ASYMMETRIES IN EEG SIGNAL PROPERTIES IN THOSE WITH TEMPORAL LOBE EPILEPSY AND PSYCHOGENIC NON-EPILEPTIC SEIZURES

By

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To my family and friends

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LIST OF ABBREVIATIONS

ADC	Analog to digital converter
AED	Anti-epileptic drug
ANOVA	Analysis of variance
AV	Amplitude variation
CPS	Complex partial seizure
DC	Direct current
EEG	Electroencephalogram
EMU	Epilepsy monitoring unit
Hz	Hertz (cycles per second)
ILAE	International League Against Epilepsy
IHA	Interhemispheric asymmetry
IRB	Institutional Review Board
MR-VAMC	Malcom Randall Veterans Affairs Medical Center
MUSC	Medical University of South Carolina
NTLE	Neocortical temporal lobe epilepsy
PLED	Periodic Lateralized epileptiform discharges
PNEE	Psychogenic non-epileptic events
PMRS	Pattern-match regularity statistics
REM	Rapid eye movement (sleep)
TLE	Temporal lobe epilepsy
UF	University of Florida
VEEG	Video EEG

Abstract of Thesis Presented to the Graduate School
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Epileptic seizures can appear clinically similar to psychogenic non-epileptic events (PNEE), which can lead to erroneous diagnosis and treatment. Differentiation of these two conditions often requires multi-day, in-patient video electroencephalogram (VEEG) monitoring to record seizures or seizure-like PNEE. Also, brief runs of "epileptiform" activity may be recorded during the times when seizures are not occurring; these periods of time are referred to as the interictal periods. However, if seizures and/or interictal epileptiform abnormalities are not noted during the VEEG monitoring, then a diagnosis cannot be made. Therefore, we developed a hypothesis-driven approach to distinguish those with epileptic seizures from those with PNEE by quantitative analysis of brief epochs of electroencephalogram (EEG) in the interictal period, when no epileptiform activity was present on visual inspection. Our goal in this hypothesis testing study was to investigate whether differences in measures of EEG signal inter-hemisphere asymmetry (IHA) exist between patients with a common form of epilepsy, temporal lobe epilepsy (TLE), and patients with PNEE.

Interictal EEG epochs (10 seconds each) were sampled from VEEG recordings obtained from 62 patients. A total of 620 epochs in the relaxed, awake state were

collected from TLE and PNEE patient groups. Within each EEG sample epoch, we calculated the signal regularity using the pattern-match regularity statistic (PMRS), and amplitude variation (AV). These calculations were performed in the F8, T4, F7, and T3 EEG channels utilizing a non-overlapping 5.12 second computation window. IHA values were then calculated as the absolute difference between left (F7 and T3) and right (F8 and T4) channels, with respect to PMRS and AV values, respectively.

We found that IHA of the PMRS from the temporal electrodes is significantly larger in patients with TLE than those with PNEE ($p=0.0182$). These results suggest measureable characteristics of the interictal EEG may be useful in distinguishing patients with TLE from those with PNEE.

CHAPTER 1
AN INTRODUCTION TO ELECTROENCEPHALOGRAPHY

A Brief History of Electroencephalography

EEG is a neurophysiologic tool by which temporal and spatial information about brain activity can be recorded. EEG electrodes can record brainwaves non-invasively by placing electrodes on the scalp or through invasive procedures brain activity can be recorded near or within brain tissue. However, scalp EEG recordings are the focus of the research performed in this thesis. Scalp EEG is widely used in many fields of neuroscience including neurology, psychology, sleep medicine, and neuroscience research.

The first electrical brain activity was recorded in animals by English physician Richard Caton (1842-1926) during the 1870s.(1) This brain activity was recorded using a galvanometer with a beam of light cast onto a mirror to reflect a large scale on a wall. However, it was Austrian neuropsychiatrist Hans Berger (1873-1941) who was deemed the father of encephalography.(1) Dr. Berger was the first to record a single channel of electrical brain activity in humans, and published this recording in 1929. He first used a sting Galvanometer (Figure 1-1), and later a double-coil Galvanometer.(2,3) Over the next several decades, several technological advances improved the quality of EEG records. Researchers began to use oscilloscopes to observe waveforms in real time. The quality of cerebral waveforms captured was improved by the development of amplifiers and filters. Also, over time the number of EEG electrodes used to record brain activity increased.

Beginning in the 1970s, mechanical apparatus used to capture and record EEG was replaced by computerized techniques.(2) Until the 1990s, centers utilizing EEG

relied on paper tracing and taped video recording of EEG data. However, since that time, most centers have begun store data using digital means, which provides greater opportunity for manipulation of the data after recording. As such, sophisticated techniques for EEG analysis have emerged.(4)

A standard system of electrode placement is essential for communication of EEG results between different laboratories. In 1958, Herbert Jasper proposed the 19 channel, International 10-20 system for electrode placement worldwide (Figure 1-2). Placement of electrodes in this system begins by distinguishing the sagittal anterior-posterior distance between the nasion and inion, placing the first two electrodes at distances 10 percent above those bony landmarks, then placing the additional electrodes in specified locations which are at 10 to 20 percent distances from previously marked landmarks. The International 10-20 system is still in place today, and was the electrode placement used for the recording of EEG data in this project.

Indications for EEG

Around the time Hans Berger was recording the first human EEGs, his observations primarily focused on describing normal human physiology. For example, he noted that alpha waves arising from the occipital region attenuated with eye opening.(1,5) As multi-channel EEG emerged, alterations in wave morphology were noted in the area of brain lesions. As such, EEG served as a non-invasive means of localizing focal, pathologic processes in the brain. Since the arrival of neuro-imaging techniques such a computed tomography and magnetic resonance imaging, EEG is not nearly so relied upon for its localizing capabilities. However, EEG remains a useful source of information that aids in diagnosis for many clinical scenarios.

Table 1-1 provides a full list of indications for EEG. However, EEG is most often used to evaluate for the presence of epileptiform appearing activity. Epileptiform activity refers to paroxysmal, sharply contoured or rhythmic activity that may be seen in the setting of epilepsy. Furthermore, the EEG can help clinicians to classify the type of seizure disorder and localize the "onset zone" of seizure activity. These concepts of seizure disorder classification and localization are discussed further in Chapter 2. Epileptiform activity may occur during the ictal or interictal period. The time during a seizure is referred to as the ictal period, and interictal period refers to the time in between seizures. During the interictal, brief epileptiform activity, generally lasting approximately 0.5 seconds to 3 seconds, may or may not be present. Interictal activity consists of sharply contoured "spikes" or "sharps," often with an after-going slow wave, higher amplitude activity than the background, and disruption of the background rhythm. (1,5) Examples of interictal epileptiform activity are displayed in Figure 1-3. Continuous ictal activity can be seen on an EEG throughout a seizure, and can last seconds to minutes, or occasionally even hours. This observation is true except in rare instances where seizure activity is confined to a small brain region that is not easily recorded with scalp EEG, such as in seizure localized to the orbital frontal regions or near the skull base. Figure 1-4 illustrates ictal activity localizing to the left temporal lobe. However, for this research project, we specifically selected 10-second samples of EEG data where no interictal or ictal epileptiform activity was visualized. This approach was important because an EEG recording may fail to demonstrate ictal or interictal epileptiform activity even if a patient has epilepsy. Increasing the time of the recording decreases the chances of missing epileptiform activity.(6)

As implied above, the duration of an EEG recording can vary from 20 minutes to several days depending on the goals of the study. Because the timing of seizure activity is largely unpredictable, baseline EEGs lasting 20 to 60 minutes generally capture the interictal period. As such, the baseline EEG is most useful for finding evidence of interictal epileptiform activity rather than ictal activity.

While EEGs recordings can last from minutes to hours to days, or even weeks, the goal of longer recordings is usually to capture seizures or ictal activity. To improve the chances of capturing seizures during a specific time, patients may be admitted into an epilepsy monitoring unit.(7,8) In these units, continuous EEG with video (VEEG) is performed. Also, provocation techniques such as tapering seizure medications, sleep deprivation, flashing lights, and hyperventilation may be used to increase the likelihood that a patient will have a seizure. All of the EEG data for this study was obtained by analyzing recorded VEEG data. This data was recorded in epilepsy monitoring units at the Medical University of South Carolina in Charleston, SC.

Technical Considerations in EEG Recording

The EEG recordings used for this project were digitally recorded. EEG data acquisition begins when electrodes placed on the on the scalp after cleaning the skin to remove oils and applying an ionic solution at the electrode site. This preparation allows current to flow from the neurons, through human tissue and an electrode wire, then into to a “jack box.” This direct current (DC) signal is adjusted with filters and amplifiers.

