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# EEG Effects of Hallucinogens and Cannabinoids Using Sleep-Waking Behavior as Baseline

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FAIRCHILD, M. D., D. J. JENDEN, M. R. MICKEY AND C. YALE. *EEG effects of hallucinogens and cannabinoids using sleep-waking behavior as baseline.* PHARMAC. BIOCHEM. BEHAV. 12(1) 99–105, 1980.—Three hallucinogens (d-lysergicacid diethylamide (LSD), mescaline, psilocybin) and two cannabinoid derivatives (tetrahydrocannabinol (THC), synhexyl) were tested for their long-term effects on the EEG of the cat. The drug-induced alterations in the EEG frequency spectrum were "drug-specific" in the sense that they would be statistically unlikely to occur during sleep-waking behavior. The two classes of compounds produced distinctly different EEG effects which were remarkably similar within each class. The duration of activity and relative potencies were consistent with those obtained by other measures, both in cats and in other species including man.

Long-term EEG frequency analysis  Hallucinogens  Cannabinoids  EEG in sleep-waking behavior.

THE work described in this report is concerned with the measurement of certain "drug-specific" and dose related alterations in the spontaneous brain electrical activity (EEG) of the cat produced by three "classical" hallucinogenic or psychedelic drugs which are contrasted with those produced by tetrahydrocannabinol (THC) and synhexyl (parahexl), a semi-synthetic analog of THC. These experiments are part of a series of investigation which have as a goal the development of relatively simple and objective procedures for utilizing the EEG of an experimental animal to classify and predict the type of central effect a drug would be most likely to produce in man. The problem has been approached by performing broadband frequency analysis of the EEG and subjecting the results to certain statistical procedures designed to abstract variables which are unique to drug effect. The initial report in this series characterized the effects of mescaline, amphetamine and four hallucinogenic amphetamine derivatives on the dorsal hippocampus and used 15 min periods of alert state as baseline for measuring drug effect [10]. In order to provide a baseline extending over hours rather than minutes of time, techniques were developed that made it possible to utilize the entire range of spontaneous EEG variation occuring during sleep-waking behavior, and the analysis was extended to include spectral changes recorded from four, rather than a single brain area [11]. Atropine and physostigmine were subsequently studied on this basis and the results showed that the "EEG-behavioral dissociation" reported to occur with these compounds was more apparent than real since each drug produced spectral changes which were uncorrelated with those occuring during sleep-waking behavior [12].

Compounds classified under the broad rubric "psychotropic" comprise the most widely used group of drugs, both for legitimate therapeutic purposes and as agents whose effects are abused by a significant percentage of the population. The problem of classifying and predicting the psychopharmacological profiles of this important group of compounds has been the subject of numerous investigations representing a wide range of biomedical disciplines. Perhaps the most successful have been those methods based on drug-induced alterations in brain electrical activity of human subjects [13, 20, 26]. One of the primary reasons humans are used in these studies is that stable baseline recordings of spontaneous or evoked brain electrical activity can be obtained, since behavioral state is relatively simple to control. While similar methods employing sub-human species would have obvious advantages, the problems of baseline control and correlating drug-induced changes with phenomena as complex as alteration in human subjective state are formidable. Although a vast literature exists concerning the effects of psychotropic drugs on brain electrical activity of experimental animals, no system for the classification and prediction of these compounds has yet emerged which is comparable to those methods using human subjects. The present paper makes a contribution in this area since drug activity is defined in terms of variables abstracted in such a way as to be statistically independent of those EEG changes occuring normally during the sleep-waking cycle. This in effect provides a stable baseline from which to measure drug activity that is valid over hours of time. In terms of these variables, the hallucinogens LSD, mescaline and psilocybin produced remarkably similar effects and had potencies and time

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courses comparable to those observed in man. The spectral changes produced by THC and its analog synhexyl were likewise similar and differed sharply from those of the hallucinogens.

