FACULTY OF INFORMATION TECHNOLOGY AND ELECTRICAL ENGINEERING

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EEG CHANGES AND C-TREND PARAMETERS IN HEALTHY PATIENTS DURING INDUCTION OF ANESTHESIA

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ABSTRACT

EEG has become technically viable tool in intensive care and there are technologies like C-Trend that compress the complex EEG recording into easy-to-interpret parameters. C-Trend Index is especially designed for evaluation of the brain function during sedation in intensive care patients. In this work, the precepts of EEG, EEG usage during anesthesia practice, including the use of EEG parameters in patients' overall assessment and C-Trend monitoring in identifying brain states under propofol were discussed. The data consisted of segments of 20 EEG recordings collected from healthy subjects who underwent anesthetic infusions while responding to stimuli to directly determine unconsciousness. The purpose of this work was to evaluate how the parameters that C-Trend provides (C-Trend Index, BSR, aEEG and ADR) behave in patients with healthy brain function during anesthesia and how they correlate with changes that we see in raw EEG and clinical signs such as loss of consciousness. It has been demonstrated that some parameters of qEEG, such as the C-Trend Index and BSR, may predict unconsciousness (results from individual t-test for C-Trend before and after loss of consciousness state are 65.70, p-value is < 0.001 for the smoothed C-Trend Index). Hence, these measures can be utilised in future studies to monitor a neurologically healthy patient's level of anaesthesia.

Keywords: EEG, slow wave activity, intensive care unit (ICU), C-Trend, anesthesia

TABLE OF CONTENTS

FOREWORD

This thesis was completed at Cerenion's suggestion and serves as the Master's Thesis for my Biomedical Engineering Master's degree. First of all, I'd want to express my gratitude to Jukka Kortelainen, my primary thesis supervisor, for introducing me to an appealing thesis topic and providing me with paid time to complete my thesis. I owe him my heartfelt gratitude for his assistance in collecting information on the subject. I'd like to thank my supervisor Tapio Seppänen, the Cerenion company as a whole, and especially my technical supervisor Eero Väyrynen for assisting me through the entire procedure and showing general interest in the thesis. I'd also want to thank the medical personnel at the Lapenranta hospital for collecting the data for my thesis. I would like to express my gratitude to my spouse, family, and friends for your vital assistance through these challenging times; I genuinely appreciate it. Finally, I'd want to thank the University of Oulu for my time there and all the friends I made along the road. I will always treasure these memories.

Oulu, June 8th, 2022

Liubov Lonishin

LIST OF ABBREVIATIONS AND SYMBOLS

ADR	alpha-delta ratio
aEEG	amplitude-integrated EEG
API	application programming interface
BEPD	benign childhood epileptiform pattern
BIS	normalized cross-correlation
BSR	burst-suppression ratio
CEEG	continuous EEG
CSV	comma-separated values
DICOM	Digital Imaging and Communications in Medicine
ECG	electrocardiography
ED	epileptiform discharge
EDF	European Data Format
EEG	electroencephalography
EMG	electromyography
EOG	electrooculography
FAR	frontal awakening rhythm
GDPR	General Data Protection Regulation
GUI	graphical user interface
ICU	intensive care unit
IFCN	International Federation of Clinical Neurophysiology
LB	longitudinal bipolar
POSTS	Positive occipital acute sleep components
R	referential montage
RMTTD	rhythmic temporal theta bursts of drowsiness
SQL	Structured Query Language
QMS	Quality management system
SCORE	Standardized Computer-based Organized Reporting of EEG
SQL	Structured Query Language
SSS	Low-amplitude biphasic spikes
TB	transverse bipolar

Cz	electrode
Kp	coefficient of rhythm asymmetry
Ps	parameter of rhythm in congruent leads across the right hemisphere
Pd	parameter of rhythm in congruent leads across the left hemisphere
V_{ij}	total charge across all electrodes

1. INTRODUCTION

Analysis of electroencephalography (EEG) has been utilised for a very long time in the identification of a wide variety of medical problems, including epilepsy and heart illnesses in particular. An EEG specialist analyzes to a recording obtained from a patient and takes notes on all of the signal characteristics that are significant from a diagnostic standpoint. When it comes to evaluating EEG recordings, there are a few different tools available on the market that may be used for therapeutic purposes as well as research. While some of them have highly extensive data models that enable the recording of events that take place at certain times, others rely primarily on free-text inputs that are generated by the reviewer.

For many years, EEG data processing has been of interest to a large number of academics. In particular, the introduction of novel approaches to machine learning has contributed to its rising popularity. The interpretation of EEG data by a human being is often thought to be challenging and requires a significant amount of training and expertise. Because of the large number of channels and the chaotic character of the signals, the data is easier for a computer to grasp than it is for a person. As a result, numerous tools have been developed to simplify the study of EEG signals for medical professionals.

EEG devices that are powered by the Cerenion C-Trend® platform bring a new level of simplicity and assurance to the process of monitoring the neurophysiological condition of patients. The C-Trend® programme, which is driven by artificial intelligence (AI), simplifies the analysis of complicated EEG recordings by producing a collection of easily understood characteristics for use by medical experts.

Patients who are under anaesthesia provide a difficulty for the diagnostic procedures that are currently in use. The C-Trend programme was developed with the specific goal of serving the needs of critical care patients. Because of this, it is essential to observe the behaviour of the parameters (C-Trend Index, BSR, aEEG, and ADR), which are used to determine the states of the brain on the healthy patients as well when propofol is being administered.

An study of the data was carried out as part of this thesis to meet the requirements outlined up top. The dataset including the EEG signals of the patient group that was gathered at the hospital will be used to analyse the trend of the quantitative parameters using statistical methods and to depict EEG data in the required level of detail.

The first two chapters will begin with a review of the EEG and the anaesthesia process. This overview will cover many aspects of the EEG, including various artefacts and parameters that have been selected for the analysis. Chapter 3 details the findings of the research along with the processes of data gathering, annotation, and analysis. Chapter 4's examination of the results and future suggestions, as well as Chapter 5's conclusions, serve as the culmination of the presentation of the thesis.

The purpose of this work is to evaluate how the parameters that C-Trend Software provides (C-Trend Index, burst-suppression ratio (BSR), amplitude-intergrated EEG parameter (aEEG) and alpha-to-delta ratio (ADR)) behave in patients with healthy brain function during anesthesia and how they correlate with changes that we see in raw EEG and clinical signs such as loss of consciousness. The evaluation of the clinical performance of the C-Trend as a method to monitor anaesthetic depth while propofol was being administered was one of the goals of this thesis. We expect to be able to prove that qEEG metrics like the C-Trend Index may indicate loss of consciousness in future studies, allowing them being used to monitor anesthetic state.

2. RELATED WORK

This chapter presents a summary of the previous research that has been conducted on the topic of the current investigation. It has four sections. In sections 2.1 and 2.2 the basics of EEG method and setup will be discussed. In 2.3 and 2.4, respectively, the emphasis is placed on providing an overall background and introduction to the EEG raw characteristics and artefacts that are present. In section 2.5, 2.6, 2.7 and 2.8 EEG procedure, importance of EEG method in diagnosis as well as general anaesthesia technology will be over-viewed. Nonetheless, Section 2.9 provides an overview of the depth of anesthesia and loss of consciousness state.

2.1. Nature of EEG

Richard Caton (1842-1926), a medical practitioner in Liverpool, gave a presentation at a conference of the British Medical Association on the 24th of August, 1875. The meeting was held in London. Data of very weak currents were produced on the brains of rabbits and monkeys, and he submitted those recordings to the scientific community in this study[1].

In the same year as Caton's work, the Russian physiologist V.Y. Danilevsky provided data in his PhD thesis about the study of brain electrical activity in dogs. These findings were gained independently of Caton's work. In his research, he discovered the existence of spontaneous potentials in addition to alterations brought about by a number of other stimuli [2].

Vvedensky began his investigation into how nerve centres function by applying the telephone technique of registration in the year 1884. By putting a telephone to one's ear and listening to the activity of the medulla oblongata of the frog and the cortex of the big hemispheres of the rabbit's brain[3]. V.V. Pravdich-Neminsky reported in 1913 the first electroencephalogram that was recorded from the brain of a dog [2, 4]. This was the event that marked the beginning of electroencephalographic research. In his investigation, he employed the usage of a string galvanometer. In addition, Pravdich-Neminsky is the one who first describes an electrocerebrogram. Hans Berger (1873-1941) is credited with obtaining the first human EEG recording in the year 1925 [5]. The work of Berger was not widely recognised until Adrian and Matthews first convincingly demonstrated the "Berger rhythm" to an English audience at the Physiological Society meeting in Cambridge in May 1934. This was the first time the "Berger rhythm" was presented to an audience in the English language [2, 5].

Electroencephalography, often known as EEG, is a technique that may be used to examine brain activity in both animals and humans. This technique is predicated on the recording of the sum total of the bioelectrical activity that occurs in the various parts, regions, and lobes of the brain. In contemporary neurophysiology, as well as in the fields of neurology and psychiatry, EEG is a common diagnostic tool[6].

The electrical activity of the brain, which may be recorded as electroencephalograms, is always present while the brain is doing work. An electroencephalogram (EEG) is a form of comprehensive record of brain activity; nevertheless, it is unrealistic to assume that such a record can be interpreted in terms of, for example, the content of a thought. For instance, professionals who are skilled in the installation and maintenance of computers are fully conversant in the "language" of pulse diagrams and the potentials that are measured at various locations in electronic circuits. However, even an expert of this level, regardless of how finely he feels the "pulse" of the computer, is only capable of saying one thing: if the computer works correctly or not.[7]. And not one of them, based solely on what they see on the screen of the oscilloscope and what the readings of the other measuring instruments show, can guess what problem the machine is attempting to solve; for example, whether it is determining the square root of an equation or processing a payroll. All what was possible is to look at the screen of the oscilloscope and the readings of the other measuring instruments.

2.2. Electrode Setup

Because the electrical activity in the brain is so minute and measured in millionths of a volt, it can only be recorded using specialised electroencephalographs, which are devices and amplifiers with a particularly high level of sensitivity. Electrodes made of metal are attached to the scalp in order to record an EEG. These electrodes are then hooked to the machine's input [8]. The electrodes are available in the following different varieties:

- When conducting an examination on patients who are able to remain sitting or semi-seated for an extended period of time and follow the instructions of a neurophysiologist, bridge electrodes are utilised (usually adults or children over 3-5 years of age who are conscious and maintain contact with others) [9].
- Cup-shaped electrodes are typically utilised for examining young children, patients who are unconscious, long-term recordings, and EEG sleep investigations. They have the appearance of a disc with raised edges and are held in place by a specialised cap that is fastened to the covering of the head [10].
- During surgical procedures, a needle-type monitor is utilised to evaluate the status of the nervous system as well as the level of anaesthesia being administered. They are administered by injections that are made directly into the patient's scalp. When neurosurgical procedures are being performed on the brain, the electrodes will be inserted directly into the tissue of the brain. The output is a graphical depiction of the variations in the live brain's bioelectrical potential differential[11].

An electroencephalogram (EEG) lead assembly, also known as an EEG lead wire, is a pattern of electrode connections. This pattern refers to the order in which the leads are organised and alternated. Calculating the potential of each electrode in relation to the two combined reference electrodes that are positioned on the right and left earlobes is the easiest way to organise this process[12].

When using electroencephalographs equipped with differential amplifiers, the potentials of the electrodes are always measured in proportion to the potentials of one or more other electrodes.

A reference (referential) or monopolar montage is a sort of measurement in which the reference electrode is positioned on a section of the head that gathers the fewest possible signals from the cortical neurons. This type of measurement is also known as a reference (reference, referential). When doing a reference recording, the reference electrode is often positioned on the mastoid, earlobe, or nasal tip of the subject[12]. The term "bipolar montage" refers to the type of recording that occurs when both electrodes are placed on the scalp over the cortical EEG generators and the power value of the electrical processes that occur in one electrode is compared to the power value of the electrical processes that occur in the other electrode. As a result, mounting is the principle that is used in order to assess EEG potentials[13].

The montage and filter settings for a digital EEG system may be determined and adjusted while the EEG is being examined, rather than when it is being recorded. This is a benefit of current digital EEG systems (compared to earlier analogue systems), which do not have this capability [14]. In most cases, the electroencephalogram is recorded with minimum restrictive analogue filter settings, and the potentials in all of the electrodes are measured relative to a single reference (such as a referent at the tip of the nose or a combined auricular referent). The computer software may then process the data as it will display on the screen or output to a printer. It is also capable of digitally filtering the data if that is required. The initial reference montage can be transformed into any reference or bipolar montage that the user desires. In the event that it is required, the same EEG fragment can be shown many times in a variety of montages and filters. In the course of its development, electroencephalography has made use of a wide variety of montages. The technical capabilities that have been made accessible to academics in the past have mostly been responsible for the variety of these montages[15].

The following configuration codes have been assigned to the assembly in accordance with the recommendations of the American Society of Clinical Neurophysiology[16]:

- longitudinal bipolar (LB);
- transversal bipolar (TB);
- reference (referential R);
- a hyphen followed by a number that represents the total number of channels (16, 18 or 20, ...);
- the last digit (the one that comes after the period) corresponds to the number of alternative installations of the specified class with the specified number of channels.

For instance, an installation denoted LB-16.2 indicates a longitudinal bipolar with 16 channels (traces), version 2 of the installation.

Bipolar mounting is when many paired bipolar leads are connected together but there is no electrode that is shared by all of the leads. A chain of electrodes will typically have neighbouring leads that share a common electrode, which is then linked to the second input of one amplifier and the first input of the next amplifier. Among the components of bipolar assemblies are [15]:

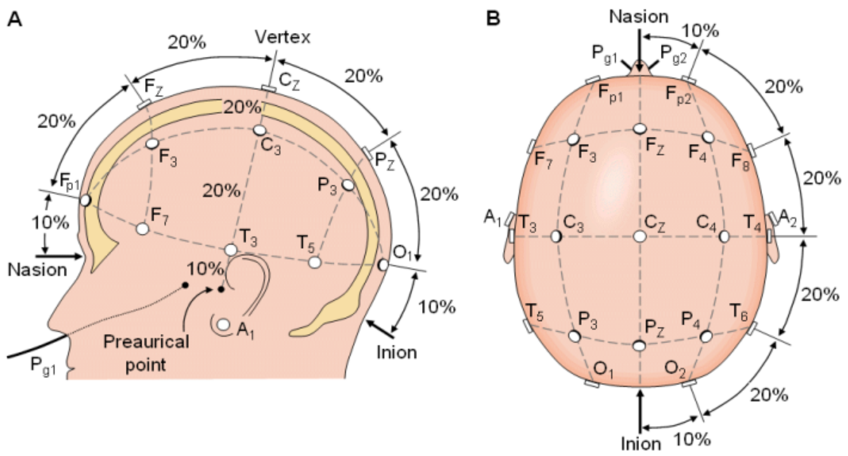

Figure 1. Scheme of the International 10–20 EEG placement system from American Electroencephalographic Society Guidelines for Standard Electrode Position Nomenclature[17]

Arrangement of bipolar electrodes in transverse rows is the goal of the transverse bipolar mounting technique, also known as the corolla bipolar mounting technique.There are different types of these montages[18]:

- bipolar assembly in longitudinal rows - this approach is quite similar to the one described before, with the primary distinction being that the electrodes are paired in longitudinal rows;
- closed bipolar assembly - the method of joining bipolar pairs of electrodes in the case when they are arranged in a closed circle;
- triangular bipolar mounting is a special variation of commutation of three pairs of bipolar lead electrodes in which three lead electrodes are placed on the vertices of a triangle. This type of mounting is used to clarify the localization of the focus of pathological activity on the electroencephalogram (EEG).

