

Near-Infrared Spectroscopy

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1. Introduction

Near infrared spectroscopy (NIRS) is an imaging technique used in both clinical and emergency medicine, as well as in research laboratories to quantify and measure the oxygenation status of human tissue non-invasively. This is done by monitoring in vivo changes of the oxygen saturation of hemoglobin molecules in the body, based on the absorbance of near-infrared light by hemoglobin. With regards to NIRS in human tissue, this chapter will primarily be concerned with discerning the oxygenation status of cerebral tissue. The importance of such a measure, especially in cerebral physiology, is that the human brain utilizes oxygen to continuously supply neurons with energy used for vital body functioning. In the absence of oxygen, as is the case during ischemic stroke or desanguination, cognitive and functional impairment resulting in death often occurs. NIRS technology makes it possible to apply critical safety thresholds with regards to cerebral tissue saturation in order to avoid dangerously low levels with the primary goal being to reduce mortality rates and cognitive deficits due to cerebral hypoxemia.

Prior to 1977, and the advent of commercially available fiber optic cables, the quantification of hemoglobin concentrations in the human body was only possible using cuvette tubes containing sampled blood and large spectrophotometer units. These spectrometers, utilized the theoretical work of Karl Vierodt in 1873, to measure the absorbance of a colored solution based on the magnitude of “visible light” attenuation per unit of the colored solution. The limitation however, was that visible light was not able to penetrate superficial human tissue, making it impossible to quantify hemoglobin concentration changes in living tissue under any circumstance and was often done using bulky expensive spectrometers. Fiber optic cables transmitting near-infrared light however, made it possible for researchers and clinicians to safely penetrate skin, bone and other tissues with minimal incident light loss and ultimately shining a literal light on cerebral tissue oxygenation. This breakthrough paved the way for multiple methods of measuring near-infrared light absorbance in oxygenated and deoxygenated hemoglobin molecules found in cerebral tissues.

The improved resolution of living tissue provided by using near-infrared light, and the additional modification of theoretical models (Beer-Lambert law, Monte Carlo technique), is proving that the NIRS technique, is quickly becoming a useful and invaluable tool in monitoring tissue hemodynamics.

2. Physical principles of NIRS

The basis of NIRS relies upon two principles: (1) that tissue is relatively transparent to near-infrared light and (2) that there are compounds in tissue in which absorption of light is dependent on the oxygenation status of the tissue (Elwell & Phil, 1995).

The propagation of light in tissue depends on the combination of absorption, scattering, and reflection properties of photons. Absorption and scatter in tissue is dependent on the wavelength. Scatter decreases with increasing wavelengths; thereby favoring the transmission of near-infrared light compared to visible light. Reflection, in contrast, is generally a function of the angle of the light beam and the tissue surface (Jöbsis, 1977).

2.1 Absorption of light

When light is absorbed its energy is dissipated as thermal energy throughout the absorber (Elwell & Phil, 1995). Absorption occurs at specific wavelengths, determined by the molecular properties of the materials in the light path (Jöbsis, 1977; Wray et al., 1988). The primary light-absorbing compounds in tissue within the near-infrared range are called chromophores (Jöbsis, 1977). Most chromophores can be considered to have stable concentrations during a measurement period (~10 min), however, their presence adds to the total light attenuation (i.e. melanin, bilirubin, water). The primary chromophores of interest are oxyhemoglobin (HbO₂), deoxyhemoglobin (Hb) and cytochrome c oxidase, because the concentration of these chromophores varies with time and oxygenation status (Elwell & Phil, 1995). Each chromophore has a unique absorption spectrum, where the specific extinction coefficient¹ (ϵ) is expressed as a function of the wavelength (Horecker, 1942; Pellicer & Bravo, 2011). ϵ describes how strongly a chromophore absorbs light at a particular wavelength. In Fig. 1 the absorption spectra for Hb, HbO₂, cytochrome c oxidase and water (H₂O) are given.

Cytochrome c oxidase changes with oxygenation status. However, it does not have a significant effect on the measurement because the effect on the attenuation signal is ten times smaller than hemoglobin (Madsen & Secher, 1999). Cytochrome c oxidase is a mitochondrial enzyme and therefore describes the intracellular oxygenation (Heekeren et al., 1999), its concentration is not entirely the result of changes in oxygen availability. Therefore, in monitoring tissue oxygenation with NIRS the chromophores Hb and HbO₂ are of interest. Hb and HbO₂ are responsible for the transport, delivery and removal of oxygen (O₂) and carbon dioxide (CO₂) throughout human body. NIRS instruments utilize light in the 700-1000 nm wavelength range to transilluminate cerebral and muscular tissues. This range follows from the increased absorption bands of H₂O above 1000 nm and increased scattering and more intense absorption bands of Hb below 700 nm. In the 700-1000 nm

¹ In literature the term specific extinction coefficient is often confused with the terms molar absorption coefficient, molar extinction coefficient and the absorption coefficient. The molar absorption coefficient describes how strongly a *chemical species* absorbs light at a particular wavelength, whereas the molar extinction coefficient describes how strongly a *substance* absorbs light at a particular wavelength. The specific extinction coefficient (in $\mu\text{molar}^{-1}\text{cm}^{-1}$) is the molar extinction coefficient multiplied by the molar mass of the compound, describing how strongly a specific chromophore absorbs light at a particular wavelength. Whereas the absorption coefficient is the specific extinction coefficient multiplied by the concentration of the compound (Elwell & Phil, 1995).

range Hb and HbO₂ have unique absorption spectra, which allows emitted light to propagate through tissue for several centimeters. The attenuation of the emitted light can be related to the change in chromophore concentration using the Beer-Lambert law as described in section 2.3.

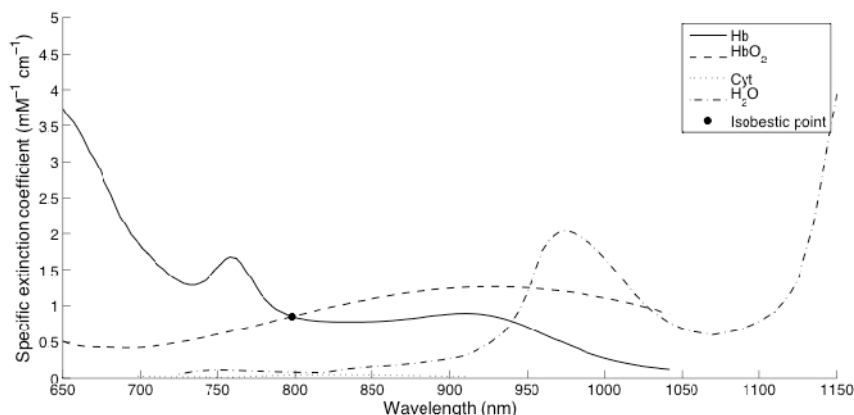


Fig. 1. Absorption spectra for deoxyhemoglobin (Hb), oxyhemoglobin (HbO₂), cytochrome c oxidase (Cyt), and water (H₂O) in the near-infrared range. The isobestic point near 800 nm is the point where the absorptivity of Hb and HbO₂ are equal (Palmer & Williams, 1974; Wray et al., 1988).

