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Early-onset cannabis use and cognitive deficits: what is the nature of the association?

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Abstract

Background: Individuals who initiate cannabis use at an early age, when the brain is still developing, might be more vulnerable to lasting neuropsychological deficits than individuals who begin use later in life. *Methods*: We analyzed neuropsychological test results from 122 long-term heavy cannabis users and 87 comparison subjects with minimal cannabis exposure, all of whom had undergone a 28-day period of abstinence from cannabis, monitored by daily or every-other-day observed urine samples. We compared early-onset cannabis users with late-onset users and with controls, using linear regression controlling for age, sex, ethnicity, and attributes of family of origin. *Results*: The 69 early-onset users (who began smoking before age 17) differed significantly from both the 53 late-onset users (who began smoking at age 17 or later) and from the 87 controls on several measures, most notably verbal IQ (VIQ). Few differences were found between late-onset users and controls on the test battery. However, when we adjusted for VIQ, virtually all differences between early-onset users and controls on test measures ceased to be significant. *Conclusions*: Early-onset cannabis users exhibit poorer cognitive performance than late-onset users or control subjects, especially in VIQ, but the cause of this difference cannot be determined from our data. The difference may reflect (1) innate differences between groups in cognitive ability, antedating first cannabis use; (2) an actual neurotoxic effect of cannabis on the developing brain; or (3) poorer learning of conventional cognitive skills by young cannabis users who have eschewed academics and diverged from the mainstream culture.

Keywords: Cannabis; Cognitive; Neuropsychological

1. Introduction

Does long-term heavy use of cannabis produce residual deficits in cognitive functioning? Most recent studies agree that heavy users exhibit temporary deficits for hours or days after stopping cannabis (Pope et al., 1995; Pope and Yurgelun-Todd, 1996; Fletcher et al., 1996; Struve et al., 1999; Patrick and Struve, 2000; Solowij, 1998; Pope et al., 2001a,b; Solowij et al., 2002)—perhaps attributable to withdrawal effects or to a residue of cannabinoids lingering in the brain (Pope et al., 1995, 2001a,b; Haney et al., 1999; Kouri and Pope, 2000). However, there is less consensus about whether cannabis can produce cumulative neurotoxicity—that is, potentially irreversible deficits associated with total lifetime cannabis exposure (Pope, 2002). A recent meta-analysis seems to argue against this possibility (Grant et al., 2001), as does a longitudinal population study of heavy cannabis users (Lyketsos et al., 1999) and recent data from our own laboratory (Pope et al., 2001a,b, 2002). Other studies, however, have suggested an association between lifetime cannabis exposure and electroencephalographic (Struve et al., 1998) or neuropsychologic abnormalities (Solowij, 1998). Recently, another study (Solowij et al., 2002) has reported a significant association between lifetime

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cannabis use and neuropsychological test performance among users seeking treatment.

One explanation for these discrepant findings may be that cannabis is more toxic for some populations than others. For example, individuals with longer durations of cannabis use have likely started use earlier in life, and perhaps cannabis is more toxic for the developing brain than for the mature brain. Evidence supporting this hypothesis comes from studies showing apparently irreversible effects on behavior and brain morphology in rats exposed to cannabinoids while immature (Stiglick and Kalant, 1985; Landfeld et al., 1988). And in humans, one recent study found that 48 early-onset cannabis users (onset before age 17), but not 51 late-onset users (onset at 17 or later), exhibited significantly longer reaction times than controls in a visual scanning task (Ehrenreich et al., 1999). Another recent study also compared 29 long-term cannabis users who had initiated use before age 17 with 28 users who had initiated use at age 17 or later (Wilson et al., 2000). Magnetic resonance images of the brain showed that early-onset users had a lower percentage of gray matter and a higher percentage of white matter, relative to whole-brain volume, than the late-onset users. Positron emission tomography studies in the same subjects showed that male early-onset users had higher cerebral blood flow than males who initiated use after age 17. Finally, early-onset users of both sexes were shorter in height and lower in weight than late-onset users. The authors speculated that these differences might be related to the effects of cannabis on gonadal and pituitary hormones in early adolescence.

To explore further the relationship between onset of cannabis use and neuropsychological dysfunction, we analyzed data from a study of cognitive performance in 122 long-term cannabis users and 87 controls, conducted at our laboratory between 1997 and 2001.

