Effect of Oral Administration of Δ^9 Tetrahydrocannabinol on Memory, Speech, and Perception of Thermal Stimulation: Results With Four Normal Human Volunteer Subjects. Preliminary Report

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SEVERAL GROUPS OF WORKERS have recently demonstrated that marihuana has a deleterious effect on memory.[1] Weil and Zinberg[2] postulated that marihuana may affect speech by interfering with retrieval of information from immediate memory storage in the brain. Employing subjective rating scales, the judges in their experiment could readily distinguish transcripts of speech produced under the influence of marihuana from control transcripts. However, no quantitative correlate of these reliable clinical judgments could be detected in the transcripts themselves. Abel[3] has studied the effect of marihuana on memory quantitatively using measures derived from signal-detection theory. He demonstrated that marihuana did not affect retrieval of information in memory when the method of free recall was used, but did affect recognition processes such that subjects were less able to discriminate between items that had been presented previously and items that had not appeared a short time before. In these studies, however, marihuana was administered by the smoking of marihuana cigarettes of undetermined tetrahydrocannabinol content, and subjective self-rating by the volunteers was relied upon to determine the magnitude of drug effect. In addition, no studies of speech were incorporated in this work.

Marihuana has also been described as an analgesic, both anecdotally in man and with quantitative animal studies.[4] No quantitative measures of the analgesic potency of the agent in man have been reported.

We now report quantitative measures of speech, memory, and thermal perception made simultaneously in the same subjects functioning under the influence of a fixed, orally administered dose of pure Δ^9 tetrahydrocannabinol.

EXPERIMENTAL PROCEDURE

Capsules containing 5 mg of pure Δ^9 tetrahydrocannabinol dissolved in sesame oil and matching placebo capsules were obtained from the National Institute of Mental Health. Male volunteers between the ages of 25 and 29 were recruited from the

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resident staff of the New York State Psychiatric Institute. Residents were excused from their day's duties by the director of the institute if they wished to participate in the study. Since volunteers were members of the residency program, they had recently been screened for gross psychopathology (at the time of their residency interviews). Volunteers were examined physically by a qualified internist shortly before participation and were screened with a battery of hematological tests, blood chemistries, and urinalysis. All volunteers were in excellent physical condition and showed no laboratory abnormalities. The four subjects, hereinafter referred to as subjects A, B, C, and D, weighed 165, 165, 148, and 215 lb., respectively.

The experiments were carried out in a neutral setting. This was a guest apartment conservatively decorated in Early American style, usually used by the psychiatric institute to house visiting scientists. It was loaned to our group temporarily for the purpose of the marihuana experimentation. All equipment was moved to this apartment, and the subjects were not relocated at any time throughout the duration of the experiment.

Subjects did not eat after midnight on the day prior to the study and received no food on the day of the study until after the second round of testing was completed. Upon arrival at the apartment, the subjects were interviewed so as to obtain a mental status covering the symptoms listed in the drug-study data sheet described by Malitz et al.,[5] slightly modified to include additional signs and symptoms such as conjunctival injection and giddiness. This mental status interview was repeated frequently throughout the day of the experiment. Pulse rates were also monitored frequently throughout the experiment.

After the initial evaluation, the subjects were administered placebo with a small amount of water and were observed clinically and interviewed for about 30 min. They then underwent a complete round of testing (described in detail below) interspersed with clinical observations and interviewing. At the completion of the first round of testing, the subjects were given 15 mg of Δ^9 tetrahydrocannabinol with a small amount of water. With administration of both placebo and active drug, the subjects were told that they were being given a certain amount of Δ^9 tetrahydrocannabinol but that we (the experimenters) were double-blind and did not know how much they were getting.

Subjects A, B, and D had an abrupt onset of drug effect $1\frac{1}{2}$ hr after administration of the dose. Subject C also had an abrupt onset of effect 1 hr after dose. The subjects noted no effect prior to this. Except for subject A, who began the second round of tests slightly prior to onset of drug effect, all subjects began the second round of tests immediately upon noting the subjective effects of the drug.

Upon completion of the second round of testing, the subjects had lunch and rested. The third round of tests began about $1\frac{1}{2}$ hr after completion of the second round, by which time the subjective sensations associated with the drug had largely passed or abated.

The testing situation included the following:

Psycholinguistic Studies. At each of the three rounds, the subject was seated comfortably in a small room with a microphone suspended 12 in. in front of his mouth. After instructions to speak extemporaneously for 5 min on any topic or topics of his own choosing, he was left alone in the room to speak, with the absence of any social context. An Ampex AG-500 tape recorder was located outside the room. Analog-to-digital conversion and analysis of each 5-min speech sample on PDP 8/I and PDP-12

computers[6,9] yielded the frequencies and mean durations of three parameters of speech rate: (1) phrases, (2) pauses, and (3) vowels.

