjects included 85 heavy and 68 light users. However, four of the self-described light users were found to display cannabinoids in their urine, and 15 of the self-described heavy users did not display cannabinoids in their urine. These 19 subjects were eliminated from the analysis, lest they had misrepresented the extent of their recent marijuana use. In addition, five of the heavy users (but none of the light users) displayed drugs other than cannabinoids in their urine (one had traces of phencyclidine, three had traces of cocaine, and one had traces of benzodiazepines). These subjects were also eliminated, leaving a final total of 65 heavy users (all with cannabinoids but with no other drugs in their urine) and 64 light users (none with any drug in the urine) for comparison.

The heavy and light users were reasonably well balanced in sexual distribution (light=31 men, 33 women; heavy=38 men, 27 women). As intended by the study design, the heavy and light groups were widely separated in their frequency of recent marijuana use. The median (range) number of days on which subjects had smoked in the last 30 days was as follows: heavy-using men, 28 (22 to 30); heavy-using women, 29 (22 to 30); light-using men, 2 (0 to 9); and light-using women, 1 (0 to 9) ($P<.001$ between heavy and light

groups within each sex; $P=.96$ between sexes in the light-using group and .80 in the heavy-using group). No significant differences were found between the overall heavy and light groups on any demographic variables, including mean age, year in college, area of residence in the United States, ethnicity, stated religious or political preferences, or type of secondary school attended (Table 1). Although marital and domiciliary status were not formally assessed, virtually all subjects in both groups were single and were living in dormitories or off-campus apartments. Although some subjects knew one another socially, no subject in either group was a biological relative of another. The two subject groups did not differ significantly on most measures of family background, including parents' marital status, political preference, or occupations. However, the heavy users reported that they came from more affluent families ($P=.01$ by trend test) (Table 1). No significant differences on any of these variables were observed when comparisons were made within the sexes separately, save for a significant relation between heavy use and higher family income among the men ($P=.02$ by trend test).

Heavy and light users did not differ significantly on self-reported scores on the verbal portion of the SAT in high school (heavy, 489 ± 98 , vs light, 512 ± 93 ; $P=.21$). However, the heavy users reported significantly lower scores than light users on the SAT quantitative portion (494 ± 96 vs 543 ± 111 ; $P=.02$) and on the total SAT (983 ± 130 vs 1055 ± 174 ; $P=.02$).

No significant differences were found between heavy and light users on lifetime prevalence of any *DSM-III-R* Axis I or Axis II psychiatric disorder. Nineteen (29%) of the heavy users vs 15 (23%) of the light users displayed a history of other substance dependence or abuse. In a majority of cases, this history was a period of heavy alcohol use lasting less than 6 months. Only one user displayed current dependence on any other substance (alcohol dependence in one heavy user). On the RAND Mental Health Inventory, no differences were found on seven of the eight composite scores generated by this instrument (anxiety, depression, loss of behavioral/emotional control, emotional ties, life satisfaction, psychological distress, and psychological well-being). However, on the remaining scale, general positive affect, which produces a range of scores from 10 to 60, heavy users scored slightly higher than light users (40.6 ± 11 vs 37.3 ± 7 ; $P=.04$).

In a separate publication,²⁴ we have compared in detail the heaviest users (those who had smoked daily for 2 years or more; $n=45$) and the lightest users (those who had never smoked more than

Table 1.—Demographic Features of Heavy vs Light Marijuana Users*

Demographic Feature	Light Users (n=64)	Heavy Users (n=65)
Age, y		
Median	21	20
Range	18-28	18-24
White, No. (%)	59 (92)	58 (89)
Public high school, No. (%)	49 (77)	43 (66)
Political orientation, No. (%)		
Conservative-moderate	32 (52)	29 (47)
Liberal-very liberal	30 (48)	33 (53)
Parents' marital status, No. (%)		
Married	37 (59)	36 (55)
Divorced	18 (29)	22 (34)
Other	8 (13)	7 (11)
Family annual income, No. (%)†		
<\$15 000	5 (8)	0
\$15 000-\$30 000	7 (11)	7 (11)
\$30 000-\$50 000	16 (25)	14 (22)
\$50 000-\$100 000	25 (39)	19 (29)
>\$100 000	11 (17)	25 (38)

*The number of subjects with missing data is as follows: for political orientation, two light users and three heavy users; for parents' marital status, one light user.

