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Characterization of sleep EEG

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ABSTRACT

The physiological relationship between the various components of sleep and its variation due to drug administration has been used as one of the primary tools to analyze the performance of drug. A number of studies have been performed in recent years in this direction. Electroencephalogram (EEG) has been characterized with the help of variables ranging from measurements of the duration of different sleep stages to the activities that define the stages themselves. Advances in computer hardware and software have improved the methods of data acquisition and storage. Analysis of long stretch of data has always been a problem considering the time and storage.

The present study is aimed at characterizing sleep data from a subject suffering from neurologic disorder. It also aims at identifying the effect of Oxycodon a Narcotic drug on the subject during sleep. The data considered for analysis is the output of a whole night recording. It is for a duration of six hours. EEG signals are analyzed using random data analysis procedures. The assumption of stationarity will be used as the basis of analysis. However the fact that analysis on long stretch of data introducing nonstationarity will not be ruled out. The analysis will be performed using Fast Fourier Transformation. Spectral analysis will be used as the primary tool in identifying the activities of various frequency components and its variation with time. The three parameters that will be considered are Mean square values and correlation function in time domain, Spectral analysis application in frequency domain and the probability density and distribution functions in the amplitude domain. Algorithms will be developed for computing these parameters and other statistical properties.

CHARACTERIZATION OF SLEEP EEG

by
Seetharamiah Sateesh

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This thesis is dedicated to
Amma, Anna and my loving Putti

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CHAPTER 1

INTRODUCTION

1.1 Introduction

In recent years a number of sleep variables have been defined that characterizes sleep. These variables range from measurements of the duration of the different stages of sleep to measurements describing the evolution of sleep through the night. Using these variables, a number of studies aimed at understanding the fundamental properties of sleep in normal subjects have been performed. These studies essentially concern sleep modifications produced by drugs or other experimental manipulations. The physiological relationships between the various components of sleep are still largely unknown. Advances in computer hardware and software have led to improved acquisition and display, as well as storage of sleep data. Strides have been made in computerized discrimination of electroencephalographic (EEG) frequency patterns and specific wave complexes. The present work aims at determining the time varying statistical properties of various sleep variables in an attempt to characterize the variations in EEG patterns following drug administration.

1.2 Normal Sleep Patterns

A normal sleep pattern has been realized after several studies of EEG. As soon as the normal subject drifts into sleep the waking voluntary eye movements which make huge deflections in electrooculogram(EOG) disappear and the high level of muscle activity decreases. The background alpha rhythm disappears and the subject enters Non Rapid Eye Movement (NREM) sleep stage 1. With the appearance of sleep spindles and K-complexes, the subject enters NREM sleep

stage 2. The K-complex, consisting of an initial negative wave, followed by a positive wave, sometimes follows a sudden environmental stimulus such as noise. Other K-complexes follow internal autonomic events such as bladder or gastrointestinal contractions [1]. The sleep spindle is a burst of 12 to 15cps activity lasting over one-half second. As NREM sleep progresses, delta activity becomes more and more predominant, the subject enters NREM sleep stages 3 and 4.

After about two hours of NREM sleep, the subject abruptly enters Rapid Eye Movement Sleep (REM) sleep. The EEG changes to a relatively low voltage, mixed frequency pattern, and the chin EMG markedly decreases its activity. Frequently a burst of theta activity heralds the onset of a REM period. The theta waves which occur during REM sleep sometimes have a notch on the rising or falling phase to give the picture of a sawteeth. These sawtooth waves, which are characteristic of REM sleep, frequently occur during or just before an eye movement. While some reports say that the eye movements of REM sleep are unlike any eye movements recorded during wakefulness, others have described somewhat similar eye movements during periods of daydreaming. Figure 1 presents a sample of typical polygraphic records from waking, REM sleep and some NREM sleep stages.

Periods of NREM and REM alternate during the night. The cyclicity of this alternation averages about 90 minutes for adults and 45 minutes for infants. In adults the first NREM period is normally dominated by stage 4. NREM periods in the early morning hours mainly consist of stage 2. The first REM period is shorter and has fewer eye movements than the later REM periods. Four to six REM periods occur during a night. As summarized in Table 1, about 20 to 25 percent of a night's sleep is spent in the REM state. Very slight decrease in REM percentage and a somewhat larger decline in NREM stage 4 may occur with

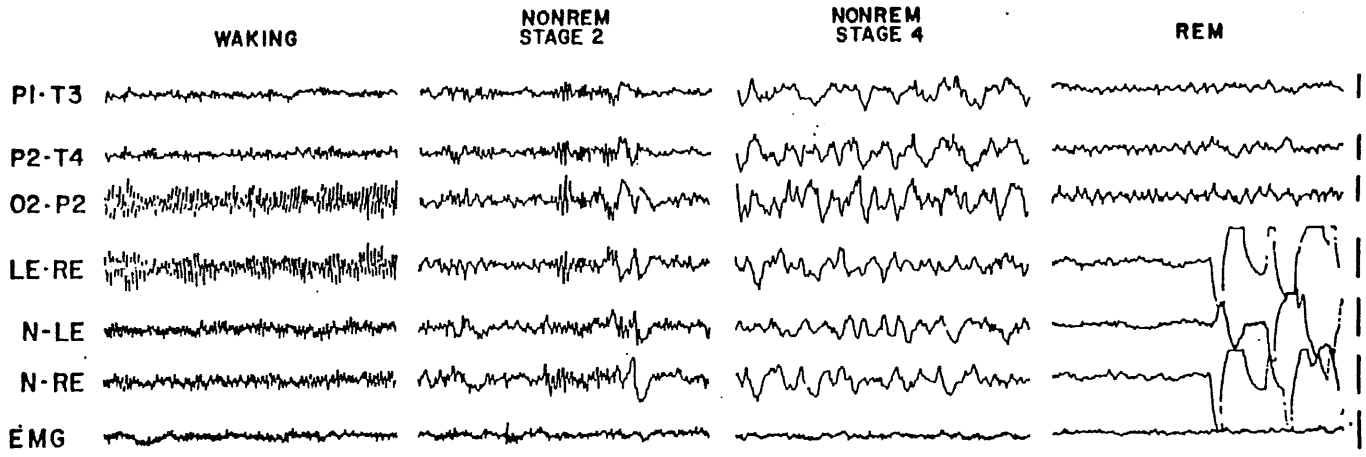

Figure 1 All-night polygraphic recording. Top three channels monitor the EEG; the next three, eye movements; and the bottom EMG.

Table 1 Sleep patterns in normal man

	N	*Average Age*	*Sleep Time*	*W*	*REM*	*Sleep Stage Percentages* 1	2	3	4	*Reference*
Preadolescent males	18	9.5	565 min	1.5	24.3	6.1	44.2	5.9	17.9	Ross et al. (1968)
Young adult males	16	24.2	—	0.9	24.1	5.4	48.7	7.7	13.2	Williams et al. (1964)
Young adult females	16	23.9	451	1.1	21.9	5.9	48.0	6.9	16.2	Williams et al. (1966)
Adult males	12	33.9	—	2.4	21.9	7.5	53.0	5.5	9.6	Agnew and Webb (1968a)
Middle aged males	16	54.1	436	4.1	22.8	10.9	51.1	8.4	2.7	Agnew et al. (1967)
Elderly (both sexes)	16	63.4	—	9.9	20.4	11.9	50.6	4.5	2.7	Agnew and Webb (1968b)
Aged males	16	80.2	365.8	—	20.1	4.2	53.9	17.2	4.5	Kahn and Fisher (1969)
Aged females	16	76.7	383.0		18.0	2.6	63.4	10.4	5.6	Kahn et al. (1970)

increasing age. Table 1 also presents the average sleep patterns of different age groups.

The sleep of normal human infant can be divided into two types. One type is characterized by no eye or body movements and regular respirations while the other type is associated with eye and body movements, irregular respiration and spontaneous suckling [2]. The first type develops into NREM sleep , the latter into REM. Sleep spindles first appear in the NREM EEG record. Unlike the adult, the infant usually passes from wakefulness directly into REM sleep. At about three months of age the infant begins to show the adult pattern of falling from wakefulness into NREM sleep. EOG during neonatal REM sleep are not identical to either eye movements of the waking newborn or of the adult REM state. It has been suggested that the changes in both REM and NREM EEG can determine conceptional age and neurological maturation in premature infants. In the case of newborn 40 to 50 percent of the sleeping time is acquired by the REM stage.

1.3 Clinical Sleep Disorders

Thousands of miles of sleep EEG data have been accumulated, and countless hours of effort have been expended by sleep researchers around the globe. Considerable information has emerged from the sleep laboratories which can be useful to the physician [3]. Some of the common disorders known are listed below .

a. Narcolepsy

This describes a condition of recurring, uncontrollable episodes of brief sleep. This disorder usually begins in adolescence or young adulthood, it continues throughout life but is generally thought to improve in later years [4]. In narcoleptics REM occurs at, or soon after, the onset of sleep when compared to normal sleep pattern. Many stimulant and antidepressant medications have been

used in the treatment of true narcolepsy, but nothing replaces an understanding discussion with the patient and his family about the illness and ways they can adjust themselves to it.

b. Cataplexy

Characterized by brief episodes of muscular weakness which are precipitated by laughter, anger, or other emotional excitement. The degree of disability may range in scope from a mere subjective feeling of weakness to almost total paralysis.

c. Hypersomnia

The subject will have tendency to sleep for excessively long periods, either as an extension of nocturnal sleep into the late morning or past noon, or at various times during normal hours of wakefulness. Unlike narcoleptics, patients with hypersomnia do not display the auxiliary symptoms of cataplexy and rarely complain of disturbed nocturnal sleep [3].

d. Insomnia

Inability to fall asleep, frequent and prolonged awakenings, early morning awakenings, in the absence of gross physical or psychological pathology is probably one of the most common sleep disturbances. Sleep EEG studies indicate that there is a physiological basis for the insomniac's complaints and it has been found that these patients have significantly longer sleep latencies, shorter sleep times and less efficient sleep.

e. Sudden Infant Death Syndrome (SIDS)

Is a sleep related phenomenon that has been strongly supported by the evidence of a high incidence of infant mortality during sleep [5]. The typical clinical syndrome is that of a generally healthy of 2 to 4 months of age who is put to sleep in its crib at night and is found dead shortly thereafter or in the morning, having died several hours before. Autopsy examination reveals no abnormalities

recognized as cause for death. The automatic inspiratory-expiratory rhythmic cycle is disrupted by recurrent periods of apnea. It is suggested that NREM sleep stages in the infant might be more prone to be correlated with a prolonged apnea than the REM sleep stage.

1.4 EEG and Drug Effect

Quantitative EEG methods have a well-documentated application in human psychopharmacology. They are used to identify drugs which affect the central nervous system, specify the times of drug activity, compare and classify drugs, and relate EEG findings to other measured effects. The EEG signal is most commonly quantified in fixed frequency bands, using power spectral density analysis. Drug effects are defined as those EEG changes from pre-drug that differ statistically from the changes after placebo.

In studies of newly developed drugs and low doses of known drugs, there is frequently a problem in deciding whether there has been an effect on the EEG. Probabilities are difficult to determine, since the many variables examined inflate the likelihood of finding differences from placebo and standard statistical adjustments are complicated by the high intercorrelations of EEG variables.

1.3 Visual and Computer Based Analysis

Sleep-waking patterns in the EEG have been studied in various species. Analysis have been done using computers and visually. Visual analysis is based on the interpretation of an individual with a good physiological background on sleep characterizing the polygraphic records. The analysis depends on the individuals view and the sleep criteria he considers. Visual analysis of the EEG remains necessary and appropriate, but is time consuming and lacks quantification. The expense and laboriousness of all-night polygraphy limits the number of subjects

and the number of nights which can be monitored in any single study. These limitations in visual analysis have opened doors for computerized quantitative analysis.

Various techniques for a computerized quantitative analysis of the EEG have been developed. Computerized method enable on-line analysis and objective classification of sleep-waking patterns recorded over large periods. Frequency domain statistics like spectral density which accurately quantify the sleep state by power-frequency distributions can be best done through computer processing. If both visual and computer analysis are performed over the same length of EEG, they seem to mutually influence each other [6]. Automatic analysis does not replace visual analysis but is helpful in handling and organizing the enormous amount of data obtained during very long records.

CHAPTER 2

TECHNIQUES FOR RANDOM DATA ANALYSIS

2.1 Random Processes

Data representing a random physical phenomenon cannot be described by an explicit mathematical relationship because each observation of the phenomenon will be unique. In other words, any given observation will represent only one of many possible results which might have occurred.

Random processes may be categorized as being either stationary or nonstationary. When a physical phenomenon is considered in terms of a random process, the properties of the phenomenon can hypothetically be described at any instant of time by computing average values over the collection of sample functions which describe the random process. The random process is said to be nonstationary if the mean value and the joint moment values vary with time. For special cases when mean and the joint moment do not vary as time varies, the random process is said to be weakly stationary or stationary in a wide sense [7]. When all possible moments and joint moments are time invariant, the random process is said to be strongly stationary.

Nonstationary process include all random processes which do not meet the requirements for stationarity. The statistical properties of nonstationary random process are time varying functions which can be only determined by performing instantaneous averages over the ensemble of sample functions forming the process. Spectral analysis is a powerful tool in characterizing such signal. Coherence spectra is used as a measure of correlation between two simultaneous signals as a function of frequency. This can be used as a useful method in medical applications.