## METHOD

### *Animal Preparations, Apparatus and Experimental Design*

Under sodium pentobarbital anesthesia, three adult, female cats were prepared with bipolar electrodes chronically implanted in the prepyriform cortex, dorsal hippocampus, lateral geniculate body, and the basolateral amygdala. In addition, monopolar electrodes were placed in the orbital plate of the frontal bone and in the body of the rectus capitis muscle to monitor eye movements and neck muscle electrical activity, respectively. At the termination of the experiments the disposition of central electrode tracts was determined from serial sections stained with thionin.

At least one month was allowed for recovery from surgery. Experiments were conducted in a sound attenuated chamber equipped with a one-way mirror for observation. Animals were connected to the recording devices via a commutator (Airflyte Electronic Co.) to prevent cable tangling.

A broad-band frequency analysis of the EEG from each of the four brain areas was performed. Briefly, brain electrical activity was amplified and recorded on a Honeywell Model 7600 tape recorder. Tape recorder output was then led to a frequency analyzer consisting essentially of eight tuned amplifiers covering the frequency range from 2.5 to 40 Hz in half-octave steps and connected through rectifying circuits to integrators with essentially infinite time constants. At one-minute intervals the integrator output were sequentially connected to an Infotronics Model CRS-30E digitizer through sample-hold circuits following immediate reset of the integrators. This device converts the analog voltage signal of the integrators to three-digit numbers representing the mean amplitude of the frequency components within the range of the eight tuned amplifiers. The digitizer was interfaced with both an IBM electric typewriter and a Model 026 printing card punch. These procedures and equipment have previously been described in detail [11,28].

A total of 48 experiments were conducted with the three animals. For each cat these included the administration of six drugs at two dose levels, an experiment during which normal saline was given and three "SFA" control experiments. The SFA controls were similar to those previously described in which the EEG was recorded during the behavioral states slow sleep (S), fast sleep or REM sleep (F), alert (A), or undetermined (U) behavior as classified during each one-min period of the experiments. Classifications of S and F were on the basis of the usual electrographic (EEG, eye movement, neck muscle EMG) and behavioral criteria. The A state was "maintained", in the sense that the animal was required to attend to various simple auditory and visual stimuli, while the U classification was reserved for those minutes during which behavioral state was transitional or could not be readily determined. Recording was continued for a period of time sufficient to obtain at least 30 min each of the S, F and A states. SFA controls were conducted during the first, middle and final week of the experimental sequence. Individual drug or saline experiments consisted of 30-min predrug recording, during which behavior was classified as S, F, A or U, followed by 2.5 hr postdrug recording, each minute of which was labeled drug (D). The test compounds were injected intraperitoneally at each of two dose levels. They included: d-lysergic acid diethylamide (LSD), 0.015 and 0.060 mg/kg; psilocybin, 0.150 and 0.600 mg/kg; mescaline sulfate, 3.000 and 12.000 mg/kg; d-bromlysergic acid diethylemide (BOL), 0.045 and 0.180 mg/kg; $\Delta^9$ tetrahydrocannabinol (THC), 2.500 and 10.000 mg/kg; synhexyl, 6.250 and 25.000 mg/kg. Experiments were conducted on a weekly basis and a balanced design was employed to insure that at least three weeks elapsed between administration of any given drug and that experiments with low and high doses of each compound had an approximately equal distribution during each month of the three month period required for drug administration. Experiments with saline were conducted following the conclusion of the drug tests.

### *Time Course Calculations*

The numerical data developed for each experiment were the minute by minute average amplitudes for each of the 8 frequency bands for each of the four brain areas. The record for each minute was completed by the entry of time from the start of the experiment and a numerical code that designated the behavioral state of the cat as S, F, A, or U. Behavioral state was not recorded following drug administration and a code corresponding to D was entered, as indicated above.