Once EEG data has been captured, it is digitized by an analog to digital converter (ADC). The ADC converts continuous information about EEG voltages into samples measured many times per second. In this study, a 256 cycles per seconds or hertz (Hz) sampling rate was used. Resolution of the EEG waveforms on a computer

monitor depends on the amount of data stored in bytes and the computer monitor screen resolution. For this study, a 12-bit recording system was used.

Montages

Voltage refers to the electric tension or potential between two points, and how voltage changes over time is the basis of EEG recordings. Since each EEG electrode is measuring current from a single brain region, a second comparison point must be used to measure the voltage between the two points.(1,5) The voltage between these two points is referred to as an EEG channel, and the two points in the channel may be adjacent electrodes, distant electrodes, or even a ground. The configuration of how electrodes channels are viewed on paper or a computer monitor is referred to as a montage.

Two main types of montages, the bipolar montage and the referential montage, are used in EEG recordings. When bipolar montages are used, each electrode is compared to an adjacent electrode in a chain-like fashion. Alternatively, referential montages produce EEG channels that compare each scalp electrode to one or two references. One advantage of using a referential montage is that all electrical amplitudes are compared to a single source. Hence, when looking at several channels, the channel with the largest amplitude waveform will be the source of that wave.(1) Also, since homologous electrodes on contralateral hemispheres (T8 on the right versus T7 on the left) will be equal distances from the reference, referential montages are ideal for assessing symmetry between the hemispheres. In our study, an average, referential montage was used. Voltage was measured by comparing the current in each electrode to the current at the mid-way point between the Cz and Pz electrodes.

Neurophysiologic Basis of EEG Activity

EEG waveforms are produced by current generated by neurons in the brain. These currents are produced by the flow of ions moving in and out of the extracellular space.(5) Single cell EEG recordings have demonstrated that waveforms noted on EEG are due to post-synaptic potentials which last 20-200 msec.(1) An excitatory post-synaptic potential (EPSP) occurs when positively charged sodium and calcium ions move into the intracellular space and the cell is depolarized. ESPS produce negative or upward deflected waveforms. Inhibitory post-synaptic potentials (IPSP) occur when cells become hyperpolarized from potassium moving out of the cell. IPSP produce downward or positive deflections. Also, an EEG best detects electric potentials that are a short distance from the scalp. As such, activity from neurons in the cerebral cortex is detected better than activity from deeper brain tissue.

Visual Analysis of EEG

Visual interpretation of EEG is a skill is mastered with years of experience, but the process that EEG readers, or encephalographers, follow can be broken down into steps including the evaluation of EEG frequency, rhythmicity, amplitude, symmetry, and synchrony. As an encephalographer scrolls through an EEG, one of the first characteristics noted is the frequency of EEG rhythms, which are measured in Hz. Brain wave activity falls into one of four frequency bands: beta (13-30 Hz), alpha (8.5-12 Hz), theta (4-8 Hz), delta (<4 Hz). Often overlapping frequencies are seen in the waveforms.

The next aspect of importance is amplitude, which is measured in microvolts (μV), and can range from low (0-25 μV) to moderate (25-75 μV) to high (>75 μV). Amplitude can be influenced by several factors, such as cortical injury, extra-axial fluid

collection (hematoma or hygroma), or increased skull thickeness, all of which can decrease the measured amplitude. Likewise, skull defect from fracture or craniotomy will decrease resistance and increase measured amplitudes.

Symmetry and synchrony are important to evaluate when determining if the left and right hemispheres of the brain are functioning similarly. If an EEG demonstrates symmetry, then equal frequencies and amplitudes are noted in the bilateral hemispheres. The EEG is synchronous if brain waves are appearing at the same points in time. Finally, brain activity can be quite rhythmic, generally with amplitudes waxing and waning in a clean sinusoidal pattern, or activity can be poorly sustained and non-rhythmical.

An additional essential skill in EEG interpretation is the ability to determine wake and sleep stages. These stages include: alert awake, relaxed awake, drowsy, N1 and N2 sleep or “light sleep,” N3 sleep, also known as slow wave sleep or deep sleep, and rapid eye movement (REM) sleep. Each stage has a characteristic pattern of brain activity on EEG.(5) Wakefulness is dominated by the presence of low amplitude beta and alpha rhythms, which attenuate, or decrease in amplitude, with eye opening. In stage N1 sleep, beta and alpha range frequencies are replaced by upper-range theta activity, and this is noted maximally in the occipital head regions. Continued infusion of slower theta rhythms occurs during stage N2 sleep along with the appearance of intermittent beta-range spindle activity in the central brain regions. Stage N3 is characterized by the presence of mixed low to moderate amplitude theta and high amplitude delta rhythms. Finally, REM brain activity is similar to that during wakefulness; however, it is slightly slower with predominantly low amplitude alpha and

theta rhythms. Also, sharply contoured, theta range “saw-tooth” waves may be seen in the central regions.

In this research project, we collected samples of EEG data in the relaxed, awake state during eye closure when alpha activity was apparent in the posterior (occipital) channels. This stage was selected because it is the easiest to recognize and would be fast to capture on a short duration EEG, and our long-term goal is to reduce the recording time and amount of EEG data needed to differentiate patients with epilepsy and non-epileptic events.

Cellular Substrates of Brain Rhythms

The cellular substrates of these brain rhythms are partially understood and described.(5) Diffuse delta waves seen in normal sleep states originate from oscillations of transient calcium currents between the thalamus and cortex. Theta activity is most commonly noted during stage N1 and N2 sleep. Though the pacemaker source for theta activity remains unclear, the medial septum and its connections to the supramammillary nucleus of the hypothalamus and brainstem reticular formation are involved. Alpha activity is seen maximally in the occipital visual cortex and is referred to as the posterior dominant rhythm. This rhythm has also been recorded in the pulvinar and lateral geniculate nucleus of the thalamus. As such, thalamocortical linkages appear to be important in the generation of this activity, which is most prominent in the relaxed wake state with eyes closed. Finally, faster beta frequencies predominantly seen in the awake, alert state are thought to originate from diffuse connections made by the mesencephalic reticular formation and intralaminal nuclei of the thalamus.
For the purposes of this study, our focus was on the right-left symmetry of amplitude variation and signal regularity of brain rhythms in the anterior temporal regions.

Table 1-1. Clinical indications for obtaining an EEG

Indication	Example
Diagnosis of seizures disorders	Prevalence of spike or sharp waves, or rhythmic delta or theta range activity
Classification of seizure disorders	Focal or Generalized
Localization of seizure onset zones	Left or right Frontal Temporal Parietal Occipital Generalized
Identification of neurologic disorders with classic EEG patterns including:	Herpes Simplex encephalitis-PLEDS Creutzfield-Jakob disease-periodic frontal sharp waves Subacute sclerosing panencephalitis-high voltage bifrontal spikes
Confirmation that altered mental status is not due to seizure	Encephalopathy Syncope Psychogenic episode
Confirmation of brain death	Electro-cerebral silence
Prognosis in coma	Based on background pattern, presence or absence of seizure activity, and reactivity to stimuli
Confirmation of diagnosis of sleep disorders	EEG channels used in polysomnography, and the multiple sleep latency test

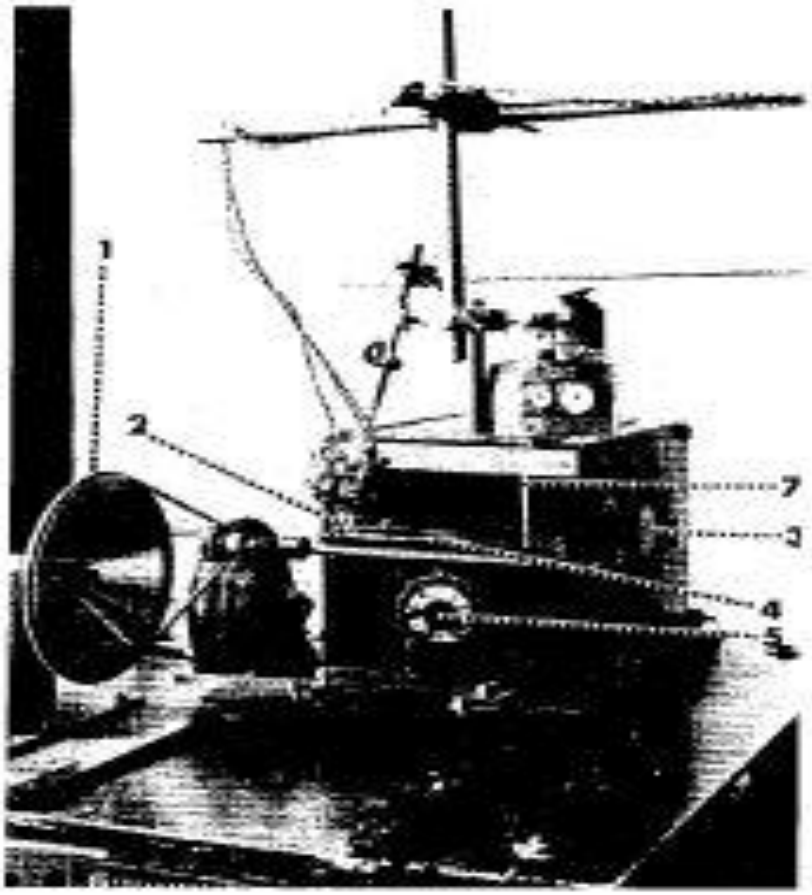


Figure 1-1. Hans Berger's first string Galvanometer Electroencephalogram. Items indicated on the figure are as follows: 1) crank, 2) marker fibers, 3) on/off switch (far right), 4) lens, 5) diaphragm, 6) paper box, 7) tuning fork. Reproduced with permission from Elsevier from the journal article: Gloor, P. Hans Berger and the discovery of the electroencephalogram. Electroencephalography and Clinical Neurophysiology.1969; S28:1–36.