2.2 Basic Properties of Random Data

Four main types of statistical functions are used to describe the basic properties of random data.

a. Mean square value

The mean square value describe the intensity of data. It is simply the average of the squared values of the time history. The mean square value for a sample time history $x(t)$ is given by

$$\Psi_x^2 = \lim_{T \to \infty} 1/T \int_0^T x^2(t)\, dt$$

Physical data is a combination of time-invariant component and a fluctuating component. The static component can be described by the mean value and dynamic component by the variance which is the mean square value of the fluctuation about the mean.

b. Probability density function

Probability density function describes the properties of data in the amplitude domain. It tries to describe the probability that the data will assume a value within some defined range at any instant of time. The probability that a sample time history $x(t)$ assumes a value within the range between x and $(x + \Delta x)$ may be obtained by taking the ratio of T_x/T, where T is the total amount of time that $x(t)$ falls inside the range $(x, x + \Delta x)$ during an observation time T. The probability density function $p(x)$ can defined as

$$p(x) = \lim_{\Delta x \to 0} \lim_{T \to \infty} 1/T \left(T_x / \Delta_x \right)$$

The principal application for a probability density function measurement of physical data is to establish a probabilistic description for the instantaneous values of the data.

c. Autocorrelation Function

The autocorrelation function for random data describes the general dependence of the values of the data at one time to the values at another. An estimate for the autocorrelation between the values of a sample time history record $x(t)$ at times t and $t + \tau$ may be obtained by taking the product of the two values and averaging over the observation time T. The autocorrelation function can be represented mathematically as

$$R_x(\tau) = \lim_{T \to \infty} 1 / T \int_0^T x(t)\, x(t+\tau) dt$$

The autocorrelation function can be used to establish the influence of values at any time over values at a future time. Autocorrelation measurement clearly provides a powerful tool for detecting deterministic data which might be masked in a random background.

d. Power spectral density function

Power spectral density function for random data describes the general frequency composition of the data in terms of the spectral density of its mean square value. A band-pass filter can be used to find the mean square value of a sample time history in a frequency range between f and $f + \Delta f$. The power spectral density function can be represented as

$$\Psi_x^2[\, f, f+\Delta f\,] = \lim_{T \to \infty} 1 / T \int_0^T x^2(t, f, \Delta f) dt$$

Power spectral density function is used to establish the frequency composition of the data which inturn bears an important relationship to the basic characteristics of the physical system involved. A final smooth estimate of the power spectral density can be found by applying Hanning Window Techniques.

2.3 Analyzing techniques for nonstationary data

The processing techniques and the statistical formulas normally do not apply when the data is nonstationary. Special considerations and procedures are required for such analysis. Nonstationary data represent a class of data whose statistical properties vary with time. Even though a vast majority of physical data fall into the class of nonstationarity, many data can be assumed to be stationary for the reasons of simplicity. The fundamental assumption made in this type of analysis is that the power contains a stationary component coupled by a nonstationary trend. Nonstationary conclusion is generally a negative statement specifying the lack of stationary properties rather than defining the precise nature of the nonstationarity [7].

In the past 3 types of models have been reported for analysing non-stationary data.

a. Time-varying mean value

For a nonstationary data the mean values can be estimated using a computer. If N different time intervals $x_i(t)$; $i=1,2,3.....N$ represent a nonstationary process $x(t)$, the estimate of mean value will vary over different choices of the N samples. One must investigate how closely an arbitrary estimate will approximate the true mean value. This can be done in two steps. The first step is to obtain mean value for each record $x_i(t)$ as a function of t. After this has been done for N samples, the average is determined by adding the records together and dividing by N.

b. Time-varying mean square value

The same analysis given for the time-varying mean is carried out to determine the variation of nonstationary mean square value.

c. Time varying power spectra

The time-averaged power spectrum can be used for describing the time varying spectral characteristics of an important special class of nonstationary random

processes which possess the following characteristics [7]

1. The lack of stationarity is due to deterministic time trends which are represented in every sample function.

2. The time trends are very slow relative to the instantaneous fluctuations of the data.

2.4 Frequency domain techniques

It is well known that when a quantity varies periodically with time it may be `analyzed into its harmonic components'. The quantities may be pressure, light, electricity etc. The variation in these quantities repeats itself at some basic frequency and the disturbances having repetition frequencies equal to the multiples of the basic frequency. Time and frequency appear as a related pair of variables in all these cases. Transformation is a technique used to change the representation of a parameter from one domain to another as shown in figure 2. In the case of a signal it is the time and frequency which form the pair of domain.

2.4.1 Fourier & Fast Fourier transformation

The basic essence of Fourier transform of a waveform is to decompose or separate the waveform into a sum of sinusoids of different frequencies. Figure 3 illustrates this interpretation. The pictorial representation of the Fourier transform is a diagram which displays the amplitude and frequency of each of the determined sinusoids. Mathematically, this relationship is stated as

$$S(f) = \int_{-\infty}^{\infty} s(t)\, e^{-j2\pi ft}\, dt$$

where $s(t)$ is the waveform to be decomposed into a sum of sinusoids, $S(f)$ is the fourier transform of $s(t)$.

It is desired to modify this fourier transformation in such a manner

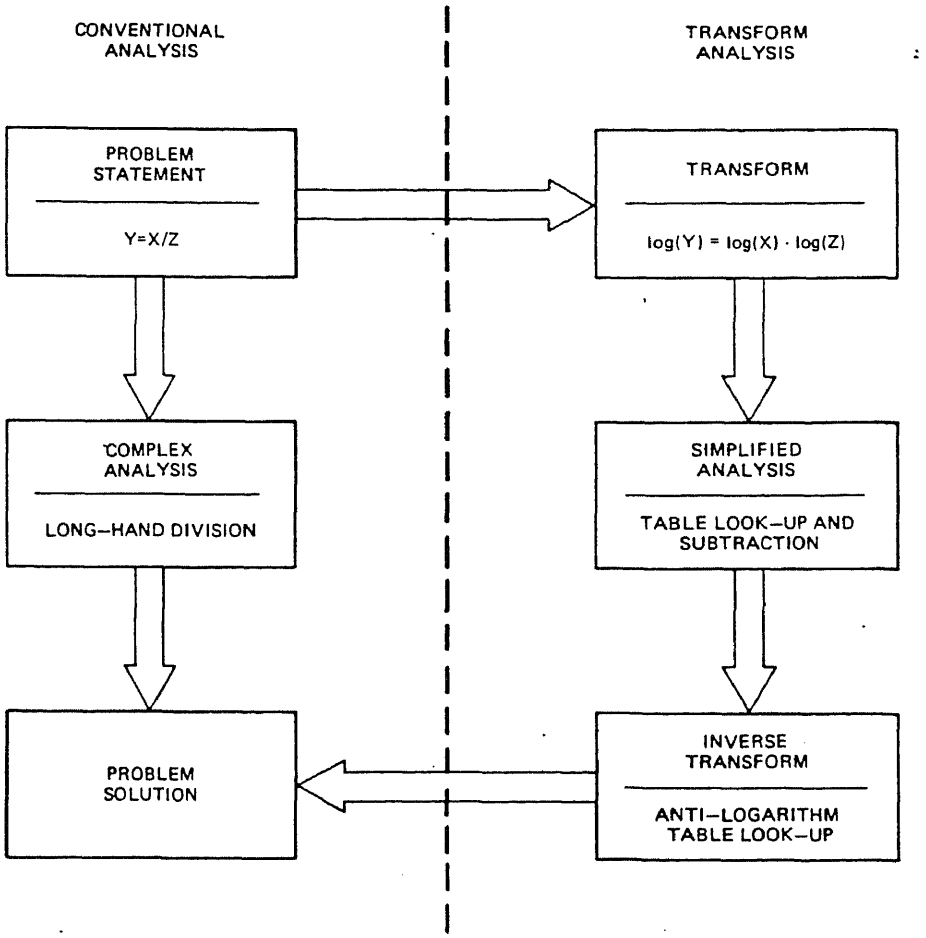

Figure 2 Flow diagram relationship of conventional and transform analysis

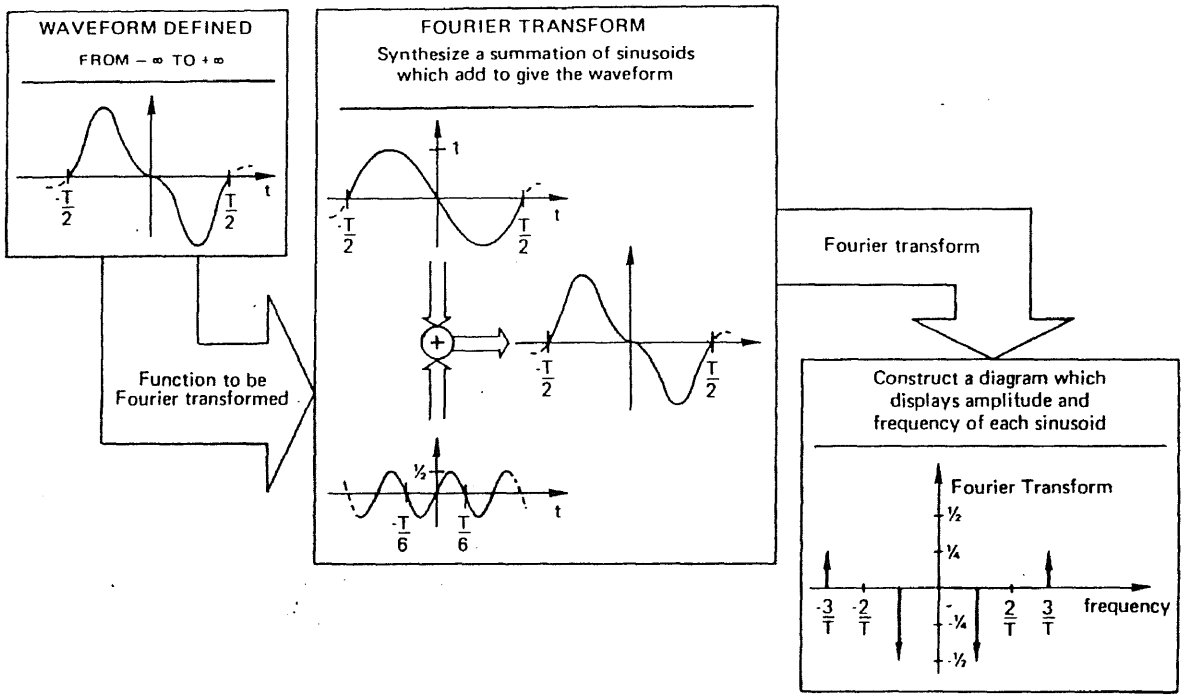

Figure 3 Interpretation of the Fourier transformation

that the pair is amenable to digital computer computation. Discrete Fourier transformation approximates Continuous Fourier transformation as closely as possible. Figure 4 illustrates a graphical development of the discrete Fourier transformation. As shown in figure 4-(a) $h(t)$ is the function whose Discrete Fourier transform has to be found. It is sampled by multiplying with a sampling function with a sample interval T. The waveform $h(t)$ is sampled at a frequency of at least twice the largest frequency component of $h(t)$ in order to avoid any loss of information. Sampled function is then truncated so that only finite number of points are considered.

If there are N data points of a function and if we desire to determine the amplitude of N separate sinusoids, then the computation time is proportional to square of N. Even for high speed computers, computation of the discrete Fourier transformation requires excessive machine time for large N.

To reduce the computational time of discrete Fourier transformation a new mathematical algorithm known as Fast Fourier transformation was developed. This algorithm makes the speed of computation time proportional to $N\log_2 N$ times. If a computer takes half an hour to do a Discrete fourier transformation on a data with $N = 8192$ samples, the calculation time required by Fast Fourier transformation is only about five seconds.

2.5 Dynamics of Electroencephalography

Changes of the Electroencephalogram during sleep were already observed in the early days of Electroencephalography [Caton, 1875; Burger, 1930]. Quantification and explanation of EEG has been a problem for long times due to tremendous amount of data generated during recording and unavailability of sophisticated quantification methods. Modern developments in information theory and statistical time series analysis have found their application also in

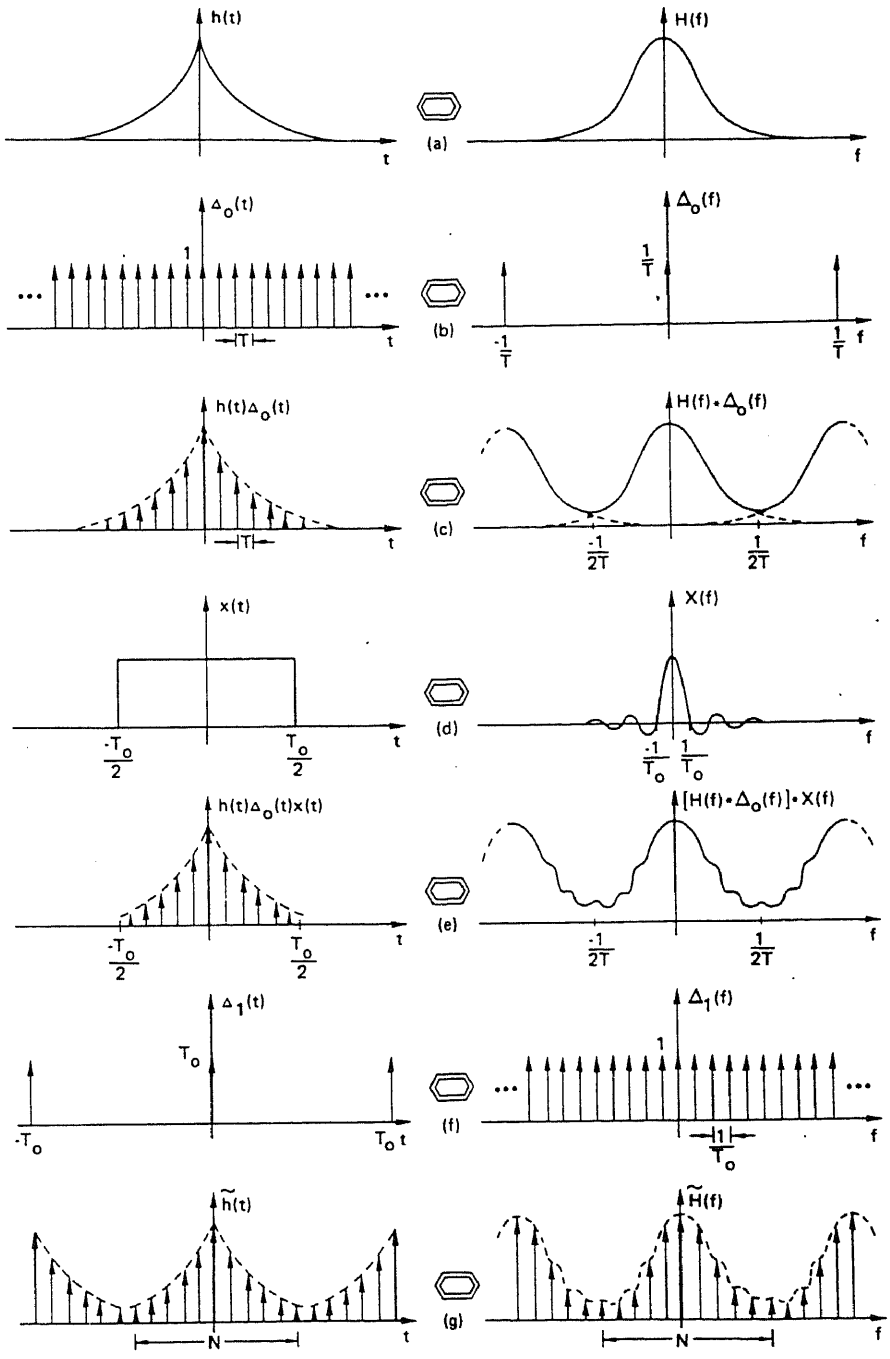

Figure 4 Graphical development of the discrete Fourier Transform

Electroencephalography. These analytical techniques provide new insight into the inherent structure and generation of neuroelectric activity, including mass activity like the EEG [9]. The mathematically best-founded method is offered by spectral analysis. The spectrum of single EEG records has already become familiar by the use of various types of analog frequency analyzers [Grass and Gibbs, 1938; Baldock and Walter, 1946; Suhara and Uemura, 1963].