† $P=.01$ by Cochran-Armitage trend test.

10 times in any 1-month period in their lives; $n=44$), drawn from our entire original sample of 159 subjects. Even these two extreme groups, who were not subject to any of the exclusion criteria used in the present study, exhibited almost no significant differences on demographic measures, prevalence of psychiatric disorders other than substance abuse, and scores on the RAND Mental Health Inventory.

The heavy and light users differed slightly on VIQs based on the WAIS-R vocabulary subscale (heavy users, 100.6 ± 12.0 , vs light users, 104.8 ± 13.5 ; $P=.06$). Because of this finding, the statistical significance of differences between groups on all subsequent neuropsychological variables was assessed using ANCOVA controlling for VIQ. However, means and SDs for the two groups presented herein and in the tables are raw figures; they would be altered only slightly if adjusted for the covariate.

Looking first at digit span, variously considered a measure of span of attention,²⁵ a measure of auditory sequential processing,²⁶ or an indirect measure of anxiety,²⁷ the two groups proved virtually identical, both in the analysis of the total sample and on separate analysis of the male subjects and female subjects (total sample: heavy users, 11.0 ± 2.4 ; light users, 10.8 ± 2.3 ; $P=.41$). Similarly, on the Stroop test, which measures sustained attention with and without an interference condition, heavy and light users again showed no significant differences on the word reading, color naming, or interference subtests. After separate analysis of male and female users, no significant differences were found between the heavy-

and light-using women, but differences appeared among the men: male heavy users were slower to name 100 colors than light users (62.5 ± 11.5 vs 56.7 ± 10.5 seconds; $P=.05$), but they also made slightly fewer errors on this task (median of one error in each group; range of zero to four errors in male heavy users and zero to six errors in male light users; $P=.05$). Male heavy users were also slower than light users on the interference portion of the Stroop test (111.7 ± 24.9 vs 97.7 ± 22.8 seconds; $P=.04$).

On the WCST, a test of mental flexibility and abstraction ability,²⁸ an overall comparison of heavy vs light users showed a significant difference in categories achieved on deck 1 (Table 2). On inspection, this difference was caused by a significantly higher number of errors among the heavy users, which in turn proved attributable to a markedly greater tendency for perseveration. Heavy users produced significantly more perseverations outside the category (an incorrect response, based on a previously correct sorting principle, following the completion of the sort) and slightly more perseverations inside the category (an incorrect response that immediately followed an identical incorrect response).²⁹ Combining the total number of perseverations of both types for both decks 1 and 2 of the WCST (Figure 1), the heavy users displayed strikingly more perseverations than the light users. These findings remained similar when heavy and light users were compared separately within each sex.

On the Benton VFT, scores represented the total number of words beginning with the letters F, A, and S

Table 2.—Neuropsychological Findings: Wisconsin Card Sorting Test*

Findings	Light Users			Heavy Users		
	Men (n=31)	Women (n=33)	All (n=64)	Men (n=38)	Women (n=27)	All (n=65)
Deck 1						
No. of sets completed	4.4 (0.8)	4.5 (0.7)	4.4 (0.8)	4.1 (0.8)	4.2 (0.8)	4.1 (0.8)†
Items sorted correctly	53.1 (3.5)	53.5 (3.7)	53.3 (3.6)	50.6 (4.4)†	52.3 (4.6)	51.3 (4.5)†
Perseverations outside, median (range)	3 (0-16)	3 (0-10)	3 (0-16)	5 (0-18)‡	4 (0-14)‡	4 (0-18)§
Perseverations inside, median (range)	0 (0-5)	0 (0-4)	0 (0-5)	1 (0-6)	1 (0-10)	1 (0-10)
Deck 2						
No. of sets completed	4.8 (0.6)	4.8 (0.5)	4.8 (0.5)	4.6 (0.6)	4.7 (0.5)	4.6 (0.5)
Items sorted correctly	56.6 (2.3)	56.0 (2.2)	56.3 (2.2)	55.1 (2.4)†	56.2 (2.3)	55.5 (2.4)
Perseverations outside, median (range)	2 (0-5)	2 (0-7)	2 (0-7)	2 (0-6)‡	2 (0-6)	2 (0-6)†
Perseverations inside, median (range)	0 (0-1)	0 (0-3)	0 (0-3)	0 (0-2)	0 (0-2)	0 (0-2)