2. Method

The detailed methods of this study, together with the results obtained from the first 180 subjects, have been presented previously (Pope et al., 2001a,b); a subsequent publication (Pope et al., 2002) presents augmented results with 29 additional female subjects. The present paper uses the full sample of 209 subjects to assess the relationship between age of onset of cannabis use and neuropsychological performance.

2.1. Subjects

A brief summary of the methods is as follows: we studied three groups of subjects age 30–55 years: (1) current heavy users who had smoked cannabis at least 5000 times in their lives and who were smoking daily at the time of study entry; (2) former heavy users who had also smoked at least 5000 times, but who had smoked fewer than 12 times within the 3 months prior to study entry; and (3) control subjects who had tried cannabis at least once, but no more than 50 times in their lives, and no more than once during the past year. We chose controls who had used cannabis to a minimal degree, rather than controls who had never used cannabis at all, because we believed that individuals who had never experimented with the drug might differ in unknown ways from those who had, thus introducing possible confounding variables into the comparison between heavy users and control subjects. All subjects signed informed consent for the study after the full study procedures had been explained.

We excluded subjects if they reported (1) use of any other class of illicit drugs more than 100 times in their lives; (2) alcohol dependence at any time in their lives; (3) current use of any psychotropic medications; (4) a history of head injury with loss of consciousness; (5) any medical or neurological condition that might affect cognitive function; or (6) a current DSM-IV (American Psychiatric Association, 1994) Axis I disorder other than social phobia or simple phobia, as determined by the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996). We also assessed subjects for a history of attention deficit hyperactivity disorder (Ward et al., 1993; DuPaul, 1991; Findling et al., 1996), antisocial behavior (Ward et al., 1993), family history of substance use disorders and other DSM-IV Axis I disorders (Hudson et al., 1987), and for levels of education and income in subjects' families of origin, since these variables all represented possible confounders that might influence cognitive performance (Pope et al., 2001a,b; Pennington and Ozonoff, 1996; Barkley, 1997; Aronowitz et al., 1994; Lueger and Gill, 1990; Gorenstein, 1987; Morgan and Lilienfeld, 2000).

2.2. Study procedures

All subjects then underwent a 28-day period of abstinence from marijuana, monitored by daily or every-other-day observed urine samples. Subjects in Groups 2 and 3 were expected to exhibit negative urines for cannabinoids and all other drugs of abuse (including alcohol) throughout the 28 days. Subjects in Group 1 were monitored for levels of 11-nor-9-carboxy-delta 9-tetrahydrocannabinol (THCCOOH) to be certain that these levels declined in a manner consistent with residual drug excretion in the absence of any new cannabis use (Huestis and Cone, 1998; Carter et al., 2001).

At the end of the 28-day abstinence period, we administered a battery of ten neuropsychological tests chosen to assess verbal and visuospatial memory, attention, and executive functions: (1) Buschke's Selective Reminding Test (BSRT; a test of memory of word lists) (Buschke, 1973), (2) Conners' continuous perfor-

mance test (CPT; a computerized measure of attention and reaction times) (Conners, 1995), (3) an auditory CPT (Weintraub and Mesulam, 1985), (4) the Benton Visual Retention Test (BVRT; a test of visuospatial memory) (Benton, 1974); (5) the Stroop Test (MacLeod, 1991); (6) the Ravens Progressive Matrices (Burke, 1985); (7) the Wechsler Memory Scale (WMS) (Wechsler, 1945); (8) the Controlled Oral Word Association Test (often known as the 'FAS' test) (Lezak, 1995); (9) the Block Design Subtest of the Wechsler Adult Intelligence Scale, Revised (WAIS-R) (Wechsler, 1981), and (10) the Wisconsin Card Sort Test (WCST) (Heaton, 1981). Four of the above tests (Buschke, 1973; Conners, 1995; Weintraub and Mesulam, 1985; Benton, 1974) were also administered on Days 0, 1, and 7 of the abstinence period, but these results were not examined in the present analysis, since we were looking for persistent cannabis toxicity associated with early age of onset, rather than temporary deficits that might be present only during the days immediately after cannabis was discontinued. Subjects also received the vocabulary subscale of WAIS-R, which is widely used to provide an estimate of verbal intelligence (VIQ) (Wechsler, 1981). This test was administered on day 0, since it not timed and unlikely to be affected by mental status changes such as residual intoxication (Luria, 1966).

