Sensitivity of Electroencephalogram after first onset seizures in patients presenting at Charlotte Maxeke Johannesburg Academic Hospital

by

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A dissertation

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DECLARATION OF WORK

I, Lebohang Matthews Ratlhankana, declare that this dissertation, submitted for the degree **MASTER OF HEALTH SCIENCES IN CLINICAL TECHNOLOGY** at the Central University of Technology, FREE STATE is my independent work, and the work upon which this research is built is original unless otherwise acknowledged. The entire work or any portion has not been submitted for a degree at this or another university.

Signature on the 28 day of March 2023

ABSTRACT

Introduction

Routine electroencephalogram (rEEG) has a significant role in diagnosing and treating epilepsy. A common requirement for the diagnosis and categorisation of epilepsy is the presence of interictal epileptiform discharges (IEDs). rEEG recording has a low sensitivity of about 30-50%. Sleep-deprived EEG (SD-EEG) can increase the yield of IEDs by about 64%, while using 24-hour ambulatory EEG (24-hour AEEG) increases the yield of IEDs by about 84%. The study aimed to determine the sensitivity of rEEG compared with the SD-EEG and 24-hour AEEG on patients with first-onset seizures presenting at the CMJAH.

Methods

The research utilised a prospective cohort, quantitative, cross-sectional, descriptive design with n=50 patients aged ≥ 16 years with first onset seizures who underwent three EEG modalities (rEEG, SD-EEG and 24-hour AEEG), creating perfectly matched EEG samples. The three EEGs were compared (specificity, sensitivity, positive predictive value, negative predictive value and assessed for IEDs.

Results

Fifty patients participated in the study group. The participants sex distribution was (n=26) females, while (n=24) were males, presenting at the median age of 29 years. The evidence of IEDs on 24-hour AEEG was 70%, SD-EEG (40%) and rEEG (22%). Sensitivity was 57.1% on the 24-hour AEEG and 55%, on a SD-EEG detecting patients with epilepsy and the rate of false positives was 45% on SD-EEG and 42.9% on the 24-hour AEEG.

Conclusions

Our findings indicate that the 24-hour AEEG was a more sensitive diagnostic tool than the rEEG and SD-EEG for diagnosing and categorising epilepsy. An important risk factor for subsequent seizures is the presence of IEDs in the EEG following the first onset seizure. Using 24-hour AEEG can reduce the time needed to find the diagnosis.

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ABBREVIATIONS AND ACRONYMS

AEEG	Ambulatory EEG
ANN	American Academy of Neurology
ASM	Anti-Seizure Medication
24-hour AEEG	24hour Ambulatory EEG
CT	Computed Tomography
CNS	Central nervous system
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CAE	Childhood absence epilepsy
CoJ	City of Johannesburg
CoE	City of Ekurhuleni
EEG	Electroencephalogram
EBC	European Brain Council
FLE	Frontal lobe epilepsy
FNR	False Negative Rate
TPR	True Positive Rate
TNR	True Negative Rate
GTCS	Generalised tonic-clonic seizure
GCP	Good Clinical Practice
HICs	High-income countries
HIV	Human Immunodeficiency Virus
HREC	Health Research Ethics Committee
Hz	Hertz
IEDs	Interictal epileptiform discharges
IGE	Idiopathic generalised epilepsy
JAE	Juvenile absence epilepsy
ILAE	International league against epilepsy
PET	Position Emission Tomography
PPV	Positive Predictive value

rEEG	routine EEG
OLE	Occipital lobe epilepsy
LMICs	Low and middle-income countries
LTM EEG	Long Term Monitoring video EEG
MRI	Magnetic Resonance Imaging
MS	Myoclonic seizures
Ms	Milliseconds
MESS	Multicentre Epilepsy and Single Seizure)
Non-REM	Non-rapid eye movement
SUDEP	Sudden Unexpected Death in Epilepsy
SSA	Sub-Saharan Africa
SA	South Africa
SD-EEG	Sleep-deprived EEG
TLE	Temporal lobe epilepsy
TIRDA	Temporal Intermittent Rhythmic Delta Activity
US	United States
WHO	World Health Organisation

Symbols

µV	Microvolt

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CHAPTER 1: INTRODUCTION TO THE STUDY

1.1 Introduction

Epilepsy is a prevalent neurological condition that affects 70 million patients worldwide (Ackermann *et al*., 2019). It affects one (1) in every 100 people in South Africa, and since 2004 Sudden unexpected death in Epilepsy (SUDEP) has increased by more than 100% (Epilepsy South Africa, Frances, 2017). In Africa, the epilepsy burden is higher than in other regions worldwide, with over 10 million individuals diagnosed with epilepsy and about 4.4 million individuals affected in Sub-Saharan Africa (SSA) (Yaria and Ogunniyi, 2020). It is estimated that approximately 75% of epilepsy begins in childhood. About 7-8% of the population in the United States experiences at least their first epileptic seizure during their lifetime (Stafstrom and Carmant, 2015; Aris, 2008).

Seizures are unusual movements or behaviors caused by aberrant electrical activity in the brain; they are signs of epilepsy. Patients with epilepsy may have multiple seizure types because seizures are merely symptomatic (Beghi, 2019). Previous studies have indicated that the diagnosis of a first seizure is subjected to substantial inter-observer disagreement, therefore correct diagnosis is crucial for appropriate investigations and managing causal conditions (Wirrell, 2010; Saleem *et al*., 2019; Van donselaar *et al*., 2006).

An epilepsy diagnosis requires evaluating the cause of epilepsy and determining if the seizure disorder falls under a defined spectrum. An epilepsy diagnosis is a multi-step procedure, typically including subsequent issues (Bandopadhyay *et al*., 2021).

1.2 History and Examination

The history and neurological assessment are the foundation of the diagnosis of seizure and epilepsy. Important aspects of the patient's history include the clinical setting in which the seizure happened and the clinical assessment examining specific symptoms that may help pinpoint cerebral disease (Stafstrom and Carmant, 2015). Examination can be in a form of neuroimaging and metabolic examinations.

1.2.1 Metabolic Examination

The extent of the metabolic workup is determined by the type of seizure and associated illness. Blood tests are performed to look for conditions such as high or low blood sugar that could have triggered a seizure and for markers that may indicate the nature of the seizure and syndrome. During a lumbar puncture, a needle is placed into the area between the two of lumbar bones (vertebrae) to extract a sample of cerebrospinal fluid. This procedure is typically performed following a seizure if the patient appears not to be recovering normally or when the patient has a fever or other indications of brain infection (Stafstrom and Carmant, 2015).

1.2.2 Neuroimaging

Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans are essential complements to the clinical examination and electroencephalogram (EEG) when evaluating a seizure patient. Neuroimaging tools are very sensitive to structural abnormalities of the central nervous system (CNS) (Stafstrom and Carmant, 2015).

1.2.2.1 Positron Emission Tomography (PET) scan

The PET scan is an imaging procedure that reveals the function of organs and tissues. It is an effectual method for analysing brain chemical activity (Stafstrom and Carmant, 2015).

1.2.2.2 Electroencephalogram (EEG)

An EEG is a recording of the electrical activity of the brain. It can detect unusual electrical impulses, such as generalised or localised spikes and sharp wave discharges (Stafstrom and Carmant, 2015).

The EEG has a significant role in diagnosing and treating epilepsy. Routine EEG is generally first called for and often the only study to detect cerebral dysfunction or epilepsy, while routine outpatient EEGs in epilepsy are often non-diagnostic (Miskin *et al*., 2015; Burkholder *et al*., 2016). Currently, there is no agreement concerning the next diagnostic action if a rEEG is normal after the first seizure; however, in the Netherlands, about 48% of clinicians order a sleep-deprived EEG, 45% a second EEG, and 3% order a 24-hour Ambulatory EEG (24-hour AEEG) recording. The International League Against Epilepsy (ILAE) advises AEEG for particular symptoms such as the categorisation of epilepsy syndrome and variation concerning

seizures and pseudo-seizure, no research exists on the diagnostic yield of AEEG following the first spontaneous seizure and usual rEEG (Geut *et al.*, 2017).

The difficulty in examining a patient following their first seizure is distinguishing those who will suffer recurrent seizures from those who will suffer only one seizure in their lifespan. The ideal EEG protocol should be able to distinguish between seizures and non-seizures, the yield of EEG abnormalities and the assurance that a negative result will increase (Leach *et al*., 2006). Furthermore, an ideal EEG protocol should help the treatment plan and envisage the possibility of seizure recurrence in patients with first-onset seizures.

The utility of SD-EEG recording might lessen the number of rEEGs needed in young people with first-onset seizures by 45% (Debicki, 2017; Leach *et al*., 2006). It has been demonstrated that 24-hour AEEG is more effective than rEEG in detecting abnormalities (Hernández-Ronquillo *et al*., 2020).

The effect of sleep-deprived EEG (SD-EEG) has been long recognised. Sleep deprivation increases the incidence of epileptic-like EEG discharges for reasons not entirely understood. Even though one research did not demonstrate the effects of sleep deprivation, several authors believe this effect increases the number of epileptiform discharges compared to normal EEG that includes sleep (Leach *et al*., 2006; Díaz-Negrillo 2013; Giorgi *et al*., 2013).

An ambulatory EEG is as valuable in offering an increase in the yield of detecting epileptiform discharges in comparison to routine EEG (rEEG) and SD-EEG, the benefit of identifying seizures over the prolonged 24-hour (hr) recording that was not seen on a sleep deprived 30 min-60min (Debicki, 2017).

Government hospitals in Gauteng do not have the 24-hour AEEG equipment, and SD-EEG is not commonly used in our hospital settings. While longer EEG recordings are likely to yield more epileptiform discharges, this has not been extensively studied comparatively in South Africa or elsewhere. Thus, the researcher sought to compare the yield of each EEG protocol to allow finding the best possible means to use the resources efficiently by decreasing the number of routine repeat EEGs required for the categorisation of seizure disorders or to convince the management of government hospitals in Gauteng or South Africa at large to purchase the 24-hour Ambulatory EEG equipment so that the patients in government hospitals can be better managed.

This study helped to clarify the sensitivity of rEEG, SD-EEG and 24-hour AEEG. The ideal EEG protocol determined the difference between seizures and non-seizures so that the yield of EEG abnormalities and the assurance of a negative result were increased. Treatment and prediction of seizure recurrence were also improved in patients with the first onset seizure.

Therefore, the study aimed to determine the sensitivity of rEEG in contrast to the SD-EEG and 24-hour AEEG in patients who present at Charlotte Maxeke Johannesburg Academic Hospital with first-onset seizures.

CHAPTER 2: LITERATURE REVIEW

2.1 Epilepsy

As a chronic disease of the central nervous system, epilepsy affects people of all races, ages, geographical locations, and social classes. The indication of epilepsy is recurrent unprovoked seizures. Seizures are a recurrent epileptic form of events marked by alterations in behaviors that reflect the brain mechanisms involved in the epileptic process. Epileptic seizures are thought to be caused by various injuries and disorders, which have varied global distributions. Epilepsy prevalence is somewhat higher in males than in women. It appears to spike in aging, given the higher incidence of stroke, central nervous system diseases, and tumours in the aging age range (Beghi, 2019).

Multiple diseases and injury mechanisms are involved in the aetiology of epileptic seizures with different global distributions; the disease mechanism's source is unknown in approximately 50% of worldwide instances (WHO, 2022). Focal seizures are more prevalent than generalised ones among adults and children (Beghi, 2019). Epilepsy is seen as a curable disorder with a high therapy success rate. Espinosa-Jovel *et al.* (2018) reported that antiepileptic medications manage 70% of epilepsy patients, and 73% of patients with active epilepsy in rural areas of low- and middle-income countries either do not obtain treatment or receive treatment inappropriately. Even though effective antiepileptic medications are available, developing countries still have a significant treatment gap due to limited financial and human resources for diagnosis and treatment (Ba-Diop *et al.*, 2014).

Epilepsy remains a significant health issue in Africa since many epileptic patients in Sub-Saharan countries do not obtain proper treatment due to late diagnosis and sometimes insufficient care. (Mukuku *et al.*, 2020), the reasons for the treatment gap in epilepsy can be categorised into two groups: 1. Healthcare system and 2. Patient-related causes. In several parts of Sub-Saharan Africa (SSA), epilepsy is still linked to witchcraft (Paul *et al.*, 2012). For this reason, individuals with epilepsy usually have psychological complications such as social stigma, workplace discrimination, and a higher mortality rate (Espinosa-Jovel *et al.*, 2018; Paul *et al.*, 2012).

Wagner *et al*. (2020) reported that 59% of patients with epilepsy in the SSA do not obtain treatment, and only 33% of those who obtain treatment are adequately controlled.

2.2 Prevalence and incidence of epilepsy

Epilepsy prevalence varies between countries based on the geographical distribution of risk and causative variables (Beghi, 2019). Low and middle-income countries (LMICs) have a higher incidence and prevalence of epilepsy than the rest of the world. Epilepsy occurs at a rate of 45 per 100,000 people per year in high-income countries (HICs) and 81.7 per 100.000 people per year in LMICs (Espinosa-jovel *et al.*, 2018). The difference in incidence and prevalence between HICs and LMICs are attributed to a variety of risk factors, including head trauma, Central nervous system (CNS) infections, and obstetric traumas are more prevalent in disadvantaged settings, especially in rural settings (Espinosa-jovel *et al*., (2018).

Tian *et al*. (2018) mentioned that about three million adults in the United States reported active epilepsy in 2015. Poorly controlled seizures create substantial burdens because of mental health comorbidities, physical dysfunction, the side effect of antiepileptic drugs, poor quality of life and increased financial cost. The prevalence of active epilepsy is high, and poor seizure control is related to unemployment, low family income and divorce (Tian *et al*., (2018).

European Brain Council (EBC) revealed a noticeably lower prevalence estimated in Europe of about 5.78 per 1000 persons from a systemic review that revealed high differences within and between countries' estimates (Linehan *et al*., 2021). The incidence of epilepsy ranges from 24–82 per 100 000 people per year to 44–162 per 100 000 people per year in the United States and Europe (Behr *et al*., 2016).

More than 85% of epilepsy cases are observed in LMICs, with more cases diagnosed in poor regions of Africa under age 15, ranking as the highest in the world's population (Paul, 2012). A previous meta-analysis study reported the prevalence of epilepsy in SSA projected at 9.4% (Bongomin *et al.*, 2021). The general information about epilepsy in SSA implies a high annual prevalence in less developed countries of about 81.7 per 100 000 compared to 45.0 per 100 000 in more developed countries (Ba-Diop *et al*., 2014).

Espinosa-Jovel *et al*. (2018) reported a prevalence of 180–250 per 100.000 people per year, with higher values in poor regions and various LMICs, including South Africa. There is still a

gap in South Africa in reporting on the incidence and prevalence of epilepsy. Eastman (2005) states that in the 1960s prevalence of epilepsy in South Africa was 2.2 per 1000 people and 3.7 per 1000 people.

Christianson *et al*. (2000) researched the prevalence of epilepsy in a predominantly rural society in the northern province of South Africa. A total of 6692 children from 2 years to 9 years of age were screened using a globally validated questionnaire designed to detect childhood impairment in developing countries, including a specific question about epilepsy. Based upon that screening, 722 children were evaluated by a paediatrician, and 49 were diagnosed with epilepsy, resulting in a lifetime prevalence of 7.3 per 1000 people.

2.3 The aetiologies of epilepsy

The 2017 International League Against Epilepsy (ILAE) report categorises epilepsy's causes into six broad groups: structural, genetic, infectious, Immune, metabolic and unknown aetiology (Scheffer *et al*., 2017).

The aetiology of epilepsy varies depending on the patient's age, with neoplasia and stroke being the most common factors among the elderly. Dahl-Hansen *et al*. (2019) report that young males are disproportionately affected by traumatic brain injuries, cerebral palsy, and abnormalities of cortical structures. In a Norwegian population study in 2018, 43% of patients had known structural-metabolic causes of their epilepsy, 20% had a genetic cause, and 36% had an unknown cause of their epilepsy (Dahl-Hansen *et al.*, 2019).

According to Beghi (2019), the aetiology of epilepsy differs depending on the socio-demographic features of the population of concern and the extent of the diagnostic workup; in about 50% of epilepsy cases from HICs, a documented cause is still lacking. Many clinical conditions symbolised by abrupt changes in awareness or behaviour surround the differential diagnosis of epilepsy. In most instances, epilepsy can be diagnosed by thorough patient history or by observing a seizure (Beghi, 2019). The main risk factors of epilepsy in SSA are family history, previous febrile seizures, head injuries, perinatal trauma and central nervous system infections such as neurocysticercosis (Ba-Diop *et al.*, 2014).

In a research of 578 African patients with epilepsy treated at Ga-Rankuwa Hospital in Pretoria, about 28% of the population had epilepsy because of neurocysticercosis, human immunodeficiency virus (HIV) infection on CNS or an opportunistic infection that may also contribute to the prevalence of seizures. In South Africa, viral illnesses such as HIV, neurocysticercosis and trauma are the leading causes of epilepsy. In many impoverished countries, the larval stage of the pig tapeworm *Taenia solium* infects the human nervous system and produces neurocysticercosis, a leading cause of epileptic convulsions (Eastman, 2005).

Whilst everyone with epilepsy suffers seizures, not everyone who experiences seizures has epilepsy. An epileptic seizure might occur following structurally toxic, metabolically, and systemically acute CNS damage. Acute symptomatic or induced seizures are considered acute expressions of harm. They may not occur again once the underlying cause has been eliminated or the acute phase has passed (Beghi, 2019).

In 2014, ILAE adopted a new definition through ILAE of epilepsy as a disease with recurrent unprovoked seizures by any of the following conditions (Fisher *et al.*, 2014):

- At least two unprovoked seizures happen less than 24 hours apart.
- One unprovoked seizure and a probability of subsequent seizures like the general recurring risk of roughly 60% after two unprovoked seizures occurred over the following 10 years.
- The diagnosis of the epilepsy syndrome.

