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Acute Effects of Marijuana on Cognition: Relationships to Chronic Effects and Smoking Techniques

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BLOCK, R. I., R. FARINPOUR AND K. BRAVERMAN. *Acute effects of marijuana on cognition: Relationships to chronic effects and smoking techniques.* PHARMCOL BIOCHEM BEHAV 43(3) 907–917, 1992.—A double-blind, placebo-controlled study assessed acute effects on human cognition of marijuana smoking involving long or short durations of inhalation and breath holding. During eight test sessions, 48 adult, male volunteers completed standardized, pencil-and-paper tests of educational development and ability, as well as computerized tests of learning, associative processes, abstraction, and psychomotor performance. Marijuana impaired all capabilities except abstraction and vocabulary. These impairments were more pervasive than those associated with heavy, chronic marijuana use in a previous study involving the same tests, but showed some similarities. Marijuana altered associative processes, encouraging more uncommon associations. Marijuana-induced impairment in learning pairs of words was influenced by associative relationships between the words. There were a few hints that prolonged breath holding increased marijuana's effects under some test conditions, but in general it did not. Prolonged breath holding itself affected performance in four tests, regardless of whether subjects smoked marijuana or placebo. Whether physiological or psychological factors (e.g., exposure to carbon monoxide in smoke or subjects' expectations) produced these effects could not be determined.

Δ^9-Tetrahydrocannabinol Associations Breath holding Carbon monoxide Cognition Iowa Tests Learning Marijuana Memory

THIS study examined immediate cognitive effects of marijuana smoking. It had three major goals:

1. One goal was to compare marijuana's acute effects with effects of chronic marijuana use observed in a preceding study that included the same battery of tests (11) to see if the three tests that showed some deficits associated with heavy, chronic marijuana use were especially sensitive to marijuana's acute effects. In the preceding study, no marijuana was administered in test sessions, and chronic marijuana users who had abstained from marijuana for 24 h were compared with nonusers. Acute and chronic effects of drugs sometimes agree, but can also differ markedly (40).
2. Two tests were included, moreover, to extend and clarify our earlier findings concerning marijuana's acute effects on associative processes and semantic memory retrieval (13–15). Using constrained association tests in which subjects gave multiple instances of a category for 2 min, or gave a single instance of a category that began with a specified letter (e.g., "Weapon-G"), Block and Wittenborn (14) found limited changes in associative processes following marijuana smoking that were consistent with the subjectively reported tendency for marijuana to promote a freer, less logically controlled flow of thought (2,9,54,55), with more unusual associations. Changes consistent with this tendency were observed with respect to the content of responses, for example, their normative frequency, but not the speed of responses (13,14). The present study included a test in which subjects had to produce free associations and constrained associations varying in content, for example, categories and opposites, as well as a test assessing memory for such associations, that is, paired associate learning. We wanted to determine if marijuana affected performance differently for free and constrained associations or associations varying in content and, in addition, if speed of response was as sensitive as content to changes in associative processes produced by marijuana that con-

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tained a higher dose of Δ^9-tetrahydrocannabinol (Δ^9-THC) than used in our previous studies (13–15).

3. A third goal was to evaluate the influence of smoking technique on marijuana's effects. Marijuana users are commonly advised that holding the smoke in their lungs for a long time increases the drug's psychological effects [(30), p. 123]. This seems reasonable, as prolonged breath holding might increase the effective dose of the primary active constituent of marijuana, Δ^9-THC. Such an increase was recently reported by Tashkin et al. (57), who observed greater rises in serum Δ^9-THC concentrations following marijuana smoking with the longer of two breath-holding durations they studied. Tashkin et al. did not examine whether prolonged breath holding increased marijuana's effects on test performance, but two other studies have (62,63). The first study examined three breath-holding durations, without benefit of placebo controls. Only one assessment, a verbal memory test (*Buschke's Test*), showed any influence of breath-holding duration on marijuana's effects. This influence was nonmonotonic and, consequently, anomalous. The second, placebo-controlled, study compared two breath-holding durations. Performance in four tests showed no influence of breath-holding duration on marijuana's effects, although a subjective assessment of sedation showed greater effects of marijuana with the longer breath-holding duration, and ratings at the session's end of the peak "high" feeling showed a marginally significant trend in the same direction. Thus, the results of these two studies were largely negative, although showing a few hints of possible influences of breath-holding duration. Increased effects of marijuana on test performance due to prolonged breath holding could be obscured if too few or too many puffs were administered, resulting in negligible or excessively strong effects on performance. A limitation of these two studies was that they examined effects of relatively few puffs of marijuana, that is, six (62) or four (63). Marijuana, relative to placebo, did not impair performance on the four tests used in the latter study (63), and the drug's effect on the one test included in the former study was uncertain because there were no placebo controls (62). Conceivably, the influence of breath-holding duration on marijuana's effects on test performance might be clearer if more than six puffs were administered.

This possibility was tested by the present study of marijuana's cognitive effects, in which subjects took a puff every 35 s until they completely smoked an entire marijuana cigarette. Long (15 s) and short (7 s) durations of inhalation and breath holding were compared, with the expectation that the former would deliver a greater effective dose of Δ^9-THC (57) and produce stronger drug effects than the latter. The long duration was comparable to that spontaneously practiced by many marijuana users (38,39,56,61). The short duration was also realistic, constituting 25% of the rest period between puffs (7 s ÷ 28 s), compared to 75% for the long duration (15 s ÷ 20 s).