A calculation objective was to develop scores that reflect over time the extent of drug activity. The method used to generate drug scores was multivariate discriminant analysis and was accomplished using the computer program BMDO7M [7]. The significance tests formally supplied by the discriminant analysis were not used partly because of the time series nature of the data but basically because the relevant sources of variation are those between experiments and between cats. The discriminant analysis was used as a data reduction calculation to provide relevant summary scores. A separate analysis was carried out in four steps for each drug experiment (regarding saline as a drug), together with the three control experiments on the same cat. In the first step the data were transformed to a logarithmic scale, following which the average of the 8 frequency bands was subtracted from the individual entry; in effect the data was transformed to the logarithm of the ratio of amplitude to geometric mean amplitude for the corresponding brain region and minute. The second step was a four group discriminant analysis, with the groups defined according to behavioral state (S, F, A or U). Because the U minutes are a more heterogeneous group than the others, the within-groups covariance matrix used for this analysis was based on the S, F and A groups only. The analysis separates information that distinguishes the groups from that with no such discriminational content (in the sense of the analysis) and prepares the latter in the form of a reduced number of residual variables; these are in the form of uncorrelated linear combinations of variables entering the analysis. In the context of drug experiments, the residual variables contain the information about drug activity that cannot be linearly accounted for in terms of spontaneous changes in EEG activity corresponding to behavioral variations during S, F, A and U. As a third step, a second discriminant analysis was done using only the residual variables from the first analysis, and contrasting non-drug minutes with minutes following drug administration. The discriminant variable, calculated by the analysis, provides a numerical score, evaluated for each minute, that is an index of the

drug-related EEG activity following drug administration. As a fourth step, the discriminant variable was rescaled so that it would have zero mean over ths predrug minutes of the drug experiment and standard deviation of 100 over the control experiments and predrug portions of the drug experiments. The resulting variable is called a drug effect score. This score was averaged over successive 5 min blocks and the resulting values were further smoothed by a single pass of a three point moving median filter.

The result of the four step analysis was a time sequence drug effect score for each drug tested on each cat. Results are averaged over cats for each drug-dose combination and these averages are plotted as representations of the time course of the drugs. Stability of the averages is indicated by standard errors computed separately from differences between cats for each five minute block with the same drug-dose combinations.

*Characteristic Profile Construction.*

A second objective was to derive profiles characteristic of each drug in terms of patterns of change in each brain region and frequency band. This was carried out by a canonical analysis between the frequency band amplitudes averaged within experiments as one set of variables and the corresponding average drug scores as the second set. The amplitude averages were taken over the part of each experiment after drug administration and adjusted for possible gain differences in electrodes by computing the deviation of the brain region average for each cat from the mean of all cats, and subtracting the deviation from the averaged data from each of the corresponding channels.

Drug related alterations of spontaneous EEG activity are presented for each drug as frequency based profiles for each of the four brain regions. The profiles were constructed as regression predictions of the change in frequency band average amplitude for the high doses of the drug. Amplitude, adjusted for cat-brain region differences and expressed on a logarithmic scale, was regressed on the informative canonical average drug score variables derived from a canonical correlations analysis (computer program BMDP6M, [7]) of the combined data from the several experiments. The canonical correlations analysis is a multivariate regression analysis [2] in which variables of one type, or set, are jointly regressed on variables of a second set. In our case the EEG frequency band amplitudes are variables forming the first set and the average drug scores of the compounds tested constitute the second set. The regression is expressed in terms of pairs of reconstituted variables, one variable of a pair summarizing information of one type and the other variable summarizing the second type. The reconstituted variables are called "canonical" variables and have the characteristics that canonical variables constructed from variables of the same type (or set), are mutually uncorrelated and that the only correlations between canonical variables across type are between those of the same pair. These correlations between pairs of canonical variables are called canonical correlations. The analysis is effective when the correlational information is summarized by a small number of pairs of canonical variables. The informative pairs are selected by a test of statistical significance [4]. As a consequence of the statistical properties of the canonical variables, the regression coefficients for the regression of amplitude, $y_i$, on drug score canonical variables, $x^*_j$, are the covariance $\mathrm{cov}(y_i x^*_j)$ so that the profile is expressed as

$$P_i = \sum_{j=1}^{m} \mathrm{cov}(y_i, x^*_j) D^*_j$$

in which $D^*_j$ denotes the value of the jth drug canonical variable evaluated at the high dose of the drug profiled, and m is the number of informative pairs of canonical variables.

