ORIGINAL ARTICLE

# Neuropsychological Performance in Long-term Cannabis Users

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**Background:** Although cannabis is the most widely used illicit drug in the United States, its long-term cognitive effects remain inadequately studied.

**Methods:** We recruited individuals aged 30 to 55 years in 3 groups: (1) 63 current heavy users who had smoked cannabis at least 5000 times in their lives and who were smoking daily at study entry; (2) 45 former heavy users who had also smoked at least 5000 times but fewer than 12 times in the last 3 months; and (3) 72 control subjects who had smoked no more than 50 times in their lives. Subjects underwent a 28-day washout from cannabis use, monitored by observed urine samples. On days 0, 1, 7, and 28, we administered a neuropsychological test battery to assess general intellectual function, abstraction ability, sustained attention, verbal fluency, and ability to learn and recall new verbal and visuospatial information. Test results were analyzed by repeated-measures regression analysis, adjusting for potentially confounding variables.

**Results:** At days 0, 1, and 7, current heavy users scored significantly below control subjects on recall of word lists, and this deficit was associated with users' urinary 11-nor-9-carboxy-Δ9-tetrahydrocannabinol concentrations at study entry. By day 28, however, there were virtually no significant differences among the groups on any of the test results, and no significant associations between cumulative lifetime cannabis use and test scores.

**Conclusion:** Some cognitive deficits appear detectable at least 7 days after heavy cannabis use but appear reversible and related to recent cannabis exposure rather than irreversible and related to cumulative lifetime use.

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DOES LONG-TERM heavy use of cannabis cause residual neuropsychological deficits? The literature has long been divided on this question.[1] A recent investigation by our laboratory found deficits on memory of word lists and on mental flexibility among 65 heavy-smoking college students, compared with 64 infrequent smokers after 1 day of abstinence from cannabis.[2] Fletcher et al[3] found significant differences between 17 older heavy cannabis users and 30 matched nonusers on memory of word lists and on selective and divided attention tasks after 72 hours of abstinence. However, these authors found no significant differences between 37 younger users and 49 matched nonusers. Another group found electroencephalographic abnormalities in chronic cannabis users after 24 hours of abstinence,[4,5] but found no significant alteration in auditory or visual P300 responses in another study of cannabis users, after controlling for potentially confounding variables.[6] By contrast, Solowij[7] found significant delays in auditory P300 responses in heavy cannabis users examined after at least 12 hours of abstinence. Cannabis users also displayed significantly slower reaction times and reduced accuracy on a selective attention task.

However, it is difficult to determine whether such deficits, observed after only 12 to 72 hours of abstinence, are temporary (eg, due to a residue of cannabinoids in the brain or to acute withdrawal effects from cannabis) or long-lasting (due to a neurotoxic effect of long-term cannabis exposure). On this critical latter question, the data are meager and conflicting. Lyketsos and colleagues,[8] examining 1318 participants younger than age 65 in the Epidemiologic Catchment Area Study, found no significant differences among heavy cannabis users, light users, and nonusers in the degree of cognitive decline on the Mini-Mental State Examination during the course of 12 years. By contrast, Struve and colleagues[9] tentatively suggested that electroencephalographic abnormalities were more pronounced in longer-duration cannabis users, even when adjusting for the

## SUBJECTS AND METHODS

### SUBJECTS

We recruited individuals aged 30 to 55 years in 3 groups: (1) current long-term heavy users reporting at least 5000 lifetime episodes of cannabis smoking (to be counted as separate, episodes had to be at least 1 hour apart), and currently smoking at least 7 times per week; (2) former long-term heavy users reporting at least 5000 episodes of smoking, but no more than 12 episodes during at least the last 3 months; and (3) control subjects reporting that they had smoked at least once, but no more than 50 times in their lives, and no more than once during the past year.

Our threshold of 5000 episodes for "heavy use" was equivalent to smoking at least once a day for at least 13 years. We considered recruiting controls who had never smoked cannabis, but elected to choose subjects who had tried the drug at least once, because individuals who had never tried cannabis might differ from individuals who had in ways that might be associated with cognitive performance. All subjects were studied at McLean Hospital, Belmont, Mass, and were required to sign informed consent for the study, which was approved by the McLean Hospital institutional review board.

