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Neuropsychological consequences of regular marijuana use: a twin study

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ABSTRACT

Background. Results of previous research examining long-term residual effects of marijuana use on cognition are conflicting. A major methodological limitation of prior studies is the inability to determine whether differences between users and non-users are due to differences in genetic vulnerability preceding drug use or due to the effects of the drug.

Method. Fifty-four monozygotic male twin pairs, discordant for regular marijuana use in which neither twin used any other illicit drug regularly, were recruited from the Vietnam Era Twin Registry. A minimum of 1 year had passed since the marijuana-using twins had last used the drug, and a mean of almost 20 years had passed since the last time marijuana had been used regularly. Twins were administered a comprehensive neuropsychological test battery to assess general intelligence, executive functioning, attention, memory and motor skills. Differences in performance between marijuana-using twins and their non-using co-twins were compared using a multivariate analysis of specific cognitive domains and univariate analyses of individual test scores. Dose–response relationships were explored within the marijuana-using group.

Results. Marijuana-using twins significantly differed from their non-using co-twins on the general intelligence domain; however, within that domain only the performance of the block design subtest of the Wechsler Adult Intelligence Scale – Revised reached a level of statistical significance.

Conclusions. Out of the numerous measures that were administered, only one significant difference was noted between marijuana-using twins and their non-using co-twins on cognitive functioning. The results indicate an absence of marked long-term residual effects of marijuana use on cognitive abilities.

INTRODUCTION

A recent meta-analysis of research relating to the residual neuropsychological effects of marijuana use found no evidence for significant long-term effects of the drug on neurocognitive processes; however, the authors noted that many of the studies included in the analysis had significant methodological shortcomings that limited the generalizability of the findings (Grant *et al.* 2003). An earlier qualitative review by the same group concluded that most studies were too fraught with methodological flaws to provide clear evidence as to the nature of the effect

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(Gonzalez *et al.* 2002). Among those studies reviewed, 55% found evidence for subtle cognitive impairments in marijuana users, ranging across a variety of specific neuropsychological domains. The most striking finding, however, was that of the 40 studies included in the survey, only 13 were able to meet all of the seven minimal methodological requirements articulated by the authors. These included the utilization of a control group, controlling for a history of neurological or psychiatric disorders, and the establishment of an abstinence period before neuropsychological testing. An earlier literature review reached a similar conclusion and argued for the use of more sophisticated research designs, as well as wide-ranging assessment batteries (Pope *et al.* 1995).

While several studies have been conducted with more sound methodologies, findings are inconsistent regarding the extent of the long-term cognitive impairments associated with marijuana use. Solowij *et al.* (2002) found evidence for memory and attention impairments in long-term marijuana users compared to non-using controls after a minimum 12-hour abstinence period. Pope *et al.* (2002) found similar memory impairments up to 7 days after marijuana use ceased, but were unable to find a significant difference between users and controls after 28 days of abstinence. Other studies provide mixed evidence regarding residual neuropsychological deficits resulting from marijuana use (Mendhiratta *et al.* 1988; Schwartz *et al.* 1989; Solowij *et al.* 1991; Lyketsos *et al.* 1999; Varma *et al.* 2000). Where differences between users and non-users have been found, they are often on only one or two tests out of a large number administered; moreover, the differences are often modest, and users' scores are usually within the range of normal cognitive variability (Block & Ghoneim, 1993).

The present study compares monozygotic twin pairs, who are discordant for regular marijuana use, on a broad spectrum of neuropsychological tests. Such a design has been referred to repeatedly in the literature as an ideal way of assessing the neuropsychological effects of marijuana while controlling for cognitive deficits that could be related to an underlying genetic vulnerability to substance use (Pope *et al.* 1995; Gonzalez *et al.* 2002; Grant *et al.* 2003). Since monozygotic twins share 100% of their genes and many of the same childhood environmental experiences, this design can control for many of the confounding factors that have made previous results inconclusive.

METHOD

Participants

Study participants were members of the Vietnam Era Twin (VET) registry. The registry, assembled from a Department of Defense computer file of 5·5 million veterans, comprises male–male twin pairs born between 1939 and 1957 in which both members served in the military during the Vietnam War era (1965–1975). Twin siblings were identified by matching veterans for same last name, date of birth and similar social security number, and confirmed by examination of military service records. Zygosity was assigned using responses to a series of questions about similarity of physical appearance, supplemented with blood group typing information. A complete description of registry construction (Eisen *et al.* 1987), characteristics of registry members (Henderson *et al.* 1990), and method of zygosity determination (Eisen *et al.* 1989) have been provided in detail elsewhere.