2.2 Scattering of light

In addition to the attenuation of light by absorption, scatter also causes attenuation of light. When NIR light is scattered in tissue the collisions are elastic, implicating that no energy is lost and the photon merely changes direction. The direction in which the scattered photon travels is dependent upon the wavelength, the different refractive indices of the tissue layers through which the photon is travelling and the size of the scattering particle (Elwell & Phil, 1995).

A complex structure such as the human head consists of multiple layers of tissue each with varying thicknesses and densities, resulting in varying degrees of scatter. These include cell membranes, transitions between different fluids and various organelles within the cell, large blood vessels as well as the boundaries between bone and soft tissue. The most important source of scatter in tissue are cell membranes since they account for a large proportion of the solid content of the tissue. However, red blood cells only account for approximately 1.5% of the solid content of tissue and as such the attenuation by scattering due to red blood cells is low (Cope, 1991; Elwell & Phil, 1995). Highly scattering tissues include bone, cerebral white matter and skin dermis (Elwell & Phil, 1995).

2.3 Attenuation by light

When light travels through tissue it is attenuated due to the effects of both absorption and scatter, hence the effects of both parameters being considered during spectroscopic

measurements. The attenuation of light caused by tissue can be related to the concentration of chromophores in tissue by the Beer-Lambert law.

$$A = \log\left(\frac{I}{I_0}\right) = \varepsilon \cdot C \cdot d \quad (1)$$

Attenuation (A) is the logarithmic ratio of two intensities, the intensity of the incident light (I_0) and the transmitted light (I). ε is the molar extinction coefficient, as shown in Fig. 1, expressed in $\text{mM}^{-1}\text{cm}^{-1}$. C is the concentration of a chromophore and d is the direct path-length of the photon from the emitting to the receiving optode, i.e. the inter-optode or geometrical distance.

Considering that there are more chromophores in tissue, the Beer-Lambert law can be written using that the absorption coefficient of each chromophore is additive (Wray et al., 1988), i.e.

$$A = [\varepsilon_1 \cdot C_1 + \varepsilon_2 \cdot C_2 + \dots + \varepsilon_n \cdot C_n] \cdot d \quad (2)$$

The typical application of the Beer-Lambert law is that A is experimentally measured (at n wavelengths for n chromophores of interest), Assuming that d is the inter-optode distance and $\varepsilon_1 \dots \varepsilon_n$ has been found previously for each chromophore, the objective is to find $C_1 \dots C_n$ (Pellicer & Bravo, 2011). Accurate estimation of chromophore concentration requires (at a minimum) the same number of wavelengths, as there are chromophores in the given tissue. A similar specific extinction coefficient of Hb and HbO₂ in the near-infrared spectrum makes measuring at a single wavelength difficult and confounds the interpretation of changes in concentration of the chromophores. Simultaneous measurements of two wavelengths can be used to separate the changes for both Hb and HbO₂ (Strangman et al., 2002). To increase the sensitivity of the estimation, two wavelengths should be chosen in order to distinguish between Hb and HbO₂ molar extinction coefficients, such that HbO₂ has the highest molar extinction coefficient at one wavelength and the lowest at the other (Klungsoyr & Støa, 1954; Refsum, 1957; Siggaard-Andersen et al., 1972). These wavelengths are normally found around the isobestic point, i.e. the wavelength at which the specific extinction coefficient of Hb and HbO₂ are equal (near 800 nm¹). In Fig. 1 the isobestic point of Hb and HbO₂ in the near-infrared spectrum is displayed. The isobestic point can be used to calculate hemoglobin concentration independent of oxygen saturation (Elwell & Phil, 1995). When three or more wavelengths are used, the changes can be extracted in other, less-absorbing chromophores such as cytochrome c oxidase and H₂O or the accuracy of the measurements of Hb and HbO₂ can be improved (Heekeren et al., 1999; Matcher & Cooper, 1994), by using multilinear regression to fit each chromophore spectrum to the measurements and performing a residual analysis to determine systematic errors (Cope, 1991).

However, if d is not equal to the inter-optode distance, the hemoglobin changes cannot be quantified and comparisons between different subjects or NIRS regions cannot be made. d depends on subjects, the measured region and the wavelength of the light. Due to scattering d will increase in an unknown manner. Approximately 80% of the total attenuation of near-infrared light in tissue is due to scattering, and the remaining 20% to absorption (Cope, 1991). Scattering is thus the biggest problem when attempting quantitative measurements

with NIRS. In a highly scattering medium, photons travel a mean distance that is far greater than d , which has been defined as the differential path-length (DP), i.e. the true optical distance between the optodes. Delpy et al. (1988) defined a scaling factor to correct for the path-length; the differential path-length factor (DPF).

$$A = \log\left(\frac{I}{I_0}\right) = \varepsilon \cdot C \cdot d \quad (3)$$

Therefore, the modified Beer-Lambert law incorporates the additions

$$A = \log\left(\frac{I}{I_0}\right) = \varepsilon \times C \times d \times DPF + G \quad (4)$$

The attenuation and the specific extinction coefficient in the modified Beer-Lambert law are no longer strictly linearly related, the degree of non-linearity is a function of the scattering coefficients. The scattering coefficient of the tissue together with the geometry of the optodes are described in the term G . G is unknown and therefore an absolute calculation of chromophore concentration cannot be derived from Eq. 4. This is a fundamental problem in tissue NIRS, making the determination of absolute concentrations of Hb, HbO₂ and cytochrome c oxidase problematic. Assuming that G has the same value for all chromophores in the medium, by using a differential equation between two chromophores, G is cleared. As a consequence, only changes in concentration of chromophores can be measured with NIRS (Matcher & Cooper, 1994). Assuming that DPF and d remain constant during the measuring period, and d and DPF are known, quantitative data on changes in the concentration of chromophores can be derived.

$$\Delta(A) = \varepsilon \cdot \Delta(C) \cdot d \cdot DPF \quad (5)$$

The changes in the concentration of chromophores can be calculated using a different wavelength for each chromophore, writing a Beer-Lambert equation for each, and solving the simultaneous equations through matrix inversion (Wahr et al., 1996). The NIRS technique can still be applied as an oxygenation trend monitor if the DPF is unknown, such as the continuous wave NIRS. There are several techniques available that can be used to calculate the DPF , i.e. by time domain (Delpy et al., 1988), frequency domain (Chance, 1990) or derivative spectroscopy (Matcher et al., 1994; Wray et al., 1988), which allow for oxygenation changes to be measured. However, without the knowledge of the term G the absolute chromophore concentration cannot be measured. Though, oxygenation trend monitoring and the measurement of absolute changes in concentration are very useful measurements as well.

