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Performance comparison among electrodes for aEEG: Impedance variability, sleep cycles recognition and gel drying assessment

Final degree project

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Abstract

Neonatal Intensive Care Units (NICUs) face significant challenges when managing neurological emergencies and providing specialized care for newborns with brain conditions. Although advances in neonatal monitoring have improved the survival rates of these infants, assessing brain function through amplitude-integrated electroencephalography (aEEG) remains an area in need of further development.

One of the main issues highlighted by neonatologists and clinical neurophysiologists is the lack of suitable electrodes for long-term brain monitoring. This limitation reduces the effectiveness of aEEG in diagnosing conditions like epilepsy in NICUs. In this study, a comparison was made between two types of electrodes: commercially available liquid gel electrodes and a new electrode specifically designed for newborns, called aCUP-E. A clinical trial was conducted with 20 neurologically healthy newborns, evaluating various aspects of the electrodes.

Certain neurophysiological criteria were established to analyze detected sleep cycles, a key parameter observable in aEEG that is crucial for diagnosis. Additionally, characteristics such as impedance (a measure of electrical resistance on the skin) and gel drying were compared. The results showed that the aCUP-E electrode recorded more sleep cycles, had better impedance stability, and provided higher quality recordings. In conclusion, this research highlights the limitations of current electrodes used in aEEG and suggests that the aCUP-E could be a more effective alternative.

Resumen

Las Unidades de Cuidados Intensivos Neonatales (UCIN) enfrentan grandes desafíos cuando se trata de manejar urgencias neurológicas y proporcionar cuidados especializados para los recién nacidos con problemas cerebrales. Aunque los avances en la monitorización neonatal han mejorado la supervivencia de estos bebés, la evaluación de la función cerebral a través de la electroencefalografía de amplitud integrada (aEEG) sigue siendo un área que necesita más desarrollo.

Uno de los principales problemas que destacan los neonatólogos y neurofisiólogos clínicos es la falta de electrodos adecuados para realizar registros cerebrales prolongados. Esta limitación reduce la efectividad de la aEEG para diagnosticar condiciones como la epilepsia en las UCIN. En este estudio, se llevó a cabo una comparación entre dos tipos de electrodos: los electrodos comerciales de gel líquido y un nuevo electrodo diseñado específicamente para recién nacidos, llamado aCUP-E. Para ello, se realizó un ensayo clínico en 20 recién nacidos neurológicamente sanos, evaluando diversos aspectos de los electrodos.

Se establecieron ciertos criterios neurofisiológicos que permitieron analizar los ciclos de sueño detectados, un parámetro clave que puede observarse en la aEEG y es fundamental para el diagnóstico. Además, se compararon características como la impedancia (una medida de la resistencia eléctrica en la piel) y el secado del gel. Los resultados mostraron que el electrodo aCUP-E registró más ciclos de sueño, tuvo una mejor estabilidad de la impedancia y ofreció una mayor calidad en los registros. En conclusión, esta investigación destaca las limitaciones de los electrodos actuales utilizados en aEEG y sugiere que el aCUP-E podría ser una alternativa más efectiva.

Resum

Les Unitats de Cures Intensives Neonatals (UCIN) s'enfronten a reptes importants quan es tracta de gestionar emergències neurològiques i proporcionar cures especialitzades als nounats amb problemes cerebrals. Tot i que els avenços en la monitorització neonatal han millorat les taxes de supervivència d'aquests nadons, l'avaluació de la funció cerebral mitjançant l'electroencefalografia d'amplitud integrada (aEEG) segueix sent un àmbit que necessita més desenvolupament.

Un dels principals problemes que destaquen els neonatòlegs i neurofisiòlegs clínics és la manca d'elèctrodes adequats per a realitzar registres cerebrals prolongats. Aquesta limitació redueix l'efectivitat de l'aEEG per a diagnosticar condicions com l'epilèpsia a les UCIN. En aquest estudi, es va dur a terme una comparació entre dos tipus d'elèctrodes: els elèctrodes comercials de gel líquid i un nou elèctrode dissenyat específicament per a nounats, anomenat aCUP-E. Es va realitzar un assaig clínic amb 20 nounats neurològicament sans, avaluant diversos aspectes dels elèctrodes.

Es van establir certs criteris neurofisiològics que van permetre analitzar els cicles de son detectats, un paràmetre clau que es pot observar en l'aEEG i que és fonamental per al diagnòstic. A més, es van comparar característiques com la impedància (una mesura de la resistència elèctrica a la pell) i l'assecament del gel. Els resultats van mostrar que l'elèctrode aCUP-E va registrar més cicles de son, va tenir una millor estabilitat de la impedància i va oferir una major qualitat en els registres. En conclusió, aquesta investigació posa de manifest les limitacions dels elèctrodes actuals utilitzats en aEEG i suggereix que l'aCUP-E podria ser una alternativa més efectiva.

Acronyms

aCUP-E: Advanced Cup Electrode

aEEG: Amplitude Integrated Electroencephalography

AS: Active sleep

CFM: Cerebral function monitoring

CNS: Central nervous system

CSV: Comma-Separated Values

DTI: Diffusion tensor imaging

EDF: European Data Format

EEG: Electroencephalography

FN: False negative

FP: False positive

GA: Gestational age

HUSJR: Hospital Universitari Sant Joan de Reus

IVH: Intraventricular hemorrhage

MRI: Magnetic resonance imaging

NICU: Neonatal Intensive Care Unit

PCA: Post conceptual age

PHVD: Post-hemorrhagic ventricular dilatation

PMA: Postmenstrual age

PNA: Post natal age

QS: Quite sleep

SNR: Signal to noise ratio

SWC: Sleep-wake cycle

TN: True negative

TP: True positive

WMI: White matter injury

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1 Context of the study

1.1 Problem statement

Neonatal Intensive Care Unit (NICU) plays a significant role in providing medical care for newborns with critical medical conditions. Despite advances in neonatal medicine, neurological pathologies remain a critical concern in this context, involving implications for the long-term neurodevelopment of infants.

Recent data from a study indicates that neurological disorders represent a significant proportion of cases treated in NICUs, accounting for up to 20% of current admissions. However, despite this high incidence, the development of specific strategies for the prevention, diagnosis, and treatment of these conditions remains limited [1].

Furthermore, there have been advances in neonatal monitoring, with the introduction of more precise tools for monitoring vital signs such as: heart rate, electrocardiogram (ECG) or blood pressure [2]. Although these progressions have improved neonatal survival rates, the assessment of brain function has received less attention, contributing to the ongoing presence of neurological problems. Therefore, several studies underscore the urgent needing to improve techniques for assessing brain activity [3].

Conducting neurological studies in neonates' infants is crucial either for early detection or intervention in potential neurological issues. These assessments provide vital insights into brain function, facilitating timely prevention or mitigating neurological damage and improving long-term health outcomes. Accurate monitoring of brain activity guides clinical decision-making, optimizes treatment, and improve overall care for neonates [4]. Early diagnosis and treatment of neurological conditions in neonates' infants can significantly enhance their quality of their lives in a future.

Significant developments have been made in neonatal monitoring, leading to the development of highly sophisticated continuous brain monitoring techniques. Among these, amplitude-integrated electroencephalography (aEEG) stands out as a nowadays tool. The aEEG provides vital information about neurological outcomes with the use of few electrodes and a quick setup [4]. Nevertheless, despite being the prevailing method today, aEEG comes with specific constraints, such as the requirement for accurate electrode positioning and other limitations, as will be explored in this study.

1.2 Objectives

This study compares the novel advanced cup electrode (aCUP-E), which is specifically designed for aEEG recordings in the neonatal intensive care unit (NICU), to the existing liquid gel electrodes.

To fulfill this proposal, the subsequent objectives were set:

1. Recognition of sleep cycles: Evaluate the efficacy of various electrodes identifying and categorizing sleep cycles from aEEG signals, considering postconceptional age as well as the sensitivity, specificity, and general accuracy of sleep stage categorization.
2. Analysis of impedance variability: Assess how stable electrical impedance of each electrode remains over time and under varying conditions.
3. Gel drying assessment: Analysis of impedance signal form aEEG recordings to obtain a gel drying rate and perform a preliminary experimental study in a thermal chamber to compare the rate of gel drying in various electrodes during extended aEEG recordings.

1.3 Structure of the study

The structure of the final degree project is as follows:

Introduction: This section presents the basic and essential concepts related to the project, highlighting similarities and differences with existing methods, as well as technical aspects. It helps define necessary notions to delve into the topic and provides the foundational knowledge that will be used throughout the work.

Methods and Materials: This section outlines the context in which the work was developed. It details the new aCUP-E electrodes and the clinical research plan. This section also includes the processing of the code for sleep cycle detection, as well as details on the electrode impedances and gel drying process.

Results and Discussion: This section reports the results of the analysis along with their interpretation. The results compare the signal acquisition based on the electrodes, either within the same patient or in general, providing a global view of all cases.

Conclusions: This section offers a global assessment of the work, commenting on the overall findings of the analyses and discussing potential future and additional work that could be undertaken in the field.

References**:** This section lists the sources from which the information is derived.

Appendix: This section includes an extension of the results presented throughout the work. It primarily refers to the results of all patients, as not all of them could be presented in the Results and Discussion section due to clarity and length constraints.

2 Introduction

2.1 Anatomy and physiology of the brain

The human brain is a highly complex organ responsible for controlling almost all bodily functions, such as movement, senses, emotions, language and memory [5]. It is composed of three main parts: the cerebrum, the cerebellum and the brainstem.

The brain is divided into two hemispheres, the right and the left, and is responsible for controlling conscious activities and processing information via the cortex. Additionally, the cerebellum modulates motor coordination and balance, while the brainstem regulates vital functions such as breathing and heart rate [5].

The interior of the brain is composed of approximately 100 billion neurons [5] and glial cells, forming up regions of gray and white matter. White matter, mainly composed of myelinated axons, refers to areas of the central nervous system (CNS) that facilitates a fast and synchronized transfer of information between different brain regions. In contrast, gray matter contains neural cell bodies, glial cells and unmyelinated axons, which are responsible for processing and interpreting information [5, 6].

Myelination is essential to accelerate the transmission of nerve impulses, thanks to the myelin sheath that covers neuronal axons. This layer acts as an electrical protector and provides nutritional support to neurons [6]. Communication between neurons takes place at the synapse, where neurotransmitters, a molecular machinery, transmit the signal between them either electrically or chemically. Related to the chemically, neurotransmitters facilitate the connection between pre- and postsynaptic neurons [7]. However, to trigger a response the postsynaptic potential must reach a specific threshold. Therefore, nerve cells must receive inputs from several neurons for activating the impulse.