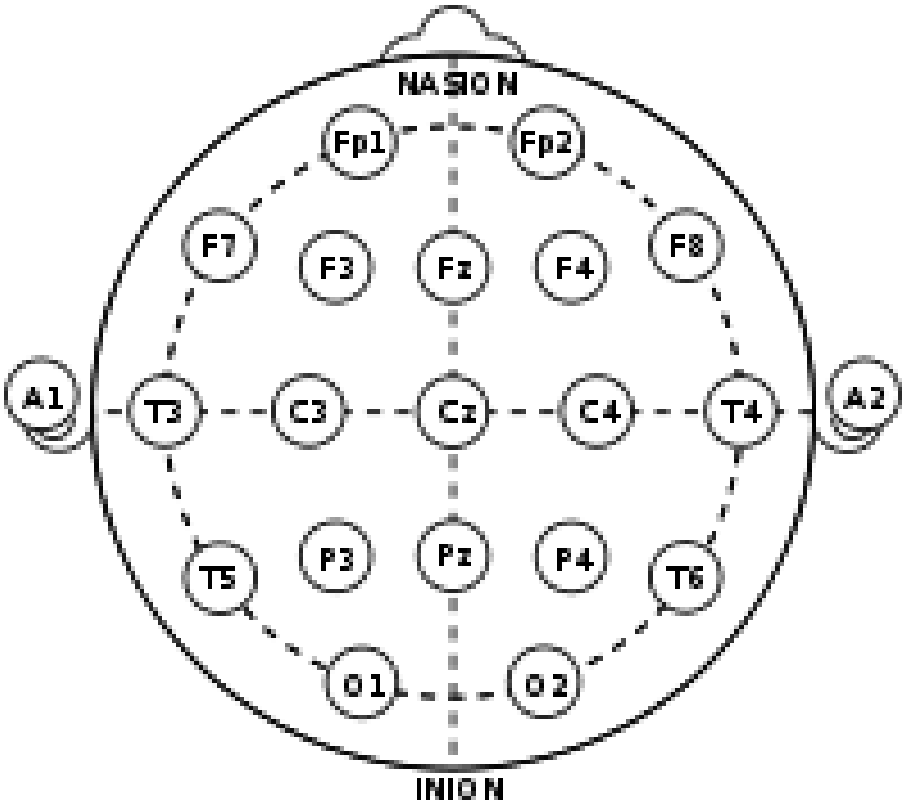


Figure 1-2. The International 10-20 System for Scalp Electrode Placement. Reproduced from the Wikipedia Commons freely licensed media file repository.

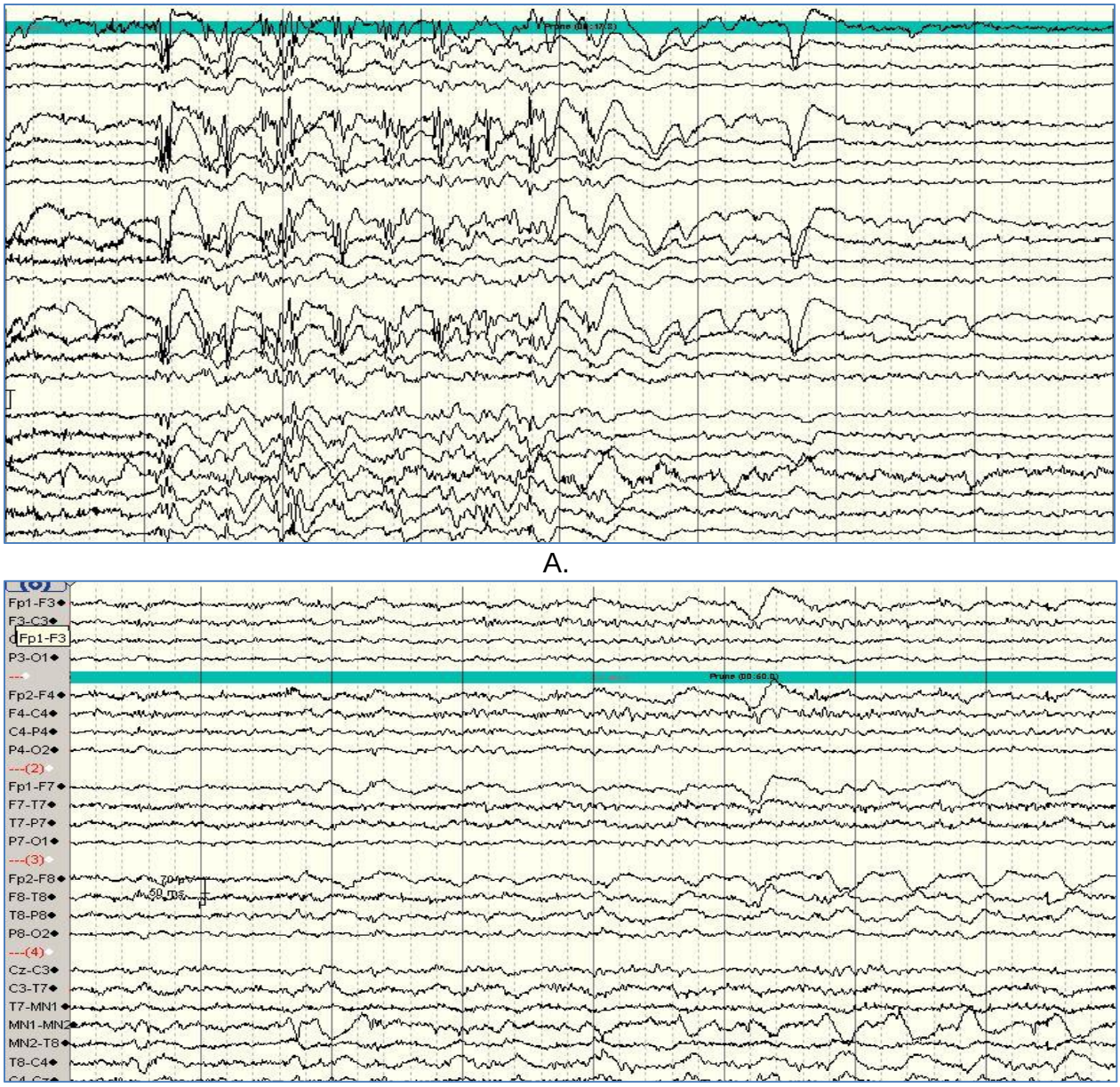


Figure 1-3. Wave discharges. A.). Diffuse, anteriorly maximal 3 hertz polyspike-wave discharges due to primary generalized epilepsy. B.) Right temporal sharp-wave discharge followed by a run of temporal intermittent rhythmic delta activity (TIRDA). Both sharp waves and TIRDA are commonly noted in patients with Temporal lobe epilepsy.

