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EFFECT OF LOW-LEVEL, LOW-FREQUENCY ELECTRIC FIELDS ON EEG AND BEHAVIOR IN MACACA NEMESTRINA

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EFFECT OF LOW HZ FIELDS ON EEG AND BEHAVIOR

Summary

A series of experiments has been done to assess the effects of low-level, low-frequency electronic fields on the behavior and EEG of monkeys. Three monkeys were implanted with subcortical and cortical EEG electrodes and trained to press a panel on a fixed interval-limited hold schedule. The monkeys were rewarded for pressing the panel once every five seconds within a 2.5-second enable period. After the animals were performing well, they were tested under low-level electric fields (2.8 volts p-p); the voltage was applied to two large metal plates 40 cm. apart so that the monkey's head was completely within the field. Fields frequency was set at 7 or 10 Hz, within the range of typical EEG recording (0-33 Hz). Four-hour daily tests of fields-on were randomly interspersed with four-hour runs with fields-off. Under the 7-Hz fields, the monkeys showed a significantly faster interresponse time in 5 of 6 experiments. Mean differences between fields on and fields off were .4 seconds or greater. The 10-Hz fields did not produce a reliable effect on behavior. Analysis of the EEG data showed a relative peak in power at the frequency of the fields (10 Hz and 7 Hz) for the hippocampus in all three monkeys. Similar peaks were seen less consistently in the amygdala and the centre median.

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A series of preliminary experiments has been done in an attempt to determine whether or not low-level electric fields have an effect on behavior and/or patterns of electrical activity in the brain of monkeys.

Very few studies of this kind have been done on either animals or man. Experimentally produced changes in reaction time in humans exposed to low-level, low-frequency (less than 12 Hz) fields havebeen reported by Hamer[7] and Konig and Ankermuller[9]. Changes in human reaction time have also been observed under low-frequency modulated magnetic fields (Friedman, Becker and Bachman[6]). Wever[19] has described the modification of circadian periods of activity in man under weak 10-Hz electric fields. It was not known what kind of primate behavior, if any, would be sensitive to field effects so that selection of a suitable behavioral task was a first consideration. Earlier pilot studies in this laboratory suggested that subjective time estimation in humans was influenced by the presence of fields. In the present study, we attempted to devise an analogous time estimation task suitable for use with monkeys, so that electrodes implanted deep in the brain could monitor brain electrical activity throughout the experiments. It is known that scheduling of reinforcements for a simple lever press can alter an animal's rate of response, or the timing of that response, or both. In the present study, monkeys were trained to press a lever under

a variation of a fixed-interval (timing) schedule of reinforcement. Under this schedule there are no external cues or signals presented to the animal; he must "time" his responses from the occurrence of his own last response. It is a schedule which has been widely employed in studies of animal behavior and has been especially useful in detecting effects of small dosages of drugs (Sidman[13]). It was expected that if there were an effect of the fields it would be seen as a shift in the distribution of the monkey's interresponse times.

Other questions of research strategy arose; it was not obvious what brain structures, if any, would show an effect of the presence of the fields. Nor was it clear what kind of changes one might expect to see in the EEG--other than a possible direct driving by the applied field--or how to assess such changes. Consequently, an array of seven bipolar cortical and subcortical electrodes were implanted in the first monkey. A slightly different array was implanted in a second monkey and electrode sites for the third monkey were selected on the basis of results from the first two. Computerized spectral analysis of the EEG was done and some special statistical tests were devised to compare fields-on vs. fields-off changes in EEG.

Low-level (2.8 volts p-p) fields were used at two frequencies, both within the range of frequencies usually evaluated in EEG work (0-33 Hz). In some of the experimental runs, 10-Hz fields were used, to correspond to Hamer's earlier experiments (Hamer [8]). In other runs, 7-Hz fields were used because they were in the range of hippocampal theta (4-7 Hz), a characteristic electrical activity of the brain that has been

shown to be important in orienting and discriminating responses Radulovacki and Adey[10], Walter, Rhodes and Adey[17]).

Methods: Experimental Design, Behavioral Data Analysis, and EEG Analysis.