2.4 Classification of Epilepsy

The new classification system suggests 1. determining if the paroxysmal incident was genuinely an epileptic seizure, 2. determining the severity of the paroxysmal incident, that is, was it generalised, focal or unknown onset and 3. determining if the epilepsy was based on certain seizure types. As discussed, seizures are classified into motor and non-motor with different presentations. Some patients will have focal and generalised onset seizures; a focal seizure may spread from a focus to become generalised, usually called focal to bilateral tonic-clonic as depicted in Figure 2.1 (Sarmast *et al.*, 2020 & Magazi *et al.*, 2018).

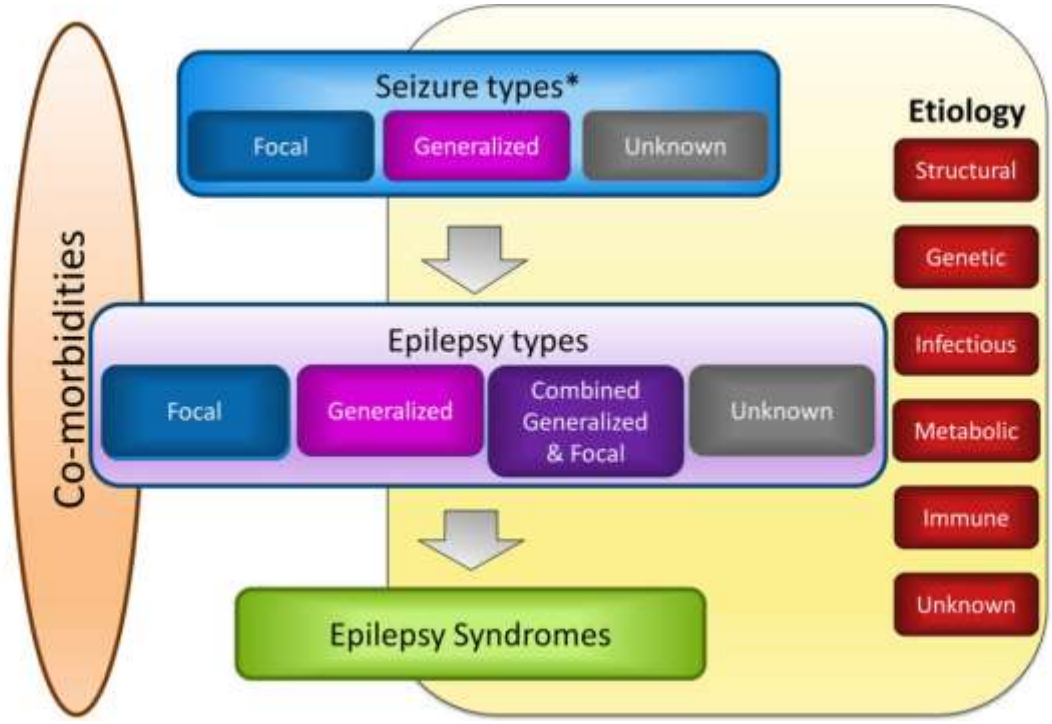

Figure 2.1: ILAE framework for classifying epilepsies

Source: (Sarmast *et al.*, 2020).

Combining an aetiology component with co-morbidities in epilepsy is a new aspect of the 2017 epilepsy classification. The ILAE recognised six aetiological axes and co-morbidities that should be reflected on a case by case when diagnosing and classifying epilepsy, including motor deficits, sleep disorders, and psychiatric and behavioural abnormalities (Scheffer *et al.*, 2017).

2.5 Types of epilepsy by syndromes

Frequently, epilepsies are categorised by a complicated combination of features that identify a subtype as a recognised syndrome. They are often characterised by their manifestations or the affected region of the brain (Koutroumanidis *et al*., 2017).

Following are some of the usual prevalent forms of epilepsy:

2.5.1 Juvenile absence epilepsy (JAE)

JAE is the primary absence syndrome of adolescence and it has onset between 8 years and 26 years of age. The seizures in JAE are longer, though and a patient can have this form of epilepsy

for the rest of their lifespan. Approximately 80% of patients with JAE experience tonic-clonic seizures (Koutroumanidis *et al*., 2017).

2.5.2 Childhood absence epilepsy (CAE)

Patients with CAE have staring spells that last for 10-20 seconds and return quickly to being alert. CAE is linked to 3-4Hz generalised sharp wave discharges on the EEG. It starts between the age of 4 years and 10 years, it then remits in the early stage of adulthood. Adulthood may bring on generalised tonic-clonic seizures (Koutroumanidis *et al*., 2017).

2.5.3 Juvenile myoclonic epilepsy (JME)

JME is the primary myoclonic syndrome of adolescence. The time of onset can vary, starting before the age of 10 (which overlaps with the CAE age range) and ending in the mid-20s or later. Patients with JME may experience generalised tonic-clonic and myoclonic seizures. (Koutroumanidis *et al*., 2017).

2.5.4 Childhood epilepsy with cento-temporal spikes

This sort of focus seizure is observed in children from 3 years to 12 years of age. The face often begins to twitch on one side, and the patient may experience facial or tongue numbness. These seizures often happen during sleep. In some patients, seizures may stop by the time they are 13 years old, while in other patients, they may last until they are 18 years old. Focal seizures can occur in childhood epilepsy with cento-temporal spikes (Koutroumanidis *et al*., 2017).

2.5.5 Sleep-related epilepsy syndrome

This syndrome is directly associated with sleep or sudden awakening from sleep. Seizures begins between 1 year and 60 years of age. In both sleep and awake, frontal lobe and temporal lobe epilepsy can manifest (Koutroumanidis *et al*., 2017).

2.5.6 Reading epilepsy

Reading-induced epilepsy is a specific type of reflex epilepsy in which reading causes all or almost all of the seizures. Between 10 and 30 years is the typical age at which seizures begin and lessen with age Specific stimuli can trigger generalised tonic-clonic seizures. The most prevalent form of reflex epilepsy is photosensitivity, in which flashing lights can cause convulsions (Koutroumanidis *et al*., 2017).

2.5.7 Temporal lobe epilepsy (TLE)

TLE usually starts in childhood or teenage years. TLE seizure may resemble staring spells, or a person may engage in pointless repetitive behaviours called automatism. This often has an aura, like an unusual smell or taste (Koutroumanidis *et al*., 2017).

2.5.8 Frontal lobe epilepsy

This type of epilepsy frequently impairs mobility; patients with frontal lobe epilepsy may experience muscle weakness and unusual motions such as arm and leg twisting and waving. Frontal lobe epilepsy occurs when a person sleeps (Koutroumanidis *et al*., 2017).

2.5.9 Occipital lobe epilepsy

Occipital lobe epilepsies (OLE) are characterised by seizures that originate in the occipital cortex, often known as occipital seizures. OLE starts between the age of 3 years and 15 years. These seizures can have a structural or unexplained cause, as well as Gastaut syndrome. This is one of the benign focal seizures of childhood. Visual changes can occur before or after a seizure (Koutroumanidis *et al*., 2017).

2.5.10 Neocortical epilepsy

It can be focal or generalised. The cortex is the brain's outermost layer, and seizure signals can range from strange sensations to emotional disturbances, visual hallucinations and convulsions (Koutroumanidis *et al.,* 2017).

2.6 Seizures

A seizure can be defined as a clinical manifestation of the electrical surge, which is cerebral and can be classified as motor or non-motor. Seizures that constitute epilepsy have non-immediately reversible causes such as infections, electrolyte imbalances, and alcohol withdrawal seizures. (Magazi *et al*., 2018).

Classification of seizure is based on the onset, into focal or generalised or unknown where onset is unknown to the patient or observer. The patient may be unaware of the onset. Depending on the patient's mental state during the seizure, focal onset seizures are further subdivided based on level of awareness into focal aware or unaware. All seizures are further subdivided into either motor or non-motor types depending on their clinical presentation,

irrespective of whether they are focal or generalised as seen in Figure (2.2) below. Fisher *et al*. (2017) state that the focal onset seizure that evolves into a generalised seizure is focal to a bilateral tonic-clonic seizure. The term unclassified can be used to describe seizures with unknown onset or with additional features such as motor, non-motor, tonic–clonic, epileptic spasms, and behaviour arrest (Fisher *et al*. (2017).

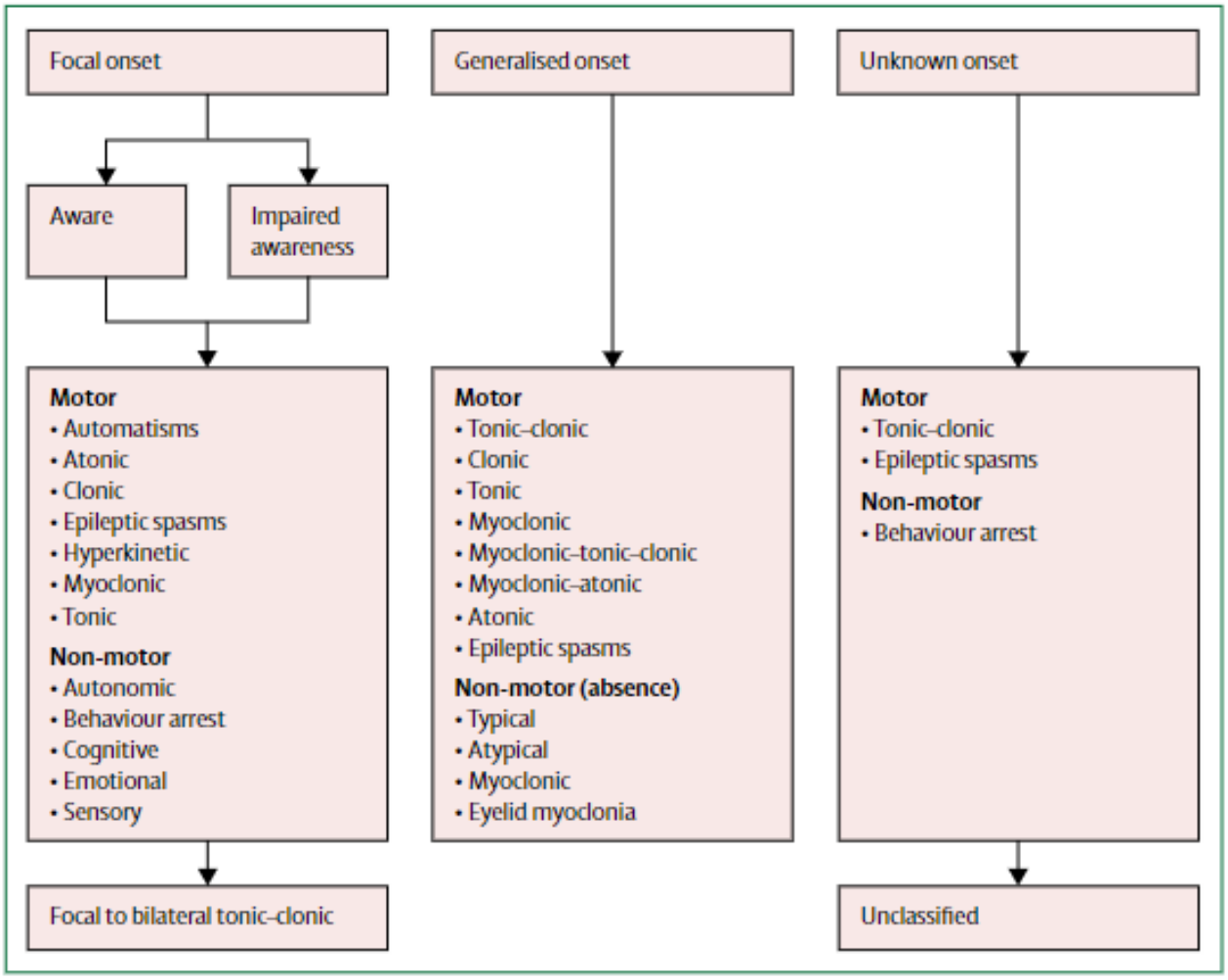

Figure 2.2: The International League Against Epilepsy framework for the classification of epileptic seizures (Thijs et al.,2019)

2.6.1 Motor seizures

A disturbance in muscle activity, such as the jerking of a finger, the stiffness of a bodily part, or the weakening of particular muscles, characterises these seizures. Other symptoms of motor seizure include automatic repetitive hand movements referred to as automatism (Reséndiz-Aparicio *et al*., 2019).

2.6.1.1 Tonic seizures

These seizures present with body spasms and stiffened limbs and may end up in backward arching followed by loss of consciousness. The episodes are short and last seconds to a few minutes (Reséndiz-Aparicio *et al.*, 2019).

2.6.1.2 Myoclonic seizures

These seizures present with short jerky movements of the muscle with a preserved consciousness (Reséndiz-Aparicio *et al.*, 2019).

2.6.1.3 Clonic seizure

These are sustained muscle contractions, which could be either focal or generalised in presentation, depending on how much brain surface is involved (Reséndiz-Aparicio *et al.*, 2019).

2.6.1.4 Tonic-clonic seizure

These seizures present with a tonic phase followed by a clonic phase. Beyond the tonic-clonic phase is the loss of consciousness and postictal confusion (Reséndiz-Aparicio *et al.*, 2019).

2.6.1.5 Atonic seizure

These seizures present with a loss of tone in the body when the patient fails to the ground in a limb form, and loss of tone may only affect the head with a head drop or nod (Reséndiz-Aparicio *et al.*, 2019).

2.6.1.6 Automatism

These are motions connected with an ictus that are less or more coordinated and occur at a distance from consciousness, such as aimless strolling (Reséndiz-Aparicio *et al.*, 2019).

2.6.1.7 Hyperkinetic seizures

These seizures present with an agitated body part movement like feet pedaling (Reséndiz-Aparicio *et al.*, 2019).

2.6.1.8 Epileptic spasm

These seizures present with an unexpected flexion of the limb and truncal muscles and often happen in series (Reséndiz-Aparicio *et al.*, 2019).

2.6.2 Non-motor seizures

These seizures include sensory, absence, emotional, autonomic and behavioral arrest (Reséndiz-Aparicio *et al.*, 2019).

2.6.2.1 Absence seizure

These are short episodes of about 4 to 20 seconds duration of halting activities with a blank stare when the patient is not responsive (Reséndiz-Aparicio *et al.*, 2019).

2.6.2.2 Cognitive and emotional seizures

A wide range of psychological and mental abnormalities, such as olfactory, visual, and tactile illusions of the body, maybe the single or predominant manifestation of particular seizures (Reséndiz-Aparicio *et al.*, 2019).

2.6.3 Sensory seizures

This seizure presentation is not frequent, with the manifestation usually being auras before the motor phenomena (Reséndiz-Aparicio *et al.*, 2019).

2.6.4 Autonomic seizures

These seizures present with sensations like gastric phenomena such as borborygmi, palpitation and piloerection, causing goosebumps. Certain syndromes have autonomic manifestation as one of the defining characteristics, such as Panayiotopoulos syndrome, which is early-onset epilepsy (Reséndiz-Aparicio *et al.*, 2019).

2.7 Seizure recurrence

Neurologists treat seizures as one of the most prevalent serious neurological disorders. In patients experiencing seizure incidents, it is estimated that about 40–50% of seizure prevalences in individuals are thought to reoccur for them to be classified as epilepsy, a condition characterised by repeated unprovoked seizures (Krumholz *et al.*, 2007). A single

seizure can be the initial indicator of epilepsy. Epilepsy is characterised by recurrent unprovoked seizures or symptoms of brain tumours, systemic disorders, infections or a syndrome that warrants special attention and treatment (Krumholz *et al.*, 2007).

Recurrence after a first seizure varies greatly depending on whether the seizure is unprovoked or acute symptomatic; nonetheless, acute symptomatic seizures have a low recurrence incidence of approximately 19% at ten years in contrast to a single unprovoked seizure at a rate of approximately 65% (Beghi *et al.*, 2015). The estimated likelihood of recurrence following a first generalised tonic-clonic seizure is around 30% at 5 years, provided there are no mild past seizures or known current risk factors (Rizvi *et al.*, 2017). For idiopathic seizures and patients with a family history of seizures, the risk of seizure recurrence increases to 29%. When the seizure is idiopathic with interictal epileptiform discharges (IEDs) on the EEG, the possibility of seizure recurrence increases to 50% (Rizvi *et al.*, 2017). Patients with symptomatic aetiology have a higher recurrence rate than those with idiopathic seizures (Rizvi *et al.*, 2017).

Berg (2008) stated that patients with a normal EEG and neurological status are in the lower risk group as the recurrence risk is about 20% at one year, 25% at two years and 30% at four years after randomisation. The Multicentre Epilepsy and Single Seizure (MESS) conducted a trial with 812 study participants with a first seizure; the rate of recurrence in the 404 participants randomised to immediate treatment was approximately 18% at 6 months, 32% at 2 years and 42% at 5 years and 8 years after randomisation versus 26%, 39%, 51% and 52% in the untreated group (Berg, 2008).

According to the American Academy of Neurology (ANN), there are four factors that increase the chance of a seizure recurrence: EEG with IEDs, cerebral injuries, newly found lesions on neuroimaging and nocturnal seizures (Gien-López *et al*., 2019). Beghi *et al.* (2015) found that established aetiology and the presence of IEDs in the EEG are the two most reliable predictors of recurrence. However, sleep-related seizures are also associated with an increased chance of recurrence.

2.8 Diagnosis of epilepsy

Diagnosing epileptic seizures is challenging, particularly in low-income countries where cultural and socioeconomic barriers impede the recognition and acceptance of the disorder. In most instances, epilepsy can be diagnosed by a patient's medical history or by observing a seizure (Beghi, 2019). Typically, the diagnosis of epilepsy relies on an observer's description of events, which can be challenging, particularly when seizures are atypical. Various tests are carried out to verify the presence of epilepsy and rule out potential causes of seizures (Beghi, 2019). A good history and strong IEDs in the EEG allow for a diagnosis with high confidence (Amin and Benbadis, 2019).

