# Patterns of Interictal Epileptiform Activity Frequency During Sleep and a Time-Matched Period of Sleep Deprivation

by

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# Chapter I

## Introduction

Epilepsy is a chronic disorder characterized by recurrent paroxysmal seizures of non-metabolic origin. Over two million Americans have epilepsy (U.S. Public Health Service, 1981; Epilepsy Foundation of America, 1986). This figure is believed to be conservative. Many people do not report seizure activity due to fear of punishment (e.g., loss of job or driver's license), fear of prognosis, or social stigma (Ozuna, 1988; Bare, 1990). Regardless, seizure activity is one of the most common neurological disorders seen today.

Epilepsy is difficult to diagnose since other problems may induce seizures or seizure-like activity (e.g., transient metabolic disturbances, psychological disorders). Since seizures occur paroxysmally and are not often observed by a trained professional, epilepsy can be misdiagnosed during a routine neurological work-up.

Fortunately, the widespread introduction of computers and video-cassette recorders has made specialized epilepsy inpatient units economically feasible. These units, known as intensive neurodiagnostic monitoring units, are essential in accurately assessing a patient's condition (Gumnit, 1986). Patients admitted to these units receive care from a number of health care professionals, who work closely together as a team. The number of nurses employed in these units is increasing as the number of hospitals installing these units

increase. The growth in the number of these units has been so great in recent years, the National Association of Epilepsy Centers was formed in 1987 to standardize the units and to establish guidelines (National Association of Epilepsy Centers, 1990). Nurses caring for patients in these units require additional skills training, and require in-depth knowledge of epilepsy care (Bare, 1990). These units provide the nurse an opportunity to expand knowledge and practice.

Interictal Epileptiform Activity

Epilepsy is manifested generally in two ways: frank seizures (ictus) and subclinical events known as interictal epileptiform activity (IEA). IEA is defined as a brief, synchronous depolarization of a group of neurons, which may be displayed on the electroencephalograph (EEG). Medications used to minimize ictus may or may not minimize IEA. In other words, medications may decrease the number of seizures, but may make the EEG look worse by increasing the number of IEA discharges displayed upon it. This prompted an old adage followed by many physicians to "treat the patient, not the EEG." Since the clinical significance of IEA has been questioned for years, treatment priorities have focused on ictus. Nurses have focused their care on ictal activity as well.

Indeed, treating ictus is of great importance. Untreated or poorly treated ictus can pose health risks, such as neuronal damage (Dam, 1980) to patients, as well as greatly disrupting their lives. Snyder (1986) found the

uncertainty of when ictus might occur was a top stressor in patients with epilepsy. Effective treatment of ictus leads to an observeable reduction of ictal manifestation, which may promote confidence in the treatment plan. Nevertheless, consideration of IEA should not be ignored.

The exact relationship between IEA and ictus remains unclear, despite the large amount of research completed in this area. The physiological mechanisms involved in producing IEA are believed to be similar, if not the same, as those involved in producing ictus (Ayala et al., 1973; Prince et al., 1983; Dichter, 1989). What remains unclear is whether IEA combines with other physiological variables to produce ictus. If IEA genesis is similar or is related to ictal genesis, it is logical to speculate that the cognitive deficits commonly seen during ictus and post-ictus may be displayed during IEA as well.

The speculation that IEA may be accompanied by ictus-like cognitive deficits has been supported by a series of recent studies. For example, Aarts et al. (1984) and Binnie et al. (1987) have found transient cognitive impairments (TCI) in half of their subjects. These studies depart from previous studies assessing TCI, since they used stringent testing criteria and research methods. These testing criteria have become a standard used by subsequent researchers, such as Trenite et al. (1988) and Siebelink et al. (1988), who demonstrated significant TCI which impaired scholastic skills and short-term verbal memory in children.

IEA is very brief in duration and is measured in milliseconds. Some health care providers may question the clinical significance of the cognitive impairments during IEA which are brief and seemingly benign. However, in patients experiencing large numbers of IEA, subsequent TCI may become highly disruptive. Aarts et al. (1984) concluded that, "Such episodic impairment may be a disability (causing problems of education or at work) or a danger (when the patient is driving, or is exposed to common domestic hazards)" (p. 295). A significant finding from Aarts et al. (1984) and Binnie et al. (1988) is that impairments related to TCI corresponded to areas of the brain producing focal IEA (IEA originating from a specific area, as opposed to IEA displayed globally throughout the brain). Some studies, such as those by Dam (1980) and Babb et al. (1984), have demonstrated actual neuronal loss in epileptogenic areas. This loss has been attributed to ictal activity. Recognition of the possible significance of TCI and of IEA has lead some practitioners to question whether the treatment adage should be changed to "treat the patient, and the EEG" (Holmes, 1991).

Research Problem Focus

In light of the recent research mentioned above, there is renewed interest in a better understanding of IEA. However, in order for this research to continue, some fundamental physiological parameters of IEA need to be investigated. An area of IEA research still in its infancy is research of the chronobiological aspects of IEA.

Chronobiology is the field of study which analyzes how biological phenomena fluctuate over time. Virtually all physiological variables heretofore studied demonstrate endogenous rhythmic fluctuations (Minors & Waterhouse, 1981, 1986). A thorough understanding of the chronobiological nature of a phenomenon ensures a better ability to predict when it will occur. Knowledge of anticipated phenomenon occurrence facilitates interpreting data and determining deviations from optimal health, as well as timing interventions which affect the phenomenon (Halberg, 1977; Smolensky & Reinberg, 1990).

Previous IEA chronobiology research has been minimal. Subsequent sections of this paper will discuss this research. Previous investigators have described the chronobiological nature of IEA as a phenomenon associated with sleep. However, previous research has lacked methods consistent with basic chronobiological principles. Consequently, the relationship between the possible chronobiological mechanisms of IEA and sleep are not well-defined.

Significance to Nursing

Nursing, by definition, strives to treat human responses to health problems (American Nurses Association, 1980). Transient cognitive impairments resulting from IEA is a response which can impact the quality of life of clients with epilepsy. Since epilepsy is a chronic condition which is often difficult to manage, nursing plays a vital role in monitoring efficacy of treatment, side effects of treatment,

and psychosocial response to treatment strategies (Shope, 1974; Leppik, 1988; Bare, 1990). Information regarding the temporal nature of IEA should be useful to nurses then caring for patients with epilepsy.

Chronobiological information is of particular importance to nursing, since nurses are responsible for timing of interventions and manipulating the environment to improve intervention efficacy. A thorough understanding of the chronobiological nature of any given variable is needed to fulfill these nursing roles (Smolensky & Reinberg, 1976; Halberg et al., 1980). Consequently, research in chronobiology is an appropriate nursing endeavor, particularly since this information is necessary to examine the effectiveness of current nursing measures, (Felton, 1987), and will be useful in developing new nursing measures.

## Purpose of Study

The purpose of this pilot study was to attempt to describe better the relationship between chronobiological characteristics of IEA and sleep, by examining IEA frequency patterns during time-matched periods of sleep and sleep deprivation. The study approached the topic by using methods consistent with basic chronobiological principles. The feasibility of these methods were evaluated along with the research questions. It was hoped that this study would provide information useful for future research on IEA chronobiology.

# Chapter II

## Literature Review and Conceptual Framework

### Current Perspectives on Genesis of Interictal Epileptiform Activity

If an ultimate treatment goal is to prevent seizures from occurring, is research on IEA appropriate? Most epilepsy researchers believe so. Ayala et al. (1973) stated that the interictal spike [a specific type of IEA] ". . . is the simplest form of epileptiform activity, hence the most susceptible to initial experimental analysis" (p. 3). Prince and Connors (1986) agreed with this view and described IEA as the simplest system with which to study basic epileptogenic mechanisms.

Analysis of IEA genesis is indicated for more than just the simplicity, and perhaps convenience, of its model, since mechanisms generating IEA are believed to be involved in the genesis of ictus. Prince et al. (1983) stated that the mechanisms that produce IEA are somehow altered and/or enhanced, resulting in ictus. The causes for these changes are not completely understood; but generally speaking, in order for IEA to develop into ictus, there must be a simultaneous increment of IEA excitatory mechanisms with a decrement of IEA inhibitory mechanisms (Prince et al., 1983; Prince & Connors, 1986; Niedermeyer, 1987; Dichter & Ayala, 1987; Engel, 1989; Dichter, 1989; Crill, 1991).

An extensive research effort has been made recently to investigate how IEA is generated initially. Ayala et al.

(1973) proposed two hypotheses to explain underlying IEA genesis mechanisms: (a) a change in a neuron's membrane resulting in increased sensitivity for epileptiform generation, and (b) abnormal firing of otherwise normal neurons. The former view supported intrinsic cell properties as generating IEA while the latter supported extrinsic mechanisms. Various investigators have attempted to support one view or the other. For example, Schwartzkroin and Wyler (1980) used the literature to support the importance of intrinsic cell properties in generating IEA. In contrast, Johnston and Brown (1981) tested several hypotheses and concluded that intrinsic properties do not lead to IEA.

Prince et al. (1983) took a more synthesizing approach in their review article. They concluded that both extrinsic and intrinsic mechanisms are involved in IEA genesis. These mechanisms included: (a) a change in the balance between inward Ca++ and Na+ currents and outward K+ currents across the neuronal membrane, (b) disinhibition of action potentials, and (c) an increase in the summated amplitudes and/or durations of excitatory post-synaptic potentials in a group of neurons. Various factors may cause or influence these mechanisms. The authors suggested also that neurons from different parts of the brain may employ these mechanisms differently. This viewpoint was supported in later articles (Prince, 1985; Prince & Connors, 1986; Dichter & Ayala, 1987; Dichter, 1989; Crill, 1991).

Prince (1985) stated that the above three mechanisms are

general requirements of epileptogenesis. These mechanisms are responsible for creating a paroxysmal depolarizing shift which could be viewed as the spark which generates IEA. However, this depolarizing shift must spread to include whole groups of neurons in a synchronous fashion to create IEA which could be displayed on the EEG. Prince (1985) and Dichter (1989) described several processes involved in synchrony and its spread. Synchrony may originate within certain pacemaker cells within the epileptogenic focus. As a depolarizing shift occurs in these pacemaker cells, synchronous depolarization may spread through a network of collateral axons to other neurons. (Of note, one thalamo-cortical relay neuron may connect with thousands of pyramidal neurons in the cortex.) The biochemical mechanisms of these possible pacemaker cells will be the core of future epilepsy chronobiological research.

In summary, three basic mechanisms at the neuronal level are believed to be involved in generating events leading to an initial PDS. A synchronous spread of the depolarization must occur to large groups of neurons in order for IEA to detected on an EEG. Pacemaker cells may be involved in producing synchrony and, ultimately, may determine patterns of epilepsy manifestation.

Although basic mechanisms for IEA generation have been hypothesized, they have not been proven. Factors influencing these mechanisms and a neuron's ability to respond to them continue to be investigated. Chronobiological principles

have rarely been discussed, or accounted for, in previous research.

Theoretical Basis for a Chronobiological Research Focus

Ever since people have observed the rhythms of the sun, moon, and seasons, people have been interested in chronobiology. Indeed, in earlier times, knowledge of rhythms such as the migratory habits of animals were key to the survival of humans. As people became more skilled at adapting to or manipulating environmental variables, natural rhythms became less prominent in the day-to-day habits of many cultures. Most natural rhythms were considered external events which influenced human behavior.

A paradigm which minimized rhythmicity was formalized scientifically in the concept of homeostasis. Homeostasis, although cognizant of the fluctuations within the body, suggests that the body works to bring physiological variables to a steady state or norm. As researchers have become more technologically adept at measuring internal variables, the concept of homeostasis in its purest form has been questioned (Minors & Waterhouse, 1986). Halberg et al. (1980) stated that the homeostatic model ignores changes of variables within a designated reference range and also ignores phenomena which are episodic or pulsatile. Moore-Ede (1986) suggested that the homeostasis model should be extended to "include the precisely timed mechanisms of the circadian . . . timing system which enables organisms to predict when environmental challenges are most likely to occur" (p. R737).

Normal values for physiological variables should depend upon at which point in time assessments are made. In accounting for the endogenous rhythm, an organism could be able to predict environmental challenges, and then employ compensatory mechanisms to meet those challenges (Moore-Ede, 1986).

Virtually all physiological and psychological variables fluctuate in patterns over time (Tom, 1976; Minors & Waterhouse, 1981 & 1986; Caradente, 1983; Felton, 1987). Since rhythmicity is a basic component of the internal human environment, it should not be overlooked when designing biological research, nor when interpreting research findings. In addition, it has been suggested that disruptions of biological rhythms may be associated with alterations in health status (Smolensky & Reinberg, 1990).

As research in chronobiology has progressed, a broad theoretical framework of chronobiological concepts has come together. This framework was outlined by Minors and Waterhouse (1981, 1986). An adaptation of this framework is diagrammed in Figure 1.

Within the deep structures of the brain, there is at least one (and possibly more) internal clock or pacemaker (Minors & Waterhouse, 1981, 1986). This clock presets the periods (cycle lengths) of numerous endogenous rhythms. Other clocks may regulate other rhythms. Czeisler and Jewett (1990) and Moore (1990) described a number of studies suggesting that the suprachiasmatic nucleus (SCN) in the

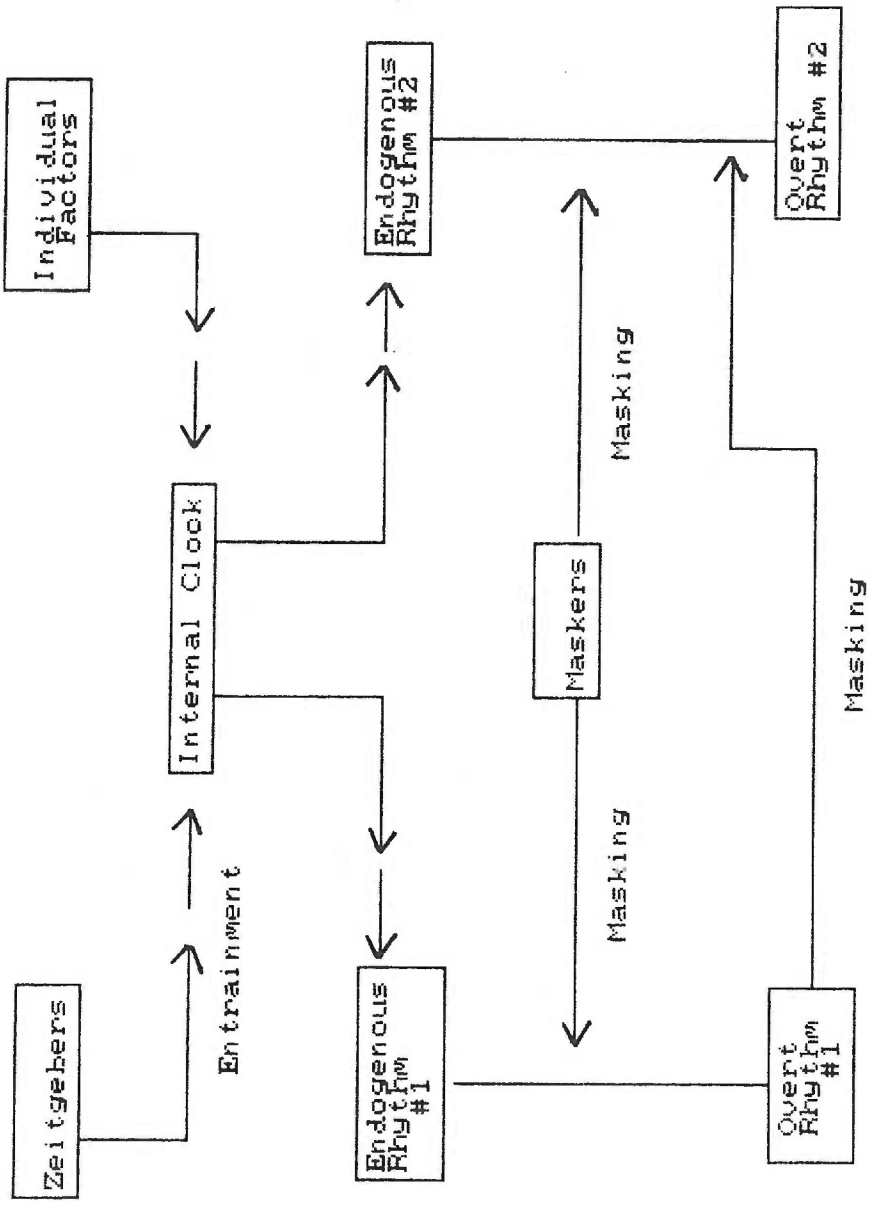



Figure 1. Conceptual framework of chronobiological principles (Adapted from Minors & Waterhouse, 1981, 1986).

hypothalamus serves as this biological clock. Moore explained that these studies do not prove that the SCN is a specific clock, but that rhythm modulation is dependent upon SCN involvement. Czeisler and Jewett (1990) stated that some investigators have described the existence of two or more clocks. Czeisler and Jewett stated that these conclusions are not based on definitive evidence, and that much more research is needed.