2.3. Age-of-onset analyses

For our primary analysis, we pooled all of the long-term cannabis users (Groups 1 and 2; $N = 122$) and then subdivided them, in the manner of both Ehrenreich et al. (1999) and Wilson et al. (2000), into those who began using cannabis prior to age 17 (early onset: $N = 69$) and those who began use at age 17 or later (late onset: $N = 53$). We compared these two groups and the 87 control subjects on baseline demographic characteristics using linear regression for continuous variables and logistic regression for binary variables. We then compared neuropsychological test scores in the three groups using linear regression, adjusting for variables that could not be effects of cannabis use and that might represent possible confounders of the association between group status and neuropsychological test performance: age, sex, ethnicity, mother's and father's educational attainment, parental household income, and presence of substance abuse or psychiatric disorders in a first-degree relative. We did not adjust for subjects' income or level of education, because these might partially reflect effects of cannabis, rather than premorbid cognitive ability. We have discussed the choice of both outcome variables and variables chosen for adjustment in previous papers (Pope et al., 2001a,b; Pope, 2002; Pope et al., 2002). On the basis of these results, we subsequently performed several a posteriori analyses (1) adjusting for VIQ; (2) adjusting for lifetime duration of cannabis use, measures of childhood attention-deficit hyperactivity disorder, and measures of childhood conduct disorder; (3) excluding control subjects who had tried cannabis at age 16 or less; and (4) changing the definition of 'early onset' to age 15 or less and then to age 14 or less. The rationale for these analyses is explained in more detail below.

Because many of the measures were correlated, it was difficult to calculate an appropriate correction for multiple comparisons. To provide some correction for the number of comparisons, we have set alpha at 0.01, two-tailed, for the purposes of our discussion below. In the tables, we have also indicated marginal findings, where $0.01 < P < 0.05$, for the interested reader. However, it must be recognized that these latter findings may represent chance associations.

3. Results

3.1. Primary analyses

The three groups differed in age, but were otherwise similar on ethnicity, sex, and levels of education and income of the subjects' parents (Table 1). However, we found significant differences between groups on the education and income of the subjects themselves. Only 22 (32%) of the early-onset users had graduated from a 4-year college, as compared with 32 (60%) of late-onset users and 71 (82%) of controls ($P = 0.001$ for early-onset vs. late onset, $P = 0.007$ for late-onset vs. controls, and $P < 0.001$ for early-onset vs. controls).

After adjustment for age, sex, ethnicity, and the five family-of-origin variables, late-onset users did not differ significantly from control subjects on any of the scores of the ten tests. However, early-onset users differed significantly from controls on several measures involving verbal functions, including VIQ, memory of word lists on the BSRT after a 30 min delay, and semantic categories on the FAS test (Table 2).

In some study populations, VIQ scores provide a good estimate of innate cognitive ability, since they tend to remain stable despite a wide range of cortical insults (Luria, 1966). Thus, the lower VIQ's of the early-onset users might reflect lower innate cognitive abilities, present even before cannabis use, rather than an effect of cannabis use itself. To pursue this hypothesis, we repeated the analysis while adjusting for VIQ–an analysis assuming that VIQ was a potential confounding variable not affected by exposure to cannabis. As shown by the representative results in Table 3, all significant differences between groups on the other test measures disappeared after adjustment for VIQ.

Table 1
Demographic features of early-onset cannabis users, late-onset users, and control subjects

Demographic feature	Early-onset users[a] ($N = 69$)	Late-onset users[a] ($N = 53$)	Control subjects[a] ($N = 87$)	P Values		
				Early versus control	Early versus late	Late versus control
Age, mean (S.D.)	36 [32.5, 41]	44 [35.5, 50]	40 [34, 45]	0.003	< 0.001	0.03
Sex, Male, N (%)	52 (75.4)	33 (62.3)	61 (70.1)	0.47	0.12	0.34
Ethnicity, White, N (%)	57 (82.6)	33 (86.8)	75 (86.2)	0.54	0.53	0.92
Father's education, High School or Less	28 (45.2) [b]	26 (50.1) [e]	31 (36.9) [g]	0.53	0.35	0.12
Mother's education, High School or Less	34 (51.5) [c]	23 (45.1) [e]	47 (54)	0.56	0.52	0.22
Subject's education, High School or Less	21 (30.4)	5 (9.4)	0	< 0.001	0.008	< 0.001
Parents' household income < $30 000	19 (28.4) [d]	8 (15.4) [f]	13 (15.1) [h]	0.056	0.11	0.98
Subject's household income < $30 000	33 (47.8)	27 (50.9)	25 (28.7)	0.015	0.73	0.009
Family history of substance abuse	35 (53) [c]	24 (47.1) [e]	24 (28.2) [j]	0.002	0.66	0.02
Family history of other disorders	11 (16.7) [c]	8 (15.7) [e]	12 (14.1) [j]	0.5	0.85	0.67
Lifetime episodes of cannabis use	17 368 [10 842, 23 218]	12 480 [9178, 21 242]	10 [5, 25]	< 0.001	0.25	< 0.001

