Cognitive Functioning of Long-term Heavy Cannabis Users Seeking Treatment

Nadia Solowij, PhD
Robert S. Stephens, PhD
Roger A. Roffman, DSW
Thomas Babor, PhD, MPH
Ronald Kadden, PhD
Michael Miller, PhD
Kenneth Christiansen, PsyD
Bonnie McRee, MPH
Janice Vendetti, MPH
for the Marijuana Treatment Project Research Group

Context Cognitive impairments are associated with long-term cannabis use, but the parameters of use that contribute to impairments and the nature and endurance of cognitive dysfunction remain uncertain.

Objective To examine the effects of duration of cannabis use on specific areas of cognitive functioning among users seeking treatment for cannabis dependence.

Design, Setting, and Participants Multisite retrospective cross-sectional neuropsychological study conducted in the United States (Seattle, Wash; Farmington, Conn; and Miami, Fla) between 1997 and 2000 among 102 near-daily cannabis users (51 long-term users: mean, 23.9 years of use; 51 shorter-term users: mean, 10.2 years of use) compared with 33 nonuser controls.

Main Outcome Measures Measures from 9 standard neuropsychological tests that assessed attention, memory, and executive functioning, and were administered prior to entry to a treatment program and following a median 17-hour abstinence.

Results Long-term cannabis users performed significantly less well than shorter-term users and controls on tests of memory and attention. On the Rey Auditory Verbal Learning Test, long-term users recalled significantly fewer words than either shorter-term users ($P=.001$) or controls ($P=.005$); there was no difference between shorter-term users and controls. Long-term users showed impaired learning ($P=.007$), retention ($P=.003$), and retrieval ($P=.002$) compared with controls. Both user groups performed poorly on a time estimation task ($P<.001$ vs controls). Performance measures often correlated significantly with the duration of cannabis use, being worse with increasing years of use, but were unrelated to withdrawal symptoms and persisted after controlling for recent cannabis use and other drug use.

Conclusions These results confirm that long-term heavy cannabis users show impairments in memory and attention that endure beyond the period of intoxication and worsen with increasing years of regular cannabis use.

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IN THE CURRENT CLIMATE OF DEBATE about marijuana laws and interest in marijuana as medicine,[1] one issue remains unresolved: Does heavy, frequent, or prolonged use of cannabis lead to a deterioration in cognitive function that persists well beyond any period of acute intoxication? Is the functioning of the brain altered in the long term? With over 7 million people using cannabis weekly or more often in the United States alone[2] and the potential for increased physician recommendations for select patients to use cannabis therapeutically,[1] answers to these questions are of significant public health concern.[3,4] Scientific evidence from past research clearly showed that gross impairment related to chronic cannabis use did not occur but was inconclusive with regard to the presence of more specific deficits.[5,6] Recent studies with improved methods have demonstrated changes in cognition and brain function associated with long-term or frequent use of cannabis. Specific impairments of attention, memory, and executive function have been found in cannabis users in the unintoxicated state (and in children exposed to cannabis in utero[7]) in controlled studies using brain event-related potential techniques[6,8-10] and neuropsychological assessments[11-15] including complex tasks.

Brain imaging studies of cannabis users have demonstrated altered function, blood flow, and metabolism in prefrontal and cerebellar regions.[16-19] Studies failing to detect cognitive decline associated with cannabis use[20] may reflect insufficient heavy or chronic use of cannabis in the sample or the use of insensitive assessment instruments. Impairments appear to increase with duration and frequency of cannabis use; however, the parameters of use that are associated with short- or long-lasting cognitive and brain dysfunction have not

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Author Affiliations: National Drug and Alcohol Research Centre, University of New South Wales, Sydney, and Department of Psychology, University of Wollongong, Wollongong (Dr Solowij), New South Wales, Australia; Department of Psychology, Virginia Polytechnic Institute and State University, Blacksburg, Va (Dr Stephens); Innovative Programs Research Group, School of Social Work, University of Washington, Seattle (Dr Roffman); Department of Community Medicine (Dr Babor and Mss McRee and Vendetti) and Department of Psychiatry (Dr Kadden), University of Connecticut Health Center, Farmington; and The Village South Inc, Miami, Fla (Drs Miller and Christiansen). **Other Members of the Marijuana Treatment Project Research Group** are listed at the end of this article. **Corresponding Author and Reprints:** Nadia Solowij, PhD, National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW 2052, Australia (e-mail: n.solowij@unsw.edu.au).

been fully elucidated. The attribution of deficits to lingering acute effects, drug residues, abstinence effects, or lasting changes caused by chronic use continues to be debated.[5,6] Animal research suggests an important role for the cannabinoid receptor in regulating the neural activity critical for memory processing.[21-24] Long-term use of cannabis may result in altered functioning of the cannabinoid receptor and its associated neuromodulator systems.

This study investigated the nature of cognitive impairments associated with long-term cannabis use employing data collected from a large clinical trial of chronic users seeking treatment for cannabis dependence. The study compared 102 cannabis users assessed prior to treatment on carefully selected neuropsychological tests with 33 nonuser controls. The parameters of cannabis use that contribute to impairment were examined. It was hypothesized that performance would deteriorate as the number of years of regular use increased.

METHODS

Design

A multisite, retrospective, cross-sectional comparison-group design was used to compare (1) long-term users with a mean of 23.9 years of regular cannabis use; (2) shorter-term users with a mean of 10.2 years of regular use; and (3) nonusers of cannabis. Key confounding variables (age, IQ, other drug use) were controlled through matching or statistical methods. The sample size required for this study was determined by estimating a 94% chance of detecting a moderate effect size of 0.5 SD units at a 2-tailed α of .05.

Recruitment Procedure and Assessment of Drug Use

Sixty-five of the 102 cannabis users were delayed-treatment participants from the Marijuana Treatment Project, a multisite US study (Seattle, Wash; Farmington, Conn; and Miami, Fla) conducted between 1997 and 2000 of the effectiveness of brief treatments for cannabis dependence.[25] The remainder were recruited through the Marijuana Treatment Project specifically for this study. Participants provided written informed consent as approved by the ethics committees of the participating institutions and were paid $75 for completing the cognitive assessments. Controls (n=33) were recruited from the general population through media advertisements at only 1 site. The controls were told that the researchers were studying the effects of exposure to drugs and alcohol on cognitive functioning, and that at present only individuals at the lighter end of the spectrum of drug experience were required. The aim was to minimize cannabis use among controls while approximating the other characteristics of the cannabis-using sample. Assessors were not blinded with regard to group assignment. Self-reported drug and alcohol use were assessed by the Addiction Severity Index,[26] a separate structured interview, and the Time Line Follow Back procedure.[27,28] The Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)* Axis I Disorders (SCID)[29] assessed cannabis dependence. Duration of regular (at least twice per month) cannabis use was an averaged composite measure derived from the Addiction Severity Index, SCID, and the structured interview. Current frequency of cannabis use was calculated from the Time Line Follow Back procedure.

