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Marijuana: Dose Effects on Pulse Rate, Subjective Estimates of Intoxication, Free Recall and Recognition Memory[1]

LOREN L. MILLER AND TERESA L. CORNETT

VA Hospital, Cooper Drive Division, Lexington KY 40507
and
Department of Psychiatry, University of Kentucky Medical Center, Lexington KY 40506

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MILLER, L. L. AND T. L. CORNETT. *Marijuna: Dose effects on pulse rate, subjective estimates of intoxication, free recall and recognition memory.* PHARMAC. BIOCHEM. BEHAV. 9(5) 573–577, 1978.—The effect of marijuana on memory as measured by free recall and recognition, pulse rate and self ratings of intoxication was evaluated in 16 male volunteers. Marijuana containing 0, 5, 10 or 15 mg Δ^9-THC was administered to all subjects by smoking in 4 sessions separated by a 1 week interval. Free recall was reduced in a dose related manner by the drug, but recognition memory was unaffected. A 2 sec word presentation rate produced inferior recall in comparison to a 4 sec rate, but this variable did not interact with drug condition. Intrusion errors increased following intoxication but this effect was not systematically related to dosage of Δ^9-THC. Both pulse rate and self ratings of intoxication increased with dosage.

Marijuana Free recall Recognition Pulse rate Self ratings Intrusions

THE EFFECTS of the cannabinoids on physiological, cognitive and subjective states have been reported to vary with the amount of tetrahydrocannabinols in the drug preparation [33]. Both smoked marijuana and orally administered Δ^9-THC produce a change in a number of physiological parameters especially pulse rate which increases directly with dosage of THC [2, 9, 14, 15, 20]. Subjective measures of intoxication which are usually measured on a potency scale of 0–100, by the Subjective Drug Effects Questionnaire [18], Addiction Research Center Inventory [13] or Cornell Medical Index have been reported also to increase with dosage of THC [2, 14, 15, 16, 20, 25, 32].

While dose response effects of marijuana on pulse rate and subjective effects have been adequately described, data concerning the effects of marijuana on behavior as a function of dosage of THC is not only less available, but less reliable. A perusal of the behavioral literature suggests that a lack of agreement exists concerning the effects of cannabinoids on a variety of behavioral measures. Factors which contribute to the discordance are individual subject variability, use of unreliable and insensitive measures, and the employment of gross performance measures which minimize the possibility that a specific locus of drug action will be found [2,22].

One of the more consistently reported effects of marijuana is to produce an impairment in various aspects of verbal memory [22,29]. Verbal memory as measured by free recall of word lists and prose has been found to be particularly affected by both smoked marijuana and orally administered THC [1, 6, 7, 8, 10, 23, 24, 26, 27, 28]. The free recall paradigm is highly refined, reliable and has strong theoretical underpinnings. For these reasons it would be important to obtain dose response data for this task.

The effect of marijuana on recognition memory, unlike free recall, has produced mixed findings. Darley *et al.* [7] reported that % correct on a delayed recognition test declined following intoxication. Other investigators have analyzed the effect of the drug on recognition memory employing parameters derived from signal detection theory [12]. This theory assumes that recognition memory can be assessed only by taking response bias into account. A recognition memory test involves responding to old and new items with a yes or no response. "Hit" rates can be artifically inflated if a subject simply responds yes to all items. In contrast, a subject could be very conservative and respond no to most items thereby keeping his "false alarm" rate low. Signal detection theory provides the parameter d' which is an unbiased indicator of memory strength and, β which represents a measure of response bias. Two studies have reported that the sensitivity parameter d' was reduced by smoked marijuana and oral THC in a recognition memory paradigm [1,34], while 3 studies have reported little or no effect [10, 25, 27]. Since dosage variables may have played a role in the discordant findings, dosage of THC contained in marijuana was varied in the present study to determine whether changes in memory strength as measured by d' would occur for recognition memory following a test for free recall.

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METHOD

Subjects

Sixteen male volunteers between the ages of 21–28 served as subjects in the study. All were considered moderate users of marijuana (2–4 times per week). Prior to the study, all subjects were screened for mental and physical health employing a brief interview, MMPI, a physical examination and a series of laboratory tests including a liver function test, urinalysis and electrocardiogram. All subjects were paid for participating. The volunteers were randomly drawn from a pool of approximately 80 subjects who had previously undergone screening prior to participating in the research project. This pool was repeatedly sampled from on a random basis for a number of studies. In the present study, each subject had served in 1 to 4 previous studies concerning the effects of marijuana on time perception, memory and/or problem solving. All had prior experience with the free recall task.

