# PERIODICITY OF HIGH-ORDER NEURAL FUNCTIONS

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# INTRODUCTION

This report describes the results of recent studies on higher order, integrative processes in the central nervous system. The purpose of these studies has been to determine whether these processes exhibit any ongoing rhythmicity which might manifest itself in alterations of attention and alertness. The presence of such alterations and their effect on perception and performance would be of more than academic interest, for such findings would be of value in scheduling critical tasks (such as an astronaut's) to coincide with periods of peak performance.

The existence of rhythmic variations in physiological processes is well established. Of particular interest to physiologists have been those rhythms with a period approximating 24 hours, the so-called circadian rhythms. Although a multitude of physiological parameters have been found to have a periodicity approximating this value, little is known of the periodicity that might be present in high-order functions of the central nervous system (CNS), such as the cognitive processes.

The most obvious periodic fluctuation in this system is the sleep-wake cycle, but sleep itself is far from being a homogeneous state. The studies of Aserinsky and Kleitman (1953) established that sleep consists of two distinct states rather than a single continuum varying only in depth. These two phases may be clearly differentiated electrophysiologically (Rechtschaffen and Kales, 1968) and behaviorally (Dement and Kleitman, 1957), and there is strong evidence

that separate neuro-chemical systems are responsible for their production (Jouvet; 1967, 1969). So-called slow-wave sleep or "quiet" sleep is characterized electrophysiologically by EEG synchronization (the presence of spindles and high voltage slow activity). Paradoxical or "active" sleep is characterized by a desynchronized EEG resembling that of the waking state. This stage is also characterized by rapid, phasic movements of the eyes and for this reason is most often called rapid-eye-movement (REM) sleep. Throughout the night, there is a cyclic alternation between REM and non-REM states (Dement and Kleitman, 1957; Rechtschaffen and Kales, 1968), the cycles having an average duration of about 70-90 minutes in man (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957).

Various behavioral and physiological parameters evidence during the waking state a periodicity which approximates that of the REM cycle (Oswald et al., 1970), and Kleitman (1970) has proposed that the changes in these parameters and the occurrence of REM sleep are all manifestations of a basic cycling of CNS activity which he has called the "basic rest-activity cycle" (BRAC). The BRAC has been shown to be present early in ontogeny (Sterman, 1970 ), supposedly before maturation of the structures responsible for quiet sleep. The BRAC of the human neonate appears to have a period of about 50-60 minutes, but this gradually lengthens until it reaches a mean value of around 90 minutes at 5-10 years of age. Conclusions regarding the significance of the BRAC are hampered by the fact that it shows considerable variation in individual cycles, a variation which might be under the

control of yet another basic rhythm with a period of 12 hours or more. But the presence of such a cycle would suggest that many physiological processes might be indirectly influenced, and it is reasonable to assume that high-order functions of the CNS (such as alertness and information-processing) may also evidence such a periodicity.

More than forty years ago, Philpott (1932) reported finding periodic fluctuations in mental and motor performance, with periods ranging from several seconds to minutes and even hours. He postulated that these periods increased exponentially from the outset of the activity, roughly doubling with each successive fluctuation, but little is known of what overall cyclic variation may be evidenced in the mental processes. Such fluctuations may well be evidenced in recordings of brain electrical activity (the EEG).

Data from our own laboratory suggest that the alpha rhythm, formerly thought to be of relatively constant frequency in any individual, can be shown by computer analyses to fluctuate considerably in wave-length spectrum. A distribution of the relative occurrence of activity at each frequency in the alpha range can be constructed, and such a distribution has been called (by Frost, in our laboratory) the "alpha profile." Similar profiles can be constructed for electrical activity in other frequency ranges. Techniques recently developed in our laboratory utilizing computer analysis of the EEG provide an even more sensitive quantitative measure of brain electrical activity. Periodicity of CNS activity, if present, should be reflected in

EEG changes sensitive to such measurement techniques.

The experiments outlined below were designed to determine if a periodicity approximating that of the REM cycle could be detected in various parameters of brain electrical activity.

Experiment 1: Periodicity in sensory-motor integration.

As has been described in previous reports to this agency (NGR 44-003-001), a slow cerebral electrical potential called the contingent negative variation (CNV) has been shown to be related to the attentive processes in man. First described by Walter et al. (1964) and later confirmed in this laboratory (Low et al., 1966), this slow potential has been the subject of intensive research by various workers. Much of the definitive work on the CNV has been performed in this laboratory. The CNV can be recorded with relative ease in subjects who are performing a fixed foreperiod reaction-time task. Warning cues are followed at a fixed interval (usually 1 second) by an "imperative" stimulus, a cue to perform some motor response. The CNV is seen as an electronegative shift in the EEG baseline during the interval between the two stimuli. A previous study (Hillyard, 1969 ) has shown that, at least in some subjects, there is a high correlation between the subject's attentiveness and various aspects of CNV wave form (Low et al. ,1967; Tecce and Scheff, 1969). Tecce (1971) has suggested that CNV amplitude is monotonically related to attention and non-monotonically related (inverted-U) to arousal. No study has yet, however, examined the possibility that the CNV wave form may fluctuate in a periodic manner. It has been suggested (McAdam, 1967) that CNV amplitude increases as the

subject learns the reaction-time task, reaches a plateau, then decreases with continued training. It is possible, however, that had the CNV been examined over a longer period of time, a second increase in amplitude might have been observed that would suggest such periodicity. If true, this would correlate with our own finding that CNV amplitude remains relatively constant over hundreds of trials when tested at the same time on successive days. This certainly is the case in monkeys, where a CNV-like, negative slow potential was found to occur in similar situations to those used to elicit the response in man. The monkeys were, again, tested at the same time every day over several months with no apparent diminution of the CNV-like potential (Borda, 1970).

As the sole electrographic correlate of such "higher nervous functions" as attention and sensory-motor integration, the CNV logically offers a simple method for determining the presence or absence of ultradian rhythms in mental performance. The techniques used to record it allow, at the same time, the analysis of reaction-time variability, another valuable clue to the existence of such fluctuations.

## METHODS

Eight subjects (5 male, 3 female), ranging in age from 21 to 30 years, were tested. Recordings were obtained from each subject every 30 minutes for $11\frac{1}{2}$ - 12 hours, except for one subject who was tested for only eight hours; all studies were initiated at 8 a.m. For each test session, the subject

was seated in a reclining chair inside an electrically shielded room. Electrode leads were coupled to the amplifiers with a quick-disconnect plug so that the subjects could leave the shielded room between recordings. The subjects' activity between these sessions was unstructured, and they were permitted to leave the recording area and to read and eat as they chose.

Each subject was asked to perform a visual signal-detection task which closely approximated the usual CNV paradigm. Details of this task are described in the enclosed reprint (Borda and Hablitz, 1973). The cathode-ray tube (CRT) display of an oscilloscope was used for presentation of visual cues. The horizontal sweep was allowed to run freely at a high rate, thus presenting an apparently solid trace. A square-wave pulse of 1.2 sec, generated by BRS-Foringer programming modules, was capacitor-coupled to the vertical input. Onset of this pulse generated an upward deflection of the beam ($S_1$), whereas its offset resulted in an identical deflection of opposite polarity ($S_2$). The CRT was viewed from a distance of 2 m through a window in the shielded room. Subjects were instructed to depress a hand-held button switch as quickly as possible following $S_2$. In order to insure cooperation and attention to the display, inappropriate responses during the $S_1$-$S_2$ interval and responses occurring later than 300 msec after $S_2$ were signaled by the occurrence of a loud tone. Subjects were told to avoid these tones by responding rapidly only after $S_2$. At least 40 trials were given during each test session.

Chlorided silver-disc electrodes (Grass Instrument Co.) were affixed

to the scalp according to the International 10-20 System at the $C_z$, $F_z$, and $F_{pz}$ positions and were referred to paired ear electrodes ($A_1$, $A_2$). An electrode placed over the infraorbital ridge of the left eye and referred to linked electrodes near each lateral canthus was used to record the electro-oculogram (EOG). All electrical potentials were amplified by a Beckman Type R Dynograph using a 1.0 sec time constant. An FM tape recorder (Ampex model FR 1200) was used for data storage.

Visual analysis of the data on an individual-trial basis was performed for the purpose of editing trials containing significant eye movements or trials on which an incorrect response was made. A PDP-12 computer was used for signal averaging and measurement of CNV area. CNV area was used as the measure of CNV magnitude, which was calculated by determining the average voltage in the prestimulus period and then summing all voltages more negative than this for a 900-msec period beginning 300 msec after $S_1$.

The data was examined for the presence of periodicity by utilizing the UCLA BMD02T computer program. Various analyses were performed using this program on an IBM System 360 computer.

## RESULTS

Visual inspection of the data indicated that the task employed was very successful in minimizing eye-movement artifacts (see Borda and Hablitz, 1973); fewer than 10% of all the trials had to be discarded. Examination of

simultaneously averaged CNVs and EOGs showed clearly that EOG artifact was absent during the $S_1$-$S_2$ interval, the period when the area measurement was made. The importance of these findings can be appreciated when one considers that data loss of up to 45% has been reported in other CNV studies, and such losses could not be tolerated in a protracted study such as this one.