The main purpose of the diagnostic process in epilepsy is to define epilepsy or epilepsy syndrome. Patient history and clinical examination are the foundation for evaluating the first seizure, as they are mostly supported by expert opinion (Nowacki *et al*., 2017).

The EEG, which captures the brain's electrical activity and can indicate abnormal electrical brain activity causing epilepsy, is one of the primary instruments used to diagnose epilepsy. Magnetic resonance imaging (MRI) and computed tomography (CT) scans are sometimes used to screen for structural abnormalities in the brain that could be the reason for seizures (Magazi *et al*., 2018; Koutroumanidis *et al*., 2017).

2.9 The role of the EEG in the diagnosis of epilepsy

The EEG is the most useful diagnostic procedure for epilepsy because it monitors voltage difference changes between scalp electrodes by measuring ionic currents within brain neurons and offers spatial and temporal information regarding the brain (Noachtar, 2009; Zhou *et al*., 2018). Epilepsy is among the few prevalent clinical conditions necessitating EEG testing nowadays (Noachtar, 2009). In suspected or newly diagnosed epilepsy patients, EEG may raise diagnostic certainty, show the risk of seizure recurrence, aid in selecting antiepileptic drugs, and provide a prognostic assessment (Noachtar, 2009).

EEG findings help identify the aetiologies in some cases, whether the seizure disorder is generalised or focal, symptomatic or idiopathic or part of epilepsy syndrome (Smith, 2005). However, it must be noted that abnormal EEG results without clinical manifestations are not considered epilepsy, as a patient with epilepsy may have a normal EEG (Gien-López *et al*., 2019).

2.10 EEG in generalised epilepsies

EEG classification in generalised epilepsy begins with the type of seizure and is undoubtedly justified by the nature of the seizure itself. (Fisher *et al*., 2014, Scheffer *et al*., 2017). EEG in generalised epilepsy can be separated into idiopathic and non-idiopathic. Idiopathic generalised epilepsy (IGE) consists of numerous epileptic syndromes that are considered to have a substantial hereditary origin (Alsaadi *et al.*, 2015). The EEG is the single test that can definitively validate the diagnosis of IGE. When the EEG is abnormal, it can reveal generalised spike and poly spike complexes of 3-4Hz or faster frequencies that are superimposed on a normal EEG background (Alsaadi *et al*., 2015).

In non-idiopathic generalised epilepsy (IGE), EEG can reveal structural abnormalities with abnormal EEG background, generalised spike and wave complex or sharp wave complexes often predominately frontally with a frequency difference 2-5Hz are the hallmark of generalised epilepsy (Rosenow *et al*., 2015).

2.10.1 Generalised tonic-clonic seizures (GTCS)

In generalised tonic-clonic seizures caused by IGE, the tonic-clonic activity should be generalised and symmetrical from the onset; in secondarily GTCS of focal epilepsies, numerous focal characteristics have been documented, aiding in localisation and lateralisation of the seizure focus. EEG would show generalised spike and poly spike complexes of 3-4Hz (Alsaadi *et al.*, 2015).

2.10.2 Myoclonic Seizures (MS)

Myoclonic seizures are characterised by bilateral, arrhythmic, and irregular contractions of proximal and distal muscles, primarily in the upper limbs. MS is characterised by the generalised bursting of polyspikes/polyspike-wave with varying side focus and anterior predominance on the EEG (Alsaadi *et al.*, 2015).

2.10.3 Absence seizures

Absence seizures are short-lasting, generalised epileptic seizures classified clinically by a sudden loss of consciousness (absence) that ends abruptly and without post-ictal symptoms. They are also electrographically identified by a generalised 3–4 Hz spike and slow-wave discharge that ends without further electrical flattening (Seneviratne *et al*., 2014).

2.11 EEG in focal epilepsies

2.11.1 Temporal lobe epilepsy (TLE)

TLE are an intermittent burst of focal spikes and sharp wave discharges in the temporal region; IED may be unilateral or bilateral. The focal Temporal Intermittent Rhythmic Delta Activity (TIRDA) is considered a good indicator of the side of the epileptogenic focus (Jan *et al.*, 2010).

2.11.2 Frontal lobe epilepsy (FLE)

IEDs are less prevalent in FLE than in TLE, at 60-80%. Compared to TLE, FLE has a lower localising value for IEDs, including secondary bilateral synchrony, which they may assume to be bilateral, lateralised, or generalised (Rosenow *et al.*, 2015).

2.11.3 Occipital lobe epilepsy (OLE)

EEG abnormalities are common in OLE patients, but scalp EEG occasionally misses IEDs produced by a central vertex on the inferior and mesial occipital areas. Spikes and sharp waves in the temporal or temporo-occipital areas are the most common IEDs in OLE, with shifting maximums in certain patients (Rosenow *et al.*, 2015).

2.12 Different EEG protocols

Clinical suspicion of an epileptic condition is the chief reason for EEG performance. It can be valuable in evaluating encephalopathies such as metabolic and infectious degeneration and focal brain lesions like cerebral infarction, haemorrhage and neoplasms. In young children, an EEG can be valuable in determining the brain's maturation level (Flink *et al.*, 2002).

EEG is particularly helpful when the clinical onset of the idiopathic generalised epilepsy type occurs in adolescence or early adulthood. The EEG is an important test that provides diagnostic information regarding epilepsy while the patient is not clinically seizing. Combined with clinical assessment, it helps classify and manage epilepsy (Hasan *et al.*, 2021). An EEG interpreter looks for the prevalence and localisation of epileptiform consisting of spike and wave discharges, sharp waves, and slow waves to support the diagnosis of epilepsy and assists in defining the category of epilepsy syndrome (Hasan *et al.*, 2021).

Interictal and ictal epileptic-form patterns were initially detected in the 1930s, distinguishing between generalised and partial seizures. Interictal discharges are divided by their morphology

as sharp waves, spikes, wave complexes and poly-spike and wave complexes (David and Benbadis, 2014).

The following definitions of interictal discharges are in use:

Sharp wave- with a sharp peak at conventional paper speed and a period of 70–200 milliseconds, transient activity easily stands out from the background activity.

Spike is similar to a sharp wave, lasting for 20 to 70 milliseconds.

Spike and wave complexes – a pattern with a spike followed by a slow wave of high amplitude than the spike.

Poly-spike and slow wave complexes- same as spike and slow wave complexes but with more than two spikes associated with one or more slow waves.

There is no clinical reason to distinguish between spike and sharp waves because they share the same implications and underlying physiological causes (Pillai and Sperling, 2006). A routine EEG is usually conducted to diagnose seizures, and it can help choose treatment with anti-epileptic drugs (Hasan *et al.*, 2021).

2.12.1 Routine EEG (rEEG)

The procedure EEG is a neurophysiological test that has been useful in predicting the likelihood that seizures would recur (Hernández-Ronquillo *et al.*, 2020). It is the first-line examination for the diagnosis of epilepsy. Nonetheless, its sensitivity is low, about 30-50%, predominantly due to a short time sample and biophysics of cortical neurophysiology signal (Batista *et al.*, 2020).

For the diagnosis of seizure, the yield of a single rEEG rises with repetitive EEGs by approximately 90% by the fourth rEEG; however, some patients with epilepsy will have no IEDs despite repeated EEGs (Benbadis *et al.*, 2020). A rEEG yields IEDs in 30%-50% of cases, and the repeat rEEG could increase the rate of IEDs to 60-70% (Mitchel *et al.*, 2015). The repeat rEEGs have been shown to increase the yield of IEDs (Hasan *et al.*, 2021).

Research conducted by Shafait *et al*. (2021) stated that a single rEEG recording of a 30 minutes duration in unselected patients with confirmed epilepsy yields IEDs of about 29%-55%, and the increased yield of IEDs of about 49%-67% was observed in doing repeated EEGs.

Pillai and Sperling (2006) stated that the sensitivity of an initial rEEG to reveal IEDs differs from 29%-55%. Some researchers have indicated that a rEEG in a patient with epilepsy will have no IEDs in about 50% of cases. Therefore, the sensitivity must be increased by incorporating activation techniques like photic stimulation and hyperventilation. A rEEG is frequently normal in patients with spontaneous unprovoked seizures or displays non-specific abnormalities (Flink *et al*., 2002; Giorgi *et al.*, 2013).

The ILAE guidelines of 2018 recommend a rEEG as the first approach to a seizure. When a rEEG is normal, the recommended approach is sleep-deprived EEG (SD-EEG). If the diagnosis is unclear, especially when a particular trigger is speculated, Ambulatory EEG (AEEG) should be considered (Batista *et al.,* 2020).

Indication for rEEG (Hasan *et al*., 2021).

- Diagnosis of epilepsy
- Categorisation of focal and generalised epilepsy
- Diagnosis of epilepsy syndromes
- Selection of Anti-Seizure Medication (ASM) and monitoring response to treatment
- Diagnosis of other diseases, such as Central Nervous System (CNS) Infections

The advantages of rEEG (Benbadis *et al*., 2020).

- The utilisation of activation procedures such as photic stimulation and hyperventilation
- It is the most basic and inexpensive test
- It can support a diagnosis of epilepsy

2.12.2 Sleep Deprive EEG (SD-EEG)

After introducing the diagnostic protocol for epilepsy, several authors describe the sensitivity increase in SD-EEG (Giorgi *et al*., 2013; Wirrell, 2010; Smith, 2005). In people with epilepsy, sleep loss is linked to increased IEDs. It is regarded as an activation procedure for EEG as some sleep stages can be linked with an increased chance of evoking IEDs in those with

underlying seizure tendencies (Debicki, 2017; Van dissen *et al*., 2014). SD-EEG has appeared to increase the frequency of IEDS by about 41% in patients with epilepsy and only 13% in a repeat rEEG (Renzel *et al.*, 2015).

On a group of young adults inferred to have epilepsy, the sensitivity of several EEG protocols, including rEEG, SD-EEG, and medication-induced sleep EEG recording, were studied. The results showed a higher sensitivity for SD-EEG. Nevertheless, it must be noted that the efficiency of the nap EEG is at least comparable to that of the nighttime EEG since IEDs are more common in slow-wave sleep and are frequently experienced during the early stages of the sleep cycle (Michel *et al*., 2015).

The study conducted by (Renzel *et al*., 2015) showed that SD-EEG is a highly specific method for detecting IEDs, as it yielded about 64% of generalised IEDs and 17% of focal IEDs. There is evidence that independent of whether sleep was present during the EEG recording, SD-EEG recordings increase the effectiveness of IEDs and aid in classifying epilepsy (Van diessen *et al.*, 2014).

Keezer *et al*. (2016) reviewed 46 patients with a previous normal rEEG; all patients were subsequently tested with 24-hour AEEG and 30- 60 minutes SD-EEG. Their findings are that SD-EEG and 24-hour AEEG were found to have IEDs in almost similar propositions of patients. Using SD-EEG as a follow-up procedure to intensify the yield of recoding IEDs encourages various interesting and unresolved issues. Sleep deprivation has been indicated to result in more activating sleep than normal sleep (Debicki, 2017).

Indication for SD-EEG (Osman *et al*., 2014).

- Patients with an inconclusive rEEG record are suspected of having epilepsy.
- Sleep deprivation EEG can assist in determining the presence of epileptiform abnormalities.
- Seizure classification and epilepsy syndromes.
- Evaluate the treatment response to anti-epileptic medication.

The advantages of SD-EEG (Osman *et al*., 2014).

- New information concerning the localisation of the epileptogenic focus.
- Further information concerning the distribution of epileptiform activity.

- Validation of the clinical results of the initial EEG recording was not seen as providing added value.
- Most evidence supports the idea that sleep deprivation activates IEDs.

2.12.3 24-hour Ambulatory EEG (24-hour AEEG)

24-hour ambulatory EEG is a monitoring procedure that permits the continuous recording of EEG for 24 hours at home or in a hospital setting, including sleep samples (Hernández-Ronquillo *et al.*, 2020). 24-hour AEEG plays a significant role in the diagnosis and clinical management of epilepsy. (Keezer *et al.*, 2016). AEEG monitoring is a modern technology that permits long-term recording in a normal environment. Some authors mentioned that AEEG appeared to be the paramount resource in a busy epilepsy clinic, and the cost of AEEG is 51-65% lower than 24-hour in-patient for video monitoring (Dash *et al.*, 2012).

Indications for 24-hour AEEG (Tatum *et al.*, 2021).

- The diagnosis of epilepsy.
- Categorisation of seizures and epilepsy syndromes.
- Quantification of IEDs and seizure burden (particularly seizures without self-awareness).
- Differential diagnosis of seizures.
- Evaluate the effectiveness of antiepileptic drug treatment.
- Confirm the historical report on seizure freedom.
- To consider prognosis while contemplating antiepileptic medication discontinuation.

The advantages of AEEG (Tatum *et al.*, 2021).

- Prolonged EEG recording in the patients' familiar environment.
- Avoiding the discomfort of hospitalisation regulations and restrictions. Family support at home from family members.
- The patient is subjected to seizure triggers and natural stressors to maximise the probability of capturing IEDs.
- Reduces the possibility of hospital-acquired infections.
- Ambulation is mobile EEG, not as strictly constrained as other EEG recordings.
- Captures normal sleep patterns and circadian changes.

- Capable of performing overnight EEG recordings for up to several days.
- Increased yield after a non-diagnostic rEEG.

In one study, the diagnostic value of SD-EEG and 24-hour AEEG recordings in 46 patients with suspected epilepsy were compared. SD-EEG showed abnormalities in 24% of the cases, and 24-hour AEEG revealed 33% of abnormalities in the cases (Michel *et al*., 2015).

Seneviratne *et al.* (2013) conducted a cohort of patients with a suspected diagnosis of epilepsy and a normal rEEG; SD-EEG and AEEG increased the interictal discharges by about 24% and 33%; there was no significant statistical difference. Furthermore, seizures were obtained in 15% of AEEG recordings compared to none in SD-EEG (Seneviratine *et al.,* 2013). AEEG has contributed about 31-84% to the clinical diagnosis in the paediatric population and can be utilised in a wide spectrum of indications with reliable results in adult patients (Dash *et al.,* 2012).

Faulkner *et al.* (2012) conducted a study where they reviewed 324 consecutive patients who underwent a 5-day ambulatory EEG between 2007 and 2010, and their findings were that the indication for ambulatory EEG was diagnostic in 193 (60%) to authenticate the frequency of subclinical seizures in 35 (10%), the provisional diagnosis for epilepsy was in 210 (65%) and a non-epileptic diagnosis in 109 (35%).

Ambulatory EEG and Long Term Monitoring video EEG (LTM EEG) have higher sensitivity and lower false negative rates than rEEG (Xinghua *et al.,* 2020). AEEG and LTM EEG are more sensitive to yield IEDs than a rEEG (Foong *et al.,* 2016). AEEG and LTM EEG can help differentiate nocturnal seizures or artefacts (Popkirov *et al.*, 2017).

The ILAE recommends long-term EEG recording when the diagnosis of epilepsy is unclear. When rEEG and SD-EEG are normal in patients with suspected seizures, an AEEG recording can show the IEDs in 12-25% of cases. In identifying IEDs of 24-hour video –EEG, an initial unprovoked seizure has been demonstrated to be a risk factor for seizure recurrence (Michel *et al*., 2015; Debicki, 2017).

2.13 The treatment outcome of epilepsy

Patients with epilepsy must contend with their condition's symptoms and their medication's side effects, the impact on their daily life activities and social stigma (Mayor *et al.*, 2022). Research done by Zewudie *et al.* (2020) revealed that the majority of epileptic patients, 72.7%, experienced one or more anti-epileptic side effects, whilst the majority of research participants, 54.5%, experienced sleepiness. Other anti-epileptic-related side effects included confusion, weakness, blurred vision and gastrointestinal irritation.

Patients with uncontrolled epilepsy are susceptible to deleterious consequences, psychological co-morbidities, cognitive deficits leading to employment restriction, physical injuries, and death (Nasir *et al.*, 2020). The concept of quality of life refers to an individual's mental, bodily, and social well-being. This is compromised in epileptic patients since epilepsy is a chronic disorder that affects the patient's personal and social life (Pamela *et al.*, 2018).

Some studies from low to middle-income countries (LMICs) revealed that incidence and mortality rates are higher than high-income countries (HICs). Approximations of prevalence from African research differ from 64 to 215 per 100.000 patients per year (Wagner *et al.*, 2015; Ngugi *et al.*, 2011; Ngugi *et al.*, 2014). In a sequence of 164 epileptic patients enlisted from a rural clinic in Tanzania, 67.1% of the patients died, with a mortality rate doubled that of the general rural Tanzanian population. In over 50% of the cases, epilepsy was a contributing factor to mortality. (Zewudie *et al.*, 2020).

According to Nasir *et al.* (2020), treating epilepsy in developing countries is inadequate due to the inaccessibility of medication and the absence of epilepsy-related information and education for patients and healthcare practitioners. Some studies have revealed that having different treatment protocols, incorrect epilepsy diagnosis, lack of modern technology, inappropriate health care provider, and lack of knowledge were the found to be factors in the treatment outcome of epilepsy (Beyene *et al.*, 2018; Panahi *et al.*, 2017).

2.13.1 Aim and objectives

The study aimed to determine the sensitivity of rEEG compared with the SD-EEG and 24-hour AEEG on patients with first-onset seizures presenting at the Charlotte Maxeke Johannesburg Academic Hospital.

2.13.1.1 ***Objectives***

The study formulated the following research objectives, namely:

- To compare the sensitivity of a routine EEG, sleep-deprived EEG and 24-hour ambulatory EEG after the first onset seizure in patients presenting at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).
- To estimate the risk of seizure recurrence.

2.13.1.2 Secondary Objectives

- To determine the latency to recording interictal epileptiform discharges with routine EEG.
- To determine the latency to recording interictal epileptiform discharges with 1hr sleep-deprived EEG.
- To determine the latency to recording interictal epileptiform discharges with 24-hour AEEG.

