

Cerebral function monitor

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**Appendices
Cerebral Function Monitor From A to Z**

Ir. Charlotte Lommen

Eindhoven, October 2007

Appendices part of report

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Cerebral Function Monitor:
from A to Z

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Eindhoven, October 2007

Contents

- A. Neonatal brain function and dysfunction5**
 - A.1 Maturational changes..... 5*
 - A.2 Common dysfunctions in the developing brain 7*
 - A.3 Neonatal seizures and brain injury 8*
 - A.4 References..... 11*
- B. The Cerebral Function Monitor 13**
 - B.2. Current thoughts and practice of CFM..... 17*
 - B.3. References..... 18*
- C. Purchase advice and implementation CFM 19**
 - C.1 Purchase advice..... 19*
- D. User protocols CFM devices 25**
 - D.1 User protocol Olympic CFM6000 25*
 - D.2 User protocol NicoletOne 27*
- E. Electrodes..... 30**
 - E.1 Characteristics of biopotential electrodes..... 30*
 - E.2 Different materials for electrodes and gels 33*
 - E.3 Types of electrodes 35*
 - E.4 References..... 38*
- F. Results inquiry among nurses..... 39**
 - Inquiry 39*
 - Results Inquiry..... 40*
- G. Handouts education for nurses 43**

H. Protocols Cerebral Function Monitoring	47
<i>H.1 Cerebral Function Monitoring (nurses protocol).....</i>	<i>47</i>
<i>H.2 Medical protocol CFM.....</i>	<i>50</i>
I. Literature study.....	59
<i>I.1 Principles for educational software design.....</i>	<i>59</i>
<i>I.2 Process of development</i>	<i>61</i>
J. Training Needs Analysis.....	62
<i>J.1 Mission and tasks of CFM.....</i>	<i>62</i>
<i>J.2 Trainee and training analysis</i>	<i>62</i>
K. Design strategy of CFM simulator	66
<i>K.1 Training Program Design</i>	<i>66</i>
<i>K.2 Training Media Specifications</i>	<i>70</i>
L. Team input.....	72
M. Automatic seizure detection	74
N. Automatic analyses EEG of prematures.....	84

Appendix A

Neonatal brain function and dysfunction

This appendix will describe the maturational changes in the newborn brain, the common dysfunctions, and seizures, which are the most distinct sign of cerebral dysfunction in the newborn. Also their relations to EEG will shortly be described.

A.1 Maturational changes (*chapter 3.1 master's thesis Loes Ruijs*)

Large changes occur in the brain during gestation and first few years postnatal. The morphological, biochemical, and physiological maturation of the central nervous system is paralleled by distinct developmental changes in the EEG. Although there have been few studies correlating specific developmental changes of the brain with developmental changes in EEG, it is thought that some processes play a key role in the remarkable changes in the EEG. Processes of which is thought of:

- Proliferation and migration of neurons and neuroglia
- Elaboration of dendritic and axonal branches
- Formation of synapses
- Myelination

These steps and the anatomical change of the brain are explained below. Extensive descriptions of brain maturation can be found in (Volpe, 2001; Augustine, 2004; Eyre, 1992; Holmes, 1986; Scheibel, 1997), information below is a summary of these references.

Neuronal proliferation and migration

In the first phase of brain development neurons and neuroglia, i.e. supporting cells of the nervous system, are formed. Subsequently, they migrate to a specific location.

The vast majority of neurons and neuroglia are generated in the germinal zone, i.e. cerebral area that is located at the ventricular surfaces. Neurons are formed till 20 weeks of gestation, neuroglia are produced till 28 weeks of gestation. Peak time of proliferation is between 12 and 16 weeks of gestation.

As cells are formed, they migrate from the germinal zone to their final destination. Migration of cells into the cortex occurs in an inside-out fashion. The deepest layers are formed first, followed successively by more superficial layers. All of the cells in each layer migrate

through prior layers to reach their final positions. The neurons reach their final positions in the cortex by following radial glial guides. By 20 to 24 weeks of gestation the cortex has essentially its full complement of neurons. Peak time period of migration for all cells is between 16 and 20 weeks of gestation.

Organizational changes of neurons and neuroglia

After the neurons and neuroglia have reached their new location several organizational changes will take place during the third trimester of gestation. These changes consist of differentiation of the neurons and formation of neuronal populations by aggregation of cells, elaboration of axons and dendrites, the connection of cells through synapses, and programmed cell death.

Differentiation of cortical neurons occurs either immediately after migration to their final positions or they continue to mature throughout development and into the postnatal period. When migrating neurons reach their definitive locations, they generally aggregate with other cells of similar kind to form cortical layers or nuclear masses. The mechanism of this selective aggregation is unknown. In most regions of the brain, neurons not only adhere to one another but also adopt some preferential orientation. In the cerebral cortex, the majority of the large pyramidal neurons are consistently aligned with their prominent apical dendrites directed toward the surface and their axons directed toward the underlying white matter. During aggregation of neurons, neurons begin to develop extensions from their cell bodies. These will progressively become longer and form the two major types of processes or branches that characterize almost all neurons: i.e. the dendrites and axons. The stimulus for the formation of dendrites and axons is not totally understood. It is likely that both genetic and environmental factors may be important. The maximal phase of dendritic and axonal growth and development of pyramidal neurons occupies a period between 18 and 24 weeks of gestation.

Synapses are formed when dendrites establish contacts with other neurons. The distribution of synapses is determined by the development of the dendritic tree and spines. The development of the synapse likely involves an interaction between the presynaptic and postsynaptic elements. However, mechanisms that control the formation of synapses are also unknown. The process of synapse formation starts at around 24 weeks' gestation and continues during life. Synaptic development differs appreciably among brain regions in the human brain. The formation of synapses in the cortex seems to be largely a postnatal event. Synapse formation proceeds at highest rate during the first 6-8 years of postnatal age.

Neuronal death during development occurs naturally throughout the nervous system because more neurons are generated than required. The phase of selective cell death occurs usually at about the time when the population of neurons is forming synaptic connections.

Myelination

Last important process involved with maturation of the brain is myelination. Myelination is growth of myelin sheaths around axons of the cerebral cortex. Myelin is a fatty substance working as an insulating sheet around the axons. Its presence allows conduction of nerve impulses to occur from ten to one hundred times as rapidly as would occur along a non-myelinated axon. Myelination starts at around 13 weeks of gestation and is finished at around adolescence. The rate of myelination is highest around 2 years of postnatal age. Within the brain, myelination starts central and spreads to more peripheral areas.

Anatomical changes

Paralleling microscopic changes in the brain, significant morphological changes of the cerebral hemispheres occur during the third trimester and postnatal months. Most visible change of the premature brain before 40 weeks of gestation is the increase in volume. Between 29 and 40 weeks of gestation the volume of the cortical gray matter increases three times. Next to this change in volume, the shape of the brain changes because of development of cortical sulci and gyri, grooves and elevations respectively. The surface of the brain is completely flat till 12 weeks of gestation, see Fig 7, but around 40 weeks the brain shows relief like a walnut. Primary sulci develop as deep grooves with walls far from each other. During maturation grooves become deeper and walls become steeper. Finally the walls come in contact with each other. Most gyri are formed between 26 and 28 weeks of gestation. Thereafter, no new gyri are formed any more, but formed gyri become more mature. Time of gyration differs for different brain areas. Occipital areas are the first, followed by temporal and central areas. Finally, frontal areas gyrate.

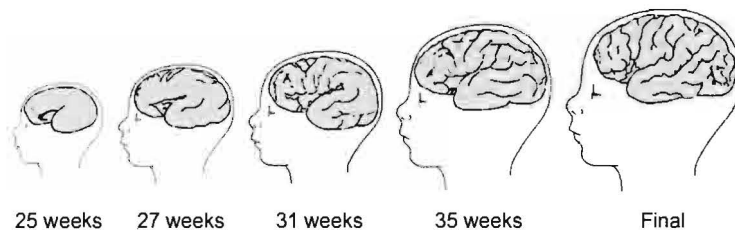


Figure 7: Gyration of the brain, schematic presentation from 25 weeks gestation till term age.

Relation of changes in brain formation and EEG

Changes in neuronal size, dendritic tree formation, synapse distribution, and myelination are associated with changes in neurophysiologic functioning of neurons. The threshold of excitation of neurons will change with increasing soma volume. Excitatory and inhibitory postsynaptic potentials in immature neurons characteristically have a slow rise time, a long duration and low peak amplitude compared with mature neurons. Temporal dispersion of impulses in immature axons may contribute to the slow rise time and long duration of the postsynaptic potentials. In the peripheral nerves the increasing fiber diameters and progressive myelination are reflected in increasing conduction velocities and decreased threshold for activation.

The sequence of above described processes is for all infants the same. However, quality and quantity of these processes for premature children at term age can be less than for full-term children. This suggests that maturation of the brain inside the womb differs from outside the womb. Moreover, animal studies have shown that several of these processes can be modulated by environmental stimuli (Gressens, 2002). Therefore, when relating changes of the EEG with brain maturation of premature infants it is important to keep the developmental phases of the brain in mind.

A.2 Common dysfunctions in the developing brain

Many dysfunctions that may occur in the newborn brain are related to the occurrence of seizures. The most important one is hypoxic ischemic encephalopathy (HIE), which is caused by a lack of oxygen or a lack of blood in the brain. Besides that, also intracranial

hemorrhages, metabolic encephalopathies and intracranial infections may cause seizures in the newborn. These dysfunctions are described in A1.3, as possible etiologies of seizures.

Not all dysfunctions are associated to the occurrence of seizures. Seizures are only rarely seen in periventricular leukomalacia (PVL). The pathogenesis of PVL is not very well understood, but is related to HIE in the premature brain and toxic injury. The injury is mainly diagnosed by ultrasound. Visible are white spots in cells just underneath the cortex, the oligodendroglia. In the EEG the occurrence of spikes can be visible. A typical pathology in the developmental period is the occurrence of malformations. There can be a wide range of malformations, but since EEG or CFM does not have an extra value concerning their diagnosis, they will not be described here. (Rennie, 2002)

A.3 Neonatal seizures and brain injury (chapter 2 master's thesis Charlotte Lommen)

Seizures are the most distinct sign of cerebral dysfunction in neonates. They may be caused by most cerebral pathologies and may cause brain injury themselves. Detection can be done based on clinical signs, although they may be subtle or absent in the newborn, and based on the electro cortical manifestation of seizures using electroencephalography (EEG).

Seizures at cellular level

In healthy neurons, a stimulus may cause depolarization, immediately followed by repolarization of the neuron. The resting potential of a neuron, -90 mV, is mainly caused by an uneven extra- and intracellular distribution of Na^+ and K^+ ions. It is maintained among others due to the Na^+-K^+ pump, which transports Na^+ out of the cell and K^+ into the cell by use of energy in the form of ATP. During depolarization Na^+ channels are opened and cause an enormous flow of Na^+ ions into the cell, which causes the membrane to rise in voltage to about +35 mV. The Na^+ channels close and rapid repolarization of the membrane is achieved by opening of the K^+ channels, that cause K^+ ions to rapidly move out of the cell. The Na^+-K^+ pump transports Na^+ ions back out of the cell and K^+ ions into the cell, and the cell can be stimulated again.

Nerve impulses are transmitted from one neuron to the other through electrical or chemical synapses. Electrical synapses conduct electricity through direct channels. Chemical synapses transmit the stimulus by the use of a neurotransmitter. An excitatory neurotransmitter is released by a neuron, causes the adjacent neuron to be more susceptible to impulses, and finally may cause depolarization. Inhibitory neurotransmitters cause the adjacent neuron to be relatively insensible to nerve impulses, due to influx of Cl^- ions (Guyton, 1996).

A seizure is an excessive synchronous depolarization of neurons within the central nervous system. Current data suggests the following mechanisms to be possible causes of neonatal seizures:

- failure of the Na^+-K^+ pump due to a disturbance in energy production;
- an excess of excitatory or a dysfunction of inhibitory neurotransmitters in the synaptic clefts;
- a lack of calcium or magnesium, the ions that should cause inhibition of Na^+ movement. (Volpe, 1995)

Regardless the underlying dysfunction, repeated neonatal seizures may cause disturbances in ventilation and circulation (Volpe, 1995) and possibly damage to the developing brain (Holmes, 2001; Scher, 2003). High activity of the Na^+-K^+ pumps during the prolonged

depolarization in seizures results in a fast decrease of ATP and increase of ADP concentration, which activates the glycolysis. This is followed by a drop in glucose levels and a large production of lactate. They cause a rise in blood pressure. Hypoventilation and apnea may occur with repeated seizures, which cause a drop in oxygen concentration, hypoxemia, and a rise in carbondioxide, hypercapnia. Finally there is evidence of high levels of excitatory amino acids at the synaptic clefts, due to the energy dependent re-uptake of the neurotransmitters which is impaired (Volpe, 1995). All these changes caused by repeated seizures, can cause brain injury in the neonate, making early detection and treatment of seizures very important.

Etiologies of seizures

Seizures may appear in most types of encephalopathies. They often have an early onset, and may be first indicators of brain disease (Lombroso, 1996).

Hypoxic-ischemic encephalopathy (HIE) is one of the most common causes of brain injury, and is often accompanied by seizures. HIE is characterized by a lack of oxygen in the brain, due to a lack of oxygen in the blood, hypoxemia, or a lack of blood perfusion in the brain, ischemia. A consequence is a decrease in energy production. HIE in newborns is mostly caused by perinatal asphyxia, a condition of decreased oxygen and increased carbon dioxide concentration in the blood, mostly caused by impairment of gas transport through umbilical cord or placenta during labour. Even though the young infants have a larger resistance to hypoxia and ischemia than adults, the long-term outcome, i.e. consequence, for them can be very poor, neurological complications or death (Volpe, 1995).

A second cause of brain injury is intracranial hemorrhage (bleeding), a pathology often causing serious neurological complications or death. Hemorrhages are mostly related to fluctuations in blood pressure, fragility of blood vessels and HIE. They are more common among preterm newborns. The different types of hemorrhages may show a variety of clinical signs among which seizures (Volpe, 1995).

There are many different types of metabolic encephalopathies; most of them may be accompanied by seizures. Hypoglycemia, a lack of glucose in the brain, may be caused by a decreased availability or production of glucose, but also by asphyxia and hypoxemia. When seizures occur during hypoglycemia, they aggravate the lack of glucose. Hypocalcemia and hypomagnesemia are also often associated with seizures. Other types of metabolic encephalopathies like bilirubin and disorders of amino acid and organic acid metabolism are more or less frequently accompanied by seizures. However most of these metabolic encephalopathies are often also accompanied by other pathologies like HIE, which makes the etiology of seizures unclear (Volpe, 1995).

Intracranial infections are causes of seizures as well. Newborns are very susceptible to infections, and they may have very poor outcome (Volpe, 1995).

Clinical and electrophysiological signs of seizures

Seizures can be classified according to clinical signs. Three well-recognisable categories are clonic seizures, which involve rhythmic movements of for example extremities or parts of the face, myoclonic movements, which are more rapid than clonic movements, and tonic movements, for example tonic extension of extremities (Volpe, 1995). A majority of seizures, however, have clinical manifestations that are easily overlooked or confused with normal newborn movements, subtle seizures, or have no clinical signs at all, silent seizures (Hellström-Westas, 2003; Volpe, 1995). Subtle seizures involve for example chewing, horizontal deviation of eyes and apnea, the last of which is well-recognisable but often has no epileptic origin (Volpe, 1995). The absence of clinical signs in silent seizures may be due to

medication like anti-convulsive treatment or due to the origin of the seizure and the immaturity of the newborn brain (Hellström-Westas, 1985; Scher, 1993; Niedermeyer, 2005). Some newborn movements may be misinterpreted as seizure. Jitteriness, which is a movement disorder, is the best example. The movements in jitteriness are generally tremulous or clonic (Volpe, 1995).

EEG is a sensitive method for the detection of seizures, and often considered as golden standard. Using 10 to 22 electrodes connected to the scalp of the newborn, the electrical activity of the cortex is measured (Stockard, 1992; Niedermeyer, 2005). In the EEG, seizures manifest themselves as rhythmic discharges, with a relatively sudden onset and termination. Within this discharge waveforms of similar morphology cause the rhythmic patterns. The waveforms within one pattern have an evolution in frequency, topology and amplitude (Niedermeyer, 2005; Shewmon, 1990). Examples of rhythmic discharges are shown in figure 2.1. Seizures can be identified electrographically as focal, multifocal or generalized seizures, by either being visible in EEG channels measured at one or more specific parts of the scalp, or being visible in all of the EEG channels (Volpe, 1995).

The minimum duration of seizures is generally defined to be 10 seconds. Rhythmic discharges with a duration shorter than 10 seconds are called brief ictal rhythmic discharges (BIRD). Prolonged seizures or repetitive seizures with a very long duration are called status epilepticus. For neonates the status epilepticus is defined as a prolonged or repetition of seizures for at least one hour and with abnormal neurological symptoms between seizures (Shewmon, 1990).

Finally, a remark has to be made that some seizures may not be visible in the EEG. Their origin is believed to be of the lateral neocortex or subcortical (Shewmon, 1990).

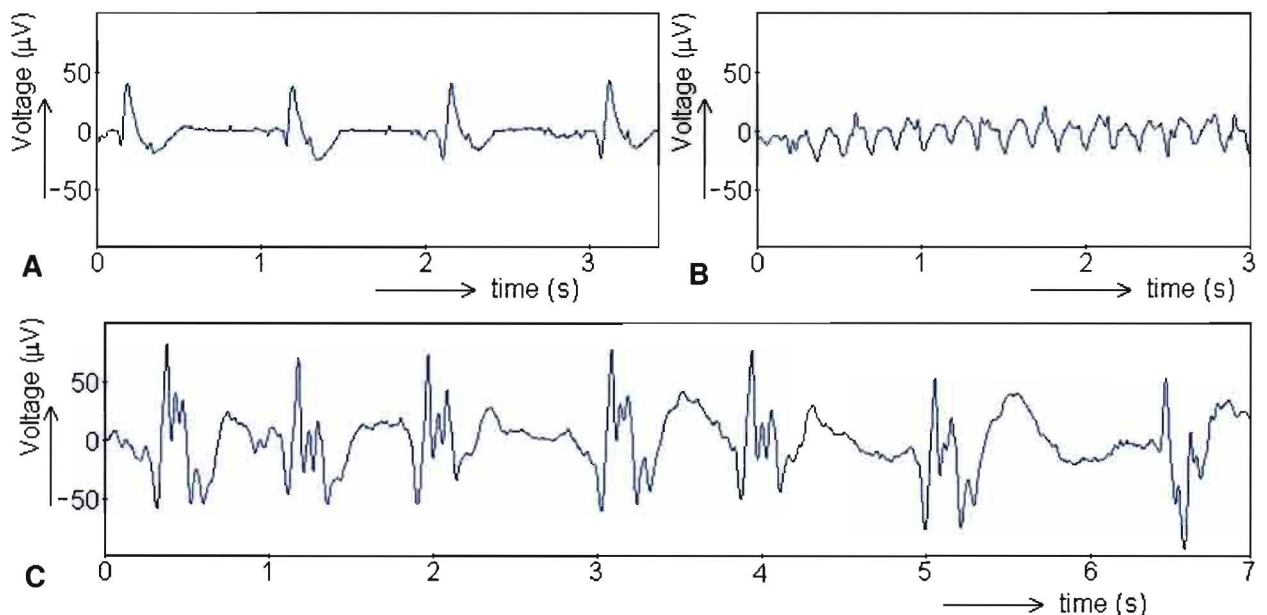


Figure 2.1: Shown are three examples of EEG signals with rhythmic discharges, seizures. Between the examples in subfigures A, B and C there is a large difference in morphology. In example C there is an evolution visible in frequency, topology, amplitude and even morphology.

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Appendix B

The Cerebral Function Monitor

B.1 The Cerebral Function Monitor (chapter 3 master's thesis Charlotte Lommen)

The Cerebral Function Monitor (CFM) is a device that measures cerebral electrophysiological activity and is used for the continuous surveillance of the cerebral function. It was constructed by Maynard in the 1960's for the monitoring of adult cerebral function (Maynard, 1969; Prior, 1986), and is now widely used in neonatal intensive care.

B.1.1 Why CFM

EEG is a generally accepted method for obtaining the cerebral function. However, the method is less suitable for long-term monitoring in the NICU environment. EEG is generally displayed at a scale of 30 mm/sec, with sample frequency of at least 256 Hz, to be able to identify all events in the signal. The complex nature of the numerous EEG signals is caused by their small amplitude, their susceptibility for artefacts and our limited knowledge of the brain. Extensive interpretation of the numerous and complex EEG signals displayed at a slow speed needs to be done by a neurophysiologist. Generally at a hospital, neurophysiologists are not available for long-term EEG measurements, which is the main reason EEG measurements are not used for continuous monitoring in the NICU. Furthermore the numerous electrodes may cause discomfort for the newborn after some time due to irritation of the skin and a limited freedom of movement. EEG measurements at the NICU generally have a duration of about half an hour.

The CFM measures a one-channel bipolar EEG signal over the mid-parietal area of the cortex, which is processed into an amplitude-integrated EEG (aEEG) signal. The aEEG signal is created to display general electrical activity of the brain, disregarding short events. This makes it possible to compress the signal in time to typically 6 cm/hour, 3 hours per page. The measured cerebral electrical activity is displayed in only positive amplitudes and compressed to a scale that enhances the visibility of abnormal patterns of low cerebral activity. The signal is relatively easy to read and interpret by skilled nurses and other doctors then neurophysiologists. Due to the use of only 3 electrodes, the single signal that is simplified and displayed in a compressed scale, measurement and monitoring of the signal can be done by

nursing staff. This makes CFM a suitable method for the continuous monitoring of the electrical cerebral activity of the newborn in the NICU.

The CFM is not designed to be a replacement of conventional multi-channel EEG. Short events are visible in the biparietal EEG signal measured by the CFM, but may be overlooked, since interpretation is often primarily done based on the aEEG signal. Because of the use of only one channel, focal events may not be noticed and there is no information about asymmetrical or asynchronous behavior. To obtain a better temporal and spatial resolution, CFM needs to be complemented with conventional multi-channel EEG.

The strength of CFM lies in its ability to monitor cerebral function for a prolonged period. It makes it possible to monitor the recovery of the brain after pathology or treatment with medication and to monitor seizures and sleep wake cycles occurring outside the short measurement time of the EEG. It is now also possible to get more information about the function of the brain of the newborn outside working hours, since no expert is needed for the measurement and interpretation. A better understanding of the newborn brain and its responses, and a better treatment can be achieved because of these long-term measurements (Maynard, 1969; Prior, 1986; Hellström-Westas, 2003).

B.1.2 Electrodes

CFM measurement only uses three electrodes. The two active electrodes are placed left and right parietal, P3 and P4 according to the International 10-20 System (Jasper, 1958), see figure 3.1. A third electrode is placed as ground electrode, to reduce the amount of electrical interference and is positioned anterior to the midline at Fz (Maynard, 1969; Prior, 1986).

The electrode positions of the active electrodes are used for different reasons. First, this electrode position is least affected by eye movement and muscle artefacts. A second reason is that the electrodes are positioned at a region that is the most sensitive to ischemia, since this region is the boundary zone of blood perfusion from the posterior, middle and cerebral arteries. A third reason is that amplitudes in waking and sleeping are relatively large in the parietal region (Maynard, 1969; Prior, 1986).

The type of electrodes used is an important aspect of the measurement. It is possible to use adhesive electrodes, though in our experience these lose contact after some hours, which can be seen in the high impedance. An alternative is the use of subdermal needles, as also suggested by de Vries *et al*, 2005. These very small needles only cause little discomfort for the newborn and can be used for prolonged recordings without the need of replacement. Like the NICU in the MMC Veldhoven, most NICU's use subdermal needles after some measurements with adhesive electrodes where the impedance was too high after a few hours.

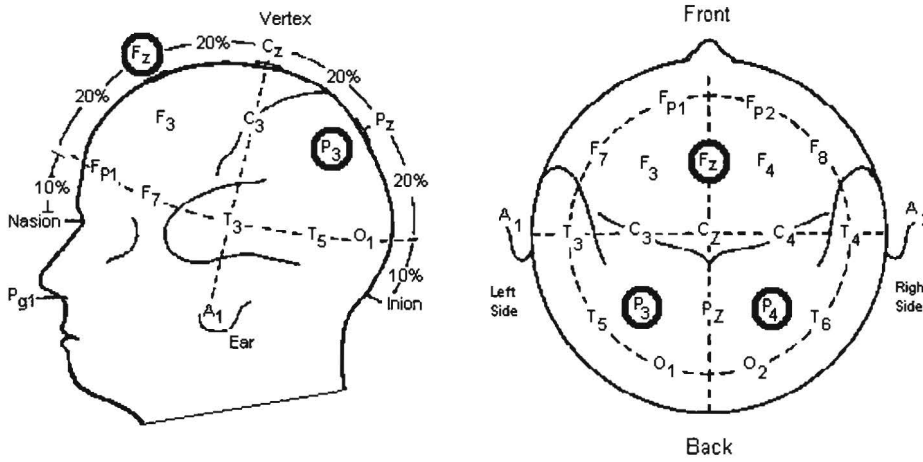


Figure 3.1: Side and top view of the placement of electrodes according to the international 10-20 System of conventional EEG; marked by circles are the electrode positions P3 and P4 for the active electrodes of the CFM measurement, complemented by a ground electrode at Fz.

B.1.3 From EEG to amplitude-integrated EEG

The aEEG signal is processed from the measured biparietal EEG signal. Most detailed information about this processing has been found in the first article of Maynard et al. 1969 and the book by Prior et al. 1986 who both created the CFM, and in a book by Hellström-Westas et al., 2003.

First the measured biparietal EEG signal with a sample frequency of 200 Hz, is filtered with an asymmetrical band pass filter, of bandwidth 2 to 15 Hz, as shown in figure 3.2. The slope of this filter is approximately 12 dB/dec, which is about the inverse of the slope of the neonatal EEG when no rhythmic alpha or beta patterns are present. The filter is designed to whiten the spectrum of the EEG thus compensate for the attenuation of EEG amplitude with increasing frequency.

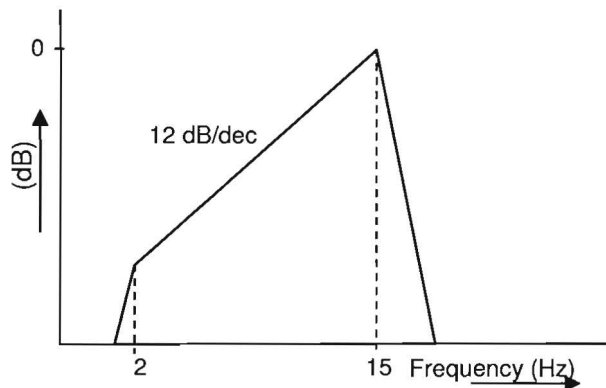


Figure 3.2: A sketch of the asymmetric bandpass filter used to convert EEG into aEEG. The slope of the filter is 12 dB/dec, which is about the inverse of the slope of neonatal EEG when no rhythmic alpha or beta patterns are present.