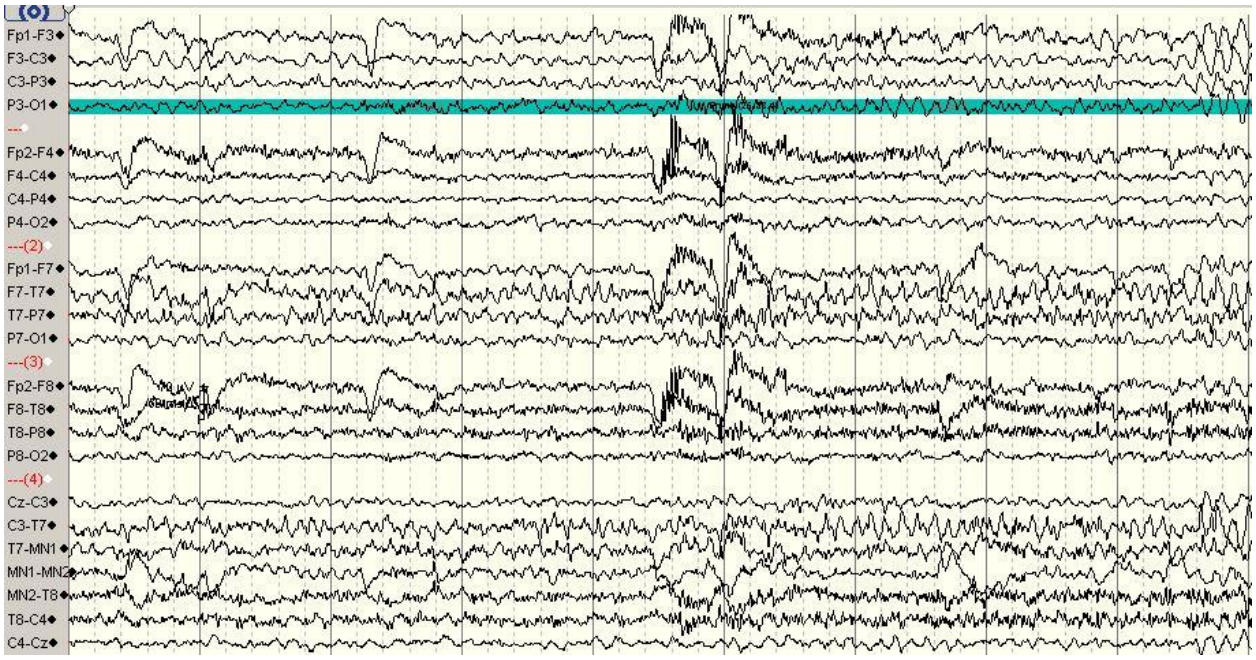


Figure 1-4. Rhythmic and sharply contoured, 7-8 Hertz theta activity at the onset of a focal seizure localizing to the left temporal lobe.

CHAPTER 2
EPILEPSY AND NON-EPILEPTIC EVENTS

Introduction to Epilepsy

Epileptic seizures are transient signs and symptoms due to abnormal excessive or synchronous neural brain activity.(9,10) Likewise, epilepsy is a brain disorder characterized by recurrent and unprovoked seizures. Epilepsy is the second most common disorder of the central nervous system, after stroke, and affects about 0.4–1% of the population.(11) An estimated 40 million people worldwide have epilepsy. (10) The term seizure, going back to its origin in Greek, means “to take hold.” An epileptic seizure is due to abnormally excessive or synchronous neuronal activity in the brain.(9)

During the onset of an epileptic seizure (i.e., the ictal period), synchronous and rhythmic discharges may originate from one part of the brain (focal or localization-related seizures) or begin simultaneously in both sides of the hemispheres (generalized seizures).(10) After the onset, focal seizures may remain localized within one part of the brain or propagate to the other side of the hemisphere and cause a wider range of synchronous neuronal activity (secondarily generalized seizures).

This research project focuses on differentiating a specific type of type of focal seizure disorder, temporal lobe epilepsy (TLE), from a condition called psychogenic, non-epileptic event (PNEE). TLE was chosen because it is the most common type of focal epilepsy seen in epilepsy monitoring units.(12,13)

Distinguishing epileptic seizure from PNEE can be difficult, as clinically they can appear quite similar.(14,15) However, making the correct diagnosis is important because therapies for the two diagnoses differ greatly. Epileptic seizures are treated with oral anti-epileptic medications, epilepsy surgeries, and special diets. Conversely,

PNEE are treated with psychotherapy, specifically, cognitive behavioral therapy. Psychotropic medications may be helpful as well.(16)

In this chapter, classification of epileptic seizure disorders is discussed to help the reader understand how a diagnosis of TLE is made. Next, clinical and EEG features of TLE will be discussed. Finally, diagnostic challenges in distinguishing epilepsy, including TLE, from PNEE are explained.

Classification of Epilepsy

Epileptic seizures are classified by type for the purposes of formulating appropriate treatment plans and offering prognosis. The most widely used system is that proposed by the International League Against Epilepsy (ILAE).(9,10) Originally drafted in 1989, this classification system was updated in 2001 and 2010. In the most recent version, a five dimension approached is used.

Dimension 1 is focused on localization of the seizure onset zone based on all known clinical data, including information obtained during the history, clinical exam, EEG, and neuro-imaging. Despite large advances in neuro-imaging over the last several decades VEEG remains the gold standard for determination of seizure onset zones.(8,14) While Dimension 1 describes the brain localization of seizure activity, it does not provide information on what type of seizures are experienced. This information is covered in Dimension 2. Most commonly, the ILAE International Classification of Epileptic Seizures is used for this purpose. This system was initially developed in 1964 and revised in 1981. The revised version categorizes seizures based on an electroclinical approach, meaning a combination of signs and symptoms during seizures and EEG findings. Dimension 3 of the ILAE classification system describes the etiology of the epileptic seizures. Dimension 4, while not particularly

useful for localization, helps to describe the severity of the condition by documenting the frequency of seizures. Finally, Dimension 5 lists related medical information that may be helpful in identifying an epileptic syndrome or seizure onset zone. This information may include focal neurologic deficits or seizure triggers.

Temporal Lobe Epilepsy

As described in dimension 1 of the ILAE classification system, localization of seizure onset zone is determined by using all available data from a patient's history, neuro-imaging, and EEG. Seizures may be focal or generalized in onset, and approximately 50% of epilepsies are focal in onset. The ILAE Commission (1989) classifies focal epilepsies according to their anatomical origin. Focal epilepsies may localize to the frontal, temporal, parietal, or occipital brain regions. Localization to the temporal region is most common, as such, the temporal lobe is considered the most epileptogenic region of the brain.(17) The true prevalence of temporal lobe epilepsy (TLE) is unknown. However, in the setting of medically refractory epilepsy patients undergoing video EEG monitoring, approximately 2/3 of focal epilepsies localize to the temporal lobes.(12,13)

Many etiologies of TLE exist. These etiologies include: current or past central infection system infections (herpes encephalitis, bacterial meningitis, neurocysticercosis), trauma brain injury that leads encephalomalacia and/or cortical scarring, cortical developmental abnormalities, hamartomas in neurocutaneous disorders, brain tumors (meningiomas, gliomas, gangliomas), vascular malformations (arteriovenous malformation, cavernous angioma), and paraneoplastic syndromes (anti-Hu , or NMDA-receptor antibodies).(17) Often, the cause is said to be either cryptogenic, meaning the cause is presumed but has not been identified, or idiopathic,

which may imply a genetic predisposition. Febrile seizures during infancy and childhood can lead to TLE later in life.

Seizure Semiology in TLE

TLE seizures are usually brief, lasting 2-3 minutes. These events may be preceded by a warning or “aura.” Olfactory, auditory, gustatory, and visual hallucinations may occur.(10,17,18) Patients may report distortions of sound or changes in the shape, size, and distance of objects. Things may appear shrunken (micropsia) or larger (macropsia) than usual.(17) Also, those with TLE may experience an aura of vertigo.

Psychic phenomena, such as a feeling of *déjà vu* or *jamais vu*, or a sense of familiarity or unfamiliarity, are common auras in TLE. Patients may experience depersonalization (i.e., feeling of detachment from oneself) or derealization (i.e., surroundings appear unreal). They may also report a sense of dissociation or autoscopy, in which they report seeing their own body from outside. Additionally, unexplained fear or anxiety may precede temporal lobe seizures. Often the fear is strong, and described as a feeling of impending doom.(17) TLE aura can also be in the form of autonomic phenomena which may include changes in heart rate, piloerection, and sweating. Patients may experience an epigastric "rising" sensation or nausea.(10)

Following the aura, a temporal lobe complex partial seizure commonly begins with a motionless stare, dilated pupils, and behavioral arrest. Oral alimentary automatisms such as lip smacking, chewing, and swallowing may be noted. Ipsilateral manual automatisms or contralateral dystonic posturing of a limb also may be observed.(17,18) Patients may continue their ongoing motor activity or react to their surroundings in a semi-purposeful manner (i.e., reactive automatisms).

A complex partial seizure may evolve to a secondarily generalized tonic-clonic seizure. Often, the documentation of a seizure notes only the generalized tonic-clonic component of the seizure. A careful history from the patient or an observer is needed to elicit the partial features of either a simple seizure or a complex partial seizure before the secondarily generalized seizure is important.

Patients usually experience a post-ictal period of confusion, which may help distinguish TLE from PNEE, as those with PNEE sometimes have an immediate return to baseline responsiveness. (14,19) In TLE, post-ictal aphasia suggests onset in the language-dominant temporal lobe. (10)

Electroencephalographic Characteristics of TLE

In temporal lobe epilepsies the interictal scalp EEG may show the following:

- -no abnormality.
- -unilateral of bilateral slowing of cerebral activity in the temporal EEG channels.
- -unilateral or bilateral epileptiform spikes, sharp waves and/or slow waves (1,10)

During a seizure, ictal EEG activity may begin at the time of aura onset or not until a complex partial seizure begins. Ictal activity includes:

- -a sudden unilateral or bilateral interruption of background activity
- -temporal or multilobar low-amplitude fast activity,
- -temporal or multilobar moderate-amplitude rhythmic spikes, sharps, or slow waves.

