The neurophysiological basis of the marijuana experience

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Summary: Experiments were done with 75 healthy young adults to explore the neurophysiological basis of the acute marijuana intoxication state. Tests included recording the scalp EEG, visual and auditory cerebral evoked-potentials, the CNV, cerebral slow potentials related to certainty of response correctness in auditory discrimination tasks, heart rate, respiration and the galvanic skin response. All variables were recorded over 45 minutes before and 45 minutes after smoking a marijuana cigarette containing either 4.8, 9.1 or less than 0.01 mg. Δ^9-THC.

High doses of marijuana induced a significant decrease in the peak power of the alpha rhythm and an increase in auditory evoked-response latency. The CNV increased in amplitude after smoking marijuana in low doses and sequential CNVs showed changes consistent with sustained attention but decreased certainty about performance following either low or high dose. Marijuana interfered significantly with performance of the discrimination task itself.

Résumé: *Les fondements neurophysiologiques des expériences sur la marijuane*

Les expériences qui ont été faites sur 75 jeunes adultes en bonne santé avaient pour objet de préciser les effets neurophysiologiques de l'intoxication aiguë provoquée par la marijuane. Parmi les épreuves utilisées figuraient: l'EGC, les potentiels corticaux évoqués par les stimuli visuels et auditifs, la "variation contingente négative" (VCN) traduisant l'incertitude du sujet sur l'exactitude de sa réaction à des épreuves de discrimination auditive, le rythme cardiaque, les paramètres de la fonction respiratoire et la réaction cutanée à la galvanisation (RCG). Toutes ces variables ont été enregistrées 45 minutes avant et 45 minutes après l'inhalation de la fumée d'une cigarette de marijuane dont la teneur en principe actif était de 4.8 mg, 9.1 mg ou moins de 0.01 mg de Δ^9-THC.

Les fortes doses de marijuane ont provoqué une diminution importante dans l'intensité spectrale du rythme alpha de l'EEG et un accroissement de la latence des potentiels évoqués par les stimuli auditifs. L'inhalation des faibles doses de marijuane a augmenté l'amplitude de la VCN. Les VCN séquentielles ont permis de montrer le maintien de l'attention du sujet et son incertitude augmentée sur son accomplissement après les doses faibles aussi bien qu'après les doses fortes. Somme toute, la marijuane a troublé notablement l'accomplissement du travail de discrimination imposé.

Despite a large and growing number of published studies of the effects of cannabis derivatives in animals and man (the Le Dain Commission[1] lists 682 publications in a compilation of selected references), the nature and degree of the physiological changes responsible for and associated with the subjective state of marijuana intoxication remain unclear. The minor character of the so far objectively measured physiological changes associated with acute cannabis intoxication is in marked contrast to the sometimes profound subjective effects reported by users of cannabis-containing substances, and to the marked changes in function indicated by neuropsychological evaluation of intoxicated subjects (reported by the authors in the preceding article). Presumably because of the absence of dramatic physiological changes, there have been no comprehensive neurophysiological models, supported by experimental evidence, proposed to explain the brain mechanisms which must underlie the subjective experiential phenomena associated with cannabis intoxication. Typical of the summaries offered by various workers after analysis of their physiological data is the statement of Gale and Guenther[2] that "The results of the present experiments support the concept that cannabis serves as an anti-anxiety agent and it is the reduction in anxiety that is desired by the long-term user."

A review of the literature relevant to the physiological changes induced in man by marijuana smoking reveals the following major findings, some of which have not yet been confirmed:

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(1) Cardiovascular system

(a) A significant and dose-related increase in heart rate.
(b) A minor decrease in systolic blood pressure.
(c) Congestion and reddening of the ocular conjunctiva.

(2) Central nervous system

(a) Minor changes in the power spectrum of the electroencephalogram.
(b) Suggestive changes in auditory evoked-potential parameters.
(c) An increase in the amplitude of the contingent negative variation (CNV).
(d) Autonomic changes including decrease in salivation and decrease in basal skin resistance.

With respect to the electroencephalographic findings associated with cannabis use, most investigators have concluded that there are no significant changes observable without computer analysis during acute intoxication.[3-6] Reports of the effects of chronic use of cannabis agents on the EEG are contradictory. Williams *et al*[7] found what was described as "little significant EEG change" in their study of subchronic users of cannabis derivatives in high daily doses. The minor alterations seen in their subjects' EEGs in some cases disappeared after the drug was discontinued. Miras[8] studied long-term users of very heavy doses of hashish and found several isolated abnormal EEGs, but he had no systematic controls and had no follow-up examination to determine whether the abnormalities would disappear after discontinuing drug use.