Scheme of the International 10–20 EEG placement system from American Electroencephalographic Society Guidelines for Standard Electrode Position Nomenclature[17] has been shown on figure 1.

In a combined instance of the auricular referent electrode potentials are measured in relation to two jointed electrodes that are positioned on the left and right earlobes using the most basic premise, which is referred to as the jointed ear electrode assembly. It is also possible to utilise the combined electrodes on the mastoid, the nasal tip, or the chin as reference electrodes. In a perfect world, the reference electrode would not produce any electrical current, meaning that its potential would remain constant during the registration process. Due to the conductive nature of the scalp, it is impossible to position a reference electrode in such a way that it would satisfy all of the requirements for an ideal reference electrode. As a result, all of the leads that are attached to the head will always be electrically active in some way. This indicates that the electrical potential that is measured from any one electrode will vary depending on the referent that is being used[18, 19].

A mounting known as a common average reference mounting is one in which the potentials of the electrodes are measured in relation to a common average reference. This reference is the potential that is produced by averaging the values recorded from all of the electrodes in the mounting.

In the early 1950s, a fitting method known as the common average reference fitting was created[20]. The process is straightforward: first, the potential is averaged over all of the electrodes to obtain what is known as the overall average potential. This value is then subtracted from each individual potential. The process may be summarised by the formula which is as follows:

$$Vi' = Vi - \sum Vj/n, \tag{1}$$

where Vi is the total charge across all electrodes.

If the head were a sphere, then the total mean number would be zero, and the total mean assembly would be the ideal answer. If the head were a sphere, then the electrodes could be put at any position on the sphere. However, this is not the situation in real life; the skull is not a sphere, and electrodes are only placed on the top and sides of the head during the procedure.

A local average mounting is a method for calculating a mounting that involves subtracting a local average potential from the potential of the electrode that is being analysed. This local average potential is obtained by averaging the potentials of a small number of electrodes that are located in close proximity to one another. There are a few distinct varieties of mounts used for averaging (Laplacian, Lemos, Hjorth) [21, 22, 23, 24].

The generation of a one-of-a-kind reference point for each electrode is what is meant by the phrase "local average referent". In this particular scenario, just a select few electrodes that are located close to the target electrode are utilised in the computation of the complex referent[23].

The variable denoted by I in the above formula is now equal to the total of the potentials measured across the electrodes that surround the i-th electrode. If we wish to find a local referent for a certain electrode, let's say Cz, for instance, we need to compute the average of the electrodes that surround Cz, which in this instance are Fz, C3, C4, and Pz. We would have the following equation for the local average if we were talking about our electrode

$$Cz : VCx' = VCx - (Vfx + VC3 + VC4 + VPx)/4, \tag{2}$$

The following is a formula that may be used to define any montage in broad terms [20]:

$$Vi' = Vi - wij * Vj, \tag{3}$$

where $w$represents the total weights. For this reason, a montage may always be identified by the weights w. Any piece of modern software will include settings where you may locate the values of the weights.

The Laplacian montage is an illustration of a local average reference montage [22]. Estimating a Laplace operator for each electrode is a necessary step in the process of creating a Laplacian montage. The Laplace operator may be thought of as the second partial spatial derivative of the potential field in terms of mathematics. According to the laws of physics, the second spatial derivative is proportional to the electric current that is flowing through the head at the corresponding place. The strength of the underlying brain oscillator may be estimated using this current, which, in turn, enables us to determine its frequency[22].

The approach was initially reported by Pitts in 1952, and it called for a three-dimensional set of electrodes that were tightly spaced [24]. Because of this, intracranial deep electrodes were necessary to carry out the procedure. In 1975 world saw the development of Hjorth's modifications for the use of surface potentials. Hjorth demonstrated that complicated computations might be simplified by making a number of assumptions about the nature of the cortical tissue. One of these assumptions was that a certain cortical layer possessed homogenous conductivity. As a direct consequence of this, the potential fields that are aligned perpendicular to each layer are homogenous. Since of this, one-dimensional derivations are the only ones that can be used because the fields they produce are aligned in a direction that is perpendicular to the cortical layer. In this approach, the second spatial derivative of the potential field is constrained by the electric current that runs perpendicular to the surface of the cortex. Lemos made several adjustments to Hjorth's approach at a later time[21].

Continuous EEG-monitoring (cEEG) has been promoted for early seizure identification and to observe the temporal evolution of the cortical recovery following cardiac arrest, but it is not always available due to a lack of resources and neurophysiology aid for setup and quality modifications. Bedside personnel may be able to apply and maintain the recording at an early stage with the use of a restricted montage that has fewer electrodes, eliminating the necessity for a 24-hour in-house neurophysiology service [25].

It was shown that a decreased montage might give crucial prognostic information and could be especially useful after cardiac arrest due to the frequently extensive anoxic brain damage that occurs after cardiac arrest [26, 27]. However, very few research have compared the effects of CA with a shortened montage to those of a complete montage, and those studies that have done so have frequently limited their evaluation to a select few predetermined EEG patterns [28]. If there were fewer electrodes required for the EEG-based detection of hypoxic brain damage, it would be more practicable for clinical use. The findings obtained with the electrodes placed on the forehead were comparable to those obtained with the complete EEG cap, which can be concluded as future use of reduced montage electrodes in the ICU as they are just as competent as the entire EEG cap [29].

2.3. Raw EEG Features

An electroencephalogram (EEG) is a convoluted curve that is made up of waves with varying frequencies and intensities. The EEG is able to differentiate between waves represented by Greek letters according to the frequency of the signal:

Alpha activity is a sinusoidal oscillation that may be identified by an EEG in the passive waking state. Its frequency ranges from 8 to 13 Hz, and its amplitude ranges from 40 to 100 V. Spindles and occipital regions are often responsible for modulating alpha activity in the mature brain (related to visual analyzer functioning) [15].

Beta activity consists of oscillations that can reach amplitudes of up to 15-20 V and frequencies ranging from 14-40 Hz. During periods of active wakefulness, it is most commonly observed in the frontal regions of the brain. The structure of beta activity differentiates between low-frequency activity (with a frequency of up to 22-24 Hz) and high-frequency activity (with a frequency of more than 22-24 Hz). Low-frequency activity has a lower frequency than high-frequency activity. Some writers regard gamma activity, or high-frequency beta activity with a frequency of 40-70 Hz and an amplitude of 5-7 v, to represent beta activity. Gamma activity may be distinguished from beta activity by its higher frequency [15].

Mu activity is mostly seen in the rolandic sulcus, which is located in the central areas of the brain (associated with proprioceptive sensitivity). Both the frequency and amplitude correlate to alpha activity; nevertheless, the distinctive form of an accurate curve is present[30].

Theta activity is a type of slow-wave activity that has a frequency of 4-7 Hz and varies in amplitude. It is known to rise both during sleep and in response to emotional arousal. A decline in the amount of functional activity of the cortex and the brain as a whole is indicated by the emergence of activity on the EEG at other time intervals [31].

Delta activity is a kind of slow-wave activity that has a frequency of 1-3 Hz and varies in amplitude. It is most prominent during sleep and has a frequency range of 1-3 Hz. A decline in the amount of functional activity of the cortex and the brain as a whole is indicated by the emergence of activity on the EEG at other time intervals [31].

Slow waves (less than 1 Hz) are the most common EEG characteristics of NREM sleep. This neurophysiological phenomena may be traced back to the neurons in the neocortex and thalamus, both of which have been found to display slow oscillations (less than one hertz), which coincide with the slow wave activity of EEG.It has been demonstrated beyond a reasonable doubt that slow waves play a physiologically significant role in higher cognitive function, and that disorders of consciousness are related with a lack of this electrophysiological phenomena[32] During general anaesthesia, healthy people often display a pattern of brain activity known as slow waves in addition to the normal sleep state. Anesthetic-induced slow waves are thought to be a consequence of an unaware brain that only occurs during sedation or anaesthesia because they originate from the same cellular and network level processes as during NREM sleep. This is because anesthetic-induced slow waves occur during NREM sleep [33].

Several different scientific research have found a connection between the presence of slow wave activity during anaesthesia and normal sleep and good brain function. For instance, it has been demonstrated that the lack of slow wave activity during cardiac arrest is indicative of hypoxia ischemic encephalopathy (HIE), which is a condition that aids in the evaluation of the neurological fate of patients. As a result, slow wave activity gives vital diagnostic and prognostic information and has the potential to be exploited in decision making regarding therapy[34].

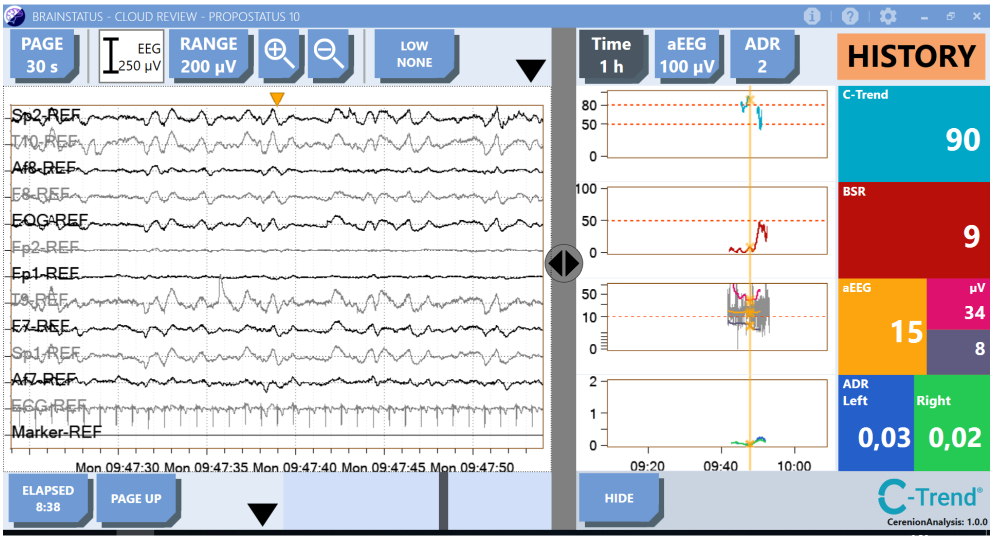

Figure 2. Example of slow wave activity (SWA) which was recorded from on of the patients in the BrainStatus device using C-Trend software.

Example of slow wave activity (SWA) which was recorded from on one of patients using C-Trend software implemented on BrainStatus device has been shown on figure 2.

The method of interpreting an electroencephalogram (EEG) involves doing so in the context of the clinical symptoms that are being experienced by the patient. The definitive diagnosis can only be determined if specific clinical indications that are bothering the patient have been identified.

The description of the recording is meant primarily for the neurophysiologist, who will utilise it for the future conclusion; however, it may also be intended for another expert, in which case it must be as objective and specific as possible.

A diagnosis cannot be derived from an EEG result. The majority of physicians operate on the assumption that the report's text has sufficient information to establish a diagnosis, and as a result, they do not look at the raw signal only.

The doctor needs a significant amount of experience as well as training before they can correctly interpret an electroencephalogram (EEG). We have collated and given all of the fundamental physiological and some commonly physiological patterns of wakefulness and sleep with full explanations so that doctors and neurophysiologists may communicate effectively with one another.

The major benign and pathological features of EEG will be discussed later in the text.

Vertex waves can be either uniphasic or biphasic, but they are always sharp waves. The first phase of a vertex wave is often negative, and it is then followed by a positive phase of low amplitude and a sluggish wave with a negative deviation. The peak is located in the vertex area. Can appear in an asymmetrical pattern, with a bias toward either the left or the right, alone or in rhythmic runs. Occurs on its own while sleeping or in reaction to a sensory stimuli while sleeping or while awake. It may be solitary or it could be repetitious. In general, the amplitude doesn't get much higher than 250 microvolts, although it can be significantly amplified and quite severe, especially in youngsters. Youngsters are more likely to experience vertex waves than adults do, and the amplitude of these waves is significantly greater in children [35, 31].

The relaxed waking period of Stage I slow-wave sleep (the first three minutes after falling asleep) is characterised by hypnagogic hypersynchronization, which consists of diffuse bursts of high-amplitude (300-600 V), bilateral-synchronous rhythmic theta or delta waves (3-5 Hz), lasting 2-6 seconds. Hypnagogic hypersynchronization is characterised by the fact that it disappears as sleep becomes deeper. It is a natural pattern of tiredness in children between the ages of 3 months and 14 years, although it is most noticeable in children between the ages of 3 and 5 years [15].

K-complexes are non-permanent discharges that are characterised by the presence of a large-amplitude negative slow wave, which is then followed by a more diminutive positive slow wave. It is accompanied by carotid spindles, which come just after the K-complexes in the order of development. In most cases, the area near the front of the vertex has the highest amplitude. Discharges are typically bilateral and synchronised, however they might be unilateral or have a permanent amplitude majority in one hemisphere when they occur in children. Typical of the slow-wave sleep that occurs throughout stage II. occur on their own or in reaction to unanticipated sensory cues; they are not particular to any one stimulus. Both adults and children might be affected [35].

Sleep spindles are rhythmic spindle-shaped waves that increase and decrease in amplitude, frequency 12-16 Hz (11-15 Hz), amplitude up to 50 V, maximum in the vertex, sometimes with a shift to the frontal regions, and lasting 0.5-2 seconds. Children under the age of 2 years old experience sleep spindles asynchronously. Sleep spindles are rhythmic and bilaterally synchronous in adults. Vertex waves can happen by themselves or in conjunction with other slow-wave sleep phase (SSP) patterns, particularly K-complexes and vertex waves in stage II. Vertex waves can also happen in stage II by themselves. Extremely seldom, something known as a "giant" spindle will occur. These spindles have a large amplitude, a frequency of 11-12.5 Hz, are most common in frontal leads, and stay for 3-5 seconds. There are two distinct types of carotid spindles that may be seen in children: one has a frequency of 11-12.5 Hz with a maximum in the frontal leads, and the other has a frequency of 13-14 Hz with a maximum in the central parietal leads. Both can be found independently. Some writers believe that "giant" sleep spindles are an indication of a pathological condition (cerebral palsy, organic lesions of the CNS, oligophrenia, drug intoxication, cognitive disorders of various degrees) [36, 37].

Positive occipital acute sleep components, also known as POSTS, are a type of acute component that consists of a high-amplitude positive monophasic or biphasic wave with a frequency of 3-5 Hz, which is then followed by a possible low-amplitude negative wave. These waves occur during the occipital region of the brain. Maximum expression in occipital leads. Occur as brief runs that can last up to three seconds, with a frequency of 4-5 Hz, bilaterally and synchronously; nevertheless, in the majority of instances, there is a noticeable asymmetry. Occurs in stages I and II of slow-wave sleep, and as sleep becomes more profound, the frequency of these waves drops below 3 Hz. In adults, the condition is most commonly documented between the ages of 20 and 30 years; nevertheless, it can first be observed in children as young as 3 or 4 years of age. The incidence of the condition gradually declines beyond the age of 50 [38].