Spectral analysis techniques have been widely used in interpreting the inherent structure of EEG. The power spectrum displays the mean square value or the average intensity of the EEG as a function of frequency. Figure 5 shows the power spectra of an all-night sleep record. The cross-spectrum gives information about the statistical interrelationship between two simultaneously recorded EEG channels. The cross-spectrum is mathematically a complex quantity composed of the cross-spectral amplitude, i.e. the average intensity of the activity shared by the two records as a function of frequency, and the phase angle which gives the average phase difference between the common frequency components. The coherence spectrum provides a measure of the correlation between two EEG records for each frequency band.

Spectral power density measurement has been used to detect the changes in the slow wave activity of EEG [1]. Figure 6 represent the power density values of EEG after drug administration. Peter Irwin has used `Spectral difference index' as a measure to determine whether a significant EEG change has occurred after drug intervention [10]. He has used Spectral density index as a measure of the difference between two relative power spectra (Figure 7). Coherence spectra can be used as a measure of correlation between two simultaneous EEG records as a function of frequency. Cross-spectrum is also of greater interest, which gives information about the statistical interrelationship between two simultaneous recorded EEG. The cross-spectrum is mathematically a complex quantity

composed of cross spectral amplitudes, i.e. the average intensity of the activity shared by two records as a function frequency and of the phase angle which gives the average phase difference between common frequency components. The coherence spectrum provides a measure of correlation between two EEG records for each frequency band.

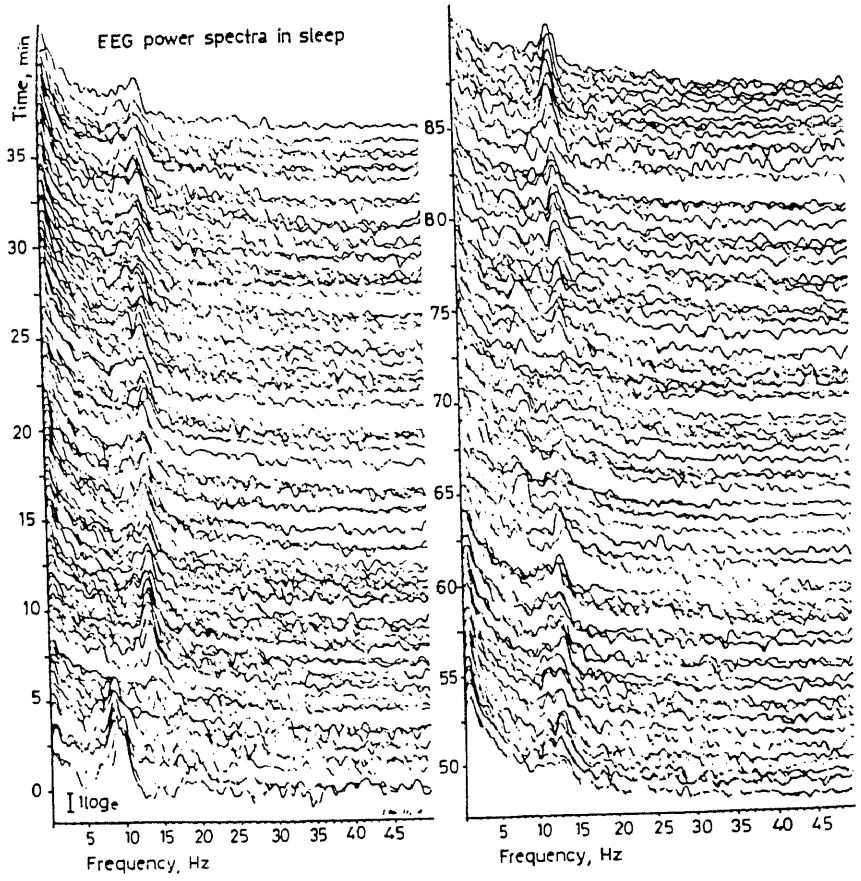

Figure 5 The power spectra of all-night sleep record displayed in consecutive samples of 20 sec

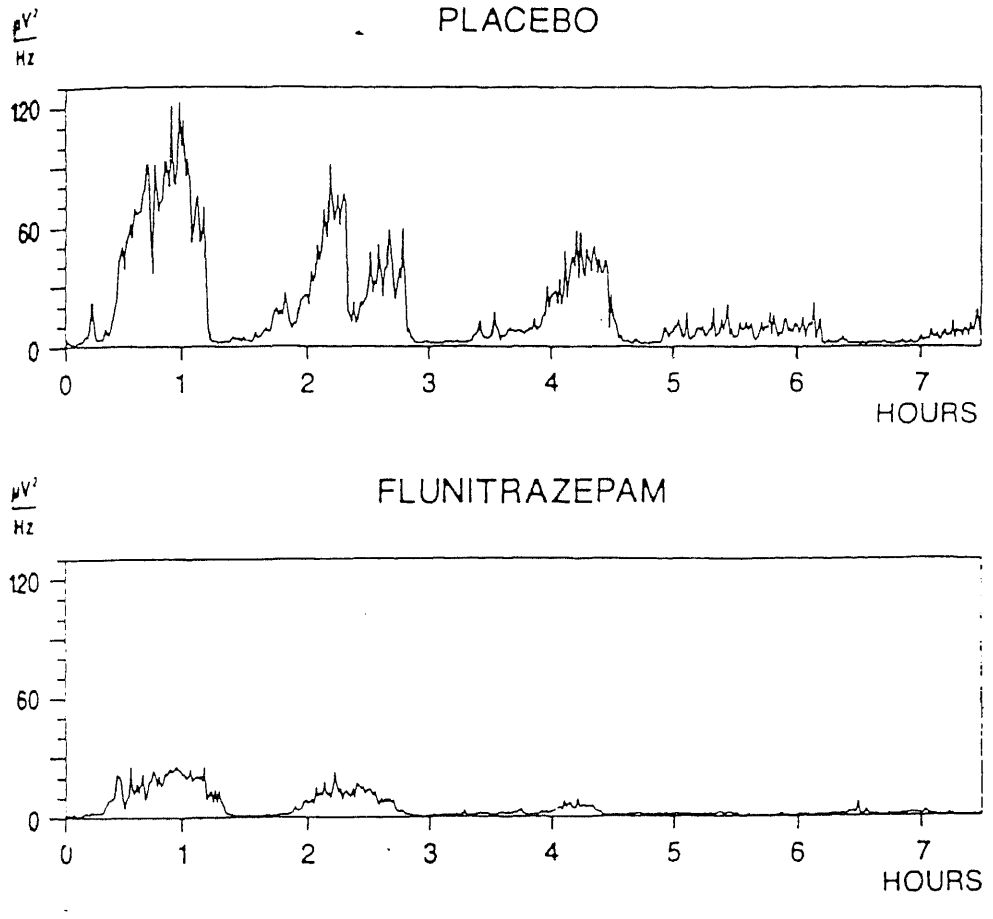

Figure 6 The curves represent power density values in the 0.75-4.5 Hz range plotted for 1-min epochs for a night following intake of flunitrazepam

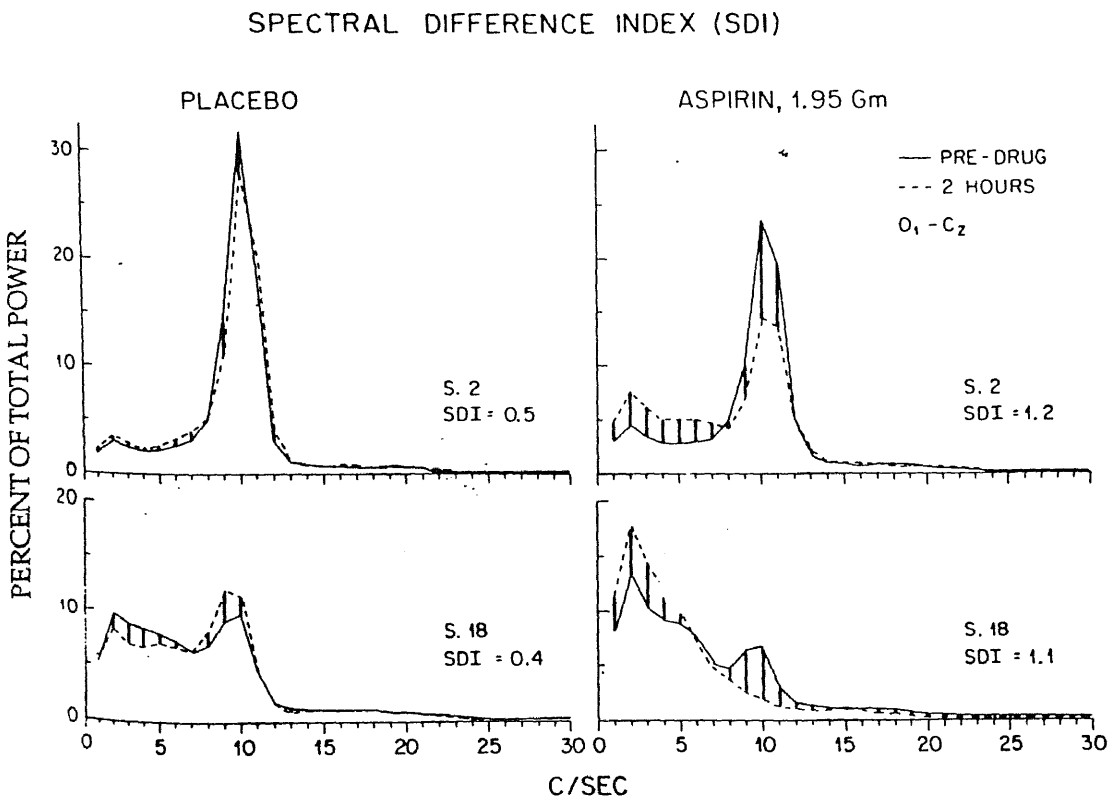

Figure 7 Spectral density index of two subjects having different pre-drug distributions of power

CHAPTER 3

MATERIALS AND METHODS

3.1 Characterization Criteria

An epoch-by-epoch approach is strongly recommended in all scoring and characterization procedures. A convenient time interval for analysis has to be selected. It should not be too short as to make the procedure cumbersome, nor so long as to lose the variations. A convenient interval for most investigators would be one page record, which is 300 mm. This interval would result in 20 to 30 sec epoch time [11]. Once an epoch duration is selected it should be maintained for the duration of analysis. During **Wake stage** alpha activity is of high or low voltage amplitude. This stage is usually, but not necessarily, accompanied by a relatively high tonic EMG, and often REMs and eye blinks are present in the EOG tracing [11]. During this stage the EEG pattern variation may consist of either decrease in amplitude, an increase in alpha activity, a paroxysmal burst of high voltage activity, or the presence of EMG activity.

Stage 1 is defined by a relatively low voltage, mixed frequency EEG with a prominence of activity in the 2-7 cps range. Stage 1 occurs most often in the transition from wakefulness to the other sleep stages or following body movements during sleep. The highest voltage about 50 - 75 microvolts [11] tends to occur irregularly. This stage is characterized by the presence of slow eye movements, each of several seconds duration. Rapid eye movements are absent.

Stage 2 is characterized by sleep spindles and K-complexes and the absence of sufficient high amplitude. The total duration of the K-complex should not exceed 0.5 sec. Waves of 12-14 cps may or may not constitute a part of complex.

Stage 3 is defined by an EEG record in which at least 20% but not more than 50% of the epoch consists of waves of 2 cps or slower which have amplitude greater than 75 microvolts from peak to peak.

Stage 4 is defined by an EEG record in which more than 50% of the epoch consists of waves of 2 cps or slower which have amplitudes greater than 75 microvolts peak to peak. Sleep spindles may or may not be present in this period.

Stage REM is defined by the concomitant appearance of relatively low voltage, mixed frequency activity and episodic REMs. Alpha activity usually somewhat predominant during stage REM than during stage 1. The frequency is generally 1-2 cps slower than during wakefulness. There is an absolute absence of sleep spindles and K complexes. Table 2 gives a concise form of criteria mentioned above. Figure 8 illustrates the placement of electrodes and the onset of EEG. Figures 9, 10, 11 and 12 shows the EEG for Stage 2, Stage 3, Stage 4 and REM stage respectively.

3.2 Experimental Setup

3.2.1 Subject

All-night EEGs, EOGs, and EMGs were recorded at the sleep laboratory of the Robertwood Johnson Research Center from a 30 year old adult female suffering from neurologic disorders. The recording was carried out in a sound-attenuated, ventilated, temperature-controlled room. The data was recorded by Medilog eight channel recorder for a period of six hours.

Two EEG channels (C3/A1 & C4/A1), two EOG channels (A1, one cm vertically upward from outer canthus of left eye; A1, one cm vertically downward from outer canthus of right eye), and one EMG channel (two electrodes placed on the jawbone) were used which is schematically illustrated in Figure 13. The five channel data obtained from the subject was amplified by

Table 2 Sleep stage scoring criteria

Stage W:	The EEG contains alpha activity associated with quiet wakefulness or low voltage activity with active wakefulness. The EMG has a high level of activity and there are frequent voluntary eye movements.
Stage 1:	The EEG shows less than half the epoch occupied by alpha waves. No spindles or K-complexes occur in the EEG record. Occasional slow, rolling eye movements occur.
Stage 2:	The EEG record shows K-complexes and bursts of 12 to 15 cycles per second rhythm and contains less than 20 percent delta activity. There are no eye movements.
Stage 3:	The EEG contains between 20 and 50 percent of the epoch occupied by delta activity. There are no eye movements.
Stage 4:	The EEG contains over 50 percent of the epoch occupied by delta activity. There may be spindle activity superimposed on the delta activity. There are no eye movements.
Stage REM:	The EEG is relatively low voltage, mixed frequency activity with bursts of theta rhythm and saw-tooth waves. Conjugate rapid eye movements occur. The chin EMG reaches its lowest amplitude.