Worthy of special mention because it is an example of the misleading type of clinical "studies" of the effects of cannabis in man is a paper by Campbell.[9] This author reports an incredibly high incidence of EEG abnormality in cannabis-using psychiatric patients and asymptomatic subjects (90 and 73%, respectively). To our knowledge there is no report anywhere in the world literature of such a high incidence of EEG abnormality associated with anything but the grossest of organic pathology. A clue to the reasons for the author's astonishing statistics may be the one illustration given as an example of "excessive theta-wave activity", apparently the most common "abnormality" encountered. The figure is not labelled with time or amplitude calibrations and the montage is not clear. The head stamp indicates a basic eight-channel montage but only six channels are shown. Much of what the author describes as theta activity appears to be artefact, and if the most obvious montage is in fact the one illustrated, this theta activity is not really bitemporal as described but appears quite asymmetrically from the right ear and the entire left frontal area. For these reasons, and because his observations regarding the EEG patterns associated with cannabis use are so grossly at variance with other reports, we do not accept Campbell's claims as established or even valid.

Tinklenberg[10] has reported findings contradictory to those of Rodin, Domino and Porzak[6] with respect to changes in auditory evoked-potential measures. Tinklenberg studied 12 college-age men, and each was given an oral dose of 0.35 mg./kg. of Δ^1-THC. Tinklenberg reports an increase in amplitude and prolonged latency of the late (approximately 200 msec.) negative and late positive components of the auditory evoked-potential after THC as compared to placebo and alcohol. The author also reports a significant increase in contingent negative variation (CNV) amplitude after THC as compared to placebo and alcohol. To date this is the only report in the literature referring to the influence of cannabis derivatives on CNV parameters. The observation has significance in that the CNV is a slowly changing brain potential which reflects the activity of brain mechanisms subserving processes of attention, motivation and preparation set.[11]

Rationale

The experiments reported here were undertaken in an attempt to define more precisely, in physiological terms, the mechanisms underlying the state of acute marijuana intoxication.

Because of the previously suggested anticholinergic effects of cannabis derivatives in observations reported by others, respiration, heart rate and galvanic skin response were recorded continuously throughout the experiments, and were used as indicators both of anticholinergic effect and autonomic tone.

The scalp EEG was also recorded continuously, primarily as an indicator of ongoing neocortical activity. Both visual and computer analyses were used to assess the EEG.

Because of the alterations in sensory perception very commonly reported during the marijuana experience and because of a conflict of reports in the literature, visual and auditory sensory evoked-potentials were recorded. Parameters of such potentials are indicators of the function of primary (classical) sensory pathways, including neocortical sensory receiving areas, and are affected by attention and subjective evaluation of the sensation.

Because of the emphasis in other literature on the learning-memory model in explaining the effects of marijuana, and because most authors proposing such models claim that the functional defects associated with cannabis intoxication are chiefly the result of diminished attention or concentration on immediate tasks, CNVs were recorded in all of our subjects. The CNV has been shown to be a very sensitive indicator of both attention and motivation.[11] It has also been shown that in auditory discrimination tasks, sequentially induced CNVs (before the discrimination and after the required response, in anticipation of a feedback signal containing information about the correctness of the response) can indicate not only the subject's immediate level of attention and interest in the task but also can reflect the effects of learning and certainty.[12] Such discrimination tasks with CNV recording were accordingly included in this study as indicators of learning, interest and certainty of response correctness.

Methods

Detailed descriptions of the over-all strategy of this investigation are given in the first paper of this series, entitled "Strategy and tactics of marijuana research." The subject population for this portion of the study included 75 unpaid volunteers, chiefly university stu-

dents and office and technical staff, whose ages ranged from 19 to 31 years. The subjects were carefully screened according to traditional psychiatric and psychological criteria and were all well adjusted and healthy. All had some casual or moderate previous experience with marijuana or hashish and none had used other psychoactive drugs within the past year. Thirty-six of the subjects were male and 39 female.

In this portion of the study 28 subjects were given placebo, 29 were given a "high" dose of drug and 18 were given a "low" dose. Marijuana and placebo were administered in cigarettes, smoked according to a timed and experimenter-supervised routine. Each "joint" (rolled by machine at U.B.C.) contained 0.7 g. plant material, assayed at least twice by Canadian Food and Drug laboratories, containing 1.3% Δ^9-THC, or 9.1 mg. per cigarette for "high dose" and 0.69% Δ^9-THC or 4.8 mg. per cigarette for "low dose". The placebo was solvent-extracted *Cannabis sativa* and assays revealed no cannabinols in 1 g. of this material. Smoking time was approximately 10 minutes. The drug was given by single-blind method and, except for the THC content of the marijuana, the experimental procedures were identical for all subjects.