Low-amplitude biphasic spikes (SSS) of very short duration, often followed by a small theta wave, occurring in the temporal regions (perhaps diffusely, but predominantly in the frontotemporal leads) during drowsiness or shallow sleep are referred to as benign epileptiform sleep components (BETS). These spikes can be classified as either benign or malignant. Benign epileptiform transients of sleep is what is meant to be abbreviated by the acronym BETS. Recordings may be made on either side of the cassette. Always appear as individual patterns by themselves. have a distinct position in the electrical field. The oscillations have a duration of less than fifty milliseconds, and their amplitudes are less than fifty microvolts. Adults are more likely to have these symptoms than children are [15, 38].

Wicket waves are runs of growing and decreasing arch-shaped sharp waves that resemble a mu-rhythm in the middle and/or anterior temporal, frontal leads. These waves have a frequency of 6-11 Hz and do not occur in conjunction with a subsequent slow wave. The waves' negative phase has a sharp edge, while the waves' positive phase has a rounded appearance. 6-11 Hz frequency, 60-200 V amplitude, occurring unilaterally, bilaterally, or independently in the temporal leads, during calm wakefulness and stage I of FMS, occuring at any age, but more commonly in adults. 6-11 Hz frequency and 60-200 V amplitude. Positive spikes with a frequency of 14-6 Hz are arc-shaped and have a frequency of 13-17 Hz and/or 5-7 Hz. They occur in short runs of 1 second (rarely up to 3 seconds), have an amplitude of no more than 75 V, and can appear unilaterally or bilaterally (synchronously or asynchronously) in the posterior temporal leads. They have a diffuse spread. It may happen at any age, but it's most frequent in teens [39].

RMTTD, also known as rhythmic temporal theta bursts of drowsiness, psychomotor variant, are rhythmic group low amplitude negative biphasic, sinusoidal, jagged or sharply outlined monotone sharp waves of 5-7 Hz that occur in short runs in the central temporal leads in adolescents and young adults [40]. These runs can last anywhere from several seconds to one minute. They manifest themselves when a person is sleepy. They can begin suddenly or gradually, can be unilateral or bilaterally synchronised, and can be independent of one another. A switch in the recording location of the EEG can sometimes be seen after it has been going on for a while. They are recorded while the subject is in stage I of the MBF and in the relaxed wakefulness state. During REM sleep, saw-tooth waves are negative vertex waves with a frequency range of 2-5 Hz that occur in sequence [40, 41].

Arch-shaped waves with a frequency of 6-7 Hz and a maximum in the fronto-central leads characterise the Ziganek central rhythm. This rhythm lasts for 4-20 seconds. Takes place during states of consciousness that are more like slumber [42].

The frontal awakening rhythm (FAR) is a cyclic run of 7-20 Hz oscillations in the frontal regions of both hemispheres that can linger for up to 20 seconds. These runs are typically intensified, giving them a jagged appearance. When youngsters first become aware of their surroundings [43].

In hypersynchrony of waking, widespread rhythmic sinusoidal (perhaps sharpened) group waves of theta-delta range in amplitude 150-300 V, lasting 4-20 seconds with amplitude preponderance in the anterior cortices, are seen. These waves have been shown to be possibly sharpened. Children aged 6 months to 5 years were observed and their awakenings were recorded [15].

Temporal deceleration is a short-term, irregular, transitory sluggish activity that occurs in the temporal area. It is more common in those over the age of 45 and has a greater tendency to have a greater predominance in amplitude on the left side of the head [31].

Lambda waves are biphasic, sharp alpha-band waves that occur in the occipital regions during the waking state and a visual task ('examining') in children ages 2-15. These waves occur less often in young adults and older people. Lambda waves are found in children's brains. The primary constituent contributes to a good impact in relation to other aspects. synchronised in time with saccadic eye movements, with a delay of around one hundred milliseconds (ms). The amplitude fluctuates, but it almost always stays within a range of 50 microvolt [44].

FIRDA is an abbreviation that stands for periodic and rhythmic waves that have a frequency of 3 Hz. Occur in a bifrontally-synchronous manner or in a unilateral fashion to the frontal leads. Recorded in wakefulness, drowsiness, generalised sleepiness (GW), which is a variety of normal in children, as well as in diffuse encephalopathies, which are organic lesions of the frontal brain [45].

OIRDA (PIRDA) are waves that repeat at regular intervals and have a frequency of 3 Hz. Biparietally, bi-occipitally, and synchronously occur in runs of two to six seconds (may be up to several minutes). During waking as well as phases I and II of non-REM sleep recording was done. M.b. in conjunction with peaks in cases of generalised epilepsy. In youngsters between the ages of 10 and 12, a variety of the normal [46].

SREDA refers to rhythmic waves that start and stop suddenly, are diffuse or bilaterally synchronised, and are most common in the occipital leads. They have a frequency of 5-6 Hz and last for a few seconds to a few minutes. Observed both while the participants were awake and while they were sleeping in people aged 50 and older [47].

Acquiring a rhythm while being stimulated by light involves positive, bilaterally synchronous oscillations in the alpha-theta region that occur "in time" with the frequency of rhythmic photostimulation, with the occipital leads playing a more prominent role than the other leads[15].

Variation in the slow background alpha rhythm - Short- or lengthy replacement of the regular frequency of the alpha rhythm by its subharmonics, such as the emergence of oscillations of 5-6 Hz instead of 10-12 Hz. This can occur for a short period of time or for a longer period of time. Waves have a rhythmic quality, and they are bilaterally synchronised. Occipital leads tend to be more prominent than other leads. Variant on the cusp between what is normal and what is abnormal, also could be an indication of a problem with the diencephalic nonspecific brain systems [48].

The term "spikes" rectus lateralis refers to artefacts that indicate adhesions of the medial rectus lateralis muscle that occur during horizontal eye movements. Sharp delta waves that are bilateral and asynchronously polyphasic. originating mostly from the muscle on the ipsilateral side. In most cases, the recording was done under the F7/F8 electrodes [49].

High-amplitude, bilaterally synchronous, monophasic, and biphasic theta-delta waves characterise eye movement artefacts. After the theta range, artefacts that represent the reflexive upward retraction of the eyes that occurs during eyelid closure are often recorded under the F7/F8 electrodes [31].

2.4. EEG Artifacts

The electroencephalographic test (EEG) gives the neurologist the ability to assess the functional condition of the brain in patients suffering from a variety of neurological illnesses. However, contemporary EEG equipment captures extremely tiny magnitudes of changes in bioelectrical potentials. Because of this, the genuine EEG activity may be substantially affected by a range of physical (technical) and/or physiological effects, which results in a variety of artefacts [15].

The following types of artefacts can be differentiated based on where the EEG recording was made: physical, the occurrence of which can be attributed to a variety of technical (technological) faults as well as a variety of physiological processes occurring within the body.

Physical artefacts

The occurrence of linear interference from the AC network at a frequency of 50 Hz in current EEG recorders is a very uncommon occurrence [50].

The main reason is malfunction of the equipment and the effect of powerful electromagnetic fields caused by mains electricity from medical equipment were the causes (magnetic resonance, radiology, physiotherapy). The mains surge can be eliminated by adjusting the encephalograph, ensuring that the device is properly grounded, and ensuring that there is no violation of contact in the electrode conductors. In the event that it is necessary to carry out research in close proximity to sources of electromagnetic radiation, it is possible to turn off all electrical appliances for a brief period of time. If this is not possible, such as in an operating theatre or intensive care ward, a high frequency filter can be used in its place. However, it is important to keep in mind that in this scenario, the appropriate frequencies of the bioelectrical activity of the subject's brain will be absent from the EEG [51].

Total and complete failure of the conductor (loss of contact with the patient) is distinguished by sharp increases in potential that are accompanied by "offsets." The most common cause of this issue is a broken connection lead, followed by improper electrode positioning, incorrect polarisation of the electrode, or a buildup of electrical charges on the body of the test subject. The problem may be fixed by ensuring that the cables in the input box of the electroencephalograph are in good condition and connected to the appropriate electrodes. In the event that there is a damaged connecting lead or a polarising potential, the electrode has to be changed [52].

The conditions of low humidity are the most likely cause of static discharge electromagnetic bursts, which might occur singly. The electrodes may be relocated, the skin under the electrode can be abraded with specific paste (fine sandpaper or sterile injection needle) to a small redness without injuring the dermis, and you can advise the patient to remove any synthetic clothes they are wearing [50].

Artifact of high electrical impedance causes include improper placement of the electrode on the patient's skin, drying out of the contact gel, or the electrode detaching itself from the skin surface. The artefact can be identified by the presence of an extended isole activity beneath one electrode, which mimics an electromyogram [50]. Restoring contact between the electrode and the patient's skin and the conducting medium is the corrective action to take.

Artifacts of the physiological system are for example ECG, EMG and EOG artifacts

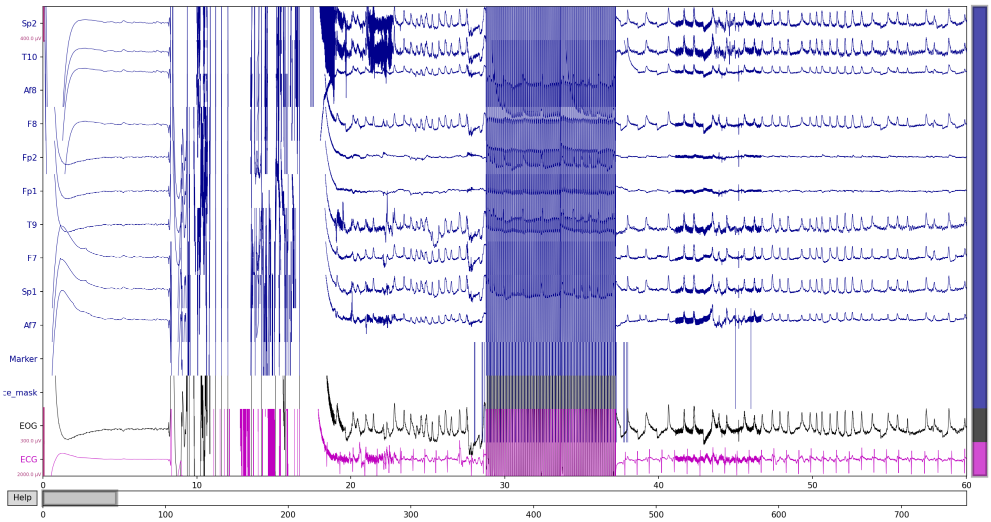

Figure 3. Example of the physical artifact such as high electrical impedance seen on the patient EEG."

ECG artefact happens more frequently in hypertensive individuals, and most frequently in monopolar and transverse bipolar leads. Its occurrence has been related to an increase in the activity of the sympathetic nervous system, which makes it easier for the ECG signal to get to the peripheral tissues. The rhythmic sharp complexes that are represented by the ECG artefact imitate epileptiform activity, specifically the benign childhood epileptiform pattern (BEPD). However, unlike BEPD, the ECG artefact does not have a slow-wave component, and in the case of BEPD imitation, its frequency is stable and coincides with the frequency of the QRS complexes on the ECG. Rhythmicity and coincidence with QRS complexes are not characteristics that are typical of BE [15].

Other type of cardiac artefacts are also known as vasopressor (vessel pulsation) or cardioballistic artefacts. Other names for them include vasopressor artefacts (myocardial contraction).

The presence of cardiac mechanical artefacts on an electroencephalogram (EEG) is attributable to the circulatory system and can be categorised as an electrode artefact. Occurs when the electrode is placed over a pulsating vessel in the head and manifests as a periodic slow wave with a regular interval (coinciding with the period of the heartbeat) that follows the peak of the ECG artefact approximately 200 milliseconds after it has occurred. This wave appears after the ECG artefact has peaked [53].

Sawtooth or sharply defined morphology can be found in some instances. It is often discovered beneath a single electrode, most frequently in the frontal and temporal leads and much less frequently in the occipital leads; nevertheless, it can be present elsewhere. Simply touching the electrode that is creating the impulse artefact is a quick and easy way to identify it. When it is pressed on, it not only reveals that there is a connection between the electrode movement and the impulse, but it also causes a change in the EEG signal. When viewed from a nearby middle mount, this feature is more easily discernible. On an EEG spectrum map, an artefact of this kind would appear as a local peak at a frequency of around 1 Hz [54].

An electromyogram, often known as an EMG, is a pointed, irregular frequency electrical activity that occurs at high frequencies (15-100 Hz). The amplitude of the electromyogram (EMG) is related to the degree of tension that is being applied to the muscle as well as its distance from the withdrawal electrodes [54].

The activation of the neck, masseter, and, to a lesser extent, the mimic muscles can cause electromyogram abnormalities in an EMG recording. These muscles are responsible for the majority of electromyogram artefacts. As a result, the most prominent EMG activity may be seen in the occipital, temporal (mostly T3, T4), or frontal leads (with tension from m. orbicularis oculi) (mainly Fp1 and Fp2). The production of myogenic artefacts is mostly associated with the frontal and temporal muscles. During photostimulation, the frontal muscles are the ones that are primarily engaged in the process of forcibly closing the eyes. When a person clenches their jaw, chews, or grinds their teeth, they are engaging their temporal muscles. This may be seen on an electroencephalogram (EEG) as recurrent bursts of polyspikes or rapid activity that is prominent in the temporal leads [15].

The eye movement artefact may be seen in virtually every normal EEG, and it is helpful in detecting the phases of sleep. This is because opening the eye inhibits the alpha rhythm, but shutting the eye promotes the alpha rhythm. There is a correlation between eyeball movement and EEG potentials, which in turn leads to shifts in the orientation of the electrical axis of the eye, which may be measured by the corneo-retinal potential [55].

The majority of the artefacts associated with eye movement are linked to the 100 mV electric dipole that is unique to each eye. The dipole has a positive charge in the corneal direction and a negative charge in the retinal direction. It is positioned along the axis that runs across the cornea and the retina. The phenomenon known as Bell's phenomenon occurs when there is an upward deflection of the signal concurrent with vertical eye movements that precede the opening and shutting of the eye. Ocular artefacts can also be caused by the movement of the eyelid, which has myogenic potentials. This occurs when the eye is opened and closed. Due to the quick movement of the eye up and down that occurs during blinking, an ocular artefact is produced, which shows up on an EEG as a bifrontal, biphasic, synchronous slow wave. As one moves further away from the orbits, one may observe a dramatic reduction in the amplitude of the artefact. The wave's amplitude is at its highest point and it has a positive sign in the frontal leads. Because the artefact is caused by an upward deviation of the eyes, the negative end of the dipoles is not seen when the antenna is mounted in its usual position [55].