The following step is rectification and smoothing of the signal. In this step an envelope is created of the EEG signal. The name of the signal leads to believe that amplitude integration is performed to create the aEEG, though this is not described in the original CFM literature

(Maynard, 1969; Prior, 1986). The name aEEG has first been seen in Greisen, 1987, where another kind of CFM device was used. Probably this device calculated the aEEG signal using amplitude integration. The CFM6000 applies peak rectification, and smoothing, like described by Maynard (1969) and Prior (1986). These steps can be approximated by taking the absolute value of the filtered EEG and smoothing it. The resulting aEEG signal has a sample frequency of 200 Hz.

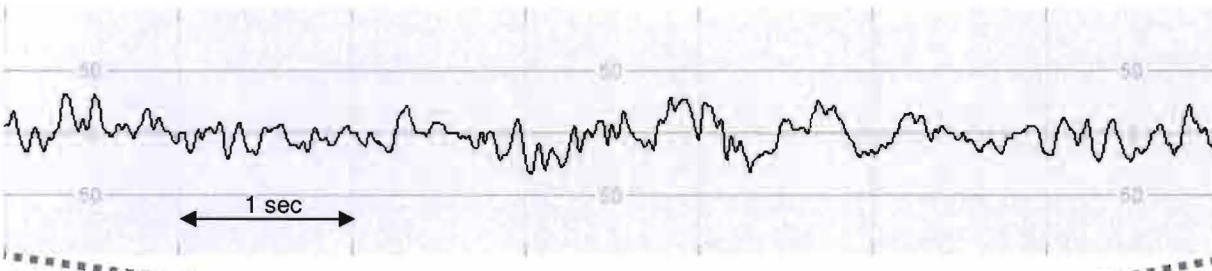
To enhance long-term visualization of the processed signal it is compressed in amplitude and in time. The amplitude is displayed semi-logarithmically; linear below 10 μV and logarithmically above 10 μV . For this semi-logarithmic compression the following formula is used:

$$\begin{aligned} y(t) &= 50x(t) & x \leq 10\mu V \\ y(t) &= 500\log(x(t)) & x > 10\mu V \end{aligned} \qquad \text{Formula 3.1}$$

The values of $y(t)$ are plotted, denoted on the y-axis by the corresponding values of $x(t)$, against time t .

Using this semi-logarithmic display, small amplitudes are displayed clearly while high amplitudes are compressed and can be displayed in the same graph. Small amplitudes are important, since they represent abnormal low electrical cerebral activity. Finally the signal is compressed to a scale of 6 cm/h where 3 hours are displayed on one screen. To achieve this, the signal with a sample frequency of 200 Hz is displayed with a pixel width 0.25 mm, corresponding to 15 seconds. These 15 seconds contain 3000 samples, which are all displayed on the same vertical line. As a result the voltages of the aEEG are displayed in a band. This band will be called ‘amplitude band’. Figure 3.3 shows an example of an EEG and an aEEG signal.

EEG



aEEG

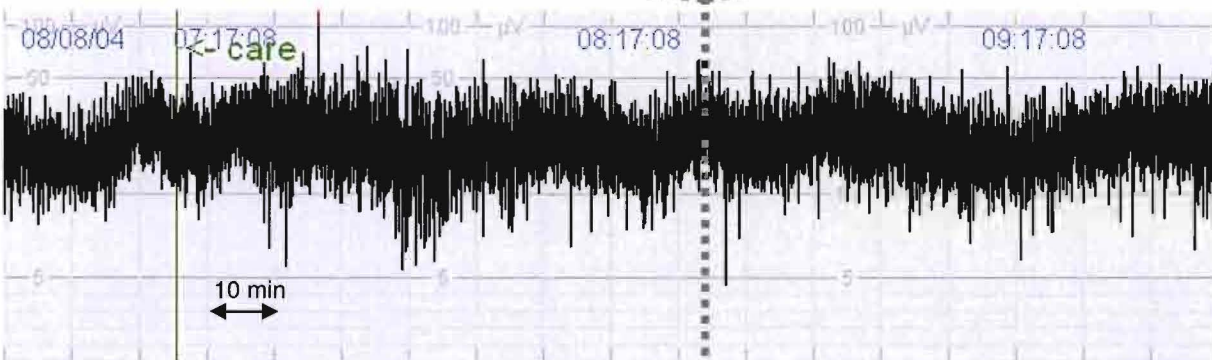


Figure 3.3: An example of an EEG signal of 7 seconds and an aEEG signal of 3 hours. The 7 seconds of the EEG signal correspond to the dotted line in the aEEG signal.

B.2. Current thoughts and practice of CFM

B.2.1 The number of channels

Since the introduction of CFM there has been a debate concerning the use of only 1 channel in CFM measurements. It is known that by measuring only in the parietal area, focal seizures in other parts of the brain will be missed. However, CFM is not a substitution, but an addition to multi-channel EEG. The use of many channels is not suitable for monitoring purposes. But there are monitors on the market for the measurement of 2-channel CFM. For these measurements the electrode positions used are P3-C3 and P4-C4 of the international 10-20 system, see figure in A3.2. The extra advantage of 2-channels, besides measurement in a larger area, is that this gives extra information concerning symmetry in the brain. Asymmetrical EEG and CFM signals are very important diagnostic indicators, especially to detect unilateral hemorrhages or lesions. (de Vries, 2005; Shah, 2006)

B.2.2 The CFM algorithm

The most remarkable thing of the CFM algorithm is that it did not change since 1969, when it has been developed to be used on adult EEG. For the sake of standardization companies chose to use the same algorithm. Although standardization in medicine is very important, it's would be very interesting to analyze the settings of the algorithm and their effect, mainly concerning the settings of the band pass filter.

A research group at the academical hospital of Maastricht investigated these settings for the detection of seizures. Their conclusion was that seizures mainly have a low frequency content, including frequencies below the 2 Hz high pass filter used in CFM. Therefore they suggest using a different filter in the CFM algorithm. (van den Bosch, 2006)

Analyzing the filters used in the current CFM devices, some differences can be observed. Feeding the monitors artificial EEG signals of known frequencies, a gain can be measured for the output of the CFM signal. Comparing the normalized gain of the two monitors used at the MMC Veldhoven, a difference as shown in figure A1 is observed. This difference causes a slight difference in amplitude between the calculated CFM signals of the two monitors.

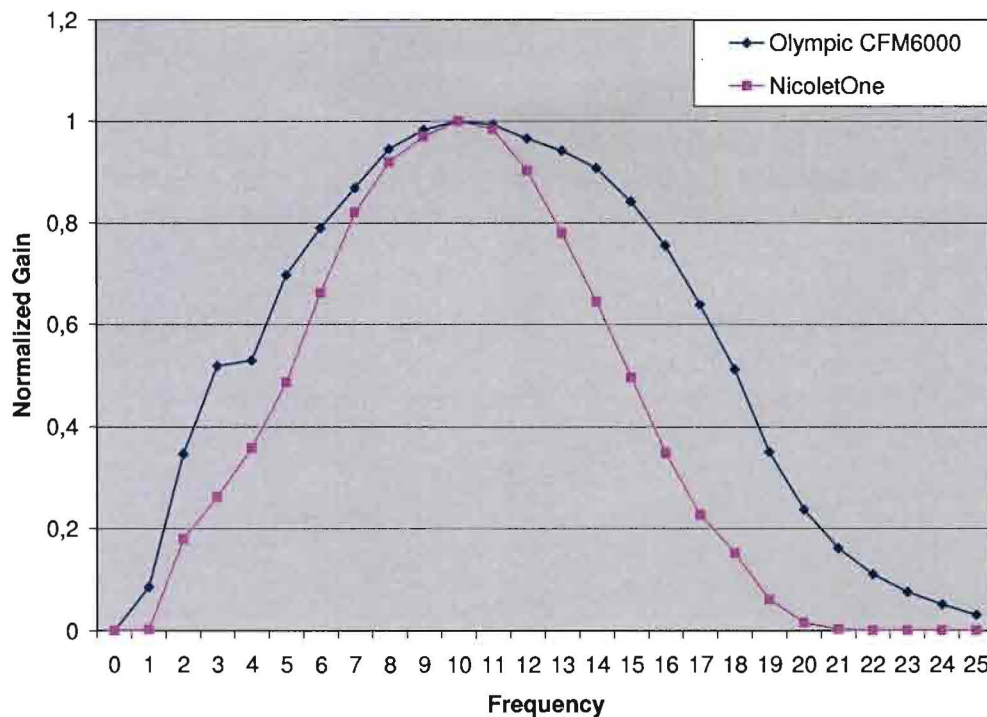


Figure B1. The normalized gain of the CFM algorithm of the Olympic CFM6000 and the NicoletOne of Viasys Healthcare. The signal of the Olympic CFM6000 is from van den Bosch, 2006.

B.3. References

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Appendix C

Purchase advice and implementation CFM

C.1 Purchase advice

There are three CFM devices on the market:

- Olympic CFM6000, from Olympic medical, Seattle. The MMC Veldhoven is already in possession of one of these devices for clinical CFM use. The monitor is used in many hospitals. However the options of this monitor are very limited. Moreover, the company does not seem to keep up with the developments in CFM research, like for example there is no option (and will not be in the near future) for 2-channel measurements.
- NicoletOne, from VIASYS Healthcare. The NICU in Veldhoven owns a NicoletOne for research purposes. The monitor has its origin at the clinical neurophysiology department, which means that there are options for the measurement of more signals, and there are many analysis methods available on the monitor. However the monitor is not as widely used for CFM, and the many options might make the monitor less user-friendly for inexperienced users.
- BRM2 Brain Monitor, from Brainz Instruments. This monitor is not yet available at the MMC Veldhoven. It is not desirable to have three different types of monitors on the department. However, GE Healthcare, from whom we own the clinical monitors at the NICU, has a distribution agreement from Brainz Instruments. An option fusing the CFM signals into the clinical monitor would be interesting, since automatically all signals would be synchronized and saved in the same format. However, in a meeting with a representative of GE healthcare this option did not seem to be one of their targets in the near future.

To investigate the suitability and user-friendliness of the 2 monitors at the NICU Veldhoven, a meeting was organized where 2 nurses compared both monitors on different aspects of user-friendliness. The results of this comparison are shown in table B1. These results were used in the list of demands, together with the demands according to a medical specialist and a resident with a lot of experience concerning the NicoletOne. The purchase advice (shown on the next pages) concluded that the NicoletOne was the best option as a second clinical CFM monitor at the NICU of the MMC. The results described in table B1 were subsequently used to implement the NicoletOne for its use at the NICU, as described in appendix B2.

Table C1. NicoletOne versus Olympic CFM6000 according to 2 nurses

Eigenschap	Olympic CFM6000	NicoletOne
Plaatsing monitor bij couveuse	+	Liever niet op trolley, maar op plank naast GE monitor te plaatsen
Gebruik touch screen/toetsbord	Pakt niet gemakkelijk. Reactie soms traag	Toetsenbord neemt meer plaats in beslag, liever bij monitor plaatsen en touch screen gebruiken.
Aantal elektrodes	3 elektrodes	4 elektrodes bij 1-kanaals meting. Enkele extra elektrodes maakt niet veel uit
Aansluiting elektrodes	Gemakkelijk, voorversterker is overzichtelijk.	Voorversterker niet overzichtelijk. Wel wordt er duidelijk weergegeven wanneer ze niet goed zijn ingeplugd.
Voorversterker in couveuse	Voorversterker kan in couveuse.	Voorversterker buiten de couveuse. Elektrodesnoeren moeten lang genoeg zijn, ook voor bewegingsvrijheid.
Starten meting	+	+
Invoering patientgegevens	Kan niet van tevoren ingegeven, wordt daardoor wel eens vergeten.	Van tevoren makkelijk in te voeren. Naderhand lastiger.
Controle impedantie vóór meting	+	+
Controle impedantie tijdens meting	+	+
Markeren signaal	Niet gemakkelijk, veel knoppen nodig	Heel gebruikersvriendelijk
Interpreteren signaal	+	+
Bekijken EEG	Naderhand wordt CFM scherm niet automatisch geactualiseerd, is risico.	Review heeft geen automatische scroll functie. Wel blijft actuele beeld zichtbaar tijdens review.
Afsluiten meting	Kan heel gemakkelijk	Moet correct gebeuren, zoals computer
Kans op fouten	Het actuele scherm is niet altijd in beeld, erg gevaarlijk!!!	Er moet een beveiliging op sommige knoppen komen die niet zomaar gebruikt mogen worden. Verder personeel goed leren dat het een computer is.
Mogelijkheden opslaan	Niet op netwerk mogelijk, branden op cd	Op netwerk
Analyse signalen	Niet mogelijk	Wel mogelijk
Hulp van bedrijf	Matig	+
Opmerking: De NicoletOne zal even wennen zijn maar heeft een aantal grote voordelen: ➤ Opslaan data op netwerk ipv cd's ➤ Makkelijker markeren ➤ Actuele scherm blijft altijd in beeld. ➤ Mogelijkheden meerdere kanalen tegelijk meten ➤ Mogelijk tegelijk ergens anders uitlezen (vooral nuttig in nieuwe VMK centrum) ➤ Meerdere analyse mogelijkheden.		

MEMO

Aan: Paul Rieter en Pieter Wijn
Kopie aan: Cees Bouter
Van: Charlotte Lommen en Chris Peters
Datum: 14-11-2006
Betreft: CFM apparaat NICU

Doelstelling

Deze memo betreft het advies van de afdeling medische technologie voor de aanschaf van een CFM monitor voor de NICU. Sinds juni 2004 wordt er op de NICU gebruik gemaakt van een klinisch CFM apparaat. Het apparaat wordt veelvuldig gebruikt en kan niet voorzien in de behoefte die op de afdeling bestaat. Om deze reden is de aanschaf van een tweede CFM apparaat voor klinisch gebruik aangevraagd. Deze aanvraag is goedgekeurd door de investeringscommissie.

Huidige situatie

Voor klinisch gebruik wordt het relatief eenvoudige CFM apparaat, de CFM6000 van Olympic Medical, ingezet. Tevens wordt er sinds september 2005 een uitgebreider CFM/EEG apparaat gebruikt voor wetenschappelijk onderzoek op de NICU. Dit apparaat is de NicoletOne van Viasys Healthcare. De ervaringen met dit uitgebreidere apparaat hebben tot het besef geleid dat de mogelijkheden van de Olympic CFM6000 erg beperkt zijn. Om deze reden is besloten om niet zonder meer een tweede Olympic CFM6000 aan te schaffen, maar te onderzoeken welke van de CFM apparaten die momenteel op de markt zijn in de huidige situatie de beste oplossing biedt.

Pakket van eisen

De belangrijkste eisen die aan het systeem gesteld worden zijn:

- Het gebruikte CFM-algoritme moet een algemeen geaccepteerd algoritme zijn
- Het systeem moet mobiel zijn en bij voorkeur te plaatsen zijn op een plank naast de bewakingsmonitor.
- Het systeem moet zeer gebruiksvriendelijk zijn voor verplegend personeel van de NICU en geen specifieke EEG kennis vereisen.
- Vanuit het oogpunt van standaardisatie verdient een van de systemen die reeds in gebruik zijn op de NICU de voorkeur.
- Het systeem moet op het netwerk aangesloten kunnen worden, zodat data eenvoudig op het netwerk opgeslagen kan worden.
- De ruwe data moeten gebruikt en bewerkt kunnen worden, bij voorkeur in EDF formaat.
- De mogelijkheid moet bestaan om zowel een 1-kanaals als een 2-kanaals meting te kunnen uitvoeren
- Bij voorkeur moet er een zoom-optie zijn voor het EEG signaal en moet frequentieanalyse mogelijk zijn.
- De voorversterker, dan wel het vooropzetblok van het systeem moet veilig en gemakkelijk in of aan de (warme en vochtige) couveuse geplaatst/bevestigd kunnen worden.
- Het systeem moet aansluiten op de MMC ICT standaard.

Overzicht beschikbare systemen

Naast de reeds in gebruik zijnde Olympic CFM6000 en de Viasys NicoletOne is ook de Brainz BRM2 monitor meegenomen. Als tweekanaals monitor overkomt de Brainz BRM2 monitor de grootste tekortkoming van de Olympic CFM6000. Sinds kort wordt de Brainz monitor door GE Health Care op de Nederlandse markt gezet. Onderstaande tabel geeft een overzicht van de beoordeling van de drie systemen. De beoordeling is gemaakt op basis van de ervaringen op de NICU, de contacten met de betreffende leveranciers en de ervaringen van experts elders.

	Olympic CFM6000	BRM2 Brainz monitor	Viasys NicoletOne
CFM algoritme	+	+	+
Mobiel	+	+	+
Gebruiksvriendelijk	+	+	+/-
Bekend bij verpleging	+	-	+
Netwerkaansluiting	-	-	+
Ruwe data	ascii	EDF	EDF
Aantal kanalen	1-kanaals	2-kanaals	1, 2, en meer-kanaals mogelijk
Zoom-optie EEG	-	+	+
Frequentieanalyse	-	-	+
Voorversterker in couveuse	+	?	- / wel aan couveuse
<u>Listprijs (incl. BTW)</u>	<u>€ 21.420</u>	<u>€ 26.180</u>	<u>€ 30.524</u>
Onvoorziene kosten (10%)	€ 2.142	€ 2.618	€ 3.052
<u>Exploitatiekosten</u>			
Onderhoudskosten (10%)	€ 2.142	€ 2.618	€ 3.052
Elektrodes	€ 1.000	€ 1.000	€ 1.000
Dataopslag CFM signalen (zonder backup)			
- Eerste 2 jaar (alle signalen)			€ 320
- Na 2 jaar (beperkte opslag)			€ 80

Opmerking NicoletOne betreffende VMK centrum

Binnen het VMK centrum zal het gewenst zijn de CFM apparatuur tijdens de meting op het netwerk aan te sluiten, zodat alarmsignalen en de EEG signalen doorgestuurd kunnen worden naar een centrale post. Hiervoor is het noodzakelijk dat er bij ieder bed een dataaansluitpunt wordt geïnstalleerd.

Conclusie

Ondanks zijn gebruiksvriendelijkheid en vertrouwdheid bij het verplegend personeel op de NICU heeft de Olympic CFM6000 te veel beperkingen. De BRM2 Brainz monitor is weliswaar een tweekanaals monitor, maar wordt verder gekarakteriseerd door een groot aantal van dezelfde beperkingen als het toestel van Olympic. Tevens is de introductie van een derde type apparaat niet gewenst.

De NicoletOne van Viasys Healthcare is een monitor met veel mogelijkheden, zoals twee- en meerkanaals metingen en uitgebreide signaalanalyse. De monitor is eenvoudig op te nemen in het reeds bestaande Viasys EEG netwerk op de NICU en KNF afdeling en voor analyse kan er gebruik gemaakt worden van de uitwerkstations die reeds aanwezig zijn op deze afdelingen. Mits er een data-aansluitpunt beschikbaar is in de nabijheid van de couveuse kunnen metingen "live" op een centrale plek bekeken worden. Dit sluit naadloos aan op de visie op het toekomstige VMK centrum. De enige kanttekening is dat de NicoletOne juist door zijn vele mogelijkheden minder gebruiksvriendelijk is. Wanneer er adequate instructie gegeven wordt aan de gebruikers zal dit niet tot problemen leiden in de klinische praktijk.

Advies

De NicoletOne van Viasys Healthcare is het meest geschikte apparaat om goede CFM functionaliteit op de NICU te kunnen bieden. De meerwaarde van dit apparaat voor de klinische praktijk weegt volledig op tegen de meerprijs van dit systeem.

C.2 Optimization NicOne for use at the NICU

As concluded from table C1, there were some items in the NicoletOne that needed improvement to optimize its use as CFM device fro the NICU.

Stand instead of trolley

In its standard form the NicoletOne is fixed to a trolley. However, on a trolley the monitor needs to be placed somewhere around the incubator. Since the monitor is used for days, it is not desirable to have a trolley around it. The monitor can also be fixed to a stand. In that case the monitor can be placed on a shelf, next to clinical monitor. This is also the routine for the Olympic CFM6000.

Tools to make it touch screen-used

Placing the monitor on a shelf about 1.7 meters above the ground, makes it inconvenient to use the keyboard and mouse. The monitor can also be used as a touch screen, except for the input of the patient name, date of birth etc. This registration of the patient can be performed before the start of the measurement. At the back of the monitor two small racks were fixed, where the keyboard, the mouse and the pre-amplifier could be stored.

For optimal use of the monitor, it was added to the protocol that the patient needed to be registered before the start of the measurement. After that, the keyboard and mouse are stored at the back of the monitor, which makes it easy for the nurse to place the monitor on top of the shelf. During the measurement only the touch screen needs to be used.

User-friendliness of the screen

All unnecessary buttons on the start-up screen and later in the measurement program were removed. For the measurement program the placement of the buttons was chosen to make it easy to use the touch screen. In this screen only buttons for starting the measurement, impedance check, review option and closing of the measurement are kept in the monitor. Other options can only be reached through scroll-down menus.

Log-book NicoletOne and CFM team

A log-book was introduced where medical personnel could write down any problems that they might encounter with the new NicoletOne monitor. In the meantime a team had been formed of 3 nurses with special interest in CFM. These nurses were specially trained to answer questions at the ward.

Instruction and protocol for the use of NicoletOne

Instructions were given to introduce the NicoletOne. Also a protocol has been written with clear instructions on how to use it, see appendix F2, which is attached to the cart on which the monitor is stored.

Appendix D

User protocols CFM devices

This appendix gives the user protocols for the Olympic CFM6000, and the NicoletOne monitor of Viasys Healthcare, inc.

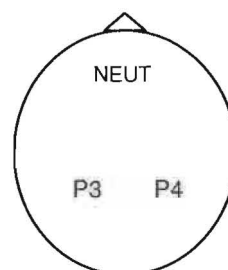
D.1 User protocol Olympic CFM6000

Gebruiksprotocol Olympic CFM

Aan/uit knop zit op de achterkant van de monitor.

1. Start de monitor op.
2. Sluit de elektrodes aan volgens protocol. Lokatie elektrodes:

De neutrale elektrode op het voorhoofd.
P3 links, P4 rechts zoals weergegeven in de tekening.



3. Klik op registreren
4. Controleer de impedantie op het scherm.

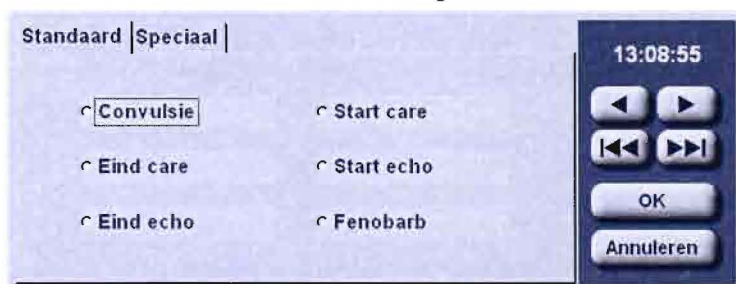
In het onderste scherm wordt de impedantie weergegeven van elektrodes P3 en P4. Deze impedantie moet onder de 10 kOhm liggen. Ligt de impedantie boven 10 kOhm, controleer dan de aansluiting van de elektrodes op de voorversterker en of het kindje op de elektrodes ligt. Controleer het contact van de elektrodes met de huid, vervang zonodig de elektrodes.

5. Klik op "Patiënt" en vul in: patiëntnaam en geboortedatum.

Nu pas is de start van de meting afgerond.

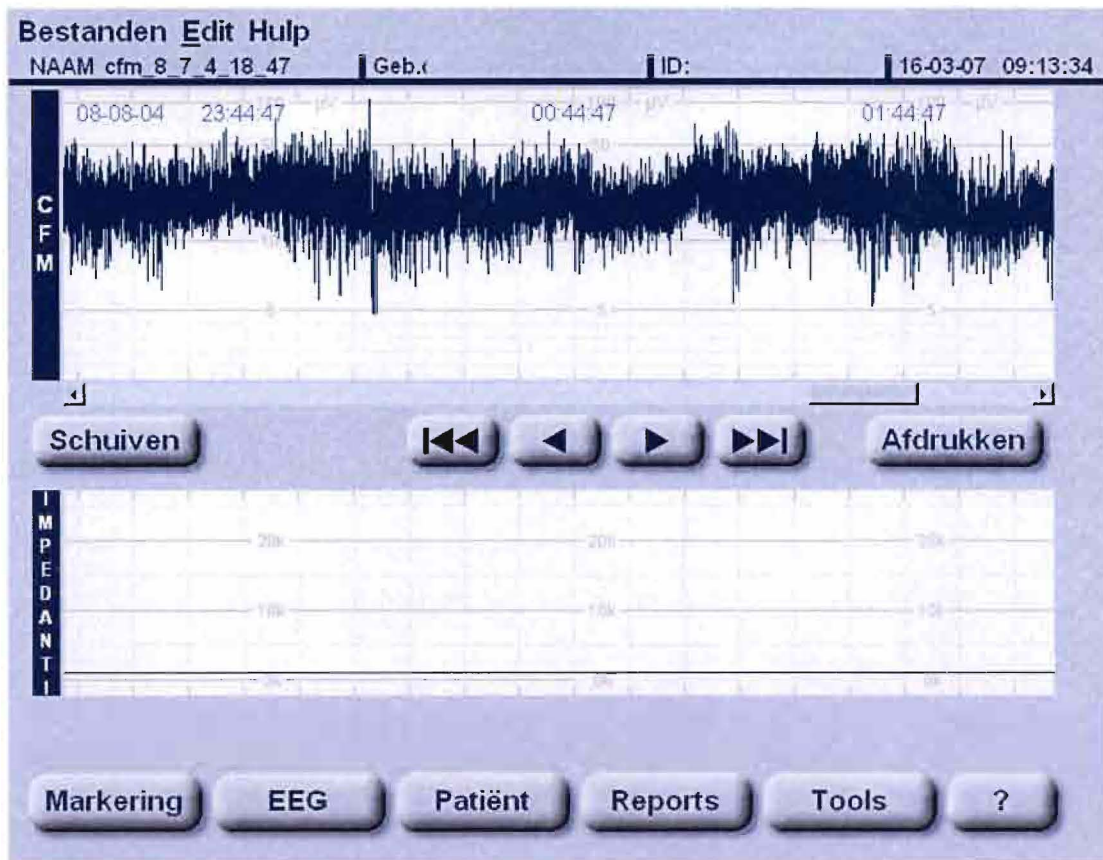
Tijdens de meting:

- **Te hoge impedantie:** de impedantie hoort onder de 10 kOhm te blijven. Bij een impedantie boven de 20 kOhm wordt een alarm gegeven. Let op: een slecht contact van de neutrale elektrode geeft geen alarm!! De kwaliteit van de meting is dan ook nog redelijk. Indien nodig controleer en herstel contact van de elektrodes zoals hierboven beschreven.
- **Markeren:** klik op "Markering" onderaan in het scherm, zodat er "Mark aan" staat. Klik vervolgens op de periode in het CFM scherm waar de marker hoort te staan; is dit aan het eind van de meting, dan kun je met behulp van de pijltjestoets in het marker scherm (zie hieronder) de marker helemaal naar het eind van de meting verschuiven.



Kies een standaard marker, of maak een "Speciaal" marker waarbij je met 11 tekens uit het toetsenbord op het scherm een marker kunt omschrijven. Let op: bij een langdurige gebeurtenis zoals verzorging (care) is een marker aan het begin en aan het eind van de gebeurtenis nodig!