*Number of sets completed and number of items sorted correctly are shown as means with SDs in parentheses. Perseverations are shown as medians with ranges in parentheses. See text for definitions of perseverations "outside" and "inside" the category. Significance is reported for all differences between comparable groups of heavy vs light users (ie, men vs men, women vs women, all vs all) by analysis of covariance controlling for Verbal Intelligence Quotient.

† $P < .05$.

‡ $P < .01$.

§ $P < .001$.

generated by the subject when allowed 60 seconds per letter. Scores were adjusted for age, sex, and education by the method of Benton and Hamsher.¹⁸ A score of 31 to 44 is considered normal, and 30 is the threshold of low normal.³⁰ Five (8%) of the heavy users, but none of the light users, scored at or below this threshold, a nearly significant difference ($P=.06$). On ANCOVA, a significant interaction ($P=.009$) was found between VIQ and marijuana use (heavy vs light) in their effect on VFT scores. On analysis of this interaction, we found that among subjects with the lowest VIQs, those who were heavy users produced fewer words than those who were light users. However, heavy and light users with average to high VIQs exhibited virtually no difference in verbal fluency. This interaction between VIQ and degree of marijuana use was the only such interaction attaining a significance of .05 or less among any of the overall comparisons between heavy and light users assessed by ANCOVA in this article.

Turning to measures of memory, the memory quotient on the WMS did not differ significantly between the groups while controlling for VIQ. Looking at specific submeasures of the WMS, no significant differences were found between groups on immediate recall for prose passages, word pairs, or figures. Delayed recall of prose passages and word pairs was also similar between groups, but delayed recall of figures was significantly reduced among heavy users. Looking at the sexes separately, this difference was contributed entirely by men (heavy users, 10.3 ± 3.2 elements recalled; light users, 12.2 ± 1.5 ; $P=.007$); women exhibited no difference (heavy users, 11.7 ± 2.3 ; light users, 11.8 ± 2.5 ; $P=.87$).

Further examining verbal memory on

the CVLT, heavy and light users differed significantly on recall of the first administration of the word list (Table 3). After five presentations of this list, heavy users still lagged significantly behind light users in their ability to learn, with fewer items recalled in each trial and in the sum of all five trials (Figure 2). Furthermore, after an interference condition that included the presentation of a different word list, the heavy users produced fewer correct words from the original list despite the short delay between the presentation of the original list and the recall condition (shown in Table 3 as "short-delay free recall"). After a 40-minute delay, heavy users again displayed a trend ($P=.07$) to recall fewer words from the original list (shown in Table 3 as "long-delay free recall"). The difference between heavy and light users in long-delay recall persisted even after cuing (see "long-delay cued recall" in Table 3), suggesting that heavy users also experienced more difficulty in retrieval of new verbal information. Of note, however, there was no decay of recall between the short-delay and long-delay conditions in either group. All these findings remained similar (though with reduced statistical power) when the male and female subgroups were analyzed separately.

Finally, looking at visuospatial memory with the ROCF, no differences were found between heavy and light users on copying the complex figure, indicating no fundamental impairment of visuospatial functioning (Table 4). However, on immediate recall of the figure, heavy-using men scored significantly lower than light-using men on the number of elements of the figure reproduced. No similar differences were observed among women. No further loss of information appeared in ei-