The postsynaptic potential allows the capture of brain electrical activity. Current non-invasive brain monitoring techniques focus on recording postsynaptic potentials of the cerebral cortex, which is the outer layer of gray matter that covers the two cerebral hemispheres.

2.2 Neonatal brain

2.2.1 Development of neonatal brain

The development of neonatal brain is a continuous process that begins in utero and continues postnatally. From the earliest stages of fetal development, the cerebral cortex begins to form neuronal layers that will specialize in cognitive and sensory functions [8].

Glio- and neurogenesis are critical processes that occur mainly during the second trimester of pregnancy, guided by genetic and molecular signals. During this period, synaptic connections are formed (synaptogenesis), establishing the foundation for the neural

networks essential for postnatal brain activity. Synaptogenesis increases during the third trimester and continues at a high rate after birth, being crucial for the cognitive and motor development of the newborn [9].

The *"Neuromorphological atlas of human prenatal brain development"* details these changes, highlighting the specific immunophenotypic profiles of brain regions, essential for understanding the interaction between different brain areas. The study of this profiles reveals the development and specialization of different brain areas in particular functions. For example, the prefrontal cortex, essential for decision-making and executive control, shows prolonged development into adolescence, while areas such as the visual and auditory cortex mature functionally earlier, necessary for early sensor perception [9].

Furthermore, research on brain asymmetry during prenatal and neonatal development has shown significant differences between the left and right hemispheres, related to the lateralization of brain functions such as language and motor skills, predominant in one hemisphere or the other [10].

2.2.2 Neonatal neurological care

Non-invasive techniques such as magnetic resonance imaging (MRI) and its variants, such as fMRI and diffusion tensor imaging (DTI), have advanced significantly, allowing detailed assessment of fetal and neonatal brain development. In utero, MRI provides accurate anatomical images of the fetal brain with millimeter resolution, making it a valuable tool for prenatal screening and identification of anomalies, like corpus callosum dysgenesis and gryi abnormalities [11, 12].

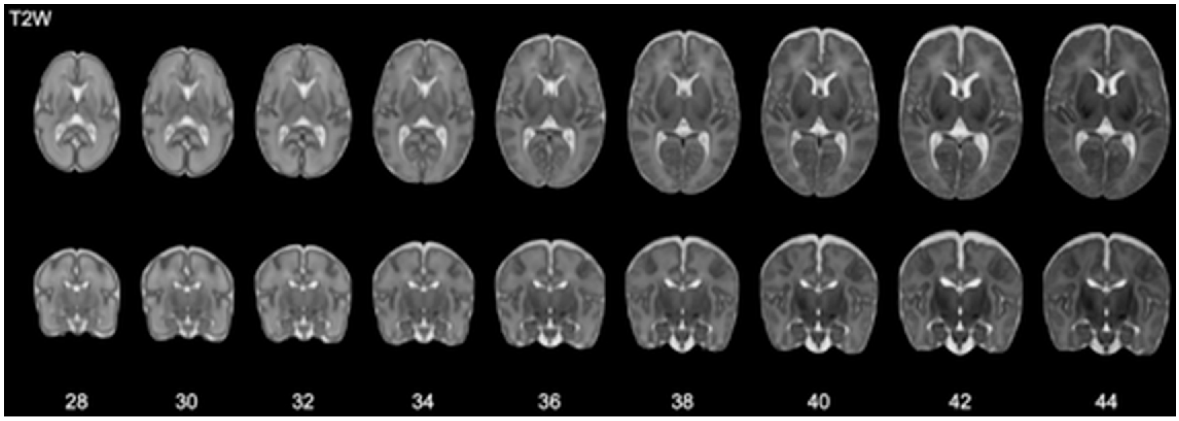

Figure 1. Growth and development of the preterm human brain with MRI images. Axial (top row) and coronal (bottom row), with the postmenstrual age (in weeks). [12]

Although MRI is extremely useful, is static, with high spatial resolution, for brain monitoring functional tests are needed as electroencephalography. In this field, amplitude-integrated electroencephalography (aEEG) allows continuous monitoring of electrical brain activity in neonates, providing crucial information about brain development and helping to predict long-term neurological outcomes [13]. This is essential during the first 1000 days of life, a critical period for neurological development [14].

Thus, aEEG complements imaging techniques like MRI by offering the ability to monitor the brain's electrical activity in real time, facilitating early intervention in cases of abnormalities. This combination of technologies used to obtain direct and indirect measurements of brain neuronal activity [14].

2.3 10-20 system

The 10-20 system is an internationally standardized protocol for the placement of electrodes on the scalps during an electroencephalogram (EEG). This system, first introduced in 1957 by Herbert Jasper, ensures uniform coverage of the different brain regions, thus allowing comparison of results between different studies and subjects [16].

The name "10-20" refers to the percentage intervals of distance between specific anatomical point on the head, such as the nasion (forehead) and the inion (back of the skull), as well as the preauricular points (on the sides). The electrodes are named with letters and numbers: the letters indicate the brain region and the numbers, the distance from the midline [16].

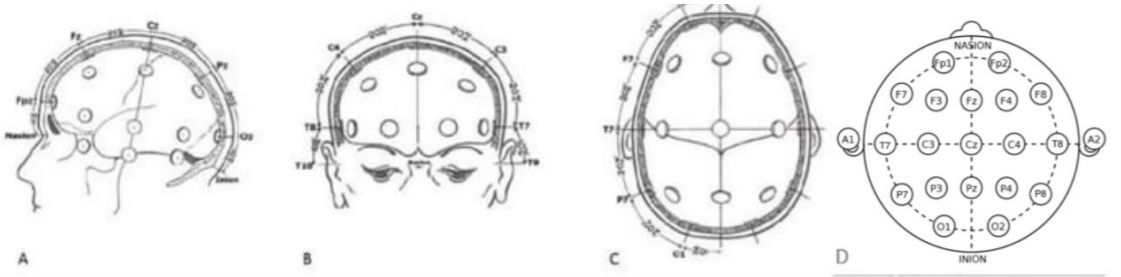

Figure 2. EEG layout of the 10-20 international system. The odd numbers are in the left hemisphere and even numbers in the right hemisphere. Furthermore, the z represents the midline. (A) Sagital Plane, (B) Coronal Plane, (C), Transverse Plane, (D) Electrode Position Scheme [31]

The 10-20 system has been instrumental in several clinical and research studies. It is used to diagnose and monitor medical conditions such as epilepsy, brain tumors, encephalopathies, and to assess the status of sedated or comatose patients [15].

In addition to the 10-20 system, there are extensions such as the 10-10 and 10-5 systems, which add more electrodes for higher spatial resolution, thus providing more detailed data on brain activity.

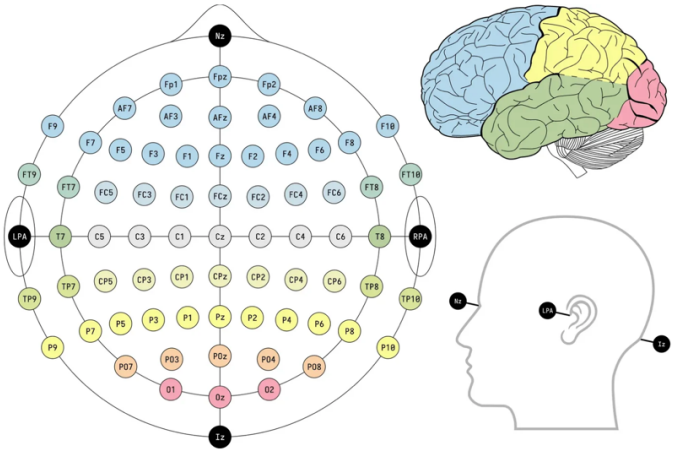

Figure 3. EEG layout with 10-10 system. [15]

2.3.1 Neonatal application

Given the small head size of neonates, a full 10-20 montage places the electrodes too close together and runs the risk of salt bridges forming between them. Thus, the neonatal montage is a scaled-down version of the 10-20 system that focuses on the central areas, and includes a cross-strand running from T7 to T8. This version is used until the baby reaches term, or at most until 46-week postmenstrual age (PMA[1]; also called conceptual or conceptional age) [19].

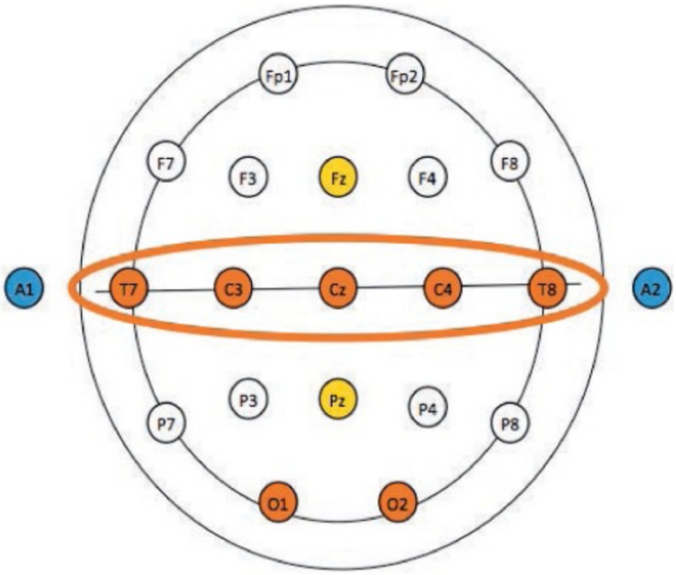

Figure 4. Diagram of the 10-20 electrode placement system in EEG adapted for neonates. [30]

Neonatal EEG is used to diagnose and monitor various medical conditions, such as:

- Differentiation of epileptic seizures
- Diagnosis of encephalopathies
- Monitoring of patients at risk of seizures

In addition, neonatal EEG is necessary for assessing the maturation of the central nervous system (CNS), detecting asymmetries and synchronization patterns that are indicative of proper brain development or possible pathologies [18].

The EEG of neonates reflects states of consciousness such as awake, active sleep and quiet sleep. Beginning at 28 weeks postmenstrual age, neonates begin to show these states, which are distinguished by specific patterns of electrical activity in the brain. For example, active sleep is characterized by irregular eye movements and respirations, whereas the awake state exhibits greater amplitude and frequency mixing in EEG activity [19].

2.4 Amplitude-integrated electroencephalography (aEEG)

aEEG is advanced technique for monitoring brain activity in neonates, especially used in neonatal intensive care units (NICU). This method is derived from a simplified configuration of the conventional electroencephalogram (EEG) and is characterized by using providing a compressed representation of brain electrical activity.

