University of Twente

Bachelor Technical Medicine

Multidisciplinary Assignment

Final Report

'A combined BIS/NIRS sensor for detecting cerebrocortical oxygenation and activity in the ICU'

Authors:
T.G.W. Boers
N. Durmus
H.J. Lievestro
M.P. Mulder

Client:
Prof. dr. J. Bakker *Erasmus Medical Centre Rotterdam*

Supervisors:
Prof. dr. J. Bakker *Medical*
Dr. E.J.O. Kompanje *Medical*
L.M. van Loon, MSc *Technical*
A.H. Jonkman, BSc *Process*

UNIVERSITY OF TWENTE.

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Abstract

PROBLEM: Currently, the state of the brain is usually not measured in the Intensive Care Unit (ICU). Especially in dying patients, it is interesting to know when irreversible brain damage has occurred. Also, the progress of ischemia in the brain, the occurrence of irreversible damage and assurance about loss of consciousness are important to know. A small sensor is needed to provide a natural looking death of the patient to prevent the discomfort of relatives.

OBJECTIVE: The goal of this multidisciplinary assignment is to develop a combined and subtle BIS/NIRS sensor, which can simultaneously measure oxygenation and activity of the brain cortex and detect differences in these parameters, as a result of performed physiological interventions in healthy subjects.

BACKGROUND: Normally, the blood flow through the brain is kept constant using sophisticated autoregulatory mechanisms. When the cerebral perfusion pressure (CPP) becomes to low and therefore out of range for the autoregulation, ischemia will develop if the ability of increasing oxygen extraction is not enough to meet metabolic needs. If the ischemia persists, a cascade of events will ultimately lead to irreversible damage of the brain.

Near infrared spectroscopy (NIRS) is based on the difference in absorption between hemoglobin and deoxyhemoglobin, and measures oxygenation of the brain cortex. Bispectral index system (BIS) uses electroencephalography (EEG) electrodes to detect differences in the electric potentials as created by the neuronal activity in the brain cortex.

DESIGN: The frontal cortex plays a crucial role in maintaining consciousness and is thus the preferred place to measure combined function and perfusion. The NIRS should measure the cerebral perfusion, at a depth of 20 mm. The spacing between light source and the detector should therefore be 40 mm. The BIS electrodes are all placed on positions of the international 10/20 sensor position system for EEG. Normally, the electrodes are placed at FPz, FP1, FT9 and AF7, but these positions may vary within the different designs during this study.

EXPERIMENTS: The NIRS and BIS are combined into various designs, from which a top 4 is tested. A comparison is made between the different locations. Also they are tested for interdependent disturbances. The chosen designs are then further tested while performing interventions like the Valsalva maneuver and crash position.

RESULTS: The lateral design has a lower average for both BIS and NIRS signals, than the frontal. Both the lateral designs have more fluctuating BIS data and show more signs of distortion. The NIRS signals of design A clearly increase or decline during the interventions, but no pattern is seen within the BIS data.

CONCLUSION: The frontal design A, which is very similar to the original of the BIS and NIRS design, is chosen to be the best design. This model showed the least distortion, while delivering the best results during the intervention trials in which the oxygenation seems to be measured. Within this research, a combination of BIS and NIRS measurements did not show any correlations.

RECOMMENDATIONS: With design A as a starting point, further research should primarily focus on the quality of the signal as captured by the sensor, eventually followed by the validation of the final design. A NIRS sensor with optical fibers is recommended to make smaller and more integrated designs. Also, it may be useful to consider using electrocardiography (ECG) electrodes instead of the BIS sensor. The disturbance should be measured on a phantom or dummy, to be certain that the two signals do not interfere with each other. In the future, other technique and applications may be studied as well.

List of abbreviations

BCI Brain computer interface

BIS Bispectral index system

CBF Cerebral blood flow

CPP Cerebral perfusion pressure

CSF Cerebral spinal fluid

ECG Electrocardiography

EEG Electroencephalography

EMG Electromyography

EOG Electrooculography

ICU Intensive care unit

LED Light emitting diode

MRI Magnetic resonance imaging

NIRS Near infrared spectroscopy

rSO_2 Regional oxygen saturation

SSVEP Steady-state visual evoked potentials

SR Suppression rate

TCD Transcranial doppler

tDCS Transcranial direct current stimulation

Preface

This is the end product of our multidisciplinary assignment, the final project of the Bachelor Technical Medicine. In a few more days we hope to receive our diploma and accompanying degree. The last ten weeks we worked hard to get to know the subject, each other and the mystery of the human brain.
We would like to thank our supervisors from the Erasmus Medical Centre in Rotterdam, Jan Bakker and Erwin Kompanje for coming up with this assignment and helping us to understand the problem. Also Alexandre Lima and Mathieu van der Jagt provided us with data and material and thought with us, even though this was not their project. We thank Debby Frenken of Covidien Nederland B.V. for arranging materials and crucial information in a very brief period of time.
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Enjoy reading,

Tim Boers, Nariç Durmus, Huub Lievestro and Marijn Mulder.

Conflicts of interest statement

The authors of this paper hereby declare that they have no financial, personal or other conflicts of interest in this study.

1 Introduction

On 27 January 2010, Medisch Contact [1] has published an article about the importance of neuromonitoring in the Intensive Care Unit (ICU). The focus of ICU monitoring is mostly on the cardiovascular and pulmonary systems. Currently, parameters like ElectroCardioGraphy (ECG) registration, systemic blood pressure, heart rate and pulse oximetry are being performed by default. In contrast, the recording of the cerebral function is unconventional. Monitoring of the brain physiology of an ICU patient is usually started when an unexplained drop or change in consciousness occurs. By that time, the underlying pathological process may have already become irreversible. According to the authors of the article, bedside cerebral monitoring is necessary to detect these events as they happen, so something may still be done about it. Preferably, the intensivists should be able to initiate and asses these recordings by themselves. Furthermore, such a monitoring device has to meet the following requirements: one or more pathophysiological variables (like cerebral metabolism, perfusion or pressure) should be recorded, this parameter should be expressed in a simple unit and the measurements should be done non-invasive and patient friendly. The authors recognize some already existing monitoring devices, which meet these criteria, as possible candidates for a cerebral monitoring system. These techniques are near infraRed spectroscopy (NIRS), the bispectral index system (BIS), transcranial doppler (TCD) and the monitoring of the autonomic nervous system using online analysis of the variations in ECG signal and blood pressure.

So, bedside cerebral monitoring within the ICU may be improved. This study will focus on the use of NIRS and BIS simultaneously in dying patients. The new device should measure two important parameters: the brain's cortical electrical activity and oxygenation. Both techniques are already being used. In the Operation Room, the anesthetist utilizes a very easy to use BIS sensor to monitor the deepness of sedation. This BIS is a simplified electroencephalography (EEG) and measures the brain's electric potentials. For measuring tissue perfusion NIRS will be used, which determines the oxygenation level of blood through near infrared light absorption. When choosing these combination of sensors, the pathophysiological processes in the ischemic brain were taken into account. Expected is that when a cardiac arrest occurs, the activity of the brain as measured by the BIS, will almost immediately drop to zero. However, it takes some time before the brain damage becomes irreversible. Therefore, another parameter should be measured to provide the full picture. In this case, the NIRS would be a good option: as the blood supply to the brain has stopped, the oxygenation of the brain cortex will slowly decline. A combination between these two techniques could make a useful device for monitoring the brain and provide the needed information of the state of ischemia in the cortex. This will provide physicians with added assurance the patient has irreversible brain damage and the cascade of ischemia in the whole brain has started.

If such a device works and gives reliable information, it could be of use in research and hospitals. Although brain ischemia can be measured with other widely used techniques, this study considers the development of a simple, non expensive, non invasive, non time-consuming and real time bedside monitoring device. Using this new sensor, more research can be done in brain ischemia and the moment irreversible damage occurs. Preferably, a dying patient should not undergo all kind of invasive tests. The death of a patient is a tough situation for the patient's family. The relatives have to be confident their loved one is really deceased and will not be aware of the following interventions. The process of dying should seem as natural as possible and therefore it is not desirable to connect a lot of devices and wires to the patient. In the ICU, or in other hospital departments, the sensor would make a difference by providing bedside information about the well-being of the brain cortex. In the case of withdrawal of life support, it would give the physician insight in the occurrence of irreversible brain damage in the cortex.

Bedside neuromonitoring is being extensively studied in a great number of clinical trails around the world.[2] Most studies focus on the use of microdialysis, NIRS, EEG and evoked potentials. Separate but simultaneous measurement of the NIRS and EEG signals has been studied by Jindal et al.[3], Cooper et al.[4] and Roche-Labarbe et al.[5] The research is not only confined to purely medical applications, like a NIRS and EEG based brain computer interface (BCI) explored by Tomita et al.[6] Also research has focused on a combined NIRS and BIS measurement, described in an article from Hayashida et al.[7] and Naguib et al.[8] Other than the researches which are already done in the field of neuromonitoring, this study will focus on a combined BIS/NIRS sensor and see if this device is useful in the ICU. The goal of this study is to design a small BIS/NIRS sensor, which can simultaneously measure oxygenation and activity of the brain cortex, without compromising the natural look of a critical patient.

The first step is to find scientific articles which provide new information, ideas and criteria for the sensor design. Next some sketches and drafts are made for different designs. The chosen designs will be tested, these measurements will take place in the Erasmus Medical Centre on healthy participants. First, it will be determined if the chosen locations are suitable for measuring and if there are any disturbances in between both sensors. Another round of experiments has to assess whether the sensor can detect changes in blood flow to the brain or brain activity. Taken all the results in consideration, an advice will be given on whether the BIS/NIRS sensor is a promising technique for neuromonitoring.

In this paper, one can read a full and detailed description of the research that has been done. First the research Objective and subquestions are given. Some of the subquestions are answered via literature, described in the Background. In the section Design more information on the choices and criteria of the sensor design are provided. Next, one can find the measurement procedure, results and conclusions of all tests under Experiments. Following is the section Discussion, where a nuanced interpretation of the results and some points that influenced this study are debated. At last, in the Conclusion the overall claim on the sensor design and the Recommendation on a final advice are given. Throughout this paper, BIS signals are printed in blue and the NIRS signals are shown in a red color.

2 Objective

The main objective of this multidisciplinary assignment is to develop a combined BIS/NIRS sensor, which can simultaneously measure the oxygenation and activity of the brain cortex. In various literature is described how EEG and NIRS can be combined.[3,4,9] When the sensors are combined, none or just a little disruption is expected. This is based on studies which already used the combination of EEG and NIRS.[10] In this clinical context, it is important that the new sensor is as subtle as possible, because the family's interests have to be taken into account. For them it is hard to lose their relative, and the death of their loved one should look as natural as possible. Also for the doctor, it is easier and faster to attach one sensor instead of two.

Based on these goals, the following research question is formed: How can BIS and NIRS be combined to measure changes in oxygenation and activity in the cortex of healthy subjects?

This research question will be answered through several subquestions:

- How are the BIS and NIRS probes build and what are the different elements in the devices?
- What is the best distance between electrodes and optodes?
- On what depth in the brain do you want to measure, and is this technically possible?
- What are, anatomically and technically, the best places to measure on the patient's head?
- What is the underlying physiological process of irreversible brain damage?
- Can both sensors (BIS and NIRS) be integrated and how?
- Are the signals disturbed by each other or the environment?
- Does the combined sensor give realistic values in healthy subjects, compared to norm values found in literature?
- Does the combined sensor react to changes in blood flow and/or brain activity?
- Is there a correlation between the BIS and NIRS signal, and how is this physiologically explained?
- What are the advantages of the BIS/NIRS sensor application?

The hypothesis is:
The BIS and NIRS sensor can be combined into one smaller, subtle sensor, without interfering with each other, which gives accurate values of the perfusion and activity of the cortex, at the designated location, in healthy test subjects.

3 Background

3.1 Brain physiology

Under normal and healthy conditions, the brain makes up only 2% of the total body weight, but receives 20% of the cardiac output.[11] This demonstrates the huge amount of oxygen and energy consumed by the brain tissue. At rest, the average human body consumes around 100 W of energy, of which 15 W is used by the brain.[12] The majority of this energy is produced through oxidative phosphorylation, with the use of oxygen and glucose. There is little possibility for storage of nutrients and the metabolic end products of the energy production should be removed as well. So, the brain is dependent on the continuous delivery of these essential nutrients and clearance of waste products, by an adequate blood supply.[12,13,14] On average, the physiological level of blood flow to the brain is about 50 - 60 ml of blood per 100 mg of brain tissue per minute.[14,15] This flow is maintained at a relatively constant rate, despite changes in perfusion pressure.

3.1.1 Autoregulation blood flow

The human brain is exquisitely sensitive to changes in cerebral blood flow (CBF). For optimal function and survival of the neurons under changing physiological conditions, mechanisms like autoregulation have evolved to maintain optimal CBF. There are several ways of autoregulation in the brain. According to Cipolla et al.[14] the blood flow is maintained constant, in a normotensive adult with a cerebral perfusion pressure (CPP) in the range of 60 to 160 mmHg. A reduction of the CBF stimulates the release of vasoactive substances, which cause arterial dilatation. When the pressure becomes higher, the smooth muscle cells in the cerebral vessels will constrict due their myogenic behavior. These smooth muscle cells also dilate in response to a decrease of CPP.[14,16]

Secondly, there is a process called neurovascular coupling. Brain activity promotes an increase in CBF. The precise function of different cells involved in this process is still unclear, even though a lot of research is done in this field. Activated neurons stimulate astrocytes or other glial cells. Metea et al.[17] found that the glial cells are crucial in neurovascular coupling. These cells secrete vasoactive ions or neurotransmitters and metabolic factors, which stimulate vasoconstriction or dilatation.[18] The amount of blood flowing through the brain's arteries is thus depending on the activity of the neurons. The elevation of potassium, one of the most important ions for maintaining the electrical conductivity of the brain and nerve transmission, and hydrogen stimulates vasodilatation. This may be a possible mechanism for neurovascular coupling, since potassium and hydrogen are promoting the blood vessels to dilate. This leads to an increased blood flow to the brain. In addition, some by-products of neuronal activity are also playing a role in neurovascular coupling. Most notable is adenosine: extracellular levels of adenosine rise with neuronal activity. A local effect of adenosine is vasodilatation of the cerebral microcirculation.[19] All of this considered: within the boundaries of autoregulation, the blood flow to the brain is promoted by the activity of the neurons, and not the other way around.

As mentioned earlier, the brain has a high oxygen consumption, compared to other organs. Generally, the blood flow through the brain does not change if tissue pO_2 stays above 50 mmHg. When the pO_2 decreases, the saturation of the hemoglobin declines from 100% at pO_2 >70 mmHg to around 50% at a pO_2 <50 mmHg. As a result, there is a drop in the ATP-production, which opens K_{ATP}-channels on smooth muscle cells, causing hyperpolarization and vasodilatation. Furthermore, the nitric oxide and adenosine production rapidly increases locally. Due to these effects, hypoxia triggers an up to 4-fold

increase of CBF, compared to resting levels. Also carbon dioxide (CO_2) has an effect on the CBF. Hypocapnia causes constriction of the cerebral arteries and arterioles, and decreases blood flow. Hypercapnia triggers dilatation of these arteries and increased blood flow.[14]

3.1.2 Irreversible brain damage

According to Cipolla et al.[14], the autoregulation mechanism is unable to maintain the flow when the CPP exceeds the range of 60 to 160 mmHg. The flow then becomes linearly dependent on the arterial pressure. When the CPP becomes lower than 60 mmHg, and the ability of increasing oxygen extraction is not enough to meet metabolic needs, ischemia will develop. A decrease of the blood flow to the brain to 10 ml/100g/min, during a cerebrovascular accident (CVA), will lead to the onset of irreversible brain damage.[15]

If ischemia arises in the brain tissue, the aerobic metabolism becomes compromised. The lack of oxygen forces the neurons to shift to anaerobic metabolism. This leads to higher lactate and lower ATP levels.[11,12] The ion pumps in the cell (in particular the Na^+/K^+-ATPase and the Ca^{2+}-ATPase) rely on this ATP as their energy source and therefore their activity becomes impaired. Ions will accumulate inside the cell, which causes an osmotic influx of water, leading to the development of edema. This edema further compromises the blood flow to the injured brain. For the excitation of neurons, ion exchange is essential. When ion pumps do not work, neural cells are not able to maintain their ion gradients and can no longer become activated. The brain's electrical activity will slowly decrease, and the ion disbalances will promote cell death by apoptosis.[11,12,15] Outside the area of autoregulation, it seems that the energy consumption, and thereby the activity, of the neurons depends on the amount of blood available. Brain activity follows the available blood supply, different from the mechanism during autoregulation.

The ischemic cascade continues with the release of cellular mediators (including proinflammatory cytokines), prostaglandins and free radicals (reactive oxygen species). These induce chemokines and adhesion molecules, leading to an inflammatory process with vasodilatation, infiltration of the injured tissue by cells of the immune system and serious disturbances of the blood-brain barrier.[11,15]

The ischemic cascade does not occur simultaneously in the whole brain, as certain areas of the brain are more sensitive to ischemia. For example, the gray matter is more sensitive to deprivation of oxygen and glucose, compared to the white matter.[15] The watershed zones are regions of the brain that are particularly sensitive to ischemia, because of their vascularisation. These areas receive their blood supply from the most distal branches of two large arteries, and are the most commonly ischemic when the cerebral perfusion is inevitable.[13] The different parts of the brain will give up one after another. This is an irreversible sequence, starting with the cortex and finally ending at the brainstem.[12] The whole process of ischemia and irreversible damage to the brain is illustrated in figure 1. The question mark indicates the segment of this process which is most relevant to our study: it indicates the moment when the brain damage actually becomes irreversible, which hopefully will become measurable.