- **Terugkijken in CFM:** je kunt in CFM terugkijken met behulp van de pijltjestoetsen onder het CFM scherm, of met behulp van de scrollbar.
- **EEG bekijken:** klik EEG. In het scherm van de impedantie verschijnt nu een EEG signaal (7 seconden per scherm). Hier kun je in scrollen met behulp van de pijltjes-toetsen. Door het knopje Schuiven aan te klikken, en vervolgens op de pijltjes toetsen te klikken, zal het EEG signaal automatisch verder of terug scrollen.
- **Naar einde van meting:** zorg na het terugkijken in het CFM of bij het bekijken van EEG dat het scherm altijd weer teruggaat naar de huidige meting. Doe dit door op de pijltjestoets van het CFM signaal te klikken, net zolang totdat de scrollbar van CFM helemaal op het eind staat.
- **Afdrukken:** door op afdrukken te klikken kun je het signaal wat op dat moment in beeld is afdrukken.
- **Pauze:** klik op "Registratie aan", er verschijnt: "Registreren". Klik wederom op Registreren om de meting te hervatten. Bij de vraag "Nieuwe patiënt starten of aan huidige meting toevoegen?", klik op "Toevoegen".
- **Lengte meting:** een meting mag niet langer zijn dan 5 dagen!! Mocht een kindje langer dan 5 dagen gemeten worden, start dan een nieuwe registratie.
- **Einde meting:** klik op "Patiënt" en "Afsluiten patiënt". Vervolgens kun je de monitor uitzetten met behulp van de knop aan de achterkant van de monitor. Verwijder elektrodes volgens protocol. Reinig de kabel/versterker met 70% alcohol.



D.2 User protocol NicoletOne

Gebruiksprotocol NicOne

NicOne is een computer, dus start op en sluit af als een computer!!!
Aan/uit knop zit links onderaan aan de achterkant van de monitor.

1. Start NicOne op. Dubbelklik op "Monitor", in het midden van het scherm. Heb even geduld, het duurt even voordat deze is opgestart!
2. Kies Protocol NICU CFM voor een 1-kanaals meting, en NICU CFM 2kanaals voor een 2-kanaals meting (links-rechts)
3. Vul in: Patiënt ID, patiëntnaam en geboortedatum in.
4. Sluit de elektrodes aan volgens protocol. Lokatie elektrodes:

De referentie (REF) en neutrale (NEUT) elektrodes, beide op het voorhoofd.

Bij 1-kanaals meting:

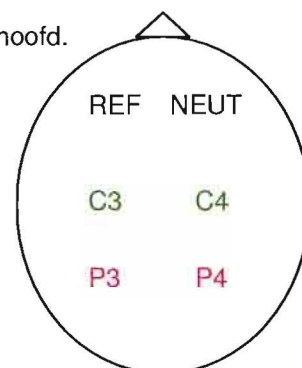
P3 links, gaat naar nummer 7 of voorversterker

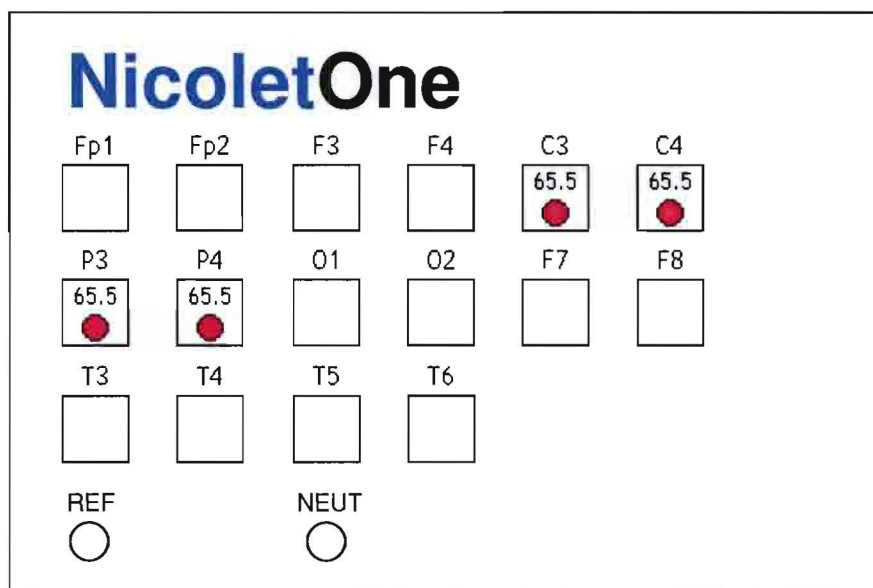
P4 rechts, gaat naar nummer 8 op voorversterker

Bij een 2-kanaals meting: P3, P4 zoals hierboven aansluiten, én

C3 iets naar voor, links, gaat naar nummer 5 op voorversterker

C4 iets naar voor, rechts, gaat naar nummer 6 op voorversterker





5. Controleer de impedantie

Op het scherm wordt de impedantie weergegeven van iedere elektrode, zoals hierboven weergegeven. De impedantie moet onder de 10 kOhm liggen, (groen weergegeven). Licht de impedantie boven 10 kOhm, is dit op het scherm in rood aangegeven. Zijn beide elektroden met hoge impedantie, dan kan het ook zijn dat de REF elektrode niet goed zit.

Na invullen patientgegevens en bij goede impedanties:

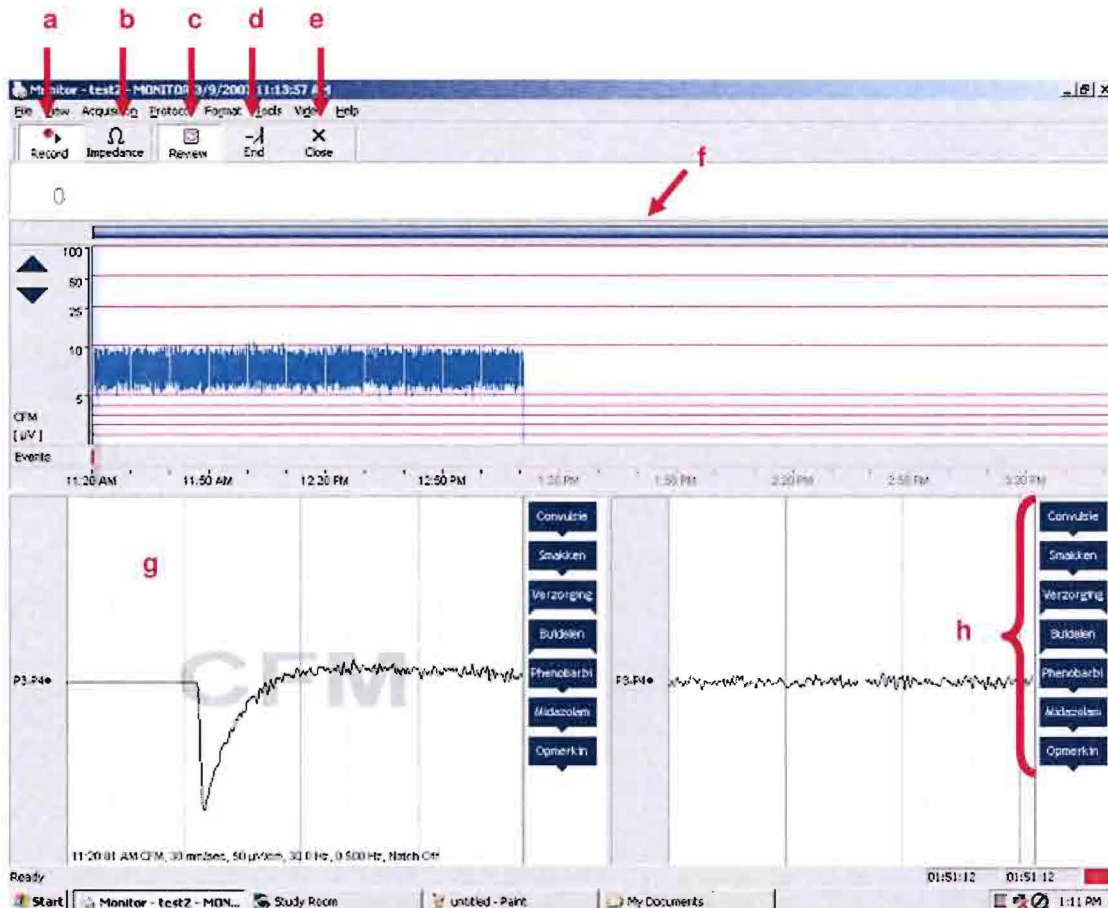
6. Klik op **Start** (start meting).

Het bovenste scherm geeft het CFM signaal weer, het onderste scherm het EEG signaal.

Tijdens de meting:

- **Bad electrode event** = te hoge **impedantie** van (één van de) elektrodes. Dit wordt weergegeven door een waarschuwingsvenster, midden op het scherm (geen geluidsalarm). Klik in dat geval op ok, en vervolgens op Impedance (b). Nu krijg je wederom het scherm met de impedanties per elektrode. Herstel de elektrodes die niet goed zitten.
- **Markeren**: gebruik de markers rechtsonder in het scherm (h). Hier hoeft je maar 1 keer op te klikken. Bij verzorging en buidelen blijft de marker doorlopen, totdat je er nog een keer op klikt, aan het einde van de verzorging of het buidelen. Weergave markers: in het EEG bovenaan het signaal. Verplaatsen markers: dit kan in de review mode.
- **Terugkijken in CFM**: je kunt in CFM terugkijken met behulp van de scroll-bar boven het CFM signaal. Zorg dat uiteindelijk weer het einde van de meting in beeld is!
- **Terugkijken in EEG**: klik de knop Review (c) aan. Er komt nu naast het huidige EEG beeld, een EEG beeld van eerder in de meting aan (g). In het CFM staat een donkere verticale streep op het tijdstip van de EEG weergave. Je kunt op het gewenste tijdstip in CFM klikken, of links of rechts in het review-EEG signaal klikken om respectievelijk een scherm eerder of later weer te laten geven. Ook kun je door het signaal scrollen met behulp van de pijltjes-toets van het toetsenbord.
- **Naar einde van meting**: klik op End (d)

- **Exporteren signalen:** Hiervoor heb je het toetsenbord nodig, en de USB stick, die rechts in de monitor moet zitten. zorg dat het scherm in beeld is dat je wilt exporteren. Klik op Print Screen (rechts bovenaan op toetsenbord). Open Paint (start -> programma's -> assechiores -> paint). Plakken (Ctrl + c). Vervolgens de afbeelding in paint, opslaan als: ga naar ... opslaan onder gewenste naam. Het signaal staat nu op de USB stick.
- **Pauze:** klik op Record (a), in het EEG scherm verschijnt "not recording". Klik wederom op Record (a) om de meting te hervatten.
- **Afsluiten meting:** klik op Close (e). Verwijder de elektrodes volgens protocol. Sluit de computer netjes af!!



Appendix E

Electrodes

E.1 Characteristics of biopotential electrodes

General characteristics

Biopotential electrodes have the function of transducer, conducting current across the interface between the body, where current is carried by ions, and a measuring circuit where it is carried by electrons. This can be represented as shown in figure E1, where in the ionic electrolyte the cations and anions carry the current and in the electrode of the electrons carry the current. Crossing of the current can be represented with the following equation:

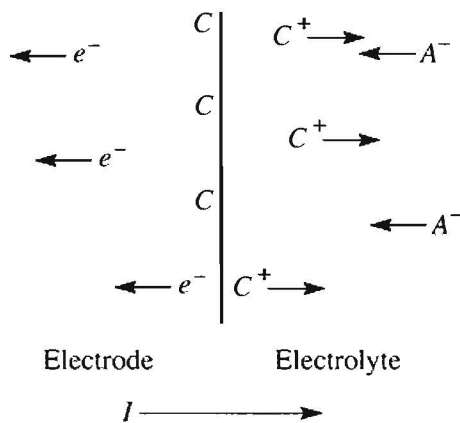
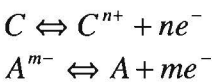


Figure E1: Electrode-electrolyte interface, the electrode consists of metal atoms C , the electrolyte consists of anions A^{-} and cations C^{+} . (Webster, 1998)

When a metal comes in contact with a solution, the reactions above will start until an equilibrium has been reached. This creates a potential difference over the interface, called the half-cell potential. The half-cell potential depends on the type of metal used. The half-cell potential cannot be measured as an absolute value, but is compared to the reference electrode. As a standard reference electrode the hydrogen electrode is used. Table E1 lists some values of half-cell potentials for different types of metals. These half-cell potentials are given by standard conditions, and will change with these conditions according to the Nernst equation:

$$E = E^0 + \frac{RT}{nF} \ln(a_{c^{n+}})$$

E = half-cell potential

E^0 = standard half-cell potential

R = universal gas constant = 8,31 J/(mol·K)

T = absolute temperature (Kelvin)

F = Faraday constant = 96,500 C·mole⁻¹·valence

n = valence of electrode material

$a_{c^{n+}}$ = activity of cation C^{n+}

Table E1: Half-cell potentials for common electrode materials at 25 °C. (Webster, 1998)

Metal and reaction	Half-cell potential (V)
$\text{Ni} \rightarrow \text{Ni}^{2+} + 2\text{e}^-$	-0.230
$\text{H}_2 \rightarrow 2\text{H}^+ + 2\text{e}^-$	0
$\text{Ag} + \text{Cl}^- \rightarrow \text{AgCl} + \text{e}^-$	+0.223
$\text{Cu} \rightarrow \text{Cu}^{2+} + 2\text{e}^-$	+0.340
$\text{Cu} \rightarrow \text{Cu}^+ + \text{e}^-$	+0.522
$\text{Ag} \rightarrow \text{Ag}^+ + \text{e}^-$	+0.799
$\text{Au} \rightarrow \text{Au}^{3+} + 3\text{e}^-$	+1.420
$\text{Au} \rightarrow \text{Au}^+ + \text{e}^-$	+1.680

The half-cell potential exists when there is no current running through the interface. When there is a current, a different potential is observed. The over potential is the difference between the observed potential and the half-cell potential. It is mainly caused by three mechanisms:

- the ohmic overpotential: this potential difference is caused by a voltage drop along the path of the current in the electrolyte caused by the resistance of the electrolyte. The voltage depends on the current, but also the resistance can be dependent on the current.
- The concentration overpotential: when a current runs through the interface, the equilibrium of the equations will change. This will cause the potential difference over the interface to change.
- Activation overpotential: the oxidation of metal atoms as well as the reduction, represented by equation 1, both use energy. These reactions may not use the same amount of energy. Because of the currents either the oxidation or reduction reaction predominates, this causes a difference in energy which appears as a difference in voltage.

Polarizable and nonpolarizable electrodes

Biopotential electrodes can be divided into polarizable electrodes and nonpolarizable electrodes. Perfectly polarizable electrodes behave as a capacitor, where current in the interface is displaced, no actual current crosses the interface. Perfectly nonpolarizable electrodes are electrodes where current passes freely across the interface. In this case there is no overpotential present. No perfectly polarizable or nonpolarizable electrodes exist. However noble electrodes, like platinum, come close to behave like perfectly polarizable electrodes. These metals are very inert, which means that they do not easily oxidize or

dissolve. These electrodes show a strong capacitive effect, due to concentration overpotential. A silver/silver chloride electrode approaches the characteristics of a perfectly nonpolarizable electrode. The electrode has a silver core and is coated with a layer of silver chloride, which is only slightly soluble in water and will therefore remain stable.

Electrode-skin interface behavior

The electrical characteristics of the electrode-electrode gel-skin interface can be modeled as shown in figure E2. Characteristics of the electrode using sinusoidal inputs have both resistive and reactive components. A good model for this behavior is a model with a resistance (R_d) and a condensator (C_d) parallel to each other; this model does not have infinite impedance at very low frequencies like in a series model. This will be connected in series to a potential difference (E_{he}) as the half-cell potential, and a resistance (R_s) associated with the resistance of the interface effects and of the conductive gel. The interface of the conductive gel with the skin will give an extra potential difference (E_{se}), since the outer layer of the epidermis can be considered as a semipermeable membrane. This potential difference is given by the Nernst equation:

$$E = -\frac{RT}{nF} \ln\left(\frac{a_1}{a_2}\right)$$

E = potential difference across semipermeable membrane
 a_1, a_2 = the activities of ions on each side of the membrane

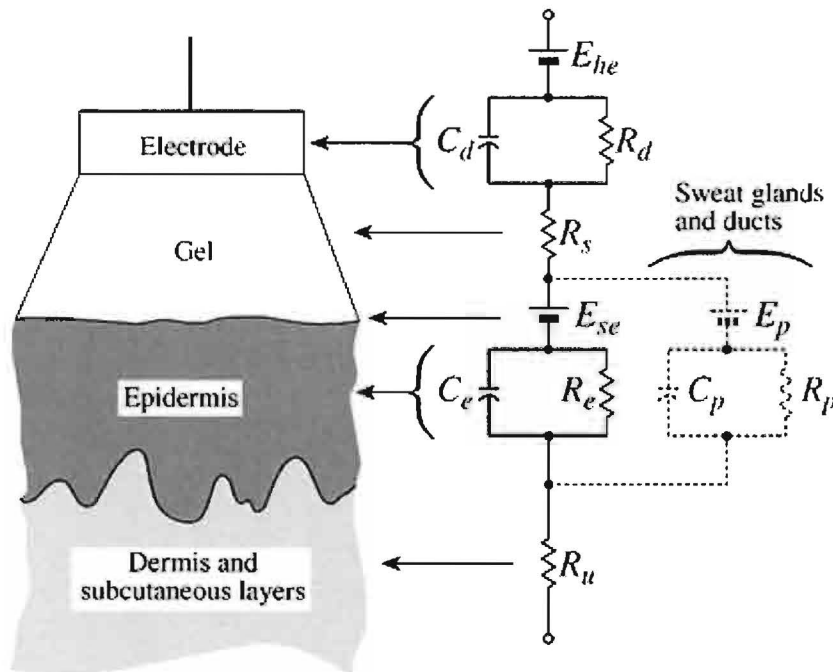


Figure E2: Model of biopotential electrode, electrode gel and skin. (ref: Webster, 1998)

The epidermis can also be modeled as a parallel circuit of a resistors (R_e) and a capacitor (C_e). The contribution of sweat glands and ducts can be modeled using extra components, however, for EEG these components can be neglected. The $R_e C_e$ circuit is the electric impedance of the epidermis. This impedance for 1 cm² contact with dry, intact adult skin may range from 15 kΩ to 1 MΩ. The impedance is highly dependent of:

- the frequency of the AC current, with a higher impedance for lower frequencies
- surface area of contact, with higher impedance for smaller contact areas
- dryness and intactness of the skin, where impedance may drop to 1% for wet or broken skin

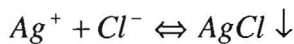
The skin of the newborn, especially the premature, is still very thin. However, after vaginal birth the skin may be oily which will increase the impedance again. A good cleaning of the skin, scrubbing of the epidermis or making a small scratch in the upper layer of the epidermis may hugely decrease the impedance.

Motion of the electrode with respect to the skin will disturb the potential differences at the electrode-gel interface and at the gel-epidermis interface. This is caused by the mechanical disturbance of the charge distribution around the interface, and resolved when the equilibrium is reestablished. Since in nonpolarizable electrodes the current passes more freely, whereas in polarizable electrodes behave as a capacitor, these mechanical disturbances around the electrode-gel interface have the least effect in nonpolarizable electrodes. They are however still effected by the disturbances around the gel-epidermis interface. This artifact can also be reduced by scrubbing the skin, or making a small scratch in the upper layer of the epidermis. It should however be noted that the conductive gel should not have an irritating effect on the skin. (Webster, 1998)

E.2 Different materials for electrodes and gels

Ag/AgCl electrodes

The silver/silver chloride (Ag/AgCl) electrode is a much used electrode with good characteristics for EEG measurements. It approaches the characteristics of a perfectly nonpolarizable electrode, where current passes easily over the electrolyte-electrode interface, and motion artifacts over that interface have minimum effect. The electrodes are easily fabricated. The chemical reactions involved in the current conductance are the oxidation of silver atoms, immediately followed by the formation of the ionic compound AgCl:



Biologic fluids, as well as most conductive gels, contain relatively high concentrations of Cl⁻ ions.

There are two types of Ag/AgCl electrodes. Both contain a Ag metal that is coated with AgCl. In the first type the coating is plain AgCl, whereas the second type has a sintered AgCl coating, where AgCl and Ag molecules are within a die. The sintered electrodes are more expensive, but have a greater stability over time and a greater endurance. (Webster)

Other types of electrode metals

Since the impedance is inversely proportional to the frequency, the direct current resistance is the highest impedance that an electrode-electrolyte interface can attain. Therefore Geddes et al (Geddes, 2001) compared this so-called Faradic resistance for different types of electrodes, using 1 cm² electrodes and a 0.9% saline electrolyte. The results are summarized in table E2.

In a study by Tallgren et al. (2005) several characteristics of electrodes for the measurement of low frequent EEG signals have been studied. Concerning the different types of metals the results are summarized in table E3. For CFM measurements no DC recording is necessary.

It can be concluded that:

- Chlorided silver has the lowest Faradic resistance and the best characteristics overall. This type of electrode is according to both studies by far the best, sintered or not.
- Tin has a reasonable Faradic resistance, however, the study of Tallgren showed poor results for the overall characteristics.
- Carbon, which is sometimes used as a radiolucent electrode, has a very high Faradic resistance.

Table E2: Faradic resistance for different electrode materials at zero current, using 0.9% saline electrolyte. (ref: Geddes, 2001)

Electrode material	Faradic resistance (Ω/cm^2)
Silver (bare)	382
Silver (chlorided)	31
Tin (electrolytically cleaned)	922
Tin (chlorided)	444
Nickel silver	765
Copper (bare)	550
Copper (electrolytically cleaned)	297
Carbon	1770

Table E3: Properties of different types of electrodes for low-frequency EEG, using chloride containing gel. (ref: Tallgren, 2005)

Electrode	Offset voltage, resistance and polarization	Rate of drift	Noise level	Suitability for DC-coupled recording	Suitability for long time-constant AC-coupled recording
Sintered Ag/AgCl	Very low	Very low	Low	Excellent	Excellent
Disposable Ag/AgCl	Low	Very low	Low	Good	Excellent
Silver	Variable	Variable	Low	Poor	Good
Gold-plated silver	Variable	Variable	Low	Poor	Good
Platinum	Very high	n.a.	Low	Poor	Good
Stainless steel	Very high	n.a.	Medium	Poor	Medium
Tin	High	High	High	Poor	Poor

Different types of gel

In the study of Tallgren et. al. (2005) nine different types of gels were tested. Two gels contained very low (15 mM) to no chloride, and showed very poor stability of the EEG measurement. The remaining seven gels contained high concentrations of Cl^- and showed high stability of the measurement. This shows that high Cl^- concentrations are necessary for stable measurements.

E.3 Types of electrodes

Cup electrodes

Often used for EEG measurements are cup electrodes. The cup electrodes can be made of Tin, Copper, Gold, but most common are Ag/AgCl electrodes, either sintered or not. These electrodes are reusable cups that need to be attached to the skin with either adhesive tape, or a gauze that is glued to the skin using collodion (figure E3). Between the cup electrode and the skin a conductive gel is used. As mentioned earlier, the skin is also scrubbed or scratched to create a low impedance and minimize motion artifacts. The placement of the electrodes is time consuming, and generally performed by assistants specialized in performing EEG measurements.

CFM measurements are often started in acute situations, where besides CFM many procedures need to be performed. The placement of cup electrodes by medical personnel of the NICU that is not specialized in EEG measurements is a time consuming and difficult procedure. Therefore these cup electrodes are not suitable for CFM measurements.

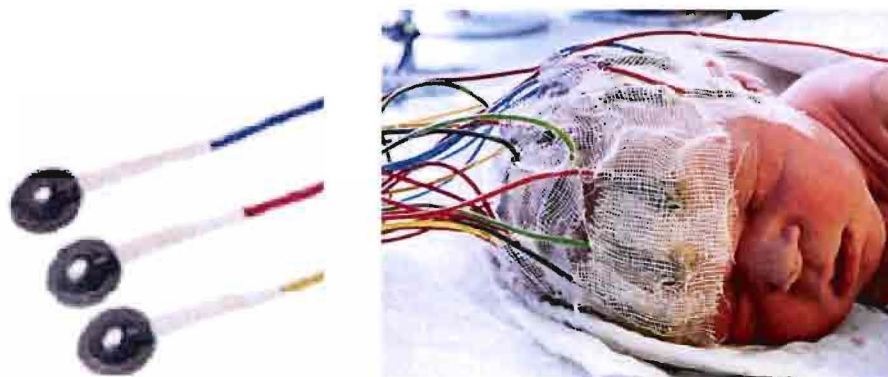


Figure E3: A) Cup electrodes; B) Cup electrodes placed on the head of a newborn using gauzes and collodion.

Subcutaneous needle electrodes

Mostly used for CFM measurements are subcutaneous stainless steel needle electrodes (figure E4). Before placement of the electrodes the skin needs to be disinfected with a chlorhexidine solution. The needle electrodes need to be fixed using adhesive tape. To minimize discomfort of the newborn, a painkilling gel may be used, called EMLA.

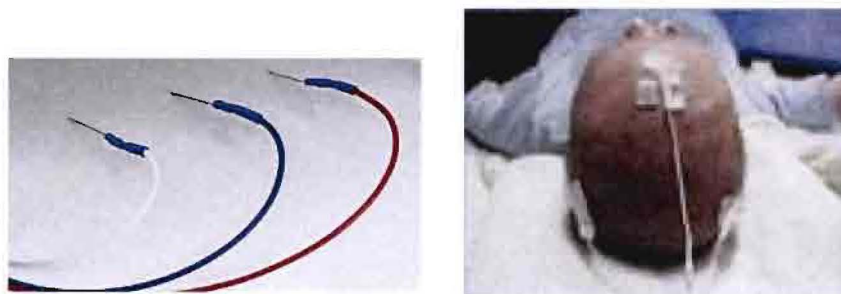


Figure E4: A) Needle electrodes; B) Placement of needle electrodes for CFM measurements.

The reason to use this type of electrodes is that they are easily placed on the head of the newborn, and secondly the impedance is very low, since they are placed subcutaneous, i.e. underneath the epidermis. However, these measurements are invasive which is inconvenient for the newborn and for the parents. Besides that, the needle electrodes detach from the skin very easily when the child is cared for or cuddled by the parents.

Adhesive electrodes

As an alternative to the needle electrodes, I have focused on adhesive electrodes. These electrodes are generally used for ECG measurements, but can be used for CFM measurements as well. The adhesive electrodes have a conductive and adhesive tape that sticks to the skin, and they are therefore not reusable. Based on the studies for electrode metal, only Ag/AgCl electrodes are used. For the adhesives there are basically three characteristics that need to be taken into account for their use for CFM:

- Long-term use
- Usability in incubator
- Skin friendly

There are mainly three types of adhesive paste on these electrodes: soft cloth, foam and clear gel. Their characteristics are summarized in table C4. The soft cloth electrodes are widely used in child care, since they are skin friendly, even for the delicate skin of prematures. However, in the warm and humid incubator they absorb moisture, and therefore will detach after 1 to 24 hours. The foam electrodes are indifferent to high humidity; however, they suck the skin to the tape, and are therefore not friendly for the delicate skin of the premature and newborn. The clear gel electrodes have a long-term usability, even in the warm and humid incubator and they are skin friendly.