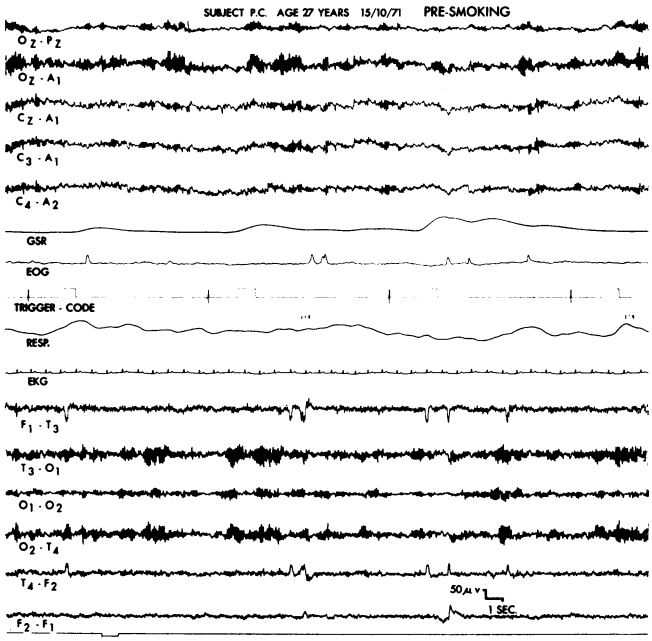

FIG. 1—Dynograph record, sample page, taken during baseline recording. The trigger code channel shows trigger pulses for computer timing, and square waves coincident with tone bursts. The calibration amplitude applies to the EEG channels only.

All electrophysiological experiments were done in the clinical investigation unit of a general hospital EEG laboratory (VGH). Throughout each experiment, continuous (except during smoking) recordings were made of scalp electroencephalogram (EEG), electrocardiogram (EKG), respiration (impedance pneumograph), galvanic skin response (GSR) and the electro-oculogram (EOG). All physiological variables were recorded continuously on paper (Fig. 1). Seven of these variables were simultaneously recorded on magnetic tape in FM mode for off-line computer analysis, including 5 EEG channels, the GSR and the EOG.

Recording was done in a shielded, sound-deadened room with the subject seated in a comfortable lounge chair and facing the translucent screen of a visual stimulus-presentation module. The subject was asked to keep his eyes open throughout the experiment and to look at a target, except during five minutes of eyes-closed EEG. Auditory stimuli were tone bursts delivered binaurally through loud-speakers hung on one wall of the recording room. Motor responses, when required, were simple button-presses using a hand-held thumb switch.

The details and order of the experimental paradigms are given in Table I. Prior to paradigm 1, approximately five minutes of resting EEG was recorded with the subjects' eyes closed. Immediately following paradigm 7 the subject was given one marijuana or placebo cigarette to smoke. As soon as smoking was finished the entire sequence was repeated. One complete sequence took approximately 40 to 45 minutes.

Data analysis

Data analysis included: visual assessment of the entire EEG record by one interpreter (MDL) according to

Table I
Electrophysiological experimental procedures

Sequence	Paradigm	Description	# Trials	Purpose
1.	S_1	Single stroboscopic light flash repeated every 4-5 secs.	64	Visual evoked response
2.	S_2	Single 1-sec. tone burst, 1000 Hz, ∞ 50 dB, repeated every 4-5 secs.	64	Auditory evoked response
3.	$S_1 \ldots S_2$	Flash followed by tone. S_1-S_2 interval 1.4 secs. Intertrial interval 2-3 secs.	32	Habituation
4.	$S_1 \ldots S_2-R$	As in 3. Subject responds to S_2 by button-press R which terminates S_2. Intertrial interval 4-6 secs.	32	CNV Measure of attention
5.	$S_1 \ldots S_{2d\Delta}$-R ... FBgb	As in 4 but S_2 (randomly) d = 1000 Hz or Δ = 1200 Hz. Subject responds to Sd by pressing right button and to S_Δ by pressing left button. Two secs. after R, a green light (good) or red light (bad) is lit. Intertrial interval 8-12 secs.	32	Auditory discrimination-feedback sequence. Measure of modality-specific memory, attention and certainty
6.	$S_1 \ldots S_{2d\Delta}$-R ... FBgb	As in 5, but $S_{2\Delta}$ = 1050 Hz.	32	Discrimination more difficult
7.	$S_1 \ldots S_{2d\Delta}$-R ... FBgb	As in 5, but $S_{2\Delta}$ = 1003 Hz.	32	Discrimination very difficult

traditional clinical EEG criteria; determination of heart rate from the Dynograph record measured during the first 20 seconds of paradigms 4, 5, 6 and 7 before and after smoking; determination of respiration rate at these same four points before and after smoking; determination of GSR reactivity as the ratio of visible changes in the GSR baseline to the number of trial sequences during paradigms 4, 5, 6 and 7; determination of the number of errors in response choice during discrimination tasks; sensory evoked-potential averaging (measurements were made from the averaged C_z-A_1 lead in all cases).

CNVs were averaged off-line from the tape-recorded C_z-A_1 EEG channel using the PDP-12 computer; during discrimination-feedback trials measurements were made of the S_1-$S_{2d\Delta}$-interval CNV area and of the post-$S_{2d\Delta}$ pre-feedback area over the 1 sec. following the end of the $S_{2d\Delta}$-evoked response. The power spectrum of ongoing EEG was derived from four 4-sec. samples of artefact-free EEGs which were selected during paradigm 2 prior to smoking and from four similar samples during paradigm 2 after smoking (all samples were from the O_z-A_1 EEG lead).