CNV areas, plotted as a function of time, are illustrated for each subject in Figures 1 and 2. Data for each of three electrode sites is plotted, with each data point being the mean CNV area for a set of thirty trials. Visual inspection revealed that CNVs persisted in each subject for the duration of the study, but were subject to significant variability. The data for some subjects did seem to contain periodic components of from $1\frac{1}{2}$ to 3 hr in duration (e.g., subjects HP and DG) and/or components of around 6 hr duration (e.g., subjects GE, AC, DG, and DC) in the recordings from the $C_z$ electrode site (see Figs. 1 and 2). Computer analysis of the autocovariance failed to substantiate the presence of such periodicity, however, with no period being significantly higher than the data variance measurement (lag=0). Plots of the autocovariance for seven of the subjects are shown in Figures 3 - 9, the data for the other subject (DG) being insufficient for such analysis.

Inspection of the distributional aspects of CNV magnitude indicates that there were two patterns present. Data from the subjects in Fig. 2 showed a consistent anterior-posterior voltage gradient, with CNV a maximum at the

vertex. A more variable pattern is seen in Fig. 1, where subjects often showed significant reversals, with the more anterior leads producing CNVs which equalled or exceeded those at the vertex. Specific examples of this are seen in Figs. 10 and 11, which show quite different distributions in subjects performing the same test under (presumably) identical conditions. This suggests that CNV is not as stable a phenomenon as previously thought. It was not possible to discern any relationship between these distributional changes and the above-mentioned variations in CNV area at the vertex.

The possibility that the variations in CNV were due to alterations in attention which might be reflected in changes in reaction time (RT) was considered, even though the use of the loud tone as an error cue had resulted in very consistent performance. Mean RTs for each averaged block of 16 trials were calculated and correlated with CNV area on a within-subject basis. The resultant correlation coefficients (Spearman's Rho) ranged from -0.09 to +0.15, but none were significant at the 0.05 level.

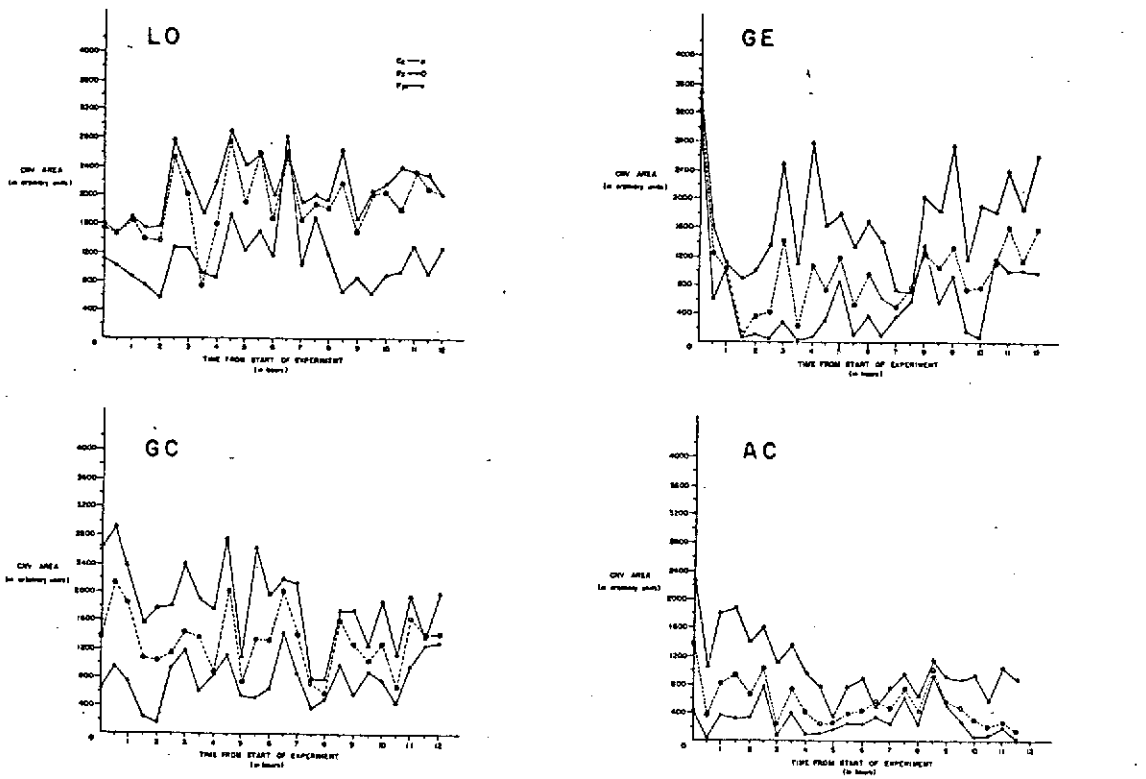


Figure 1. CNV area as a function of time in four subjects. Each point is an average of 30 trials, and data is plotted for each of three electrode sites.

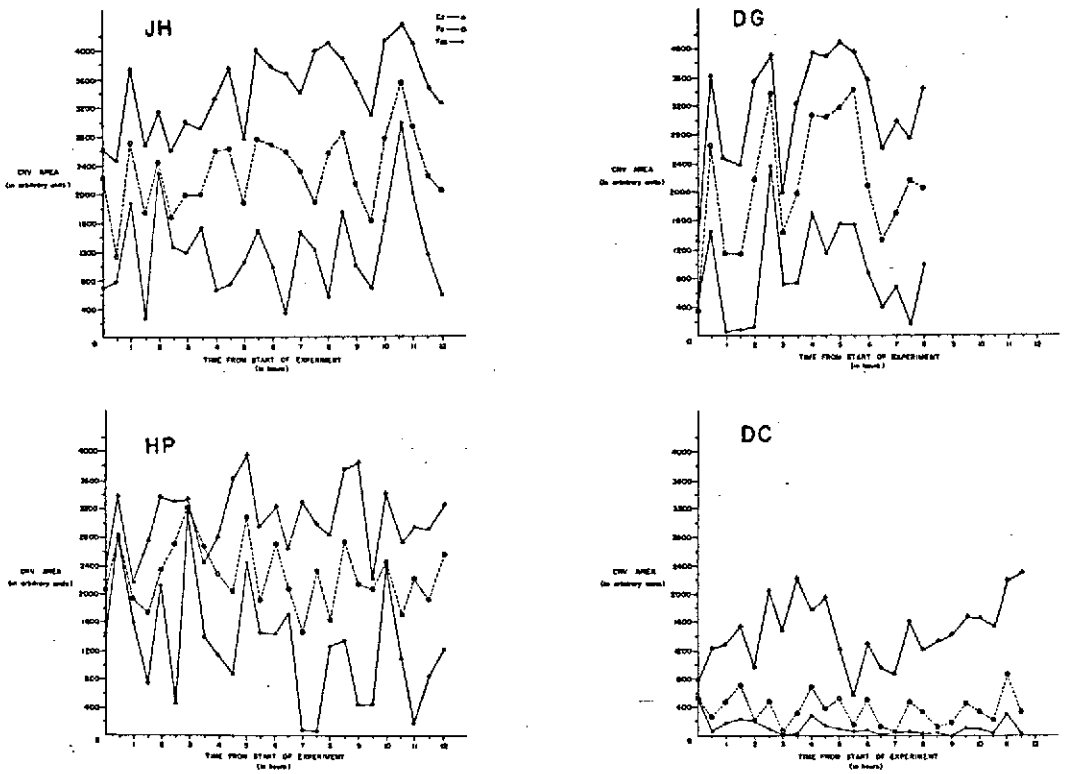


Figure 2. CNV area as a function of time in four additional subjects.

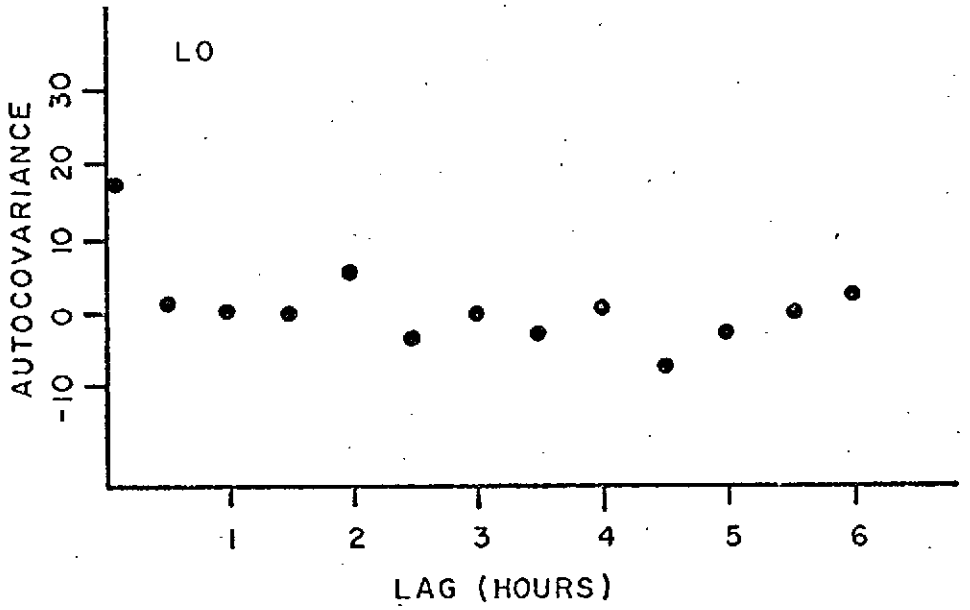


Figure 3. Autocovariance of data shown in Figure 1 for subject LO.