Drug Administration

Marijuana cigarettes supplied by the National Institute on Drug Abuse were employed as smoking materials. In each of 4 sessions, subjects smoked a single marijuana (M) cigarette containing 5, 10 or 15 mg Δ^9-THC or a placebo (P) cigarette from which all THC had been exhausted. All sessions were separated by a 1 week interval. Subjects were run in groups of 4 with each subject receiving 1 of the 4 doses. They were allowed to smoke in any manner they desired but were instructed to finish as much of the butt as possible. Smoking lasted about 10 min with all testing being completed in a quiet comfortable room.

Pulse rate measures were taken before smoking, 15, 50, and 90 min following smoking with the last measure occurring at the termination of testing. At the end of testing each subject rated the intensity of his high (potency) and its pleasantness on a 0–100 point scale.

Design and Procedures

The design was counterbalanced with 4 subjects being assigned to each of 4 possible orders of dosage. In any session all doses were represented. On arrival in the laboratory, subjects were randomly assigned to a dosage conditon. In successive sessions, the dosage was changed so that each subject was eventually run under all treatment conditions. Subjects were initially given a 10 min rest period and then provided with instructions regarding the task they were to perform. Smoking was then initiated. Following smoking, subjects were presented with eight 40 item word lists. The words were typed individually on clear 2×2 inch slides. Four lists were presented at a 2 sec rate and 4 at a 4 sec rate. New lists were used in each session and both lists and presentation rate were counterbalanced as equally as possible across sessions. Following presentation of each list, an *immediate free recall* test was administered during which subjects were required to write down all the words they could remember in any order. Subjects were allowed 2 min to recall each list. Following the recall interval a new list was immediately presented. The total time for list presentation and recall for the immediate free recall test was approximately 32–35 min. Fifteen min following completion of the immediate free recall tests, *a delayed recall* test was administered. Five min was allowed for delayed recall. Following the completion of the delayed test, a *delayed recognition* test was administered. Subjects were presented with a list of 192 words. From each list of 40 words 16 were chosen with 2 being drawn from each successive 1/8 of a list. Sixty-four "lures" or new items were also chosen. Subjects' task was to circle those words they had seen before. All words for both recall and recognition tests were chosen from Thorndike-Lorge [31] norms. Lists were equated in terms of frequency of occurrence of individual words in the English language.

RESULTS

Pulse Rate

Pulse rate varied significantly following intoxication with M in comparison to P, $F(3,45)=10.56$, $p<0.0001$. These results are presented in Fig. 1. Pulse rate increased directly and remained more elevated during the 90 min testing period as the dosage of THC contained in the marijuana increased. All 3 marijuana doses were still active at 90 min. The maximum change in pulse rate occurred with the 15 mg dose with a mean increase to 108 BPM 15 min following smoking. This represented an increase of approximately 30 BPM over P levels. The mean pulse rate values collapsed over 4 time measurements including P were 78, 84, 87 and 91 BPM respectively for each of the doses.

Potency and Pleasantness Ratings

Following M smoking, potency ratings increased significantly, $F(3,45)=22.67$, $p<0.0001$ as did pleasantness ratings, $F(3,45)=15.93$, $p<0.0001$. These ratings are presented in