Inclusion/Exclusion Criteria

Cannabis users were included if they had used cannabis regularly for at least 3 years, were currently using at least once a week, were seeking treatment to assist them to cease or reduce their use of cannabis, and were willing to participate in the treatment program offered. Participants were excluded if they had ever had a serious illness or injury that may have affected the brain, any psychotic disorder, met a current *DSM-IV* diagnosis of dependence on any other drug or alcohol, or had a poor command of the English language.

Sample Characteristics

TABLE 1 provides demographic information and cannabis use parameters.

Table 1. Demographic and Cannabis Use Details of the Sample*

	Cannabis Users			
	All	Shorter-term Users	Long-term Users	Controls
No.	102	51	51	33
Sex, male (%)	75 (74)	36 (71)	39 (76)	22 (67)
Age, mean (SD) [range], y	35.4 (8.6) [19-55]	28.7 (5.5) [19-45]†	42.1 (5.2) [34-55]†	34.8 (11.1) [19-65]
Education, mean (SD) [range], y‡	14.3 (2.3) [10-22]	14.1 (2.5) [10-22]	14.5 (2.0) [11-20]	14.8 (1.8) [12-18]
Full-scale IQ, mean (SD) [range]§	105.4 (6.7) [87.4-118.5]‖	105.1 (7.4) [87.4-118.5]	105.7 (5.9) [92.7-118.3]	107.9 (4.7) [94.5-117.2]
Duration of use, mean (SD) [range], y¶	17.1 (7.9) [2.7-31.7]	10.2 (3.8) [2.7-17.0]	23.9 (4.1) [17.3-31.7]	. . .
Frequency of use, median (range), d/mo#	27.9 (3.5-30)	28.3 (5.2-30)	27.4 (3.5-30)	. . .

*Ellipses indicate not applicable.
†Significantly different from controls at $P<.001$.
‡The self-reported number of years of formal education completed.
§Estimated from a combination of North American Adult Reading Test, Wide Range Achievement Test–Revised reading subtest scores, and the Barona Index.
‖Significantly different from controls at $P<.05$.
¶The number of years that cannabis had been used since regular use commenced (at least twice per month), composite from self-report, Addiction Severity Index, and Structured Clinical Interview Axis 1 Disorders assessments.
#The median number of days per month that cannabis was used at entry to the study, based on average use per 30 days from self-reported use during the past 14 weeks.

The user group was split at the median for duration of cannabis use to enable comparisons of long-term users, shorter-term users, and controls. No meaningful division of groups could be achieved on the basis of frequency of cannabis use, which was almost daily for the majority of the sample. Sex distribution and years of education did not differ between groups. The majority of users (68.6%) and controls (63.6%) were white. Overall, users and controls did not differ in age, but long-term users were significantly older and shorter-term users were significantly younger than controls ($P<.001$). Premorbid intelligence was estimated by several methods and averaged: the Wide Range Achievement Test—Revised reading subtest (WRAT-R READ)[30,31]; the North American Adult Reading Test (NAART)[32]; and the Barona Index.[33] The mean estimated full-scale IQ (FSIQ) did not differ between the 3 groups based on duration of cannabis use. The majority of the sample (82.4% long-term, 88.2% shorter-term users) reported experiencing problems with memory, attention, or concentration, which they attributed to their use of cannabis.

Cannabis Use, Required Abstinence, and Urinalysis

Users first tried cannabis at a mean age of 15.3 (SD, 2.6) years with regular use (at least twice a month) commencing at age 17.5 (SD, 3.2) years. Cannabis had been used on a median 29 of the past 30 days (range, 1-30). Almost the entire sample (98%) met the *DSM-IV* criteria for cannabis dependence. The median amount of cannabis smoked per week was 1 quarter of an ounce (range, 0.01-2.00 oz) with 2 average-sized joints typically smoked per day (range, 0.12-20.00). None of these cannabis-use parameters differed between the long- and shorter-term user groups. Twenty-two controls had either never tried cannabis or used it 10 or fewer times in their lives and 11 had used cannabis weekly to monthly while at school or college between 4 and 30 years ago. Controls with a history of cannabis use were excluded from "pure sample" analyses.

Participants were required to abstain from cannabis for at least 12 hours prior to testing and to provide 2 urine samples (1 the night before testing, another during the test session). The median self-reported time since last use of cannabis was 17 hours (range, 7-240 hours); this did not differ between long- and shorter-term users. At the time of testing, 70% of the sample reported that they were not experiencing any discomfort after abstaining from cannabis. Twice as many shorter-term users than long-term users ($P=.03$) reported mild withdrawal symptoms such as cravings, irritability, depression, anxiety, sleep, or appetite disturbances. In 78.3% of cases, creatinine-normalized urinary cannabinoid metabolite (THC-COOH) levels on the day of testing were less than or equivalent to those from the night before.[34-37] Abstinence from cannabis was supported by significant correlations between the level of normalized urinary cannabinoid metabolite on the day of testing and the self-reported time since last use (bivariate correlation coefficient [r], –0.46; $P<.001$), and the quantity used on the last occasion divided by the time since last use (r, 0.39; $P<.001$). The effects of these measures of recent use were examined in relation to test performance. "Pure sample" analyses excluded users with higher metabolites in the second urine sample. No cannabinoid metabolites were detected in the urine of the control participants.

Other Drug Use

No other drug metabolites were detected in any urine sample. Tobacco and alcohol use was minimal. Alcohol was consumed on a median of 3.4 and 1.7 days per month among users and controls, respectively. Almost one third of users and 46.8% of controls drank less than once a month or not at all. Forty-eight percent of the cannabis users had only tried drugs other than cannabis a few times or never; 52% had used other drugs socially/recreationally primarily during high school and college. Past histories of regular drug use included cocaine (n=24), amphetamines (n=11), hallucinogens (n=17), and sedatives/hypnotics or minor tranquilizers (n=7). Current use of other drugs was less than once a month or not at all for 93.1% of the sample. More than half of the controls (51.5%) had never tried any other drug and the remainder had only tried other drugs experimentally. "Pure sample" analyses excluded all participants with histories of regular or heavy use of alcohol or other drugs.