The data analyzed consisted of 75 sets of 8(frequency bands) × 4(brain regions)=32 average amplitudes obtained as follows. For each of the 6 (drug) × 2 (doses) × 3 (cats)=36 drug experiments, the number entered was the logarithm of the amplitude for the recorded period following drug administration. Saline experiments, one for each of the three cats, were treated as drug experiments with a single dosage. An additional 4 (states) × 3 (cats) × 3 (control experiments)=36 cases were formed using the logarithm of the amplitude averaged over the minutes corresponding to the classified behavioral state (sleep, fast sleep, alert, or unclassified). An adjustment for electrode associated factors was made by computing for each cat-brain region the average over the eight frequency bands of the log average amplitude for the saline experiment. The 3 (cats) × 4 (brain regions) array which was obtained was processed by a standard two-way analysis of variance and the resulting interactions (residuals from fitting cats and regions) provided adjustments to be subtracted from the corresponding log average amplitudes for the 75 "cases". Values for an additional seven variables, the drug variables for the canonical analysis, six of which correspond to the drugs and one to saline, were formed for each of the 75 cases by entering the value zero if the case did not correspond to an experiment in which the drug was injected and by entering the average drug score from the discriminant analysis for experiments in which the drug was tested. For this purpose saline was treated as a drug. The resulting 75 cases by 32 + 7=39 variables array was the data processed to produce the drug profiles.

## RESULTS

*Time Courses*

Figures 1 and 2 depict the time course of effect following injection of the test compounds as estimated from changes in the EEG spectrum. In each case the peak drug effect appears to have occurred within the 150 min postinjection period and, except for synhexyl, all of the compounds tested which produced significant alterations in the EEG of the cat showed clear dose-response relationships with regard to the magnitude of drug effect. The low and high doses of synhexyl appeared almost equal in potency, and although the degree of activity was less than the other drugs, it had the most consistent effect on the brain of the cat (note the relatively small standard errors over the entire time course in Fig. 2). Neither saline nor BOL produced drug scores deviating significantly from zero.

*Characteristic Profiles*

The configuration of the characteristic profiles presented in Fig. 3 clearly separate the test compounds into three groups. The profiles for the cannabinoid analogs THC and synhexyl closely resemble each other, as do those for the hallucinogenic compounds mescaline, psilocybin and LSD. It is evident that the two groups of drugs produced quite different "drug-specific" alterations in the EEG frequency