Statistical analyses (F tests with 1° of freedom) were done in the U.B.C. Computing Center, comparing mean values for each observed measure during high and low drug conditions as follows (using difference scores): placebo-drug, placebo-baseline, drug-baseline.

Results

Visual assessment of the EEG

Of the 75 baseline records obtained, only five were abnormal by clinical criteria. The abnormal records included three with paroxysmal, generalized slow and sharp activity and two with focal slow activity. This represents an abnormality rate of 6.6%, which is well within the expected range for a normal population. The focal abnormalities were both occipital-temporal in location, one left- and one right-sided.

None of the records changed significantly after smoking, except one with a right occipital-temporal slow focus which showed a very slight increase in slowing after placebo, and one with paroxysmal slow and sharp activity which improved slightly after a high dose of active marijuana.

Computer analysis of EEG

The results of the computer-derived power density spectral analysis of occipital EEG activity are summarized in Table II. Peak power (mean) was very close to 10 Hz during baseline recording and this peak point was not changed significantly by administration of placebo or either dose of drug. There was a slight tendency, however, for the peak power point to shift to the left under low-drug condition.

There was a significant decrease in power at the peak frequency (10.2 to 10.5 Hz) following high dose of the drug and a tendency, not statistically significant, to an increase in power at the peak frequency (9.8 to 10.0 Hz) following low dose.

Visual and auditory evoked-potentials

Measuring peak latency and peak-to-peak amplitude of the late negative deflection, visual evoked-response parameters were unchanged following either drug dose. The auditory evoked-response latency was slightly but significantly ($P < 0.05$) prolonged following high drug-dose (137 msecs.) as compared to placebo (119 msecs.).

Respiration

Mean respiration rate was 16.3/min. during baseline trials, 15.7/min. during placebo trials, and tended to be slightly but not significantly higher during drug trials, with means of 16.4 and 16.6/min. after low and high drug-doses respectively.

Heart rate

Fig. 2 illustrates the observed heart rate changes. Mari-

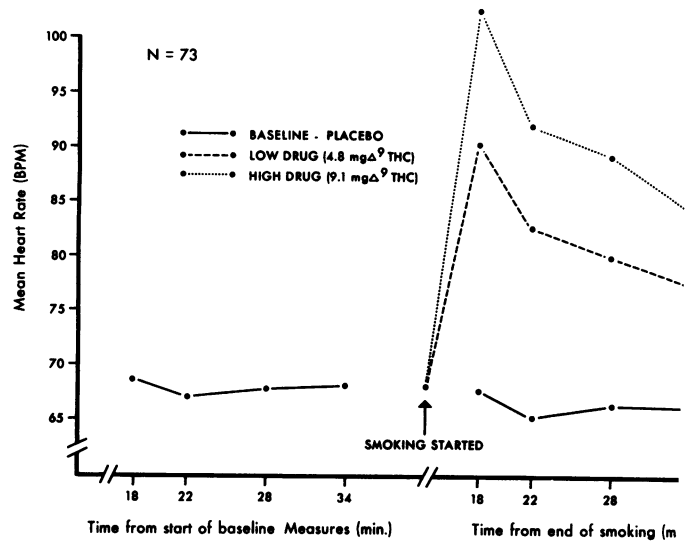

FIG. 2—Graph of observed heart rate vs. time through baseline and post-smoking recording. Each mean heart rate observation following either high or low dose of marijuana is significantly higher than the corresponding baseline and placebo value ($P < 0.05$ at least). Note that total (baseline) N = 73, placebo N = 29, low drug N = 16 and high drug N = 28.

Table II
EEG power spectral analyses

Measured parameter	N	Baseline	N	Placebo	N	Drug low	N	Drug high
Mean of peak power (value)	75	309	28	308	18	310	29	181†
Mean of peak power (freq.)	75	10.0	28	10.0	18	10.0	29	10.2
Peak of mean spectra (value)	75	218	28	211	18	232	29	143†
Peak of mean spectra (freq.)	75	10.4	28	10.2	18	9.8	29	10.5

†Sig. diff. from baseline $P < 0.05$

juana smoking induced a very rapid, significant dose-related increase in heart rate which began to diminish within 22 minutes after smoking was completed. The rate diminished progressively thereafter, but was still significantly higher than baseline levels near the end of the recording period (44 minutes after beginning smoking).

GSR reactivity

The GSR reactivity decreased throughout both baseline and placebo trials, showing a significant decrease in reactivity as compared to both placebo and baseline conditions (Fig. 3).

CNV

The only significant change was in the magnitude of the CNV after smoking marijuana containing 4.8 mg. Δ^9-THC. Under low-dose conditions subjects developed significantly larger amplitude CNVs (22.3 μV) than during placebo trials (15.6 μV).