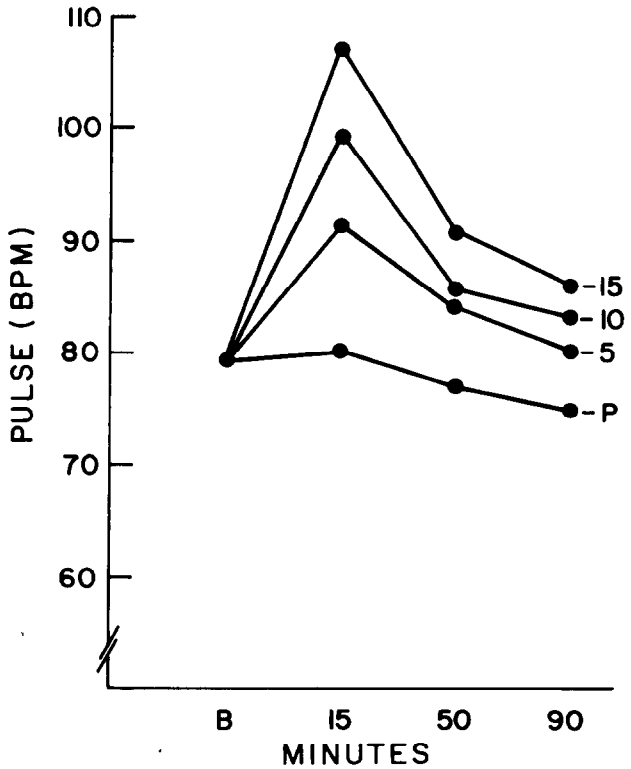

FIG. 1. Mean pulse rate changes over time as a function of dosage of Δ^9-THC contained in marijuana. P=placebo; B=baseline.

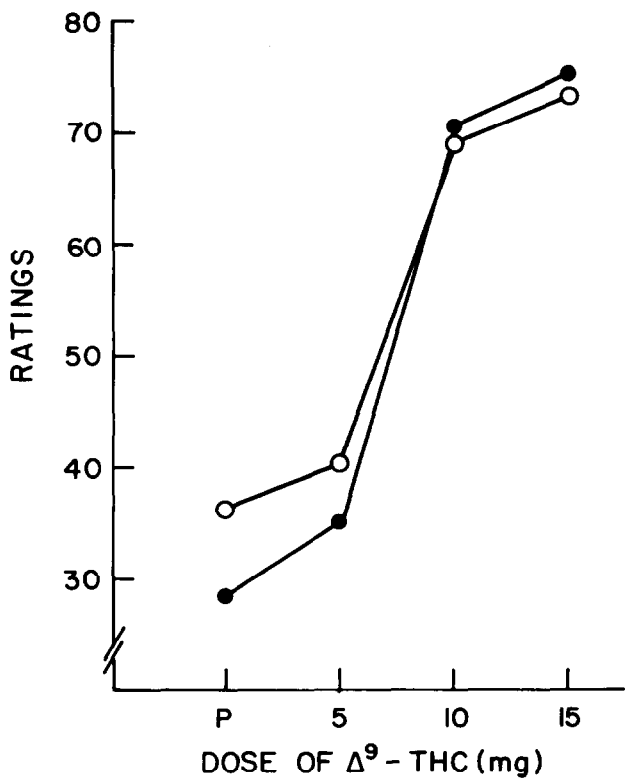

FIG. 2. Mean potency (open circles) and pleasantness (closed circles) ratings as a function of dosage of Δ^9-THC contained in marijuana. P=placebo.

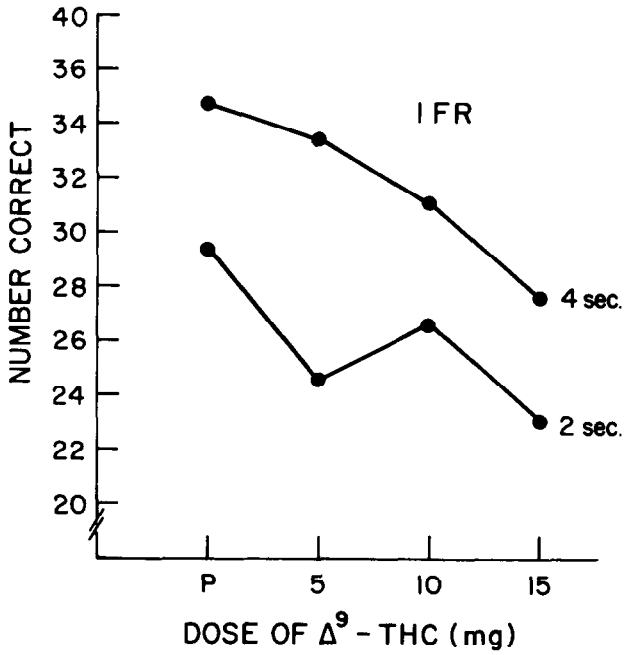

FIG. 3. Mean number of words correctly recalled on the immediate free recall test (IFR) as a function of dosage of Δ^9-THC contained in marijuana and presentation rate. Each closed circle represents mean recall for four word lists. P=placebo.