[a] Shown as N (%) for proportions and median [interquartile range] for continuous variables.
[b] $N = 62$ due to missing data.
[c] $N = 66$ due to missing data.
[d] $N = 67$ due to missing data.
[e] $N = 51$ due to missing data.
[f] $N = 52$ due to missing data.
[g] $N = 84$ due to missing data.
[h] $N = 86$ due to missing data.
[j] $N = 85$ due to missing data.

3.2. Secondary analyses

We also carried out a series of a posteriori analyses (data not shown), the first of which compared the early-onset and late-onset users on all test measures while adjusting for log-transformed number of episodes of cannabis use in the subjects' lifetimes. This adjustment had little effect on the results, changing the estimated difference between early- and late-onset users by no more than 0.13 S.D. units on any of the measures in Table 2. Interestingly, however, lifetime episodes of use was itself associated with VIQ ($P < 0.001$), BRST total recall, and WMS total score (both $P < 0.01$) even after allowing for age of onset. Next, we repeated the analyses while adjusting for scores on the ADHD rating scale (DuPaul, 1991) and again while adjusting for ratings of childhood antisocial behavior (see reference 7 for details on the derivation of these scores). The adjustments for these variables again produced only small changes in the estimate of average effect of group on each of the neuropsychological measures, and did not alter any qualitative conclusions. We also repeated all of the analyses with 'early-onset' redefined before age 16 (thus splitting the users into 53 early-onset vs. 69 late-onset cases) and also redefined as before age 15 (a split of 34 early- vs. 88 late-onset users). These divisions produced results closely resembling those obtained with the original 'early-onset' definition of age 16 or less. Finally, we repeated the analyses while eliminating the 19 control subjects who had themselves tried cannabis before age 17, to allow for the possibility that even brief exposure to cannabis at an early age might itself be toxic–although these subjects had used the drug a median of only 12 times and a maximum of 45 times in their entire lives. The results were again essentially unchanged.

4. Discussion

We compared 69 long-term cannabis users who had begun smoking cannabis before age 17 ('early-onset users'), 53 long-term users who had begun smoking at age 17 or later ('late-onset users'), and 87 control subjects who had smoked cannabis only a few times in their lives. Subjects with a significant history of other forms of drug or alcohol use, or with potentially confounding medical or psychiatric disorders, were excluded. All subjects received a battery of ten standard

Table 2
Neuropsychological test performance in early-onset cannabis users, late-onset users, and control subjects

