

N72-24088

CR115551

FINAL REPORT

Contract NAS 9-11120

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FINAL REPORT

Contract No. NAS 9-11120

Title:

Analysis of Bioelectric Records and Fabrication
of Prototype Sleep Analysis Equipment

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Date: February 25, 1972

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The work carried out under this contract consisted of two independent but closely related tasks designed to implement the Manned Spacecraft Center's programs concerned with the application of EEG and EEG analysis to the study of sleep-wake cycles in man.

TASK I

This study was designed to evaluate analytic EEG computer programs developed by the Neurophysiology Group at Baylor/Methodist to extract information not available through standardized visual (clinical) reading of the analog trace, or to provide quantitative information concerning the analog trace which can only be characterized in subjective, non-numerical terms by visual analysis (see Carrie and Frost, 1971). A small general-purpose computer system for EEG wavelength-amplitude profile analysis, developed with the support of a previous contract for the Manned Spacecraft Center (NAS 9-9418), was employed for the analysis of tapes that were developed for inclusion in the NASA/Baylor Normative EEG Library. These tapes were developed for the unique purpose of making a quantitative analysis of changes elicited in the electroencephalograms of young male adults by a drug known to produce subtle EEG changes in therapeutic doses.

Because sleep-promoting drugs are carried in space missions for emergency use, it was decided that the agent to be utilized should be of this character. The agent selected, flurazepam hydrochloride (a benzodiazepine derivative), was chosen because it has been demonstrated to be a clinically useful hypnotic agent (Jick, 1969; Kales et al., 1969) that promotes sleep without excessively suppressing the REM stage, as do other hypnotics. Also, other benzodiazepine derivatives such as chlordiazepoxide and diazepam had been shown to produce fairly marked and consistent EEG changes in therapeutic doses (Lairy, 1962; Towler et al., 1962). Preliminary visual analysis of the EEGs of patients receiving flurazepam hydrochloride had shown that similar EEG changes were induced by this derivative also.

Method

Subjects. Five male, volunteer subjects were selected on the basis of interviews and screening tests to participate in the study. All subjects were free of known major medical or psychiatric disorders, had received no medication during the preceding 30-day period, and presented normal screening EEG evaluations.

Procedure. On the day after the routine clinical EEG screening test, the EEG of each subject was recorded at 90-minute intervals over a period of 8 hours to establish his usual waking pattern (baseline test). During recording, subjects were at rest with eyes closed, at rest with eyes open, and provided 3 minutes of voluntary overventilation. After the baseline test, each subject received 30 mg of flurazepam hydrochloride nightly for 2 weeks, after which a placebo was substituted for a second 2-week period. An 8-hour test similar to the baseline study was performed weekly, and a single clinical EEG test was run every other day. In two subjects who showed some residual effects at the end of the 2 weeks of placebo administration, a final 8-hour test was carried out after a third week, during which neither drug nor placebo was administered.

Only one of the investigators knew whether drug or placebo was being administered. The subjects were not told the name of the drug that was under evaluation until the end of the project.

Visual EEG interpretation. The EEG records for each 8-hour test and for each of the intervening shorter tests were interpreted visually by a clinical electroencephalographer. Each record was examined individually to detect the presence of any EEG change or any unusual or abnormal electrographic event. The amount of fast (beta) activity that was present in each recording was rated according to an arbitrary scale.

EEG recording and quantification. EEGs were obtained with a Beckman Type R electroencephalograph and were recorded simultaneously on analog magnetic tape to permit off-line computer analysis. EEG signals were quantified by a modified version of the system described by Carrie and Frost (1971). The outputs from 2 EEG channels were subjected simultaneously to bandpass filtering (Krohn-Hite 333B filters) in order to limit the range of EEG frequencies contained in the signals. The settings on the filters were adjusted in separate analysis runs to give essentially flat responses between 3 c/sec and 7 c/sec (theta range), 6 c/sec and 14 c/sec (alpha range), and 14 c/sec and 38 c/sec (beta range) with a relatively high degree of attenuation of frequencies above and below these range limits. The filtered signals were then analyzed with a LINC-8 computer during each analysis run in real time. Consecutive waves in each of the filtered signals were sorted automatically into 60 different wavelength categories in each band. The limits of the passbands defined by the digital programs were 136.07 and 370.46 msec (theta range), 55.99 and 173.18 msec (alpha range), and 77.04 and 24.96 msec (beta range).