CHAPTER 3: ARTICLE-1

SENSITIVITY OF ELECTROENCEPHALOGRAM AFTER FIRST ONSET SEIZURES IN PATIENTS PRESENTING AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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Abstract

Introduction

Routine electroencephalogram (rEEG) has a significant role in diagnosing and treating epilepsy. A common requirement for the diagnosis and classification of epilepsy is the presence of interictal epileptiform discharges (IEDs). rEEG recording has a low sensitivity of about 30-50%. Sleep-deprived EEG (SD-EEG) can increase the yield of IEDs by about 64%, while the use of 24-hour ambulatory EEG (24-hour AEEG) increases the yield of IEDs by about 84%.%. The study aimed to determine the sensitivity of rEEG compared with the SD-EEG and 24-hour AEEG in patients with first-onset seizures presenting at the CMJAH.

Methods

The research study utilised a prospective cohort, quantitative, cross-sectional descriptive design with a total of n=50 patients aged ≥ 16 years with first onset seizures who underwent three EEG modalities (rEEG, SD-EEG and 24-hour AEEG), creating perfectly matched EEG samples. The three EEGs were compared (specificity, sensitivity, positive predictive value, negative predictive value) and assessed for IEDs.

Results

Fifty patients participated in the study group. The patient's sex distribution was (n=26) females, while (n=24) were male patients. The median age of the study group was 29 years. The evidence of IEDs on 24-hour AEEG was 70%, rEEG(22%) and SD-EEG(40%). In an SD-EEG on detecting patients with epilepsy, sensitivity was 55%, and the rate of false positives was 45%. The 24-hour AEEG on detecting patients with epilepsy sensitivity was 57.1%, and the rate of false positives was 42.9%.

Conclusions

Our findings indicate that the 24-hour AEEG was a more sensitive diagnostic tool than the rEEG and SD-EEG for the diagnosis and classification of epilepsy.

Keywords: Epilepsy, Diagnosis, Electroencephalogram, Sensitivity, Interictal Epileptiform Discharges

3.1 Introduction

Neurologists continue to face a significant clinical challenge when evaluating patients with first-onset seizures because an abnormal rEEG that suggests epilepsy raises the risk of future seizures by a factor of 2.1. Therefore, they should decide whether the first seizure is a real epileptic seizure, whether a patient should begin taking anti-epileptic medication, or whether there is a probability of seizure recurrence (Hasan *et al*., 2017). Unprovoked seizures affect 4-6% of the population by age 74 (Adelow *et al*., 2009). In 1 to 2 years after their first onset seizure, about 30% of patients will experience another seizure (Hernández- Ronquillo *et al*., 2020). The first seizure has serious life-threatening consequences, such as driving restrictions, injuries, unemployment, and accidents. The potential for seizure recurrence places a considerable psychological and social burden on patients, especially their families (Geut *et al*., 2017).

The sensitivity of a rEEG following an initial onset seizure is poor, ranging from 25% to 50%, while symptomatic aetiologies and the presence of IEDs on the EEG are the main predictors for seizure recurrence (Krumholz *et al*., 2007). However, longer-duration EEG and a sleep EEG improve the yield from 50% to 75% (Geut *et al*., 2017). Previous studies have reported that 13% of patients with unprovoked seizures and a negative rEEG were subsequently found to have positive SD-EEG results (Geut *et al*., 2017; Gustafsson *et al*., 2014; Renzel *et al*., 2016).

A study by Haq *et al.* (2019) ascertained the prevalence of patients with epilepsy with an unprovoked seizure but a negative rEEG. The authors found a greater detection rate of roughly 41% of IEDs on SD-EEG. Geut *et al.* (2017) compared the yield of IEDs from AEEG and sleep deprivation in patients with single unprovoked seizures. They assessed a group of patients in their study who had only an AEEG and compared their results to those of patients with an SD-EEG. After a year of follow-up, a diagnosis of epilepsy was found.

The authors concluded that both the SD-EEG and AEEG were equally accurate. Hence, it is necessary to evaluate the sensitivity of rEEG, 24-hour AEEG and SD-EEG in patients with first-onset seizures and its relationship with seizure recurrence. Therefore, the study aimed to determine the sensitivity of rEEG compared with the SD-EEG and 24-hour AEEG on patients with first-onset seizures presenting at the CMJAH.

3.2 Methods

3.2.1 Study design

This prospective cohort, quantitative, cross-sectional descriptive study was conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Department of Neurology, Gauteng Province, South Africa. Before the study commenced, ethical clearance was obtained from the University of Witwatersrand Research Ethics Committee (M210933) and the Gauteng Department of Health. Each participant provided informed consent before inclusion in the study, attached as Appendix A.

3.2.2 Study population

The study group (n=50) included Adult patients over the age of 18 years with clinically confirmed first-onset seizures, referred to CMJAH for epileptic seizure diagnosis. Patients with a history of previous epileptic seizures and previous diagnoses of epilepsy were excluded.

3.2.3 Data collection

Demographic, anthropometric and clinical data during the recruitment visit (visit 1). The clinical data included; medical history using a validated questionnaire by Azar *et al.* (2010) to investigate patient seizure and epilepsy history by the nurse at the epilepsy clinic and a neurologist, who booked the first rEEG after the consultation, triaged referrals.

Three EEG protocols were performed on each patient.
(1) rEEG data was recorded the same day after the patient consultation with the neurologist.
(2) SD-EEG data was recorded 5 days post the initial rEEG. SD-EEG data was recorded according to the minimum recording standards of the International Federation of Clinical Neurophysiology and the International League Against Epilepsy (Peltola *et al.*, 2023).)
(3) 24-hour AEEG data was recorded 2 days post the SD-EEG. 24-hour AEEG was recorded in accordance with the clinical practice guidelines by the International League Against Epilepsy and the International Federation of Clinical Neurophysiology (Tatum *et al.*, 2022)

3.2.4 Electroencephalogram

rEEG was recorded for 30 minutes on the recruitment visit, SD-EEG within 5 days after the rEEG for 60 minutes and 24-hour AEEG after 2 days of SD-EEG using 32-channel Nihon Koden EEG system, with scalp electrodes placed in accordance with the International 10-20

system (Seeck *et al*., 2017). rEEG and SD-EEG were recorded with hyperventilation and photic stimulation according to minimum recording standards of the International Federation of Clinical Neurophysiology and the ILAE (Peltola *et al*., 2023).

24-hour AEEG electrodes were secured with collodion, or conformed bandages were wrapped to minimize artefact and to ensure that the electrodes remained secured; skin impedances were confirmed below 5.000 ohms (Ω). The patients were told to push the event button for auras and spells. Patients and family members and patients further described events with a documented diary that included the clinical description, time and duration of each occurrence (Azar *et al.*, 2010).

Data were reviewed and interpreted by two qualified neurologists and one clinical technologist (neurophysiology) at CMJAH. Each interpreter had access to clinical data for all three EEGs. The findings were reported based on two categories: 1). EEG records showed the presence of focal spike/ sharp wave discharges and their location or generalised spike/sharp wave discharges. 2). EEG records with abnormal slowing activities with no IEDs were coded as abnormal but not suggestive of epilepsy, and only records with IEDs during the study period were considered diagnostic.

3.3 Statistical analysis

The analysis was conducted in Stata version 17 at a 95% confidence interval, and inferential results were interpreted at a 5% significance level. The study indicates that the P value was ≥ 0.05 level of significance. The analysis is stepwise, starting with frequency tables that provide counts and percentages, followed by a bivariate analysis of McNemars tests of association between the exposure variable (abnormal EEG) and the demographic predictors, followed by sensitivity tests in the form of Return on curves (roctab) analysis. Finally, logistic regression determines the factors that may affect EEG.

3.4 Results

3.4.1 Demographic information

Table 3.1: Demographic information

		Frequency	Valid Per cent
Location	COJ	35	70,0
	COE	15	30,0
Age_Group	18-34 years	28	56,0
	35-49 years	22	44,0
	Median=29 years (IQR: 22-41 years)		
Gender	Female	26	52,0
	Male	24	48,0
Ethnicity	African	37	74,0
	Indian	7	14,0
	White	6	12,0
	Total	50	100,0

Fifty patients were included in the study group. Patient sex distribution was almost identical, with slightly above half of the patients (n=26; 52%) being females, while (n=24; 48%) were male. The median age of the study group was 29 years, with an Interquartile Range of between 22 years (25th Quartile) and 41 years (75th Quartile). Thirty-five (35;70%) of the population was from Central Johannesburg, and the remaining 30% was from Central Ekurhuleni. Noteworthy, 74% of the population was of African ethnicity.

3.4.2 Clinical characteristics

3.4.2.1 Objective: To estimate the risk of seizure recurrence.

A total of 50 patients underwent Electroencephalography (EEG) between February 2022 and December 2022 at CMJAH. The following table presents interictal epilepticform discharges (IEDs) of rEEG, SD-EEG and 24-hour AEEG after the first onset seizure.

Table 3.2: Diagnostic findings in patients with a rEEG, SD-EEG, and 24-hour AEEG Abnormal implies the presence of interictal epileptiform discharges (IEDs)

	interictal epilepticform discharges/ Normal	Frequency	Valid Percent
ROUTINE EEG	Normal EEG. No interictal epilepticform discharges(IEDs)	39	78,0
	Abnormal EEG, Evidence of IEDs.	11	22,0
SLEEP DEPRIVED EEG	Normal EEG. No interictal epilepticform discharges(IEDs)	30	60,0
	Abnormal EEG, Evidence of IEDs,	20	40,0
24 HOURS AEEG	Normal EEG. No interictal epilepticform discharges(IEDs)	15	30,0
	Abnormal EEG, Evidence of IEDs,	35	70,0
	Total	50	100,0

Table 3.2 indicates that the prevalence of abnormal EEG on a 24-hour AEEG, suggestive of epilepsy with 24-hour AEEG with evidence of IEDs, was 70%, which is much higher compared to patients with rEEG (22%) and SD-EEG (40%).

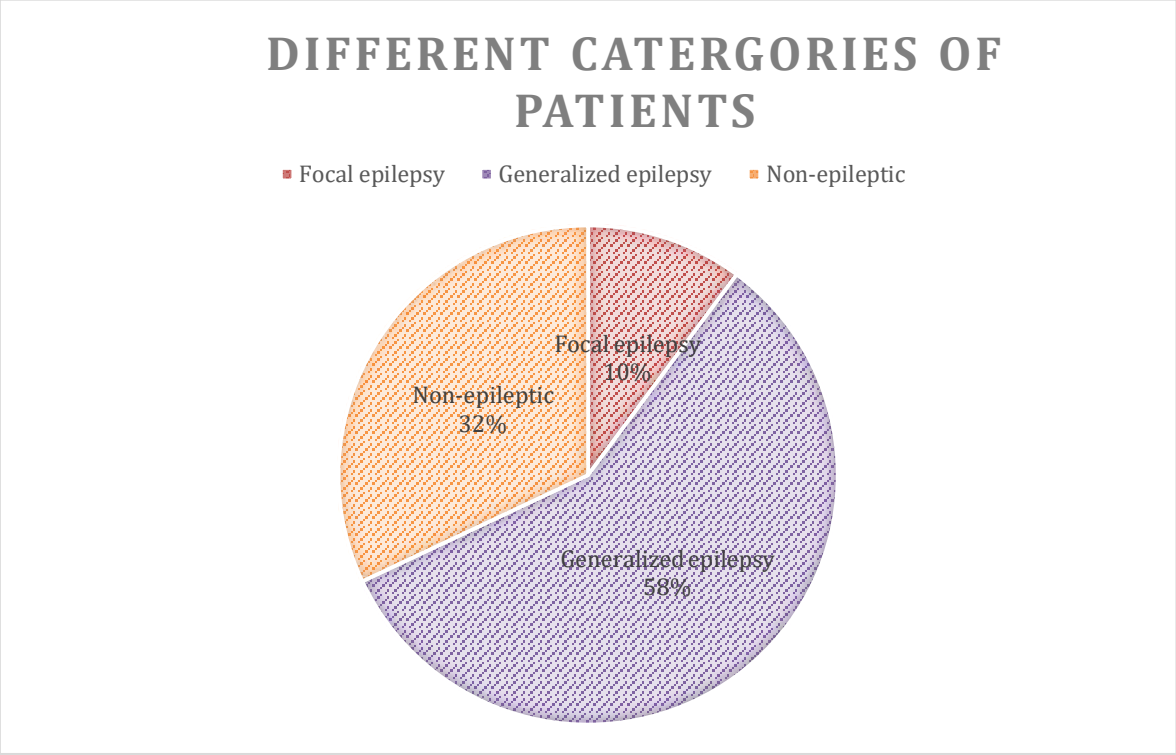

Figure 3.1: Graphical depiction of different categories of non-epileptic, focal epilepsy and generalised epilepsy.

Figure 3 shows a graphical depiction of several patient types with or without IEDs on their EEGs. Patients without epilepsy made up 32% of the population, patients with focal epilepsy made up 10%, and patients with generalised epilepsy made up 58%.

Table 3.3: Latency of recording IEDs

		Routine EEG IEDS	SD-EEG IEDS	24-hour AEEG IEDS
N	Valid	11	20	35
	Missing	39	30	15
Mean		**16.91**	**22.85**	**12.54**
Median		**17.00**	**20.00**	**10.00**
Skewness		-0.054	0.449	1.776
Std. Error of Skewness		0.661	0.512	0.398
Minimum		5	6	3
Maximum		28	48	45
Percentiles	25%	9.00	9.25	7.00
	50%	17.00	20.00	10.00
	75%	25.00	37.50	15.00

Table 3.3 depicts the median time in hours that IEDs were recorded. SD-EEG recorded a higher median time in recording IEDs, 20 hours (interquartile range: 9.25-37.5) compared to the rEEG-17 hours (interquartile range: 9.0-25.0). The 24-hour AEEG recorded the least time to record IEDs, 12 hours (interquartile range: 7.0-15).

3.4.3 Subgroup Analysis

Three subgroup analyses were conducted, stratified by duration of the three EEG protocols, age group, gender, ethnicity and location (hospital).

Table 3.4: Chi-square tests EEG by age

		Electroencephalography (EEG)			
	Age group	Normal	IEDs(abnormal)	Total	Exact Sig. (1-sided)
Routine	18-34 years	23	5	28	0,323
		82,1%	17,9%	100,0%	
	35-49 years	16	6	22	
		72,7%	27,3%	100,0%	
	Total	39	11	50	
		78,0%	22,0%	100,0%	
Sleep Deprived	18-34 years	17	11	28	0,568
		60,7%	39,3%	100,0%	
	35-49 years	13	9	22	
		59,1%	40,9%	100,0%	
	Total	30	20	50	
		60,0%	40,0%	100,0%	
24 Hours EEG	18-34 years	5	23	28	*0,036
		17,9%	82,1%	100,0%	
	35-49 years	10	12	22	
		45,5%	54,5%	100,0%	
	Total	15	35	50	
		30,0%	70,0%	100,0%	

*Significant at 5% level

Table 3.4 indicates significant associations between the age group and 24-hour AEEG. Patients aged 18-34 years subjected to 24-hour AEEG were more likely to have IEDs in the EEG; there was evidence of IEDs suggestive of epilepsy (82.1%) compared to those aged 35-49 years (54.5%). These results are suggestive that the intensity of IEDs in the EEG was highest among patients with 24-hour AEEG with significant differences across age: the middle age 18-34 years more likely to have epilepsy.

The results on the association between rEEG and SD-EEG were not statistically significant; however, they provide some insights. Proportionally, patients aged 18-34 years subjected to rEEG were more likely to have normal rEEG, with no IEDs (82.1%) compared to those aged 35-49. This means those aged 35 and above were more likely to have IEDs in the EEG (27.3% vs 17.9%).

Patients aged 18-34 years subjected to SD-EEG had an equal likelihood to have IEDs in the EEG; there was evidence of IEDs suggestive of epilepsy (60%) compared to those aged 35-49 years (59%).

Table 3.5: Chi-square tests EEG by gender

		Electroencephalography (EEG)			
Electroencephalography (EEG),	Gender	Normal	IEDs	Total	Exact Sig. (1-sided)
Routine	Female	20	6	26	0,560
		76,9%	23,1%	100,0%	
	Male	19	5	24	
		79,2%	20,8%	100,0%	
	Total	39	11	50	
		78,0%	22,0%	100,0%	
Sleep Deprived	Female	15	11	26	0,477
		57,7%	42,3%	100,0%	
	Male	15	9	24	
		62,5%	37,5%	100,0%	
	Total	30	20	50	
		60,0%	40,0%	100,0%	
24 Hours EEG	Female	6	20	26	0,211
		23,1%	76,9%	100,0%	
	Male	9	15	24	
		37,5%	62,5%	100,0%	
	Total	15	35	50	
		30,0%	70,0%	100,0%	

Table 3.5 indicates that the results on the association between gender and rEEG, SD-EEG, and the 24-hour AEEG were not statistically significant; however, they provide some insights. Female patients subjected to the rEEG had a slightly higher proportion of those with IEDs in the EEG (23.1%) than male patients (20.8%). Female patients subjected to SD-EEG had a slightly higher proportion of those with IEDs in EEG (42.3%) than male patients (37.5%). The results also show that female patients subjected to the 24-hour AEEG had a slightly higher proportion of those with IEDs in EEG (76.9%) than male patients (62.5%).