Regardless of how many clocks there may be, rhythmicity of physiological variables is modulated by neural structures. A simple diagram of the relationship between two rhythms and a clock is depicted in Figure 1. Broken arrows in the diagram indicate that a number of undetermined physiological mechanisms may be present.

Before a rhythm is seen overtly, it may be influenced by a masker. Wever (1985) defined a masker as an environmental condition which changes some aspect of a biological rhythm. Maskers alter the waveform of a rhythm by changing its amplitude, its mean, or its smoothness. This process is called masking. Maskers do not change the period (cycle length) of a rhythm. An example might be the ingestion of a large meal (masker) altering the rhythm of mental alertness by briefly increasing somnolence (masking effect). In addition, some rhythms may have a masking effect on other rhythms.

Internal clocks are influenced by several factors. One group of factors, known as zeitgebers, are rhythms which

synchronize other rhythms from their pure period to the period of the zeitgeber. An example would be the adjustment of the endogenous temperature rhythm (which has a preset period of approximately 25 hours) to the 24-hour period of the night and day rhythm. The process by which zeitgebers synchronize preset rhythms of the internal clock to another period is known as entrainment. In addition, zeitgebers can shift the timing of a rhythm along the time axis in a process known as phase shifting.

Other factors which influence internal clocks are individual factors (e.g. genetics, gender, age). Minors and Waterhouse (1981) suggested from their literature review that internal clocks are established genetically. It remains unclear how large an impact inherited components have on internal clocks. Minors and Waterhouse concluded that inherited components, as well as external components, must be considered when discussing biological rhythms.

Thus, the overt rhythm easily measured by the researcher or clinician is influenced by external and internal variables. These influencing variables will modify the magnitude, the waveform, and the timing of a rhythm. However, the rhythm itself is derived from an internal clock. This framework provided the theoretical foundation for this study. Concepts specific to this study will be diagrammed within this framework at the end of this chapter.

An examination of previous research on IEA demonstrated that chronobiological principles, although not

predominant, have not been completely ignored. A review of this literature follows.

## Chronobiological Aspects of Epilepsy

Introduction. Much of the earlier chronobiological research in epilepsy focused on observable ictal events, and attempted to determine the cause of seizures by assessing when they occurred and noting the events which may have precipitated them. Although using self or observed report of ictal events may miss large amounts of data (Stevens et al, 1972; Pierelli, 1989), studies using these data-collection methods have revealed a variety of non-random, temporal patterns of epilepsy manifestation (Langdon-Down & Brain, 1929; Griffiths & Fox, 1938; Halberg & Howard, 1958; Janz, 1962; Newmark & Dubinsky, 1990; Balish et al., 1991: Tauboll et al., 1991).

Research on the chronobiological aspects of IEA was found less frequently in the literature. This type of research is often less feasible, since subjects must be studied while connected to an EEG. Recently, intensive neurodiagnostic monitoring studios, now found in many hospitals, have offered researchers access to the continuous EEG data needed to study IEA chronobiologically. It is hoped that these studios will encourage continued IEA chronobiological research.

Level of analysis. Generally, chronobiological research examines the fluctuation of some variable over time. Examining patterns of frequency is an indirect method of

examining the patterns of the underlying, always present physiological mechanisms of some phenomenon. Assessment of frequency patterns has been used in other fields of study characterized by paroxysmal events, such as cardiology, to explore underlying physiological mechanisms (Hjalmarson et al., 1989; Muller, 1989).

Generally speaking, one is either in epileptic activity or not. With the notable exception of status epilepticus, one is not in a sustained state of epileptic activity. Therefore, researchers cannot measure variations of epileptic activity over time in the same way serum glucose can be measured over time. Ideal models of chronobiological measures in epilepsy are probably at the cellular and molecular levels (e.g. the measure of a neuron's ability over time to respond to neuromodulators within the synapse). A thorough understanding of epileptogenic mechanisms and the development of sophisticated research designs and measurement capabilities would be necessary to use these models. Assessment of frequency patterns may assist in obtaining these models (Martins da Silva et al., 1984). At this time, chronobiological research in epilepsy may be limited to researching frequency patterns.

Research on interictal epileptiform activity frequency patterns. Although much research addressing IEA has been completed, little research has attempted to identify IEA frequency rhythms. Unfortunately, this research has neglected basic chronobiological principles.

Stevens et al. (1971) examined EEG records totalling 18 days from five subjects who had a variety of epilepsy types. Eight scalp electrodes provided three EEG channels and one electro-oculogram channel, transmitted per radio telemetry. Electrode placement varied among subjects in order to produce the best display of IEA.

The investigators quantified IEA and ictal activity with a computer-assisted spike recognition device. This automatic spike recognition based tabulation of spikes (a type of IEA) on pre-determined EEG parameters. Although the investigators recognized the inaccuracy of this method, they concluded that measurement error would be more consistent than the measurement error made by the "intuitive recognition [of IEA] by the electroencephalographer" (p. 315). Still, the investigators hand-counted portions of the EEG and concluded that the tabulations were "similar".

The investigators examined the EEG for a number of items, including temporal patterns of spike frequency (defined by the investigators as the number of spikes per four-minute epoch). Frequencies were graphed for a visual display of the data. In two subjects (both having generalized epilepsy with absence seizures), spike frequency cycles with periods of 90-120 minutes were noted, with a suppression of spike activity lasting 15-20 minutes between each cycle. These cycles persisted both day and night. During sleep, these times of spike suppression occurred during rapid eye movement (REM) sleep.

The investigators calculated means and standard deviations of cycle periods from the graphed data. They found periods of 100 ± 20 minutes. Noting that this method is a poor measure of biological periodicity, the investigators completed spectral analysis on the data and found significant rhythms with periods of 124 and 164 minutes. It is unclear whether or not times of spike suppression were excluded from the analysis.

In a follow-up study, Stevens et al. (1972) examined the EEG's of three of the subjects from the original study, as well as the EEG's of two new subjects. Three subjects had generalized epilepsy characterized by absence seizures. Two subjects with focal epilepsy had complex partial seizures. During the day, four channels of EEG were recorded using radio telemetry. During sleep, two channels of EEG were converted to electro-oculogram and electromyogram channels. Recordings were continuous, and varied from 17-72 hours in length.

Computer-assisted spike recognition was used again. Verification of spike tabulation was completed by hand-counting of data from "several [records yielding] generally good agreement" (p. 412). The investigators found times of spike suppression occurring every 90-150 minutes. Spectral analysis of the data revealed significant spike frequency rhythms with periods of 90 minutes in three subjects. Periods of 124 and 164 minutes, noted in the previous study, were not discussed in the follow-up study.

These investigators made an initial attempt at describing IEA frequency rhythms. Limitations of these two studies are noteworthy.

First, a limited number of EEG channels were utilized to record data. Ebersole and Leroy (1983) compared EEG recording devices; one with three EEG channels, the other with eight channels of EEG. The eight channel EEG device detected 20% more epileptiform activity than the smaller device. Small numbers of EEG channels may greatly limit the ability to gather complete IEA data.

Second, a computerized counting device was used to tabulate spikes. Although computerized scanning of EEG's for epileptiform activity may be highly practical in clinical diagnostics (Pauri et al., 1992), the utility of computer devices in research requiring highly accurate tabulation is unclear. Computer devices cannot always differentiate between true epileptiform activity and muscular or sleep artifact (Gotman, 1986; Pauri et al., 1992). In addition, the computer device used by Stevens et al. counted all spikes, both ictal and interictal, providing a summed total of two, possibly separate, phenomena. The investigators did not specify the level of agreement between computerized and hand-counted spike totals.

Third, although the investigators found cycles of spike frequency which persisted 24 hours a day, during sleep periods spike frequency cycles were associated with sleep cycles. The implications of this association were not

explained. Despite the emphasis the authors made on sleep cycles, they did little to control for possible variations of accustomed sleep patterns in their subjects. They standardized the sleep time during the data collection, but subjects were habituated to this schedule for only one night before data collection began. Minors and Waterhouse (1981) concluded from their literature review that at least five to six nights are required to adjust to a new sleep schedule.

Kellaway et al. (1980) examined the EEG records of 19 subjects who were monitored with 14-24 channels of EEG for 24-36 hours. All patients had primary generalized epilepsy with 3 Hertz (Hz) spike-and-wave formations (a specific type of IEA), which were hand counted, using video recordings of the monitoring sessions to assist in rejecting artifact.

The frequency of IEA was graphed using 15-minute epochs. Data were analyzed from these graphs only. Although no cycles were found in any daytime recordings, fourteen subjects demonstrated nocturnal IEA frequency cycles. These cycles were characterized by a step-like augmentation of frequency with abrupt attenuations of frequency during REM sleep. Frequency peaks occurred an average of every 100 $\pm$ 11 minutes (range 84-120 minutes). During the sleep period, amplitudes of these cycles showed either a decrease as the night progressed, a decrease for two or three cycles followed by an increase, or an increase until the middle of the sleep period followed by a decrease. The investigators concluded that these varying amplitudes resulted from the culmination

of two rhythms: a hypothesized circadian rhythm of IEA probability, and the ultradian rhythm (rhythm with a period of less than 20-24 hours) of IEA frequency found during sleep. The investigators did not address several key points.

First, the investigators did not mention if the epilepsies of the subjects were primarily nocturnal, diurnal, or both. Billiard (1982) examined 320 patients with primary generalized epilepsy and categorized them using the classification system refined by Janz (1962). Billiard found that 36.3% of his patients had strictly diurnal epilepsy. Of this group 54% showed IEA on a routine daytime EEG. However, of those patients with strictly nocturnal epilepsy, only 9% showed IEA on a daytime EEG. These findings suggest that analysis of epilepsy type beyond what Kellaway et al. provided was indicated.

Second, the investigators proposed a model to explain their findings which was not well-supported. This model suggested that IEA frequency rhythms are demonstrated only during sleep. The investigators did not test this model with sleep deprivation. In addition, the investigators did not describe the accustomed sleep patterns of their subjects, nor how alteration of those sleep patterns may have influenced their findings.

Martins da Silva et al. (1984) examined a variety of phenomena from 18 EEG records. Each record was at least 48 hours in length, and contained 16 channels of EEG. Subjects were kept under a standardized sleep regimen, and pre-study

AED regimens were maintained.

Although the investigators did not discuss analysis of frequency patterns in detail, Spearman rank correlation tests revealed significant consistency in the number of interictal epileptiform discharges per 30 seconds between each 24-hour block in 89% of the records. Also, the maximum values of the number of discharges occurred less than two hours apart between days one and two in 67% of the records. Subjects with generalized 3 Hz spike-and-wave activity had lower IEA frequencies than subjects with focal discharges.

Three major limitations of this study were noted.

First, the circa 100-minute rhythms of IEA identified by investigators mentioned previously were not evaluated in this study. Second, the investigators calculated IEA frequencies using 30-minute epochs. Organizing data in this fashion would make discussion of circa 100-minute rhythms difficult, if not impossible. Third, no mention was made of the habitual sleep patterns of the subjects, nor of the possible desynchronization which may have occurred when the subjects' sleep schedules were standardized. This is particularly important since sleep was staged in this study and some of the findings were interpreted using sleep data.

In their introductory comments, Martins da Silva et al. (1984) stated that " . . . few authors have investigated possible endogenous circadian or ultradian rhythms modulating epileptic phenomena independently of sleep, wake, or the REM/non-REM cycle" (p. 1). However, the investigators in

this study did not experiment with sleep pattern alterations, nor sleep deprivation with their subjects in order to investigate this possible modulation either. Still, the investigators concluded from their study that REM/non-REM sleep directly influences the fluctuations of seen in the number of epileptiform discharges via a masking process. (The investigators did refer to their previous study in which subjects were sleep deprived. In that study, fluctuations IEA frequency with periods of 80-90 minutes with an abrupt reduction of IEA at the habitual time of awakening were found in both sleep nights and sleep deprivation nights. The investigators concluded that these findings suggested an endogenous component to IEA frequency patterns.)

Using the same database, Binnie et al. (1984) analyzed IEA chronobiologically also. Although they calculated IEA frequency, they did not report the frequency distribution of IEA. Instead, Binnie et al. examined the length of the intervals between individual discharges, and whether or not a pattern existed in these interdischarge intervals.

Other studies investigating IEA are less specific on identifying and describing frequency patterns than they are on correlating rates of IEA with the genesis of ictus (Gotman & Marciani, 1985; Gotman & Koffler, 1989).

Summary. The above research does not describe IEA frequency patterns conclusively. Stevens et al. (1971, 1972) and Kellaway et al. (1980) have identified ultradian rhythms (more specifically, circa 90-164 minute rhythms) of

IEA frequency. Martins da Silva et al. (1984), although finding some circadian consistency, did not report ultradian rhythms of IEA frequency. Binnie et al. (1984) analyzed patterns in the lengths of interdischarge intervals. None of the research reviewed above adequately described IEA patterns independent of sleep. This point is particularly important since IEA patterns were described in terms of sleep stages. Therefore, assessment of IEA patterns independent of sleep was crucial to the design of this study. A review of the literature discussing the relationship between sleep deprivation and IEA follows.

Sleep Deprivation and Interictal Epileptiform Activity

Various forms of sleep deprivation (e.g. half-night or full night of sleep deprivation) have been used historically to induce epileptiform activity for diagnostic purposes (Scollo-Lavizzare et al., 1977; Arne-bes et al., 1982). Sleep deprivation is a measure used routinely in inpatient intensive neurodiagnostic monitoring units.

Numerous studies have described rates of activation of epileptiform activity (percentage of normal EEG's converting to EEG's with epileptiform activity) after using sleep deprivation. Molaie and Cruz (1988) reviewed studies which revealed activation rates ranging from 6.9% to 83.0%. They explained that these variable rates resulted from loose control over influencing variables. Also, these studies used varying lengths of sleep deprivation. Montplaisir (1990) noted an activation rate of 30-50% in his review, and

noted that sleep deprivation has greater activation potential in patients with generalized epilepsy.

Arne-bes et al. (1982) studied activation rates in 93 adults and 42 children. Adults were deprived of sleep for one night, followed by EEG recordings the next afternoon. Children were deprived of sleep after 0200. Activation rates were 40% for adults and 38% for children. The investigators compared their results with the findings of nine other studies. Eight of these studies had findings which varied by no more than six percentage points to the results of the investigators.

Sleep deprivation can increase the frequency of both ictal and interictal activity in patients whose baseline EEG's are abnormal as well. Molaie and Cruz (1988) found an 8-83% increase in the number of IEA in 6 of 8 subjects after 36 hours of sleep deprivation.

The mechanisms by which sleep deprivation increases the incidence of epileptiform activity remain unclear. Bowersox and Drucker-Colin (1982) argued that the theories which suggested that sleep deprivation increases shifts toward synchrony do not explain all models of epileptiform activation. These authors described how sleep deprivation suppresses the synthesis of brain macromolecules (such as neuromodulators). They suggested that this suppression could be the primary mechanism involved in activation. Perhaps several mechanisms are involved. Nevertheless, fatigue from sleeplessness is well-documented in the literature as a

precipitator of ictal activity (Epilepsy Foundation of America, 1986; Hickey, 1986; Gumnit, 1990).

Influencing Variables

Many variables could have influenced this study. When assessing the impact variables may have had, one must review the literature for information on how each variable impacts EEG parameters (more specifically, IEA if known), biological rhythms, and sleep, since these were primary components of this study. The following sections will review the literature on the potential influencing variables identified by this author.

