ELSEVIER

Drug and Alcohol Dependence 38 (1995) 25–34

DRUG and ALCOHOL DEPENDENCE

The residual neuropsychological effects of cannabis: the current status of research

Harrison G. Pope Jr.*, Amanda J. Gruber, Deborah Yurgelun-Todd

Biological Psychiatry Laboratory, McLean Hospital, 115 Mill Street, Belmont, MA 02178, USA
Department of Psychiatry, Harvard Medical School, Boston, MA, USA

Received 15 June 1994; accepted 30 December 1994

Abstract

Evidence for the residual neuropsychological effects of cannabis must first be separated from evidence regarding (i) the acute effects of the drug, (ii) attributes of heavy cannabis users, and (iii) actual psychiatric disorders caused or exacerbated by cannabis. The remaining evidence must then be subdivided into (a) data supporting a 'drug residue' effect during the 12–24 h period immediately after acute intoxication and (b) data suggesting a more lasting toxic effect on the central nervous system which persists even after all drug residue has left the system. We reviewed the literature, comparing both 'drug-administration' studies in which known amounts of cannabis were administered to volunteers, and 'naturalistic studies' in which heavy marijuana users were tested after some period of abstinence. The data support a 'drug residue' effect on attention, psychomotor tasks, and short-term memory during the 12–24 h period immediately after cannabis use, but evidence is as yet insufficient to support or refute either a more prolonged 'drug residue' effect, or a toxic effect on the central nervous system that persists even after drug residues have left the body. We describe possible study designs to address these latter questions.

Keywords: Cannabis; Marijuana; Neuropsychological effects; Residual effects

Does cannabis use produce important residual neuropsychological effects? Although use of cannabis dates to the beginnings of history, the question is still much debated. Below, we attempt to clarify the term, 'residual effects', then discuss the relevant studies in this area.

1. What is a residual effect?

Residual effects must first be distinguished from acute effects of cannabis. There is no question that cannabis produces a syndrome of acute intoxication, with characteristic cognitive and perceptual changes, lasting for some hours after the drug is ingested. Individuals who consume the drug several times a day — as is often the case in some cultures, and sometimes the case even in American college students — may thus display acute effects almost continuously. To study residual effects in such individuals, it would be necessary to remove them from the drug for a known period — which ideally should be supervised to prevent surreptitious use. Thus, studies which examined users only during the period of acute intoxication are excluded from this review.

Next, residual effects must not be confused with simple attributes of heavy cannabis users as compared to non-using or infrequently-using controls. Some studies, though by no means all, have found that heavy users of cannabis differ from non-users on various psychological or neuropsychological measures. Although part of this difference might be attributable to residual effects of cannabis, much of the difference might be due to (i) acute effects, which may become virtually continuous as described above, (ii) premorbid differences between users and non-users in intellectual, cognitive, or psychological functions, or (iii) other risk factors which covary with cannabis use, such as use of other drugs, or different values with respect to academic or occupation-

* Corresponding author.

SSDI 0376-8716(95)01097-I

al achievement. With these many confounding factors, it is virtually impossible to draw conclusions about the residual effects of cannabis from a simple comparison of the attributes of users versus non-users. Therefore, studies of this design are also excluded from our review.

Third, residual neuropsychological effects of cannabis must be distinguished from actual psychiatric disorders, such as psychotic disorders or anxiety disorders, which might be induced by cannabis. In a recent review (Gruber and Pope, 1994), accompanied by a study of nearly 10 000 psychiatric hospital admissions, we have argued that there is little evidence that cannabis can actually induce a psychotic disorder in previously asymptomatic individuals. However, a substantial possibility remains that cannabis might exacerbate the course of a pre-existing DSM-IV Axis I disorder. For example, we have anecdotally observed several bipolar patients who appeared to develop manic episodes, often associated with psychotic symptoms, after smoking marijuana heavily. Because of the potential confounding effects of such phenomena, if they in fact occur, we have confined the following review to studies of individuals without frank psychiatric disorders, either before or after cannabis use.

The above exclusions reduce our analysis to studies of (a) specific neuropsychological measures, (b) performed after the acute effects of cannabis have dissipated, in (c) individuals without diagnosed psychiatric disorders. But still further clarification is required: 'residual' effects can mean either those which are (i) attributable literally to a residue of the drug in the system (i.e., effects which represent the 'tail' of the acute effects of the drug, or what might be called 'drug residue' effects) or (ii) effects which persist even after the drug has left the body, which are due to a lasting alteration of central nervous system (CNS) function. Various investigators have used the term 'residual' to imply only the first, only the second, or both of the above concepts.

These two forms of 'residual effects', which we have termed, for convenience, 'drug residue' effects and 'CNS alteration' effects, are diagrammed in Fig. 1. As can be seen, some studies have examined exclusively the 'drug residue' effect (Fig. 1a) by investigating impairments of functioning at various time points shortly after a known dose of cannabis is administered. On the other hand, studies have only rarely assessed 'CNS alteration' by looking at heavy cannabis users weeks after their last exposure to the drug, when cannabis components would reasonably be expected to have disappeared from the CNS (Fig. 1c). Instead, the majority of studies have examined heavy users a short time after their last cannabis ingestion, so that it is difficult to assess whether observed impairment was attributable to a protracted 'drug residue' effect from a large accumulated CNS burden of cannabis, or to a frank 'CNS alteration' above and beyond the 'drug residue' effect (Fig. 1b).