Test score [a]	Early-onset users ($N = 69$)	Late-onset users ($N = 53$)	Control subjects ($N = 87$)	Estimated mean differences (SE) between groups [b]		
				Early versus control	Early versus late	Late versus control
Verbal IQ	103.5 (15.2)	115.6 (17.7)	117.8 (13.3)	−11.8 (2.3)***	−8.7 (3.2)**	−2.6 (2.5)
BSRT, Total recall	115.4 (13.6)	119.4 (13.7)	121.0 (13.5)	−5.2 (2.2)*	−3.3 (2.7)	0.1 (2.4)
BSRT, 30 min delay	9.2 (2.5)	9.3 (2.4)	10.3 (2.2)	−1.1 (0.4)**	−0.1 (0.5)	−0.7 (0.4)
CPT, Comission errors	0.4 (1.4) [c]	0.4 (1.5)	0.5 (1.2)	0 (0.1)	0 (0.1)	0.1 (0.1)
CPT, Omission Errors	0.6 (1.5)	0.5 (0.9)	0.4 (1.1)	0.3 (0.2)	0.4 (0.3)	0 (0.2)
CPT, Reaction time	551.2 (151.3)	524.3 (103.3)	517 (110)	32.0 (22.6)	14.9 (30.3)	9.8 (24.7)
BVRT, No correct	7.8 (1.5)	7.9 (1.8)	8.1 (1.5)	−0.2 (0.3)	−0.1 (0.4)	0 (0.3)
BVRT, Errors	2.5 (1.9)	2.4 (1.9)	2 (1.6)	0.4 (0.3)	0 (0.4)	0.2 (0.3)
WMS, Total score	68.5 (8.2)	69.1 (8.7)	70.4 (6.4)	−1.6 (1.2)	−0.6 (1.7)	−0.4 (1.3)
FAS, Raw Score	47 (10.6)	48.2 (12)	50.4 (11.2)	−3.6 (1.9)	−0.6 (2.5)	−1.8 (2.1)
FAS, Semantic categories	22.1 (4.3)	22.3 (5.1)	24.4 (5.7)	−2.5 (0.9)**	−0.8 (1)	−1.4 (0.9)
WCST, Total categories	7.8 (2)	7.5 (2.1)	8.5 (1.7)	−0.8 (0.3)*	−0.3 (0.4)	−0.7 (0.3)*
WCST, Total perseverations [d]	2.3 (0.8)	2.6 (0.8)	2.1 (0.7)	0.2 (0.1)	0 (0.2)	0.3 (0.1)*
WAIS Block design, raw score	11.7 (2.5)	11.3 (2.7)	11.7 (2.8)	−0.3 (0.4)	0.2 (0.5)	0 (0.5)
Stroop, Interference time, (s)	106.4 (24.8)	106.2 (26)	103.7 (26.2)	4.5 (4.4)	1.6 (5.7)	−0.7 (4.7)
Ravens, Total score	48.5 (6.9)	48.9 (8.2)	50.6 (6.9)	−2.4 (1.2)*	−1.7 (1.6)	−0.4 (1.3)

[a] Shown as mean (S.D.).
[b] By linear regression adjusted for age, sex, ethnicity, and family-of-origin variables (see text).
[c] One outlier with 89 errors excluded from the analysis.
[d] Shown and analyzed as logarithm of total perseverations because of right-skewed distribution.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

neuropsychological tests after a period of 28 days of abstinence from cannabis and all other drugs, monitored by observed urine samples. Given this prolonged abstinence period, it seems unlikely the differences among the groups could be attributed to temporary deficits due to a residue of cannabinoids in the brain, or to acute withdrawal effects from stopping cannabis. We found no significant differences between late-onset users and controls on the test measures, but early-onset users differed markedly from the controls on several measures, particularly those involving verbal abilities. Most notably, early-onset users scored much lower than either controls or late-onset users on VIQ as measured by the vocabulary subtest of the Wechsler Adult Intelligence Scale. Interestingly, when we repeated our analysis with adjustment for VIQ, all of the differences between early-onset users and the other two groups ceased to be significant.

It should be recognized that these findings may be subject to both Type I and II errors. On the one hand, we might have found spurious differences between groups in some cases because of chance associations

Table 3
Neuropsychological test performance in early-onset cannabis users, late-onset users, and control subjects, adjusting for VIQ

Test score [a]	Estimated mean differences (SE) between groups			Significance of differences		
	Early versus control	Late versus control	Early versus late	Early versus control	Late versus control	Early versus late
BSRT, Total recall	−2.2 (2.4)	1.4 (2.4)	−1.7 (2.9)	0.37	0.55	0.55
BSRT, 30 min Delay	−0.9 (0.4)	−0.6 (0.4)	−0.1 (0.5)	0.028	0.19	0.84
FAS, Raw score	−1.5 (2.1)	−1.0 (2.1)	0.3 (2.7)	0.48	0.65	0.91
FAS, Semantic categories	−0.9 (0.9)	−0.9 (0.9)	0.5 (1.0)	0.35	0.31	0.61
WCST, Total categories	−0.3 (0.3)	−0.5 (0.3)	0.1 (0.5)	0.45	0.15	0.86
WCST, Total perseverations [b]	0.1 (0.1)	0.2 (0.1)	−0.2 (0.2)	0.55	0.15	0.28
Ravens, Total score	0.4 (1.2)	0.4 (1.2)	0.8 (1.5)	0.74	0.72	0.62

[a] Shown as mean difference (S.D.).
[b] Log of total perseverations.

due to the large number of comparisons, selection bias affecting the subjects who presented for study, or unrecognized confounders (such as use of other drugs, psychiatric disorders, or other conditions not disclosed by the users). Conversely, we might have failed to reject the null hypothesis in some instances due to lack of sensitivity of the neuropsychological tests or to selection and information bias working in the opposite direction (such as recruiting control subjects who displayed greater cognitive deficits than would occur in a completely unbiased control population). We have discussed these limitations in more detail previously (Pope et al., 2001a,b; Pope, 2002).