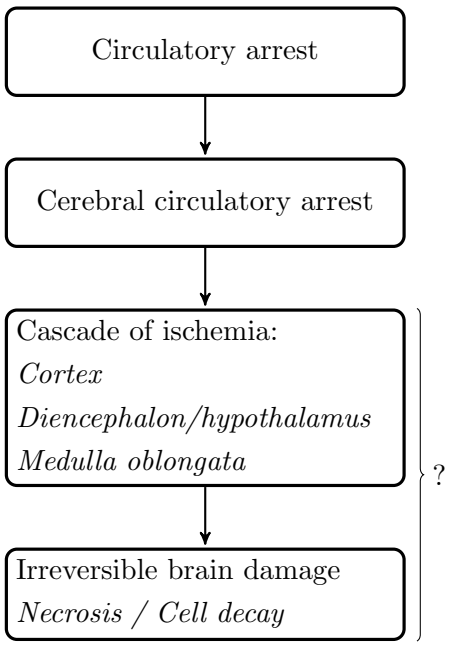


Figure 1: Schematic overview of the process leading to irreversible brain damage[12]

The whole process of brain injury develops relatively fast. During the first minute of ischemia, intracellular acidosis and ion disbalance begins. Irreversible neuronal death occurs after 4 to 5 minutes, and in 30 minutes cellular swelling affects all cells of the brain. And within hours to weeks, the injured tissue will be replaced by scar tissue.[11,13,15] At this point, the brain damage is considered as being "irreversible".

3.2 Measuring the brain

As indicated in the Introduction of this paper, the future monitoring device will assess the oxygenation and the electrical activity of the brain's cortex. Using the insights of cerebral (patho)physiology, these two parameters are identified as possible markers for irreversible brain damage. To gain information about the blood flow trough the brain, as an indicator of oxygenation, there are a few gold standards: TCD measures the velocity of the flow through the blood vessels of the brain. The main advantages of the technique are the portability of the TCD system and the use of non-harmful ultrasound. Performing TCD measurements is relatively cheap, but it requires the expertise of a well trained sonographer. Computed tomography angiography (CTA) and cerebral angiography also visualize the CBF, but the use of contrast agents poses a problem in the presence of renal failure or allergies to intravenous contrast. Another disadvantage is the need of transporting the patient across the hospital to the radiology department. Both techniques use ionizing radiation and are more expensive than TCD. The same applies to cerebral scintigraphy, which uses a radioactive tracer sensed by a gamma camera to perform measurements. Magnetic resonance imaging/angiography (MRI/MRA) uses magnetic field gradients to construct an image of the CBF, without exposing the patient to ionizing radiation. However, it is a relatively slow and expensive technique and it also requires the transportation of the patient to the scanner. Concerning the electrical activity in the brain, EEG is the most widely used technique. Besides TCD and EEG, these techniques are not suited for real time bedside monitoring. In the case of a dying patient, this is not desirable as continuous measurements should be carried out. It is important to know the patient is no longer aware, will not wake again and lost his consciousness indefinitely. Therefore, the measurements should be performed in the parts of the brain that maintain consciousness. Damage in these brains regions indicates the onset of irreversible brain damage.

Anatomically, the state of consciousness relies on different structures involved in arousal and awareness functions. These structures are the ascending reticular activating system, located in the postero-superior part of the brainstem, the thalamus and it's surrounding, the basal forebrain and the fronto-parietal association cortices.[20] The brainstem is the center of several ascending neural pathways. These pathways affect the activity of the cerebral cortex, either directly or through the thalamus and the basal forebrain. The brainstem can affect either local regions of the cortex or the whole cortex. The process of activating the cortex results in wakefulness and attention, which are essential parts of consciousness. The ascending reticular activating system, with it's origin in the reticular formation in the brainstem, can also activate the cerebral cortex.[21] Considering this information, the ideal place to measure activity regarding the state of awareness would be in the brainstem. But due technical deficiency it is currently impossible to measure non-invasive brainstem activity. However, non-invasive measuring of the cortex is possible. It is known that the cerebral cortex plays a significant role in pain perception and modulation.[22] Damage of the cerebral cortex can provide assurance about the absence of pain sensation. Englot et. al[23] showed that a disorder of consciousness can be seen with damage of the bilateral fronto-parietal association cortex. Assuming that irreversible damage of the fronto-parietal association cortex will lead to unconsciousness and not being able to become awake again, the cascade of irreversible damage of the whole brain will start inevitability.

With a non-invasive measurement method, the signal from the brain has to pass certain structures before reaching the probe. As seen from the outside, the scalp is the first part of the head where the signals of the measurement go through. The scalp is composed of five layers: the skin, connective tissue, aponeurosis, loose areolar tissue and the pericranium. Under the scalp lies bone tissue, also called the skull. The area inside the skull is named the intracranial space. Directly beneath the bone tissue are the cranial meninges, consisting of the dura mater, arachnoid and pia mater. Between the meninges lies the cerebrospinal fluid (CSF).[24] The different layers are shown in figure 2.

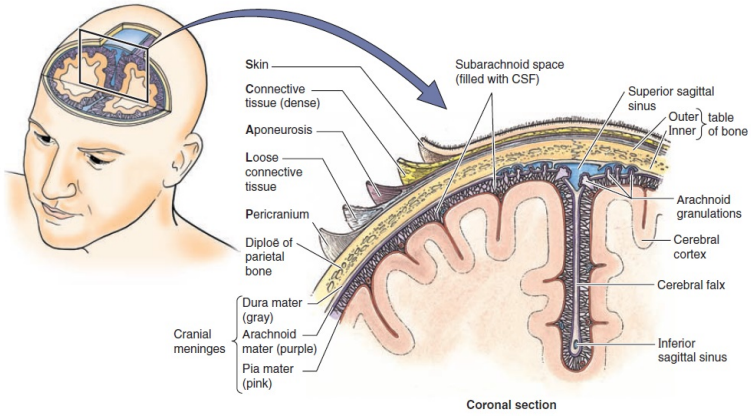


Figure 2: Coronal section of the head with different layers of the scalp, skull and cranial meninges[24]

The thickness of the various layers is different for each individual and can vary widely. There are standards that are used for research of the brain: the depth of the scalp is 4 mm, the skull 6 mm and the cranial meninges 3 mm.[25] Combining those values, the signal of the measurement should pass approximately 13 mm to reach the surface of the cortex.

3.2.1 Near infrared spectroscopy

NIRS is a measurement technique used in various fields, including medical sensing. Pulse oximetry is a well-known example. NIRS is based on the difference in absorption between agents, in this case hemoglobin and deoxyhemoglobin. The binding with oxygen gives the hemoglobin molecule other optical properties, and therefore a different light absorption. Near infrared light (700-1100 nm) is used because it has a great penetration depth, even for dense tissues like bone.[26] Most sensors contain two or three different wavelengths. The NIRS probe sends light into the tissue, where it will scatter. The reflected light is detected and analyzed by two photo-detectors of the NIRS device.[27] A schematic overview of the NIRS system can be found in figure 3. The parameters that can be measured are regional oxygen saturation (rSO_2), heart frequency, blood volume and the oxygenated state of cytochrome-aa3.[28] NIRS is a non-invasive technique that is simple to use. It is not harmful at all for the patient, due to the low light intensity and wavelengths.[26]

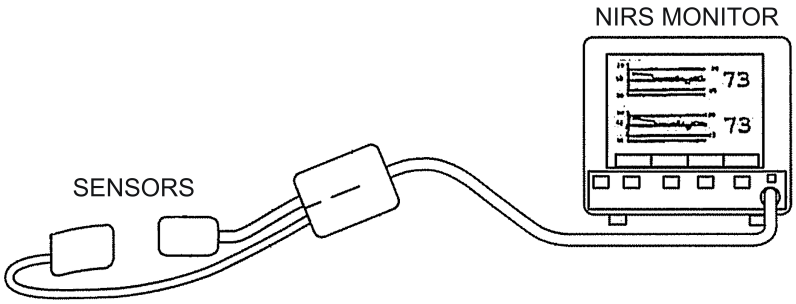


Figure 3: Schematic overview NIRS system with NIRS monitor and two connected sensors [29]

Unlike pulse oximetry, NIRS not only detects arterial blood, but also venous oxygen saturation. The contribution of venous and arterial oxygenation to the signal are respectively 75% and 25%. The norm values are therefore a bit lower and lie at 60-80%. [30] The normal value can differ for each individual and sensoring system. For the INVOS system from Covidien, as used in this study, this is about 67%. [31]

The blood flow to the brain stops in case of a circulatory arrest. This does not mean that the NIRS signal will immediately drop to zero. Oxygen is still present in the blood, and this oxygen will be used by the brain cells. The oxygen level will slowly decrease, due to the brain cells metabolism and lack of tissue perfusion. [11] The research of Al-Rawi et al. [32] showed that a 13% decrease in NIRS signal is an indicator of cerebral ischemia. This threshold has 100% sensitivity and 93.2% specificity. However Covidien, the manufacturer of the INVOS system, says the intervention threshold lies at 20% and the critical threshold at 25% from the baseline. [33]

The INVOS cerebral oximetry adult sensor has three important elements, as shown in figure 4. First there is a light source, a light emitting diode (LED), that sends out two different wavelengths of near infrared light, 730 and 810 nm. [34] Then there are two detectors, one measures the superficial area and the other one the deep area. Only information from the brain cortex is desired, and not from the overlying tissue. The superficial detector catches the reflected light from the scalp and skull. This data will be subtracted from the signals of the deep detector. The remaining signal now only consists of information of the brain tissue. The use of two detectors makes sure the extracranial contamination will be eliminated. [27]

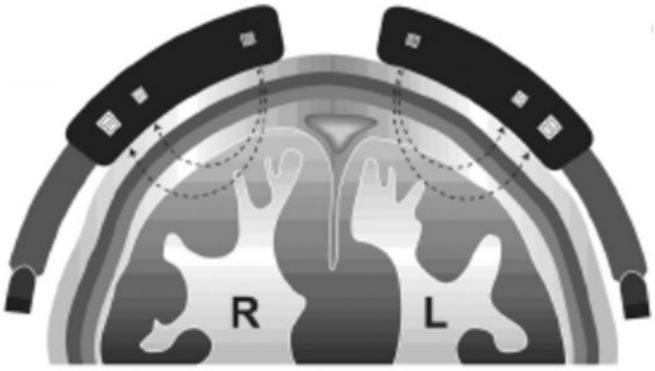


Figure 4: Schematic drawing of path traveled by the near-infrared light and the detection by the NIRS sensors [35]

To obtain information from different depths inside the patient's head, the source and detectors need to have different distances. The more space between the light source and the sensor, the deeper it will measure. The relationship is defined as D=0.5 • L, where D stands for depth and L is the length between light and detector.[30] Several researches are done to determine the optimal distance between light source and detector. Strangman et al.[36] found that the bigger the distance, the greater the sensitivity to the gray matter of the brain. However, this effect is gone beyond 40-50 mm. They also found that the depth sensitivity decreases exponentially, when source and detector are further apart. A consideration has to be made between brain cortex sensitivity and depth sensitivity. Strangman came to the conclusion that the best measurement depth is 10 to 15 mm intracranial.[36] Other researchers, who combined NIRS and EEG sensors, took standard 30 mm for the source-detector separation.[6,9]

3.2.2 Bispectral Index System

Clinically, the BIS is used to measure the level of consciousness in sedated people. It uses EEG electrodes to detect the electrical currents emitted by the brain. This data is processed through multiple filters and subparameters of the raw EEG are calculated.[37] Afterwards, the subparameters are compared to a dataset of subjects with a known sedation level. The output of the system is an index ranging from 0 to 100. A fully isoelectric signal gives an index score of 0, which indicates no brain activity. A score of 100 indicates fully awake brain activity, see figure 5. According to this figure, a score of 60 denotes that the patient is sedated.

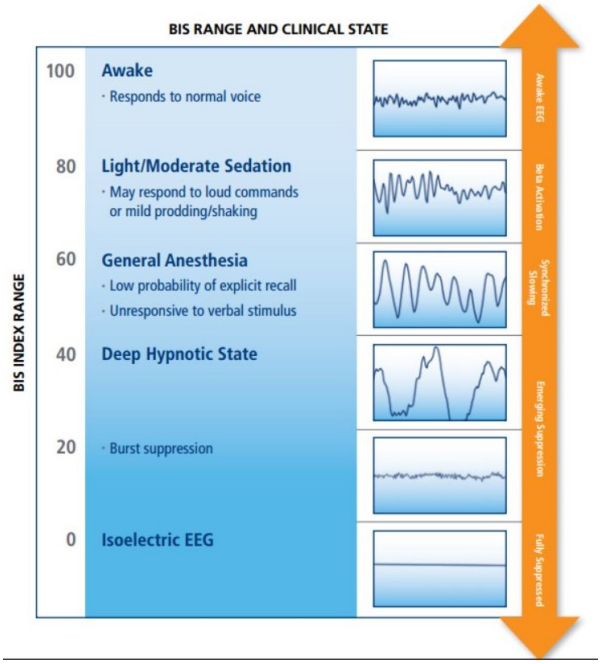


Figure 5: The BIS index range and it's corresponding clinical state[38]

Among other things, the BIS records delta waves, which are associated with deep sleep and are captured from the frontal part of the brain.[39] The sensor consists of 4 EEG-electrodes (see figure 6 and 7). These are placed on the skin surface of the forehead (see figure 6). The various components of the BIS are shown in the figure: 16A, 16B, 16C and 16D are the four electrodes, number 20 is the paddle connector and 22 the connector cable. Furthermore, the monitor is displayed with number 14 and the digital signal converter with 28.

Electrode 1 and 3 are used to measure the EEG signal, whereby electrode 1 is the reference electrode. These electrodes are placed the furthest apart from each other, as a result of this, the amplitude of the EEG is bigger than when they were to be placed closer together.[40] However, with a bigger amplitude, also more noise appears in the EEG signal.[40] Electrode 2 is the ground, it is used to subtract all kind of noise from the EEG signal. The ground electrode can be placed anywhere on the head or body.[41] The last electrode, number 4, detects electromyography (EMG) signals. This is the electric activity of the muscles and it should be filtered from the EEG signal.[39] All electrodes are required to get a reliable BIS score. An image of the whole BIS with monitor is given in figure 7.

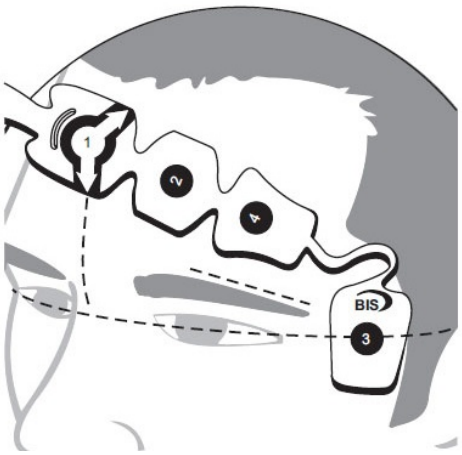


Figure 6: BIS system sensor with the four electrodes placed on the patients head [42]

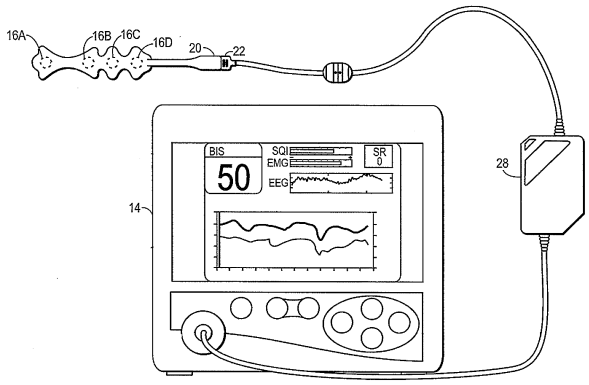


Figure 7: Overview BIS system with monitor (14), digital signal converter (28) and BIS sensor (16) [43]

EEG signals are often contaminated with various kind of noises. The most common noises on the measured signal are originating from EMG, ECG and powerline frequencies. [44] These disturbances have to be removed before the data is analyzed, otherwise they could affect the accuracy of the BIS monitor. A major drawback is that the frequencies of these noises overlap with the frequencies present in the EEG signal, therefore some of the EEG signal will also be removed along with the noise. The BIS monitor analyses frequencies ranging from 0 to 60 Hz. Within these frequencies, noises are originating from the EMG ranging from 0-200 Hz, electrooculography (EOG) ranging from 0-20 Hz and standard disturbance of 50 Hz caused by the air and powerlines. [44] The BIS Vista monitor from Covidien uses a bandpass filter from 2 to 70 Hz. A notch filter for both 50 and 60 Hz is used to exclude the powerline interference in the signal. [37] The main reasons why EEG is considered to measure the depth of the anesthetics are [44]:

- EEG-signals show the cortical activity of the brain;
- The effect of anesthetics is connected to the blood flow and metabolism of the brain, which is further related to the different activity state of the brain;
- The EEG is influenced by anesthetics: EEG-patterns change when anesthetics are administered.

Some research has shown that the BIS system is fairly reliable, even though the effects of anesthetics on the BIS are not fully clear. [45] When an index score of 65 is chosen as the threshold of someone being sedated, the system has a sensitivity of 0.86 and a specificity of 0.98. [46] However, some other researchers doubt the reliability of the BIS, like Renna et al. [47] and Vivien et al. [48] Their research described some remarkable events, which seemed to indicate interference from the EMG.

When the brain becomes ischemic the BIS value will rapidly decline to 0. Note that a score of 0 does not mean directly that the brain is damaged. Only when the brain stays ischemic for too long, approximately 4 to 5 minutes, the brain becomes irreversibly damaged. [13] During this time the suppression rate will slowly rise to 100. The suppression rate (SR) is a parameter which stands for the percentage in extent to which the EEG signal is isoelectric during over one sample time of 63 seconds. [49] The combination of the index value of 0 and a SR of 100 correlates with no activity of the cortex but are not sufficient to diagnose for irreversible damage. [49,50,51] Moreover, the BIS only monitors local activity and is therefore no indicator for loss of activity elsewhere in the brain.