Caffeine. Chemically, caffeine belongs to the xanthine family. Xanthines are known stimulants of the central nervous system. Caffeine's excitatory action is believed to be due to its ability to block adenosine receptor sites. Endogenous adenosine is an inhibitory neuromodulator, therefore, caffeine creates excitation by preventing natural inhibition from occurring (Dews, 1984; Chou et al., 1985; Ault & Wang, 1986; Ault et al., 1987). Caffeine is most often consumed through caffeinated beverages such as coffee, tea, and cola.

Caffeine can greatly influence EEG data due to its ability to increase neuronal excitation. Chou et al. (1985) found increased neuronal firing in reticular neurons in caffeine-supplied rats. Ault & Wang (1986) and Ault et al. (1987) supported these findings when they studied hippocampal slices in caffeine-supplied rats. This excitation may lower

the threshold for epileptiform activity occurrence. In addition to increased firing, increased epileptiform activity has been demonstrated in humans who have received caffeine. Hinkle et al. (1987) demonstrated significant increases in seizure length in humans undergoing electroshock therapy after caffeine was infused intravenously. Itil (1982) reported that caffeine is used commonly to promote epileptiform activity, and that caffeine should clearly be viewed as an analeptic (pro-convulsant agent).

Caffeine may influence biological rhythms also. Farr et al. (1985) found phase advances (shifts in the peak of a rhythm to an earlier time) in temperature and locomotor rhythms in rats after administering caffeine. After performing surgery on the rats, the investigators found better stabilization of rhythms in the rats given caffeine.

Caffeine has been used historically to increase mental alertness and allay sleep, possibly by promoting excitation in the reticular activating system. The efficacy of caffeine's ability to promote alertness can be demonstrated by the increased fatigue seen in caffeine withdrawal.

Griffiths et al. (1986) described caffeine withdrawal symptoms as including headaches, increased fatigue, and decreased mental alertness. After reviewing 37 clinical reports and studies, Griffiths and Woodson (1989) concluded that headache and fatigue were the most common symptoms of caffeine withdrawal. They also noted that withdrawal had an

onset from 12-24 hours and peaked between 20-48 hours. Chou et al. (1985) suggested that prolonged caffeine consumption increased the number of adenosine receptor sites. When caffeine is withdrawn, fatigue and decreased alertness is seen due to an elevated number of sites able to bind to endogenous adenosine.

Nicotine Withdrawal. Smoking is not allowed in most monitoring studios due to the highly flammable nature of materials used in the studios (e.g. oxygen, adhesive paste). Therefore, nicotine withdrawal, not nicotine use, is the germane influencing variable in IEA research conducted in these studios.

Nicotine is a central nervous system stimulant. Nicotine increases the rate of neuronal discharge in animals (Egan & North, 1986; Grenhoff et al., 1986). EEG changes seen after nicotine use correlate with increased mental alertness (Itil, 1982). Not surprisingly, symptoms of nicotine withdrawal include initial lethargy and drowsiness as seen by EEG changes and by observations of smokers deprived of nicotine for 10-19 hours (Herning et al., 1983). Knott and Vernables (1977) noted EEG changes signifying cortical hypoexcitation in smokers deprived for 13-15 hours.

These symptoms of lethargy and drowsiness may become less noticeable as symptoms such as irritability and restlessness become apparent with extended nicotine withdrawal (Snyder et al., 1989). EEG changes remain significant up to seven days post-cigarette (Pickworth et

al., 1989). In addition, cognitive functioning remains decreased up to nine days post-cigarette (Snyder et al., 1989).

The influence nicotine withdrawal may have on biological rhythms is unclear. However, disturbances in sleep during nicotine withdrawal have been noted. Clavel et al. (1987) and Niaura et al. (1989) reported insomnia in their nicotine-deprived subjects. Hatsukami et al. (1988) reported a significant increase in wakefulness after the onset of sleep (WASO) in smokers who quit abruptly. Cigarette substitutes, such as nicotine gum, contain variable amounts of nicotine (Benowitz et al., 1989), and may not be an equivalent replacement for cigarettes for subjects in research studies. Subjects continue to experience subjective symptoms of withdrawal when using nicotine gum (Pickworth et al., 1986; Niaura et al., 1989).

Another important aspect of nicotine withdrawal is its influence on caffeine metabolism. Smokers metabolize caffeine quicker than non-smokers (Parsons & Neims, 1978; Brown & Benowitz, 1989). How caffeine metabolism may change during nicotine withdrawal is unclear, but such a change may nevertheless be significant.

Antiepileptic Drugs (AEDs). The literature discussing the influence AEDs have on IEA is variable. Stevens et al. (1972) and Martins da Silva et al. (1984) did not specify which AEDs their subjects were taking, but the investigators stated that AED regimens were maintained. AED use did not

prevent these investigators from finding periodicity or consistency in IEA frequency. Likewise, Kellaway et al. (1980) did not detail which AEDs were used by subjects, but rhythms were found nevertheless. Kellaway et al. (1980) added ethosuximide to their subjects' medications in increasing doses until they noted an elimination of IEA frequency rhythmicity.

During withdrawal of carbamazepine, no change in IEA frequency was noted by Gotman and Marciani (1986) and Gotman and Koffler (1989). However, Martins da Silva et al. (1984) demonstrated a negative correlation between serum carbamazepine levels and IEA frequency. Duncan et al. (1990) found a significant increase in the number of seizures when carbamazepine was withdrawn from patients on polytherapy. Duncan et al. did not report IEA frequency.

No changes in IEA frequency have been reported with varying levels of phenytoin, valproic acid, phenobarbital, nor primidone (Martins da Silva et al., 1984; Gotman & Marciani, 1985; Gotman & Koffler, 1989).

Changes in biological rhythms from AED use has been reported. Rietveld and van Schravendijk (1987) reported that sodium valproate shortens the period of food intake rhythms in rats under free-running conditions (conditions absent of time cues). Ebihara and Oshima (1988) found that pentobarbital injections could either phase advance or phase delay locomotor rhythms in rats, depending upon when the injections were given.

Johnson (1982) reported that only mild changes in sleep are seen in patients with chronic AED use. He stated that AEDs "stabilize the sleep pattern . . . by reducing nocturnal seizures " (p. 392). Johnson concluded that AED use allows subjects with epilepsy to sleep with parameters which more closely resemble the sleep parameters of normals. Drake et al. (1990) measured a variety of sleep parameters in patients taking either phenytoin, carbamazepine, valproic acid, or clonazepam. The investigators found significant disruptions in sleep parameters for all of the AEDs assessed, but they compared their sleep data with sleep data of published norms. The lack of a true control group of epileptics not taking AEDs in this study makes interpretation of their results difficult.

Caffeine metabolism appears to be influenced by AEDs also. Wietholtz et al. (1989) reported that phenytoin more than doubled caffeine clearance, and reduced the half life of caffeine by half. Since AEDs are often withdrawn during a stay in an inpatient monitoring studio, changes in caffeine metabolism from phenytoin withdrawal could be significant. Wietholtz et al. did not find an effect on caffeine from carbamazepine nor valproic acid.

Sedatives. Short-acting benzodiazepines, such as triazolam, are often given to promote sleep in hospitalized patients. Itil (1982) and Gevins et al. (1988) reported that benzodiazepines (quazepam, triazolam, and flurazepam) significantly changed delta, theta, and sigma waves on the

EEG in normals. It is unclear how patterns of IEA frequency may be impacted by these drugs.

Turek and Van Reeth (1989) used triazolam in hamsters and found phase advances in luteinizing hormone and locomotor rhythms. Benzodiazepines have also been used to entrain sleep-wake rhythms in humans (Okawa et al., 1987; Seidel et al., 1984).

Exercise. While in a monitoring unit, subjects are continuously monitored by EEG and video recording. This requires that the subject remain confined to a small area in the studio. For a relatively active person, this creates a significant change in physical activity.

The influence such a change in activity might have on EEG parameters is unclear. However, Nakken et al. (1990) did study seizure frequency changes before and after an exercise program. They examined 21 adults before, during, and after an intensive four-week physical training program. Programs were individualized to match each subject's fitness level. No significant changes in seizure frequency occurred in any subject during the study, but fourteen subjects did report a small decrease in seizure frequency during the exercise period. Interestingly, seizures which did occur during the four week exercise program occurred during periods of inactivity. Also of importance, serum AED levels showed no significant change during the entire study.

The influence on biological rhythms from changes in exercise patterns is also unclear. Obviously, physiological

changes during the exercise itself (e.g. changes in temperature, blood pressure, heart rate) will mask corresponding rhythms. However, Piercy and Lack (1988) manipulated the timing of outdoor exercise in their subjects. While maintaining steady sleep-wake patterns in their subjects, they were able to phase delay body temperature rhythms by 2.1 hours and urine formation rhythms by 2.7 hours with evening exercise.

The literature describing the impact of exercise on sleep is extensive. The literature does not show conclusively a positive influence exercise has on sleep quality using objective measures such as polysomnography. (Anch et al., 1988; Trinder et al., 1988; Vuori et al., 1988). However, this is not true of subjective reports. For example, Vuori et al. (1988) questioned 1600 adults (between age 36-50). One-third of these adults reported that light to moderate exercise in the early evening was the best sleep-enhancer. Driver et al. (1988) reported subjective improvements in sleep quality after their subjects went through a 12-week exercise program. The investigators were unable to demonstrate this improvement in sleep quality with polysomnography at a significant level. This same inconsistency was found in three experiments done by Montgomery et al. (1988), who also examined gender, age, and type of exercise used when assessing the influence exercise had on sleep quality.

Bonegio et al. (1988) suggested an interesting

hypothesis on how evening exercise may improve sleep quality. They raised the core body temperature in young men after they had fallen asleep. When temperature was raised, sleep quality was significantly decreased. The investigators hypothesized that the usual drop in core body temperature seen in the first three hours after sleep onset is responsible for optimal sleep quality. The investigators suggested that light evening exercise would artificially raise core body temperature, thus increasing the extent of the drop in temperature seen after sleep onset, thus improving sleep quality.

Age. Aminoff (1986) stated that, although highly variable, EEG patterns in normals change across the life-span, and that age must be taken into account when interpreting EEG data. Pollock et al. (1990) studied various EEG parameters in normal subjects with ages between 56-76 years. The investigators found significant differences from pre-established normal values for some parameters. They stated that these "normal" reference values were often determined in studies using adolescents and young adults and should not be used when interpreting EEG data in older subjects.

The influence age may have on EEG patterns in epileptics is less certain. Hughes (1982) stated that there are changes in epileptic activity depending upon age. These changes are particularly noticeable in infants and children. However, Sundaram et al. (1990) examined 203 epileptics between age

16-60+ years (specific range not given). The investigators found no significant difference in IEA among age groups.

Age appears to have a strong effect on biological rhythms. Casale and de Nicola (1984) studied 42 biological variables in elderly patients (specific ages not given). Although the results were variable, the investigators found a general decrease in rhythm amplitudes and mesors (mean values as determined by cosinor analysis) when compared to pre-established normal values for these rhythms. Touitou et al. (1986) also demonstrated a decreased amplitude in core body temperature rhythms in elderly subjects (age 75.5 $\pm$ 6.6 for men; 78.2 $\pm$ 9.1 for women) when compared to young controls (age 22.4 $\pm$ 0.5 for men, 21.8 $\pm$ 0.8 for women). After reviewing the literature, Minors and Waterhouse (1981) commented that despite the use of pooled data in many studies, it is noteworthy that the literature continually demonstrates decreased rhythm amplitudes and means in elderly persons. An exception is a study done by Ishii et al. (1990). These investigators examined blood pressure rhythms in various adult age groups. They found no significant changes in rhythm amplitudes, but did find a trend for earlier acrophases (time of rhythm peaks) in older age groups.

After reviewing the literature, Williams et al. (1988) concluded that the elderly have changes in sleep, most notably an increased sleep latency, increased WASO, and decreased sleep efficiency. These changes were noted in

elderly subjects independent of pathology. The authors noted that diseases commonly found in the elderly may exacerbate the above sleep changes. Ehlers and Kupfer (1989) found the same sleep changes which were most pronounced in the 51-70 year old population.

In examining the influence age has on variables, one must remember that the ideal study design would follow cohorts longitudinally. Simply comparing age groups may be like comparing apples and oranges, even though such a comparison might produce some preliminary data.
Even though longitudinal studies were not present in the above review, age was considered a variable in this study.

Gender. The effect gender may have on EEG parameters is unclear. However, Wever (1984) discussed the effect gender has on sleep-wake rhythms. He found that males have longer periods than females under free-running conditions (conditions free of time cues). He concluded that males need stronger zeitgebers to set rhythms to a 24-hour period. However, he did not find a difference in temperature rhythms. This discrepancy could be explained by the hypothesis that these two rhythms originate from two different internal clocks (Moore-Ede, 1982). Gender may have a differential effect on these two clocks.

Ruler and Lack (1988) reviewed studies which assessed sleep by subjective report. They found that a significant number of these studies showed that females had more difficulty falling asleep and more WASO. However, in six

other studies using polysomnography, males had more difficulty. The investigators felt that questionnaires used in the studies using subjective report may have had a gender bias depending on how questions were worded. They devised three questionnaires; one with positively-worded statements, one with neutral wording, and one with negatively-worded statements. The investigators found variable results, but regardless of question type, females reported more WASO. Rediehs et al. (1990) conducted a meta-analysis of 27 studies examining gender differences in sleep in subjects older than 58 years. The investigators assessed the findings of a number of sleep parameters. Despite some small variability, no significant differences in most sleep parameters between elderly men and elderly women could be concluded. The investigators did find consistent findings that elderly men had more nocturnal myoclonus and respiratory disturbances. The investigators discussed the limitations of the studies reviewed, and suggested that longitudinal studies are needed. They concluded that ". . . the role of gender in . . . sleep changes is uncertain" (p. 421).

Seizures. One characteristic shared by all subjects in this study was that they all had epilepsy. People with epilepsy have seizures. The literature suggests that seizures influence the concepts of concern of this study.

Stevens et al. (1972) found a sharp change in background IEA preceding ictus. This change was not investigated by Kellaway et al. (1980). However, Gotman and Marciani (1985)

could not support Stevens et al. with their findings. Gotman and Marciani found a sharp increase in IEA immediately after both partial and generalized seizures, but no change was noted pre-ictally. This change in IEA frequency lasted for an undefined period of up to several days. These findings were supported by Gotman and Koffler (1989). It is interesting to note however, that the last two studies examined IEA frequency only, and did not examine possible changes in the patterns of IEA frequency.

Seizures may exert a clear masking effect on biological rhythms. Rao et al. (1989) examined serum levels of various hormones in patients with epileptic seizures and in patients with psychogenic seizures. Hormone levels were assessed every 15 minutes for two hours post-ictally, and were compared to levels from the same patient during a corresponding time on a seizure-free day. No changes in serum hormone levels were seen in patients with psychogenic seizures. Significant and sharp increases in serum prolactin, growth hormone, thyrotropin, and cortisol levels were seen immediately post-ictal in five of six patients with epileptic seizures. These increases returned to baseline levels within two hours in most cases. Increases were not found in serum levels of serotonin, melatonin, dopamine, nor epinephrine. The investigators noted that their findings of serum prolactin changes post-ictally support the findings of previous studies. The investigators suggested that epileptic seizures stimulate the hypothalamic-pituitary axis. If this

hypothesis is true, the influence seizures may have on biological rhythms may be significant since the suprachiasmatic nucleus is located within the hypothalamus (Minors & Waterhouse, 1981; DeGroot & Chusid, 1988).

The relationship between epileptiform activity and sleep is a complicated one, and is not completely understood. This relationship has been the topic of much study. Poor sleep quality in subjects with epilepsy has been noted by numerous investigators. Sleep problems noted have included increased wakefulness after sleep onset (WASO) (Hoeppner et al., 1984; Baldy-Moulinier, 1982; Montplaisir, 1990; Sammariatano, 1991); increased REM latency (Hamel & Sternman, 1982); decreased REM sleep time (Hamel & Sternman, 1982; Baldy-Moulinier, 1982); and increased latency of sleep onset (Montplaisir, 1990). Alterations in sleep quality may depend heavily on when epileptiform activity occurs. Besset (1982) noted that subjects who had nocturnal seizures had significantly impaired sleep quality compared to subjects who had diurnal seizures.