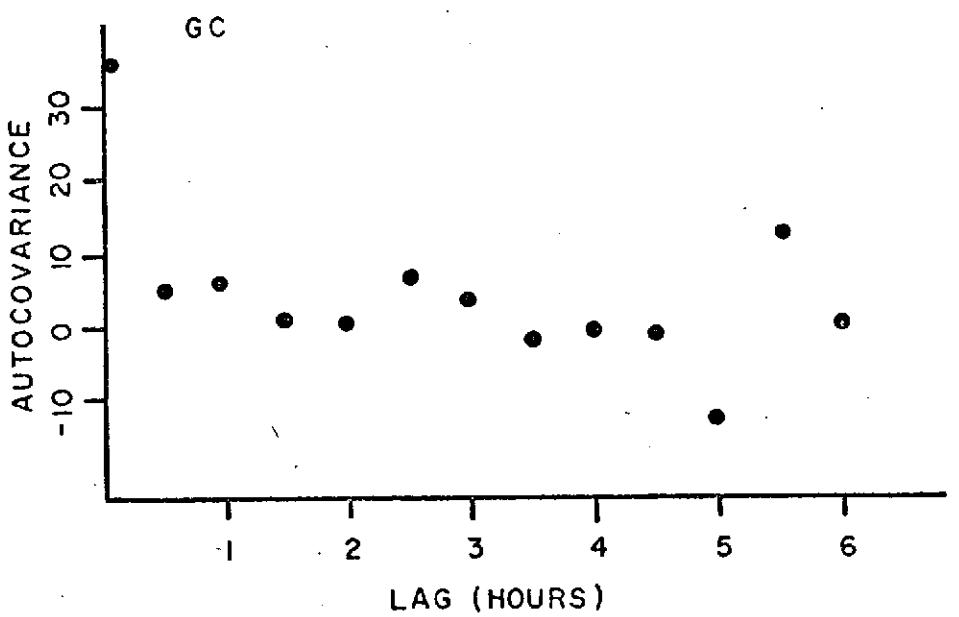


Figure 4. Autocovariance of data shown in Figure 1 for subject GC.

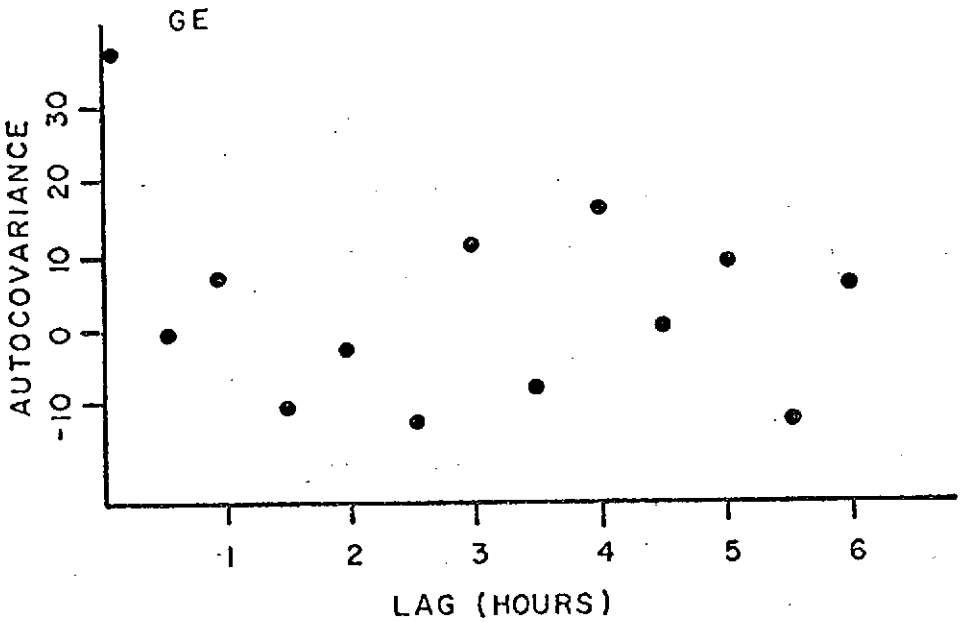


Figure 5. Autocovariance of data shown in Figure 1 for subject GE.

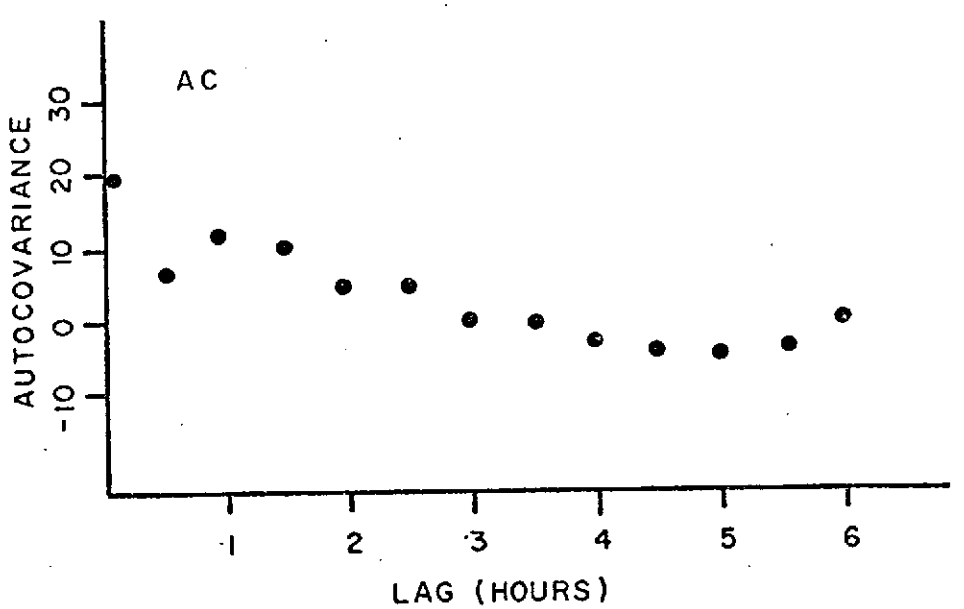


Figure 6. Autocovariance of data shown in Figure 1 for subject AC.

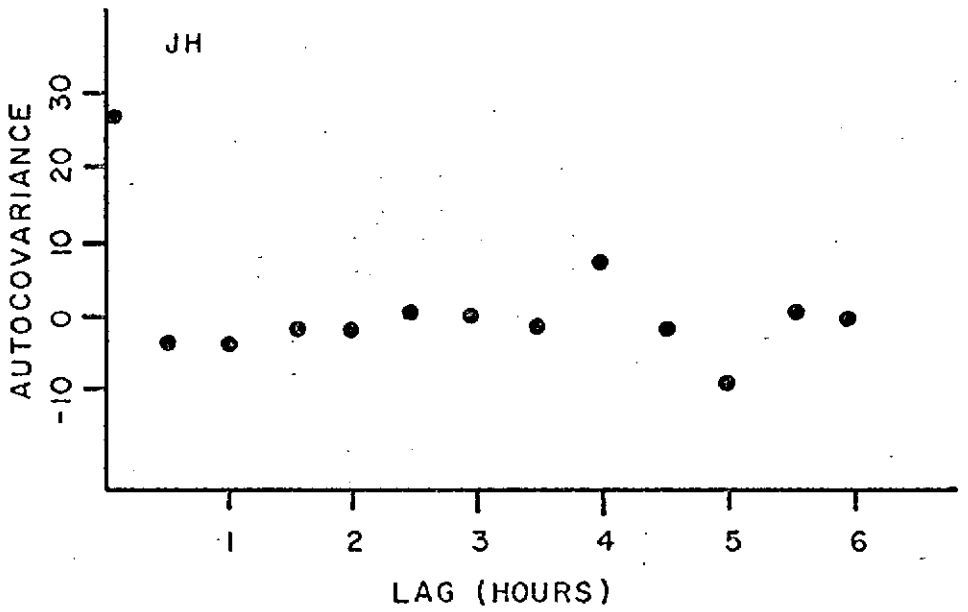


Figure 7. Autocovariance of data shown in Figure 2 for subject JH.

