dicative of the decay of an early memory phase and the subsequent consolidation of a memory trace (*6*). Conceiving the fish's latency as an index of memory retention, the one-trial method can be a concise technique to determine how memory itself varies over time.

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9. We thank A. Von Thun for suggesting the basic water-flow technique and R. O. Meinecke for exploratory experimentation.

21 January 1971; revised 18 March 1971 ■

Electroencephalographic and Behavioral Alterations Produced by Δ^1-Tetrahydrocannabinol

Abstract. *The administration of small doses of Δ^1-tetrahydrocannabinol to cats with indwelling electrodes produced a disruption of both the electroencephalogram and behavior. Some of these alterations, including the appearance of a high-voltage slow wave electroencephalogram in the awake and moving animal, have been observed in cats that had been administered other drugs known to cause hallucinogenic states in man.*

Several recent reports (*1–4*) have dealt with the disruptive influences exerted by active constituents of *Cannabis* on various behaviors in different species. In one of these studies, Lipparini *et al.* (*4*) showed that the disrupted discriminative behavior observed in cats after the administration of Δ^1-tetrahydrocannabinol was accompanied by an increased electroencephalographic (EEG) synchronization.

Scheckel *et al.* (*3*) pointed out that many earlier investigations with *Cannabis* showed inconsistencies due primarily to problems encountered in determining the actual amount of active ingredients in the crude extracts. In recent years, however, advances in cannabinoid chemistry (*5*) have led to the isolation of the major active component of marijuana and to the elucidation of its structure. In the present experiments, this constituent, namely Δ^1-tetrahydrocannabinol (THC), was found to alter behavior and induce a concommitant EEG disruption in the freely moving cat.

Under halothane anesthesia, stainless steel monopolar electrodes were stereotaxically placed in regions of the ventromedial hypothalamus, midbrain reticular formation, basolateral amygdala, and ventral hippocampus. Ball electrodes were placed over the dura above the coronal, suprasylvian, and lateral gyri, which are usually considered to correspond to the frontal, association, and occipital areas of the cerebral cortex, respectively. A stainless steel screw over the frontal sinus served as a reference. All electrode placements conformed to the system of coordinates developed by Snider and Niemer (*6*).

At least 1 week was allowed for recovery from the surgical procedure, following which each animal was placed in a recording cabinet (Lehigh Valley Electronics) for a 1-hour period on each of six consecutive days. After habituation to the cabinet, each cat was subjected to three daily 60-minute control sessions during which electrical activity was recorded for 100-second intervals from all placements at 5, 10, 15, 30, 45, and 60 minutes, and displayed on a model VI Grass electroencephalograph.

Each experimental session consisted of a 90-minute period, the first 30 minutes serving as an additional control. During this predrug period, electrical activity was sampled at 10, 15, 20, and 30 minutes. Then THC dissolved in 3 ml of polyethyleneglycol was administered intraperitoneally, and electrical activity was sampled at 5, 10, 30, 45, and 60 minutes after drug administration. Each of six cats received three dosages of THC, namely, 0.5, 1.0, and 4.0 mg/kg. The order of drug administration was counterbalanced, and from 4 to 7 days elapsed between doses. In an additional experimental session, each animal received 3 ml of the diluent alone. During all sessions, protocols were kept of each animal's behavior.

After having been administered the drug, all animals showed a mydriasis which persisted for as long as 2 hours after an experimental session. While we are unable to state precisely the moment of onset of this response, it was present 5 minutes after THC (at all dose levels), and the pupils of all animals were fully dilated at 30 minutes. The corneal reflex was normal.