Drug use data collected previously by our group in the course of the Harvard Twin Study of Drug Abuse and Dependence were available from 1806 pairs of identical twins from the VET registry (Tsuang *et al.* 2001). Participants were interviewed by telephone using the Diagnostic Interview Schedule, Version III – Revised (DIS-III-R; Robins *et al.* 1988). This permitted lifetime psychiatric diagnoses to be made for a wide variety of disorders according to the *Diagnostic and Statistical Manual for Mental Disorders, Third Edition Revised* criteria (DSM-III-R; APA, 1987). Using these data, 117 monozygotic twin pairs (234 individuals) were identified who met the following criteria: (1) one twin used marijuana at least once weekly for a minimum of 1 year, while his co-twin never used marijuana more than five times in his life; (2) the marijuana-using twin reported not using marijuana for at least 1 month prior to the DIS-III-R telephone interview; (3) neither sibling reported regularly using, at least once weekly, any other illicit drug; and (4) neither sibling reported ever experiencing symptoms of alcohol withdrawal (e.g. 'shakes', difficulty sleeping, feeling anxious

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or depressed, sweating, rapid heart beat, delirium tremens, hallucinations, seizures). Twin pairs in which either one or both siblings reported alcohol withdrawal symptoms were excluded because of concern that the adverse health consequences associated with very heavy alcohol use might complicate the attempt to identify the adverse effects of marijuana (Fadda & Rossetti, 1998).

Recruitment letters were mailed in 1995 to eligible members of the VET Registry. The 62 twin pairs who agreed to be examined were offered the opportunity to travel to one of two research sites, Boston (Harvard University) or St Louis (Washington University), or the option of having a research assistant travel to their hometown for an evaluation at a local hotel. Travel and hotel costs associated with participation were paid by the study, and $225 compensation was offered. Before the in-person evaluation, a research assistant explained the research procedures and obtained written informed consent. This method of consent was approved by all appropriate institutional review boards.

In total, data from eight twin pairs were eliminated from the analysis for the following reasons. Five twin pairs were removed because one sibling had used marijuana within the preceding 12 months. Another pair was excluded because one member had been misclassified as a non-user. One pair was excluded because one of the twins had experienced a stroke and had been treated for it surgically. A final pair was excluded because one of the twins had AIDS and a history of a psychotic illness. The present investigation, therefore, utilized data from 54 twin pairs.

Measures

Past marijuana use

The minimum number of days on which marijuana was used during the participant's lifetime was derived from responses to the following DIS-III-R questions administered in 1992: 'Have you ever used marijuana (hashish, bhang, ganja)?' 'Have you ever used marijuana (hashish, bhang, ganja) more than five times?' 'Have you ever used marijuana (hashish, bhang, ganja) regularly, that is, once a week or more?' 'How many days per week did you use marijuana during your period of most frequent use?' 'How old were you when you started your period of most frequent use?' 'How old were you when you ended your period of most frequent use?' and 'What was the longest period that you used marijuana almost every day?'

The minimum number of days on which marijuana was used was the greater of the following calculations: (*a*) number of days per week marijuana was used during the period of most frequent use multiplied by the number of weeks that period lasted, or (*b*) the total number of weeks of regular marijuana use, assuming one use per week. Days of marijuana use between 1992 and the present study, 1995–1996, were added to the minimum number of days used.

Table 1. *Neuropsychological assessment battery*

Cognitive domain	Measure
General intelligence	Wechsler Adult Intelligence Scale – Revised Raven's Advanced Progressive Matrices – Set I Wide Range Achievement Test – Revised
Attention	Cancellation Test, Verbal and Nonverbal Time Continuous Performance Task, AX and X-degraded conditions Trail Making Test, Part A
Memory	Wechsler Memory Scale – Revised, logical memory and visual reproduction California Verbal Learning Test Rey–Osterrieth Complex Figure Test, accuracy scores
Executive functioning	Wisconsin Card Sorting Test Stroop Test, Color/Word Score Cancellation Test, Organization Scores Trail Making Test, B – A Rey–Osterrieth Complex Figure Test, organization scores
Motor skills	Finger Tapping Test (FTT) Grooved Pegboard

Neuropsychological tests

Participants were administered a comprehensive neuropsychological test battery by a research assistant blind to the twin's drug use history. Neuropsychological tests were chosen to assess the following cognitive domains: general intelligence, attention, memory, executive functioning and motor skills. Table 1 shows a breakdown of the neuropsychological tests used in each domain. General intelligence was assessed with the Wechsler Adult Intelligence

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Scale – Revised (WAIS-R) Verbal, Performance and Full Scale IQ scores, as well as subtest scaled scores (Wechsler, 1981). This domain also included a measure of general nonverbal problem solving as assessed by the number correct from the Raven's Advanced Progressive Matrices – Set I (Raven, 1982); and a measure of reading achievement as assessed by the standard score from the Wide Range Achievement Test – Revised (WRAT-R; Jastak & Wilkinson, 1984). Attention was assessed with the Cancellations Test time and organization scores of the visual attention and speed/random verbal and non-verbal conditions (Mesulam, 1985); Trail Making Test, time score for part A; and the Continuous Performance Test (CPT), mean reaction time, number correct, omissions, number incorrect, omissions and sensitivity for both AX- and X-degraded conditions (Rosvold *et al*. 1956; Davies & Parasuraman, 1982). The memory domain was assessed with the Wechsler Memory Scale – Revised (WMS-R), recall for the immediate and delayed conditions of the Logical Memory and Visual Reproductions subtests (Wechsler, 1987); the California Verbal Learning Test (CVLT), list A total trials 1–5, short delay free and cued recall, long delay free and cued recall, and recognition hits (Delis *et al*. 1987); and the Rey–Osterrieth Complex Figure Test, accuracy scores for the copy, immediate and delayed recall conditions (Rey, 1941; Osterrieth, 1944). Executive functioning was assessed with the Wisconsin Card Sorting Test (WCST), number of categories and perseverative errors (Heaton, 1981); the Stroop Test, age-corrected *T* score for the Color/Word condition (Stroop, 1935); Trail Making Test, time score for part B – part A; and the Rey–Osterrieth Complex Figure Test, organization score for the copy, immediate and delayed recall conditions (Rey, 1941; Osterrieth, 1944). Finally, the motor skills domain was assessed by the Finger Tapping Test (FTT), the average number of taps across trials for the dominant and non-dominant hands (Halstead, 1947); and the Grooved Pegboard, time for the dominant and non-dominant hands (Matthews & Klove, 1964).