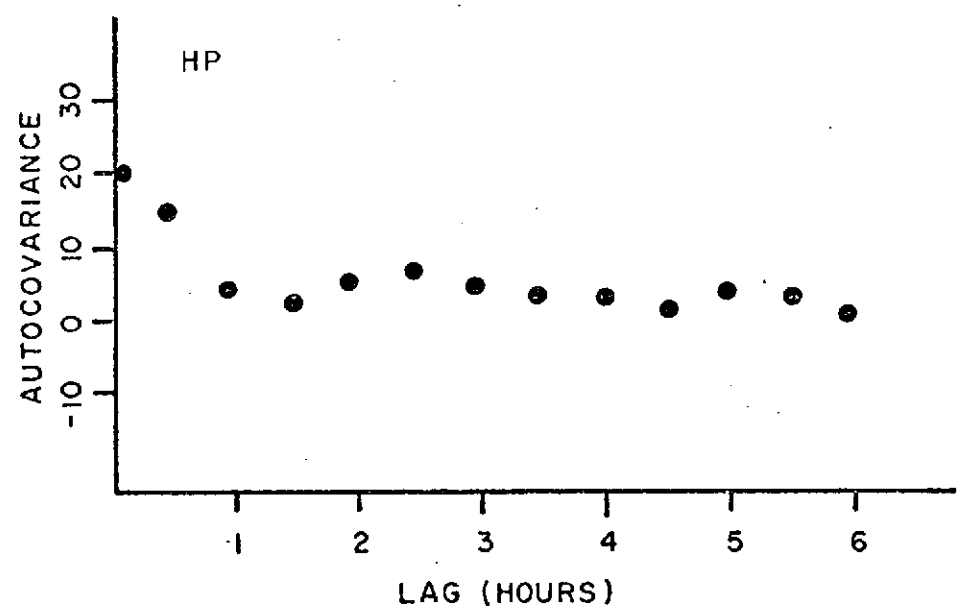


Figure 8. Autocovariance of data shown in Figure 2 for subject HP.

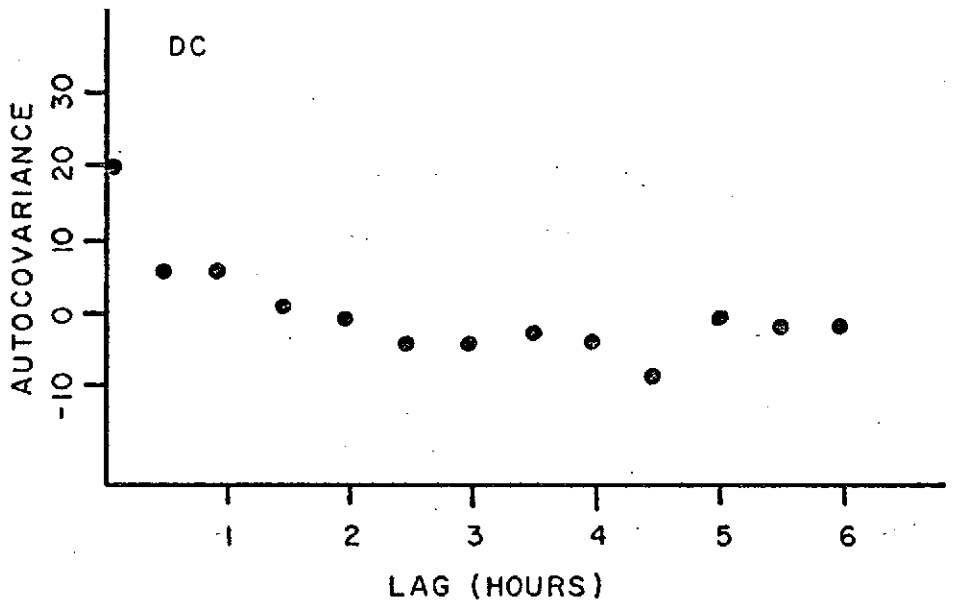


Figure 9. Autocovariance of data shown in Figure 2 for subject DC.

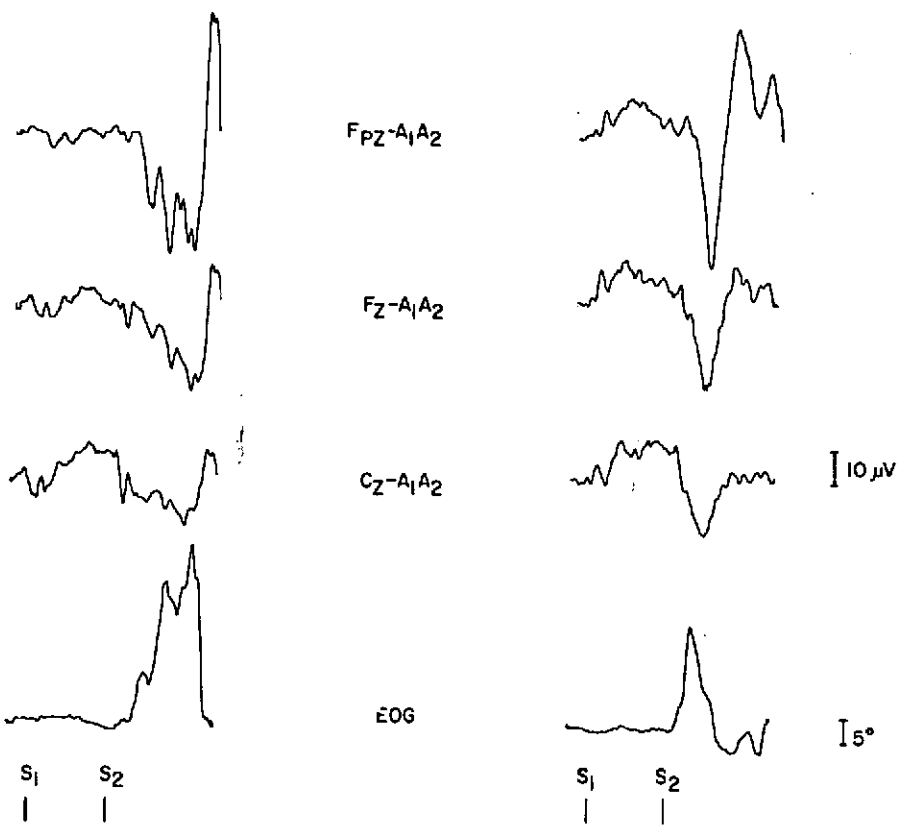


Figure 10. Comparison of CNV wave forms at three electrode sites in the same subject during different recording sessions (under identical conditions with no significant eye movements). A more central dominant potential is evident in the recordings in the column on the left, whereas a more widespread, frontocentral distribution is evident in the other set.

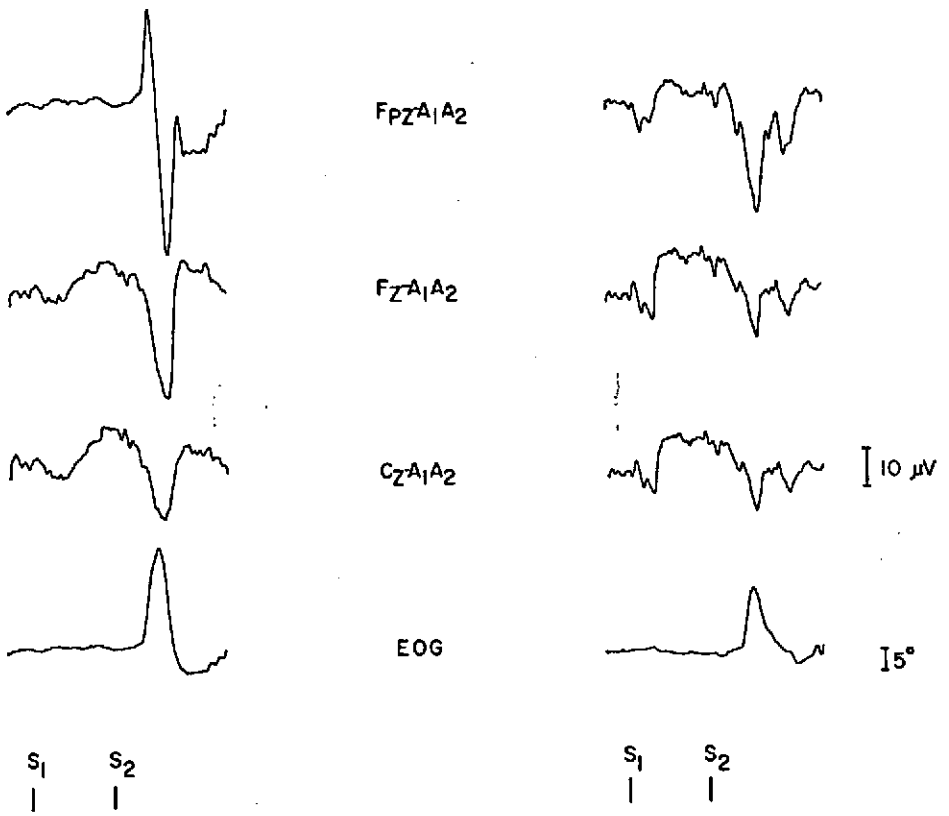


Figure 11. Comparison of CNV wave forms at three electrode sites in another subject during different recording sessions (under identical conditions with no significant eye movements). The column on the left illustrates a central-dominant distribution, whereas a more frontal dominant distribution is evident in the other sample.

