# Shining light on the newborn brain

For over 30 years, cerebral haemodynamics and oxygenation in the newborn brain has been studied using near-infrared spectroscopy. The technology has advanced considerably over the years; this article reviews some of these developments and highlights the work of neoLAB, a collaborative group of clinicians, engineers and scientists at University College London and Cambridge. neoLAB is based in the Evelyn Perinatal Imaging Centre, a unique newborn functional brain imaging facility at the Rosie Hospital, Cambridge, which contains an infant scanning room, physics laboratory and a recently installed magnetic resonance imaging scanner.

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**Keywords**

perinatal brain injury; NIRS; optical imaging; neonatal brain injury

**Key points**

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1. neoLAB is a collaboration between physicists, engineers and clinicians in London and Cambridge, based at the Evelyn Perinatal Imaging Centre, Cambridge, a dedicated newborn functional brain imaging unit.
2. The development of novel optical and electrophysiological imaging technologies to study the newborn brain will help to identify vulnerable infants at an early stage.

The idea of using light to study the newborn brain is not new. In 1831, Richard Bright, a London physician, describing the examination of a patient with hydrocephalus, wrote: *'If a candle was held behind his head, or the sun happened to be behind it, the cranium appeared semi-transparent'*.[1] Fast forward nearly 150 years and Professor Frans Jobsis of Duke University first described the technique of near-infrared spectroscopy (NIRS).[2] The haemoglobin molecule strongly absorbs visible light passing through biological tissue; however as you move towards the red and near infrared (700-1000nm) part of the spectrum, absorption decreases. This can be simply observed by shining a thin torch over a finger; the light appears red. More importantly, the light is absorbed in different amounts by oxy- and deoxy-haemoglobin ($HbO_2$ and HHb, respectively). Therefore, if you shine light of very specific wavelengths, it is possible to measure the amount of $HbO_2$ and HHb.

This is the principle behind pulse oximetry, a universal tool to measure arterial oxygen saturation. By applying light sensors and detectors (together known as optodes) on the head and monitoring the intensity of light passing through brain tissue at two or more wavelengths, observed changes in light attenuation can be converted into changes in the cerebral concentrations of $HbO_2$ and HHb.

## Development of NIRS

An early application of NIRS was in the study of neonatal cerebral haemodynamics. Absolute quantification of cerebral blood flow (CBF) and cerebral blood volume (CBV) were possible by manipulating inspired oxygen or injecting an inert optical dye, indocyanine green.[3,4] However, continuous measurements could only detect *changes* in $HbO_2$ and HHb. This is because, as well as being absorbed, light is highly scattered, and mathematically it is very difficult to account for the scattering. That said, light scattering is essentially a feature of the underlying tissue structure, which during measurement periods can be assumed to be constant, so any change in light attenuation can be assumed to be due to changes in absorption and hence $HbO_2$ and HHb concentration.

Spatially resolved spectroscopy (SRS) is a development of NIRS. By using a single light source and multiple closely spaced detectors, the scattering component of light attenuation can be accounted for and an absolute assessment of the ratio of $HbO_2$ and total haemoglobin can be made, expressed as percentage oxygen saturation. Measured over the head, this is known as the regional cerebral oxygen saturation ($rScO_2$).[5] A number of commercial systems employ SRS technology. NIRS has been routinely used clinically to monitor $rScO_2$ in cardiac surgery and several studies have shown an association between pre-operative and intra-operative low cerebral oxygenation and poor post-operative outcome in infants.[6]

Recently the European SafeBoosC (Safeguarding the brains of our smallest children) consortium completed a phase II randomised controlled trial of continuous monitoring of $rScO_2$ with a dedicated treatment guideline in combination with cerebral NIRS monitoring. The study showed that in the 86 infants randomised to the experimental group, the mean

burden of hypoxia was significantly less than in the control group, demonstrating that $rScO_2$ can be stabilised in extremely preterm infants using a dedicated treatment guideline in combination with cerebral NIRS monitoring.[7] Whether a 'cerebral oxygen' targeted approach to the early management of these infants improves long-term neurodevelopmental outcome will require a much larger study.

## NIRS in sick infants

Several research groups, including the author's, have been interested in using NIRS to study cerebral autoregulation in sick newborn infants. Continuous measurements of CBF can be inferred from measurements of $rScO_2$ and changes compared with spontaneous fluctuations of other haemodynamic variables such as arterial blood pressure (ABP) and heart rate (HR). In the healthy brain, cerebral autoregulation limits CBF variation over a range of cerebral perfusion pressures (CPP). Loss of autoregulation is associated with brain injury in newborn infants, children and adults. In neonatal intensive care, there is a lot of focus on blood pressure management even though the effects of changes in ABP on CBF are not measured and the 'optimal' ABP ($ABP_{opt}$) to maintain adequate cerebral perfusion in any single patient is not known. Defining 'optimal' ABP based on the strength of cerebral autoregulation has been studied in adults with traumatic brain injury.[8] The author's research group has recently described a novel index of cerebral vascular reactivity using the correlation coefficient between ABP and HR, known as TOHRx.[9] Using this index to study preterm infants soon after birth, it was possible to define values of $ABP_{opt}$ where cerebral vascular reactivity was strongest and show that preterm infants who died had a higher mean absolute deviation from $ABP_{opt}$ than patients who survived.[10]