METHOD

Subjects and Screening

Forty-eight subjects were tested. Paid, male volunteers were recruited through advertisements. During preliminary screening visits, informed consents were obtained after the nature and possible consequences of the study were explained. Volunteers then provided information about their medical history, demographic characteristics, and use of marijuana and other drugs (26). Portions of the Diagnostic Interview Schedule (DIS) Version III-A (43), a structured psychiatric screening interview for use by research staff, were administered. A urine sample for drug screening and routine urinalysis and a blood sample for blood chemistry and complete blood count were obtained.

To maintain comparability with procedures followed in our preceding study of effects of chronic marijuana use on cognition (11), we retrieved subjects' scores during the 4th grade of grammar school on the *Iowa Tests of Basic Skills* (tests for younger age groups comparable to the 12th-grade *Iowa Tests of Educational Development*, which were administered to subjects during the experiment). Fourth-grade scores, which correlate substantially with 12th-grade scores obtained years later (11), did not differ significantly for subjects who smoked with long and short breath-holding durations, whose respective mean scores (±SE), expressed as grade equivalents, were as follows: *Vocabulary*, 5.3 ± 0.2 and 5.7 ± 0.3; *Reading Comprehension*, 5.6 ± 0.3 and 5.9 ± 0.2; *Language Skills*, 5.1 ± 0.2 and 5.3 ± 0.2; *Work-Study Skills*, 4.9 ± 0.2 and 5.3 ± 0.2; *Mathematics Skills*, 4.8 ± 0.2 and 4.9 ± 0.2; and *Composite Score*, 5.2 ± 0.2 and 5.4 ± 0.2.

Subjects were restricted to adults (age range 18–42 years) who had attended the fourth grade in Iowa so that their fourth-grade scores could be retrieved. Subjects were also restricted to individuals whose health was adequate for administration of marijuana, based upon their medical history information, blood tests, and urinalysis. Volunteers who were not experienced marijuana users were excluded, as were those who had a history of dependence upon any illicit drugs other than marijuana (43).

Drug

The mean weight of the marijuana cigarettes was 755 mg, and their mean content of Δ^9-THC was 2.57%, or 19 mg. Placebo cigarettes contained inactive, cannabinoid-extracted marijuana with only trace amounts of Δ^9-THC. The cigarettes were provided by the National Institute on Drug Abuse.

Smoking Procedure

Using a stopwatch, the research assistant guided subjects in a paced smoking procedure. The research assistant said "in" every 35 s, cuing subjects to inhale deeply and hold the smoke in their lungs. For the long and short breath-holding durations, which were each used with half the subjects, the research assistant said "out" 15 s and 7 s after "in," respectively, cuing subjects to exhale and pause. Subjects smoked the cigarettes as completely as possible, using a holder while consuming the butts. Numbers of puffs were recorded. At the beginning of the study, all subjects smoked with a long breath-holding duration. Four subjects quit or had to be dropped from the study due to adverse reactions following marijuana smoking during the initial 22% of the data collection period. To help understand these unanticipated effects of smoking with a long breath-holding duration, a short breath-holding duration was subsequently added and subjects were assigned to one or the other.

Test Procedure

Subjects were tested individually. Multiple sessions for subjects were necessary to assure that they completed all tests while effects of marijuana smoking remained substantial, as the total length of the test battery exceeded the duration of substantial marijuana effects. So that test performance would not be influenced by effects of self-administered drugs, subjects had to promise to abstain from alcohol on the day of each session and after 6:00 p.m. on the preceding evening and from marijuana and other drugs on the day of each session and the preceding 3 days. Each subject participated in eight sessions, which were separated by intervals of at least 4 days and commonly 1 week or more.

In each session, subjects smoked a marijuana or placebo cigarette under double-blind conditions. The smoking procedure for each subject was the same in all his sessions. Orders of administering marijuana and placebo were counterbalanced by assigning subjects to four different sequences of drug administration. For all sequences, each successive pair of sessions (sessions 1-2, 3-4, 5-6, and 7-8) involved smoking marijuana once and placebo once. The same tests were given within each pair of sessions. In the first four sessions, cognitive and psychomotor tests were administered by an Apple II+ computer system. Subjects responded orally or by pressing buttons. They were administered Buschke's Test, *Free and Constrained Associations*, and *Psychomotor Tests* (*Critical Flicker Fusion* and *Discriminant Reaction Time*) in sessions 1-2 and *Concept Formation, Text Learning*, and *Paired Associate Learning* in sessions 3-4. In the last four sessions, four tests from the Iowa Tests of Educational Development (Level II) were administered along with the *Short Test of Educational Ability* (Level 5), a test of general academic ability standardized with the Iowa Tests (48). The tests were administered according to procedures specified in the test manuals (24,47). All were pencil-and-paper tests in multiple-choice format. Subjects were administered *Ability to Do Quantitative Thinking* and *Ability to Interpret Literary Materials* in sessions 5-6 and *Correctness and Appropriateness of Expression, Vocabulary*, and Short Test of Educational Ability in sessions 7-8.

Details of the computerized tests were as follows.

1. *Buschke's Test*. A list of 16 nouns, half "high-imagery" words that were easy to visualize (e.g., "bouquet") and the remainder "low-imagery" words that were difficult to visualize (e.g., "replacement") (37), was presented on the monitor at a rate of 3 s per word. The subject tried to recall as many words as possible. Seven learning and test trials were given consecutively. The subject tried to recall the whole list on each test trial, but on learning trials after the first he was reminded only of the words missed on the immediately preceding test trial.