Statistical analyses

Demographic differences between marijuana using and non-using twin pair members were examined using McNemar's χ^2 test for paired proportions for dichotomous response variables, and the matched pairs *t* test for continuous variables. Intra-pair median differences of ordinal scale variables were evaluated using the Wilcoxon signed rank test. To assess for a non-response bias, data collected in 1992 from the 54 pairs who participated in the present study were compared with data from the 55 twin pairs who chose not to participate for differences in age, race, employment status, educational level, alcohol abuse/dependence status and marijuana days of use as of 1992. The two groups were also compared for the lifetime prevalence of the following psychiatric disorders: alcohol and nicotine abuse or dependence, mania, bipolar disorder, major depression, dysthymia, generalized anxiety disorder, pathological gambling and panic disorder.

To control for multiple tests, we took a sequential approach to comparing the marijuana users to their non-using co-twins. We first examined differences on the five neuropsychological domains between using and non-using twin-pair members using a multivariate approach with a repeated-measures general linear model. This model used each pair as a case and the two members of the pair as the within-subjects factor. If the multivariate test of a neuropsychological domain was significant, we followed this with a univariate approach. First, we used the Kolmogorov–Smirnov test to determine whether the neuropsychological test scores were normally distributed. For those scores that were normally distributed, we compared groups using matched-pairs *t* tests. For those scores that were not normally distributed, we compared groups using the Wilcoxon signed rank tests. Within the user group, dose-response relationships between the number of days of marijuana use and neuropsychological test scores were examined using Pearson correlation coefficients for normally distributed variables and Spearman correlation coefficients for those that were not normally distributed. Significance levels were set at $p < 0{\cdot}05$ (two-tailed) for all analyses.

In order for the difference between marijuana users and non-users on a specific measure to be formally designated as 'significant', we required that the multivariate test of the domain achieve statistical significance and that the follow-up univariate test of the individual measure also

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Table 2. *Number of lifetime marijuana use days in the user group*

Marijuana use days	Number of users (%)
50–100	3 (5·6)
101–200	7 (13·0)
201–300	10 (18·5)
301–400	3 (5·6)
401–500	5 (9·3)
501–1000	13 (24·1)
1001–3000	9 (16·7)
3001–5000	3 (5·6)
5001–7000	1 (1·9)

achieve significance. Given the widespread *a priori* expectation that marijuana has adverse effects on cognitive functioning, we wanted to balance the risk of type I error (incorrectly concluding that marijuana users were significantly different from their non-using co-twins) with the risk of type II error (incorrectly concluding that marijuana users did not differ from their non-using co-twins). In general, a conservative scientific approach places a higher priority on the avoidance of type I error; however, we wanted to balance this against the risk of missing actual differences that did exist and making a type II error. Therefore, we calculated the means and effect sizes along with the nominal statistical significance of every possible univariate test comparing marijuana using twins to their non-using co-twins.

We did not consider univariate tests to reach our criterion for statistical significance if the multivariate significance test of the domain to which they belong did not reach statistical significance. However, in the interest of providing readers with as much relevant information as possible, we chose to report the nominal probability of each univariate test. Because these values are not adjusted for the numerous comparisons that we conducted, we do not consider a probability below 0·05 to be statistically significant. These probabilities are presented for descriptive, not inferential, purposes. Our group has successfully used this method in a similar study of twins discordant for stimulant use (Toomey *et al*. 2003).

RESULTS

At the time of neuropsychological assessment, participants' ages ranged from 38 to 51 years (mean = 46·3 ± 3·1). Former marijuana users were not significantly different from their co-twins in the proportion who were currently married (users 79·2%, non-users 81·5%; $\chi^2 = 0{\cdot}08$, $p = 0{\cdot}78$) or employed (users 98·1%, non-users 94·4%; $\chi^2 = 1{\cdot}0$, $p = 0{\cdot}31$), and were in the same median household income bracket ($50,001–$60,000, $Z = -0{\cdot}93$, $p = 0{\cdot}35$). Education level did not differ between the two groups (users 13·9 years, non-users 14·3 years, $Z = -1{\cdot}49$, $p = 0{\cdot}14$), nor did the groups differ on indicators of learning problems in school such as being in a special school (0 users, 3 non-users), being in a special academic class (users 11·1%, non-users 3·7%; $\chi^2 = 2{\cdot}67$, $p = 0{\cdot}10$), or getting special help for academic problems (users 14·8%, non-users 18·5%; $\chi^2 = 0{\cdot}40$, $p = 0{\cdot}52$). In the user group, no subject reported ever being diagnosed with a learning disability or with attention deficit disorder. In the non-user group, one subject reported having been diagnosed with a learning disability and one subject reported having been diagnosed with attention deficit disorder. The groups did not differ in having ever had a head injury (users 53·7%, non-users 46·3%; $\chi^2 = 0{\cdot}62$, $p = 0{\cdot}43$).