Subjects qualifying on telephone screening were evaluated by one of us (H.G.P. or A.J.G.) at a baseline (day 0) interview, which included demographic questions, detailed questions about frequency of use of cannabis and other drugs throughout the subject's lifetime, the Structured Clinical Interview for *DSM-IV*,[10] assessment for history of attention-deficit/hyperactivity disorder (ADHD) using the Wender Utah Rating Scale[11] and a modified ADHD rating scale,[12,13] semistructured questions regarding family history of *DSM-IV* Axis I psychiatric disorders,[14] and laboratory tests for standard chemistries, hematology, and urinalysis. Ratings of ADHD were introduced only during the second year of the study and, hence, were limited to 109 of the 180 subjects (33 current users, 31 former users, and 45 controls). We calculated a conduct disorder score by adding the scores on 4 items on the Wender Utah Rating Scale: "ran away from home"; "get in fights"; "trouble with authorities, trouble with school, visits to the principal's office"; and "trouble with the police, booked, convicted."

We excluded subjects who reported (1) use of any other class of drugs of abuse (such as hallucinogens, cocaine, stimulants, or opiates) more than 100 times in their lives; (2) a history of *DSM-IV* alcohol abuse or dependence; (3) a current *DSM-IV* Axis I disorder other than simple phobia or social phobia; (4) a history of a head injury with loss of consciousness requiring hospitalization; (5) current use of any psychoactive medication; or (6) a medical, psychiatric, or neurological condition that might affect cognitive function. We also screened urine by immunoassay (EMIT II; Behring Diagnostics, Cupertino, Calif) for 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THCCOOH), creatinine, cocaine metabolites, benzodiazepines, barbiturates, phencyclidine hydrochloride, opioids, and amphetamines, and by enzymatic assay for ethanol. The immunoassay threshold for detection of cannabinoids was 20 ng/mL; ethanol detection was considered positive if it exceeded 0.02 g/dL. Samples positive for THCCOOH were then tested by gas chromatography-mass spectroscopy to obtain quantitative THCCOOH and creatinine concentrations. Samples showing evidence of ethanol levels above 0.02 g/dL, or evidence of any of the other 6 classes of drugs listed, were also confirmed by gas chromatography–mass spectroscopy.

### ABSTINENCE PERIOD

Following the baseline evaluation, subjects were required to abstain from cannabis and other drugs of abuse for 28 days, monitored by observed urine samples daily (current users) or every other day (former users and controls). All subjects were permitted to consume caffeine and tobacco, and up to 2 alcoholic drinks (defined as 12 oz of beer, 4 oz of wine, or 1½ oz of distilled liquor) per day. Subjects were withdrawn from the study if urine samples indicated noncompliance with these requirements. Current users, who by definition were smoking regularly up until day 0, were judged to be abstinent provided that their urinary THCCOOH concentrations, normalized to urinary creatinine concentrations, decreased in a manner consistent with residual drug excretion in the absence of any new cannabis use.[15]

### NEUROPSYCHOLOGICAL TESTING

On days 0, 1, 7, and 28, an investigator, blinded to the subjects' group status, administered the neuropsychological tests described in this subsection. To maintain blindness, the tester worked in a separate building. Before testing, subjects were instructed not to reveal to the tester any information about their prior cannabis use or current frequency of urine samples.

#### Day 0

At baseline, subjects were administered the vocabulary subtest of the Wechsler Adult Intelligence Scale–Revised, a measure correlated with general intellectual ability[16] and relatively insensitive to cortical insults.[17]

#### Days 0, 1, 7, and 28

On all 4 testing days, subjects were administered (1) a computerized Continuous Performance Test (Conners'

greater age of these subjects. Most ominously, Solowij[7] found a strong correlation between duration of cannabis use and increased processing negativity to complex irrelevant stimuli in a selective attention task, even in users with a mean of 2 years' abstinence.

To augment these limited data on the cognitive consequences of long-term cannabis use, we examined neuropsychological performance in 108 long-term heavy users of cannabis throughout 28 days of monitored abstinence from the drug.