   This procedure allowed scoring of several measures of memory—long-term retrieval, long-term storage, short-term retrieval, and consistent long-term retrieval—in addition to total recall (16). In essence, recall of a word without an immediately preceding reminder (i.e., recall on two successive trials) indicated that the word had entered (and presumably remained in) long-term storage. Recall of the word before this occurrence was attributed to short-term retrieval; after it, to long-term retrieval. Long-term retrieval was designated "consistent" when the word was never subsequently omitted. Long-term retrieval and consistent long-term retrieval were also expressed as ratios of long-term storage to control for differences among subjects in the amount of information stored.
2. *Concept Formation*. The stimuli for this test, which assessed abstraction ability, were schematic faces (31,42) with seven varying features, each having three possible values. For example, the eyes could be facing left, right, or center. The subject studied a card picturing five members of the "Smith" family and five members of the "Jones" family for 1 min. Then, 20 new schematic faces, half Smiths and the remainder Jones, were shown on the monitor at a rate of 10 s per face, and the subject classified each as Smith or Jones, pressing a button to indicate his decision. The card remained present while the subject classified the first 10 new faces and then was taken away. Following this testing, the entire procedure was repeated with a different card defining Smith vs. Jones. Of the two cards, one portrayed a "clear" concept that involved a well-defined rule, for example, "faces with large beards and round noses are Smiths, smiling faces with no hair are Jones." The other portrayed a "fuzzy" concept (45) that followed a similar pattern but had some exceptions, for example, 80% of the Smiths had small beards and 80% of the Jones had frowning faces. Every Smith bore more resemblance to the Smith family than to the Jones family and vice versa, but there was no simple logical rule for defining Smith vs. Jones.
3. *Text Learning*. The subject read a paragraph from an article in *Reader's Digest* on the monitor at his own pace, pressed a button when finished, and then recalled as much as he could in 3 min. He then reread the paragraph and recalled it again. Following this, the entire procedure was repeated with a different paragraph. The subject's recall was tape recorded for later scoring of the propositions recalled (33). Reading times were determined based upon the subject's button presses.
4. *Free and Constrained Associations*. For each of 100 words presented at a 10-s rate on the monitor, the subject gave a single word as an association. Response times were measured by a voice-activated relay. For 50 words, the subject was cued to provide a "free association," that is, any kind of association that came to mind; for 10 words each, the subject was to provide one of five types of "constrained associations," that is, his response was to relate to the stimulus in a specified way, cued by the words "another," "category," "example," "opposite," or "property." Examples of these types are "book-magazine," "aluminum-metal," "fruit-apple," "night-day," and "banana-yellow," respectively. The words were drawn from those used in a pilot study (10) involving introductory psychology students so that for each response in the present study the number of pilot subjects giving that response ("dominance") could be scored, for example, eight pilot subjects gave "sandal" in response to "shoe."
5. *Paired Associate Learning*. A list of 30 pairs of words was presented at a 3-s rate on the monitor. Then, the initial word from each pair was presented at a 5-s rate and the subject tried to respond with the second word from each pair. Response times were measured by the voice-activated relay. These learning and test trials were then repeated. Following this, the entire procedure was repeated with a different list of pairs of words. Each list consisted of 3 pairs representing each of the 5 types of constrained associations used in Free and Constrained Associations, mixed with 15 other pairs, of which equal numbers involved moderately strong free associates, weak free associates, and unassociated words, for example, "plumber-pipe," "tell-secret," and "carpet-laughter," respectively (10).
6. *Psychomotor Tests*. a) *Critical Flicker Fusion*: The subject viewed two light-emitting diodes. One was flickering and the other remained constantly illuminated. During the 2-s

period of flickering or the following 3-s interstimulus interval, the subject indicated which diode was flickering. The computer determined the flicker fusion threshold by increasing or decreasing the rate of flickering depending upon the correctness of the subject's responses (8). The task was repeated twice, with two threshold estimates produced each time. b) *Discriminant Reaction Time*: The subject viewed a series of digits flashed for 0.1 s each and pressed a button as fast as possible following each "4." The interstimulus interval, initially 0.4 s, was increased or decreased by the computer depending upon the correctness of the subject's responses to determine the most rapid rate at which accuracy could be maintained. Digits were presented for 50 s, and the mean interstimulus interval during this period served as a measure of the subject's sustained response speed (8). The task was repeated four times.

Details of the functions assessed by the standardized, pencil-and-paper tests were as follows:

1. *Ability to Do Quantitative Thinking*. Solving mathematical word problems and answering questions assessing understanding of basic mathematical concepts.
2. *Correctness and Appropriateness of Expression*. Recognizing misspelled words and deciding which of alternative versions of a specified portion of text best expressed the idea, made the statement grammatically correct or most precise, or was correctly punctuated or capitalized.
3. *Vocabulary*. Picking which of several words was the closest synonym for a specified word.
4. *Ability to Interpret Literary Materials*. Answering questions assessing comprehension of a short text. The subject read the text first and could refer back to it while answering the questions.
5. *Short Test of Educational Ability*. Answering four types of questions involving vocabulary, arithmetic computation, letter series (recognizing patterns in series of letters), and symbol manipulation (recognizing symbolic quantitative relations).

The order of administration of tests within each session was counterbalanced to control for changes in marijuana's effects over time except that two short tests in the first pair of sessions, Critical Flicker Fusion and Discriminant Reaction Time, were always administered together in constant order, as were two short tests in the final pair of sessions, Vocabulary and Short Test of Educational Ability.

Two alternate forms of all computerized tests except Critical Flicker Fusion and Discriminant Reaction Time were constructed, using stimuli carefully balanced on relevant characteristics (10,37). Published, equated forms (X-8 and Y-8) were available for the Iowa Tests of Educational Development (25), but not for the Short Test of Educational Ability, so alternate items were used to construct two forms of the latter test. Alternate forms were used in the two administrations of tests to each subject in sessions involving smoking of marijuana and placebo. Alternate forms were counterbalanced over drug conditions. When more than one set of stimuli was used during a single administration of a test (i.e., in Concept Formation, Text Learning, and Paired Associate Learning), the orders of stimuli were also counterbalanced.