I. Experimental Design.

Three pigtailed macaques were implanted with cortical and subcortical bipolar electrodes, and were adapted to Foringer monkey chairs. They were then trained to push a panel in front of them on a fixed interval-drl (differential reinforcement of low rates) limited hold schedule of reinforcement; (drl-h schedule). The animal was gradually conditioned to wait 5 seconds between pushes, and to push within a 2.5 second reward-enable interval. If the animal pushed within the specified time interval, he was rewarded with a squirt of apple juice. If he pushed too early, or too late, he did not receive a reward, and the timer recycled to the beginning of another 5 second interval. The behavioral task was completely automated with logic modules manufactured by B.R.S. Electronics. The monkeys were maintained throughout training and experiments on a standard controlled diet of monkey pellets, fruit, and restricted fluids. A liquid reinforcer was chosen in order to eliminate chewing artifacts in the EEG. The animal was trained until he was performing at a high rate of accuracy (70-80%) and his performance was relatively stable from one day to the next. All of the training was done in an isolated and sound-proofed booth. Task electronics and recording apparatus were in an outer room and the monkey's behavior was continuously monitored on closed-circuit TV.

After the animal was performing well, his behavioral records over a 24-hour period were examined to determine periods of free responding during the day, and a four-hour segment of time was selected for scheduling daily experimental runs. The low-level (2.8 volts p-p), low-frequency fields were administered by applying the voltage to two larger metal plates, 40 cm. apart, which were fastened to the monkey's chair so that the head of the animal was completely within the fields. Four-hour daily tests with the fields on were randomly interspersed with four-hour daily control runs without the fields. A total of twenty such tests were done on the three well-trained monkeys. All monkeys were given two tests with 7-Hz fields and two comparable control tests without fields. Two of the three monkeys were also given two tests with 10-Hz fields and two control runs without the fields. EEG and behavioral data were continuously monitored throughout all runs. In addition, EEG was monitored in one monkey during two four-hour nonperformance runs (7-Hz fields-on and fields-off) before he was trained to the drl-h task.

II. Data Analysis of Behavioral Changes.

Interresponse time data (IRTs) were collected by the computer for each experimental run; each response of the animal was tallied as a function of time elapsed since the immediately preceding response. Two-tenths of a second bin widths were used; 144 bins were counted and interresponse times greater than that were tallied as 144 (28.8 seconds). Mean and standard deviations were calculated for each four-hour run, and t tests were used to compare IRT distributions for experimental runs and

the appropriate matched control runs.

III. Data Analysis of EEG Changes: Spectral Intensity, Coherence, Discriminant Analysis.

EEG data was continuously recorded on a Grass polygraph and an Ampex analog tape recorder. In the first monkey (J.) EEG was recorded from the left hippocampus, right hippocampus, right amygdala, midbrain reticular formation, right visual cortex, left visual cortex and motor cortex. In the second monkey (Z) EEG was monitored from the right hippocampus, left hippocampus, left centre median, right visual cortex, and right amygdala. In the third monkey (A.) records were taken of the electrical activity of the right hippocampus, left hippocampus, right centre median, left centre median, right amygdala, and left amygdala.

Four sets of EEG data from comparable epochs from each day's run were selected for computer analysis. A set of correct (i.e., properly timed) responses was selected from the beginning of the run and a second set from the end of the run; similarly, a set of predominantly incorrect responses was sampled from the beginning of the run and a comparable set from the end of the run. Each epoch was approximately 80 seconds in length. These epochs were spectrally analyzed in consecutive 10-second samples and then averaged over the total 80 seconds.

The selected data epochs were converted to digital form by the SDS 930 computer system of this laboratory and spectral analysis of this data was performed, using the BMDX92 program and the IBM 360/91 computer of the Health Sciences Computing

Facility. Spectral resolution was set at 2 Hz over the range 0-28 Hz for survey purposes. Spectra and coherences (Walter, Rhodes, Brown and Adey[18]) were averaged for each structure, within condition, and plotted; spectra were converted before plotting to relative units (by dividing by the total intensity in that structure in that condition) in order to compensate for day-to-day variations in total intensity; the result is called "percent power" at each frequency.