## RESULTS

On telephone screening, 246 subjects appeared to meet criteria for 1 of the 3 study groups. Of these, 66 were either excluded at the baseline interview or subsequently withdrawn during the study (**Figure**), leaving 180 evaluable subjects. The 3 groups (63 current users, 45 former users, and 72 control subjects) were similar in age, ethnic distribution, and sex (the latter because of matching) (**Table 1**). Interestingly, subjects in all groups reported similar edu-

version 3.0)[18]; (2) an Auditory Continuous Performance Test[19] to assess measures of attention; and (3) the Buschke Selective Reminding Test (BSRT)[20] to assess verbal learning and memory. On days 0, 7, and 28, subjects also received the Benton Revised Visual Retention Test[21] to assess visuospatial memory. The BSRT and Benton Revised Visual Retention Test were administered in alternate forms to minimize learning effects.

### Day 28

On the final testing day, subjects were administered 6 additional tests: (1) the Wisconsin Card Sorting Test[22]; (2) the Wechsler Memory Scale[23]; (3) the block design subtest of the Wechsler Adult Intelligence Scale–Revised[16]; (4) the Controlled Oral Word Association Test (often known as the "FAS" test)[24]; (5) the Stroop Test[25]; and (6) the Raven Progressive Matrices.[26] These measures of attentional and executive functions and verbal and visuospatial memory were chosen because of their known sensitivity to various forms of brain dysfunction[17,24] and because they had demonstrated possible deficits in heavy cannabis users in previously published studies.[1-3] Because these 6 tests were not available in multiple versions, they could be administered on only a single occasion and, thus, were reserved for day 28.

## STATISTICAL ANALYSIS

For baseline demographic characteristics, we compared groups using the Fisher exact test for binary variables and the Wilcoxon rank sum test for continuous variables. For neuropsychological test scores, we compared current users and former users separately with controls via multivariate linear regression analysis. We used 2 sets of adjustments for possible confounding variables. Analysis 1 adjusted only for variables that could not have been affected by cannabis use: sex, age, ethnicity (white vs nonwhite), mother's and father's educational level, parents' household income, presence of substance abuse or dependence in a first-degree relative, and presence of any other psychiatric disorder in a first-degree relative. Analysis 2 adjusted for verbal IQ (VIQ), as determined by the vocabulary subtest of the Wechsler Adult Intelligence Scale-Revised in addition to the other variables.

Because VIQ is generally well preserved despite cortical insults,[16,17] analysis 2 was intended to adjust for the effects of premorbid intelligence. This adjustment is potentially important, because the heavy users displayed lower VIQs than did controls (see the "Results" section). However, we cannot exclude the possibility that the lower VIQs of heavy users might be partially a consequence, rather than an antecedent, of cannabis use. Therefore, the 2 analyses effectively provide upper and lower bounds for the neuropsychological effects of cannabis use: analysis 1 (VIQ-unadjusted) assumes that the lower VIQ of heavy users is entirely a consequence of cannabis use and entirely unrelated to premorbid differences in intelligence, while analysis 2 (VIQ-adjusted) assumes that lower VIQ is entirely a consequence of premorbid differences and entirely unrelated to cannabis use. If one assumes that the truth lies somewhere between these extremes, then the VIQ-unadjusted analysis would be expected to overestimate the true neuropsychological deficits associated with heavy cannabis use, whereas the VIQ-adjusted analysis would tend to underestimate such deficits.

For tests involving serial measures at different time points, we used the methods of longitudinal analysis with generalized estimating equations, with compound symmetry as a working covariance structure, to account for correlation of observations within individuals.[27] We used appropriate transformations for variables in which there appeared to be a dependence of the variance on the mean.

We also tested the association between neuropsychological measures and lifetime use of cannabis in current and former users, and between these measures and baseline THCCOOH-creatinine ratio. For these analyses, we used multivariate linear regression as already described in this subsection, except that we restricted the analysis to a single group and entered as predictor variables lifetime use (modeled as log of the total number of lifetime episodes of use) and baseline THCCOOH-creatinine ratio. Using this ratio allowed us to correct for differences in the concentration of urine samples provided by subjects at day 0 and, thus, provided a rough approximation of the subject's recent exposure to cannabinoids. We modeled this value as log (ratio + 1).

We had complete information on the most important covariates: age, sex, ethnicity, and VIQ. For the small number of missing observations for other covariates, we assigned the median value for the total sample for purposes of analysis.

We also fitted a model that included terms for scores on the ADHD rating scale and the conduct disorder scores calculated as described in the "Subjects" subsection of the "Subjects and Methods" section. This was a secondary analysis, because these data were limited to 109 subjects and because we could not exclude the possibility that some features of ADHD and conduct disorder represented effects of cannabis use.