Table E4: *Basic characteristics of adhesive tape.*

	Soft cloth	Foam	Clear gel
Longterm use (> 48h)	+	+	+
Use in incubator (90% humidity)	-	+	+
Skin friendly (for prematures)	+	-	+

To attach adhesive electrodes it is necessary to scrub the skin, in order to remove dead cells of the skin. This process is also unpleasant for the newborn. To compare this effect with the needle electrodes, a pain score test has been performed (PIP-test), based on the reactions of the newborn, and the look of the skin after removing the electrodes. The PIP scores were lower for the scrubbing of the skin. Furthermore the adhesive electrodes do not detach when a nurse cares for the newborn, or when it is cuddled by its parents.

There are different types of reusable Ag/AgCl clear gel electrodes. Currently mostly used at the NICU are the 3M Red Dot electrodes 2269T. They are easy to use, even though the skin does need to be scrubbed. However, for use with the NicoletOne monitor, these electrodes have leads that are not long enough. The amplifier of the NicoletOne is attached to the outside of the incubator, since due to hygienic and electric properties of the amplifier, it cannot stay inside the incubator. Therefore the leads of the electrodes need to be at least 90 cm, and preferably over 1m. The leads of the 2269T electrodes are only 60 cm.

A second type of electrode has been introduced: Kendall ARBO electrodes H207PGT. These

electrodes have micropore adhesives that are very similar to clear gel. They are so far the only electrodes with suitable characteristics and cables that are just long enough, 90 cm. Another type of partly reusable electrodes are the click electrodes, shown in figure C4 C. These electrodes can be used with reusable cables of any length. The prices of these electrodes are also lower (beneath 1 euro each, compared to 2-3 euro each for the disposable electrodes (C4 A and B)). However, for neonatal or pediatric purposes this type of electrode has been manufactured with soft cloth and foam adhesives.

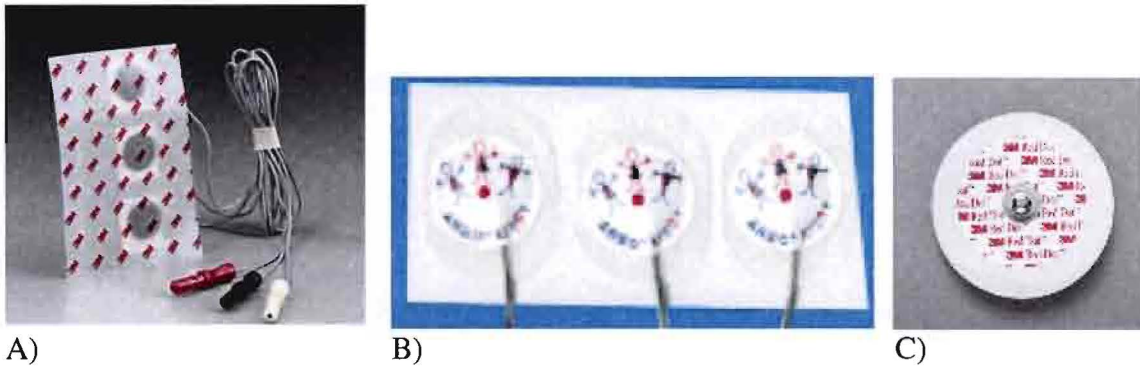


Figure E4: Different types of adhesive electrodes: A) 3M Red Dot 2269T electrodes; B) Kendall ARBO H207PGT electrodes; C) Click electrodes with soft cloth 3M Red Dot 2258.

Caps

The widely used caps are the Electro-Caps (figure E5 A). They do have infant caps down to 34 cm diameter. The electrodes used are generally tin-electrodes, which are made into relatively large plastic cups in the cap. For more comfortability and more stability they have sponge disks that are stuck to the skin, and fit around the plastic cups. These sponge disks prevent gel bridges as well. The fabric used in the cap is elastic spandex. These caps can be disinfected using alcohol.

The company ANT-neuro put a cap product on the market, born from a research based need for more sophisticated caps, the Waveguard cap (figure E5 B). Their caps are made with sintered Ag/AgCl electrodes and the fabric used is an elastic and breathing fabric. The plastic cups are rather small and thin, which is more comfortable for the patient. They use a kind of suction cups, to be less prone to movement and movement artifacts. These, however, can be replaced by more skin friendly rubber rings, also to prevent movement and gel bridges. The wires are all made into the fabric of the cap, making it more patient friendly. They can be disinfected, including the rubber rings. Furthermore, they have shown to have measurements with an impedance below 10 kOhm, without the necessity to scrubb or scratch the skin of the newborn. ANT is working together with a doctor in Finland, Vanhatalo (Tallgren, 2005), to improve the caps and the electrode gel for neonatal use. They are willing to start a pilot study in cooperation with the MMC Veldhoven to evaluate the long-term use of these caps for CFM measurements.



A)

B)

Figure E5: A) *Electro-Cap for neonates*; B) *ANT Waveguard cap*.

E.4 References

Geddes LA, Roeder R. Measurement of the direct-current (Faradic) resistance of the electrode-electrolyte interface for commonly used electrode materials. *Ann Biomed Eng.* 2001;29:181-6.

Tallgren P, Vanhatalo S, Kaila K, Voipio J. Evaluation of commercially available electrodes and gels for recording of slow EEG potentials. *Clin Neurophysiol.* 2005;116:799-806.

Webster JG. *Medical instrumentation, application and design*. 3rd ed. New York: John Wiley & Sons, Inc. 1998.

Appendix F

Results inquiry among nurses

This appendix gives an inquiry and its results, performed in 2005 concerning the experience and questions of nurses about CFM.

Inquiry

Veldhoven, 16 februari 2005

Betreft: voorlichting CFM-apparaat.

Beste verpleegkundigen van de NICU,

Sinds een jaar staat op de NICU het CFM (cerebral function monitor) apparaat. Sommige van jullie zullen hier al mee gewerkt hebben, en anderen misschien nog niet. Natuurlijk roept deze nieuwe manier van monitoren vragen en onduidelijkheden op.

We willen jullie nog meer vertrouwd maken met het continu monitoren van de cerebrale functie. Daarom hebben wij besloten een voorlichting te organiseren over het CFM apparaat. Om deze echter zo volledig en efficiënt mogelijk te kunnen laten verlopen, willen we jullie graag een paar vragen stellen over jullie ervaring met het CFM apparaat.

Na het invullen (gaarne voor 1 maart) van deze vragen kan dit formulier in een van onze postvakjes gedeponneerd worden.

Bij voorbaat dank.

Jacqueline van der Sluijs, kinderarts / fellow neonatologie
Charlotte Lommen, onderzoeker CFM

1. Hoe vaak heb je zelf al een CFM-meting opgestart?
2. Hoe vaak ben je bij een CFM-meting betrokken geweest?
3. Hoe ervaar je het werken met CFM? Positieve en/of negatieve punten?
4. Wat is voor jou onduidelijk over het werken met de CFM?
5. Wat zou je graag nog meer willen weten over de CFM?
6. Is volgens jou de handleiding bij de CFM duidelijk genoeg? Wat zou je er graag anders in zien?
7. Heb je nog suggesties voor de voorlichting?

Results Inquiry

Reacties op enquête over voorlichting CFM

26

Aantal reacties:

Hoe vaak heb je zelf al een CFM-meting opgestart?

0	1	2	3	4	5	6	Aantal keren
11	7	3	1	3			1

Hoe vaak ben je bij een CFM-meting betrokken geweest?

0	1	2	3	4	5	6	Aantal keren
2	9	3	4	1	1	3	3

Hoe ervaar je het werken met CFM? Positieve en/of negatieve punten?

Negatief:

Naaldjes gaan snel uit het hoofdje, ook bij goede fixatie.	3
Vaak alleen rugligging mogelijk. Mag kind er niet op liggen?	3
Kindje moet in houding liggen/op rug verzorgd worden	3
Naaldjes moeten soms herplaatst moeten worden voor optimale meting	1
Te weinig mee gewerkt (nog onwennig)	5
Naaldjes inbrengen zonder pijnstillen; paracetamol gewenst	2
Er kan niet/moeilijk gebuideld worden	1
Plakkers gaan makkelijk los	1
Om na een paar uur weer te <u>moeten</u> wisselen van kind	1
Indien er veel handelingen/onderzoeken moeten gebeuren is het intikken vervelend.	1
Inbrengen naaldjes: onzeker of ze goed zitten	1
Kinderen verpleegd met hoofd in middenstand, jammer	1
Onhandig met de draden -> pleisters/naaldjes gaan snel los	1
Naaldjes inbrengen. Is er niet iets anders ontwikkeld? Elektrodes?	1
Je vergeet snel om bij iedere handeling te 'registreren'	2
	1

Positief

Na 24 uur wordt het weer gestopt, duurt geen dagen.	1
Geeft meer waarde mbt observatie/ behandeling/veel informatie	2
Om convulsies geregistreerd te zien	1
Duidelijk apparaat	1
Bediening apparaat, werkt makkelijk	2
Protocol is duidelijk	1
Kinderen zijn ook in andere houdingen te verplegen dan alleen rugligging	1

Verder

Als je het 1 keer gedaan/gezien hebt wordt het al een stuk makkelijker	1
Je moet er wel goed aan denken om elke actie/ handeling te markeren	1
Blijkt minder belastend dan in eerste instantie lijkt	1

Wat is voor jou onduidelijk over het werken met de CFM? (open vraag, meerdere antwoorden mogelijk)

Engels kaartje van voorbeelden van hersenactiviteiten, liever Nederlands	1
Hoe zie je precies een convulsie?	1
Te weinig ervaring	1
CFM lezen is moeilijk/beoordelen	5
Basisprincipes zijn duidelijk	2
Pijnstilling	1
Buideling	1
Rapportage bijhouden nog onduidelijk	1
Verwerking van gegevens, hoe vindt dat plaats?	1
Interpreteren scherm	1
Altijd nodig om te markeren? Incident zie je toch wel?	3
Na hoeveel tijd is CFM meting betrouwbaar bij een kind?	1
Wanneer en hoe op het CFM apparaat beschreven moet worden welke handelingen je doet.	1
Kan de knoppen nog niet zo goed vinden (weinig ervaring)	1
Betekenis onduidelijk	1
Tussen 2 patiënten wisselen om de paar uur, hoe patiënten aanmelden?	1
Wat wordt er met de gegevens gedaan?	1
Hoeveel patiënten doen mee aan het multi-center onderzoek?	1
Nog zo'n beetje alles	1
Soms denk ik een incident te herkennen n.a.v. de plaatjes uit het protocol, maar dan blijkt het toch acceptabel te zijn.	1
De indruk er te vaak een arts bij gehaald te hebben	1

Wat zou je graag nog meer willen weten over de CFM?

Wanneer is er een afwijkend patroon te zien? Uitleg patronen	4
Hoe zie je precies een convulsie?	1
Alles (wat belangrijk is voor verpleegkundigen)	4
Meer ervaring	1
Strookje CFM met EEG-meting in verband brengen? Meer verband	1
Verwerking van gegevens, hoe vindt dat plaats?	1
Wat zie ik precies? Meer voorbeelden, meer diepgang	2
Interpreteren scherm / beoordelen	5
Altijd nodig om te markeren? Incident zie je toch wel?	1
Voortgang onderzoeken en evt behaalde resultaten tot nu toe	1
Wat moet ik doen met welke knoppen/toetsen?	1
Wat wordt ermee gedaan?	1
Hoe werkt het CFM precies?	2
Wat kan er van mij (verpleegkundige) verwacht worden als ik met CFM werk	1
Duidelijke uitleg over het apparaat. Instructieles	3
Uitleg over instellingen	1
Invoeren gegevens, markeren	1
Meer theoretische vorming over neurologie	1

Is volgens jou de handleiding bij de CFM duidelijk genoeg? Wat zou je er graag anders in zien?

Duidelijk genoeg.	14
Herkenning convulsie	1
Duidelijker aangeven dat het kind niet op naaldjes mag liggen en ook niet met steunen in contact mag komen	1
Nog niet mee gewerkt	2
Plaatjes CFM-beelden: als er een kind aan ligt is het moeilijk te beoordelen bij welk plaatje het CFM beeld van het kind past	1

Heb je nog suggesties voor de voorlichting?

Op een pop (hoofdje) naaldjes inbrengen + fixeren.	2
Meer voorbeelden en eventueel syllabus met plaatjes van verschillende soorten convulsies op CFM.	1
Patronen leren herkennen, hoe interpreteer je de gegevens? + akties	3
Niet precies, maar meer duidelijkheid is wenselijk	1
Meer uitleg/diepgang	1
Andere mogelijkheid plakkers?	1
Gebruik skillslab	1
Materiaal ter voorbereiding	1
Demonstratie hoe CFM precies werkt	1
Hoe mogen deze kinderen verpleegd worden? Vb wisselligging, buidelen enz	1
Apparaat doornemen stap voor stap	1
Klinische lessen over neurologie EEG	1
Hoe het werkt dmv klinische les	1
Alles nog eens goed op een rijtje zetten.	1

Samenvatting resultaten enquête:

Belangrijkste punten:

- Doel CFM
- Herkenning patronen / interpreteren gemeten signaal
- Naaldjes
 - pijnlijk
 - gaan makkelijk los, fixatie
- Houding pasgeborene
 - alleen rugligging?
- Werking CFM-apparaat
- Markeren/registreren
 - hoe?
 - wanneer?
- Lopend onderzoek, wat wordt er met de signalen gedaan?
- Theorie neurologie

Appendix G

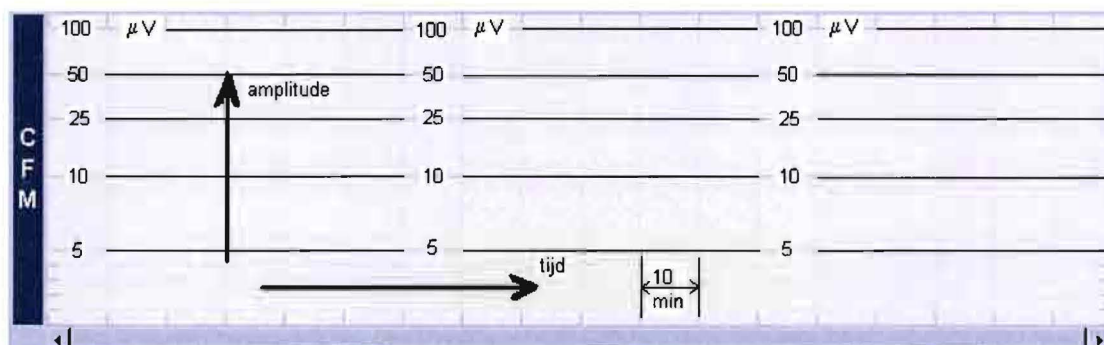
Handouts education for nurses

Cerebral Function Monitor (CFM)

De Cerebral Function Monitor is een apparaat dat het mogelijk maakt continu het brein van de pasgeborene te monitoren. Het meet de elektrische hersensignalen van de neonat, net als het EEG. Maar het CFM meet maar 1 signaal, een afleiding van 2 elektroden, waarbij een derde elektrode dient als neutrale elektrode. Verder wordt dat ene signaal in amplitude en tijd gecomprimeerd, waardoor een overzichtelijk signaal ontstaat, waarbij in 1 oogopslag, 3 uur signaal zichtbaar is.

Het CFM signaal (ook wel amplitude-integrated EEG, of aEEG genoemd) geeft dus globale informatie over de toestand van het brein van de neonat, en gaat voorbij aan heel kort durende events, of heel plaatselijk voorkomende events. Door al deze vereenvoudigingen wordt een signaal gecreëerd dat overzichtelijk lange perioden weergeeft, en dat relatief eenvoudig te lezen is door niet-gespecialiseerd personeel. Hierdoor wordt het mogelijk neonaten voor zelfs dagen lang met behulp van de CFM te monitoren.

Figuur 1 geeft de grafiek waarin de CFM signalen worden weergegeven. De amplitude is hierbij uitgezet in μV , maar de schaal geeft geen lineaire afstanden tussen bijvoorbeeld 10, 25 en 50 μV . Dit is gedaan zodat signalen met kleine amplitudes duidelijk weergegeven worden, en tegelijkertijd amplitudes tot 100 μV in dezelfde grafiek passen. In de tijdschaal is steeds om de 10 minuten een verticale streep zichtbaar. Eén scherm komt overeen met 3 uur.



Figuur 1: het scherm van de CFM.

Zichtbaar in het CFM signaal zijn:

- Achtergrondpatroon; binnen welke voltages het CFM-sigitaal zich over het algemeen bevindt. Hieronder worden de verschillende soorten achtergrondsignalen kort beschreven.
- Slaap-waak cyclussen; deze zijn pas zichtbaar vanaf een bepaalde conceptionele leeftijd. Ze zijn herkenbaar door veranderingen in de bandbreedte van de amplitude.
- Convulsies; deze kenmerken zich als een abrupte verhoging van de ondergrens, en een vernauwing van de bandbreedte van het CFM-sigitaal, voor een beperkte tijd. Een convulsie kan van 10 seconde tot een half uur of zelfs nog langer duren.

Er zijn verschillende soorten achtergrondsignalen, die zich voornamelijk karakteriseren door verschillen in amplitude:

- Continuous Normal Voltage, CNV: dit sigitaal heeft een amplitude voornamelijk tussen de 10 en 25 μV (tot 50 μV).
- Discontinuous Normal Voltage, DNV: met een amplitude voornamelijk boven de 5 μV .
- Burst suppression, BS: Heel laag voltage, onder de 5 μV , afgewisseld door hoge pieken, de bursts, die minimaal 10 per 10 minuten voorkomen.
- Continuous extremely Low Voltage, CLV: heel laag gevolteerd patroon, tussen 0 en 10 μV .
- Flat Trace, FT: activiteit beneden 5 μV . Deze kan een enkele hoge piek hebben, maar minder dan bij de burst suppressie.

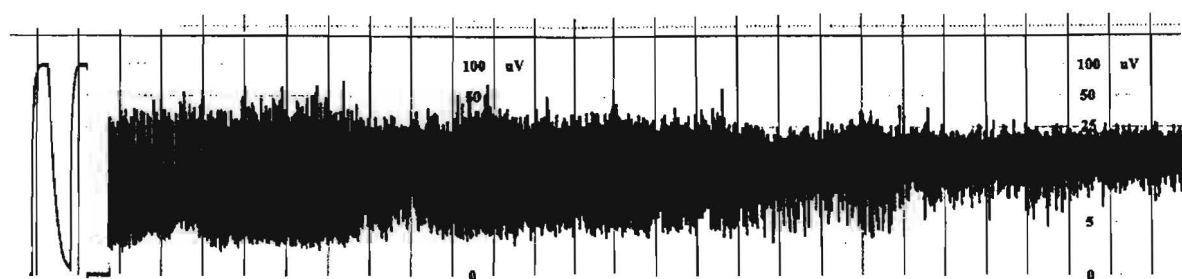
Het CFM achtergrondpatroon is afhankelijk van de conceptionele leeftijd. Bij een prematuur is DNV een normaal patroon. Naarmate de conceptionele leeftijd stijgt, stijgt ook het CFM sigitaal. Bij voldragen neonaten is CNV een normaal achtergrondpatroon, en DNV redelijk abnormaal. BS is abnormaal, maar kan nog altijd leiden tot een normale uitkomst en CLV en FT zijn extreem abnormaal, voor prematuren en voldragen neonaten.

Voorbeelden van de patronen zijn weergegeven in de figuur op de volgende bladzijde. Zichtbaar zijn:

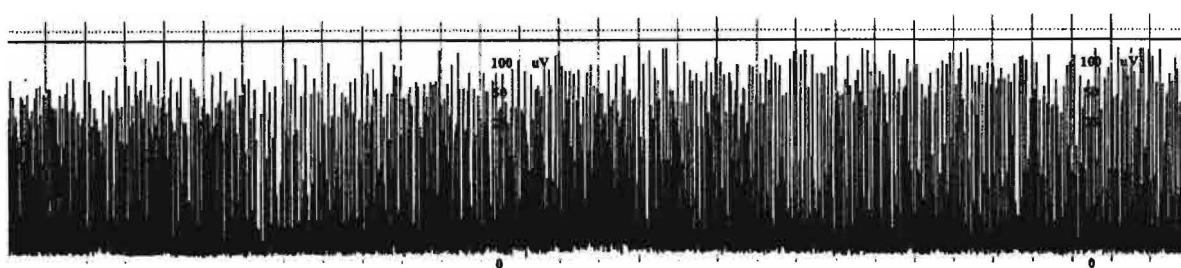
- a. Een DNV, dat langzaam overgaat in CNV.
- b. Een BS patroon. In dit sigitaal is er een hoge dichtheid van hoge pieken (bursts).
- c. CLV patroon. De kortdurende verhogingen in het sigitaal komen waarschijnlijk door beweging van de pasgeborene; dit zijn waarschijnlijk bewegingsartefacten.
- d. FT patroon. Bij het begin van dit sigitaal zou je ook kunnen spreken van BS met een hele lage dichtheid van bursts.

Overige voorbeelden zijn te vinden in het protocol dat aan het CFM apparaat hangt.

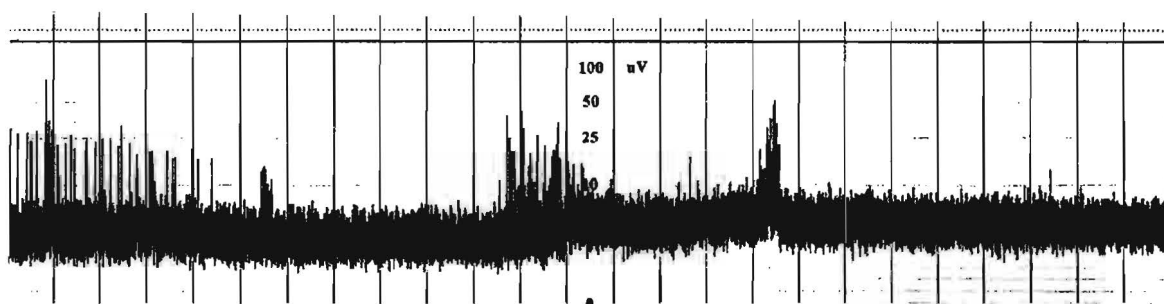
Verder wil ik graag dat jullie er even bij stilstaan dat bewegingen van de neonaat, of bewegingen aan de elektroden zichtbaar zijn in het CFM sigitaal, zoals in figuur c. Ga voor jezelf na, wat jij denkt dat gebeurtenissen/handelingen/behandelingen op de NICU zijn, die effect zouden kunnen hebben op het CFM sigitaal. Het markeren van deze gebeurtenissen is van groot belang voor het achteraf beoordelen van het sigitaal.



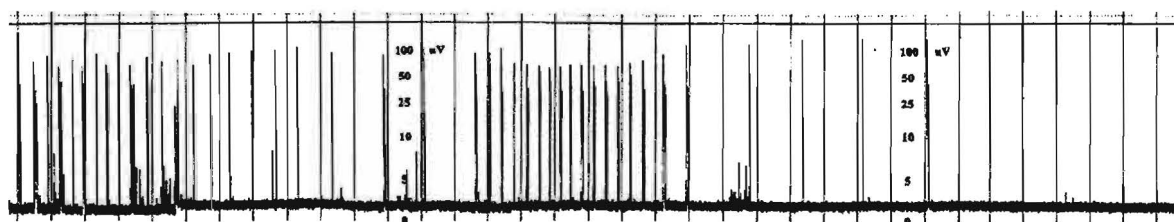
a



b



c



d

Appendix H

Protocols Cerebral Function Monitoring

H.1 Cerebral Function Monitoring (nurses protocol)

Cerebrale functie monitoring bij pasgeborenen

Doel van de handeling

- Monitoring van de hersenfunctie.
- Research

Indicaties

- Alle kinderen die participeren in de multicenter studie over subklinische neonatale convulsies:
 - G.A. >37 wkn.
 - Perinatale asfyxie en/of convulsies
 - Binnen 24 uur opgenomen op een neonatale intensive care
- Alle a terme kinderen waarbij er neurologische schade of convulsies te verwachten zijn (asfyxie, neurologische infectie, zeer zieke kinderen), maar die buiten de criteria van de studie vallen of waarvan de ouders niet willen participeren in de studie
- Alle a terme kinderen die verslapt zijn, waardoor je de neurologie niet meer kunt beoordelen
- Alle preterme kinderen waar het vermoeden op convulsies bestaat en je neurologische schade kunt verwachten, zoals asfyxie en vermoeden van sepsis en/of meningitis

Opmerkingen

- In de multicenter (Utrecht) studie wordt het effect van behandeling van niet-klinische convulsies onderzocht. Deze studie wordt op onze NICU gecoördineerd door de neonatologen.

- Convulsies op het CFM worden behandeld als ze ook klinisch zichtbaar zijn, of als er een status epilepticus wordt geconstateerd. Bij meerdere convulsies op het CFM per uur moet behandeling overwogen worden.

Benodigdheden

- CFM-monitor
 - Bij pasgeborenen van de multicenter studie: Olympic CFM
 - Bij 2-kanaals metingen: NicOne
 - Overig: beide monitoren kunnen gebruikt worden
- Elektrodes
 - Bij pasgeborenen van de multicenter studie: naald-elektrodes
 - Overig: in eerste instantie plakelektrodes. Mochten deze een te hoge impedantie geven, toch naald-elektrodes gebruiken

Algemene werkwijze

- Volg gebruiksaanwijzing van de desbetreffende monitor. Sluit elektrodes aan volgens protocol.
- Let op impedantie, deze moet onder 10 kOhm blijven (zie gebruiksaanwijzing monitor)
- Waarschuw een arts bij convulsies

Voorbeelden van CFM patronen, zie medisch protocol.

Advies in relatie tot pijn

(Adviezen geformuleerd door de Landelijke Pijnwerkgroep NICU's)

Wat doet er precies pijn bij deze handeling:

- Het liggen op de naaldjes
- Manipulatie aan het hoofd

Adviezen ter voorkoming van pijn:

- Hoofd zodanig positioneren dat patiënt niet op de naaldelektrode ligt
- Bij manipulatie aan het hoofd tractie aan de draden voorkomen

Bijbehorende protocollen

Protocol: Inbrengen en fixeren van naald-electrodes voor CFM bij pasgeborenen

Protocol: Verwijderen van naald-electrodes voor cfm bij pasgeborenen

Protocol: Aanbrengen van plakelektrodes voor CFM bij pasgeborenen

Protocol: Gebruiksprotocol Olympic CFM

Protocol: Gebruiksprotocol NicOne CFM

H.2 Medical protocol CFM

PROTOCOL CFM

Januari 2007. C Lommen; H Niemarkt; J van der Sluijs; J Buijs.

Inleiding

In dit protocol worden besproken de indicaties voor het gebruik van de CFM, de keuze van de elektrodes (naalden, plakkers), de verschillende apparaten (Olympics, NicoletOne) en de patronen op de CFM (achtergrond, convulsies, slaap-waak cycli).