Fig. 2. It can be seen that the increase in both ratings is dose related with the biggest jump in both occurring between the 5 and 10 mg doses. Newman-Keuls multiple comparison tests indicated that significant differences existed between the P and 5 mg doses, $p<0.05$, the 5 and 10 mg doses $p<0.001$, and 10 and 15 mg. doses $p<0.05$ for both ratings.

Free Recall

The number of words correctly recalled was reduced following M intoxication, $F(3,45)=2.68$, $p<0.006$ and this effect was dose related. The rate at which words were presented also affected recall with the 2 sec presentation rate producing inferior recall in comparison to the 4 sec rate $F(1,15)=19.59$, $p<0.0007$. The interaction of these two variables was not significant. These results are presented in Fig. 3. Newman-Keuls multiple comparison tests performed on the combined means for the 2 and 4 sec presentation times indicated that both the 5 and 10 mg doses differed significantly from P, $p<0.05$, but not from each other in terms of number of words recalled. The 15 mg dose produced significantly inferior recall in comparison to P, $p<0.01$ and the 5 and 10 mg doses, $p<0.05$.

The delayed recall test data are displayed in Fig. 4. The free recall deficit was again evident following intoxication and was dose related, $F(3,45)=4.43$, $p<0.008$. Recall also remained superior if words were originally presented at a 4 sec rather than 2 sec rate of presentation, $F(1,15)=18.27$, $p<0.0009$. Newman-Keuls multiple comparison tests indicated that the 5 mg dose did not differ significantly from P. However, the 10 and 15 mg doses differed significantly from P and the 5 mg dose, $p<0.01$. No other comparisons were significant.

Intrusions

Intrusion errors which consisted of extra list words introduced on the recall test were elevated significantly following intoxication with M, $F(3,45)=4.34$, $p<0.009$, but did not increase directly with dosage. The number of intrusion errors did not differ significantly for the two presentation rates although intrusions were slightly higher for the 2 sec rate of presentation. The mean number of intrusion errors made were 1.78, 4.06, 3.09 and 3.97 per word list for each of the 4 dosage conditions respectively.

Recognition Memory

Recognition memory was analyzed by calculating the hit rates (correctly identifying an item as being seen before) and false alarm rates (incorrectly identifying a distractor item as being seen before) for each dosage condition. The total number of both of these types of errors did not differ for any of the dosage conditions.

Two measures derived from signal detection theory [12] were calculated, "d" an unbiased indicator of memory strength and β, a measure of response bias. Analysis of variance performed on both of these measures indicated that no significant changes in either measure occurred as a result of drug treatment.

DISCUSSION

Pulse rate, subjective estimates of intoxication and immediate and delayed free recall were all found to vary systematically with dosage of Δ^9-THC contained in M. Intrusion

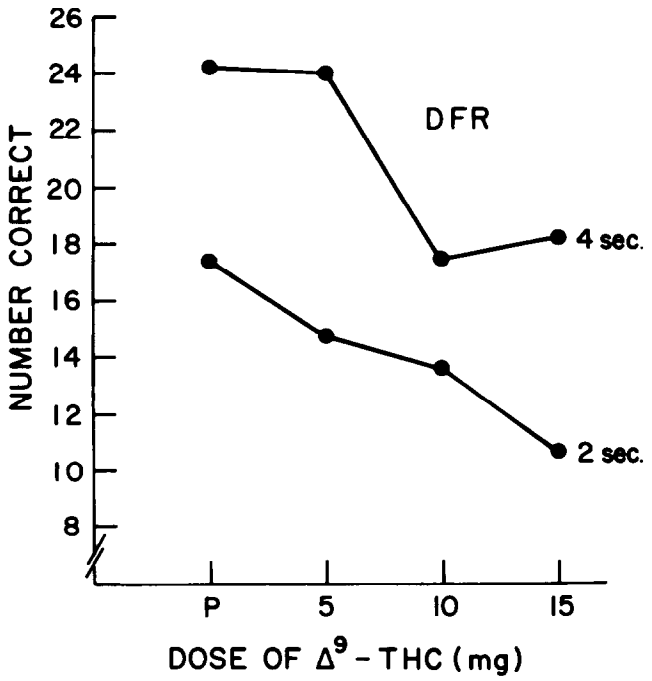

FIG. 4. Mean number of words correctly recalled on the delayed free recall test (DRF) as a function of dosage of Δ^9-THC contained in marijuana and presentation rate. P=placebo.

errors increased following intoxication but not directly with dose while the distribution of hit and false alarm rates in a recognition task were unaffected by M at any drug dose.