Table 3. *Repeated measures MANOVA comparing marijuana users and non-users on neuropsychological tests*

Cognitive domain	*F* value	*p* value
General intelligence ($n = 53$)	1·96867	0·045*
Attention ($n = 49$)	0·49116	0·92
Memory ($n = 52$)	1·06870	0·41
Executive functioning ($n = 53$)	1·17883	0·33
Motor skills ($n = 53$)	1·27812	0·29

* $p < 0{\cdot}05$.

No significant differences were observed between former marijuana users and their non-using co-twins in lifetime prevalence of alcohol abuse/dependence (users 63·0%, non-users 51·9%; $\chi^2 = 1{\cdot}64$, $p = 0{\cdot}20$), total number of years drinking alcohol (users 24·1, non-users 23·9; $t = 0{\cdot}14$, $p = 0{\cdot}89$), proportion of current drinkers (users 74·0%, non-users 69·2%; $\chi^2 = 0{\cdot}29$, $p = 0{\cdot}59$), and average number of drinks per day during the preceding year among currently drinking twins (users 0·92, non-users 0·66; $t = 1{\cdot}64$, $p = 0{\cdot}11$). No significant differences were observed between former marijuana users and non-users in lifetime prevalence of

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Table 4. *Comparison of users and non-users on neuropsychological tests*

Measures	Mean (S.D.) score: Users ($n=54$)	Mean (S.D.) score: Non-users ($n=54$)	t or z value†	Nominal p	Effect size
General intelligence					
WAIS-R					
Verbal IQ	106·00 (11·63)	107·06 (11·77)	$t=-1·03$	0·31	0·09
Performance IQ	109·83 (13·27)	107·54 (13·29)	$t=1·76$	0·09	0·17
Full Scale IQ	107·98 (12·74)	108·13 (12·94)	$t=-0·14$	0·89	0·01
Information Scaled Score	10·81 (2·13)	10·94 (2·51)	$t=-0·60$	0·55	0·06
Digit Span Scaled Score	10·81 (2·43)	10·30 (2·45)	$t=1·60$	0·12	0·20
Vocabulary Scaled Score	10·91 (2·18)	10·93 (2·46)	$z=-0·12$	0·91	0·01
Arithmetic Scaled Score	10·35 (2·84)	10·78 (2·92)	$z=-1·15$	0·25	0·15
Comprehension Scaled Score	11·06 (2·62)	11·44 (2·25)	$t=-1·06$	0·29	0·12
Similarities Scaled Score	10·04 (2·50)	10·43 (2·45)	$t=-0·99$	0·33	0·16
Picture Completion Scaled Score	10·41 (2·29)	10·00 (2·55)	$t=1·08$	0·29	0·17
Picture Arrangement Scaled Score	10·85 (2·61)	10·17 (2·89)	$t=1·84$	0·07	0·25
Block Design Scaled Score	10·22 (2·54)	10·70 (2·48)	$t=-1·97$	0·05*	0·19
Object Assembly Scaled Score	9·80 (2·47)	9·65 (2·63)	$t=0·49$	0·63	0·06
Digit Symbol Scaled Score	8·89 (2·02)	8·69 (2·21)	$z=0·58$	0·56	0·09
Raven's					
Number correct	8·28 (2·13)	8·51 (2·23)	$t=-0·69$	0·50	0·11
WRAT-R					
Reading Standard Score	97·31 (10·63)	95·69 (12·43)	$t=1·71$	0·09	0·14
Attention					
Cancellation test					
Nonverbal, time in seconds	99·33 (28·33)	103·30 (31·40)	$t=-0·83$	0·41	0·13
Verbal, time in seconds	108·89 (31·32)	107·31 (31·18)	$t=0·37$	0·71	0·05
CPT					
X-degraded, reaction time (seconds)	48·36 (7·28)	47·31 (9·44)	$z=-0·19$	0·85	0·12
X-degraded, number correct	46 (19·22)	46·69 (18·58)	$t=-0·46$	0·65	0·04
X-degraded, omissions	27·73 (18·93)	26·82 (18·23)	$t=0·60$	0·53	0·05
X-degraded, number incorrect	20·06 (14·88)	23·92 (24·21)	$z=-0·87$	0·38	0·19
X-degraded, sensitivity	0·8422 (0·141)	0·8417 (0·150)	$z=0·00$	1·00	0·00
AX, reaction time (seconds)	33·72 (4·91)	34·20 (6·14)	$t=-0·51$	0·61	0·09
AX, number correct	73·76 (3·15)	73·06 (5·21)	$z=-0·85$	0·40	0·16
AX, omissions	1·96 (3·05)	2·63 (5·09)	$z=-0·83$	0·41	0·16
AX, number incorrect	3·39 (6·09)	3·80 (6·50)	$z=-0·23$	0·82	0·07
AX, sensitivity	0·9902 (0·012)	0·9872 (0·022)	$z=-0·71$	0·48	0·17
Trail Making Test					
Part A, time in seconds	31·35 (9·42)	31·83 (9·23)	$t=-0·30$	0·76	0·05
Memory					
WMS-R					
Logical memory, immediate recall	24·74 (5·57)	25·15 (5·46)	$t=-0·52$	0·60	0·07
Logical memory, delayed recall	21·75 (6·51)	22·04 (6·46)	$t=-0·29$	0·77	0·04
Visual reproduction, immediate recall	33·50 (4·10)	33·78 (3·42)	$z=-0·21$	0·84	0·07
Visual reproduction, delayed recall	30·93 (5·55)	29·87 (6·33)	$t=1·09$	0·28	0·18
CVLT					
Trials 1–5, total correct	46·04 (8·14)	47·60 (8·46)	$t=-1·10$	0·28	0·198
List B, total correct	5·77 (1·59)	6·08 (1·45)	$z=-0·94$	0·35	0·20
Short delay free recall, no. correct	9·55 (2·42)	9·40 (2·53)	$t=0·37$	0·71	0·06
Short delay cued recall, no. correct	10·92 (2·27)	11·00 (2·43)	$t=-0·20$	0·84	0·03
Long delay free recall, no. correct	9·91 (2·41)	10·66 (2·51)	$t=-2·22$	0·03	0·31
Long delay cued recall, no. correct	10·72 (2·27)	11·38 (2·42)	$t=-1·86$	0·07	0·28
Recognition hits	14·38 (1·71)	14·53 (1·56)	$z=-0·39$	0·70	0·09
Rey-Osterrieth					
Copy accuracy	64·65 (0·76)	64·70 (0·72)	$z=-0·40$	0·69	0·07
Immediate recall accuracy	50·11 (8·28)	50·93 (7·82)	$t=-0·87$	0·39	0·11
Delayed recall accuracy	49·52 (9·55)	50·96 (8·08)	$t=-1·26$	0·21	0·16
Executive functioning					
WCST					
Categories completed	4·93 (1·90)	4·65 (1·85)	$z=-0·90$	0·37	0·15
Perseverative errors	16·87 (13·94)	15·70 (9·95)	$z=-0·51$	0·61	0·10
Stroop Test					
Color/word, age-corrected raw score	45·77 (8·60)	43·83 (8·43)	$t=1·42$	0·16	0·23