Neuropsychological Tests and Procedures

Nine neuropsychological tests were administered in the order listed in TABLE 2,[38-46] along with the 2 tests used to assess premorbid IQ.[30-32] A 10-minute rest break was given after the Rey Auditory Verbal Learning Test (RAVLT) Recognition test. Tests were administered by trained assistants and took approximately 2 hours to complete. Quality assurance procedures were adopted to ensure that procedures were standardized at each site with ongoing supervision and review of audiotaped assessments by centralized staff throughout the course of the study.

Data Analysis

Each cognitive test was analysed using SPSS version 10.0 (SPSS Institute, Chicago, Ill) with analysis of covariance (ANCOVA) for normally distributed variables or nonparametric tests of group differences for skewed data. The FSIQ and age were included as covariates in analyses where they correlated with test performance. All participants were initially included in analysis, with the overall cannabis user sample first compared with the control group (evaluated at $P<.05$), followed by comparisons on the basis of duration of cannabis use (long- vs shorter-term users vs controls, evaluated at $P<.01$). For 2-way interactions, the Greenhouse-Geisser method was used to adjust the *df* where appropriate and for multiple comparisons, a Bonferroni adjustment controlled for type I error. Analysis of covariance was repeated on a purer sample that strictly

Table 2. Neuropsychological Tests Administered and Cognitive Functions Assessed*

Neuropsychological Test	Cognitive Functions Assessed
Wide Range Achievement Test–Revised reading subtest (WRAT-R READ)[30,31]	Premorbid IQ
Speed of Comprehension (SOC) test (Speed and Capacity of Language Processing [SCOLP])[38]	Rate of verbal information processing
Rey Auditory Verbal Learning Test (RAVLT)[39-41]	Memory span, verbal learning and retrieval efficiency, susceptibility to interference
Stroop Test[42] with additional interference condition[43]	Attention, cognitive flexibility, inhibition of distractor stimuli, suppression of habitual response
Wisconsin Card Sorting Test (WCST), computerized[44]	Problem solving, conceptual ability
Alphabet Task†	Cognitive flexibility, executive function
Omitted Numbers‡	Working memory
Time Estimation and Production§	Temporal judgment
RAVLT 20-minute delay trial (VII), Recognition test	Long-term retention, recognition memory
North American Adult Reading Test (NAART)[32]	Premorbid IQ
Auditory Consonant Trigrams (Brown-Peterson)[45]	Short-term retention under distractor conditions
Paced Auditory Serial Addition Test (PASAT)[46]	Information processing, working memory, divided and sustained attention

*Tests were administered in the order listed.
†Composed of timed loud, silent, and alternating recital trials.
‡Recognition of omitted item from a jumbled aural list of numbers from 1 to 10 (10 trials).
§Composed of 3 trials: unwarned estimation of time to complete the preceding task (mean, 3 minutes 18 seconds) (Time Estimation A); time production (1 minute 40 seconds); and warned passive estimation (2 minutes) (Time Estimation B).

excluded those participants with either a history of other drug use or possible recent use of cannabis prior to testing. Semipartial correlations examined the unique contributions of FSIQ, age, duration of cannabis use, and recency of cannabis use to the variance in cognitive test performance.

RESULTS

Results from the 9 neuropsychological tests are shown in TABLE 3 for cannabis users overall, for groups based on duration of cannabis use, and for controls. Effect sizes are calculated between long-term users and controls using the SD of the controls.

Speed of Comprehension

Cannabis user groups did not differ from controls in the number of items completed (range, 23-100) but users overall made more errors ($P=.03$) (range, 0-5). These results suggest that cannabis users are more likely to sacrifice accuracy for speed.

Rey Auditory Verbal Learning Test

Mean words recalled on each trial are depicted in the FIGURE. The learning curves of shorter-term users and controls were similar but long-term users showed a learning curve with a less steep gradient and long-term users recalled fewer words on every trial. The sum of words recalled across all trials I through VII inclusive of trial B (referred to here as RAVLT sum; range, 37-114) correlated significantly and inversely with the duration of cannabis use after controlling for age and FSIQ (partial r, –0.23; $P=.01$). When analysed by ANCOVA, there was a significant effect of group ($F_{2,127}=8.36$; $P<.001$) whereby long-term users recalled significantly fewer words than either shorter-term users (95% confidence interval [CI] for difference, 3.84-19.18; $P=.001$) or controls (95% CI for difference, 2.83-19.93; $P=.005$) with no difference between shorter-term users and controls. When all trials were included in a repeated measures ANCOVA, a significant interaction between group and trial ($F_{14,889}=2.84$; $P=.007$) suggested that long-term users recalled fewer words than shorter-term users or controls on every trial ($P<.05$ for each comparison) except the first, with a trend on trial B (the interference list presented only once; $P=.08$).

The proportion of subjects with a very poor learning ability (acquisition <3 words over 5 trials) was greater among long-term users (13.7%) than controls (0%) ($P=.007$) but not shorter-term users (5.9%). The proportion of long-term users recalling fewer than 10 words on trial V (27.5%) was more than among shorter-term users (8.5%) or controls (3.0%) ($P=.002$). Significantly more long-term users (23.5%) lost 3 or more words over the 20-minute delay between trials VI and VII than shorter-term users (4.3%) or controls (3.0%) ($P=.003$). Long-term users showed a smaller primacy effect in the serial position curve than either other group ($P=.02$). Groups did not differ in the recency effect or in words recalled from the middle of the list.

Users overall and long-term users recognized fewer words than controls from list A (overall, $P=.03$; long-term, $P=.01$) and list B (overall, $P=.01$; long-term, $P=.04$) but long-term users did not differ from shorter-term users. More than half of the long-term users (55%) had a recognition score for list A of 12 or less compared with 28% of shorter-term users and 21% of controls ($P=.002$). Long-term users misassigned more words (median, 2) than shorter-term users and controls (each median, 0) ($P<.001$). A greater proportion of long-term users (13.7%) compared with shorter-term users (6.4%) and controls (0%) actually identified fewer words on recognition than they had just prior during recall on trial VII ($P=.02$). Long-term users' performance was significantly poorer than published norms[47] for the general population on most measures from the RAVLT.