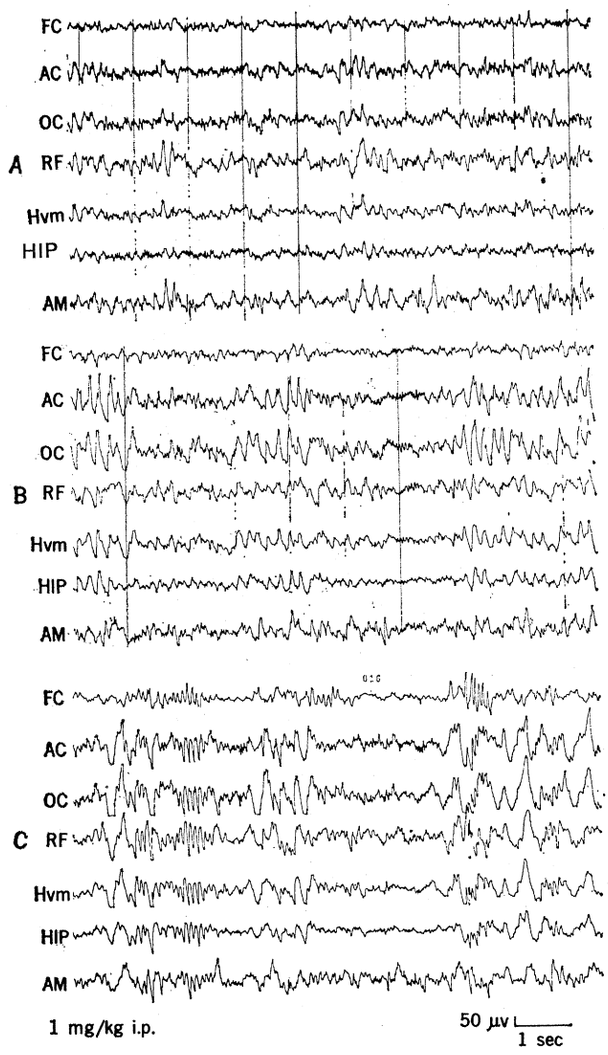
All cats displayed variable amounts of locomotor activity during control and predrug sessions, and all dosage levels of THC had a quietening effect on all animals with two exceptions: one cat spent the latter 30 minutes of a session after the 4-mg dose walking around the cabinet with occasional leaps in the air, and another animal spent most of the experimental session after the 1-mg dose walking around the enclosure. In all other sessions, the animals assumed either a standing, sitting, or prone position which they maintained throughout the experimental period. Although the tranquilizing effect of the drug made the study of motor deficits difficult, we did observe alterations in postural attitudes which included bobbing and weaving of the head, swaying from side to side, and an ataxic, broad-based gait. If an animal was placed in a standing position, it tended to retain a stance, and displayed extremely poor coordination in altering this attitude.

With all dosages of THC, the animals stared into space, and often appeared to be following stimuli with their eyes even though no moving stimulus was discernible by the experimenter. Scheckel *et al.* (*3*) assumed that similar behavior in the monkey was indicative of visual hallucinations; however, there is no evidence to support this contention.

All drug dosages produced an increase in synchrony from all electrode placements in the quiet but awake animal (only one animal slept during the latter part of an experimental session).

Lipparini and his colleagues (*4*) reported only moderate synchrony in their cats with doses of THC up to 6 mg/kg, whereas Bicher and Mechoulam (*2*) observed increased beta activity in the EEG of the rabbit following a dose of 10 mg of THC per kilogram of body weight. Since it has been suggested that rabbits are more sensitive to THC than cats are (*4*), the dosage used by Bicher and Mechoulam may be functionally much higher than those used in the present experiments. We found that the increase in synchrony usually began between 5 and 15 minutes after injection of the drug. During this period, the hypersynchronous pattern alternated with epochs of electrical activity that often resembled the sleep pattern (*7*). This is illustrated in Fig. 1. These tracings are from an animal in the prone position, and were recorded 45 minutes after the 1-mg dose of THC. The animal was very quiet and appeared to be gazing into space. On other occasions, the hypersynchronous pattern gave way to high-voltage waves of two to three per second that lasted from 5 to 100 seconds. The tracings in Fig. 2 were recorded 30 minutes after a 4-mg dose. This pattern has also been recorded from the hippocampus. Although the hippocampal lead was shorted in this animal, these tracings were chosen because the animal was sitting and appeared to be following "nonexistent" stimuli.

The high-voltage activity usually reached a peak between 30 and 45 minutes after drug administration, and an appreciable decline was observed during the 60-minute sample of activity. This was seen in five out of six animals with dosages of 0.5 and 1.0 mg of THC; however, with the larger dose (4 mg), four out of six animals did not show the decline at 60 minutes. It should be pointed out, however, that the amount of high-voltage activity observed after the 0.5- and 1-mg doses was much greater than that recorded