There is strong evidence for the existence of grammatical phrase structure in short-term memory during both production and understanding of speech. Our prior work has shown that silences > 200 msec segment the speech stream such that the average phrase duration is estimated.* Silences > 200 msec are defined as pauses. They tend to occur at the syntactic boundaries of phrases and may be the occasion for taking a breath prior to resumption of speech. Silences < 200 msec occur, by the above definition, within phrases.** They are associated with consonants and are not usually perceived as discontinuities by the naive listener. These low-energy consonant signals alternate with relatively high energy vowel signals, and the resultant cycle is highly correlated with the syllabic microstructure of phrases. Variation in syllable duration is mainly referable to the duration of its high-energy vowel nucleus.[9] Thus careful examination of the energy envelope of the speech signal permits the automated computation of three important phonetic decision units in speech: (1) the decision to begin speaking, i.e., to terminate a pause by beginning a phrase; (2) the decision concerning what and how much to say within any phrase, i.e., the number of syllables per phrase; and (3) the decision concerning how rapidly to execute the phrase, i.e., the syllable rate, which is mainly determined by vowel length.

Theoretically, variations in the duration of these three parameters (pause, phrase, and vowel, singly or in combination) define many possible modes for change of speech rate. Until such time as empirical dependencies are firmly established, the three parameters are treated separately. There is also evidence[7,8,10] that these parameters are differentially affected by psychoactive drugs, as well they might be, since they represent such very different types of decision units. Based on prior experiments with the hallucinogen LSD-25, we hypothesized a slowing of speech rate referable to increased mean pause duration and decreased phrase duration.[7,8] No hypothesis was made regarding vowel duration, since this is a new measure in our work.

Memory-Lag Recognition. The subjects were presented with 192 three-consonant trigrams at intervals of 3 sec on a memory drum. Forty-eight of these trigrams were repeated once, with varying numbers of other nonrepeating trigrams intervening between the first appearance of the trigram to be repeated and its repetition. A new set of 192 trigrams was used in each round of the study. The numbers of nonrepeating trigrams intervening between the repeating trigrams (referred to as lags) were 0, 1, 5, 10, 20, and 30, corresponding to time intervals of 0, 3, 15, 30, 60, and 90 sec between trigrams and their repetitions. There were eight repeats in each lag category.

The subjects were asked to respond "old" or "new" to each trigram, depending upon whether the subject believed he had or had not seen the trigram previously. Correct re-

*We prefer the term phrase to the term sentence because considerable editing of most extemporaneous speech is necessary in order to discover grammatically correct sentences. Phrase is equivalent to the vocalization or phonemic clause of our previous work.[6-8] It is a string of 2 to 10 words, averaging 5, with one primary stress, lasting 1 to 2 sec. Successive phrases may be spliced, omitting the criterion silence. Conversely, a silence greater than the criterion may break up a phrase, occurring at a syntactically impermissible point. These splicings and subdivisions cancel each other out in the estimation of mean phrase length.[6]

**The precise physical definition of these unperceived gaps is given elsewhere,[9] where the high-energy bursts are called vocalic segments and the low-energy gaps are intervocalic segments.

sponses ("old" to old) and false affirmatives ("old" to new) were utilized to obtain measures of response criterion (L_x) and recognition memory (d') according to signal-detection theory.

Pain. Radiant heat at fixed intensities of 0, 75, 150, 225, 270, and 300 mcal/sec/cm^2 was delivered sequentially in a random manner to each of six 3.5-cm-diameter patches of india ink applied symmetrically on and about the midline of the volar surface of the nonpreferred (left in all subjects) forearm between wrist and elbow. Details of this procedure are described elsewhere.[11]

RESULTS

Clinical. Clinical findings in each of the four subjects varied considerably, except in certain respects: onset of drug effect was seen rather abruptly 90 min after administration in three subjects and 60 min after administration in the fourth. Prior to this onset, no effects were observable or reported by the subject, except that a sharp rise in pulse rate was noted 5 min prior to the onset of subjective effects. After onset of drug effect, pulse rate varied but remained elevated, so that mean pulse rate during drug effect was about 50% higher than mean pulse rate during the placebo period in all subjects. Drug effect lasted approximately 5 hr from onset of effect and approximately 6 hr from time of dose. We were not able to state with precision a discrete time for end of drug effect, since the subjects continued to feel ill-defined subjective effects such as drowsiness and mild depersonalization for prolonged periods and we could not follow them clinically over this period. Pulse rate came down toward baseline only slowly in two subjects, returned abruptly toward normal in one subject $5\frac{1}{2}$ hr after dose, and remained elevated in the fourth subject at the termination of testing.