In all sessions, the tests were completed within about 1.5 h after smoking,a period during which effects of smoked marijuana remain substantial. Subjects were required to stay in the laboratory for 3 h after smoking to assure that marijuana's effects had abated and to agree not to drive home from the session or later on the days of the sessions. About 15 min before being released in sessions 3-4, they were asked to recall the paragraphs presented earlier during each session in Text Learning.

Statistical Analyses

To assess effects of marijuana and breath-holding duration, the data were submitted to analyses of variance (ANOVAs). These analyses included a within-subjects factor representing drug (marijuana vs. placebo) and between-subjects factors representing breath (long vs. short breath-holding durations), the four sequences of drug administration, and the counterbalancing of alternate forms over drugs. From one to three additional within-subjects factors representing test manipulations appropriate for the individual computerized tests were included in the analyses (11). The significance level for all F-tests was $p < 0.05$.

RESULTS

Characteristics of Subjects

On average, subjects were 21.2 ± 0.6 years old and had attended school for 13.5 ± 0.3 years. One subject described himself as Hispanic and the remainder described themselves as Caucasian. One subject was unemployed and the remainder were in school (42%), employed (21%), or both (35%). One subject had a history of noncurrent major depression and one had a history of noncurrent major depression and atypical bipolar disorder (43). None had a history of schizophrenia.

On average, subjects started using marijuana in grade 9.9 ± 0.3. The median reported frequency of marijuana use among those who were currently using it (88%) was one to four times weekly, and the mean duration of use at their indicated frequencies was 3.7 ± 0.4 years. Most subjects (85%) did not report using any illicit drugs other than marijuana more than twice in the last month or show any in urine specimens. The remainder reported using an illicit drug other than marijuana three to nine times in the last month and/or showed cocaine in their urine. Apart from marijuana and alcohol, the drugs with which subjects had the most experience were stimulants, psychedelics, and amyl or butyl nitrites.

Effects of Marijuana

The left part of Table 1 shows mean test performance as a function of drug condition. As the table indicates, marijuana impaired performance on most tests relative to placebo. Marijuana reduced thresholds for discriminating a flickering light (Critical Flicker Fusion), slowed sustained reaction speed (Discriminant Reaction Time), slowed response time for giving associations (Free and Constrained Associations), slowed reading of paragraphs of text and reduced both immediate and delayed recall of these paragraphs (Text Learning), reduced learning of associations between pairs of words (Paired Associate Learning), reduced recall of words (Buschke's Test), and decreased correct answers on the Short Test of Educational Ability and on three tests of the Iowa Tests of Educational Development dealing with comprehension of text (Ability to Interpret Literary Materials), verbal expression (Correctness and Appropriateness of Expression), and mathematics (Ability to Do Quantitative Thinking).

In Buschke's Test, besides reducing overall recall marijuana impaired long-term retrieval and consistent long-term retrieval both when the scores for these aspects of memory

TABLE 1

EFFECTS OF MARIJUANA AND BREATH-HOLDING DURATION ON MEAN TEST PERFORMANCE

Test and Dependent Variable	Drug Condition: Marijuana	Drug Condition: Placebo	Breath-Holding Duration: Long	Breath-Holding Duration: Short
Psychomotor tests				
Critical Flicker Fusion				
Threshold (Hz)	36.0 ± 0.2*	38.2 ± 0.2	37.1 ± 0.2	37.1 ± 0.2
Number of trials	35.7 ± 0.6*	40.8 ± 0.6	37.5 ± 0.6	39.0 ± 0.6
Discriminant reaction time (s/100)	38.1 ± 0.2†	37.5 ± 0.2	38.4 ± 0.2‡	37.2 ± 0.2
Concept formation				
Percentage correct	71.5 ± 1.4	74.5 ± 1.4	71.5 ± 1.4	74.3 ± 1.3
Response time (s/100)	271.5 ± 9.6	263.0 ± 8.7	281.1 ± 9.4	254.5 ± 8.9
Free and constrained associations				
Dominance of responses	41.7 ± 1.3*	44.6 ± 1.3	41.2 ± 1.3‡	45.1 ± 1.3
Percentage of commonest responses¶	42.4 ± 1.1¶	45.6 ± 1.1	41.1 ± 1.1#	46.9 ± 1.1
Response time (s/100)	197.5 ± 2.8†	189.1 ± 2.6	212.4 ± 3.0**	174.7 ± 2.0
Text learning				
Number of propositions recalled††				
Immediate recall	12.4 ± 0.6*	13.9 ± 0.6	12.7 ± 0.6	13.6 ± 0.6
Delayed recall	8.4 ± 0.6†	9.8 ± 0.6	8.4 ± 0.6	9.9 ± 0.6
Reading time (s)	38.7 ± 0.7†	37.1 ± 0.7	38.7 ± 0.8	37.1 ± 0.6
Paired associate learning				
Percentage correct	73.1 ± 0.8†	75.7 ± 0.7	70.2 ± 0.8#	78.9 ± 0.7
Response time (s/100)	153.4 ± 1.4	153.8 ± 1.5	164.8 ± 1.5#	142.2 ± 1.3
Buschke's Test				
Number of words‡‡				
Total recall	5.2 ± 0.1†	5.5 ± 0.1	5.1 ± 0.1‡	5.7 ± 0.1
Long-term storage	4.9 ± 0.2	5.2 ± 0.1	4.7 ± 0.1‡	5.5 ± 0.2
Short-term retrieval	0.9 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.7 ± 0.1
Long-term retrieval	4.4 ± 0.2†	4.7 ± 0.1	4.2 ± 0.1‡	4.9 ± 0.2
Consistent long-term retrieval	2.9 ± 0.2†	3.3 ± 0.2	2.8 ± 0.1‡	3.4 ± 0.2
Percentage of long-term storage				
Long-term retrieval	84.4 ± 1.8†	89.5 ± 0.8	85.5 ± 1.6	88.5 ± 1.1
Consistent long-term retrieval	50.8 ± 2.6†	58.0 ± 2.2	51.5 ± 2.3	57.5 ± 2.5
Short test of educational ability				
Number correct	21.3 ± 0.6†	22.8 ± 0.5	21.3 ± 0.6	22.8 ± 0.5
Iowa Tests of Educational Development (standard scores)				
Vocabulary	26.7 ± 0.5	27.2 ± 0.5	26.8 ± 0.5	27.0 ± 0.5
Ability to interpret literary materials	23.0 ± 0.8*	26.1 ± 0.6	24.2 ± 0.7	24.9 ± 0.7
Correctness and appropriateness of expression	19.4 ± 0.9*	22.3 ± 0.8	20.5 ± 0.9	21.3 ± 0.9
Ability to do quantitative thinking	23.7 ± 1.0¶	26.5 ± 0.8	24.5 ± 1.0	25.8 ± 0.9