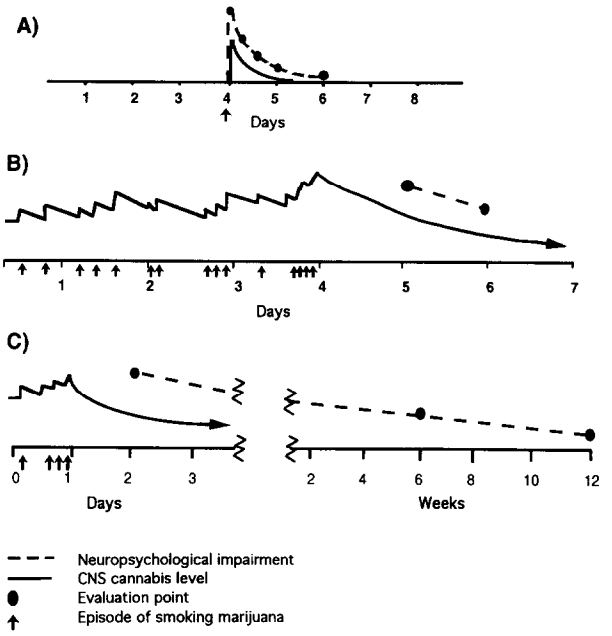

Fig. 1. Three types of study design used to assess residual effects of cannabis. The residual effects of cannabis CNS concentration of psychoactive cannabis alkaloids is shown by a solid line, and neuropsychological impairment is shown by a dotted line; episodes of cannabis smoking are indicated by arrows at bottom of each figure. 'CNS cannabis level' (solid line) represents the presumed total level of active cannabis components and their active metabolites within the CNS. However, since the actual pharmacokinetics of these substances within the CNS are poorly understood (see text), the solid lines represent only a crude approximation for purposes of illustration. (A) Acute study of 'hangover' effects. On day 4, cannabis is administered to subjects with no recent prior cannabis use. Impairment is documented during acute intoxication and at 6, 12, 24, and 48 h afterwards. (B) Study of chronic cannabis effects. Subjects who smoke frequently (several times per day) are withdrawn from cannabis and supervised starting on day 4 to ensure abstinence. They are then tested after 24 and 48 h of abstinence. It is difficult to assess whether impairment is due to residual cannabis still in the CNS or to actual alterations of the CNS due to chronic cannabis exposure. (C) Study of chronic cannabis effects. Subjects who smoke frequently are withdrawn from cannabis and supervised after day 1. They are then tested 24 h, 6 weeks, and 12 weeks later. In the hypothetical study shown above, neuropsychological impairment is found long after cannabis would be expected to have disappeared from the CNS, implying that residual impairment is due to a lasting alteration of CNS function, rather than merely a residue of drug in the CNS.

In comparing the study designs, one must also bear in mind the complex pharmacokinetics of cannabinoids. The principal active component of cannabis, delta-9-tetrahydrocannabinol (Δ^9-THC) displays a plasma half-life of 2–60 h (Wall and Perez-Reyes, 1981; Johannson et al., 1988; Seth and Sinha, 1991), but much of this decline reflects redistribution of drug from the plasma compartment into tissues. Thus Δ^9-THC may persist at CNS receptor sites far longer than in plasma, and serial plasma levels will not reflect the time course of CNS activity. In chronic users, both Δ^9-THC and other

Table 1
Cannabis administration studies

Study	N[a]	Prior drug use[b]		Toxic screen[c]	Blinded evaluation[d]	Abstinence period[e]	Time to testing[f]	Past use of cannabis[g]	Neuro-psychological tests done[h]	Return to baseline[i]
		Alcohol	Other							
Barratt et al., 1972	7 ?	No	No	No	No	Unknown	See text	NR	D,F,Q	See text
Dornbush et al., 1972	5 M	NR	NR	No	No	Unknown	See text	L	B,D	See text
Rafaelson et al., 1973a, b	8 M	Yes	NR	Yes[j]	Yes	Unknown	105 min–16 h	None–L	G	By 16 h
Kielholz et al., 1972, Kielholz et al., 1973	54 ?	NR	NR	No	Yes	Infinite	1–18 h	None	D,E,Q	By 18 h
Cohen et al., 1976a, b	28 M	Yes	Yes	No	No	Unknown	See text	M–H	A,E,F,Q	See text
Frank et al., 1976	36 M	Yes	Yes	No	No	Unknown	See text	M–H	E,Q	See text
Jones and Benowitz, 1976	12 M	No	No	No	No	Unknown	See text	L–H	B,E,F	See text
Barnett et al., 1985	8 M	Yes	Yes	Yes[j]	NR	Unknown	0.2–22.7 h	L	D,E	By 7.1 h
Chait et al., 1985	13 M	NR	NR	Yes[k]	No	Unknown	25 min–9 h	H	B,E,Q	No[l]
Yesavage et al., 1985	10 ?	NR	NR	Yes[j]	Yes	Unknown	1–24 h	L–M	G	No[l]
Leirer et al., 1989	18 ?	NR	NR	Yes[j]	Yes	Unknown	1–48 h	L–M	G	By 8 h
Chait, 1990	9 M, 3 F	Yes	Yes	No	Yes	12 h S	12 h	L	B,D,E,Q	No[l]
Heishman et al., 1990	3 M	NR	NR	Yes	Yes	3 days S	10 min–24 h	L	E,Q	No[l]
Leirer et al., 1991	9 ?	NR	NR	Yes	Yes	Unknown	15 min–48 h	NR	G	By 48 h

