3

Functional Near-Infrared Spectroscopy (fNIRS): Principles and Neuroscientific Applications

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1. Introduction

fNIRS is a device designed to detect changes in the concentration of oxygenated (oxyHb) and deoxygenated (deoxyHb) haemoglobin molecules in the blood, a method commonly used to assess cerebral activity. Over the last decade, functional near-infrared spectroscopy (fNIRS) has widely extended its applications due to its capacity to quantify oxygenation in blood and organic tissue in a continuous and non invasive manner (Chance & Leigh, 1977; Villringer & Chance, 1997). This technique is an effective, albeit 'indirect', optical neuroimaging method that monitors hemodynamic response to brain activation, on the basis that neural activation and vascular response are tightly coupled, so termed 'neurovascular coupling'. Different studies show that neural activity and hemodynamic response maintain a lineal relationship (Arthurs & Boniface, 2003; Logothetis et al., 2001), suggesting that these changes in hemodynamic response could provide a good marker for assessing neural activity. In neuroscience, functional near-infrared spectroscopy (fNIRS) is used to measure cerebral functions through different chromophore mobilization (oxygenated haemoglobin, deoxygenated haemoglobin and cytochrome c-oxidase) and their timing with concrete events. Due to methodological and theoretical problems associated with cytochrome c-oxidase functioning (Cyt-Ox) (see section 3.2.), current neuroscience studies on cerebral functions only assesses and analyzes oxyHb and deoxyHb mobilizations. These chromophore mobilizations are directly related to the cerebral blood flow (CBF) associated with an event and the physiological reactions provoked by the brain's functional state (fNIRS measures these reaction in the cerebral cortex). The assessment of these task-related mobilizations performed in light of a base line established by the researcher him/herself. The difference in oxyHb and deoxyHb concentrations at baseline and at task performance determines the location in the cortex of an increase or decrease in CBF. An increase in CBF is associated with cerebral activity, making the temporal and spatial correlation between CBF and task a determinant of cerebral function. This capacity to study cerebral functions, both spatial and temporal, is what gives name to the technique described in this chapter: functional near-infrared spectroscopy (fNIRS).

fNIRS has become a valuable neuroimaging technique, novel in its easy application and characterized by its small size, portability, and reliability. Although relatively new to the

field of health care, fNIRS use is growing rapidly in clinical settings and research, particularly in work involving higher level cognitive control. fNIRS measures of hemodynamic response have been used in numerous studies to assess cerebral functioning during resting state (Lu et al., 2010) and tasks on motor skills (Leff et al., 2011; Obrig et al., 1996_a), vision (Gratton et al., 1995; Herrmann et al., 2008), hearing (Zaramella et al., 2001), speech (Cannestra et al., 2003) social skills (Ruocco et al., 2010), learning (León-Carrión et al., 2010), emotion (León-Carrión, 2006, 2007_a, 2007_b), and executive functions (Chance et al., 1993; León-Carrion et al., 2008; Nakahachi et al., 2010). fNIRS is a proven medical device for monitoring hemodynamic activity through the intact brain cortex in normal adult subjects, a powerful and original functional neuroimaging technique which charts cerebral functioning in a non-invasive and relatively low-cost manner. The application of fNIRS in cerebral functioning studies has been validated by other neuroimaging techniques, showing that the NIR signal maintains a strong correlation with PET measures of changes in regional cerebral blood flow (rCBF), and the fMRI Blood Oxygen Level Dependent (BOLD) signal (Hock et al., 1997; Huppert et al., 2006; Kleinschmidt et al., 1996; MacIntosh et al., 2003; Toronov, 2001, 2003; Villringer and Chance, 1997). Yet compared to traditional neuroimaging technology, fNIRS is non-invasive, safe, portable and inexpensive (Gratton, et al. 1995; Strangman, 2002; Totaro et al., 1998; Villringer & Chance, 1997; Wolf, et al., 2002; Zabel & Chute, 2002). Given these characteristics, fNIRS makes it possible for research to be done more ecologically, in clinical and social settings, without the restrictions of more traditional scanners. Furthermore, fNIRS technology is ideal for studies in which subjects may have a more difficult time with traditional neuroimaging techniques, namely children, patients with dementia, etc. The flexibility of fNIRS also makes it ideal for studies involving patients who are in movement (Milla et al., 2001), patients who are bed-ridden (von Pannwitz et al, 1998), and new-borns (Goff et al., 2010).

In this paper, we review the literature to determine the principles of fNIRS, which could help create experimental designs and data analysis techniques objectively and effectively. We also provide a description of articles carried out by our research team on the use of fNIRS as a paradigm in the study of cognitive functions and in clinical applications. Specifically, we consider fNIRS use in studies on learning processes and affective dimensions in dorsolateral prefrontal cortex (DLPFC), and their influence on evoked hemodynamic changes.

2. The principles of fNIRS

Spectroscopy is based on the study of light signals. Many fields of science use this technique to study the composition of objects, both organic and inorganic. In 1949, Hill and Keynes (1949) reported that nervous system cell activity was associated with changes in the optical properties of light. NIRS has thus far the unique feature of being able to measure intravascular (oxyHb and deoxyHb) (Jöbsis, 1977) and intracellular (cytochrome c-oxidase) (Heekeren et al., 1999) events simultaneously.

In the study of cerebral functioning, a ray of light is used near the visible spectrum of light (NIR). More specifically, a light source known as a light-emitting diode (LED), emits a ray of quasi-infrared light at the scalp, half the wave absorbed by the chromophores (oxyHb, deoxyHb and cytochrome c-oxidase) found in the nervous tissue. A photo detector captures the light wave resulting from the interaction with the chromophores,

following a banana-shaped path back to the surface of the skin (see Fig 1.) (Gratton et al, 1994). The characteristics of this light wave have changed in respect to the original emitted by the LED due to the absorption and dispersion capacity of the nervous tissue and chromophores.

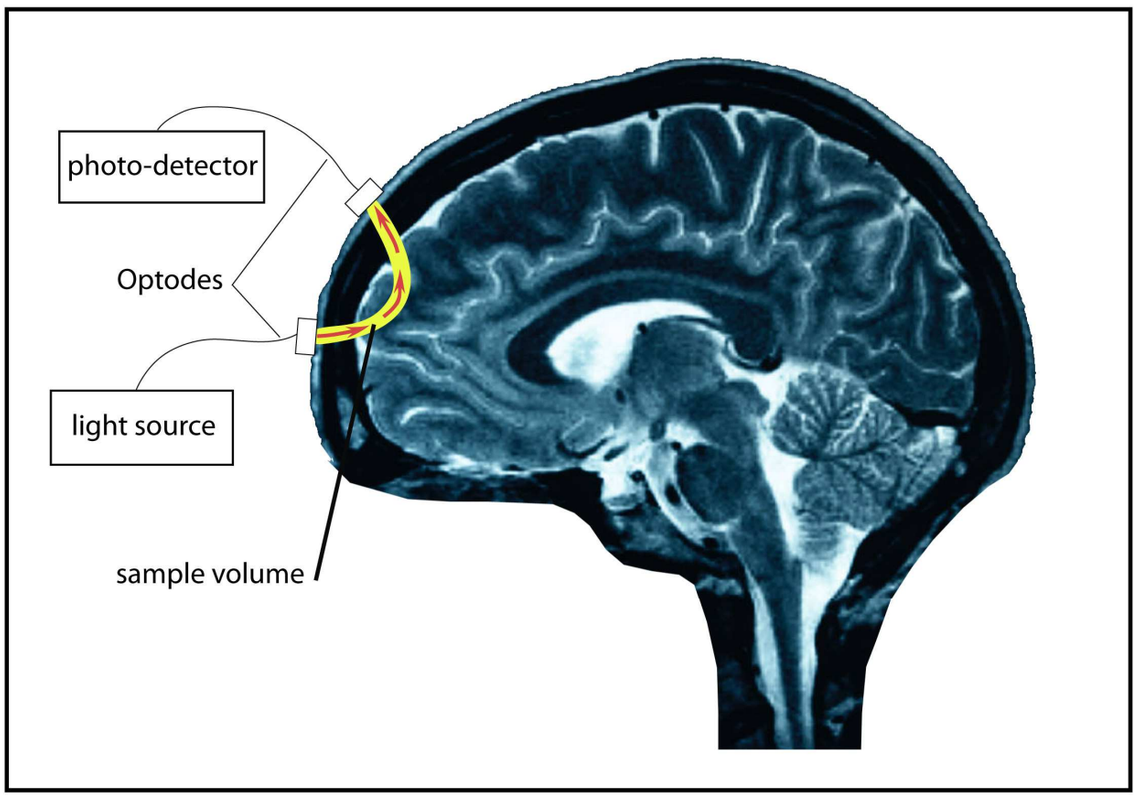

Fig. 1. Light from the light source is guided to the head by an optode. A photo-detector will collect the light which leaves the head at a distance of some centimetres. The photons follow a banana-shaped path from light source to detector.