All values are means ± SE. Significance levels are based upon the main effects of drug (marijuana vs. placebo) and breath (long vs. short breath-holding durations) in the ANOVA described in the text.

*$p < 0.001$, †$p < 0.05$, ¶$p < 0.01$ for difference from placebo.

‡$p < 0.05$, #$p < 0.01$, **$p < 0.001$ for difference from the short breath-holding duration.

§For scoring the percentage of commonest responses, the commonest responses were determined from previously obtained normative data (10).

††Immediate and delayed recall are scores for the tests immediately after reading the paragraphs and 15 min before the ends of the sessions, respectively.

‡‡The scores, which are averaged over trials and types of imagery, are based upon eight words.

were expressed in "raw" form (numbers of words) and "adjusted" form (as percentages of long-term storage). Marijuana's tendency to impair long-term storage itself was not significant, although it was marginal, $F(1, 30) = 3.6$, $p = 0.07$, for drug effect.

Marijuana produced additional effects in two tests that could not be characterized either as impairment or improvement. In Free and Constrained Associations, subjects gave lower dominance (i.e., normatively less common) responses to stimuli on average and gave the normatively commonest responses less frequently under the influence of marijuana compared to placebo. Both these effects indicated more unusual associations following marijuana smoking. In Critical Flicker Fusion, marijuana reduced the number of trials required for threshold determination, probably due to its effect of decreasing the threshold.

There were two tests that were not affected by marijuana, the ones assessing abstraction ability (Concept Formation) and picking of synonyms (Vocabulary).

Influence of Breath-Holding Duration on Marijuana's Effects

If marijuana's effects had been greater when the breath-holding duration was long than short, this would have been reflected in the analyses as a drug × breath interaction. This interaction was significant in one test, Correctness and Appropriateness of Expression, $F(1, 32) = 4.3$, $p < 0.05$. Following placebo smoking, the mean scores for long and short breath-holding durations were similar, 22.5 ± 0.9 and 22.1 ± 1.3, respectively. Following marijuana smoking, the corresponding means appeared to differ in the expected direction, being 18.4 ± 1.3 and 20.5 ± 1.2, respectively. However, follow-up analysis for marijuana alone showed that these means did not differ significantly, $F(1, 32) = 1.1$, $p > 0.05$, making interpretation of the drug × breath interaction in this test problematic.

Effects of Breath-Holding Duration

In contrast, breath-holding duration affected performance in several tests regardless of whether subjects smoked marijuana or placebo. The right part of Table 1 shows mean test performance as a function of breath-holding duration. A long breath-holding duration, compared to a short one, had the following effects that were in the same direction as the effects of marijuana: slowed sustained reaction speed (Discriminant Reaction Time); slowed response time for giving associations, giving lower dominance responses, and giving normatively commonest responses less frequently (Free and Constrained Associations); reduced learning of associations between pairs of words (Paired Associate Learning); and reduced recall of words, and impaired long-term retrieval and consistent long-term retrieval when the scores for these aspects of memory were expressed as numbers of words (Buschke's Test). A long breath-holding duration, compared to a short one, also produced two impairments not matched by marijuana: slowed response time in providing answers during testing of paired associates (Paired Associate Learning) and a reduced score for long-term storage of words (Buschke's Test). On the other hand, marijuana produced other effects that a long breath-holding duration did not, that is, impaired long-term retrieval and consistent long-term retrieval when the scores for these aspects of memory were expressed as percentages of long-term storage (Buschke's Test), as well as altered performance in other tests (Critical Flicker Fusion, Text Learning, Short Test of Educational Ability, Ability to Interpret Literary Materials, Correctness and Appropriateness of Expression, and Ability to Do Quantitative Thinking).

Influence of Test Manipulations on Marijuana's Effects

There were two computerized tests in which within-test manipulations influenced the effects of marijuana.

In Text Learning, the impairment by marijuana in immediate recall was greater on the first recall trial than the second, $F(1, 32) = 5.9$, $p < 0.05$, for drug × trial effect. A second reading of the text, which naturally improved recall under both drug conditions, $F(1, 32) = 417.1$, $p < 0.001$, for trial effect, in addition allowed subjects to compensate slightly for the marijuana-induced impairment. The mean number of propositions recalled was 8.5 ± 0.6 for marijuana and 10.6 ± 0.6 for placebo on the first trial. The corresponding figures on the second trial were 16.3 ± 0.6 and 17.1 ± 0.6, respectively.