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Table 4 (*cont.*)

Measures	Mean (S.D.) score: Users ($n=54$)	Mean (S.D.) score: Non-users ($n=54$)	t or z value†	Nominal p	Effect size
Cancellation					
Nonverbal, organization score	1·76 (0·75)	1·78 (0·69)	$z=-0·16$	0·88	0·03
Verbal, organization score	1·65 (0·83)	1·59 (0·71)	$z=-0·47$	0·64	0·08
Trail Making Test					
B – A, time in seconds	67·56 (35·33)	68·83 (33·08)	$z=-0·27$	0·78	0·04
Rey-Osterrieth					
Copy organization	10·91 (2·26)	10·52 (3·09)	$z=-0·50$	0·62	0·14
Immediate recall organization	9·87 (3·35)	10·26 (2·71)	$z=-0·40$	0·69	0·13
Delayed recall organization	10·00 (3·38)	10·61 (2·21)	$z=-0·90$	0·37	0·21
Motor skills					
Finger Tapping					
Average dominant hand	54·03 (5·41)	55·42 (6·44)	$t=-1·50$	0·14	0·23
Average non-dominant hand	48·17 (4·43)	49·99 (6·58)	$t=-2·11$	0·04	0·32
Grooved Pegboard					
Time, dominant hand	71·90 (7·08)	70·84 (9·59)	$t=0·81$	0·42	0·13
Time, non-dominant hand	75·74 (10·12)	73·74 (9·61)	$t=1·46$	0·15	0·20

CPT, Continuous Performance Task; CVLT, California Verbal Learning Test; WAIS-R, Wechsler Adult Intelligence Scale Revised; WCST, Wisconsin Card Sorting Test; WMS-R, Wechsler Memory Scale – Revised; WRAT-R, Wide Range Achievement Test – Revised.

* $p<0·05$.

† For variables that were normally distributed, paired-samples t tests were conducted and the t value was reported. For variables that were not normally distributed in either one or both groups, Wilcoxon signed rank tests were conducted, and the z value was reported.

nicotine dependence (users 50·0%, non-users 53·7%; $\chi^2=0·29$, $p=0·59$).

Twin pairs that chose to participate in this study did not significantly differ from twins that did not participate in terms of age, race, employment status, education level, alcohol abuse/dependence, marijuana use days as of 1992, and the lifetime prevalence of the following psychiatric disorders: alcohol abuse/dependence, nicotine dependence, mania, bipolar disorder, major depression, dysthymia, generalized anxiety disorder, pathological gambling and panic disorder.