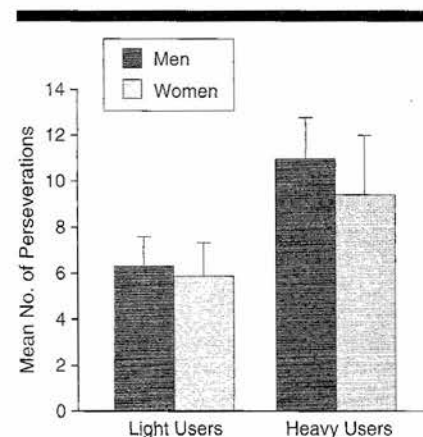


Figure 1.—Total perseverations on the Wisconsin Card Sorting Test. The error bars represent the 95% confidence interval for each mean value shown. The significance of differences was computed by analysis of covariance controlling for Verbal Intelligence Quotient. For all heavy users vs all light users, $P < .001$; for male heavy users ($n=38$) vs male light users ($n=31$), $P=.002$; for female heavy users ($n=27$) vs female light users ($n=33$), $P=.01$.

ther sex on delayed copying of the figure after approximately 40 minutes.

We then performed additional analyses to assess for possible confounding effects in the study. We first considered the important question of whether the differences in observed neuropsychological performance between heavy and light users might be due to premorbid differences between these groups in cognitive function, rather than to an effect of marijuana use.

The lower VIQ scores of the heavy users, as well as their lower self-reported SAT scores, raises this possibility. However, as discussed herein, when we performed ANCOVA controlling for VIQ, we nevertheless continued to find equally or more strongly significant differences

Table 3.—Neuropsychological Findings: California Verbal Learning Test (Selected Items)*

Findings	Light Users			Heavy Users		
	Men (n=31)	Women (n=33)	All (n=64)	Men (n=38)	Women (n=27)	All (n=65)
Items recalled, trial 1	7.9 (1.9)	8.3 (2.6)	8.1 (2.3)	6.6 (1.8)†	7.3 (1.8)	6.9 (1.8)†
Items recalled, trial 5	13.7 (2.1)	14.3 (2.2)	14.0 (2.2)	12.5 (2.1)	14.2 (1.4)	13.2 (2.0)‡
Short-delay free recall	12.4 (2.9)	13.7 (2.2)	13.0 (2.6)	11.4 (2.3)	12.6 (2.5)	11.9 (2.4)‡
Long-delay free recall	12.6 (3.2)	13.9 (2.5)	13.3 (2.9)	11.6 (2.4)	13.3 (2.2)	12.3 (2.4)
Long-delay cued recall	15.1 (1.3)	15.6 (0.8)	15.3 (1.1)	14.8 (1.3)	15.0 (1.7)	14.9 (1.5)‡

*All data shown are means with SDs in parentheses. Significance is reported for differences between comparable groups of heavy vs light users (ie, men vs men, women vs women, all vs all) by analysis of covariance controlling for Verbal Intelligence Quotient.

† $P < .01$.

‡ $P < .05$.

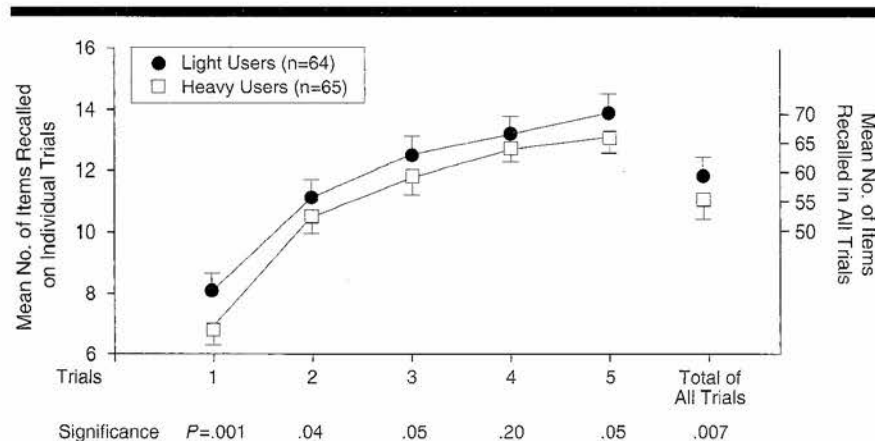


Figure 2.—Number of items recalled on successive trials of the California Verbal Learning Test. The error bars represent the 95% confidence interval for each mean value shown. The significance of differences was computed by analysis of covariance controlling for Verbal Intelligence Quotient, comparing light users vs heavy users for each trial and for the sum of all trials.