Psychogenic Non-epileptic Events

PNEE are paroxysmal changes in behavior that resemble epileptic seizures, but have no electrophysiological correlate or clinical evidence for epilepsy.(16) Also, positive evidence for psychogenic factors that may contribute to these events are often present. Point prevalence of PNEE has been estimated to be low in the range of one person per 30,000–50,000. The incidence rate is equivalent to 4% of that of

epilepsy.(20) None the less, approximately 25-30% of patients undergoing in-patient video EEG monitoring for medically refractory epilepsy have PNEE.(16) A major complication to the issue is that between 5 and 40% of the patients with PNEE have a concomitant diagnosis of epilepsy or have a past history with epileptic seizures.(16)

Clinical Manifestations of PNEE

PNEE are more often composed of purposeful, asynchronous, apparently consciously integrated motor activity such as thrashing movements of the entire body, opistotonic posturing of trunk, out-of-phase limb movements, side-to-side head movements, forward pelvic thrusting.(19,21) PNEE patients were more likely to have forceful sustained eye closing at any stage of the seizure and jaw clenching in the tonic phase of convulsive seizures.(22,23) PNEE is often accompanied by moaning, crying (ictal weeping), and stuttering throughout the events. (19,24) The most common ictal characteristic of PNEE was unresponsiveness without predominant motor manifestations.(19)

Patients with PNEE often describe fluctuating, but more or less continuous, levels of conscious mental activity during their events without the discrete gaps of missing memory that are characteristic of the impaired consciousness during complex partial epileptic seizures.(19) More often than in epilepsy, PNEE occur in the presence of others and have a more gradual onset (slow increase of symptoms) with abrupt recovery.(14,19) Pre-ictal pseudosleep, in which the seizure arises while the patient seems to be asleep despite electrographic evidence of wakefulness, has been reported to be specific for PNEE.(19) Autonomic changes can occur with epileptic seizures and PNEE (e.g., coughing, palpitations and pupillary dilatation). In the setting of PNEE,

these autonomic symptoms are likely part of the heightened arousal response attached to panic or other extreme emotional states.

Etiologies of PNEE

PNEE are almost infinitely heterogeneous and are quite different from person to person. Even if the PNEE behaviors of very different people are morphologically similar, clinical experience reveals that the psychogenic causes may be quite divergent.(16,19)

Psychological factors describe the underlying causation of these seizure-like behaviors. A common factor is a history of abuse during any time in life prior to PNEE onset. Abuse may have been sexual (most common), physical, or verbal. (16,19) While not all patients who have suffered from abuse will develop PNEE, the risk for developing PNEE is clearly increased. Other common examples of such psychological etiology may be personality disorders, post-traumatic stress disorder, malingering, depression or chronic anxiety, dissociation, somatization disorder, behaviorally oriented concepts of secondary gain and assumption of the sick role (mainly in intellectually impaired persons), personality disorders, and organicity.

Shaping factors are also important in the development of PNEE.(16,19) These factors contribute to “shaping” the symptoms in the form of seizures-like events, as opposed to other movement disorders or other somatic symptoms. A well-known shaping factor is living with a relative who has epileptic seizures.

Differentiating Epilepsy from PNEE

The gold standard diagnostic modality for distinguishing PNEE from epilepsy is inpatient continuous VEEG monitoring.(7,14) However, there are many limitations to this procedure. First, in order to make a diagnosis, patients must stay in the hospital until all of their typical seizure-like events are recorded. A typical stay is 3 to 5 days.

VEEG monitoring is a resource that is not universally available, especially in rural areas, and patients with PNEE are misdiagnosed with epilepsy for an average of 7 years.(19) Furthermore, once undergoing VEEG, if one does not have their events before discharge, then a definitive diagnosis cannot be made. Also, VEEG can be quite expensive depending on the patient's insurances provider's willingness to pay for the procedure. In some cases, hospital bills for thousands of dollars may be charged to the patient. As a common seizure provocation technique, patients are taken off their seizure medications either immediately or over several days; the speed of removal depends on baseline seizure frequency. Those with epilepsy are at risk for prolonged seizures, status epileptic, need for intubation, transfer to an intensive care unit, and injury. All patients can suffer side effects from rapid withdraw of seizure medication. For all the reasons listed above, a need exists for the development of alternative diagnostic techniques whereby PNEE can be distinguished from epilepsy. This technique should be one that can be performed safely and in the out-patient setting.

CHAPTER 3
MEASURING INTRAHEMISPHERIC EEG ASYMMETRY IN TLE AND PNEE

Asymmetry of EEG activity: In the setting of focal epilepsy, single photon emission tomography, positron emission tomography, and magnetic resonance spectroscopy studies have revealed that, interictal hypoperfusion, glucose hypometabolism, decreased benzodiazepine binding, and metabolic disturbances lateralized to the side of an epileptic focus or "onset zone."(25) These findings are even true when conventional computed tomography or magnetic resonance imaging studies fail to identify a lesion. Studies utilizing spectral power analysis, a technique that measures the amplitude of physiologic frequency bands, have shown greater entropy of the spectral power in electrodes where interictal discharges appear.(26) This findings provides electrophysiological evidence of brain activity asymmetries in focal epilepsy.

Furthermore, previous research has demonstrated that analyzing hemispheric asymmetries in EEG characteristics may be useful for differentiating focal epilepsy from other controls. For example, when comparing patients with focal epilepsy with normal controls or controls with tension headache, those with focal epilepsy had greater left-right asymmetry of total power and alpha power than the control groups.(27) Also, greater asymmetries in sleep spindle intensity (amplitude) have been noted in those with focal epilepsy than those with idiopathic generalized epilepsy.(25) Furthermore, those with focal epilepsy demonstrated decreased synchrony of brain activity in the area of seizure onset zone than non-seizure producing brain regions. These epileptic subjects also have decreased overall brain synchrony when compared to subjects with chronic facial pain. (28)

For the purpose of this study, we used a novel approach and compared the (left-right) interhemispheric asymmetry (IHA) of two quantitatively derived EEG variables of 1) signal regularity and 2) amplitude variation in patients with TLE and PNEE. The first variable was the pattern-matched regularity statistic (PMRS) and the second was the amplitude variation (AV). Both are discussed below.

Pattern-match regularity statistic (PMRS): Motivated by calculations of approximate entropy in thermodynamic systems, the PMRS is a probabilistic statistic quantifying signal regularity, as shown in Equation 3-1.(29,30)

Pr{difference of the next points of *xi* and *xj* <r | *xi* and *x j* and value matched} (3-1)

This variable has previously been shown to be useful in a seizure prediction model.(31) The rationale of applying this pattern match method (instead of amplitude or "value" match) is that pattern match is more robust compared to scalp amplitude match, which are usually more unstable than their up-and-down trends.(6) The procedure for calculating PMRS is described below:

Given a time series $U = \{u_1, u_2, \cdots, u_n\}$ with standard deviation σ_n, a tolerance coefficient e, and a fixed integer m, the two segments in U ($x_i = u_i, u_{i+1}, \cdots, u_{i+m-1}$, $x_j = u_j, u_{j+1}, \cdots, u_{j+m-1}$) are considered pattern-matched to each other when Equation 3-2 is fulfilled.

$$u_i - u_j \leq e\sigma_n \wedge u_{i+m-1} - u_{j+m-1} \leq e\sigma_n \wedge sign\ u_{i+k} - u_{i+k-1} = sign\ u_{j+k} - u_{j+k-1}, k = 1,2,\cdots,m-1 \quad (3\text{-}2)$$

In Equation 3-2, the first two criteria require value match to some extent at both the beginning and ending points of two segments, where e was set to be 0.2 empirically.

The third criterion requires pattern match between x_i and x_j within a range of m (set as 3 in this study). To calculate PMRS, we first define a conditional probability, p_i.

$$p_i = Pr\ sign\ u_{i+m} - u_{i+m-1} = sign\ u_{j+m} - u_{j+m-1}\ \ x_i and\ x_j\ are\ pattern\ match \quad (3\text{-}3)$$

Given m, p_i can be estimated as p_ι as in Equation 3-4.

$$p_\iota = \frac{\#\ of\ \begin{matrix} x_j's\ pattern\ match\ with\ x_i\ \wedge \\ sign\ u_{i+m} - u_{i+m-1} = sign\ u_{j+m} - u_{j+m-1}) \end{matrix}}{\#\ of\ \ x_j's\ pattern\ match\ with\ x_i}, 1 \le j \le n-m \quad (3\text{-}4)$$

In Equation 3-5, $1 \le i \le n-m$. Finally a *PMRS* can be estimated.

$$PMRS = -\frac{1}{n-m} \sum_{i=1}^{n-m} \ln(p_\iota) \quad (3\text{-}5)$$

As the time series U develops into a more regular state, p_ιs become larger and *PMRS* decreases as a result.