[a]M, male; F, female; ?, sex not specified.
[b]No, no attempt was made to exclude subjects with a prior history of alcohol or other drug use; Yes, some attempt was made to exclude subjects with a history of other substance use; NR, not reported.
[c]Yes, subjects gave a urine or blood sample which was screened for psychotropic substances; No, no objective method was used to screen for psychotropic substances.
[d]Yes, either the rater was blind to whether or not the subject had received cannabis prior to testing or the evaluation was done by a machine; No, the raters were aware that the subject had received cannabis prior to testing.
[e]Abstinence period, the time from the last personal use of cannabis to baseline testing; S, supervised abstinence period; U, unsupervised abstinence period.
[f]Time to testing, time from cannabis administration to test.
[g]L, light use (less than or equal to once per week); M, medium use (between one and four times per week); H, heavy use (greater than once per day).
[h]A, intelligence tests or tests measuring or estimating general intellectual capacity; B, tests of short-term or delayed memory (includes both verbal and visuospatial tests); C, visuo-constructional ability; D, tests of reaction time or psychomotor speed; E, tests of executive or attentional 'frontal functions'; F, tests of visuospatial ability; G, flight or driving simulator; Q, other.
[i]Return to baseline, time after administration of cannabis that the performances of subjects returned to baseline levels.
[j]Toxic screens were performed, but the results were not reported.
[k]Plasma levels prior to testing the morning after smoking were 3 ng/ml after placebo and 5 ng/ml after active marijuana.
[l]Subjects demonstrated a slight but still statistically significant impairment at the last time tested.

metabolites accumulate in fat stores, from which they are slowly released back into the circulation (Seth and Sinha, 1991). Thus, chronic users may display cannabinoid metabolites in the urine after weeks or even months of abstinence (Ellis et al., 1985). Chronic users also differ from infrequent users in their rates of metabolism of cannabinoids (Seth and Sinha, 1991), and may display effects of both tolerance and withdrawal (Jones and Benowitz, 1976; Jones et al. 1976; Hunt and Jones, 1980). Thus, when single doses of cannabis are administered to relatively drug-naive volunteers, a simple decay in residual effects may be observed, as Δ^9-THC is quickly redistributed into various tissue compartments. But in naturalistic studies of chronic users, the duration of impairment due to 'drug residue' may be much longer and more difficult to estimate. These distinctions must be borne in mind when considering the studies reviewed below.

2. Studies in which cannabis was administered to subjects

We review first those studies in which cannabis was actually administered to volunteers, who were then assessed at various time points after ingestion to assess for acute and residual effects. These studies are summarized in Table 1. As will be seen, the typical study of this type administered a known dose of cannabis to subjects with a history of modest prior marijuana use (note that we rated past use in most of these studies as 'L' = light, or less than once per week; or 'M' = medium, or less than four times per week). Some, but not all, of the studies attempted to exclude subjects who exhibited abuse of alcohol or drugs other than cannabis, either by self-report (columns 3 and 4 of Table 1) or by laboratory screening for drugs of abuse (column 5). Unfortunately, most studies failed to specify the interval between the last personal use of cannabis by the subjects and the date of cannabis administration in the laboratory (column 7).

The studies used a wide range of neuropsychological measures, as summarized in column 10 of the table. These included tests of general intellectual ability, verbal and visuospatial memory, attention and concentration, psychomotor speed, and visuospatial and visuoconstructional ability. Several investigations also used specialized tests of flight and driving abilities. Unfortunately it is difficult to make comparisons between the studies or to clearly identify neural systems affected by cannabis, because most studies used only a subset of available neuropsychological tests. Investigations based only on selected cognitive measures are, for the most part, insufficient for comparisons between functional domains.

The amount of cannabis administered in these studies also varied considerably. Several authors (Barnett et al., 1985; Yesavage et al., 1985; Leirer et al., 1989, 1991) administered a single dose of THC by allowing subjects to smoke a marijuana cigarette (although different subjects received different doses in some of these studies). Two other investigators (Rafaelson et al., 1973a; Rafaelson et al., 1973b; Kielholz et al., 1972; Kielholz et al., 1973) administered a single dose of marijuana orally (also with different doses to different subjects) so that a longer duration of action might be expected. Heishman et al. (1990) administered two doses, of two marijuana cigarettes each, over a one-day period; Chait (1985) used a similar design, also allowing for subjects to smoke two marijuana cigarettes 90 min apart. In a more recent study, Chait (1990) administered five sessions of smoking, at eight puffs per session, over a three-day period. Finally, several investigators have used more complex designs with longer periods of drug administration over periods of 10 days (Barratt et al., 1972), 11–16 days (Jones and Benowitz, 1976), 21 days (Dornbush et al., 1972), 28 days (Frank et al., 1976) and intermittently for 94 days (Cohen, 1976 a, b). However, despite these varying designs, some including relatively extensive marijuana administration over prolonged periods, none of the studies provides clear evidence for a measurable neuropsychological deficit persisting more than 48 h after the last marijuana exposure.

Admittedly, many of these studies have methodologic deficiencies, such as lack of blindness, failure to control for extent of prior marijuana exposure, and failure to control for use of alcohol and other drugs. But these deficiencies would seem likely to yield, if anything, false positive findings of residual effects rather than false negative findings. The only problem tending to produce a false negative finding might be failure to use adequately sensitive and sophisticated neuropsychological tests. But given the wide range of tests used in these many studies, it seems unlikely that a robust residual effect of marijuana would have been missed.

Up to this point, then, it might be concluded that it is unwise to undertake a calculus examination or to fly an airliner on the morning after smoking marijuana, but one cannot conclude that marijuana produces more than a simple 'drug residue' effect. However, two questions remain: are there more prominent or lasting 'drug residue' effects in individuals who smoke several times per day over weeks or months of time? And are there temporary or permanent 'CNS alterations' produced by months or years of heavy cannabis exposure — alterations which persist even after the drug has left the brain? These latter two questions can be addressed only through naturalistic studies.