between groups. We also performed ANCOVA examining all the neuropsychological test results while controlling for verbal, quantitative, and total SAT scores. These latter calculations would be expected to produce, if anything, an overly conservative estimate of the neuropsychological effects of marijuana, since lower SAT scores may have represented in part a consequence of heavy use in high school, rather than a consequence of lower premorbid cognitive abilities. Nevertheless, ANCOVA controlling for SAT scores yielded essentially the same results as that controlling for VIQ. These observations argue against the possibility that the impairment observed in the heavy users was attributable to some premorbid deficiency in this group.

Also relevant to this question is our previously published analysis, cited earlier,²⁴ which found few demographic or psychiatric differences even when comparing the 45 heaviest users and the 44 lightest users in our overall sample of 159 subjects. These results also argue against an innate or premorbid difference between groups and thus further suggest that the reduced test performance among heavy users in the present study was an effect of marijuana itself.

The more frequent abuse of other substances among heavy users represents another potentially confounding variable: greater alcohol use, history of dependence on another substance, or recent use of another substance might all be expected to contribute to impaired neuropsychological performance. To test for this possibility, we performed comparisons of heavy vs light users after deleting (1) all subjects with a history of abuse of or dependence on any other substance (this yielded a comparison of 46 heavy vs 49 light users); (2) all subjects who reported that they currently consumed more than 12 alcoholic drinks per week (yielding 36 heavy vs 52 light users); and (3) all subjects who reported use of any illicit substance other than marijuana within the past month (yielding 35 heavy vs 57 light users). Finally, we excluded all subjects who met any of these three criteria, creating particularly "purified" samples of 16 heavy users vs 36 light users. In all these exercises, the differences between heavy and light users remained similar or even widened. As shown in Table 5, on three of four measures previously found to differentiate heavy users from light users, the difference between the "purified"

groups actually exceeds that found between the original groups.

These analyses suggest that the differences observed in this study were indeed due to residual effects of marijuana use, rather than to premorbid differences between groups or to the effects of other substance use. However, this observed impairment might represent merely a temporary effect, due to either a drug residue of cannabinoids lingering in the brain^{1,31} or an abrupt withdrawal from heavy use.³²⁻³⁴ Alternatively, the impairment might represent a lasting CNS alteration effect due to some actual damage to the CNS related to overall lifetime exposure. In an effort to distinguish between these possibilities, we performed two analyses. First, we compared the 13 light users who at a previous time in their lives had been heavy users (smoking 25 or more days per month) with the 32 light users who had never smoked more than nine times per month at any time in their lives. Unexpectedly, the former group displayed a much higher VIQ (114 ± 11 vs 103 ± 14 ; $P = .01$). We then chose only the 13 always-light users with the highest VIQs, thereby matching the two groups on VIQ. On comparing these two groups of 13, no differences approaching significance were found on any neuropsychological variables—although it must be recognized that the sample sizes in this comparison were small.

As a second test, we divided the entire group of 64 light users into three equal subgroups on the basis of lifetime use of marijuana (group 1=17 to 70 joints smoked in their lifetimes, $n=21$ subjects; group 2=80 to 400 joints in lifetime, $n=21$; and group 3=400 to 4500 joints in lifetime, $n=22$). We then performed ANCOVA examining each neuropsychological test score with group status (1, 2, or 3) and VIQ entered as covariates. Although many of the test scores were significantly associated with VIQ in this analysis (as might be expected), on none of the variables was performance significantly related to total lifetime consumption of marijuana. Thus, these analyses, though of low statistical power,