## DISCUSSION

It is readily apparent from the results of this study that CNV amplitude does not, as previously reported (Walter et al., 1964), reach a plateau and remain relatively constant, but rather tends to vary over a considerable range. The changes in amplitude were accompanied by variations in the scalp distribution of CNV. A differentiation of the topographic changes according to behavioral task, such as performed by Jarvilehto and Fruhstorfer (1970), was not possible in this stidy, since the task remained constant. Therefore, it appears that, at least to some extent, CNV distribution may vary randomly. Tecce (1972) has suggested that the early reports of prominent frontal-dominant CNVs (Walter et al., 1964; Low et al., 1966) were in error because of spurious enhancement from eye-movement potentials. The current results indicate that large frontal CNVs can be recorded in the absence of contamination by eye-movement artifact. The sporadic occurrence of these large frontal potentials is consistent with the observations of Walter (1967) that during direct cortical recordings in humans, the presence of CNV was "patchy," with some areas generating large slow potentials and other locations simultaneously showing no activity. Presence of the frontal-dominant potential reinforces the association of CNV with higher nervous function and underscores the complex nature of this potential. Clearly, recording the CNV from a single "active" electrode at the vertex can no longer be considered adequate.

Although computer analysis failed to confirm the presence of ultradian

periodicity in the CNV, several factors may have biased these findings. First, the assumption that the CNV is a fairly stable phenomenon appears to be invalid, and the reliable detection of periodicity in the face of such high sample variability will require a higher sampling rate than was used in this study. Second, the program used assumes that only stationary processes (time series) are involved, and this assumption may also be invalid. Clearly, a higher sample rate would help solve the first problem, but a sampling interval of much less than the thirty minutes used in this study may exceed subject acceptance. Another approach would be to record from each subject on several different days, and pool the data from each of these sessions.

Still another possibility is that CNV, as suggested from the studies in monkeys, is a non-unitary process with components varying from trial-to-trial. If such is the case, then any single electrode site would be inadequate to measure what must be considered a "topographically mobile" event, and a composite recording from multiple electrodes over the frontal region would be necessary. The application of such techniques must await a more thorough understanding of the basic processes underlying the CNV.

Experiment 2: Periodicity in endogenous cerebral electrical activity.

Unlike the CNV, the endogenous electrical activity of the brain (the EEG) may be sampled at will without any behavioral demands being placed

upon the subject. The alteration in the EEG which accompanies the "sleep cycle" suggests that ultradian modulation may be present during waking hours as well.

Although the waking EEG is generally characterized by relatively fast rhythms, i.e., those in the alpha and beta ranges, the study by Ivanov et al. (1965) showed that activity in the lower frequency ranges (delta and theta) was present but at greatly reduced power. Since it is the disappearance of alpha and the emergence of activity in the theta range which signals the onset of sleep, it is logical to assume that periodic fluctuation in the EEG produced by the BRAC might be detected by examining activity in this mid-range of frequencies.

## METHODS

For a preliminary inspection of ultradian rhythmicity, a monkey (Macaca mulatta) was chosen as a subject. Transcortical platinized-platinum electrodes were chronically implanted over the frontal and central regions, and the cortical electrical activity recorded while the subject sat in a plastic restraining chair (Foringer) inside an electrically shielded cubicle (Ray Proof). Samples were obtained every six minutes for twelve hours. Data was digitized on-line by a PDP-12 (Digital Equipment Corporation) computer after pre-filtering the analog signal to a bandwidth of 3-7 $H_z$ (rolloff more than 6db/octave). The digitized data was subsequently submitted to a wavelength/amplitude analysis (on the PDP-12) which yielded

the following measures for each 100 sec sample: (1) wavelength of the waves with the largest amplitude, (2) mean wavelength, (3) number of waves, and (4) average wave amplitude. Each of these measures (in time-series form) was then analyzed using the UCLA BMD02T program for the IBM System 360 computer.

## RESULTS

Plots of the power spectral estimates and autocovariance functions for each of the four measures for recordings obtained at one electrode site (left central) are presented in Figures 12 -19. In this data no marked ultradian rhythmicity is evident in the frequency range (theta) examined. Sample variability was quite high, and even though there was some suggestion of periodic components approximating 20 and 50 minutes in duration, these did not exceed the "noise level" of the data and thus were not statistically significant.

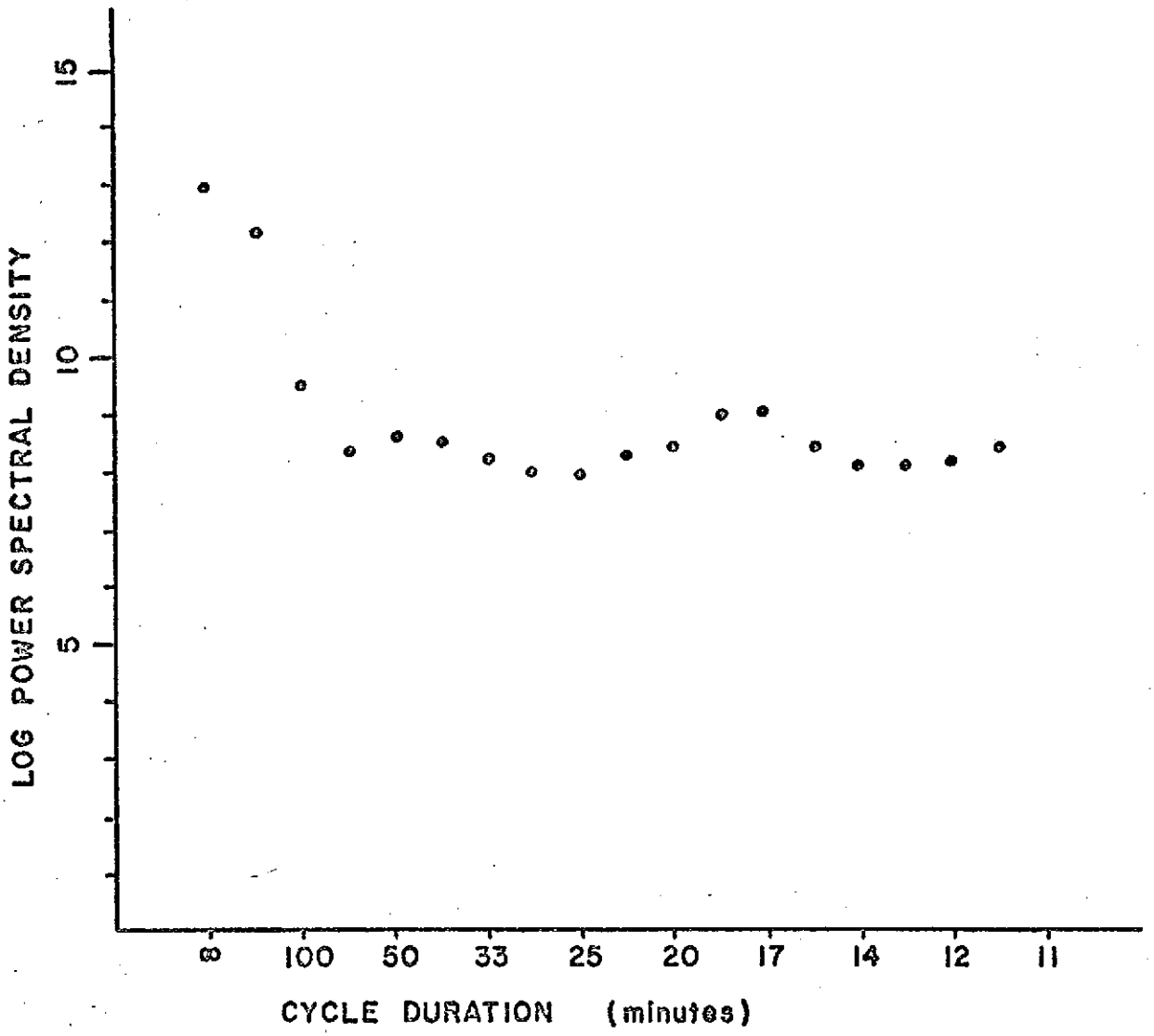


Figure 12. Power spectral estimates (log scale) of theta analysis (wavelength of waves with highest amplitude) as a function of cycle duration. Recordings obtained from left central region.