Spectral Intensity. A specialized statistical test for the effect of the imposed field on recorded activity was devised as follows. In the frequencies from 4-20 Hz, at least, the spectra were close to exponential in shape, in the absence of fields. If this were exactly true, the logarithm of the spectral curve would be a linear function of frequency, over this range. Then any activity contributed by the field would be above the line containing those points not at the field frequency (or its harmonics). Accordingly, we tabulated the statistic ("peak quotient") for the 10 Hz field.

$$\log_e(S_{10}) - 1/2\,[\log_e(S_{12}) + \log_e(S_8)]$$

When the field was at 7 Hz, more care was required. The 7-Hz signal appeared both in the filter band centered at 6 Hz and (to a lesser extent) in that centered at 8 Hz. We chose to test only the value at 6 Hz, and to compare it with the line based on 4 Hz and 10 Hz; thus, the peak quotient for the 7-Hz field became

$$\log_e(S_6) - [2/3\ \log_e(S_4) + 1/3\ \log_e(S_{10})]$$

The spectral estimates have a sampling distribution like chi^2/d.f., with d.f. calculated by the program (according to

formulas adapted from Blackman and Tukey[4]) as approximately 200 in our case. Thus, the natural logarithm of a single spectral intensity has an approximately normal distribution, with variance 2/d.f., and a coefficient of skewness of -0.1 (Abramowitz and Stegun[1]). Our peak quotient statistic, then, is close to normally distributed with variance .01. Its response to application of the field in the two experiments for each animal could be tested by the t-statistic, with the two fields-off values providing the mean corresponding to the null hypothesis of no effect of the field.

Coherence. An additional parameter calculated by the spectral analysis program is the coherence between the imposed field and the activity in each structure, as well as between the brain structures themselves. It is essentially analogous to the squared coefficient of correlation, and hence, a measure to the linear predictability between the two wave forms, taking into account spectral intensity, frequency and phase lag. Although the purity of the imposed sinusoidal field invalidates the usual distributional assumptions about the coherence statistic, we felt these results might be suggestive.

Discriminant Analysis. In seeking for less obvious field effects, we applied step-wise discriminant analysis (Anderson[2], Rao[11]) to spectral and cross-spectral parameters, with the exclusion of the frequency band containing the field frequency, or else of that band and all bands containing any harmonics of that frequency. Applications of this computer program, Discan (based on BMD 07M, Dixon[5]) to spectral analysis of EEGs have

been described previously (Walter, Rhodes and Adey[17]; Rhodes, Walter and Adey[12]; Hanley, Walter, Rhodes and Adey[9]; Berkhout, Adey and Campeau[3]).

Results

Behavioral data. Consistent differences in interresponse time distributions were observed in the 7-Hz experiments. The 10-Hz field condition failed to produce a reliable effect on the behavior. For one animal (Z.) the mean interresponse time was unchanged by the 10-Hz field; responses were slightly faster (but not significantly so) in the replication. In animal J., interresponse times were faster in the first 10-Hz experiment and slower in the second.

Under the 7-Hz condition, however, rather large and consistent differences were observed in all animals. Animal Z. showed a shift in mean interresponse time toward shorter IRT's; the difference was approximately one-half second in the first experimental-control run. This finding was replicated in a second experiment (See figure 1) and these differences were highly significant statistically ($p = .01$ or better). In general, the whold distribution was shifted towards faster responses, while overall number of responses did not increase or decrease consistently. For the second animal (J.), the IRT mean shifted significantly in the direction of faster responses in the first experiment; however, this difference was not replicated in the second experiment. The third animal (A.), like the first, showed a shift in the direction of faster responses under the 7-Hz field. This difference was statistically significant

and was replicated in the second experiment. Percent of correct responses (those falling between 5 and 7.5 seconds) did not differ significantly under fields-on conditions for monkeys J. and Z.; monkey A., who had a large number of very long IRTs in the fields-off condition, showed gains of 16% correct and 21% correct when the fields were on. In summary, five of the six experiments showed a shift to significantly faster inter-response times under the 7-Hz fields compared with fields-off performance. All of these mean differences were .4 seconds or greater. Shifts in modal values also occurred in all 5 experiments and were all .2 seconds or greater. The distributions and means for all monkeys are shown in Figure 1. It may be observed that the overall output of responses and the variability of those responses differs considerably from monkey to monkey. Nevertheless, the direction of the mean shift under the fields is remarkably consistent and the size of the shift is relatively large.

EEG data: Visual inspection of the EEG data during the experiments did not reveal any marked effects due to the fields. An examination of the percent power graphs, however, revealed small peaks in power from some brain structures at the fields frequency, for epochs of predominantly incorrect responses near the end of the run. A sample of EEG data and percent power graphs is shown in Figure 2.