2.4.1 aEEG configuration

aEEG uses a smaller number of electrodes compared to conventional EEG. Generally, one or two channels are employed. Typical configurations include biparietal recordings with symmetrical electrode pairs such as P3-P4 and C3-C4 [13].

The raw aEEG signal is compressed in time at a rate of 6 cm/hour, allowing long recording durations to be displayed in a manageable format. This compression facilitates the identification of long-term trends in brain activity.

In addition, the representation of the aEEG signal is on a semilogarithmic scale, linear in the range of 0 to 10 μV and logarithmic from 10 to 100 μV, which highlights changes in low voltages and minimizes the significance of high-amplitude variations.

The aEEG signal is characterized by two amplitude bands: the lower margin, reflecting low-voltage activity, and the upper margin, indicating high-voltage activity. The evolution of these bands is essential for identifying pathological patterns in brain activity.

The above can be seen in Figure 5. The raw EEG signal (upper curve) is processed, resulting in the amplitude-integrated EEG band (lower curve). High amplitudes form the upper border, while low amplitudes from the lower border. A strong variation in amplitude height produces a wide aEEG band, while a minimal variation results in a narrow band. The y-axis scale is linear up to 10 μV and logarithmic above 10 μV.

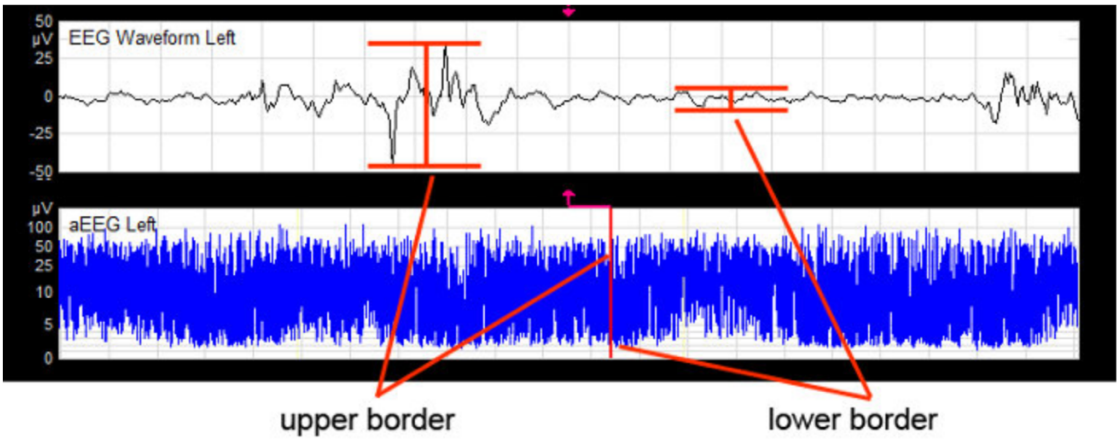

Figure 5. Formation of the aEEG tracing

Furthermore, in modern equipment, electrode impedance is continuously recorded and can be displayed on screen by changing the EEG signal using simple touch commands. This allows clinicians to check and adjust the quality of electrode contact in real time, ensuring better quality of the recorded signal.

2.4.2 State of the art

Amplitude-integrated electroencephalography (aEEG) is a valuable technique for the continuous neurological assessment of preterm and term infants. It plays a crucial role in reducing, and in some cases, even preventing permanent brain damage before it becomes irreversible [14]. Since aEEG monitors brain activity continuously, unlike magnetic resonance imaging (MRI) provides only snapshots at specific times, it is especially useful for tracking brain maturation in these vulnerable children and detecting changes in their neurological status.

To delve deeper into the origins and evolution of brain monitoring techniques, it is essential to highlight the contribution of Douglas Maynard in the 1960s. This pioneering figure, together with his team, innovated in the field of neurological monitoring by developing the cerebral function monitoring (CFM), initially developed for adults [15]. This innovation established the foundations for continuous monitoring of electroencephalogram activity in critically ill patients, representing a significant advance in intensive care medicine and neurology. Maynard's work will highlight the importance of monitoring brain activity as a key indicator of brain function in general, both in medical emergencies and during surgical procedures, thus making the brain function monitor an essential tool for physicians in making treatment decisions.

Pamela Prior played an important role in the introduction of CFM into clinical use, in close collaboration with Maynard. Her research highlighted how continuous EEG monitoring, assisted by CFM, can provide crucial indications of changes in brain function, including early detection of seizures that are not visually apparent. This has enabled

professionals to make informed decisions about the care of patients with severe neurological disorders. Prior's studies have been key in assessing patient recovery or deterioration following brain damage or drug overdose, as well as during open heart surgery. CFM has established itself as a valuable method for monitoring brain function in critical circumstances [16].

In the early 1980s, Bjerre, I et al. and Viniker et al. began to use CFM to monitor brain function in neonates [17], [18]. The use of CFM allowed physicians to monitor the brain activity of critical preterm and term infants without the need to use invasive procedures. This was a breakthrough in neonatal care, as it helped to identify neurological problems early on, especially in neonates who experienced asphyxia or other brain lesions [17], allowing effective correlation between the initial EEG recordings and the first 12 hours of CFM tracings. This advance allowed the identification of baseline activity, whether continuous or intermittent, as a significant prognostic indicator [18]. Furthermore, the introduction of statistical analysis of CFM data provided a new perspective for assessing the development of sound patterns in relation to conceptual age and other variables, such as weight, highlighting the use of CFM not only in the detection of problems but also in the understanding of the neurological development of the unborn.

Lena Hellström-Westas conducted important studies establishing the use of EEG as a valuable tool in neonatal practices. In a 1995 study, Hellström-Westas, together with Rosén and Svenningsen, shows the importance of continuous EEG recordings in predicting outcomes after severe birth asphyxia in term infants [19]. This research underscores that the patterns of aEEG fons during the first six hours of life may accurately predict future development, indicating that aEEG could be an effective method for identifying children at high risk of brain damage after asphyxia who may benefit from later interventions.

In the late 1990s, Niran Al Naqeeb and coworkers conducted a study to define normal and abnormal patterns of aEEG, as well as to assess interobserver variability and prognostic accuracy of aEEG shortly after the onset of neonatal encephalopathy [20]. This study included consecutive cases of neonatal encephalopathy and singleton infants as controls, establishing criteria for pattern identification and demonstrating a close relationship between the findings at aEEG and the subsequent neurological outcomes of the infants. The research highlighted this test as a simple but accurate and reproducible clinical tool useful in the evaluation of infants with encephalopathy, underlining its importance as a method for early prediction of neurological prognosis in children with encephalopathy.

In 2006, Lena Hellström-Westas published a classification of aEEG patterns, which has been fundamental for clinical practice in neonatology. This classification allows professionals to identify more effectively the different stages of maturation and possible brain damage in neonates, facilitating early diagnosis and intervention. Each of these patterns in aEEG provides key information about the neurological status of the neonate and aids clinical decisions. Early detection of abnormalities in the aEEG pattern allows the

implementation of timely treatments and interventions to optimize the neurological outcome of the neonate. Accurate interpretation of these patterns requires specific expertise and training, given the complexity and individual variability of neonatal brain development [21], [22].

The contribution of Hellström-Westas to the field of neonatology has been instrumental in establishing aEEG as an accurate and noninvasive clinical tool, especially in the assessment and monitoring of neonates with encephalopathy and other neurological risk conditions, as discussed in the article by L.S. de Vries and L. Hellström-Westas (2015) [23].

Since 2006, monitoring with aEEG has significantly improved neonatal care, allowing early detection of neurological disorders in neonates, especially those with extremely low birth weight and those with critical conditions such as hypoxia-ischemia [23],[24]. Other studies have emphasized the importance of the aEEG for detailed neurological assessments, identification of seizures, and understanding of sleep cycles, reaffirming its usefulness in predicting neurodevelopmental outcomes and improving treatment strategies in this vulnerable population [25], [26].

This situation is further complicated by the lack of electrodes specifically designed for neonates, resulting in a qualitative deficit of the recorded signal. The research by Cordeiro et al. (2021), which explores the assessment of different types of electrodes in the use of aEEG or cEEG in extremely premature infants, together with the study by El Ters et al. (2018), which presents a detailed comparison between cup and hydrogel electrodes in long-duration EEG studies for preterm infants, become a turning point in the discussion about the technical problems associated with aEEG monitoring [27], [28]. This study, along with other research on improving the quality of the aEEG signal and reducing the invasiveness of monitoring methods, highlights the importance of innovating in the design of electrodes and developing standardized protocols for their application in neonatology. Usually, subdermal electrodes are used, which, although they allow higher quality recordings, are invasive and are not indicated in preterm infants [29]. The lack of adequate electrodes may increase the risk of skin injury and make it difficult to obtain accurate readings and repeat tests if necessary. These challenges underline the importance of improving existing technology and training specialists in neonatal neurophysiology.

Furthermore, the lack of an open database and the need for a more accurate review of aEEG patterns, considering postconceptional age and expected birth cycles, reveal a gap in the research that prevents a deeper understanding of neonatal neurodevelopment. The need to re-evaluate the patterns of aEEG classified as normal (both continuous and discontinuous voltage) in the context of the actual postconceptional age of the newborn and the expected birth cycles is a step towards a more nuanced understanding of brain maturation and birth cycles. This approach highlights how the standard interpretation of aEEG patterns may not be sufficient to capture the complexity of neonatal brain development. Especially when

compared with age-specific markers, such as the duration of non-REM sleep periods, it is possible to identify discrepancies that may not be evident in a more general assessment.

Another significant barrier is that aEEG has important limitations with reduced spatial and temporal resolution compared to conventional EEG, which involves a susceptibility to artifacts, and limited ability to provide a detailed view of the different phases of sleep. Artifacts can be caused by a variety of factors, such as patient movements, electrical interference from the environment, and problems with electrode contact. These artifacts can distort the data and make accurate interpretation of aEEG recordings difficult. The presence of artifacts requires continuous monitoring and correction by trained personnel, which can be a challenge in resource-limited settings and an important limitation to detect correctly the sleep-wake cycles.

In addition to the above, there is a long way to go in research and development in the use and interpretation of aEEG in neonatology. These challenges include the complexity in the interpretation of newborn signs, the lack of electrodes specifically designed for neonates, and the need for an open database and a more accurate framework for the interpretation of newborn patterns. It also highlights the importance of specialized training in neonatal neurophysiology and the adaptation of assessment tools such as the Burdjalov scale to improve the interpretation of brain development.

2.5 Sleep-wake cycles

Sleep is an essential biological process that allows for the physical and mental restoration of the organism. Sleep cycles are composed of different stages that alternate throughout the night and are characterized by specific patterns of brain, eye and muscle activity. These cycles are crucial for maintaining health and well-being, as each phase of sleep has specific functions, such as memory consolidation, metabolic regulation and cellular repair [32].