Of particular interest is a study conducted by Manni et al. (1990). These investigators studied the sleep EEG's of 14 subjects with partial epilepsy receiving carbamazepine monotherapy and EEG's of normal controls. Six subjects had poor seizure control with a mean frequency of 2.7 seizures per month. Polysomnographic recordings of subjects were made at least 48 hours post-ictally. All subjects had therapeutic serum carbamazepine levels during data collection.

Regardless of the amount of seizure control, all subjects with epilepsy had significantly poorer sleep than the normals. More specifically, REM latency and WASO was increased, and the amount of REM sleep was decreased. No significant differences were found between subjects with poor seizure control and subjects with good seizure control.

Specific sleep stages may impact the manifestation of epileptic activity. Stevens et al. (1972) and Kellaway et al. (1980) reported sharp drops in IEA frequency during REM sleep. Manni et al. (1990) noted that, despite stable carbamazepine levels, subjects with poor seizure control had increased IEA frequency during stages 1 and 2 non-REM sleep. Montplaisir (1990) suggested that the display of epileptiform activity during various sleep stages will differ depending upon the epilepsy type of the patient. However, Hamel and Sternman (1982) and Sammaritano et al. (1991) noted increased IEA frequency during stages 3 and 4 non-REM sleep in subjects with a variety of epilepsy types. In reviewing the relationship between sleep and epilepsy, one must step back from a paradigm which emphasizes causal relationships. In other words, does sleep modulate epileptiform activity, or does epileptiform activity alter sleep parameters, or do both processes occur? Findings of variable IEA frequencies in different sleep stages suggest that sleep modulates IEA. However, findings of altered sleep parameters in subjects with epilepsy suggests the reverse. A complex relationship between sleep and epilepsy in which both processes occur

simultaneously is perhaps the most accurate paradigm (Montplaisir, 1990).

Sleep Pattern Alterations. Humans are creatures of habit. Many people have predictable times at which they go to sleep and wake up. Sleep patterns among individuals may differ greatly due to lifestyle and personal preference. Few of the studies heretofore discussed have mentioned sleep patterns as a possible variable. If subjects slept in laboratories, sleep times may have been scheduled for the convenience of the laboratory staff, rather than to accommodate the accustomed sleep patterns of the subject.

Little is known about the possible influence changing sleep patterns may have on EEG data. However, if one considers sleep deprivation as shifting accustomed sleep-wake rhythms, EEG changes have been noted, and were discussed earlier.

Due to the influence one rhythm may have on another, changing sleep patterns may in turn alter other biological rhythms. This was demonstrated by Gundel and Wegmann (1987), who studied body temperature rhythms after transmeridian flights which resulted in nine hour phase shifts in sleep-wake rhythms. Westbound flights resulted in a disruption requiring two to seven days to resynchronize temperature rhythms to its baseline relationship to sleep-wake rhythms. Eastbound flights required three to nine days for resynchronization. In addition, both types of flights resulted in decreased amplitudes of temperature rhythms.

Changing sleep patterns alters sleep parameters. After reviewing the literature, Minors and Waterhouse (1981) and Anch et al. (1988) reported that a decreased total sleep time, increased WASO, decreased latency to rapid eye movement sleep, and increased fatigue result from shifting sleep patterns. Some of these symptoms are commonly seen from jet lag. As mentioned earlier, Minors and Waterhouse (1981) reported that five to six nights are required to adjust to a new sleep schedule. Studies such as the one by Gundel and Wegmann (1987) examined large changes in sleep patterns. Small changes of two to three hours have not been examined as thoroughly, but Minors and Waterhouse (1981) and Wagner (1990) suggested that the impact on rhythms is proportional to the size of the shift in sleep-wake rhythms.

Menstrual Cycle. The changes in hormone levels seen during the menstrual cycle could have influenced the phenomena of concern in this study.

Newmark and Penry (1980) reported that their review of the literature revealed nothing conclusive on the influence the menstrual cycle may have on epilepsy. However, Zimmerman (1986) disagreed. He stated that the literature demonstrates well that progesterone decreases cortical irritability and estrogen increases cortical irritability. He explained that exacerbations of seizures before or during menstruation is correlated with a rapid fall of progesterone and a decrease in the progesterone/estrogen ratio. He suggested that decreased progesterone levels do not cause seizures, but that

they lower the seizure threshold.

Backstrom (1976) noted this influence of progesterone as well. He studied six menstrual cycles in five women and found an increase in secondarily generalized seizures when progesterone levels were low which reversed when levels were high. Mattson et al. (1982) conducted a clinical trial of medroxy-progesterone acetate administration to women with uncontrolled seizures. No increase in seizure frequency was reported, and six women experienced a 50% decrease in seizure frequency. The other women either showed no improvement or were removed due to side effects of the medication. Jacono and Robertson (1987) found results which do not support the above studies. They found seizure frequency highest when progesterone levels were highest in women with primary generalized epilepsy.

Backstrom et al. (1984) studied seven women during the first week of their cycles when both progesterone and estrogen levels were low. They administered progesterone intravenously in concentrations commonly found during the luteal phase (when progesterone levels are high). Four women showed a reduction of baseline IEA frequency ranging from 24%-91%. The other three showed no significant change.

The regular fluctuation of hormone levels during the menstrual cycle may serve as a zeitgeber for other rhythms. In studies of healthy, ovulating women, circatrigintan (about 30 days) periods were found in temperature rhythms measured rectally (Caradente et al., 1987), esophageally (Stephenson &

Kolka, 1985), and on the skin surface (Simpson et al., 1990a, 1990b). Circatrigintan rhythms have been demonstrated in thyroid volume in ovulating women also (DeRimigis et al., 1990). In addition, Stephenson and Kolka (1985) demonstrated a significant difference in the threshold for initiation of heat loss during exercise during different times in the menstrual cycle. Unfortunately, none of these studies compared their results with non-cycling women or with men.

The impact the menstrual cycle has upon sleep is not yet clear. Regestein et al. (1981) studied hypogonadal women who were either started on estrogen or placebos. Of the eight women who had reported insomnia before the study, four showed a decrease in time needed to fall asleep during the study, and four showed an increase. The investigators did not specify which of these women were on estrogen however, and results were tabulated by the subjects by checking a box on a symptom card. Parry et al. (1989) examined sleep EEG's across the menstrual cycle in women with pre-menstrual depression and matched controls. The investigators found a significant increase in WASO in both groups during the pre-menstrual phase when both estrogen and progesterone levels were low. Lee et al. (1990) were unable to support these findings in their study. Lee et al. described a significant decrease in REM sleep latency during the luteal phase, but no other significant changes were noted. However, the investigators examined only four nights from a circatrigintan cycle, so possible changes may have been missed.

Mendelson (1987) reviewed the literature, and concluded that overall significant changes in sleep architecture across the menstrual cycle have not been identified.

Summary. The above sections have reviewed literature discussing the influence variables may have on EEG data, biological rhythms, and sleep. Although the review is non-exhaustive, it did suggest that the variables mentioned needed to be addressed in the design of this study. Other unidentified variables may have been pertinent to this study, but as with any research, it was hoped that unforeseen variables impacted the study minimally.

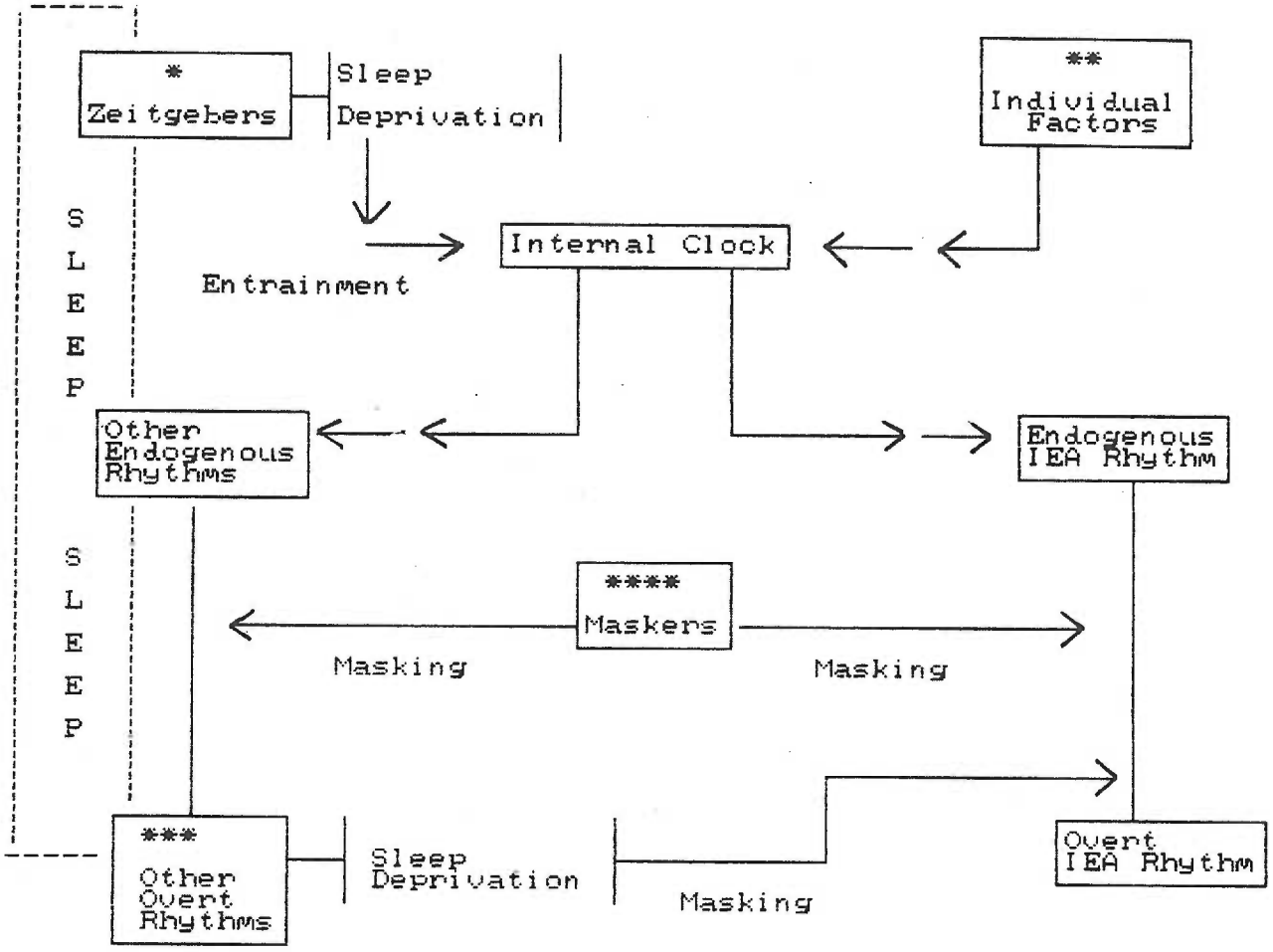
The next section will present the conceptual framework used in this study. This framework is based on the chronobiological framework presented earlier in Figure 1. Variables previously discussed will be included in this framework.

## Conceptual Framework

The purpose of the conceptual framework was not to provide only a theoretical foundation, but also to clarify possible relationships among variables germane to this study. This framework is displayed in Figure 2.

As mentioned in the previous chapter, the purpose of this study was to describe patterns of IEA frequency during sleep and sleep deprivation. Sleep deprivation (e.g., the absence of sleep) was the independent variable; overt patterns of IEA frequency were the dependent variables.

According to Minors and Waterhouse (1981), sleep, with




Note: Placement of Variables

* Caffeine, Nicotine, AED's, Sedatives, Exercise, Seizures, Sleep Pattern Disruptions, Menstrual Cycle

** Age, Gender

*** Seizures, Sleep Pattern Disruptions, Menstrual Cycle

**** Caffeine, Nicotine, AED's, Sedatives, Exercise, Seizures

Figure 2.

Conceptual framework used in study.

its own internal rhythmicity, may serve as a masker, a zeitgeber, or both. Its exact role may depend upon which internal clock or overt rhythm is being examined. Since the role of sleep on IEA frequency rhythms is unclear, sleep is displayed in the conceptual framework as both a zeitgeber and as an overt rhythm serving as a masker. Thus sleep deprivation may be an interruption of an entraining process, a masking process, or a combined process.

The review of literature of the influencing variables discussed earlier suggested possible entraining or masking properties. As is with sleep, some of these variables may be either zeitgebers, maskers, or both. This study was not intended to sort out all these relationships. Consequently, variables may be displayed more than once in the framework in order to account for their possible influence. How each of these variables was managed in this study will be discussed in the next chapter.

Research Questions.

Based upon the research problem, purpose of study, review of literature, and conceptual framework, the specific research questions for this study were:

1. What are the temporal patterns of IEA frequency during two episodes of sleep in individual subjects with focal epilepsy?

2. What happens to these patterns during a time-matched episode of sleep deprivation?

# Chapter III

## Methods

### Sample

A convenience sample of five subjects was selected from patients admitted to the Seizure Telemetry Unit, located at the Portland, Oregon Veterans Administration Medical Center. This unit was the inpatient component of the Comprehensive Epilepsy Center, and was equipped with 24-hour video/EEG monitoring. All subjects were admitted for diagnostic purposes. Demographic information is presented in Table 1.

All subjects gave signed informed consent to participate in the study. All subjects were instructed that participation was voluntary, and that they could withdraw from the study at any time without consequences. Subjects were instructed that they would not benefit directly from this study, nor would they receive payment for their participation. Consent forms, as well as this study's procedures, were approved by Institution Review Boards from the V. A. Medical Center and Oregon Health Sciences University. Sample consent forms from each institution are located in Appendix B.

Inclusion criteria. All subjects met the following inclusion criteria:

1. Had partial epilepsy, characterized by focal IEA identified by a staff electroencephalographer during the subject's first night in the unit. (The first night was not a night of data collection for this study.)

Table 1
Subject Demographics

| Subject | Gender and age | Seizure type(s)[a] | Origin of IEA[b] | Years with seizures | AED's used during study[c] | Caffeine, nicotine habits | Day in menstrual cycle |
|---|---|---|---|---|---|---|---|
| One | F 29 | CP CP->TC | Left temp. | 17 | CBZ | 2 colas/day Non-smoker | 4-7 |
| Two | M 25 | CP CP->TC | Left, right temp. | 9 | CBZ | No caffeine Non-smoker | N/A |
| Three | M 55 | CP | Right temp. | 6 | None | 20 cups coffee 1 pack of cigarettes/day | N/A |
| Four | M 44 | CP | Right temp. | 32 | PB | No caffeine Non-smoker | N/A |
| Five | F 35 | CP CP->TC | Right front. | 10 | CBZ | 2 cups coffee 1 pack of cigarettes/day | 3-6 |

Note. [a]CP = complex partial CP->TC = complex partial, secondarily generalized [b]temp. = temporal lobe; front. = frontal lobe. [c]CBZ = carbamazepine; PB = phenobarbital

2. Had a customary bedtime between the hours of 2100 and 0100.

3. Was between the ages of 18-50 years.

4. Provided signed informed consent.

Exclusion criteria. Subjects were excluded from the study if any of the following criteria were met:

1. Unable to maintain accustomed caffeine consumption habits during the stay in the unit.

2. Required sedatives during the stay in the unit.

3. Strayed away from usual sleep habits for more than three nights during the week prior to admission.

4. Required intracranial EEG electrodes.

Management of Influencing Variables

Optimal management of the influencing variables presented earlier was attempted during the study. Table 2 summarizes the methods used to manage variables which could potentially have confounded the study's results.

Caffeine was a variable which was easily controlled. Subjects were instructed to adhere to their usual caffeine consumption habits while staying in the unit. Caffeinated beverages were supplied by staff in order to assist maintenance of caffeine habits.