3.3 Prior research

In the last years, a lot of research is done in the field of neuromonitoring. Some other scientists thought about the combination between NIRS and EEG or BIS in various circumstances. It is important to look into these researches; to see what they did, experienced and found out. Their conclusions and discussion might be useful for this study. Some of these studies are noted below.

At the University of Tokyo, Hayashida and his team [7] studied 65 children having a hypothermic cardiopulmonary bypass. The purpose was to detect which children suffered from cerebral ischemia during the surgery. With BIS and NIRS placed separately on the head, the brain was measured. When BIS and NIRS both abruptly decreased during hypotension, cerebral ischemia was diagnosed. The outcome of this study was that children under 4 years have more episodes of cerebral ischemia by hypotension, probably because the cerebral autoregulation is ineffective. They noticed an agreement in both signal drops. It can be hypothesized that the BIS and NIRS may correlate with each other. Also, a strong relation is found between the mean arterial pressure (MAP) and the NIRS signal. Furthermore, the change in the NIRS and BIS values correlated with the patient's level of consciousness. In the case report by Naguib [8], which uses NIRS and BIS separately on the head as additional monitoring during a tilt-table examination of a 14 years old patient, is found that the changes in NIRS values occurred before changes in blood pressure or the appearance of clinical symptoms. If a tilt-table experiment will be performed, this information could be taken into account while processing the data.

Besides a combination of BIS and NIRS, a combination of EEG and NIRS is of interest, because a BIS is derived from an EEG and also uses scalp electrodes. Cooper et al. [4] designed a novel probe design which they called opto-electrode. The opto-electrode enables simultaneous EEG and near infrared (NIR) optical imaging to be performed. This new design is easy to apply and maximizes the number of sensors applied to a given area. The opto-electrode is tested on human motor cortex experiments and has demonstrated it's effectiveness and suitability. Any disturbance inbetween the EEG or near infrared (NIR) is not mentioned. This research shows how a possible design of an EEG and NIRS, or BIS and NIRS, could be made.

If a combination of the EEG and NIRS sensors has an added value, this should appear in combinated and practically used designs. Roche-Labarbe et al. [5] from the Groupe de Recherches sur l'Analyse Multimodale de la Fonction Cérébrale (GRAMFC) carried out a study about coupled oxygenation oscillation as measured by NIRS and EEG. They performed simultaneous EEG and NIRS recordings on six healthy premature neonates and four premature neonates with neurological pathologies. Their goal was to determine whether changes in the oxygenation of the brain were related to the occurrence of spontaneous burst of cerebral electrical activity. Their study provided evidence that spontaneous physiological neuronal activity in premature infants is coupled with a transient stereotyped hemodynamic pattern, consisting of deoxygenation followed by a strong oxygenation. They could not completely rule out the possibility that these patterns have completely different origins. In the neonates with cerebral impairment, these patterns were found to be modified. With respect to the interpretation of a NIRS measurement, they point out that the signal also depends on spontaneous, physiological activations, combined with various regulatory processes. This article provided an introduction to the coupled hemodynamic response of the brain, and a working example of a simultaneous measurement with a NIRS and EEG system.

Another study that uses NIRS and EEG simultaneously is Jindal et al.[3] The paper presents a testing device, a combination of EEG and NIRS, to asses the relationship between local neural activity and subsequent changes in CBF. The EEG and NIRS are recorded during anodal transcranial direct current stimulation (tDCS) in healthy subject and patients who have had a stroke. tDCS uses a constant and low current, delivered to the brain area of interest via electrodes on the scalp. These techniques are limited to 2 NIRS detectors, 8 NIRS sources and 8 EEG channels. These restrictions are chosen to reduce the costs, as well as the complexity. The healthy and stroke study showed detectable neural and hemodynamic changes without any artifact from the EEG and NIRS on each other, which demonstrated the potential of combined measuring. Based on this information, it can be concluded that it is possible to measure EEG and NIRS simultaneously without disturbance from each other and it is also possible to detect changes in neural and hemodynamic activity in healthy subjects.

Another application of the combined EEG and NIRS, which is not purely medical, is a brain computer interface (BCI). A BCI based on EEG showed room for improvement in terms of reliability. So, Tomita et al.[6] designed a cap which records NIRS data as well as EEG. They detected hemodynamic fluctuations in the brain during stimulation with steady-state visual evoked potentials (SSVEP) in thirteen healthy subjects, who did not suffer from any brain disorder and with normal or corrected to normal vision. A flickering checkerboard was used to activate the occipital lobe of the brain, which was alternating with different frequencies, ranging from 4.8 Hz to 11.8 Hz. The joint use of EEG and NIRS was shown to improve the SSVEP classification, despite there was interference of the two measurements and some artifacts were created.

In summary, it can be said that it is possible to combine the BIS sensor with a NIRS sensor. Also, a correlation between these two measured parameters can be expected. Furthermore, simultaneously used EEG and NIRS provided more and more reliable information about the state of the brain and were able to detect changes in neural and hemodynamic activity in healthy subjects. It is expected that a combination of BIS and NIRS will have the same result, although some interference inbetween both signals may occur when measuring too close to each other.

4 Design

Irreversible brain damage and it's underlying process are described in the section Background. In that section, it is also debated which part of the brain controls consciousness. The features of the BIS and NIRS sensor are given as well. Using this information, the designs of the new sensor are shaped.

4.1 Materials

The BIS Quatro sensors and the INVOS Cerebral/Somatic Oximetry sensors are both from Covidien Nederland B.V. To make the designs some craft materials were needed: 2 mm thick foam sheets from Rayher Hobby, double-sided tape by Le Suh and Kruidvat textile sticking plasters.

4.2 Location

The best place to measure the lack of brain activity would be the brainstem, because this is the last part of the brain that will be irreversibly damaged.[12] No activity in this location indicates that the remaining parts of the brain are presumably no longer functioning as well. The problem is that these places are hard to reach and only invasive techniques can measure there. Unfortunately, neither the BIS nor the NIRS are able to measure brainstem activity. They only provide reliable information about the higher parts of the brain. A good alternative may be measuring on the cortex of the frontal or parietal lobe. The fronto-parietal lobe along with the brainstem regulates consciousness.[20,23] When it is set that the frontal or parietal lobe is irreversible damaged, it can be assumed that the patient has lost consciousness. Other parts of the cortex can be measured as well, but these are worse indicators of awareness.

4.3 Position elements

The NIRS probe provides information about the oxygenation of the cortex. Based on literature, one can assume that the average depth of the cortex is 13 mm, consisting of 4 mm scalp, 6 mm skull and 3 mm cranial meninges, however those values are very variable.[25] Therefore, the minimum depth the NIRS signal should pass to reach the cortex is 13 mm. To be sure about the origin of the measured values, keeping in mind the intention to measure the cerebral cortex, a depth of 7 mm within the cortex is chosen. This results in a total depth of 20 mm, as measured from the skin. The relation between measuring depth and source-detector separation of the NIRS is defined as D=0.5 • L.[30] With a desired depth of 20 mm the distance between the light source and the deep detector should be 40 mm. The superficial detector should measure the light returned from all the tissue layers above the cortex. The depth for this detector is 13 mm, this results in a source-detector separation of 26 mm. It is known that the thickness of the skull and skin can vary widely between individuals. But also within an individual, the thickness of the skull can vary between parts of the head.[25] For example, the mastoid is a very thick bone. This should be taken in consideration before placing the NIRS sensor on a person's head.

All BIS electrodes are placed on positions of the international 10/20 sensor position system for EEG.[52] Normally, the electrodes are placed at FPz, FP1, FT9 and AF7, but these positions may vary within the different designs during this study. The ground electrode can be placed anywhere on the head, and even elsewhere on the body.[41] The potential difference measured between electrode 1 and 3 depends on the distance the electrodes are placed from each other. The further away from each other the bigger the potential difference is, however the disturbance by noise also increases.[40] The electrodes can be placed on adjoining EEG points, but not closer to each other, due the small signal amplitude. The last electrode, number 4, may be placed on any point close to electrode 1 and 3, as it detects the interfering EMG signal.

Furthermore, the relative placement of the BIS to the NIRS has to be taken into account. The NIRS has a LED inside it's probe, which is powered by electricity and therefore produces an electromagnetic field. As said before, the BIS measures the electric waves sent out by the brain, but might also pick up the electromagnetic field sent out by the NIRS when placed too close to the NIRS. This may interfere with the recording electrodes and therefore give incorrect BIS readings. This effect will be evaluated in this study (see section 5.4).

Concluding: all elements of the sensors, both detectors and all BIS electrodes, have to be integrated in the new design, otherwise the data of the probes cannot be retrieved properly. Also, all elements have to be placed on the patient skin and therefore cannot overlap. The whole sensor has to look as subtle as possible, and preferably has a small surface area.

4.4 Methods

With knowledge gathered from the literature, by analyzing the sensors, taking the demands stated above into account and with the use of some creativity, thirteen designs were made (see Appendix VI). These were compared with each other using a scoring matrix. The most important criteria were summarized into 6 groups. For each group 1, 0.5 or 0 points could be earned, whereby 1 point stands for full compliance with the criteria. These groups are: subtlety, surface area, location, complexity, practical issues and whether it is necessary to shave any hair of a patient. If a design is subtle it gets 1 point, less subtle designs receive 0.5 or 0 points. If the design takes a relatively small surface area 1 point is given, and when it takes a large surface 0 points are given. Because it is preferred to measure the parietal or frontal lobe, the location of the design is considered important. The complexity of the designs depends to what extend the original designs of the BIS and NIRS are changed, like taking apart the different BIS electrodes and NIRS components. Practical issues that would make the design hard to use are for example the situation when the patient has to lay on top of the design, which could give incorrect outcomes. Finally, it is important for the design to have a natural look. So it is not desirable to shave the hair of the patient. Based on these criteria and scorings, table 1 is made. The top 4 best scoring designs at these criteria were chosen to be tested in our experiments. These designs are further illustrated in the concluding section of the Design part of this paper.

4.5 Results

Table 1: Scoring table for different sensor designs on 5 criteria. A score of 1 indicates the design is in full compliance with the criteria and 0 indicates the opposite.

Sensor design	**Total score**	**Subtlety** *1 = hidden* *0 = visible*	**Surface area** *1 = small* *0 = large*	**Location** *1 = frontopar* *0 = other*	**Hair removal** *1 = none* *0 = shave*	**Complexity** *1 = simple* *0 = difficult*	**Practical issues** *1 = none* *0 = yes*
Frontal 1	**4.5**	0	0.5	1	1	1	1
Frontal 2	**4.5**	0	0.5	1	1	1	1
Frontal 3	**2**	0	0	1	1	0	0
Frontal 4	**4.5**	0.5	0.5	1	0.5	1	1
Occipital 1	**2.5**	1	0.5	0	0	1	0
Occipital 2	**3**	1	0.5	0	0	1	0.5
Lateral 1	**3**	0.5	0.5	0	0	1	1
Lateral 2	**4**	0.5	1	0.5	1	0	1
Lateral 3	**2**	0.5	0	0.5	1	0	0
Lateral 4	**3.5**	1	1	0	0.5	0	1
Lateral 5	**4.5**	0.5	1	1	0.5	1	1
Lateral 6	**4.5**	0.5	1	1	0.5	1	1
Lateral 7	**4.5**	0.5	1	1	0.5	1	1

4.6 Discussion

Eventually, the four prototypes of designs A, B, C and D are not exactly shaped like drawn in the sketches. The BIS electrodes were found to be expired, and the use of supplemental EEG gel proved necessary. As a result, the quality of the signal may become compromised. When the NIRS sensors finally arrived, it turned out they could not be disassembled. This resulted in a different light source-detector distance than calculated before. The distances of the manufacturer had to be used, which were 30 mm and 40 mm for the two detectors, respectively. Furthermore, it was impossible to place the NIRS light source and detectors in between the BIS electrodes, like shown in the design figures. For that reason, some changes had to be made during the construction of the prototypes. Sometimes, there was no other option than placing the NIRS components outside the BIS electrodes, on locations different than planned. This lead to larger and less subtle prototypes, in conflict with our criteria of subtlety and a small surface area.

4.7 Conclusion

There are 6 designs with a score of 4.5. Not all of them could be made with the available materials, so it was chosen to manufacture only two frontal en two lateral designs. The four designs that were selected are: frontal 1 and 2, and lateral 6 and 7. They are extensively described below, and will be indicated with the letters A to D. Frontal 4 is not chosen because it possibly overlaps with the hairline. It has been tried to put lateral 5 together, but this proved technically impossible. Alternatively, lateral 7 was made instead. For the placement of the BIS sensors, the 10-20 system for EEG is used to accurately

describe the location of each individual sensor. The electrodes are shown in the figures with their number in green. The NIRS components are displayed with red boxes in the figure. Within the figure, the light source is marked with a S and the two photo-detectors with D1 and D2.

4.7.1 Design A: frontal 2

BIS position
Electrode 1: Fpz
Electrode 2: Fp1
Electrode 3: FT9
Electrode 4: AF7

NIRS position
Light source: between AF7 and Fp1
Detectors: between Fp1 and Fpz

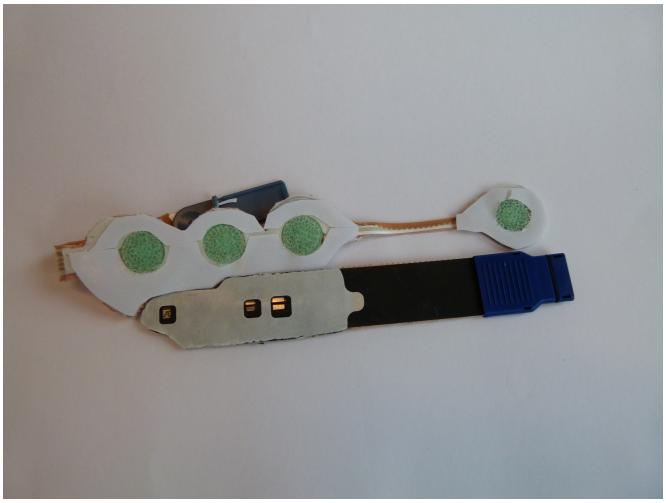


Figure 8: Photograph of design A

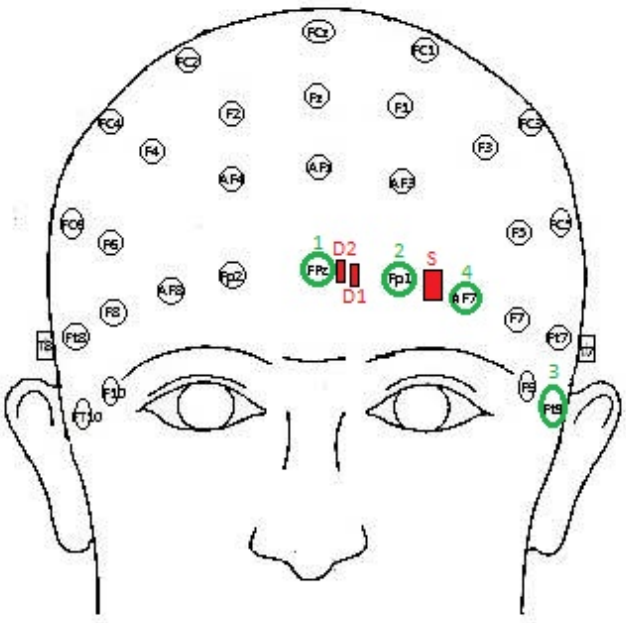


Figure 9: Element positions of design A (frontal 2)

The BIS sensor will be positioned at the conventional positions (as indicated by the manufacturer), as mentioned above. The NIRS will be incorporated in the design, also at the original configuration. Because the conventional positions are used and no major changes are made to the design of the BIS sensor or NIRS, the same performance is expected of this sensor as for the conventional sensors (used separately). Although this design is more compact than two separate sensors, it can still be made smaller and more subtle. However, the design must be changed radically to do so. Whether these smaller designs give reliable measurements must be examined, but only some basic initial steps will be taken in this study.

4.7.2 Design B: frontal 1

BIS position
Electrode 1: FPz
Electrode 2: FP1
Electrode 3: FT9
Electrode 4: AF7

NIRS position
Light source: to the right of FT9
Detectors: to the left of AF7

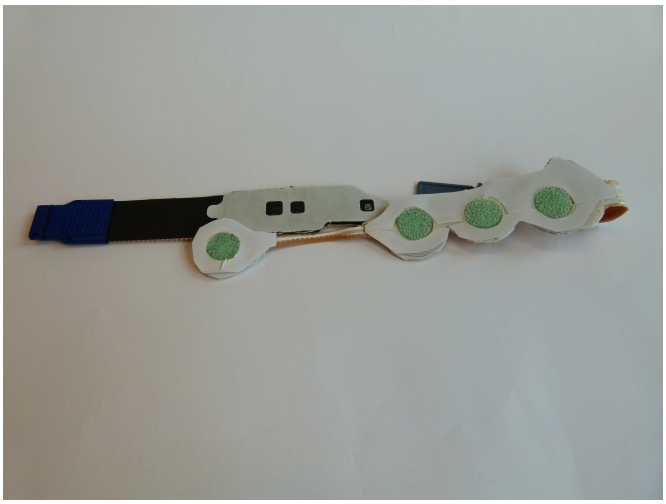


Figure 10: Photograph of design B

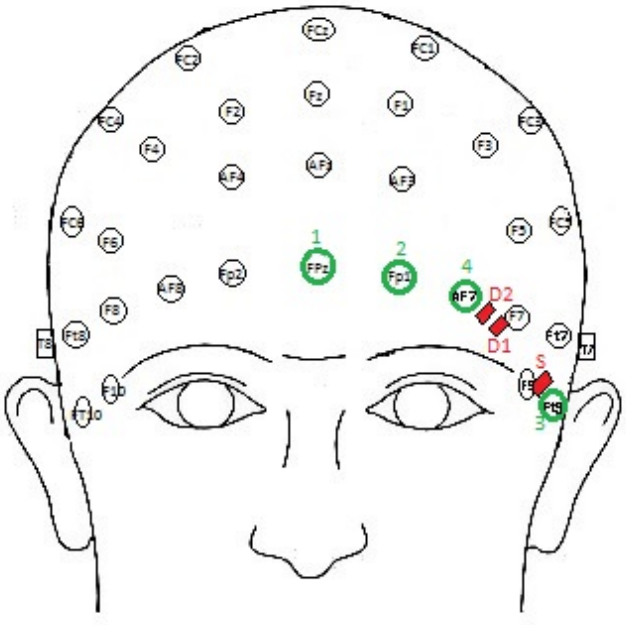


Figure 11: Element positions of design B (frontal 1)

This design is very similar to design A. The main difference is that the NIRS sensor is positioned between electrodes 4 and 3. The BIS sensor is, like design A, placed on the conventional place. In this design the NIRS sensor curves around the head of the patient, and whether this causes any differences in the measured results will be investigated whether this causes any differences in the measured signals. The advantage of this design over design A is that the NIRS sensor is moved to the side of the face. This leaves more empty space on the face of the patient, so that the patient looks more restful to the relatives.