Peak quotients (as described in the methods section) were compared via t-tests for these epochs in fields-on versus fields-off conditions, for each animal and for each structure. (See Figure 3). In the first animal (J.), significant differences

were observed in the left hippocampus, the right hippocampus and the right amygdala for both the 7-Hz and the 10-Hz condition. In the third animal (A.), 7-Hz fields only were tested. Differences at the .01 level or better were observed in right hippocampus, left hippocampus, and left centre median. EEG records were also evaluated for this animal while he was sitting quietly and before he had been trained to do the drl-h task. Differences in peak quotients for 7-Hz fields-on vs. fields-off were observed in four of six structures tested: right hippocampus, right centre median, left hippocampus, and left amygdala.

Coherence measures between the 7-Hz sinusoidal wave form and the responsive EEG structures were always higher for the fields-on condition than for the fields-off condition. Sample measures are shown in Figure 4. Coherences between responsive brain structures did not reveal a consistent pattern of change.

No effects on EEG at non-field frequencies were visually noticeable, but the discriminant analysis program Discan (see Methods) was applied to the data of one animal (J.), and identified strong driving (increased intensity and increased coherences) at harmonics of the field frequency. Although such harmonic response is perfectly compatible with biological transduction (Walter and Adey[16], Van der Tweel and VerduynLunel[15]), it does not exclude artifactual transduction. Further application of Discan, this time excluding all bands containing any harmonics of the field frequency, still showed a clear discriminability of fields-on from fields-off EEGs, principally in that intensity was raised in the fields-on condition, even in non-harmonic frequency bands.

Discussion. The behavioral results suggest that imposing a 7-Hz field on the performing animal resulted in shorter interresponse times. Results with 10-Hz fields were not reliable. Experimental/control differences for the 7-Hz runs were statistically significant for five of six experiments, and these differences could be observed in all three monkeys. In spite of large differences in total output of responses from monkey to monkey, the shift in interresponse times was very consistent (towards faster responses) and rather large (.4 seconds or greater).

Increases in EEG intensity (peak quotients) at the frequency of the fields were observed in all three animals in the hippocampus, and less consistently in the amygdala and centre median. These differences were observed both in the 7-Hz and 10-Hz conditions. Coherences between the sine wave and responsive brain structure at the fields frequency were always higher in the fields-on condition.

The analysis of the EEG data presents special problems. The difficulty of isolating effects of biological transduction from those of transduction at the electrode/tissue-fluid interface is considerable, being almost parallel to the impossible question of "what the tree looks like when no one is looking at it." Nevertheless, the discriminant analysis program has provided preliminary evidence of subtle EEG changes at non-field frequencies that cannot be easily explained as electrode/tissue artifacts.

The concordance of evidence for a fields effect on behavior and on electrical activity of the brain is encouraging. We

intend to pursue additional demonstrations of these same kinds as well as others. One new technique to be applied is a frequency "sweep" from 5 to 20 Hz, with enough time spent at each frequency to allow coherence estimates to be reliably made there; our prediction is that, as occurred with wholebody vibration in the monkey (Walter and Adey[16]), and as seems to occur with sinusoidally modulated light stimulation in the human (van der Tweel and VerduynLunel[15]) there will be a band of incoherent driving. It may even be possible to establish some specific non-linear model, along the lines successfully pursued by Spekreijse[14] for the visual system.

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FIGURES

Figure 1. Behavioral data showing shifts in interresponse time under 7-Hz fields. The abcissa shows time between responses in .2 sec. bins; the ordinate shows percent of total responses at each interval. (Note that only bins 15-45 are plotted; bins 0-144 were used in calculation of means and standard deviations).

Figure 2. Sample records of EEG and percent power graphs before conversion to peak quotients.

Figure 3. Significance levels for EEG peak quotients: fields-on vs. fields-off.

Figure 4. Sample records of EEG and 7-Hz sinusoidal wave form with corresponding coherence tables.