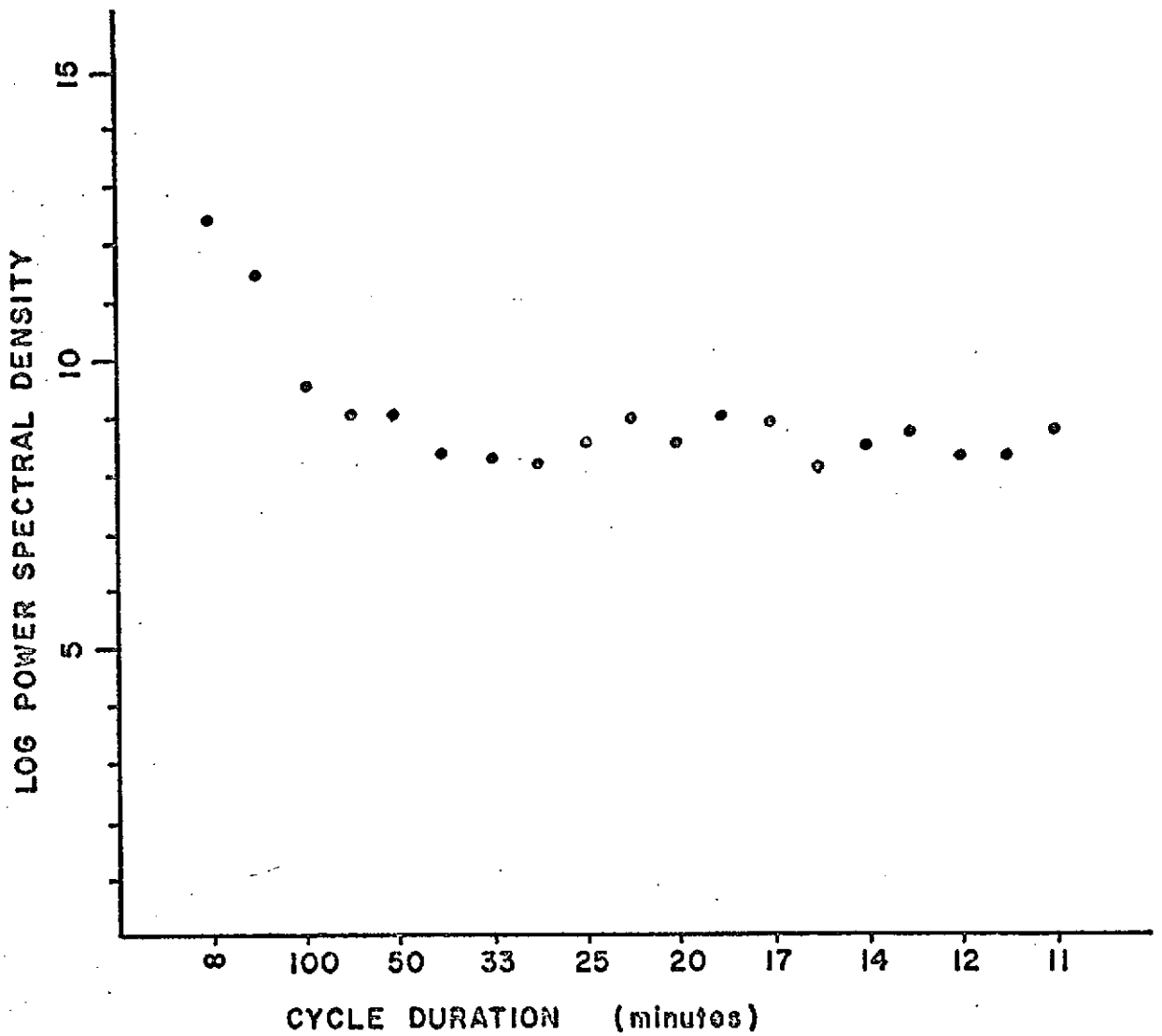


Figure 13. Power spectral estimates (log scale) of theta analysis (mean wavelength of sample) as a function of cycle duration. Recordings obtained from left central region.

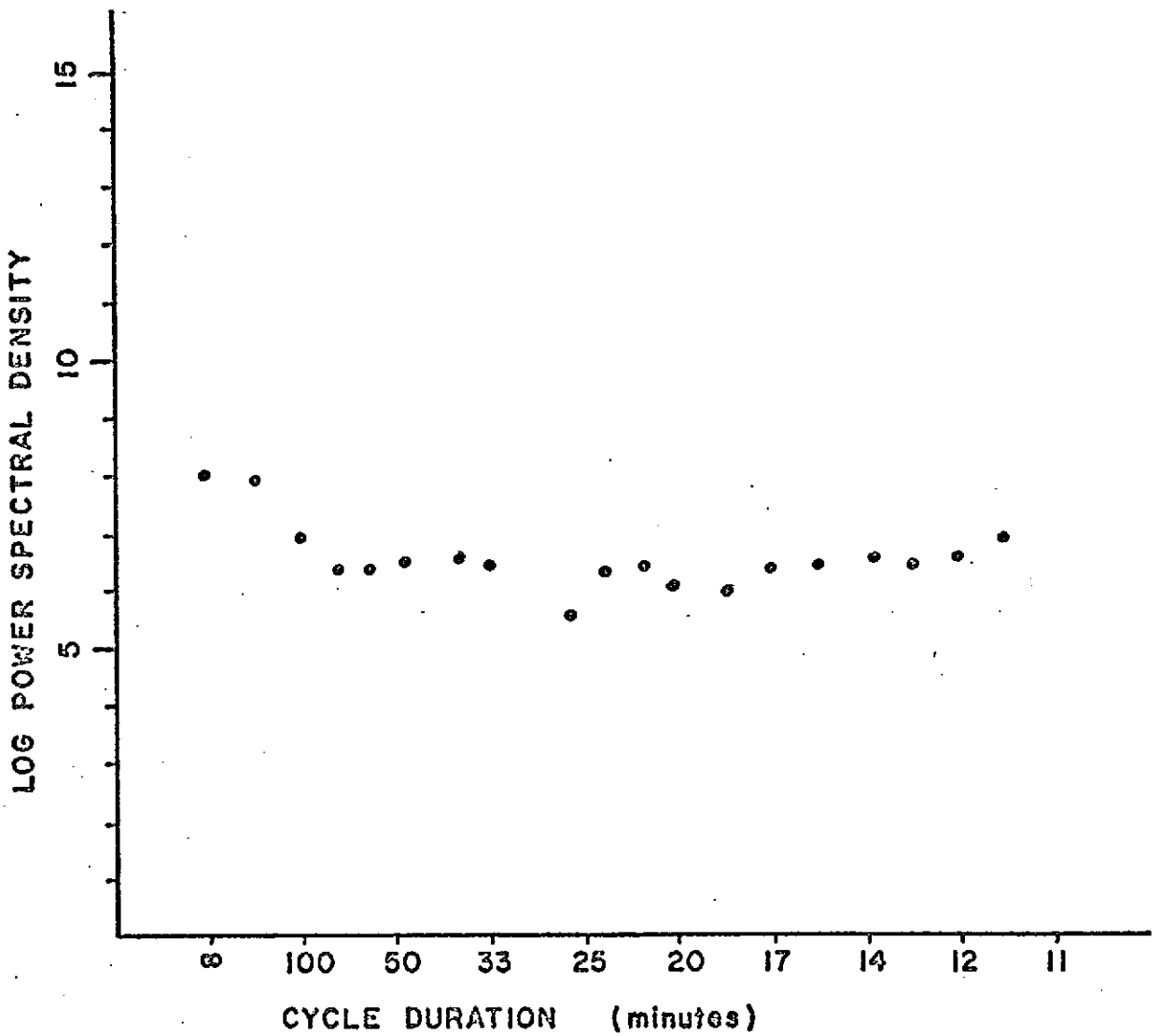


Figure 14. Power spectral estimates (log scale) of theta analysis (number of waves in sample) as a function of cycle duration. Recordings obtained from left central region.