Stroop Test

Cannabis users did not differ significantly from controls after inclusion of covariates in any condition or on interference scores. While there were no performance differences between Color-Word (CW) and Color-Read (CR) in the control group, performance on CR was, however, poorer than on CW in both long- ($P<.001$) and shorter-term

users ($P = .03$). Color-Read was the additional interference condition designed to increase demands on executive function.[43] There was an inverse relationship between duration of cannabis use and number of items completed on CR (partial $r, -0.27$; $P = .003$) and CW (partial $r, -0.27$; $P = .004$) after controlling for age and FSIQ. These results suggest that cannabis users are vulnerable to task complexity with increasing demands creating more sources of interference that adversely affect performance.

Wisconsin Card Sorting Test

There were no significant group differences on any Wisconsin Card Sorting Test (WCST) measure but a trend on one: long-term users failed to maintain the set more often than shorter-term users ($P = .05$) or controls ($P = .07$). Research suggests that this measure best represents attentional dysfunction.[39] There was no evidence of impaired performance with increasing years of cannabis use after controlling for covariates.

Table 3. Neuropsychological Test Results

Test	Cannabis Users*			Controls (n = 33)	Effect Size	*P* Value for Comparisons			
	All (n = 102)	Shorter-term Users (n = 51)	Long-term Users (n = 51)			All vs Controls	Shorter-term Users vs Controls	Long-term Users vs Controls	Shorter- vs Long-term Users
SCOLP-SOC, median (range)†									
Correct	10 (3-18)	11 (6-18)	10 (3-17)	10 (6-15)	. . .	.06	.07	.10	.65
Errors	1 (0-8)	1 (0-8)	1 (0-6)	0 (0-3)	. . .	.03	.05	.05	.99
RAVLT, mean (SD)‡									
Trial I	6.3 (1.9)	6.5 (1.9)	6.1 (1.9)	7.0 (1.9)	0.47	.12	>.99	.15	.59
Trial II	9.3 (2.7)	9.9 (2.6)	8.5 (2.5)*	9.9 (2.3)	0.61	.27	>.99	.05	.004
Trial III	10.8 (2.5)	11.5 (2.3)	10.1 (2.6)*	11.4 (2.2)	0.59	.37	>.99	.07	.003
Trial IV	11.5 (2.3)	12.1 (2.2)	10.9 (2.4)*	12.4 (2.2)	0.68	.10	>.99	.02	.01
Trial V	12.2 (2.3)	12.7 (2.1)	11.5 (2.4)*	12.9 (1.6)	0.88	.19	>.99	.03	.005
Trial B	6.0 (2.3)	6.5 (2.4)	5.5 (2.2)	6.9 (2.5)	0.56	.18	>.99	.05	.07
Trial VI	10.0 (3.0)	10.9 (2.8)	9.2 (3.1)*	11.4 (2.2)	1.00	.07	>.99	.005	.002
Trial VII	9.8 (3.5)*	11.1 (3.1)	8.5 (3.5)*	11.0 (2.7)	0.93	.13	>.99	.004	<.001
RAVLTsum	75.6 (17.2)*	81.4 (15.8)	70.3 (16.8)*	82.9 (14.8)	0.85	.14	>.99	.005	<.001
Recog_A	12.1 (3.1)*	13.1 (2.3)	11.1 (3.4)*	13.3 (1.7)	1.29	.03	>.99	.01	.14
Recog_B	6.1 (3.7)*	7.2 (3.7)	5.0 (3.5)*	8.2 (3.2)	1.00	.01	>.99	.04	.26
Stroop, mean (SD)§									
Word	101.3 (15.1)	100.2 (16.4)	102.2 (14.0)	107.0 (15.9)	0.30	.13	.99	.34	>.99
Color	75.6 (12.2)	75.8 (13.4)	75.4 (11.1)	74.5 (13.3)	0.07	.50	>.99	>.99	>.99
Color-Word	45.4 (9.2)*	46.8 (9.4)	44.0 (8.8)	44.4 (10.2)	0.04	.25	.55	>.99	>.99
Color-Read	40.1 (7.9)*	42.2 (9.0)	37.7 (6.2)	41.4 (7.9)	0.47	.92	>.99	>.99	.42
WCST, median (range)‖									
Errors	28 (16-81)	27 (16-77)	29 (17-81)	30 (15-78)	. . .	.67	.29	.77	.08
Perseverative responses	16 (7-49)	16 (7-45)	15 (8-49)	14 (8-63)	. . .	.95	.55	.49	.17
% Concept	72.7 (12.5-86.7)	73.1 (14.8-85.9)	71.9 (12.5-86.7)	71.9 (16.4-88.3)	. . .	.82	.38	.64	.12
Trials	13 (10-75)	13 (11-64)	12 (10-75)	13 (10-101)	. . .	.75	.90	.67	.74
Failures	1 (0-7)	1 (0-5)	2 (0-7)	1 (0-4)	. . .	.42	.74	.07	.05
Alphabet Task, median (range)¶									
Alternating	18.6 (10.4-52.4)*	16.8 (10.4-37.2)	19.8 (13.0-52.4)	17.5 (11.5-33.2)	. . .	.31	.91	.08	.07
Difference	11.3 (4.8-39.9)*	10.3 (5.0-29.6)	12.3 (4.8-39.9)	8.8 (3.2-24.7)	. . .	.14	.54	.04	.09
Omitted Numbers, mean (SD)#	6.7 (1.8)	7.0 (1.8)	6.4 (1.9)	6.3 (2.1)	0.05	.13	.64	.53	>.99
Time Estimation, s**									
Unwarned Task A, mean (SD)	−64.4 (53.5)*	−61.3 (54.1)*	−67.7 (53.2)*	−7.6 (88.6)	0.68	<.001	<.001	.01	>.99
Warned Task B, median (range)	−1.0 (−55 to 85)	−1.5 (−55 to 85)	−0.5 (−40 to 75)	5 (−70 to 102)	. . .	.65	.67	.70	.96
Time Production, mean (SD)	−15.6 (24.6)	−14.9 (25.7)	−16.4 (23.6)	−19.0 (26.2)	0.10	.24	>.99	.34	.79
Auditory Consonant Trigrams, mean (SD), seconds of delay††									
9	11.4 (2.7)*	12.1 (2.3)	10.7 (2.9)*	12.9 (1.9)	1.16	.03	>.99	.002	.007
18	11.3 (2.5)	11.7 (2.0)	10.9 (3.0)	11.5 (2.8)	0.21	.79	.92	>.99	.23
36	10.9 (2.9)	11.2 (2.9)	10.7 (2.9)	11.0 (2.7)	0.11	.84	>.99	>.99	.94