The absorption spectra of light absorbing molecules (chromophores) are used to interpret the attenuated light levels as changes in chromophore concentration. The low absorption capacity of biological tissue (composed mostly of water) is one reason why light waves pierce different extracerebral tissue with hardly any absorption of NIR rays. In contrast, chromophores have characteristic optical properties which absorb rays close to the light. The transparency of the biological tissue, along with the absorption capacity of the diverse chromophores, makes it possible for optic methods to be used to measure hemodynamic responses (Chance, et al. 1998; Villringer and Chance, 1997). The optimal light spectrum for studying cognitive functions ranges between 700-900nm, which could be considered the biological "optical window", framed by chromophore mobilization (Jöbsis, 1977) (see Fig 2). This optical window lends itself to non-invasive, low-risk methods for studying cerebral processes.

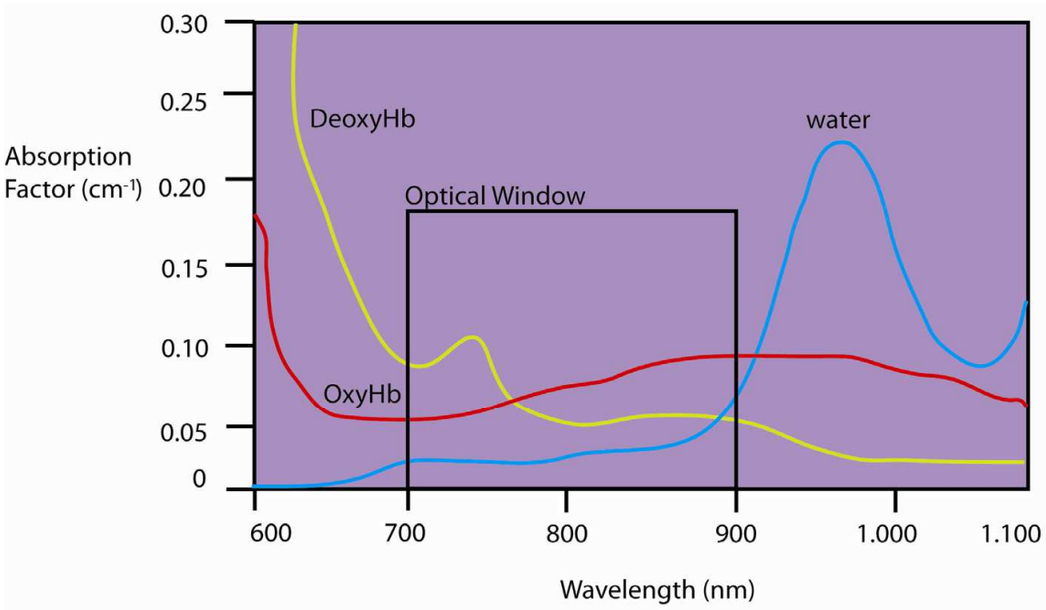

Fig. 2. Absorption spectrum in NIR window: different absorption spectra of oxyHb and deoxyHb at 700-900 (optical window) allow spectroscopy methods to assess their respective concentrations. Beyond 900 nm, the majority of the photons are absorbed by the water, making measurements difficult.

One of the limitations of the fNIRS is its scarce depth measurement capacity. This depth is determined mostly by two factors: wavelength and interopmode distance (IOD). Wavelength is one of the variables which determine a light's penetration capacity. In confocal microscopy at 488/514 nm, a penetration into cerebral tissue of approximately 0.25mm can be achieved (Dirnagl et al., 1991). When using dual photon technology with an excitation of 830 nm (Kleinfeld et al., 1998), penetration depth can surpass 0.6 mm below the brain surface. Nevertheless, penetration depth is limited by the optic window, given that a wavelength greater than 900nm penetrates tissue poorly due to the spectrum's high water absorption capacity at those depths (See Fig 2). The other parameter determining light penetration into nervous tissue is the distance between light source and detector. In general terms, the greater the source-detector distance, the deeper the penetration. However, a greater distance can also lead to a lower intensity of light captured by the detector. The ideal distance between source and detector depends on the capillary depth and demographic variables of the subjects being studied. Dark skin and very dark hair can absorb most wavelengths, hence a shorter distance between light source and detector would be recommended, which increases the intensity of the wavelength.

The main interaction between light and tissue is absorption, although the latter coexists with another phenomenon capable of modifying the optic characteristics of a light wave. This phenomenon, known as dispersion, illustrates photon loss which is not due to chromophore absorption (the loss depending on the size of the photo detector and the system's geometry). A photon's trajectory could vary when crossing nervous tissue with chromophores. A few photons will reach the photo detector without undergoing any dispersion or absorption effects (ballistic photon), some will be absorbed by chromophores (absorption), others--scattered out of the sampling volume--will not reach

the photo detector (scatter), and the remainder will make it, but by travelling a path longer than the geometrical distance between light source and detector (scatter) (See Fig 3). Dispersion alters the attenuated light wave captured by the photo detector and hence the reflected chromophore absorption capacity. If we interpret this light wave solely on the basis of chromophores absorption, we would lose analytic access to the biological processes which underlie cerebral functions.

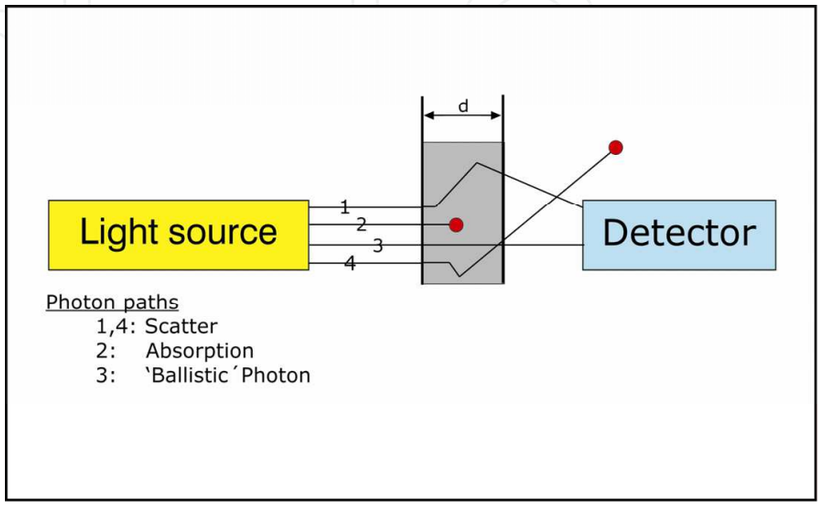

Fig. 3. Possible trajectory of a photon passing through biological tissue.

To offset dispersion and obtain a wider analytical scope of a light wave's optical characteristics, we applied the modified Beer-Lambert Law (Table 1). This version differs from the original in its conception of the effect of dispersion. In a typical trans-cranial study of the human brain, the mean path length of light is six times as long as the distance between sender and receiver (Duncan et al., 1995). In the modified Beer-Lambert Law, a new term (B) is added to represent the longest path length of light. A second modification to this equation is also necessary, given that not all photons reach the photo detector due to the dispersion effect. A second term is added (G) which measures photon loss due to dispersion. The process of modification of this law is as follows:

Original/Modified Beer-Lambert Law	Equation
Original Beer-Lambert Law	$A= \varepsilon \times c \times d$
Modified Beer-Lambert Law	$A= \varepsilon \times c \times d \times B + G$
Assuming constant B and C gives	$\Delta A= \varepsilon \times \Delta c \times d \times B$

Table 1. Variations of the original Beer-Lambert Law due to the dispersion effect.
A: absorbance, light attenuation (no units, since A = log10 P0 / P); **ε** is the molar absorption with units of L mol^{-1} cm^{-1};**c**: concentration of the compound in solution, expressed in mol^{-1}; **d**: path length of the sample; **G**: photon loss due to dispersion; **B**: longer path length due to dispersion effect.