2.4 NIRS device

A NIRS device exists out of a light source (emitting optode) to deliver light to the tissues at a known intensity and at two (or more) wavelengths surrounding the isobestic point, and a light detector (receiving optode), which measures the intensity of the exiting light. A computer translates the change in light intensity to clinical useful information.

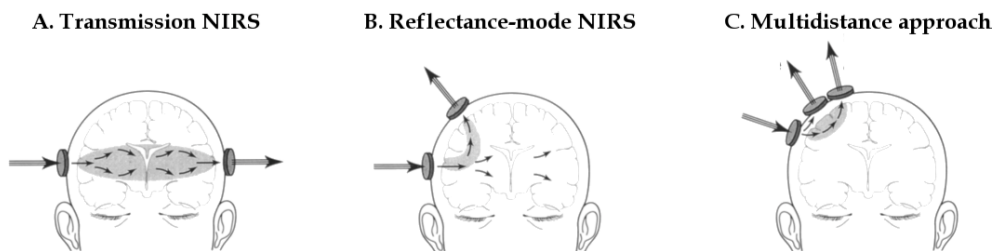


Fig. 2. Different type of NIRS set-ups: (a) transmission NIRS, (b) reflectance-mode NIRS, (c) multi-distance approach NIRS with several receiving optodes to differ between oxygenation changes in different tissue layers (modified from Wahr et al., 1996).

The receiving optode can be either contralateral (transmission NIRS) or ipsilateral (reflectance-mode NIRS) located to the receiver, see Fig. 2A and B. Transmission cerebral NIRS, in which a near-infrared light source is placed contralateral to the receiver, is most frequently used in infants. In adults this is not believed to be sensitive enough, primarily because of the reduced intensity of the exiting near-infrared light (Jöbsis, 1977) and poor signal-to-noise ratio (Germon et al., 1999). In reflectance-mode NIRS the near-infrared light source is placed ipsilateral to the receiver, it has been developed to overcome the problems of transmission NIRS. This approach assumes that there is homogeneous light absorption and constant optical scattering effects. If these assumptions are correct, then the mean path-length of the travelling photons should describe an ellipse whose mean depth is proportional (i.e. $1/3$) to the optode spacing (Germon et al., 1999; Strangman et al., 2002).

In Fig. 2C a NIRS device that uses two receiving optodes is displayed. This device attempts to differentiate between light attenuation caused by skull and overlying tissues and light attenuation caused by cerebral tissue. This is called the multi-distance approach and is used in several types of spectrometer, such as spatially resolved spectroscopy and functional NIRS. In most of the NIRS instruments, the distance between source and detector on the surface of the tissue varies between 3 and 5 cm. Measurements at larger distances are difficult because of the fast decay of the signals with the inter-optode distance (Liebert et al., 2011).

3. Types of spectrometer

Three main categories of near-infrared light spectrometers have been developed: continuous wave, time domain and frequency domain spectrometers. The type of information one needs to collect basically determines the choice of spectrometer. The principles, advantages and disadvantages are discussed per category instrument; also other types of spectrometers are discussed.

3.1 Continuous wave NIRS

Continuous wave (CW) NIRS instruments are the earliest and most common commercial NIRS devices. These instruments generally employ either a multiple discrete wavelength source or a filtered white light source, they measure the light attenuation using either a photomultiplier, photodiode or a avalanche photodiode detector (Delpy & Cope, 1997).

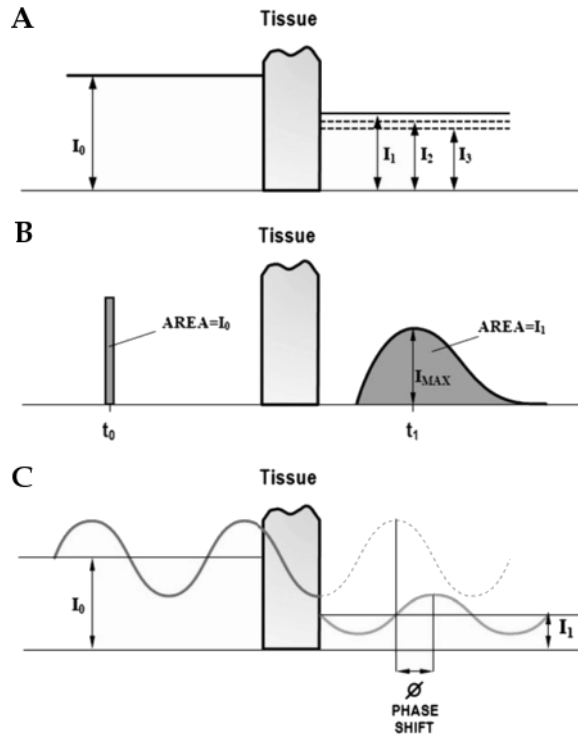


Fig. 3. Schematic presentation of the three main categories of NIRS. (a) Continuous wave NIRS, (b) time domain NIRS (c) and frequency domain NIRS (modified from Pellicer & Bravo, 2011).

The measured attenuation (A) at the receiving optode cannot be quantified in CW NIRS, as it contains an unknown light loss due to tissue scattering, increased path-length and thereby increased absorption. However, the changes in measured attenuation (ΔA) can be linearly related to the specific extinction coefficient (ε), according to the Beer-Lambert law, see Eq. 6. Which assumes that the direct path-length (d) is a constant value and that changes in attenuation can only arise from variations in the concentrations (ΔC) of Hb, HbO₂ and the cytochrome c oxidase. Considering this, the changes in concentration of these chromophores can be separately identified (but not quantified) from measurements of ΔA made at three different wavelengths (Delpy & Cope, 1997).

$$\Delta A = \varepsilon \cdot d \cdot \Delta C \quad (6)$$

The main advantages of CW NIRS are the sampling rate, the size of the instrument, the weight, the simplicity and the cost, which makes CW NIRS ideal for bedside monitoring. However, CW NIRS has a few disadvantages, including the penetration depth and the difficulty to separate absorption and scattering effects. CW NIRS is only fit to do oxygenation trend monitoring, however, over the years several possibilities to quantify the changes in concentrations of chromophores were investigated. Applications of CW NIRS as

a concentration monitor are for example second derivative spectroscopy and spatially resolved spectroscopy, which are described in the next sections. In section 3.1.3 functional NIRS is described which allows for three-dimensional reconstruction of the oxygenation in the brain.