All tests were 2-tailed. The large number of correlated outcome measures makes proper adjustment for multiple comparisons difficult. To control partially for the effects of multiple comparisons, we set the $\alpha$ level at .01.

We used commercially available statistical software (Stata 6.0[28]) for all analyses.

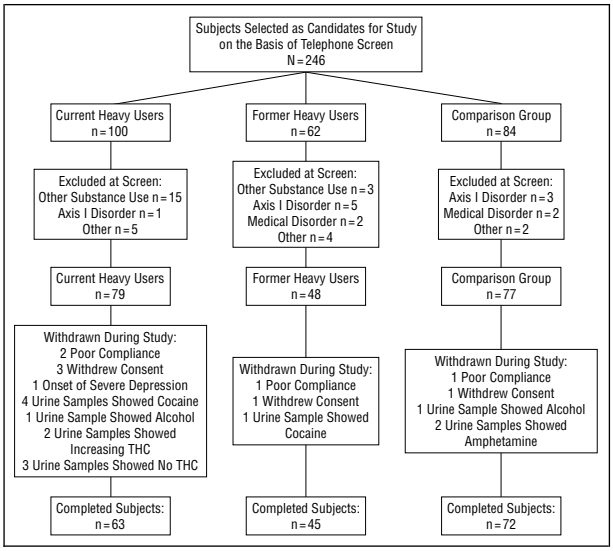
cational levels and household income in their families of origin, whereas the subjects themselves differed markedly on these same indices, with users reporting much lower educational attainment and income than controls.

Of the 4 neuropsychological tests performed serially during the 28 days of abstinence, 2 (the Auditory Continuous Performance Test and Continuous Performance Test) revealed no significant differences between control subjects and current users, in analyses with and without VIQ adjustment, on any of the 4 testing days on any of the measures tested (total correct responses and total errors). On the Benton Revised Visual Retention Test, the groups did not differ significantly at any time point on the number of correct responses, but current users made more errors on day 0, although this difference met our proposed $\alpha = .01$ only in the analysis without VIQ adjustment (adjusted mean difference [SE], 1.2 [0.3], $P = .001$ without VIQ adjustment; 0.8 [0.3], $P = .02$ with VIQ adjustment). However, memory of word lists on the BSRT more consistently distinguished the current users

from control subjects at days 0, 1, and 7, although generally not at day 28 (**Table 2**). The former users, by contrast, were not significantly different from controls on all measures of all 4 tests at all time points, in the VIQ-adjusted and VIQ-unadjusted analyses.

Scores on the 6 neuropsychological tests administered exclusively at day 28 appeared consistent with these findings. We found no significant differences between either the current or former users and the control subjects, using either the VIQ-adjusted or VIQ-unadjusted analyses, on the standard measures generated by these tests, as shown in **Table 3**. In addition to the measures shown in Table 3, we also failed to find significant differences in any of these same comparisons on times for word reading and color naming on the Stroop Test; immediate and delayed memory for stories, figures, and pairs on the Wechsler Memory Scale; digit span on the Wechsler Memory Scale; and total categories achieved on deck 1 of the Wisconsin Card Sorting Test. On categories achieved on deck 2 of the Wisconsin Card Sorting Test, we found one significant difference: in the VIQ-unadjusted analysis, current users achieved fewer categories than did controls (estimated difference [SE], –0.5 [0.2] categories, $P = .003$). However, this difference largely disappeared in the VIQ-adjusted analysis (–0.2 [0.2], $P = .25$) and failed to achieve significance in the comparison of former users vs controls (VIQ-unadjusted, –0.3 [0.2], $P = .09$; VIQ-adjusted, –0.3 [0.2], $P = .17$). Overall, these findings suggest that cognitive deficits associated with cannabis use persisted at least 7 days, but could not be detected with our measures after 28 days.

We then performed additional analyses to test the impression that reduced cognitive performance was associated with recent exposure to cannabis, rather than total lifetime use of the drug. First, as described in the "Subjects and Methods" section, we examined the association between subjects' estimated lifetime number of episodes of use and performance at day 28 on all of the measures shown in Tables 2 and 3. Subjects' lifetime cannabis use varied more than 10-fold, from 5000 to more than 70 000 estimated episodes, thus permitting a test of the association between total use and test measures. In current and former users, however, none of these asso-




Flow sheet showing subjects recruited and withdrawn in the 3 study groups. THC indicates tetrahydrocannabinol.