3. Technical approaches for functional near-infrared spectroscopy and neuroimaging

Neuroscience interprets the optical characteristics of wavelengths reflected by different endogenous chromophores in nervous tissue, to discern the locations of cerebral functions at a specific moment. The functional state of the chromophores will determine how much spectrum light is absorbed, thereby revealing the functional state of the cortex. For example, the absorption spectrum for haemoglobin depends on whether or not it is oxygenated (venous vs. Arterial blood) (see Fig 2). Another important chromophore is cytochrome c-oxidase (Cyt-Ox), the terminal enzyme of oxidative phosphorylation whose absorption spectrum depends on its redox-state. Many other agents with absorption capacity are found in cerebral tissue, including melanin or water, although the spectral light of near-infrared rays practically nullifies their absorption capacity.

Apart from the changes in concentration of molecules with absorption capacity, dispersion causes changes in light's optical characteristics. The changes provoked by dispersion have been described as a result of changes in neural basal state. It is believed that rapid dispersion changes are temporally linked to changes in membrane potential (Stepnoski et al., 1991), whereas slow changes in dispersion probably reflect changes in cellular volume. The following section provides a description of the different parameters and elements used to analyze wavelengths and interpret study results.

3.1 OxyHb and DeoxyHb

To create cerebral activity, neurons require nutrients in order to generate energy and produce action potentials. Glucose, like oxygen and other substances, are sent to metabolically active neurons by means of blood perfusion via capillaries, which produces an increase in rCBF and in regional cerebral blood oxygenation (rCBO). Hence, changes in rCBF or rCBO can be used to map brain activity with high spatial resolution ("functional neuroimaging").

During functional activation, oxygen metabolism (cerebral metabolic rate of oxygen, $CMRO_2$) increases substantially (Ances et al., 2001_a; Dunn et al., 2005; Gjeddeet al., 2002) This increased oxygen consumption during neuronal activity results in a decrease in tissue oxygenation which is counteracted by the increase in O_2 supply when CBF and cerebral blood volume (CVB) increase (Ances et al., 2001_b; Enager et al., 2009; Offenhauser et al., 2005; Thompson et al., 2003), thanks to a mechanism known as neurovascular coupling. If the stimulus is lasting, glucose and oxygen consumption must be kept constant by increasing capillary density, which in turn increases total cerebral blood volume (Clarke & Sokoloff, 1994; Gross et al., 1987; Klein et al., 1986). However, when the stimulus is short-lived, the aforementioned hemodynamic and metabolic changes are not produced in the same manner.

CBF and oxygen metabolism is produced not only to counteract the effects of tissue oxygenation, but also to oxygenate haemoglobin. When haemoglobin transports oxygen, it is called oxyhaemoglobin (oxyHb). When it releases oxygen via an increase in oxygen metabolism, it transforms into deoxyhaemoglobin (deoxyHb). A cerebral region, therefore, could be considered active when its rCBF increases, producing a decrease in deoxyHb and an increase in oxyHb (Lindauer et al., 2001; Obrig et al., 1996_b), which in experimentation is generally associated with a specific event.

The increased oxygen transported to the brain area typically exceeds the local $CMRO_2$ utilization, causing an overabundance of cerebral blood oxygenation in active areas (Fox et al., 1988; Frostig et al., 1990; Lin et al., 2008; Lindauer et al., 2001; Mayhew et al., 2001). When there is an increase in CBF, tissue hyperoxygenation takes place (See Fig 4). Different optic studies using fNIRS and fMRI have reported that when neural activity commences, hyperoxygenation (due to an increase in CBF--increased oxyHb) is preceded by low oxygenation (increase in deoxyHb). This vascular response is difficult to measure and very controversial (Buxton, 2001; Frostig et al., 1990; Malonek & Grinvald, 1996; Obrig & Villringer, 2003).

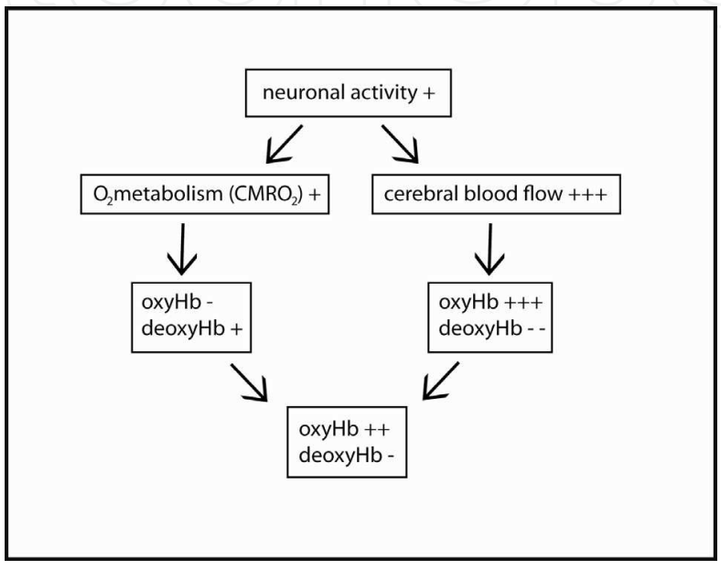

Fig. 4. Diagram of metabolic and hemodynamic changes during brain activity.

Scientific debate ensues as to which molecule possesses the highest discriminatory capacity for measuring neural activity. Currently, this is attributed to the deoxyHb molecule, the gold standard neuroscience neuroimaging technique. The deoxyHb molecule for cortical activity analysis has a high correlation with the BOLD response in fMRI ($R=0.98$; $P<10\text{-}20$), compared to that of the oxyHb molecule ($R=0.71$) or the Hb_{TOTAL} ($R=0.53$) (Huppert et al., 2006). These same results were obtained by other researchers (MacIntosh et al., 2003; Toronov 2001, 2003). In addition, concentrations of deoxyHb are reported to have more discriminatory power in humans than oxyHb (Herrmann et al., 2008).

In current research, our team is studying deoxyHb mobilization in different levels of consciousness during general anaesthesia. This mobilization has been correlated using Bispectral Index System (BIS) technology, the gold standard for controlling depth of anaesthesia. Preliminary results show a strong correlation between an increase in deoxyHb and a decrease in BIS as the patient reaches the lowest levels of consciousness. These results highlight the discriminatory power of the deoxyHb molecule in measuring deactivation in different brain areas.

As we mentioned earlier, oxyHb and deoxyHb possess characteristic optical properties in the near-infrared light range as well as wide-ranging sensibility to different wavelengths (See Figure 2), making it possible to use optics methods to quantify changes in chromophore concentration during neurovascular coupling (Chance et al., 1993; Chance et al., 1998;

Gratton et al., 1995; Hoshi et al., 1993; Villringer et al., 1993; Villringer & Chance 1997). To calculate the different levels of oxyHb, deoxyHb, and Hb_{TOTAL} concentration, the modified Beer-Lambert Law is used. The attenuation of light intensity after absorption and scattering by biological tissue is expressed as:

$$I = GI_0e^{-(\alpha_{HB}C_{HB}+\alpha_{HBO2}C_{HBO2})L}$$

where *G* is a factor that accounts for the measurement geometry and is assumed constant when concentration changes. I_o is input light intensity; a_{HB} and a_{HBO2} represent molar extinction coefficients; C_{HB} and C_{HBO2} indicate concentrations of deoxyHb and oxyHb chromophores, respectively; and *L* represents the photon path, a function of absorption and scattering coefficients μ_a and μ_b (Izzetoglu et al., 2007).