3.1.1 Second derivative spectroscopy

Wray et al. (1988) suggested that CW NIRS could also yield estimates of the differential path-length factor (*DPF*) and thereby quantifies the measured changes in concentration. Its principles are that in the near infrared range, the water spectrum contains three major features, a prominent peak centered around 965 nm and two other small peaks around 820 and 740 nm. The 965 peak is large enough to allow accurate curve-fitting of its shape to the known spectrum of water. The concentration of water in the brain is usually known to within 2% to 3%; therefore it is possible to estimate the *DPF* at 965 nm using the ratio of the peak amplitudes and the known inter-optode spacing (Delpy & Cope, 1997; Wray et al., 1988).

The actual comparison is performed on the second derivative of the spectra, which will eliminate most of the effects of tissue scattering (Wahr et al., 1996). The principle of this technique is that if the measured spectrum has an unknown constant attenuation, this can be removed by taking the first derivative of the spectrum with respect to wavelength. If there is an additional unknown, but linearly wavelength-dependent, attenuation present, this will appear as a constant in the first derivative, which can be removed by taking the second derivative. This should leave a flat spectrum containing only features corresponding to the second derivative of the absorption spectra of any chromophores in the tissue. In the near infrared, the second derivative of the water spectrum has three components corresponding to the previous named peaks. Hb has a large peak at 760 nm, but HbO₂ and cytochrome c oxidase have negligible features (Delpy & Cope, 1997). Therefore, it is possible to calculate the ratio of the Hb concentration to the water concentration and thereby obtain an absolute measure of changes in the Hb concentration (Wahr et al., 1996).

The advantage of this technique is that it uses CW NIRS, which are easy to use on the bedside. Additionally, changes in chromophore concentrations can be measured. However, at shorter wavelengths the *DP* is underestimated (Matcher et al., 1994).

3.1.2 Spatially resolved spectroscopy

Spatially resolved spectroscopy (SRS) is one of the most used NIRS systems. The SRS system incorporates several detectors housed in a single probe, with an inter-optode distance of 4–5 cm. The combination of the multi-distance measurements of optical attenuation allows calculation of the relative concentrations of HbO₂ and Hb in the illuminated tissue. This calculation is derived from the relative absorption coefficients obtained from the slope of light attenuation at different wavelengths over a distance measured at several focal points from the light emission. The opinion about NIRS in adults has been influenced by the additive effect of the extracerebral tissues on the light attenuation. By using a SRS approach, the superficial layers of brain tissue affect all the light bundles similarly and therefore the influence of the extracerebral tissues on the light attenuation cancel out. Only deeper tissue layers have an effect on the values (Choi et al., 2004).

The main advantage of spatially resolved spectroscopy is that it also uses the small, light CW NIRS technology. Additionally it can measure online hemoglobin concentration changes and the TIO. However, the scattering factor included in the TIO calculation make spatially resolved spectroscopy less reliable for multilayered structure like in cerebral oxygenation measurements. However, Al-Rawi et al. (2001) showed that the NIRO 300, a spatially resolved spectrometer, has a high degree of sensitivity and specificity to intracranial and extracranial changes. SRS is technically simpler than TRS and provides measurements with a good signal-to-noise ratio and a high time resolution (Perrey, 2008).

3.1.3 Functional NIRS

After the development of multichannel CW NIRS imaging systems, which allow the generation of images of a larger area of the subject's head with high temporal resolution, and thereby the production of maps of cortical oxygenation changes (Quaresima et al., 2002), functional NIRS was developed. In multichannel CW NIRS multiple source-detector probes are used, which for example can result in a 7 by 7 cm measurement surface. The development of three-dimensional reconstruction methods resulted in the present functional NIRS (fNIRS) (Quaresima et al., 2002). If a sufficient number of sources and detectors are placed around the head it is feasible to generate cross-sectional or three-dimensional (3D) images of the optical properties of the brain. This approach, known as either functional NIRS, diffuse optical imaging (DOI) diffuse optical tomography (DOT) or near-infrared imaging (NIRI), requires sophisticated image reconstruction algorithms to convert the transmittance measurements into 3D images (Minagawa-Kawai et al., 2008).

However, fNIRS is far from routine use, mainly because of its slow acquisition and reconstruction speed, and high cost. Optical tomography of the entire brain is also limited to newborn infants, since the attenuation of light across a larger head is too great to sample the inner regions of the brain. Because of the high attenuation, data acquisition is relatively slow, and imaging of evoked response requires averaging over several activations (Gibson et al., 2005).

3.2 Time domain NIRS

Time domain spectrometers are also called time-of-flight or time-resolved systems. They generally employ a semiconductor or solid state laser to generate ultrashort pulses. They measure the attenuation by either a synchroscan streak camera or a time-correlated single photon counting in which a photon counting detector detects and sorts the received photons by their time of arrival (Delpy & Cope, 1997).

In time domain spectrometers a light pulse of a few picoseconds long propagates in the tissue and, as a result of scattering, the timeline of photons exiting the tissues has a broad distribution, this distribution is called the temporal point spread function (TPSF). A typical tissue TPSF is characterized by a relatively rapidly rising intensity, peaking around 600-1000 ps and then a slow decay often several nanoseconds in duration (Chance et al., 1988b), see Fig. 3. The TPSF data can be analyzed in four different ways; (1) The DP can be derived from the mean of the integrated TPSF (Delpy et al., 1988). (2) When the TPSF data is plotted on a logarithmic scale, the slowly decaying final slope is observed to be almost linear and, from diffusion theory, a simple relationship between the asymptotic limit of this final slope and the specific extinction coefficients of the chromophores can be obtained (Chance et al.,

1988a). (3) The TPSF of the tissue is measured at two different wavelengths and then the ratio of the intensities at corresponding times calculated. As time can be related to distance (knowing the speed of light and tissue refractive index), the resulting plot is essentially attenuation ratio as a function of distance. Changes in chromophore concentration can be calculated from these if the difference in the chromophore specific extinction coefficients is known and assuming that the scattering coefficient is constant over the wavelength measurement range (Oda et al., 1996). (4) A variant of this technique takes the above attenuation ratio versus time data and then extrapolates the resulting linear relation back to a time when the first light, which can be considered as unscattered light, would have exited the tissues (Yamada et al., 1993). The attenuation at this point is theoretically the absorption ratio one would obtain in the absence of scattering. This is the so-called temporally extrapolated absorbance method (TEAM) (Yamada, 1993).

The main advantages of time domain spectrometers are the spatial resolution; the penetration depth and that time domain spectrometers are the most accurate spectrometers in separating absorption and scattering effects. However, there are several disadvantages including the sampling rate, the instrument size, the instrument weight, the necessity for cooling, the lack of stabilization and the cost.