Among the marijuana-using members of the 54 twin pairs, 37% reported using marijuana a minimum of between 52 and 300 days during their lifetime, 39% a minimum of between 301 and 1000 days, and 24% a minimum of between 1001 and 7000 days (Table 2). The mean number of days on which marijuana was used was 916 (S.D. = 1201). The mean age of initiating regular marijuana use was $21·3\pm3·8$ years (range = 17–38 years), of last regular marijuana use was $27·1\pm6·0$ years (range = 19–43 years), and the mean duration of regular marijuana use was $5·8\pm5·3$ years (range = 1–22 years).

As would be expected from previous twin research on cognitive abilities, we observed a substantial degree of resemblance within twin pairs (Cardon & Fulker, 1993). Cross-twin correlations for the WAIS-R Full Scale ($r=0·82$), Verbal ($r=0·79$), Performance ($r=0·74$), and all 11 subtests (range = 0·32–0·78) were significant at the $p<0·01$ level (except for Similarities and Picture Arrangement, which were significant at the $p<0·05$ level), as was the WRAT-R Reading standard score ($r=0·83$). Cross-twin correlations for WCST (range = 0·38–0·42) and FTT (range = 0·36–0·41) scores were all significant at the $p<0·01$ level. Correlations for three CVLT scores were significant at the $p<0·01$ level, two at the $p<0·05$ level, while two did not attain statistical significance (range = 0·09–0·56).

Table 3 presents the results from the multivariate analysis of the five cognitive domains. Of these domains, only general intelligence was found to differ significantly between marijuana users and non-users ($F=1·968$; $p=0·045$). Univariate analyses of the specific measures indicated that only one reached our criterion for statistical significance (Table 4). An inspection of univariate analyses in all of the domains indicated that very few had a nominal p value less than 0·05. Marijuana users performed significantly worse than non-users on the WAIS-R block design subtest ($t=-1·97$; $p=0·05$). The CVLT long delay free recall ($t=-2·22$; $p=0·03$), and the average for the non-dominant

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Table 5. *Correlation of total days of marijuana use and neuropsychological tests*

Measures	Marijuana use days ($n=53$) Correlation coefficients, r	p value
General intelligence		
WAIS-R		
Verbal IQ	0·102	0·469
Performance IQ	−0·053	0·706
Full Scale IQ	0·046	0·742
Information Scaled Score	0·152	0·276
Digit Span Scaled Score	0·012	0·930
Vocabulary Scaled Score†	0·057	0·686
Arithmetic Scaled Score†	−0·046	0·744
Comprehension Scaled Score	0·199	0·154
Similarities Scaled Score	0·056	0·690
Picture Completion Scaled Score	0·142	0·311
Picture Arrangement Scaled Score	−0·156	0·264
Block Design Scaled Score	0·060	0·671
Object Assembly Scaled Score	0·010	0·945
Digit Symbol Scaled Score†	−0·004	0·976
Raven's		
No. correct	−0·039	0·784
WRAT-R		
Reading Standard Score	0·134	0·340
Attention		
Cancellations		
Nonverbal, time	0·050	0·725
Verbal, time	0·122	0·384
CPT		
X-degraded, reaction time†	−0·062	0·665
X-degraded, no. correct	−0·075	0·599
X-degraded, omission	0·080	0·579
X-degraded, no. incorrect†	−0·022	0·876
X-degraded, sensitivity†	−0·087	0·552
AX, reaction time	−0·103	0·464
AX, no. correct†	−0·143	0·308
AX, omission†	0·172	0·219
AX, no. incorrect†	−0·135	0·335
AX, sensitivity†	−0·036	0·796
Trail Making Test		
Part A, time in seconds	−0·087	0·536
Memory		
WMS-R		
Logical Memory, I	0·195	0·161
Logical Memory, II	0·090	0·572
Visual Reproduction, I†	0·001	0·993
Visual Reproduction, II	0·023	0·868
CVLT		
Trials 1–5, total correct	0·110	0·437
List B, total correct†	0·013	0·926
Short Delay Free Recall, no. correct	0·113	0·425
Short Delay Cued Recall, no. correct	0·226	0·108
Long Delay Free Recall, no. correct	0·041	0·775
Long Delay Cued Recall, no. correct	−0·021	0·883
Recognition Hits†	0·113	0·427
Rey-Osterrieth		
Copy Accuracy†	−0·017	0·906
Immediate Recall Accuracy	−0·032	0·821
Delayed Recall Accuracy	−0·094	0·503
Executive functioning		
WCST		
Categories completed†	0·019	0·895
Perseverative errors†	0·030	0·830
Stroop Test		
Age Corrected Color/Word Score	0·174	0·218
Cancellations		
Nonverbal, Organization Score†	0·095	0·494
Verbal, Organization Score†	0·039	0·780
Trail Making Test		
B – A, time in seconds†	0·087	0·534
Rey-Osterrieth		
Copy Organization†	0·034	0·807
Immediate Recall Organization†	−0·195	0·161
Delayed Recall Organization†	0·004	0·977
Motor skills		
Finger Tapping		
Dominant hand	−0·183	0·190
Non-dominant hand	0·088	0·523
Grooved Pegboard		
Time, dominant hand	0·181	0·196
Time, non-dominant hand	0·055	0·697

CPT, Continuous Performance Task; WAIS-R, Wechsler Adult Intelligence Scale – Revised; WRAT-R, Wide Range Achievement Test – Revised.