Amplitude variation: Amplitude variation (AV) is simply the standard deviation of the EEG amplitudes within a detection window. This variable has been used in seizure prediction models. (29,31). However, as far as the investigators in this study are aware, neither the PMRS nor AV have not yet been applied to interictal EEG samples for the purpose of distinguishing those with epilepsy from controls.

CHAPTER 4
STUDY DESIGN AND OUTCOME

In this study, we tested our hypothesis that inter-hemispheric asymmetry (IHA) of the interictal EEG is greater in those with temporal lobe epilepsy (TLE) than those with PNEE. We compared IHA of signal regularity using the pattern-match regularity statistic (PMRS) and the IHA of amplitude variation (AV). The PMRS calculates the probability that two points will have the same change in slope at the same time, given that two previous points were patterned matched. Further details on the PMRS can be read in the paper by Shiau et al., Cybernetics and Systems Analysis 2010.(29)

Methods

All EEG data for the project were recorded in the adult Epilepsy Monitoring Unit at the Medical University of South Carolina (MUSC) in Charleston, SC USA. Collection and analysis of the EEG data were approved by the MUSC Institutional Review Board (IRB), and participants signed informed consent prior to inclusion. EEG samples were collected and analyzed at Optima Neuroscience in Alachua, FL, USA.

Subjects' data were included in the study if a diagnosis of TLE or PNEE was confirmed based on a single or multiple typical events having been recorded on VEEG. All subjects were adults age 18 years or old. Exclusion criteria included VEEG recordings where a diagnosis was not confirmed because the subject did not have events during the recording. Also, subjects' data were excluded if both epileptic and PNEE were recorded from the same individual, or if epileptiform ictal activity localized to other brain regions besides the temporal lobes.

EEG recordings were obtained using the XLTEK EEG monitoring systems (Oakville, Ontario, Canada) with a 256 Hz sampling rate. A 19-electrode scalp

electrode configuration was used according the international 10–20 system (Fig. 1-2). A referential montage was utilized and the referential channel was at a location between Cz and Pz. In order to reduce the effects from muscle and movement artifacts, each of the EEG signals were band-pass filtered with a low cut filter = 1 Hz and high cut filter = 20 Hz. Interictal EEG epochs (at least 10 seconds each) were sampled from recordings obtained from 61 patients (29 with PNEE and 32 with TLE {Left temporal onset in 14, right temporal onset in 10, and independent bilateral temporal onsets in 8}). A total of 610 epochs (10 epochs from each recording) in the relaxed, awake state were sampled from TLE and PNEE patient groups. To reduce confounding effects, included interictal EEG epochs were constrained to the following three conditions: 1) no epileptiform discharges; 2) no eye-blinking; and 3) presence of a clear bi-posterior alpha rhythm.

Within each EEG sample epoch, we calculated the PMRS and AV in the F8, T4, F7, and T3 EEG channels utilizing a non-overlapping 5.12 second computation window. IHA values were calculated as the difference between right (F8 and T4) and left (F7 and T3) channels, with respect to PMRS and AV values, respectively. Within each recording, outlier PMRS and AV values were excluded using Grubb's test. Both the PMRS and AV variable were found to follow a non-normal distribution (Figure 4-3). The Whitney-Mann-U test was used to test for significant differences ($p<0.05$) in the inter-hemispheric differences between the two groups.

For a priori power analysis, we are planned a study with 30 TLE subjects and 30 PNEE subjects. The mean and standard deviation of the IHA of the PMRS and AV were not known. The PMRS value (unilateral meansurement) was known to range from approximately 0.01 to 0.06. The AV value (unilateral measurement) was known to

range from approximately 1 to 10. For the IHA of the PMRS, a power of 0.995 was calculated based on a standard deviation 0.02, if the true difference in the TLE and PNEE group means was 0.03. A type I error probability of 0.05 was used. A power of 0.861 was calculated for the IHA of the AV assuming a standard deviation of 2.0 and a true differences in the group means of 2.5, with a Type I error rate of 0.05.

Results and Conclusion

Both groups included more females than males (TLE 20/29, PNEE 23/32), and gender ratios were not significantly different (p=0.8035) (Figure 4-1). The mean age was 36.9 years in the TLE group and 43.3 years in the PNEE group, but the age differences were not significant (p=0.6030) (Figure 4-2). Although length of EEG recording was longer in the TLE group than the PNEE group (84.50 hours versus 70.56 hours), these values were not significantly different.

A total of 71 outlier values were excluded (60 AV and 11 PMRS). No significant difference was found in AV IHA values (2.9261 vs. 2.6379, p=0.5065) (Figure 4-5). However, TLE samples had significantly higher PMRS asymmetry than PNEE (0.0399 vs. 0.0196, p=0.0182) (Figure 4-4).

We calculated the sensitivity of the PMRS for separating out TLE from PNEE groups, based on empiric “true positive” PMRS values being greater than the mean PMRS asymmetry value for the PNEE (control) group +2 standard deviations (0.0196 + (2*0.01388)). Therefore, all PMRS values ≥ 0.04736 were considered positive. Based on this calculation, 11/32 TLE patients had positive values and the sensitivity of this test was only 34.3%.

We found that IHA of the PMRS from the temporal electrodes is significantly larger in TLE subjects than in NES subjects. Our finding is likely due to interruptions in signal

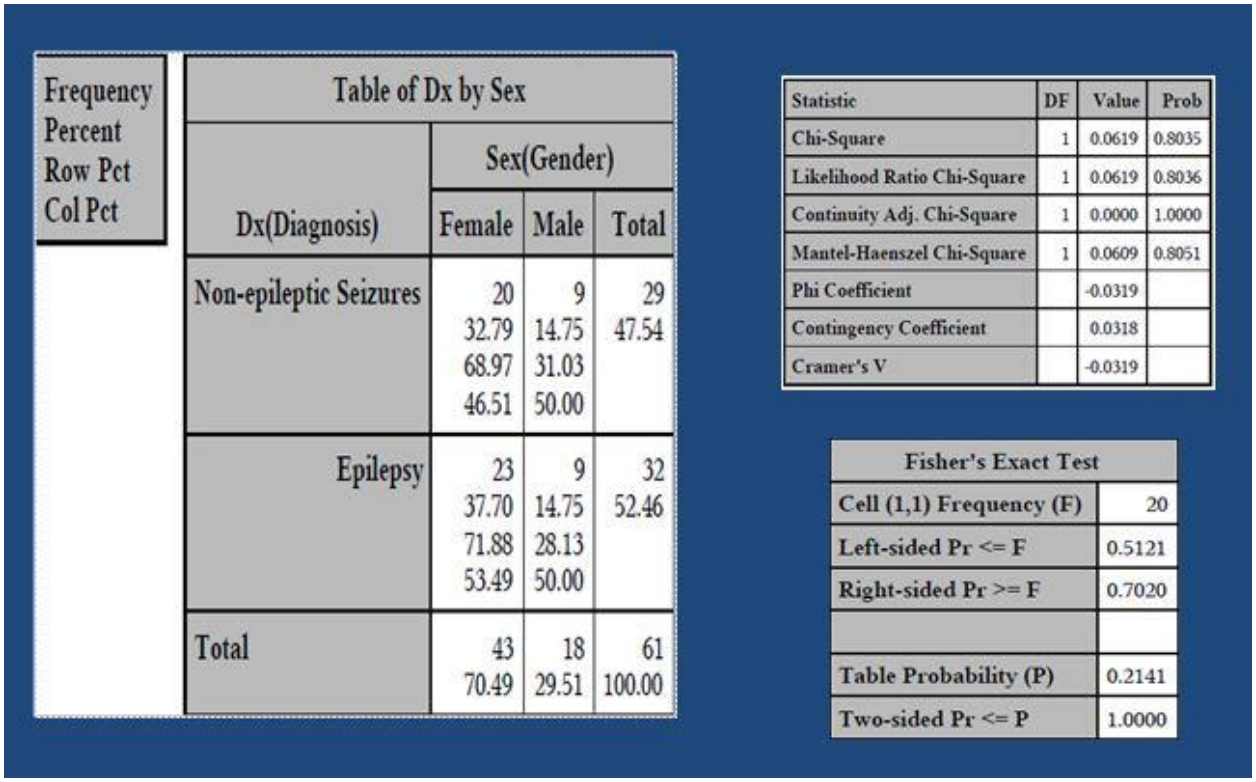
regularity caused by the focal epileptic process in the temporal regions. Patients with focal epilepsy have been shown to have greater asymmetry in spectral power analysis and more delta activity lateralizing to the epileptic focus.(27,32). This intermixed delta activity may be responsible for interruptions in signal regularity.