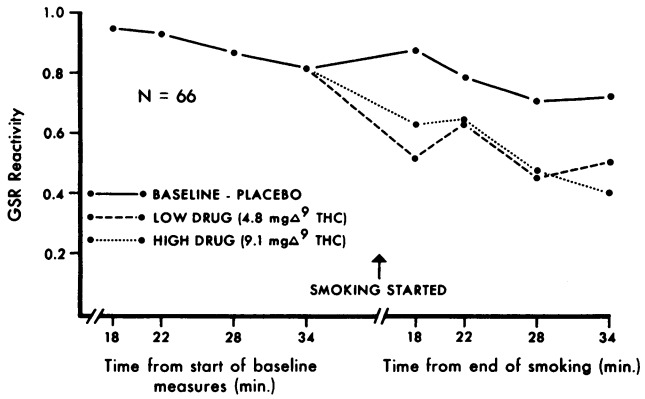

FIG. 3—Graph of observed GSR reactivity vs. time through baseline and post-smoking recording. Values at 18, 28 and 34 mins. after both high and low dose of marijuana are significantly lower than corresponding baseline and placebo values ($P < 0.05$ at least). Note that total (baseline) N = 66, placebo N = 27, low drug N = 16 and high drug N = 23.

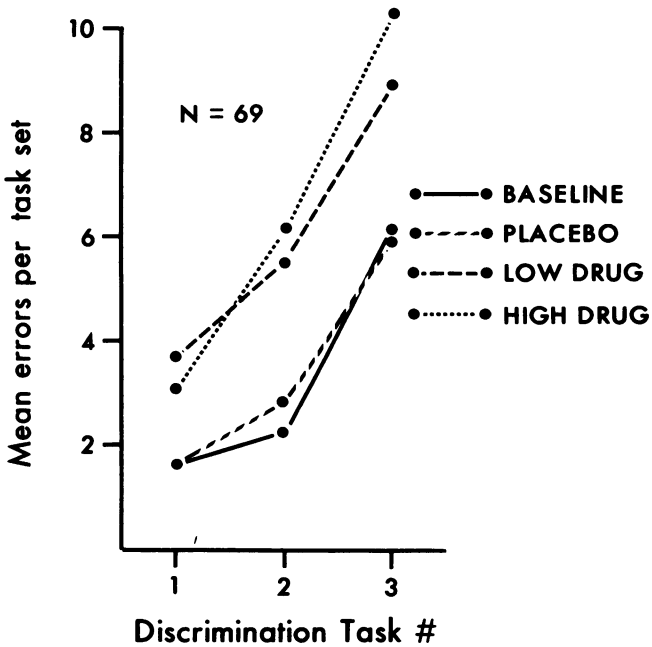

FIG. 4—Graph of mean number of errors made during discrimination trials. Each mean error observation following either high or low dose of marijuana is significantly higher than the corresponding baseline and placebo value ($P < 0.05$ at least). Note that total (baseline) N = 69, placebo N = 28, low drug N = 16 and high drug N = 25.

Discrimination-feedback CNVs

There was a slight but insignificant tendency for the CNV area to decrease and for the post-response area to increase as the discrimination task became more difficult during both baseline and placebo trials. The difficulty in discrimination is indicated by the increase in the number of response errors from paradigm 5 to paradigm 7 (Fig. 4).

Following marijuana smoking there was a marked change in the relative magnitudes of the pre-$S_{2d\Delta}$ CNV and the post-R CNV, with the post-R area tending to become larger than the pre-$S_{2d\Delta}$ CNV. This tendency is illustrated in the averaged traces from one subject shown in Fig. 5.

The mean number of errors was significantly higher during all three discrimination trial sets after smoking either dose of marijuana than during baseline or placebo trials (Fig. 4). There was a slightly higher response-error rate during paradigms 6 and 7 after high drug-dose as compared to low drug-dose, but no clear-cut dose effect as in the heart rate changes.

Discussion

Our heart rate data are consistent with those of many other investigators.[6,13,14] It is clear that marijuana smoking produces an almost immediate tachycardia, that this tachycardia is dose-related, and that the initial rate increase is sustained for only a relatively short period of time. However, marked subjective and objective effects of the drug may persist while the heart rate returns toward resting levels.

There is no clear parallel between heart rate and GSR reactivity changes, although they both show a suggestively bimodal pattern, with initial short-lived changes which could be attributed to marked anticholinergic activity, either central or peripheral. That these initial effects give way to qualitatively different effects within approximately 30 to 35 minutes after starting to smoke is suggested by the rapidly decreasing heart rate near the end of this time period, and by the change in GSR reactivity pattern to follow more closely the pattern obtained with placebo.

The EEG spectral analysis during low drug-dose conditions shows trends (statistically not significant) similar to those described by Hollister, Sherwood and Cavasino,[3] Volavka *et al*[4] and Rodin, Domino and Porzak,[6] i.e. a very slight shift downward in the peak frequency and a slight increase in the power of the peak frequency of the occipital EEG. These trends are reversed, however, under high drug-dose conditions, in which we found a significant decrease in the power of the peak frequency. This decrease could indicate desynchronization of alpha activity, and may reflect a greater or qualitatively different effect of high doses of THC on corticodiencephalic function than is induced by low doses.