In 2 subjects, 1000 consecutive waves in the alpha range were acquired from each channel during each analysis run. In the other 3 subjects, the analysis time for alpha was 100 seconds. The analysis time for all subjects was 100 seconds for theta and 30 seconds for beta. Alpha and theta activity in the C₃-O₁ and C₄-O₂ derivations and beta activity in the F₁-C₃ and F₂-C₄ derivatives were quantified. During the recording of the EEG for alpha and theta analysis, the subjects closed their eyes; samples for beta analysis were obtained under both the "eyes-closed" and the "eyes-open" conditions. The digital computer counted the number of waves in each of the 60 wavelength categories; the summated peak-to-peak amplitude in each wavelength category also was computed. Following the acquisition of this information in real time, 14 measurements and statistical variables that described quantitatively the characteristics of the EEG signal were calculated for each channel. Three of these measurements were used in this study for the examination of the effects of the drug on the EEG.

Additional quantitative analysis was performed using an IBM 360/50 computer (see Results).

Results

Visual analysis

No consistent change was detected in alpha or theta activity throughout the study in any of the subjects.

Visual examination showed an increase in the amplitude of beta activity in the EEGs of all the subjects during administration of the drug. This increase was rated as "minimal" in 2 subjects, "very slight" in one, "clear-cut" in one, and "very pronounced" in one. No other changes consistently associated with drug administration were reported by the electroencephalographer.

One subject showed episodes of 14 and 6/sec positive spikes in the majority of his records. The same subject showed bursts of generalized "abortive" spike and wave patterns which were not present in the baseline recording but which were maximal in amplitude and frequency of occurrence at 2 and 3 weeks after withdrawal of the drug.

Computer analysis

Graphic plots. The mean wavelength, the average wave amplitude, and the number of waves during the fixed analysis time were

each plotted as a function of test days. Examination of these plots supported the results of visual interpretation of the EEG tracings in that no changes in the alpha and beta activity that were associated consistently with the administration of the drug could be defined. However, in all 5 subjects there was a clearly detectable change in fast, or beta, activity during the period of flurazepam administration. This change was characterized by an increase in the number of waves in the 30-second epoch during which the EEG was analyzed. There was a less definite increase in average wave amplitude with no detectable change in mean wavelength. The change in beta activity was most striking during periods when the subjects' eyes were open. There was a considerable degree of variability in the magnitude and persistence of the EEG response to drug administration. In 3 subjects, the EEG returned to the starting level within 2 weeks of drug withdrawal. The other 2 subjects showed a relatively marked change in beta activity during drug administration, and 3 weeks elapsed before restoration of the baseline pattern occurred. The findings from one subject, which are typical of those from the whole group, are shown in Fig. 1.

Statistical analysis

An IBM 360/50 computer was used via a remote access statistical system to obtain a quantitative assessment of the information displayed in the graphic plots of beta activity. The significance of the difference between scores obtained during the baseline 8-hour test and each of the other 8-hour tests was calculated for each subject. In 2 subjects, 12 samples of EEG were obtained from each channel during an 8-hour test for beta analysis; in the other 3 subjects, the 8-hour tests yielded 24 samples for beta analysis. It was found that most of the scores obtained during drug administration, and also some of the scores obtained 2 and 3 weeks after drug withdrawal, differed from the baseline observations beyond the 5% level of significance.