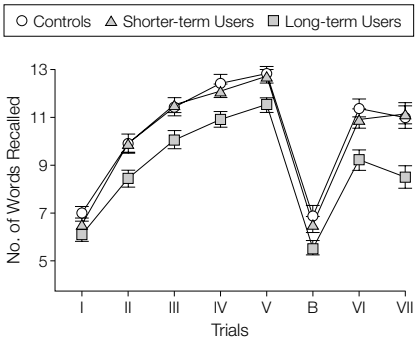
(continued)

Table 3. Neuropsychological Test Results (cont)

Test	Cannabis Users			Controls	Effect Size	*P* Value for Comparisons			
	All (n = 102)	Shorter-term Users (n = 51)	Long-term Users (n = 51)	(n = 33)		All vs Controls	Shorter-term Users vs Controls	Long-term Users vs Controls	Shorter- vs Long-term Users
PASAT, median (range)‡‡									
PR Trial 1	2.56 (2.40-4.56)	2.51 (2.40-3.60)	2.58 (2.40-4.56)*	2.56 (2.40-3.55)	. . .	.92	.16	.23	.007
PR Trial 2	2.23 (2.00-3.53)	2.18 (2.00-2.83)	2.28 (2.00-3.53)	2.24 (2.00-3.05)	. . .	.43	.84	.10	.03
PR Trial 3	1.79 (1.60-3.56)	1.78 (1.60-3.56)	1.81 (1.60-2.52)	1.76 (1.60-2.63)	. . .	.20	.49	.11	.35
PR Trial 4	1.36 (1.20-2.31)	1.35 (1.20-1.80)	1.38 (1.20-2.31)	1.33 (1.20-2.00)	. . .	.25	.54	.15	.22
Total PR	8.07 (7.32-10.81)	7.90 (7.36-9.95)	8.21 (7.32-10.81)	7.85 (7.37-10.53)	. . .	.32	.87	.05	.02
Total attempted	142.5 (74-191)	146.0 (96-191)	139.0 (74-188)	145.5 (110-190)	. . .	.75	.99	.56	.45
Total correct	127.0 (26.5)	132.0 (26.8)	121.9 (25.4)	131.6 (28.9)	0.34	.74	>.99	.84	.22
% Correct	64.8 (13.5)	67.3 (13.7)	62.2 (13.0)	67.1 (14.7)	0.33	.74	>.99	.84	.22
Seconds	2.78 (1.88-5.88)	2.64 (1.88-4.67)	2.94 (2.09-5.88)	2.71 (1.89-4.54)	. . .	.52	.97	.23	.14

*Significant correlation with the number of years of cannabis use after controlling for covariates ($P<.05$).
†SCOLP-SOC indicates Speed and Capacity of Language Processing-Speed of Comprehension test. Median scaled scores for the number of SOC test items completed in 2 minutes and errors (n = 96 users, n = 32 controls). Ellipses indicate not applicable.
‡RAVLT indicates Rey Auditory Verbal Learning Test. Mean words recalled on each trial of the RAVLT, total recalled across all trials (RAVLTsum), and median words recognized from lists A and B (98-102 users varied on each trial).
§Mean items completed in 45 seconds for the Word, Color, and Color-Word conditions of the Stroop (age-corrected, n = 100 users) and the modified Color-Read condition (n = 101 users).
‖WCST indicates Wisconsin Card Sorting Test. Median errors, perseverative responses, percentage of conceptual level responses, trials to complete the first category, and failures to maintain the set (n = 101 users, n = 32 controls).
¶Median time to recite the alphabet alternating from loud to silent and median difference between the loud and alternating trials in seconds (n = 94 users, n = 29 controls).
#Mean number of correctly identified items from the Omitted Numbers task.
**Mean difference between actual time elapsed and estimated time in unwarned Time Estimation task A, negative scores indicate underestimation (n = 94 users, n = 31 controls), median difference in warned Time Estimation task B (n = 98 users, n = 32 controls), and mean difference between time produced and time required in the Time Production task (n = 102 users, n = 30 controls).
††Mean letters recalled with 9-, 18-, and 36-second delays (n = 31 controls).
‡‡Paced Auditory Serial Addition Test (PASAT). Median processing rates (PR) for PASAT trials 1-4, total PR, total attempted, total correct (mean [SD]), percentage correct (mean [SD]), and seconds per correct response across the 4 trials (n = 98-100 users, n = 32 controls).

Figure. Mean Number of Words Recalled on Each Trial of the Rey Auditory Verbal Learning Test by Long- and Shorter-term Cannabis Users and Controls



Error bars represent SDs.

Alphabet Task and Omitted Numbers

Groups did not differ in the time taken to complete any trial of the Alphabet Task or in the number of items correct in the Omitted Numbers task. The log time to complete the alternating trial of the Alphabet Task increased as a function of duration of cannabis use (partial r, 0.26; $P=.006$), as did the square root difference between times taken to complete the alternating and loud trials, an index of interference and lack of flexibility (partial r, 0.26; $P=.006$).

Time Estimation Tasks

Cannabis users differed from controls ($P<.001$) in Time Estimation Task A where they estimated the time taken to complete the preceding (Omitted Numbers) task. Both long- and shorter-term users underestimated the time by about one third of the actual time taken (64.4 seconds) and differed significantly from controls ($P=.01$ and $P<.001$, respectively). Groups did not differ in the simple and brief warned passive Time Estimation Task B or Time Production, where they could use strategies such as counting. Time estimation measures did not correlate with duration of cannabis use.

Auditory Consonant Trigrams

Long-term users recalled significantly fewer items than shorter-term users ($P=.007$), controls ($P=.002$), and published norms[48] on only the 9-second delay condition. The number of items recalled did not correlate with duration of cannabis use. In the general population, the greater the delay interval the worse the performance. In cannabis users, this general pattern was apparent, though there was greater interference at the shorter-delay interval than would be expected.