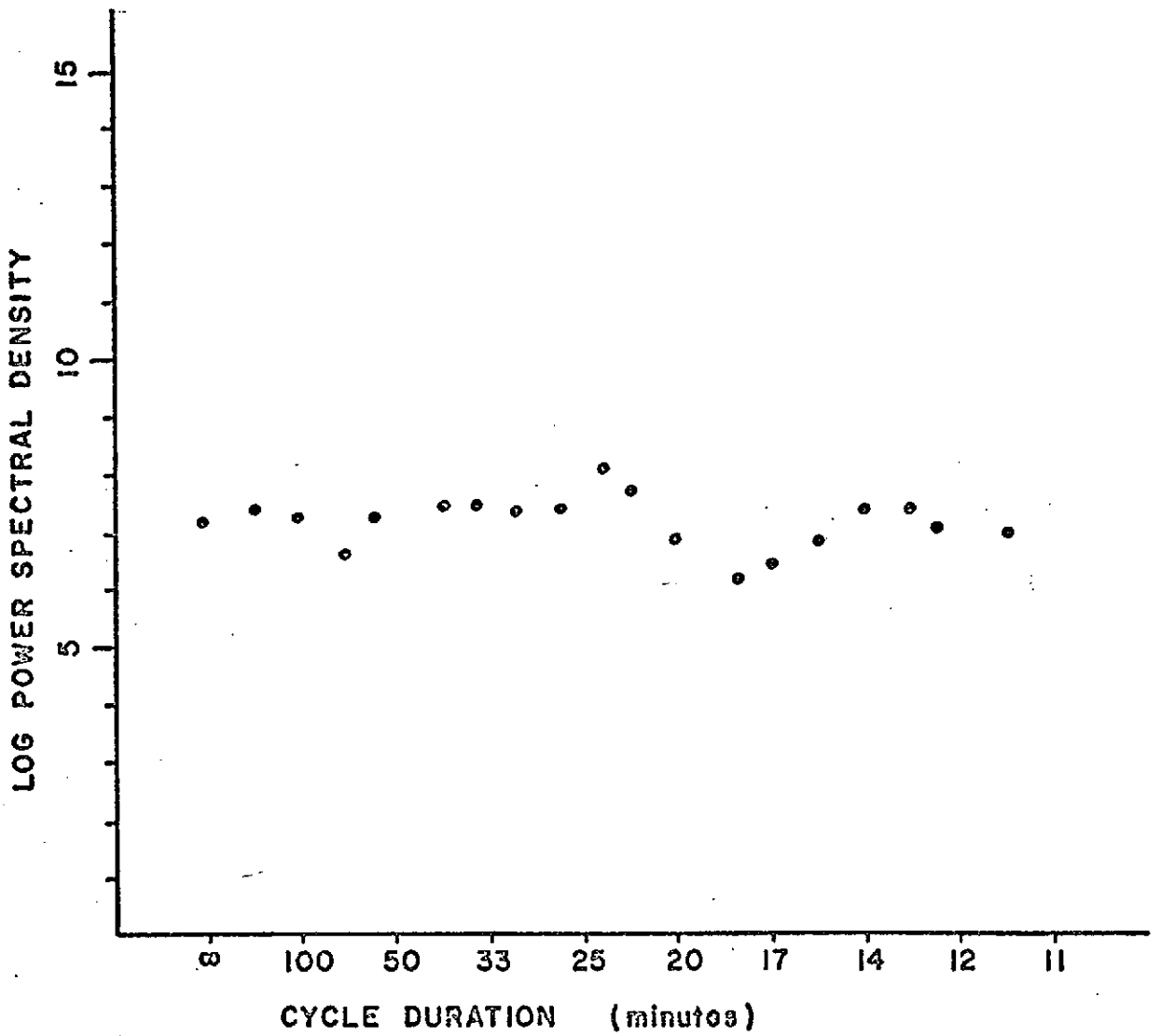


Figure 15. Power spectral estimates (log scale) of theta analysis (average wave amplitude) as a function of cycle duration. Recordings obtained from left central region.

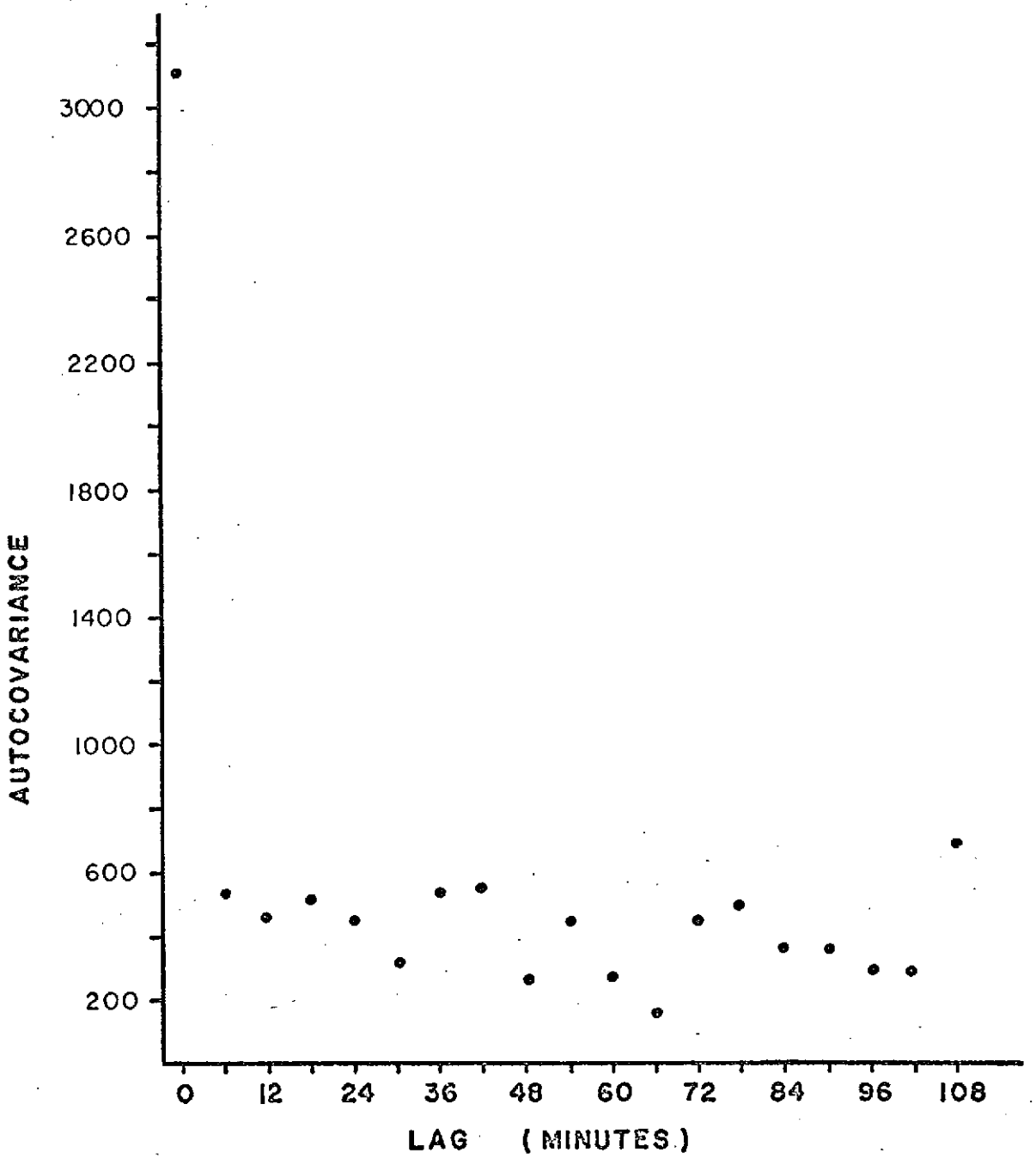


Figure 16. Autocovariance of series shown in Figure 12 (theta analysis wavelength of waves with highest amplitude).

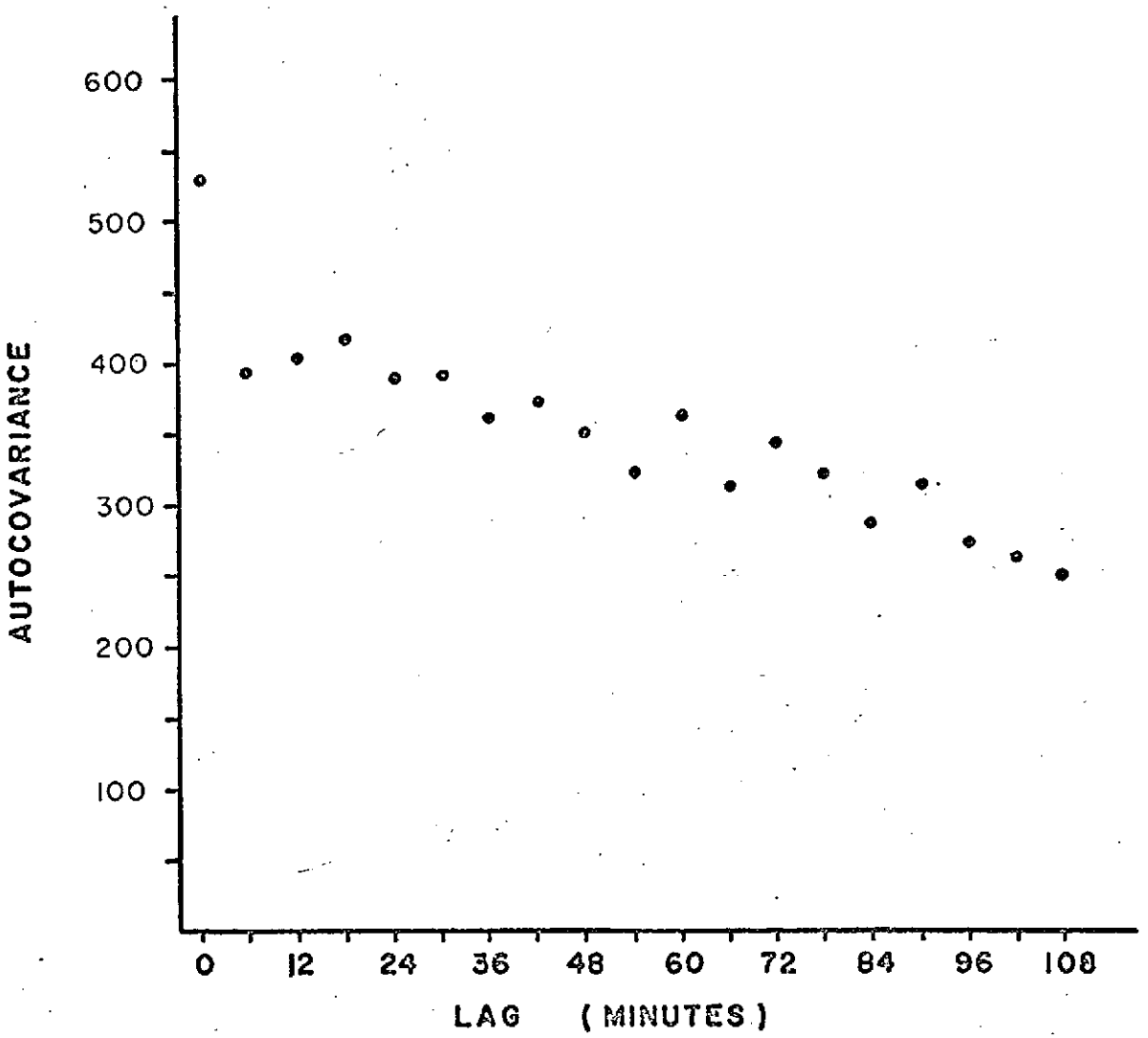


Figure 17. Autocovariance of series shown in Figure 13 (theta analysis, mean wavelength).