In order to detect changes consistently related to administration of the drug, the results for all 5 subjects for both sides were pooled for each EEG variable and for each test. The number of tests showing P values of more than 0.05, and the numbers showing P values of less than 0.05 for increases and decreases in the variables as compared with the 8-hour baseline levels, were determined using the Wilcoxon matched-pairs signed-ranks test (Siegel, 1956). The results are displayed in the form of a series of block histograms in Fig. 2. The most consistently significant change from the baseline that was related to drug administration was an increase in the number of beta waves during the analysis epoch, with a less consistent tendency for the wave amplitude to increase.

Discussion

In this investigation, visual evaluation of EEG records indicated that administration of flurazepam hydrochloride was associated with an increase in the prominence of relatively high frequency components of the signal. This type of EEG change is also often caused by other widely used benzodiazepine derivatives, such as chlordiazepoxide (Kaim and Rosenstein, 1960; Winfield and Aivazian, 1961; Lairy, 1962; Geissman et al., 1962) and diazepam (Towler et al., 1962; Réquin et al., 1963).

The results of computer analysis confirmed the findings obtained by visual analysis and also demonstrated an aspect of the drug effect that was not obvious on visual inspection of the original EEG tracings. It was found that the increase in the prominence of beta activity was characterized mainly by a consistent increase in the incidence of waves in the 14-38 c/sec range with a much less consistent increase in their average amplitude and with no detectable change in average wavelength (frequency).

Although the most consistent changes in EEG characteristics were associated with flurazepam administration, some significant differences were detected by the highly sensitive techniques used in this study between the baseline measurements and those obtained up to 3 weeks after withdrawal of the drug. This finding may have been the result of an inadequate baseline measurement, or of normal temporal variability in EEG characteristics as measured by the technique used in this study, or of real drug effects that persisted for at least 3 weeks after withdrawal. Further investigation will be required before any conclusions can be drawn.

Summary

A computer-analysis technique was used to evaluate the changes in the waking EEGs of 5 normal subjects which occurred during the oral administration of flurazepam hydrochloride (Dalmane). While the subjects were receiving the drug, there was an increase in the amount of beta (14-38 c/sec) activity in fronto-central EEG leads in all 5 subjects. This increase in beta activity was characterized by a highly consistent increase in the number of waves that occurred during an EEG recording interval of fixed duration and by a less consistent increase in average

wave amplitude. There was no detectable change in mean EEG wavelength (frequency) within the beta frequency range. The EEG patterns reverted to their baseline condition during 2-3 weeks after withdrawal of the drug.

Analysis of the alpha, theta and delta components of the EEG indicated no changes during or following administration of the drug.

This study clearly illustrates the usefulness of specific computer-analysis techniques in the characterization and quantification of sleep-promoting drugs upon the EEG of the normal young adults in the waking state. The influence of such drugs in modifying the stages of sleep has been well established, but no quantitative studies have yet been made of the effects of such drugs upon the wave components of the various sleep stages.

The 33 tapes used in this study have been entered and inventoried as a permanent part of the Normative EEG Library.

TASK II

This task consisted of the fabrication for DB4 MSC certain items of EEG sleep-monitoring and analysis equipment developed by the Neurophysiology Group at Baylor/Methodist. These items are unique in that they represent the products of applied research carried out by the Neurophysiology Group over a period of several years and are prototypes basic to anticipated flight-hardware development for a proposed Skylab I sleep-monitoring experiment.

Fabricated and delivered to DB4 MSC were two preamplifiers and 150 EEG monitoring caps with electrodes. These conformed to the specifications outlined in the final report to NASA of Contract NAS 9-10747 under which these items were finally developed.

FIGURE LEGENDS

- Fig. 1. Three measurements of EEG characteristics plotted as a function of test days. The thicker bars on the time axis indicate that relevant points are the averages of measurements obtained during an 8-hour test. There is a clear-cut increase in the number of waves in the 14-38 c/sec band, with a much less definite increase in average wave amplitude, during drug administration.
- Fig. 2. Each block histogram shows pooled results from all 5 subjects and both sides of the head for each 8-hour test. The number of tests giving P values (Wilcoxon matched-pairs signed-ranks test) of less than 0.05 for increases or decreases in the measurements as compared with the 8-hour baseline levels, or P values of more than 0.05 (N.S.) are shown. The most consistent drug-related change was an increase in the number of waves during an EEG recording interval of fixed duration, with a less definite increase in average wave amplitude.