Nicotine withdrawal and exercise were problematic. Smoking was not allowed in the unit. Subjects were confined to the unit, since they were continuously attached to EEG cables. Consequently, subjects were not able to smoke, nor were they able to maintain their accustomed physical activity

Table 2

Management of Influencing Variables

| Variable | How managed |
|---|---|
| Caffeine | Controlled--usual caffeine habits maintained |
| Nicotine withdrawal | Taken into account |
| Sedatives | Controlled--no subjects required sedatives |
| Sleep pattern disruption | Controlled--usual sleep times maintained |
| Exercise | Not controlled--subjects confined to unit |
| AEDs | Taken into account |
| Age and gender | Taken into account<br>Data not pooled |
| Seizures | Taken into account<br>Adjusted times of data used for analysis |
| Menstrual cycle | Taken into account<br>Subjects in follicular phase of cycle |

level. These variables were accounted for but not controlled. Two subjects experienced nicotine withdrawal during the study. Neither subject accepted nicotine-containing gum to help reduce withdrawal symptoms.

Attempts were made to control sleep pattern disruptions. Subjects went to bed at the same time on sleep nights, which corresponded to their usual bedtime at home. In addition, exclusion criteria for the study required that subjects had no more than three nights of sleep pattern disruption during the prior week.

Use of sedatives was easily controlled. No subject required the use of sedatives to promote sleep during hospitalization.

Antiepileptic drugs (AEDs) were not controlled for this study. The original diagnostic purposes of the subjects' admissions required fluctuating dosages of AEDs. All subjects were on monotherapy during data collection.

Age and gender are individual characteristics which were not controlled. However, since each subject served as his or her own control, these variables had no impact on data from the same subject. The sample included two women and three men. Ages ranged from 25 to 55 years.

Seizures, though not controlled, were taken into account during data collection. One subject experienced a seizure during data collection. Two subjects had seizures within 24 hours of the beginning of data collection. The process used to account for seizures in data collection will be detailed

in the data analysis section of this chapter.

Menstrual cycling was a variable which was taken into account. Both female subjects were in the early follicular stage of the menstrual cycle during data collection. This stage is characterized by relatively low and stable levels of estrogen and progesterone. Since data collection occurred on consecutive nights, changes related to hormone levels between nights should have been negligible.

Procedures

Procedures were divided into three stages: pre-data collection period, data collection period, and post-data collection period. A detailed protocol is located in Appendix A.

Before data were collected, the investigator reviewed the study with staff nurses and discussed how the protocol would impact their routine work duties. After a patient was admitted to the unit and had already been monitored for one night, participation in the study was solicited.

At this point, the data collection period began. The investigator worked with staff to ensure that subjects maintained accustomed caffeine consumption habits and sleep patterns. The investigator was present during sleep nights to ensure that sleep was as uninterrupted as possible. On the sleep deprivation night, the investigator was present to ensure that subjects stayed awake.

During the post-data collection period, the investigator thanked each subject for participating in the study and

informed staff that the study was completed for the individual subject. Printing of the EEGs and data tabulation began after the subject was discharged.

Instrumentation

Description of equipment. EEG data were printed using a Grass 8-20D electroencephalograph (Grass Instrument Company of Quincy, MA). Gold-plated surface EEG electrodes were used since they required less maintenance than silver electrodes, and were used routinely in the unit. Staff technicians placed all electrodes with collodion gel, and utilized the International 10-20 System, which is the standard placement in most EEG laboratories (Aminoff, 1986). Staff technicians were responsible for daily maintenance of the electrodes as well. This maintenance included verification of electrode placement and cleansing of the electrodes.

Electrical safety was maintained during the study. Subjects were protected from electrical shock by a grounded surface electrode placed on the forehead. The electroencephalograph was grounded also. Instrument grounding was verified by the V.A. Medical Center's biomedical engineer every six months during data collection. The Grass Model 8-20D electroencephalograph was in compliance with Underwriter's Laboratories (UL) safety standards according to the manufacturer (Grass Instrument Company, Quincy, MA).

The scalp EEG electrodes led to a transducer worn about the chest. The chest unit combined multiple electrodes into

a single cable which was then connected to a wall unit transducer. From here, electrical signals were sent to a computer, where they were recorded onto a computer disk, as well as onto a track on the videotape. Hardcopy EEG data were printed from the videotape, using wide EEG paper (3D18-6-18 inch DWG: Graphics Control, Incorporated, Tustin, CA.) at a chart speed of 30 millimeters per second.

Instrument specifications. The instrument specifications germane to this study were sensitivity and impedance. Sensitivity is defined as the ratio of input voltage to output pen deflection and is measured in microvolts per millimeter (Grass, 1983). The Grass Instrument Company has listed the maximum sensitivity for the Model 8-20D printer as 0.5 microvolts per millimeter. The Center's staff maintained calibration of the printer to a sensitivity to 7.0 microvolts per millimeter. Impedance is the obstruction of flow of alternating electrical current (Grass, 1983). Grass has listed the minimum input impedance as 20 megohms. The Center's staff routinely accepted any impedance under 5000 megohms and usually could obtain impedance readings less than 3000 megohms. Sensitivity and impedance were checked by the Center's staff daily. The investigator accepted all instrumentation checks.

IEA was defined in terms of what was printed on the hardcopy EEG. Therefore, information regarding the validity and reliability of the EEG's representation of the electrical activity in the brain was not needed.

Montaging. The montage describes how the information from pairs of electrodes is displayed on the EEG paper. Any montage could be selected from the EEG data stored on the videotape. A routine montage was developed by the Center's staff for the purposes of this study. This montage allowed for ease of IEA recognition, and was used for most records. However, due to diagnostic needs, two nights from Subject 2 and all nights from subject Five required a different montage. These other montages did not prevent IEA recognition, but instead, displayed IEA in different channels. The medical center's electroencephalographers reviewed all montages with the investigator. All montages used in the study are detailed in Appendix C.

## Data Analysis

Definitions. Data were tabulated from the EEG from two periods of sleep and a time-matched period of sleep deprivation. Periods of sleep were determined generally by interruptions of sleep (seizures or wakefulness) which may have occurred. These interruptions may have threatened the validity of sleep data. If a subject experienced a seizure or a period of wakefulness after sleep onset lasting more than 15 minutes, data collection was stopped, and EEG data preceding the interruption were used. No EEG data were used until subjects had been asleep for at least thirty minutes (per observation). If a subject experienced no interruption of sleep, EEG data were used beginning one hour after the subject had fallen asleep and continuing for the following

four hours. EEG data from sleep deprivation nights were used from periods of time corresponding to each subject's previous sleep nights. The resulting time blocks of EEG data used for data analysis across subjects and across nights ranged from 2.75 to 4.50 hours in length.

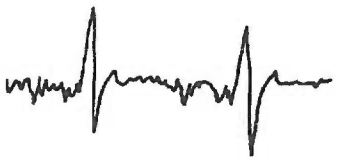
From this EEG database, IEA (spikes and sharp waves) were tabulated and totaled per 10-second and per 1-minute epoch. Definitions and examples of spikes and sharp waves are listed in Figure 3. The guidelines of Maulsby (1971) were used to assist in IEA identification and classification. These guidelines are recognized as the professional standard for EEG interpretation (personal communication, L. Morehead, 1991).

Some epochs were filled with artifact, preventing clear IEA identification. These epochs were removed from the EEG used in IEA tabulation, resulting in missing data points in data analysis. The number of these epochs was small, resulting in less than six minutes per night. However, Subject Five fell asleep for 25 minutes during the sleep deprivation night. IEA from this sleep episode was not included in data anlysis.

After data were tabulated, a random 10% of the EEG records from 75% of the nights recorded were selected by a certified electroencephalographer in order to verify IEA tabulation. Interrater agreement was determined as the ratio between the number of IEA tabulated by the investigator and the number of IEA tabulated by the medical

Interictal epileptiform Activity (IEA): activity displayed on the EEG indicative of epileptic activity occurring between ictus. Specific forms of IEA are displayed below.

Spike: a single, sharp transient with a duration between 20-70 milliseconds.



Spike

Sharp wave: a single, sharp transient with a duration between 70-200 milliseconds.

Sharp wave

Figure 3. Data definitions for study

Note. To differentiate these transients from other types of EEG data, the guidelines from Maulsby (1971) were used.

center's electroencephalographer. This method did not account for IEA agreed upon by chance. Agreement ranged from 77-87%. (This level of agreement is consistent with agreement levels ranging from 65-92% among EEG readers reported by previous investigators [Gevins et al., 1977a, 1977b; Salinsky et al., 1988].) In addition, selected EEG sections were used to review IEA recognition techniques.

Data collected post-ictally might not be reliable for the purposes of study. How long a seizure may influence IEA frequency is unclear, but hormone levels (such as prolactin levels) were noted in the literature to return to pre-ictal levels within two hours after a seizure (Rao et al., 1989). Since the impact of hormone levels was defined more clearly in the literature, this two hour time span was used as the time span for editing of post-ictal IEA. Therefore, EEG data were not used if a seizure identified by an epileptologist occurred within two hours of data collection.

Statistical analysis. A diagram of the steps used in data analysis is located in Figure 4. The frequencies of IEA from each record were graphed initially for a visual display of the data. Then, fast Fourier transforms and periodogram analyses were completed utilizing data of IEA per minute epoch. One minute epochs were used to facilitate mathematical computations.

Fast Fourier transform analysis uses an algorithm to solve mathematical equations more quickly (hence, fast) and

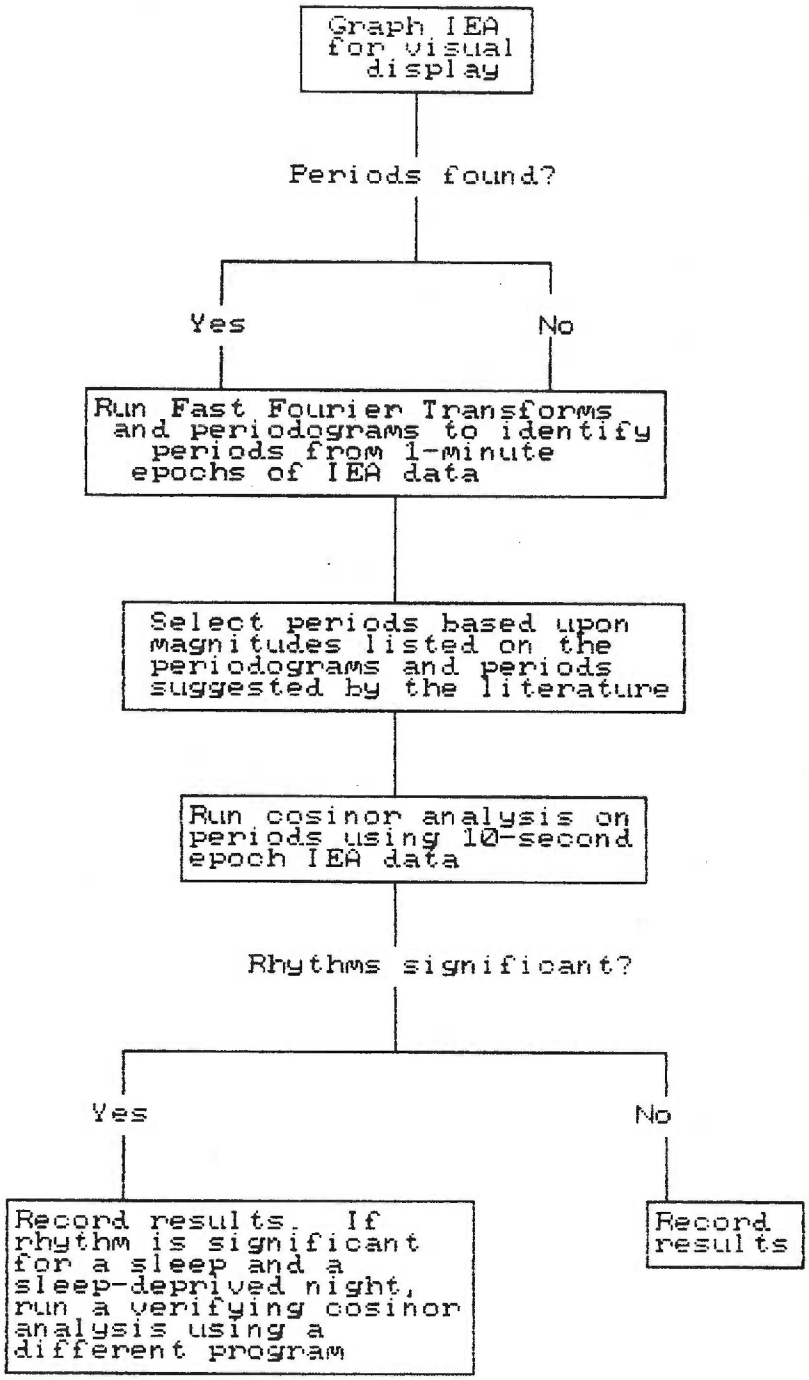



Figure 4.

Data analysis procedures.

is based upon a theorem by Jean Fourier (1768-1830). Fourier's Theorem states that every curve, no matter what its nature may be or in what way it was originally obtained, can be exactly reproduced by superimposing a sufficient number of single harmonic curves (Bracewell, 1986). This analysis may be likened to a prism which splits white light into a rainbow. Fast Fourier transform analysis detects the periods of any cycles present in the data. This analysis requires a series of complicated mathematical steps, so procedures have been incorporated into the process of solving the equations to facilitate efficiency (hence, transform). The cycles detected by fast Fourier transform analysis, when summed, will reproduce the waveform of the data. This analysis is suitable for data which may or may not be equidistant, and may be used when small amounts of data are missing.

Certain assumptions of the data must be met in order to use fast Fourier transform analysis. First, the value of the waveform function at any given time must exist within infinity. Second, the function must be periodic, with a least one period of specific length. Third, in any given cycle length, the function must have a finite number of discontinuities, and a finite number of maxima and minima. (Champeney, 1973; Weaver, 1983; Bracewell, 1986).

In addition, the function must fulfill the requirement of stationarity. Stationarity is an extension of the third assumption listed above, and requires that the waveform maintains stable parameters over time. The current study did

not test these assumptions.

The periodogram is a display of the fast Fourier transform analysis results. The periodogram lists the periods of the cycles detected and their magnitudes. These magnitudes are used to determine which cycles most account for the waveform of the data.

The investigator examined the periodograms from each night individually. Periods were selected for the next stage of data analysis if their magnitudes were relatively large by subjective inspection, or if magnitudes of a series of periods peaked to a relatively large value. Periods of rhythms reported as significant by Stevens et al. (1971, 1972) and Kellaway et al. (1980) were used if they were not already suggested in the periodograms. Periods less than 10 minutes were not selected, since rhythms with such periods are of questionable clinical utility.

It is important to note that periodograms reveal periods from a fixed graph determined by the number of data points used. Hence, in this study, periods of 62.5 minutes were listed in the periodogram, but periods of 60.0 minutes were not. Therefore, periods which the periodogram did describe and which were selected for continued analysis were rounded to a more clinically useful value. (For example, a period of 62.5 minutes was rounded to 60 minutes.) Both fast Fourier transform and periodogram analyses were performed using the SYSTAT (Evanston, IL) statistical package on a Macintosh SE computer.

The next stage in data analysis was cosinor analysis of the data. Cosinor analysis uses a simple least squares regression approach to fit a cosine function to the data. This approach is based on the hypothesis that the sum of the squared deviations will be smallest about the best-fit curve. Cosinor analysis provided a method to determine the acrophase (time or degree of the curve's peak), the mesor (the mean value of the fitted curve), and the amplitude (peak-to-mesor difference) of a waveform. Cosinor analysis tests the significance of a rhythm with an assumed period (Lentz, 1990) by disproving the null hypothesis. (The null hypothesis states that the rhythm has an amplitude of zero.) The equation of the best-fit curve and curve parameters is presented in Figure 5.

Cosinor analysis requires two assumptions (Lentz, 1990). First, the data must fit a sinusoidal cycle with a fixed period length, phase, and amplitude. This assumption requires stationarity of the rhythm. The second assumption requires that the period of the rhythm is known. This second assumption required the investigator to complete fast Fourier transform and periodogram analyses before running cosinor analysis, since periods of IEA frequency rhythms could not be ascertained definitively from the findings of previous investigators.