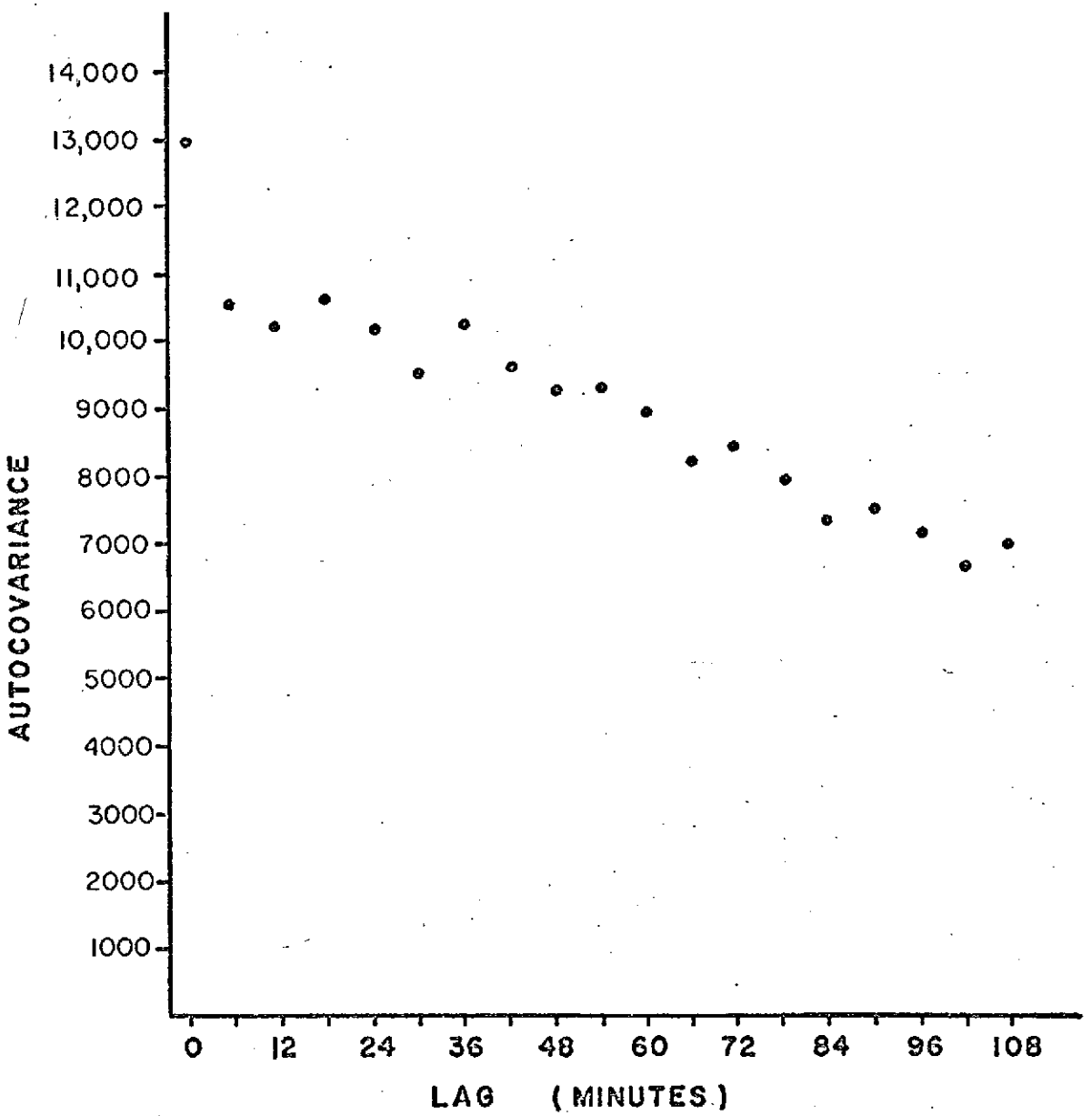


Figure 18. Autocovariance of series shown in Figure 14 (theta analysis, number of waves in sample).

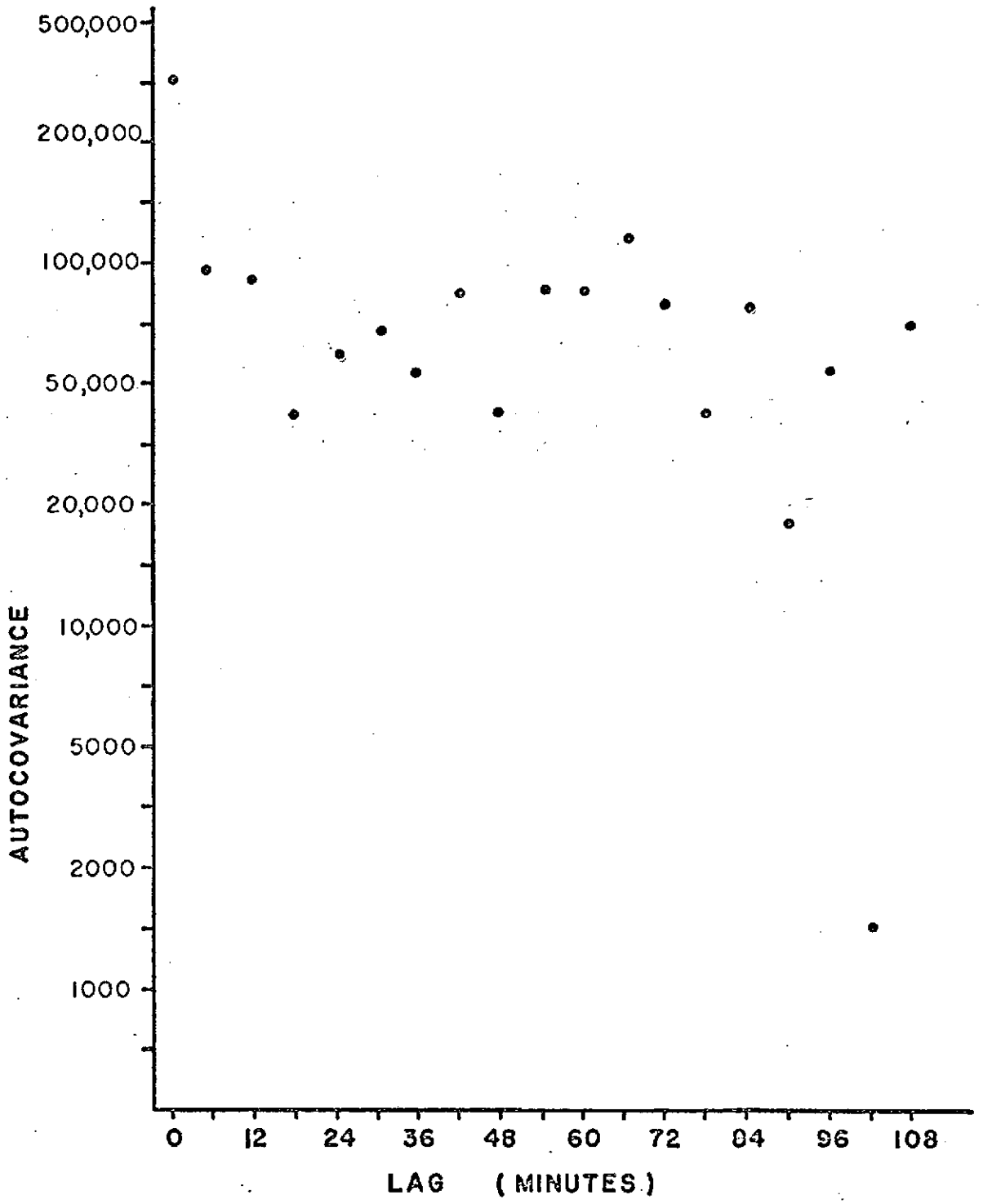


Figure 19. Autocovariance of series shown in Figure 15 (theta analysis, average wave amplitude).

## DISCUSSION

The experiment described above demonstrates that techniques have been developed which will allow us to examine the EEG and other parameters of cerebral activity for the presence of ultradian periodicity. Although the preliminary analysis of cortical activity in the monkey failed to demonstrate any rhythmic fluctuation in the theta band approximating the monkey's 50-60 min REM cycle, the analysis clearly can be extended to other frequency bands and other electrode locations. The data analysis itself also can be improved by applying such techniques as detrending and prewhitening of the data so that the assumptions underlying the computer analyses are more closely approximated. Other improvements can be made in the sampling procedure itself (e. g., by increasing the sampling frequency) and in the recording technique (e. g., by improving the acoustic isolation of the subject). The variability of the data might also be reduced by "smoothing" over several different recording sessions.

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