The majority of the time, they manifest themselves as uniphasic, biphasic, or monophasic positive or positive-negative oscillations with a period ranging from 0.3 to 1 second. Involuntary eyelid and ocular motion can cause the EOG frequency to be much higher, ranging from 4-6 Hz. Because the frequency range of eye movements overlaps with the - and -waves on the EEG, there is a chance that an incorrect diagnosis might be made. [15]

The spatial distribution of artefacts that result from eye movements is one of the characteristics that sets them apart. Their amplitude is reported as being at its highest in the frontal leads, and it quickly declines as one moves towards the front or rear. In addition, the shape of these artefacts is extremely distinctive and archetypical, to the point where, when laid on top of one another, they almost entirely correspond. EOG artefacts, like other types of artefacts, are unconnected to the rhythm of the present EEG and appear as though they are independent of changes in the EEG [55].

Figure 4. Example of artifact of eye batting and eye moving seen on the patient EEG recorded on the BrainStatus device using the C-Trend programme.

2.5. EEG Procedure

An EEG does not cause any harm and is totally painless. During the examination, the patient will either sit in a chair or lie down on a couch, and will keep their eyes closed the whole time. In order to conduct an EEG, a specialised helmet with built-in electrodes must be worn by the patient, and those electrodes must be hooked to the electroencephalograph. The potentials that are obtained from the sensors are multiplied by hundreds of thousands of times by the machine, and either written out or stored in the memory of the computer [56].

When a kid is brought in for an exam, the parent or caregiver should prepare the child for what to expect during the test and reassure the child that it will not be painful. Before the examination, the patient shouldn't have a feeling of hunger because this might create abnormalities in the EEG. Before beginning the EEG test, the patient's head should be thoroughly cleansed; doing so will enable the electrodes to make better contact with the scalp and produce more accurate findings. Children in preschool should have practise putting on a "helmet" (by playing cosmonaut, tanker, or other such roles) and keeping still with their eyes closed, as well as learning to breathe deeply and often. This should be done in addition to learning to stay still [56].

If the patient experiences a seizure while they are getting an EEG, the findings will be much improved since it will be easier to pinpoint the precise site of the electrical activity in their brain. On the other hand, in order to keep the patient as safe as possible, seizures are never purposefully brought on. It is fairly uncommon for individuals to skip taking any medications before having an EEG done on them. This is not something that should be done [57].

The electroencephalogram (EEG) is performed by a neurologist who has undergone extensive further training and is also referred to as an electroencephalographer or neurophysiologist. He presents his interpretation of the findings of the examination after describing them. Nevertheless, the neurophysiologist is unable to provide a conclusive diagnosis in the absence of more comprehensive clinical evidence. Many of the changes that might occur on an EEG have the potential to be nonspecific, which means that their accurate interpretation can only be achieved in conjunction with the clinical picture of the disease and, in some cases, after an additional test[57].

2.6. The Importance of the EEG in Diagnosis

In recent years, electroencephalography (EEG) has frequently been compared with cutting-edge imaging techniques for the brain such as positron emission tomography (PET) and functional magnetic resonance imaging (MRI) (PET and fMRI). These approaches provide very precise pictures of brain areas that are either engaged in the regular functioning of the brain or are damaged when pathological processes are present [58].

What are the benefits of utilising EEG? Some of these are quite self-explanatory: EEG is very user-friendly, economical, and does not need the individual to be exposed to any risk (non-invasive). The patient's EEG can be recorded at the bedside and utilised for long-term monitoring of brain activity as well as tracking the stage of epilepsy the patient is experiencing. However, EEG also has another benefit that is not as readily apparent but is extremely advantageous []. In point of fact, PET and fMRI are predicated on the measurement of secondary metabolic changes in brain tissue as opposed to primary metabolic changes (i.e. electrical processes in nerve cells). The electroencephalogram (EEG) is capable of revealing one of the most important criteria of the nervous system, which is the quality of rhythmicity. This attribute indicates the coherence of the various regions of the brain. As a consequence of this, the neurophysiologist is able to gain access to the real information processing systems of the brain by recording an electrical (in addition to a magnetic) encephalogram. This helps to disclose the pattern of processes engaged in the brain, demonstrating not just "where" but also "how" information is processed in the brain. This helps to highlight the pattern of processes involved in the brain. This capacity is what distinguishes EEG as a distinctive diagnostic tool that is unquestionably beneficial [58, 57].

Examinations using electroencephalography shed light on how the human brain makes use of its available functional reserves.

2.7. Basics of Anaesthesia

Anaesthesia is a condition of artificially caused reversible inhibition of the central nervous system that leads in loss of consciousness, sleepiness, forgetfulness, pain alleviation, skeletal muscle relaxation, and loss of control over certain reflexes. Anaesthesia is created intentionally and may be reversed. This will take place as a result of the administration of one or more general anaesthetics. The anesthesiologist will determine the optimal dose and combination of these anaesthetics based on the specific characteristics of the individual patient as well as the kind of medical procedure that will be performed [33].

The primary objective of administering anaesthesia is to postpone the physiological reaction of the body to a surgical treatment, in particular the experience of pain. However, the induction of sleep by means of medical treatment, with which the word "anaesthesia" is most generally associated, is only one component of anaesthesia, albeit the most important one. When giving anaesthesia, it is also important to suppress or significantly reduce the severity of the body's autonomic (automatic) reactions to surgical trauma. These reactions are manifested by an increased heart rate (tachycardia), increased blood pressure (arterial hypertension), and other phenomena that may occur even when the consciousness of the patient has been turned off. Anaesthesia and analgesia are both terms that refer to the inhibition of autonomic reflexes. Myorelaxation, often known as muscle relaxation, is the third component of anaesthesia. It is important to ensure that surgeons have a proper working environment in which to perform their jobs [59].

The word "anaesthesia" refers, more particularly, to the body's generalised state of being unconscious. When discussing "local" or "local" anaesthesia, you should refer to either phrase as "local anaesthesia" or "local anaesthesia" (with the adjective "local" is often omitted). Because unconsciousness (also known as narcosis or falling asleep) is the foundation of this type of anaesthesia, the phrases anaesthesia and anaesthesia refer to fundamentally distinct states of awareness and are not interchangeable [59].

Infusions and decoctions of numerous plants (such as opium, cannabis, hemp, hemlock, and scurvy, among others) were used to create the earliest anaesthetics. These "sleeping sponges" were also a common practise. After being doused in the liquid produced by the plants, the sponges were then set ablaze. The patients fell asleep after taking in the vapours of the medication [60].

R. Lullius, a Spaniard, is credited with discovering ether in the XIII century, and Paracelsus, writing in 1540, detailed the analgesic qualities of this substance [61]. William Thomas Green Morton gave the first public demonstration of ether anaesthesia on October 16, 1846, in a clinic in Boston, Massachusetts, in the United States. The procedure involved the excision of submandibular tumours. On February 7, 1847, F. I. Inozemtsev was the first person in Russia to utilise ether narcosis, and on February 14, 1847, Russian scientist and physician Nikolai Ivanovich Pirogov was the first person to use it to anaesthetize a patient before to a surgery [62].

J. Simpson, a Scottish obstetrician, is credited with being the first person to utilise chloroform for the purpose of administering anaesthesia during delivery in the year 1847[63].

In the latter part of the 20th century, xenon was first utilised in the field of anaesthesia[64].

There are several distinct types of anaesthesia, including inhalational, parenteral (intravenous, intravenous with AV, intramuscular, rectal, etc.), and combination anaesthesia (anaesthesia is achieved by using a series of different narcotic agents and methods of their administration)[65]. It is possible to have anaesthesia with spontaneous (independent) breathing or anaesthesia with mechanical lung ventilation, and the differentiation between the two is based on the circumstances surrounding the patient's breathing while under anaesthesia (AVR). The second option typically requires tracheal intubation, which is when a specialised tube is inserted into the airway of the patient after they have been put to sleep, or other methods that enable air, oxygen, or gas mixtures to be blown into the patient's lungs using a ventilator or a special bag. Tracheal intubation is performed after the patient has been put to sleep[33].

Because different parts of the brain and spinal cord are involved in the inhibition process at different stages, each stage has its own distinct features, which are in turn dictated by these differences.

The initial stage of analgesia is characterised by a condition that appears to be externally pronounced stupefied. The animal either appears to be standing there dazed or displays signs of restlessness. The patient's pulse is quick, their ocular movement is voluntary, and their breathing is deep and regular. The tone of the muscle either stays the same or slightly increases. Reflexes are intact. The feelings of pain are dulled or eliminated entirely, although the receptions of touch and temperature are unaffected[66].

In order to create analgesia, the pain-sensitive centres in the reticular formation and the optic tubercles of the brain stem must first be disabled. Meanwhile, the bioelectrical activity of the cerebral cortex must even be boosted[66].

Continuing to take the medication causes the activity of the medicine to become more profound, and it also causes the second stage, motor excitation, to commence. This can be observed as an elevated tone in the skeletal muscles, disorganised contraction of the limbs, efforts to get up, or movements in space that are out of sync with one another. Both the respiration and the pulse are erratic. There is an elevation in blood pressure. There is a lack of focus in the eyeballs. The pupil has become more open. There is an increase in the amount of secretion produced by the sweat, salivary, and bronchial glands. Swallowing occurring frequently. Against this backdrop, increasing levels of analgesia can be observed. Urination, vomiting, reflex respiratory arrest, cardiac fibrillation, and maybe even death are all possible side effects of this medication[67].

The third stage of anaesthesia, known as surgical anaesthesia, occurs as the effects of the anaesthetic drug become more intense. This stage is broken up into four different levels according to anaesthesiology:

1. Anesthesia of a superficial kind. There is a total absence of discomfort as well as physical feelings. There is a halt to the swallowing. The corneal reflex is no longer visible. The eyeballs are displaced in a manner that is eccentric, and the pupils are constricted. Snoring occurs as a result of the relaxation of the vocal chords, which causes deep, rhythmic breathing. Blood pressure stabilises, pulse is fast. Skeletal muscles are not relaxed. Reflexes of the anal sphincter and visceral-visceral reflexes, which are responsible for stretching the peritoneum and mesentery, are both retained [68].

2. A mild form of anaesthesia. The eyeballs are positioned such that they are in the middle of the head. The pupils are narrowed and have a minimal reaction to light. There is some looseness in the skeletal muscles, but not total relaxation. Lack of a stretch reflex in the abdomen region Both the heartbeat and the breathing have a regular pattern. It is possible to undertake superficial surgical procedures[68].

3. Complete sedation or anaesthesia When CO2 is added to the air that is breathed in, the breaths are regular and shallow, and the rate of breathing quickens. A regular pulse is there, but its filling is less, which indicates a drop in blood pressure. However, reflexes continue to be present from the aortic and sinocarotid zones, which ensures

proper operation of the respiratory and circulatory centres. Reflexes from the surface and body cavities are not obvious. In some cases, it is possible to generate impaired bladder and rectal reflexes. The pupils of the eye start to become more open. The skeletal muscles become relaxed, and the tongue may droop if it is not held in place. This can lead to asphyxiation since the tongue is blocking the airway leading into the larynx[68].

4. Ultra-deep anaesthesia, a state that poses a risk to the patient's life. The breaths are short, laboured, and diaphragmatic in nature. The blood pressure is low, the pulse is feeble, and the filling is low as well. Mucosal membranes are affected by cyanosis. The eyeballs are not moving and are located in their typical location. Additionally, the cornea is dry, and the pupil has expanded[68].

Tracking of the patient's heartbeat, blood pressure (assessed manual or automatic, directly and indirectly), persistent registration of the electrocardiogram (ECG), and oxygen concentration in blood (from observation of the skin and mucous membranes colour or by using a pulse oximeter to evaluate blood oxygen saturation levels, or lab tests), core and body surface temperature, pupil response, diuresis rate, and blood tests for gases, electrolyte composition, and acid-base status are all used to control the patient's condition while they are under anaesthesia [69].

Inhalation anaesthesia is kept at the appropriate level by specialised devices (rotameters, vaporisers), which enable precise control of the concentration of anaesthetic gases or vapours of liquid anaesthetics in the breathing mixture. This allows inhalation anaesthesia to be administered safely and effectively. Anaesthesia and respiration devices allow for the monitoring of several parameters of AV, and current anaesthesia monitors allow for the monitoring of the concentration of gases (oxygen, nitrous oxide, carbon dioxide, and anaesthetic vapours) in the inhaled and exhaled gas [70].

Recovery from anaesthesia, often known as waking, is just as important as the delivery and maintenance of anaesthesia. However, the loss of reflexes will be progressively repaired, and the results may not be satisfactory for some time. Due to the fact that this is linked to a variety of anaesthetic issues, anesthesiologists are required to continue monitoring the patient after the procedure has been completed [66].

2.8. Propofol-Induced General Anaesthesia

Propofol (diprivan) is a compound emulsion for intravenous administration containing 10 mg propofol in 1 ml (1 per cent propofol). It has a significant hypnotic effect, therefore it is used for administration in anaesthesia and in combination with other agents for maintenance of anaesthesia in operations of various volume and nature. In this study propofol was used as an anaesthetic agent [67]. Usually if necessary, cholinolytics, analgesics, sedatives, and antihistamines are included in the medical preparation. Intravenous bolus slow infusion of propofol at a dosage of 2-2.5 mg/kg is used to administer introductory anaesthesia during surgical procedures. After around 30 to 35 seconds, unconsciousness is no longer present. After a delay of 40–60 seconds, surgical staging will begin. It is not possible for a single dose of propofol to have an effect that lasts longer than five to ten minutes. If the level of anaesthesia no longer has to be maintained, it is possible to keep the patient under anaesthesia with either a continuous infusion of the anaesthetic agent or frequent bolus injections [67].

As is the case with the vast majority of intravenous anaesthetic drugs, the mechanism of action is not completely understood. It has been hypothesised that the injection of this substance will impede GABA mediator transmission in the upper central nervous system[71].

Propofol, when given intravenously, causes a quick onset of hypnotic sleep with just a little amount of wakefulness. This often takes place within the first forty seconds after the injection has been started. Inhibition of glottic and laryngeal reflexes occurs during the induction phase of propofol administration, despite the fact that the anaesthetic has no impact on the tone of the voluntary muscles. Following a propofol-induced state of anaesthesia, the patient will often experience a speedy return to full awareness along with an unimpaired capacity for orientation in both place and time [71].

Post-anesthetic waking is characterised by a quick recovery of awareness (on average lasting just five to six minutes) as well as activation of motor processes, including breathing. Because of this trait, propofol is distinguished from the other anaesthetics that are currently in use, which makes the use of propofol particularly favourable for outpatient surgery and for short-term treatments. Disorders in the patient's external respiration (bradypnoea, apnoea) and abnormalities in the patient's hemodynamics are the propofol side effects that are most characteristic (bradycardia, lower blood pressure) [72].

During the injection process, patients can experience muscle fibrillation and motor excitation. In extremely unusual instances, symptoms such as stridor, increased salivation, and masticatory muscle spasms may be present [72].

Only a small percentage of people experience symptoms such as nausea, vomiting (despite the fact that propofol has an anti-emetic effect), and a transient headache when they are awake. Sensitized individuals frequently suffer allergic responses, particularly in response to the repeated administration of propofol. The allergic reaction that manifests itself most frequently is erythema, whereas partial bronchospasm and anaphylactic shock manifest themselves much less frequently. In individuals who have chronic hepatitis or liver cirrhosis, an increase in the amount of time spent awake can be as much as twenty minutes or longer. The fact that the liver is responsible for deactivating propofol helps to explain this phenomenon. Local responses to an injection of propofol can include the relatively common occurrence of unpleasant feelings at the injection site, as well as the less common development of phlebitis. Both of these conditions are classified as local reactions [71].