3.3 Frequency domain NIRS

Frequency domain spectrometers are also called frequency-resolved or intensity modulated systems. They generally employ a laser diode, LED or modulated white light sources. They measure the attenuation, phase shift (Φ) and modulation depth (M) of the exiting light by either a photon counting detector or gain modulated area detector (Chance et al., 1990; Delpy & Cope, 1997).

In frequency domain spectrometers radio frequency modulated light propagates through tissue. The resulting signal is the Fourier transform of the TPSF, relating time domain results to frequency domain results. Therefore, the same information as measured with the time domain spectrometers can be found with the frequency domain spectrometers. There are three different principles of frequency domain spectrometers, which are all based on diffusion theory. The frequency domain spectrometers perform measurements of changes in intensity, phase and modulation using either (1) a single wavelength and a fixed inter-optode distance. (2) multiple wavelengths and a fixed inter-optode distance. (3) Or a single wavelength and multiple inter-optode distances (Delpy & Cope, 1997).

The main advantages of frequency domain spectrometers are the sampling rate and the relative accurate separation of absorption and scattering effects. A limitation of frequency domain spectrometers is that the radio frequency modulated light cannot exceed 200 MHz, because a linear relationship between phase shift and path-length no longer applies above 200 Mhz (Arridge et al., 1992). However, the main disadvantage is the penetration depth of frequency domain spectrometers.

4. Utility of NIRS

Cerebral injury due to hypoxic/ischemic and hyperperfusion are common issues associated with clinical and surgical practice. Monitoring of cerebral oxygenation during surgery, eg;

cardiac and cerebral endarterectomy, has been shown to improve patient outcomes and reduce the risk of negative surgical outcomes. In addition to surgical monitoring, NIRS technology provides useful insight into cerebral hemodynamics when used in combination of other cerebral monitoring systems. NIRS monitoring and comparisons have been made with transcranial Doppler (TCD) and electroencephalography (EEG) in its ability to accurately predict cerebral ischemia and hyperperfusion. In addition to peri-operative monitoring in clinical settings, many researchers utilize the various NIRS systems to reflect on the cerebral tissue oxygenation status during environmental and exercise interventions despite strong evidence and proper analytical techniques. The following sections will outline the above utilities associated with NIRS technology.

4.1 Cardiovascular procedures

Post surgical outcomes of cardiac surgeries like are often confounded with poor neurological outcomes. Despite advanced techniques in the operation protocol, (ie: arterial line filtering and aortic arch ultrasound) complications still arise. Stroke occurs in 1-3% of patients during these surgeries, with an increasing number of those who undergo cardiovascular procedures developing cognitive impairments (Murkin et al., (2007)). A study performed by Murkin et al., (2007) demonstrated that prolonged cerebral de-saturation in the control group of a coronary artery bypass surgical population resulted in a higher incidence of peri-operative stroke, and longer post surgical ICU durations. Additionally, the control group while suffering from longer time spent de-saturated below the experimental mean of 84% also had a higher frequency of organ morbidity and death compared to the intervention group who remained above or near the 84% cerebral saturation point. The NIRS device, although apparent in its usefulness in reducing intra and post surgery complications, is further exalted in its ability to guide cardiac surgeons with temporally targeted cerebral de-saturation limits while maintaining a non-invasive and relatively viable and cost effective technology.

4.2 Cerebrovascular procedures

The neurological outcome of a patient undergoing cerebrovascular surgery, which often requires the supplementary artery blood flow to the brain, is dependent on the successful management of brain oxygenation. Carotid endarterectomy (CEA) is a surgery involving intra-operative clamping of the carotid artery, resulting in a change in blood supply to the brain via the ipsilateral vertebral artery and contralateral vertebral and carotid arteries (European Carotid Surgery Trialists' Collaborative Group, 1998). Since the first CEA surgery in 1954, there have been regular incidences of peri-operative stroke. Approximately 3-5% of all subjects undergoing this procedure in the aforementioned study suffered either embolic or ischemic stroke. Peri-operative monitoring of cerebral oxygenation enables surgeons to set ischemic thresholds, typically in the range of 12-20% reduction in cerebral oxygenation, aimed at identifying crucial periods when implementing a cerebral shunt. To allow for measurement of adequate oxygenation levels during the implementation of the shunt, it requires a highly specific and sensitive monitoring device to correctly identify ischemic conditions. Implementing a carotid shunt too early can increase the risk of an embolic stroke, thereby reducing the benefit of using the peri-operative monitoring device (Botes et al., 2007; Matsumoto et al., 2009; Samra et al., 2000). In the literature, three primary methods

of non-invasive monitoring of cerebral oxygenation and perfusion can be found: transcranial Doppler (TCD), electroencephalography (EEG) and (NIRS). Each technique has its own limitations and advantages. In TCD it is possible to monitor bilateral anterior and posterior cerebral perfusion with good specificity and sensitivity to changes in blood pressure, but remains to have implementation issues as not every patient has optimal temporal acoustic windows. Approximately 15% of all subjects do not have ecogenic cerebral arteries (Willie et al. (2011)). EEG on the other hand remains a highly specific monitoring tool, yet it fails to be as sensitive to changes in BP and ischemia as TCD and NIRS during peri-operative monitoring, additionally it often requires trained operators thereby decreasing the cost effectiveness and efficiency. Botes et al., 2007 compared the ability of EEG and NIRS during CEA surgery, and demonstrated that NIRS was able to recognize changes in brain perfusion earlier than EEG (Botes et al., 2007). However, the low specificity and high sensitivity may also have resulted in false positive ischemic findings and could possibly lead to a premature carotid shunt. Since the application of continuous peri-operative monitoring during CEA, incidences of intra-operative stroke have decreased, however few multisurgical designs investigating the combined and individual use of NIRS as an improved device over TCD and EEG have been done. Although it may be cost-effective and useful on occasion, little direct evidence supporting the wide spread use of NIRS as a CEA technique is available.

4.3 Exercise and cerebral tissue oxygenation

In addition to practical clinical applications, researchers have attempted to use the NIRS device to measure and quantify the differences between muscular, cerebral, and respiratory tissue oxygenation during exercise. However, NIRS as a stand-alone device to quantify cerebral tissue oxygen kinetics have not been validated. The use of NIRS as a sports medicine and exercise tool should be used with caution as studies are often time consuming and frequently difficult to interpret. One example of how to utilize NIRS during exercise can be seen in a study performed by Nielsen et al. (1999) where the authors had world-class rowers perform two 6-min bouts of all out rowing on a rowing ergometer while breathing two different mixtures of oxygen. Cerebral tissue saturation during normal exercise (normoxic inspired fraction of oxygen, $F_{I}O_2=0.21$) as measured by NIRS indicated that the frontal lobe of the brain dropped from 80 to 63% cerebral saturation. However, when subject performed the same trial while inspiring a higher O_2 mixture ($F_{I}O_2=0.30$) cerebral saturation was maintained at baseline levels. The authors of the study suggested that the high $F_{I}O_2$ resulted in a reversal of the exercise induced cerebral de-saturation. The study provided a unique look into the brain's response to exercise, however issues with measuring the NIRS signal during exercise continue to arise. The primary difficulty stems from the knowledge that hyper and hypoventilatory responses associated with exercise result in Cerebral blood flow and volume. CBF and cerebral blood volume changes may interfere with accurate signal interpretation due to issues with arterial-venous differences which are to be discussed in the oncoming sections.

