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Celebrating 25 Years of *NIR news*

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Medical near infrared spectroscopy: a prestigious history and a bright future

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This article provides an overview of the present and the bright future of near infrared (NIR) spectroscopy applications in the medical field with special regard to brain oximetry and functional NIR spectroscopy (fNIRS).

Introduction

Although the first applications of medical near infrared (NIR) spectroscopy go back to 1977,[1] when Frans Jöbsis (Professor of Physiology at Duke University, NC, USA) reported that the relatively high degree of transparency of brain tissue in the NIR range (the "optical window") enabled real-time, non-invasive detection of haemoglobin (Hb) oxygenation using trans-illumination spectroscopy, the first commercial NIR system (brain oximeter) was not built until 1989 by Hamamatsu Photonics K.K. (Japan). The 16 (mainly review) articles published in the 2012 *Journal of Near Infrared Spectroscopy* Special Issue on Medical Applications,[2] have nicely summarised the most important aspects of medical NIR spectroscopy. Brain/muscle oximetry[3] and functional NIR spectroscopy (fNIRS)[4,5] represent the most established clinical and/or basic research areas. More recently, several review articles have been dedicated to brain oximetry, the technique that continuously measures cortical Hb saturation.[6,7]

Most successful applications: brain oximetry and fNIRS

Examples of two commercially-available brain oximeters are shown in Figures 1 and 2. Functional activation of the human cerebral cortex can be successfully explored by fNIRS, optical topography, NIR imaging, diffuse optical imaging (DOI) or diffuse optical tomography (DOT).[4,5] fNIRS is a non-invasive, vascular-based neuroimaging technology that measures concentration changes of oxygenated-Hb (O_2Hb) and deoxygenated-Hb (HHb) in cortical microcirculation blood vessels by means of the characteristic Hb absorption spectra in the NIR range. Cerebral blood flow (CBF) adequate for brain activity and metabolic demand is maintained through the processes of autoregulation and neurovascular coupling. Coupling between neuronal activity and CBF is fundamental to brain function. When a specific brain region is activated, CBF increases in a temporally and spatially coordinated manner tightly linked to changes in neural activity through a complex sequence of coordinated events involving neurons, glia, arteries/arterioles and signalling molecules. fNIRS relies on this coupling to infer changes in neural activity that are mirrored by changes in blood oxygenation in the region of the activated cortical area (i.e. the concomitant increase in O_2Hb and the decrease in HHb, as observed by fNIRS). fNIRS systems vary in complexity from two to several dozen channels ("whole-head' arrays; Figures 3 and 4). fNIRS data processing and analysis methods permit topographical assessment of real-time, regional cortical haemodynamic changes. fNIRS

Figure 1. Commercial brain NIR oximeter: "SenSmart™ Universal Oximetry System" (Nonin). The NIR spectroscopy oximeter is equipped with five optical probes for monitoring the tissue Hb saturation over the forehead or in other parts of the body. Photo courtesy of Nonin Medical, Inc., USA.

Figure 2. Commercial brain NIR oximeter: "O3™ Regional Oximetry" (Masimo). The instrument can support up to six optical probes. Photo courtesy of Masimo International.

Figure 3. High density DOT optical fibre array covering two-thirds of the head. Photo courtesy of Professor Culver, Washington School of Medicine, St Louis, Missouri, USA.

data from multiple simultaneous measurement sites are displayed by fNIRS systems in the form of an O_2Hb/HHb map or an image covering a specific cortical area.

In 2014, the journal *Neuroimage* dedicated a special issue to commemorate the first 20 years of fNIRS research.[8] Its 9 review articles and 49 contributed papers offer a comprehensive survey of the exciting advances driving the field forward and of the myriad of applications that will benefit from fNIRS. So far, fNIRS has lacked the combination of spatial resolution and wide field of view sufficient to map distributed brain functions in detail. The emergence of high-density DOT represents the most recent generation of fNIRS systems which open up more potential clinical applications by offering regional comparisons of brain oximetry and mapping higher-order, distributed brain functions either at rest or in response to interventions.[9,10] Figure 3 depicts an example of a high-density DOT imaging array that has been recently used to map, for example, multiple resting-state networks including the dorsal attention and default mode networks, cortical responses during language tasks and brain function in patients with Parkinson's disease and implanted deep brain stimulators.[9]

More recently, the "hyperscanning" approach, consisting of the measurement of brain activity simultaneously on two or more people, has been adopted by fNIRS, as reported in several recent studies, for investigating inter-personal interactions in a natural context.[11] Examples of "hyperscanning" fNIRS measurement are shown in Figures 5 and 6. fNIRS, more than any other neuroimaging modality, is suitable for investigating real social interactions by using a "hyperscanning" approach.