* $p<0·05$.

hand on Finger Tapping ($t=-2·11$; $p=0·04$) did not meet our first criterion for significance, but did have nominal p values less than 0·05. Based on the nominal p values there was a 'trend' ($0·05<p<0·10$) for users to perform worse than non-users on the CVLT long delay cued recall ($t=-1·86$; $p=0·07$). Also based on nominal p values, 'trends' for users to perform better than non-users were observed for the WAIS-R performance IQ ($t=1·76$; $p=0·09$), the WAIS-R picture arrangement ($t=1·84$; $p=0·07$), and the WRAT-R reading ($t=1·71$; $p=0·09$).

The correlation of total days of marijuana use and neuropsychological test performance (Table 5) revealed no significant dose response effects. Analysis of the distribution of scores for total days of marijuana use revealed one case to be a significant outlier from the rest of the sample (6188 marijuana use days; 4 S.D. above the mean). Inclusion of this case in the dose–response analysis resulted in significant correlations with the number of correct responses ($r=-0·29$; $p=0·03$) and the number of omissions ($r=0·31$; $p=0·02$) on the CPT AX condition. The removal of this case from the dose–response analysis resulted in non-significant

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correlations for the number of correct responses ($r = 0{\cdot}036$; $p = 0{\cdot}798$) and the number of omissions ($r = -0{\cdot}04$; $p = 0{\cdot}775$) with marijuana use days.

DISCUSSION

We examined neuropsychological functioning in 54 male monozygotic twin pairs discordant for prior regular marijuana use. To address the risk of Type I errors, we first performed a small number of multivariate tests, comparing users and non-users on their performance across specific cognitive domains. Multivariate analysis yielded significant group differences on the general intelligence domain. We then examined group differences on individual subtests. Out of the 16 tests making up the general intelligence domain, marijuana users performed significantly worse than non-users on only the block design subtest of the WAIS-R. There was a trend in this domain for users to have a higher performance IQ than non-users as measured by the WAIS-R, a higher score on the picture arrangement subtest of the WAIS-R, and a higher reading standard score on the WRAT-R. Based on finding only one significant comparison between users and non-users on the tests comprising this domain, and the fact that there existed a trend of users performing better than non-users on several tests, we concluded that the effects observed in our multivariate analysis do not support the existence of meaningful long-term residual effects of regular marijuana use. The absence of any significant dose–response relationship between the increased use of marijuana, as measured by the number of use days, and cognitive abilities further strengthens this conclusion.

We considered the possible implications of the nominal p-values comparing users to non-users on both the long delay free and cued recall conditions of the CVLT, the latter at the trend level. Previous studies found differences between heavy and light users on these two CVLT conditions, but also found differences on several other CVLT measures that failed to reach significance in our sample (Pope & Yurgelun-Todd, 1996). Users, in our sample, performed no worse than non-users on the WMS-R Logical Memory II subtest, which assesses delayed recall for contextually meaningful verbal material. Similarly, while the possibility of poorer performance on the FTT (non-dominant hand only) suggested by the nominal p value could be a sign of reduced manual dexterity, users performed equally well as non-users on the Grooved Pegboard, an even more complex and neurologically sensitive measure of motor dexterity and speed (Lezak, 1995). The lack of supporting evidence for these cognitive deficits leads us to believe that, once again, our findings may simply reflect the large number of significance tests performed. Pope & Yurgelun-Todd (1996), while acknowledging the large number of individual comparisons they made, nevertheless point out that almost every difference, whether significant or not, was in the direction of poorer performance by heavy users than by light users. This is not true of our results.

Given our failure to detect much in the way of differences between users and their co-twins, we considered the possibility that low statistical power could account for this. To evaluate this possibility, we examined the statistical power of our matched pairs t tests. One factor that influences the power of a matched pairs t test is the correlation within the pair. For the variables on which we conducted t tests, the within pair correlations ranged from a low of $r = 0{\cdot}22$ to a high correlation of $r = 0{\cdot}83$ with a mean correlation of $r = 0{\cdot}50$. Based on 54 pairs of twins, an alpha of 0·05, and Cohen's (1988) definitions of effect sizes, we calculated that for the variable with the lowest within pair correlation we had a power of 21·1% to detect a small effect, a power of 82·4% to detect a medium effect, and a power of 99·6% to detect a large effect. For the variable with the highest within pair correlation we had a power of 68·4% to detect a small effect and power greater than 99% to detect a medium effect. For the average within pair correlation we had a power of 30·2% to detect a small effect size, a power of 95% to detect a medium effect, and a power of over 99% to detect a large effect. Thus, we do not believe that our failure to observe consistent differences between marijuana using twins and their non-marijuana using identical co-twins is likely to reflect inadequate statistical power. Real differences too small to be detected by our study are unlikely to have much practical importance.