Times for reading the two paragraphs of text that were tested, in addition to showing an overall slowing by marijuana (Table 1), showed a four-way interaction, $F(1, 32) = 4.9$, $p < 0.05$, for drug × breath × trial × paragraph effect. This interaction primarily reflected an influence of breath-holding duration on marijuana's effects like that discussed above—greater marijuana effects when the breath-holding duration was long than short—which was, however, restricted to only two of the four reading times measured, that is, times for subjects' second reading of the first paragraph and first reading of the second paragraph.

Within-test manipulations also influenced the effects of marijuana in Paired Associate Learning. Percentage correct showed an interaction of drug × associative type, $F(7, 217) = 2.3$, $p < 0.05$, which was further qualified by an interaction of drug × breath × associative type, $F(7, 217) = 2.2$, $p < 0.05$. Figure 1 illustrates both these interactions, as well as the overall impairments in learning produced by marijuana and the long breath-holding duration (Table 1). The drug × breath interaction is shown separately for each associative type, with constrained associations on the left and free associations on the right. Follow-up analyses done for constrained and free associations separately clarified the drug × associative type and drug × breath × associative type interactions by indicating that they were attributable solely to constrained associations: These interactions were both significant for constrained associations, $F(4, 124) = 4.0$, $p < 0.01$, and $F(4, 124) = 3.3$, $p < 0.05$, respectively. Neither of these interactions was significant for free associations ($F < 1$), although there was a large overall effect of associative type, $F(2, 62) = 257.6$, $p < 0.001$.

Examination of Fig. 1 revealed that the drug × breath × associative type interaction for constrained associations partly reflected an influence of breath-holding duration on marijuana's effects like that discussed above—greater marijuana effects when the breath-holding duration was long than short—which occurred for three associative types ("category," "property," and "another"), but not the others. Examination of Fig. 1 also revealed that the "example" associative type was primarily responsible for the drug × associative type interaction for constrained associations. The overall impairment in leaning produced by marijuana was shown by all the other associative types but was reversed for the example associative type.

Other Effects

There were other significant effects, but for the sake of brevity those not falling under the preceding headings have not been discussed except where essential. There were numerous effects of within-test manipulations independent of drug condition. For example, in the test of abstraction ability (Concept Formation) although neither the drug nor the breath-holding duration influenced performance percentage correct was lower and response times were slower for fuzzy concepts than clear concepts, as expected, $F(1, 30) = 51.9$, $p < 0.001$, and $F(1, 30) = 15.2$, $p < 0.001$.

DISCUSSION

In our earlier work, analyses of the content of responses indicated that marijuana produced some changes in associative processes in the direction of encouraging more uncommon associations (14). In the present study, subjects gave more uncommon associations in Free and Constrained Associations

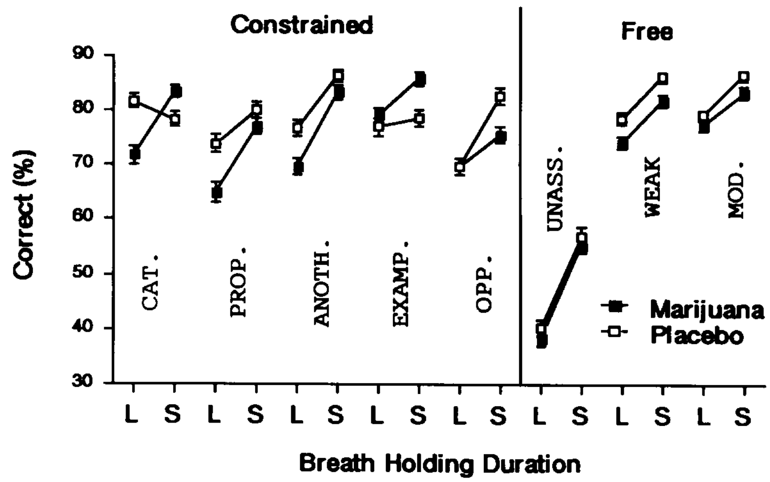

FIG. 1. Drug × breath × associative type interaction for percentage correct in Paired Associate Learning. The drug × breath interaction is shown separately for each of five associative types of constrained associations (left) and three associative types of free associations (right). The bars indicate SE. CAT., category; PROP., property; ANOTH., another; EXAMP., example; OPP., opposite; UNASS., unassociated words; WEAK, weak free associates; MOD., moderately strong free associates; L, long breath-holding duration; S, short breath-holding duration.

after smoking marijuana relative to placebo, consistent with our previous results, but this effect did not differ for associative types varying in content or free vs. constrained associations. In contrast, such differences did occur with respect to marijuana's effect on learning associations in Paired Associate Learning. The marijuana-induced impairment in learning, which was shown by seven of eight associative types of free or constrained associations, was reversed for the example associative type. This drug × associative type interaction should be interpreted cautiously until future verification, but suggests that marijuana's effects on learning were influenced by content.

In our earlier work, the evidence that marijuana encouraged more uncommon associations derived from analyses of the content of responses but not their speed (13,14). The present study examined whether speed of response was as sensitive as content to changes in associative processes produced by marijuana. The results were unclear: Marijuana both slowed responses and encouraged more uncommon associations in Free and Constrained Associations. However, these effects were not influenced by associative type; and while associative type did influence marijuana's detrimental effect on learning in Paired Associate Learning, marijuana did not slow responses at all in this test. Marijuana slowed responses in two of the other three tests in which speed was measured (i.e., in Discriminant Reaction Time and Text Learning, but not Concept Formation), giving the impression that speed was generally a sensitive measure of the drug's effects in the present study, possibly because we used marijuana cigarettes with a Δ^9-THC content of 19 mg compared to only 10 mg in our earlier work on associative processes and semantic memory retrieval (13–15).