It is recommended that injections be given into big veins in order to reduce the likelihood of experiencing these adverse effects. Indications: Introductory anaesthesia, mono anaesthesia for the analgesia of short-term surgery and manipulations, and total intravenous anaesthesia (in combination with low doses of narcotic analgesics, tranquillizers, and ketamine) for the anaesthesia of nontraumatic medium-duration surgical interventions. Considerations to the contrary are patients who have a history of adverse responses following the administration of propofol; patients who have phlebitis or thrombophlebitis; and patients who have respiratory or cardiovascular insufficiency are not good candidates for receiving propofol treatment [72].

Following the conclusion of the anaesthetic procedure, the patient may be sent immediately to the specialty department, skipping by the recovery chamber in the process. The anaesthetic itself, oxygen, analgesics, equipment for preserving upper airway patency (laryngeal masks, airways of various diameters), and venous access, monitor, aspirator, drugs for symptomatic treatment in case of side effects and problems are all required resources for anaesthesia.

Propofol has a central depressive effect on the respiratory system, meaning that it slows down both the rate and the depth of breathing. The use of propofol for anaesthesia frequently results in apnea (60 sec or more). In most cases, maintaining anaesthesia at a dosage of 6 mg/kg/h will result in some suppression of breathing along with an elevation in RAS2, the magnitude of which is depending on the dose. Apnea, blockage of the airway, and a drop in blood oxygen levels are common side effects of the fast injection of dosages [73].

Propofol has several side effects on the central nervous system. The anesthetic decreases cerebral blood flow, cerebral oxygen uptake, and intracranial pressure while simultaneously raising cerebral vascular resistance without having an effect on cerebral vasoreactivity in response to variations in CO2 concentration. When the anaesthetic is administered to individuals who have normal intraocular pressure, this leads to a drop in that pressure, which may be the result of a simultaneous reduction in systemic vascular resistance[73].

2.9. Depth of Anesthesia

It is a difficult undertaking to properly monitor the level of anaesthetic being administered during a surgical operation. Inadequate depth of anaesthetic might result in patients experiencing intraoperative consciousness, which can have detrimental psychological repercussions on the patient. In addition to this, clinical signs such as blood pressure, heart rate, sweat, or limb movement can be utilised to determine the extent to which anaesthetic has been administered. However, these traditional approaches do not always permit a reasonable estimate of the level of anaesthesia, and the accuracy of such an estimate might differ from patient to patient and depending on the type of operation being performed. In addition, the simultaneous administration of various medications, such as muscle relaxants, vasodilators, and so on, in conjunction with anaesthetics, has made the interpretation of these indications both challenging and unreliable [74].

Over the course of the past few decades, the primary objective of research has been to identify a method that is both dependable and non-invasive for monitoring the extent of anaesthesia. Due to the fact that an anaesthetic medication primarily affects the central nervous system, there has been an increased emphasis placed on the study of brain activity. EEG analysis is regarded to be one of the most important methods of study and evaluation of the level of anaesthesia in clinical applications due to the fact that electroencephalogram (EEG) signals give vital information about brain functions [75]. EEG analysis has led to the development of a number of methods that can assess the patient's state of awareness while they are under general anaesthesia. These approaches include the 95 percent spectral edge frequency (SEF95), the spectral central frequency, and the bispectral index [74]. The bispectral index, often known as the BIS, is a complicated frequency-time parameter that is made up of multiple subparameters. These subparameters have meanings that shift based on the patient's depth. In specifically, two of these BIS index characteristics are the burst suppression ratio (often referred to as BSR), and the relative beta ratio (RBR).

The degree of complexity and variation in the communication that takes place between different parts of the brain is connected to the individual's level of consciousness. When a person is under anaesthesia, their brain loses some of the varied functional connections that it has when they are awake [75]. During anaesthesia, there is an increase in the phase synchronisation of the frontal brain's electroencephalography (EEG) signals, as well as changes between these signals, which indicates a reduction in the amount of communication variety. It has been found that the temporal dynamics of the functional network configuration are more closely associated to the state of consciousness than the strength of the static connectivity. During anaesthesia, the state of awareness may be measured using brain function monitors, which include the processed EEG data as an essential component [76].

However, anesthesiologists often do not possess any trustworthy methods for determining whether or not a patient is unconscious. Unconsciousness is a necessary condition for general anaesthesia to take place. In the majority of instances, loss of consciousness (LCV or LOC) is associated with a rise in slow wave range (1 Hz) EEG activity, the disappearance of spatially coherent alpha rhythms (8–12 Hz) in the back, and the development of spatially coherent alpha oscillations in the front. During the process of regaining awareness, these dynamics are eventually flipped - recovery of conscoiusness(ROC).[77]. During anaesthesia with propofol, sevoflurane, and ketamine, there have been reports of alterations in the functional connectivity of the brain as well as interruptions in the communication of the frontal EEG in the brain [78].

The evaluation of the clinical performance of the C-Trend as a method to monitor anaesthetic depth while propofol was being administered was one of the goals of this thesis.

2.10. BrainStatus Device

The Bittium BrainStatus gadget and C-Trend Software were utilised in the process of gathering the parameters that have been gathered over the course of the investigation. Bittium [79] is a firm that specialises in the creation of trustworthy, secure communications and connectivity solutions. The company has a history of knowledge spanning 30 years in the field of sophisticated radio communication technology. The traditional full-head helmet used for EEG measurements is not comparable to the modern EEG cap in terms of both the number of electrodes and their placement. In place of completely covering the scalp with electrodes, just 10 EEG electrodes, together with electrooculography (EOG), electrocardiography (ECG), and marker (reference) signals, are shown across the frontal lobe of the head. The Bittium BrainStatus headband is designed to be both flexible and sturdy so that the electrodes may be automatically positioned in the appropriate locations without the need for the patient's head to be moved. This allows the headband to provide the benefits that were previously outlined. Because of the material that the electrode set is made of, it is not necessary to take it off in order to do a computerised tomography scan [79].

The Bittium BrainStatus electrode device is being used in the study that is now being conducted in order to capture the EEG data from the patients so that the study can assess all of the patients' EEG signals. The EEG measurement system consists of 10 EEG data electrodes, which have been given names in accordance with the 10/20 international system; an EOG; an ECG; reference signals; and an information channel, which includes data such as the recording device, the start date and time; the duration; and the channel physical characteristics. The reference signals are composed of the average of all reference signals (dimension, physical maximum and minimum value, sampling frequency, among others). This complies with a record that is made up of thirteen signal channels and one auxiliary channel that contains environmental information. The live data can be also accessed after the recording on the medical tablet, as data is usually stored in the cloud. The example of how the data is looked like for the medical specialists can be seen on Figure 5.

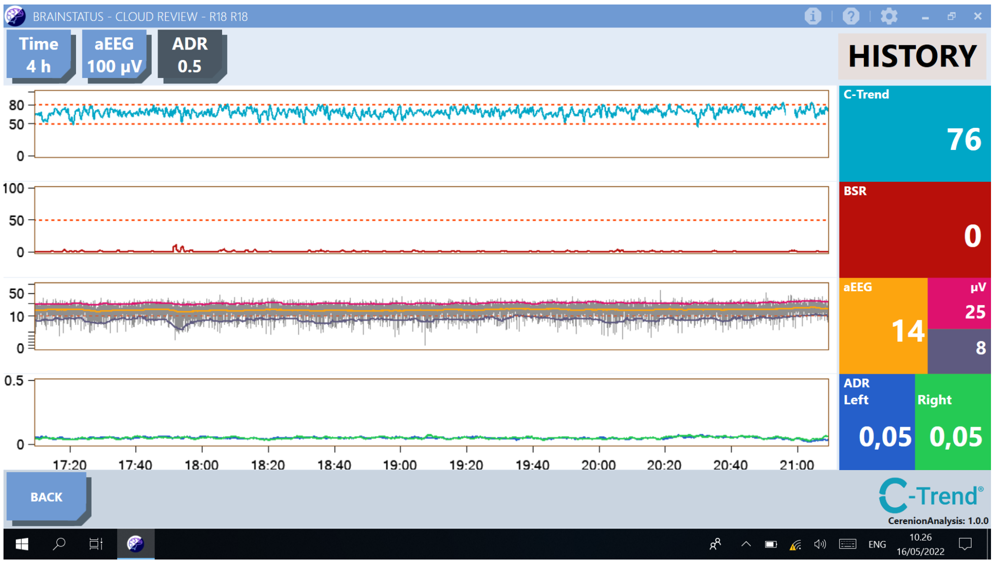

Figure 5. Example of several hour C-Trend data analysis on the BrainStatus. On the first two plot from above blue signal represents the C-Trend Index parameter, red colour signal represents the burst-suppression ratio parameter. On the third plot blue and red colour represent the lower and upper margin of the amplitude-integrated EEG parameter, the gray colour represents the raw aEEG signal and the orange colour represents the mean value. On the fourth plot green and blue colours represents alpha-to-delta ratio on right and left hemisphere. On the X axis time is in hours and minutes, the y axis is in micro-volts.

2.11. Quantitative Parameters of EEG

For EEG interpretation, the "gold standard" is considered to be a visual analysis of the patient's original EEG data performed by a neurophysiologist who has received board certification. In addition, quantitative EEG trends, also known as QEEG, are shown to aid in the interpretation of this visual data. For the purpose of monitoring the brain condition of a patient who is receiving critical care, continuous EEG monitoring that lasts for several days is required. This is especially true in cases where it is suspected that the patient is experiencing nonconvulsive seizures [80]. In the event that long-term, uninterrupted visual EEG evaluation by a neurophysiologist is not practicable in clinical practise, continuous monitoring of qEEG parameters at the patient's bedside can be an aid in monitoring the patient's condition. This can be achieved by notifying the personnel working in the intensive care unit (ICU), in addition to acting as a trigger for neurologic and radiologic consultations [81].

One of the criteria for EEG analysis is symmetry, which refers to the degree of overlap in the frequency, amplitude, and phase of activity over identical (homotopic) regions of both hemispheres of the brain. Symmetry is used to determine whether or not a person has a brain disorder. A reflection of the functional asymmetry of the brain may be seen in the asymmetry of electrical activity between the right and left hemispheres of the brain. Expression, amplitude, and index are the three metrics that may be used to evaluate asymmetry for each beat [82]. An interhemispheric asymmetry coefficient is utilised in order to measure symmetry. This coefficient is the severity (often expressed as a percentage) of the difference in EEG parameters (amplitude, index) over comparable regions located on the right and left sides of the brain. The formula that may be used to get the asymmetry coefficient Kp is as follows:

$$Kp = (Ps + Pd)/(Ps - Pd), \tag{4}$$

where Cp is the coefficient of rhythm asymmetry according to the specified parameter, and Ps and Pd are the chosen parameters of rhythm in congruent leads across the right and left hemispheres, respectively.

The term "pattern" is used for the purpose of providing an all-encompassing description of the total EEG as well as the nature of activity distribution over the convexital surface. A pattern is the broad picture that is formed by fluctuations of biopotentials on a "running electroencephalographic canvas" [80].

Multiple parameters of the qEEG and properties of the EEG have been linked to a variety of disorders and their consequences. The alpha-to-delta ratio, the amplitude-integrated EEG parameter, the burst-suppression ratio, and the C-Trend index will each receive an in-depth analysis in this chapter.

2.11.1. Burst-Suppression Ratio

The "burst-suppression" effect in the EEG signal is characterised by the temporal sub-parameter known as "BSR." These measurements, on the other hand, are very susceptible to artefacts and are also characterised by a temporal lag in reaction to changes in EEG. Numerous studies [83, 84] have demonstrated that a non-linear analysis may be utilised to provide an accurate estimation of the level of anaesthesia present on the EEG. Using such an approach makes it possible to linearize the information, which is something that cannot be done using the methods of EEG spectrum analysis that are traditionally used. Because of this, approaches from non-linear dynamics and information theory, such as entropy, are utilised to estimate the level of anaesthetic that is being administered [83]. Calculating the entropy of a signal may be done in a number of different ways. In the contemporary day, it is feasible to do calculations such as those for estimated entropy and Shannon entropy, for instance. Calculations of spectral entropy, often known as SE, may be done in the frequency domain. The frequency distribution of the EEG is altered when anaesthetics are used. In most cases, a combination of alpha and beta rhythms may be seen on the participants' EEGs. Alterations in the electrical activity of the scalp induced by going from a state of wakefulness to one of profound unconsciousness are reflected in the EEG as a movement of the signal's spectral components toward the lower end of the frequency range. The frequency of the EEG signal drops, which is another evidence that these changes are taking place. In addition, the condition of profound anaesthesia is characterised by oscillations in the EEG signal that are characterised by a significant high amplitude and a low frequency [83].

In addition, there are distinct alterations that may be seen in the electroencephalogram (EEG), such as the "burst-suppression" effect, which is typical of profound anaesthesia. This may be observed as a succession of signal segments with extremely low amplitude and brief waveforms with a high amplitude signal. This indicates that anaesthetic medicines generate a full set of neurophysiological changes, which cannot be accurately measured by a single indication by itself. Therefore, a complicated collection of characteristics is required in order to provide a description that is appropriate of these intricate events that occur during the transition from wakefulness to profound anaesthesia [84].

The sub-parameter BSR is used to assess the flash-by-pressure effect during deep anesthesia. The BSR subparameter is used to estimate the flash-for-pressure effect during deep anesthesia. To calculate this parameter, the pressure segments are identified as periods of at least 0.5 s, during which the electrode voltage does not go beyond ± 5.0 µV. The total time in the pressure state is calculated and the BSR is calculated as the fraction of the total length of the epochs where the EEG meets the suppression criteria.

This Figure 6 illustrates a typical burst-suppression pattern that may be seen on the BrainStatus device when the C-Trend software is used.

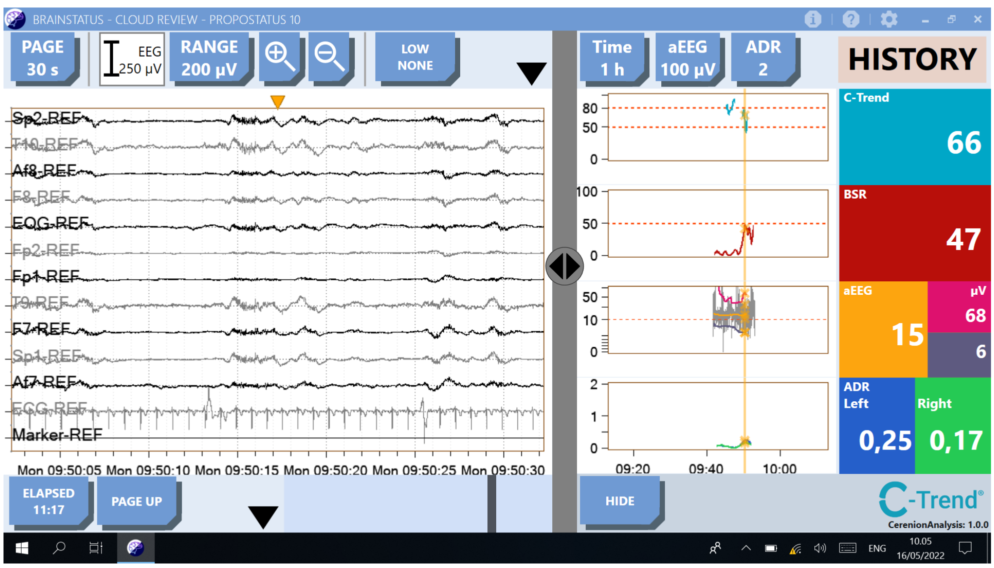

Figure 6. Clear burst-supression pattern recorded from one of the patients on the BrainStatus device using the C-Trend programme.