By measuring optical density (OD) changes at two wavelengths, the relative change of oxy- and deoxy-haemoglobin versus time can be obtained. If the intensity measurement at the initial time (baseline) is I_b, and at another time is I, the OD change due to variation in C_{HB} and C_{HBO2} during that period is:

$$\Delta OD = \log (I_b/I) = \alpha_{HB}\Delta C_{HB} + \alpha_{HBO2}\Delta C_{HBO2}.$$

Measurements performed at two different wavelengths allow the calculation of ΔC_{HB} and ΔC_{HBO2}. Oxygenation and blood volume (Hb_{TOTAL}) can then be deduced (Izzetoglu et al., 2007):

1. Oxygenation = $\Delta C_{HBO2} - \Delta C_{HB}$
2. Blood Volume (Hb_{TOTAL}) = $\Delta C_{HBO2} + \Delta C_{HB}$

When baseline is taken, it is important to take into account that the subject is medicated or anxious, variables which could have a quantitative effect on CBF. Since NIRS measures changes in oxyHb and deoxyHb concentrations in the arterial and venous intracerebral compartments, comparisons of different measurements depend on the assumption that the proportion of arterial and venous compartments remains constant. For this reason, factors that alter venous volume should be considered. Changes in head position, likely to occur in the clinical use of NIRS, might influence venous pressure and alter the proportion of arterial and venous compartments in the cerebral vasculature. In addition, body position might modify the tone of the resistive vessels to maintain a constant cerebral blood flow. According to Toraro et al (1998), cerebrovascular reactivity measurements may be performed without taking into account changes of head position.

Other variables to take into account when interpreting oxyHb and deoxyHb results are those which affect CBF:

1. In hypercapnia, when baseline perfusion was increased by up to 100% (stronger hypercapnia), the deoxyHb response almost disappeared (Jones et al., 2005).
2. During hyperoxia, the deoxyHb outwash was significantly reduced under normobaric conditions (Lindauer et al., 2003) or even abolished under hyperbaric conditions of 3 or 4 ATA (Lindauer et al., 2010), while neuronal activity and CBF responses remained unaltered.
3. OxyHb and deoxyHb effects remained lineal when the stimulus lasted between 6-24 seconds. However, during shorter stimulation periods, strong nonlinear effects came into play (Wobst et al., 2001).
4. Although hypothermia reduced baseline CBF by almost 50%, neurovascular coupling was preserved. Reduction of functional changes in CBF, deoxyHb and $CMRO_2$ followed reductions in neuronal activity during hypothermia (Royl et al., 2008)

5. A recent study reported that the amplitude of the functional deoxyHb decrease in rat somatosensory cortex was reduced when ICP was elevated to 7 mmHg. At an ICP of 14 mmHg, the deoxyHb response was close to 0 and even reversed at an ICP of 28 mmHg (Füchtemeier et al., 2010).
6. Changes in oxyHb, deoxyHb and Hb_{TOTA} correlated significantly with changes in blood velocity (Totaro et al., 1998).
7. NIRS parameters, induced by CO, reflect variations in resistive vessels, and could thus be considered an index of cerebrovascular reactivity (Totaro et al., 1998).

3.2 Cytochrome-c oxidase

Cytochrome-c oxidase (Cyt-Ox), an enzyme found in the mitochondria, is responsible for more than 90% of cellular oxygen consumption. In isolated mitochondria, Cyt-Ox redox states showed transient oxidation during increased cellular activity (Chance & Williams, 1956), indicating that Cyt-Ox redox state could provide a good approximation for assessing transitory changes in cellular metabolism during neuronal activity (Wong Riley, 1989). Cyt-Ox has a characteristic light absorption pattern in the visible (Keilin, 1925) and near-infrared parts of the electromagnetic spectrum (band centred around 830 nm) (Wharton and Tzagoloff, 1964), and it is in principle feasible to measure changes in the Cyt-Ox redox state in vivo (Cooper et al., 1994; Ferrari et al., 1990; Jöbsis, 1977).

Cytochrome-c oxidase theoretically could be a biological marker for cellular metabolic demand, with the potential to provide more direct information on neuronal activity than haemoglobin (Heekeren et al., 1999; Jöbsis, 1977). The theoretical advantage of using this enzyme as a marker for neuronal activity is that it is much more exact than oxyHb and deoxy-Hb, given that the demand by neurons for oxygen exceeds the need for their activation (Fox et al., 1988). Nevertheless, while Cyt-Ox may be a more precise marker for measuring neuronal activity, its use in neuroscience as a parameter has been limited by two fundamental issues:

1. The use of non-invasive NIRS to detect redox changes in Cyt-Ox in response to cerebral activation is hampered by methodological spectroscopic issues related to the modification of the Beer-Lambert law. However, the separation of the haemoglobin signal from the Cyt-Ox signal has been regarded as questionable and mere cross talk (Cooper 1994, 1998; Matcher et al., 1995). Methodologically, the calculation of the enzyme's redox change may be erroneous due to the simplified assumptions inherent in the modified Beer – Lambert approach.
2. From a physiological standpoint, there is ongoing debate on as to whether or not the redox state of Cyt-Ox changes in response to the functional activation of cerebral cortex.

Recent studies have attempted to resolve these two questions. New algorithms are being developed that can help discern the role of Cyt-Ox and its functions during cerebral activity. A recent study reported that the differential stimulation of areas rich and poor in cytochrome-c-oxidase content results in optical changes which cannot be solely explained by the presently available models of cross talk (Uludağ et al., 2004). One of the most renowned studies tackling the physiological question reported that the spectra obtained in a state of increased brain activity cannot be explained solely by the well-known changes in oxyHb and deoxyHb, but must include Cyt-Ox in the analysis. The inclusion of Cyt-Ox to explain spectra changes is also applied to explain how Cyt-Ox transient oxidation increases significantly during visual stimulation in 9 out of 10 subjects (Heekeren, 1999).

For these reasons, Cyt-Ox is not widely used in research on normal cerebral functions, whereas other fields are finding use for its capacity as a direct maker for tissue oxygenation to study pathologies related to metabolic dysfunction of the mitochondria (Atamna et al., 2010; Levy et al., 2007; Pickrell et al., 2009). The mechanisms and control of this enzyme have been discussed in various reviews (Cooper, 1990; Brown, 1992).

3.3 Fast and slow light scattering signals

Another method used for measuring neuronal activation is known as the event-related optical signal, or EROS, which capitalizes on the changes in the optical properties of the cell membranes themselves that occur as a function of the ionic fluxes during firing (Gratton et al., 1995). It is well established that the optical properties of cell membranes change in the depolarized state relative to the resting state (Obrig & Villringer, 2003; Rector et al., 1997; Stepnoski et al., 1991). Optical technology can be used to study these changes.

The ability to measure neuronal membrane depolarization provides us with the opportunity to study neuronal activity more directly. There are two approaches to studying neuronal depolarization via light wave dispersion, one with fast and the other with slow scattering signals. These signals differ both in terms of duration (milliseconds vs. seconds) and magnitude and their subsequent physiological processes. Fast light scattering signals occur in milliseconds (Hill & Keynes, 1949). In isolated nerves cells, Stepnoski et al. (1991) showed that changes in light scattering were associated with membrane potentials. Slow light scattering signals, reported in bloodless brain slices, occurred in seconds after the onset of stimulation (MacVicar & Hochman, 1991). The origin of slow light scattering is still unclear, although the primary candidates are changes in intracellular volume and/or in extracellular volume (MacVicar & Hochman, 1991; Holthoff & Witte 1996).

The study of cerebral functions in humans using EROS signals is hampered by numerous limitations. The principal shortcoming is that the fast scattering signal represents the low signal-to-noise ratio (SNR) resulting from optical properties in the skin, skull and cerebral-spinal fluid, which are traversed by the quasi infra-red light wave. Furthermore, basic sensory and motor movements such as tactile stimulation and finger tapping require between 500–1,000 trials to establish a reliable signal (Franceschini et al., 2004).