We did not find differences in the IHA of AV. Possible reasons include that AV IHA may depend on duration of epilepsy, seizure type or severity, or etiology of TLE. However, these variables were not collected for this study, so their role remains unclear.

A limitation of the study is that subjects were taking anti-epileptic medication. Also, tapering seizure medication is a popular technique for provoking seizures while patients are being monitored in an epilepsy monitoring unit. Therefore, the subjects may have been in the process or tapering, holding, or restarting medications during the recording of the EEG epochs which were selected for analysis. Furthermore, recording of PNEE patients were compared only recordings of TLE patients. Whether or not AV or PMRS are useful in distinguishing PNEE from other types of focal epilepsy or even idiopathic generalized epilepsy remains unclear. Finally, we analyzed IHA only in the relaxed, awake state. Different stages of wakefulness and sleep have well-described natural fluctuations in frequency, amplitude, and rhythmicity would require separate measurements and analysis for each stage. However, this is an area that may deserve future investigation.

In conclusion, our findings suggest that characteristics of the interictal EEG may be useful in distinguishing patients with TLE from those with PNEE. Future studies should focus on more diverse groups of epilepsy patients, additional measures of IHA,

other brain regions (electrodes), and different sleep-wake stages in order to improve the potential clinical applicability for separating PNEE from epilepsy.



Frequency
Percent
Row Pct
Col Pct

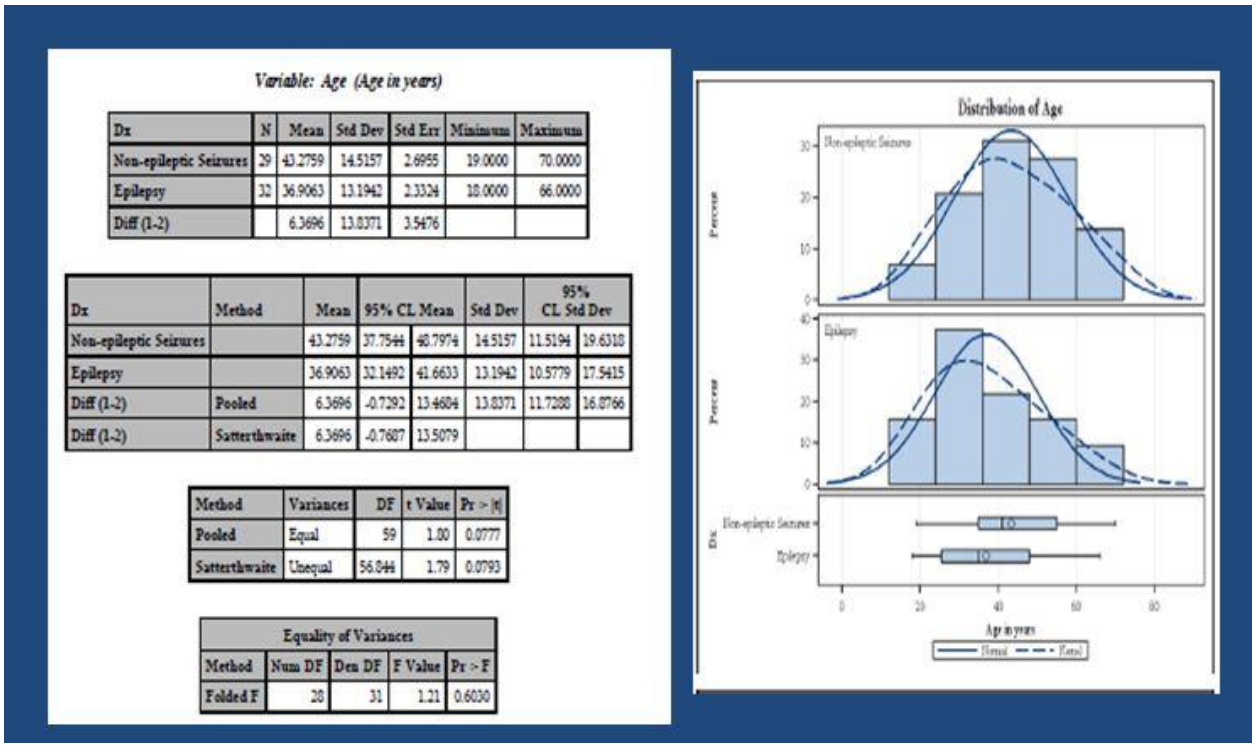
Table of Dx by Sex

Dx(Diagnosis)	Sex(Gender) Female	Male	Total
Non-epileptic Seizures	20 32.79 68.97 46.51	9 14.75 31.03 50.00	29 47.54
Epilepsy	23 37.70 71.88 53.49	9 14.75 28.13 50.00	32 52.46
Total	43 70.49	18 29.51	61 100.00

Statistic	DF	Value	Prob
Chi-Square	1	0.0619	0.8035
Likelihood Ratio Chi-Square	1	0.0619	0.8036
Continuity Adj. Chi-Square	1	0.0000	1.0000
Mantel-Haenszel Chi-Square	1	0.0609	0.8051
Phi Coefficient		-0.0319	
Contingency Coefficient		0.0318	
Cramer's V		-0.0319	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	20
Left-sided Pr <= F	0.5121
Right-sided Pr >= F	0.7020
Table Probability (P)	0.2141
Two-sided Pr <= P	1.0000

Figure 4-1. Bi-variate analysis of diagnosis and gender. In the table, “epilepsy” = temporal lobe epilepsy, and non-epileptic seizures=psychogenic non-epileptic events. Gender ratios were not significantly different in the two groups.



Variable: Age (Age in years)

Dx	N	Mean	Std Dev	Std Err	Minimum	Maximum
Non-epileptic Seizures	29	43.2759	14.5157	2.6955	19.0000	70.0000
Epilepsy	32	36.9063	13.1942	2.3324	18.0000	66.0000
Diff (1-2)		6.3696	13.8371	3.5476		

Dx	Method	Mean	95% CL Mean		Std Dev	95% CL Std Dev	
Non-epileptic Seizures		43.2759	37.7544	48.7974	14.5157	11.5194	19.6310
Epilepsy		36.9063	32.1492	41.6633	13.1942	10.5779	17.5415
Diff (1-2)	Pooled	6.3696	-0.7292	13.4684	13.8371	11.7288	16.8766
Diff (1-2)	Satterthwaite	6.3696	-0.7687	13.5079			

Method	Variances	DF	t Value	Pr > |t|
Pooled	Equal	59	1.80	0.0777
Satterthwaite	Unequal	56.844	1.79	0.0793

Equality of Variances				
Method	Num DF	Den DF	F Value	Pr > F
Folded F	28	31	1.21	0.6030

Figure 4-2. Bi-variate analysis for diagnosis and age (in years). In the tables above "epilepsy" = temporal lobe epilepsy, and non-epileptic seizures=psychogenic non-epileptic events. Age was not significantly different in the two groups.