2.11.2. Amplitude-Integrated EEG (AEEG)

Amplitude-integrated EEG (AEG) is a technology of compressed presentation of a continuous electroencephalogram (EEG) recording, which allows, by determining typical patterns in the AEG trend, to quickly conclude the current state of cerebral function and assess its dynamics. The AEG method is now widely used in neonatal intensive care units to monitor cerebral function in newborns. AEEG is also used in the intensive care wards of adult patients [85].

This Figure 9 illustrates a typical amplitude-integrated EEG parameter that may be seen on the data of cardiac arrest patient.

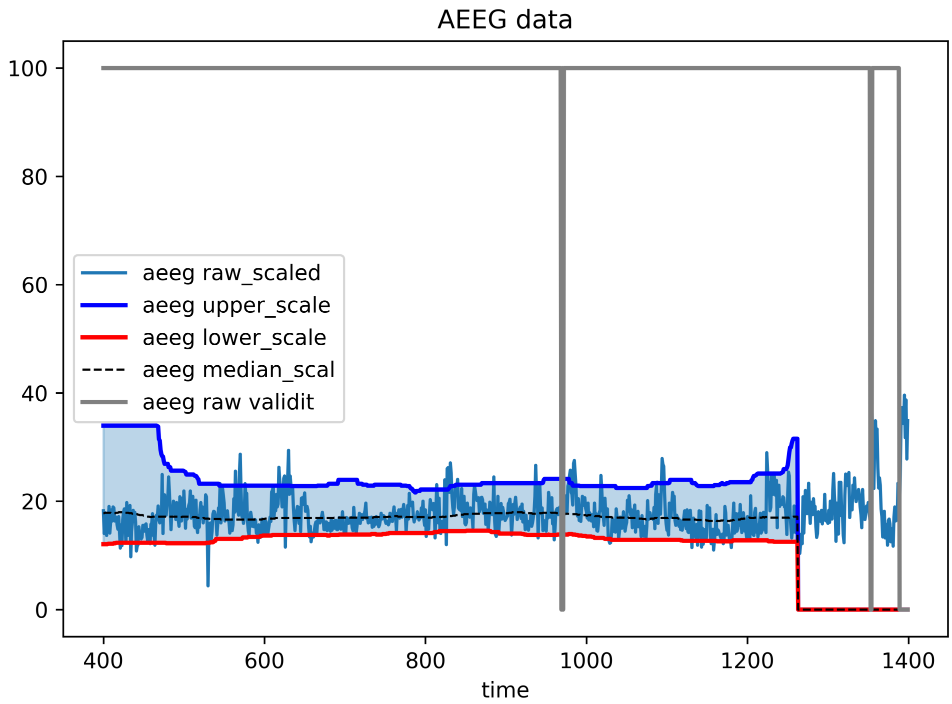

Figure 7. Example of Amplitude-integrated EEG recording from one of the patient. Blue and red lines represent upper and lower borderlines of the signal, gray color line represents the validity of the signal.

The clinician is able to swiftly analyse the current status of the patient's central nervous system (CNS) using an aEEG trend, and they may also watch its dynamics, such as in reaction to the administration of a medicine. In addition, it is always feasible to look at the original EEG curves in detail for a more precise evaluation. This may be done whenever necessary [15].

The approach offers three primary benefits to its users. In contrast to a lengthy EEG recording, a single screen of aEEG patterns can display the results of many hours' worth of data, which significantly speeds up the decision-making process. A expert simply needs to give the EEG patterns a cursory check in order to identify seizure activity and assess whether or not there is background bioelectrical activity. Ease of analysis: the patterns of an AEG can swiftly determine the level of functional development in a newborn central nervous system. Promptness refers to the fact that the approach is sensitive enough to allow for prompt tracking of functional changes that occur in the CNS during therapy.

2.11.3. Alpha-To-Delta Ratio

The alpha-to-delta ratio, or ADR, is a metric that indicates the ratio of signal strength in the alpha (8-13 Hz) to the delta (1-4 Hz) range. An increase in the ADR values shows that there has been a relative shift in power away from the delta frequencies and toward the alpha frequencies [15]. On the other hand, levels of ADR that are decreasing suggest that there has been a relative transfer of power from alpha frequencies to delta frequencies. Alterations of this nature in the power spectrum of the signal may take place under a variety of distinct circumstances. However, when oxygen is depleted in a particular region of the brain, as is often the case, the activity there often switches from higher frequencies to lower ones. This is a normal occurrence. Because the shift in the raw EEG could be difficult to perceive with the naked eye, quantitative factors like ADR might be able to assist in the detection of such occurrences. The scientific literature has explored the use of ADR for EEG waveform analysis. There is no need to use any fresh clinical data for the derivation of the manufacturer's ADR parameter because the method is well known and has been published in the relevant literature. Instead, it is ensured that the parameter in question is equivalent to the one described in published works and in items sold in the marketplace. In most cases, the parameter has been utilised in the process of identifying signal alterations that are associated with hypoxia. This may be the case, for instance, in a patient who is experiencing subarachnoid haemorrhage (SAH). Vasospasm, a condition in which arterial spasm leads to vasoconstriction, commonly occurs after an episode of subarachnoid haemorrhage (SAH). This disorder might potentially result in hypoxia and the loss of tissue in the brain. However, if it is discovered at an early enough stage, there is a chance that the harm can be mitigated by intervention. It has been observed that ADR is a helpful tool in assessing the EEG waveform for patients with SAH, which helps in the diagnosis of vasospasm. An example of such a research is shown below [86].

2.11.4. C-Trend Parameter

Several different scientific research have found a connection between the presence of slow wave activity during anaesthesia and normal sleep and good brain function. For instance, it has been demonstrated that the lack of slow wave activity during cardiac arrest is indicative of hypoxia ischemic encephalopathy (HIE), which is a condition that aids in the evaluation of the neurological fate of patients. As a result, slow wave activity gives vital diagnostic and prognostic information and has the potential to be exploited in decision making regarding therapy [87].

The C-Trend Index is a metric that was developed with the intention of capturing the activity of slow waves. A machine learning (ML) strategy was utilised during the development of the algorithm that underpins the parameter, and this strategy was also utilised throughout the validation process [88]. The C-Trend Index indicates the slow wave activity (1 Hz) of EEG and is designed to assist in the monitoring of the neurophysiological condition of patients who are sedated with certain anaesthetic drugs such as propofol.

The values for the index range from 0 to 100, with values higher than 80 indicating high normal slow wave activity, values between 80 and 50 indicating moderate normal slow wave activity, and values lower than 50 indicating abnormal or low slow wave activity. The index is expressed as a dimensionless units.

The values of the C-Trend Index are derived from EEG sequences that last for roughly sixty seconds. However, rather than relying on a single number, it is recommended that the index be read over a period of many minutes because the occurrence of slow waves may be fleeting.

When used in conjunction with the BrainStatus electrode and device, the C-Trend index is derived from a reference montage that makes use of all of the BrainStatus EEG channels (Fp1, Fp2, F7, F8, Af7, Af8, T9, T10, Sp1, and Sp2) in order to arrive at a value.

When doing an analysis of C-Trend data, there are a number of considerations that must be given careful attention. One of them is the possibility that the C-Trend Index values will be reduced if the depth of anaesthesia administered was excessive.

In addition, spike artefacts have the potential to influence the results of the C-Trend Index. The C-Trend Library is able to identify spikes and label a signal sequence as having spike artefacts if more than two percent of the signal has an amplitude that is more than three hundred microvolts when it is included inside a C-Trend Index analysis window. For sequences that are determined to have spike artefacts, the C-Trend index will not be shown (missing C-Trend index contour points are indicated UI by dashes in the respective value box). Predicting the neurological prognosis of a patient who has experienced cardiac arrest is one of the indications for using the C-Trend Index.

3. MATERIALS AND METHODS

Data from the PropoStatus clinical trial were utilised for the purpose of conducting an analysis of the C-Trend Index as well as other quantative EEG characteristics. The experiment was carried out in an observational and non-interventional manner and was started by the investigator. As a result of the fact that Cerenion's participation in these research was that of a collaborator, the company has the legal authorization to make use of the study data. Cerenion has not served as the investigation's Sponsor in any capacity. Later, a detailed description of the clinical investigation will be available.

3.1. Data Collection

The PropoStatus research was a prospective observational study that looked at the changes in EEG patterns that occurred in patients with neurologically healthy after the induction of general anaesthesia with propofol. Changes in the EEG were studied throughout various levels of anaesthesia, ranging from a fully awake condition to a profound level of unconsciousness, during which a burst suppression pattern is observed in the EEG. In addition, research was conducted to investigate the link between changes in EEG and clinically measured levels of anaesthetic depth.

The patients who participated in the trial made up the population (N = 20), and all of them were neurologically healthy adults who were scheduled to have elective surgery at South Karelia Central Hospital that required general anaesthesia. The patients were not given any pre-medication before to the procedure. They agreed to take part in the research and supplied their written consent. The vital signs were monitored in accordance with the procedure that is customary in the operating room while the anaesthetic was being administered. The electrode and wireless amplifier that included with the Bittium BrainStatus were used to record the EEG. During the recording, an evaluation of the EEG was performed on a laptop.

Propofol was used to start the anaesthetic at a rate of 30 mg/(kg*h), and the rate remained constant throughout the procedure. The patient was given instructions to repeatedly apply pressure to the anesthetist's hand every 10 seconds. The patients were regarded to have lost consciousness at the point in time when they ceased to respond to the order. The infusion was maintained until burst-suppression pattern appeared in the electroencephalogram. After that, the infusion was kept going for another three minutes, after which the EEG recording was discontinued. Afterwards, the administration of the anaesthetic was carried on for as long as the surgery required.

3.2. Data Preprocessing and Annotation

Each individual patient's file has an information structure as well as thirteen channels that hold signals. The 10/20 International method was used to come up with the names for these signals. These include the following: Sp2, T10, Af8, 'F8, EOG, Fp2, Fp1, T9, F7, Sp1, AF7, ECG, and Marker. It was noticed, for instance, whether electrodes put more frontally would work better than temporal electrodes since they represent electrodes placed symmetrically above various hemispheres. This is possible due to the fact that they represent electrodes. Additionally, because the reference is located in the centre, the activity in unipolar channels may be significantly reduced, at least in the channels that are near to the reference.

Annotation Tool was used for the annotation, which was developed by Erika Niemela for her master's thesis 7 [89]. The tool's graphical user interface enables for manual annotation and analysis of EEG signals. The utility was written in Python. Because it is the most commonly used machine learning programming language, it is simple to integrate with other tools and libraries. Because of its reliability, performance, and business understanding, PostgreSQL is used in tool. For the database, SQLAlchemy created an ORM with a Python interface. ORM protects against SQL injections. The REST API was created using Flask-RESTful, a plugin to the popular WSGI framework Flask. As a web server and reverse proxy, NGINX was used. The Python GUI toolkit Tkinter was chosen as a user-interface option. It's platform-agnostic and has few dependencies, which is significant given that the users can run it both on Windows and Linux. The annotations were performed by the guidelines which comes along with the tool.

Matplotlib was chosen to plot qEEG signals because it gives similar figures to MATLAB, which is used in many EEG annotation and analysis tools, including the company's prototype. It offers a tkinter backend for integrating figures into GUIs. Frontend array calculations require Numpy. Some downsampling calculations are improved with Numba, a just-in-time (JIT) compiler that can increase the speed of numerically oriented Python computations.

Annotations of the EEG data are done using a purpose-built tool that is capable of both human and semi-automatic annotations (e.g. in the tool, very common artefacts such as spikes and suppressions can be first marked by automatic algorithm with user selected input parameters and then reviewed and completed manually in the annotation tool UI). The following are the annotation segment labels which have been utilised for the analysis: 'attenuation', 'bsp', 'burst' ,'clipping', 'decoupling', 'emg','epileptiform', 'isoelectric', 'movement', 'reference', 'spike', 'suppression', 'unspecified'. These labels used to define quality and artefacts for segments in annotated EEG data. Segments labelled as "reference" were used as data of neurologically healthy patients' slow-wave activity after loss of consciousness. During analysis, each segment that has been labelled in a certain way is disqualified from the later analysis (i.e. only good signal quality EEG data segments are included).

3.3. C-Trend Software Analysis

The C-Trend Library was created so that clinicians may evaluate the neurophysiological state of their patients. Patients who are receiving critical care are the target audience for this product. The electroencephalogram (EEG) measurement that is traditionally used in conjunction with sophisticated signal processing and machine learning algorithms is what the C-Trend Library offers. It results in the production of four metrics that describe the patient's neurophysiological condition. The parameters give skilled medical practitioners vital information about the patient's brain function, including diagnostic and prognostic information. This information may be found in the parameters. The parameters, which should always be evaluated in conjunction with evaluation of the original EEG waveforms, have the goal of advancing an easy, reliable, and ongoing assessment of the patient's brain activity. The C-Trend Library was designed for the purpose of reviewing and analysing EEG recordings that were created using an EEG equipment that is compatible with C-Trend Library. The data from the EEG are given for use as an input in the C-Trend Library. After that, the C-Trend Library does the calculations for the parameters and gives them to you as the output. The display of the parameters is handled by a separate device, which is why the C-Trend Library does not include this functionality. Nowadays C-Trend Library is available for the BrainStatus platform offered by Bittium.

To define the slow-wave EEG input characteristics, describe the slow-wave power and connection across channels, and give the mapping to an index range (i.e. 0-100 value interval) for the C-Trend index parameter, machine learning of the C-Trend Library 1.0.0.0 (medical) is utilised. In the ML approach, the method that is used to improve the performance of the C-Trend index is to maximise the distance of index value distributions between patient outcome groups (i.e. good and poor based on the classification of CPC scores) in the training data. This is done in order to adapt the configurations for a particular EEG device and/or electrode platform. EDF files were the product of the software, and the data contained inside them were then analysed and plotted with the help of code written in Python. The most important libraries for the study were MNE, matplotlib, pandas, and seaborn. MNE is a free and open-source Python application that allows users to explore, display, and interpret human neurological data such as electroencephalogram.[90].

3.4. Statistical Analysis

The use of linear regression models as the primary technique for statistical analysis was the primary focus of this particular research. The basic technique was deemed unsuitable for this situation due to the huge numbers of outliers; hence, the robust method derived from the seaborn and statsmodels python packages was selected as the solution. Since the confidence interval around the regression line is computed using a bootstrap procedure, the solution was to fit a robust regression in such a way that the regression line showed the estimated probability of $y = 1$ for a given value of x. The robust regression estimate required significantly more computational effort than the simple regression estimate.