2.5.1 Types of sleep

The sleep cycle in preterm infants is characterized by the presence of cyclic variations in brain activity that can be detected through the amplitude-integrated EEG (aEEG). The cycles are an important indication of brain maturation status, and its interpretation can provide critical information about the neurological health of preterm infants [33].

There are two main types of sleep that can be observed in these infants: active sleep (AS) and quite sleep (QS) [33]:

2.5.1.1 Active sleep

Active sleep (AS) in preterm neonates, also known as REM sleep, is characterized by brain activity showing a narrow region in the aEEG. Neonates in active sleep exhibit rapid eye movements, frequent body movements, and fluctuation in heart rate and respiratory rate.

These cyclic patterns in the aEEG develop and mature with gestational age being fundamental for the diagnosis and neurological monitoring of preterm infants. Variations in trace amplitude reflect the alternation between states of cortical and subcortical activity.

2.5.1.2 Quite sleep

Quite sleep (QS), also called non-REM sleep, manifests in preterm neonates with brain activity that becomes the wider bands in the aEEG. This state is characterized with fewer body movements and a more regular heart and respiratory rate.

Quite sleep is important for brain rest and recovery in preterm infants, correlating directly the maturation of the CNS.

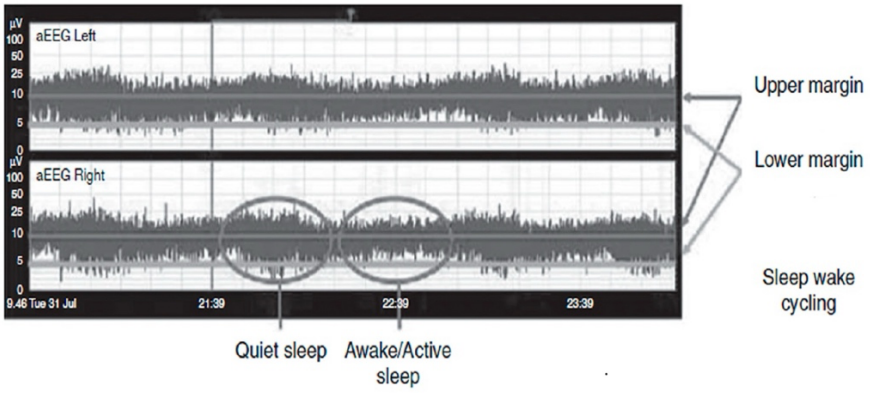

Figure 6. Sleep-wake cycle of a neonate. Narrow periods represent AS or REM sleep, while wide band periods correspond to QS or non-REM sleep [39].

2.5.2 Representation of sleep-wake cycles in aEEG

The sleep-wake cycle (SWC) is a pattern of brain activity that reflects the alternation between sleep and wake states. In aEEG, this cycle manifests as periodic variations in the amplitude of the tracing. In preterm neonates, SWC is an important measure of neurological maturation and can provide critical information about brain development and health.

The presence of SWC in preterm neonates is well documented, although there is considerable variation in reports of the gestational ages (GA) at which SWC may be visible. Thornberg et al. observed that the cyclic variability in preterm neonates resembles that of term neonates [34]. Curzi-Dacalova et al. confirmed that sleep state differentiation is present as early as 27 weeks GA [35]. Other studies have corroborated these findings, indicating that cyclic activity can be detected in neonates as early as 23 weeks GA [33].

Nevertheless, some studies have detailed the evolution of SWC with GA in preterm neonates as follows:

- **Before 30 weeks:** SWC is observed as an increase in both the upper and lower margin voltages during the active sleep stage, creating a wave-like appearance.

- **Between 30 and 32 weeks:** The lower margin voltages rise during both active and quite sleep, while the upper margin gradually begins to lower, resulting in a subtle alternating narrowing (during AS) and broadening (during QS) of the tracing.
- **After 32 weeks GA:** Clear and discernible cyclic activity appears, often taking on a spindle-shaped pattern, indicating a more established and regular sleep-wake cycle.

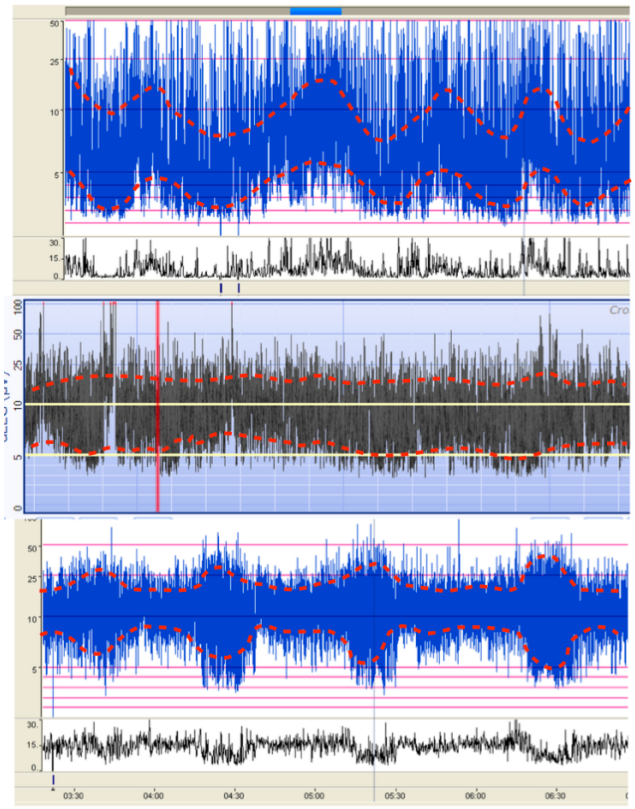

Figure 7. Patterns of sleep–wake cycling in preterm and full-term infants. The first image shows a case in which the preterm neonate is < 30 weeks GA. The second image corresponds to a neonate between 30 - 32 weeks GA. The last image represents a neonate with > 32 weeks GA [33].

Identification of the SWC is essential to assess brain maturation and detect possible neurological pathologies in preterm infants. A well-defined SWC suggests adequate neurological development, while the absence or irregularity of this cycle may be indicative of neurological problems.

Discontinuous patterns without cyclicity may represent a normal background in a preterm neonate, but moderate suppression in a term neonate. Burst suppression patterns indicate suppressed electrical brain function in both term and preterm neonates and are associated with significant pathology. Interruptions or absence of SWC may be related to brain lesions such as intraventricular hemorrhage (IVH), white matter injury (WMI), and post-hemorrhagic ventricular dilatation (PHVD) [33].

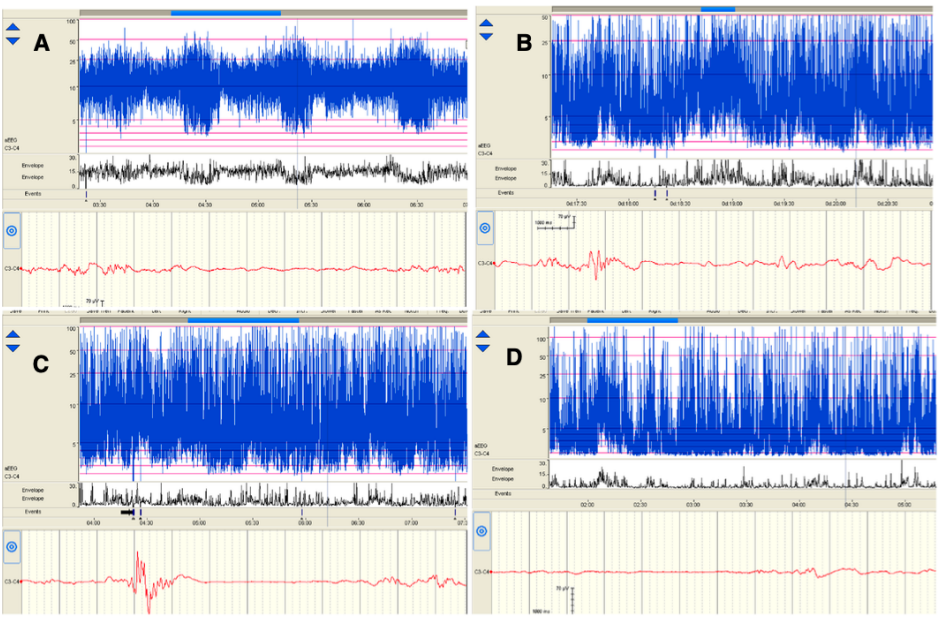

Figure 8. Differences between term and preterm aEEG in health and disease. Panel A shows a continuous normal pattern with SWC which represents a “healthy” full-term infant. Panel B illustrates a discontinuous pattern with cyclicity in a neonate with 27 weeks GA. Panel C shows a discontinuous pattern without clear cyclicity, which may be normal for a preterm infant but indicates moderate suppression in a full-term infant. Panel D depicts a burst suppression pattern, probably associated with a neurological pathology [33].

Monitoring SWC through aEEG allows clinicians to not only follow neurodevelopmental progress, but also to intervene early in case of deviations, potentially improving long-term outcomes for preterm infants.

2.6 Impedance

Impedance in the context of amplitude-integrated electroencephalogram (aEEG) is a crucial factor in ensuring the quality of the recorded signal. Impedance refers to the electrical resistance of the electrodes and the patient's skin to the passage of electrical current, influenced by factors such as hydration, the fat layer of the epidermis and the amount of hair. In neonates, the skin has a lower impedance due to increased hydration, although skin preparation is still necessary to obtain a good recording [4]. If impedance is high, it can affect the accuracy of the aEEG signal and, consequently, the clinical interpretation of the data.

To achieve good recordings in aEEG, it is important to understand how the interface between the skin and the electrodes affects impedance. This interface can be modeled with a non-lineal RC circuit, which includes components that depend on both frequency and electrical current. To improve impedance, work is done primarily on the outer layer of the skin, cleaning it to remove sweat and oil, and ensuring good contact with the electrode. Needle electrodes, although they penetrate deeper and have better impedance, are not used in neonates due to their invasive nature.

The impedance is composed of several layers that hinder the flow of electrical current from the brain. The dermis and deeper layers are pure resistors that do not vary with

frequency. In contrast, the epidermis is frequency dependent: At high frequencies, it behaves as a short circuit and impedance is low, while at low frequencies, resistance predominates, and impedance is constant [36].