These differences are paralleled by differences in auditory evoked-response latencies and CNV magnitude, and emphasize the crucial importance of specify-

ing dose when discussing the effects of drugs like the cannabis derivatives. Under low drug-dose conditions, we observed a significant increase in CNV magnitude as compared to placebo during the simple reaction-time paradigm. No significant changes in this CNV measure were induced by high drug-doses, however. These data confirm the report of Tinklenberg[10] and lend support to the idea that during the initial phase of the marijuana experience the brain mechanisms subserving attention are enhanced rather than diminished.

We have observed a slight increase in auditory evoked-response latency under high drug-dose conditions, but no significant changes in AER amplitude or in visual evoked-response parameters. These findings support partially the conclusions of Tinklenberg[10] and, together with the CNV data, suggest that while attention mechanisms are undisturbed, high doses of THC may alter perception by interfering with cognitive readout functions. The observed change in AER latency was in the relatively late negative component, the amplitude of which has been shown to be diminished during inattention,[15] and whose latency is presumably related to the efficiency of cognitive processes occurring after the arrival of the sensation in the primary auditory cortex.

That attention mechanisms *per se* are not necessarily disturbed by marijuana is also suggested by the results of the discrimination-feedback experiments. During the first discrimination task set the pre-$S_{2d\Delta}$ CNV tended to be higher under low drug-dose than placebo conditions, although this difference was not statistically significant; only under high-dose conditions relatively late in the recording session was there a significant diminution in the magnitude of the pre-discrimination CNV compared to placebo.

This significant diminution in the pre-$S_{2\Delta}$ CNV area under high drug-dose during discrimination tasks 2 and 3 must be interpreted in the light of the subject's involvement in the whole task and of the changes occurring after the response. The difference between the pre-$S_{2d\Delta}$ CNV and the pre-feedback CNV is interpreted as an indication of the subject's certainty of correctness of response choice, since the post-R pre-feedback CNV directly reflects interest in the information conveyed by the feedback signal. If one subtracts post-R area from CNV area, the result is positive in some relation to the subject's degree of certainty of the correctness of his choice of response to $S_{2d\Delta}$. That this is a reasonable interpretation is supported by previous evidence[12] and by the plots in Fig. 6. These plots of pre- and post-R CNV differences clearly show the effects of learning (smaller differences during placebo than during baseline practice) and the complete reversal of relative magnitudes of the two shifts under drug conditions. In all but one instance the post-R CNV is larger than the pre-$S_{2d\Delta}$ CNV.

The absolute measure of correctness of response choice is the number of response errors, fewer errors indicating better discrimination. The large number of errors made during drug trials, even while the subjects were interested and attentive and were receiving specific feedback information about correctness of response, clearly indicates a performance deficit induced by the drug.

In context with the results of our neuropsychological experiments and with other reported findings, these observations can form the basis of a reasoned hypothesis of the neural mechanisms responsible for the marijuana experience.

First, it is clear that smoked marijuana has at least a qualitative bimodal effect over time, with an initial relatively brief "rush" lasting approximately 30 to 35 minutes, and a subsequent longer period of "quieter" ac-