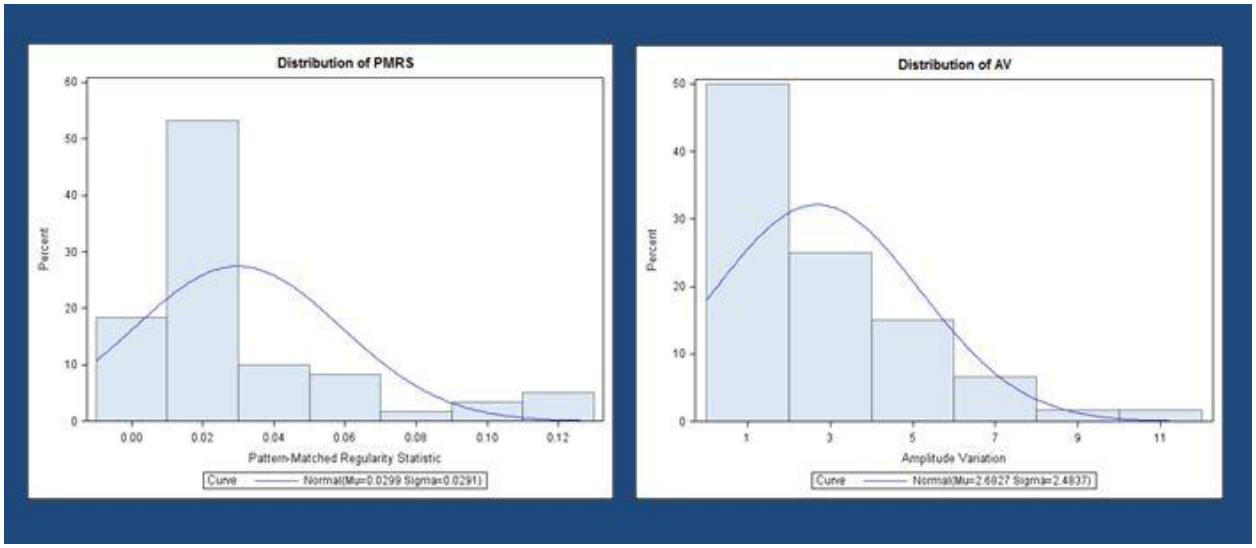
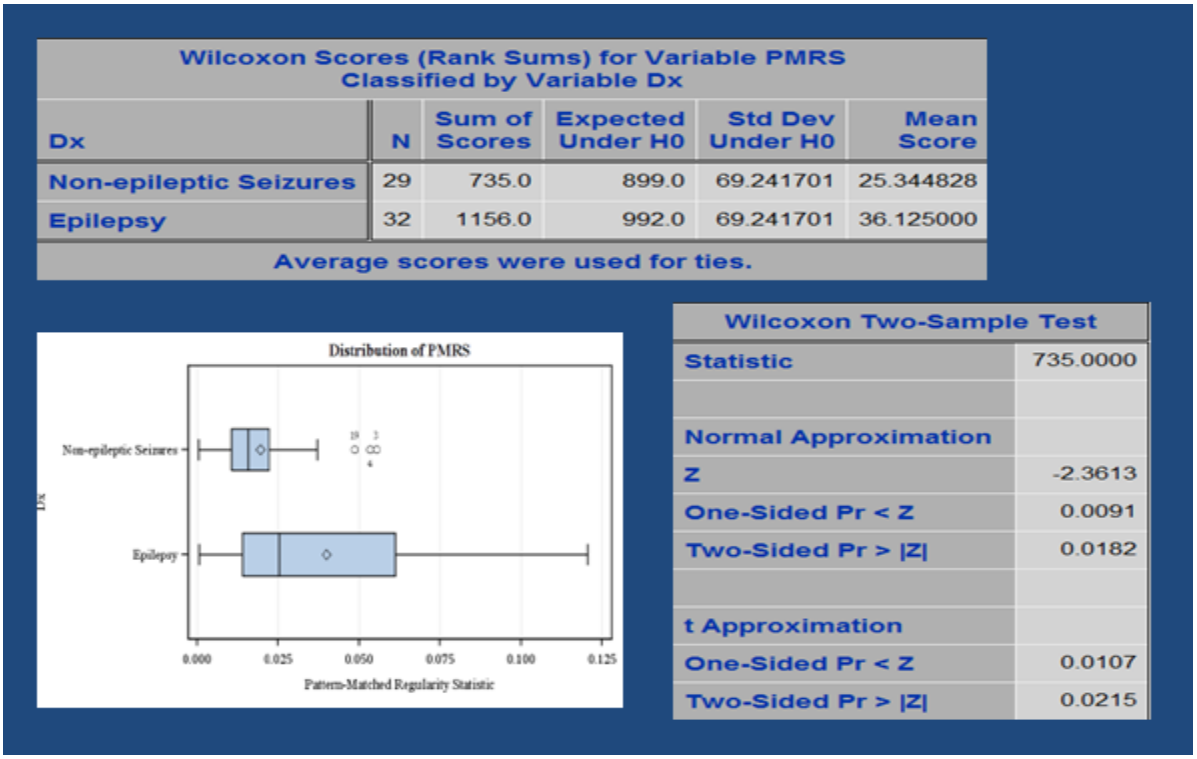


Figure 4-3. Distributions of the interhemispheric asymmetry. (Non-normal) distributions of the interhemispheric asymmetry of the PMRS=pattern matched regularity statistic (left) and the AV=amplitude variation (right).



Wilcoxon Scores (Rank Sums) for Variable PMRS Classified by Variable Dx					
Dx	N	Sum of Scores	Expected Under H0	Std Dev Under H0	Mean Score
Non-epileptic Seizures	29	735.0	899.0	69.241701	25.344828
Epilepsy	32	1156.0	992.0	69.241701	36.125000

Average scores were used for ties.

Wilcoxon Two-Sample Test	
Statistic	735.0000
Normal Approximation	
Z	-2.3613
One-Sided Pr < Z	0.0091
Two-Sided Pr > |Z|	0.0182
t Approximation	
One-Sided Pr < Z	0.0107
Two-Sided Pr > |Z|	0.0215

Figure 4-4. Bi-variate analysis of the interhemispheric differences in the PMRS=pattern matched regularity statistic. The interhemispheric PMRS asymmetry was greater in the “epilepsy”=temporal lobe epilepsy group.

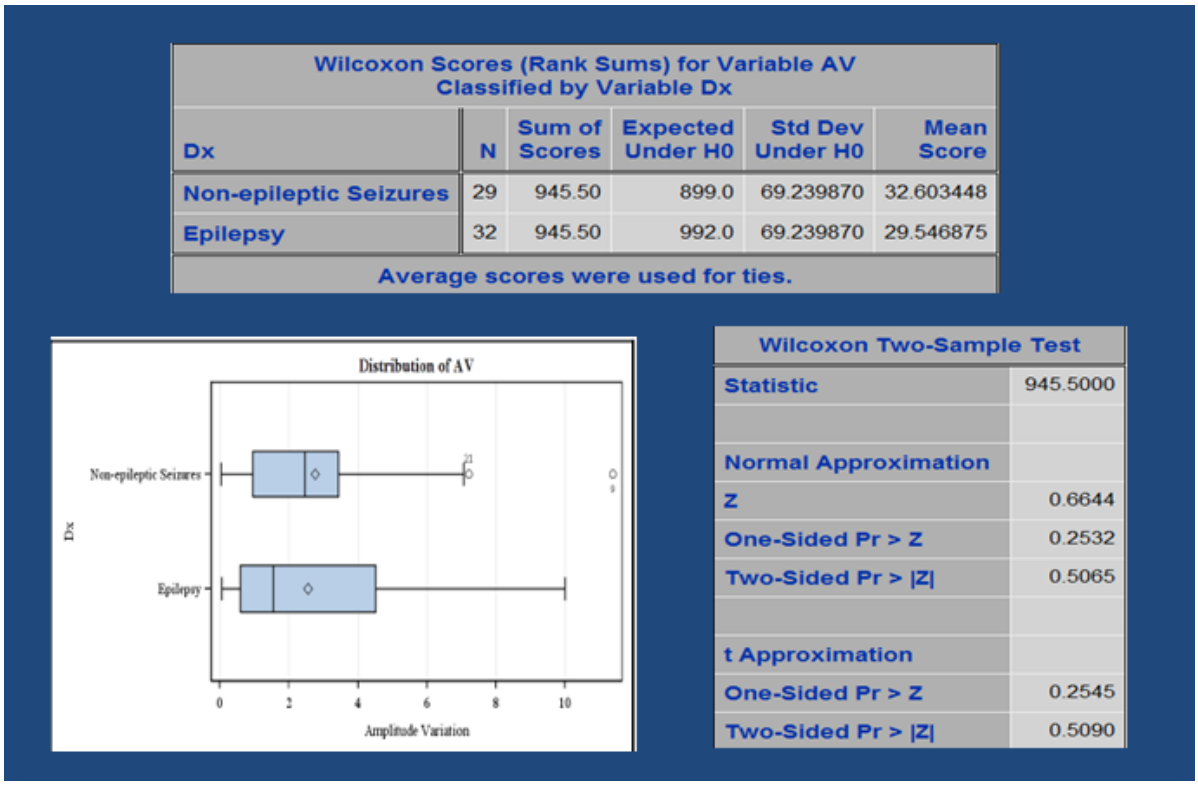


Figure 4-5. Bi-variate analysis of the interhemispheric differences in the AV=amplitude variation. The interhemispheric AV asymmetry was not significantly different between groups.

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BIOGRAPHICAL SKETCH

Holly Skinner was born in Orlando, FL, USA. In 1983 she moved with her family to Tallahassee, FL where she lived until 2001. While in Tallahassee, she graduated from Lincoln High School in 1997, and earned her Bachelor of Science degree in Exercise Physiology from Florida State University in 2001. She then moved to Fort Lauderdale, FL for medical school at Nova Southeastern College of Osteopathic Medicine.

Upon completion of medical school in 2005, she moved to Charleston, SC for a one-year medicine Internship, then a four-year residency in adult neurology. After residency, she moved to Gainesville, FL in 2009. While in Gainesville, she completed a one-year fellowship in clinical neurophysiology at the University of Florida (UF). Then, she worked for the UF Department of Neurology as a clinical lecturer (neurologist) and participated in the UF Advanced Post-graduate Program for Clinical Investigation. Through the program, she was afforded the opportunity to complete a master's degree with a concentration in clinical and translational science, for which this thesis is written.

Under the supervision of her primary mentor, J. Chris Sackellares, she was introduced to Optima Neuroscience Inc., a neurodiagnostic research company. Through mentorship and collaboration with the researchers at Optima, she was able to complete this project. She intends to pursue her research interests in distinguishing PNEE from epilepsy by way of analysis of brief EEG epochs.