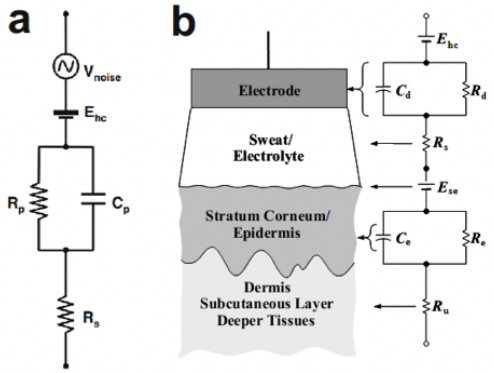

Figure 9. Models of the electrode-skin impedance. Case A shows a simplified electrical model of the electrode-electrolyte interface. While case B depicts a generalized model of the electrode-skin interface. [36]

In addition, the skin acts as a semi-permeable membrane with a potential difference. The interface between electrode and electrolyte is also frequency dependent and has a characteristic half-cell potential due to electrochemical reactions.

In aEEG, a bipolar setup is used that amplifies the difference between the signals from two electrodes in one hemisphere of the brain. If one electrode is disconnected, it will not pick up brain activity, affecting the output of the amplifier. Therefore, it is crucial that the impedances of both electrodes match closely to avoid biases in the measurements and to minimize the pickup of environmental noise. The use of instrumentation amplifiers helps to cancel common interferences [37].

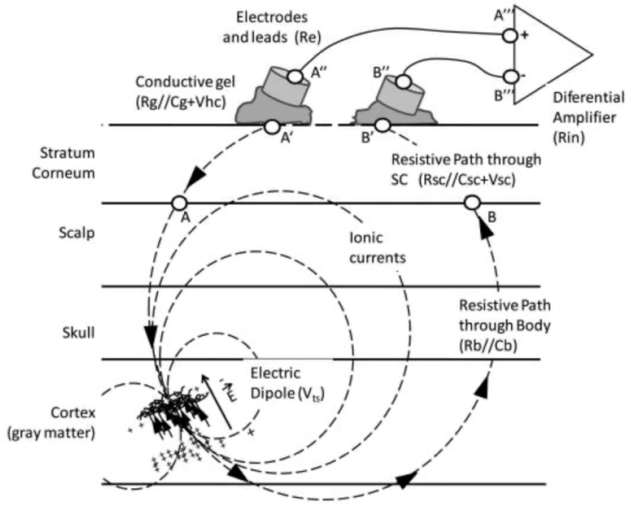

Figure 10. Schema of electric dipole, ionic currents and differential measure. [37]

Therefore, to obtain accurate aEEG recordings, it is vital to prepare the skin well, use appropriate conducting gels, and design electrodes that maintain low and stable impedance. Modern aEEG monitors continuously record impedances, allowing clinicians to adjust their interpretations as needed.

3 Materials and methods

3.1 Clinical research plan

This study was carried out at the *Hospital Universitari Sant Joan de Reus* (HUSJR) as a part of clinical investigation under the direction of clinical neurophysiologist Dr. Vicenç Pascual Rubio. It is noteworthy that this project had an existing foundation before such work began and this same study formed the basis for Ángel Rodríguez Ballabriga's final degree project. Despite this, a recap of the project's description and evolution will be provided to a better understanding.

3.1.1 Description of the study

Dr. Vicenç Pascual identified several issues with the use of adult electrodes on neonates due to the artifacts in the recordings. There are many drawbacks of surface adult electrodes to be used in aEEG but mainly they are related to bad adhesion and gel drying. To address these problems, Dr. Pascual collaborated with Dr. Albert Fabregat from the Department of Mechanical Engineering at *Universitat Rovira i Virgili*.

Their collaboration resulted in the development of a new electrode (aCUP-E), created especially for amplitude integrated electroencephalography (aEEG) in neonatal intensive care units (NICUs). The primary objective of this project is to compare the performance of the aCUP-E electrode with the conventional liquid gel electrode (Neuroline 720).

The hypothesis is that the aCUP-E electrode offers significant advantages, including better adhesion, consistent impedance, and greater comfort for medical professionals, while maintaining safety and signal quality standards comparable to those of the liquid gel electrode. For this reason, a clinical trial with NICU neonates that were neurologically healthy was performed.

3.1.2 Electrode comparison

To evaluate a newborn's health and neurological development, electrodes are essential to collect precise information on brain activity. This study focuses on two types of electrodes: aCUP-E and Neuroline 720, named as commercial electrode in this study.

3.1.2.1 aCUP-E (Advanced cup electrode)

The advanced cup electrode (aCUP-E) was designed especially for prolonged neonatal monitoring in NICUs. It is customized to be safe for a newborn's sensitive skin, offering flexibility and secure attachment. Because of its consistent impedance, strong adhesion, easy of refilling the electroconductive gel, and convenience of handling for medical staff, it is perfect for long-term studies. While the specific technical details of the aCUP-E are protected by intellectual property and they are not essential for this study, Figure 11 provides an illustrative depiction of the electrode.

Figure 11 The advanced aCUP-E electrode designed for aEEG in NICU

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3.1.2.2 Neuroline 720™

The Neuroline 720™ electrode from Ambu®, a self-adhesive electrode with an Ag/AgCl sensor and highly conductive liquid gel for stable signal transmission, was selected as the commercial electrode type for this study. Its measurement area is 95 mm^2, with dimensions of $30x20$ mm (Fig. 12).

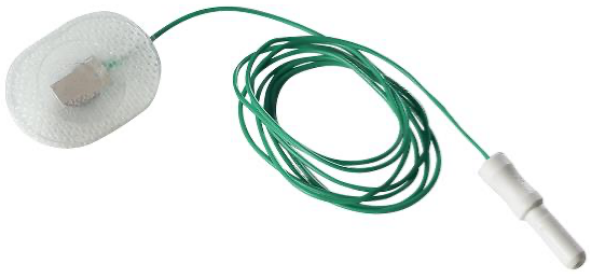

Figure 12 The Neuroline 720TM electrode from Ambu

Additionally, the Neuroline 720™ is the industry standard for continuous monitoring of neonates due to its high-quality aEEG recordings, easy of application, durability, and non-invasiveness [38]. For this reason, it has been utilized as a benchmark for comparing and assessing the aCUP-E capabilities.

3.1.3 Development of the study

As previously explained, two types of electrodes are used for electrode placement: liquid gel electrodes and aCUP-E electrodes. Following the conventional 10-20 international system, two electrodes of each type are placed on the right hemisphere and two on the left.

Electrodes P3 and C3 are positioned in the parietal and central regions, respectively, on the left side. Similarly, P4 and C4 are placed in equivalent positions on the right side. Furthermore, a ground electrode designated as Cz is included. This ground electrode which is an aCUP-E electrode, serves as a reference for accurately measuring the signals from the other electrodes.

The montage is shown in figure 13, with commercial electrodes on the left hemisphere and aCUP-E electrodes on the right. In contrast, figure 14 depicts the montage with the electrodes switched between the hemispheres.

Figure 13 Electrode montage with commercial electrodes on the left hemisphere and aCUP-E electrodes on the right hemisphere

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Figure 14 Electrode montage with commercial electrodes on the right hemisphere and aCUP-E electrodes on the left hemisphere

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This setup allows for a direct comparison between the two types of electrodes used in the study, guaranteeing equitable representation of both cerebral hemispheres.

After determining the placement of electrodes, meticulous care is taken to ensure optimal signal transmission. The first step is preparing the newborn's scalp for skincare. Any possible causes of interference, such as grease, sweat or dead skin cells, are removed from the scalp using soap and alcohol applied with cotton swabs. The monitoring procedure is then started by positioning the electrodes in their assigned locations.

In the case of commercial electrodes, they come embedded with liquid gel from the factory, so there's no need to apply electroconductive gel. However, it implies that once the package with 12 electrodes has been opened, the other electrodes not used dries and nurses add gel to the electrodes [38] to use the other electrodes. However, the manufacturer does not guarantee good adhesion if gel is added to the electrodes.

In contrast, for aCUP-E electrodes, there is no problem with electrodes gel because they come without gel. Gel must be added after placement to ensure the gel does not interfere with adhesion. These electrodes facilitate easy addition of more electroconductive gel every 8 hours to prevent drying without detaching it from the skin.

3.2 Data acquisition

The CFM Olympic Brainz Monitor (Natus Medical Incorporated) was used to acquire aEEG signals. The raw EEG signals and continuous impedance data were extracted from the monitor in European Data Format (EDF) files, as the device does not provide an option to download aEEG files directly.

For the analysis of aEEG in neonates and to evaluate the performance of aCUP-E against liquid gel electrodes, the signals were primarily processed using MATLAB (The MathWorks, Inc., 2024a). However, the EDF files were converted to CSV (Comma-Separated Values) format using the Python MNE package, which was more efficient at handling the extracted EDF files.

After extracting the signals to CSV format, the files were converted to MATLAB (.m) format to reduce their size and make them more manageable for further processing and

analysis. This conversion was performed using MATLAB (The MathWorks, Inc., 2024a), ensuring that the data files are optimized for storage and analysis while maintaining the integrity and accessibility of the data. By converting the CSV files to .m format, the efficiency of data handling and processing in MATLAB is significantly improved, facilitating a smoother workflow for subsequent analysis steps. The files of interest and their sampling frequencies are detailed in Table 1.

File name	Channel	Sampling frequency (Hz)
LeftEeg	C3 signal	200
	P3 signal	200
RightEeg	C4 signal	200
	P4 signal	200
LogicalImpedanceC3	C3 impedance	100
LogicalImpedanceC4	C4 impedance	100
LogicalImpedanceP3	P3 impedance	100
LogicalImpedanceP4	P4 impedance	100

Table 1 List of files and their sampling frequencies after conversion to .m format

3.3 Study population

This study involved performing aEEG analysis on neonates during their NICU stay. The subjects were carefully selected based on predetermined inclusion criteria, ensuring they exhibited no signs suggestive of neurological damage. Ultimately, the sample size for this study was refined to include 16 neonates, 12 preterm neonates and 4 term neonates.

Table 2 Demographic information and sample size of neonates included in the aEEG study

This table has been removed for confidentiality reasons.

3.4 Data analysis

The first step in the data analysis process involved extracting the recordings from the Cerebral Function Monitor (CFM) in EDF (European Data Format) format. The specific CFM used in this study is the Olympic Brainz Monitor, manufactured by Natus Medical Incorporated (Natus). Natus specializes in providing medical equipment, software, supplies, and services aimed at diagnosing, monitoring, and treating disorders that impact the brain or neural pathways.

The Olympic Brainz Monitor is particularly suited for this study because it has the capability to record raw EEG, continuous impedance (without interrupting the recording

process), and amplitude-integrated EEG (aEEG), which is consistently displayed at the top of the screen. The design of the monitor allows users to seamlessly switch between viewing the raw EEG and the impedance signals via an on-screen button, enhancing the usability and functionality of the device during monitoring.