Other difficulties have been encountered in attempts to replicate experiments both on fast and slow scattering signals, limiting data collection, for example, on the optic characteristics of the fast scattering signal in response to a visual stimulus among normal adult humans (Obrig & Villringer, 2003). A final constraint is that these methods, apart from requiring a more expensive and cumbersome laser-based light source, have an increased risk of inadvertent damage to the eyes in comparison to other systems measuring hemodynamic response. In spite of these current limitations, the fast optical signal continues to be an important area of investigation because it offers glimpses of the "holy grail" of neuroimaging: the direct measurement of neuronal activity with millisecond time resolution and superior spatial resolution (Izzetoglu et al., 2004).

4. Instrumentation

Functional near-infrared (fNIR) instrumentation is composed of various light-emitting diodes (LEDs) and photo detectors which pick up light waves after they have interacted with brain tissue. The fNIRS normally used for neuroimaging has numerous channels. Each channel represents a cerebral region covered by the light wave and which coincides with the separation between the LED and its corresponding photo detector. Due to the dispersion

effect, a photo detector, which can detect light coming from cerebral tissue, is placed 2-7 cm from the LED. The relative contribution of extracranial tissue decreased as the interoptode distance increased, for an interoptode distance greater than 4.5 cm, the extracranial contribution was negligible (Smielewski 1995, 1997). The contribution of the scalp might be minimized by applying moderate pressure on the optodes (Owen et al., 1996). The ideal separation between source and photo detector is 4 cm, given that the fNIR signal becomes sensitive to hemodynamic changes within the top 2–3 mm of the cortex and extends laterally 1 cm to either side, perpendicular to the axis of source-detector spacing. Studies have shown that at interoptode distances as short as 2–2.5 cm, gray matter is part of the sample volume (Chance et al., 1998).

Three distinct types of fNIR implementation systems have been developed: time-resolved, frequency-domain, and continuous wave spectroscopy, each with its own strengths and limitations. (For review, see Minagawa-Kawai et al., 2008; Wolf et al., 2007). Our research team used the fNIRS system developed by Drexel University's Optical Engineering Team. This low-cost functional neuroimaging system provides a variety of clinical, research, and educational applications. Our NIRS system (NIM, Inc., Philadelphia, PA) applies light to tissue at constant amplitude and can provide measurements of oxy- and deoxy-Hb relative to baseline concentrations (see Bunce et al., 2006). The fNIRS probe is 17.5 cm long and 6.5 cm wide. It contains four light sources surrounded by ten detectors, for a total of 16 channels of data acquisition, covering an area of 14 X 3.5 cm on the forehead (see Figure 1). A source-detector distance of 2.5 cm provides a penetration depth of 1.25 cm. The probe positioning is such that the line of sources is set at the line of fronto-polar electrodes [FP1–FP2] (in the International 10–20 system). This is designed to image cortical areas that correspond to DLPFC (Izzetoglu, 2005). The DLPFC generally occupies the upper and side regions of the frontal lobes. It is comprised of BA 9 and 46. Area 9 occupies the dorsal region of lateral PFC and extends medially to the paracingulate of humans. Area 46 is generally located at the anterior end of the middle frontal sulcus. The fronto-polar PFC, BA 10, is a region positioned above the Orbito Frontal Cortex (OFC), inferior to Area 9, and anterior to Area 46, serving as a junction point between the OFC and DLPFC (Krawczyk, 2002). A complete data acquisition cycle lasts approximately 330ms, making the temporal resolution approximately 3 Hz.

5. fNIRS research

5.1 Prefrontal activity and learning processes

Understanding the processes which underlie learning has become a central theme in current society, whether it is in the scope of education or in the field of neurorehabilitation. The proper functioning of learning processes can determine the efficacy of an individual's adaptation in society. By identifying these processes, we can identify learning problems early on in childhood and intervene. This is also true in the rehabilitation of patients with brain injury, or with memory-related neuropathology, where learning processes can determine the path of neurorehabilitation within a therapeutic program.

During learning, different brain structures begin to function, regardless of content, channel or mode of information. PFC participates in memory control (Luria 1973; Blumenfeld & Ranganath, 2006), particularly dorsolateral PFC (DLPFC), which plays a relevant role in temporal integration by means of functions that are complimentary and temporally reciprocal. The capacity to learn and remember highlights the plastic, adaptive ability of the neural system to change in response to experience. This capacity to integrate information is

widely considered to be a product of working memory (WM) (D'Esposito et al., 1998; Owen, 1997, 2000). The following two articles provide evidences on how prefrontal cortex is related to learning capacity and working memory.

The first study (León-Carrión et al., 2010) was designed to measure the physiological effects of repetition on learning and working memory using an adaptation of Luria's Memory Word-Task (LMWT). The study focused on the physiological effects of repetition on learning and working memory. We have used an adaptation of Luria's Memory Word-Task (LMWT) to study functional hemodynamic changes related to learning by verbal repetition. Functional near infrared spectroscopy (fNIRS) is used to test the hypotheses that repeated verbal presentation of information will produce an increase in DLPFC activation only during learning, followed by a decrease in activation once the information has been learned. This study assessed the hemodynamic response of DLPFC in 13 healthy subjects while performing a Luria task. All subjects successfully completed the task. A significant result from our data was that during the learning process, an increase in activation takes place in right and left DLPFC, which then decreases or ceases when the learning is complete. Our findings show neural repetition suppression (NRS) (see Grill-Spector et al., 2006 for a review) in DLPFC after effective verbal learning, an adaptation of hemodynamic activity in DLPFC during multiple repetitions. The correlations between memory recall and fNIRS activation evidences the neurophysiological substrates related to LWMT (see Tables 1 and 2). In psychobiological terms, this indicates that NRS must be present in successful verbal learning to maximize the effectiveness and accuracy of learning, and also to free up space in working memory. This optimization of neural responses stems from a verbal learning process that to be effective, requires time and repetition of the material being learned. Thus effective learning by repetition produces a reduced demand on WM through decreased DLPFC oxygenation as a consequence of a shift from controlled to automatic processing. Our results also point out that NRS is necessary not only to complete or close learning, but to keep DLPFC free and available for engagement in other tasks upon demand.

The second study used fNIRS and the N-Back paradigm to assess prefrontal activation. The N-Back paradigm and its variations have been used in numerous neuroimaging studies investigating the neural bases of working memory processes (Owen et al., 2005). In the current study, a modified version of the N-back task is applied (see Fig 5), which includes working memory manipulation to explore PFC activation during tasks requiring working memory (Baddeley, 1986).

The N-back task is designed to increase the manipulative character of information, producing more activation in regions associated with working memory. We hypothesized that as task difficulty increased, so would the differentiation in activation among different areas of DLPFC. The study included 20 healthy volunteers (14 female, 6 male), all right-handed and between 22 – 39 years of age (mean age = 26.6; SD = 4.15). fNIRS and oxyHb molecule mobilization were also used to measure DLPFC activation. The preliminary results showed that like classic verbal N-back tasks, the modified version activated the same regions of PFC but with greater intensity. The main result showed that while both N-back tasks (modified and classic) activated the same left DLPFC regions, the modified version registered greater differential activation. One possible explanation for the differential activation could be that the modified N-back had a deeper processing of information, with its manipulation involving semantic category and chronological order (days of the week). This higher information processing implies greater executive control, and an increase in regional cerebral blow flow in areas related to verbal working memory. In our study, areas