4.7.3 Design C: lateral 7

BIS position
Electrode 1: AF7
Electrode 2: F9
Electrode 3: FT7
Electrode 4: FT9

NIRS position
Light source: between AF7 and AF5
Detectors: between FT7 and F9

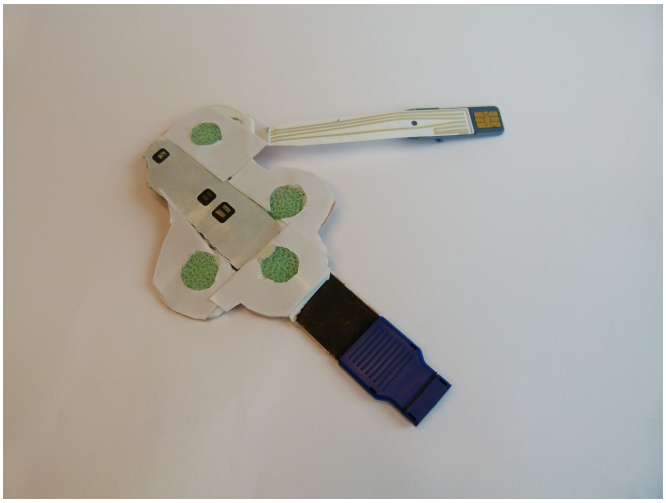


Figure 12: Photograph of design C

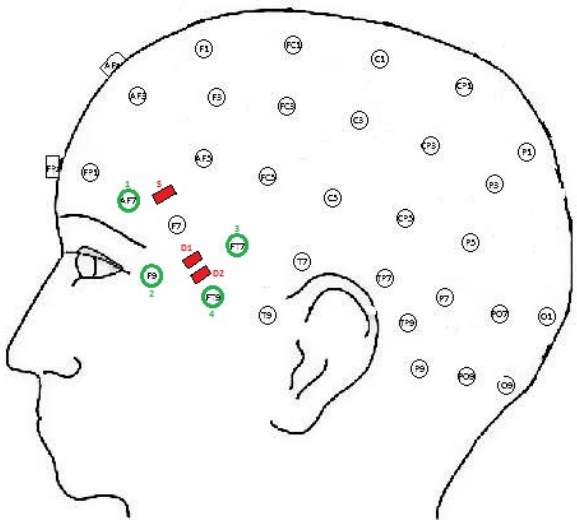


Figure 13: Element positions of design C (lateral 7)

This design is more compact in comparison to the other designs, because it covers less of the face of the patient. A drawback of this design is that it measures less of the frontal brain activity, which the BIS sensor is designed to process. Whether this may have any effects is currently not known, and will analyzed during this study.

4.7.4 Design D: lateral 6

BIS position
Electrode 1: FT7
Electrode 2: TP7
Electrode 3: AF7
Electrode 4: F7

NIRS position
Light source: between AF7 and F7
Detectors: between F7 and FT7

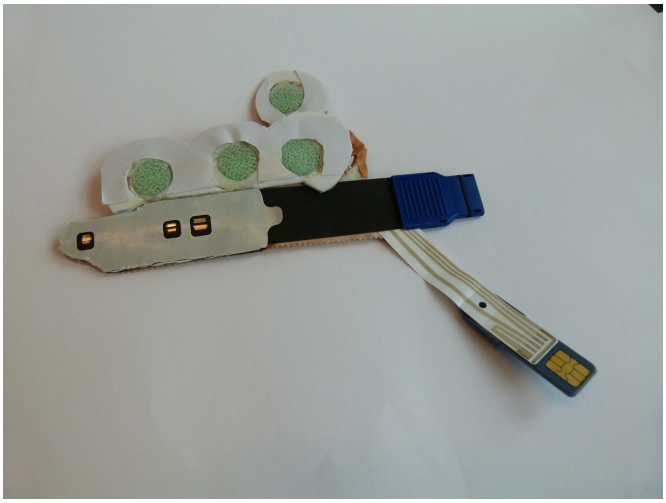


Figure 14: Photograph of design D

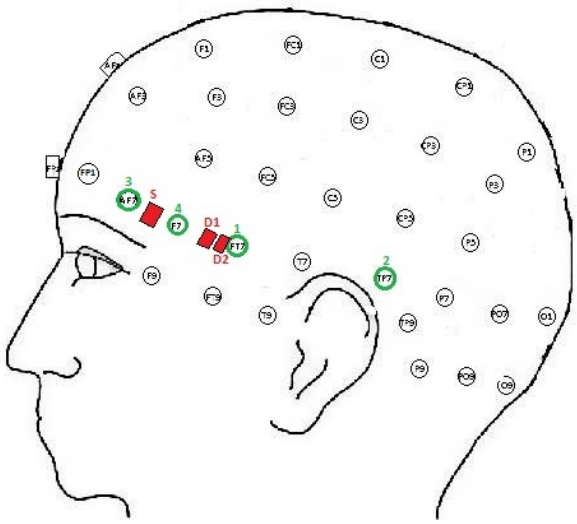


Figure 15: Element positions of design D (lateral 6)

This design is a little more subtle than design A and B, since it is positioned at the side of the patients face. Electrode 2 (the ground electrode) of the BIS sensor is detached from the rest of the sensor and placed behind the ear. Moving electrode 2 behind the ear results in a more hidden sensor which will presumably not lose any signal quality.

5 Experiments

To determine whether the chosen designs work properly, measurements had to be done. The measurements took place in the Erasmus Medical Centre. On the first day the disturbance and performances at various locations were measured. On the second day, the effect of physiological changes on the NIRS and BIS signal was evaluated. These measurements were done following protocols, which can be found in the Appendix. Before each measurement, a form was filled in by each participant (see Appendix V). This concerned the gender, age and presence of diseases which possibly interacted with the performed experiments. Persons with an interfering disease were excluded from this study. The participants also needed to be 18 years or older, and a verbally informed consent was required before participation. Each participant was coded, so the data is fully anonymous (without the coding key). All participants and researchers were quiet during all the tests and they only spoke when giving instructions to the participants.

5.1 Data extraction

The sensors were connected to an INVOS and BIS Vista monitor, both from Covidien BV. The signals were retrieved from the monitors via the RS-232 port. A RS-232 to USB converter from BB Electronics Ulinx and the manufacturer's drivers were used. It's important to note that the serial port of the NIRS was connected via a null modem cable to the converter. The converters were then connected to the USB ports on a computer, on which a serial port emulator converted the data. The emulator used in this study was HyperTerminal Private Edition by Hilgreave, version 6.3. The input parameters for both monitors were set using confidential information from Covidien. At the moment that the sensors were connected, data will be transferred to the PC. Then the data was saved for further analysis with Matlab [53] and SPSS [54]. Any further details may be obtained by contacting the authors.

5.2 Data analysis

First, the raw data was cropped to the start and end timecodes of the measurements. The designs could sometimes be measuring before the experiment started or remain active when the experiment was stopped. This is corrected by deleting the values that were not measured during the actual experiment. In the raw BIS data, columns were separated by a pipe character (|). To be able to import this raw data, these vertical lines were changed manually to an empty space. Also, all letters were deleted from the raw data of the BIS and NIRS. These characters in the data files caused problems with the import of the data, because different types of data in the same column could not be read. Only the columns that include the time, the NIRS values and the BIS scores were used for the analysis.

When the BIS and NIRS data were loaded in Matlab, the values were read as a string and not as integers. To solve this, `str2num()` was used. This command converts the chosen string into a numeric value, which could be used in further analysis. It was chosen to remove NIRS or BIS values of zero, because the NIRS returns a value of 0 as an error code and the BIS should never be 0 in a healthy subject. Time series were used to save the measured values, assigned to the proper timecode. These time series were used when making plots of the data. To indicate the time of the interventions, a patch was used. The exact timecode of an intervention could be extracted from the raw data. The used scripts can be found in the Appendix VII.

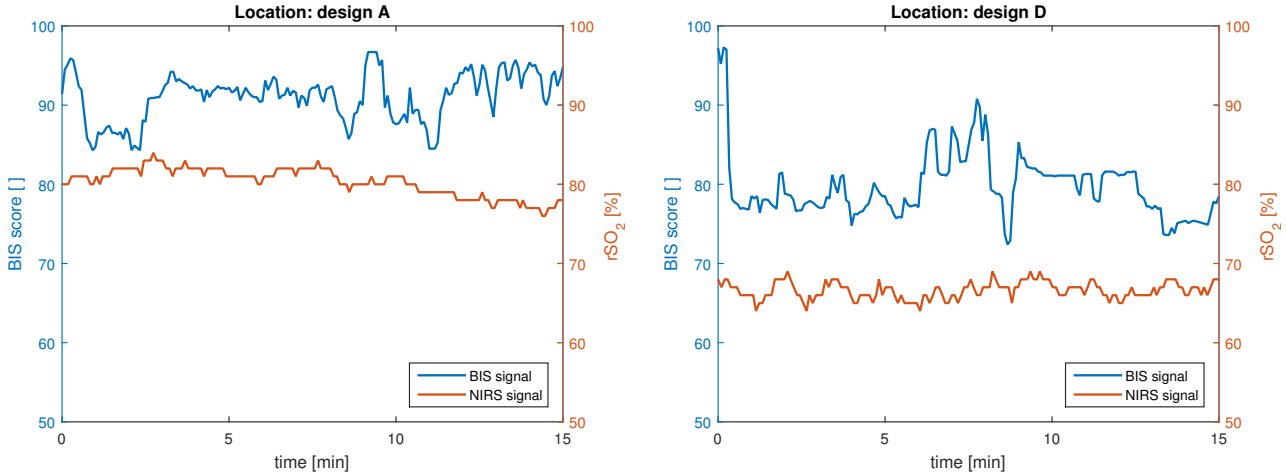
5.3 Location

The designs that are made, are meant for different locations on the head, namely frontal and lateral. To find out whether the position of the sensor affects the performances, design A and D are chosen to represent frontal and lateral measurement sites. The differences between their results and their correlation with the norm values are investigated.

5.3.1 Methods

The difference between sensor locations is measured according to measurement protocol I (see Appendix). The metering took place on one individual (subject 1) and lasted 15 minutes, for both one frontal (A) and one lateral (D) design. The designs could not simultaneously perform measurements, as they cannot be placed on the head together. Moreover, there were just one NIRS and one BIS monitor to measure with. The NIRS and BIS sensors (of the same design) were running at the same time. The subject sat quietly with his eyes closed during the test.

5.3.2 Results



(a) Frontal design (A)

(b) Lateral design (D)

Figure 16: BIS (blue) and NIRS (red) data measured with a frontal (A) and lateral (D) design separately

The signals of the different locations are plotted figure 16; the BIS values are shown in blue and the NIRS signals are printed in red. The designs did not measure at the same time, only the BIS and NIRS, of a single design, were obtained simultaneously. Figure 16 shows that the frontal design was measuring a higher NIRS signal in comparison with the lateral sensor. Furthermore, the mean rSO_2 values for the lateral design is 67%, and for the frontal design 80%. The mean and standard deviations of the datasets are printed in table 2. As can be seen clearly from figure 16, the frontal design was measuring higher BIS values than the lateral design. Also, the mean value of the frontal design is 91.1 and the mean value of the lateral design is 79.7 (see table 2).

Table 2: Mean and standard deviation of the measured data during the location experiment

Monitor	Design	Mean	Std. deviation
NIRS	A	80%	1.78
	D	67%	1.08
BIS	A	91.1	3.06
	D	79.7	4.23

5.3.3 Discussion

The frontal design returned higher rSO_2 in comparison with the lateral design. This may be due to various reasons. First, it is possible that the distance between the NIRS sensor and detector is different in the two designs, because the lateral sensor curves around the head. This may cause the light to travel a smaller distance in the lateral designs, which may alter the depth of the NIRS measurements. The second reason that could explain the difference is the inequality of blood flow at different places of the cortex. The norm rSO_2 values of a NIRS sensor are between 60 and 80%.[30] This means that the results from both of the designs, the lateral (68%) and frontal (80%), match with the values as found in the literature. Eventually, the ability to detect the declining saturation of a ischemic brain should be evaluated, experiments III and IV might give some first clues. Unfortunately, such a decrease in cerebral saturation could not be easily tested in the healthy subjects as used in this study.

The BIS values as measured by the frontal design were higher than the BIS indices on the lateral side. This difference can also be explained in various ways. First of all, the lateral design was more difficult to put together, and the whole BIS sensor had to be disassembled. This could cause damage and consequently disturbance of the signals. This could lead to lower values being measured. Also, the sequence of the BIS sensors and their location on the scalp was changed in the lateral design, in relation to the original lay out (by the manufacturer). This could cause problems within the data analysis performed in the BIS monitor, which processes the raw EEG data through multiple filters and complex mathematical algorithms.[37] The accuracy of the BIS reading is not validated for locations other than set by the manufacturer. Another reason that the measured values are different can be due to the diverse activity in the different places of the brain, where the different designs performed their measurements. According to the manufacturer, the normal BIS index of a fully awake brain should be around 100 and a BIS index around 80 means light to moderate sedation.[38] Based on these normal values from Aspect, the BIS index of 91.1 measured by the frontal design appeared more realistic than the mean of 79.7 as measured by the lateral design in an awake subject.

5.3.4 Conclusion

The NIRS sensor in the frontal design reported higher rSO_2 values than the lateral sensor. In the clinical context of this research, the goal is to assess the decline of the NIRS signal when a patient is dying. So, differences in baseline may not be an issue. Both designs are in line with the norm values of 60-80%. Concluding: both designs seem usable in terms of NIRS performance.

The BIS values of the frontal frontal design also were higher than the lateral one, as confirmed by their means. The lateral design deviated from the reference value. However, in this application the decline of the signal (during intervention) is of more interest. So, in this context the lateral design is not considered less functional. As concerning BIS, both design seem usable in further experiments.

5.4 Disturbances

Both the BIS and the NIRS make use of electrical currents to carry data signals from the sensor to the monitor. In addition, the NIRS sensor contains an electrical powered LED. These currents could possibly distort each other. This disturbance can influence the data and lead to misinterpretations, which impact could be huge when a wrong conclusion is drawn form such data.

5.4.1 Methods

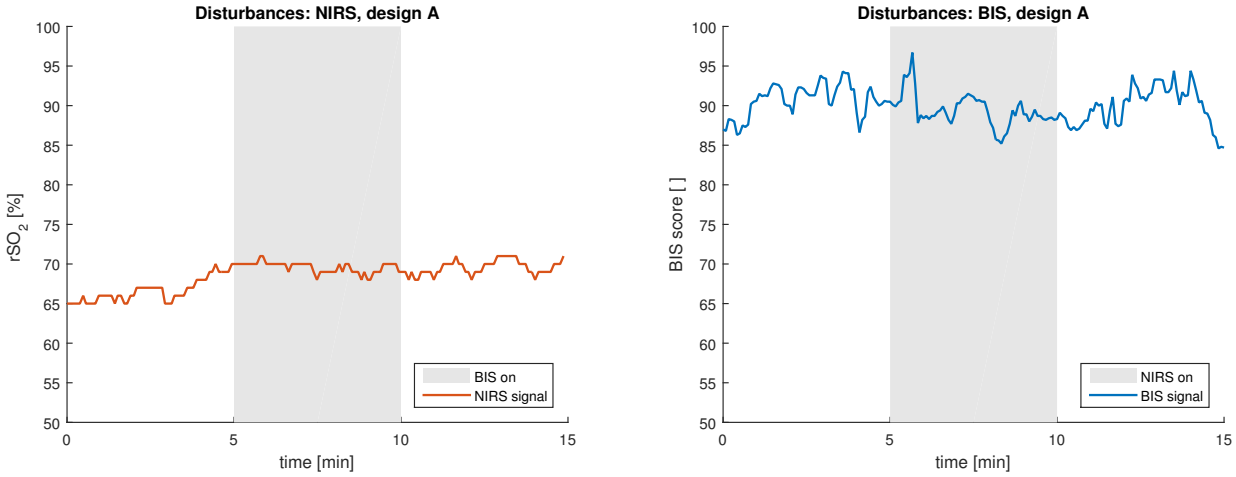
The interdependent disturbance between the BIS and NIRS sensor was measured according to measurement protocol II (see Appendix). The testing took place on one individual with a duration of two times 15 minutes for each design. The designs cannot be tested simultaneously. The first 15 minutes the BIS was tested on disturbances caused by the NIRS sensor. The BIS was switched on, five minutes after the BIS was switched on the NIRS was started. After ten minutes, of the start of the test, the NIRS was shut down and the BIS continued for another five minutes. The same routine is followed when testing the NIRS on disturbance caused by the BIS sensor but conversely. On all of the four chosen designs these routines are used. By switching one of the two sensors on/off, the disturbance of that sensor can be measured with the other one. An other way to determine the disturbance is by switching the sensor on and off more frequently for a short amount of time. The contribution of the physiological variation to the BIS signal is considered relatively constant during this experiment, in contrast to the method described above. During the testing the NIRS was turned on every minute for 10 seconds. Due a shortage of time this method of measuring was only used with design B, and not in both ways.