Using a smoother to fit a nonparametric regression model is an entirely new strategy that may be used. This method has the fewest assumptions of any of the others, but it is also quite computationally costly; as a result, confidence intervals are not computed at all in the package at the moment, which is why it is not utilised in this study.

4. RESULTS

The population of the study (N = 20) consisted of neurologically healthy adults who were scheduled for surgical interventions at South Karelia Central Hospital that required general anaesthesia. The demographic data of these patients are shown in Table 1.

	Age	Weight	Height
count	20	20	20
mean	50.60	71.91	170.65
std	15.84	14.34	9.58
min	18.00	47.00	153.00
25%	42.50	64.75	163.00
50%	51.00	69.50	170.00
75%	63.25	86.00	179.00
max	76.00	100.00	185.0

Table 1. Statistics of the patients group. Std refers to a standard deviation, min and max to the minimum and maximum values and 25%, 50% and 75% are quarters correspondingly.

Because the patients were under the influence of propofol throughout the EEG recording, the dataset was deemed suitable for the assessment of the slow wave activity and, as a result, the quantitative EEG parameter analysis. The anaesthetic also caused some of the recordings to have a pattern of burst suppression, and these were included in the dataset. As a consequence of this, the dataset was also regarded to have the potential to be used in studies involving the burst-suppression rate.

Of the 20 patients, two were excluded because of a technical error during recording with the sensor electrode. Therefore, 18 patients were included in the statistical analysis.

4.1. Alpha-To-Delta Ratio

The clinical manifestations of alpha-to-delta ratio among the 18 patients were not substantially different from one another. The behaviour of the signal is consistent throughout all of the recorded EEG data; for example, high values were reported at the beginning of the recording, but they fell following the condition of loss of consciousness. The behaviour of an alpha-to-delta ratio (ADR) is depicted as an example in the figure 8, which shows a plot of the data from one of the patients.

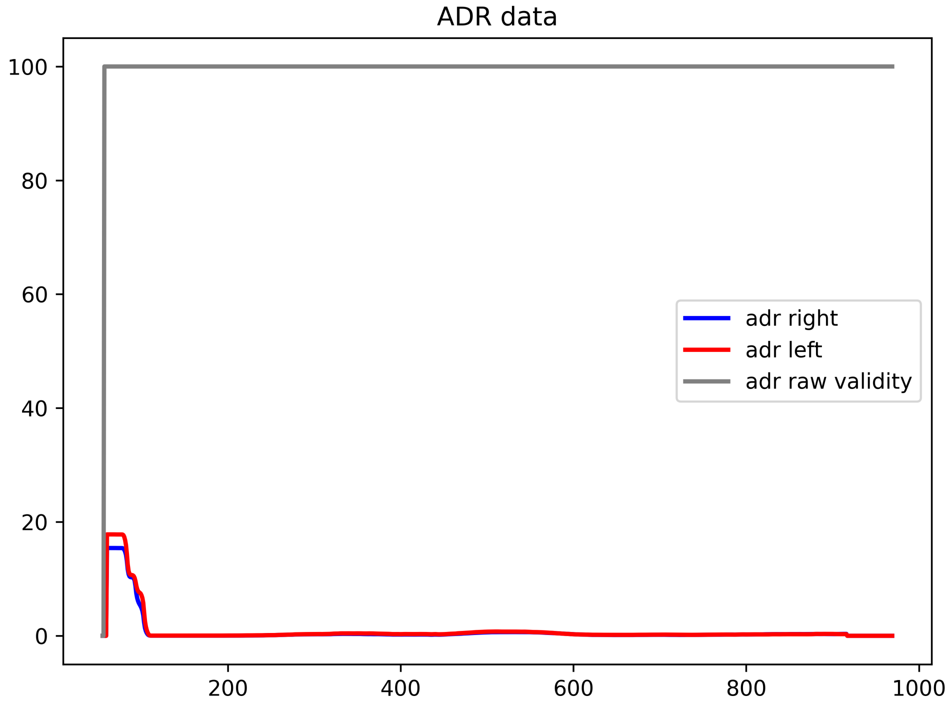

Figure 8. Example of alpha-to-delta ratio from one of the patient. Blue and red lines represent signal from right and left hemisphere, gray color line represents the validity of the signal. X axis represents time in seconds, y-axis represents alpha-to-delta ratio parameter in dimensionless units.

4.2. Amplitude-Integrated Electroencephalogram Parameter

The values of amplitude-integrated EEG among the 18 patients did not differ from one another in a significant way either. The aEEG tracings show that normal amplitudes are being produced. The behaviour of the signal is stable throughout the entirety of the EEG data that was captured; for instance, high values were reported towards the end of the recording. Throughout the entirety of the recording, the reliability of the signal did not remain consistent. It was determined that the start and end minutes of more than half of the recordings were invalid. The behaviour of an amplitude-integrated electroencephalogram (aEEG) is represented as an example in the image 9, which displays a plot of the data from one of the patients.

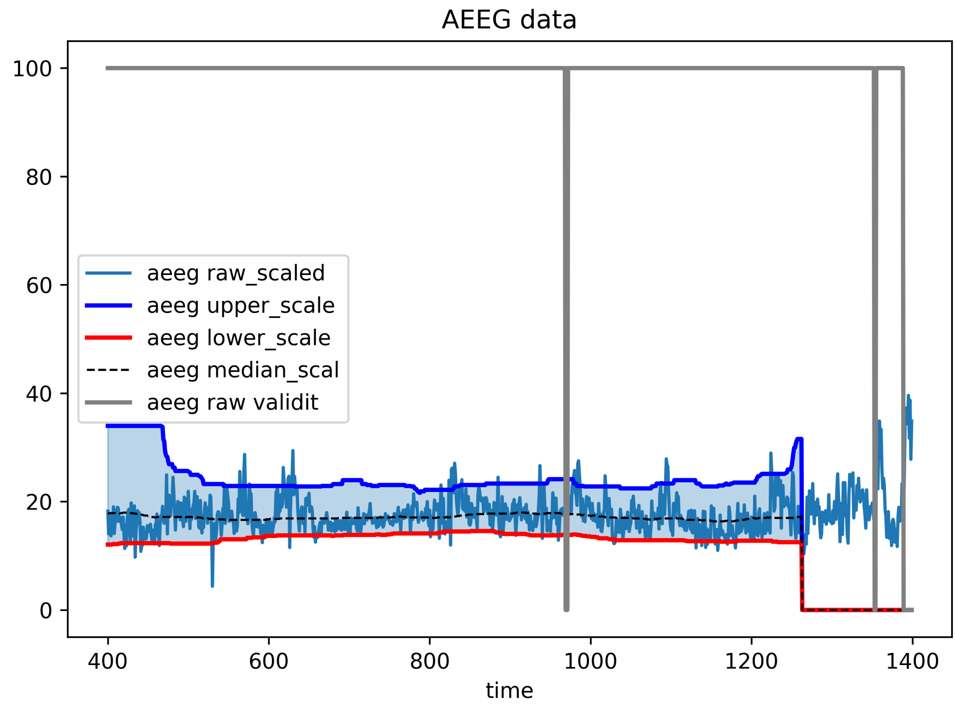

Figure 9. Example of Amplitude-integrated EEG recording from one of the patient. Blue and red lines represent upper and lower borderlines of the signal, gray color line represents the validity of the signal. Black dashed line represents the medium values of the amplitude-integrated EEG parameter. Light blue line refers to the raw aEEG parameter data. X axis represents time in seconds, y-axis represents amplitude-integrated EEG parameter in micro volts.

4.3. Burst-Suppression Ratio

The burst-suppression ratio of the 18 patients were significantly different from one another. The tracings of the BSR show amplitudes that are normal. There was a considerable rise in the values in the majority of the patients (11 out of 18), who were affected under propofol anaesthesia. The settings for the remaining 7 patients remained constant during the entirety of the recording. Throughout the entirety of the recording, the reliability of the signal did not remain consistent. The behaviour of a burst-suppression rate (BSR) is presented as an example in the figure 10 which depicts a plot of the data from one of the patients.

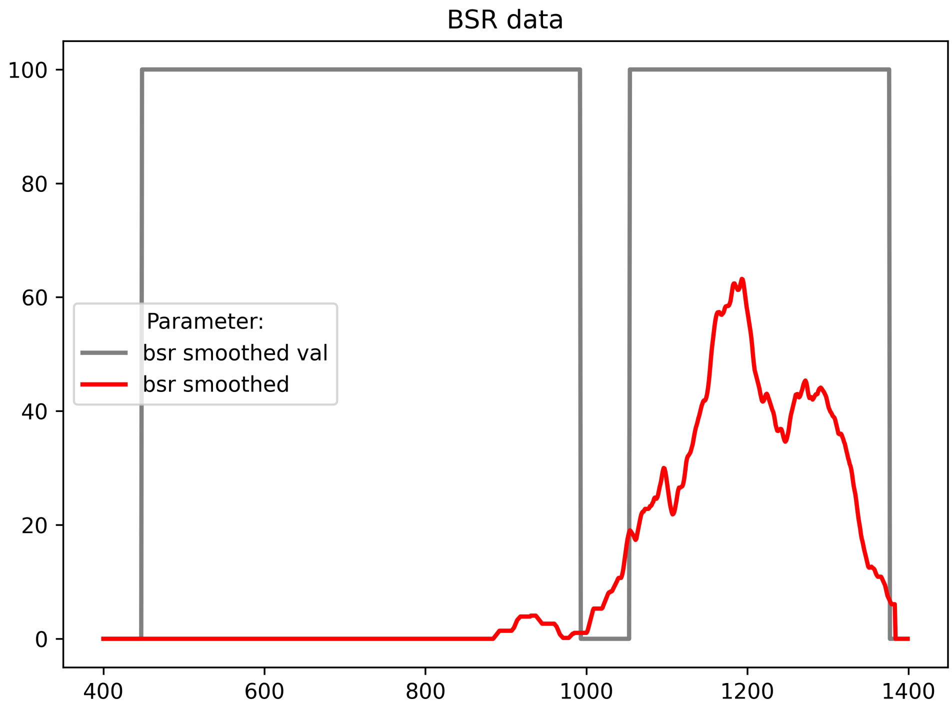

Figure 10. Example of burst-suppression ratio from one of the patient. Red line represent the smoothed signal, gray color line represents the validity of the signal. X axis represents time in seconds, y-axis represents burst-suppression ratio parameter in dimensionless units.

4.4. C-Trend

The values of the C-Trend parameter varied greatly from one patient to the next among the group of 18 individuals. The values of the C-Trend parameters show amplitudes that are normal. The C-Trend parameter from one of the patients is displayed as an example in the figure referred to above as 11. In general, there is a distinguishable difference between the condition of loss of consciousness before and after the anaesthetic injection time in each and every recording. Because of this, and also because the hospital had data regarding the exact moment when LCV occurred, the dataset was split up into two distinct states in order to facilitate further research: before and after LCV.

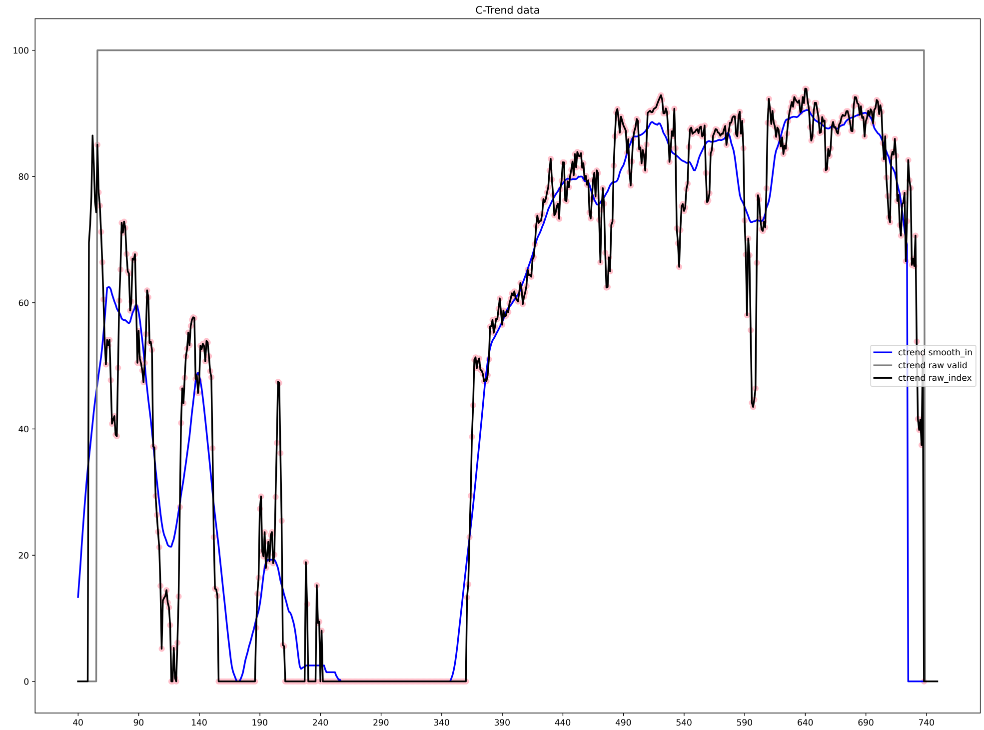

Figure 11. The change in C-Trend values during propofol anesthesia. Pink dots represents discrete C-Trend values, while black line shows the line plot connecting all of them. The blue line represents the smoothed C-Trend index values. Gray color line represents the validity of the signal, X axis represents time in seconds, y-axis represents C-trend parameter in 0-100 units.

In order to do a comparison between these two datasets, violins plots have been drawn and individual two-way t-tests have been carried out. The figure 12 demonstrates that the median value of the C-Trend parameter is lower before LCV than it is after the individual has lost consciousness. Although the interquartile ranges are very comparable (as seen by the lengths of the boxes), the total range of the data set is somewhat larger for the dataset that was collected prior (as shown by the distances between the ends of the two whiskers for each boxplot and the density from the violin plot).

Although it would appear that both batches of data have an up-skew, the batch of data obtained after the LCV state is more skewed than the data obtained before the LCV state was obtained; nonetheless, the degree of skewness is not very pronounced in either scenario. (In point of fact, both skewnesses are positive; the value for the post LCV state is somewhat bigger, which corresponds to a lack of symmetry that is more severe; nonetheless, neither skewness is extremely substantial.)

In both sets of data, there are instances of outliers that consider for more examination, although raw data in general has a greater number of these instances than smoothed data does. The majority of the dataset's outliers may be found in the vicinity of the 0 values before LCV was applied. In general, it appears as though the two batches of data were usually dispersed in a manner that was comparable to one another, although one batch is placed to the upper (>50) of the other batch. It is possible to see that the quartile of the 25th percentile of the post LCV state is much higher than the median of the state before LCV (that is, over three-quarters of the data was greater than the median of before LCV state values). It would appear that we are in a position to confidently assert that C-Trend is capable of displaying high values for healthy individuals when they are under the influence of propofol anaesthesia.