FIG. 1

SUBJECT: R. K. W.
BETA BAND (14-38 Hz)
EYES OPEN
C3-A1 (LEFT)
C4-A2 (RIGHT)

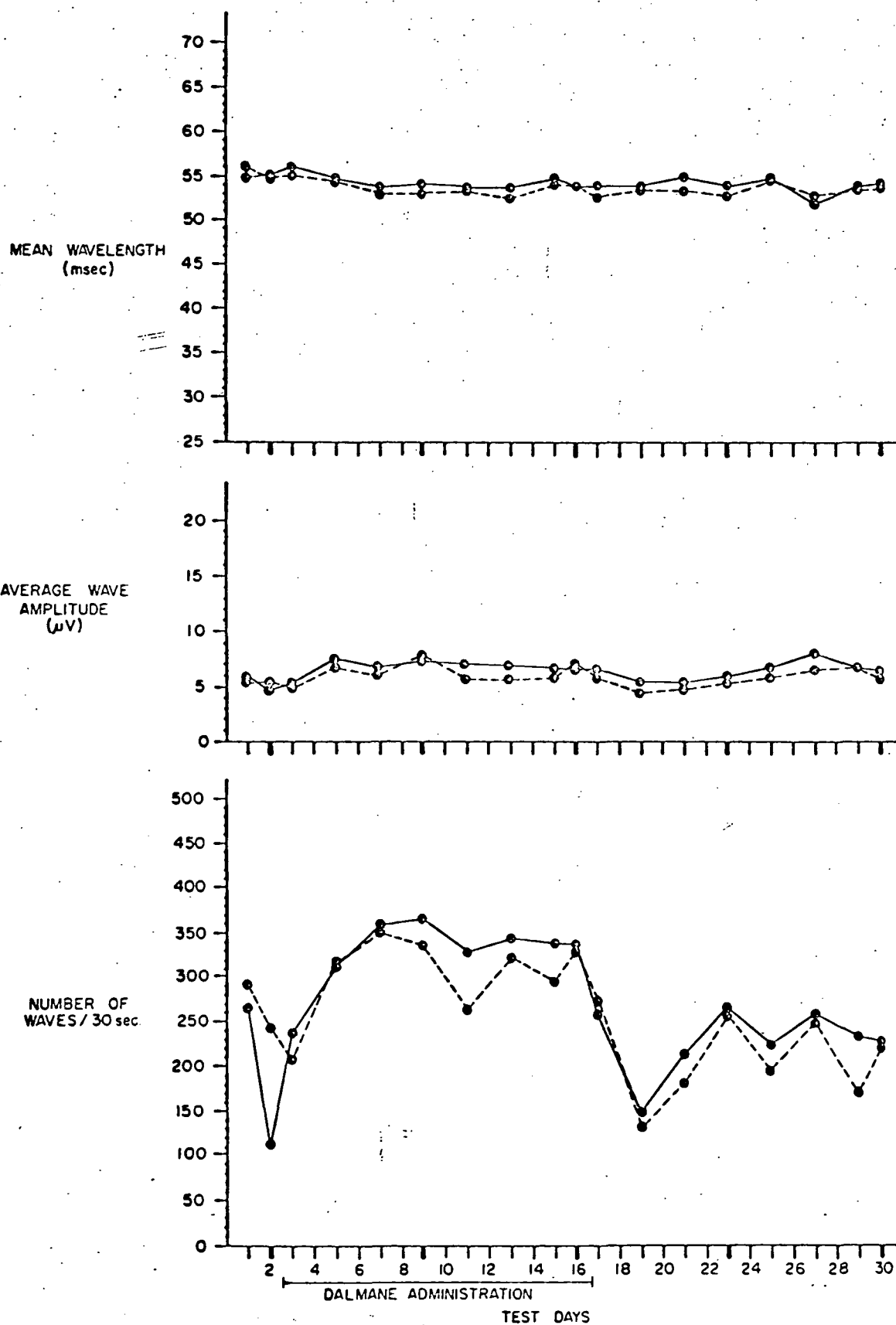
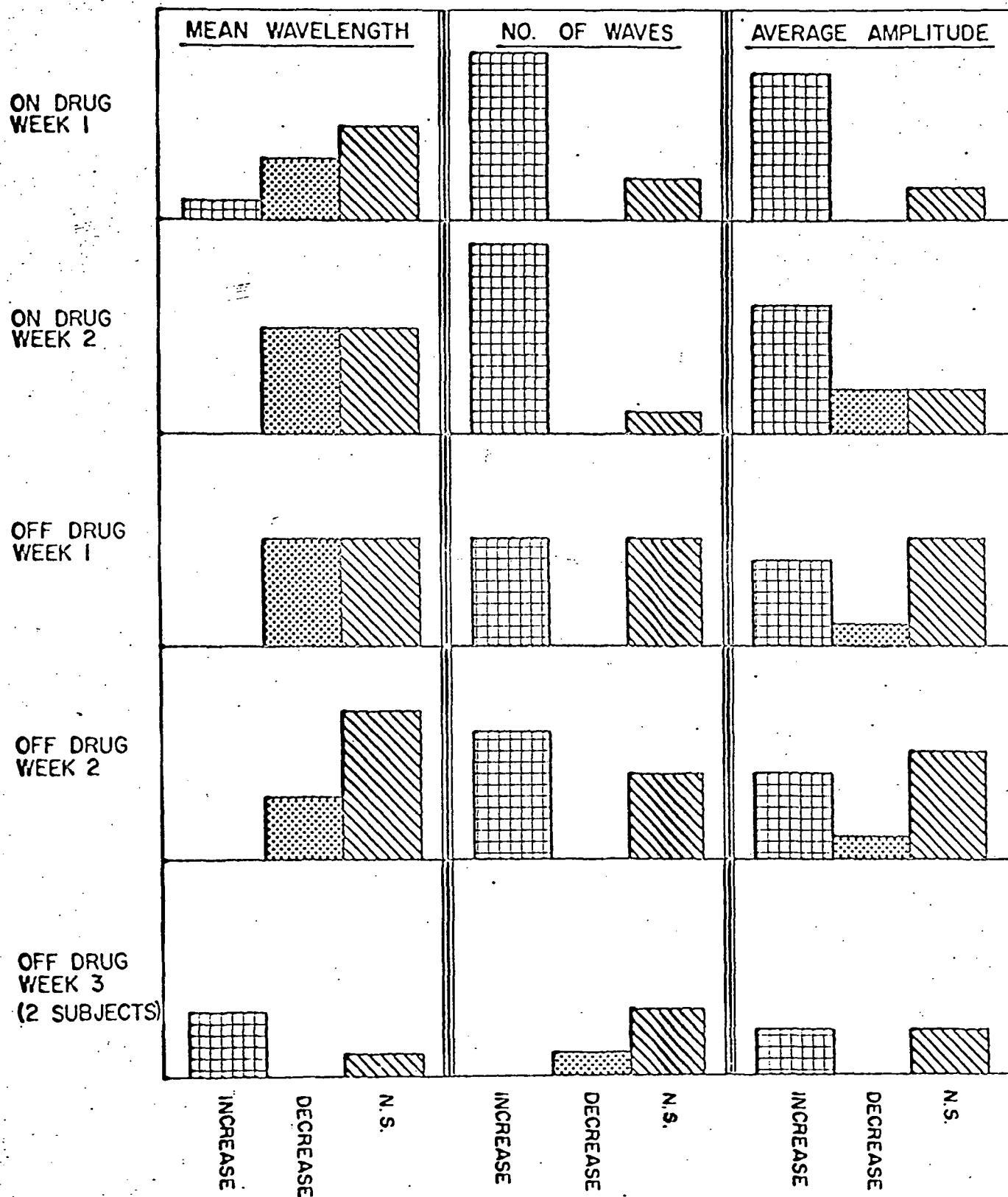