Diagnostiek

Indicaties voor het gebruik van de CFM

1. Alle a terme pasgeborenen die in de CFM Trial (wel/niet behandelen subklinische convulsies) participeren.
2. Alle a terme pasgeborenen waarbij er neurologische schade of convulsies te verwachten zijn (asfyxie, neurologische infectie zoals meningitis, ernstig zieke kinderen), maar die buiten de criteria van de CFM Trial vallen of waarvan de ouders niet willen participeren in deze trial.
3. Alle a terme kinderen die verslapt zijn, waardoor de klinische beoordeling ernstig verstoord wordt.
4. Alle preterme kinderen waar het vermoeden op convulsies bestaat en neurologische schade verwacht kan worden, zoals asfyxie en vermoeden van sepsis en/of meningitis.

Dit betekent dat CFM bij deze groep gebruikt wordt voor bevestiging van de kliniek (bewegingen verdacht voor convulsies) en monitoring van de hersenfunctie voor wat betreft achtergrondpatroon en slaap-waak cyclus.

Bij een tekort aan CFM apparaten gaat de CFM Trial vóór het klinische gebruik op de afdeling.

ELECTRODES

1. NAALDELECTRODES:

- a. Patiënten die geïnccludeerd kunnen worden in de CFM Trial krijgen primair naaldelectrodes. Inclusiecriteria zijn:
- Gestational Age > 37 weken
 - Asfyxie (volgens Trial protocol)*
 - Neonatale convulsies binnen 24 uur post partum opgenomen op NICU

Exclusiecriteria:

- Chromosomale of congenitale afwijkingen
- Verslachte patient
- Diphantonine gehad voor onderzoek
- Midazolam ter sedatie

* Criteria asfyxie CFM Trial (minstens 3 van de volgende criteria): teken van intra-uteriene asfyxie:-meconium houdend vruchtwater of deceleraties op CTG; arteriële navelstreng pH<7,10; vertraagd op gang komen spontane regulier ademhaling > 5 minuten postpartum; Apgar score <5 na 5minuten;-Multi Organ Failure.

- b. Patiënten bij wie plakkers niet lukken en CFM meting klinisch noodzakelijk wordt geacht.
- Plakkers laten los
 - Impedantie > 10 kOhm
 - NB. Probeer altijd te overleggen met Hendrik of Charlotte als het niet lukt**

2. PLAKKERS:

- a. Patiënten die niet voldoen aan inclusie criteria CFM Trial
- b. Prematuren
- c. CFM ter uitsluiting convulsies (bijvoorbeeld bij kind met apneus)
- d. Als NicoletOne monitor gebruikt wordt
- e. Wetenschappelijk onderzoek

NB: er is een protocol voor het plakken van de CFM plakkers (op CFM kar!)

Probeer bij problemen met de plakkers Hendrik te bereiken. Telefoonnummer: 3371;Thuis: 06-21825013 (schroom niet te bellen buiten kantooruren/ bij niet opnemen: spreek voicemail in).

APPARATUUR

1. **Olympic** wordt gebruikt: CFM Trial (beslist door supervisor) of CFM op klinische indicatie (beslist door supervisor).
2. **NicoletOne** wordt gebruikt: wetenschappelijk onderzoek; klinisch: alleen als daar harde klinische reden voor is (dit dan ook vermelden in status)

De NicoletOne is een kostbaar apparaat. Wees er zuinig op! -Na gebruik **direct** terugzetten in PINO hok (sleutel op secretariaat NICU aan gele Pino sleutel hanger).

Geen vloeistoffen in de buurt van het EEG apparaat laten komen, ook niet in het mandje!

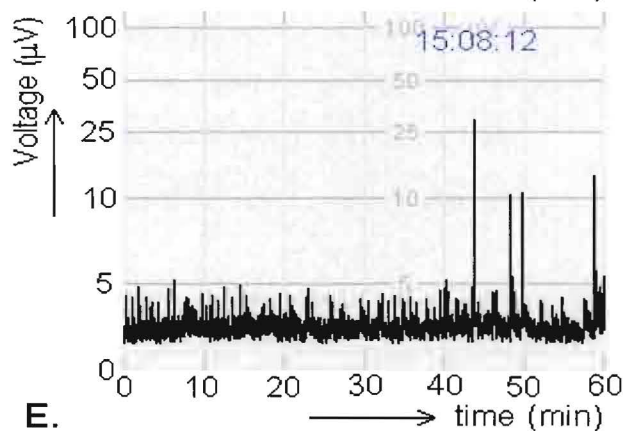
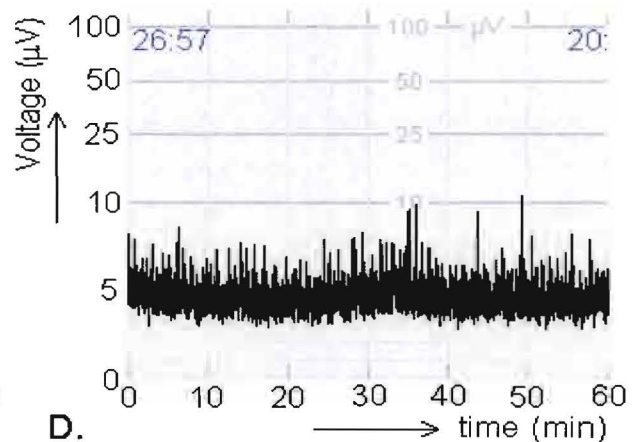
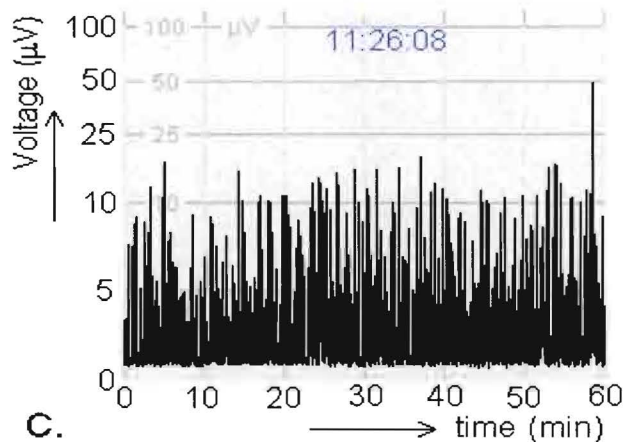
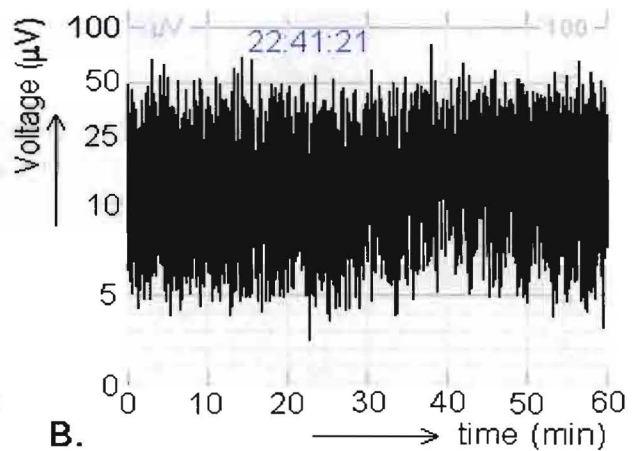
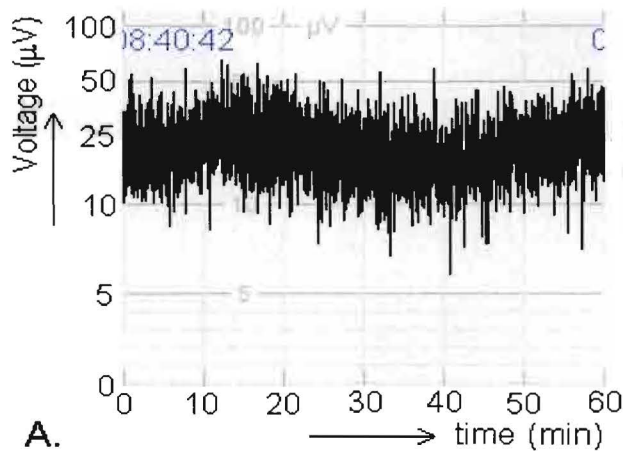
PATRONEN IN CFM

In het CFM zijn te herkennen:

- Achtergrondpatroon; de algemene activiteit van de hersenen
- Convulsies; te herkennen aan plotselinge stijging van de ondergrens in combinatie met stijging van de boven grens
- Slaap-waak cyclus; te herkennen aan een cyclische wisseling in bandbreedte.

Let op: CFM is een vereenvoudigde versie van het EEG. Het EEG blijft de gouden standaard.

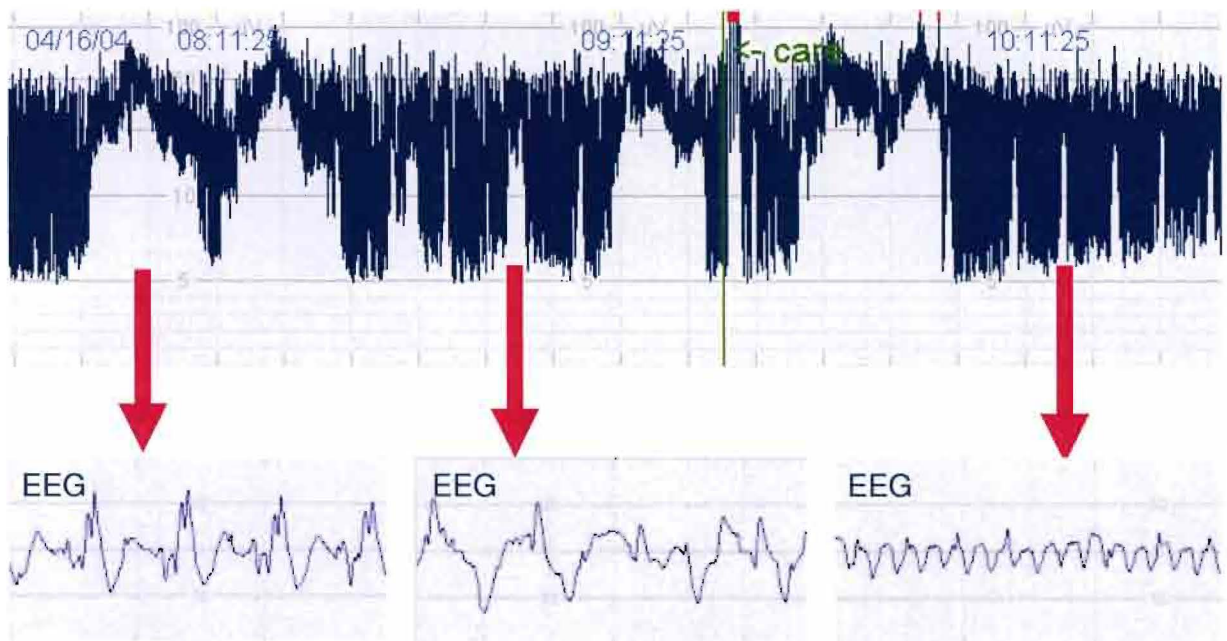
Sommige CFM signalen zijn moeilijk te interpreteren. In dat geval is een EEG vereist voor de juiste interpretatie.



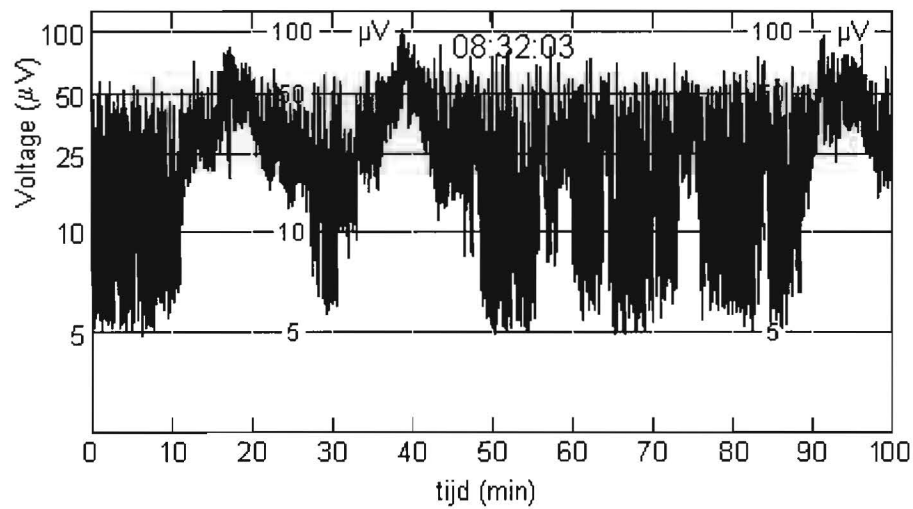
- A) CNV(Continuous Normal Voltage) amplitude ondergrens: 5-10 μV ; bovengrens: 10-50 μV .**
- B) DNV(Discontinu Normaal Voltage) amplitude ondergrens < 5 μV ; bovengrens >10 μV .**
- C) BS(Burst Suppression) discontinue activiteit met weinig variërende ondergrens: 0-1 μV .**
- D) CLV (Continuous Low Voltage) continue activiteit met laag voltage <5 μV .**
- E) FT (Flat Trace) inactieve achtergrond <<5 μV ; iso-electrisch.**

NB: BS, CLV en FT zijn bij á terme neonaten afwijkende achtergrondpatronen!

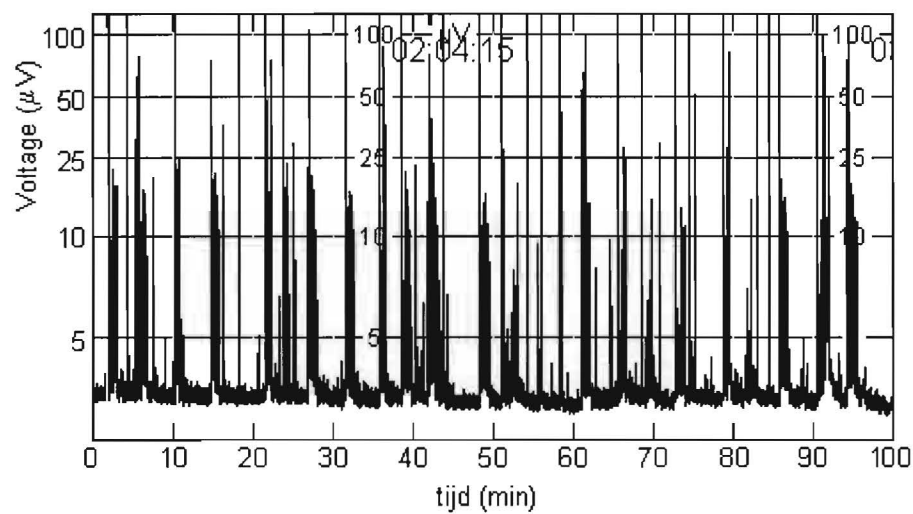
Convulsies



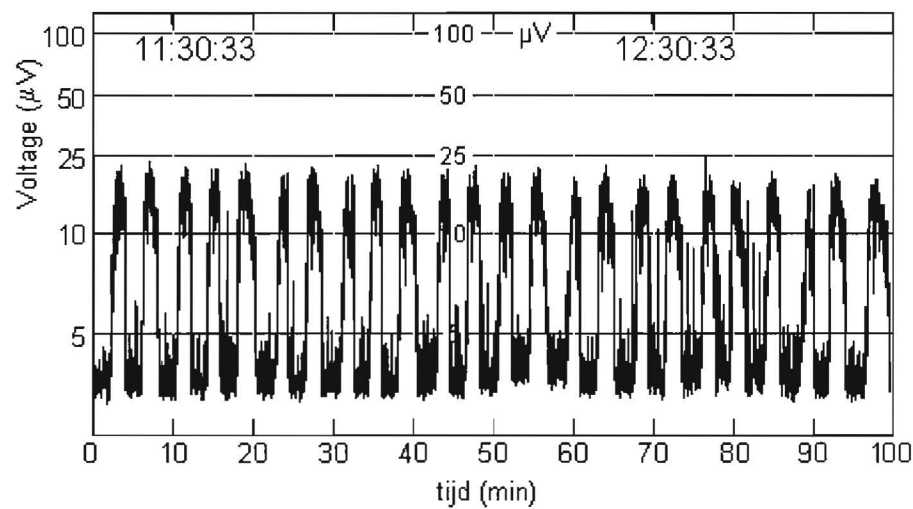
Convulsies zijn te herkennen in het CFM beeld aan de stijging van de ondergrens van het signaal in combinatie met de bovengrens. Mocht het onduidelijk zijn of een stijging daadwerkelijk een convulsie is, kijk dan naar het EEG signaal. Bij convulsies zal hierin een repeterend patroon te zien zijn. De repeterende patronen kunnen echter wel verschillende vormen hebben, zoals te zien in het EEG van 3 verschillende convulsies uit hetzelfde CFM signaal hierboven.



A.



B.



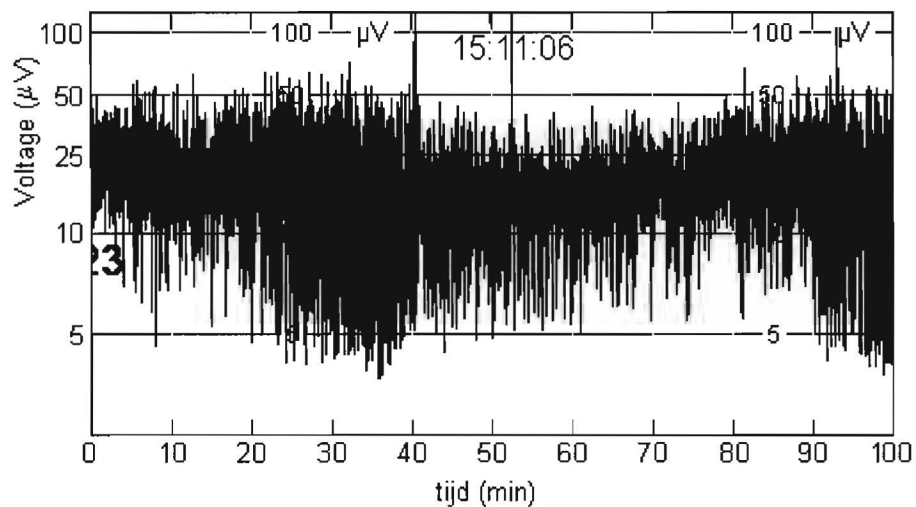
C.

A. Convulsies

B. Burst suppressie met convulsies, de strakke ondergrens van de BS wordt onderbroken door kleine stijgingen.

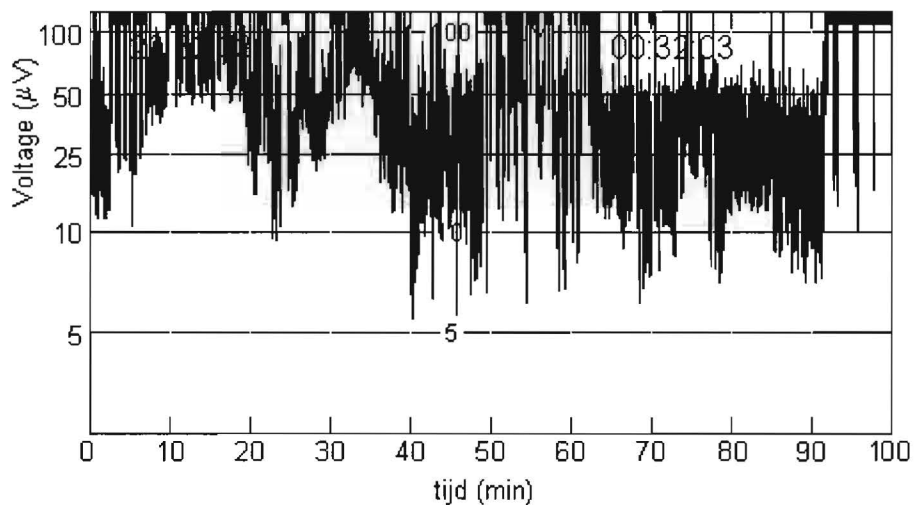
C. Status epilepticus: een toestand van voortdurende convulsies.

Slaap-Waak Cycli

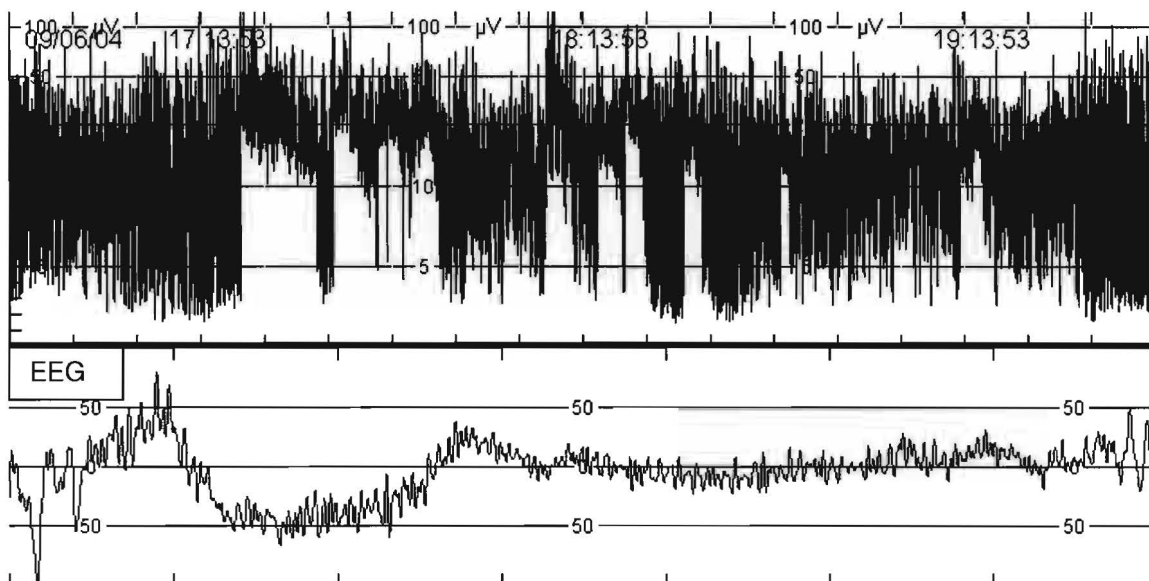


Slaap-waak cycli, te herkennen aan de verandering in breedte van de CFM band. Het brede gedeelte is rustige slaap, het smalle gedeelte REM-slaap of waak.

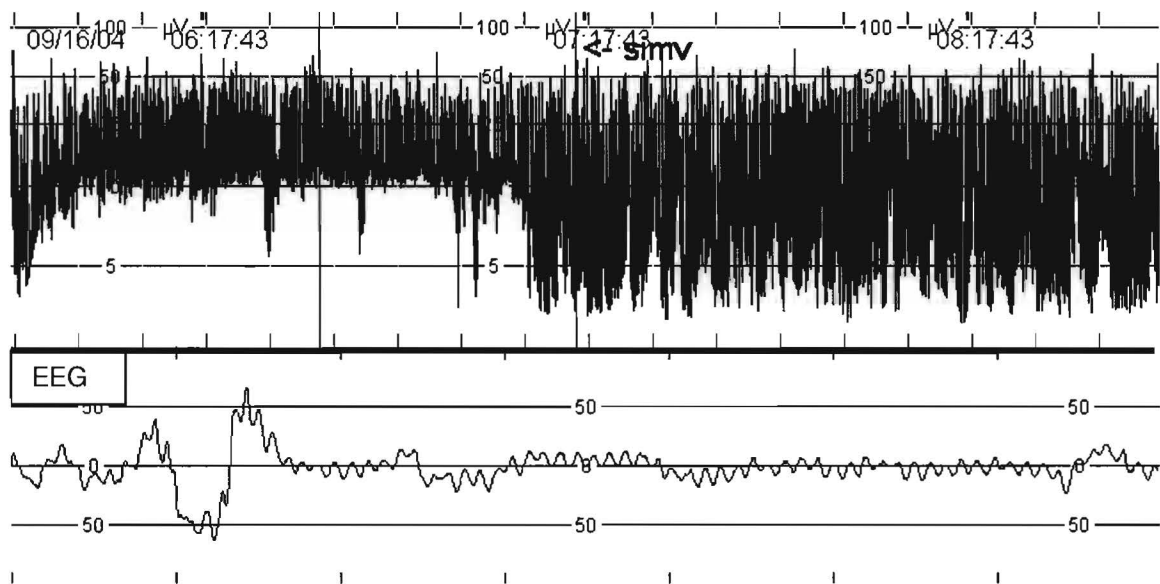
Artefacten.



Dit CFM signaal is erg hoog, en met name uigerekt naar boven. In het begin zijn nog twee patronen zichtbaar die op convulsies lijken, maar verderop in het signaal is het onduidelijk. In dit geval zat een elektrode los.



Spierartefacten: in sommige gevallen kan spieractiviteit gemeten worden door de elektrodes. Deze activiteit kan in het CFM signaal dezelfde patronen geven als convulsies, zoals hierboven. Als echter het EEG signaal erbij genomen wordt, is een snelle fluctuatie in het signaal zichtbaar. Dat is een aanwijzing dat spieractiviteit is gemeten op dat moment. Let op: als spieractiviteit wordt gemeten, betekent dat over het algemeen dat de elektrodes te ver naar voren zijn geplaatst.



HFO artefacten. Tijdens HFO metingen kan het signaal vervormd zijn, zoals hierboven. Op het moment dat SIMV is aangegeven, is de conventionele beademing weer ingeschakeld. Voordat de conventionele (SIMV) beademing is ingeschakeld lijkt CFM patroon lijkt het beeld van een convulsie te tonen. In het EEG is ook een ritmisch patroon zichtbaar, dit patroon heeft echter een duidelijk constante frequentie van 10 Hz (10 golven per seconde) en is dus veroorzaakt door HFO.

Let op: Tijdens HFO kunnen nog wel convulsies gemeten worden, deze zijn zichtbaar als een extra stijging in de ondergrens van het signaal.

Behandeling

Ten aanzien van de behandeling van [convulsies](#) in relatie tot de CFM geldt het volgende:

Een status epilepticus die alleen op de CFM wordt geconstateerd, dus zonder klinische verschijnselen, wordt **wel** behandeld.

Convulsies die op de CFM worden gezien , maar niet klinisch, worden **niet** behandeld, tenzij kinderen in de CFM Trial geïnccludeerd zijn.

Appendix I

Literature study

1.1 Principles for educational software design

For the development of educational software there are some principles and guidelines that are useful to make the program efficient. These include pedagogical principles and usability guidelines for software interface. The pedagogical principles used in education, both medical and general, have severely altered in the last decades. Traditional education was mainly based on tutorials by a teacher, passive learning, and motivation due to examination. Current education is preferably based on learner centered learning, where motivation is coming from the learner, learning is an active and collaborative process and a variety of instructional methods are used. (Amin, 2003) In this appendix the pedagogical principles for educational software are described as well as some usability guidelines.