The more dramatic effects of the drug, such as visual, tactile, and temporal distortions, marked depersonalization, body-image distortion, euphoria, difficulty in concentrating, giddiness, and hilarity, were seen mainly in the first 2 hr after the onset of drug effect and were then replaced by drowsiness, mild euphoria, and milder feelings of unreality and perceptual distortion.

Subject B had a "bad trip" and experienced most of the perceptual distortions, but with dysphoria, and became anxious and paranoid and later experienced moderate depression. The spectrum of symptoms varied from subject to subject, but in these four subjects virtually all the findings described by other investigators and reviewed by Hollister[1] were seen in one subject or another. In addition to those mentioned above, there were dreamlike states, dizziness, increased verbal productivity (in a social context), mild ataxia, and uncoordination.

No changes in pupil size were observed. Blood pressure either tended to remain the same or fall slightly. No severe hypotension or orthostatic hypotension was encountered. Conjunctival injection was consistently associated with onset of drug effect. At this dose, no frank hallucinatory phenomena were encountered, although three of four subjects definitely had marked perceptual intensification and distortion. Subject B, who became paranoid, had feelings about the experiments in which he was participating (especially thermal perceptions) that were borderline delusional, and he reported that he "felt psychotic and had a thought disorder" at the time of maximum effect. Subjects A, C, and D enjoyed their experiences, but expressed regret at having to partake of them in a highly structured experimental setting rather than in a social setting. All subjects were completely recovered by the following day and reported no prolonged residual effects or "flashbacks."

Table 1. Speech-Rate Parameters for Extemporaneous Speaking Task: Mean Pause, Phrase, and Vowel Duration for Each Subject

Subject	Round	Mean Pause (sec)	Mean Phrase (sec)	Mean Vowel (sec)
A	1	0.695	1.27	0.217
	2	0.749	1.20	0.250
	3	0.627	1.44	0.247
B	1	0.522	1.58	0.243
	2	1.04	1.16	0.275
	3	0.533	1.24	0.251
C	1	1.52	1.29	0.150
	2	1.82	1.13	0.179
	3	1.27	1.14	0.193
D	1	0.438	1.82	0.177
	2	0.685	1.46	0.179
	3	0.885	1.36	0.206

Psycholinguistic. From placebo (round 1) to the height of the drug effect (round 2), a consistent pattern of change occurred in all three parameters for all four subjects. Table 1 shows that mean pause and mean vowel duration increased, whereas mean phrase length decreased. Thus speech has slowed in three ways: prolonged decision time to begin speaking (pause), fewer syllables (vowels) per phrase, and prolongation of the syllables themselves. A tendency to dissociation of the parameters was seen in the recovery period (round 3). This is best seen in Table 2, which summarizes the group mean statistics for the three parameters. In round 3, where mean pause and mean phrase duration tended to return toward baseline (which rules out explanations due simply to fatigue), the vowel duration remained elevated. A computation from the values in Table 2 confirmed that syllables per phrase returned toward baseline.

Memory. Table 3 summarizes the mean values for all four subjects for d' and L_x (recognition memory and response threshold, respectively) in the lag-recognition experiment. Means are given for overall d' and L_x for all lag periods taken together. Overall mean discrimination of old from new trigrams fell during round 2 (under maximum effect of drug) and returned to slightly better than baseline post-drug effect. Overall mean response criterion also fell and then returned exactly to baseline; that is, the drug caused the subjects to become less cautious—they reported "old" frequently. The return of parameters to baseline or better is indicative of the effect being attributable to drug rather than to fatigue.

Thermal Perception. Table 4 summarizes the mean values of d' and L_x for each of the four subjects and the overall means for all subjects for rounds 1, 2, and 3. Overall mean discrimination (d') fell in round 2 under maximum drug effect and improved somewhat in round 3, but did not return to baseline. It should be noted, however, that d' remained unchanged or continued to fall in round 3 in three of four subjects, and if it were not due to the unusual increase in discrimination seen in subject C alone in

Table 2. Overall Means for Speech-Rate Parameters

	Mean Pause (sec)			Mean Phrase (sec)			Mean Vowel (sec)		
Round	1	2	3	1	2	3	1	2	3
Mean	0.794	1.07	0.834	1.49	1.24	1.30	0.197	0.221	0.224
SD	0.496	0.521	0.324	0.262	0.151	0.132	0.041	0.049	0.029

Table 3. Recognition Memory (d') and Response Criterion (L_x) for Lag-Recognition Memory Task

Subject	Round	d'	L_x
A	1	1.69	1.01
	2	1.52	0.84
	3	1.78	0.75
B	1	1.85	2.12
	2	1.55	0.60
	3	1.35	0.91
C	1	1.14	0.76
	2	0.86	0.74
	3	1.29	0.52
D	1	1.06	0.96
	2	1.25	1.52
	3	1.28	2.69

Overall Means for All Lag Times

	d'			L_x		
Round	1	2	3	1	2	3
Mean	1.44	1.30	1.43	1.21	0.925	1.21
SD	0.394	0.320	0.239	0.615	0.409	0.995

round 3 (perhaps due to differences in metabolism of the drug), overall mean d' for all subjects would have continued to diminish in round 3.