In SPSS the means and standard deviations of the signals were calculated. For all designs the function *analyse* >*descriptive statistics* >*explore* was used in SPSS. This allows for an analysis between the different phases and designs. No mean value was calculated for the experiment with fast disturbances applied to design B, because the intervals of 10 seconds only contained one or two samples.

5.4.2 Results

The following graphs show the results of the experiments to disturbance. Figures 17a, 18a, 20a and 21a contain the NIRS signal during measuring. In figure 17b, 18b, 19, 20b and 21b and the BIS signals are shown during the experiments. The gray bar inside the graph represents the on-state of the disturbing sensor. At some places the graph is disrupted due to signal loss.

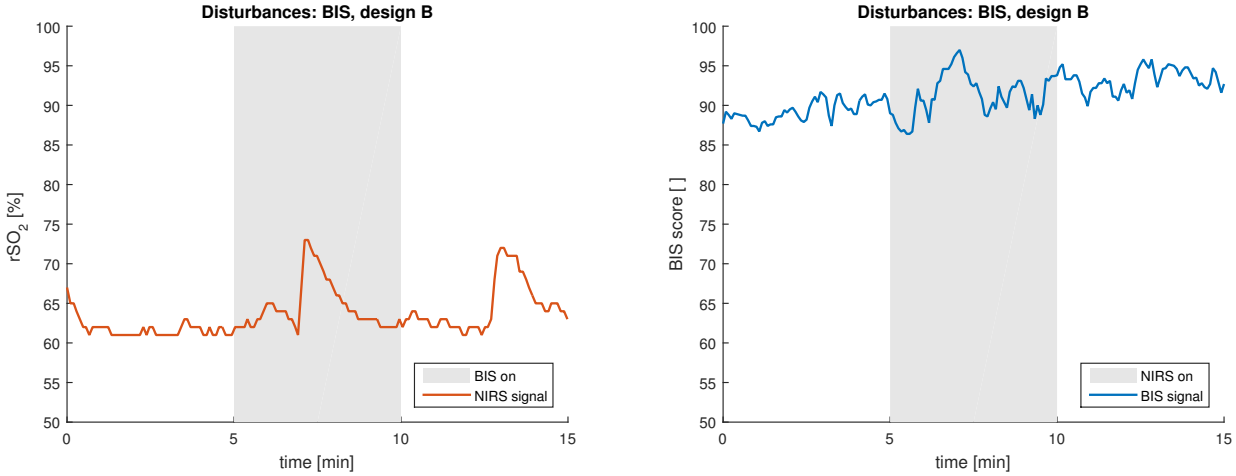
In design A the BIS does not seem to affect the NIRS signal. No big changes in the NIRS signal are seen in figure 17a. Figure 17b shows fluctuations of the BIS signal during the whole experiment but a pattern is not identified.



(a) NIRS tested (b) BIS tested

Figure 17: Separate NIRS (red) and BIS (blue) recordings with design A. From 5 till 10 minutes a disturbance is applied to the signal

The NIRS of design B, in figure 18a shows two peaks approximately at 7 and 13 minutes after the experiment started. Like in design A, in the BIS signal of design B also no pattern of the fluctuations of can be seen, see figure 18b.



(a) NIRS tested (b) BIS tested

Figure 18: Separate NIRS (red) and BIS (blue) recordings with design B. From 5 till 10 minutes a disturbance is applied to the signal

The BIS signal of design B when NIRS is quickly switched on and of is shown in figure 19. When the NIRS is on, the BIS signal shows peaks at 1, 2 and 5 minutes, which decline directly as the NIRS is put off. At 3, 4 en 6 minutes after the experiment has started this phenomenon is not seen.

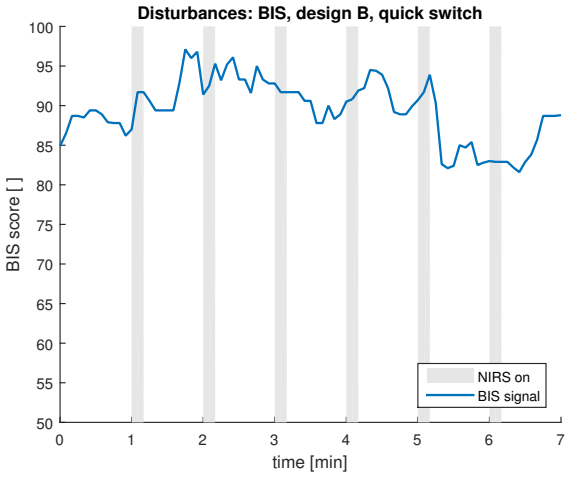
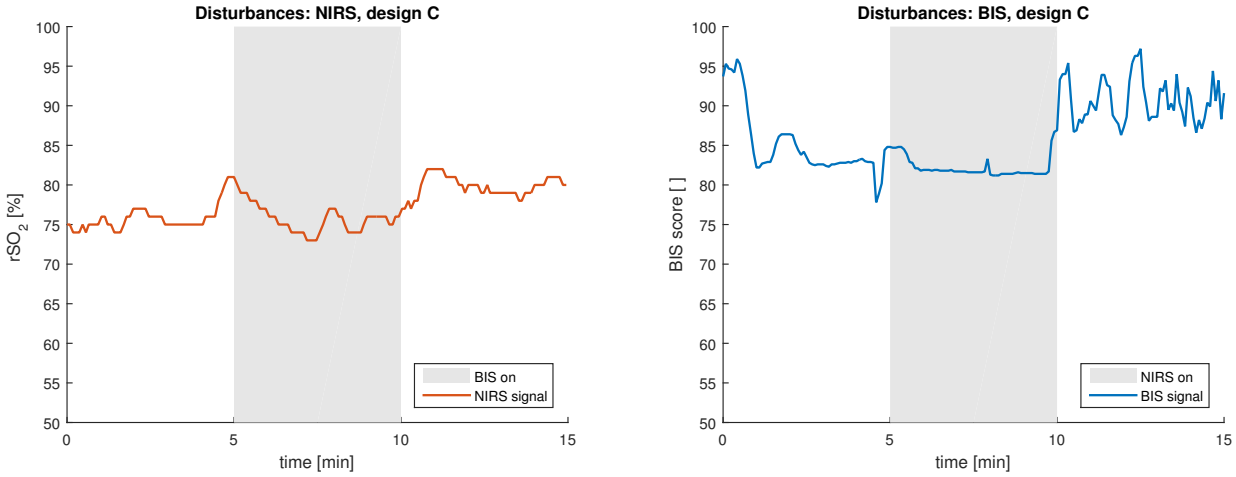


Figure 19: BIS data recording with design B. Every minute a disturbance is applied for 10 seconds

Design C shows in figure 20a some peaks in the NIRS signal, before and after the BIS has started to measure. The BIS signal shows in figure 20b has an increase of 10% in mean value after the NIRS is switched off. In addition, more fluctuations of the BIS signal occurred than before or while the NIRS was measuring.

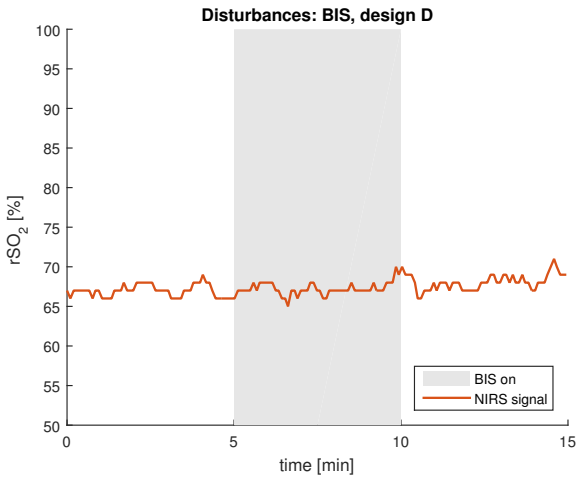


(a) NIRS tested

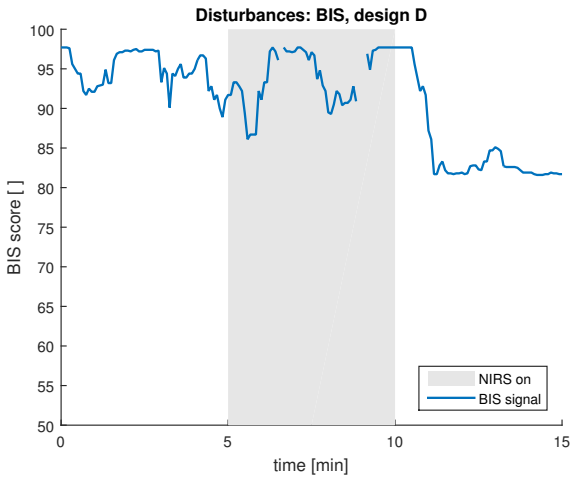
(b) BIS tested

Figure 20: Separate NIRS (red) and BIS (blue) recordings with design C. From 5 till 10 minutes a disturbance is applied to the signal

Figure 21a shows a relatively stable NIRS signal of design D with a mean value between 66.96 and 68.09. The mean value of the BIS signal as shown in figure 21b drops 10% after the NIRS is switched off.



(a) NIRS tested



(b) BIS tested

Figure 21: Separate NIRS (red) and BIS (blue) recordings with design D. From 5 till 10 minutes a disturbance is applied to the signal

For further analyze of these data the mean and standard deviation were calculated out of figure 17, 18, 20 and 21. These numbers show, over an interval of approximately 5 minutes, how much the mean differs from the other intervals within the same design and monitor. Also the standard deviation shows whether the signals within the same interval changes significantly, and could therefore function as a value for how stable the signal is. The mean and standard deviations of these figures are placed in table 3 and table 4. In all designs the mean NIRS signal changes no more than 5% between each interval within the same design. Except for design B, the standard deviation does not peak above 2, see table 3. Unfortunately table 4 shows that this does not count for the BIS sensor. During stage 2 of design D the standard deviation equals 24.56. Only in design A the means are ranging no further apart than 2 and standard deviations not higher than 2.5.

Table 3: Mean and standard deviation of NIRS stages during the disturbance experiment

Design	**Stage**	**Mean**	**Std. dev.**
A	1	66.56	1.46
	2	69.57	0.69
	3	69.57	0.93
B	1	61.79	1.20
	2	64.60	3.11
	3	64.60	3.24
C	1	75.92	1.80
	2	75.56	1.58
	3	79.77	1.34
D	1	66.96	0.78
	2	67.18	0.81
	3	68.09	1.00

Table 4: Mean and standard deviation of BIS stages during the disturbance experiment

Design	**Stage**	**Mean**	**Std. dev.**
A	1	90.66	2.04
	2	89.35	2.11
	3	89.87	2.49
B	1	89.30	1.32
	2	91.24	2.69
	3	93.27	1.41
C	1	85.06	4.16
	2	81.95	1.03
	3	90.60	2.79
D	1	94.84	2.37
	2	86.97	24.56
	3	86.24	6.26

5.4.3 Discussion

Because in both design C and D the BIS signal fluctuates at the time a stage changes, it seems highly likely that the NIRS causes disturbance on the BIS sensor. Furthermore, design C and D are harder to attach firmly to the head. While measuring design C and D, the BIS monitor has given warnings during the measurements to indicate an attachment fault. This could cause the fluctuations of the BIS signals in both designs. But it should also be considered that because the attachment to the head was less firm, the BIS was more susceptible to disturbances caused by the NIRS sensor. The NIRS of design B and C shows a quite unstable signal, the relatively high standard deviation confirms this. These values are most likely due to bad contact of the sensor to the skin. Du,ring all tests the sensors were exposed to similar but variable external disturbances, so any influence of these possible interference sources should not be excluded. While experimenting quick switch of the NIRS sensor, some peaks of the BIS signal occurred. The peaks could be caused by the NIRS signal, but it could also be the standard fluctuations of the BIS signal. With the previous procedure of testing disturbance the BIS showed continuously fluctuations of the signal. Therefore nothing can be concluded of the quick switch test.

5.4.4 Conclusion

All the NIRS values lie in the range of the norm value 60-80%. In all designs the signal was fairly stable. Design B and C have a higher standard deviations caused by the peaks than the others designs, and are therefore less stable. Design C and D both show high fluctuations in the BIS signal. The fluctuations are more clearly when the NIRS is turned off than when it is turned on. On the other hand, the BIS signal stays above the boundary for awakeness. Based on the results the following can be noted: design A has the smallest amount of disturbance between the signals and is the most stable and therefore seems the most reliable device.

5.5 Valsalva maneuver

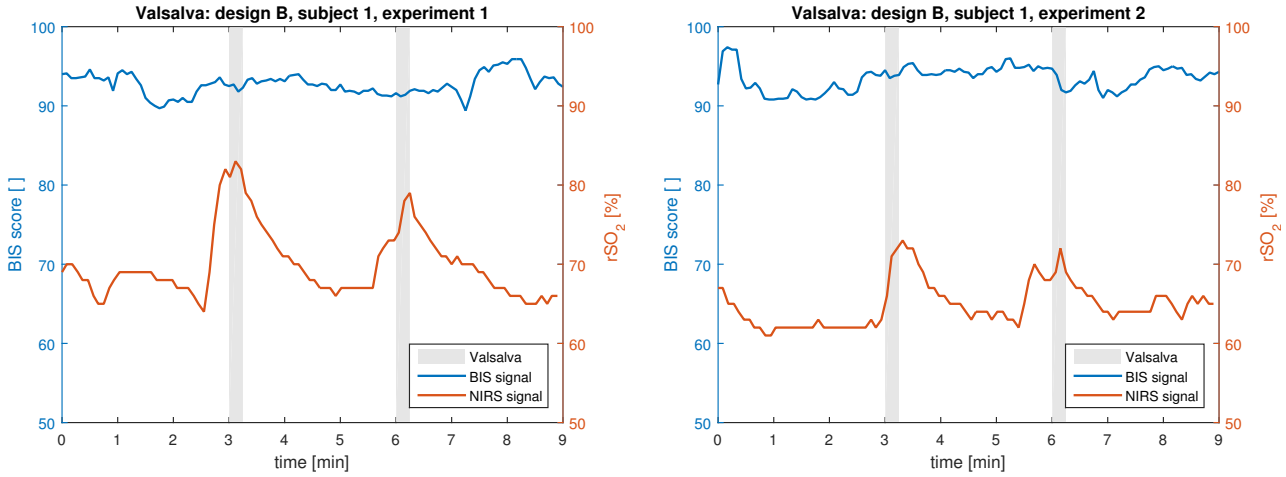
Now it is important to look if the fabricated sensors can measure relevant differences in brain activity and perfusion. In the context of this study, one actually wants to measure what happens to the brain when the blood flow is stopped, like during a cardiac arrest. This is not easily done in healthy subjects, so a less rigorously procedure is chosen. The Valsalva maneuver is a simple method to alter the blood flow to the brain, but not completely stop it. A change in blood flow will affect the oxygenation in the brain that will lead to a changed rSO_2 value. The Valsalva maneuver is executed by performing a forceful exhalation attempt against a closed airway. When the Valsalva maneuver is performed, the pressure inside the chest rises, which immediately increases the aortic pressure. The increased aortic pressure will lead to a short-term increased blood flow to the brain. The blood supply, and thus the oxygenation of the brain will increase. This will not hold for long because the cardiac output will fall, the aortic pressure will consequently decrease and eventually the blood flow to the brain will decrease. Furthermore, because of the pressure inside the chest, the return of venous blood is also reduced. There will be engorgement of venous blood in the brain. When the subject is breathing normal again, the pressure on the chest will be release and the venous blood will return to the heart. This will cause a rapid increase of the cardiac output. With return of the original blood pressure, the pulse rate returns towards normal.[55]

5.5.1 Methods

The frontal design A and B and lateral design C are tested to determine if the designs are able to measure difference in blood flow. The sensor reaction to different blood flows is tested according to measurement protocol III (see Appendix). To affect the blood flow, the Valsalva maneuver was performed, which was practiced before the experiment. The subjects had to perform this maneuver for 15 seconds. This time seemed suitable, because most people can sustain this task for this period of time, and this duration is often being used in other Valsalva protocols.[56] A standard time is highly favorable, because this makes the exercise much more reproducible. At least two experiments for each design are performed for a time of 2 x 9 minutes. Three and nine minutes after the measuring started, the subject had to perform the Valsalva maneuver. Design C had other time intervals, compared to designs A and B. The duration of the experiment was 15 minutes and the Valsalva maneuver is performed after 5 and 10 minutes. The BIS and NIRS were measuring at the same time.

5.5.2 Results

The moments when the flow was altered using the Valsalva maneuver are shown as a grey patch in figure 24, figure 25, figure 22, figure 23. The NIRS results for the frontal design B for subject 1 is presented in figure 22. When the Valsalva maneuvers are performed, clear peaks ranging from 6 to 30% increase in rSO_2 are seen in the figures of both experiments. Very little change can be found in the BIS signal in both experiments with design B subject 1, see figure 22a and figure 22b.



(a) experiment 1

(b) experiment 2

Figure 22: NIRS (red) and BIS (blue) data from subject 1 measured with design B. Valsalva is performed 15 seconds long, at 3 and 6 minutes.

Design Lateral C is tested ones and the results are shown in figure 23. The NIRS signal shows peaks ranging from 12 to 14% increase. The BIS signal shows fluctuations over time, without an obvious reason.