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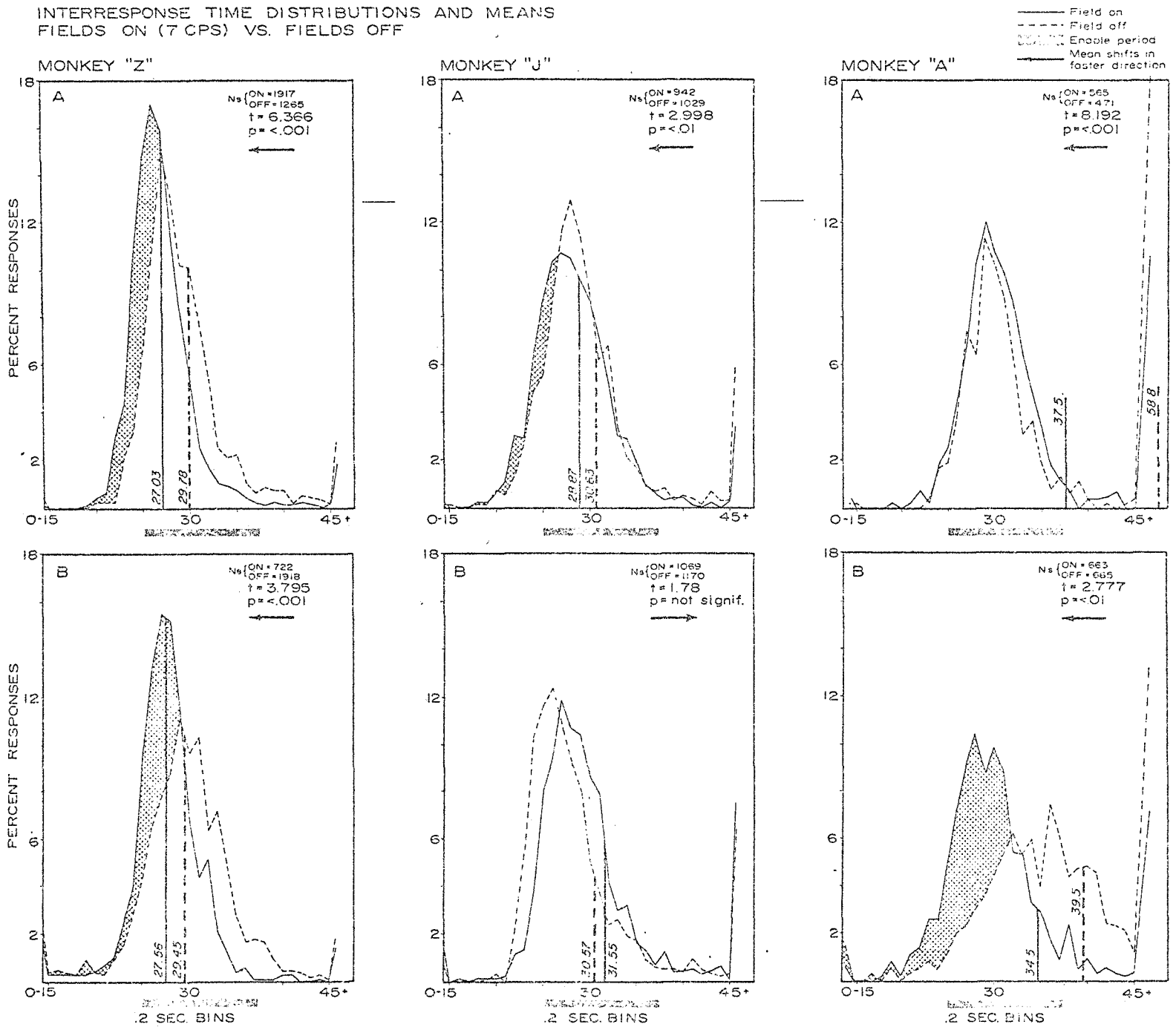
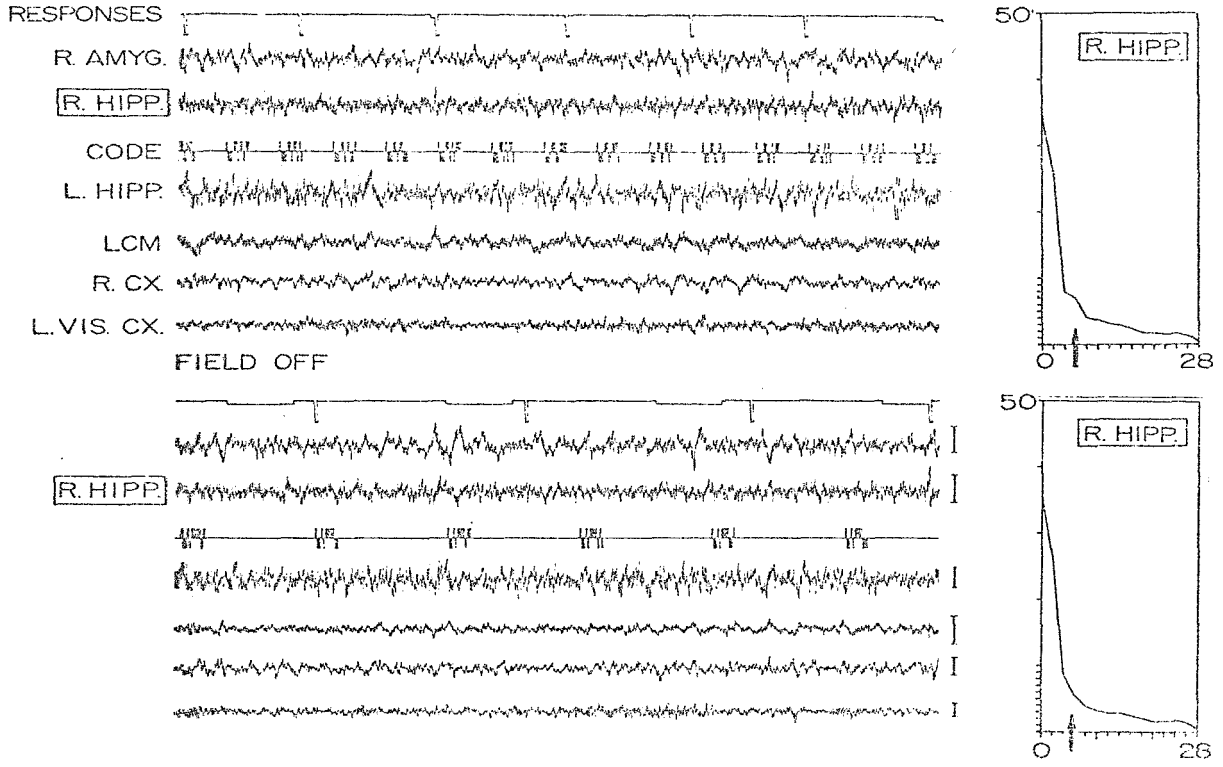
INTERRESPONSE TIME DISTRIBUTIONS AND MEANS
FIELDS ON (7 CPS) VS. FIELDS OFF