Learning is personal

One of the main pedagogical principles is that learning is personal. (Talavera, 2001; de Marisco, 2006; Rubens, 2005; Squires, 1999; Keulers, 2006) Everybody has their own preference in learning style, and also their own learning needs. The reason for these different preferences is based on cultural differences between different countries and different institutes, educational background, and individual differences. To meet these individual preferences, it is suggested to give the user some control over the learning methods for example by flexibility in the interface and modularity of the learning environment (Squires, 1999; Rubens, 2005). Moreover from this arises the importance to analyze the training needs prior to the development of the training program. (Keulers, 2006; Talavera, 2001)

Active learning

Another educational principle involves active learning of the students, also referred to as knowledge building (Rubens, 2005; Amin, 2003). This is in contrast to passive learning or assimilation of knowledge as used to be the regular educational method. In active learning knowledge is constructed through actively solving problems of understanding by for example problem based learning or projects. Active learning is both more motivating and creates a more efficient learning process than passive learning. (Amin, 2003; Keulers, 2006)

Scaffolding

Scaffolding information is building new knowledge with help of, and on top of previous knowledge. (Rubens, 2005) One educational method that involves scaffolding is experiential

learning. (Amin, 2003) In experiential learning past experience is used in new settings, this is followed by observation and reflection and subsequently the development of new general principles. These new general principles are tested in a new simulation, which results into new experience and knowledge.

Progress analysis

A fourth important principle is the progress analysis, or in other words following the progress of the trainee. (Rubens, 2005; Amin, 2003) This is important for the tutor, but just as important for the trainee. For a trainee, following his/her own progress is motivating, and will therefore make training more efficient. In these progress reports it is important to give feedback to the trainee. (Squires, 1999) For the tutor the progress is important as well, however, his role in this type of learning is generally as a facilitator. (Rubens, 2005)

Collaborative learning

One of the educational principles seen in literature is collaborative learning (Squires, 1999) or community building (Rubens, 2005). There are many facets to this principle. Learning in a group is a motivating factor. Furthermore, asking for help to coworkers is easier and more fun than asking help from the tutor. Finally, explaining things to a coworker is the highest level of learning. When a trainee explains a theory, it is most likely that this trainee will understand and remember this knowledge.

Cosmetic authenticity

Cosmetic authenticity of educational software will make the emotion of the trainee more as in the real life situation. Therefore the learning experience will be more enduring. (Squires, 1999) In simulation cosmetic authenticity is a main factor.

Adult learner

Some more specific pedagogical principles follow from the specification of the learner to adult learner. Some of their learning characteristics include wanting to have control over their own learning, being very critical of their own achievements, and learning most efficiently when the process is based on their life experience. This leads to some principles useful in creating an educational process or program. First it is very important to realize that the adult learner does not want to feel naïve, but does need to be intellectually challenged in the learning process. Connected with this is the need for a good learning needs assessment. Most effectively is an individual learning needs assessment, to create individual learning goals. Moreover, individual learning, based on these individual learning goals is preferred by adults. Finally, an internal motivation for learning and methods for reviewing own learning progress is important for adult learning. (Amin, 2003)

Motivation

As already described in several of the earlier principles, the motivation to learn is very important in the efficiency of learning. Most efficient is when the motivation is coming from the learner himself, as opposed to reinforced motivation by for example examination.

Usability interface

Finally, some design principles concerning usability of interfaces are important to create an efficient training program. The principles are straightforward, but easily overlooked in the design process. Most used usability principles are described in a book by Nielsen. (Nielsen, 1993) They include simple and natural dialogue with terminology based on the user. Consistency in the interface is very important. Furthermore, clearly marked exits and

shortcuts should be included. Naturally the design process should include to prevent errors, but when errors do occur it is important to show clear error messages. Finally, help and documentation are very important, as well as heuristic evaluation and good feedback.

Team involvement

As described above, many different types of principles and guidelines exist, that need to be taken into account in the development process. Moreover, a good knowledge of the trainee in the design process is fundamental. For these reasons it is very useful to create a team of experts of different disciplines that can help in the development process of educational software. (Keulers, 2006; Kofránek, Dornan, 2005)

1.2 Process of development

The educational software will be based on simulation. Simulation uses active learning, it can easily be used for scaffolding information, and cosmetic authenticity is a main feature. Furthermore, simulation is very useful to train situations that are rare and situations where in real life time and/or scale are limiting factors for the learning process. CFM is used for about 15 % of the newborns at the NICU. The signals are measured for days, which means that with changing shifts, personnel often loses the educational moment of the rest of the signal. Furthermore, CFM is often started during acute situations, when attention of medical personnel is divided between different procedures and monitors. Decisions concerning diagnosis and treatment need to be made on these signals. Simulation is a good method to practice the decision-making process. The trainee can practice in interpretation of signals and making of decisions based on them, in a time that no other acute situations concerning a patient arrive. Finally, simulation is very useful in educational software to be used in combination with game elements. This makes the educational experience more motivating and more fun. (Aldrich, 2005)

As seen in the pedagogical principles that learning is personal and that adults are very critical of their own achievement, it is very important for an analysis of the training needs before the development of the educational software. These training needs should be the driving factor of the development. Other factors like financial and technological (im)possibilities have to be secondary, compared to the specific training needs.

The 'handbook of simulator based training' by Farmer (Farmer, 1999) describes steps to build an educational simulator, based on the specific training needs. This book was recommended to us by dr. Willem van Meurs, head of a simulator research group at the Instituto de Engenharia Biomédica, Porto. The book is primarily written for simulator development for military purposes. However, the steps described are suitable for simulator development in any professional/educational area. These steps can be used for screen-based as well as non-screen-based simulators. This makes the described development process suitable as well for other intended research projects at the Máxima Medical Center in Veldhoven.

In the first step the training needs of the different target groups is analyzed. The second step in the guidelines is the design of the training program based on the specific training needs. In the third step the training media specifications are described, to specify how the program design can be realized. These steps for the CFM simulator are described in appendix G2 through G4.

Appendix J

Training Needs Analysis

In the training needs analysis (TNA) the need of training is assessed. This is done by first analyzing the mission of the CFM, followed by the tasks that need to be performed to achieve the mission. After that the target groups for training, their current level of knowledge and skills and their expected level of knowledge and skills of the defined tasks are analyzed.

J.1 Mission and tasks of CFM

The mission of CFM is to monitor the function of the brain of newborns. This is monitored using 3 to 6 electrodes on the head of the newborn. The measured signal needs to be checked for reliability and marked in case of events that may effect the recording. Finally the artefacts need to be detected and the signal needs to be interpreted according to background pattern, seizures, and sleep-wake cycles.

The tasks that are required to fulfill the mission of CFM are given in table J1. These tasks are split into different categories of knowledge and skills. This will give insight into means needed to train these different tasks.

J.2 Trainee and training analysis

The different target groups that need to be trained are the medical specialists, the residents and the nurses in neonatology. Medical specialists are mainly neonatologists, but also pediatricians that regularly work at the neonatal intensive care. Their full agenda's make it difficult for them to be trained by regular instructions. Residents in pediatrics are substituted every two years, and therefore regularly new residents appear with a very low level of skills and knowledge. The nursing team of the NICU at the MMC Veldhoven count about 70 members. Many of them work part-time and some of them work mostly in night shifts. This makes it difficult to give all of them regular training concerning CFM.

The current level of knowledge is different for the three target groups (table J2). Medical specialists have generally a basic level of knowledge and skills, while the residents, because of their frequent renewal, are regarded as having no current knowledge and skills concerning CFM. The main skills of the nurses concerns the performance of the measurements. The level of skills concerning the interpretation of CFM recordings is diverse, and therefore considered to be low to absent.

The expected level of skills to fulfill the mission of CFM adequately is shown as well in table G2. Mostly an advanced level is expected of all medical personnel. The knowledge and skills concerning EEG for the medical specialists is regarded as basic, since this is used as a backup for the interpretation of CFM. The level of expected skills and knowledge for residents is equal to medical specialists. The nurses do not need to have an advanced level of skills in interpretation of CFM, except for the interpretation of seizures, since this is necessary for early detection and treatment of the seizures.

From table J2 it becomes clear what the training need of the different target groups is. This is necessary to know, to be able to develop an efficient tool for their training.

Table J1. Tasks required to fulfill the mission of CFM, split into different categories of knowledge and skills.

	Kennis		Vaardigheden				
	Feiten	Concepten	Perceptuele motorische vaardigheden	Procedurale vaardigheden	Cognitieve vaardigheden	Team	Tijdsplanning
Opstarten/ afsluiten CFM meting			X	X			
Positioneren van elektrodes				X			
Fixeren van elektrodes - Naald elektrodes - Plak elektrodes			X	X			
Controleren betrouwbaarheid meting			X				
Reageren op onbetrouwbare meting				X	X		
Markeringen bijhouden			X	X			
Detecteren artefacten			X		X		
Theoretische kennis CFM signaal	X						
Theoretische kennis EEG signaal	X						
Interpreteren CFM signaal - Convulsies - Achtergrondpatronen - Slaap-waak cycli			X		X		
Interpreteren EEG signaal			X		X		
Waarschuwen medisch specialist				X			

Tabel J2. Huidige en verwachte kennis van de verschillende doelgroepen, in categorieën:

1. geen tot weinig ervaring / kennis

2. basis ervaring / kennis

3. geavanceerde ervaring / kennis

nvt = niet van toepassing.

	Kinderartsen- neonatologen		Arts-assistenten		Verpleegkundigen	
	Huidig	Verwacht	Huidig	Verwacht	Huidig	Verwacht
Opstarten/ afsluiten CFM meting	2	3	1	3	2	3
Positioneren van elektrodes	2	3	1	3	1	3
Fixeren van elektrodes						
- Naald elektrodes	2	3	1	3	2	3
- Plak elektrodes	1	3	1	3	1	3
Controleren betrouw- baarheid meting	2	3	1	3	2	3
Reageren op onbetrouwbare meting	2	3	1	3	1	3
Markeringen bijhouden	2	3	1	3	2	3
Detecteren artefacten	2	3	1	3	1	2
Theoretische kennis CFM signaal	2	3	1	3	1	2
Theoretische kennis EEG signaal	1	2	1	2	1	1
Interpreteren CFM signaal						
- Convulsies	2	3	1	3	1	3
- Achtergrondpatronen	2	3	1	3	1	2
- Slaap-waak cycli	1	3	1	3	1	2
Interpreteren EEG signaal	1	2	1	2	1	1
Waarschuwen medisch specialist	nvt	nvt	1	3	1	3

Appendix K

Design strategy of CFM simulator

The design strategy is as described in a book by Farmer (1999), based on the training needs analysis as described in appendix J. In the training program design (TPD) a global set up of the training program, based on the specific training needs that were analysed, is given. Also the different scenarios included will be described. Subsequently the training media specifications are described.

K.1 Training Program Design

Figure K1 gives the flow diagram of the training program design. The different aspects are described below.

Entry CFMsim

- Entry of personnel ID. The trainee will be identified, and placed in category of medical specialist, resident or nurse.
- Choice for the trainee:
 - Continue where the trainee left off last time
 - Go to an earlier level
 - Go to review mode, to review typical CFM recordings

Level 0

Theoretical introduction

Medical specialist and residents	Nurses
Importance of CFM	Importance of CFM
EEG: what is measured	
How is CFM calculated from EEG	CFM: what is measured
Electrodes	Electrodes
Important aspects of measurement: impedance/ marking of events	Important aspects of measurement: impedance/ marking of events
Classification CFM	Classification CFM
Possible sources of artifacts	Possible sources of artifacts
Showing protocol of department	Showing protocol of department

Evaluation: this part will be evaluated with multiple choice questions

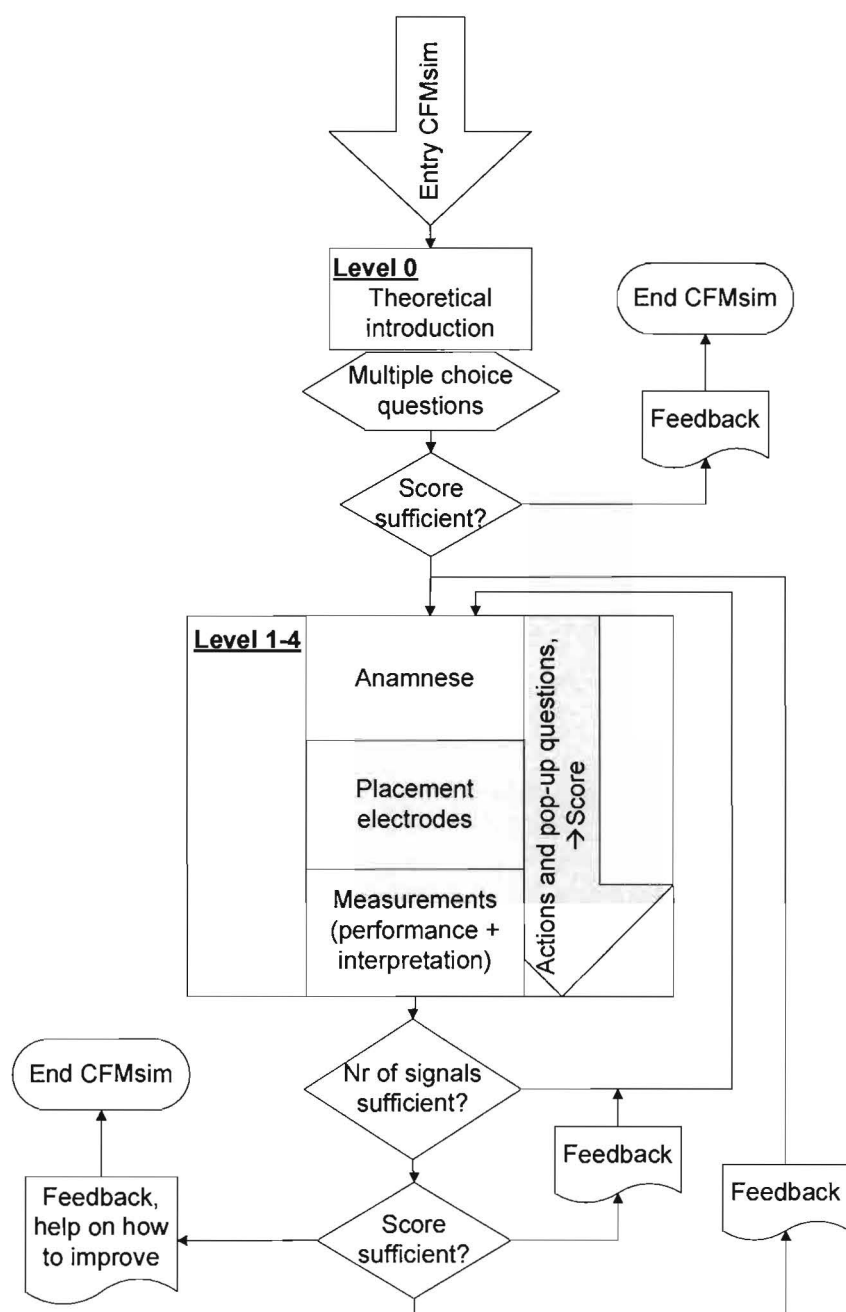


Figure K1: Flow diagram of the training program

Level 1-4:

Anamnese

The anamnese and background of a newborn in need of CFM is described.

Placement of electrodes

- Choose the monitor
- Choose the type of electrodes
- Position the electrodes: drag them to the right place on the head of the newborn
- Fixate the electrodes: short description/illustration how to fixate the electrodes
- Check reliability: if the impedance exceeds 10 kOhm, the electrodes need to be checked and possibly replaced.

This step should mainly be practiced in the skills lab, and should therefore not take too much time in the training program.

Measurements (performance + interpretation)

Performance of the measurement

- Impedance is given on the monitor. When the impedance exceeds 10 kOhm, the trainee should react by checking the electrodes. If necessary, the electrodes need to be replaced.
- On the screen certain events (like parents cuddling the newborn) or medical procedures are given, like care, medication, etc. These procedures as well as clinical seizures, need to be marked in the recording.
- When an according to protocol number of seizures has occurred, a medical specialist needs to be warned and needs to make a decision about medication.

Whenever the trainee does not take the appropriate action, a warning will be given by the training program, with argumentation concerning the expected action.

Interpretation of the signal

- The trainee needs to have the same options available in the CFM simulator as on the real CFM monitor, concerning looking back into the recording and looking at the underlying EEG signal.
- When events like artefacts and seizures occur, a pop-up will appear in the screen asking a multiple choice question concerning the pattern. The measurement will be paused in the mean time.
- With a change of background pattern or the occurrence of sleep-wake cycles, questions may appear as well.
- At the end of the signal questions will be asked concerning the background patterns and events in the signal. A relation to the possible state of the newborn will be asked as well.

Feedback is very important, both positive and negative. An explanation should be included concerning the right answer.

K.1.1 Included scenarios

The scenarios included into the training program are:

- Cerebrally healthy
- Asphyxia, SARNAT 1,2,3
- Suspected seizures

Included patterns within these scenarios:

- 5 background patterns (C, DC, BSA, LV, FT)
- Sleep-wake cycles
- Different speeds of recovery after asphyxia, as well as deterioration
- Seizures
 - On all different background patterns
 - Single, repetitive and status epilepticus
 - After medication with/without effect
- Fasciculations
- Influences of medication: phenobarbital, midazolam, lidocaine

- Artefacts
 - Muscle artefacts
 - Movement artefacts
 - HFO artefacts
 - High impedance artefacts

K.1.2 Levels 1-4/5 for different target groups

Levels 1-4 include CFM recordings of increasing difficulty, mainly based on the types of patterns. Moreover, the performance of the measurements does not need to be practiced for every trainee in every level. Based on the training needs of appendix J, a content for levels 1-4 for the different target groups is given in table K1. The residents have an extra level, level 5, since for them the difference between current and expected knowledge is the largest.

Tabel K1. Levels 0-4/5 for different target groups.

Level	Medical specialists	Residents	Nurses
0	Theoretical knowledge	Theoretical knowledge	Theoretical knowledge
1	Cerebrally healthy newborns, with sleep-wake cycles. Clear background patterns and seizures. Some artefacts Placement of electrodes and performance of measurements included	Cerebrally healthy newborns, with sleep-wake cycles. Placement of electrodes and performance of measurements included.	Cerebrally healthy newborns, with sleep-wake cycles. Placement of electrodes and performance of measurements included.
2	Unclear background patterns, unclear seizures. More artefacts.	Clear background patterns and seizures. Some artefacts.	Clear background patterns and seizures. Some artefacts. Placement of electrodes and performance of measurements included.
3	Status epilepticus, recovery patterns and artefacts	Unclear background patterns, unclear seizures. More artefacts.	Unclear background patterns, unclear seizures. More artefacts. Placement of electrodes and performance of measurements included.
4	Everything mixed, signals included by own department, fasciculations.	Status epilepticus, recovery patterns and artefacts	Status epilepticus, recovery patterns and artefacts Placement of electrodes and performance of measurements included.
5		Everything mixed, signals included by own department, fasciculations.	

K.2 Training Media Specifications

In the training media specifications (TMS), general specifications, choice of software and some specifications concerning the database will be given. The extended requirements will be given in Appendix G6.

General specifications

- Program recognizes by the personnel ID earlier use and achievements in the CFM simulator.
- An option to pause or save the training program should be given any time
- The simulated monitor needs to have the same options as the real monitor
- Every question will be divided into a category. Scores need to be sufficient for all categories before a trainee can move to the next level. Feedback will be given according to the score based on categories.
- Many mistakes → refer to literature and the owner of the program
- Possibilities of extending and changing the training program:
 - Extend database with more signals
 - Extend scenarios to premature and other scenarios
 - Which monitors or electrodes are available
 - When a medical specialist needs to make a decision about treatment of the newborn
 - Making the instructor interface not anonymous: give scores of individual trainees.

Writing of signals

- Signals will not be more than 48 hours, minimal 4 hours (exceptions allowed)
- Signals will be written in 5 seconds per hour, 1 minute per screen (for each signal this is 1.20 to 16 minutes). For the NicOne monitor, the EEG signal will not be shown at this speed.
- The writing speed can be moved up or down. The speed can also be put to “true speed”. For the NicOne the EEG will only be shown at true speed.
- The signal will automatically go to true speed when the trainee will look back into the signal or will go to the EEG signal.
- To clearly show these speeds of the signal, an analogue clock will be shown, that will go at true speed (accelerated when the signal is shown accelerated). Moreover, to give the trainee a good perspective of time, the clock will turn black during night time.

Choice of software: JAVA

The choice of software is based on different aspects, see table K2. The choice is to use JAVA for the training program. JAVA is supported by most PC's, is a generally often used program that I have some personal experience with. It has a nice program to build user interfaces (JAVA Builder).

Table K2: Demands for software that will be used for the training program, and a comparison of three software languages.

Demands software	Phyton	JAVA	C++
Supported by most PC's	- (Extra software needed)	+ (Java Virtual Machine)	+
Relatively easy to learn	+	+ (Personal experience)	-
Easily adapted/extended	+	+	+-
Calculation time	+-	+	++
Constructing interfaces	+	+ (Java Builder)	+ (C++ builder)
Intranet possibilities	+-	+ (JVM or javascript)	+

Evaluation of knowledge and skills

In the TNA the different tasks have been divided into knowledge and skills. These tasks need to be evaluated in the training program. This will be done as follows:

Factual knowledge:

- Evaluated with questions in theoretical knowledge

Perceptual / motor skills

- In combination with procedural skills: test indirectly through reactions of trainee.
- In combination with cognitive skills: test using pop-up multiple choice questions.

Procedural skills:

- Trainee must perform procedures, evaluation based on this.

Cognitive skills:

- These tasks are perceptual / motor skills as well, and will be tested accordingly.

Database

There will be an extended database of signals, see table K3. The required storage for these 80 signals, assuming a mean duration of 24 hours - corresponding to 44 MB - is 3.52 GB.

Signals will be saved in EDF+ format. EDF+ is an efficient format to save large EEG files, and gives the opportunity to save annotations in these signals. The annotations will be used to mark the types of background, the types, length and place of events. This information will be used by the program as cues to give questions to and expect actions from the trainee.

Table K3: Number of signals included in the database

Category	Type of CFM signal	Number of signals
1	Cerebrally healthy newborns, with sleep-wake cycles.	8 signals
2	Clear background patterns and seizures. Some artefacts.	10 without seizures 10 with seizures (At least 3 for each background pattern)
3	Unclear background patterns, unclear seizures. More artefacts.	10 unclear background patterns 10 unclear seizures
4	Status epilepticus, recovery patterns and artefacts	10 status epilepticus 10 recovery patterns
5	Everything mixed, signals included by own department, fasciculations.	10 new signals Others from categories 2-4 Signals included from own department

Appendix L

Team input

As has been concluded in the pedagogical principles, it is important to include people from different disciplines in the development of the educational software. During the development of the CFM simulator regularly the advice of doctors and residents has been asked for. After concluding the training needs analysis, the training program design, and the training media specifications, a team has been formed including members of each target group and an educational scientist. This team received a presentation of the CFM simulator. They were asked for any comments they had on the program, new ideas to include and different opinions they might have. This appendix summarizes the ideas that have not already been included in the training program design and media specifications.

Nurse practitioners

In the training needs analysis three target groups have been described: medical specialists, residents, and nurses. However, there is a fourth group of medical personnel that have not been described yet, the nurse practitioner. The nurse practitioners have at first been grouped together with nurses. However, this group needs to have a higher level of knowledge and skills. Their expected level is equal to that of a resident. The current level of knowledge and skills is higher than residents. However, since it concerns a very small group, only two in the MMC, no new target group will be described. The nurse practitioners will be grouped together with the residents.

Knowledge of nurses

The expected level of knowledge for nurses is for theoretical knowledge of EEG and CFM lower than for residents and medical specialists. However nurses may be interested in receiving extra information concerning the origin of CFM and EEG signals. Therefore the option should be given to the nurses to receive this theoretical knowledge. In this case it is very important to make clear to the nurses that they will not be examined on these topics, and the opportunity must be given for the nurses to skip this topic within the CFM simulator.

Authenticity

As already has been described in the pedagogical principles, authenticity is a very important factor for the learning process. It has been mentioned by the team that it is very important to use images in the CFM simulator that are authentic to the devices used at the department.

Technological explanations

Some of the technological concepts regarding CFM are need to be explained clearly to the non-technical medical personnel. The examples mentioned in the team meeting concerned the explanation of the neutral and reference electrodes, and the explanation of the frequency filter in the processing of CFM. Especially concerning the frequencies some examples need to be use to explain what is happening in this process and why.

Personnel ID

In the training program design it has been suggested that the trainee enters his/her personnel ID, so the program will be able to recognize to which target group the trainee belongs and whether or not he has already used the CFM simulator before. The team mentioned that there will be a possibility that colleagues will use other personnel IDs to train with the CFM simulator. They suggested that each member can make his own password to enter the CFM simulator. This will prevent the possibility of identity theft when training with the program.

Clinical and subclinical seizures

The training program so far only deals with seizures within the CFM signal. However, it is very important to know whether the seizures are only subclinical, i.e. only appear in the CFM signal, or are clinical as well. This has consequences for treatment of the newborn, and should therefore be included in the CFM simulator.

Looking back in time in the CFM signal

In the Olympic CFM6000 a problem has been recognized occurring whenever people look back into previous screens of the measured signal. The screen does not automatically return to its current position. Because of this the situation has occurred that medical personnel diagnosed the current status of a newborn based on a CFM signal that had been measured hours earlier. This is a very serious flaw that needs to be included into the training program. For all target groups at least one example of this will be included in both levels 1 and 2.

Multiple-choice questions

This item had already been scheduled, but has not yet been described explicitly. Multiple-choice questions are given at the end of level 0. It is very important that trainees who have to repeat this level, will not be able to complete the level based on their memory of the questions and their answers in their first attempt. This means that a list of questions needs to be built, that will be used in the simulator in a randomized way. To be sure that different types of questions are used, the questions will be categorized. For level 1 through 4, a similar problem may occur when the same signals are repeated for the trainees. In this case a database of categorised signals should be built, that will be used randomized in each level.

Automatic seizure detection

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REGULAR ARTICLE

An algorithm for the automatic detection of seizures in neonatal amplitude-integrated EEG

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Cerebral function monitor, Detection, Neonatal seizures

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Abstract

Aim: To develop and evaluate an algorithm for the automatic screening of electrographic neonatal seizures (ENS) in amplitude-integrated electroencephalography (aEEG) signals.**Methods:** CFM recordings were recorded in asphyxiated (near)term newborns. ENS of at least 60 sec were detected based on their characteristic pattern in the aEEG signal, an increase of its lower boundary. The algorithm was trained using five CFM recordings (training set) annotated by a neurophysiologist, observer 1. The evaluation of the algorithm was based on eight different CFM recordings annotated by observer 1 (test set observer 1) and an independent neurophysiologist, observer 2 (test set observer 2).**Results:** The interobserver agreement between observer 1 and 2 in interpreting ENS from the CFM recordings was high (C coefficient 0.82). After dividing the eight CFM recordings into 1-min segments and classification in ENS or non-ENS, the intraclass correlation coefficient showed high correlations of the algorithm with both test sets (respectively, 0.95 and 0.85 with observer 1 and 2). The algorithm showed in five recordings a sensitivity $\geq 90\%$ and approximately 1 false positive ENS per hour. However, the algorithm showed in three recordings much lower sensitivities: one recording showed ENSs of extremely high amplitude that were incorrectly classified by the algorithm as artefacts and two recordings suffered from low interobserver agreement.**Conclusion:** This study shows the feasibility of automatic ENS screening based on aEEG signals and may facilitate in the bed-side interpretation of aEEG signals in clinical practice.