These results are compatible with previous findings by our group, which found that a

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history of regular marijuana use was not associated with adverse effects on socio-demographic characteristics, physical health, or mental health (Eisen *et al.* 2002), as well as those of other studies that found no, or few, differences between marijuana users and non-users on neuropsychological functioning. The research design used in the present study provides several methodological advantages over prior research on the cognitive effects of marijuana use. First, the sample is drawn from the VET registry, which is population-based. Many previous studies have used subjects obtained from treatment-seeking clinical samples (Gonzalez *et al.* 2002). Individuals with cognitive impairment may be disproportionately represented among clinical groups, thus increasing the observed effects of marijuana use. Second, the use of monozygotic twins as controls minimizes the problem of confounding variables, such as premorbid differences in cognitive functioning, as monozygotic twins share all of their genes and many of the same childhood experiences. Third, the marijuana-using twin had smoked a considerable amount of marijuana. The mean number of days on which marijuana was used was 916 over a mean of 5·8 years, with 39% of users reporting a minimum of between 301 and 1000 days of use, and 24% reporting a minimum of between 1001 and 7000 days. Fourth, a minimum of 1 year had passed since the marijuana-using twin had last used the drug, and a mean of almost 20 years had passed since the last time marijuana had been used regularly. This precluded the possibility that positive results could be attributed to either a withdrawal effect or a drug residue effect. Any cognitive deficiencies observed could reasonably be attributed to a long-term CNS alteration effect. Finally, our study excluded twin pairs in which either member reported ever using any other illicit drug at least once weekly at any time in his life, or ever experienced symptoms of alcohol withdrawal. This reduced the likelihood that observed differences between twin siblings might be attributable to drugs other than marijuana.

Our study does have several potential limitations. First, because only about half of the eligible pairs participated in the study, it is possible that our results were influenced by non-response bias. Individuals whose functioning had been compromised by heavy marijuana use may have been unable or unwilling to participate. We attempted to examine this possibility by comparing 1992 data on the eligible pairs who did not participate to corresponding data from participating pairs. No differences were detected in age, race, employment status, educational attainment and a variety of psychiatric disorders. Nevertheless we cannot exclude the possibility that participation bias may have prevented us from detecting adverse effects of marijuana use on cognitive functioning.

Second, the assessment of regular marijuana use is based on retrospective self-report, and thus its validity is unknown. While the reliability and validity of self-reported drug use data have generally been demonstrated to be satisfactory (Brown *et al.* 1992; Harrison *et al.* 1993), it is not known if this validity extends to recall of marijuana use patterns 20 years after regular use has ended. Similarly, although subjects denied recent substance use, we cannot be absolutely certain that some participants had not used drugs or alcohol in the days immediately prior to testing, leaving a possible drug residue in their bodies. Because of the possibility that marijuana-using twins might be more likely to use other substances, any drug residue effects might be more likely in the marijuana-using twin, biasing the results in the direction of greater impairment. Additionally, if the marijuana users had consumed in the past greater quantities of drugs other than marijuana that could produce more neuropsychological impairment among the marijuana users as a consequence of the other drugs. But the absence of impairment in the marijuana group reduces both of these concerns.

Third, it should be noted that the subjects in our sample by and large displayed moderate levels of marijuana use, and that our findings may not generalize to the effects brought on by very heavy marijuana use. Bolla *et al.* (2002) found evidence of neurocognitive deficits even after 4 weeks of abstinence in subjects who used marijuana as frequently as 13 times per day. Although we used a different method to determine the frequency of marijuana use, we can conclude that our sample did not approach this level of abuse. Our data, however, are probably more reflective of the typical marijuana user, and as such provide more generalizable results.

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Fourth, although our design allows us to control for pre-existing differences in the family environment or genetic factors between regular marijuana users and non-users, it does not preclude the possibility that some environmental factor not shared by twins (e.g. an early childhood head injury) might increase the risk of future marijuana usage and produce neuropsychological impairment. This possibility of a third factor predisposing towards both marijuana usage and neuropsychological impairment independent of genetic and family environmental influences would be more of a concern if we had observed significant differences between the groups.

Fifth, our sample consisted entirely of males, and thus our results may not generalize to females. As women have been underrepresented in research on the consequences of drug abuse, and as Pope *et al.* (1997) found sex-specific residual effects of marijuana use on cognitive functioning, it is important to study marijuana-using women before conclusions can be drawn regarding the drug's effects.

Finally, a recent study by Pope *et al.* (2003) has provided evidence of a possible significant effect for early versus late onset marijuana use and subsequent cognitive deficits. Specifically, they found that individuals who began smoking marijuana before age 17 showed significant deficits when compared to those who began at age 17 or later. The authors hypothesize that this difference could be due to an innate cognitive deficit that predisposes an individual to begin using marijuana at an early age, a disruption in education brought on by the early use, or a neurotoxic effect of marijuana during early adolescence. In our sample only two subjects reported having tried marijuana before age 17, and none initiated regular marijuana use prior to that age. As a result, we were unable to separate our sample into early and late onset users, and could not appropriately address age of onset in our analyses. Therefore, if an innate cognitive impairment predisposes an individual to early but not late onset marijuana use, our study would not be able address this effect. The lack of early onset users in our sample could be the result of prior screening at the time of military induction, with early regular users being found unfit for military service.

Despite employing a rigorous research design, this study fails to find clear evidence in support of the hypothesis that regular marijuana use causes long-term residual CNS alternations. This suggests the need to study other illicit drugs whose regular use is assumed to have detrimental effects on long term-cognitive functioning.

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DECLARATION OF INTEREST

None.

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