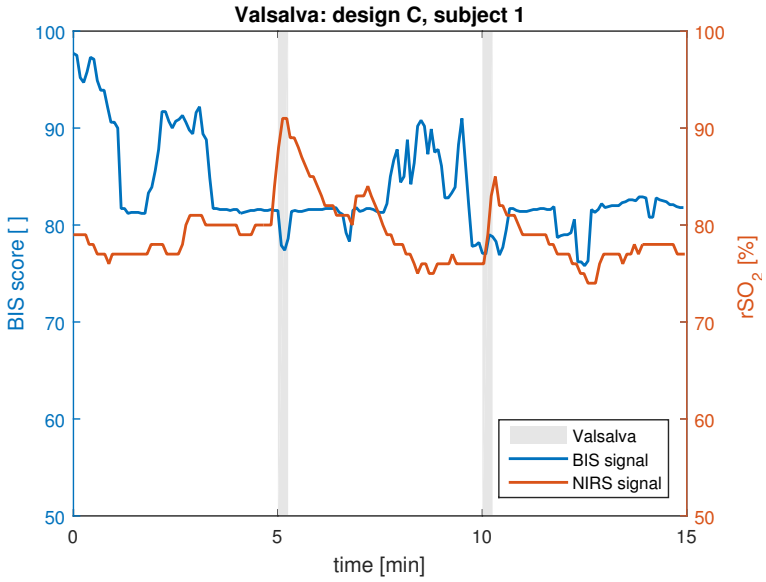
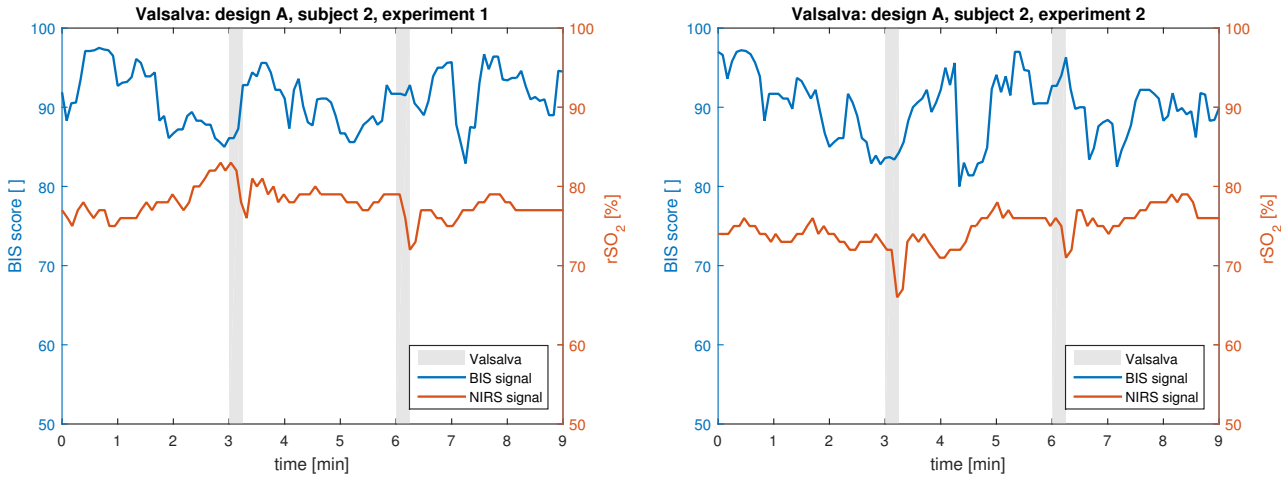


Figure 23: NIRS (red) and BIS (blue) data from subject 1 measured with design C. Valsalva is performed 15 seconds long at 5 and 10 minutes.

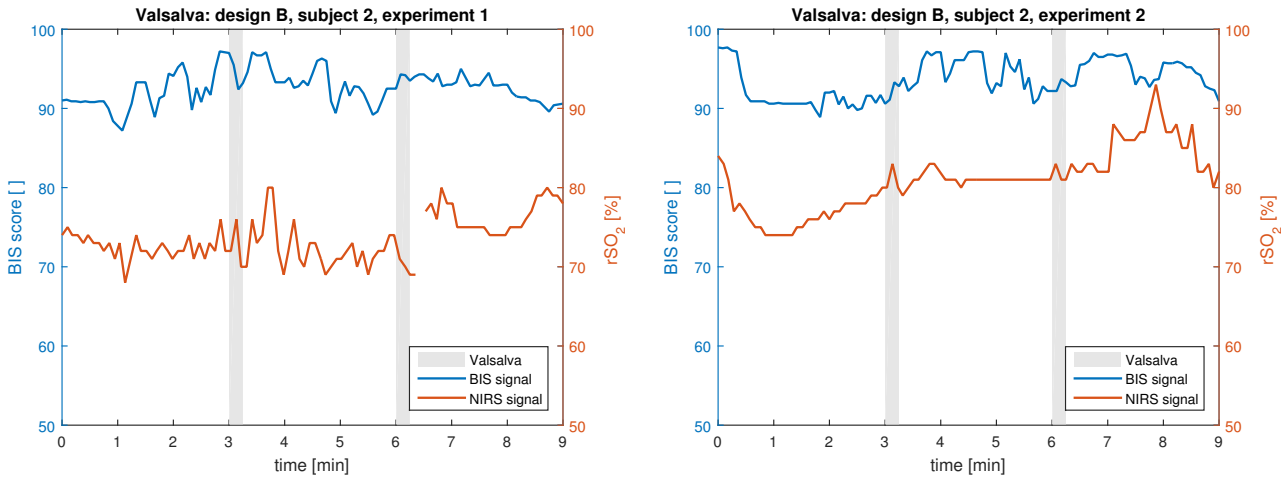
The following figures 24 and 25 show the NIRS and BIS values while the Valsalva maneuver is performed by subject 2. Subject 2 performed the maneuver with design A and design B. Design A shows in figure 24 in both experiments a depression of the rSO_2 value during the intervention, a decrease of 7-10%. The NIRS signal of design B has in experiment 1 various fluctuations during the measuring, see figure 25a. None of them are considered real peaks or depressions. Also, the NIRS signal of design B during experiment 1 disappears for a few seconds after the Valsalva maneuver is performed. Experiment 2 of design B shows a significant increase in NIRS value after 7 minutes, while no intervention is performed at that time, this is shown in figure 25b. The BIS values of design A and B did not show any differences before, after or during the intervention.



(a) experiment 1

(b) experiment 2

Figure 24: NIRS (red) and BIS (blue) data from subject 2 measured with design A. Valsalva is performed 15 seconds long at 3 and 6 minutes.



(a) experiment 1

(b) experiment 2

Figure 25: NIRS (red) and BIS (blue) data from subject 2 measured with design B. Valsalva is performed 15 seconds long at 3 and 6 minutes.

5.5.3 Discussion

There could be different reasons for the peaks that are shown in the figure 22 and figure 23 or depressions shown in figure 24 and figure 25. It would be errors in the signals, perhaps due to movement artifacts. It is expected that the pressure in the chest will lead to a short-term boost of the blood flow to the brain while performing the Valsalva maneuver. The oxygen consumption is unchanged in this situation. The subject is still sitting with his/her eyes closed while performing the Valsalva maneuver. An unchanged oxygen consumption with a changed blood flow through the brain will lead to a higher oxygenated blood level in the venous system. This will cause a peak in the signal. The venous blood can not return to the heart because of the pressure in the chest. As the brain cells still consume oxygen and little new blood is supplied, the oxygen levels slowly decrease. Because the experiment has a short duration, only the increase in oxygenation will be visible in the NIRS signal like in figure 22 and figure 23. To have more assurance, the Valsalva maneuver should be performed several times by the same person with a mouthpiece, because repeating tests improves reliability. Random errors do not repeat themselves, unfortunately systematic errors will not be filtered out. A mouthpiece will make the experiment be more reproducible, because a mouthpiece makes sure that the epiglottis is open during the experiment, while still making sure a pressure is build inside the lungs. The difference of the NIRS signal between subject 1 and 2 can be caused due the difference of pressure in the chest caused by the Valsalva maneuver. If the pressure in the chest caused by the Valsalva maneuver would be the same by each experiment the data could be compared better. Also the participant's scalp turned red, due to increased blood flow. This can result in that higher NIRS values are being measured, if any interference is present. The peaks in figure 22a appear just before the intervention is provoked, in contrast to the other graphs, where a peak or depression starts exactly when the Valsalva is performed. Two possible explanations are that the timing in this experiment was not correct or that the participant breathed deeply just before the intervention and in this way the pressure in the chest was already building up.

During the Valsalva maneuver peaks in the NIRS signal of subject 1 can be seen unlike the NIRS signal of subject 2 that shows depressions. This could be explained due to the change of pressure that is formed while performing the maneuver between the subjects. It is possible that subject 2 has build more pressure in the chest which leads to an immediate decrease of the blood flow to the brain. This could

cause a decrease in venous oxygenation. It could also be possible that engorgement of venous blood and the need of oxygen in the brain will lead to less oxygenated blood which could also cause the decrease in the NIRS signal. In case of the second situation it is expected that the NIRS signal would show an increase in signal first and afterwards a decrease.

Based on the experiment of subject 2, of the two frontal designs A and B, A seems to detect changes in oxygenation better. The NIRS values change clearly changes during testing, as seen in graph 24. In design B this change is less obvious, because the signal is less stable. This could be caused due to the place of the NIRS sensor on the head. In this experiment no correlation could be seen between the NIRS and BIS signal. All the figures are showing simultaneously measuring of a BIS and NIRS signal while performing the Valsalva maneuver. The BIS signal of design B seems to stay relatively stable, with a BIS score around 95, while the NIRS is showing peaks. This could be due to the short period of intervention that could not cause changes in neuronal activity of the brain. To say more about the autoregulation of the brain and the correlation between NIRS and BIS the duration of the Valsalva maneuver or another similar intervention should be longer. The lateral designs C and D were hardly tested, due to the insufficient amount of time, as a result of practical reasons. Priority was given to the more stable designs A and B.

5.5.4 Conclusion

The lateral and frontal designs were able to detect changes in cerebral oxygenation, caused by a Valsalva maneuver. Of the two frontal designs, frontal A was better in detecting changes when compared by subject 2. The BIS system did not detect any differences with all designs when the Valsalva maneuver was performed. This short-term intervention did not show any correlation between the BIS and NIRS.

5.6 Crash position

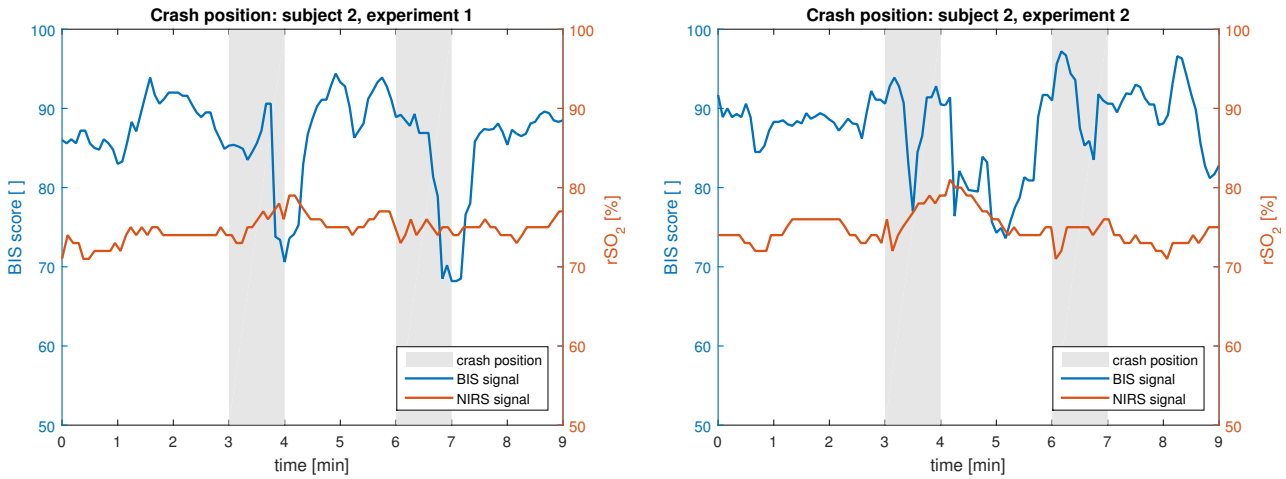
The previous experiment turned out to be useful, but had some difficulties with the reproducibility of the Valsalva maneuver. Another, easier way to alter the blood flow to the brain is chosen to perform next. The crash position is a common maneuver for people who are lightheaded or going to faint. The problem is mostly a low blood pressure, which results in a decreased blood flow to the brain. One puts his head between his knees to increase the blood flow. With an increased blood flow the saturation in the brain will also increase, because the oxygen consumption stays approximately the same.

5.6.1 Methods

The experiment is done following measurement protocol IV in the Appendix. During nine minutes, BIS and NIRS signals are being measured. The subject sits on a chair with his eyes closed. At three minutes the participant is asked to put his head between his legs for one minute, and thereafter raise it to it's original position. The same procedure is repeated at six till seven minutes.

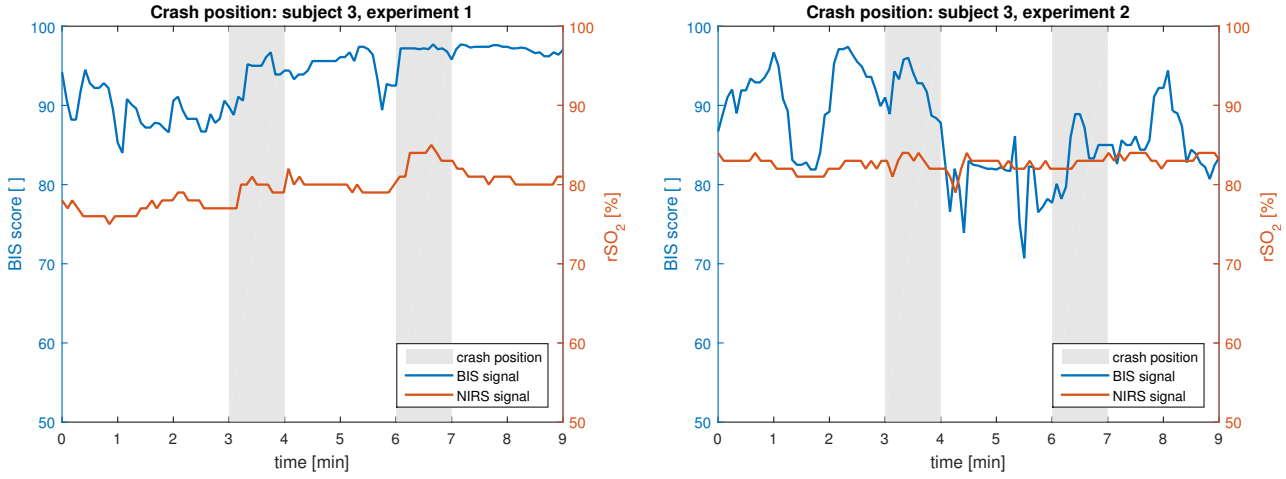
5.6.2 Results

The graphs beneath show the information of two subjects (2 and 3) performing the crash position, being measured by design A. Each subject has performed two experiments.



(a) experiment 1 (b) experiment 2

Figure 26: NIRS (red) and BIS (blue) data from subject 2 measured with design A. Crash position is performed at 3 till 4 and 6 till 7 minutes.



(a) experiment 1 (b) experiment 2

Figure 27: NIRS (red) and BIS (blue) data from subject 3 measured with design A. Crash position is performed at 3 till 4 and 6 till 7 minutes.

In figure 26 the BIS and NIRS signals from the first two experiments with subject 2 are shown. In these experiments there is an increase of 8.2% in experiment 1 and an increase of 12.7% in rSO_2 as the first crash position was performed. As soon as the participant sits up straight the value decreases again. In the second crash position this phenomenon is not seen. Subject 3 has also done two experiments, the results can be found in figure 27. In this subject there is not a very clear change in rSO_2. Experiment 1 in figure 27a shows two peaks during the time the subject has his head between his knees, but they are not as obvious as in the first crash positions of subject 2. The NIRS signal in experiment 4 in this figure has nearly no change during crash position. In figure 26a the BIS data shows two depression of circa 25% when the subject sits up straight again. But in experiment 2 in the figure 26b depressions are found within the minute the subjects head is down. The BIS data of the other two experiments seems pretty random and it looks like it has no pattern or correlation with the performed intervention. No relation can be found between the different experiments.

5.6.3 Discussion

Higher rSO_2 values, during the crash position, were expected, because an increased blood flow to the brain will lead to a higher saturation of brain tissue. Due to a well functioning autoregulation these changes are not found every time the maneuver was performed. During the crash position the participant's scalp became red, due to increased blood flow. This can result in higher rSO_2 values than can be actually measured within the brain. The BIS signal differs too much within the subjects and experiments. Some elevation during the performed movement is expected, because one has to use one's brain to make a move. Also, the EMG activity could increase during head movement. Unfortunately, this interference cannot be seen, because the BIS signal fluctuates too much. Due to the movement of the head and the upper body, some artifacts can be generated. The sensors could be detached or displaced. This may have led to the big fluctuations, but it may also be caused by the several reuse of the sensor, since this was the last experiment. Similar to the Valsalva experiments, the most stable designs were given priority over the least stable designs. So, in this case only design A could be tested. Unfortunately, no comparison can be made between the designs.

5.6.4 Conclusion

In half of the cases, the crash position resulted in higher rSO_2 values. The experiments with subject 2 clearly show that design A is able to detect the expected changes in saturation during crash position. No clear conclusion can be drawn from the BIS signal. In this experiment the BIS data was not at all trustworthy. Also, no correlation in BIS and NIRS signals can be found within this design and experiment.

6 Discussion

6.1 BIS and NIRS sensor

A critical look at this research is given in the following section. First, the choice of materials was limited by the client demands. The given monitors, the INVOS cerebral oximeter and the BIS Vista, had to be used. No further investigation was done in other options, so it is possible that these techniques are not the ideal solutions for this problem. Other sensors or methods might give the same, worse or even better information about the state of the brain.