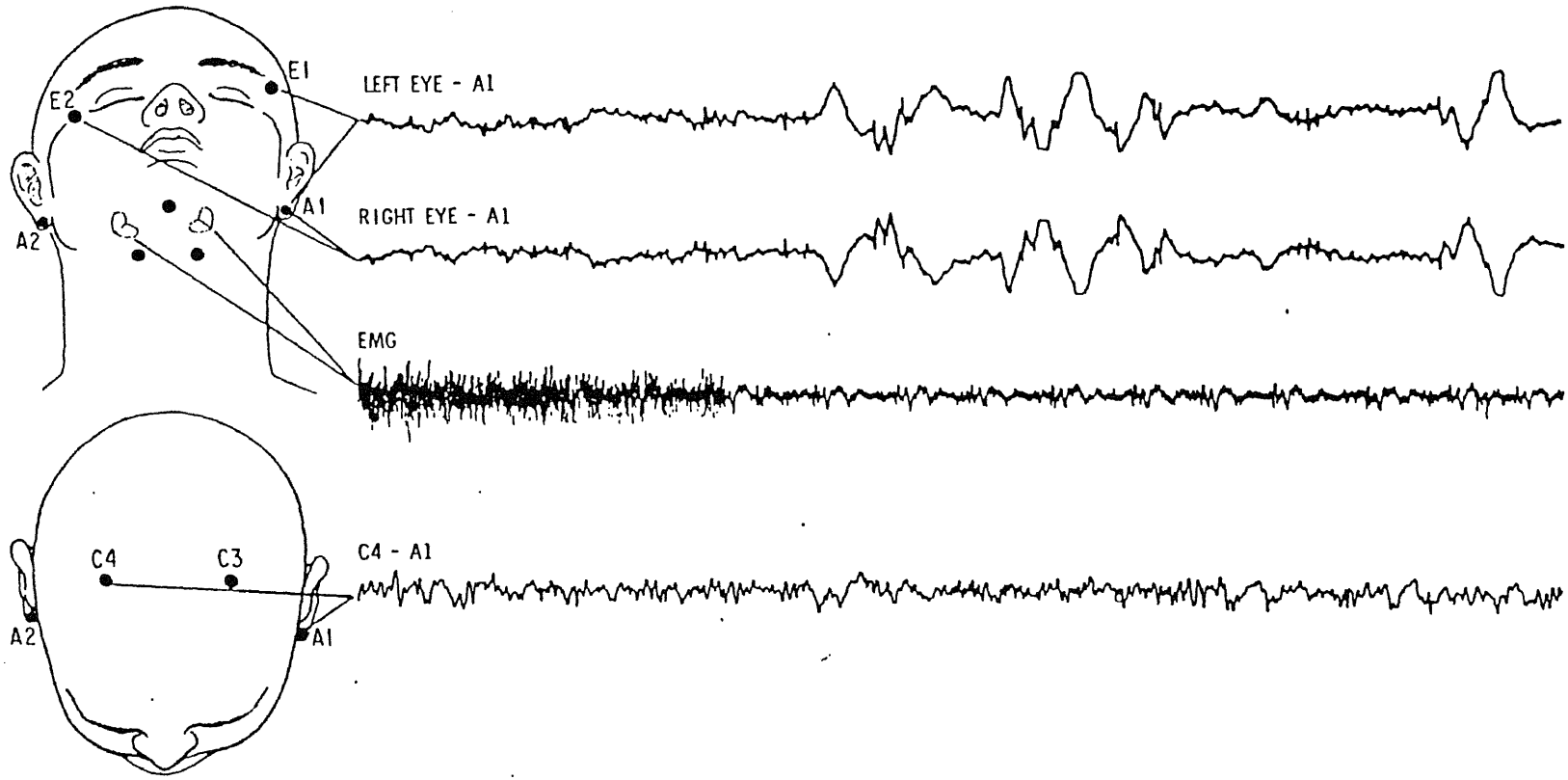

Figure 8 Placement of electrodes and the onset of EEG

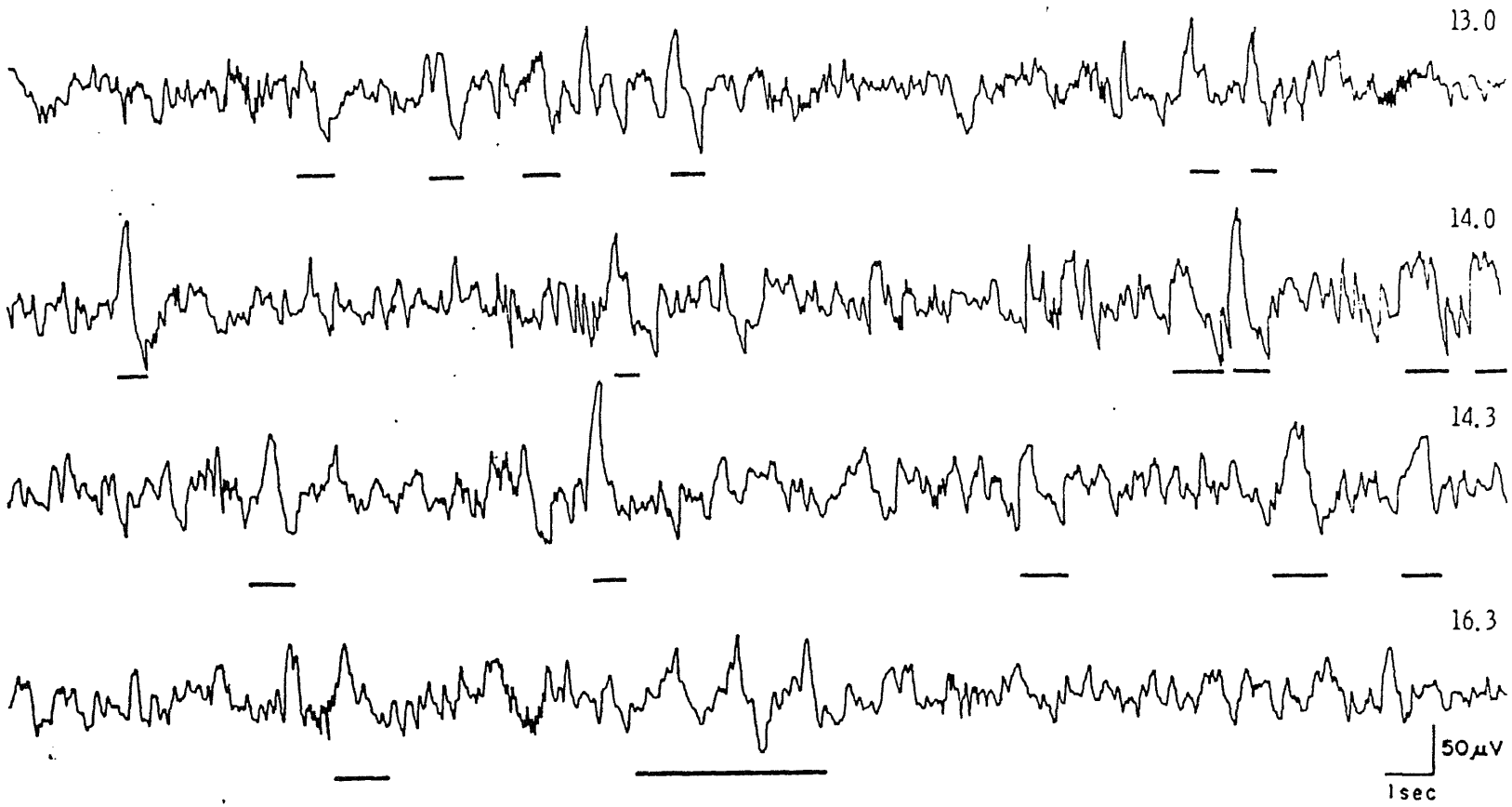

Figure 9 Standard tracings of sleep EEG in stage 2 for four continuous 30 sec epoches

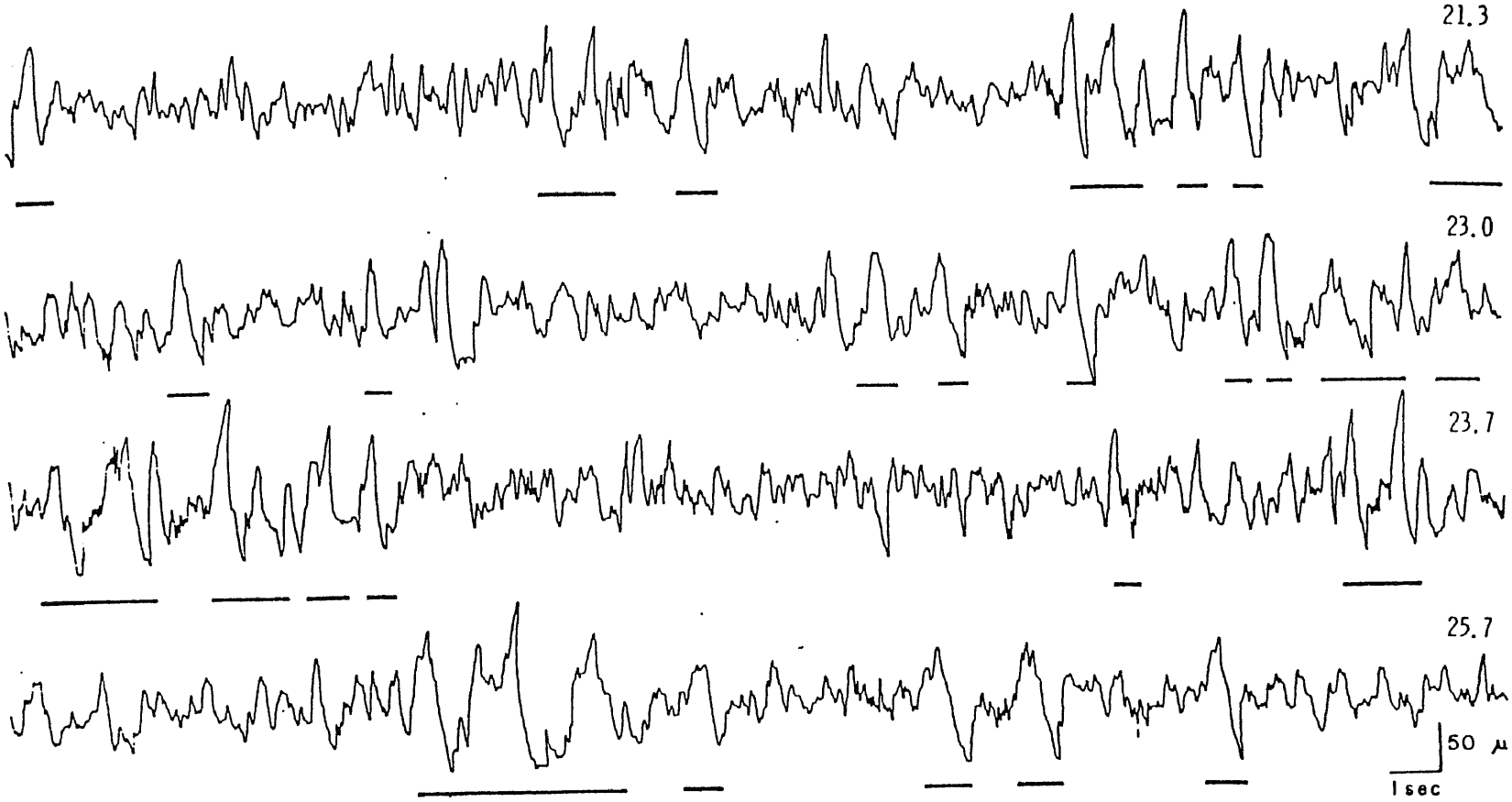

Figure 10 Standard tracings of sleep EEG in stage 3 for four continuous 30 sec epoches

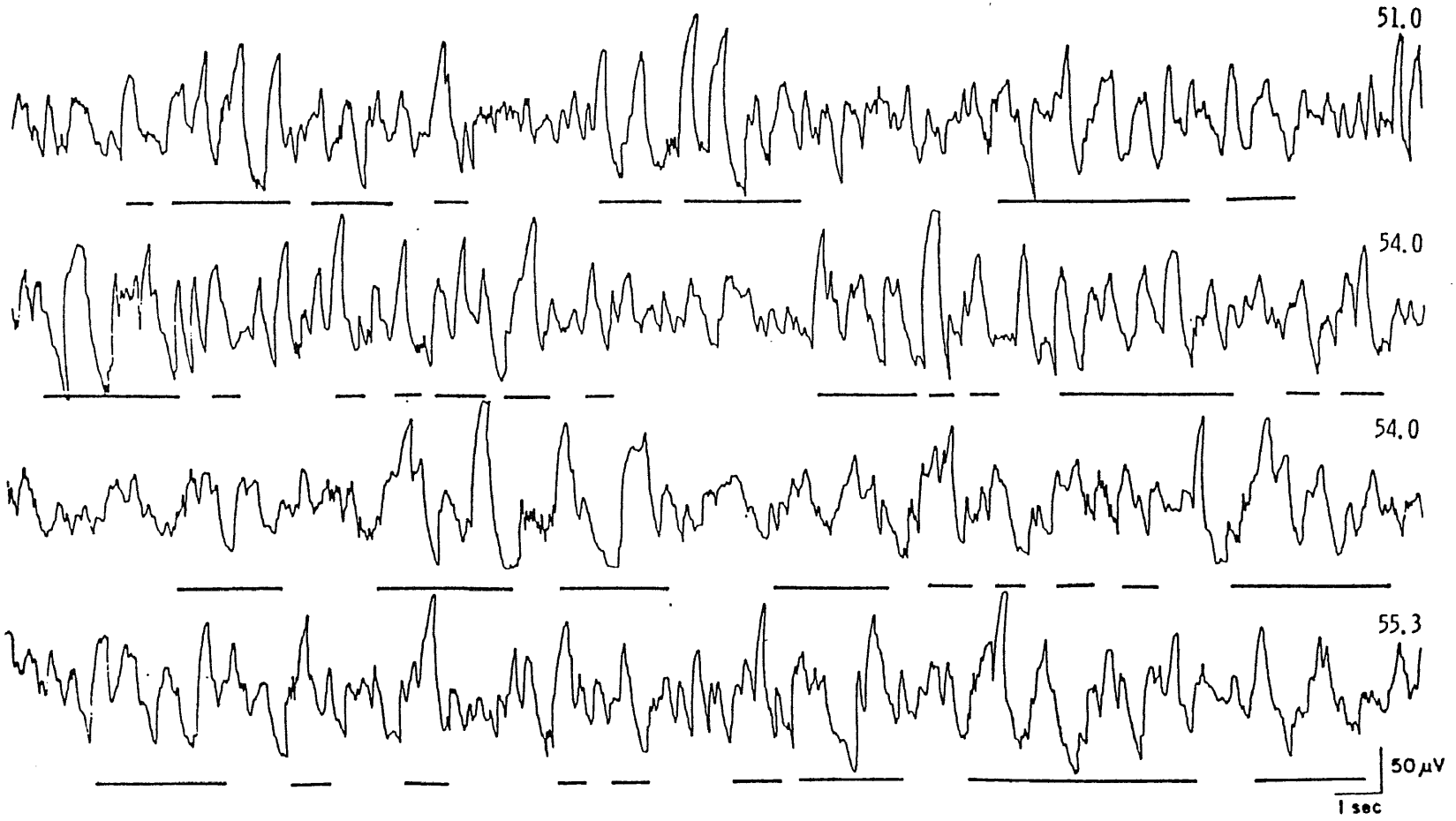

Figure 11 Standard tracings of sleep EEG in stage 4 for four continuous 30 sec epoches