SAMPLE EEG RECORDS FIELD ON (7 Hz) VS. FIELD OFF

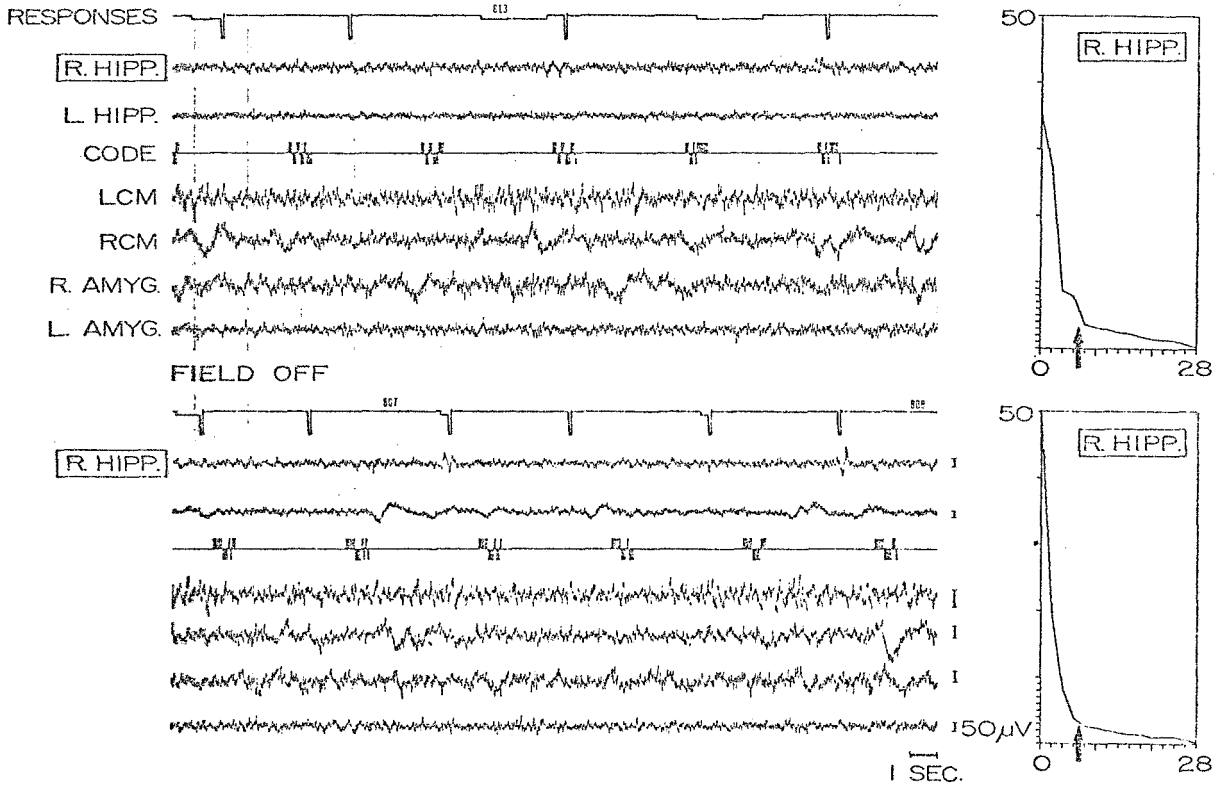
SAMPLE PERCENT POWER SPECTRAL INTENSITY. FIELD ON (7Hz) VS. FIELD OFF.