INTRODUCTION

For the neurological assessment of critically ill newborns electroencephalography (EEG) is an important tool. The clinical relevant characteristics of the EEG are the background pattern and electrographic neonatal seizures (ENS) (1).

Seizures are one of the most distinct signs of cerebral dysfunction in newborns (2). They may be caused by most common cerebral pathologies of the newborn like hypoxic-ischemic encephalopathies, intracranial hemorrhages, metabolic encephalopathies, cerebral infarctions or cerebral infections (2). They often have an early postnatal onset and may be first indicators of cerebral disease (2,3). Repetitive seizures may cause disturbances in ventilation and a rise in blood pressure (2), and may cause damage to the developing brain (4,5).

For the detection of ENSs in newborns electroencephalography is a sensitive method and considered as the golden standard. Clinical signs of seizures in newborns are often subtle, difficult to differentiate from normal newborn movements, or even absent (silent seizures) (2,6). Especially after medication seizures are often clinically silent (7). In neonatal EEG the electrical cortical activity is measured

using 9–21 electrodes connected to the scalp of the newborn (8,9). ENSs are characterized by rhythmic discharges of waveforms of similar morphology. They have a relatively sudden onset and termination as well as an evolution in frequency, topology and amplitude (9,10). They may either be focal, multifocal or global and are generally defined to have a minimum duration of 5 or 10 sec (1).

Practical considerations make the EEG less suitable for long-term monitoring of the brain function in the neonatal intensive care unit (NICU) environment. This is mainly due to the time consuming interpretation of the numerous signals. The complex nature of the signals makes interpretation by experts necessary. Therefore, EEG measurements at the NICU are generally performed for the duration of about 45–90 min.

The cerebral function monitor (CFM) (11) facilitates long-term monitoring of cerebral electrical activity at the NICU (12). The CFM measures only one channel, biparietal EEG. This EEG is converted into an amplitude-integrated EEG (aEEG), which shows clinically useful information even when displayed at 6 cm/h, resulting in a clear overview of several hours on a monitor. The amplitude of the signal shows the relative power of cerebral electrical activity. The CFM is relatively easy to install and to interpret by doctors

and nursing staff with limited expertise, and therefore suitable for long-term monitoring (13).

CFM is predominantly used to detect ENSs outside the period of the EEG measurement and outside office hours. Using CFM only generalized and focal parietal ENSs will be measured. However, focal ENSs often migrate or spread to other areas in the cortex (8) and then can be detected by CFM, as reported in a study by Toet et al. (14).

Still some difficulties in the interpretation of the CFM recording remain, especially concerning the detection of ENSs. Because of hypersynchronisation, i.e. the simultaneous discharge of large groups of neurons, seizures cause a rise in the amplitude of the aEEG signal (6,13). A similar rise is known to be caused by different types of artefacts (15,16). Furthermore, it is often difficult to detect ENSs of short duration and/or low amplitude (17,18).

The objective of this study was to develop an algorithm as a screening tool for the automatic detection of ENSs in aEEG signals of newborns. The algorithm should be able to recognize artefacts that can be mistaken for ENSs. The purpose of the algorithm is to assist doctors and nurses in the interpretation of the aEEG signal and as an alarm function on the CFM monitor. This study describes the algorithm and its evaluation.

METHODS

Subjects

In this study 13 CFM recordings were included of 13 newborns. Ten of these newborns were full term and 10 of them were diagnosed with asphyxia. The clinical details of these newborns are given in Table S1.

Recordings

Recordings have been obtained using the CFM6000 (Olympic Medical, Seattle, WA, USA). These digital CFM recordings contain both the EEG and aEEG signal. For these measurements needle electrodes were placed parietal at locations P3 and P4 according to the international 10–20 system (13).

CFM measurements were a part of standard clinical monitoring of severely ill neonates, the main indication being detection of epileptic seizure activity. Therefore, the medical ethics committee did not consider it necessary to evaluate this study. Measurements have been performed between June 2003 and November 2004 at the Máxima Medical Centre Veldhoven, the Radboud University Nijmegen Medical Centre, and at the Wilhelmina Children's Hospital Utrecht, the Netherlands and one recording at the Hammersmith Hospital in London, UK. Inclusion of the recordings was based on their variability in types of background patterns (19) and presence of ENSs, given for each recording in Table S1.

The presence of ENSs is specified in either repetitive ENSs or status epilepticus, i.e. an ENS that is so prolonged or frequently repeated as to create a fixed or lasting epileptic condition (9). The duration of the recordings varied from 9 to 24 h (total: 222 h). Figure 1 shows 100 min of recording

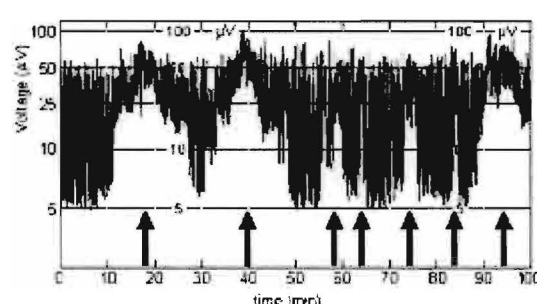


Figure 1 Repetitive ENSs in an aEEG signal of 100 min, belonging to recording 1. The ENSs, characterized mainly by the sudden increase of the lower boundary, are indicated by arrows.

1. containing repetitive ENSs, characterized mainly by the sudden increase of the lower boundary.

The algorithm

In this study only ENSs with a duration of at least 60 sec were included. The minimum duration of ENSs is generally defined to be 5 or 10 sec (1). However, due to the compressed nature of the aEEG signals, these ENSs may not be recognizable. Moreover, ENSs of short duration may be difficult to differentiate from bursts. The goal of the algorithm is to be a screening tool for the detection of ENSs, to help neonatologists in detecting non-clinical seizures that might have damaging effects on the brain. Therefore we arbitrarily decided to start with only including ENSs with a duration of at least 60 sec.

The algorithm has been written in the mathematical program MATLAB® (The MathWorks, Massachusetts, USA).

Before detecting ENSs, artefacts were detected and rejected in a way similar to artefact detection of the CFM6000 monitor. In the monitor amplifier saturation and high impedance are marked as artefact. During amplifier saturation the aEEG signal reaches its maximum amplitude. In the algorithm these parts of the signal were classified as artefact as well. The signal is also classified as artefact when the impedance exceeds 20 k Ω , like in the monitor. Since an impedance beneath 5 k Ω is preferred (13), our algorithm marked the aEEG signal corresponding to impedances between 5 and 20 k Ω .

The ENS detection was based on the main characteristic change in the aEEG signal due to ENSs; a sudden increase of the lower boundary of the signal (Fig. 1). A lower boundary was defined every 10 sec of the signal as the 10th percentile of the samples, see Figure 2A. The reference boundary, i.e. the lower boundary of the background pattern, was calculated for each segment of 10 sec. It was defined as a weighted average of the lower boundaries over the last 6 min. ENSs and artefacts that occurred during the last 6 min were not included in the calculation of the reference boundary. Figure 2B gives an example of this reference boundary.

Subsequently, a sudden rise of the lower boundary of the aEEG signal was classified as a pattern of interest. The

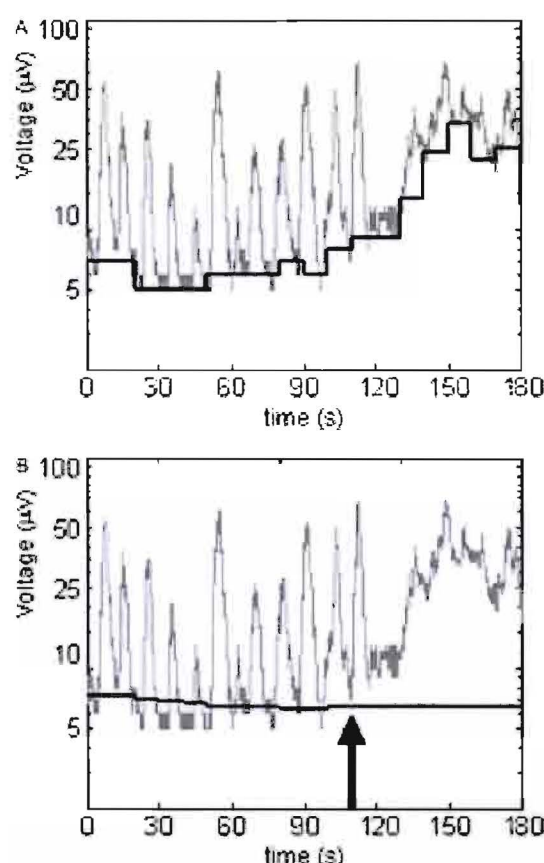


Figure 2 An aEEG signal of 180 sec. (A) The black line represents the lower boundary calculated for every segment, i.e. every 10 sec. (B) The black line represents the reference boundary calculated for every segment as a weighted average over the last 6 min. During the detected ENS, which starts in the graph at 110 sec (indicated by an arrow), the reference boundary does not change.

algorithm detected a pattern of interest whenever the lower boundary of the aEEG signal was at least an empirically determined threshold (EDT) higher than the reference boundary for a period of at least 60 sec. Whenever an artefact was detected during this increase, the parts of the pattern of interest not classified as artefact needed to have a total duration of at least 60 sec. Otherwise, the increase would be considered as artefact. The EDT value has been determined using a training set of five CFM recordings (recordings with ID A–E) annotated by a neurophysiologist.

Patterns of interest in the training set were caused by either ENSs or muscle activity. Muscle activity is characterized in the EEG signal by its high frequent fluctuations, containing frequencies reaching up to over 100 Hz (9). Cerebral electrical activity only contains frequencies of up to 30 Hz (1). Accordingly a pattern of interest containing in the EEG signal a high percentage of frequency power above 30 Hz was classified as muscle artefact. All other patterns of interest were classified as ENSs.

Evaluation of the algorithm

In this study it was intended to evaluate the ability of the algorithm to detect ENSs in CFM recordings, not the ability of CFM recordings to detect ENSs compared to standard EEG. Therefore evaluation was based on the CFM recording, containing both 1-channel EEG and aEEG signals.

Two neurophysiologists, observer1 and observer2, visually examined the CFM recordings for the presence of ENSs with a minimum duration of 60 sec. The examinations were performed independently with no preliminary consultation between the observers. They were not aware of the diagnosis of the newborns. Clear ENSs were annotated accordingly as well as patterns where the observer doubted if they were ENSs. Annotations were based mainly on the one-channel EEG signal displayed at 2.5 cm/sec and the aEEG and impedance signals, displayed at 6 cm/h. There were no options for scaling or frequency analysis.

From the two neurophysiologists, observer1 annotated the full length of the recordings and observer2 the first 6 h of each of the recordings. The recordings were divided into a training set and two test sets (Table S1):

- Training set: recordings A–E, annotated by observer1.
- Test set 1: recordings 1–8, annotated by observer1.
- Test set 2: the first 6 h of recordings 1–8, annotated by observer2.

The degree of agreement for these sets between the detections of the observers and the algorithm were found by comparing timeframes of 10 sec. The training set was used to train the algorithm and set its EDT value. Hypothetically this set would therefore have the highest agreement with the detections of the algorithm. The CFM recordings in the test sets were different from those in the training set. Test set 1 was annotated by the same observer as the training set. Test set 2 was annotated by an independent observer, observer2. This set had the least correlation with the training set, and would therefore hypothetically have the lowest agreement with the detections of the algorithm.

Statistical analysis

The interobserver agreement was determined based on notable ENS activity (NEA) for each of the first 6 h of the 13 recordings. We used an arbitrary threshold for NEA of at least three ENSs or an ENS of at least 3 min in 1 h recording (21). Subsequently we used the G coefficient (22) for the calculation of interobserver agreement. The G coefficient divides the variance of the data into different components related to their source. In our case the different components, the different patients (or CFM recordings) and for each patient the time within the recording. The G coefficient is then calculated as the extend to which the observers influence the total variance. The value of the G coefficient is therefore between 0 and 1, where 0 will be calculated when all the variance between the data is related to the variance between the observers, and 1 when the variance is not at all related to

the variance between the observers, i.e. there is no variance between the observers.

To evaluate the algorithm the sensitivity and false positives per hour (FPh) for each recording of each of the three sets have been calculated. However, sensitivity and FPh do not take into account the variability of ENS length and amount of ENSs between the CFM recordings. Therefore the recordings have been divided into segments of 1 min, each classified as ENS or non-ENS for each of the observers and the algorithm. This was used to calculate an intraclass correlation coefficient (ICC) (23,24) to compare the different sets. The ICC uses components of variance to calculate the correlation between pairs of observations, i.e. the reliability of these observations. The ICC was calculated separately for each of the sets explained above, compared to the algorithm.

RESULTS

Interobserver agreement

Two neurophysiologists, observer1 and observer2, independently analyzed the CFM recordings. We determined an interobserver agreement based on NEA for each of the first 6 h of the 13 recordings. Results are shown in Table S2.

A full interobserver agreement of NEA was found in nine of the 13 recordings. A high G coefficient of 0.82 has been found as overall interobserver agreement.

All interobserver disagreements were based on a higher amount of ENSs detected by observer1 compared to observer2. These disagreements were mostly caused by patterns in the EEG signals of high frequency and some rhythmic character. Especially in recordings 4 and 8 these patterns caused a large fluctuation in the lower boundaries of the aEEG signals (Figs 3B and C).

Evaluation of the algorithm

The algorithm is evaluated with the three sets described in the methods. The results are summarized in Table S3 A, B and C, respectively.

The values of ICC for comparison with each of these sets are given in Table S4.

Evaluation with the training set (Table S3A)

Since the algorithm has been trained on this set, the ICC value was very high, 0.99. For recordings A, C and E there was almost full agreement between observer1 and the algorithm, with sensitivities of 99–100% and FPh 0–0.42. Recording C showed a neonatal status epilepticus of frequently repeating ENSs that were all but one detected by the algorithm. Recording D, a recording with a relatively low interobserver agreement, had the lowest sensitivity, but still 81%. Recording B showed no ENSs. However this recording contained many muscle artefacts. Most of these artefacts were detected as such by the algorithm, but a mean of 1 FPh remained.

Evaluation with test set 1 (Table S3B)

This set of different CFM recordings had still a high ICC value of 0.95. In recording 1, a recording of 12 h that showed

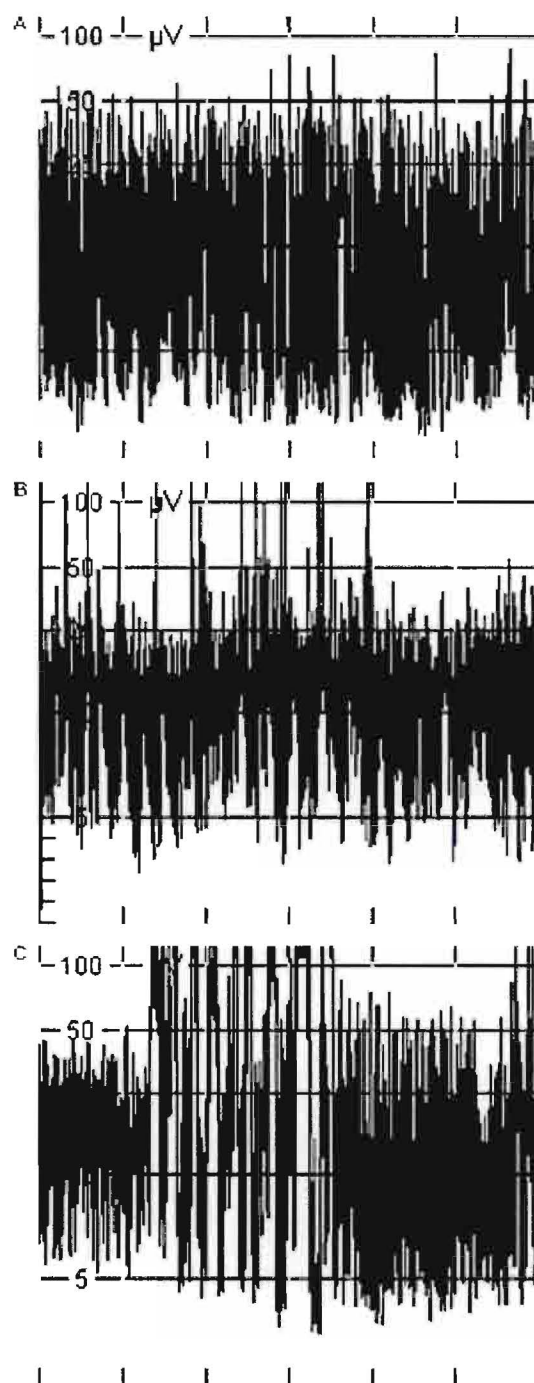


Figure 3 aEEG signals of 60 min. (A) Recording 4. (B) Recording 8. Both (A and B) show large fluctuations in the lower boundary that cause false and missed detections by the algorithm. (C) Recording 6. This part of the signal contains seizures where the amplitude of the aEEG signal immediately rises to its maximum value, i.e. amplifier saturation. The algorithm classified these patterns as artefacts.

no ENS, only one pattern was falsely detected as ENS by the algorithm. Of the remaining seven recordings, four had a sensitivity of 93–100%, including one recording that showed a status epilepticus. The FPh was in four recordings at highest 0.58 and overall at highest 1.89.

Three recordings had a low sensitivity. Recordings 4 and 8 had low interobserver agreements as well. These recordings showed large fluctuations in the lower boundaries of the aEEG signals, as shown in Figures 3A and B. For the algorithm these large fluctuations caused, depending on the durations and amplitudes, either false positives, or a rise in the reference boundary. Rises in the reference boundary may cause following ENSs to remain undetected. Recording 6 showed five ENSs with in the aEEG signal an immediate rise in amplitude to the maximum value as shown in Figure 3C. This so-called amplifier saturation caused these patterns to be detected as artefacts by the algorithm.

Evaluation with test set 2 (Table S3C)

This data set, containing different CFM recordings than the training set and annotated by an independent observer, was the least related to the training set. The ICC value of the ENS detections of the algorithm compared to this set was, as expected, the lowest value but was still good, 0.85. The set only included the first 6 h of each of the recordings.

The recordings with a full interobserver agreement of NEA had sensitivities of 90 to 100%. This was comparable to the values found for test set 1 in Table besides for recording 6. In recording 6 the ENSs that were falsely detected by the algorithm as artefacts, were not within the first 6 h of the recording, so were not included in test set 2. Therefore, the sensitivity was in this case 100%. The values for FPh were in all but one recording equal or slightly higher than in Table S3B, but never exceeding 1.33. For the recordings with low interobserver agreements, in recording 4 observer2 did not annotate any ENS and in recording 8 only one, which was not detected by the algorithm. The amount of FPh for these two recordings was as high as 4, caused by the large fluctuations in the lower boundaries of the aEEG signals.

DISCUSSION

In the present study, an algorithm for automatic screening of ENSs in neonatal CFM recordings is proposed. The purpose of the algorithm is to assist doctors and nurses in the interpretation of the aEEG signal and as an alarm function on the CFM monitor. A part of the algorithm detected artefacts, in order to distinguish them from ENSs. ENSs were detected based on their characteristic pattern in the aEEG signal, i.e. an increase of the lower boundary. Muscle activity, that may cause a similar rise in the lower boundary of the aEEG signal, was differentiated from ENSs by using the high frequency content of its pattern in the EEG signal. Other artefacts were detected by using the amplitude of the aEEG signal and the magnitude of the impedance.

Two neurophysiologists, observer1 and observer2, analyzed 13 CFM recordings for training and evaluation of the algorithm. For nine of the 13 recordings there was a full in-

terobserver agreement of NEA for each hour. An overall interobserver agreement of G coefficient 0.82 was found. Five CFM recordings annotated by observer1 were used to train the algorithm, the so-called training set. Eight recordings were used for further evaluation of the algorithm, test set 1 and test set 2 annotated by observer1 and an independent second observer, observer2, respectively.

For the recordings with full interobserver agreement of NEA the evaluation of this automatic seizure detection algorithm showed very high sensitivities and low FPh for most CFM recordings. All but one showed a sensitivity of 90% or higher when compared with either of the observers. The recording with a low sensitivity contained ENSs where the amplitude of the aEEG signal immediately rose to the maximum value. The algorithm therefore classified these patterns falsely as artefacts. The amount of FPh was only for two of the 10 recordings higher than 1, but never more than 1.33.

Of the four recordings with a lower interobserver agreement, two had sensitivities below 80% and FPh higher than 1 when compared to the annotations of observer1. These two recordings, both from the test set, showed large fluctuations in the lower boundaries of the aEEG signals. This caused the missed ENSs and false detections of the algorithm. Observer2 only detected 0 and 1 ENS in these recordings. In a second review of these two recordings, the observers advised that clarification about the presence of ENSs should be given by standard EEG measurements.

The ICC values for the different sets were high and decreased for sets that were less related to the training set. This relationship was expected and indicates the reliability of the evaluation method.

Automatic ENS detection methods based on standard EEG recordings have been described earlier, based on minimum ENS durations of 10 sec. Liu et al. (25) described an automatic ENS detection based on the repetitive character of seizure induced EEG signals. He found a sensitivity of 84% and a specificity of 98%. Another important study of Gotman et al. (26) was more comprehensive, and also included detection of spikes that may not be rhythmic. His thorough evaluation resulted in a sensitivity of 69% and 2.3 false positives per hour (27). More recent algorithms were based on time-frequency (28) or wavelet analysis (29), that detect the repetitive structures by their characteristic evolution of frequency in time. These algorithms were not evaluated. An algorithm based on synchronization likelihood, detected statistical interdependencies between EEG channels. A sensitivity of 65.9% and a specificity of 89.8% were found in its evaluation (30). Finally Navakatikyan recently published an interesting algorithm comparing intervals, amplitudes and shapes of consecutive waves to detect ENSs. The evaluation showed a sensitivity of 83–95% with 2.0 false positives per hour (31).

EEG is the golden standard for the detection of ENSs. However, for long-term monitoring and ENS detection outside office hours when EEG may not be available, CFM is a useful tool. Automatic ENS detection in EEG signals is extremely complex due to the variation in morphology and

frequency between and within ENS patterns. This makes algorithms for their automatic detection complex and still in need of validation by medical specialists. CFM processes the EEG signal into a relatively easy to interpret aEEG signal. In these signals ENS patterns have similar morphologies: the rise of the lower boundary of the aEEG signal. Remarkable is, the relatively straightforward detection of these patterns, including artefact rejection, resulted in high sensitivities in combination with low false positives per hour for ENSs of at least 60 sec.

Some remarks need to be made here. First, although high sensitivities and low false positives per hour were reached, the detections of the algorithm are still in need of validation by clinicians, i.e. the final decision about the presence of seizure activity still needs to be made by the clinicians. The second remark concerns the limited amount of channels measured in CFM. Due to this type of measurement some focal ENSs can be missed. However, CFM measurements are not intended to be a substitute for standard EEG. The standard EEG measurements for detailed registrations and a more extensive spatial examination of the brain function are complemented by the CFM measurements that facilitate long-term monitoring. Third, we arbitrarily chose to include only ENSs of at least 60 sec in this study, due to the compressed nature of the aEEG signal and the aim to use the algorithm as a screening tool. Future research will aim to decrease this minimum duration of included ENSs. Finally, some false or missed episodes occur in recordings with extremely high fluctuations in the lower boundaries of the aEEG signals and ENSs that cause immediate amplifier saturation.

Clinical relevance of automatic ENS detection is related to the question if seizures cause damage to the brain of the newborn. The newborn brain is more susceptible to seizures, but also more resistant to brain injury. Furthermore, neurological sequelae following neonatal seizures are mainly due to the aetiologies of these seizures (32). However, due to their energy-consuming mechanisms, seizures may effect activity-dependent changes in the developmental processes of the brain (33). Both Scher (5) and Ben-Ari (34) indicate that prolonged or frequent seizures do have a long-term effect on the newborn brain, mainly due to the interference with its development.

This study introduced an algorithm for the screening of neonatal ENSs in aEEG signals with rather good results. The algorithm facilitates the interpretation of aEEG signals in clinical practice and can be used as an alarm function on the CFM monitor. However, some points of improvement could increase the reliability of the algorithm in terms of sensitivity and FPh. First, ENSs with an extremely high amplitude (Fig. 3C) need to be detected as true ENSs. Second, a function should be included to recognize recordings with a large fluctuation in the lower boundary of the aEEG signal, which reduces the reliability of the ENS detection. In this case human validation is necessary and possibly the measurement of a standard EEG. Third, in the training of the algorithm as well as in the evaluation, more recordings should be included. These recordings should be annotated by more than

one neurophysiologist, since the algorithm replicates the detections of these neurophysiologists. Besides these points of improvement, also ENSs with a duration less than 60 sec should be included. These are new goals for our future research.

CONCLUSIONS

An automatic detection algorithm for neonatal seizures in aEEG signals was developed and evaluated in this study. In the evaluation rather good results were found for recordings with clear ENSs. The algorithm developed, facilitates the interpretation of aEEG signals in clinical practice and may be used as an alarm function on the CFM monitor.

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Supplementary material

The following supplementary material is available for this article:

Table S1 Clinical details of the patients and their CFM recordings that were used in this study. The aEEG background patterns are categorized as continuous normal voltage (CNV), discontinuous normal voltage (DNV) or burst suppression (BS) (19). The ENSs are categorized as either repetitive ENSs (RS) or status epilepticus (SE)

Table S2 Notable ENS activity (NEA) in the first 6 h of the 13 recordings according to observer1 and observer2, and their disagreement. For NEA we used an arbitrary threshold of at least three seizures or a seizure of at least 3 min/h

Table S3 Comparison of the ENS annotations by one of the observers with the ENS detections of the algorithm, given in number of ENSs (nr) and amount of ENS minutes (min). Sensitivity and false positives per hour (FPh) were calculated from the number of ENSs. (A) The training set compared to the algorithm. (B) Test set 1 compared to the algorithm, containing the full recordings 1–8, annotated by observer1. (C) Test set 2 compared to the algorithm, containing only the first 6 h of each recordings, annotated by observer.

Table S4 The intraclass correlation coefficient (ICC) calculated for the ENS detections of the algorithm compared to the training set and the two test sets. Test set 1 was annotated by the same neurophysiologist as the training set, test set 2 by an independent neurophysiologist.

This material is available as part of the online article from: <http://www.blackwell-synergy.com/doi/abs/10.1111/j.1651-2227.2007.00223.x>

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Supplementary material

TABLE S1. Clinical details of the patients and their CFM recordings that were used in this study. The aEEG background patterns are categorized as continuous normal voltage (CNV), discontinuous normal voltage (DNV) or burst suppression (BS) [19]. The ENSs are categorized as either repetitive ENSs (RS) or status epilepticus (SE).