**Table 1. Demographic Features of Current Users and Former Users vs Control Subjects***

| Demographic Feature | Current Users (n = 63) | Former Users (n = 45) | Controls (n = 72) |
|---|---|---|---|
| Age [range], y | 36 [32-41] | 41 [37-48] | 39.5 [34-44] |
| Male | 55 (87) | 30 (67) | 61 (85) |
| White | 54 (86) | 39 (87) | 60 (83) |
| High school education or less | 18 (29)† | 6 (13)‡ | 0 |
| Annual household income <$30 000 | 32 (51)‡ | 23 (51)‡ | 19 (26) |
| Mother's education high school or less§ | 37 (61) | 17 (40) | 42 (58) |
| Father's education high school or less‖ | 26 (46) | 22 (50) | 27 (38) |
| Parents' annual household income <$30 000¶ | 16 (25) | 11 (25) | 13 (18) |
| Family history of any Axis I disorder# | 37 (60) | 21 (50) | 26 (37) |
| Lifetime episodes of cannabis use | 18 720 [11 700-27 000]** | 11 000 [8400-16 000]** | 10 [5-25] |
| Years smoking cannabis ≥7 times per week | 19 [15-24]** | 15 [11-19]** | 0 |
| Lifetime alcoholic drinks | 4700 [2100-7700] | 3900 [1100-10 100] | 2800 [1100-5500] |
| Lifetime packs of cigarettes | 730 [0-5100]** | 420 [0-4400]** | 0 |
| Lifetime caffeinated drinks | 13 800 [3000-23 200] | 15 300 [3200-26 100] | 12 400 [3600-20 000] |
| Conduct disorder score‡‡ | 1 [1-3]†† | 1 [0-2] | 0 [0-1] |
| Attention-deficit/hyperactivity disorder score‡‡ | 10 [4-14] | 10 [7-13] | 7.5 [5-15] |
| Verbal IQ | 106 [95-118]** | 115 [99-127] | 115 [110-126] |

*Data are given as number (percentage) for proportions and as median [interquartile range] for continuous variables. *P* values are significance of differences vs controls. All statistical tests were 2-tailed. Numbers of users and controls vary because of missing data.
†$P<.001$, Fisher exact test.
‡$P<.01$, Fisher exact test.
§61 current users and 43 former users.
‖56 current users, 44 former users, and 71 controls.
¶44 former users.
#62 current users, 42 formers users, and 70 controls.
**$P<.001$, Wilcoxon rank sum test.
††$P<.01$, Wilcoxon rank sum test.
‡‡Thirty-three current users, 31 former users, and 45 controls.