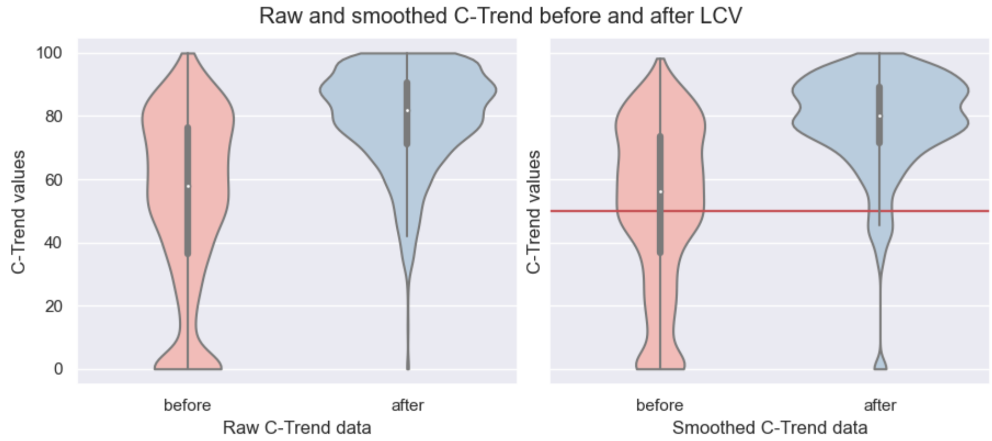

Figure 12. The change in C-Trend values during propofol anesthesia. The violin and box and whiskers plots show C-Trend values before and after loss of consciousness(LCV) state and for raw and smoothed parameter.a For raw data, individual t-test is 64.38, p-value is < 0.001. b For smoothed C-trend data, individual two-way t-test is 65.70, p-value is < 0.001. Abbreviations: LCV, loss of consciousness. The boxes show the values at the median as well as the 1/4 and 3/4 percentiles (lower whisker = -1.5 inter-quartile range, higher whisker = + 1.5 inter-quartile range). X axis represents time in seconds, y-axis represents C-trend parameter in 0-100 units.

Through the use of linear regression, we were able to get an approximation of the C-Trend parameter as well as visualise the linear trend. The grid for each of the 18 patients is displayed in figure 13, together with the smoothed C-Trend index and the linear regression trend. The overall trend is slightly upward, coming in at 0.0059 (standard deviation = 0.006), while the intercept comes in at 86.0064 (standard deviation = 3.777). This indicates that the overall trend is calculated to be extremely high, as it should be for healthy individuals, despite the fact that there are a lot of artefacts and the data during the awake time is quite noisy.

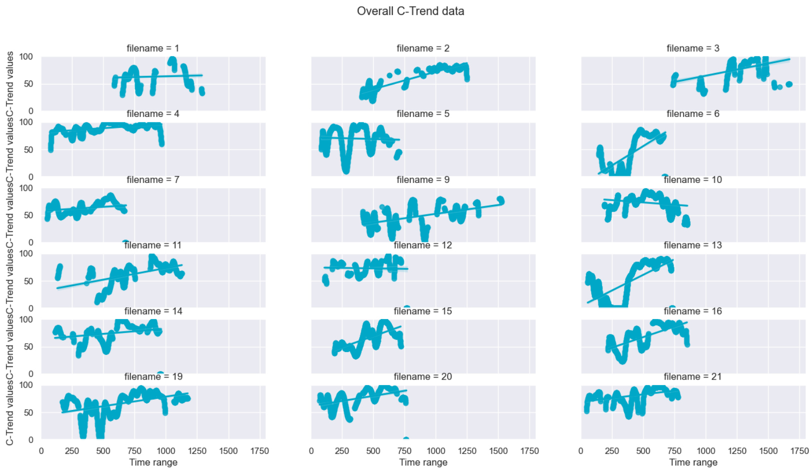

Figure 13. The change in C-Trend values during propofol anesthesia before loss of consciousness state. Blue curve line represents the smoothed C-Trend data, blue straight line represents plotted linear regression. X axis represents time in seconds, y-axis represents C-trend parameter in 0-100 units.

The LCV state datasets from before and after the change were processed using the exact same manner.

Before the event that caused the patient to lose consciousness, the grid shown in figure 14 depicts all 18 patients with a smoothed C-Trend index and a linear regression trend. The overall trend is somewhat downward, coming in at -0.0019 (standard deviation = 0.002), while the intercept comes in at 52.8937 (standard deviation = 0.634). When compared to the total computations of the C-trend linear regression, the intercept is significantly smaller. This is something that may happen since the data around the time of the injection were noisy, and the artefact data from the awakened patient were comparable to the activity of slow waves.

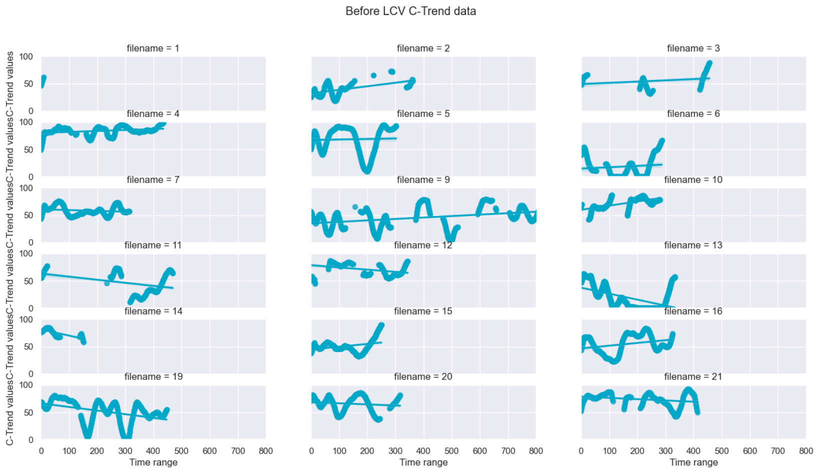

Figure 14. The change in C-Trend values during propofol anesthesia before loss of consciousness state. Blue curve line represents the smoothed C-Trend data, blue straight line represents plotted linear regression. X axis represents time in seconds, y-axis represents C-trend parameter in 0-100 units.

The grid for all 18 patients is displayed in figure 15, together with a smoothed C-Trend index and a linear regression trend after the incident that caused them to lose consciousness. The overall trend is somewhat upward, coming in at 0.0021 (standard deviation = 0.001), while the intercept comes in at 79.0801 (standard deviation = 0.626). When compared to the general average and the results of the linear regression calculations performed before the C-trend, the intercept is somewhat larger. The C-Trend values often drop down as the recording comes to a close in practically almost in every single case. The burst-suppression pattern, which was one of the conditions for the recording to come to an end, is to blame for the current state of affairs. Some of the recordings show a significant decrease in quality near the conclusion due to the fact that it is quite challenging to evaluate the exact same instant when this pattern becomes predominant. This behaviour of the C-Trend index is well-known and highly predictable.

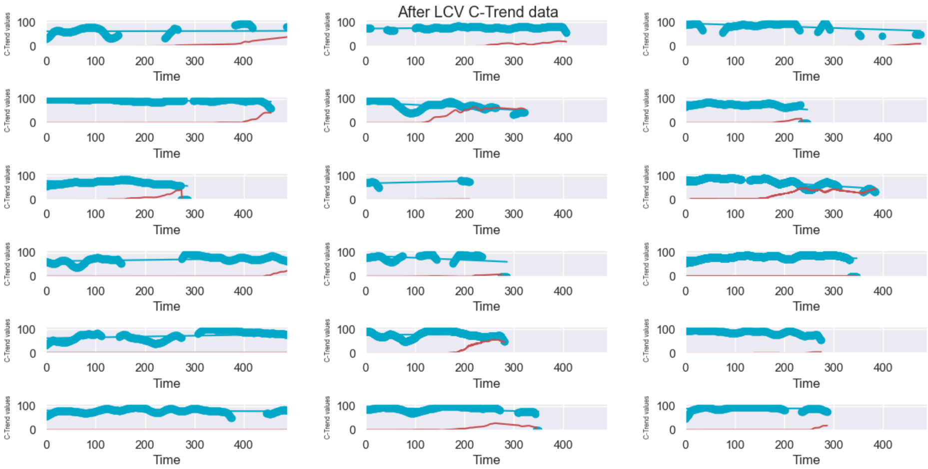

Figure 15. The change in C-Trend values during propofol anesthesia before loss of consciousness state. Blue curve line represents the smoothed C-Trend data, blue straight line represents plotted linear regression. X axis represents time in seconds, y-axis represents C-trend parameter in 0-100 units. Red line represent the burst-suppression ratio smoothed signal, y-axis represents burst-suppression ratio parameter in dimensionless units

5. DISCUSSION

There have been no studies conducted about the C-Trend Index estimated on healthy individuals who were given propofol prior to having anaesthesia. Nonetheless, various attempts have been made to employ EEG quantitative characteristics as an outcome predictor or as a loss of consciousness marker [69, 91].

EEG backdrop has proved to be a significant predictor of LCV, while other commonly used metrics have shown to be a solid predictor of a poor outcome in unhealthy patients. The most significant dissimilarity between the studies is that typically, a longer time of continuous EEG testing is necessary for patients who have survived cardiac arrest or stroke in order to determine the likely level of damage and the result. The length of the recordings that were analysed in this work were significantly shorter than usual because of the way the experiment was designed. However, even over such a short period of time, the C-Trend has shown a good outcome trend (positive for both the overall and post LCV datasets) for all of the patients.

In the past ten years, there has been an increase in the utilisation of quantitative EEG, which is now recognised as one of the most essential instruments for the continuous EEG monitoring of neurocritical care patients. Since it was first used in clinical settings, a number of difficulties have been resolved; as a result, worldwide guidelines now make use of standardised nomenclature and indications and relate to the same technical problems. Despite this, clinical grounds for the use of such parameters are frequently disregarded, and the method continues to be an underutilised tool.

The requirement of a neurophysiologist to read the EEG 24 hours a day, seven days a week and a technician to set and check the electrodes is one of the most significant barriers to the general use of this technology. It has been demonstrated in a number of papers that physicians and nurses working in intensive care units (ICUs) may reach an adequate degree of proficiency in addressing technical difficulties and recognising the primary EEG patterns after only a brief time of training [92, 93]. Neurological health specialists are in for an intriguing task with this one.

In addition, proof that cEEG may enhance patient outcome is still insufficient at this time. Because of this, it was very crucial to discover, with the help of the C-Trend parameter, that even for shorter periods of time, we are still able to evaluate the patient's status. ICU physicians may largely concentrate on atypical discoveries, where the C-Trend suggests bad result, or review the raw EEG data for artefacts in the regions where there is a lack of validity of the signal. The availability of summary data in the historical mode is another thing that makes C-Trend much more comfortable for clinicians to use.

The majority of the patients have stable and smooth ADR with peak values in the beginning of the signal. This could be because of the physiological artefacts recorded form the patients, since the were still in the awake state in the beginning.

In this study's aEEG data, there were no significant differences reported between normal aEEG and abnormal aEEG. There are a few peaks that are rising, and they largely correlate to the artefacts on the raw data. Tracings of aEEG and ADR can also be affected by a number of other parameters, including muscular activity, respiratory movements, interelectrode spacing, scalp oedema, ECG artefacts, and interference from other technologies, such as high-frequency oscillatory ventilation. In addition, a poor quality of contact between the skin and the electrode may be one of the causes of artefacts in the impedance of the aEEG. Inadequate contact or a high impedance might have been the cause of the enhanced artefact, which would have resulted in an artificially raised voltage of the aEEG background [94].

The most common applications for the amplitude-integrated EEG are the diagnosis of hypoxic ischemic encephalopathy and the detection of epileptic seizures [85]. These kinds of results provide us with an accurate picture of the parameter's performance in this study because the patients who participated in the research were in good neurological health.

The burst-suppression ratio (BSR) and C-Trend values have been discovered to have a considerable association with one another, once more especially towards the later phases of severe sedation (the drop of the C-Trend lower than 50 and the significant rise of the BSR values of up to 40 percent). This highlights how important it is to make use of the BSR during intensive care unit procedures as an independent variable (rather than an integrated variable that is merely a component of the C-Trend), in order to determine the level of anaesthesia that is provided. [91, 95]

On the basis of the results that were obtained and the analysis that was performed, we are able to confirm that the C-Trend Index and the burst-suppression ratio (BSR) is, in fact, a possible solution to the issue of determining the state of loss of consciousness while the patient is under the influence of propofol anaesthesia. However, in order to validate the results of this study, it has to be repeated with a larger sample size of patients, on par with those used in previous studies. The following are some of the problems with our research.

Despite of this findings, a number of steps must still be taken before the results that were given in this paper may be used in clinical practise. To begin, and most importantly, the greatest weakness of this work lies in the lack of patients who are participating in the study. This necessitates the validation with larger data sets, for which setting the limit and threshold for each individual patient ought to be addressed in a manner that is less manual. There is still opportunity for development for the data to become more accurate and for stronger conclusions to be drawn, despite the fact that a bigger data set will still require manual input from health professionals to establish the particular time for LCV.

First, because the data were gathered while the patient was undergoing preparations for the operation, a large number of movement artefacts have been observed. This has had a significant impact on the signal in the awake area.

Second, there was a substantial standard deviation in the amount of disagreement that existed between the qEEG parameters at each time point. This may be due to the fact that various calculation windows and smoothing rates are used by the algorithms. This is because some of the parameters take longer to respond to changes and artefacts in the EEG.

Despite the fact that we have shown that the dataset after LCV exhibits high C-Trend values than the dataset before LCV, this body of work is not yet able to answer the issue of how accurate this method is and whether or not it can be used to forecast the result in a clinical environment. It is recommended that a more comprehensive study be carried out to investigate how early on from the LCV state the C-Trend would recognise it and whether or not it correlates with age, weight, or any other characteristics that might affect the strength of the EEG signal. Additionally, the response of the C-Trend to large artefacts on the electroencephalogram has not yet been tested for individuals who are healthy.

6. SUMMARY

A quantitative study of the EEG signal was carried out on healthy individuals under the treatment of propofol and is presented in this thesis. The goal of this study was to determine how the parameters that C-Trend offers (the C-Trend Index, BSR, aEEG, and ADR) behave in patients who have normal brain function while under anaesthesia, as well as how these parameters correlate with the changes that are observed in raw EEG and clinical signs such as loss of consciousness. It has been demonstrated that some parameters of qEEG, such as the C-Trend Index and BSR, may predict unconsciousness; hence, these measures can be utilised in future studies to monitor a neurologically healthy patient's level of anaesthesia.

In the first part of this thesis, there is a presentation of a literature review that focuses on background information concerning EEG data, artefacts, and existing parameters. The essential characteristics of EEG are presented, and a variety of applications for EEG montages and features are described. Throughout the entirety of the literature study, it is clear that new methods are required to accurately determine the status of the patient, particularly the degree to which they have lost awareness.

It was possible to get C-Trend to display us proper results for the health patient data (more than 50, according to the intended usage standards), but the clinical use of the programme is now limited to the cardiac arrest patients who are being treated in the intensive care unit. These results will serve as an important tool for continuing to work with them in further research, and they will provide sufficient resources to ensure that the conclusions may be enhanced when the study group has been increased in size.

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