The dose related effects of M on pulse rate and subjective indices of intoxication supports previous findings [2, 9, 14, 15, 16, 20, 25, 32]. It should be noted that these dose related effects were found with an ad lib smoking procedure in which no instructions were given with regard to number of puffs to be taken or length of inspiration. Thus, it is suggested that a constrained smoking procedure is not a prerequisite for obtaining orderly dose response curves for behavioral as well as physiological measures providing the same subjects are run under repeated treatments.

The reduction in free recall following M intoxication confirms the results of a number of studies conducted in our laboratory [23, 24, 26, 27, 28] as well as the findings of other investigators [1, 6, 7, 8, 10]. However, it is unlikely that the effect of the drug on memory is nonspecific or due to some change in volitional control of attention or level of intoxication as suggested previously [21]. All subjects were experienced research participants and all appeared to be highly motivated to perform. Although other studies have indicated that the subjective feelings induced by M can be influenced by motivational variables, expectancy, setting or previous experience with the drug [3,4], there is at least 1 study which indicates that M induced deficits in memory as measured by free recall are not reversed by altering motivational state [3]. The consistency with which free recall deficits occur following intoxication with M even in well practiced participants suggests that this effect is centrally mediated. While a specific locus of action of marijuana on neural substrates has not been elucidated, it has been suggested that subcortical areas especially in limbic system may in part mediate the effect of M on both memory and mood [11,21].

The finding that M reduced immediate and delayed free recall while not affecting recognition memory indicates that information was stored under drug but not effectively retrieved. However, other findings suggest that viewing the effects of M in terms of a simple storage—retrieval dichotomy may be tenuous. Marijuana appears to act on memory processes in a varied manner. It definitely impairs the formation of a memory trace as measured by immediate and delayed free recall tasks. However, information which is encoded under the drug can be retained although it appears to be in a state of flux if consistency of recall is employed as a criterion of adequate remembering [26]. Repetition allows learning to occur under the drug state [27], but the employment of retrieval cues does not eliminate recall deficits [23,24]. However, presenting items in a recognition task does provide access to information [25,27]. Recall of pictures appears to be more affected than recall of words under drug [28], and memory for complex learning material such as prose which may require sequential organization is particularly affected [24]. Intrusion errors are consistently elevated in free recall tasks under M but are not highly correlated with total recall [27]. These findings suggest that marijuana not only affects amount of information that is incorporated into memory but may act mainly on processes by which information is encoded into memory.

A memory trace can be considered to be a record of encoding operations performed on input. The function of these operations is to analyze and specify the attributes of to-be-remembered items. Memory performance depends on the elaborateness of the final encoding process. That is, how many and what type of operations are performed on stimulus input. This conception can be likened to the levels of processing approach proposed by Craik and Lockhart [5]. They hypothesize that differences in initial levels of processing of to-be-remembered material result in different memory codes. Stimuli processed on a superficial sensory level give rise to transient memory traces while stimuli which are analyzed and enriched by associations or imagery yield a deeper encoding of a given event. Thus, marijuana may affect the encoding process by interfering with attention [8], rehearsal [1] or by acting on any number of as yet unspecified operations. This results in poor retrieval from episodic memory because of improper or inadequate encoding. On the other hand, recognition involves the representation of the original stimulus which provides more information from which the initial encoding can be reconstructed. For this reason, it may be difficult to disrupt recognition memory with drugs generally unless very high doses are employed or the recognition test is made very difficult.

Intrusion errors were elevated in the intoxicated state but this effect appeared to be nonspecific. An equivalent increase occurred under all doses. This finding along with data from a previous study which indicated that intrusion errors were not correlated with total recall [27] suggests that these errors may not be systematically related to the memory process and may constitute a factor which appears to be independent of recall.

In conclusion, the actions of M on memory might be best described in terms of retrieval deficit from episodic memory which is due to impaired encoding operations involving semantic and cognitive integration.

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