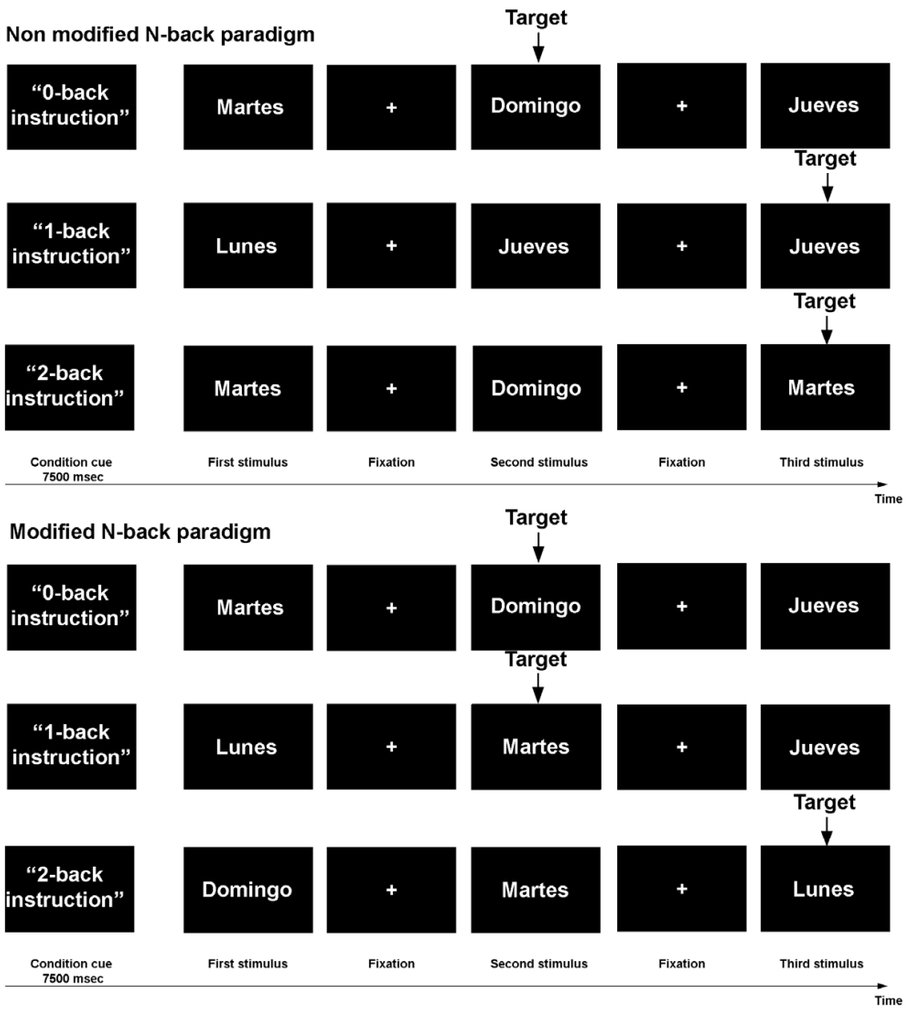

Fig. 5. Paradigms for unmodified N-back tasks (above) *and modified N-back task*s (below). The *0-back condition for both sets of tasks* required a response when the word "Domingo" appeared. A fixation point (+) was located between stimuli. In the *unmodified 1-back condition,* the subject had to respond when a stimulus was repeated. In the *unmodified 2-back condition*, the subject had to respond when the present stimulus coincided with the prior stimulus. The *modified 1-back condition* required the subject to respond if the stimulus coincided with day after the prior stimulus. The *modified 2-back condition* requested a response if the present stimulus coincided with the day after the stimulus presented two positions back.

with significant differential activation, associated with verbal manipulation and maintenance, corresponded with DLPFC and left frontal operculum (Brodmann Areas 9, 10, 45 y 46) (See Fig 6).

Overall, these two studies carried out with fNIRS indicate the importance of DLPFC in learning processes. The learning of verbal information, both auditory and verbally, is determined by the capacity of working memory to load information temporarily and manipulate it. The increased load and manipulation of verbal information result in increased physiological activation in related zones. This increased activation translates to an increase in CBF in areas related to verbal tasks, mostly in the left hemisphere.

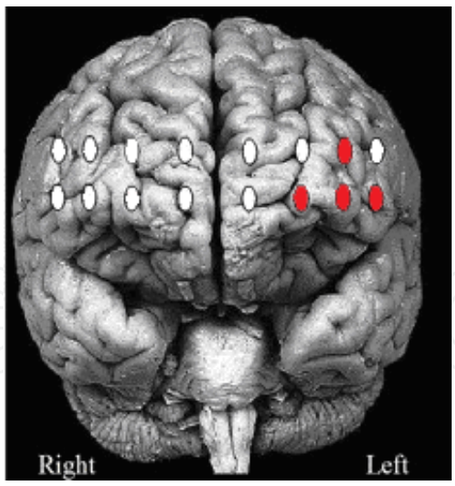

Fig. 6. Channels significantly activated during *modified* N-back task

5.2 Prefrontal activity and the affective dimension

The fNIRS is an excellent tool for studying the temporal dimension of hemodynamic activity, in terms of both reaction time (measured in ms) and residual activation after stimulus cessation. This residual activation could shed light on the characteristics of human behaviour. It is generally accepted that brain activation is elicited by direct cognitive/affective stimulation and that this activation decreases with stimulus cessation (Huettel & McCarthy, 2001). The DLPFC (Brodmann areas 9 and 46) has been selected as region of interest (ROI) based on a review of the literature which guarantees that emotional stimuli will produce some kind of activation in our ROI. These findings include DLPFC's sensitivity to emotional and motivationally significant aspects of stimuli (Hikosaka & Watanabe, 2000; Williams et al., 2001). The following articles display DLPFC activation during the viewing of scenes with different emotional content.

This first paper introduces a new paradigm in the study of emotional processes, emphasizing the role of affective dimensions in DLPFC and their influence on the neuroimaging of evoked hemodynamic changes (Leon-Carrion et al., $2007_{a)}$. Two affective dimensions have been studied extensively in neuroimaging research on emotional stimuli: arousal (exciting or calming) and valence (positive or negative) (Bradley et al., 1992). Another question that needs to be studied is whether the value (valence) and intensity (arousal) of an emotional stimulus evokes the same type of neural activation.

By using fNIRS, our intent was to image PFC oxyHb (oxygenated haemoglobin) changes and the duration of activation in relation to how subjects rated emotional stimuli (valence and arousal). We studied evoked-cerebral blood oxygenation (CBO) changes in DLPFC during direct exposure to emotion-eliciting stimuli ('on' period) and during the period directly following stimulus cessation ('off' period). Our hypothesis was that the evoked-CBO, rather than return to baseline after emotional stimulus cessation, would show either a significant increase (overshoot) or a significant decrease (undershoot) in oxyHb.

This study used visual emotional stimuli (film clips) of moderate length (approx. 20 s) and different emotional content to study the duration of DLPFC activation and provoke strong, lasting responses that could be easily registered. The content of the scenes ranged from mutilation, repulsive acts, and violence to walking along the street, cartoons, and scenes with explicit sex. The results showed that by using subjective ratings in analyzing PFC activation to account for individual differences in emotional response to salient stimuli, and

by incorporating subjective data on emotional arousal, more robust activation occurred within DLPFC during the 'off' period than the 'on' period. In other words, when the subjective degree of arousal is high, the representation of the stimulus remains in the prefrontal cortex, even when the stimulus is no longer present. The persistence of sources of DLPFC activation during the 'off' period is closely related to the degree of arousal that the subject assigns to the stimulus (Fig 7).