3. Naturalistic studies

Naturalistic studies investigate residual effects of cannabis in individuals who use the drug more heavily or over longer periods than could be ethically duplicated in

Table 2
Naturalistic studies, negative results

Study	Subjects[a]	Controls[a]	Prior drug use[b]		Toxic screen[c]	Blinded evaluation[d]	Abstinence period[e]	Past use of cannabis[g]	Neuro-psychological tests done[h]
			Alcohol	Other					
Bowman and Pihl, 1973	16 M	10 M	Yes	No	No	No	4 h U	H	B,D,E,F
Grant et al., 1973	29 ?	29 ?	NR	No	No	Yes	NR	L	A,D,E,Q
Culver and King, 1974	28 ?	28 ?	No	No	No	No	7 days U	L–H	A,B,C,D,E,F,Q
Reed 1974	10 M, H[i]	10 M, L[k]	No	No	No	NR	NR	L–H	D,E,Q
Mendelson et al., 1976	15 M, H[j]	12 M, L[l]	No	No	No	Yes	NR	L–H	A,B,D,E
Satz et al., 1976a, b	27 M	30 M	Yes	NR	No	NR DB	NR	H	A,B,D,Q
Stefanis et al., 1976	47 M	40 M	No	Yes	No	NR	NR	H	A,F
Rochford et al., 1977	41 M	41 M	Yes	NR	No	NR	NR	>50X/life	D,F,Q
Weckowicz et al., 1977	24 M	24 M	NR	No	No	No	NR	H	B,E,F,Q

Please refer to corresponding letters a–h from Table 1. Note that in the naturalistic studies, blinded evaluation indicates that the rater was blind to whether the subject was a user or a control, and the abstinence period indicates the time from the last personal use of cannabis to testing.
[i]H, heavy user, defined as an average of 33 uses per month for between 2 and 9 years.
[j]H, heavy user, defined as an average of 42 joints per month for an average of 5.6 years.
[k]L, light user, defined as an average of 8 uses per month for greater than one year.
[l]L, light user, defined as 11.5 joints per month for an average of 5.3 years.

Table 3
Naturalistic studies, positive results (1973–1981)

Study	Subjects[a]	Controls[a]	Prior drug use[b]		Toxic screen[c]	Blinded evaluation[d]	Abstinence period[e]	Past use of cannabis[g]	Neuro-psychological tests done[h]
			Alcohol	Other					
Entin and Goldzung, 1973	12 M, 14 F	20 M, 17 F	Yes	Yes	No	No	Unknown	H	B
Agarwal et al., 1975	40 M	0	No	No	No	No	8–10 h U	H	A,B,C,Q
Rubin and Comitas, 1975	37 M	23 M	No	No	No	No	3–4 days S	L–H	A,B,D,E,F,Q
Gianutsos and Litwack, 1976	25 M and F	25 M and F	NR	NR	No	No	Unknown	L–H	B
Soueif, 1971, 1975, 1976a, b	850 M	839 M	NR	NR	No	No	12 h S	L–H	C,D,E,F
Carlin and Trupin, 1977	7 M, 3 F	10 ?	No	Yes	No	No	24 h U	H	A,B,C,D,Q
Wig and Varma, 1977	23 M	11 M	NR	NR	No	No	NR (prisoners)	H	A,B,D,Q
Mendhiratta et al., 1978	50 M	25 M	Yes	No	No	No	12 h ?S	H	D,E,F,Q
Sethi et al., 1981	50 M	0	No	No	No	No	Unknown	H	A,B,F

Please refer to corresponding letters a–h from Table 1.

Table 4
Naturalistic studies, positive results (1988–1993)

Study	Subjects[a]	Controls[a]	Prior drug use[b]		Toxic screen[c]	Blinded evaluation[d]	Abstinence period[e]	Past use of cannabis[g]	Neuro-psychological tests done[h]
			Alcohol	Other					
Varma et al., 1988	26 M	26 M	No	No	No	No	12 h, 'some' S	H	A,B,D,E,Q
Mendhiratta et al., 1988	25 M	15 M	Yes	No	No	NR	12 h S	H	D,E,F,Q
Page et al., 1988	25 M, 1 F	24 M, 1 F	No	No	No	NR	NR	H	A,B,C,D,E,Q
Schwartz et al., 1989	9 M ,1 F	9 M, 8 F	No	No	Yes[i]	Yes	6 wks S	H	A,B,C
Solowij et al., 1991	6 M, 3 F	6 M, 3 F	No	No	Yes[j]	Yes	12 h U	M–H	E
Block et al., 1990, Block and Ghoneim 1993	144, 80% M	72, 30% M	No	No	Yes[k]	NR	24 h U	L–H	A,B,C,D

Please refer to corresponding letters a–h from Table 1.
[i]Screens were positive for cannabis in 'some' of the subjects at day 2 when first testing was done.
[j]Screens considered negative if the second level (on test day) was lower than the first level (from the night before).
[k]Subjects with positive screens were not excluded.

the laboratory. Many of these studies have been performed in other countries where cannabis preparations are widely used, such as India, Egypt and Costa Rica. Most of the remaining studies have been performed in students in the United States. The studies are summarized in Tables 2–4.

As shown in Table 2, nearly half the published studies of this design produced negative results: cannabis users were indistinguishable from controls on various neuropsychological tests. The reader is referred to the table for details of the methodology of these studies. However, although these studies failed to reject the null hypothesis, they do not provide great reassurance that cannabis is devoid of residual effects. Many of the studies, for example, examined only light to moderate marijuana smokers; of those studies examining subjects who smoked once a day or more, most did not specify the interval between last cannabis ingestion and the time of testing.

Similar methodological reservations apply to many of the earlier studies which produced positive results: these studies, conducted between 1973 and 1981, are summarized in Table 3. Two of the studies lacked a control group. In one (Agarwal et al., 1975) users performed below population norms, but they were drawn from lower socio-economic classes. In the other (Sethi et al., 1981), users showed at most mild impairment as compared to population norms. In another study (Carlin and Trupin, 1977) users actually scored better than non-users after a 24-h unsupervised abstinence. Thus these three studies provide little convincing evidence of residual effects.