Figure 15 Olympic Brainz monitor used for EEG and aEEG recording and monitoring

After obtaining all the recordings in EDF format, the data was converted to CSV (Comma-Separated Values) format to facilitate easier handling and analysis. Subsequently, the CSV files were converted to MATLAB (.m) files. This conversion step was crucial as it significantly reduced the file size, making storage and further analysis more manageable. The detailed procedure for data acquisition and conversion is outlined in section 3.2 (Data Acquisition).

To proceed with the analysis, the raw EEG data needed to be converted to aEEG. This transformation was achieved using a MATLAB script specifically developed for this purpose by Ángel Rodríguez Ballabriga in his final project [40]. The MATLAB code processes the raw EEG signals and generates aEEG traces, which are essential for evaluating brain function over time in a simplified and clinically relevant format.

The conversion to aEEG, along with the continuous impedance data, allows for comprehensive visualization and analysis of the recordings. This dual visualization capability is critical for interpreting the data accurately and making informed decisions based on both the aEEG and impedance signals.

3.5 Evaluation of sleep cycles detection in neonates

Given that the detection of sleep cycles is crucial for the brain development and general well-being of neonates, a MATLAB code has been developed for this purpose. This code allows for the evaluation of sleep cycles in the right and left hemispheres separately. This is important because it enables a detailed analysis of brain activity in each hemisphere, helping to identify possible differences in the neurological development of the neonate. Additionally,

this approach facilitates the comparison between two types of electrodes, aCUP-E and commercial.

The general behavior of sleep cycles in neonates is characterized by alternating phases of active sleep (REM) and quiet sleep (No REM). During quiet sleep, brain activity decreases and the aEEG shows higher peaks in the upper margin and lower peaks in the lower margin. However, in active sleep, brain activity increases, which is reflected in lower and more constant values of the upper margin and higher values of the lower margin because of the desincronized neuronal activity. Therefore, the key to accurately identifying and analyzing sleep cycles lies in the constant fluctuations of the lower margin of the aEEG.

Each sleep cycle can be recognized by a specific pattern, independently of the brain maturation of the neonate: a valley in the lower margin, which is usually preceded by a progressive decrease in voltage activity (descending slope) and followed by an increase in voltage brain activity (ascending slope). This pattern – descent to a valley and subsequent ascent – indicates that a sleep cycle is occurring.

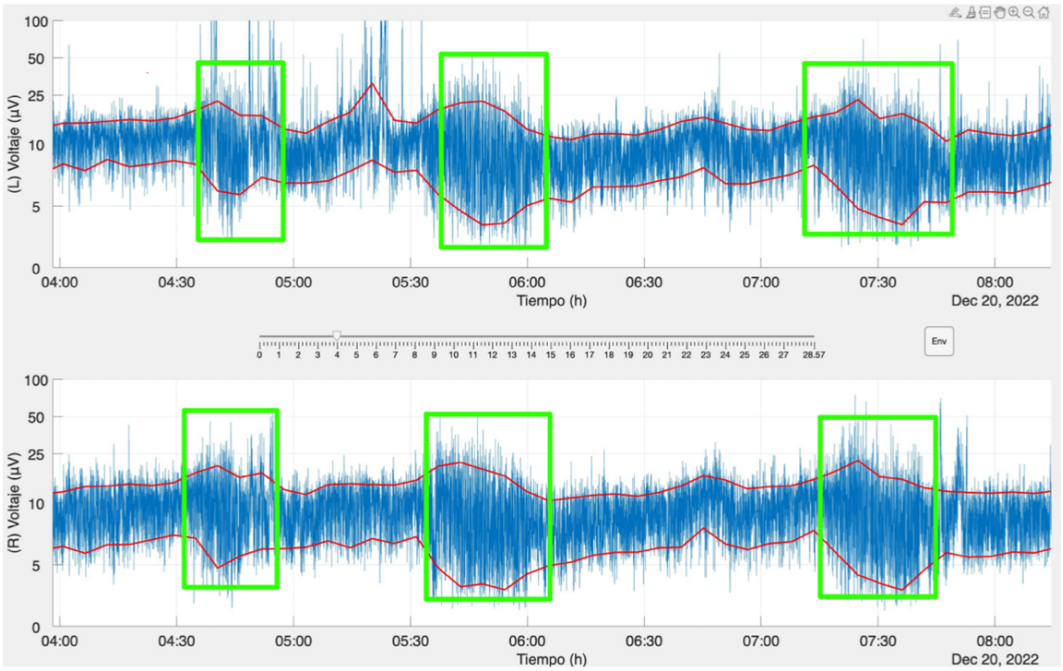

Figure 16 aEEG patterns for identifying sleep cycles based on fluctuations in brain activity

Therefore, all the valleys in the lower margin have been identified, as this is one of the indicative characteristics of neonatal sleep states. Once the valleys in the lower margin were identified, a series of criteria were established to determine if each valley could be considered part of a sleep cycle. This process was conducted in collaboration with Dr. Vicenç Pascual, who provided his expertise in identifying sleep cycles in the aEEG through continuous visual analysis of the data. Based on the doctor's identification of sleep cycles, the following criteria were defined for a valley to be considered a sleep cycle:

- Calculate the average brain activity, using the envelope of the aEEG signal, 30 minutes before and 30 minutes after the valley. The difference between this average and the lower margin of the valley must be greater than 1µV.
- The lower margin must meet certain conditions:
    - 10 minutes before and after the valley, the value must be less than 40 µV.
    - The valley itself must be between 1 and 10 µV.
- The upper margin must also meet several conditions:
    - 10 minutes before and after the valley, it must be between 7.5 and 50 µV
    - 15 minutes before and after, it must be below 50 µV
    - 20 minutes before and after, it must be below 55 µV
    - The upper margin of the valley itself (the point aligned in time with the identified valley) must be between 8 and 45 µV.
- The slope of the brain activity, specifically of the lower margin, must be greater than 0.04 μV during the 20 minutes before and 20 minutes after the valley. However, if there is another valley within those 20 minutes before or after the identified valley, the slope should be checked 25 minutes before or 15 minutes before the originally valley. This ensures that the slope is truly greater than 0.04 μV and not just the result of a slope between two valleys. This way, it guarantees that the slope reflects a real change in brain activity and not an artifact or normal oscillation within the same sleep cycle.
- There must not be any valleys considered as sleep cycles within 20 minutes before the evaluated valley.

The valleys that meet the previously established criteria are considered sleep cycles.

Once the valleys considered as sleep cycles according to the established criteria were identified, it was necessary to verify if these cycles were correctly detected. This was done by comparing them with the sleep cycles identified by Dr. Vicenç Pascual. This process involved counting false positives (FP), false negatives (FN), true positives (TP), and true negatives (TN):

- TP: Sleep cycles correctly detected by both the algorithm and Dr. Vicenç Pascual.
- TN: Moments where both the doctor and the program agree that there are no sleep cycles.
- FP: Sleep cycles identified by the algorithm but not by Dr. Vicenç Pascual.
- FN: Sleep cycles identified by Dr. Vicenç Pascual but not by the algorithm.

TP, FN, and FP are straightforward to calculate in the context of sleep cycle detection. The clarity in calculating these metrics lies in the direct comparison of each detected valley against Dr. Pascual's annotations. If a detected sleep cycle matches Dr. Pascual's identified sleep cycle, it is considered a TP. If Dr. Pascual identified a sleep cycle that the algorithm missed, it is an FN. If the MATLAB identifies a sleep cycle that Dr. Pascual did not, it is an FP.

A time margin of error of up to 10 minutes is used for this comparison. This means that if Dr. Pascual detects a sleep cycle at 11:00 AM, the algorithm's detection is considered valid only if it occurs between 10:50 AM and 11:10 AM. Detections outside this 10-minute window, such as at 11:20 AM, would not be considered valid as they exceed the acceptable time margin.

To identify the TNs the process was more complex. Initially, all valleys not detected as sleep cycles by MATLAB were considered as TNs. However, it became clear that not all these valleys could be considered as non-sleep cycle moments since some might be artifacts and not have the same time scale as TPs.

At this point, to identify the TNs, additional processing was required in MATLAB. This involved discarding valleys that didn't meet the criteria for being a possible sleep cycle, ensuring the elimination of points that could be signal artifacts, and applying a restriction on how frequently a valley could occur. Therefore, the TNs had to meet the following requirements:

- For 10 minutes before and after the valley, the lower margin must be < 40 μV.
- The valley itself must be between 1 and 10 μV.
- There must be no valley 20 minutes before. (This limit was defined by calculating the distance between all TPs and applying the same minimum distance between two TNs.)

The purpose of separately calculating TP, TN, FP, and FN is to determine the sensitivity and specificity of the algorithm in detecting neonatal sleep cycles. This analysis allows us to evaluate the effectiveness of the automated method in comparison with the expert assessment of Dr. Vicenç Pascual, ensuring that the detected sleep cycles are reliable and precise. Additionally, this validation also enables a comparison between the functionality of the two types of electrodes, aCUP-E and commercials.

Sensitivity (Equation 1) measures a test's ability to correctly identify TP, which in this context means accurately detecting sleep cycles. A higher sensitivity indicates that the algorithm effectively detects the sleep cycles present according to Dr. Vicenç Pascual's annotations.

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP+FN}} \qquad (1)$$

This calculation shows the proportion of actual sleep cycles correctly identified by the MATLAB code, ensuring that the algorithm misses as few sleep cycles as possible.

On the other hand, specificity (Equation 2) measures a test's ability to correctly identify TN, meaning correctly recognizing periods that are not sleep cycles. A higher

specificity indicates that the algorithm effectively avoids FP, ensuring non-sleep periods are not mistakenly identified as sleep cycles.

$$\text{Specificity} = \frac{\text{TN}}{\text{TN+FP}} \qquad (2)$$

This calculation shows the proportion of non-sleep periods correctly identified by the MATLAB code, ensuring that the algorithm avoids mistakenly identifying non-sleep periods as sleep cycles.

3.6 Impedances

Impedances play a crucial role in achieving high-quality aEEG readings, making them a key focus of this final degree project. Maintaining low and stable impedances, ideally below 5 kΩ, is essential. Fluctuations in impedance levels can be caused by factors such as bed friction, gel drying, or electrode detachment, which can negatively impact the aEEG results. Therefore, this project includes an analysis of various factors affecting impedances, comparing the results obtained from different types of electrodes, specifically aCUP-E and commercial ones. This comparison aims to evaluate which electrodes provide more reliable impedance levels for accurate aEEG measurements.