We previously found no impairment of learning in a paired associate test using marijuana with a Δ^9-THC content of 10 mg (12), whereas 19 mg in the present study produced clear impairment. To explain why marijuana cigarettes with a Δ^9-THC content of 10 mg did not impair paired associate learning, whereas comparable doses have been shown to impair memory assessed by other tests such as free recall (1), we speculated that retrieval deficits might contribute to marijuana-induced memory impairments and that paired associate learning might be less vulnerable to such deficits because the stimulus always provided a cue for the response (12). The present study, while demonstrating that marijuana with a higher Δ^9-THC content impaired paired associate learning, provided other evidence of marijuana-induced retrieval deficits. Marijuana impaired long-term retrieval and consistent long-term retrieval in Buschke's Test both when the scores for these aspects of memory were expressed as numbers of words and as percentages of long-term storage, whereas the drug's tendency to impair long-term storage itself was only marginally significant. We previously reported that heavy, chronic marijuana use (defined by use seven or more times weekly) while not producing any overall impairments in Buschke's Test was associated with selective retrieval deficits for words that were easy to visualize (11). Using Buschke's methods, others have also observed retrieval impairments associated with acute and chronic marijuana use (34,36).

The impairments associated with heavy, chronic marijuana use in our previous study (11) were much less pervasive than the immediate effects of marijuana smoking on the same tests in the present study. Only two tests showed overall impairments associated with heavy, chronic marijuana use, whereas all but two tests showed impairments immediately after marijuana smoking. Concept Formation was one of the tests that showed no acute effects of marijuana smoking. This test also stood out in our study of chronic marijuana use, as use of "intermediate" frequency (five to six times weekly) was associated with superior performance in one test condition (fuzzy concepts), the only suggestion of superior performance in any test associated with any frequency of marijuana use.

To judge the similarity between marijuana's acute and chronic effects, a "profile" of its acute effects was obtained by calculating for each test the percentage by which performance was changed following smoking of marijuana relative to placebo using the dependent variable of primary interest for each test, that is, the one listed first in Table 1. This comparison indicated reasonable, albeit imperfect, agreement between acute and chronic effects of marijuana. The two tests that showed overall impairments associated with heavy, chronic marijuana use, Correctness and Appropriateness of Expression and Ability to Do Quantitative Thinking, ranked first and fourth among the tests, respectively, in percentages of change attributable to marijuana's acute effects. On the other hand, the tests ranking second and third with respect to marijuana's acute effects—Ability to Interpret Literary Materials and Text Learning, respectively—showed no effects of chronic marijuana use. The profile of acute effects would be altered by considering additional dependent variables in some tests, for example, in Critical Flicker Fusion the threshold showed a smaller acute effect than the number of trials. Conceivably, the profile might also depend upon dose, which we did not vary; we assumed that dose would influence the magnitude of effects much more than their profile.

Although marijuana smoking impaired performance in most tests, holding the smoke in the lungs for a long time did not substantially increase these impairments. A drug × breath interaction occurred only for Correctness and Appropriateness of Expression, and even for this test the results were equivocal. In two tests, greater marijuana effects when the breath-holding duration was long than short appeared under some conditions but not others, that is, for three of eight associative types in Paired Associate Learning and two of four reading times in Text Learning. While these influences of breath-holding duration on marijuana's effects were intriguing, their dependence upon test conditions mandates caution in interpretation, that is, they could be Type I errors and should be considered tentative until future verification. Although our subjects smoked substantially more marijuana than those in prior studies that examined whether prolonged breath holding influenced the drug's effects on test performance (62,63), the results of our tests were compatible with the conclusions of these studies, that is, the few hints of possible influences of prolonged breath holding were insufficient to conclude that it increased the effective dose of Δ^9-THC.

However, Tashkin et al. (57) measured serum Δ^9-THC concentrations directly and found that they increased more following marijuana smoking with the longer of two breath-holding durations studied, suggesting that marijuana users may not be completely misguided in advocating prolonged breath holding. Marijuana users advocate this smoking technique to produce stronger subjective effects. Conceivably, prolonged breath holding may increase marijuana's subjective effects more than its effects on test performance. Tashkin et al. did not assess test performance, but found a marginally significant effect of prolonged breath holding on subjects' "high" feeling. In subjects described in the present report and some additional ones, we found that marijuana's subjective effects were somewhat more sensitive than its effects on test performance to influences of prolonged breath holding, although not dramatically so. Subjective effects will be described in a separate report because the data were extensive and the results were complex.

The present study lacked some features that would have helped clarify the influence of prolonged breath holding, primarily because this influence was not a focus of the original study design but was addressed after four subjects experienced adverse reactions following smoking with a long breath-holding duration. These features included: manipulation of breath-holding duration within subjects; quantitation of serum Δ^9-THC concentrations; measurement of smoke exposure, for example, alveolar carbon monoxide (CO) levels; assessment of physiological effects, for example, changes in heart rate; and measurement or control of additional parameters of smoking topography, for example, puff volume. Our manipulation of breath-holding duration did not separate inhaling from breath holding, as do some paced smoking procedures (17,18), and was much less controlled than other techniques for administering marijuana smoke, for example, syringe methods (62,63). On the other hand, it may have been somewhat more naturalistic.