Three possible hypotheses, individually or in combination, might explain the differences between early-onset cannabis users and the other two groups. The first is that early-onset cannabis users had lower innate cognitive capacity than the other groups even before they started smoking cannabis. In favor of this hypothesis is that in many neurologic populations, VIQ tends to be preserved despite a wide range of cortical insults (Luria, 1966), suggesting that early onset of cannabis use, per se, would be unlikely to cause lower VIQ scores. Under this hypothesis, individuals with limited intellectual ability might be more prone to experiment with cannabis at an earlier age and to go on to use it heavily. Because of their lower cognitive capacity, these individuals would tend to do poorly across the board on neuropsychological testing, not because of cannabis use, but simply as a result of their innate limitations. This latter prediction is consistent with our observation that, after VIQ adjustment, early-onset users no longer differed significantly from the other groups on most of the test measures.

Since verbal IQ is estimated on the basis of a vocabulary test, a second possible hypothesis is that early-onset users were not innately lacking in cognitive capacity, but simply failed to acquire comparable verbal skills because of their more limited education. Under this hypothesis, individuals who begin smoking cannabis at an early age, for whatever reason, are less motivated to pursue an education (which would be consistent with our observations in Table 1, as well as those of other investigators (Bray et al., 2000; Hammer and Vaglum, 1990; Lynskey and Hall, 2000)), and would thus remain particularly disadvantaged on tests requiring verbal abilities. This prediction is consistent with our observation that early-onset users were sharply distinguishable from controls primarily on tests requiring verbal abilities, including VIQ itself, memory of word lists on the BSRT, and semantic categories on the FAS test. By contrast, early-onset users showed no significant differences from the controls on the non-verbal tests, as shown in Table 2.

The third and most ominous hypothesis is that cannabis produces a potentially irreversible neurotoxic effect in individuals who begin using it at an early age. This hypothesis would be consistent with the observations of Wilson et al. (2000), who found morphological and physiological abnormalities in early-onset users possibly attributable to neuroendocrine effects of cannabis. Similarly, Ehrenreich et al. (1999) found that early-onset cannabis users displayed significantly longer reaction times on a visual scanning task. However, the subjects in this study did not display significant deficits on tasks requiring verbal skills, as was found in our study. Unfortunately, our study measured reaction time only on the CPT–a much easier task than the visual scanning task used by Ehrenreich et al. Thus, our failure to find a difference on reaction time may have represented a ceiling effect, because our task was too easy to produce meaningful differences among the groups.

Our study, like virtually all other retrospective studies of cognitive performance in cannabis users, is limited in its ability to distinguish among the above three hypotheses. An ideal study would obtain neuropsychological testing results from a large sample of individuals when they were approximately 10 years old, before they had ever tried cannabis, and then obtain neuropsychological results many years later, after some of the individuals had become long-term cannabis users. Such a study could then control accurately for premorbid cognitive abilities by adjusting for childhood test scores. We are aware of only one major study that has used such a design (Block and Ghoneim, 1993), but this study required only 1 day of abstinence from cannabis before users were tested, so that it is uncertain whether the deficits observed were temporary residual effects or potentially irreversible effects of cannabis.

Furthermore, even assuming perfect adjustment for differences in premorbid cognitive abilities among study groups, a study design based solely on neuropsychological testing could not discriminate accurately between the second and third hypotheses listed above. Individuals who smoke cannabis heavily as young teenagers may miss numerous opportunities for academic, social, and practical learning. As members of a drug-using culture, spending considerable amounts of time in drug-related behavior, they diverge from mainstream culture in their interests, skills, and vocabularies. Thus, a cannabis-associated 'cultural divergence' might lead to almost irreversible deficits on skills as measured by neuropsychological tests that were developed for and standardized to individuals in mainstream culture—even if cannabis itself were not directly toxic to the brain.

The challenge posed by our findings, therefore, is to determine the relative contributions of the above three factors to the cognitive deficits observed in early-onset cannabis users. In particular, to establish that cannabis can produce frank neurotoxicity, future studies would be required to demonstrate deficits in cannabis users

beyond those potentially explainable by premorbid differences or by 'cultural divergence.'

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