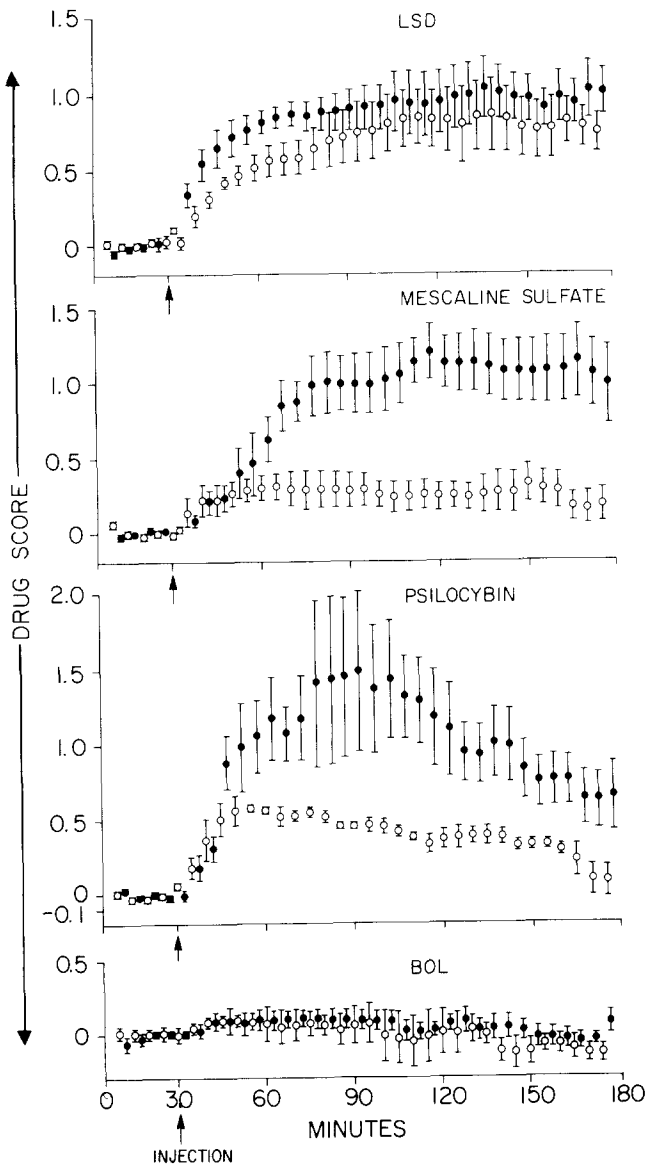


FIG. 1. Time courses of drug-induced changes in the EEG averages over all cats for the low (○) and high (●) doses of LSD, mescaline, psilocybin and BOL. The ordinate is the mean value over successive 5 min epochs of the drug score. The standard error of the mean was calculated from score differences between cats (see Methods).

spectra. The very small profiles for BOL and saline indicate that those substances produced only minimal changes in EEG frequency spectra different from those occurring as the result of spontaneous changes in behavioral state. The similarity in patterns for the two groups can also be appreciated by inspecting Fig. 4. Here the potency of drug effect for the high dose of each test compound is depicted in terms of the regression predicted changes in the two statistically significant canonical response variables.

## DISCUSSION

In their review of the pharmacology of the hallucinogens Brawley and Duffield [6] pointed out that two classes of

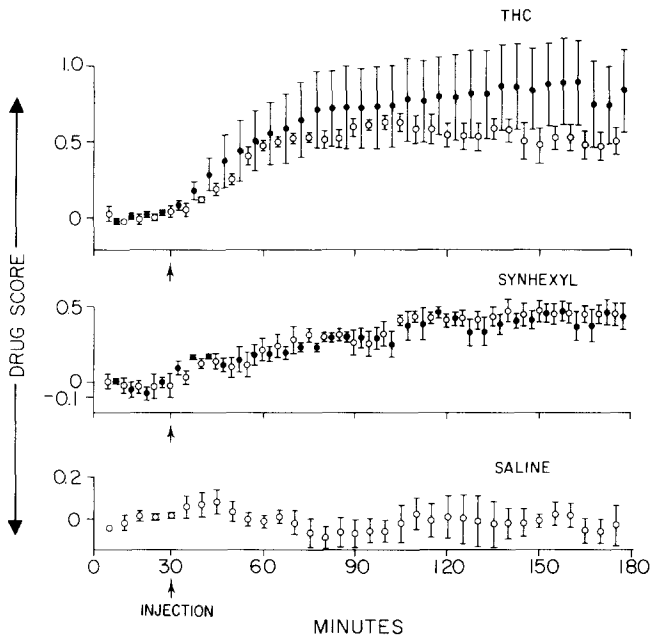


FIG. 2. Time courses for the low and high doses of THC and synhexyl and for saline calculated as in Fig. 1.

"Phantastica" [23] could not reasonably be classified as "psychotomimetic" drugs. These included substances derived from the plant *Cannabis sativa* and the unsubstituted amphetamines. The former group appeared to have mixed deliriant, euphoriant and hallucinogenic effects and the latter, while causing marked paranoid reactions when taken chronically, did not produce hallucinations in single doses. In a former report [10] we demonstrated that alterations in the frequency distribution of the cat EEG produced by amphetamine could be clearly distinguished from that resulting from mescaline and several hallucinogenic amphetamine derivatives and further that the degree of change in the frequency spectra characteristic of hallucinogenic activity accurately reflected the relative potency of these compounds in man. The experiments described in this article have demonstrated that a similar distinction can be made between the changes in EEG frequency spectra produced by the "classical" hallucinogens LSD, mescaline and psilocybin and the cannabinoid derivatives THC and synhexyl.

In spite of the certain similarities in the clinical effects of the hallucinogens and the cannabinoid derivatives [16,18] it is now generally recognized that the two types of compounds probably act through different central mechanisms and should be regarded as "separate and distinct pharmacological classes" [22]. They fail to show cross-tolerance, both in man [19] and in experimental animals [3,31] and also produce different behavioral [9, 15, 21, 24, 27, 32] and neurophysiological [5,8] effects when tested together in a variety of experimental paradigms.