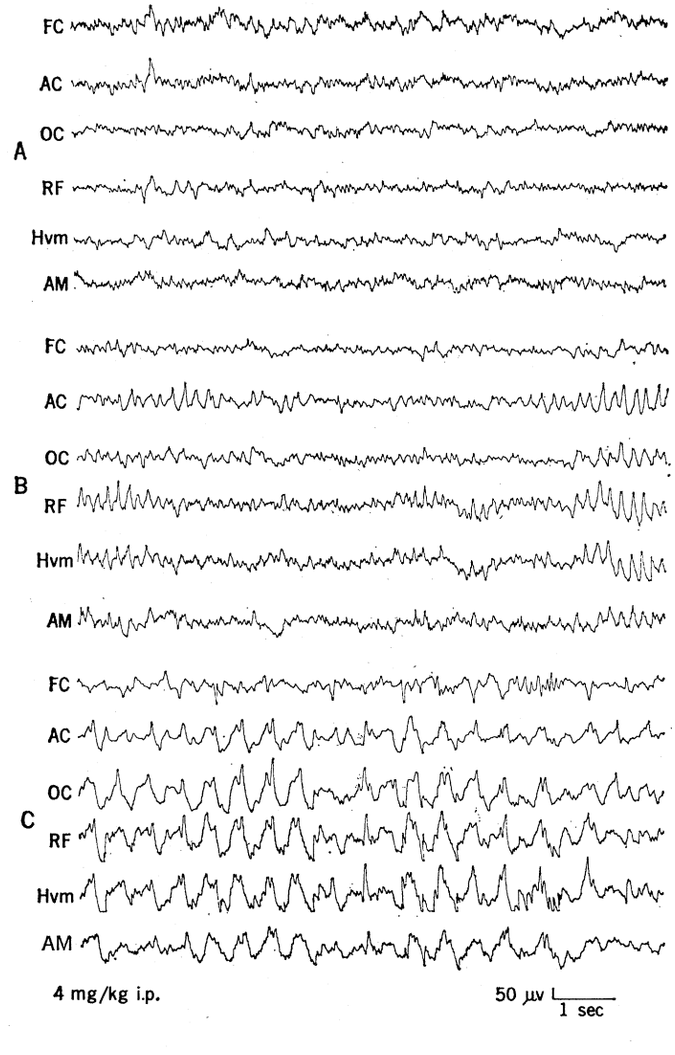


Fig. 1 (left). The predrug tracings in (A) are from an awake animal in the prone position. The increased synchrony seen in (B) occurred 10 minutes after the administration of 1 mg of Δ^1-tetrahydrocannabinol per kilogram of body weight. In (C), 45 minutes after the drug, the synchronized pattern seen in (B) alternated with one that resembled that of light sleep, although the animal was awake. *FC*, frontal cortex; *AC*, association cortex; *OC*, occipital cortex; *RF*, midbrain reticular formation; *Hvm*, ventromedial hypothalamus; *HIP*, hippocampus; and *AM*, amygdaloid complex. Fig. 2. (right). In panels (A), (B), and (C) the animal was in the "sitting position." The tracings in (A) were recorded during the predrug control session. In (B), the increase in synchrony occurred 10 minutes after administration of 4 mg of Δ^1-tetrahydrocannabinol per kilogram of body weight. And in (C), 30 minutes after the drug, a high-voltage pattern of two or three waves per second alternated with the hypersynchronous activity seen in (B). Electrode placement designations are the same as in Fig. 1.

after the 4-mg dose, as illustrated in Fig. 3. Each animal is represented by an individual line, and the plotted points at each dose level are based on the total amount of sampled time (seconds) occupied by high-voltage activity during a recording session. No significant difference ($P > .05$) was found between the slopes [$F = 1.36$ (d.f. = 5, 6)]. There was, however, a highly significant difference between cats ($P < .01$), indicating a differential sensitivity to the drug [$F = 20.1$ (d.f. = 5, 11)]. And a definite dose-response relationship is indicated by the significant effect ($P < .05$) of the average slope (in the line regression) of log time versus log THC [$t = 3.32$ (d.f. = 11)]. The fact that the high-voltage activity lasted for a longer time after the high dose than after the lower doses, yet occupied a smaller fraction of the total sampling time, suggests that this activity was being partially masked by some supervening effect at the high dose. Such a supervening effect might correspond to the increased beta activity reported by Bicher and Mechoulam (*2*), or the stimulant effects observed in the monkey by Scheckel *et al.* (*3*). Three milliliters of the diluent administered to each animal during a control session had no observable effect either on behavior or on the EEG.

All doses of THC induced both vomiting and defecation, and the animals seemed oblivious of this. In most cases they sat in their excrement, which is very unusual behavior in the cat.