Several other studies from the 1970s examined users after an unknown (and possibly very brief) period of abstinence: for example, Entin and Goldzung (1973) did not specify the interval between last cannabis use and the time of testing; if the subject arrived 'high' for testing, these investigators simply requested him to return for testing at a later time. Similarly, Gianutsos and Litwack (1976) also simply requested users not to smoke before testing. Thus, immediate 'drug residue' effects from very recent smoking might easily explain the findings of these two groups of investigators.

This leaves three other positive studies from the 1970s, two from India and one from Egypt. Using very similar designs, Wig and Varma (1977) and Mendhiratta et al. (1978) investigated heavy cannabis users, using a battery of neuropsychological tests, after at least 12 h of abstinence (which was apparently partially but not rigorously supervised). Both authors found significant impairment on a wide variety of neuropsychological tests in users as compared to non-users. However, both studies were subject to several of the methodologic limitations common to most studies of this type (lack of control for use of other drugs, possibly insufficient matching of users and controls, and non-blind testing). Also, since the period of abstinence was only 12 h, the results might again be easily explained as a simple 'drug residue' effect from a large accumulated CNS burden of cannabis components, as suggested earlier in Fig. 1b.

The study of Souief (1971, 1975, 1976a, 1976b), by contrast, examined prisoners in Egypt who had presumably lacked access to cannabis for a prolonged period (although the length of incarceration and the possibility of cannabis use within the prison are not discussed). Thus, this study is the only one from the 1970s to assess what we have termed a possible 'CNS alteration' as opposed to a simple 'drug residue effect' from cannabis. The investigators compared 850 male prisoners who had used hashish at least once per month for at least a year with 839 non-user controls, using a substantial battery of tests. Users performed significant-

ly more poorly than non-users on a wide variety of these measures. Unfortunately, however, although users were matched with controls on age, sex, urban versus rural residence, education, and employment level, they were not matched on other variables, such as use of other drugs or premorbid measures of intelligence. For example, users were slightly more likely to be illiterate and less likely to have attended high school or university than non-users. Further, the modest level of use required for inclusion in the study group weighs against the possibility that the differences observed were actually residual effects of cannabis. A within-group comparison of heavy users versus light users in this study would have helped to resolve these questions, but is not reported. Thus, the intriguing findings of this study remain difficult to interpret.

Methodological quality improves substantially when we move to recent studies of cannabis effects, summarized in Table 4. Varma et al. (1988) were the first to rigorously supervise a group of users for a 12-h period to ensure abstinence before testing. On a battery of numerous tests, users performed below non-users on only three tests (pencil tapping, time estimation, and size estimation) — suggesting at most a modest residual effect. Mendhiratta et al. (1988), examining a subsample of those subjects which they had previously tested in 1978, also employed formal supervision of subjects for an abstinence period of 12 h or more. Users performed more poorly than non-users on virtually all tests in the study. On response time and the Bender visuomotor gestalt test, users had deteriorated more from their performance 10 years earlier than had the non-users. This latter finding suggests a possible 'CNS alteration' effect, over and above a 'drug residue' effect, in this sample. However, despite matching on age, sex, education and occupation, various confounding variables may have differentially affected users and non-users in this study. Among other things, the groups were not matched on use of other drugs: for example, 22 (73%) of the 30 users, but only 1 (7%) of the 15 non-users reported opiate use. Given the possibility of such confounding variables, together with the modest degree of deterioration documented, these data provide only very tentative evidence for a 'CNS alteration' effect.

In a similar longitudinal design, Page et al. (1988) examined a subset of the Costa Rican subjects previously studied by Satz et al. (1976a, 1976b). In the original 1976 study, the 41 users could not be distinguished from 41 non-user controls on a battery of tests, despite the fact that users had consumed a mean of 9.6 marijuana cigarettes per day for a mean of 17 years! In 1988, however, examining 27 of these same users and 30 of the same controls, Page et al. found users significantly more impaired than non-users on three of the approximately 20 tests administered (Bushke's verbal selective reminding, underlining test and the continuous performance test). Unfortunately, the authors did not report whether either group had changed between 1976 and 1988, or whether the cannabis-using group had deteriorated more than the controls. But given the massive cumulative exposure to marijuana among users (a mean of 30 years and 105 000 joints per subject), it is striking that the study failed to show more than a few differences on neuropsychological testing. And given that testing was performed only 12–24 h after last use, and that even this interval was unsupervised, it appears that 'drug residue' effects might well explain the few significant differences observed. Thus, the study would actually seem to weigh somewhat against the hypothesis that extended cannabis use can cause a 'CNS alteration'.

Weighing on the opposite side of this argument, however, are the results of Schwartz et al. (1989). These investigators compared 10 'cannabis-dependent' adolescents with 9 non-user controls and 8 abusers of other drugs. The cannabis users were in a treatment program where they were denied access to drugs, thus permitting testing after an extended period of abstinence. The cannabis-dependent group performed significantly worse than both control groups on the Benton visual retention test and the Wechsler memory scale prose passages, both after two days and again after six weeks of abstinence. The finding of differences even at six weeks, despite the fact that users were matched with non-users on age, socio-economic status, home environment, parents' education, and IQ, favors the hypothesis of a lasting 'CNS alteration' due to cannabis. On the other hand, the small sample sizes render the study vulnerable to the effects of one or two 'outliers' in a given group.

Small sample size may have also affected the study of Solowij et al. (1991) who compared 9 users and 9 controls, using a computerized selective attention test, 12 h after drug exposure. Given the brief period of abstinence, a short 'drug residue' effect might again explain the observation that users performed significantly more poorly than non-users on this measure.