5. NIRS limitations

NIRS, like most technology, has various limitations. The most important of those limitations are as follows: interference from non targeted chromophores; indefinite differential path-length; unknown scattering loss factor; and complicated signal interpretation.

5.1 Influence of other chromophores

Before the NIR light reaches the brain it must first pass through the different tissue layers, see Fig. 4. In some of these layers there are chromophores present, which will cause light attenuation independent of brain oxygenation.

The skin is composed of the epidermis and the dermis. The epidermis contains melanin, at near-infrared wavelengths melanin has a constant specific extinction coefficient. Melanin also has a significant optical effect on skin reflectance. Caucasian skin causes two times more reflection than negroid skin in the 600-1000 nm region. Attenuation by melanin only increases the sensitivity required of the instrument. Since its absorption is constant and oxygenation independent, it does not produce attenuation changes that are time dependent (Cope, 1991).

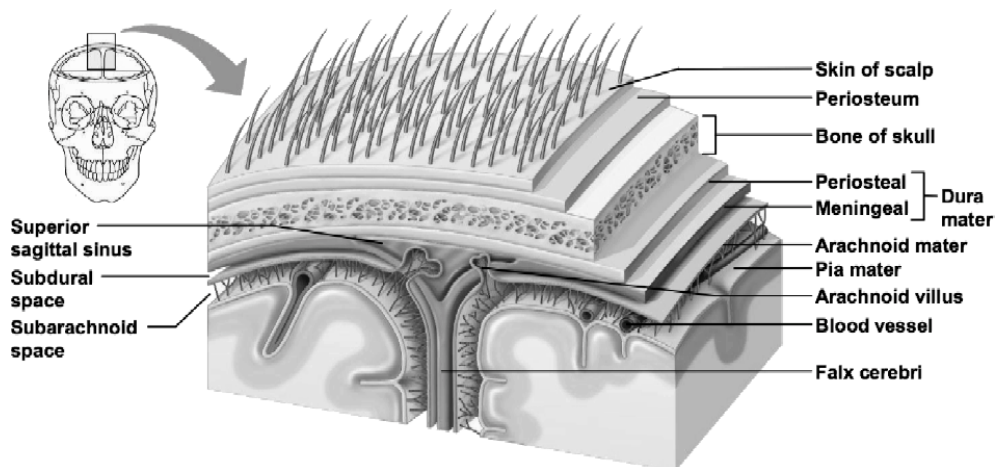


Fig. 4. Different tissue layers of the human head (modified from Hammoudi, 2011).

The dermis and the skull contain the chromophores *bilirubin*, *hemoglobin* and *cytochrome c oxidase*. Overall, the skin and the skull provide a barrier which must be penetrated before light enters the brain tissues. The attenuation caused by this region will also change with oxygenation (due to the presence of hemoglobin), the magnitude of this effect being proportional to its thickness and chromophore concentration. It is recommended that the thickness of brain tissue illuminated is therefore much greater than that of the surface tissues. Bilirubin can be found in blood plasma. Bilirubin systematically lowers brain oxygenation and attenuates the detection of changes in cerebral oxygenation (Madsen & Secher, 1999). In liver disease the bilirubin level can be increased in severe manners, so that the NIRS signal is seriously confounded (Murkin & Arango, 2009).

In the surface layers covering the skull a small amount of muscle can sometimes be found, the thickness of which is spatially dependent. This is important because muscle additionally contains the chromophore myoglobin. NIRS is unable to differentiate between the signal attenuation from hemoglobin and myoglobin; the absorbency signals of these two chromophores overlap in the NIR range. Myoglobin is much less sensitive to tissue oxygenation than hemoglobin; therefore oxygen delivery must be greatly reduced before the myoglobin spectrum is affected (Doornbos et al., 1999; Ferrari et al., 2004).

In the brain water and lipids are present together with bilirubin, hemoglobin, and cytochrome c oxidase. The average water content of neonatal brain is 90% (Fillerup & Mead, 1967) and 80% (Woodard & White, 1986) for an adult brain. This obviously implies that any absorption band of water will have a large optical effect. An infant's brain consists of about 80% of water, lipids constitute about 5% of the total wet weight. This percentage increases to 8% of the grey matter and 17% of the white matter in adulthood (Fillerup & Mead, 1967). The extinction coefficient for lipids is similar in magnitude to that of water. Lipids will not significantly add to the overall extinction coefficient of brain tissue as it is only present at approximately one tenth the proportion compared to water, although it is possible that lipids have a significant effect on the light attenuation (Cope, 1991).

5.2 Differential path-length

There are several factors influencing the optical path-length including tissue type, wavelength, scattering coefficients, optode geometry and blood volume changes. In reality there is no unique optical path through a scattering medium but rather a distribution of paths (Cope, 1991). The DPF is mainly influenced by scatter. It increases the optical path-length in an unknown manner, which leads to an increased absorption. With several techniques an estimation of the mean optical path-length can be made. However, this is not very accurate for the whole measurement. Further, the differential path-length factor generally decreases with increasing wavelength (Essenpreis et al., 1993). For this reason it is always important when quoting DPF values to also quote the wavelength at which the measurements have been made (Elwell & Phil, 1995). Also, the DPF depends on the geometry of the optodes, i.e. the angular position of the optodes on a spherical object, such as the human head (van der Zee et al., 1990).

The brain can move or expand to a limited degree in the skull, and it is possible that the thickness of the cerebrospinal fluid (CSF) layer varies during the NIRS measurements or because of changes in posture. Changes in the thickness of the CSF layer alter the intensity of detected light, therefore any brain movement and expansion during the measurement would affect the NIRS signal. The optical path length in the brain for a certain inter-optode distance depends to a great extent on the thickness of the skull whereas the thickness of the CSF layer scarcely affects the optical path-length in the brain (Okada & Delpy, 2003).

When the DPF is not determined accurately cross talk might occur, i.e., a change in the concentration of one chromophore might yield an artifactual change in the concentration of another unless the algorithms for deconvoluting the spectral contributions were without error (Heekeren et al., 1999).