Since cosinor analysis uses a least squares regression approach, assumptions for regression methods must be met also. These assumptions require that data are of at least

$$Y(t) = B_0 + B_1\cos(2\pi\ t/P) + B_2\sin(2\pi\ t/P) + E$$

Where: $B_0$ = mesor

$B_1$ and $B_2$ = constants

t = time

P = period

$K + \arctan(-B_2/B_1)$ = acrophase

K = multiple of 90 degrees

$\sqrt{B_1^2 + B_2^2}$ = amplitude

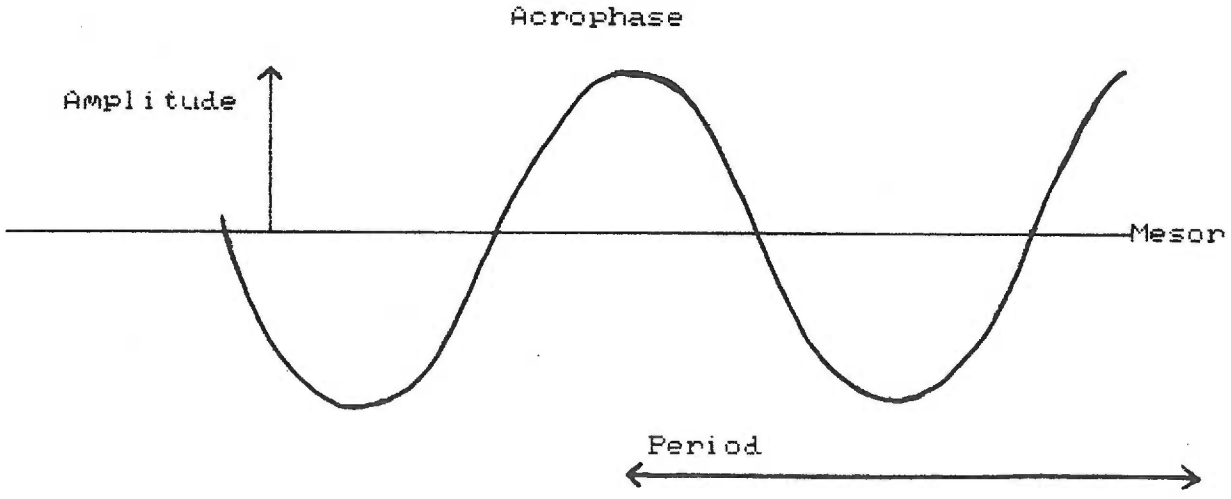



Figure 5.

Equation for cosinor analysis and parameters.

interval level, that values of the variables are normally distributed, that values of variables have equal variability (homoscedasticity), and that there is independence among the variances of data intervals. When data is collected closely in time (as was done in this study), independence of variance may have been violated. However, DePrins (1986) stated that the lack of independence of variances usually does not effect the parameters given by cosinor analysis. This study did not test the assumptions listed above.

Cosinor analysis was completed using a FORTRAN program developed by Johannes (Johannes, 1984) and modified by Zucker, Reith, and Felver (personal communication, L. Felver, 1991). Cosinor analysis was completed on the data of IEA per 10-second epoch in order to represent real time more closely. Based on the conceptual framework presented earlier, the investigator anticipated results from the cosinor analysis to be most incongruent between a sleep night and the sleep deprivation night within subjects. Therefore, when significant rhythms (significance was defined <u>a priori</u> as $< 0.05$) were found in at least one sleep night and one sleep deprivation night in the same subject, a second cosinor analysis utilizing a different computer program was performed to verify significance. The next chapter will discuss the results and interpretation of the findings.

# Chapter IV

## Results

Three types of results were derived from data analysis: overall IEA frequency, periods from the fast Fourier transforms and periodogram analysis, and significance of rhythms from cosinor analysis.

### IEA Frequency

Data were collected from two nights of sleep and one night of sleep deprivation from each subject (data from one night of sleep from Subject Four was lost). The amount of time assessed from each night ranged from 2.75 to 4.50 hours. Since the amounts of time varied among nights, analysis of the total number of IEA counted per night was not helpful. Therefore, overall IEA frequency per night was analyzed per epochs of 10 seconds, one minute, and one hour (see Table 3).

IEA frequencies ranged widely among subjects, from as low as 0.92 per hour in night 2 for Subject One to 3427.05 per hour in night 3 of Subject Four. Interestingly, most nights varied widely within subjects. IEA frequency remained relatively consistent among nights only in Subject One, who experienced very little total IEA.

In Subjects One, Two, and Three, IEA frequency dropped during the night of sleep deprivation. Conversely, IEA frequency rose dramatically during the night of sleep deprivation in Subject Four. IEA frequency of the sleep deprivation night in Subject Five was very similar to one night of sleep and considerably lower than the other sleep

Table 3
Total Tabulation of IEA and Overall IEA Frequency

| Night | Time[b] | # IEA | Overall IEA Frequency per Epoch[a] | | |
|---|---|---|---|---|---|
| | | | 10 second | 1 minute | 1 hour |
| | | | Subject One | | |
| 1 | 4.20 | 16 | 0.01 | 0.06 | 3.81 |
| 2[c] | 3.25 | 3 | 0.00 | 0.02 | 0.92 |
| 3 | 3.25 | 7 | 0.01 | 0.04 | 2.15 |
| | | | Subject Two | | |
| 1 | 3.08 | 157 | 0.15 | 0.88 | 52.68 |
| 2 | 2.97 | 67 | 0.06 | 0.38 | 22.79 |
| 3[c] | 3.00 | 19 | 0.02 | 0.11 | 6.33 |
| | | | Subject Three | | |
| 1 | 3.08 | 284 | 0.29 | 1.72 | 103.27 |
| 2 | 2.75 | 484 | 0.51 | 3.06 | 184.03 |
| 3[c] | 2.83 | 71 | 0.07 | 0.42 | 25.36 |
| | | | Subject Four | | |
| 1 | 4.50 | 9666 | 5.84 | 35.02 | 2101.30 |
| 2[c] | 4.47 | 15079 | 9.52 | 57.11 | 3427.05 |
| | | | Subject Five | | |
| 1 | 4.00 | 158 | 0.11 | 0.67 | 40.00 |
| 2 | 3.92 | 48 | 0.03 | 0.21 | 12.37 |
| 3[c] | 3.80 | 48 | 0.04 | 0.25 | 15.24 |

Note. [a]10 second epochs in which artifact prevented IEA tabulation were eliminated from total time in frequency calculations. [b]Length of the block of time (in hours) used for data analysis. [c]Night of sleep deprivation.

night.

Fast Fourier Transforms and Periodogram Analysis

Fast Fourier transforms and periodogram analysis provided relative magnitudes of the periods contained within the data. These periods ranged from 2 to 256 minutes, with finer discrimination between periods of shorter length.

This analysis revealed a number of periods whose magnitudes were considerably higher than the magnitudes of the other periods. However, these periods varied among nights and among subjects.

In all subjects except Subject One, periods of 2.00 and 1.50 hours were identified for every night. Otherwise, each night from each subject revealed a variety of periods. Analysis of the sleep deprivation night from Subject Four revealed seven periods, more than with any other subject. Periods of 1.00, 0.75, 0.50, 0.40, 0.33, and 0.25 hours were revealed overall from the data in addition to the periods listed previously.

Cosinor Analysis

Periods identified by the fast Fourier transforms and periodogram analysis were used in cosinor analysis to test the significance of rhythms. In addition, a period of 2.75 hours was used in cosinor analysis, since this rhythm was identified by Stevens et al. (1981, 1972) (discrimination within the periodogram analysis was not at a level to evaluate the magnitude of a period of 2.75 hours directly). Cosinor analysis revealed significant rhythms in all subjects

except Subject One (see Table 4).

At least one night from Subjects Two through Five included significant rhythms with periods of 2.75, 2.00, 1.50, and 1.00 hours. No rhythm maintained significance for the three nights within a subject, but Subjects Three through Five had at least one rhythm which maintained significance for a sleep night and a sleep deprivation-night. (Subject Two approached this with a 1.00-hour rhythm for nights one and three). A verifying cosinor analysis was completed on records in which at least one sleep night and one sleep deprivation night contained a significant rhythm of the same period; this accounted for 55% of the records. This confirmatory analysis revealed identical significance levels in nearly all records, and the same overall significance in all records. Complete results from the cosinor analysis utilizing the FORTRAN program on all significant rhythms are presented in Tables 5 through 8.

In all subjects with significant rhythms, there was a general trend for longer periods to account for more of the variance ($R^2$) in IEA than for shorter periods within the same night. The variance explained by the rhythms across all subjects ranged from 0.40% to 7.55%.

The mesors (time-adjusted means of the fitted curve) of the rhythms were low, approaching zero in all subjects except Subject Four. This is understandable since mesor values correspond to IEA frequency at 10 second time intervals. Not surprisingly, mesor values of rhythms for each night within

Table 4

Significance Levels of Periods Revealed Through Fast Fourier Transforms and Periodogram Analysis

| | Subject One nights | | | Subject Two nights | | | Subject Three nights | | | Subject Four nights | | Subject Five nights | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Periods | 1 | 2* | 3 | 1 | 2 | 3* | 1 | 2 | 3* | 1 | 3* | 1 | 2 | 3* |
| 2.75 hours | NS | | NS | .001 | NS | NS | <.0001 | <.0001 | NS | <.0001 | <.0001 | <.0001 | NS | .020 |
| 2.00 hours | NS | | NS | <.0001 | AS | NS | <.0001 | <.0001 | NS | <.0001 | <.0001 | .001 | NS | .002 |
| 1.50 hours | NS | | NS | <.0001 | .009 | NS | .001 | <.0001 | NS | NS | <.0001 | .018 | .003 | NS |
| 1.00 hours | | | NS | .002 | NS | AS | NS | .001 | NS | <.0001 | .016 | NS | .040 | NS |
| 0.75 hours | | | | NS | NS | .040 | NS | .038 | NS | <.0001 | .003 | | | |
| 0.50 hours | | | NS | NS | NS | NS | | | | .024 | .004 | | | NS |
| 0.40 hours | | | | | | | NS | NS | NS | NS | .043 | | | |
| 0.33 hours | NS | | | .009 | NS | NS | NS | .003 | <.0001 | NS | NS | .003 | NS | NS |
| 0.25 hours | | | | | | | | | | NS | .006 | | | |

Note: NS = not significant. AS = approached significance with p between 0.05 and 0.06

*Night of sleep deprivation

Table 5

Results of Cosinor Analysis for Subject Two

| Night | Period (hrs) | p | $R^2$ | Mesor +- SE | Amplitude +- SE | Acrophase[a] +- SE |
|---|---|---|---|---|---|---|
| One | 2.75 | .001 | 1.58% | 0.14 +- 0.10 | 0.01 +- 0.02 | 0218 +- 6 min |
| | 2.00 | <.0001 | 2.62% | 0.16 +- 0.02 | 0.12 +- 0.02 | 0253 +- 4 min |
| | 1.50 | <.0001 | 1.76% | 0.15 +- 0.02 | 0.10 +- 0.02 | 0253 +- 3 min |
| | 1.00 | .002 | 1.19% | 0.14 +- 0.02 | 0.08 +- 0.02 | 0159 +- 3 min |
| | 0.33 | .009 | 0.89% | 0.15 +- 0.02 | 0.07 +- 0.02 | 0139 +- 1 min |
| Two | 2.00 | .053[b] | 0.55% | | | |
| | 1.50 | .009 | 0.87% | 0.06 +- 0.01 | 0.03 +- 0.01 | 0256 +- 5 min |
| Three[c] | 1.00 | .053[b] | 0.56% | | | |
| | 0.40 | .040 | 0.62% | 0.02 +- 0.01 | 0.02 +- 0.02 | 0144 +- 3 min |

Note. [a]Acrophases for each rhythm occur at the clock time listed +- n hours; where n = period length. Acrophases can be determined only for clock times which occur during the hours of data collection. [b]This rhythm approached significance at the 0.05 level. [c]Night of sleep deprivation.

Table 6

Results of Cosinor Analysis for Subject Three

| Night | Period (hrs) | p | $R^2$ | Mesor +- SE | Amplitude +- SE | Acrophase[a] +- SE |
|---|---|---|---|---|---|---|
| One | 2.75 | <.0001 | 3.71% | 0.29 +- 0.02 | 0.18 +- 0.03 | 0212 +- 4 min |
| | 2.00 | <.0001 | 2.81% | 0.30 +- 0.02 | 0.14 +- 0.03 | 0122 +- 4 min |
| | 1.50 | .002 | 1.23% | 0.30 +- 0.02 | 0.10 +- 0.03 | 0129 +- 4 min |
| Two | 2.75 | <.0001 | 1.93% | 0.51 +- 0.02 | 0.15 +- 0.04 | 0249 +- 6 min |
| | 2.00 | <.0001 | 6.02% | 0.50 +- 0.03 | 0.28 +- 0.03 | 0108 +- 2 min |
| | 1.50 | <.0001 | 7.55% | 0.52 +- 0.02 | 0.29 +- 0.04 | 0120 +- 2 min |
| | 1.00 | .0001 | 1.63% | 0.51 +- 0.03 | 0.14 +- 0.04 | 2419 +- 3 min |
| | 0.75 | .039 | 0.69% | 0.51 +- 0.03 | 0.09 +- 0.04 | 2436 +- 3 min |
| | 0.33 | .003 | 1.21% | 0.52 +- 0.02 | 0.12 +- 0.03 | 2425 +- 1 min |
| Three[b] | 0.33 | <.0001 | 1.92% | 0.07 +- 0.01 | 0.06 +- 0.01 | 2433 +- 1 min |

Note. [a]Acrophases for each rhythm occur at the clock time listed +- n hours; where n = period length. Acrophases can be determined only for clock times which occur during the hours of data collection. [b]Night of sleep deprivation.

Table 7

Results of Cosinor Analysis for Subject Four

| Night | Period (hrs) | p | $R^2$ | Mesor +- SE | Amplitude +- SE | Acrophase[a] +- SE |
|---|---|---|---|---|---|---|
| One | 2.75 | <.0001 | 5.57% | 6.30 +- 0.10 | 1.35 +- 0.15 | 0134 +- 3 min |
| | 2.00 | <.0001 | 6.79% | 6.11 +- 0.10 | 1.50 +- 0.14 | 2426 +- 2 min |
| | 1.00 | <.0001 | 3.75% | 6.16 +- 0.10 | 1.09 +- 0.14 | 2440 +- 1 min |
| | 0.75 | <.0001 | 2.59% | 6.13 +- 0.10 | 0.90 +- 0.14 | 2432 +- 1 min |
| | 0.50 | .024 | 0.48% | 6.13 +- 0.10 | 0.38 +- 0.14 | 2402 +- 2 min |
| Three[b] | 2.75 | <.0001 | 1.90% | 9.66 +- 0.11 | 0.81 +- 0.15 | 0159 +- 5 min |
| | 2.00 | <.0001 | 1.67% | 9.72 +- 0.11 | 0.81 +- 0.16 | 2436 +- 4 min |
| | 1.50 | <.0001 | 1.59% | 9.70 +- 0.11 | 0.76 +- 0.15 | 2410 +- 3 min |
| | 1.00 | .013 | 0.56% | 9.72 +- 0.11 | 0.46 +- 0.15 | 2428 +- 3 min |
| | 0.75 | .003 | 0.74% | 9.70 +- 0.11 | 0.52 +- 0.15 | 2442 +- 2 min |
| | 0.50 | .004 | 0.71% | 9.70 +- 0.11 | 0.51 +- 0.15 | 2420 +- 1 min |
| | 0.40 | .043 | 0.40% | 9.69 +- 0.11 | 0.39 +- 0.15 | 2416 +- 2 min |
| | 0.25 | .006 | 0.65% | 9.69 +- 0.11 | 0.49 +- 0.15 | 2406 +- 1 min |

Note. [a]Acrophases for each rhythm occur at the clock time listed +- n hours; where n = period length. Acrophases can be determined only for clock times which occur during the hours of data collection. [b]Night of sleep deprivation.