**Table 2. Scores of Study Groups on the Buschke Selective Reminding Test on Successive Testing Days**

| | Mean (SD) Scores | | | Estimated Mean Differences (SE) Between Groups* | | | |
|---|---|---|---|---|---|---|---|
| | | | | Current Users vs Controls | | Former Users vs Controls | |
| | Current Users (n = 63) | Former Users (n = 45) | Controls (n = 72) | With VIQ Adjustment | Without VIQ Adjustment | With VIQ Adjustment | Without VIQ Adjustment |
| **Total Recall** | | | | | | | |
| Day 0 | 104.5 (15.0) | 109.1 (13.4) | 113.6 (16.3) | −6.1 (2.7) | −9.1 (2.6)† | −3.0 (2.4) | −3.9 (2.5) |
| Day 1 | 106.7 (17.0) | 114.9 (11.3) | 115.5 (15.7) | −5.8 (2.8) | −8.8 (2.8)† | 0.9 (2.2) | 0.0 (2.2) |
| Day 7 | 111.7 (15.4) | 118.7 (12.9) | 120.9 (13.6) | −6.3 (2.4)† | −9.3 (2.4)‡ | −0.6 (2.1) | −1.6 (2.2) |
| Day 28 | 116.4 (12.9) | 117.9 (13.5) | 121.1 (13.6) | −1.8 (2.4) | −4.8 (2.1) | −1.7 (2.3) | −2.6 (2.2) |
| **Long-term Storage** | | | | | | | |
| Day 0 | 96.5 (22.7) | 104.5 (21.1) | 108.6 (21.9) | −8.5 (4.1) | −11.9 (3.8)† | −1.5 (3.8) | −2.8 (3.8) |
| Day 1 | 99.4 (22.5) | 108.2 (16.5) | 109.0 (21.2) | −6.0 (3.9) | −9.4 (3.7) | 1.7 (3.3) | 0.4 (3.2) |
| Day 7 | 105.7 (22.0) | 115.1 (18.3) | 117.2 (16.6) | −7.8 (3.5) | −11.2 (3.3)† | 0.4 (2.9) | −0.8 (3.0) |
| Day 28 | 112.4 (18.6) | 112.4 (19.6) | 117.2 (19.0) | −1.2 (3.5) | −4.5 (3.1) | −2.3 (3.4) | −3.6 (3.2) |
| **Consistent Long-term Retrieval** | | | | | | | |
| Day 0 | 58.0 (29.2) | 64.4 (27.7) | 77.1 (33.0) | −13.7 (5.4) | −19.3 (5.1)‡ | −10.3 (5.1) | −12.4 (5.2) |
| Day 1 | 62.0 (33.4) | 75.0 (28.4) | 81.7 (36.3) | −14.3 (6.0) | −19.9 (5.7)‡ | −4.3 (5.1) | −6.3 (5.3) |
| Day 7 | 70.8 (32.8) | 86.9 (30.9) | 91.5 (35.2) | −15.3 (5.6)† | −20.9 (5.4)‡ | −2.2 (5.4) | −4.3 (5.5) |
| Day 28 | 79.4 (31.2) | 82.2 (32.6) | 91.9 (31.7) | −7.1 (5.6) | −12.7 (5.0) | −7.3 (5.3) | −9.4 (5.4) |
| **30-Minute Delayed Free Recall** | | | | | | | |
| Day 0 | 8.8 (2.3) | 9.4 (2.2) | 9.7 (2.4) | −0.6 (0.4) | −1.0 (0.4) | −0.3 (0.4) | −0.4 (0.4) |
| Day 1 | 8.3 (2.7) | 9.6 (2.4) | 9.6 (2.6) | −0.8 (0.4) | −1.2 (0.4)† | 0.0 (0.4) | −0.1 (0.5) |
| Day 7 | 8.6 (2.6) | 9.9 (2.3) | 10.1 (2.0) | −1.1 (0.4)† | −1.5 (0.4)‡ | −0.2 (0.4) | −0.2 (0.4) |
| Day 28 | 9.1 (2.3) | 9.2 (2.5) | 10.2 (2.2) | −0.8 (0.4) | −1.1 (0.4)† | −0.9 (0.4) | −1.0 (0.4) |

*VIQ indicates verbal IQ. *P* values are significance of differences vs controls.
†$P<.01$.
‡$P<.001$.

**Table 3. Scores of Study Groups at Day 28 on Representative Test Measures**

| | Mean (SD) Scores at Day 28 | | | Estimated Mean Differences (SE) Between Groups* | | | |
|---|---|---|---|---|---|---|---|
| | | | | Current Users vs Controls | | Former Users vs Controls | |
| Test Score | Current Users (n = 63) | Former Users (n = 45) | Controls (n = 72) | With VIQ Adjustment | Without VIQ Adjustment | With VIQ Adjustment | Without VIQ Adjustment |
| Total score on Wechsler Memory Scale | 69.3 (8.4) | 68.9 (6.8) | 70.3 (6.2) | 0.2 (1.3) | −1.6 (1.2) | −0.1 (1.2) | −1.2 (1.2) |
| Raw score on Controlled Oral Word Association Test | 47.1 (10.8) | 48.2 (10.3) | 51.4 (11.0) | −2.3 (2.3) | −4.9 (2.0) | −2.7 (2.2) | −3.2 (2.2) |
| Total perseverations on Wisconsin Card Sorting Test† | 2.4 (0.8) | 2.4 (0.8) | 2.1 (0.7) | 0.1 (0.1) | 0.3 (0.1) | 0.1 (0.2) | 0.2 (0.1) |
| Scaled score on block design subtest of the Wechsler Adult Intelligence Scale–Revised | 11.7 (2.5) | 11.4 (2.5) | 11.9 (2.6) | 0.1 (0.5) | −0.5 (0.4) | −0.1 (0.5) | −0.3 (0.5) |
| Color interference time on Stroop Test, s | 105.5 (26.5) | 107.4 (24.1) | 101.5 (23.5) | 5.5 (5.3) | 7.4 (4.5) | 3.5 (5.1) | 3.8 (4.8) |
| Total score on Raven Progressive Matrices | 49.3 (6.5) | 49.4 (6.9) | 51.1 (6.7) | −0.5 (1.3) | −2.3 (1.1) | −1.1 (1.3) | −1.9 (1.3) |