Most of the commercial fNIRS systems utilise fibre optic bundles. The disadvantage of using such bundles is that the fibres are often heavy and of limited flexibility, perhaps provoking discomfort (especially in patients). In addition, these fNIRS systems

Figure 4. Integrated portable imaging system consisting of diffuse optical imaging "optodes" and EEG electrodes used at the Evelyn Perinatal Imaging Centre in Cambridge, UK. A cap is used to apply the fibre optics and wires to the infant's head. Because the device is portable, it can be placed next to the cot in the neonatal intensive care unit and used to scan vulnerable infants, such as those suffering from seizures. NeoLAB, a collaborative research group involving Cambridge University and University College London , are working to develop novel biomarkers for assessment and treatment of neonates using this instrument.

Figure 5. 22-channel wearable fNIRS system (WOT-220, Hitachi High-Technologies Corporation, Japan) mapping the prefrontal cortex activity. The flexible probe unit covers the dorsolateral and the rostral prefrontal cortex. The processing unit is worn on the waist. Multiple people measurement (up to four people) is possible. Photo courtesy of Hitachi.

Figure 6. "Hyperscanning" measurement performed in two children playing with a puzzle (NIRSscout extended, NIRx Medical Technologies, LLC, USA). Photo courtesy of NIRx Medical Technologies.

Figure 7. Time-domain brain NIR oximeter: tNIRS-1 (Hamamatsu Photonics Systems Division, Japan). The instrument is equipped with two optical probes. Photo courtesy of Hamamatsu.

Figure 8. Commercial DCS NIRS system for measuring the adult head rCBF: αιμα-FloMo (Hemophotonics S.L., Spain). Photo courtesy of Hemophotonics.

Figure 9. Commercial DCS NIRS system: MetaOx (ISS, USA). The instrument provides concomitant measurements of O_2Hb/HHb concentrations and Hb saturation (using frequency-domain NIR spectroscopy) and rCBF (using DCS) of the newborn head. The instrument can also monitor regional cerebral oxygen consumption. Photo courtesy of ISS.

require that the subject's head position does not move beyond the length of the fibre optic bundles. Since 2009, different battery-operated, multi-channel, wearable/wireless systems have been commercialised,[5] allowing fNIRS measurements on the adult prefrontal cortex. An example of a 22-channel wireless system is shown in Figure 5. This most advanced version of fNIRS systems is a suitable tool for evaluating brain activation in response to cognitive tasks executed in normal daily activities.

So far, the most commonly used tissue oximeters and fNIRS instruments utilise continuous-wave light sources,[5] while the high-cost, time-domain NIR devices utilise a short pulse of laser light (a few picoseconds) and measure the temporal broadening of the pulse as it propagates through the tissue.[12] As a consequence, time-domain NIR instruments measure the absolute concentration of O_2Hb/HHb and provide a better depth discrimination than what is possible using continuous-wave NIR instruments.[12] The first clinical time-domain brain oximeter will be soon commercialised by Hamamatsu Photonics Japan (Figure 7). On-going developments in time-domain diffuse optics could generate compact and even wearable time-domain oximeters and fNIRS systems.[12]

However, a better understanding of brain pathophysiology can be achieved by monitoring regional CBF (rCBF). Recently developed diffuse correlation spectroscopy (DCS) offers the opportunity of evaluating a continuous quantitative index of rCBF by measuring the decorrelation of the intensity fluctuations in the detected coherent NIR light that is induced by moving red blood cells.[13,14] This technology also makes possible an estimation of the relative cerebral oxygen metabolism. So far, two DCS-NIRS systems have become commercially available (Figures 8 and 9). A different approach for measuring rCBF has been utilised by Ornim Inc. (USA), a company that has developed the CerOx 3210F oximeter using NIR spectroscopy and weak acoustic beams to identify light emerging from deep tissue layers.

The sector of wearable health technology is arousing apparently endless interest. The use of low-cost, wearable monitoring devices or wearable biosensors that allow constant monitoring of physiological signals is essential for the advancement of both the diagnosis and the treatment of diseases as well as for monitoring an active lifestyle. Wearable wireless fingertip pulse oximetry devices for arterial saturation measurement are already available for smart phones. Recently, a wireless and smartphone controllable NIR system has been presented.[15] Foetal/neonatal head Hb saturation has been also obtained by the examiner's finger-mounted oximeter (Toccare, Astem, Japan) (Figure 10).[16] Very recently, a textile NIR system has been utilised for monitoring arterial Hb saturation and O_2Hb/HHb muscle oxygenation changes.[17]

Figure 10. Oximeter probe attached to the examiner's finger pulp measuring Hb saturation on the newborn head (Toccare, Astem, Japan). Photo courtesy of Astem.

Conclusions

Medical NIR spectroscopy has already found and will continue to find several other unexpected interesting applications. For instance, since the beginning of the nineties, NIR mammography has being utilised to support and further understand lesions of the breast found with other imaging modalities. Different optical signatures of breast cancer are currently exploited for early detection and a rapid outcome measure to guide intervention.[18] In conclusion, the applications of NIR in the medical field are still growing, as witnessed by the high number of publications (about 80 and 280 in brain oximetry and fNIRS, respectively; source: SCOPUS 2014, Elsevier BV). This growth reflects the increasing number of clinicians and researchers who utilise NIR spectroscopy together with the new technological developments of NIR spectroscopy for a broad range of medical applications.

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