3.6.1 Impedances with sleep cycle detection

The impedances have been reviewed during all the sleep cycles considered by the algorithm, whether they were TP or FP. This was done to determine if the sleep cycles were accurately detected despite high impedances.

By analyzing the impedance values during each detected sleep cycle, the aim is to assess the reliability of sleep cycle detection in the presence of high impedance levels according to the two types of electrodes. This analysis ensures that the algorithm's performance remains robust even when encountering potential signal artifacts. The results have helped us determine whether either type of electrode, aCUP-E or commercial, maintains the same quality in recording sleep cycles despite high impedances.

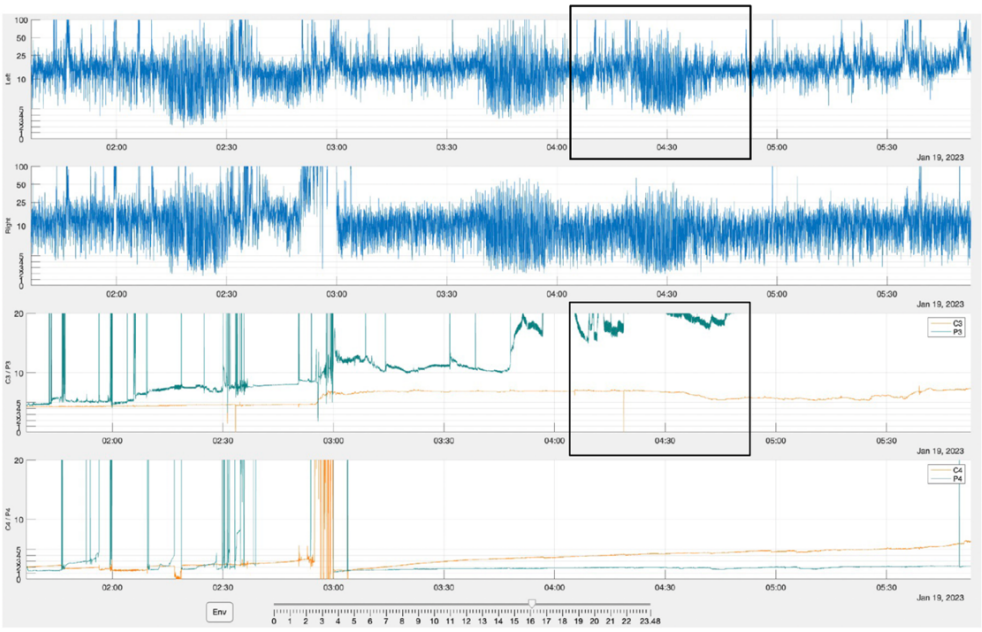

Figure 17 Impedance levels during sleep cycle detection

3.6.2 Impedance analysis

In his final project [40], Ángel Rodríguez Ballabriga calculated various parameters to assess electrode impedance. He observed that electrodes located in the parietal region exhibited worse impedances compared to those in the central region, likely due to friction with the mattress. However, it was later discovered that the issue was not specific to the parietal electrodes but rather due to noise interference. To analyze and certify that the worse results is caused due to the noise, a MATLAB program was developed to calculate the ripple noise for each electrode.

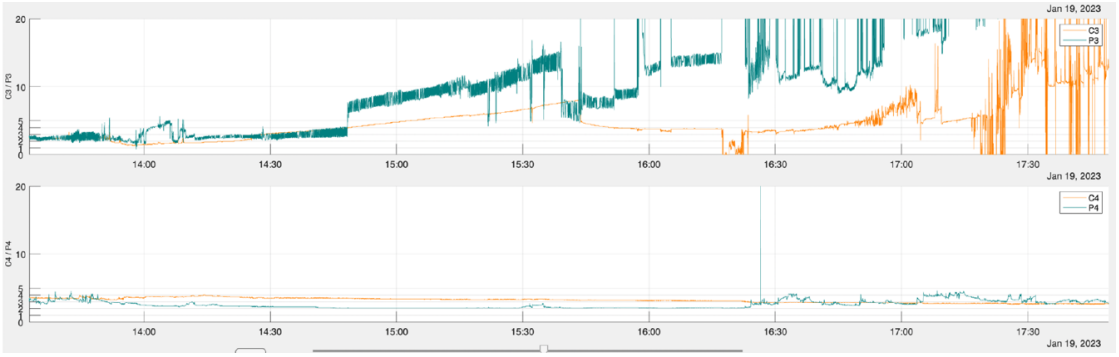

Figure 18 Ripple of electrode impedance signal in MATLAB

The program calculated the ripple noise by first identifying the total minutes in the recording where the impedance difference between the maximum and minimum of each minute was greater than 1 kΩ. Then, the percentage of ripple was determined using the formula:

$$\% = \frac{\text{Minutes with difference}>1\ \text{k}\Omega}{\text{Total minutes}} * 100 \qquad (3)$$

To ensure that the calculated percentage represented only the ripple and not significant impedance fluctuations, one conditions to the previous calculation was applied:

- Ensure that the difference between the average impedance at minute thirty and minute one was less than 2 kΩ.

This condition excluded minutes where the fluctuation was due to significant impedance changes rather than ripple. After applying these conditions, the final percentage of ripple was calculated using the same formula.

Additionally, several parameters were computed to analyze impedance across 16 cases, according to electrode and hemisphere:

- The average impedance for the entire recording.
- The average impedance for the first 24 hours, divided into five equal parts, with the standard deviation calculated from these five averages.
- The standard deviation of the impedance for the entire recording.

3.6.3 Analysis of impedance increase

If impedance increases due to gel drying or poor electrode adhesion, the quality of the aEEG recording can be compromised. Therefore, the increase in impedance has been analyzed according to the type of electrode and its location developing a MATLAB code created to find a trend line for each electrode, resulting in a total of four trend lines (Parietal aCUP-E, Central aCUP-E, Parietal commercial, Central commercial).

First, the recording was divided into 5-hour segments: from hour 1 to 6, and from hour 6 to 11, both for aCUP-E and commercial electrodes, in parietal and central regions for each case. The first hour was excluded to avoid initial instability and allow the recording to stabilize. The following table defines the segments of the recording that were considered.

aCUP-E		**Commercial**	
Central	**Parietal**	**Central**	**Parietal**
1 hour – 6 hours	1 hour – 6 hours	1 hour – 6 hours	1 hour – 6 hours
6 hours – 11 hours	6 hours – 11 hours	6 hours – 11 hours	6 hours – 11 hours

Table 3 Defined 5 - Hour segments of recording for aCUP-E and commercial electrodes in parietal and central regions

The trend line for each 5-hour segment was calculated, considering both the type of electrode and the location area. Below, you can find a figure showing the trend lines along

the first 5 hours with the impedance values for the 16 cases using the aCUP-E electrode placed in the parietal area. The rest of the data can be found in Appendix 1.

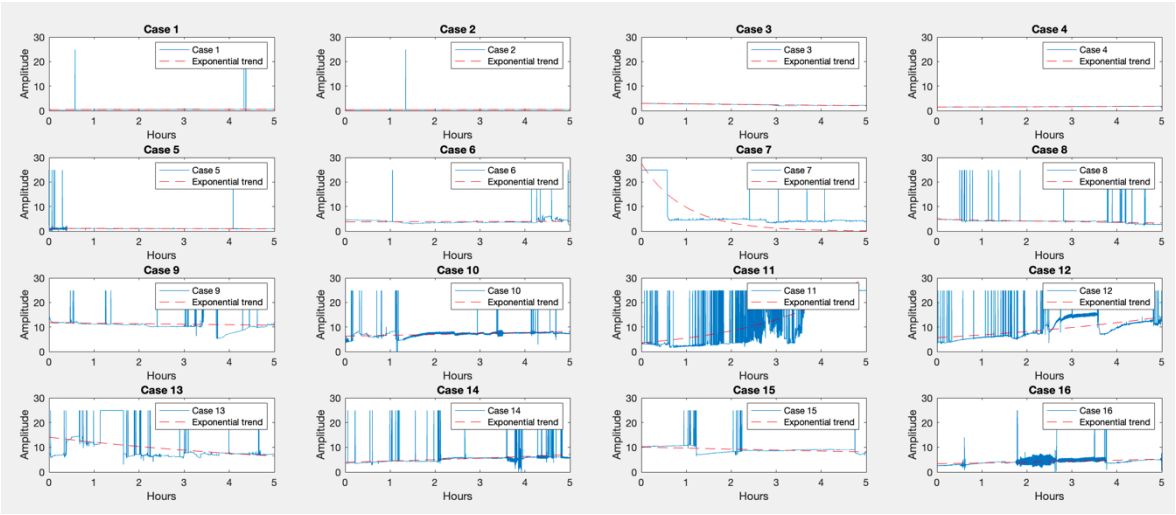

Figure 19 Trend lines of impedance over the first 5 hours for aCUP-E electrodes in the parietal area across 16 cases

The trend line that best matched the impedance increase for all cases was exponential. The formula used is:

$$y = a * e^{bx} \qquad (4)$$

To calculate the average trend line, certain segments were excluded from the analysis based on the following criteria:

- Segments with a continuous 10-minute period where impedances exceeded 24,8 kΩ. Because these can alter the trend line negatively, creating an inaccurate representation of impedance increases.

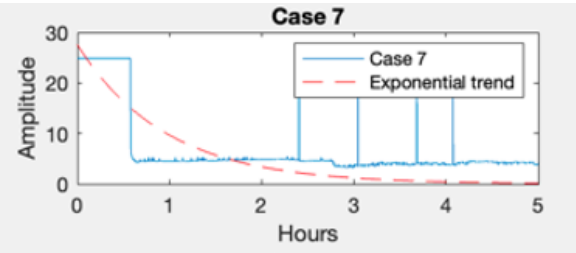

Figure 20 Exclusion criteria for calculating average trend lines based on impedance thresholds

- Segments with negative *b* greater than 0.1 Eq.4. These were excluded because such trend lines could skew results towards a negative average trend line, which does not accurately represent the typical behavior of impedance increases.

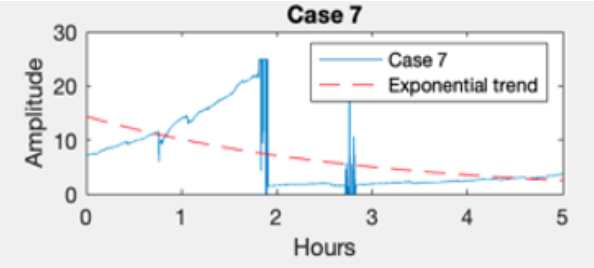

Figure 21 Exclusion of segments with significant negative slopes (b > 0.1) to ensure accurate impedance trend lines

Based on the previously provided case for the aCUP-E electrode in the parietal area from hour 1 to hour 6, certain regions were excluded from the analysis as they did not meet one or both previous conditions. The other regions and cases can be found in Appendix 2.