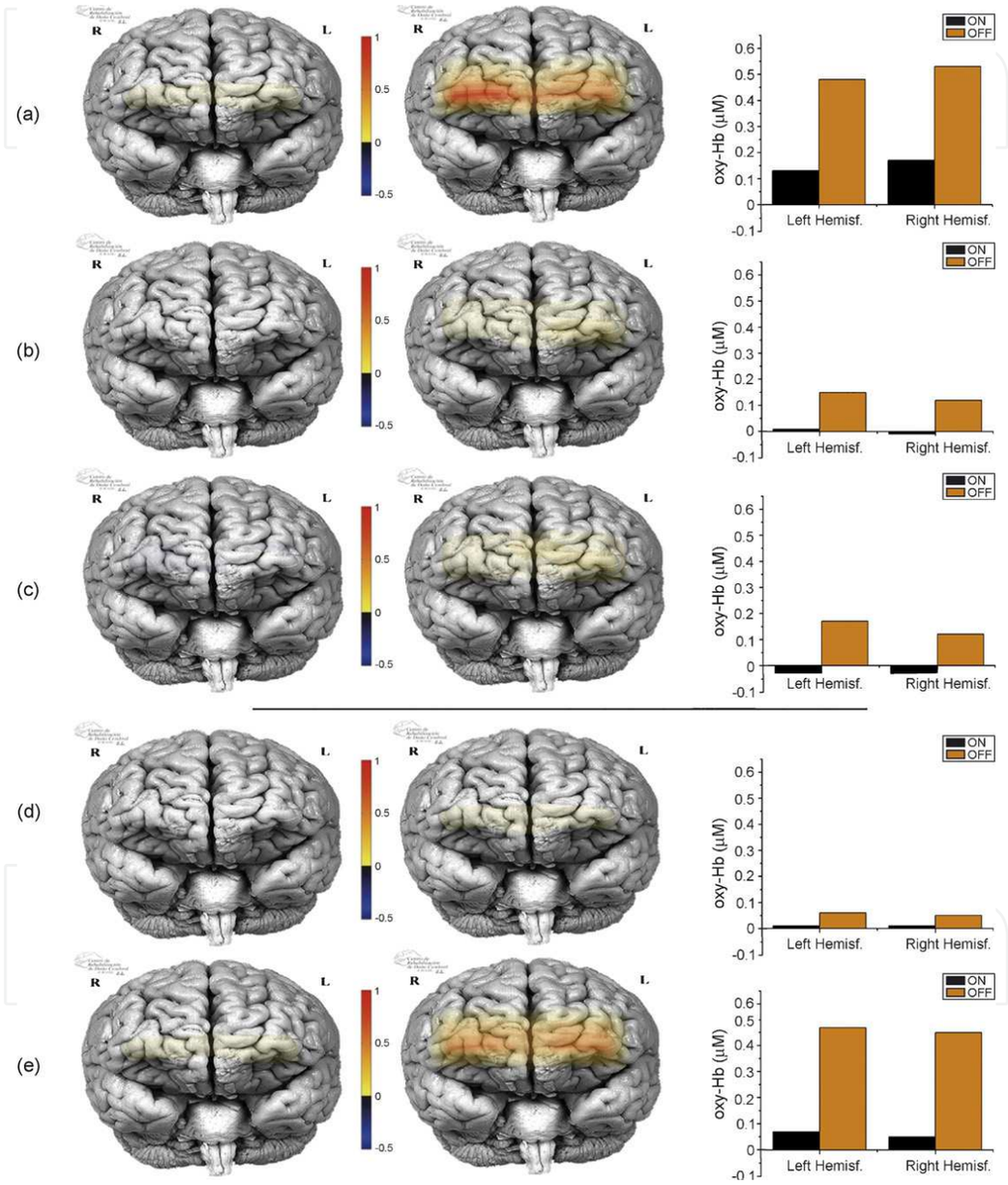

Fig. 7. Figure displays relative oxyHb concentrations, interpolated from the DLPFC channels of data acquisition in both on and off period for each emotional condition. The brain templates on the left and right represent the mean oxygenation during 'on' and 'off' periods, respectively. Valence category: (a) for unpleasant clips; (b) for neutral; and (c) for pleasant. Arousal category: (d) for non-arousing; and (e) for arousing. (Leon-Carrion et al., 2007$_a$)

The principle finding of this study was that an overshoot related to level of arousal in the DLPFC persists even when the arousing stimulus has disappeared. Our data also confirmed that valence and arousal have different effects on the course of evoked-CBO response in DLPFC. We also found significant post-stimulus overshoot related to arousal ratings. Significant differences between 'on' and 'off' periods of DLPFC activation based on valence ratings were not observed. In conclusion, our findings provide the first fNIRS evidence directly showing that an increment in subjective arousal leads to activation within DLPFC. This paper introduces a new paradigm in the study of emotional processes using functional neuroimaging techniques. Since arousing stimuli produce longer periods of brain activation than do non-arousing stimuli, neuroimaging studies must consider the duration and affective dimensions of the stimulus as well as the duration of the scanning. It will be necessary to specify how long a subject is exposed to a stimulus and how much of the recorded response is analyzed.

The second study (Leon-Carrion et al., 2007$_b$) explored DLPFC structures involved in the processing of erotic and non-sexual films. DLPFC plays a specific role in working memory in order to guide the inhibition or elicitation of sexual action. Different neurosurgery studies have demonstrated that frontal cortex is involved in the inhibitory control of human sexual behaviour (Freeman, 1973; Terzian & Ore, 1955). Here, we measured stimulus response both during direct viewing of the stimulus and for a short time after stimulus cessation, and recorded the temporal course of activation in DLPFC. Our hypothesis was that the sexual stimulus would produce a DLPFC overshoot during the period of direct perception ("on" period) that would continue after stimulus cessation ("off" period), whereas the non-sexual stimulus would not produce overshoot during either period.

Changes in pre-frontal concentrations of oxygenated haemoglobin (oxyHb) were measured during the two experimental conditions ("on" and "off" periods). Figure 8 shows a diagram of stimuli presentation and the sequence of fNIRS data acquisition. At the end of the presentation, participants were asked to rate each scene from 1 to 9 on a 2-dimensional scale. The first dimension, valence, corresponded to the subject's personal evaluation of the degree of pleasantness/unpleasantness of each scene, and the second, arousal, referred to how exciting or relaxing the subject perceived the scene to be.

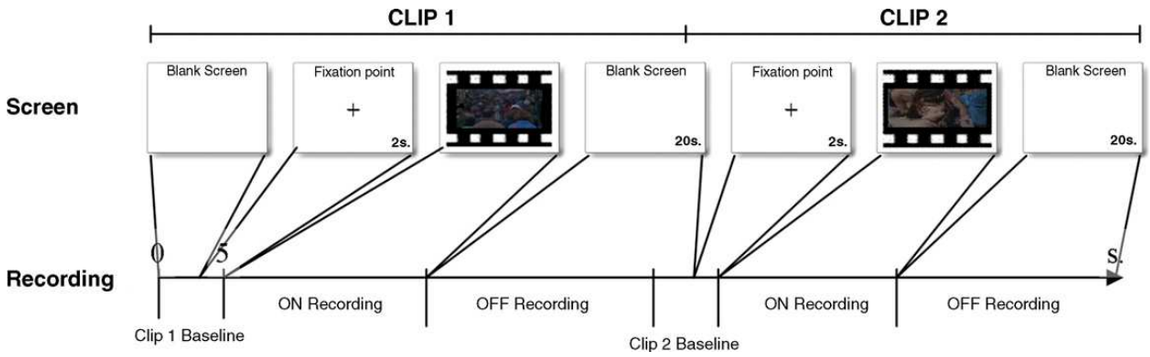

Fig. 8. Diagram of stimuli presentation and sequence of fNIRS recording. Note that to avoid accumulative effect, independent local baselines were recorded. (Leon-Carrion et al., 2007$_b$)

This is the first study to show that exposure to a sexually explicit scene produces strong overshoot in DLPFC, while exposure to a non-sexual scene does not. A significantly rapid and ascendant course in DLPFC overshoot was observed during direct viewing ("on" period) of the sexual scene, which became even more pronounced directly after viewing

("off" period), whereas a strong undershoot was observed for the non-sexual condition during the "off" period. We also found that the hemodynamic response to visual sexual stimuli differed between genders, with men registering higher oxyHb levels in DLPFC than women. Men seemed to be more interested in arousing visual stimuli as soon as these were perceived, and they experienced greater conflict in controlling their response. Men and women could differ in the urgency of response to a sexual stimulus, with men experiencing a greater degree of urgency than women. Compared to baselines, both genders showed significant overshoot in response to the sexual stimulus, but men showed a higher activation in absolute values. In men, activation was rapid and quickly increased, right from the onset of the stimulus, whereas women generally had a more delayed initial activation, which remained more stable than in men. This indicates that women, in general, would be more capable than men of controlling their response once aroused, and that this control, in both men and women, is a function of DLPFC. We therefore conclude that DLPFC plays a critical role in the self-regulation of sexual arousal. This study also demonstrates the feasibility of examining brain activation/sexual response relationships in an fNIRS environment.

Summarizing, the fNIRS is proven to be a useful tool for research on cognitive as well as emotional processes. Its high temporal resolution facilitates research of cerebral processes in their most dynamic and lasting form.