ID	GA (weeks)	BW (kg)	Apgar 5'	pH	SARNAT [20]	diagnosis	aEEG age (days)	Background pattern aEEG [19]	ENS
A	41	3.04	8	6.98	III	asphyxia	0	DNV	RS
B	34	2.45	7	-	-	-	2	BS	-
C	38	4.58	2	6.88	II	asphyxia	1	BS	SE
D	40	3.50	10	-	-	hypoglycemia	3	DNV/BS	RS
E	39	4.22	8	6.82	II	asphyxia	1	BS	RS
1	40	2.48	6	7.14	II	asphyxia	2	CNV	-
2	38	2.43	8	-	II	asphyxia	2	DNV	RS
3	41	4.06	1	6.7	III	asphyxia	1	BS	SE
4	33	2.23	4	6.73	II	asphyxia	2	BS/DNV	RS
5	40	3.59	8	-	-	Fam. benign seizures	3	CNV	RS
6	42	3.90	5	-	II	asphyxia	3	CNV/DNV	RS
7	40	3.70	5	6.94	II	asphyxia	2	DNV	RS
8	40	3.20	5	6.88	III	asphyxia	3	DNV/BS	RS

TABLE S2. Notable ENS activity (NEA) in the first 6 hours of the 13 recordings according to observer1 and observer2, and their disagreement. For NEA we used an arbitrary threshold of at least 3 seizures or a seizure of at least 3 minutes per hour.

ID	NEA Obs1	NEA Obs2	Dis-agreement
A	6	5	1
B	0	0	0
C	6	6	0
D	3	1	2
E	4	4	0
1	0	0	0
2	3	3	0
3	5	5	0
4	3	0	3
5	1	1	0
6	1	1	0
7	0	0	0
8	1	0	1

TABLE S3. Comparison of the ENS annotations by one of the observers with the ENS detections of the algorithm, given in number of ENSs (nr) and amount of ENS minutes (min). Sensitivity and false positives per hour (FPh) were calculated from the number of ENSs. A) The training set compared to the algorithm. B) Test set 1 compared to the algorithm, containing the full recordings 1 through 8, annotated by observer1. C) Test set 2 compared to the algorithm, containing only the first 6 hours of each recordings, annotated by observer2.

A

ID	Total length (min)	ENSs found by:				sensitivity (%)	FPh
		Observer1		Algorithm			
		(nr)	(min)	(nr)	(min)		
A	827	40	258	45	269	100	0.36
B	720	0	0	12	47		1.00
C	880	161	446	172	463	99	0.82
D	695	13	58	15	65	81	0.42
E	1080	2	117	2	117	100	0

B

ID	Total length (min)	ENSs found by:				sensitivity (%)	FP/h
		Observer1		Algorithm			
		(nr)	(min)	(nr)	(min)		
1	720	0	0	1	2		0.08
2	1320	14	60	39	112	93	1.18
3	540	45	151	47	160	98	0.33
4	1078	38	89	56	128	57	1.89
5	709	5	18	12	36	100	0.58
6	1260	8	28	5	22	25	0.14
7	720	1	3	3	8	100	0.17
8	1397	6	15	31	104	17	1.49

C

ID	Total length (min)	ENSs found by:				sensitivity (%)	FP/h
		Observer2		Algorithm			
		(nr)	(min)	(nr)	(min)		
1	360	0	0	1	2		0.17
2	356	10	47	14	52	90	0.83
3	360	31	108	34	119	100	0.50
4	356	0	0	22	54		4.00
5	358	4	14	10	36	100	1.33
6	351	2	9	5	13	100	0.50
7	360	1	4	2	7	100	0.17
8	346	1	2	6	13	0	1.00

TABLE S4. The intraclass correlation coefficient (ICC) calculated for the ENS detections of the algorithm compared to the training set and the two test sets. Test set 1 was annotated by the same neurophysiologist as the training set, test set 2 by an independent neurophysiologist.

Algorithm compared to:	ICC
Training set	0.99
Test set 1	0.95
Test set 2	0.85

Appendix N

Automatic analyses EEG of prematures

This appendix concerns the automatic analyses of EEG of prematures, for the description of maturation of the brain. This project is part of the PhD program of drs. Hendrik Niemarkt, and is the master's thesis of MSc Loes Ruijs, who did the project under my supervision. The appendix gives chapter 1 and parts of chapters 4 and 6 as a summary of this project.

Chapter 1 Introduction

In the Netherlands, 7-8 % of all babies are born premature, i.e. born before 37 weeks of gestation [5;6]. Due to prematurity, these infants may have underdeveloped and malfunctioning organs. As a consequence, they are at higher risk for disorders of vital functions.

With follow-up of premature born infants into school age and adolescence, it has become apparent that about 40 % of these infants are exhibiting neurobehavioral problems [7;8]. These problems consist, among other things, of moderate cognitive impairment, attention deficits and behavioral disturbances. Remarkable is that many of the premature infants who have brain dysfunction, do not show detectable brain lesions [7;8]. This makes early recognition of the neurobehavioral problems more difficult.

The exact etiology of the neurobehavioral problems of premature infants has not been clarified yet. Possibly, the problems are caused by the exposure of the immature developing brain to noxious factors that normally do not reach the fetal brain in utero. Many clinical factors (e.g. apnea, bradycardia and nutritional deficiencies) as well as stressful environmental conditions (including medical care interactions, constant noise, and bright light) may act in combination to impact on the developing brain [9;10]. The premature brain is probably more susceptible to these factors than the brain of a full-term infant, because critical steps in human brain development take place in the third trimester of gestation, i.e. 28 till 42 weeks of gestation [10;11].

Since the pathogenesis of the neurobehavioral problems of premature infants is still unclear more research regarding this topic is necessary. First of all, it is important to have a description of brain development of the cerebral healthy premature infant. This description can be used as a reference for determination of pathological conditions that have an adverse influence on brain development and for studying effectiveness of possible therapeutic interventional strategies.

In continuation of this study the focus will be on brain maturation of cerebral healthy premature infants. Next, a method for the description of brain maturation and its drawbacks are described. From these, the aim of this study will follow.

1.1 Changes in the electroencephalogram reflect brain maturation

Electroencephalography is regarded as the gold standard in the assessment of cerebral function and is one of the most powerful tools for predicting neurological outcome in preterm and term infants [12;13].

Changes in the electroencephalogram (EEG) reflect functional brain development from preterm to term age [14-16]. Typical EEG patterns change as a function of gestational age (GA), postmenstrual age (PMA, GA plus the time elapsed from birth in weeks [17]) and the infant's state of wakefulness [18]. The states of wakefulness are categorized in phases of sleep and awake. The difference between GA and PMA is made, because it is assumed that brain maturation within the womb progresses different from outside the womb [18].

Characteristics of EEG patterns at different ages can be described in terms of: continuity, amplitude and frequency, interhemispheric synchrony, and presence of specific maturational patterns and transients [15;19;20]. The progressive development of continuity of activity provides the most immediate visually striking aspect of the EEG reflecting brain maturation.

Continuity of EEG activity

For the premature infant two distinct background patterns are recognized that together form the components of continuity, see Fig 1. A background pattern refers to the characterization of EEG activity in terms of stability or fluctuation of amplitude and the variation in time without taking artifacts and characteristic patterns into account. The two background patterns for the premature are:

- Continuous: characterized by medium-high voltage slow waves, Fig 1.A.
- Discontinuous: bursts constituted by high voltage slow waves, separated by low amplitude waves, the interburst intervals (IBI), see Fig 1.B.

The continuous pattern, burst, and IBI are the three components of continuity. Henceforth, "events of continuity" is used to cover the bursts, IBI and the continuous pattern together.

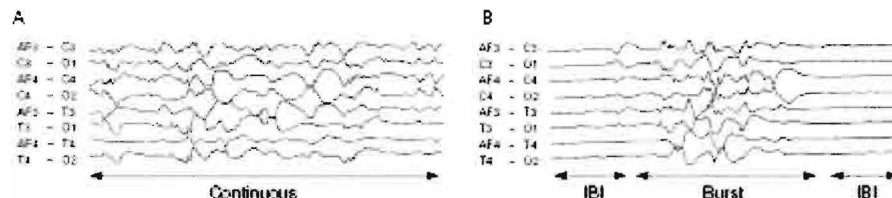


Figure 1: EEG background patterns of a very preterm infant (PMA 24 wk). A) Continuous pattern; B) Discontinuous pattern, IBI = interburst interval. [4]

An overall trend seen in continuity of the EEG background pattern of preterm infants till term age is a gradual change from a discontinuous pattern to a continuous pattern [3;4;12-15;21]. For the infant younger than 30 weeks PMA, most recordings will consist of only discontinuous EEG. As an indication, the percentage of discontinuous activity decreases from about 64% at 27-28 weeks to approximately 45 % at 31-32 weeks and is no longer present in any state after 46 weeks PMA [22]. On the other hand, EEG continuity increases in percentage of recording time with increasing PMA. The changes in continuity comprise increasing duration of burst, a decrease of burst amplitude, reducing lengths of IBIs, and increase of IBI amplitude to the appearance of continuous patterns [3;4;12-15;21].

1.2 Difficulties EEG assessment

Even though there is a consensus of the trend of development of continuity, no clear definition of development of continuity of the cerebral healthy premature brain is stated yet. Potential parameters describing maturation are: time percentages, minimum and mean duration, and numbers of each event of continuity [1;4;12;23-26]. Studies using these parameters show the same trend in changes of continuity, but the values vary between different studies. For example, two studies [12;23] determined maximum IBI lengths for infants of 29-30 weeks PMA. This resulted in 12 s for one study [23] and 30 s for the other study [12].

Factors influencing the variation in parameter values describing changes in continuity consist of: the different GAs of prematures included in a study group, obscure definitions of cerebral healthy infants, use of different definitions for events, and visual scoring of the observers. Starting with the difference in GA, some studies classified infants by PMA irrelevant of the GA [12]. Due to this, a group of infants with a PMA of 32 weeks can consist of infants with a GA of 27 weeks who are 5 weeks old and infants with a GA of 31 weeks who are 1 week old. However, these infants have passed through different periods of extra uterine life, which is believed to influence brain maturation [18]. Second, the condition of the infant was not well defined in several studies. Of these studies it was not clear if the infants included were cerebral healthy and / or used medication. As a rule, only EEG registrations are made if it is expected that the infant will show abnormal behavior. As a consequence, for the

description of maturation of the cerebral healthy infant no EEGs of cerebral healthy infants were available and the EEGs of the cerebral healthiest infants were used instead [16]. However, cerebral healthiest does not indicate that the infants were indeed cerebral healthy. Moreover, many of these infants use medication that may as well affect the EEG. For example, of morphine it is known that it increases discontinuity [27]. Third, great variations of definitions were used for burst, IBI, and the continuous patterns in former studies. Differences in definitions consisted, among other things, of considerably varying amplitude criteria that even were overlapping for the different events of continuity [4;12;18;23-25;28]. Moreover, some studies did not differentiate between the continuous pattern and bursts [24;25]. Finally, traditionally EEG scoring has been performed by visual inspection of records. This procedure requires an expert neurophysiologist and is because of that subject to interobserver variability. Moreover, it is time-consuming and expensive.

1.3 Goal and outline

An unambiguous description of brain maturation of the cerebral healthy premature infant is necessary to serve as a reference for determination of causes of neurobehavioral problems affecting 40 % of the premature born infants. However, due to differences in research conditions of former studies and disagreement on thresholds within visual inspection, a clear description of brain maturation of the cerebral healthy premature infant does not exist yet.

To overcome the differences in ages and conditions of the infants included in a study, strict criteria of infants participating must be formulated. Furthermore, consistent definitions of the events of continuity have to be formulated and EEG assessment has to become less subjective. A solution for these last mentioned requirements could be the use of a computer-based method for EEG assessment. A computer-based method will identify the events of continuity based on absolute values and is therefore not dependent of subjective interpretations of human observers. The use of absolute values forces the physician to formulate consistent definitions of the events of continuity. Besides, a benefit of a computer-based method for analyzing EEG is that it will be timesaving for the physician.

Therefore, the aim of this project was to develop an automatic detection method of the events of continuity for the description of the development of continuity of cerebral healthy premature infants. For the description of development of continuity, bursts, IBIs, and the continuous patterns had to be detected from the EEG first. Later on, the parameters changing with continuity related to the events of continuity, e.g. numbers, percentages, and lengths, can be determined based on the detected events of the cerebral healthy premature infant.

For this purpose, infants included in the study were born before thirty weeks of gestation. Due to this conditions it was restricted that the infants included had a large difference in GA. Besides that, each infant had to meet strict requirements regarding cerebral health. Each infant was measured weekly from the first week after birth. Obtained data varied from 29 weeks PMA up to 34 weeks PMA. The developed algorithm detected burst, IBI and continuous patterns of the EEG based on common characteristics of these events: amplitude of the EEG signal, time of duration and amount of channels in which activity was detected at the same time. For training and validation of the algorithm, detections of the algorithm were compared with annotations of two clinical neurophysiologists.

This Master thesis first provides background information about EEG signals and recording (chapter 2), followed by a description of physiological maturation of the brain and changes in EEG characteristics from preterm up to term age (chapter 3). Next chapter describes the development of the algorithm based on literature and annotations of the two clinical neurophysiologists. Results of the evaluation of the algorithm are shown in chapter 5. Finally, this report will be ended with a discussion of obtained results and used methods, recommendations for further research, and a conclusion.

Examples of discontinuous and continuous EEG signals.

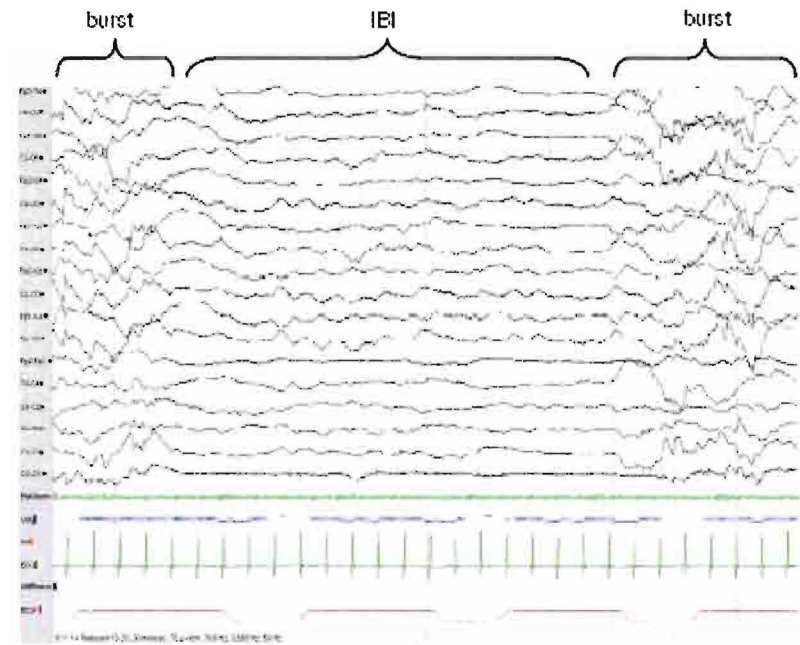


Figure 23: Example of 12 s of discontinuous background pattern consisting of burst and IBI events. The events detected by the algorithm were assessed as correct by the observers.

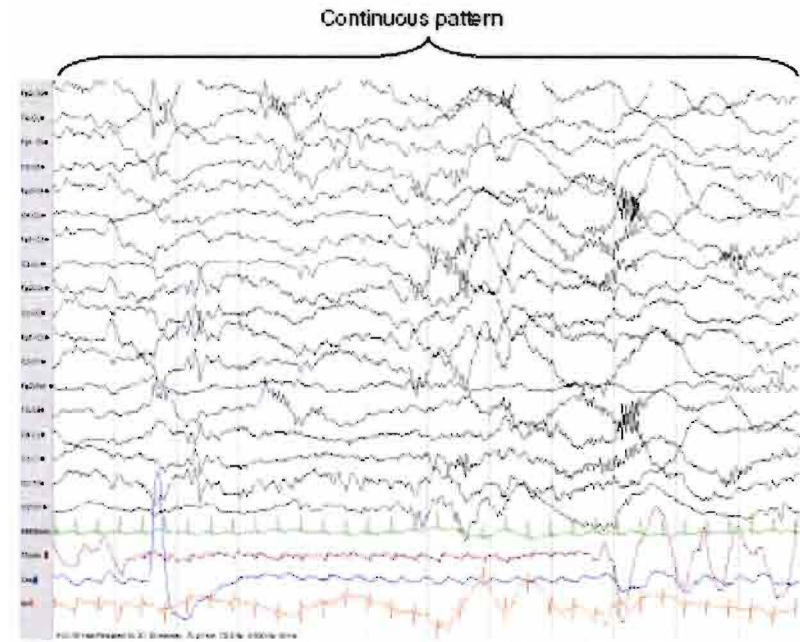


Figure 24: Example of 12 s of a continuous pattern detected by the algorithm, which was examined as correct by the observers.

From chapter 4, an overview of the detection of bursts and continuous patterns (figure 14) and interburst interval (IBI) detection (figure 15).

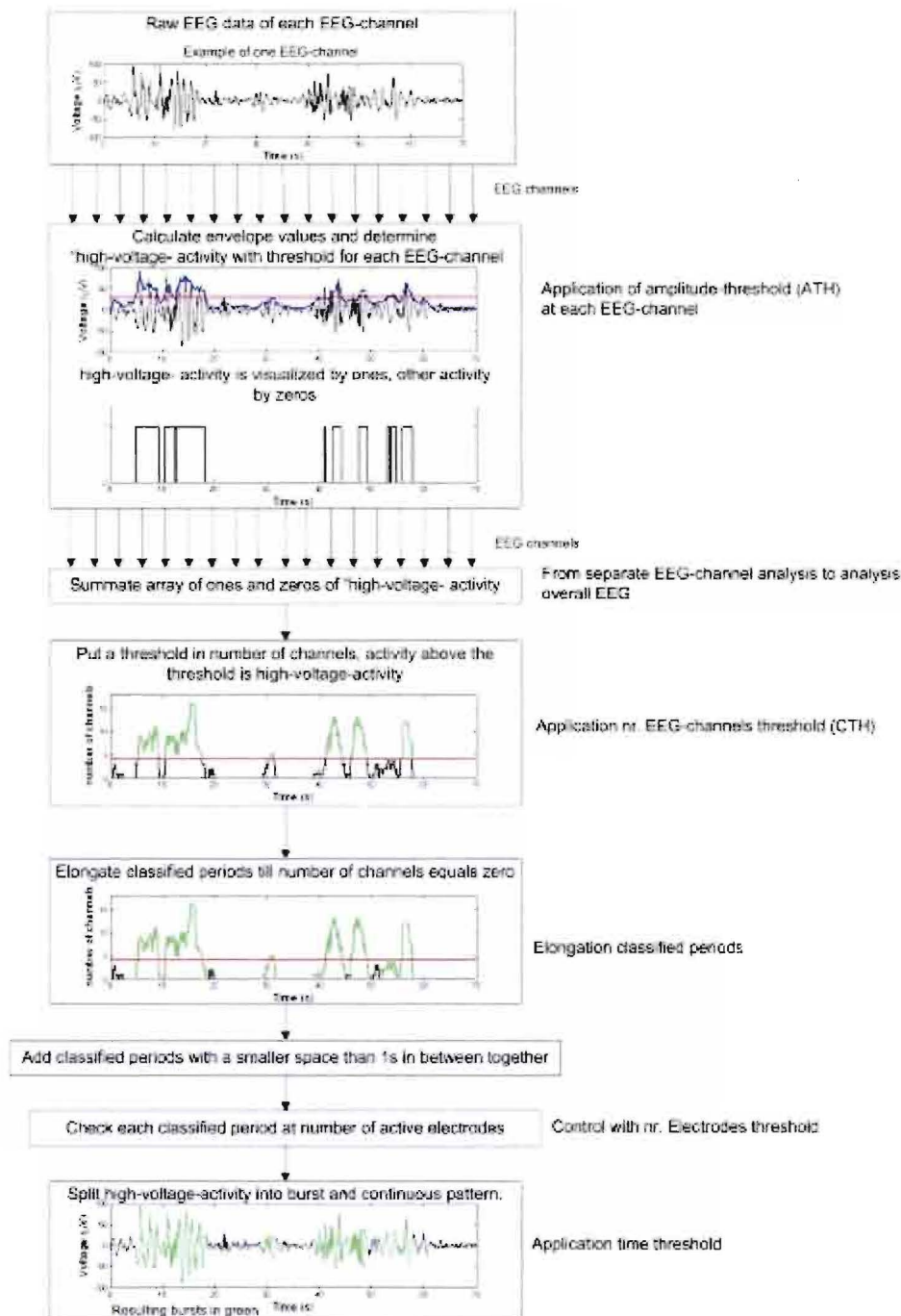


Figure 14 : Overview of procedure for detection of bursts and continuous patterns. The procedure is started with analysis of each EEG-channel separately. At the end, one overall detection is made for the EEG-channels. More information of the steps carried out can be found in the text corresponding with the headlines next to the figures.

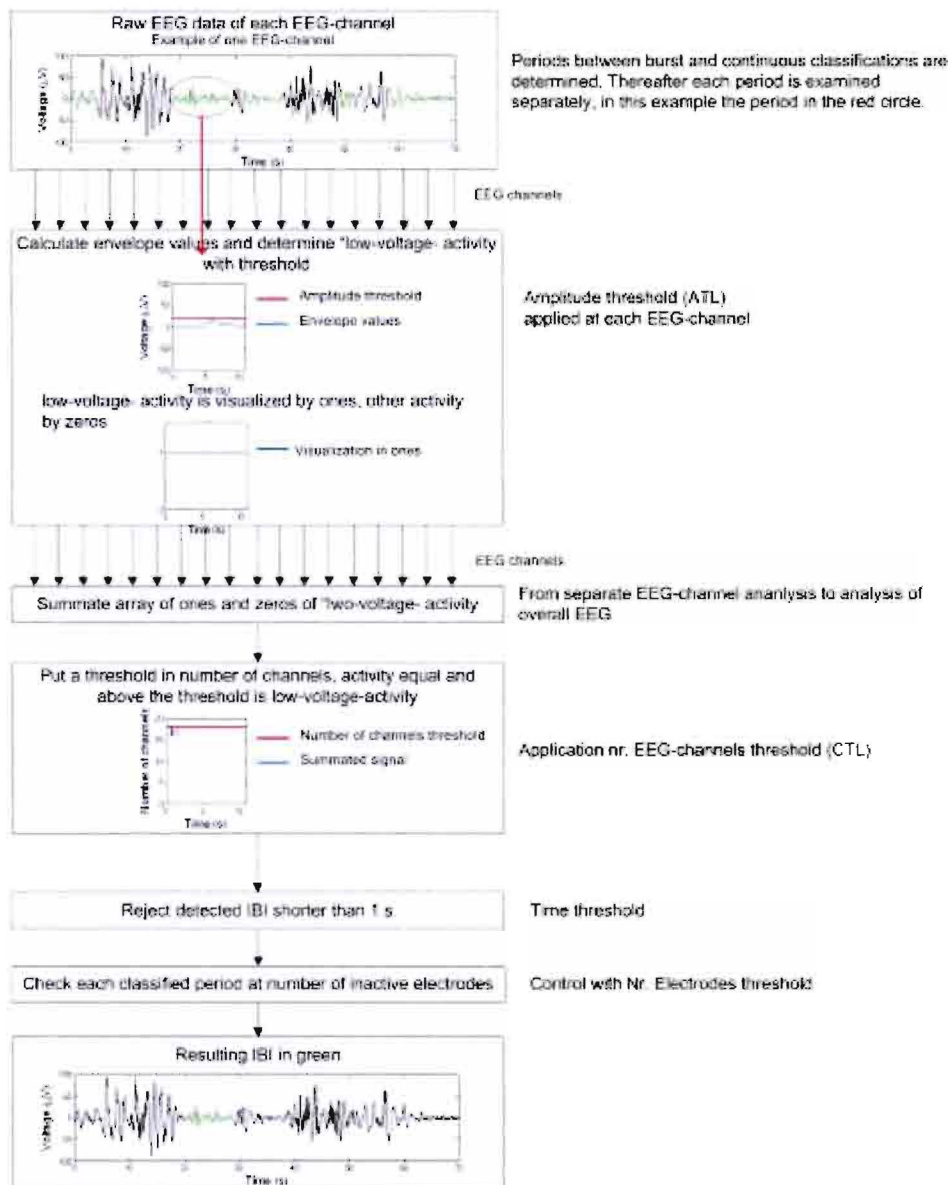


Figure 15: Schematic overview the procedure of IBI detection. More information of the steps carried out can be found in the text corresponding with the headlines next to the figures.

From chapter 6, some comments concerning the training and the evaluation of the algorithm, and a final conclusion.

For training of the algorithm annotations of two independent observers were used. The overview of the annotations made by the observers showed to be similar. However, when viewing the annotations in detail the agreement of the observers was small. The annotations of burst and IBI resulted in a fair agreement. The annotations of the continuous patterns had a slight agreement. It was not expected that the agreement of the observers was so small. Although the annotations were used to train the algorithm, for the future it is recommended that some factors influencing the way the annotations were made by the observers are avoided.

Results of evaluation of the algorithm indicated that both observers did agree on average with more than 80% of all detections. For the detection of IBI, the mean PPV for both observers was even 96%. Mean SNS values were also above 90 %, except for IBI detection according to observer1 who had a mean SNS of 75%. Highest mean SNS value was scored for the continuous pattern, both observers had a mean SNS above 94 %. Overall, observer1 scored higher PPVs and SNS values than observer2. Within the values of PPV and SNS for each of the events of continuity no trends relating to age were visible. The high mean values of PPV and SNS are promising for the usability of the algorithm to detect bursts, IBIs, and continuous patterns of the cerebral healthy premature infant born before 30 weeks GA with a PMA of 29-34 weeks. However, because correct on- and offset was not taken into account with the evaluation of the algorithm the detected events cannot be used directly to describe development of continuity. Because, for the description of development of continuity the time percentages, numbers and lengths of events are important. More research regarding events detected visually by observers and detected by the algorithm is necessary before it is sure that the algorithm detects events of correct time span. Recommendations for further research regarding the annotations and detection of events of continuity are further worked out in the next two paragraphs.

6.4 Conclusion

The aim of this project was to develop an automatic detection method of the events of continuity to describe the development of continuity of cerebral healthy premature infants. An algorithm was developed for premature infants born before thirty weeks of gestation with postmenstrual ages of 29 up to 34 weeks. Detection parameters distinguishing the events of continuity from each other consisted of amplitude, time span, and number of channels involved. Moreover, each detected event was checked at the number of electrodes involved with the event. Evaluation of the developed algorithm resulted in high values for the sensitivity and positive predictive value for both observers who checked the detection of the algorithm. However, before the algorithm can be used to follow development of continuity of the premature infant more research has to be devoted to it. With evaluation of the algorithm no correct on- or offset of the events was taken into account, therefore it is not known if exact lengths of events are detected. Discussion of the FalseNegatives and FalsePositives of the algorithm showed already that IBI are not detected as a whole. Further, the definition of the continuous background pattern needs more attention to specify the difference between tracé alternant and tracé continu. For the detection of bursts it is recommended that movement-artifact detection will be implemented in the algorithm to avoid that movement-artifacts are detected as bursts. Furthermore, annotations of more children of exact the same gestational age and annotations of more observers using the same annotation protocol are necessary to make the algorithm more robust for the detection of the events of continuity.