Finally, Block et al. (1990, 1993) compared 144 users with 72 non-users, following an unsupervised 24-h period of abstinence. The groups were carefully matched, not only on age, education, use, work status, income and occupation, but also on fourth grade Iowa test scores. However, users were more frequently male than controls (80% of users versus 30% of controls), and were more likely to have abused other drugs. Specifically, among the 52 heaviest users, the number reporting lifetime use of another drug more than 100 times were six (12%) for amphetamines, six (12%) for cocaine, three (6%) for hallucinogens other than LSD, and three (6%) for LSD. On urine testing at the time of the study, one (2%) of the heavy users showed codeine, and four (8%) heavy users and three (11%) of the intermediate users showed cocaine. Among the non-users, it appears that none reported a history of using other drugs (not in-

cluding alcohol) more than 100 times, or displayed other drugs in the urine.

On a battery of neuropsychological tests, including the twelfth grade Iowa test, users performed significantly below controls on the 'quantitative thinking' and 'correctness and appropriateness of expression' subtests of the Iowa, and on Buschke's selective reminding test. Given that this study employed unusually rigorous matching of users to controls, especially with fourth grade test scores, the evidence is persuasive that the differences observed were truly attributable to marijuana. However, because of the relatively short abstinence period, lack of supervision during the abstinence period, and modest differences observed, these results may again be attributable to short-term 'drug residue' effects, rather than to lasting 'CNS alteration' effects.

4. Discussion

Residual effects of cannabis must be distinguished from (i) the known effects of acute intoxication, (ii) the traits of individuals who use cannabis heavily, and (iii) actual psychiatric disorders which may be induced or exacerbated by cannabis. After these exclusions, residual effects must be divided into (a) those due to a residue of psychoactive cannabis components in the CNS during the hours or days after acute intoxication (phenomena which we have termed 'drug residue' effects), and (b) those effects due to a lasting toxic effect of cannabis on the central nervous system (CNS) which persists even after the drug has left the body (effects which we have called 'CNS alteration'). We reviewed the literature to assess the evidence that cannabis use can produce these two types of residual effects.

Available studies divide into cannabis administration studies, in which a known quantity of drug is administered to volunteers in the laboratory, and naturalistic studies, in which chronic heavy users of cannabis are compared with non-users or infrequent users, usually after a period of abstinence varying from hours to days. Both study designs, unfortunately, are subject to frequent methodologic limitations. Cannabis administration studies have the advantage that a known dose of cannabis is administered, and subjects can serve as their own controls (i.e., each subject is tested before, during, and after administration of the drug). But for technical and ethical reasons, the period of drug administration is brief and follow-up is short. Thus, these studies may assess short-term 'drug residue' effects, but not the long-term 'drug residue' effects, much less 'CNS alteration' effects, that might result from chronic heavy exposure.

Naturalistic studies solve the latter problem by testing chronic heavy users who may have accumulated years or decades of daily exposure. But these studies are bedevilled by the difficulty of adequately matching non-using or infrequently-using controls, by lack of control for frequency of use prior to the neuropsychological assessments, and by brief and/or unsupervised periods of abstinence before testing.

It is not surprising, then, that we can presently draw only very limited conclusions about the residual effects of cannabis. First, there is reasonable evidence for a brief 'drug residue' effect of 12–24 h after even a single episode of smoking. Given laboratory evidence that frequent daily smoking may accumulate a large CNS burden of Δ^9-THC and other psychoactive substances, one might reasonably expect this 'drug residue' effect to persist longer in chronic heavy users, but evidence is as yet inadequate to support or refute this speculation. Similarly, the evidence is inadequate to answer the 'CNS alteration' question. Given that many studies have found modest or absent differences between even heavy users and controls, one might be tempted to assume that any 'CNS alteration' with cannabis is slight or nonexistent. But findings such as the deterioration noted by Mendhiratta et al. (1988) on a ten-year follow-up of an earlier sample of users, or the impairment found by Schwartz et al. (1989) even after six weeks of abstinence, indicate that the case is not closed on the issue of lasting CNS toxicity.

In studies where residual effects have been reported, the most consistent findings are impairment of performance on tests of focused attention, visual and verbal memory, and visuomotor functions. However, as mentioned earlier, comparisons between individual studies are difficult because most studies have examined only a subset of cognitive measures. Given that the ability to learn new information, or memory, is dependent on a number of cognitive components — including the ability to organize, encode, store and retrieve new information — future studies of cannabis must examine the specific subprocesses which are compromised by the residual effects of the drug.

Unfortunately, resolving these many questions will be time-consuming and expensive. Several designs might suit the task. One would be a protracted cannabis administration study, in which subjects are given large doses of marijuana over a prolonged period in order to mimic natural use (say, 5 episodes of smoking per day for 30 days), followed by neuropsychological testing for at least two weeks afterwards — and longer if clear differences persist. Another would be a more refined naturalistic study, in which heavy users were compared with a rigorously matched control group (composed perhaps of infrequent users, rather than frank non-users, since this choice might reduce confounding variables and better isolate frequency of use as the variable under study). Assuming that differences were found between heavy users and matched controls after a day or two of abstinence, retesting after a longer period of supervised abstinence would be performed to assess whether these differences vanished (arguing for a 'drug

residue' effect) or persisted (arguing for a 'CNS alteration'). Longitudinal studies of chronic users in Western industrialized countries, using designs similar to those of Mendhiratta et al. (1988) or Page et al. (1988) in India and Costa Rica, might also assess the possibility of 'CNS alteration' in an ethically acceptable manner. Finally, twin studies, if feasible, might compare genetically identical individuals with different degrees of cannabis exposure. In all of these studies, a detailed battery of neuropsychological measures, assessing individual subprocesses of cognitive function, should be employed. In particular, these tests should assess focused attention, verbal and visuospatial memory, time estimation, and visuomotor functions. A wide-ranging battery of neuropsychological tests is important, since no single test, or type of test, has consistently proven more sensitive than others to the residual effects of cannabis in the studies which we have reviewed.