In contrast to the relatively consistent changes seen in d', changes in the subjective criterion for reporting pain (L_x) varied from subject to subject: subjects B and C showed an increase in L_x under maximum drug effect, subject A showed a decrease, and subject D remained unchanged. Overall mean L_x for all four subjects remained essentially unchanged in all three rounds, despite great intrasubject variability. Subject

Table 4. Thermal Stimulation Discrimination (d') and Response Criterion (L_x)

Subject	Round	d'	L_x
A	1	1.07	0.64
	2	0.93	0.42
	3	0.94	0.59
B	1	1.62	0.60
	2	1.33	0.70
	3	1.22	0.94
C	1	0.83	0.97
	2	0.62	1.12
	3	1.50	0.75
D	1	1.87	0.48
	2	1.56	0.48
	3	1.14	0.90

Overall Means

	d'			L_x		
Round	1	2	3	1	2	3
Mean	1.35	1.11	1.20	0.67	0.68	0.80
SD	0.480	0.418	0.232	0.210	0.317	0.159

B set a much lower criterion under the drug condition. His reports of "pain" in response to mild, barely warm, thermal stimuli reflect his paranoid ideation—he thought he was about to be injured. The other possibility—that the drug had induced a hyperalgesia—may be discounted since the measure of sensitivity (d') did not increase.

DISCUSSION

The diminished recognition memory (d') in the lag-recognition task under the effect of Δ^9 tetrahydrocannabinol (Table 3) indicates that subjects were less able to discriminate between a previously seen item and a new item under the influence of the drug. The return toward normal after peak drug effect indicates that the observed phenomenon is not attributable to fatigue. The results indicate that the drug interferes with short-term recognition memory.

Unrehearsed extemporaneous speech was recorded immediately after completion of the lag-recognition memory task in each round. The acute drug effect on three different speech-rate parameters (Tables 1 and 2) paralleled the effect on recognition memory d' (Table 3). As postulated by Weil and Zinberg,[2] there may be some functional relationship between these parallel findings; that is, semantic coherence, keeping to the subject, maintaining a train of thought, etc., during unrehearsed speech involves the retrieval from short-term memory of one's own previous comments, along with their associates, and recognition of those items actually spoken from the multitude of peripheral thoughts. If this discrimination breaks down, new thoughts will not be distinguished from prior ones. Thus continuity may be lost and the argument may appear to wander. At the height of the drug effect, the number of phonetic decisions was markedly reduced, suggesting some difficulty in information processing during speech generation. Two of the three parameters returned toward baseline in the recovery period, along with recognition memory d'.

Table 4 shows that the overall mean discrimination of thermal stimulation decreased under the effect of the drug, and remained diminished in round 3. These results are compatible with the anecdotal and clinical reports in humans and the results in animals demonstrating that marihuana is an analgesic. It should be noted that in terms of subjective reports of the volunteers, one subject felt that the drug was an analgesic, two reported no subjective change in thermal sensitivity, and one (subject B, who became anxious and paranoid) reported markedly enhanced sensitivity to stimulation, so that considerable effort was required to get him to continue the thermal-stimulation experiment. In spite of this, signal-detection theory analysis demonstrated diminished thermal discrimination in all subjects under the effect of the drug, irrespective of the subjects' verbal reports. Moreover, the persistence of diminished thermal discrimination, even when memory, pause, and phrase measurements were returning to baseline, may indicate that the analgesic effect of the drug is more prolonged than the cognitive effect.

The time course of mean vowel duration is similar to that found for the thermal response, in that neither recovers in round 3. In contrast, the time course of change in mean pause and phrase length parallels that for recognition memory d', suggesting a more cognitive aspect of speech. These results suggest a twofold action of Δ^9 tetrahydrocannabinol with different time courses.

The very large standard deviations for the overall (group) means seen in Tables 2, 3, and 4 preclude statistical conclusions with the small group of subjects in this pilot

study. Individual differences are marked on the indices employed; however, the consistency in direction of change noted above suggests that nonparametric techniques would yield significant results without undue expansion of the subject population.[12]

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