While the outcome of our experiments supports the concept that cannabinoid derivatives act through different central mechanisms than the hallucinogens, they also clearly demonstrate that the individual compounds within each class have remarkably similar effects on the spontaneous brain electrical activity of the cat and that these effects are reasonably consistent with the relative potency and duration of action of the central activity of the test compounds in man.

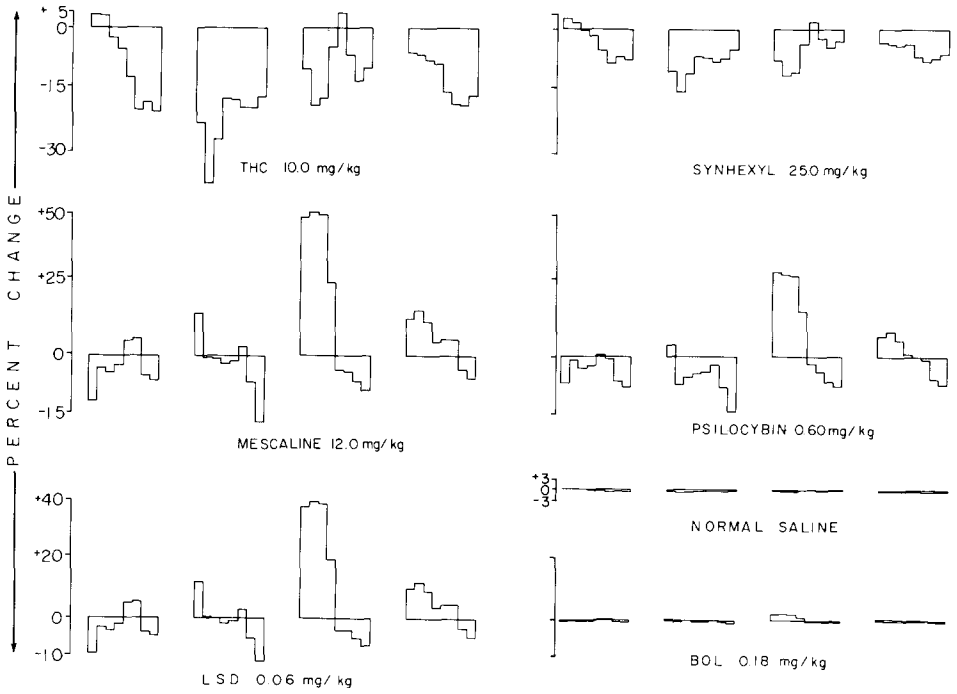


FIG. 3. Characteristic profiles for "drug-specific" changes in EEG frequency distribution in the four brain areas produced by the high dose of test compound. Individual histograms within each profile represent the 8 frequency bands between 2.5 and 40 Hz. The four brain areas are, from left to right: prepyriform cortex, dorsal hippocampus, lateral geniculate nucleus, basolateral amygdala. Calculations are based on the pooled data from all three cats (see Methods).

The similarity of their effects on the EEG of the cat is readily apparent from the appearance of the characteristic profiles of frequency distribution shown in Fig. 3.

The relative potencies are shown in Fig. 4. Psilocybin was administered at a dose 10 times, and mescaline at a dose 200 times that of LSD and it can be seen that their potencies are approximately equal in the hallucinogenic direction depicted by the frequency pattern corresponding to variable 1 and that they do not differ significantly from zero in terms of the patterns representing variable 2. The nonhallucinogenic LSD derivative BOL does not differ significantly from the origin. In man, the relative hallucinogenic potency of LSD compared to psilocybin and mescaline has been reported to be at least an order of magnitude greater than we found in the cat. This is perhaps not surprising since the effective dose of the hallucinogens is known to vary widely in different species and only in man is there the advantage of verbal reporting [6]. Synhexyl, a semi-synthetic homologue of THC, and THC itself have very similar psychotropic effects in man, with synhexyl having approximately one third the potency [17,25]. In the cat, we found synhexyl to be even less potent; a dose 2.5 times that of THC had about one half the effect in terms of the EEG frequency pattern changes depicted by variable 2 in Fig. 4. Neither synhexyl nor THC differed significantly from zero in the hallucinogenic direction represented by variable 1.