5.3 Scattering loss factor

The main reason why concentrations in chromophores cannot be quantified is the unknown loss due to scattering. Several models have been developed for prediction of near-infrared light through tissue; (1) To seek an analytical solution of the diffusion equation. However, this has only succeeded under restricted geometries and in a homogeneous medium. (2) The MC method, which can be applied to an inhomogeneous medium, has the advantage of being able to calculate the path-length directly and can offer the individual photon histories, but which requires considerable computation time. (3) To solve the diffusion equation

numerically by the finite-difference method, which has been successful under restricted conditions for an inhomogeneous medium. (4) To solve the diffusion equation by the finite-element method, which can be applied to the complex geometries of an inhomogeneous medium and has the advantage of fast calculation time, but it does not calculate individual photon histories (Hiraoka et al., 1993).

However, these models can only approximate the scattering loss factor. There is still an uncertainty in every model because it will not predict nonlinearities, which will probably arise in human tissue.

5.4 Interpretation of the NIRS signal

The measured attenuation of near-infrared light is influenced by many factors. Although the NIRS signal can be related to the regional oxygenation, it cannot differentiate between venous, arterial or capillary blood, or between an increase utilization of oxygen or decreased saturation. Also, the changes in Hb and HbO₂ concentrations in the blood flow of the skin or additional to the total attenuation. These issues are addressed in the next sections.

5.4.1 A/V ratio

An advantage of NIRS is that it measures the regional saturation. However, this also comes with a disadvantage because the regional blood flow consists of venous, arterial and capillary blood flow. Cerebral NIRS devices measure mean tissue oxygen saturation and, as such, reflect hemoglobin saturation in venous, capillary, and arterial blood comprising the sampling volume. For cerebral cortex, average tissue hemoglobin is distributed in a proportion of 70% venous and 30% arterial (McCormick et al., 1991), based on correlations between position emission tomography (PET) and NIRS (Ohmae et al., 2006). However, clinical studies have demonstrated that there can be considerable biological variation in individual cerebral arterial/venous (A/V) ratios between patients, further underscoring that the use of a fixed ratio can produce significant divergence from actual *in vivo* tissue oxygen saturation, thus confounding even 'absolute' measures of changes in cerebral oxygenation (Watzman et al., 2000).

NIRS results are not only influenced by oxygenation changes. For example, an increase in arterial oxygen saturation causes an equal increase and decrease in the cerebral HbO₂ and Hb concentration respectively (and *visa versa*). However, an increase in cerebral oxygen consumption would lead to an equal decrease and increase in the cerebral HbO₂ and Hb concentration respectively (and *visa versa*). Note that an arterial saturation monitor would allow the changes in arterial and venous systems to be differentiated from each other. Further, an increase in cerebral blood flow leads to an increase in cerebral blood volume, which is largely taken up by the HbO₂ concentration (and *visa versa*). However, an increase in blood pressure in the venous system (i.e. blocking venous return) would lead to an increase in blood volume in the venules, a much larger fraction of which would be made up of Hb compared to the case of increased cerebral blood volume. Deliberately increasing venous pressure has been suggested as a method of measuring absolute venous saturation (Cope, 1991). This suggests that the NIRS results are not only influenced by oxygenation changes but other factors are also of importance. This should be considered when the interpretation of the results is done, especially in critical care situations.

5.4.2 Cerebral vs extracerebral blood flow

A serious problem connected with the application of the NIRS technique is contamination of the measured signals with the components originating from the extracerebral tissue layers (Liebert et al., 2011). An increase of inter-optode distance leads to better determination of intracerebral changes in tissue absorption, i.e. the volume of cerebral tissue which is interrogated by NIRS increases (Germon et al., 1999). Also, when using the multi-distance approach, see Fig 2C, the oxygenation changes in cerebral and extracerebral tissue can be separated.

Since mean depth of photon penetration approximates 1/3 of the transmitter/receiver separation, by utilizing two differentially spaced receiving optodes—one spaced more closely and the other spaced farther from the transmitter—a degree of spatial resolution can be achieved. The closer receiver (e.g. 3 cm separation) detects primarily extracerebral tissue, whereas the farther optode (e.g. 4 cm separation) reflects extracerebral and cerebral tissue. Incorporation of a subtraction algorithm enables calculation of the difference between the two signals and thus a measure of deeper, cortical tissue saturation. Thus the multi-distance approach can provide spatial resolution to distinguish signals from cerebral vs extracerebral tissue. Approximately 85% of cerebral regional oxygen saturation is derived from cerebral tissue with the remaining 15% derived from the extracerebral tissue (Murkin & Arango, 2009).

However, most NIRS devices do not incorporate the multi-distance approach and therefore do not differentiate between cerebral and extracerebral blood flow. An increase in extracerebral blood flow, as can occur, during exercise, induces an unknown change in the total attenuation due to extracerebral blood flow, while cerebral blood flow might not have changed.

5.5 Hospital setting

Practical optical measurements are commonly contaminated by constant (or temporally uncorrelated) background illumination. Frequency domain systems are able to reject uncorrelated signals by the use of lock-in amplifiers, while time domain systems reject photons that reach the detector outside a finite temporal window. However, frequency domain systems are unable to identify unwanted light that is temporally correlated with the measurement, such as light that has leaked around the object being imaged. In the time domain inspection of the TPSF can enable these contaminated measurements to be rejected (Hebden et al., 2004).

6. Future directions

NIRS has various limitations as discussed in section 5, which result in the possibility to measure only the quantitative changes in chromophore concentration. These results should be analyzed carefully to exclude other causes of altered attenuation. In contradiction to the inability of NIRS to measure absolute chromophore concentrations, it can measure cerebral blood volume (CBV) and cerebral blood flow (CBF) with the use of a dye, indocyanine green, and without using radioisotopes or X-rays, as is used in CBF measurements with single-photon emission computed tomography (SPECT) or positron emission tomography (PET).

Another future direction is brain mapping using multimodality approaches; this could enhance the knowledge about neurovascular coupling. Simultaneous measurements of EEG or fMRI with fNIRS results provide more information about cerebrovascular responses to neural stimuli.

6.1 Indocyanine green

As mentioned earlier, NIRS cannot quantify the chromophore concentrations in tissue, however, when using NIRS in combination with indocyanine green (ICG) cerebral blood volume (CBV) and cerebral blood flow (CBF) can be determined. ICG is a highly absorbing intravascular chromophore. It is a tricarboyanine dye that binds to albumin and therefore remains in the plasma. It shows strong absorption in the NIR range with maximal absorption at 805 nm. Because ICG is normally not present in the human tissue, a zero-concentration reference point is available before any dye is administered. This enables NIRS to quantify absolute tissue concentrations of ICG (Hopton et al., 1999).