The most intriguing and unexpected finding of the study was that performance in several tests was affected by a long breath-holding duration compared to a short one regardless of whether subjects smoked marijuana or placebo. A long breath-holding duration altered associative processes, slowed sustained reaction speed, and impaired memory for words (Buschke's Test) and pairs of words (Paired Associate Learning). It seems unlikely that these results were due to differences in intellectual abilities between subjects who smoked with long and short breath-holding durations, as the most pertinent information available, subjects' scores during the fourth grade on the Iowa Tests of Basic Skills, showed no such differences. Nor did subjects who smoked with long and short breath-holding durations differ significantly in the number of puffs during smoking, their means being 15.2 ± 0.2 and 15.5 ± 0.2 puffs, respectively.

Both physiological and psychological explanations of the effects of prolonged breath holding are possible. Physiologically, prolonged breath holding produces greater exposure to CO in smoke, as demonstrated by measures of expired air CO (63,64) and blood carboxyhemoglobin (COHb) (57), which is produced by combination of CO with hemoglobin. Increased blood COHb concentrations may produce behavioral changes, presumably due to CNS hypoxia. But, the plausibility of explaining the effects of prolonged breath holding in this way hinges on whether the COHb concentrations attained in our study were large enough to produce behavioral changes.

Although we did not measure COHb concentrations, they can be estimated from prior reports based upon number of puffs during smoking, with conversion, when necessary, of measurements of alveolar CO levels to COHb concentrations (32), with which they correspond reasonably well (27). Data from three studies (17,57,63) yielded estimated COHb increases over baseline concentrations from 3.7–6.1% for our subjects who smoked with a long breath-holding duration. These estimates are probably conservative because in these studies, unlike ours, subjects were not required to smoke their cigarettes as completely as possible, which may have resulted in lower CO delivery per puff (44,58). Moreover, in the two studies that included a placebo (17,63) no differences between marijuana and placebo in CO levels were observed, whereas placebo sometimes has produced greater CO levels or yields than marijuana that has a higher Δ^9-THC content (18–20,46).

Small increases in COHb concentrations, comparable to those probably experienced by our subjects, have been reported to impair test performance in numerous studies of CO effects on visual perception, critical flicker fusion, time perception, reaction time, vigilance, and tracking [(4,5,21,23, 41,49); for review, see (6) and (50), pp. 75–88]. Although this work did not utilize the tests that showed effects of prolonged breath holding in our study, the effects that we observed could have been mediated by effects on capabilities reported to be impaired by small increases in COHb concentrations, including visual perception (4) and visual reaction time (41). Although our tests required up to about 1.5 h after smoking to complete, COHb concentrations should have remained substantial for this period (17,22,51,64). The major objection to the speculation that elevated COHb concentrations produced the effects of prolonged breath holding in our study is that the behavioral effects of exposure to low CO concentrations are controversial. While many studies have reported such effects, more have been unable to replicate these reports or observe impairments in other tests from exposure to low CO concentrations or even substantially higher concentrations (7,35,53,60). While many authors seem willing to accept that impairments occur at COHb concentrations of 3% and above [(50), p. 77], others believe that impairments are absent, suspect, or small at COHb concentrations below 5% (52) or even 20% (6). The plausibility of explaining effects of prolonged breath holding in our study by elevated COHb concentrations depends upon which view is correct. This cannot presently be determined with confidence.

Psychological explanations of the effects of prolonged breath holding in our study are also possible. The long breath-holding duration in our study was comparable to that spontaneously practiced by many marijuana users, with average combined inhalation and breath-holding periods of 13–18 s observed in several studies (38,39,56,61). Consequently, subjects may have expected greater marijuana effects with the long than the short breath-holding duration. These expectations may have produced greater effects, both with marijuana and placebo. Using an even longer breath-holding period of 30–40 s, Jones (28) observed substantial effects from smoking placebo, which he viewed as nonpharmacological responses attributable to subjects' attitudes and expectations following smoking of materials with the characteristic taste and smell of marijuana. This interpretation was supported by evidence that frequent marijuana users showed greater placebo effects than infrequent marijuana users from smoking but not from orally administered placebo marijuana extract. Analogously, subjects' expectations about the optimal duration of breath holding may have contributed to nonpharmacological changes in test performance associated with the long relative to the short breath-holding duration in our study. Such an explanation might have been more convincing if each subject experienced both breath-holding durations and if the effects of prolonged breath holding involved subjectively reported responses, as did the placebo effects observed by Jones (28). However, such an explanation is not precluded by the facts that each subject experienced only one breath-holding duration and that the effects involved objective changes in test performance. Effects of expectations are not restricted to subjectively reported responses. Kirsch and Weixel (29) found that subjects' expectations about effects of a drug (caffeinated coffee) on psychomotor performance correlated with changes in performance produced by a placebo (decaffeinated coffee). Moreover, manipulating subjects' expectations by telling some that they would receive the active drug and others that they might receive either the active drug or placebo affected physiological responses to the placebo. Studying effects of passive exposure to tobacco smoke, Urch et al. (59) found that physiological responses were at least slightly augmented by suggestibility.

Changes in performance with the long relative to the short breath-holding duration were observed in some tests, but not others, and this specificity seems inconsistent with an explanation solely in terms of expectations. It seems unlikely that subjects would expect prolonged breath holding to have such specific effects.

It is possible, of course, that both CO and expectations contributed to the changes in test performance observed with the long relative to the short breath-holding duration. Whatever the explanation of these findings, they have implications for everyday marijuana use and laboratory research concerning marijuana. Although similar to the spontaneous practices of many marijuana users, the long breath-holding duration in our study was shorter than the combined durations of inhalation and breath holding practiced by some users (46) or required by paced smoking procedures followed in some experimental studies of marijuana's effects, for example, 25–40 s in studies of Barnett et al. (3) and Jones (28). This suggests that some of the effects of marijuana observed both on the street and in the laboratory may be attributable not only to Δ^9-THC but to other physiological or psychological factors, or both.

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