Paced Auditory Serial Addition Test

Long-term users had slower processing rates than shorter-term users on trial 1 ($P=.007$), with trends on trial 2 ($P=.03$) and the total processing rate across all trials ($P=.02$). Group differences on all other measures failed to reach significance but the performance of the long-term users was poorer in comparison with one set of norms[49] but not another.[50]

Pure Effects Attributable to Cannabis Use and Effects of Recent vs Chronic Use

Excluding all participants with histories of regular other drug or alcohol use, dependence or treatment, and controls with any history of regular cannabis use within the past 20 years reduced the sample to 27 long-term users, 33 shorter-term users, and 26 controls. Despite the

reduction in power to detect differences between groups, there remained a significant difference with $\alpha = .05$ between long-term users and controls on RAVLTsum ($P = .03$), recognition of lists A ($P = .004$) and B ($P = .01$), and between users overall and controls on the unwarned Time Estimation task ($P = .02$). These results support the hypothesis that impaired memory function and time estimation are specific to chronic use of cannabis.

In a separate analysis, exclusion of users whose urinary cannabinoid metabolite levels exceeded those from the night before testing by 50 ng/mg or more (n=18) still resulted in significant differences between long- and shorter-term users, and long-term users and controls on RAVLT sum ($P = .002$ and $P = .002$, respectively), on recognition of lists A ($P = .005$ and $P = .006$) and B ($P = .01$ and $P < .001$), on the 9-second delay of the Auditory Consonant Trigrams test ($P = .02$ and $P = .03$), and users still differed from controls on time estimation ($P = .005$). When the sample was split at the median for time since last use or level of urinary cannabinoid metabolite on the day of testing and analyzed by ANCOVA, there were no differences on any measure between those who had used cannabis within the past 17 hours and those who had used cannabis 17 or more hours ago, or those with high vs low levels of urinary metabolites and no interactions with duration of cannabis use. Including measures of recent use as covariates in ANCOVA did not change the significance of differences between long- and shorter-term users. These results support the hypothesis that impaired performance is not a consequence of recent use prior to testing or the extent of cannabinoid residues present.

To explore further the influences of duration of cannabis use and recency of use, semipartial correlations were calculated using the following predictors: FSIQ, age, duration of cannabis use, and hours since last use of cannabis. As shown in TABLE 4, the unique contribution of duration of cannabis use to the variance of each test variable was superior or at least equivalent to that of recency of use in all 6 test variables that had significant contributions from at least 1 cannabis use parameter. Recent use contributed only to performance on the memory tests. The fact that a minority of the sample, primarily shorter-term users, reported experiencing mild withdrawal symptoms, yet shorter-term users' performance was not impaired, supports the interpretation of the cognitive impairments observed as a long-term consequence of cannabis use and not a manifestation of overtly experienced withdrawal.

COMMENT

The results of this study have confirmed and extended previous findings of cognitive impairments among chronic heavy cannabis users. Long-term users with a mean 24 years of regular cannabis use performed significantly less well on tests of memory and attention than nonuser controls and shorter-term users with a mean of 10 years' use. The greatest impairment on almost every measure was from the RAVLT, indicating a generalized memory deficit with impaired learning, retention, and retrieval. Long-term users recalled 2.5 fewer words than controls on the delayed recall trial where 49% of the long-term users' scores were more than 1 SD, and 21.6% were more than 2 SDs, below the control mean and normative data.[47] A large proportion of long-term users' recognition scores were more than 1 SD (51%) or 2 SDs (31.4%) below the control mean and norms.[47] Effect sizes for measures that differed significantly between long-term users and controls ranged from 0.56 to 1.29 across all tests, indicating moderate to large effects.

These results do not indicate a severe memory problem but could nevertheless translate into clinically significant cognitive impairment and could impact functioning in daily life. There were significant differences between long-term users and controls on 6 of the 9 tests administered and performance on 4 tests worsened as a function of increasing years of cannabis use. Despite this and a range of up to 17 years of cannabis use in the shorter-term user group, they differed significantly from controls only on time estimation.

Table 4. Predictor Correlations Between Hypothesized Predictors and Select Test Variables*

	Full-Scale IQ			Age			Duration of Cannabis Use			Recency of Cannabis Use†		
Test Variables	Zero-Order	Semipartial	*P* Value	Zero-Order	Semipartial	*P* Value	Zero-Order	Semipartial	*P* Value	Zero-Order	Semipartial	*P* Value
SCOLP-SOC, No. correct ($\sqrt{\ }$)	0.55	**0.52**	<.001	0.12	**0.24**	.005	0.01	**−0.24**	.005	0.11	**0.05**	.53
Stroop												
Color-Word	0.27	**0.29**	.002	−0.26	**0.09**	.33	−0.34	**−0.24**	.01	0.09	**0.05**	.58
Color-Read	0.36	**0.36**	<.001	−0.19	**0.12**	.17	−0.27	**−0.24**	.008	0.18	**0.13**	.15
RAVLT												
RAVLTsum	0.21	**0.22**	.02	−0.31	**0.06**	.54	−0.37	**−0.21**	.02	0.25	**0.21**	.02
RAVLT recency	0.11	**0.10**	.32	−0.19	**0.12**	.20	−0.27	**−0.22**	.02	0.24	**0.23**	.02
Alphabet Task Alternating, log	−0.21	**−0.21**	.03	0.12	**−0.17**	.09	0.21	**0.25**	.01	−0.04	**−0.02**	.81

*SCOLP-SOC indicates Speed and Capacity of Language Processing-Speed of Comprehension; RAVLT, Rey Auditory Verbal Learning Test. *P* values are for semipartial correlations. Test variables were significantly predicted by at least 1 cannabis use parameter.
†Defined as hours since last use of cannabis.

Altered brain metabolism in shorter-term users may be detected with sensitive techniques, such as functional magnetic resonance imaging and positron emission tomography, but the clinical significance of such changes remains obscure. The strength of this study is in its assessment of overtly relevant cognitive processes; our results suggest that shorter-term cannabis users are not impaired to an extent that would interfere with cognitive functioning in their daily lives. The fact that the frequency of use was near daily among long- and shorter-term users suggests that the duration of cannabis use is a more salient contributor to the development of cognitive impairment than quantity or frequency of use.

While most cannabis users cease using in their mid-20s to late 20s, approximately 20% continue to use through their 30s and beyond.[2] This is the first study to our knowledge of a relatively large sample of long-term entrenched cannabis users seeking treatment. Concern about perceived cognitive impairment was one of many problems associated with cannabis use that led the users in this study to seek treatment. This concern is unlikely to have biased the results of this study since a slightly higher proportion of shorter-term vs long-term users reported experiencing cognitive problems, yet shorter-term users mostly did not differ from controls on the cognitive tests. Nevertheless, it is possible that long-term cannabis users in the community who are not seeking treatment may not experience impairments to the same degree as those assessed in this study.