Table 3.6: Chi-square tests EEG by location

		Electroencephalography (EEG)			
Electroencephalography (EEG)	Gender	Normal	IEDs	Total	Exact Sig. (1-sided)
Routine (30 minutes)	COJ	28	7	35	0,430
		80,0%	20,0%	100,0%	
	COE	11	4	15	
		73,3%	26,7%	100,0%	
	Total	39	11	50	
		78,0%	22,0%	100,0%	
Sleep-Deprived (1 hour)	COJ	20	15	35	0,380
		57,1%	42,9%	100,0%	
	COE	10	5	15	
		66,7%	33,3%	100,0%	
	Total	30	20	50	
		60,0%	40,0%	100,0%	
24 Hours EEG (24 hours)	COJ	20	15	35	0,248
		57,1%	42,9%	100,0%	
	COE	10	5	15	
		66,7%	33,3%	100,0%	
	Total	30	20	50	
		60,0%	40,0%	100,0%	

Table 3.6 indicates that the results on the association between the City (location) and rEEG, SD-EEG, and the 24-hour AEEG were not statistically significant. However, they provide some insights. City of Johannesburg (CoJ) patients subjected to rEEG had a slightly lower proportion of those who had IEDs in the EEG (20%) compared to City of Ekurhuleni (CoE) patients (26.7%). CoJ patients subjected to SD-EEG had a slightly higher proportion of those with IEDs in the EEG (42.9%) than CoE patients (33.3%). The results also show that CoJ patients subjected to the 24-AEEG had a slightly higher proportion to those who had IEDs in the EEG (42.9%), compared to CoE patients (33.3%)-a similar trend to those who had SD-EEG.

3.4.4 Sensitivity Analysis

It is crucial to compare the difference in specificity or sensitivity between an examination and the reference standard when determining its effectiveness. This section compares the sensitivity of a rEEG, SD-EEG and 24-hour AEEG after the first onset seizure in patients presenting at the CMJAH. The McNemar chi (2) test was first utilised to compare the discordance of two dichotomous responses (1=abnormal, 0=normal) for the paired EEG samples.

Table 3.7: McNemar's test (exact) comparing the paired SD-EEG and rEEG samples.

		SLEEP DEPRIVED EEG					
		Normal		IEDs (Abnormal)		Total	
ROUTINE EEG	Normal	30	76,9%	9	23,1%	39	100,0%
	Abnormal	0	0,0%	11	100,0%	11	100,0%
Total		30	60,0%	20	40,0%	50	100,0%
Exact Sig. (2-sided)	McNemar Test	.004c					

c. Binomial distribution used.

For each observation, a positive test was defined as the presence of IEDs, coded 1 in the data. The results indicate that the SD-EEG could identify all patients with IEDs in the EEGs when using the rEEG. However, SD- EEG identified 23.1% of normal rEEG as abnormal, having IEDs in the EEG. Among the 30 recorded as normal using rEEG, nine were recorded as having abnormal EEG with the presence of IEDs using the SD-EEG.

Table 3.8: Detailed report of sensitivity and specificity for the SD-EEG, compared to rEEG.

Cutpoint Sensitivity	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= Normal)	100.00%	0.00%	40.00%	1.0000	
(>= Abnor..)	55.00%	100.00%	82.00%		0.4500
(> Abnor..)	0.00%	100.00%	60.00%		1.0000

Sensitivity explains what proportion of the positive results were accurately classified. In this case, the proportion of the actual epileptic patients whom the SD-EEG model correctly detected was 55%. Specificity explains what proportion of the results were accurately classified. The proportion of non-epileptic patients whom the model correctly identified was 100%.

These results suggest that compared to rEEG, the SD-EEG test for detecting patients with epilepsy was sensitive 55% of the time. Further analysis was done to confirm these results, a logistic regression analysis followed by a classification analysis (based on the regression). The following tables of results confirm these results.

Table 3.9: Logistic regression showing the strength and effect of SD-EEG on rEEG.

ROUTINE_EEG	Odds Ratio	Std. Err.	z	P>z	[95% Conf. Interval]
SLEEP_DEPR	1				
_cons	1.222	0.549	0.45	0.655	0.506-2.949

The logistic regression was run to test the strength of the effect of the SD-EEG on the Routine EEG. The results were not significant, as the p-value was above 0.05 (CI: 0.506-2.949). The results suggest that the performance of the SD-EEG was 0.2 times stronger than the Routine EEG (β=1.2, $p<0.05$), which is a negligible difference. The following table provides results on the sensitivity of the SD-EEG based on the regression.

Table 3.10: Logistic model for SD-EEG

Sensitivity		Pr(+ D)	100.00%
Specificity		Pr(-~D)	0.00%
Positive predictive value		Pr(D +)	55.00%
Negative predictive value		Pr(~D -)	.%
False + rate for true ~D		Pr(+~D)	100.00%
False - rate for true D		Pr(- D)	0.00%
False + rate for classified	+	Pr(~D +)	45.00%
False - rate for classified	-	Pr(D -)	.%
Correctly classified			55.00%

Classified + if predicted Pr(D) >= .5
True D defined as SD-EEG != 0

In table 3.10, an observation is classified as positive if its predicted probability is 1 (abnormal). The overall correct classification rate of the positive (abnormal) is estimated to be 55%. A false positive was classifying a patient as normal when abnormal; in this case, only 45% of the patients without epilepsy were correctly classified. The Positive Predictive value (PPV) for the SD-EEG was 55%; this means that the proportion of the patients with epilepsy whom SD-EEG correctly detected was 55%.

In conclusion, SD-EEG on detecting patients with epilepsy was sensitive 55% of the time; it classified false positives (patients without epilepsy) 45% of the time when they had no epilepsy (correct classification). However, the difference between the SD-EEG and the rEEG was not statistically significant.

3.4.5 24-hour AEEG versus SD-EEG

Hypothesis: 24-hour AEEG will increase the latency to record interictal, epilepticform discharges compared to SD-EEG**.**

Table 3.11: McNemar Test -24-hour AEEG and SD-EEG

		SLEEP DEPRIVED EEG			
		Normal	Abnormal	Total	Exact Sig. (1-sided)
24 HOURS EEG	Normal	15	0	15	McNemar Test
		50,0%	0,0%	30,0%	
	Abnormal	15	20	35	
		50,0%	100,0%	70,0%	
Total		30	20	50	
		100,0%	100,0%	100,0%	.000c

Table 3.11 indicates that 15 of the 30 patients (50%) recorded as abnormal by the SD-EEG were classified as abnormal by the 24-hour AEEG. Both methods agreed on the abnormal classification.

Table 3.12: 24-hour AEEG level compared to the SD-EEG

Cutpoint S	Sensitivity	Specificity	Classified	LR+	LR-
(>= Normal)	100.00%	0.00%	70%	1.0000	
(>= Abnor..)	57.4%	100.00%	70.00%		0.428
(> Abnor..)	0.00%	100.00%	30.00%		1.0000

The resulting sensitivity and specificity are 100% and 0%, respectively. The 24-hour AEEG correctly classified 57.4% of the 50 patients in this case, compared to the SD-EEG. This means that the proportion of patients with epilepsy whom 24-hour AEEG correctly detected was 57.4%. The proportion of patients without epilepsy whom 24-hour AEEG correctly identified was 100%.

Further analysis is done to confirm these results, a logistic regression analysis followed by a sensitivity analysis based on the regression. The following tables of results confirm these results.

Table 3.13: Logistic regression showing the strength and effect of the 24-hour AEEG

SLEEP_DEPR	Odds Ratio	Std. Err.	Z	P>z	[95% Conf. Interval]
T_24_HOURS_EEG	1	(omitted)			
_cons	1.333333	.45542	0.84	0.400	.6826499-2.60423

The logistic regression was run to test the strength of the effect of the 24-hour AEEG on the SD-EEG. The results were not significant, as the p-value was above 0.05 (CI: 0.682-2.604). The results suggest that the performance of the 24-hour AEEG was 0.3 times stronger than the SD-EEG (β=1.2, $p<0.05$), which is also a negligible difference. The following table provides results on the sensitivity of the 24-hour AEEG based on the regression.

Table 3.14: Logistic model for 24-hour AEEG

Classified + if predicted Pr(D) >= .5
True D defined as 24-hour AEEG != 0

Sensitivity		Pr(+ D)	100.00%
Specificity		Pr(-~D)	0.00%
Positive predictive value		Pr(D +)	57.14%
Negative predictive value		Pr(~D -)	.%
False + rate for true ~D		Pr(+~D)	100.00%
False - rate for true D		Pr(- D)	0.00%
False + rate for classified	+	Pr(~D +)	42.86%
False - rate for classified	-	Pr(D -)	.%
Correctly classified			57.14%

Table 3.14 indicates that the overall rate of correct classification of positive patients with epilepsy is estimated to be 57.1%, slightly higher than the SD-EEG. The false positive was estimated at 42.9%, meaning that 42.9% of the patients without epilepsy were correctly classified. The Positive Predictive value (PPV) for the 24-hour AEEG was 57.1%; this means that the proportion of patients with epilepsy whom 24-hour AEEG correctly detected was 57.1%.

In conclusion, the 24-hour AEEG on detecting patients with epilepsy was sensitive 57.1% of the time; it classified false positives (patients without epilepsy) 42.9% of the time when they had no epilepsy (correct classification). However, the difference between the SD EEG and the 24-hour AEEG was not statistically significant.

3.4.6 Logistic Regression Analysis

To determine demographic factors that determine the sensitivity of a rEEG, SD-EEG and 24-hour AEEG after the first onset seizure in patients presenting at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). Three logistic regression models were run to check if the EEG was sensitive to demographic factors, such as gender, age and hospital. The 24-hour AEEG was the only one with significant results at the 5% level; hence, we present only those results.

Table 3.15: Logistic regression showing factors that could affect rEEG

rEEG	Odds Ratio	Std. Err.	Z	P>z	[95% Conf. Interval]
Gen					
Male	.9574705	.6861357	-0.06	0.952	.2350409 -3.900384
Location					
COE	1.408311	1.125099	0.43	0.668	.2942215-6.740978
1.Age_Group	1.519508	1.098698	0.58	0.563	.3683252-6.268654
_cons	.2083669	.140916	-2.32	0.020	.0553569-.7843067

Table 3.15 indicates that gender, location and age of the patients were not factors that affected the rEEG sensitivity; the results are not statistically significant (p>0.05).

Table 3.16: Logistic regression showing factors that could affect SD-EEG

SLEEP_DEPR	Odds Ratio	Std. Err.	z	P>z	[95% Conf. Interval]
Gen					
Male	.7739282	.4629371	-0.43	0.668	.2396301-2.499539
Location					
COE	.6569134	.4644737	-0.59	0.552	.1643093-2.62636
1.Age_Group	.9270924	.5642138	-0.12	0.901	.2812517-3.055983
_cons	.884685	.4754919	-0.23	0.820	.308527-2.536788

Table 3.16 indicates that gender, location and age of the patients were not factors that affected the SD-EEG performance/sensitivity; the results are not statistically significant (p>0.05).

Table 3.17: Logistic regression showing factors that could affect 24-hour AEEG

(Significant at 5% level)

T_24_HOURS_EEG	Odds Ratio	Std. Err.	z	P>z	[95% Conf. Interval]
Gen					
Male	.2846477	.2159256	-1.66	*0.098	.0643592-1.25894
Location					
COE	.4887994	.4037678	-0.87	0.386	.0968287-2.4675
1.Age_Group	.1676061	.128182	-2.34	*0.020	.0374375-.7503654
_cons	16.11518	13.88237	3.23	0.001	2.978313-87.19672

*

Table 3.17 indicates that gender was a predictor of the 24-hour AEEG outcomes (abnormal EEG) in this study; male patients were less likely to have abnormal EEG, with weak results at a 10% level (OR=0.29, p<0.1). Age was also a predictor of the 24-hour AEEG; patients aged 18-34 years were less likely to have abnormal 24-hour AEEG outcomes. Location was not a factor that influenced 24-hour AEEG. These results imply that the 24-hour AEEG was also sensitive to gender to a lesser extent and the patient's age to a larger extent.

3.5 Discussion

This study aimed to expand our understanding of electrodiagnostic testing in patients presenting with first onset seizure at CMJAH, identify the sensitivity and latency of IEDs, and estimate the risk of seizure recurrence associated with IEDs presence in rEEG, SD-EEG, and 24-hour AEEG. Given that, the most recent definition of epilepsy by the ILAE considers the presence of a single unprovoked seizure, and the presence of IEDs in the rEEG remains essential for epilepsy diagnosis (Hernández-Ronquillo *et al*., 2020; Fisher *et al*., 2014).

The rEEG has proven to be useful in the prognostic determination of seizure recurrence. The American Academy of Neurology (AAN) states that adults have a 47% likelihood of having another seizure after the first and a 77% chance if the EEG shows signs of IEDs (Shafait *et al*., 2021). However, due to a limited time sample and the biophysics of the cortical neurophysiology signal, the rEEG sensitivity as a diagnostic tool is low, approximately 30–50% (Batista *et al*., 2021). There is proof that SD-EEG, serial routine EEGs and investigations conducted soon after an epileptic seizure all boost the overall diagnostic yield (Keezer *et al*., 2016).

In comparing AEEG to rEEG, a higher increase rate in IED detection has been identified in AEEG (Dash *et al*., 2012). The findings in this study suggest that the SD-EEG performed 0.2 times better than the rEEG, while the 24-hour AEEG performed 0.3 times better than the SD-EEG. Of the 50 patients, 11 (22%) had IEDs on their rEEGs, while seven to eight out of ten (78%) had normal rEEGs, indicating that none of the patients had IEDs. This suggests that if the study had solely focused on a rEEG, about 50% of the EEG recordings containing IEDs would have been lost. Our results are consistent with those of Wyman *et al*. (2017), who reported that a single conventional EEG has limited sensitivity in detecting IEDs following the first unprovoked seizure, which varies from 21 to 48%. In an rEEG recording, Stages I and II Sleep were not attained.

The prevalence of abnormal EEG with the evidence of IEDs, which are suggestive of epilepsy with SD-EEG, was 20 (40%); six out of ten (60%) patients had normal SD-EEG, and they were no signs suggestive of IEDs among them. IEDs detected were focal and generalised spike/sharp and wave. IEDs in SD-EEG were exclusively seen during sleep in 10 patients (50%). SD-EEG on detecting patients with epilepsy was sensitive 55% of the time, and it classified false positives (patients without epilepsy) 45% of the time when they had no epilepsy (correct classification). This is in agreement with previous studies, which reported the sensitivity of SD-EEG (45%) when detecting IEDs (Geut *et al*., 2017; Giorgi *et al*., 2013).

However, our findings differed from one of Keezer *et al.* (2016), who reviewed the findings of 46 patients with previously normal rEEGs who underwent 24-hour AEEGs and 30 to 60-minute SD-EEGs. They found that the percentage of patients with IEDs was the same for 24-hour AEEG and SD-EEG (24-33%) and that 24-hour AEEG was more likely to find IEDs than SD-EEG. However, without the assistance of a neurologist, their EEGs were analysed by Stellate Systems Harmonie software with an automated seizure pattern detector and two electroencephalographers.

In this study, the duration of the AEEG was 24 hours, the rEEG was 30 minutes, and the SD-EEG was 1 hour. Most IEDs were found during non-rapid eye movement (Non-REM) stages I and II of sleep. The increased detection of IEDs in the 24-hour AEEG in this study may be due to sleep, which is thought to be a potent IED activation process.

Our study evaluates the IEDs' latency in assessing the first onset seizure. The latency of the first IEDs differed from 8 minutes to 24 hours. Twenty-two per cent (11/50) of the patients had their IEDs in the 30-minute rEEG recording. The percentage increases to 40% (20/50) who had their first IEDS within the 1 hour of SD-EEG recording. In most IEDs, 70% (35/50) of patients had their first IEDs within 24 hours. Thirty per cent (15/50) of the patients had no IEDs in their EEG recordings. Our data indicate that, out of the 50 patients in the study, 58.1% of patients had generalised epilepsy, and 10.15% had focal epilepsy (TLE). This classification of seizures was based on the EEG.

All patients with generalised epilepsy got IEDs within eight hours, while those with focal epilepsy required closer monitoring since IEDs took between 12 and 24 hours to be obtained. For detecting IEDs, the sensitivity of rEEG was 23% in females and 20.8% in males. Compared to male patients (37.5%), female patients who underwent SD-EEG showed greater IEDs in rEEG (42.3%). The results also reveal that compared to male patients (62.5%), female patients who underwent the 24-hour AEEG had a greater percentage of IEDs in SD-EEG (76.9%). Except that females detected more IEDs than males, there was no statistically significant difference between the detection of IEDs in males and females. Our results are consistent with those of Siddiqi *et al*. (2017), who found no statistically significant differences between the genders and stated that the yield of AEEG to capture IEDs was 39% in females and 21% in males.

The patients in this study ranged in age from 18 to 39 years, with a median age of 29. Although our results between rEEG and SD-EEG in this study did not reach statistical significance, certain conclusions can still be drawn. Patients between the ages of 18 and 34 who underwent rEEG had a higher proportion of normal rEEGs (82.1%) without IEDs than patients between the ages of 35 and 49. This indicates that patients above 35 years had a higher likelihood of having IEDs in the EEG (27.3% vs. 17.9%). Patients between the ages of 18 and 34 who had SD-EEG had a similar risk of having IEDs; there was evidence of IEDs suggestive of epilepsy (60%) compared to those between the ages of 35 and 49 (59%). Significant correlations were found between the age groups.

Those between the ages of 18 and 34 who underwent 24-hour AEEG showed IEDs indicative of epilepsy in a higher percentage (82.1%) than patients between the ages of 35 and 49 (54.5%). Patients between 18 and 34 were less likely to have abnormal 24-hour AEEG outcomes.

These results imply that the 24-hour AEEG was also sensitive to gender to a lesser extent and the patient's age to a larger extent. Our findings indicate that a rEEG and SD-EEG were able to detect the first IEDs in generalised epilepsy, and 24-hour AEEG was able to detect more IEDs in both generalised epilepsy and focal epilepsy. All patients with generalised epilepsy had their IEDs within 8 hours, but the patients with focal epilepsy needed to be monitored more as IEDs were obtained between 12-24 hours. Due to a lack of power, this study does not find any statistically significant differences in the sensitivity and latency to the IEDS between the rEEG, SD-EEG, and 24-hour AEEG.