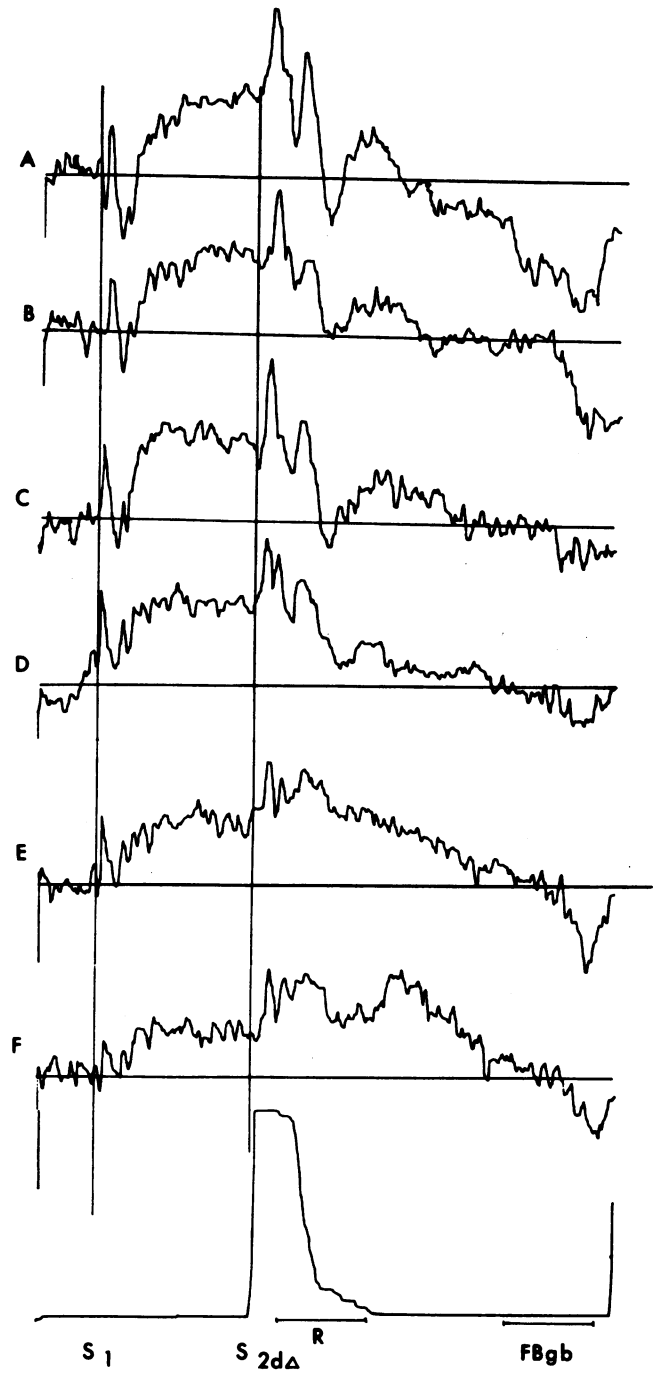

FIG. 5—Sample averaged vertex potential tracings from one subject in each of the three discrimination paradigms (5, 6, 7) listed in Table I. Traces A-C were taken during paradigms 5-7 baseline trials and traces D-F were taken during paradigms 5-7 after smoking marijuana. S_1 = warning stimulus (light flash); S_2 = imperative stimulus (tone); R = reaction time (button press); FBgb = feedback stimulus (good or bad). Lower trace shows duration of tonal stimulus. Horizontal bar showing reaction time distribution = 1 sec., and the height of the pulse in the bottom trace = 25 μV.

tion. This sequence fits almost exactly with the known time-frame of biotransformation of Δ^9-THC to 11-OH THC[16] and with the subjective reports of many users. It is possible that Δ^9-THC is itself in general terms an "activator" or stimulant, while its metabolites such as 11-OH THC are predominantly "depressant" to the CNS.

Second, dose is critically important in determining not only the duration of effects as has been claimed by some, but also the qualitative nature of the effects themselves, perhaps in a successive-threshold fashion.

Third, marijuana induces changes in brain function which can be profound but which are associated with only relatively minor measurable changes using standard electrophysiological recording techniques such as the EEG. This fact alone strongly implicates subcortical, medial or basal brain structures as being primarily responsible for the experiential and performance changes induced.

We have demonstrated in these experiments that marijuana interferes with performance in a manner which cannot be explained on the basis of decreased attention or altered retention of learned information. The results of the neuropsychological experiments in particular indicate that the functional change produced is one which results in altered concept formation or appraisal. The neurophysiological data support this conclusion in demonstrating changes in AER latency and marked disturbances in sensory discrimination task performance.

Appropriate action in response to any sensory input depends upon a complex neural pathway serving sensation, perception, appraisal, evaluation or concept formation, and motor response. According to Arnold[17] and MacLean[18] the appraisal or evaluation function is likely mediated by relays from cortical sensory receiving-areas to the adjoining limbic system.

Shute and Lewis[19] have shown that the main afferent pathways to the hippocampus are cholinergic in type. Our experiments and others have demonstrated that marijuana exerts an anticholinergic effect.

Clinical evidence has shown that abnormal discharges in or near the limbic cortex may produce feelings of depersonalization, distortions of perception, alterations

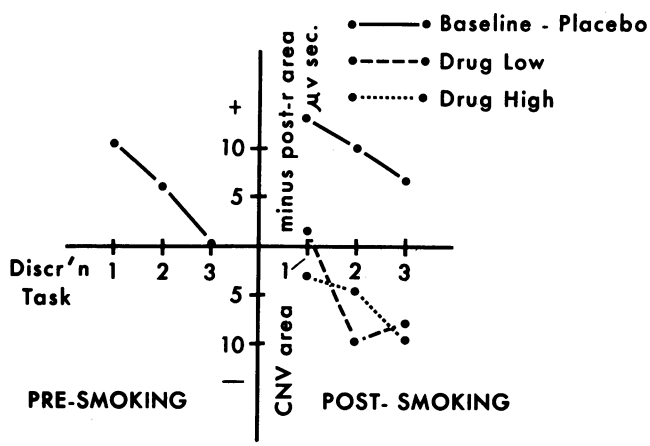

FIG. 6—Plots of differences between pre-response and pre-feedback CNV areas (pre-R minus pre-feedback) during discrimination paradigms before (N = 68) and after smoking placebo (N = 25), high dose marijuana (N = 26) and low dose marijuana (N = 17). Positive values result only when pre-feedback CNV is smaller than pre-response CNV.

in time sense, and feelings of fear or paranoia.[20] All of these subjective states may occur, and some are very common as part of the marijuana experience. Pleasant feelings, euphoria, happiness and placidity are also very common elements of the marijuana experience, and it is notable that the septal region, which appears to function as a major coordinating centre for the entire limbic system, is by far the most effective target for self-stimulation experiments with a variety of mammals, including man. Delgado[21] has demonstrated that electrical stimulation of limbic structures, especially the hippocampus, often produces pleasant sensations, elation, deep thoughtful concentration, relaxation and coloured visions in human subjects with chronically implanted depth electrodes.