Table 4.—Neuropsychological Findings: Rey-Osterreith Complex Figure Test*

Findings	Light Users			Heavy Users		
	Men (n=31)	Women (n=33)	All (n=64)	Men (n=38)	Women (n=27)	All (n=65)
Elements of figure correctly identified						
Initial copying	34.6 (1.6)	34.0 (1.8)	34.3 (1.7)	34.2 (2.0)	33.7 (2.2)	34.0 (2.1)
Immediate recall	23.8 (4.7)	19.5 (6.5)	21.6 (6.1)	20.1 (6.2)†	20.6 (4.8)	20.3 (5.6)
Delayed recall	23.2 (4.5)	19.5 (6.3)	21.3 (5.8)	20.2 (6.1)	20.6 (6.0)	20.4 (6.0)

*All data shown are means with SDs in parentheses. Significance is reported for differences between comparable groups of heavy vs light users (ie, men vs men, women vs women, all vs all) by analysis of covariance controlling for Verbal Intelligence Quotient.

† $P < .05$.

Table 5.—Neuropsychological Findings: Total Sample vs "Pure" Cases*

Findings	Light Users		Heavy Users	
	All Cases (n=64)	"Pure" Cases (n=36)	All Cases (n=65)	"Pure" Cases (n=16)
Stroop test				
Interference subtest, time in seconds	99.6 (19.6)	99.6 (17.7)	106.8 (23.5)	110.5 (32.1)
Wisconsin Card Sorting Test				
Total perseverations, median (range)	5 (0-18)	4 (0-18)	9 (0-28)†	12.5 (0.25)†
Wechsler Memory Scale				
Delayed recall of figures, elements recalled	12.0 (2.1)	11.8 (2.6)	10.9 (2.9)‡	10.0 (3.9)
California Verbal Learning Test				
Total items remembered on 5 trials combined	59.2 (8.7)	58.5 (9.0)	55.0 (8.0)§	56.9 (7.3)

*"Pure" cases represent individuals who (1) displayed no current or past history of any substance abuse or dependence (other than cannabis) by the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised*; (2) currently reported drinking fewer than 12 alcoholic drinks per week; and (3) reported no use of any illicit drug other than marijuana during the past month. All data shown are means with SDs in parentheses, with the exception of total perseverations on the Wisconsin Card Sorting Test, which are shown as medians with the ranges in parentheses. Significance is reported for differences between comparable groups of heavy vs light users (ie, all cases vs all cases, "pure" cases vs "pure" cases) by analysis of covariance controlling for Verbal Intelligence Quotient.

† $P < .001$.

‡ $P < .05$.

§ $P < .01$.

weigh tentatively against a CNS alteration hypothesis.

COMMENT

We compared 65 college students who smoked marijuana regularly with 64 students who smoked only occasionally. The heavy users had smoked a median of 29 days (range, 22 to 30 days) in the past 30 days, and all displayed cannabinoids in their urine. Light users had smoked a median of 1 day (range, 0 to 9 days) in the past 30 days, and none displayed urinary cannabinoids. Students displaying a current psychotic disorder, schizotypal personality disorder, major mood disorder, or history of severe head injury with loss of consciousness were excluded, as were students currently taking any medication with psychotropic effects and those displaying any substance other than cannabinoids in their urine. We also attempted to recruit roughly equal numbers of male and female students in each group so that results could be analyzed within each sex separately, as well as for the heavy users vs the light users as a whole. All 129 students received a battery of neuropsychological tests after a supervised overnight period of abstinence from marijuana and other drugs of abuse.

The findings on this battery of tests suggest that heavy marijuana use was associated with reduced function of the

attentional/executive system, as exhibited by decreased mental flexibility and increased perseveration on the WCST, and reduced learning, as seen on the CVLT. In addition, verbal fluency on the Benton VFT was impaired with heavy use, but only in subjects with lower VIQs, perhaps because their fluency was more vulnerable to attentional impairment. However, the ability to retain newly learned information after a temporal delay appeared to remain relatively intact in the heavy users, as exhibited by the absence of decay on the delayed recall conditions of the CVLT and ROCF. In short, although marijuana use may produce some compromise in memory function, it appears that the principal effect is in the attentional/executive system, with recall memory functions per se remaining relatively unaffected. Our data suggest that multiple brain systems may be affected by marijuana, but the most pronounced effects may be in sustained attention, mediated by brain stem structures, and in the capacity to shift attention, associated with prefrontal cortical regions.