Because all patients in this study recovered to their pre-seizure baseline after the seizure, the patient history and physical examination performed on each patient did not predict the most prevalent metabolic disturbances, such as glucose abnormalities and hyponatremia. Consequently, not all of the study's patients had metabolic tests completed. The American College of Emergency Physicians' clinical policy states that when a patient returns to normal baseline after complaining of a new-onset seizure, complete metabolic testing is not advised (Huff *et al*., 2014).

3.6 Conclusion

The study results indicated that patients with the first seizure onset present at the CMJAH at a median age of 29 years, and 70% of the affected population is from Central Johannesburg of African ethnicity.

To the best of our knowledge, the sensitivity of rEEG, SD-EEG and 24-hour AEEG in patients presenting with first-onset seizures has not been directly compared in any previous African studies**.** This prospective study comparing the rEEG, SD-EEG, and 24-hour AEEG was reasonable and practical, demonstrating the sensitivity of a rEEG, SD-EEG, and 24-hour AEEG and their significance in the diagnosis of first-onset seizures. Our findings suggest that the SD-EEG was more sensitive in detecting IEDs than the rEEG, and additionally, the 24-hour AEEG was shown to be more sensitive in detecting IEDs than the rEEG and SD-EEG.

Overall, the results of this study found that the 24-hour AEEG was a more sensitive diagnostic tool than the rEEG and SD-EEG for the diagnosis of epilepsy. The need for further research with a large sample size and an adult population with suspected epilepsy might assist in clarifying the sensitivity of the three EEG modalities and epilepsy diagnosis variables affecting the sensitivity.

3.6.1 Limitations

This study had a few limitations.

1. The limitations encountered during the study include receiving an ethical clearance letter from the ethics committee later than expected, which delayed our data collection process.
2. Because of the study's small sample size and lack of power to detect differences between the three EEG protocols, the results were not statistically significant.
3. Artefacts were present in rEEG, SD-EEG and 24-hour AEEG. These artefacts were more in 24-hour AEEG than rEEG and SD-EEG. This might have made it challenging to interpret the EEG recordings.

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CHAPTER 4: GENERAL CONCLUSION

To the best of our knowledge, the sensitivity of rEEG, SD-EEG and 24-hour AEEG in patients presenting with first-onset seizures has not been directly compared in any previous studies in the African continent. A rEEG remains an important test in the management of patients with epilepsy. It can characterize epilepsy after first-onset seizures and detect epilepsy in people of all ages and genders. Compared to rEEG, an SD-EEG demonstrated a higher rate of IEDs detection.

Compared to rEEG and SD-EEG, our study demonstrates that 24-hour AEEG had a greater IED detection rate and a strong positive predictive value. This highlights the need for 24-hour AEEG as an additional diagnostic tool in patients with first-onset seizures, especially if the results of the rEEG and SD-EEG are unclear.

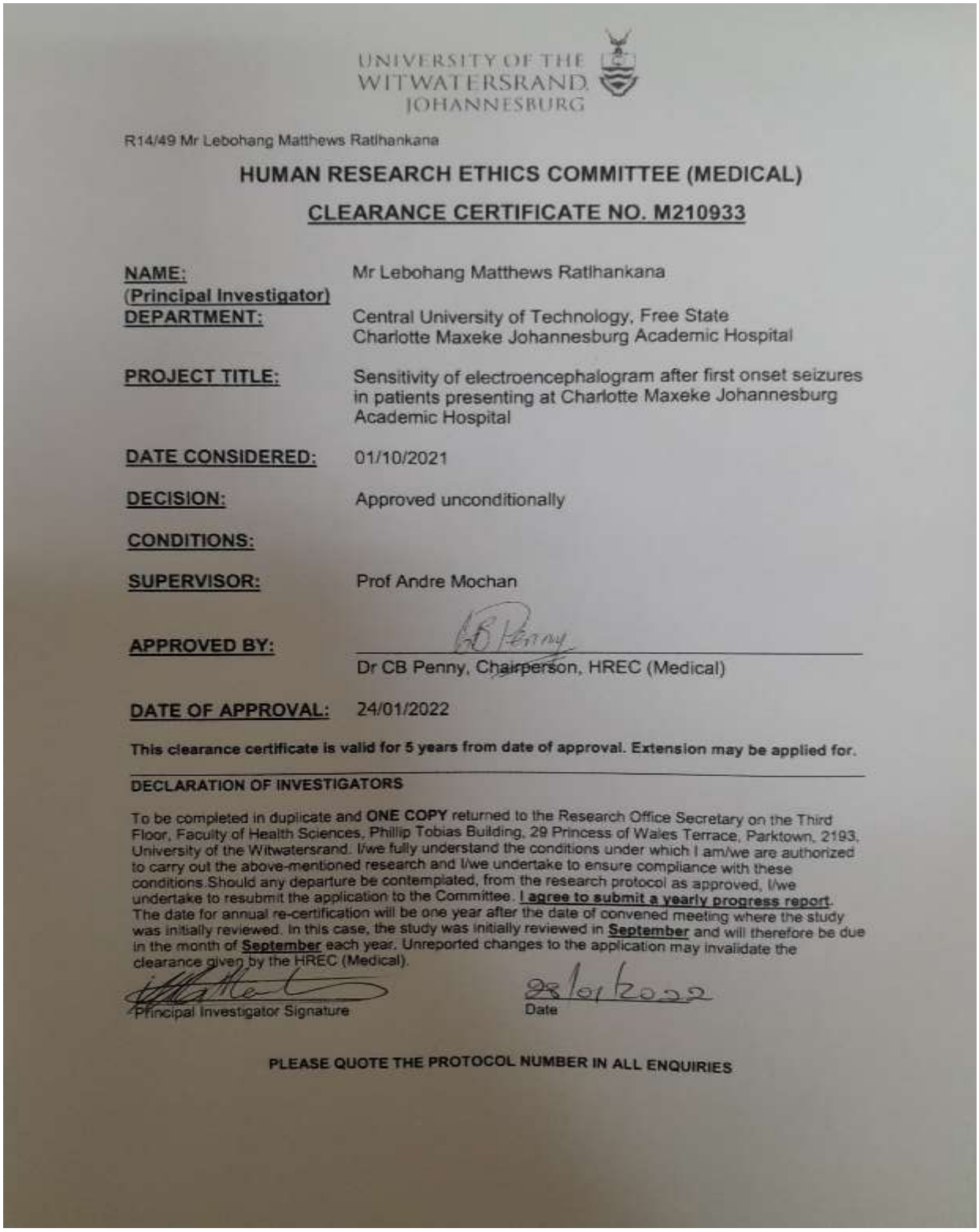
We conclude that the 24-hour AEEG is an effective diagnostic tool in adult patients with epilepsy for a variety of reasons, including the evaluation of patients with non-epileptic episodes, the diagnosis of suspected epilepsy, suspected seizures of sleep disturbances and the classification of seizure type for the selection or adjustment of anti-epileptic medication. In our clinical setup, we recommend that all patients who present with first-onset seizures and have a normal rEEG and SD-EEG undergo a 24-hour AEEG.

While our study has a crucial advantages to compare three different EEG protocol records. As a result, we could control any general predictors that might have impacted the sensitivity of the rEEG, SD-EEG and 24-hour AEEG.

We recommended that further research be conducted with an adult population and a large sample size to understand better the sensitivity of the rEEG, SD-EEG and 24-hour AEEG. To address the issues that this study has identified since this is an important element for future research in the field of Clinical Neurophysiology in individuals experiencing their first seizure.

APPENDICES

Appendix A1: HREC Approval Letter



UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Mr Lebohang Matthews Ratlhankana

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M210933

NAME: (Principal Investigator)	Mr Lebohang Matthews Ratlhankana
DEPARTMENT:	Central University of Technology, Free State Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Sensitivity of electroencephalogram after first onset seizures in patients presenting at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	01/10/2021
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Andre Mochan
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	24/01/2022

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193. University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **September** and will therefore be due in the month of **September** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

28/01/2022
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix A2: Department of Health Approval Letter

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
OFFICE OF THE SENIOR CLINICAL MANAGER

Enquiries: Ms. TT Mahlangu
Email: Thandi.Mahlangu4@gauteng.gov.za
Tel: 011 488 3365
Ref: 1/7/2
Date: 24 March 2022

GP_202106_025

To: Lebohang Matthews Ratlhankana

RE: FINAL APPROVAL OF STUDY

TITLE: SENSITIVITY OF ELECTROENCEPHALOGRAM AFTER FIRST ONSET SEIZURES

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported/~~Not Supported~~
Signed by: Jayshna Punwasi
Signed at: 2022-03-25 07:09:02 +02:00
Reason: Witnessing Jayshna Punwasi

Dr J. Punwasi
Senior Clinical Manager

Approved/~~Not Approved~~

Ms. G Bogoshi
Chief Executive Officer

Appendix B1: Detailed Methodology

B1.1 Study site

The research study was conducted at Charlotte Maxeke Johannesburg Academic Hospital, Department of Neurology, Charlotte Maxeke Johannesburg Academic Hospital is located in South Africa, Gauteng Province, Johannesburg, Parktown, Jubile road 2001.

B1.2 Study design

This is a prospective cohort, quantitative, cross-sectional study.

B1.3 Study population

The targeted population in this study included adult patients older than 16 years of age referred to CMJAH who experienced an epileptic seizure and whose first onset seizure was clinically corroborated and were sequentially asked to participate in the study. The researcher presented the purpose of the study and its limitations (i.e., routine EEG, sleep-deprived EEG and 24-hour AEEG) of being a participant in this study. After signing consent, patients were booked for a routine EEG, Sleep Deprived EEG and 24-hour Ambulatory EEG on the next available date.

There was no attempt to influence how procedures were performed regarding factors such as EEG recording technique and summation potentials. Thus, the study results represent the practice at the time of diagnosis at the research site.

Fifty-six patients' EEG data were captured in the database over the 11 months, of which 6 were excluded from the study due to missing follow-up and 24-hour AEEG appointments.

B1.4 Pilot study

A total of 20 participants took part in a pilot study where the rEEG, SD-EEG and 24-hour ambulatory EEG were done, and the results were compared among the three EEG modalities. The pilot study participants were not included in the main study. This was done to check whether the data collection tools answered the study's objectives. The results of the pilot study warranted further research.

B1.5 Sampling approach

B1.5.1 Convenience sampling

The primary sampling approach used in the research study was convenience sampling, a non-probability sampling technique that allowed the researcher to use those accessible and available (Oyen, 2013). In this study, epilepsy clinic patients or outpatients referred to the neurophysiology department at CMJAH who have experienced a first-onset epileptic seizure were enrolled according to their availability and accessibility

B1.5.2 Sample Size

A sample is a portion of a population considered representative of the wider population without bias (Suresh *et al.*, 2011). This study implemented a confidence level of 95%, which

implies that the sample was generated 100 times, and at least 95% of these samples accurately reflected the population's characteristics. A power analysis was used to estimate the minimum sample size needed for the study, given a desired significance level (95%), effect size, and statistical power. This study sample consisted of all patients who had experienced a first-onset seizure and were referred to CMJAH between February 2022 and December 2022.

B1.6 Criteria for patients included and excluded in the study

B1.6.1 Inclusion criteria

- Patients with epilepsy or clinical suspicion of epilepsy.
- Patients aged between 18 years and 50 years.

B1.6.2 Exclusion criteria

- Refusal to give informed consent.
- Patients younger than 18 years and older than 50 years.
- Patients with a suspicious history of a previous epileptic seizure.
- Patient with a previous diagnosis of epilepsy

B1.7 Subject Identification

Patients were identified by their hospital-assigned numbers (GT numbers), and a study number was allocated to each participant (P1).

B1.7.1 Confidentiality

Throughout the study, patient confidentiality was upheld, and there was never a confidentiality violation. Only the research team leading this study had access to patient information, including patient names.

B1.1 Figure: Conceptual framework for data collection

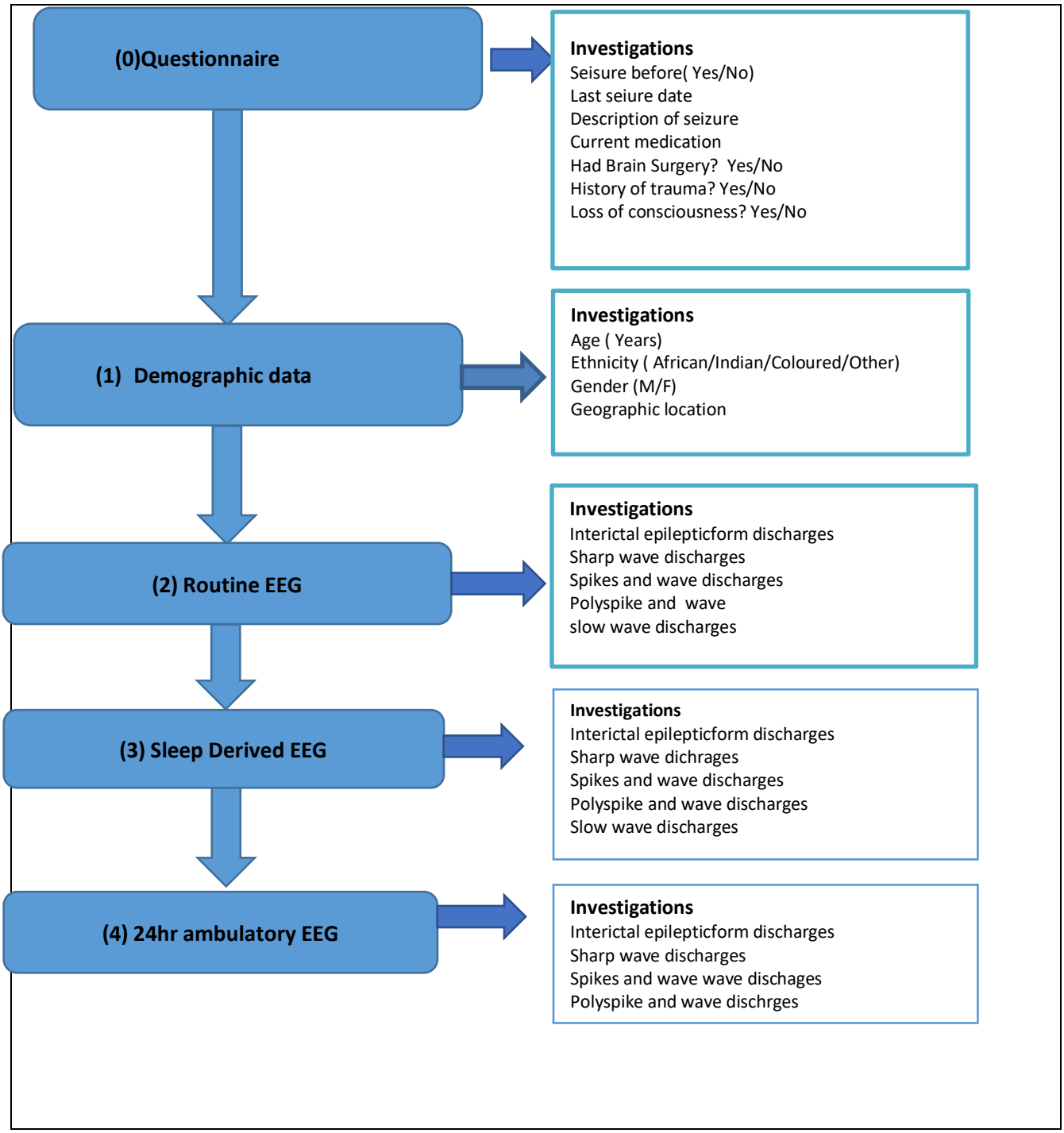


Figure B1.1 above provides a conceptual framework for data collection for the study

B1.9 Special investigations

All of the special investigations included in this study were routine ones for a patient who had just experienced their first seizure. Patients were not subjected to additional tests simply because they agreed to participate in the research study.

B1.10 Clinical and demographic information

The nurses at CMJAH obtained the demographic information from a standardized questionnaire used at the hospital. The clinical information included data on the first onset seizure, the initial assessment, the date of the referral physician, the time of the initial assessment and the impression by the neurologist.

B1.10.1 Demographic data

The following demographic information was collected for each participant:

- Age (Years)
- Ethnicity (African/Indian/Coloured/Other)
- Gender (Male/Female)
- Geographic location

B1.11 Electroencephalogram (EEG)

Electroencephalogram information was collected from the study participants who consented to participate using the Nihon Kohden Neuropack digital EEG instrument. The EEG recordings were obtained by placing electrodes on the scalp with conductive gel, usually after preparing the scalp area by light abrasion to reduce impedance due to keratinised skin cells.

The international 10-20 system specified the electrode's location and names…. 25 recording electrodes were used (Seeck *et al.*, 2017). Since an EEG voltage signal represents a difference between the voltages at the two electrodes, the display of EEG for the reading encephalogram will be seen in several ways. The representation of the EEG channels is called montage (Trujillo *et al*., 2017).

B1.11.1 The following EEG frequency bands were recorded.

Although the EEG signal varies significantly, the EEG waveform is considered to be between 0.3 and 30Hz based on clinical importance. The alpha, theta, delta, and beta frequencies are the four different frequency bands that make up the clinically significant frequency range of the EEG signal. The various nervous system actions produce these frequencies. The normal EEG

waveform's classification is based on frequencies and occurrence when a subject undergoes EEG recording (Medithe *et al.*, 2016). When one frequency band displays characteristics of a higher or lower frequency band, the EEG waveform is deemed abnormal. Every frequency band has distinct characteristics, such as shape, amplitude, and level of consciousness. Some EEG waveforms, such as sleep spindles, appear spontaneously in some episodes and stage II of NREM sleep. (Medithe *et al.*, 2016).

Table B1.1 EEG waves classification based on frequencies (Medithe *et al.*, 2016).