With these various more sophisticated designs, it may be increasingly possible to resolve questions about the residual effects of cannabis which still linger after decades of research.

Acknowledgment

This research was supported in part by NIDA grant RO1 DA06522.

References

Agarwal, A.K., Sethi, B.B. and Gupta, S.C. (1975) Physical and cognitive effects of chronic bhang (cannabis) intake. Indian J. Psychiatry 17, 1–7.

Barnett, G., Licko, V. and Thompson, T. (1985) Behavioral pharmacokinetics of marijuana. Psychopharmacology 85, 51–56.

Barratt, E., Beaver, W., White, R., Blakeney, P. and Adams, P. (1972) The effects of the chronic use of marijuana on sleep and perceptual motor performance in humans. In: Current Research in Marijuana (Lewis, M.F., ed.), pp. 163–193. Academic Press, New York.

Block, R.I., Farnham, S., Braverman, K., Noyes, R. Jr and Ghoneim, M.M. (1990) Long-term marijuana use and subsequent effects on learning and cognitive functions related to school achievement: preliminary study. NIDA Res. Monogr. Ser. 101, 96–111.

Block, R.I. and Ghoneim, M.M. (1993) Effects of chronic marijuana use on human cognition. Psychopharmacology 110, 219–228.

Bowman, M. and Pihl, R.O. (1973) Cannabis: psychological effects of chronic heavy use. Psychopharmacologia (Berlin) 29, 159–170.

Carlin, A.S. and Trupin, E.W. (1977) The effect of long-term chronic marijuana use on neuropsychological functioning. Int. J. Addict. 12 (5), 617–624.

Chait, L.D. (1990) Subjective and behavioral effects of marijuana the morning after smoking. Psychopharmacology 100, 328–333.

Chait, L.D., Fischman, M.W. and Schuster, CR. (1985) 'Hangover' effects the morning after marijuana smoking. Drug Alcohol Depend. 15, 229–238.

Cohen, S. (1976a) The 94-day cannabis study. Ann. NY Acad. Sci. 282, 211–220.

Cohen, S., Lessin, P.J., Hahn, P.M. and Tyrrell, E.D. (1976b) A 94-day cannabis study. In: The Pharmacology of Marijuana (Braude, M.C. and Szara, S., eds.), pp. 621–626. Raven Press, New York.

Culver, C.M. and King, F.W. (1974) Neuropsychological assessment of undergraduate marijuana and LSD users. Arch. Gen. Psychiatry 31, 707–711.

Dornbush, R.L., Clare, G., Zaks, A., Crown, P., Volavka, J. and Fink, M. (1972) 21-Day administration of marijuana in male volunteers. In: Current Research in Marijuana (Lewis, M.F., ed.), pp. 115–128. Academic Press, New York.

Ellis, G.M. Jr, Mann, M.A., Judson, B.A., Schramm, N.T. and Taschian, A. (1985) Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. Clin. Pharmacol. Therap. 38, 572–578.

Entin, E.E. and Goldzung, P.J. (1973) Residual effects of marijuana usage on learning and memory. Psychol. Rec. 23, 169–178.

Frank, I.M., Lessin, P.J., Tyrrell, E.D., Hahn, P.M. and Szara, S. (1976) Acute and cumulative effects of marijuana smoking in hospitalized subjects: a 36-day study. In: The Pharmacology of Marijuana (Braude, M.C. and Szara, S., eds.), pp. 673–679. Raven Press, New York.

Gianutsos, R. and Litwack, A.R. (1976) Chronic marijuana smokers show reduced coding into long-term storage. Bull. Psychonomic Soc. 7 (3), 277–279.

Grant, I., Rochford, J., Fleming, T. and Stunkard, A. (1973) A neuropsychological assessment of the effects of moderate marijuana use. J. Nerv. Ment. Dis. 156 (4), 278–280.

Gruber, A. and Pope, H.G. Jr. (1994) Cannabis psychotic disorder: does it exist? Am. J. Addict. 3, 72–83.

Heishman, S.J., Huestis, M.A., Henningfield, J.E. and Cone, E.J. (1990) Acute and residual effects of marijuana: profiles of plasma THC levels, physiological, subjective, and performance measures. Pharmacol. Biochem. Behav. 37, 561–565.

Hunt, C.A. and Jones, R.T. (1980) Tolerance and disposition of tetrahydrocannabinol in man. J. Pharmacol. Exp. Ther. 215, 35–44.

Johansson, E., Agurell, S., Hollister, L.E. and Halldin, M.M. (1988) Prolonged apparent half-life of delta-1-tetrahydrocannabinol in plasma of chronic marijuana users. J. Pharm. Pharmacol. 40, 374–375.

Jones, R.T. and Benowitz, N. (1976) The 30-day trip — clinical studies of cannabis tolerance and dependence. In: The Pharmacology of Marijuana (Braude, M.C. and Szara, S., eds.), pp. 627–642. Raven Press, New York.

Jones, R.T., Benowitz, N. and Bachman, J. (1976b) Clinical studies of cannabis tolerance and dependence. Ann. NY Acad. Sci. 282, 221–239.

Kielholz, P., Goldberg, L., Hobi, V., Ladewig, D., Reggiani, G. and Richter, R. (1972) Haschisch und Fahrverhalten. Deutsch. Med. Wschr. 97 (20), 789–794.