Finally, the paper previously referred to by Heath[5] and one by McIsaac *et al*[22] provide objective evidence that the primary physiological and chemical changes induced by marijuana do occur in limbic-diencephalic structures. Heath recorded electrical activity from multiple subcortical brain regions and from scalp electrodes in one psychiatric patient. Recordings were made repeatedly over several weeks during all states of consciousness and during intoxication with marijuana, alcohol and amphetamines, and while smoking tobacco. Only during marijuana intoxication and only associated with "rushes" of euphoria, Heath recorded marked changes in electrical activity patterns from the septal region. There were no significant changes in the activity in any other area including the scalp-recorded EEG.

McIsaac *et al* injected squirrel monkeys with radioactive Δ^9-THC, and using radioautographic techniques showed that very high concentrations appeared in the limbic system, diencephalon (excluding hypothalamus) midbrain, and frontal and cerebellar cortex within 15 minutes, and remained in these regions at higher concentrations than in other brain areas for up to four hours. They also noted a differential effect of dose on the behaviour of the monkeys, with low doses producing apparently diminished anxiety, moderate doses inducing stimulation and high doses producing incapacitation.

This may be the most inclusive neural model of the physiological basis of the marijuana experience: Δ^9-THC and its metabolites act primarily to alter the normal functional relationship between paleocortical limbic system structures and the neocortex. This alteration may vary from stimulation of limbic activity to depression (or disinhibition to increasing inhibition) depending upon dose, time, prior set and current setting. The major elements of the marijuana experience, including altered perception, mood and performance may all be explained on this basis. The most striking objective change, i.e. a general cognitive performance decrement, may be the result of the loss of an accurate concept formation, appraisal or evaluation stage in the stimulus cue → performance sequence, normally subserved by neocortical-limbic circuits. The occasional "bad trip", which occurred with three of our subjects only, and which from our observations appears to occur only if the individual is already feeling badly or is apprehensive about the experimental situation, emphasizes the importance of set and setting in determining the quality of the emotional aspects of the experience.

The model would explain not only the major ele-

ments of the acute marijuana experience itself, but also the occasionally reported "flashback" phenomenon and possibly some of the cannabis-mobilized psychoses. It is well known to neurophysiologists that the limbic system, and the hippocampus in particular, has a very low threshold for activation by mechanical, chemical or electrical stimulation. Once activated, neuronal discharges tend to spread throughout all limbic circuits without very readily involving other brain areas. These phylogenetically old neural structures also have a marked tendency to persist in an altered functional state for long periods after the initial stimulus has been withdrawn. In this regard, it is perhaps significant that Heath[5] has recorded bursts of high voltage spike and slow activity from limbic areas as the only consistent electrographic abnormality in a large number of patients during periods of psychotic behaviour.

Because of the intense current interest of society in the subject of drugs and their effects on people, it is inevitable that investigators with research data will be asked for interpretations of those data in philosophical-sociological terms. While such interpretations can mislead the unwary if it is not made clear where the evidence stops and speculation begins, if carefully made they can provide a valuable perspective for laymen and may stimulate other scientists in different disciplines to seek new directions for future investigation.

With the disclaimer, then, that what follows here is a speculative interpretation on a social level, we believe that the neurophysiological model proposed might also explain the devotion to the marijuana experience of millions of young and not-so-young individuals in present-day society. In terms of the relationships among the three brain levels suggested by McLean,[18] cannabis drugs may allow the individual to exist at a phylogenetically old mammalian level, literally within the emotional brain itself, free from the conflict which is constant between the old sensory and feeling-oriented system and the newly imposed "civilization brain".

Such "regression in service of the ego" is not new in our society, nor is it unique to the marijuana experience. It is practiced regularly with at least some cultural approval and even encouragement in the form of tobacco smoking, alcohol consumption, some forms of psychotherapy, the use of tranquillizers, "back to earth" activities and even in the rituals, ceremonies and ordinances of many lodges, fraternal organizations and religions.

Rational man will of course perceive that the crucial questions regarding the marijuana experience have to do with the degree of certainty about the transient or temporary nature of the regression measured against the survival value to the individual of that particular form of experience. Since a great deal of effort has, to this date, adduced no major detrimental side effects to the casual or moderate and selective use of marijuana by rational adults (and each of these qualifications is justified by current knowledge) perhaps it is time for scientists to begin to explore the "other question", i.e. of what possible value can this sort of experience be, to the individual and to society.

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