Type of waveform	**Characteristics**	**State of occurrence**
Alpha waves	Frequency range 8-13Hz Amplitude is mostly less than 50µV.	When the patient is Awake but calm, with their eyes closed.
Beta waves	Frequency range 13-30Hz Small in amplitude symmetric	When the patient demonstrates Alertness, mental exertion, Having taken drugs
Theta waves	Frequency range 4-8Hz Larger amplitude than beta	Early stages of drowsiness.
Delta waves	• Frequency range 1-4Hz or less • Large amplitude	Deep sleep, non-REM sleep unconscious

Table B1.2. EEG waves classification based on sleep features (Medithe *et al.*, 2016).

Type of Waveform	Characteristics	State of occurrence
K- complex waves	Delta frequency, large amplitude, sharp apex. Symmetric. Rhythmic theta waves follow it.	Stages 2 and 3 of sleep
Vertex sharp waves	Occur in Parasagittal regions	During sleep stage-2
Sleep spindles	Frequency more than 13Hz. Occur in Parasagittal regions.	During stage 2
Positive Occipital Sharp Transients of Sleep (POSTS)	Bilaterally positive waves, Triangular in shape Seen in the Occipital region	During stage 2 of sleep

Normal EEG: Alpha rhythm

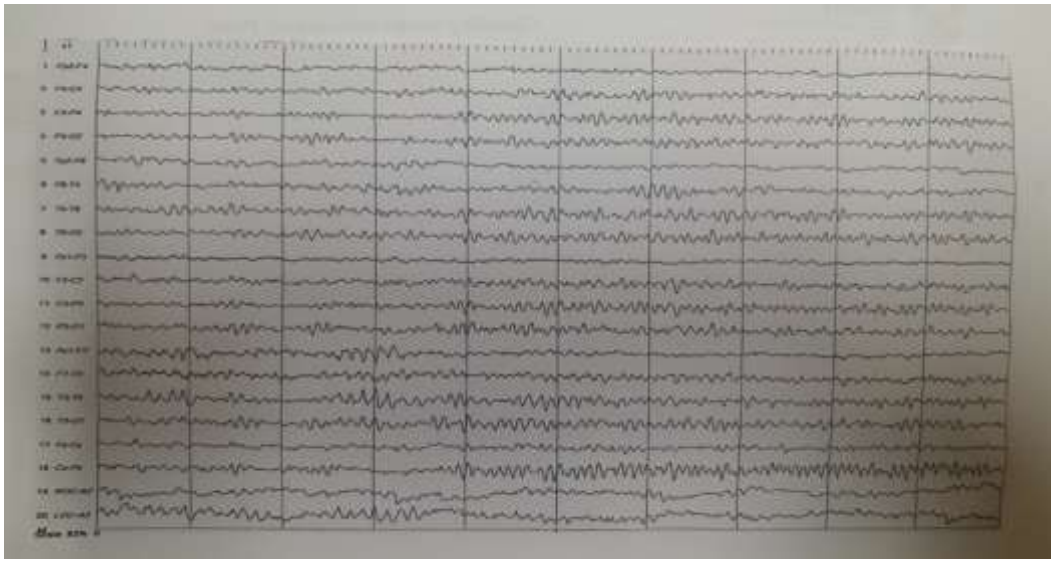


Figure B1.2. Indicates a low to medium voltage, mixed frequencies of 12–13 Hz posterior alpha rhythm, and fast frequency beta in frontal areas signify a typical EEG recording. It was said that this EEG was normal.

Generalised IEDs: Absence seizure

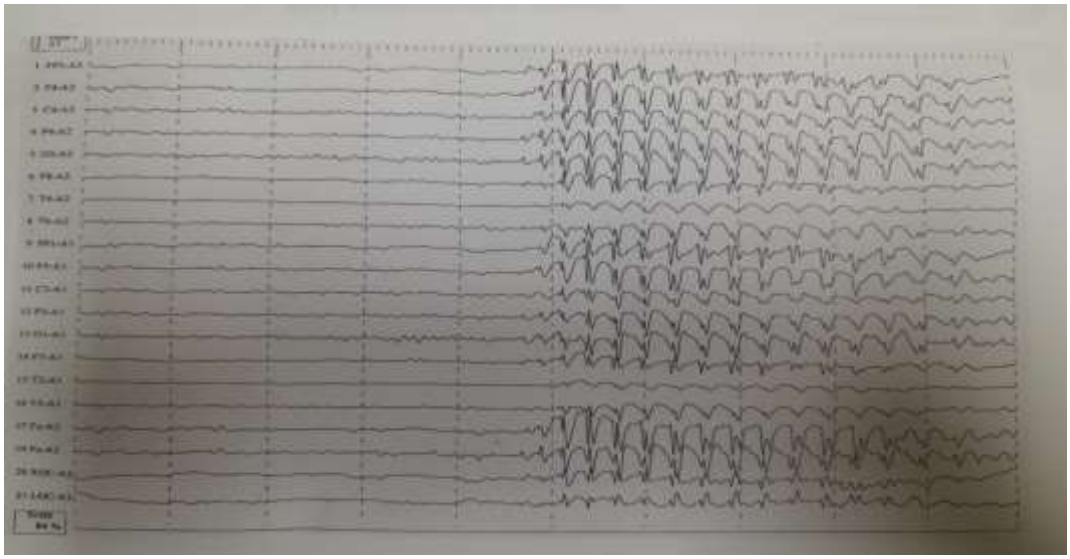


Figure B1.3. Indicates a 3 per second spike and wave interictal epilepticform discharges. Common reference montage was used to display better the configuration of these generalised events than bipolar montage. This EEG was reported as suggestive of absence seizure.

Generalised IEDs: Generalised tonic-clonic seizure

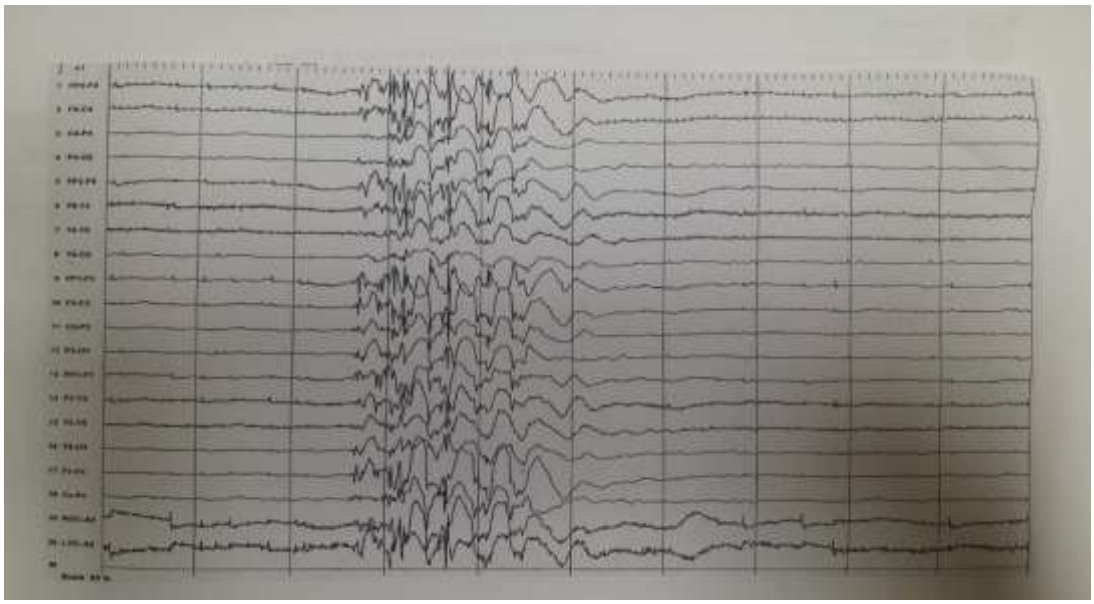


Figure B1.4. A Generalised interictal epilepticform discharges of poly spikes and 2-4Hz slow waves. This EEG was reported as suggestive of a generalised tonic-clonic seizure.

Focal IEDs: Temporal Lobe Epilepsy

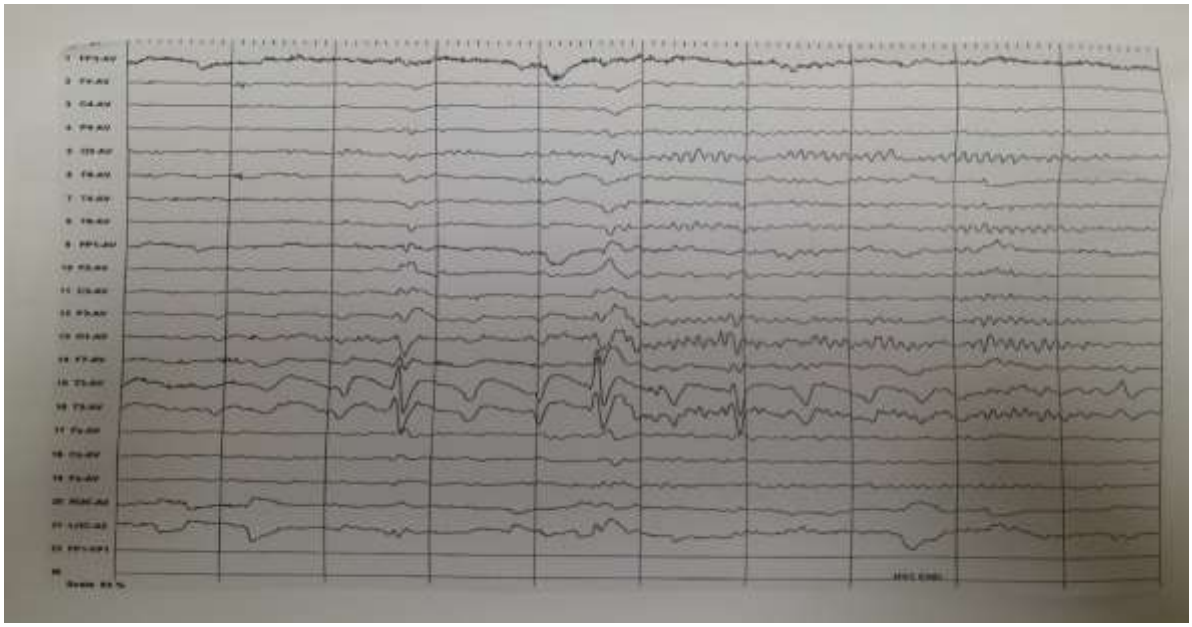


Figure B1.5 Indicates a high voltage focal left mid and post temporal IEDs and delta-theta slow wave activity. This EEG was reported as suggestive of Temporal Lobe Epilepsy.

In the digital signal processing circuit, the accuracy of the analogue to digital converter, filter characteristics and setting of the number of the averaging times were the important items to consider. Therefore, EEG analyses were performed using the same filter setting in all patients. rEEGs were on the day of the booking, whereas succeeding EEG recordings were separated by at least two weeks.

B1.11.2 rEEG

A rEEGs were recorded for each patient after the first onset seizure. Silver cup electrodes were attached to the scalp following the 10-20 international system for electrode placement. We have used 24-channel digital recording with bipolar and referential montages with the following filter settings, High-frequency filter of 70 Hertz (Hz), and a time constant of 0.3, paper speed of 30mm /s and sensitivity of 7 or 10 microvolts. Impedances were kept at 5-kilo ohms or less. Activation procedures included photic stimulation and hyperventilation. The photic stimulus was done with eyes open and close. In hyperventilation, patients were requested to breathe deep in and out with their mouths open for 3 minutes. Interictal epilepticform discharges were defined as sharp waves, spikes and waves or polyspike waves and slow wave discharges (Li *et al*., 2020).

B1.11.3 SD-EEG

SD-EEGs were recorded for each patient after the first onset seizure. Silver cup electrodes were attached to the scalp following the 10-20 international system for electrode placement. 24-channel digital recording with bipolar and referential montages with the following filter settings, High-frequency filter of 70 Hertz (Hz), time constant of 0.3, paper speed of 30mm/s and sensitivity of 7 or 10 microvolts were used. Impedances were kept at 5-kilo ohms or less.

Activation procedures included photic stimulation and hyperventilation. Photic stimuli were applied with eyes open and close. In hyperventilation, patients were requested to breathe deep in and out with their mouths open for 3 minutes. Patients were asked to get 3-4 hr sleep during the day before the test and stay awake from midnight.

B1.11.4 24-hour AEEG

24-hour AEEG were recorded for each patient after the first onset seizure. Silver cup electrodes were attached to the scalp following the 10-20 international system for electrode placement using a collodion, and the head was wrapped with a bandage. EEG systems and filters used were the same as routine and Sleep deprived EEG. After the 24-hour AEEG set-up, patients were asked to go home with the AEEG machine and come back the next day after the 24-hour recording to end the record and remove electrodes from the scalp.

B1.11.5 Statistical analysis

The data collected was captured on Microsoft Excel 2016 spreadsheet and analysed by a statistician using Stata version 17. The results were interpreted using frequency distribution, where graphs and charts represented the percentage per analysis.

B1.11.5.1 Validity (Precision) and Reliability (Consistency)

How accurately the research measures what it sought to measure (Golafshani, 2003; Heale and Twycross, 2015) determines the fundamentals of medical research. Precision in comparing the sensitivity of a routine EEG, sleep-deprived EEG and 24-hour ambulatory EEG after the first onset of seizures in epileptic patients depended on the results' reliability and validity. In the present study, the three EEG tests were used as an instrument and were considered reliable because the results were consistent over time.

A measuring instrument has high validity (accuracy) if it captures precisely what it is intended to measure. Collectively, reliability and validity determine the measurement's precision, which is necessary for drawing meaningful statistical conclusions from medical research (Heale and Twycross, 2015).

A pilot study was conducted, Tseng and Sim (2021) cite a general flat rule to utilise at least 30 subjects or greater to estimate a parameter, whereas Teresi *et al*. (2022) suggest a minimum sample size of 10 subjects per treatment arm in a randomised trial. In line with these pilot study guidelines, 20 participants took part in a pilot study where the rEEG, SD-EEG and 24-hour AEEG were done, and the results were compared among the three EEG tests. Those who participated in the pilot study were excluded from the main study. In this case, the pilot results indicated that the data collection tools were reliable and valid, answering the study's objectives.

B1.12 Ethical aspects and good clinical practice

B1.12.1 Ethical clearance

The University of Witwatersrand Research Ethics Committee granted ethical approval for the research, which was then submitted to the CMJAH ethics committee for further approval. The ethical clearance Certificate and the research proposal were submitted to the head of Internal Medicine to seek authorisation to conduct the research.

B1.12.2 Patient safety

The patient was not exposed to any additional risks during the research study beyond those involved in routine/standard practice for seizures.

B1.12.2.1 Discontinuation and withdrawal criteria

A Neurophysiology clinical technologist from the Department of Neurology monitored participants who participated in this study.

The decision to participate was entirely voluntary. Patients could leave the research at any moment, for any reason and without suffering consequences**.**

B1.12.2.2 Good clinical practice

The Good Clinical Practice guidelines were applied to all clinical work for this study endeavour. The third basic principle of the Declaration of Helsinki stipulates that individuals with scientific training should only carry out research and under the supervision of experts with the necessary qualifications (South African Good Clinical Practice guidelines, 2006; World Medical Association Declaration of Helsinki, 2013. Essentially, GCP calls for oversight by the local ethics commission, confirmation of the investigator's credentials, a study protocol,

informed consent, necessary documents to carry out the study, monitoring, report submission, and record-keeping. The public can have confidence that the participants' well-being, safety and rights will be safeguarded and that the study data will be reliable because the GCP guidelines were followed in this study.

B1.12.3 Financial implications to the patient

Every investigation was a normal practice. For their participation in the study, the patients were not paid anything.

B1.12.4 Subject information and informed consent

Participation in this study was voluntary. The participants were given a consent form to sign before they could participate, and they had the right to withdraw at any moment without penalty. The consent forms confirmed that the participants understood the study's purpose and willingly participated. Additionally, they received an information sheet that they kept. All patients' documentation, including the information sheet and informed consent, was available in English and Isizulu.

B1.13 Research team

Principle Investigator

Mr Lebohang Matthews Ratlhankana

Supervisors

Ms Joy Mofokeng (Promotor)

Prof Andre Mochan (Co-promotor)

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Appendix C: Informed consent

Title: Sensitivity of electroencephalogram after first onset seizures in epileptic patients at Charlotte Maxeke Johannesburg Academic Hospital

Name of researcher: Lebohang Matthews Ratlhankana

1. I confirm that I have read and understood the information sheet for the above study.	☐
2. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	☐
3. I understand that my participation is entirely voluntary and that I am free to withdraw at any time or to decline to answer any particular questions.	☐
4. I fall within the age range of 18-60 years.	☐
5. I agree to complete the questionnaire	☐
6 There is no reward for participating in this study.	☐
7. I agree to participate in the additional sleep deprivation and 24 EEG recordings.	☐
8. I agree to take part in the above study	☐

Name of participant: _____

Date: _____

Signature: _____

Witness: _____

Date: _____

Signature: _____

Appendix D: Information guide

STUDY TITLE: SENSITIVITY OF ELECTROENCEPHALOGRAM AFTER FIRST ONSET SEIZURES IN EPILEPTIC PATIENTS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Information guide

I am Lebohang Matthews Ratlhankana, studying for an MHSc at Central University of Technology Free State and currently employed at Charlotte Maxeke Johannesburg Academic Hospital. I would like to invite you to participate in a research study. Before you decide to participate in this research, you need to understand why the research is being done and your role. Please take time to read the following information carefully.

What is the purpose of the study?

An Electroencephalogram (EEG) is important in diagnosing and treating epilepsy. The challenge in evaluating a patient after a first onset seizure is to identify those participants who will go on to develop recurrent seizures from those who will have only a single seizure in their lifetime.

Three types of EEGs can be used to identify seizures, namely Routine EEG, 24-hour ambulatory (AEEG) and sleep-deprived EEG; in government Hospitals, the most commonly used is Routine EEG due to lack of Equipment, although it has been discovered that longer EEG recording is likely to yield more epileptic form discharges.