Kielholz, P., Hobi, V., Ladewig, D., Miest, P. and Richter, R. (1973) An experimental investigation about the effect of cannabis on car driving behaviour. Pharmakopsychiat. 6, 91–103.

Leirer, V.O., Yesavage, J.A. and Morrow, D.G. (1989) Marijuana, aging, and task difficulty effects on pilot performance. Aviat. Space Environ. Med. 60, 1145–1152.

Leirer, V.O., Yesavage, J.A. and Morrow, D.G. (1991) Marijuana carry-over effects on aircraft pilot performance. Aviat. Space Environ. Med. 62, 221–227.

Mendelson, J.H., Babor, T.F., Kuehnle, J.C., Rossi, A.M., Bernstein, J.G., Mello, N.K. and Greenberg, I. (1976) Behavioral and biological aspects of marihuana use. Ann. NY Acad. Sci. 282, 186–210.

Mendhiratta, S.S., Varma, V.K., Dang, R., Malhotra, A.K., Das, K. and Nehra, R. (1988) Cannabis and cognitive functions: a re-evaluation study. Br. J. Addict. 83, 749–753.

Mendhiratta, S.S., Wig, N.N. and Verma, S.K. (1978) Some psychological correlates of long-term heavy cannabis users. Br. J. Psychiatry 132, 482–486.

Page, J.B., Fletcher, J. and True, W.R. (1988) Psychosociocultural perspectives on chronic cannabis use: the Costa Rican follow-up. J. Psychoactive Drugs 20 (1), 57–65.

Rafaelson, L., Christrup, H., Bech, P. and Rafaelson, O.J. (1973b) Effects of cannabis and alcohol on psychological tests. Nature 242, 117–118.

Rafaelson, O.J., Bech, P., Christiansen, J., Christrup, H., Nyboe, J. and Rafaelsen, L. (1973a) Cannabis and alcohol: effects on simulated car driving. Science 179, 920–923.

Reed, H.B.C. (1974) Cognitive effects of marijuana. In: The Use of Marijuana: A Physiological and Psychological Inquiry (Mendelson, J.H., Rossi, A.M. and Meyer, R.E., eds.), pp. 107–114. Plenum Press, New York.

Rochford, J., Grant, I. and LaVigne, G. (1977) Medical students and drugs: further neuropsychological and use pattern considerations. Int. J. Addict. 12 (8), 1057–1065.

Rubin, V. and Comitas, L. (1975) Psychological assessment. In: Ganja in Jamaica: A Medical Anthropological Study of Chronic Marijuana Use (Rubin, V. and Comitas, L., eds.), pp. 111–119. Mouton, The Hague.

Satz, P., Fletcher, J.M. and Sutker, L. (1976b) Neuropsychologic, intellectual and personality correlates of chronic marijuana use in native Costa Ricans. Ann. NY Acad. Sci. 282, 266–306.

Satz, P., Krauskopf, D., Fletcher, J.M. and Sutker, L. (1976a) Neuropsychological, intellectual, and personality correlates. In: Chronic Cannabis Use in Costa Rica (Carter, W.E., Coggins, W.J. and Doughty, P.L., eds.) Chapter XVI, pp. 1–69. NIDA, Washington DC.

Schwartz, R.H., Gruenewald, P.J., Klitzner, M. and Fedio, P. (1989) Short-term memory impairment in cannabis-dependent adolescents. Am. J. Dis. Child 143, 1214–1219.

Seth, R. and Sinha, S. (1991) Chemistry and pharmacology of cannabis. Prog. Drug Res. 36, 71–115.

Sethi, B.B., Trivedi, J.K. and Singh, H. (1981) Long-term effects of cannabis. Indian J. Psychiatry 23 (3), 224–229.

Solowij, N., Michie, P.T. and Fox, A.M. (1991) Effects of long-term cannabis use on selective attention: an event-related potential study. Pharmacol. Biochem. Behav. 40, 683–688.

Souief, M.I. (1971) The use of cannabis in Egypt: a behavioral study. Bull. Narc. 23 (4), 17–28.

Souief, M.I. (1975) Chronic cannabis users: further analysis with objective test results. Bull. Narc. 27 (4), 1–26.

Souief, M.I. (1976a) Some determinants of psychological deficits associated with chronic cannabis consumption. Bull. Narc. 28 (1), 25–42.

Soueif, M.I. (1976b) Differential association between chronic cannabis use and brain function deficits. Ann. NY Acad. Sci. 282, 323–343.

Stefanis, C., Boulougouris, J. and Liakos, A. (1976) Clinical and psychophysiological effects of cannabis in long-term users. In: The Pharmacology of Marijuana (Braude, M.C. and Szara, S., eds.), pp. 659–665. Raven Press, New York.

Varma, V.K., Malhotra, A.K., Dang, R., Das, K. and Nehra, R. (1988) Cannabis and cognitive functions: a prospective study. Drug Alcohol Depend. 21, 147–152.

Wall, M.E. and Perez-Reyes, M. (1981) The metabolism of delta-9-tetrahydrocannabinol and related cannabinoids in man. J. Clin. Pharmacol. 21, 1785–1795.

Weckowicz, T.E., Collier, G. and Spreng, L. (1977) Field dependence, cognitive functions, personality traits, and social values in heavy cannabis users and non-user controls. Psychol. Rep. 41, 291–302.

Wig, N.N. and Varma, V.K. (1977) Patterns of long-term heavy cannabis use in North India and its effects on cognitive functions: a preliminary report. Drug Alcohol. Depend. 2, 211–219.

Yesavage, J.A., Leirer, V.O., Denari, M. and Hollister, L.E. (1985) Carry-over effects of marijuana intoxication on aircraft pilot performance: a preliminary report. Am. J. Psychiatry 142 (11), 1325–1329.