A. MONKEY Z
FIELD ON 7 Hz



B. MONKEY A
FIELD ON 7 Hz

MONKEY A



EEG PEAK QUOTIENTS
FIELDS ON VS. FIELDS OFF
PROBABILITY OF OBSERVED DIFFERENCES
(T-TESTS)

Performing DRL task. 80 sec. segments near end of the 4 hr. runs. Combined data from 2 experimental-control runs

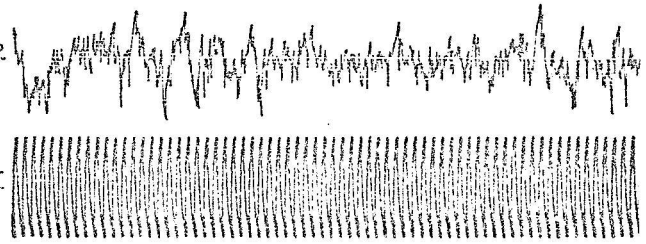
		7 CPS On vs. Off	10 CPS On vs. Off
MONKEY J	L. HIPPOCAMPUS	p = .048	p = .025
	R. HIPPOCAMPUS	p = .001	p = .011
	R. AMYGDALA	p = .003	p = .001
(OTHER STRUCTURES OBSERVED: LMBRF, L.V. CX, R. M. CX, R.V. CX)			
MONKEY Z	R. HIPPOCAMPUS	p = .006	p = .020
	L. CENTRE MEDIAN	p = .001	p = .001
(OTHER STRUCTURES OBSERVED: AUD CX, R.V. CX, R. AMYG, L. HIPP)			
MONKEY A	R. HIPPOCAMPUS	p = .001	
	L. HIPPOCAMPUS	p = .001	No run
	L. CENTRE MEDIAN	p = .059	
(OTHER STRUCTURE OBSERVED: L. AMYG)			

Non-performing: Sitting quietly

		7 CPS On vs. Off
MONKEY A	R. HIPPOCAMPUS	p = .001
	L. HIPPOCAMPUS	p = .036
	R. CENTRE MEDIAN	p = .045
	L. AMYGDALA	p = .003
(OTHER STRUCTURES OBSERVED: LCM, R. AMYG)		

Sample EEG Records

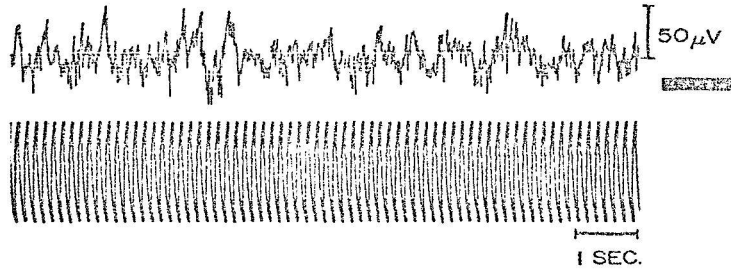
FIELD ON 7Hz



Sample Coherences of Averaged Data

Hz	Coherence
2	.038
4	.014
6	.146
8	.016
10	.005
12	.008
14	.015
16	.012

FIELD OFF



Hz	Coherence
2	.010
4	.002
6	.003
8	.003
10	.004
12	.006
14	.005
16	.009