Table 8

Results of Cosinor Analysis for Subject Five

| Night | Period (hrs) | | $R^2$ | Mesor +- SE | Amplitude +- SE | Acrophase[a] +- SE |
|---|---|---|---|---|---|---|
| One | 2.75 | <.0001 | 1.67% | 0.10 +- 0.01 | 0.07 +- 0.01 | 0146 +- 5 min |
| | 2.00 | .0001 | 1.15% | 0.11 +- 0.01 | 0.06 +- 0.01 | 0228 +- 5 min |
| | 1.50 | .018 | 0.57% | 0.11 +- 0.01 | 0.04 +- 0.01 | 0233 +- 5 min |
| | 0.33 | .003 | 0.83% | 0.11 +- 0.01 | 0.05 +- 0.01 | 0139 +- 1 min |
| Two | 1.50 | .003 | 0.82% | 0.03 +- 0.01 | 0.03 +- 0.01 | 0203 +- 4 min |
| | 1.00 | .040 | 0.46% | 0.03 +- 0.01 | 0.02 +- 0.01 | 0202 +- 4 min |
| Three[b] | 2.75 | .020 | 0.75% | 0.05 +- 0.01 | 0.03 +- 0.01 | 0210 +- 9 min |
| | 2.00 | .001 | 1.25% | 0.05 +- 0.01 | 0.04 +- 0.01 | 0306 +- 5 min |

Note. [a]Acrophases for each rhythm occur at the clock time listed +- n hours; where n = period length. Acrophases can be determined only for clock times which occur during the hours of data collection. [b]Night of sleep deprivation.

each subject matched the subject's overall IEA frequency (10 second) listed in Table 1.

The amplitudes (mesor-to-peak distance) of the rhythms were very small, usually less than 0.50 IEA/10 sec. occurrence. Subject Four demonstrated half-amplitudes greater than 1.00 IEA/10 sec. occurrence in rhythms with periods of 2.75, 2.00, and 1.00 hours.

The acrophases (times of the rhythm peaks) were of particular interest. Acrophases for like rhythms occurred within 30 minutes of each other within the same subject, regardless of whether the night was a sleep night or not. Consistent acrophases occurred despite the inconsistency in overall IEA frequencies among nights within a subject.

Summary of Results

Overall IEA frequency was highly variable among nights and among subjects. Only one subject maintained consistent IEA frequency among nights, but low IEA totals from this subject is noteworthy. Interestingly, no significant rhythms were found in the data from this subject.

Significant rhythms were found in the remaining subjects. Although no rhythm maintained significance for three nights within a subject, three subjects had at least one rhythm which maintained significance for one sleep night and one sleep deprivation night.

Rhythms accounted for little of the variance in IEA, but generally, rhythms with longer periods explained more of the variance than rhythms with shorter periods. Significant

rhythms were generally very flat (low amplitudes) and had mesors which approached zero. Within a given subject, acrophases for a specific rhythm occurred within 30 minutes of each other in both sleep and sleep deprivation nights. A discussion of these results follows in the next chapter.

# Chapter V

# Discussion

## Discussion of Findings

Tabulation of IEA from the EEG records of subjects revealed high variability in IEA frequency both within and between subjects. This finding is not consistent with those of Martins da Silva et al. (1984). Although these investigators utilized 30-minute epochs for IEA frequency, they found significant correlations between time-matched epochs 89% of the time. However, their subjects were maintained on stable AED, exercise, and sleep regimens. Variability in IEA frequency in the current study may have resulted from the following influencing variables.

Subjects in the current study were maintained on stable sleep and caffeine regimens. No subjects required sedatives. Female subjects were in the early follicular stage of their menstrual cycles. These variables, in addition to age and gender, most likely had a minimal impact on IEA frequency in the current study.

Subjects Three and Five underwent nicotine withdrawal. Withdrawal promotes cortical hypoexcitation, and should promote a decrease in IEA frequency over time. This decrease was noted in Subject Three, but Subject Five had a slight increase in IEA frequency on the third night.

None of the subjects who experienced tapering of their AED dosages maintained stable IEA frequencies, as would be anticipated from the literature. Seizures occurred within 24

hours of data collection (never less than 12 hours) in three subjects. No consistent rise or fall in IEA frequency peri-ictally was found in this group.

The most consistent variable among the group was poor sleep. Subjects were required to sleep in a very unnatural environment. Although EEG records were not scored for sleep, subjective observation during sleep nights revealed inconsistent amounts of wakefulness after sleep onset within subjects. An exception was Subject Five. This subject had two very similar and very quiet sleep nights, yet this subject's IEA frequency between sleep nights varied by more than 300%. The poor sleep found in these subjects was consistent with the findings from previous investigators discussed earlier who noted poor sleep quality in subjects with epilepsy (e.g., Hoeppner et al., 1984; Montplaisir, 1982).

In addition to sleep quality, the stage of sleep experienced by subjects during data collection should be considered a variable. Data were collected during the early and middle portions of a sleep night in subjects. These portions of sleep are generally characterized by less frequent and shorter episodes of REM sleep in normals. Stevens et al. (1971, 1972) and Kellaway et al. (1980) have reported sharp decreases in IEA frequency during REM sleep, although changes IEA frequency during non-REM sleep is unclear (Hamel & Sternman, 1982; Manni et al., 1990; Montplaisir, 1990; Sammaritano et al., 1991).

Records were not scored for sleep in the current study; yet the investigator noted that the record for the first night of Subject One contained no REM sleep. Variability in the sleep staging within subjects may have accounted for some of the IEA frequency variability.

As mentioned, data were collected from records which did not span the entire night. If data were collected from longer sleep periods which contained each subject's full sleep cycling (assuming complete cycling occurred), IEA frequency may have been more consistent among nights within subjects.

No clear pattern of overall IEA frequency emerged from the data which could be explained by identified influencing variables. The impact various combinations of variables or unforeseen variables may have had was undetermined.

Significant rhythms were displayed in four of five subjects. Some of these rhythms had periods consistent with periods of sleep cycles (e.g., 90 to 120 minutes). However, these rhythms maintained significance during sleep nights in which subjects may not have had normal sleep cylces as well as during sleep deprivation nights.

Perhaps the most important finding from the current study is the presence of significant rhythms of IEA frequency during sleep deprivation in all but one subject. In addition, rhythms were found during sleep deprivation whose periods matched those of rhythms in at least one sleep night in three subjects, and nearly so in a fourth subject. These

findings indicate that IEA frequency has rhythmicity independent of sleep.

The presence of IEA frequency rhythms during sleep deprivation is not completely consistent with the findings of Kellaway et al. (1980), who reported rhythms only during sleep. However, these investigators did not examine data from non-sleep episodes during the night hours. The rhythms they reported had periods of 84 to 120 minutes. The current study found rhythms with periods of 90 and 120 minutes. It is important to note that Kellaway et al. examined data from subjects with generalized epilepsy, whereas the current study examined data from subjects with focal epilepsy. Although etiological factors stemming from structural and/or gross biochemical processes define the neurophysiological differences between generalized and focal epilepsy, the epileptogenic neuronal mechanisms are similar, if not identical, in both types of epilepsies. Therefore, comparisons of findings between the current study with those of Kellaway et al. seem warranted.

The presence of IEA frequency rhythms during sleep and sleep deprivation in the current study is more consistent with the findings of Stevens et al. (1971, 1972). They reported rhythms during non-sleep states, but did not evaluate non-sleep states during the habitual sleep times of subjects. Rhythms with periods of 90, 124, and 164 minutes identified by Stevens et al. were also found to be significant in the current study.

The confirmation of rhythms identified by both Kellaway et al. and Stevens et al. is noteworthy. Similar findings occurred despite the differences in subjects' epilepsy types, IEA frequency calculations, and statistical analyses in these studies.

Rhythms found in the current study accounted for little of the variance in the data. However, the number of data points from each record ranged from 888 to 1656. Unless values are extremely consistent, the odds that so many data points will correlate highly to a fitted curve are limited. Indeed, the number of IEA discharges from individual 10-second epochs varied highly (from 0 to 25 in night 3 of Subject Four). Previous investigators did not report variance accountability levels. Consequently, it remains unclear as to whether the levels found in the current study are congruent with previous research. Despite the high variability in the data, it is noteworthy that significant rhythms were found at all.

Amplitudes of the rhythms found were low as well. Low amplitudes suggest that values for the variable of interest do not fluctuate greatly around the mesor (mean). Low amplitudes call into question the clinical importance of a demonstrated rhythm. However, the cosinor analysis utilized in the current study was performed on data tabulated from 10-second epochs, in order to represent real time more closely. The clinical utility of 10-second epochs is difficult to imagine. If data were condensed into larger

epochs, mesors, and possibly amplitudes, might be larger. Stevens et al. (1971, 1972) used 4-minute epochs; Kellaway et al. (1980) used 15-minute epochs. Although these epochs were larger, they were still of questionable clinical importance. Clinical utility may require epochs of 30 minutes or more in length. However, the current study tabulated data from records totaling no more than 4.50 hours. Utilization of 30-minute epochs in the current study would have provided too few data points for an appropriate analysis. In addition, such long epochs may have biased the fast Fourier transform and periodogram analyses into suggesting periods which would not have been significant. Longer epochs would have changed the values for time utilized in cosinor analysis. If true rhythms with low amplitudes and low variability accountability were present in the data, significance may have been lost by using longer epochs.

Another intriguing finding from the current study was the closeness of acrophases of like rhythms within a subject, regardless of sleep or sleep deprivation. This finding might suggest that sleep deprivation, as a possible modulator of IEA frequency rhythms, does not shift the phase of rhythms more than 30 minutes. This finding is consistent with the theory that IEA frequency has rhythmicity independent of sleep.

Other explanations are possible for the findings. The maintenance of significant rhythms between sleep and sleep deprivation nights, and the consistency of acrophases for

like rhythms may be the result of possible modulating effects of other variables. These possible modulators could include the suspected consistency among nights of sunlight and darkness, body posture, serum hormone and electrolyte levels, and body temperature. These possible modulators were not examined or taken into account in the current study, and hence, cannot be ruled out as explanations for the findings.

Still another alternative explanation for the findings may be the influence ongoing REM /non-REM rhythms had on IEA frequency. The similarity between some of the periods found in this study and the 90 to 100-minute REM /non-REM cycle (Johnson, 1980) is noteworthy. Some investigators have proposed that the REM /non-REM cycle continues throughout the day as part of the basic rest-activity cycle (BRAC) (Kleitman, 1963 as cited by Johnson, 1980; & Kerkhof, 1985). Consequently, any possible influence of this cycle may be seen during sleep deprivation nights. However, Johnson (1980) proposed that the REM /non-REM cycle is clearly a sleep-dependent rhythm. Regardless, the REM /non-REM cycle may have impacted IEA frequency rhythms with periods of 90 and 120 minutes.

Implications of Findings

The scientific implications of these findings are three-fold. First, confirmation of periodicity of IEA frequency is crucial in understanding the manifestation of IEA. This understanding is needed to interpret the findings of IEA research more accurately, to interpret EEG data more

accurately, and to design better research methods for many topics in epilepsy research. Second, confirmation of IEA periodicity supports chronobiological theories, including revisions to the homeostasis paradigm (which proposes that physiological mechanisms work to maintain biological values within a narrow and constant range). Third, confirmation of IEA periodicity may promote a better understanding of epileptogenic mechanisms and phenomena which may modulate those mechanisms.

The clinical implications of the findings of the current study are more obscure, and can only be speculative at this time. In general, clinical research utilizes a physiological knowledge base to discover, predict, and evaluate treatment modalities. The validity of clinical research is greatly hampered if this physiological knowledge base is limited or unknown. Chronobiological knowledge is part of a knowledge base for any given physiological phenomenon. The importance of chronobiological knowledge in clinical practice was discussed earlier. Chronobiological knowledge is prerequisite to employing chronotherapy (the timing of treatment to maximize treatment efficacy and minimize unwanted treatment effects). Epilepsy is a chronic disorder which is often difficult to manage. The application of chronobiological principles to epilepsy care is potentially an important adjunct to the treatment plan, although this potential is yet unrealized. The findings of the current study support chronobiological principles in epileptogenesis,

and can be used as a springboard for further research on this topic, with an ultimate goal of chronobiological clinical epilepsy research.

The findings of the current study contribute to understanding of the relationships between sleep and IEA manifestation described by numerous investigators. As discussed earlier, some epilepsies have been defined in sleep parameters. People with epilepsy have poorer sleep than non-epileptics. Poor sleep increases fatigue and may precipitate more seizures. Obviously, promoting optimal sleep hygiene is desirable in people with epilepsy. The current study suggests that continued research is needed to define the modulating relationships between sleep and IEA frequency. Knowledge generated from continued research may be applied clinically to improve sleep hygiene and possibly to minimize epilepsy manifestation.

Limitations of the Study

An obvious limitation to the current study is its lack of generalizability since only five subjects were examined. These subjects were homogeneous in seizure type and medications, and consequently, do not represent the epilepsy population. However, finding rhythms which matched the periods of rhythms found by others using different epilepsy populations was encouraging.

Another limitation was the inability to examine rhythms with periods greater than four hours, since data were not collected for longer time blocks. Consequently, the study

was not able to address the mathematical model of the circadian rhythm of IEA probability suggested by Kellaway et al. (1980). In addition, due to the large number of data points, graphs from the current study were too dense to evaluate the 15 to 20 minute periods of IEA cessation between IEA frequency rhythms noted by Stevens et al. (1971, 1972) and Kellaway et al. (1980). However, in examining the graphs provided in those investigators' reports, it is questionable whether these periods of IEA cessation are truly inter-rhythm phenomena, or simply troughs of ongoing IEA frequency rhythms.

The study did not include sleep scoring of the records. The lack of sleep scoring made it impossible to evaluate the extent a specific sleep stage may have influenced the study's results.

The study used multiple statistical tests of the data. The likelihood of finding significance by chance is increased when multiple tests are run. However, the high level of significance of many of the rhythms determined is encouraging. In addition, the assumption of stationarity for cosinor analysis was not met convincingly, since data were collected from short time blocks. The variable effect different sleep stages may have on IEA frequency poses a serious threat to this assumption.

Although the study described rhythms in sleep and sleep deprivation nights, the study did not test whether or not these rhythms differed significantly. In order to

demonstrate that rhythms did not change significantly, coherence analysis should be completed. This analysis would require a larger and more heterogeneous sample, data from larger time blocks, and better control of possible influencing variables. Coherence analysis would evaluate the consistency between the findings and the *a priori* hypothesis.

These limitations must be taken into account when interpreting the findings of the current study and determining its contribution to the body of IEA knowledge. The results obtained in the study do not address conclusively all questions regarding IEA chronobiology, thus continued research on this topic is indicated.

## Suggestions for Further Research

The findings of the current study could be enhanced in several ways. First, cosinor analysis could be performed on significant rhythms using data condensed into 4-minute and 15-minute epochs. This information would allow for better comparisons between the current study and previous investigations. Second, the EEG records could be scored for sleep. Information regarding which sleep stage was present during rhythm peaks and troughs would be most valuable, as well as information on what happens to IEA frequency during REM sleep. This information could be compared to the findings of previous investigations.

The current study was used as a pilot, in which methods could be assessed. For continued research on IEA chronobiology, subjects should remain on steady AED doses in

order to minimize the impact of this variable. Data should be tabulated from periods longer than 24 hours in order to address possible circadian rhythmicity.

If data are tabulated from such long blocks of time, one must seriously consider the practicality of hand-counting. The current study was extremely labor-intensive. Future researchers must weigh the reported inaccuracies of computer-assisted counting devices against the high cost of hand-counting. A compromise is possible. Parameters on computer devices could be calibrated to correspond with the unique IEA characteristics of individual subjects. In addition, randomly-selected time blocks could be chosen for data tabulation verification utilizing hand-counting. Computerized sleep scoring could be addressed similarly.

Subjects in future studies should be selected on the basis of overall IEA frequency. Stevens et al. (1971, 1972) and Kellaway et al. (1980) did not describe the IEA frequencies of their subjects. However, Martins da Silva et al. (1984) included subjects with IEA frequencies of 1 or more event per hour. Subjects with such low IEA frequencies (such as Subject One of the current study) may not provide enough events for statistical description of rhythms with short periods. It is unclear at this time which minimum IEA frequency would be most helpful.

Summary

This study identified significant rhythms of IEA frequency in four of five subjects with focal epilepsy during

periods of sleep. In three subjects, at least one rhythm maintained significance during a time-matched period of sleep deprivation. Some rhythms corresponded to rhythms found by previous investigators. Despite the variability in overall IEA frequency, acrophases of like rhythms occurred within 30 minutes of each other within subjects. These findings indicate that IEA frequency has rhythmicity characterized during sleep and sleep deprivation.