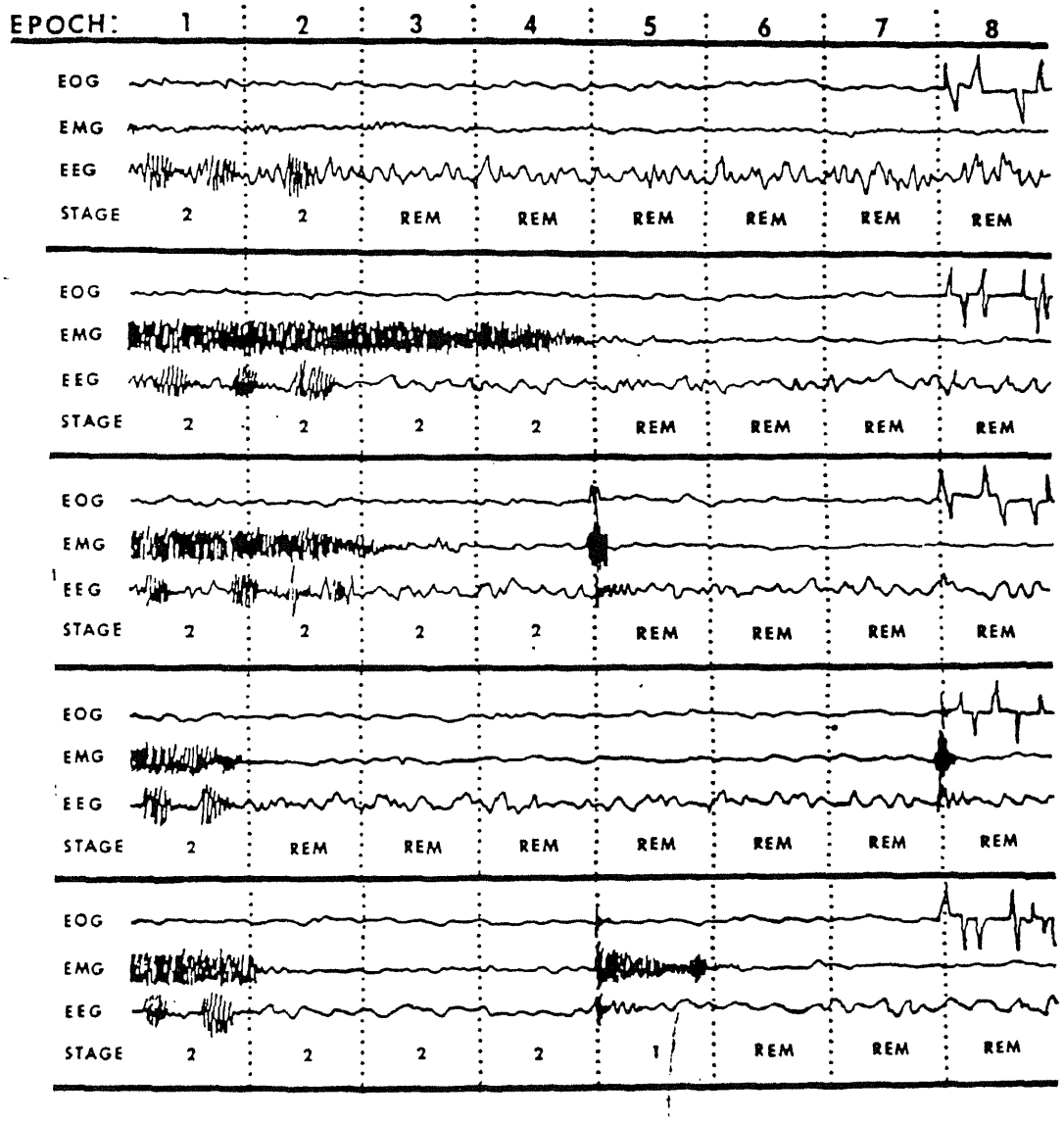

Figure 12 Schematic illustrations of starting of REM sleep

Gould Universal amplifier with Band-pass filter across 0.3 to 100 Hz, and continuously digitized at 256 Hz by a Data Translation Board. Figure 14 shows the experimental setup.

3.2.2 Data Porting

The digitized data had to be transferred from the recording Center to the Sun workstation which had the requisite tools for analysis. The binary data file, the result of a six hour five channel recording was 66MB in size. Due to nonavailability of INTERNET access at the time of this work, other means for data transfer had to be thought of. An attempt to transfer the data through an optical disk failed due to the mismatch of optical reader formats.

Alternative ways of transferring were through Floppy Disks, Laptop with an ETHERNET card, Magnetic tapes etc. Storing onto floppy disks was not feasible considering the size of the data. Laplink, a package which supports the transfer of data between two computers, was used for this purpose. Laplink is a sophisticated package having capabilities to transfer any form of data. Data can be transferred to either a local or a remote machine. Local data transfer was achieved at a rate of 33Kb/sec. The data was loaded onto the Sunsparc mainframe using File Transfer Protocol. The binary file had to be converted into a readable form. The size of converted file was three times its counterpart which precluded its storage on the mainframe. Data Cartridge was employed to store the 200MB of readable data.

3.3 Procedure

Analysis of overnight recording of EEG, EMG and EOG was performed on a Sun Spark station. Matlab which supports mathematical and robust graphical applications was used as an aid for analysis. Normally analysis is conducted on

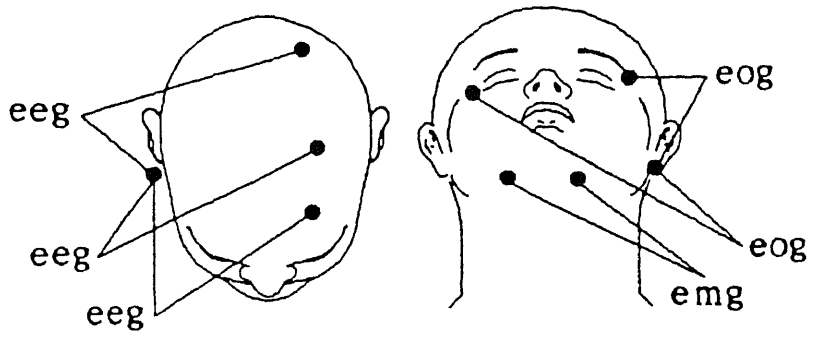

Figure 13 Electrode placements

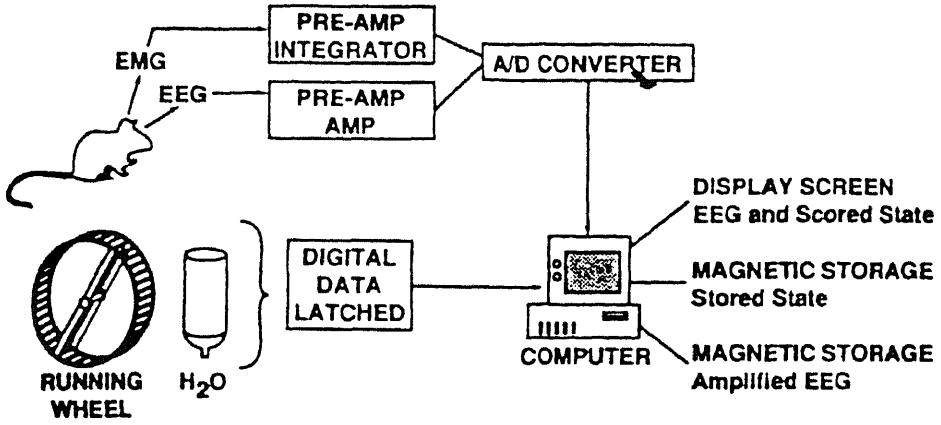

Figure 14 Experimental setup for the data collection

small lengths of data which are later stacked to get a overall picture of the signal. Following the steps analysis was performed for various lengths of epoch. Due to the enormous size of data and the following computational problems, to start with a smaller length of signal was considered.

The basic approach in analyzing the data was by using the Fast Fourier Transformation. Spectral analysis was the tool used to detect the variations in the signal. The use of other orthogonal functions such as Walsh and Haar was also considered but Fourier transformation was applied in the present study. Initially the digitized and filtered data was preprocessed for analysis by removing the dc component. The dc component inherent in the signal was removed in two ways depending upon the type of analysis. First the mean value was calculated for each epoch and subtracted from the epoch amplitude. To say a few words about the decision of epoch length, there are some standard approaches. Normally the epoch length recommended is 30 seconds. There are other cases where smaller durations have been considered. It is a customary to reduce the duration of epoch when finer details within a given length is required. The 30 second epoch is a practise to characterise long stretch of data. Continuing on the dc shift, the mean value calculated for each epoch was applied on the same. The second way was by calculating mean value for the whole length of data and subtracted from each epoch. The data was reduced by 1000 times to get a realistic scale. Figure 15 shows a small stretch of demagnified data with its dc component reduced.

Various methods were considered to obtain spectral plots depicting subtle changes in the behaviour of the signal. As a test epoch with a duration of 5 sec was subjected into Fast Fourier Transformation (Routine FFT, Matlab subroutine). A program was designed to read assigned length of data and to perform the transformation. This routine was made to run over the whole length of data. Consecutive power spectrums thus obtained were stacked onto a matrix

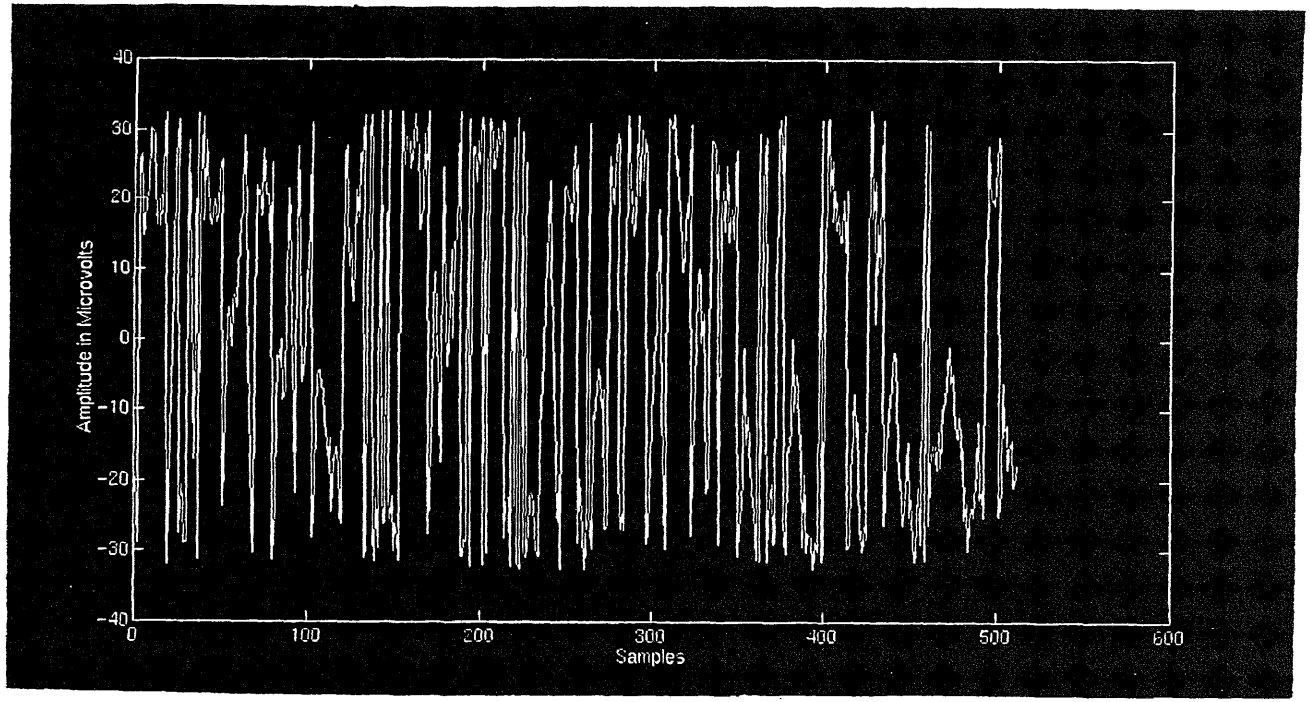

Figure 15 Sample EEG signal of two minutes used for analysis

to get a complete picture of the nature of the signal. Figure 16 shows the power spectrum of one such epoch. Figure 17 shows the 3D graph obtained through the algorithm. Due to computational and memory restrictions the whole stretch could not be depicted in the three dimensional form.

The overall power of data can be described by computing mean square value, which is simply the average of the squared values of the time history. This has been estimated for the whole length of data using an algorithm. It performs this operation by calculating the square of each digitized sample and by averaging it for a given length of epoch. The mean square value obtained for each epoch is stored in an array. This array is used to plot a graph of mean square variation with respect to time. The moving mean square model thus obtained will be used for analysis and discussion in the later paragraph. Figure 18 shows the plot of mean square variation.

For nonstationary data, a basic statistical parameter is to estimate the nonstationary mean value change with time. A similar algorithm as that of mean square value has been used to get the mean value. It calculates the mean for each epoch and stores in a form that can be used to plot the change with respect to time. Figure 19 gives the output of this moving mean value model.

An epoch length of 30 sec was used. Mean power spectra was calculated in two ways for each epoch. 15 spectras of consecutive 2 sec segments was averaged to find the outcome of the 30 sec stretch of signal. This computation resulted in 30 degrees of freedom. Another procedure was aimed at considering the effect of history on the signal. Moving Power Spectral Analysis was carried out by applying Fourier Transforms on overlapping data segments each of 30 seconds, divided and overlapped by 2 seconds (512 samples of data). The spectral estimates were smoothed using Hanning window in the frequency domain. Figure 20 shows a moving power spectral model with this approach.