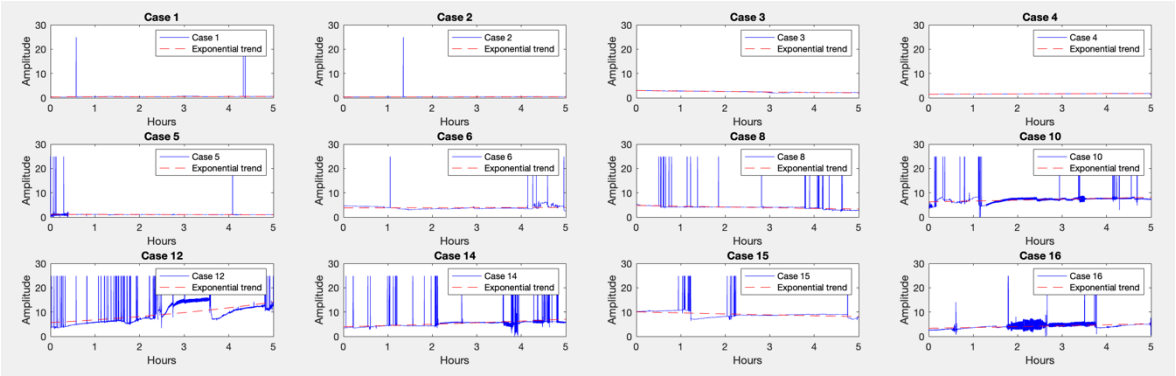

Figure 22 Excluded regions from parietal aCUP-E electrode analysis (Hour 1 to hour 6) due to non-compliance with exclusion criteria

To analyze the trend lines of impedance increases across different segments of the recording, we focus on segments that meet the specified criteria. Once we have all segments that qualify, we calculate the average of the exponential trend lines. The process for determining the average trend line is as follows:

- **Calculating the geometric mean of coefficients *a*:** Since the coefficients a are multiplicative in the exponential function, it is appropriate to use the geometric mean to find the average value of a. This is calculated using the formula:

$$a_{mean} = \left(\prod_{i=1}^{n} a_i\right)^{\frac{1}{n}} \qquad (5)$$

- **Calculating the arithmetic mean of coefficients *b*:** For the coefficients b, which have a linear relationship with x within the exponent, we use the arithmetic mean:

$$b_{mean} = \frac{1}{n}\sum_{i=1}^{n} b_i \qquad (6)$$

- **Forming the average exponential curve**: With the calculated values of a_{mean} and b_{mean}, the average exponential trend line can be represented as:

$$y = a_{mean} * e^{b_{mean} * x} \qquad (7)$$

3.7 Gel drying

One significant factor affecting the quality of aEEG recordings is the drying of the conductive gel. The aCUP-E electrodes allow for gel reapplication as needed by the nursing staff, whereas the gel in commercial electrodes tends to dry out, leading to a significant increase in impedance and compromising the quality of the aEEG recordings.

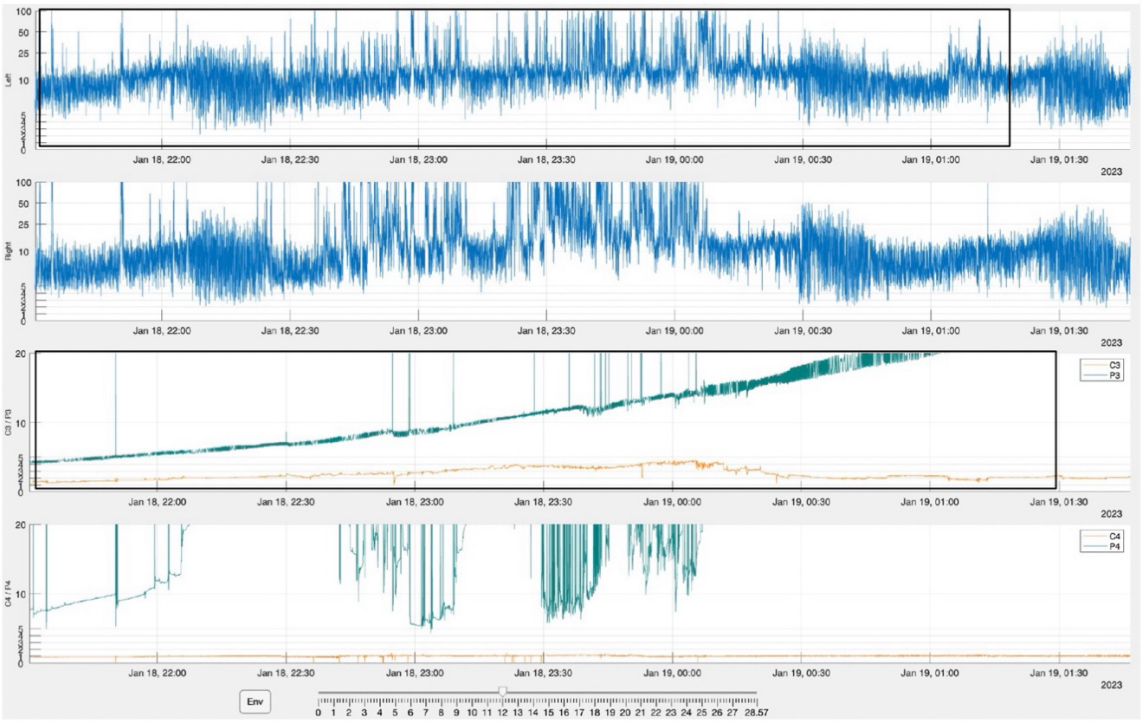

Figure 23 Impact of conductive gel drying on impedance levels and aEEG recording quality

To study the gel drying process, an experiment was conducted …

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3.8 Comparative performance analysis of aCUP-E v1 with aCUP-E v2 electrode

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4 Results and discussion

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4.1 Sleep cycles detection

4.1.1 Results of performance analysis

4.1.2 Specificity and sensibility

4.2 Impedances

4.2.1 General overview of recording impedances

4.2.2 Impact of high impedance on sleep cycles detection

4.2.3 Impedance analysis

4.2.3.1 Ripple noise

4.2.3.2 Mean comparison according to type of electrode

4.2.3.3 Standard deviation comparison according to type of electrode

4.2.4 Analysis of impedance increase

4.3 Gel drying

4.4 Updated findings on the performance of the aCUP-E v2 electrode

4.4.1 General overview of recording impedances

4.4.2 Evaluation of sleep cycles

4.4.2.1 Specificity and sensitivity

4.4.3 Impedance

4.4.3.1 Impedances percentage

4.4.3.2 Turns count of impedance values over 20 kΩ

4.4.4 Survival analysis

4.4.5 Impedance stability

4.4.6 Susceptibility to different frequency ranges

4.4.7 Impedance analysis

4.4.7.1 Mean

4.4.7.2 Standard deviation

4.4.8 Optimal brain activity

4.4.9 Impedance increase

5 Conclusions

The results of this study demonstrate that aCUP-E electrodes exhibit better adhesion and greater impedance stability compared to those currently used in clinical practice. This translates into improved signal quality for aEEG recordings, leading to better interpretation of aEEG signals for enhanced diagnosis and treatment of newborns. Although this final degree project has shown that the performance of aCUP-E is superior, it is important to emphasize the overall work conducted.

In this study, a code was developed to identify the number of sleep cycles per hemisphere and their occurrence. This, combined with sleep cycle evaluations by a physician, enabled a study on the specificity and sensitivity of different electrodes. The results show that aCUP-E records sleep cycles better than commercial electrodes, with higher specificity and sensitivity.

An impedance study was also conducted. The impedance values were first examined in the context of sleep cycle detection according to the developed code. It was concluded that high impedances in aCUP-E electrodes do not affect sleep cycle recording. In contrast, high impedances in commercial electrodes lead to poorly recorded sleep cycles, increasing false positives due to artifacts being misinterpreted as sleep cycles.

Other parameters, such as the overall mean impedance (including and excluding values above 24.9 kΩ), standard deviation, and the percentage of minutes above 24.9 kΩ, were also analyzed. The results indicate that aCUP-E electrodes have better, and more stable impedances compared to commercial electrodes.

Additionally, a study on impedance increases over 5-hour periods, simulating gel drying, concluded that the parameter "a" of the exponential formula is higher for aCUP-E, while "b" and the trend of the function generally increase more for commercial electrodes.

Finally, impedance results were compared with those from Ángel Rodríguez Ballabriga's final project for an aCUP-E v2 design. The aCUP-E v2 appears to have better performance and thus better aEEG quality. Although not all average results surpass the old aCUP-E, this is mainly due to poor parietal impedance in the first case of the aCUP-E v2. With only four cases, this significantly impacts the final average. Nonetheless, the aCUP-E v2 shows improved optimal signal recording compared to both commercial and aCUP-E v1 electrodes.

In conclusion, the aCUP-E v2 design demonstrates superior performance in terms of impedance stability and overall signal quality, making it a promising alternative for clinical use in aEEG recordings.

5.1 Future work

For future work, it is essential to analyze more cases to determine if the aCUP-E v2 design is genuinely a better version than the old one, as the current study's four cases are insufficient to draw significant conclusions.

Additionally, the gel drying experiment should be performed with better methodology. The in vitro experiment indicated gel drying, but it needs to be conducted with a conductive liquid on a plate to measure the conductivity as the gel dries. Moreover, placing the electrode on a model shaped like a neonate's head would be beneficial. This approach would help establish a correlation between gel drying and impedance changes.

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7 Appendix

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Appendix 1: 5-hours impedance data analysis

Appendix 2: 5-hours impedance data analysis for regions meeting specific conditions

Appendix 3: Table of sensitivity and specificity case-by-case

Appendix 4: Table of ripple for each electrode and case

Appendix 5: Table of verified ripple for each electrode and case

Appendix 6: Table of mean impedances for each electrode and case

Appendix 7: Table of mean impedances for each electrode and case non including saturated impedance values > $24,9\ k\Omega$

Appendix 8: Table of percentage of minutes for each electrode and case above $24,9\ k\Omega$

Appendix 9: Table of standard deviation of mean impedances for each electrode and case of all the recording

Appendix 10: Table of standard deviation impedances for each electrode and case

Appendix 11: Moving standard deviation

Appendix 12: Impedance increase of 5-hour segment of v2 aCUP-E and commercial

Appendix 13: Table of sensitivity and specificity case-by-case with the v2 of aCUP-E