The findings of this study will contribute to the body of knowledge of IEA manifestation and its relationship to sleep. Study limitations including lack of generalizability, lack of sleep scoring of records, lack of data collected over entire sleep nights, and lack of coherence analysis indicate that continued research is indicated. This study should be used as a springboard for further research in order to prepare a knowledge base foundation for clinical research of IEA chronobiology.

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# Appendix A

## Protocol for Study

### Pre-Data Collection Period

1. Instruct staff nurses and EEG techincians on purpose of study and how the protocol may impact their routine duties before any subjects are included into the study.

2. When a patient is admitted to the Seizure Telemetry Unit, have the staff nurses ascertain the patient's usual bedtime and caffeine habits. Have the nurses promote the continuation of these habits.

3. The morning after a patient has spent the first night in the Seizure Telemetry Unit, have Laura Morehead verify that the nighttime EEG displays IEA.

4. Determine if patient meets all inclusion/exclusion criteria.

5. If criteria are met, seek participation in the study from the patient. The material detailed on the consent forms will be discussed in detail. All questions will be answered.

6. If the patient agrees to participate, and gives signed informed consent, the patient will become a subject in the study.

7. Obtain from the subject a detailed history of sleep habits, caffeine habits, exercise habits, seizure patterns, and medications as it pertains to this study. For women, determine menstrual cycle status.

8. Caffeine intake will be monitored and documented separately on the I/O sheet by the nursing staff.

9. All EEG electrode placement and instrumentation calibration will be done by the EEG technicians per routine.

10. EMG leads will be placed in the evening before the technicians leave for the day.

### Data Collection Period

1. The subject's second night in the unit will be Night # 1 for the study.

2. The investigator will arrive before the subject's bedtime.

3. Caffeine records for the day will be reviewed. Questions the investigator or subject may have will be answered.

4. The subject will go to bed at his or her accustiomed bedtime.

5. The investigator will maintain a sleep-conducive environment as much as possible. Lights will be off (except the infrared light needed to maintain visualization of the subject), doors closed, and noise kept to a minimum.

6. The subject will not receive any interruptions from staff (e.g. vital signs) unless medically indicated and ordered by the physician. Phlebotomy draws will be done at 1000, instead of 0600, unless contraindicated per physician order.

7. Any emergent care (e.g. seizure activity) will be provided by the investigator and staff nurses.

8. The investigator will monitor the cameras and video-cassette recorder during the night to ensure that they are running properly. The investigator will be responsible for videotape changes as is needed.

9. Night # 2 will continue the same protocol as above.

10. Night # 3 will be the sleep deprivation night.

11. On Night # 3, the investigator will arrive on the unit at the same time as the previous two nights.

12. The investigator will instruct the subject on the sleep deprivation aspect of the study.

13. The subject will be instructed to refrain from caffeinated beverages (since the subject is ordinarily asleep at this time), eating, or using the exercise bicycle. In order to reduce muscle artifact, the subject will be encouraged to maintain light activity such as reading a book or watching television.

14. At the accustomed bedtime, the investigator will leave the subject's room, and monitor the subject from the laboratory.

15. Two-way intercom will be used to alert the patient to stay awake if needed.

16. The investigator will alert the staff nurse before he leaves the unit to go home.

17. A four-hour epoch is desired from each night. The investigator must be confident that this data has been recorded before leaving the unit for the night.

18. Situations which might disrupt data collection (e.g. seizure activity) are described in the text of the study proposal, as well as how to manage data.

19. Only one subject at a time will be monitored in this study.

20. During each night, the investigator will maintain a narrative of pertinent information (e.g. problems, disruptions, time subjects went to bed, time investigator went home, etc.). This information will be used in data analysis as is needed.

Post-Data Collection Period

1. After data have been collected, the investigator will thank the subject for participating, and answer any questions the subject may have.

2. If a subject withdraws from the study, the investigator will assure the subject that no consequences will result, and thank the subject for his or her effort.

3. Once a subject has completed participation, the investigator will prepare for the inclusion of a new subject.

4. The investigator will notify staff that data collection for this subject has been completed, and that the protocol no longer needs to followed.

5. The investigator will print the data as is convenient to the Center's needs (data will most likely be printed after hours).

6. The investigator will begin data tabulation from the EEG record. Tabulation for one subject will be completed before tabulation begins on another subject. Data tabulation and data analysis will occur on a schedule determined by the investigator.

Appendix B

Consent Forms

Department of Veterans Affairs

# VA Research Consent Form

**Subject Name:** _____ **Date:** _____

**Title of Study:** Patterns of Interictal Epileptiform Activity During Sleep and a Time-Matched Period of Sleep Deprivation

**Principal Investigator:** Chad Ellis, RN **VAMC:** ext. 6133

## Description of Research By Investigator

TITLE: Patterns of Interictal Epileptiform Activity Frequency During Sleep and a Time-Matched Period of Sleep Deprivation

PRINCIPAL INVESTIGATOR: Chad R. Ellis, RN
220-8262 ext. 6133
Nsg 118-P Ward 5-D

PURPOSE:

This research study is designed to examine how short-term lack of sleep might change a person's brainwave pattern. This study will examine the electroencephalogram (EEG) record after it is collected during your stay in the Seizure Telemetry Unit.

PROCEDURES:

You have already consented to be videotaped and have your EEG recorded during your stay in the Seizure Telemetry Unit. This recording is routine procedure. Part of your stay includes staying up for a night to see if any changes occur on your EEG. This study will examine part of your EEG from three of the nights you stayed in the Unit.

For the purposes of this study, you will be asked to go to bed at your usual bedtime for two nights. You will also be asked to drink caffeinated beverages in amounts and at times you ordinarily do so at home and/or work. If you currently exercise regularly, an exercise bicycle will be provided. You should use the exercise bicycle at times you ordinarily exercise.

Subject's Identification (I.D. plate or give Name-last, first, middle)

Department of Veterans Affairs

# VA Research Consent Form

Continuation Page 2 of 4

**Subject Name:** _____ **Date:** _____

**Title of Study:** Patterns of Interictal Epileptiform Activity During Sleep and a Time-Matched Period of Sleep Deprivation

**Principal Investigator:** Chad Ellis, RN **VAMC:** ext. 6133

During the night you stay awake, you will be instructed to not drink any caffeinated beverages, eat any food, nor use the exercise bicycle. None of these procedures are experimental.

INCLUSION CRITERIA

You must meet the following conditions to be included into this study:

1. Have epilepsy
2. Are between ages 18-50 years
3. Usually go to bed between 9 pm and 1 am.
4. Give your signed consent to participate

RISKS:

This study will not add any health risks or side effects to your stay in the Seizure Telemetry Unit. Registered Nurses will be caring for you during your stay.

BENEFITS:

You will not personally benefit from this study, but by serving as a subject, you may contribute new information which may benefit patients in the future.

WITHDRAWAL FROM STUDY:

Your participation in this research study is voluntary, and you may withdraw from this study at any time without prejudice to yourself or to any future medical care with this institution or with the Department of Veterans Affairs (VA).

CONFIDENTIALITY:

The results of your participation in this study may be used for publication or for scientific purposes, but your identity will not be disclosed unless you give separate, specific consent to this, or unless as required by law.

Department of Veterans Affairs

# VA Research Consent Form



**Subject Name:** _____ **Date:** _____

**Title of Study:** Patterns of Interictal Epileptiform Activity During Sleep and a Time-Matched Period of Sleep Deprivation

**Principal Investigator:** Chad Ellis, RN. **VAMC:** ext. 6133

COSTS:

There will be no costs to you for participating in this study.

LIABILITY:

Every reasonable effort to prevent any injury that could result from this study will be taken. In the event of physical injuries resulting from the study, medical care and treatment will be available at this institution. For eligible veterans, compensation damages may be payable under 38 USC 251 or, in some circumstances, under the Federal Tort Claims Act. For non-eligible veterans and non-veterans, compensation would be limited to situations where negligence occurred and would be controlled by the provisions of the Federal Tort Claims Act. For clarification of these laws, contact District Counsel at (503) 326-2441. You have not waived any legal rights or released the hospital or its agents from liability for negligence by signing this form.

Department of Veterans Affairs

# VA Research Consent Form

(Continuation Page 4 of 4 )

**Subject Name:** _____ **Date:** _____

**Title of Study:** Patterns of Interictal Epileptiform Activity During Sleep and a Time-Matched Period of Sleep

**Principal Investigator:** Chad Ellis, RN **VAMC:** ext. 6133

RESEARCH SUBJECTS' RIGHTS: I have read or have had read to me all of the above. Chad Ellis, RN has explained the study to me and answered all of my questions. I have been told of the risks and/or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of VA or other benefits to which I am entitled.

The results of this study may by published, but my records will not be revealed unless required by law.

In case there are medical problems or questions, I have been told I can call Dr. Martin Salinsky at x 7019 during the day and the neurologist on call after hours. If any medical problems occur in connection with this study the VA will provide emergency care.

I understand my rights as a research subject, and I voluntarily consent to participate in this study. I understand what the study is about and how and why it is being done. I will receive a signed copy of this consent form.

_____ _____

Signature of Subject Date

_____ _____

Signature of Witness Witness (print)

_____

Signature of Investigator

IF MORE THAN ONE PAGE IS USED, EACH PAGE (VAF 10-1086A) MUST BE CONSECUTIVELY NUMBERED AND SIGNED.

OREGON HEALTH SCIENCES UNIVERSITY
Consent Form

TITLE: Patterns of Interictal Epileptiform Activity Frequency During Sleep and a Time-Matched Period of Sleep Deprivation

PRINCIPAL INVESTIGATOR: Chad R. Ellis, RN
220-8262 ext. 6133

PURPOSE:

This research study is designed to examine how short-term lack of sleep might change a person's brainwave pattern. This study will examine the electroencephalogram (EEG) record after it is collected during your stay in the Seizure Telemetry Unit.

PROCEDURES:

You have already consented to be videotaped and have your EEG recorded during your stay in the Seizure Telemetry Unit. This recording is routine procedure. Part of your stay includes staying up for a night to see if any changes occur on your EEG. This study will examine part of your EEG from three of the nights you stayed in the unit.

For the purposes of this study, you will be asked to go to bed at your usual bedtime for two nights. Also, you will be asked to drink caffeinated beverages in amounts and at times you ordinarily do so at home and/or work. If you currently exercise regularly, an exercise bicycle will be provided. You should use the exercise bicycle at times you ordinarily exercise.

During the night you stay awake, you will be instructed to not drink any caffeinated beverages, eat any food, nor use the exercise bicycle. None of these procedures are experimental.

RISKS:

This study will not add any health risks or side effects to your stay in the Seizure Telemetry Unit. Registered Nurses will be caring for you during your stay.

BENEFITS:

You will not personally benefit from this study, but by serving as a subject, you may contribute new information which may benefit patients in the future.

CONFIDENTIALITY:

All personal identification information will be removed from the data collected during this study. Records will be identified by a code number. Neither your name nor your identity will by used for publication or publicity purposes.

COSTS:

There will be no costs to you for participating in this study.

LIABILITY:

The Oregon Health Sciences University, as an agency of the State, is covered by the State Liability Fund. If you suffer any injury from the research project, compensation would by available to you only if you establish that the injury occurred through the fault of the University, its officers or employees. If you have further questions, please call Dr. Michael Baird at (503) 494-8014.

Participation in this study is completely voluntary. You may refuse to participate, or you may withdraw from this study at any time without affecting your relationship with or treatment at the Oregon Health Sciences University. No consequences to you health will result should you choose to withdraw from this study.

You will be removed from the study by the researcher only if you are unable to follow the procedures previously discussed or if you choose to withdraw.

Chad Ellis, RN (220-8262 ext. 6133) has offered to answer any questions you might have. You will receive a copy of this form.

Your signature below indicates that you have read the foregoing and agree to participate in this study.

_____ _____

Participant Date

_____ _____

Witness Date

# Appendix C

## Routine Montage Used for Study

| Channel | Electrodes |
|---|---|
| 1 | Cz -> C3 |
| 2 | C3 -> T3 |
| 3 | T3 -> T1 |
| 4 | T1 -> T2 |
| 5 | T2 -> T4 |
| 6 | T4 -> C4 |
| 7 | C4 -> Cz |
| 8 | Fp1 -> F7 |
| 9 | F7 -> T3 |
| 10 | T3 -> T5 |
| 11 | T5 -> O1 |
| 12 | Fp2 -> F8 |
| 13 | F8 -> T4 |
| 14 | T4 -> T6 |
| 15 | T6 -> O2 |
| 16 | Electrocardiogram |
| 17 | Electro-oculogram |
| 18 | Electro-oculogram |
| 19 | Electro-oculogram |
| 20 | Electromyogram |
| 21 | Time code |

Note: Montage assembled by Laura Morehead.

Montage Used for Two Nights for Subject Two

| Channel | Electrodes |
|---|---|
| 1 | Cz -> C3 |
| 2 | C3 -> T3 |
| 3 | T3 -> T1 |
| 4 | T1 -> T2 |
| 5 | T2 -> T4 |
| 6 | T4 -> C4 |
| 7 | C4 -> Cz |
| 8 | Fp1 -> T1 |
| 9 | T1 -> LOC |
| 10 | LOC -> T3 |
| 11 | T3 -> T5 |
| 12 | Fp2 -> T2 |
| 13 | T2 -> ROC |
| 14 | ROC -> T4 |
| 15 | T4 -> T6 |
| 16 | LOC -> ROC |
| 17 | Electrocardiogram |
| 18 | Electro-oculogram |
| 19 | Electro-oculogram |
| 20 | Electromyogram |
| 21 | Time code |

Note: Montage assembled by Laura Morehead.

Montage Used for Subject Five

| Channel | Electrodes |
|---|---|
| 1 | Fp1 -> F7 |
| 2 | F7 -> T3 |
| 3 | T3 -> T5 |
| 4 | Fp2 -> F8 |
| 5 | F8 -> T4 |
| 6 | T4 -> T6 |
| 7 | F7 -> F3 |
| 8 | F3 -> Fz |
| 9 | Fz -> F4 |
| 10 | F4 -> F8 |
| 11 | Cz -> C3 |
| 12 | C3 -> T3 |
| 13 | T3 -> T1 |
| 14 | T1 -> T2 |
| 15 | T2 -> T4 |
| 16 | T4 -> C4 |
| 17 | C4 -> Cz |
| 18 | Electrocardiogram |
| 19 | Electromyogram |
| 20 | Electro-oculogram |
| 21 | Time code |

Note: Montage assembled by Laura Morehead.

## Abstract

Title: Patterns of Interictal Epileptiform Activity Frequency During Sleep and a Time-Matched Period of Sleep Deprivation

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This descriptive study examined the temporal patterns of interictal epileptiform activity (IEA) frequency during sleep, and how those patterns were manifested during a time-matched period of sleep deprivation. Data were collected from EEG records from one to two nights of sleep and one night of sleep deprivation from a convenience sample of five subjects with partial epilepsy admitted to an inpatient epilepsy monitoring unit for diagnostic purposes. Subjects' accustomed sleep and caffeine habits were maintained during the study. Dosages of antiepileptic drugs, nicotine withdrawal, and seizure occurrence were not controlled. Data were analyzed with fast Fourier transforms and periodogram and cosinor analyses to identify periods of cycles and rhythm significance. Significant rhythms with periods of 2.75, 2.00, 1.50, and 1.00 hours were found in at least one night in four of five subjects. Other rhythms with periods of 0.75, 0.50, 0.40, 0.33, and 0.25 hours were found in various

nights. Four of five subjects had at least one significant rhythm during a night of sleep deprivation; three of five subjects had rhythms maintain significance during sleep and sleep deprivation. Acrophases of like rhythms occurred within 30 minutes of each other within subjects. This study found rhythms which were consistent with the significant rhythms reported by previous investigators. This study's findings indicate rhythmicity of IEA frequency independent of sleep, however other interpretations of the findings may be drawn. Although the sample size was too small to support generalization of the findings, the study provided suggestions for further research. Research of IEA chronobiology may lead to a better understanding of the sleep characteristics in people with epilepsy, as well as a better understanding of epilepsy manifestation.