While acknowledging the limitations of retrospective designs, if carefully controlled and analyzed, this approach is the most efficient way to evaluate the long-term cognitive effects of cannabis, given the costs and logistical difficulties in using prospective research designs. The matching of groups on measures of premorbid intellectual functioning that are resilient to brain damage, together with the observed relationships between duration of cannabis use and test performance, support the assumption that the cognitive impairments observed in the long-term users were not preexisting but developed as a result of their prolonged use of cannabis. Impairment appeared unrelated to withdrawal phenomena. The cognitive functions assessed in this study are dependent on the intact functioning of the hippocampus, prefrontal cortex, and cerebellum,[39,51-55] which are dense with cannabinoid receptors.[56] The effects that exogenous cannabinoids exert on the cannabinoid receptor system and the role of endogenous cannabinoids as suggested by animal research[6,21-24] provide a credible neurophysiological explanation for the development of cognitive impairments as the result of hypothesized long-term changes occurring over many years of exposure to the drug.

In conclusion, our results confirm that cognitive impairments develop as a result of prolonged cannabis use, they endure beyond the period of acute intoxication, and they worsen with increasing years of use. Impairments develop gradually but may only become clinically significant and detectable by standard neuropsychological tests after 1 to 2 decades of cannabis use. Nevertheless, altered brain function with subtle impairment has been shown to manifest earlier.[6,8,9,11,17,18] It is also likely that impairments would be greater among comorbid substance-dependent persons. The risk to most medical cannabis users is likely to be small, as long as they are not maintained at high doses for many years. For habitual users, the kinds of impairments observed in this study have the potential to impact academic achievements, occupational proficiency, interpersonal relationships, and daily functioning. The extent to which these cognitive impairments may recover following cessation or reduction of cannabis use will be addressed in a follow-up of this sample subsequent to treatment for cannabis dependence.

Author Contributions: *Study concept and design*: Solowij, Stephens, Roffman.
Acquisition of data: Stephens, Roffman, Kadden, Miller, Christiansen, McRee, Vendetti.
Analysis and interpretation of data: Solowij, Stephens.
Drafting of the manuscript: Solowij.
Critical revision of the manuscript for important intellectual content: Solowij, Stephens, Roffman, Babor, Kadden, Miller, Christiansen, McRee, Vendetti.
Statistical expertise: Solowij, Stephens.
Obtained funding: Solowij, Stephens, Roffman, Babor, Kadden, Miller.
Administrative, technical, or material support: Solowij, Roffman, McRee, Vendetti.
Study supervision: Solowij, Stephens, Roffman, Babor, Kadden, Miller, Christiansen, McRee, Vendetti.
Other Members of the Marijuana Treatment Project Research Group include Kathleen Carroll, PhD, Karen Steinberg, PhD, (Coordinating Center, University of Connecticut Health Center, Department of Community Medicine), Mark Litt, PhD (Farmington Clinical Research Unit, University of Connecticut Health Center, Department of Psychiatry), Jean Donaldson, MA, and James Herrell, PhD (Center for Substance Abuse Treatment).
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REFERENCES

1. Watson SJ, Benson JA, Joy JE. Marijuana and medicine: assessing the science base: a summary of the 1999 Institute of Medicine report. *Arch Gen Psychiatry*. 2000; 57:547-552.
2. Substance Abuse and Mental Health Services Administration (SAMHSA). *National Household Survey on Drug Abuse Series: H-6: Preliminary Results from the 1997 National Household Survey on Drug Abuse.* Rockville, Md: Office on Applied Studies; 1998. DHHS publication SMA 98-3251.
3. Hall W, Babor TF. Cannabis use and public health: assessing the burden. *Addiction.* 2000;95:485-490.
4. Voelker R. "Decent research and closure" needed on medical marijuana, says head of NIH panel. *JAMA.* 1997;278:802.
5. Pope HG, Gruber AJ, Yurgelun-Todd D. The residual neuropsychological effects of cannabis: the current status of research. *Drug Alcohol Depend.* 1995; 38:25-34.
6. Solowij N. *Cannabis and Cognitive Functioning.* Cambridge, England: Cambridge University Press; 1998.
7. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol.* 1998;20:293-306.