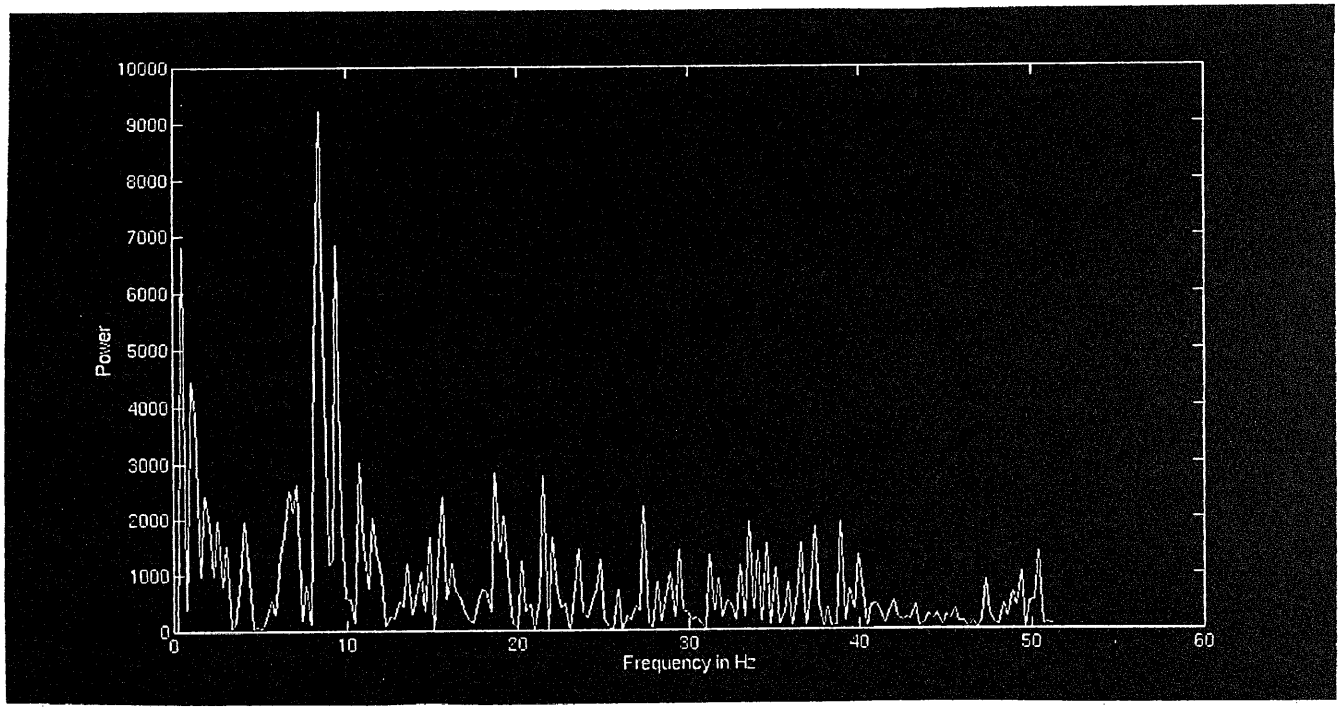

Figure 16 Power Spectrum of EEG for a thirty second epoch

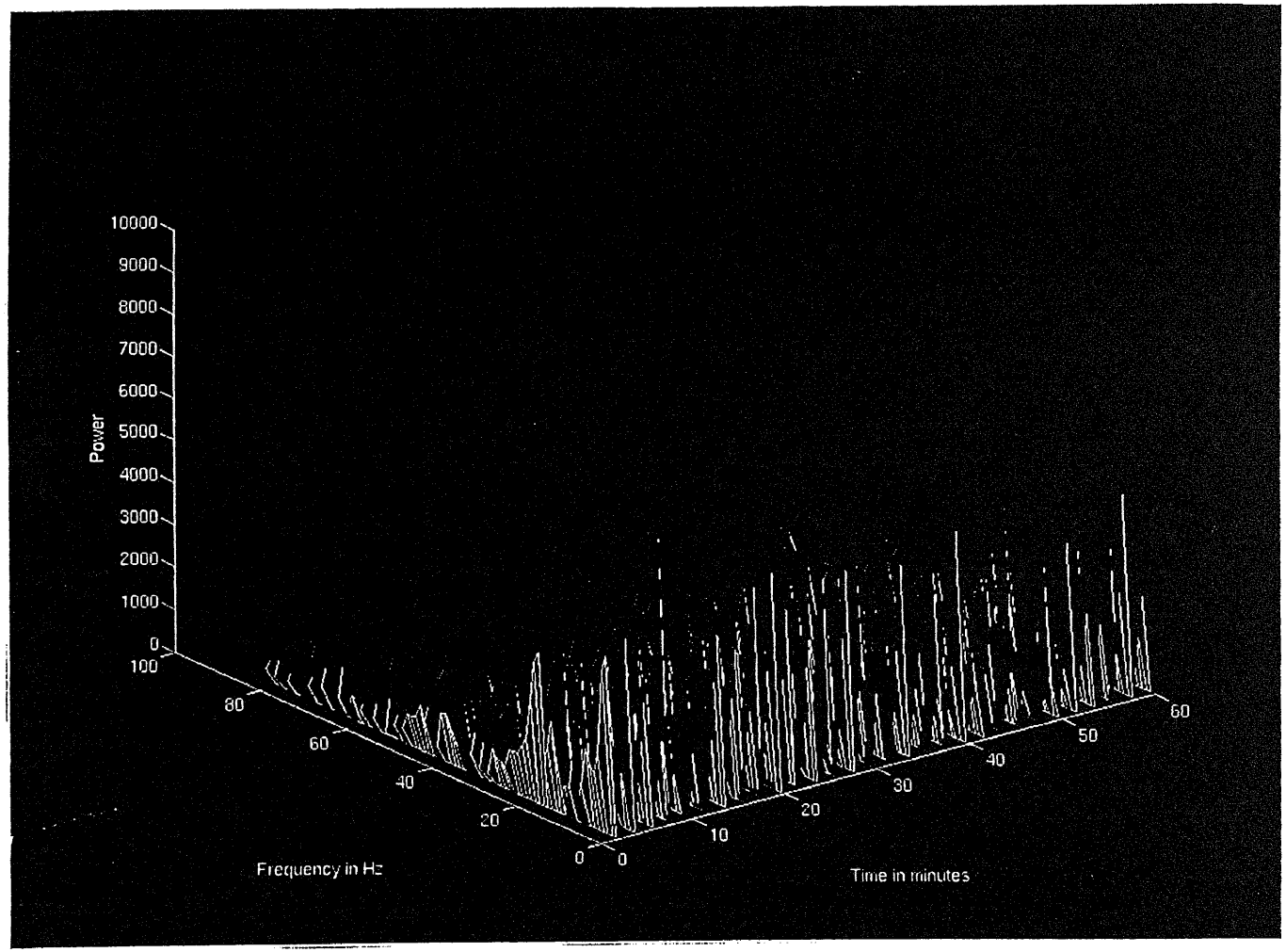

Figure 17 Three dimensional plot of power spectra of one hour EEG

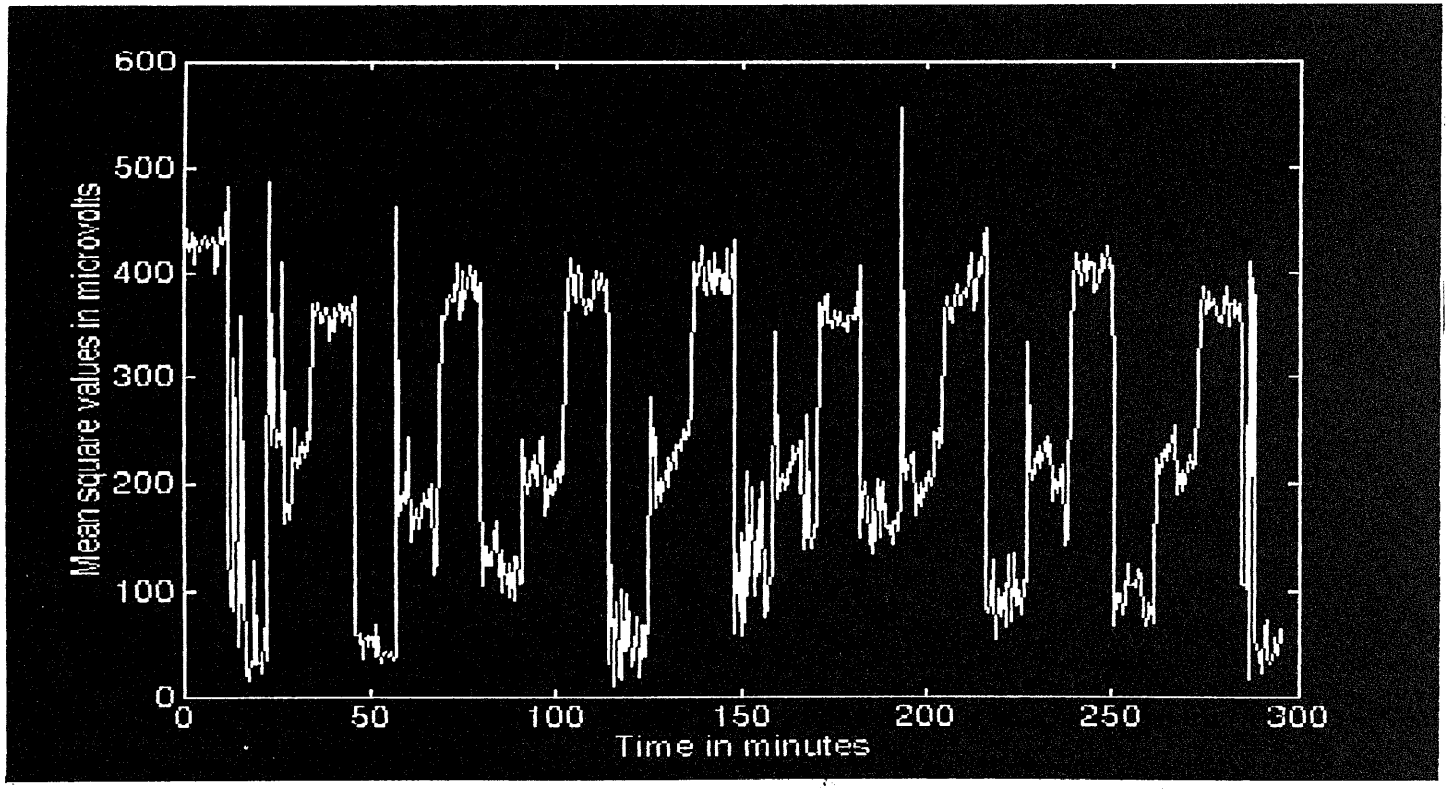

Figure 18 Mean square variation for a five hour EEG with a epoch length of 30sec.

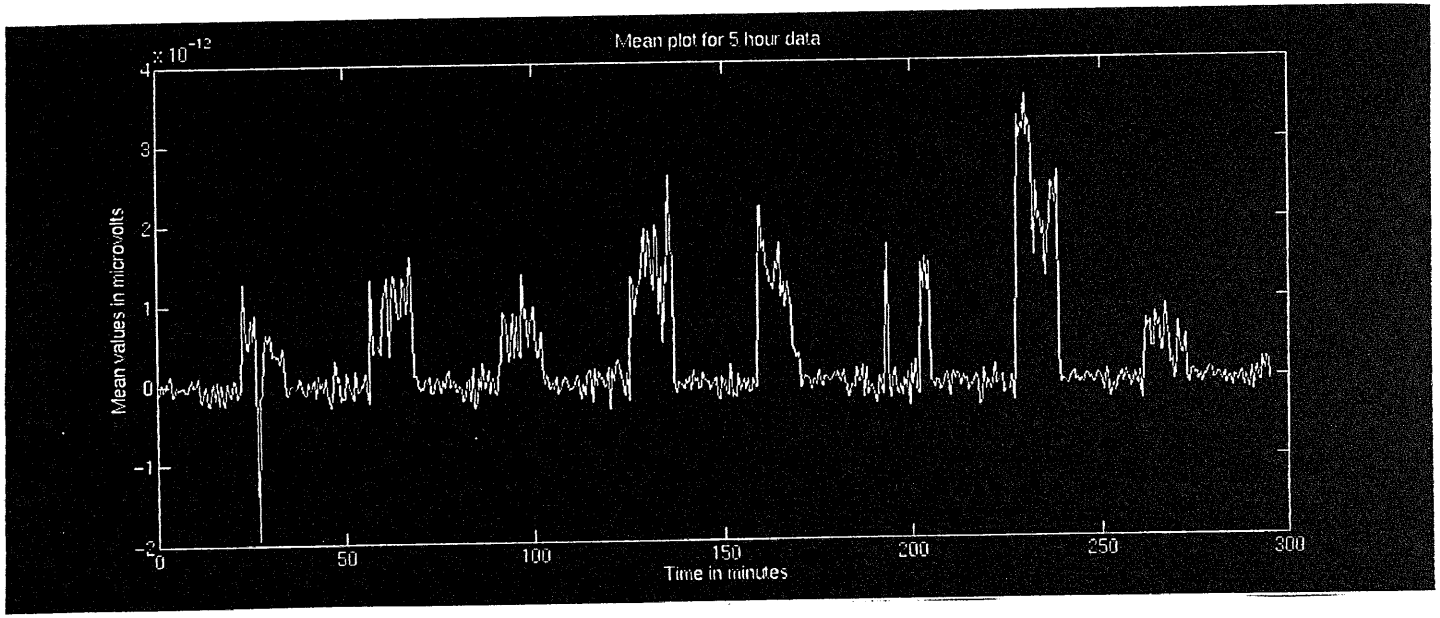

Figure 19 Mean value variation for a five hour EEG with a epoch length of 30sec.