In general, these findings were somewhat more prominent among men than women, even though male heavy users did not differ from female heavy users in their reported recent or lifetime marijuana consumption. Nevertheless, the possibility remains that men were ac-

tually ingesting a greater total dose of cannabinoids during their individual episodes of smoking.

The differences between heavy users and light users did not appear to be due to fundamental demographic or psychological differences between these groups, as evidenced by our comparisons in the present study and our previously published comparison of the heaviest vs the lightest users from our larger original sample.²⁴ Similarly, the differences observed did not appear attributable to premorbid differences between heavy and light users in neuropsychological function—since the differences in test scores remained significant, or even increased in significance, when we performed ANCOVA controlling for VIQ or for self-reported verbal or quantitative high school SAT scores. Finally, the differences did not appear attributable to use of other drugs or large amounts of alcohol, since analyses excluding individuals with these possible confounding factors failed to change the differences observed, and in some instances even widened them.

Despite these analyses, however, certain methodological limitations must be acknowledged. First, it must be recognized that a large number of individual comparisons were performed; therefore, some results may have achieved statistical significance by chance alone. On the other hand, the trend of the data was consistent: virtually every difference, whether significant or not, was in the direction of greater impairment among heavy users.

Second, it is conceivable that heavy and light users did differ on certain premorbid cognitive abilities and that the analyses controlling for VIQ and SAT scores did not fully correct for such differences. Only a standardized test, administered to all subjects in a uniform manner before their first marijuana use, would fully address this issue. Only one published study, to our knowledge, has utilized such test results¹¹ and, despite this control, nevertheless found residual impairment in heavy users similar to that found in our study.

Third, it might be argued that non-users would have represented a better

comparison group than light users. However, we reasoned that light users might be less likely to differ from heavy users on possible confounding variables, such as aspects of lifestyle, study habits, or background, than would nonusers. Thus, our comparison, while perhaps producing a slightly conservative estimate of the effects of marijuana, may also be less vulnerable to confounding.

Fourth, most historical data, including subject's SAT scores, prior use of other substances, and even prior marijuana use, were obtained from self-reports without external validation. However, inaccurate self-reports appear unlikely to have imposed marked bias, since subjects would have derived no particular benefit from distorting their reports in this study. Further, our conclusions would be seriously affected only in the unlikely event that subjects' self-reports were distorted in some systematic manner that was correlated with neuropsychological test scores.

Fifth, several studies have suggested that abrupt discontinuation of heavy cannabis use, as was required by our supervised abstinence period, may precipitate a withdrawal syndrome char-

acterized by insomnia, restlessness, and irritability.³²⁻³⁴ Such a syndrome might have influenced our findings; only a study with a much longer abstinence period could fully resolve this issue. Of studies using longer abstinence periods, one found few neuropsychological deficits among 37 heavy users after 3 to 4 days,³⁵ but another found memory impairment in 10 users after 6 weeks⁹ and another found deficits on an auditory selective attention task in 28 users after a mean abstinence of about 2 years.³⁶ These latter two findings suggest a CNS alteration effect of marijuana, not explainable by drug withdrawal or by a drug residue in the CNS.

Sixth, it should be recognized that our study might have underestimated the potential residual effects of marijuana because of the young age of the sample. Although many students had smoked marijuana daily for 2 years or more, as noted earlier, none had smoked regularly for more than a decade. Thus, a comparison of middle-aged heavy marijuana users, with longer histories of use, might produce more robust findings.

In short, the findings of our study, together with those of other recent, well-

controlled investigations,^{1,6-11,36} raise several questions that must be pursued. These questions include how long marijuana-associated neuropsychological impairment lasts, whether it is related to cumulative lifetime use, whether it interacts with normal aging, and to what extent, if any, it compromises the actual functioning of users in their daily lives. Specifically, although marijuana use may not cause overt psychopathology or serious academic impairment,^{24,37} subtle drug-induced deficits in sustaining and shifting attention may nevertheless cause important difficulties in adapting to intellectual and interpersonal tasks. Only by further study of these issues can it be judged whether neuropsychological impairment associated with marijuana use should be considered a public health problem.

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