The time courses of activity for altering EEF frequency distribution in the cat also seems consistent with the duration of the psychotropic effects of the test compounds in man. For instance, psilocybin is known to have a shorter duration of activity than either LSD or mescaline in man [1,30] and unlike either LSD or mescaline it also demonstrated recovery from the effect on the EEG of the cat within the 150 min post-drug period (see Fig. 3). Both THC and synhexyl are active for a number of hours in man [17] and their time courses of activity in the cat did not show recovery within the post-drug period (see Fig. 2). The onset of effect appeared slower with synhexyl and this has also been observed in man [17].

The current investigations have provided additional evidence that long-term, broad band frequency analysis of the EEG can yield quantitative and objective measures of psychotropic drug activity in the cat which are dose related and relatively independent of those sources of frequency variation occurring spontaneously during the sleep-waking cycle. It has further been demonstrated that the "drug-specific" parameters abstracted from the EEG of the cat, utiliying the statistical techniques described, are reasonably related to the known effects of the test compounds in man and thus hold promise of providing a logical method for utilizing an experimental animal to obtain meaningful predictions of psychotropic drug activity in man.

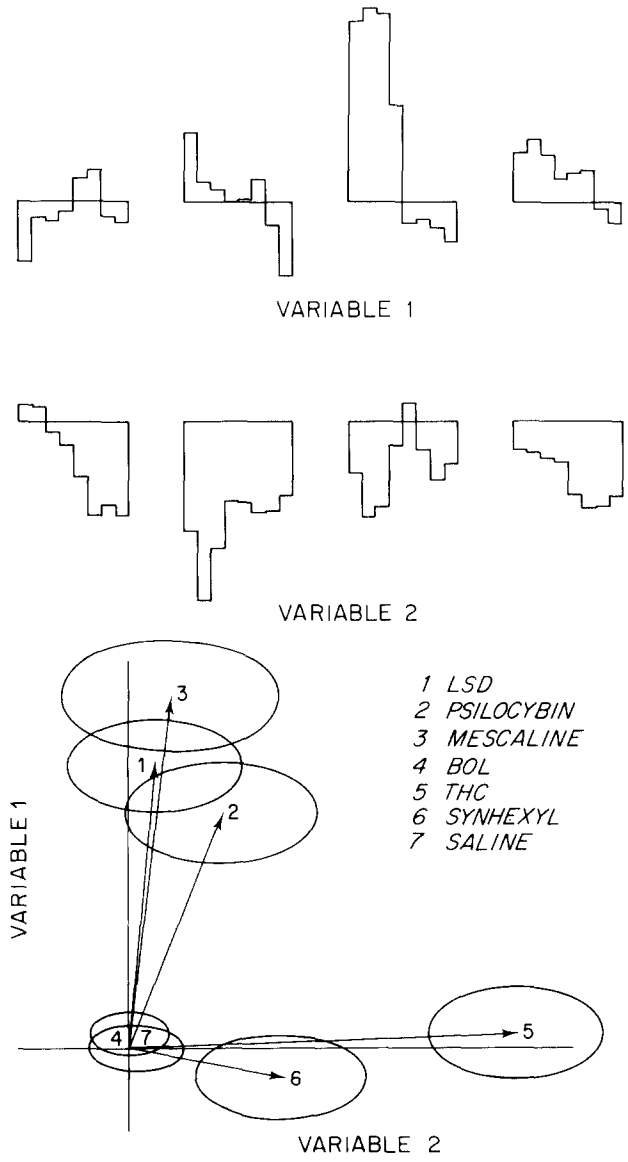


FIG. 4. Summary of canonical analysis of drug effect in the four brain regions, using pooled data from all experiments on all cats. The values of the coordinates, for each drug, are the regression predicted changes, corresponding to the high dose, in the response canonical variables that correspond to statistically significant canonical correlations ($p<0.001$). Alterations of frequency band average amplitudes are mixtures of the patterns corresponding to the coordinate axes, with weights given by the coordinates of the point representing the drug effect. The ellipses depict 95% confidence regions.

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