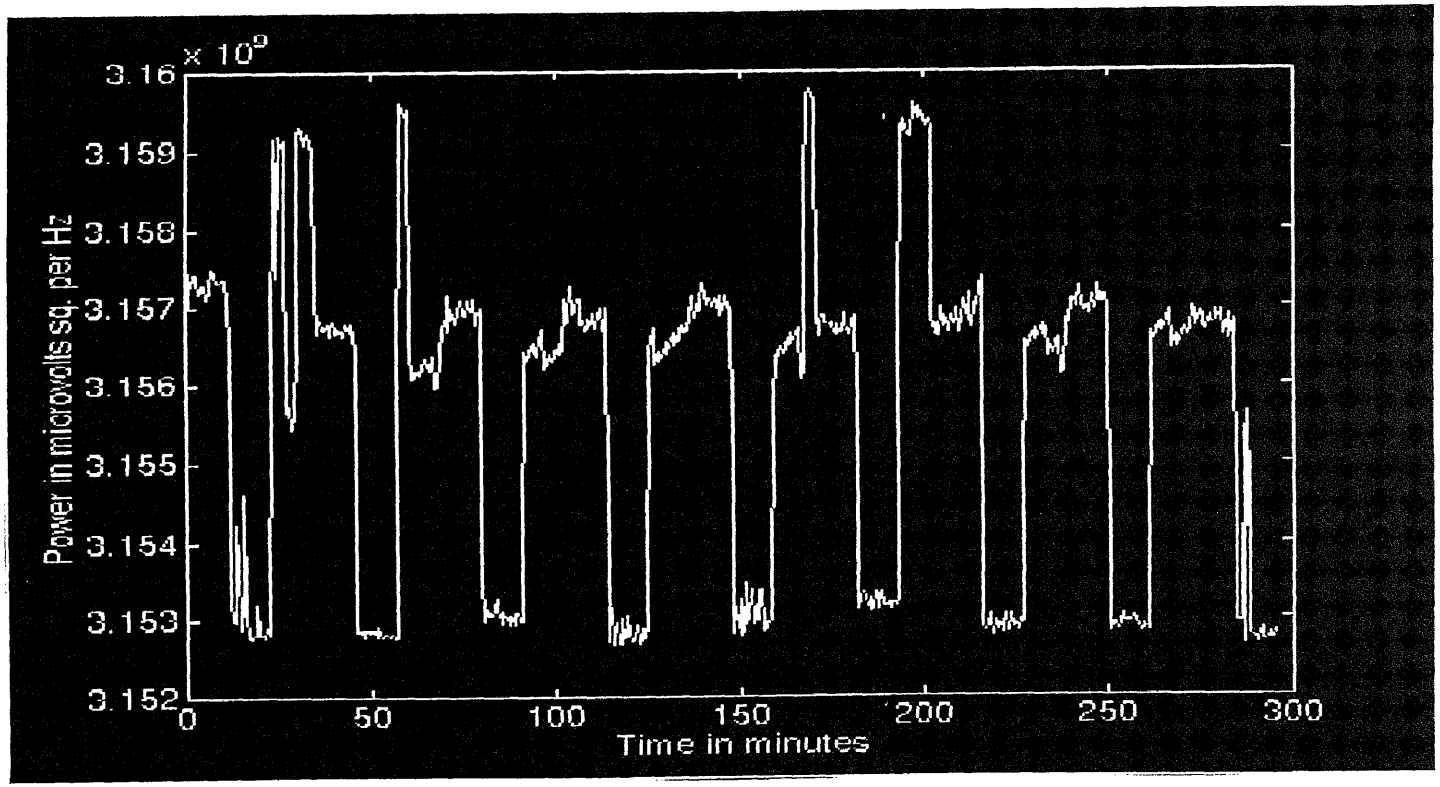

Figure 20 Power variation for a five hour EEG with a epoch length of 30sec.

The same procedure was applied for the second EEG which has been derived from a different part of the brain. Figure 21 shows the spectral graph of both EEGs at the same section of time. This relational plot helps us in studying the common properties and behaviour of the different sections of brain at the same instant of time.

3.4 Results and discussions

This thesis presents a few results with spectral analysis of sleep activity. Because of the large amount of computation various calculations had to be limited to small lengths of data ranging up to 5 hours. Keeping this in mind the results of analysis should be considered preliminary. A couple of questions that immediately came to mind were the following. Is the technique of spectral analysis a useful tool for characterization and does spectral analysis provide new insights into the physiological mechanisms underlying the different EEG patterns at different stages of sleep?

Spectral analysis if not the only tool, is atleast a good way to get a feel of the composition and characteristics of signals like EEG. Spectra displays the distribution of average intensity of the different frequency components. This also allows us to quantify the background activity during various stages of sleep, especially regarding frequency and intensity of peaks in the δ-, α-, σ- and β-band. Figure 21 will be the centre of discussion to figure out the variation of different bands. δ (0.25 - 2.0 hz) activity as expected increased its power as it passed from awake to NREM. A peak in δ band appears at around 1.5 hz during stage 2. Its intensity increased as the subject got into the REM sleep. Something which can be slightly noticed in the graph is the shift of the δ peak to around 1.8 to 2.0 hz as we get into REM. This means that the frequency has slowed down during the REM stage. This slow wave activity can be noticed more dominantly in a

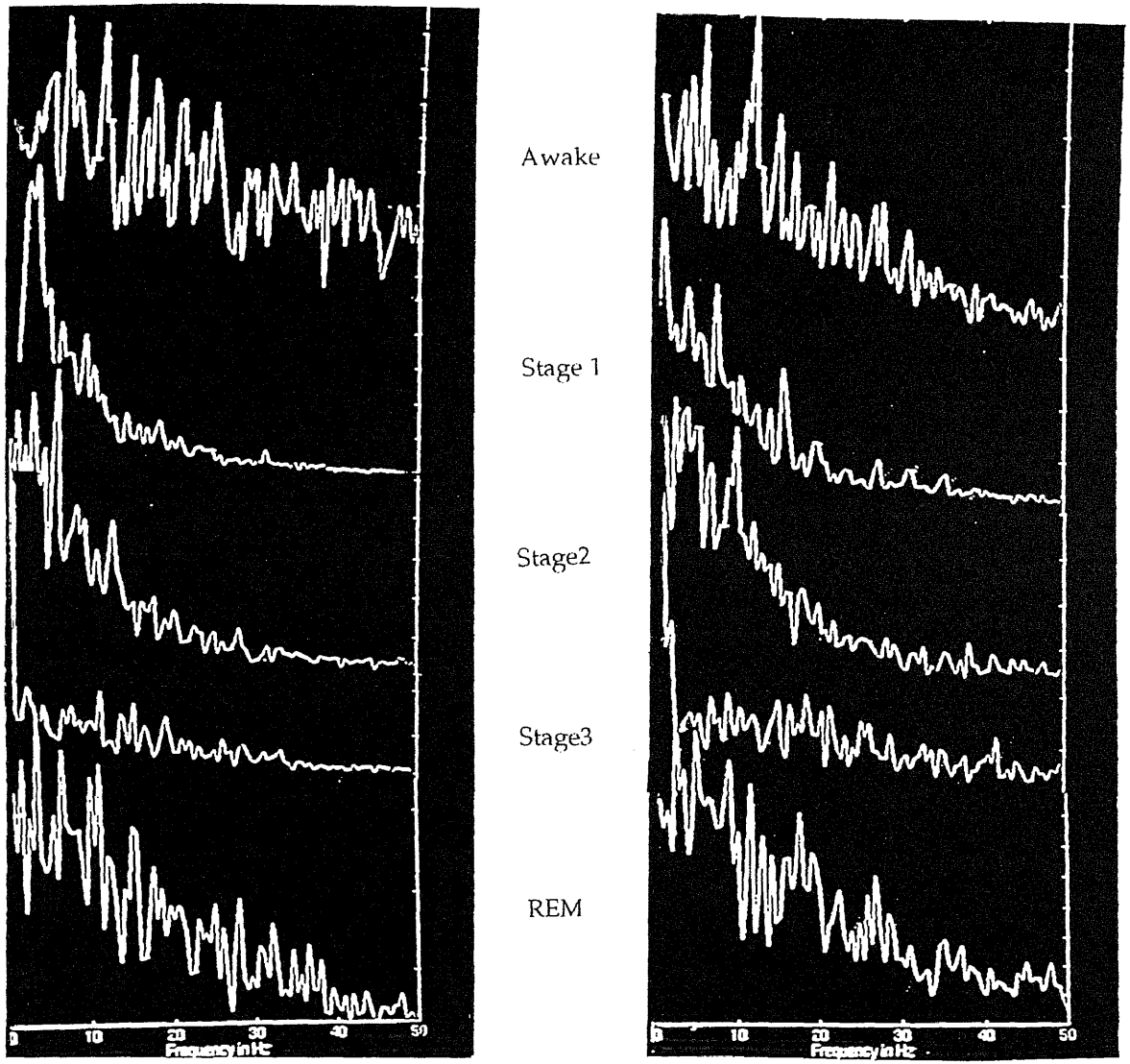

Figure 21 Averaged power spectra of EEG samples from various stages of left derivation is shown in the left half. On the right half is the power spectra for the right derivation.

conventional EEG, but not in this spectra. θ activity (7 hz) is seen to be similar to frequency that of δ activity. The α activity (9.5 to 11 hz) is seen to be as expected in the wake and in stage 1. In one of the papers it was mentioned that harmonic distortion of the α activity was a frequent feature of healthy subjects. In this analysis a great detail of α activity variation could not be noticed. The σ activity (13 and 15 hz) showed peaks during stages 2 and 3. A small peak can also be observed during paradoxial sleep. β activity (20 to 30 hz) decreased its intensity with increasing depth of sleep. Its intensity can be noticed during the initial stages of sleep. In the three dimensional graph shown in figure 17 the activity of β band can be noticed clearly in the initial part of the EEG recording. The moving power spectra shown in figure 20 is a bit confusing. The activity of signal seems to be quite varied. Even though the spectras at different stages relate to the expected activity of EEG, the overall power variation does not follow the usual pattern.

Before we discuss about the results mentioned above, it is important to remember that phenomena like K-complexes are not dealt in this analysis. The reason is due to the fact that its frequency content is spread over large parts of the frequency scale which we are unable to detect by spectral analysis. Since the activity of various bands are quantified by averaging for the analyzed epoch, intermittent spindles with high amplitude are not clearly distinguishable. This shows that spectral approach is not suitable for EEG classification schemes which use K-complexes, vertex potentials and spindle shaped activity. Haar transformation is another suitable technique for analysis due its superior convergence property, but has the disadvantage of losing resolution in the estimated power spectrum.

One of the contradicting observations was the existence of σ activity in the paradoxial sleep. Strong feeling that came about during this analysis was the lack

of information regarding other activities that characterize EEG. This means to say that spectral analysis alone cannot be used for characterization purpose. Strong statistical tools and pattern recognition techniques are necessary. One of the physiological remarks that can be made from the observations of two recordings of EEG is the possibility of one source for certain components of the signal. Close observation of figure 21 the variation of signal between 13 and 17 hz in both the recordings vary similarly. In the analysis performed long intervals of time have been considered and an average spectrum has been calculated. This long interval averaging has the disadvantage of ignoring the short-term changes. The attempt to characterize the unexpected variation in the moving power spectra for any possible drug effect was not successful. However the analysis on this stretch of time was performed by choosing comparitively a smaller length. Faster EEG waveforms that occur concurrently with slow-wave may not be detected, unless certain filtering techniques are used.

APPENDIX A

MATLAB

MATLAB is a technical computing environment for high performance numeric computation and visualization. MATLAB integrates numerical analysis, matrix computation, signal processing, and graphics in an easy-to-use environment where problems and solutions are expressed just as they are written mathematically - without traditional programming.

The name MATLAB stands for matrix laboratory. MATLAB was originally written to provide easy access to matrix software developed by LINPACK and EISPACK projects, which together represent the state of the art in software for matrix computation.

MATLAB is an interactive system whose base data element is a matrix that does not require dimensioning. This allows you to solve many numerical problems in a fraction of time it would take to write a program in a language such as Fortran, Basic, or C.

MATLAB has evolved over a period of years with input from many users. In university environments, it has become the standard instructional tool for introductory courses in applied linear algebra, as well as advanced courses in other areas. In industrial settings MATLAB is used for research and to solve practical engineering and mathematical problems. Typical uses include general purpose numeric computation, algorithm prototyping, and special purpose problem solving with matrix formulations that arise in disciplines such as automatic control theory, statistics, and digital signal processing.

MATLAB also features a family of application-specific solutions that it calls as Toolboxes. Very important to most users of MATLAB, toolboxes are

comprehensive collections of MATLAB functions(M-files) that extend the MATLAB environment in order to solve particular classes of problems. Areas in which toolboxes are available include signal processing, control system design, dynamic systems simulation, systems identification, neural networks, and others.

Probably the most important feature of MATLAB, and the one that MATLAB people took care to perfect, is its easy extensibility. This allows us to become a contributing author too, creating our own applications. In the years that MATLAB has been available, the company has enjoyed watching many scientists, mathematicians, and engineers develop new and interesting applications, all without writing a single line of low level code.

External Interfaces to MATLAB

Although MATLAB is a complete, self-contained environment for programming and working with data, it is often very useful to interact with data and programs external to MATLAB. Shell escape functions and MEX-files are the two methods for calling your own C or Fortran subroutines.

a. Shell Escape Functions

Shell escape functions use shell escape command ! to make external stand alone programs act like new MATLAB functions. A shell escape M-function is an M-file that

1. Saves the appropriate variables on disk.
2. Runs an external program (which reads the external data file, processes the data, and writes the result back out to disk).
3. Loads the processed file back into the workplace.

Shell escape functions are less efficient than MEX-files because they incur the overhead associated with invoking an external program each time they are called and because their arguments are passed via disk files. In situations where

relatively large amount of processing is performed in the external program, this overhead can be negligible, and converting to MEX-files offer no real advantage.

If the computation time of the external program is short compared to the time spent loading the program and passing the variables, MEX-files may be more suitable since the object code of a MEX-file is physically linked into MATLAB.

b. Dynamically Linked Subroutines: MEX-Files

One can also call C and Fortran subroutines from MATLAB as if they were built-in functions. MATLAB-callable C and Fortran programs are referred to as MEX-files. MEX-files are dynamically linked subroutines that the MATLAB interpreter can automatically load and execute. MEX-files have several applications:

1. Large pre-existing Fortran and C programs can be called from MATLAB without having to be rewritten as M-files.
2. Bottleneck computations (usually for-loops) that do not run fast enough in MATLAB can be recorded in C or Fortran for efficiency.
3. A/D cards, D/A cards, and other hardware can be accessed directly for data acquisition and control applications.

MEX-files are not appropriate for all applications. MEX-files offer an avenue that unsuspecting users may follow when they would be much better of programming in the MATLAB language. MATLAB is a high-productivity system whose specialty is eliminating time consuming, low-level programming in compiled languages like C and Fortran.

Techniques for importing and exporting data to and from the MATLAB environment are also available. The most important approach is MAT-files-the file format that MATLAB uses for saving data to disk. MAT-files offer a simple and convenient mechanism for transporting our data between different platforms.