It is noteworthy that among the observations that we have described, the disrupted or *dissociated* EEG pattern and the apparent following of "nonexistent stimuli" were also reported by Rougeul (*8*) following the administration of psilocybin and Ditran (JB 329), which produce hallucinogenic effects in man. Winters and Wallach (*9*) suggested that the action of various compounds could be located along a continuum of central nervous system excitation. Along this progression, hypersynchrony, with its concomitant bizarre behavior, would characterize drugs that produce hallucinations in man.

Extreme caution must always be exercised in any attempt to extrapolate results from animal experimentation to man. However, suitable doses of THC in human subjects are known to cause disturbances in perception, and dissociation and hallucinations (*10*). The present findings are thus consistent with those observed in the cat after administration of other substances known to be hallucinogenic in man. It is also of interest that, despite obvious species differences, the EEG effect in the present study was produced by a dose of THC (0.5 mg/kg) quite similar to that which was found to be hallucinogenic when smoked by humans (*10*). When the dosage is expressed in relation to surface area to permit interspecies comparisons, good agreement is found: the hallucinogenic dose in man (*10*) was equivalent to approximately 16 mg/m^2; the cataleptic dose in the mouse (*11*) was about 15 mg/m^2; and the lowest dose in the present study was 7 mg/m^2.

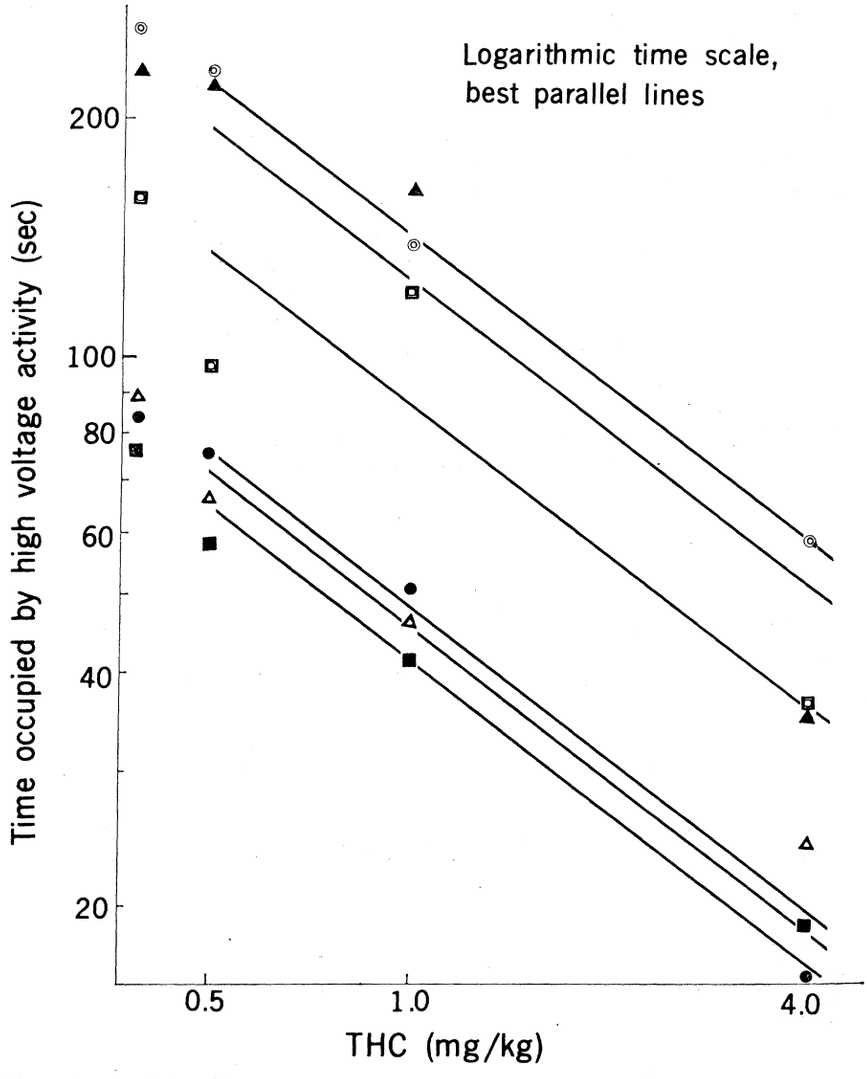


Fig. 3. Each of six animals is represented by one of the best individual parallel lines. The plotted points at each dose level correspond to the total amount of sampled time occupied by high-voltage activity during a session (recording time = 600 seconds). Symbols next to ordinate are for purposes of identification.

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2 March 1971