The BIS and NIRS techniques certainly seem to offer opportunities, but there are some aspects that need attention. There is a skeptical image about the application at the NIRS sensor for the brain. Physicians noted that when a force was applied to the NIRS sensor, the NIRS monitor displayed different values. The applied force only manipulates the characteristics of the skin. This suggests that the signal as measured by the NIRS is originating from the skin instead of the cerebral cortex. [57,58] There are also some doubts about the BIS technique and the origin of the signal, both within University of Twente and in the literature. [47,48] It is possible that the BIS system particularly measures EMG signals. Moreover, it is only measuring regional brain activity in the frontal cortex and not of the whole brain or brainstem. Therefore no conclusion can be made about the activity in other parts of the brain. [50,51]

Ideally, the brainstem would be the best place to measure the oxygenation and brain activity of a dying person. This because this region regulates the respiration and heart rate, and is the last part of the brain that is affected by ischemia. However, the chosen technology does not allow monitoring of this area. The results of the combined BIS/NIRS sensor can give an indication of what is going on deeper in the head, but do not measure exactly there. This has to taken into account when evaluating the results. Another limitation is the locations on the head where the original sensors are designed to measure. BIS and the NIRS are designed for specific places on the human body. By changing these locations, the same accuracy can not be guaranteed because the systems are not properly tested and validated for those locations.

Besides the measuring locations, the dimensions of the original sensors are also changed. The chosen sensor dimensions and the measured values depend on dimensions of the head. It should be remembered that individuals are different from each other and that signals therefore can show differences. This is also the case when looking at the participants and the depth of the different layers of their head. A general assumption is made of the skull, the thickness of the layer CSF and depth of the brain cortex. This can result in incorrect NIRS values, if the assumptions that were made do not correspond to the actual values of the participants.

6.2 Designs

Another problem with the used devices are the high costs of the original sensors. Only a few could be used to make the combined sensor, otherwise the costs would become immense. This resulted in less prototypes being made. Furthermore, the time available to perform experiments was limited, due to distance between Rotterdam and Enschede. As a result of these two limitations, not all possible designs could be tested. So, the perfect design may not be mentioned in this research, despite efforts to minimize this chance by making reasoned choices.

Furthermore, the original BIS and NIRS sensors are disposable and made for single use. The sensors in this research were used on several individuals and for repeated measurements, because of cost reduction. This may have resulted in a decrease in signal quality. By taking of the sensor of a participant's forehead, the sensor can get damaged. Also the sticker will not adhere as good as before, which can lead to poorer signal transduction and thus less signal quality. In addition to that, it is not hygienic and for measurements with patients not acceptable.

During the making of the designs, the construction work had to be performed very carefully. The cables of the sensors are very fragile which sometimes led to trouble, it may be possible that while making the new designs the cables of the sensors become damaged. Especially the BIS sensor has a lot of vulnerable wires which have to be separated to create the new designs. This could create false or even no values for the BIS component of the resulting sensor. The NIRS sensor was disassembled to a lesser degree, because this was almost not possible without damaging the sensor. This led to designs with a bigger area than expected and less subtlety. By shortage of time and material, neatly finished new designs could not be created and trial versions were made.

6.3 Methods

The experiments were performed on healthy participants. The application of this sensor would be in comatose or dying patients, not in healthy subjects. It is difficult to say that the results of this study can be transferred to the actual patient group. The healthy subjects have very different BIS and NIRS values compared with comatose or dying patients, and may react differently to changes in blood flow or brain activity. Additionally, one can not really measure what happens during a circulatory arrest in the healthy subjects. Due to practical reasons, the blood flow to the brain cannot be stopped. The small change in blood flow in this study might be compensated by the brain's autoregulatory system. Another difference is the presence of possible confounders in the dying patient. There may be a lot of sweat, blood or a greasiness present on the skin of the forehead. This may lead to different results, but could not be tested in the healthy participants.

In this research, the brain activity has not been altered. It is not clear what kind of activities will change the electric state of the brain with such a degree that it can be measured by BIS and/or NIRS. When trying to reproduce the clinical situation, it is hard to reduce brain activity. The participant has to go to sleep for example, which is difficult to do in just 5 minutes. Or one could give some anesthetic drugs, but this would make the study more complicated. The Medisch Ethische Toetsings Commissie (METC) has to give approval for research done with the use of pharmaceuticals.

Furthermore, only three subjects were used to test the chosen design. This relatively small number of participants may not be an accurate representation of the whole population. Additionally, comparative analysis with the use of these small amount of subjects are not reliable. Besides, there is no blinding or masking used during this study. Both participants and researchers were able to identify which design was tested in a specific experiment and on a specific subject. This might lead to a placebo effect and/or misinterpretation of the result.

6.4 Performed experiments

The experiments took place in a hallway of the Erasmus MC (Rotterdam). This is a non enclosed space, so that the performed tests were being exposed to various and variable sources of interference. The level of (ambient) light and sound varied randomly during the tests, for example when people walked past or a freezer turned on and off. This could alter the neural activity of the subject, mimicking reaction on stimuli and leading to the possibility of misinterpretation of the resulting data.

In addition, electrical interferences were present. Due to limited space, the laptops were placed close to the sensors. Next to the experimental set up, a printer (with RFID), a varying number of cellphones and a large freezer were present. All this may have interfered with the measurements that are done, especially the BIS. Some more disturbances likely will being measured within the EEG signal, like EMG, EOG, ECG or power line signals. These noises on the signal could influence the interpretation of the signals. As a result, wrong conclusions may be drawn from the misinterpreted results. On the other hand, all kinds of disturbance and noise will be present in the ICU as well, because a lot of the existing equipment is powered by electricity.

On our second day in Rotterdam, the BIS electrode in the frontal design stopped working because of too many reconnections to the monitor. To measure some disturbances (slow and fast) and physiological interventions (Valsalva and crash position), a new sensor had to be arranged. A BIS sensor was already used on a patient and needed to be cleaned with alcohol. It is not known what happened to the sensor between unpacking and the delivery to the experimental site. Furthermore, it was not an expired sensor like the other BIS electrodes that were used. Also, the effect of cleaning with alcohol on the BIS sensor is not known. This may have influenced the data obtained with this specific sensor.

More specific discussion points for each experiment can be found in the corresponding discussion sections.

7 Conclusion

The goal of this study was to investigate how the BIS and NIRS could be combined to measure changes in perfusion and activity in the cortex of healthy subjects. The NIRS sensor showed little room for altering, therefore the number of possible BIS/NIRS designs was limited and could not be made much smaller. Ultimately, four designs were chosen to be tested. The new designs unfortunately did not look more subtle than the two separate sensors. Combining all data from the experiments together, it can be concluded that design A is the best performing design. This model showed the least distortion, while delivering the best results during the intervention trials in which the oxygenation seems to be measured. The BIS signal was overall not very useful during the interpretation of the results. No relevant conclusions can be drawn from that data. Within this study a combination of BIS and NIRS measurements did not provide any correlations. In the clinical context of this study, it is important to have more insight in the irreversible damage to the brain following a cardiac arrest. After testing, a prototype is realized, which only seems to measure meaningful oxygenation differences in the brain.

8 Recommendations

This project is only the start of something that could become a clinically useful monitoring device of brain cortex physiology. Concluding from our study, the use of the BIS and NIRS sensors as shown in design A is recommended. Further research should primarily focus on the quality of the signal as captured by the sensor, as mentioned earlier in the discussion section. This should be done on a small scale, starting with healthy subjects. The establishment of a gold standard to compare with the new designs and the development of a standard scoring procedure are both highly advisable. The design of the sensor should be changed if needed, to meet the demands of the patients, their relatives and the health care professionals.

The INVOS™ 5100C Cerebral/Somatic Oximeter that is used in this research has a relatively large NIRS sensor, which works with a LED and is hard to dismantle. It would be better to use a smaller sensor, with the light being conducted by fibers. These fibers will not create disturbance on the BIS signal and will be more subtle. Furthermore, a NIRS with fibers is easier to disassemble and this will lead to subtler and more possible options for designs. In this study, BIS sensors are used as well. A limited amount of sensors were available because of the high costs. Instead of BIS electrodes, EEG or ECG electrodes could also be used, these electrodes are cheaper and in several other researches they were successfully used.[59,60] Ideally, each electrode should be used once and be disposed afterwards. The use of the BIS system is seen as unsuitable in this application, due to the questionable performances of the device during this study. In the ICU, a monitoring system should be robust and reliable.

To make good analysis of the disturbance of the BIS and NIRS signal on each other, it is important to pay attention to the various characteristics of the signals. Those are for example fluctuation, width, frequency spectrum or the mean value. A set of meaningful markers of interference should be established. Also in this research is disturbance of the signals tested on a human subject, so the physiological processes in a person are causing fluctuations in the signal. To have minimum effect of the subject itself on the signal, a phantom or dummy is required while measuring disturbance.

If BIS and NIRS are simultaneously measured, it would be useful to present the two values on one screen and/or could be combined into one score as a value for the brain's state. The values would be easier to read and interpret. If the combined sensor proves to measure meaningful information about the brain, then validation trials need to be set up. This should also start at a small scale, and develop into large multicentre randomized controlled trials. After the sensor being validated, the mass production of the resulting product could be launched. To have a better sensor than the created BIS/NIRS sensor and to have as much as information about the brain, it is desired to measure the intracranial pressure and the cerebral blood flow as well. A new design with all these components would be a design that provides more information and is more reliable than a combination of merely NIRS and BIS.

Eventually, the concept of the combined monitoring of the activity and oxygenation of the brain also promises potential uses for other patient groups. Other critical patients could possibly benefit from this development, for example people who endured severe head trauma. Currently on the ICU, almost every organ function is being continuously monitored, like blood pressure and heart rate. However, being one of the most important organs, the real time monitoring of the brain may be improved. Physicians mostly gather information about the state of the brain through indirect neurological tests, computed tomography (CT) and/or MRI. Unfortunately, continuous measurements are not possible with those

technologies. The BIS/NIRS sensor possesses the ability to measure easily, continuously and in real time and could therefore be an addition to the conventional monitoring standards. But this has to be investigated in future research, and should be well validated before put into practice.

The prototypes are the result of an evaluation of a limited set of options in a limited time span. Furthermore, this study only demonstrates the use of an combined BIS/NIRS-design. So, other options should not be ruled out automatically. The exploration of the use of other similar techniques (like EEG and TCD) is highly recommended. Hereby, it is important to realize the final system will be used as a continuous bedside monitoring system, this restricts the possible options (as seen in section 3.2). The use of the most suitable, up to date, direct and reliable techniques in the future design process is essential to create a useful and purposeful addition to the monitoring toolbox in the ICU.

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Appendix

Appendix I Measurement protocol Location

Location: Erasmus MC, 6th floor (ICU staff).
Duration: 2x 15 = 30 minutes
Requirements:

- The 4 chosen BIS/NIRS sensor designs
- BIS monitor (Aspect)
- NIRS monitor (Invos)
- 2x RS-232 to USB converters (BB Electronics Ulinx USO9ML2)
- Null modem cable
- Laptop (with USB serial driver and Hyperterminal)
- Stopwatch
- Alcohol and gauze pads

Only two designs (A and C) are being measured.
Preparation:
Give information to subject; and ask informed consent
Complete the participants form
Clean the participant's head with alcohol and gauze pads
If necessary, use EEG-gel to wet the BIS electrodes
Place the sensor on it's position and press firmly from inside out, to ensure the sensor is securely fixed to the subject and the edges are properly attached to the skin
Press each BIS electrode for 5 seconds
Connect the sensor with the monitors, make sure all settings are correct (see manufacturer's manual)
Connect the BIS monitor with the laptop using the RSR-323 to USB converter
Connect the NIRS monitor with the laptop using a null modem cable and the RS-232 to USB converter
Check if calibration and impedance checks were successful
Experiment:
The subject sits on a chair with his/her eyes closed
Turn BIS and NIRS measuring on and start time
End measurements at 15 minutes
Repeat this experiment for the other design
Completion:
Save and upload data
Remove sensor from participant and disconnect the sensors and monitors
Note any abnormalities or particularities for this experiment in the lab journal

Appendix II Measurement protocol Disturbance

Location: Erasmus MC, 6th floor (ICU staff)
Duration: 4x 2x15 = 120 minutes
Requirements: see Measurement Protocol I
Preparation: see Measurement Protocol I
Experiment:
The subject sits on a chair with his/her eyes closed
First round
Start time and BIS measurement
After 5 minutes: start NIRS measurement
After 10 minutes: end NIRS measurement
End BIS and time measurement at 15 minutes
Second round
Start time and NIRS measurement
After 5 minutes: start BIS measurement
After 10 minutes: end BIS measurement
End NIRS and time measurement at 15 minutes
Repeat the whole experiment for all 4 designs
Completion: see Measurement Protocol I

Appendix III Measurement protocol Valsalva maneuver

Location: Erasmus MC, 6th floor (ICU staff) .
Duration: 7 x 9 = 63 minutes
Requirements: see Measurement Protocol I
Preparation: see Measurement Protocol I
Experiment:
The subject sit on a chair with his/her eyes closed
Turn BIS and NIRS measuring on and start time
After 3 minutes: let the subject perform a Valsalva maneuver for 15 seconds.
After 6 minutes: let the subject perform a Valsalva maneuver for 15 seconds.
End measurements at 9 minutes
Repeat this experiment with the other subjects and/or designs.
Completion: see Measurement Protocol I

Appendix IV Measurement protocol Crash position

Location: Erasmus MC, 6th floor ICU staff
Duration: 4x 9 = 36 minutes
Requirements: see Measurement Protocol I
Preparation: see Measurement Protocol I
Experiment:
The subject sits in a chair with his/her eyes closed
Turn BIS and NIRS measuring on and start time
After 3 minutes: Ask subject to put his/her head between the knees for 1 minute.
After 6 minutes: Ask subject to put his/her head between the knees again for 1 minute.
End metering at 9 minutes
Repeat this experiment with the other participants and/or designs.
Completion: see Measurement Protocol I

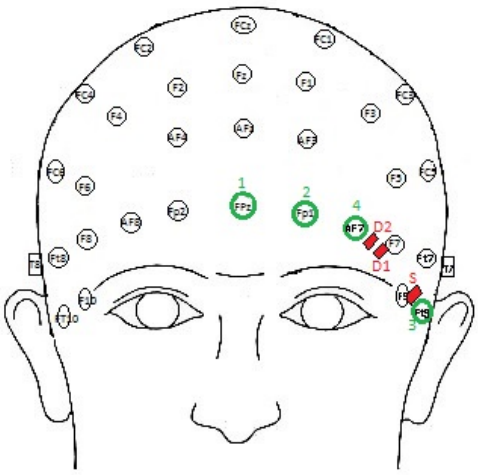
Appendix V Participation Forms

Subject ID: 1
Gender: ~~M~~ / V
Age: 21
Familiar with:
~~Heart diseases~~
~~High or low blood pressure~~
~~Vascular diseases~~
~~Neurological diseases~~
~~Skin/scalp disorders~~
None of the above

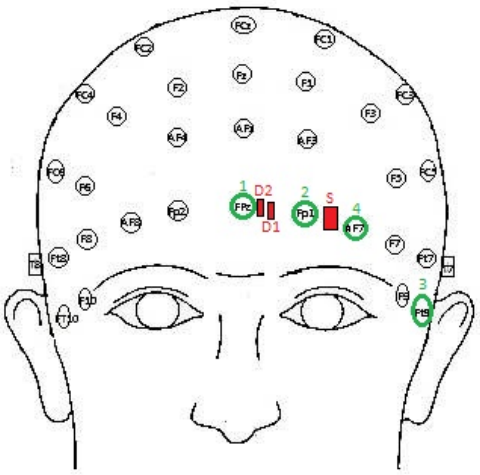
Subject ID: 2
Gender: M / ~~V~~
Age: 22
Familiar with:
~~Heart diseases~~
~~High or low blood pressure~~
~~Vascular diseases~~
~~Neurological diseases~~
~~Skin/scalp disorders~~
None of the above

Subject ID: 3
Gender: M / ~~V~~
Age: 21
Familiar with:
~~Heart diseases~~
~~High or low blood pressure~~
~~Vascular diseases~~
~~Neurological diseases~~
~~Skin/scalp disorders~~
None of the above