Our aim with this research is to compare the yield of each EEG protocol to allow us to find the best possible way to use our resources efficiently by decreasing the number of routine repeat EEGs needed for the classification and prediction of recurrent seizure episodes as well as to guide improved treatment in participants with first onset seizure.

Brief description of three types of EEGs.

1. **Routine EEG**

To prepare you for the test, measurements will be done on your head, and marks will be made on your scalp with a special pencil to indicate where to attach the electrodes and then rubbed with a cotton bud with some abrasive paste. A sticky paste will be used to make it easy for 23 disc electrodes that are to be attached from the scalp on your head to pick up small impulses from the brain.

During the test, we will ask you to do different simple actions.

- Opening and closing eyes
- Hyperventilation is taking deep breaths in and forcing them out as if you are blowing a candle out; this will take 3 minutes.
- Photic stimulation- watching a flashing light. A lamp in front of you flashes on and off at different speeds. You will be asked to look at it.
- The recording time would be an hour.

2. **Sleep deprived EEG**

This test is similar to a routine EEG, as described above, except that you are requested to wake up four hours before the test and not to eat or drink anything containing caffeine between midnight and the time of your test. A sleep-deprived EEG will take between 1-2 hours.

3. **24-hour ambulatory EEG**

This test is similar to a routine EEG, as described above. During 24-hour AEEG, you will go home carrying or wearing a portable EEG recorder for 24 hours. Once the test is completed, you will bring the portable EEG machine back to the neurophysiology unit in CMJAH and have electrodes removed from your scalp.

Why have I been invited?

You have been invited to participate in this study because you are a participant who had a seizure.

Do I have to take part?

No. Participation is entirely voluntary, and if you do not wish to participate in the research, you need not consent to it. You do not have to give any reasons for not participating in the research. If you indicate an interest in participating, you will be asked to sign a consent form showing that you have agreed to participate.

What will happen to me if I take part?

I, the principal researcher Lebohang Mathews Ratlhankana, would perform three EEG tests to measure your brain waves from 30 minutes to 24 hours.

The first test is routine and takes about 1 hour; the second test, which is sleep deprived, will take between 1 to 2 hr; the third test will take about 24 hrs, and all three tests are non-invasive.

What are the possible benefits and disadvantages of taking part?

Benefits

There will be no remuneration or added benefits for participating in the research study, but their participation will help clarify the sensitivity of routine EEG, sleep-deprived EEG and 24-hour ambulatory EEG.

Reimbursements:

The routine EEG is done when the participant visits the epilepsy clinic for a routine investigation.

For sleep-deprived EEG 2ND visit and 24 ambulatory EEG 3RD visit, participants will be given transport fees between R100.00 and R150.00 per visit, determined by their residential address and associated transport costs.

The participants taking part in the study will be given a transport fee between R100.00 and R150.00 per visit for sleep-deprived EEG and 24-hour AEEG; no remuneration will be given to them.

Disadvantages

You will need to commit time to participate in the EEG recordings that will last a maximum of 24 hours.

Has Ethical Approval been gained?

HREC has approved this research protocol.

Will my taking part in the study be kept confidential?

Personal information will be kept confidential. Participants who enter the study will be assigned numbers, which will be used to report all results.
Organisations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Ethics Committee for Medical Research and the Medicines Control Council *(where appropriate)*.

This is very important, and you need to be assured that the information you provide and your recorded EEG will only be accessible to the assisting neurologist who will be interpreting the recorded EEG and me.

This information will be saved onto a password-protected computer in accordance with the Protection of Personal Information Act 2013. The questionnaires used will be destroyed by shredding after capturing data from the principal investigator's computer. For anonymity, the EEG recording of each study participant will be coded during recording and in the final dissertation.

These codes will only be made known to my supervisors and me. No one will be informed that you have participated in the research, so your contribution will be kept anonymous.

Risks

As with any medical procedure, risks will be involved, but as all the tests and investigations to be performed are standardised medical practices for participants who had a seizure, no additional risks will be incurred by any participants. The EEG has been used for many years and is considered safe.

What will happen to the findings of the research?

The findings will be published in a peer-reviewed journal and presented at a health conference.

The participant will be given pertinent information on the study while involved in the project and after the results are available.

A copy of the complete report of the research findings will be kept in the Central University of Technology Free State library.

Thank you for taking the time to read this, and I look forward to your reply and participation in the research study.

Contact details of the researcher(s)

Name: Prof A Mochan/ Mr Ratlhankana

Email address: Andre.Mochan@wits.ac.za

Lratlhankana@mail.com.

Tel: 011 488 4431/011488 4432

Contact details of the Human Research Ethics Committee (HREC) chair – for reporting complaints/problem

Human Research Ethics Committee Chair

Name: Dr Clement Penny

Email address: Clement.Penny@wits.ac.za : Tel: 011 717 2700/123

Appendix E: Data Collection Sheet

Age

Sex

Male	Female

Race

Black	Indian	Asian	Coloured	Other
0	1	2	3	4

EEG Analysis

Routine EEG	Sleep deprived EEG	24-hour ambulatory EEG
Background	Background	Background
Activation procedures (hyperventilation and photic stimulation)	Activation procedures (hyperventilation and photic stimulation)	Activation procedures (hyperventilation and photic stimulation)
Normal/Abnormalities	Normal/Abnormalities	Normal/Abnormalities
Assessment	Assessment	Assessment

Appendix F: Seizure Questionnaire

Name: Record No.:_____

Investigator initials:_____

1. Date: _____

2. Sex: Male Female Place of investigation:_____

3. Age:_____

5. Domicile classification (circle) a) urban b) rural c) suburban d) tribe

6. Do you have someone in your family with seizures or epilepsy?

a) yes _____ (relationship) b) no_____

7. Have you ever had to tremble in your arms or legs? Yes No

8. Have you had seizure events where you fall down and become pale? Yes No

9. Have you ever lost your consciousness? Yes No

10. Have you had seizures where you fall and bite your tongue? Yes No

11. Have you had momentary seizures in your arms, legs, or either side of the face? Yes No

12. Have you had episodes where you stay absent/out of touch? Yes No

13. Have you had seizures where you smell strange odours? Yes No

14. How old were you at your first seizure? _____

15. How old were you at your last seizure? _____

16. Do you know the cause of your seizures? Yes, No Reason _____

17. Have you ever had seizures with fever before 5 years of age? Yes No

18. Have you ever taken drugs for seizure treatment? Yes No

19. Are you taking drugs for seizures now? Yes No Name _____ Dose _____ Name _____ Dose _____ Name _____ Dose _____ Name _____ Dose _____

20. Have you ever used other treatments for your seizures? Yes No If the answer is yes, circle the _____)Others _____ exams done to you? (circle) Yes No a) EEG b) CT scan/MRI e) others f) none

21. Have you ever had 2 or more continuous seizures or many continuous seizures without stopping? Yes No

22. Had you stopped taking your drugs for seizures just before you had those seizures? Yes No

The epilepsy survey questionnaire was used to interview patients from the Honduran outpatient epilepsy clinic at Hospital Escuela. Questionnaire was then used in a nationwide survey of people with epilepsy seen in private and public clinics in 12 of 18 departments in Honduras. Developed by the National Autonomous University of Honduras Neurology Postgraduate Program, Greenwood Genetic Center, and the Epilepsy Foundation (Durón *et al*., 2009).

Isijobelelo C: Ifomu Locwaningo Elinemvume

Isihloko: Lolu cwaningo luphathelene nokufunda kabanzi ngokuzwela kwe electroencephalogram (EEG) / ubuchwepheshe bokuhlola okwenzakalayo engqondweni emva kwesiwomba sokuqala sokuhlaselwa isifo sokudlikiza komzimba okuye kubange isifo sokuwa, ucwaningo luzokwenzeka esibhedlela esihlanganyele nezemfundo egoli icharlotte Maxeke Academic Hospital.

Igama lo Mcwaningi: Lebohang Matthews Ratlhankana

1. Ngiyaqinisekisa ukuthi ngiyifundile futhi ngayiqonda yonke imininingwane equkethwe ekhasini lemininingwane mayelana no cwaningo oludalulwe ngentla.	☐
2. Ngilitholile ithuba elanele loku cabangisisa kahle ngalemininingwane, nganikwa ithuba lokubuza imibuzo futhi lemibuzo iphenduleke ngokugculile.	☐
3. Ngiyaqonda ukuthi ukubamba kwami iqhaza kulolucwaningo kungokuzithandela ngokuphelele, futhi ngingayeka nganoma yisiphi isikhathi uma ngingasafuni ukuqhubeka. Nginelungelo futhi lokweqa yinoma yimuphi umbuzo noma imibuzo ethile uma ngingafuni ukuyiphendula.	☐
4. Ngokweminyaka ngiphakathi kweminyaka engu 18 kuyela ku 60.	☐
5. Ngiyavuma ukuthi ngizoyiphendula imibuzo emayelana nalolu cwaningo.	☐
	☐

6. Ngiyaqonda ukuthi angizukuhlomula ngokwemali futhi asikho isinxephezelo thizeni engizosizuza ngokuvuma kwami ukubamba iqhaza kulolu cwaningo.	
7. Ngiyavuma ukubamba iqhaza kulolu cwaningo olumayelana nomthelela wokuswela ubuthongo okwengeziwe futhi nokuthi ku qoshwe imiphumela yokuhlolwa kwami nge i24 EEG - ubuchwepheshe bokuhlola okwenzakalayo engqondweni.	☐
8. Ngiyavuma ukubamba iqhaza kulolu cwaningo.	☐

X _____ X _____

X _____

Igama lobambe iqhaza Usuku Isignesha

Isijobelo D: Imininingwane ephathelene no cwaningo

Ngithanda ukuk'mema ekutheni ube iqhaza kulolu cwaningo. Ngi ngu Lebohang Matthews Ratlhankana ofundela i-master's degree yobuchwepheshe bezokwelapha nezempilo phecelezi i-mhsc esikhungweni sezemfundo ephakeme yezobuchwepheshe icentral University of Technology yase Free State; ngokusebenza ngisebenza esibhedlela esihlanganyele nezemfundo egoli icharlotte Maxeke. Ngaphambi kokuba uthathe isinqumo kudingena ukuthi uqonde isizathu salolu cwaningo, nokuthi uzozimbandakanisa kanjani kulolu cwaningo. Ngokuzithoba ngicela uzinikeze isikhathi esanele sokufunda nokuqonda lemininingwane kabanzi.

Ungangabazi ukubuza imibuzo nokucela ingcazelo yalemininingwane, uvumelekile ukucela imniningwane eyongeziwe uma kunesidingo. Thatha isikhathi sokucabangisisa kahle ukuthi uyafisa yini ukuba ingxenye yalolu cwaningo noma Cha.

Iyini inhloso yalolu cwaningo?

Lolu cwaningo lumayelana nobuchwepheshe bokuhlola okwenzakalayo engqondweni i-EEG obudlala indima ebalulekile ekuhlolweni nakwezokwelashwa kwesifo Sokuwa phecelezi i-Epilepsy. Ukuhlohwa ngalobuchwepheshe okujwayelekile kuye kusetshenziswe ukufunda kabanzi nokuthola okungahambi kahle oketshezini lwengqodo noma ukuhlola amathuba woku hlaselwa isifo sokuwa.

Lolu cwaningo luhlose ukuthola umehloku kumiphumela phakathi kokuhlolwa okujwayelekile kweziguli ezingakaze zibe nesifo sokuwa, lezo eziqwashayo kanye nokucubungula imiphumela eqoshiwe ngobuchwepheshe bokuhlola okwenzakalayo engqondweni i-EEG kulabo abake bahlaselwa isifo sokuwa.

Kungani ngimenyiwe ukubamba iqhaza kulolu cwaningo?

Isizathu sokucelwa kwakho ukuthi ubambe iqhaza kulolu cwaningo yingoba ungomonye weziguli ezake zahlaselwa ukudlikiza komzimba phecelezi i-Seizure.

Ngiphoqelekile yini ukuba ingxenye yalolu cwaningo na?

Cha, ukuba ingxenye kwakho kololu cwaningo kungokwentando yakho, uma ungafisi ukubamba iqhaza kulolu cwaningo unelungelo lokunganikezeli imvume yokuba inxenye yalo. Awuphoqekelanga ukuchaza isizathu noma izizathu ezibangela ukuba ungafisi ukubamba iqhaza ocwaningweni. Uma ukhomibisa ukuthanda ukuba ingxenye yalolu cwaningo uzocelwa ukuba usayine ifomu lwemvume okuzochaza ukuthi uzivumele ngokuthanda kwakho ukubamba iqhaza kulocwaningo.

Kuzokwenzakalani Kumina uma ngivuma ukubamba iqhaza kulolu cwaningo ?

Mina, Lebohang Mathews Ratlhankana oyinthloko yalolu cwaningo ngizosebenzisa ubuchwepheshe bokuhlola okwenzeka emqondweni i-EEG ukuze ngikuhlole izihlandla ezintathu ngizokwazi ukuthola imiphumela eqoshiwe mayelana nenqgondo yakho. Lokuhlolwa kuzokwenzeka esikhathini esiphakathi kwemizuzu engu-30 ukuya emahoreni awu-24.

Ukuhlolwa kokuqala kuzothatha imizuzu engu-30 yilokhu okujwayelekile, ukuhlolwa kwesibili okokuhlola imiphumela yomuntu oqwashayo - lokho kuhlolwa kuthatha ihora elilodwa / 1-hour bese ukuhlolwa kwesithathu kube amahora awu-24. Zonke lezihlandla zokuhlolwa ezintathu ngeke zikuzwise ubuhlungu emzimbeni ngoba akuzweli lutho. Akukho okunye ukuhlolwa ozophoqeleka ukuba ingxenye yakho ngaphandle kwa lokuhlolwa okudalulilwe ngentla, angeke kudingeke ukuhlinzwa noma ukuthatha imithi ezokubangela izinhlungu, noma okuzoba nomthelela omubi empilweni yakho.

Lmiphumela eqoshiwe ngobuchwepheshe boku hlola ezengqondo i-EEG izotholakala ngokuthi kubekwe izintambo ezincane zomshini wobuchwepheshe bengqondo, lezizintambo zingepheshana elinyamatheliswa esikhumbeni sekhanda ngoketshezi oluyi-gel(incamathela) noma okunye okoyincamathela okuphephile futhi okusheshayo ukusuka esikhumbeni. Lezintanjana zinama gama ahlukene njengokudalulwa kwawo i-international 10-20 system esetshenziselwa ezempilo, kuzosetshenziswa lamapheshana nemicu yezintambo ezingu-25 ukuze ziqophe imiphumela yokuhlolwa kwe ngqondo.

Imiphi imiphumela emihle nengemihle yokubamba iqhaza kulolu cwaningo?

Imiphumela emihle

Ukubamba kwakho iqhaza kulolu cwaningo kuzosiza ekudwebeni Imibandela nemithetho emkhakheni wobuchwepheshe bezengqondo.

Umthelela omgemuhle

Uzodinga ukunikezela isikhathi sakho ukuze ube ingxenye yalolu cwaningo nokuhlolwa ngobuchwepheshe bezengqondo i-EEG okungevile emahoreni angu-24.

Ngabe lolucwaningo luyitholile yini Imvume yokuziphatha kwaba cwaningi?

Isicelo sokuthola imvume yenqubo yalolu cwaningo sizofakwa kwi-komidi lokuziphatha kwaba Cwaningi (bezokwelapha) i-CMJAH Research ethics committee (medical).

Ngabe ukubamba iqhaza kwami kuzo gcinwa kuyimfihlo na?

Lokhu kubaluleke kakhulu futhi siyakuqinisekisa ukuthi lonke ulwazi oluzoqoqwa kulolu cwaningo kanye nemiphumela yakho eqoshiwe izo finyelela kumnikazi wocwaningo kanye nomsizi wakhe ozobe etolika imiphumela eqoshiwe ezokhishwa umshini wokuhlola ngobuchwepheshe bezengqondo i-EEG.

Lonke ulwazi nemiphumela izogcinwa ku mqhafazo(computer) ogcina imiphumela, lomqhafazo(computer) uvikelwe nge-Pin noma i-Password ngokuqendene nemigomo yomthetho wokuvikeleka kwemininingwane ephathelene nabantu yango 2013, phecelezi i-Protection of Personal Information Act 2013. Imibuzo esetshenzisiwe izoshabalaliswa ngokusikwa ngomshini wokusika okuphindaphindiwe kwamaphepha emva kokuthi idluliselwe ku mqhafazo(computer) womnikazi walolucwaningo evikelekile. Ukuze kungadaluleki amagama abantu abazobe beyingxenye yalolu cwaningo, okuqoshiwe ngamuntu munye azofakwa ama-khodi uma eshicilelwa naku phepha lezifundo ze master’s degree.

Lama khodi azokwaziwa abaphathi bami kwezocwaningo kanye nami kuphela, akekho omunye umuntu ozobanolwazi lokuthi ukewaba ingxenye yalolu cwaningo futhi konke okuphathelene nawe kanye nama nemiphumela yakho kuzogcinwa kuyimfihlo.

Ngabe kuzo kwenzakalani ngemiphumela yalolu cwaningo?

Izifundo ezizotholakala kulolu cwaningo zizo shicilelwa encwadini yaba cwaningi bese zethulwa engqungutheleni yezempilo ngaphandle kokudalulwa kwamagama abantu.

Ikhophi lwemibiko yezifundo ezitholakele kulolu cwaningo olungadaluli amagama abantu lizo gcinwa e-mtapweni wezincwadi wase Nyuvesi yobuchwepheshe i-Central University of Technology efree State.

Ngiyabonga ithuba olithathile ufunda lemininingwane futhi ngingakujabulela ukuthola impendulo nokuthi ube ingxenye yalolu cwaningo.

Lebohang Matthews Ratlhankana

Intloko Kwezobuchwepheshe bokwelapha

Echarlotte Maxeke Johannesburg Academic Hospital. Inombolo yocingo: 011 488 4431