FIG. 2 - COMPARISON WITH BASELINE MEASUREMENTS

(WILCOXON TEST)

BETA (14-38 Hz)

EYES OPEN



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APPENDIX

The alpha-analysis program, IA and IB, and examples of II, a wavecount/wavelength profile, III, a summated peak-peak amplitude/wavelength profile and IV, mean-wave amplitude/wavelength profile from a single electrode pair on the left side of the head.

ALPHA ANALYSIS/LEFT

SUMMATED PEAK/PEAK AMPLITUDES
DURING DATA ACQUISITION= 15287 MICROVOLTS

MEAN WAVE AMPLITUDE/WAVELENGTH
PROFILE ANALYSIS...

WAVELENGTH OF WAVES WITH
LARGEST MEAN AMPLITUDE= 0096 MILLISECS

LARGEST MEAN AMPLITUDE= 0020.2 MICROVOLTS

MEAN= 0102 MILLISECS

VARIANCE= 0786 MILLISECS

STANDARD DEVIATION= 0028 MILLISECS

MEDIAN= 0094 MILLISECS

INTER-QUARTILE RANGE= 0028 MILLISECS

WAVECOUNT/WAVELENGTH
PROFILE ANALYSIS...

WAVECOUNT AT MODAL WAVELENGTH= 0126 WAVES

MODAL WAVELENGTH= 0086 MILLISECS

MEAN= 0088 MILLISECS

VARIANCE= 0133 MILLISECS

STANDARD DEVIATION= 0012 MILLISECS

MEDIAN= 0084 MILLISECS

INTER-QUARTILE RANGE= 0008 MILLISECS

ANALYSIS TIME= 0090 SECS

AVERAGE WAVE AMPLITUDE= 0015.3 MICROVOLTS

ANALYSIS OPTIONS...

SELECT DESIRED OPTION:

- 1 NAME
- 2 BLOCK NO.
- 2

ENTER DESIRED BLOCK NUMBER:

120

SELECT ANALYSIS REQUIRED:

- 1 ALPHA
- 2 BETA
- 3 THETA
- 1

SELECT DESIRED SIDE:

- 1 LEFT SIDE
- 2 RIGHT SIDE
- 3 BOTH SIDES
- 1

STATISTICAL MEASURES REQUIRED:

- 1 ALL MEASURES
- 2 SOME MEASURES
- 1

SELECT DESIRED OPTION:

- 1 CALIBRATION FACTOR
- 2 SCALING FACTOR
- 3 BOTH FACTORS
- 4 NEITHER FACTOR
- 1

ENTER CALIBRATION FACTOR:

1.7

SELECT DESIRED OPTION:

- 1 DETAILED PRINT-OUT
- 2 QUICK PRINT-OUT
- 1

BLOCK NO. 120
OPTION NO. 3

II

50

100

150

200

I-----I-----I-----I-----I
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I
IX
IX
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IXX
14 -XXX
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13 -XXXXXXXX
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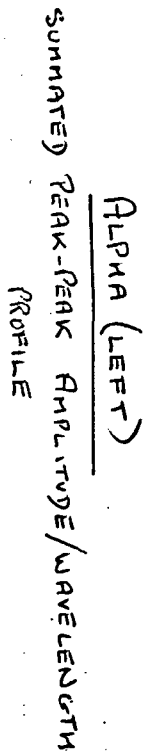
ALPHA (LEFT)
WAVECOUNT/WAVELENGTH PROFILE

III

1

400

800



1
-----I-----I-----I-----I-----I
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ALPHA (LEFT)
MEAN WAVE AMPLITUDE/WAVELENGTH
PROFILE