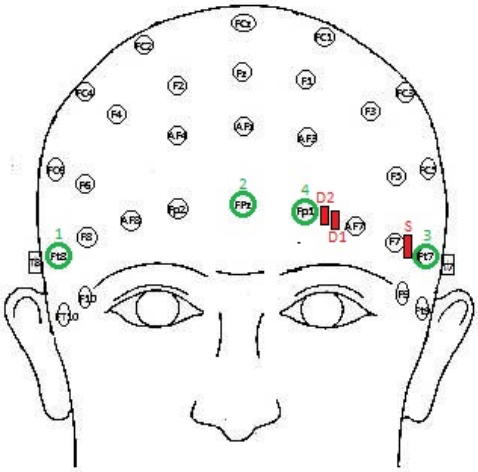
Appendix VI Sketches All Designs



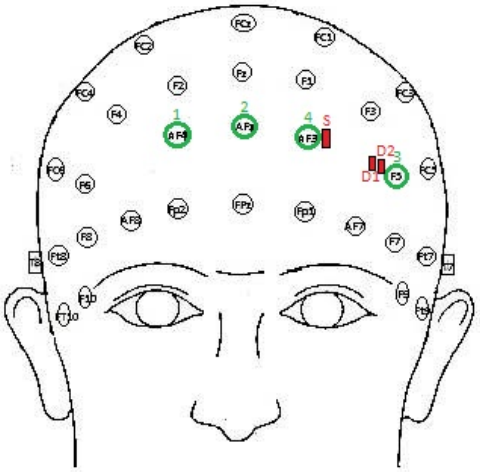
(a) Frontal 1



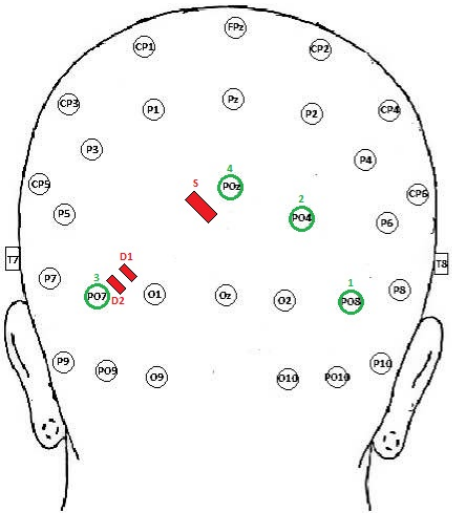
(b) Frontal 2



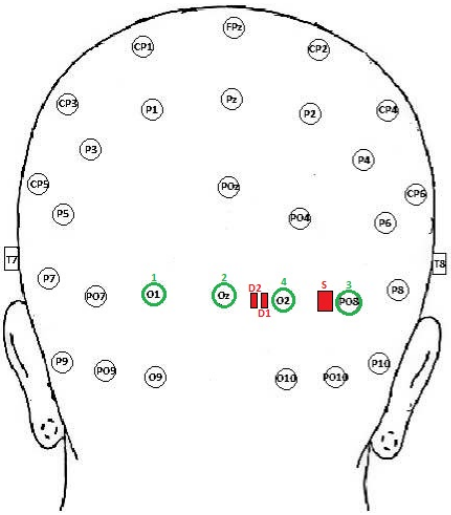
(c) Frontal 3



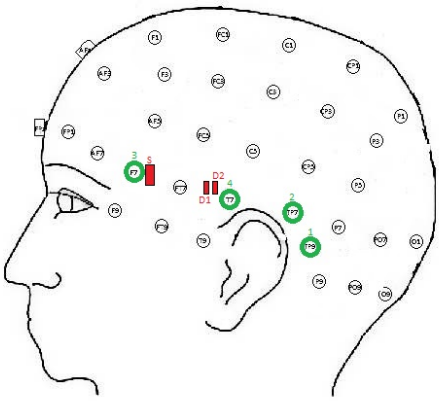
(d) Frontal 4



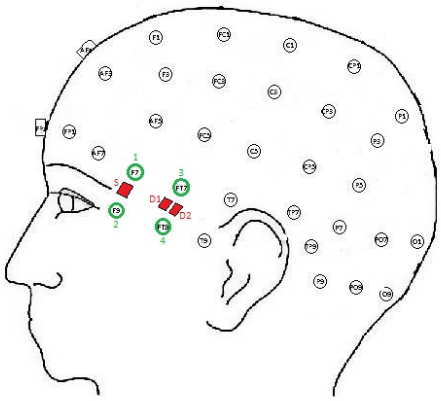
(e) Occipital 1



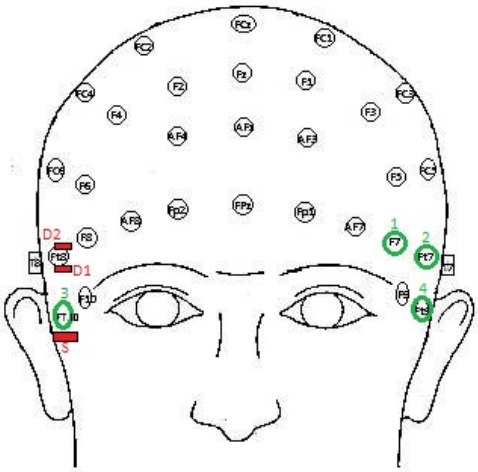
(f) Occipital 2



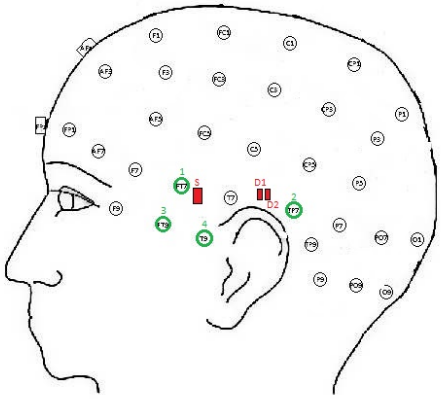
(g) Lateral 1



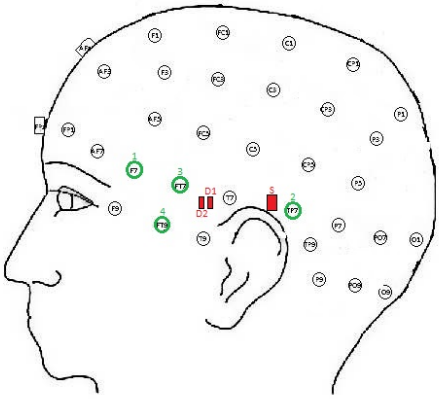
(h) Lateral 2



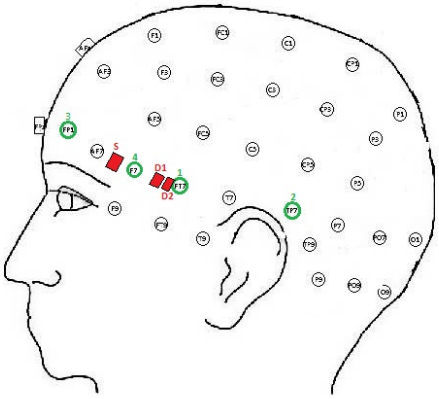
(i) Lateral 3



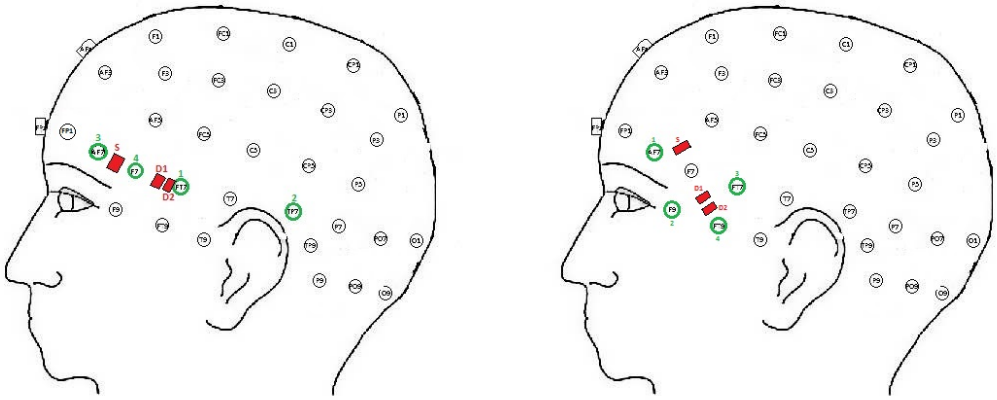
(j) Lateral 4a



(k) Lateral 4b



(l) Lateral 5



(m) Lateral 6 (n) Lateral 7

Figure 28: Overview of all designs

Appendix VII Matlab

VII.1 Matlab Functions

VII.1.1 READ_BIS.m

```
function [timeserie_BIS] = READ_BIS(userMessage)
% TG MDO-15 - Read NIRS file into timeserie
% (c) Narik, Tim, Marijn en Huub
% University of Twente
% version: 13 jun 2015

%Read data from files
fileName= uigetfile('*.*',userMessage,mfilename('fullpath'));
DATA = importdata(fileName,' ');

% BIS data-tables merge
   % dimensions table
    a = size(DATA.data);
    b = size(DATA.textdata);
    c = a(1,1);
    d = b(1,2);
    e = d + 1;
   % preparation table
    DATA.data = num2cell(DATA.data);
    data1 = zeros(a(1),36);
    data1 = num2cell(data1);
   %construction of table
    data1(1:c,1:d) = DATA.textdata;
    data1(1:c,e:36) = DATA.data;

%Convert data
   % select data
    BIS = (data1(:,13))';
    TIME = (DATA.textdata(:,2))';
    DATE = (DATA.textdata(:,1))';

   % preprocessing dataset and timevector
   if iscellstr(BIS) == 0;
        BIS_num = cell2mat(BIS);
    elseif iscellstr(BIS) == 1
        BIS = cell2mat(BIS');
        for i=1:length(BIS)
            bis(i) = str2num(BIS(i,1:4));
        end
        BIS_num = bis;
   end
   for j=1:length(BIS_num)
        %reading of 0 when sensor turned off: filter out
        if (BIS_num(j) == 0)
            BIS_num(j) = NaN;
        end
   end
   for t=1:length(DATE)
       DATIM{t} = strcat(DATE(t),{' '},TIME(t));
   end
% Create time-series
```

```
    timeserie_BIS = timeseries(BIS_num, [TIME(:)]','Name','BIS');
    timeserie_BIS.TimeInfo.Units = 'minutes';
    %timeserie_BIS.TimeInfo.StartDate = TIME{1};
        %do not use if measurements are not performed simultaneously
    timeserie_BIS.Time = timeserie_BIS.Time - timeserie_BIS.Time(1);
    timeserie_BIS.Time = (timeserie_BIS.Time*24*60);
```

VII.1.2 READ_NIRS.m

```
function [timeserie_NIRS] = READ_NIRS(userMessage)
% TG MDO-15 - Read NIRS file into timeserie
% (c) Narik, Tim, Marijn en Huub
% University of Twente
% version: 13 jun 2015

%Read data from files
fileName= uigetfile('*.*',userMessage,mfilename('fullpath'));
DATA = importdata(fileName,' ');

%Convert data
   % select data
    rSO2 = (DATA.textdata(:,5))';
    TIME = (DATA.textdata(:,3))';
    DATE = (DATA.textdata(:,2))';
  % preprocessing dataset and timevector
    for i=1:length(rSO2)
        rSO2_num(i) = str2num(rSO2{i});
        % NIRS reading of 0 means error: remove from data
        if(rSO2_num(i)==0)
            rSO2_num(i) = NaN;
        end
    end
    for t=1:length(DATE)
       DATIM{t} = strcat(DATE(t),{' '},TIME(t));
    end
% Create time-series
    timeserie_NIRS=timeseries(rSO2_num,[TIME(:)]','Name','NIRS');
    timeserie_NIRS.TimeInfo.Units='minutes';
    %timeserie_NIRS.TimeInfo.StartDate = TIME{1};
        %do not use if measurements are not performed simultaneously
    timeserie_NIRS.Time = timeserie_NIRS.Time - timeserie_NIRS.Time(1);
    timeserie_NIRS.Time = (timeserie_NIRS.Time*24*60);
```

VII.2 Matlab Scripts

VII.2.1 PLOT_BISNIRS.m

```
% TG MDO-15 - Plot BIS and NIRS file
% (c) Narik, Tim, Marijn en Huub
% University of Twente
% version: 19 jun 2015

%Clean variables and workspace
clear all;
close all;

%Create time-series
tslB = READ_BIS('Select the BIS file');
tslN = READ_NIRS('Select the NIRS file');

% Plot two NIRS datasets in one figure
figure('name','Combined BIS and NIRS recordings vs time');
hold on
title ('Combined BIS and NIRS recordings vs time');
[Ax,hLine1,hLine2] = plotyy(tslB.Time,[tslB.Data(:)],tslN.Time,[tslN.Data(:)]);
hLine1.LineWidth = 1.5;
hLine2.LineWidth = 1.5;
xlabel('time [min]')
ylabel(Ax(1),'BIS score [ ]') % left y-axis
ylim(Ax(1),[50 100])
ylabel(Ax(2),'rSO_2 [%] ') % right y-axis
ylim(Ax(2),[50 100])
set(Ax(1),'YTick',[50:10:100])
set(Ax(2),'YTick',[0:10:100])
set(Ax(1),'YLim', [50 100])
set(Ax(2),'YLim', [50 100])
legend ([hLine1,hLine2],'BIS signal', 'NIRS signal', 'Location', 'southeast')
hold off
```

VII.2.2 PLOT_BISNIRS_disturbances.m

```
% TG MDO-15 - Plot BIS/NIRS and disturbance
% (c) Narik, Tim, Marijn en Huub
% University of Twente
% version: 19 jun 2015

%Clean variables and workspace
clear all;
close all;

%Ask for tested sensor (choice: 1 = BIS, 2 = NIRS)
choice = menu('Choose tested sensor','BIS','NIRS');
%Ask for applied disturbance (choice: 1 = slow, 2 = fast)
disturbance = menu('Choose applied disturbance','Slow (standard)','Fast (standard)','User Specifed (c

if choice == 1 %BIS
tsl = READ_BIS('Select the BIS file');
%-------[OR]-----------------------------------------------------------
elseif choice == 2 %NIRS
tsl = READ_NIRS('Select the NIRS file');
```

```
%-------[OR]-----------------------------------------------------------
else
    error('Invalid sensor type');
end
%--------------------------------------------------------------------

% Plot signal and disturbance in one figure
figure('name','Sensor recordings and disturbance(s) vs time');
hold on
title ('Sensor recordings and disturbance(s) vs time');
if disturbance == 1
    disturbanceMarker = patch([5 10 10 5],[0 0 100 100],[0.9 0.9 0.9], 'edgecolor','none'); %slow
elseif disturbance == 2
    for t = 1:6 %each minute, 10 sec disturbance
    disturbanceMarker = patch([t (t+10/60) (t+10/60) t],[0 0 100 100],[0.9 0.9 0.9], 'edgecolor','none
    end
elseif disturbance == 3
    input_start = str2double(input('Enter start of disturbance (min): ', 's'));
        while isnan(input_start) || fix(input_start) ~= input_start
         input_start = str2double(input('Please enter and INTEGER: ', 's'));
        end
    input_end = str2double(input('Enter end of disturbance (min): ', 's'));
        while isnan(input_end) || fix(input_end) ~= input_end
         input_end = str2double(input('Please enter and INTEGER: ', 's'));
        end
    tsl = addevent(tsl,{'START_Disturb' 'END_Disturb'},{input_start input_end});
    disturbanceMarker = patch([input_start input_end input_end input_start],[0 0 100 100],[0.9 0.9 0.
else
    error('Invalid experiment type');
end
xlabel('time [min]')
title('Sensor recording and disturbances vs time');
if choice == 1 %BIS
signal = plot(tsl.Time,[tsl.Data(:)]);
ylabel('BIS score [ ]') % y-axis
ylim([50 100])
legend ([disturbanceMarker,signal],'NIRS on','BIS signal', 'Location', 'southeast')
elseif choice == 2 %NIRS
signal = plot(tsl.Time,[tsl.Data(:)],'color','[0.8500 0.3250 0.0980]');
ylabel('rSO_2 [%] ') %y-axis
ylim([50 100])
legend ([disturbanceMarker,signal],'BIS on','NIRS signal', 'Location', 'southeast')
else
     error('Invalid sensor type');
end
signal.LineWidth = 1.5;
hold off
```

VII.2.3 PLOT_BISNIRS_intervention.m

```
% TG MDO-15 - Plot BIS, NIRS and intervention
% (c) Narik, Tim, Marijn en Huub
% University of Twente
% version: 19 jun 2015

%Clean variables and workspace
clear all;
close all;

%Ask for experiment type (choice: 1 = val, 2 = head)
choice = menu('Choose experiment','Valsalva (standard)','Head down/up (standard)','User Specifed (cmd

% Create time-series
tslB = READ_BIS('Select the BIS file');
tslN = READ_NIRS('Select the NIRS file');

% Plot BIS and NIRS signal in one figure
figure('name','Sensor recordings and intervention(s) vs time');
hold on
title ('Sensor recordings and intervention(s) vs time');
if choice == 1
    intervention = patch([3 3.25 3.25 3],[0 0 100 100],[0.9 0.9 0.9], 'edgecolor','none' ); %Valsalva
    patch([6 6.25 6.25 6],[0 0 100 100],[0.9 0.9 0.9], 'edgecolor','none' ) %Valsalva
elseif choice == 2
    intervention = patch([3 4 4 3],[0 0 100 100],[0.9 0.9 0.9], 'edgecolor','none'); %Head
    patch([6 7 7 6],[0 0 100 100],[0.9 0.9 0.9], 'edgecolor','none' ) %Head
elseif choice == 3
    input_start = str2double(input('Enter start of intervention (min): ', 's'));
        while isnan(input_start) || fix(input_start) ~= input_start
         input_start = str2double(input('Please enter and INTEGER: ', 's'));
        end
    input_end = str2double(input('Enter end of intervention (min): ', 's'));
        while isnan(input_end) || fix(input_end) ~= input_end
         input_end = str2double(input('Please enter and INTEGER: ', 's'));
        end
    tslB = addevent(tslB,{'START_Intervention' 'END_Intervention'},{input_start input_end});
    tslN = addevent(tslN,{'START_Intervention' 'END_Intervention'},{input_start input_end});
    intervention = patch([input_start input_end input_end input_start],[0 0 100 100],[0.9 0.9 0.9], '
else
    error('Invalid experiment type');
end
[Ax,hLine1,hLine2] = plotyy(tslB.Time,[tslB.Data(:)],tslN.Time,[tslN.Data(:)]);
hLine1.LineWidth = 1.5;
hLine2.LineWidth = 1.5;
xlabel('time [min]')
ylabel(Ax(1),'BIS score [ ]') % left y-axis
ylim(Ax(1),[50 100])
ylabel(Ax(2),'rSO_2 [%] ') % right y-axis
ylim(Ax(2),[50 100])
set(Ax(1),'YTick',[50:10:100])
set(Ax(2),'YTick',[0:10:100])
set(Ax(1),'YLim', [50 100])
set(Ax(2),'YLim', [50 100])
legend ([intervention,hLine1,hLine2],'Intervention','BIS signal', 'NIRS signal', 'Location', 'southea
hold off
```