*None of these differences achieved statistical significance. VIQ indicates verbal IQ.
†Shown and analyzed as logarithm of total perseverations because of right-skewed distribution.

ciations proved significant in either the VIQ-adjusted or VIQ-unadjusted analyses.

Turning to the issue of recent cannabis exposure, we also examined the association between baseline THCCOOH-creatinine ratios and the neuropsychological measures at each time point for the current users. This analysis, with VIQ adjustment, produced significant associations between baseline ratios and BSRT Total Recall at day 1 (estimated decrease in words recalled for every increase of 1 in log of ratio [SE], −5.7 [2.0], $P = .005$) and Consistent Long-term Retrieval on day 1 (−11.8 [4.3], $P = .006$). Without VIQ adjustment, we also found significant associations with BSRT Total Recall at day 1 (−6.6 [2.1], $P = .002$), Consistent Long-term Retrieval at day 1 (−13.3 [4.4], $P = .002$) and day 7 (−11.8 [4.2], $P = .005$), and 30-Minute Delayed Recall at day 28 (−0.9 [0.3],

$P = .003$). However, we found no significant association between baseline ratios and scores on the other 3 serial tests or on the 6 tests given exclusively at day 28.

We also examined the effects of sex. On all of the measures in Tables 2 and 3, we found no significant gender-by-group interaction. However, the power of this analysis was limited by the small number of female subjects.

Given evidence that ADHD and antisocial behavior may be associated with neurocognitive deficits,[29-34] we also performed analyses adjusting for ADHD and for conduct disorder scores among the 109 subjects for whom we possessed these data. However, adjustment for these variables produced only small changes in the estimate of mean effect of group on each of the neuropsychological measures and did not alter any qualitative conclusions (ie, whether a result was statistically significant).

## COMMENT

In a study of cognitive function among long-term heavy cannabis users, we found deficits on memory of word lists, detectable at least 7 days after discontinuing the drug and related to initial urinary concentrations of THCCOOH. After 28 days of abstinence, however, users showed virtually no significant differences from control subjects on a battery of 10 neuropsychological tests. Former heavy users, who had consumed little or no cannabis in the 3 months before testing, showed no significant differences from control subjects on any of these tests on any of the testing days. The paucity of significant differences between the cannabis and control groups at day 28, together with the lack of significant associations between test scores and lifetime cannabis consumption, suggests that cannabis-associated cognitive deficits may be reversible phenomena associated with recent drug exposure, rather than irreversible phenomena associated with cumulative lifetime use.

Deficits on memory of word lists, persisting for days after discontinuing cannabis use, might be attributable to cannabinoids lingering in the central nervous system or to withdrawal from abruptly stopping use. Although we cannot clearly discriminate between these hypotheses, measures of aggression[35] and subjective indices[36,37] in the users suggest that withdrawal-associated agitation, often lasting at least 7 days, may have compromised their neuropsychological performance. A withdrawal hypothesis might explain why deficits on the BSRT in current users were at least as great on day 7 as on days 0 and 1 (Table 2).

Our findings are generally congruent with those of previous studies[1-6] showing neuropsychological deficits within the first few days after cannabis use is stopped. Also, in agreement with another recent study,[8] we failed to find an association between cumulative lifetime use of cannabis and cognitive deterioration. Only the findings by Solowij[7] appear somewhat discrepant with ours, in that she found significantly increased processing negativity to irrelevant stimuli in former heavy users after a mean of 2 years' abstinence, whereas we found little evidence of neuropsychological deficits after 28 days of abstinence. Possibly, cannabis produces irreversible effects detectable on electroencephalographic measures, but too subtle to be detected on our neuropsychological test battery. Alternatively, the differences between the 2 studies may have been because of unmeasured or inadequately controlled confounding variables.