6.1.1 CBV

The ratio between the blood and tissue concentration of ICG over a measurement period can be used to derive a mean CBV, by using blood and tissue time integrals. Thereby minimizing changes due to alterations in blood pressure and pCO_2 .

$$CBV = \frac{\int_{t_1}^{t_2} [ICG]_{tissue} dt}{\int_{t_1}^{t_2} [ICG]_{blood} dt} \quad (7)$$

Where $[ICG]_{tissue}$ is the concentration of ICG in the tissue measured by NIRS, $[ICG]_{blood}$ is the concentration of ICG in cerebral blood estimated by analysis of a peripheral venous sample, compensating for the Fahraeus effect and t_1 and t_2 are respectively the start and finish times of the measurement period. After administration of a bolus of ICG, ICG concentration decreases, as there is hepatic uptake and biliary excretion (Kuebler et al., 1998). The integrated tissue and blood concentrations over a period of time (usually from 3 to 20 minutes after the ICG bolus) are determined by calculating the areas under the elimination curves for NIRS tissue measurements and peripheral venous concentration measurements of ICG (for a more detailed explanation see Hopton et al., 1999).

6.1.2 CBF

The measurement of CBF is based on the principles of the direct Fick method (Fick, 1870) and the later adapted Kety-Schmidt technique (Kety & Schmidt, 1945), i.e. the rate of proportionality, or the balancing of venous content and arterial content, of an inert gas dependent upon the volume of blood flowing through the brain (Kety & Schmidt, 1945). ICG can act as a Fick tracer, similar to that of an inert gas. The rate of arrival of ICG in the brain, a few seconds after the rapid injection of ICG, can be observed by NIRS (Gora et al., 2002). ICG is introduced rapidly and its rate of accumulation is measured over time. Blood flow can be measured as a ratio of ICG accumulated to the quantity of ICG introduced over a given time (Perrey, 2008). The accumulation of ICG in the brain will be dependent on both arterial inflow and venous outflow (Gora et al., 2002). The method of measuring CBF relies

on several assumptions: first, blood flow must be constant for the period of measurement. Second, there must be linearity and stability of the tracer dose response in tissue. Third, the tracer must not be metabolized or permanently retained in the tissue during the period of measurement (Perrey, 2008). And finally, the measurements should be made within the cerebrovascular transit time (four to six seconds), because then the venous outflow is negligible and the measured increase in cerebral ICG concentration can be assumed to be entirely the result of arterial inflow of the tracer. ICG meets up with these assumptions and can thus be used as the specific tracer in CBF measurements (Gora et al., 2002). The amount of tracer delivered to the brain can be calculated from the area under the curve of the arterial ICG concentration change measured by the dye-densitometer

A disadvantage of CBV and CBF determinations with NIRS in combination with ICG is that it is invasive since it requires arterial cannulation, repeated blood withdrawals, and reinfusions (Guenette et al., 2011). It is still less invasive than SPECT or PET (radioisotopes and X-rays, respectively), but nonetheless invasive. However, NIRS in combination with ICG could be feasible on the bedside, in contradiction to SPECT or PET. Exploring and validating this technique should be an aim in the nearby future.

6.2 Multimodal approach

Human brain mapping by multimodality approaches has been proposed as an integrated methodology towards a deeper understanding of cortical response and neurovascular coupling. Integration of functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) with functional near-infrared spectroscopy (fNIRS) has the potential to monitor neuronal and vascular response and provide new insights into the origin and development of cortical activation (Torricelli et al., 2011; Wallois et al., 2011).

6.2.1 EEG-fNIRS

Since electrical and hemodynamic changes involve subtle, complex mechanisms, EEG-fNIRS coregistration is a promising approach to study language related, neural and cerebral functional activity (Wallois et al., 2011). NIRS combined with video EEG is a promising upcoming development for the evaluation of epileptic patients. fNIRS in combination with EEG could become an essential tool for the management of epileptic patients in daily clinical routine, particularly in neonates and children (Wallois et al., 2010).

EEG has very high temporal resolution whereas fNIRS is not affected by electromagnetic interference and is not as susceptible to movement artefact as EEG. By using both modalities on the same area of cortex, extra information about the cortical activity can be recorded. As this implements a combined electrical and hemodynamic recording of cortical activity, we are making direct observations of neurovascular coupling. Such information may prove to be vital for research into stroke rehabilitation, epilepsy and language related studies. An advantage of a multimodal approach is that for the same measurement space on the head, more information about the underlying neurovascular relationship is being recorded. An EEG of fNIRS alone system can only record the electrical or hemodynamic response in an area of cortex. A multimodal approach records fNIRS and EEG but also records information about the relationship between them, even if that relationship is not fully understood. Investigation into dual-modality measurement is

of importance due to the potential gains in classification accuracy while utilizing the same area of cortex (Leamy et al., 2011).

6.2.2 fMRI-fNIRS

fMRI is the golden standard to image neuronal processes in the brain in-vivo, The golden standard to detect activation in the brain during neural stimulation is fMRI. It relies on an indirect signal, the blood oxygenation level-dependent (BOLD) contrast, which is caused by an increase in oxygen delivery (Steinbrink et al., 2006; Toyoda et al., 2007).

However, the details of the translation of firing neurons to an increase in focal cerebral blood flow remains controversial. fNIRS has the potential to resolve some of the key issues concerning the basis of the vascular response, since it measures the physiological changes of total hemoglobin, Hb and HbO₂ concentration. The BOLD signal correlates with changes in Hb, HbO₂ and total hemoglobin concentration (Steinbrink et al., 2006).

NIRS offers superior temporal resolution (40 ms versus 2000 ms), whereas BOLD offers superior spatial resolution and whole brain coverage (Tong & Frederick, 2010). Combined fMRI-fNIRS studies have been used to elucidate the biophysics of the BOLD response. However, most studies have focused on the correlation of the BOLD signal to the changes in the hemoglobin concentrations, but there is a lack in studies of the transient effects of the BOLD signal. For example, the interplay of the vascular dynamics in flow, volume and oxygen extraction and the origin of the BOLD signal due to the differential behavior in CBV and Hb concentration (Steinbrink et al., 2006).

Multimodal fMRI-fNIRS may provide a novel contrast mechanism that can be exploited as a tool for characterizing cerebral blood flow directly. And that further optimization of the technique may allow for quantification of other blood flow parameters (Tong & Frederick, 2010), for example, the oxygen extraction fraction and CBV (Toyoda et al., 2007).

7. References

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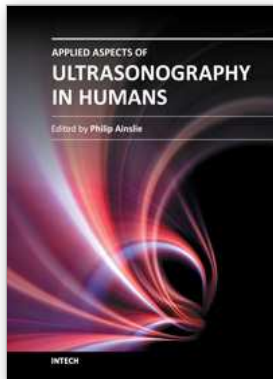
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