APPENDIX B

"SIGNA" SIGNAL PROCESSING PACKAGE

The package supports a biomedical signals processing system. As a research tool the system offers the potential to acquire and analyze experimental and clinical data obtained in the form of photographs, polygraphic paper charts etc. In its role as an adjunct to biomedical education, several self-teaching features are implemented which enable the student of biomedical signals processing to gain hands-on experience in the application of signals processing methodologies to the analysis of clinical and experimental data. These features include a software function generator and a help option. The modular approach employed in the system design provides a great deal of flexibility to the investigator such that when a new analysis is desired one can simply add on the particular user-developed module to the system without causing any undue system constraints.

The types of analyses that are currently implemented include numerical integration, curve fitting, Fourier, Walsh and Haar transformations, spectral analysis and frequency response measurements. The system is being used for a wide range of applications which include the analysis of electrical signals generated at the neuromuscular junction, the computation of input impedance of the arterial system, the analysis of pressure waveforms obtained during anesthesia and in the characterization of respiratory dynamics in studies pertinent to asthma.

APPENDIX C

CLINICAL PHARMACOLOGY OF SLEEP

Table 3 Lists a few drugs and their effect on sleep. The column numbered through 1 through 4 refer to control (+) of lack of control (0) for some major problems in drug research. These conclusions have been made by analysing a portion of data less than the entire night.

Study	*Drug*	*Subjects*	*1*	*2*	*3*	*4*	*Results*
Dunleavy et al. (1971)	Debrisoquine, 40 to 60 mg	3 normal	+	+	+	0	Decreased rem; withdrawal rem rebound.
	Guanethidine, 40 mg	2 normal					Decreased delta sleep.
	Propanolol, 120 mg	3 normal					No effect on sleep stages.
Haider and Oswald (1971)	Amylobarbitone, 200 mg	6 normal	0	+	+	0	Decreased rem; increased stage 2.
	Nitrazepam, 10 mg						Decreased rem; increased stage 2.
Hartmann et al. (1971)	Tryptophan, 120 mg/kg	10 normal	+	0	0	0	Increased rem sleep.
A. Kales et al. (1971)	Levodopa	4 parkinson	+	+	0	0	Decreased rem sleep.
		4 normal					No effect on sleep stages.
J. Kales et al. (1971)	Methapyrilene, 50 mg and Scopolamine, 0.5 mg	5 insomnic	+	0	+	0	Decreased rem in first part of night only.
Kupfer et al. (1971)	Chlorpromazine, 100 mg	9 mixed	+	0	0	0	No effect on sleep stages; increased total sleep time.
Lester et al. (1971)	Chlorpromazine, 150 mg	12 normal	+	+	0	0	No effect on sleep stages: decreased latency to first rem period.
Wyatt et al. (1971b)	Phenelzine, 60 mg/24 hr	6 mixed	+	0	0	0	Total rem suppression without tolerance.
Wyatt et al. (1971c)	5-Hydroxytryptophan, 600 mg	8 normal	+	+	0	0	Increased rem sleep.

Study	*Drug*	*Subjects*	*1*	*2*	*3*	*4*	*Results*
Kales et al. (1970f)	Glutethimide, 500 mg	5 normal	+	0	+	0	Decreased rem; increased stage 2; withdrawal rem rebound.
	Methyprylon, 300 mg	7 normal					Decreased rem; withdrawal rem rebound.
	Pentobarbital, 100 mg	4 normal					Decreased delta sleep.
Kupfer et al. (1970b)	Lithium, 1.8 gm/24 hr	7 manic-depressive	+	+	0	0	Decreased rem; increased delta sleep
Lewis (1970)	Fenfluramine, 40 mg	8 normal	+	+	+	0	No effect on sleep stages
	Chlorphenteramine, 50 mg						Decreased rem sleep.
	Diethylproprion, 25 mg						Decreased rem sleep.
	Amphetamine, 7.5 mg						Decreased rem; increased stage 2.
Wyatt et al. (1970a)	Levodopa, variable dose	7 movement disorder	+	0	0	0	Decreased rem sleep.
Wyatt et al. (1970b)	Tryptophan, 7.5 gm	5 normal	+	0	0	0	Decreased rem; increased delta sleep.
		7 insomnic					No effect on sleep stages.
• • •	• • •						• • •
Baekeland and Lundwall (1971)	Methyldopa, 1.25 gm/24 hr	10 normal	+	+	+	0	Increased rem and decreased delta sleep in first 3 hours only.
Coulter et al. (1971)	Reserpine, 1 mg	10 normal	+	0	0	0	Increased rem and decreased delta sleep on day after medication taken.

Study	*Drug*	*Subjects*	*1*	*2*	*3*	*4*	*Results*
Evans and Ogunremi (1970)	Chloral hydrate, 800 mg	4 normal	0	+	0	+	Decreased rem sleep.
	Dichloralphenazone, 1.3 gm						No effect on sleep stages.
	Methaqualone, 250 mg and Diphenhydramine 25 mg						No effect on sleep stages.
Firth et al. (1970)	Fenfluramine, 40 mg	7 normal	+	+	0	0	No effect on sleep stages.
Kales et al. (1970b)	Flurazepam, 30 mg	3 insomnic	+	0	+	0	No effect on sleep stages.
	Chloral hydrate 1 gm	4 insomnic					No effect on sleep stages.
	Glutethimide, 500 mg	4 insomnic					Decreased rem; withdrawal rem rebound.
Kales et al. (1970d)	Flurazepam, 30 mg	4 normal	+	0	+	0	No effect on sleep stages.
	Flurazepam, 60 mg	not given					Decreased rem sleep.
	Chloral hydrate, 1 gm	5 normal					No effect on sleep stages.
	Methaqualone, 300 gm	5 normal					Decreased rem; withdrawal rem rebound.
	Methaqualone, 150 mg	5 normal					No effect on sleep stages.

Study	*Drug*	*Subjects*	*1*	*2*	*3*	*4*	*Results*
	Mebanazine, 15 mg	1 depressed					Decreased rem; withdrawal rem rebound.
	Phenelzine, 45 mg	1 depressed					Decreased rem.
	Pargyline, 100 mg	1 normal					Decreased rem.
Zung (1969a)	Desipramine, 75 mg/24 hr	6 depressed	+	0	0	0	Increased delta sleep.
Zung (1969b)	Desipramine, 75 mg/24 hr	17 normal					Decreased rem and increased delta sleep on fourth day of drug.
• • •	• • •						• • •
Akindele et al. (1970)	Nialimide, 10 mg/kg	5 normal	+	0	+	0	No effect on sleep stages.
	Phenelzine, 90 mg	4 normal					Decreased rem; increased stage 2; withdrawal rem rebound.
	Phenelzine, 90 mg	3 depressed					Decreased rem; increased delta sleep.
Bricolo et al. (1970)	Levodopa, 4 gm/24 hr	14 parkinson	+	+	0	0	No effect on sleep stages.
Davison et al. (1970)	Methaqualone, 250 mg and Diphenhydramine, 25 mg	14 normal	+	+	0	0	No effect on sleep stages.
	Quinalbarbital, 100 mg and Amylobarbital, 100 mg						Decreased rem sleep.

Study	*Drug*	*Subjects*	*1*	*2*	*3*	*4*	*Results*
Sagales et al. (1969)	Scopolamine, 0.006 mg/kg	8 normal	0	+	0	0	Decreased rem sleep.
	Chlorpromazine, 0.4 mg/kg						No effect on sleep stages.
H. L. Williams et al. (1969a)	Reserpine, 1 mg	16 normal	+	+	+	0	Increased rem on second drug night.
	Tryptophan, 7.5 gm	11 normal					Increased delta sleep.
	Phenylalanine, 7.5 gm	11 normal					Increased delta sleep.
H. L. Williams et al. (1969b)	Alpha-chloralose, 500 mg	10 normal	+	+	0	0	Decreased rem; increased delta sleep.
R. L. Williams and Agnew (1969)	Pentobarbital, 200 mg	9 normal	0	+	0	+	Decreased rem; increased stage 2.
	Meprobamate, 800 mg						No effect on sleep stages.
	Glutethimide, 500 mg						Decreased rem sleep.
	Methaqualone, 300 mg						No effect on sleep stages.
Wyatt et al. (1969a)	Parachlorophenylalanine, 4 gm/24 hr	4 carcinoid	+	0	0	0	Decreased rem with no tolerance.
Wyatt et al. (1969b)	Isoniazid, 400 mg	1 normal	+	0	+	0	No effect on sleep stages.
	Isocarboxazid, 60 mg	1 normal					Decreased rem sleep.

Study	*Drug*	*Subjects*	*1*	*2*	*3*	*4*	*Results*
Brebbia et al. (1969)	Lithium, 1 gm/24 hr	6 mixed	+	+	0	0	No effect on sleep stages.
Feinberg et al. (1969c)	Phenobarbital, 200 mg	6 mixed	+	+	0	0	Decreased rem sleep.
	Chlorpromazine, 200 mg						Decreased rem sleep.
Greenberg et al. (1969)	Nitrous oxide by inhalation	7 normal	+	0	0	0	No effect on sleep stages
Haider (1969)	Amylobarbitone, 200 mg	6 normal	+	+	+	0	Decreased rem; increased stage 2.
	Nitrazepam, 10 mg						Decreased rem; increased stage 2.
Hoffman and Domino (1969)	Reserpine, 0.14 mg/kg	20 prisoners	+	0	0	0	Increased rem, prolonged effect.
Kales et al. (1969)	Glutethimide, 500 mg	5 normal	+	+	0	0	Decreased rem; withdrawal rem rebound.
	Methyprylon, 300 mg	7 normal					Decreased rem; withdrawal rem rebound.
	Chloral hydrate, 500 mg	10 normal					No effect on sleep stages.
Lewis and Evans (1969)	Chlorpromazine, 25 mg	7 normal	+	?	0	0	Increased rem after the first night.
	Chlorpromazine, 100 mg						Decreased rem sleep.
Rubin et al. (1969)	Glutethimide, 1 gm	4 normal	+	0	0	0	Decreased rem sleep.

Study	*Drug*	*Subjects*	*1*	*2*	*3*	*4*	*Results*
Hartmann (1966)	Reserpine, 2 mg	6 normal	+	0	0	0	Increased rem sleep.
Lester and Guerrero-Figueroa (1966)	Chlorpromazine, 100 mg	8 normal	+	0	+	0	Increased delta sleep.
	Alpha-chloralose, 500 mg						Decreased rem; increased delta sleep.
	Phenobarbital, 120 mg						Increased delta sleep.
	Thiopental, 300 mg IV						Decreased rem; increased delta sleep.
Muzio et al. (1966)	LSD, 30 mcg	12 normal	+	0	+	0	Increased rem in first part of night.
Oswald et al. (1966)	Tryptophan, 5 gm	16 normal	+	+	+	0	Increased rem (2 hr. recording only).
Toyoda (1966)	Atropine, 10 mg	9 mixed	+	0	+	0	No effect on sleep stages.
Yuko et al. (1966)	Alcohol, 1 gm/kg	3 normal	+	+	+	0	Decreased rem in first half of night; rem rebound on withdrawal.
• • •	• • •						• • •
Baekeland (1967)	Pentobarbital, 100 mg	20 normal	+	+	+	+	Decreased rem sleep.
	Amphetamine, 15 mg						Decreased rem sleep.
Hartmann (1967a)	Tryptophan, 120 mg/kg	8 normal	+	0	0	0	Increased rem; increased total sleep time.
Ritvo et al. (1967)	Imipramine, 50 mg	7 enuretics	0	0	0	0	Decreased rem; increased stage 2 (first drug night discarded).

Study	*Drug*	*Subjects*	*1*	*2*	*3*	*4*	*Results*
Yules et al. (1967)	Alcohol 1 gm/kg	4 normal	+	+	+	0	Decreased rem; rem rebound on withdrawal
• • •	• • •						• • •
Evans and Lewis, (1968)	Amylobarbitone, 400 mg	2 normal	+	+	0	0	Decreased rem; rem rebound on withdrawal; rem rebound blocked by chlorpromazine.
Hartmann (1968b)	Pentobarbital, 100 mg	8 normal	+	+	0	0	Decreased rem sleep.
	Amitryptyline, 75 mg						Decreased rem sleep.
	Chlordiazepoxide, 100 mg						No effect on sleep stages.
Knowles et al. (1968)	Alcohol, 180 ml	1 normal	+	0	+	0	Decreased rem in first half of night; rem rebound on withdrawal.
Lester et al. (1968)	Secobarbital, 200 mg	14 normal	+	0	+	0	No effect on rem; delta sleep increased in first half of night, decreased in second half.
Oswald et al. (1968)	Diethylproprion, 50 mg	6 normal	+	+	+	0	Decreased rem; withdrawal rem rebound (2 hr. recording).
	Fenfluramine, 40 mg						No effect on sleep stages (2 hr. recordings).
Torda (1968)	LSD, variable, given during third rem period.	2 normal	0	0	+	0	Decreased latency to fourth rem period.
• • •	• • •						• • •
Brannen and Jewett (1969)	Promethazine, 50 mg	7 normal	0	+	+	0	No effect on sleep stage percentages; sleep cycle length increased.
	Trifluoperazine, 5 mg						Increased rem sleep.

Study	*Drug*	*Subjects*	*1*	*2*	*3*	*4*	*Results*
Gresham et al. (1963)	Alcohol, 1 gm/kg	7 normal	0	+	+	0	Decreased rem sleep.
Oswald et al. (1963)	Heptabarbitone, 400 mg	6 normal	0	0	+	0	Decreased rem sleep.
		6 depressed					
• • •	• • •						• • •
Rechtschaffen and Maron (1964)	Amphetamine, 15 mg	8 normal	+	+	0	0	Decreased rem; decreased total sleep time; rem rebound upon drug withdrawal.
Toyoda (1964)	Chlorpromazine, 50 mg	6 mixed	+	+	0	0	Increased rem sleep.
	Imipramine, 50 mg						Decreased rem sleep.
• • •	• • •						• • •
Freemon et al. (1965)	Meprobamate, 1200 mg	8 normal	+	+	+	+	Decreased rem; increased stage 2.
Green (1965)	LSD, 300 mcg	1 alcoholic	+	+	+	0	Increased rem sleep.
Oswald and Priest (1965)	Amylobarbitone, 400 mg	4 normal	+	+	+	0	Decreased rem sleep; withdrawal rem rebound.
	Nitrazepam, 15 mg						Decreased rem sleep; withdrawal rem rebound.
• • •	• • •						• • •
Baekeland (1966)	Methylphenidate, 5 mg	6 normal	+	+	+	0	Decreased rem; increased stage 2.
Evans and Oswald (1966)	Tryptophan, 5 gm	7 narcoleptic	+	+	+	0	Increased rem (not an all-night recording).

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