The cannabis users and controls in our study reported similar educational levels and income in their families of origin, whereas the users themselves exhibited significantly lower educational attainment, income, and estimated VIQ than controls. We cannot determine whether these differences are because of premorbid attributes of the users or because of cannabis effects. Even if cannabis produces little or no irreversible cognitive deficit, chronic cannabis intoxication might still compromise educational ambitions, income potential, and the acquisition of new verbal information.

Several limitations of our study should be considered. The first is a possible selection bias caused by our study requirements. For example, users with severe neuropsychological deficits might have been less likely to enter the study, although a similar bias might also have affected the control group. In any event, we cannot exclude the possibility that we might have underestimated the cognitive deficits associated with cannabis use because severely impaired individuals were underrepresented.

A second limitation is the possibility of residual confounding, because of either unmeasured confounders or inadequate adjustment for measured confounders. However, it seems unlikely that such confounders could explain the lack of differences between users and controls at day 28, because the most plausible unmeasured confounding variables in the users—such as undetected psychopathologic conditions, unrecognized premorbid cognitive deficits, unreported prior use of other drugs, or undetected surreptitious use of cannabis during the study—would all be expected to militate against our finding of an absence of differences. Similarly, users' greater lifetime consumption of alcoholic drinks and cigarettes would also be expected to militate against our finding, barring the remote possibility that nicotine from possible compensatory cigarette smoking among abstinent users might actually improve neuropsychological performance.[38]

Third, subjects' histories, including information on cannabis and other drug use, were obtained by self-report without external validation. However, as mentioned in the "Subjects" subsection of the "Subjects and Methods" section, subjects were interviewed about their drug histories without knowledge of the answers necessary to gain acceptance into the study. Furthermore, previous studies[39-41] have suggested that self-reports of use of cannabis and other drugs are fairly reliable. Finally, our principal positive findings—the initial cognitive deficit of the current users and its association with THCCOOH concentrations at study entry—were largely independent of self-report, because THCCOOH concentrations were measured on observed urine samples, using a sophisticated method likely to detect all but the most minimal levels of surreptitious cannabis use.[15]

Fourth, it might be argued that we should have chosen control subjects who had never used cannabis, as opposed to individuals who had used the drug 1 to 50 times. However, we reasoned that "minimal-user" controls would more closely resemble the heavy users on possible confounding variables (measured and unmeasured) than would "never-used" controls, while still differing more

than 1000-fold from the heavy users in their median level of exposure to cannabis (Table 1).

Fifth, our study design included only a limited assessment of premorbid intellectual functioning, based on the vocabulary subtest of the Wechsler Adult Intelligence Scale–Revised. Although this measure has been shown to provide reliable estimates of premorbid IQ in other populations,[17,24] it is possible that lower VIQ is, at least partly, a consequence, rather than an antecedent, of long-term cannabis use. As discussed in the "Statistical Analysis" subsection of the "Subjects and Methods" section, we addressed this question by performing analyses with and without adjustment for VIQ, thus providing upper and lower bounds for our estimate of the neuropsychological deficits associated with cannabis use. However, in the non–VIQ-adjusted analysis, which would be expected to be the least favorable to cannabis users, we still found virtually no significant differences at day 28 between users and controls on the test measures.

Sixth, it is possible that long-term cannabis use might produce long-term cognitive deficits, but that our neuropsychological tests were not sufficiently sensitive to detect them. For example, practice effects on the BSRT, combined with a possible ceiling effect, might have reduced the ability of this instrument to detect differences between groups on the fourth administration, on day 28. The sensitivity of the study is also limited by its sample size. For example, in the VIQ-adjusted analysis for current users, the 99% confidence intervals for the day 28 test measures shown in Tables 2 and 3 do not exclude an effect of 0.4 to 0.8 (median, 0.6) SD units (the estimated difference between groups divided by the SD in the control group). Therefore, the possibility remains that more sophisticated neurocognitive assessment measures, such as electroencephalographic or functional magnetic resonance imaging measures, might reveal deficits in long-term cannabis users below the threshold detectable with our neuropsychological test battery.

In summary, our findings do not support the hypothesis that long-term heavy cannabis use causes irreversible cognitive deficits, at least at the level detectable with our test instruments and our sample size. However, in agreement with previous reports, we found evidence that heavy users exhibit some cognitive deficits lasting for many days, and possibly for weeks, after discontinuing cannabis use.

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