5.3 Near-Infrared Spectroscopy and its clinical use

In recent years, the use of near-infrared spectroscopy (NIRS) has steadily increased. It is now being applied in clinical settings, primarily in the field of medical monitoring and diagnosis (Frangioni, 2008; Kurth et al., 1995; Ward et al., 2006). One significant development has been the Infrascanner©, a tool which uses NIRS technology for the early diagnosis of cerebral haematomas (Leon-Carrion et al., 2010).

Traumatic brain injury (TBI) is a leading cause of death and disability and a major public health problem in the US, Canada (Leon-Carrion et al., 2005; Zygun et al., 2005) and Europe (Bruns & Hauser, 2003; Tagliaferri et al., 2006). Delayed medical attention is the strongest independent predictor of mortality in TBI patients. Early detection and surgical evacuation of mass-occupying lesions have decreased mortality and improved outcome in these patients. This reduction in mortality and morbidity requires rapid identification of the patient's cerebral and cranial status. Any further delay in haematoma evaluation severely increases mortality and worsens functional outcome in patients who survive (Seeling et al., 1985). NIRS technology could improve existing methods of identification of intracranial haematomas in these patients in situ. The Infrascanner test lasts 3 minutes and is easy to use in assessment applications as well as data organization and transmission. The purpose of this pilot investigation was to evaluate the Infrascanner as a handheld medical screening tool for the in situ detection of brain haematomas in patients who sustained a head injury.

The Infrascanner includes two main components: a NIRS-based sensor and a wireless personal digital assistant (PDA). The sensor includes a safe Class I NIRS diode laser, optically coupled to the patient's head by means of two disposable light guides in a 'hairbrush' like configuration. This configuration allows the sensor to contact the skin of the scalp. The 4.0cm separation between light source and detector allows NIRS absorbance measurement (~2cm wide and 2–3cm deep) in tissue volume. The light source uses an

808nm wavelength. The detector is covered by a band pass filter to minimize interference from background light. Electric circuitry is also included to control laser power and detector signal amplifier gain. Signals acquired from the detector are digitized and transmitted by a wireless link to the PDA. This link is also used to receive and set the sensor's hardware parameters. The PDA receives the data from the sensor and automatically adjusts its settings to ensure good data quality. The data is further processed and the results are displayed on the PDA screen (Fig 9).

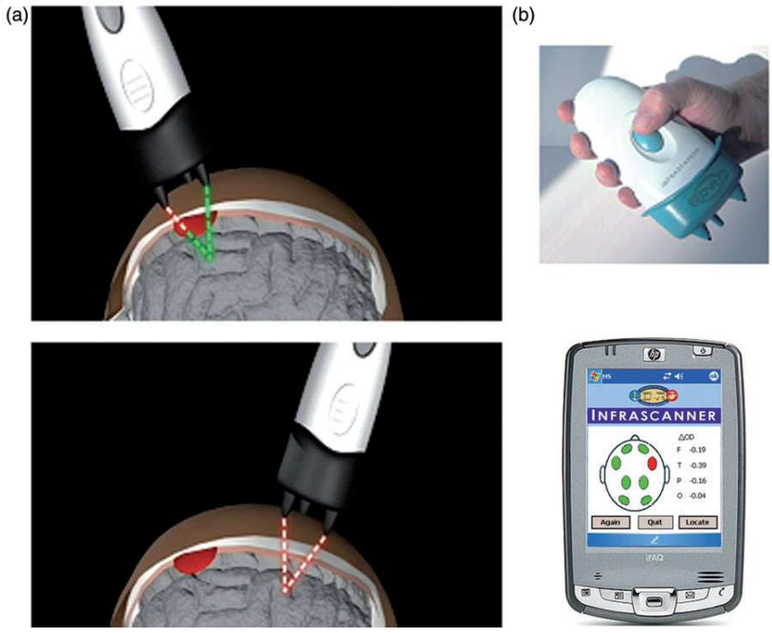

Fig. 9. Scanning sequence for brain haematoma. (a) The NIRS Sensor has two components: a 808nm diode laser and a silicon detector. The NIRS light source emits a light that penetrates the brain and is registered by the NIRS detector connected to the scalp through two optical fibres. The light intensity determines approximately how much blood volume is present. The Infrascanner performs symmetrical readings in the four main brain lobes: frontal, temporal, parietal and occipital. Haematoma detection derives from the difference in optical density between left and right readings for each brain lobe. (b) The detected signal is digitized and transmitted to a Bluetooth wireless personal digital assistant (PDA) that displays the results on the screen. (Leon-Carrion et al., 2010).

The results of this pilot study showed that handheld near-infrared Infrascanner demonstrates high sensitivity and specificity in detecting intra- and extra-axial hemorrhagic haematomas and, even more importantly, it could detect small haematomas (<25 mL) within the first 24 hours following injury. Data showed that the Infrascanner achieves 89.5% sensitivity when used on patients with TBI. Its on-site capacity to identify patients that have suffered an intracranial haematoma may be considered very high. The Infrascanner also

showed excellent specificity (81.2%) or the capacity to detect true negatives, identifying patients with TBI that have not suffered an intracranial haematoma. When compared to gold standard CT scans, its probability of positive predictive value was 85% and 86.7% for negative predictive value. This means that the Infrascanner is very accurate when confirming the presence or the absence of a haematoma.

This study demonstrated that the Infrascanner is a useful tool in the initial examination and screening of patients with head injury. It has proven utility as an adjunct to CT scans or as a preliminary exam given within 24 hours post-injury, when a CT scan is not available. In conclusion, the data shows that the Infrascanner is a sound portable device for detecting pre-operative intracranial subdural, epidural and subarachnoid haematomas in intensive care fields and emergency care units. It could aid paramedics, emergency room physicians and hospital staff, permitting earlier treatment and reducing secondary injury caused by present and delayed haematomas.

6. Conclusion

fNIRS has been approved by the FDA for clinical purposes and can be used simultaneously with other neuroimaging technologies. Studies show that fNIRS is a valid and reliable assessment tool for task-associated oxygenated blood, and while it may be early to define all the applications of this new technology, we believe it promises to find utility far beyond this in clinical practice. There are several types of clinical applications that could benefit from the unique attributes of fNIRS neuroimaging technology (Izzetoglu et al., 2004):

- Populations that may not be able to readily tolerate the confines of an fMRI magnet or be able to remain sufficiently still, e.g., schizophrenics, autistic children, neonates.
- Populations that require the long-term monitoring of cerebral oxygenation, e.g., premature and other high-risk infants.
- Studies that require repeated, low-cost neuroimaging, e.g., treatment studies that image the cortex for efficacy.
- Applications where an fMRI system would be too expensive or cumbersome, e.g., for use in a clinical office.
- Applications that require ecological validity, e.g., working at a computer or in an educational setting.

Furthermore, its current use is widely accepted by the neuroscientific community for studying cerebral functions due to its high level of consistency with findings based on traditional neuroimaging techniques. Like these, it measures neuronal activity indirectly via hemodynamic response. However, fNIRS is the only technique which can measure both extracellular and intracellular activation, with the latter still under development. fNIRS holds great potential for growth and application in clinical and research settings, offering new possibilities in neuroimaging techniques and expanding our knowledge about the functional organisation of the brain.

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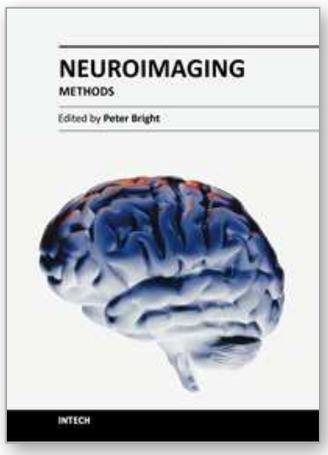

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Neuroimaging methodologies continue to develop at a remarkable rate, providing ever more sophisticated techniques for investigating brain structure and function. The scope of this book is not to provide a comprehensive overview of methods and applications but to provide a 'snapshot' of current approaches using well established and newly emerging techniques. Taken together, these chapters provide a broad sense of how the limits of what is achievable with neuroimaging methods are being stretched.

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