8. Solowij N, Michie PT, Fox AM. Effects of long term cannabis use on selective attention: an event-related potential study. *Pharmacol Biochem Behav.* 1991;40:683-688.
9. Solowij N, Michie PT, Fox AM. Differential impairments of selective attention due to frequency and duration of cannabis use. *Biol Psychiatry.* 1995;37:731-739.
10. Solowij N. Do cognitive impairments recover following cessation of cannabis use? *Life Sci.* 1995;56:2119-2126.
11. Pope HG, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. *JAMA.* 1996;275:521-527.
12. Pope HG, Jacobs A, Mialet JP, Yurgelun-Todd D, Gruber S. Evidence for a sex-specific residual effect of cannabis on visuospatial memory. *Psychother Psychosom.* 1997;66:179-184.
13. Fletcher JM, Page JB, Francis DJ, et al. Cognitive correlates of long-term cannabis use in Costa Rican men. *Arch Gen Psychiatry.* 1996;53:1051-1057.
14. Elwan O, Hassan AAH, Naseer MA, et al. Brain aging in a sample of normal Egyptians: cognition, education, addiction and smoking. *J Neurol Sci.* 1997;148:79-86.
15. Solowij N, Grenyer BFS, Peters R, Chesher G. Long term cannabis use impairs memory processes and frontal lobe function. In: *1997 Symposium on the Cannabinoids.* Burlington, Vt: International Cannabinoid Research Society; 1997:84.
16. Loeber RT, Yurgelun-Todd DA. Human neuroimaging of acute and chronic marijuana use: implications for frontocerebellar dysfunction. *Hum Psychopharmacol Clin Exp.* 1999;14:291-301.
17. Block RI, O'Leary DS, Hichwa RD, et al. Cerebellar hypoactivity in frequent marijuana users. *Neuroreport.* 2000;11:749-753.
18. Block RI, O'Leary DS, Hichwa RD, et al. Effects of frequent marijuana use on memory-related regional cerebral blood flow. *Pharmacol Biochem Behav.* In press.
19. Block RI, O'Leary DS, Augustinack JC, et al. Effects of frequent marijuana use on attention-related regional cerebral blood flow. *Abstr Soc Neurosci.* 2000;26:2080.
20. Lyketsos CG, Garrett E, Liang K-Y, Anthony JC. Cannabis use and cognitive decline in persons under 65 years of age. *Am J Epidemiol.* 1999;149:794-800.
21. Hampson RE, Deadwyler SA. Cannabinoids, hippocampal function and memory. *Life Sci.* 1999;65:715-723.
22. Hampson RE, Deadwyler SA. Cannabinoids reveal the necessity of hippocampal neural encoding for short-term memory in rats. *J Neurosci.* 2000;20:8932-8942.
23. Reibaud M, Obinu MC, Ledent C, et al. Enhancement of memory in cannabinoid CB1 receptor knockout mice. *Eur J Pharmacol.* 1999;379:R1-R2.
24. Bohme GA, Laville M, Ledent C, Parmentier M, Imperato A. Enhanced long-term potentiation in mice lacking cannabinoid CB1 receptors. *Neuroscience.* 2000;95:5-7.
25. Marijuana Treatment Project Research Group. Treating marijuana dependence: findings from a multisite study. *Arch Gen Psychiatry.* In press.
26. McLellan AT, Kushner H, Metzger D, et al. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat.* 1992;9:199-213.
27. Sobell LC, Sobell MB. Timeline follow-back: a technique for assessing self reported alcohol consumption. In: Litten RZ, Allen JP, eds. *Measuring Alcohol Consumption: Psychological and Biochemical Methods.* Totowa, NJ: Humana Press; 1992.
28. Miller WR. *Form 90: A Structured Assessment Interview for Drinking and Related Behaviors: Test Manual: Project MATCH Monograph Series, Vol. 5.* Bethesda, Md: National Institute on Alcohol Abuse and Alcoholism; 1996. NIH Publication 96-4004.
29. First MB, Gibbon M, Spitzer RL, Williams JB. *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders—Research Version.* New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 1996.
30. Jastak S, Wilkinson G. *The Wide Range Achievement Test: Manual of Instructions.* Wilmington, Del: Jastak Associates; 1984.
31. Kareken DA, Gur RC, Saykin AJ. Reading on the Wide Range Achievement Test-Revised and parental education as predictors of IQ: comparison with the Barona formula. *Arch Clin Neuropsychol.* 1995;10:147-157.
32. Blair JR, Spreen O. Predicting premorbid IQ: a revision of the National Adult Reading Test. *Clin Neuropsychol.* 1989;3:129-136.
33. Barona A, Reynolds CR, Chastain R. A demographically based index of pre-morbid intelligence for the WAIS-R. *J Consult Clin Psychol.* 1984;52:885-887.
34. Bell R, Taylor EH, Ackerman B, Pappas AA. Interpretation of urine quantitative 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid to determine abstinence from marijuana smoking. *Clin Toxicol.* 1989;27:109-115.
35. Dackis CA, Pottash ALC, Annitto W, Gold MS. Persistence of urinary marijuana levels after supervised abstinence. *Am J Psychiatry.* 1982;139:1196-1198.
36. Ellis GM, Mann MA, Judson BA, Schramm NT, Tashchian A. Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. *Clin Pharmacol Ther.* 1985;38:572-578.
37. Fraser AD, Worth D. Urinary excretion profiles of 11-nor-9-carboxy-delta-9-tetrahydrocannabinol: a delta-9-THCCOOH to creatinine ratio study. *J Anal Toxicol.* 1999;23:531-534.
38. Baddeley A, Emslie H, Nimmo Smith I. *The Speed and Capacity of Language-Processing Test Manual.* Bury St Edmonds, England: Thames Valley Test Co; 1992.
39. Lezak MD. *Neuropsychological Assessment.* 3rd ed. New York, NY: Oxford University Press; 1995.
40. Rey A. *L'examen clinique en psychologie.* Paris, France: Presse Universitaire de France; 1964.
41. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests: Administration, Norms and Commentary.* 2nd ed. New York, NY: Oxford University Press; 1998.
42. Golden CJ. *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses.* Wood Dale, Ill: Stoelting; 1978.
43. Bohnen N, Jolles J, Twijnstra A. Modification of the Stroop Color Word Test improves differentiation between patients with mild head injury and matched controls. *Clin Neuropsychol.* 1992;6:178-184.
44. *The Wisconsin Card Sorting Test: Computer Version.* Alpharetta, Ga: Psychological Assessment Resources Inc, CyberMetrics Testing Software Services; 1989.
45. Stuss DT, Stethem LL, Poirier CA. Comparison of three tests of attention and rapid information processing across six age groups. *Clin Neuropsychol.* 1987;1:139-152.
46. Levin HS, Mattis S, Ruff RM, et al. Neurobehavioral outcome following minor head injury: a three-center study. *J Neurosurg.* 1987;66:234-243.
47. Geffen G, Moar KJ, O'Hanlon AP, Clark CR, Geffen LB. Performance measures of 16- to 86-year old males and females on the Auditory Verbal Learning Test. *Clin Neuropsychol.* 1990;4:45-63.
48. Stuss DT, Stetham L, Pelchat G. Three tests of attention and rapid information processing: an extension. *Clin Neuropsychol.* 1988;2:246-250.
49. Roman DD, Edwall GE, Buchanan RJ, Patton JH. Extended norms for the Paced Auditory Serial Addition Task. *Clin Neuropsychol.* 1991;5:33-40.
50. Brittain JL, La Marche JA, Reeder KP, Roth DL, Boll TJ. Effects of age and IQ on Paced Auditory Serial Addition Task (PASAT) performance. *Clin Neuropsychol.* 1991;5:163-175.
51. Levy R, Goldman-Rakic PS. Segregation of working memory functions within the dorsolateral prefrontal cortex. *Exp Brain Res.* 2000;133:23-32.
52. Herman BP, Seidenberg M, Wyler A, et al. The effects of human hippocampal resection on the serial position curve. *Cortex.* 1996;32:323-334.
53. Middleton FA, Strick PL. Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science.* 1994;266:458-461.
54. Schacter DL. Memory and awareness. *Science.* 1998;280:59-60.
55. Schmahmann JD, ed. *The Cerebellum and Cognition.* San Diego, Calif: Academic Press; 1997.
56. Herkenham M, Lynn AB, Little MD, et al. Cannabinoid receptor localization in brain. *Proc Natl Acad Sci U S A.* 1990;87:1932-1936.