## Optical topography and neurovascular coupling

Studies using single channel NIRS systems have been described but the use of multiple optodes on the head would provide an opportunity to obtain regional information and reconstruct images of cerebral oxygenation in the brain. The most straightforward approach is optical topography. This involves obtaining multiple measurements at small source-detector separations from the surface of the head. By frequency-modulating the light, it is possible to interrogate large areas of the brain simultaneously and make measurements of rapid changes in haemodynamics associated with functional brain activation. At neoLAB, an optical tomography system – the University College London NTS system – has been combined with a standard clinical electroencephalogram (EEG). The rationale here is to investigate the relationship between electrical activity and blood flow, both in health and in response to injury. Although the temporal response is not as fast as EEG, it provides better spatial localisation and the opportunity to measure deeper changes within the brain. Using this system, dramatic changes in CBV associated with seizures have been observed (**FIGURE 1**).[11] A consistent pattern emerges of a small increase in CBV followed by a more profound and sustained fall in CBV. Interestingly these phenomena, not seen in healthy infants, persisted even when the seizures were terminated by anticonvulsant medication. More recently, the author's research group has been able to image haemodynamic changes associated with burst suppression in infants with hypoxic-ischaemic encephalopathy. In this case, the burst is associated with an increase in blood volume, and in some of the infants studied these changes appear to be localised to the area of brain injury when compared to the magnetic resonance imaging (MRI) scans of the infants.

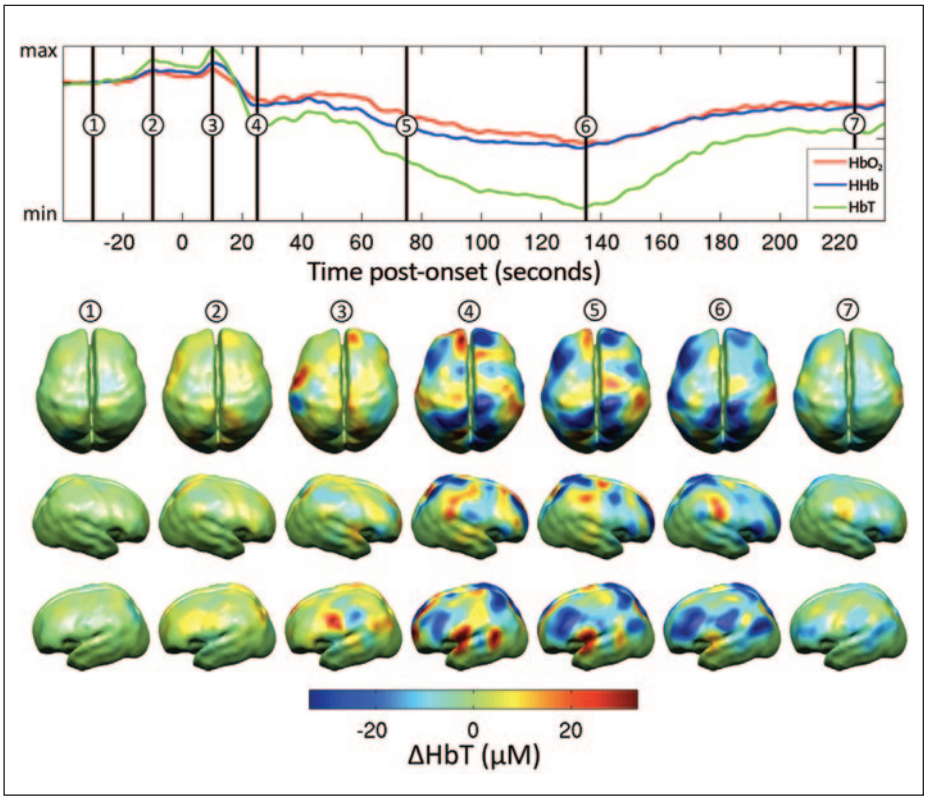


**FIGURE 1** A sequence of images showing the changes in total haemoglobin (HbT) associated with a clinical seizure in an infant. The upper axes show the changes in haemoglobin concentration spatially averaged across the cortical surface. Seven distinct time points are identified and the associated reconstructed images of the changes in HbT concentration are shown in dorsal and left and right lateral views. All data are changes relative to a baseline defined as the mean of the period between 60 and 30 seconds prior to the electrographic seizure onset. *Adapted from Singh et al.*[11]
Key: $HbO_2$ = oxyhaemoglobin, HHb = deoxyhaemoglobin, HbT = total haemoglobin.

Another application of optical topography is in the study of functional connectivity in the developing brain. Resting state functional connectivity (RSFC) networks consist of coherent regions of spontaneous brain activity that represent functional neural networks in the absence of movement or stimulus. In the developing brain, RSFC has been shown to emerge during the third trimester and is possibly incomplete in preterm infants.[12] The majority of studies on RSFC use functional MRI (fMRI); there are obvious logistical and environmental limitations of

scanning newborn infants in an MRI scanner and optical topography offers a relatively simple and safe cotside system to undertake these studies.[13] As well as providing insight into development of the preterm brain, RSFC could become an important imaging biomarker, identifying infants at risk of neurodevelopmental problems at an early stage.

## Optical tomography

While optical topography results in surface maps of cortical changes in haemodynamics, a more challenging approach, known as optical tomography, is to obtain three-dimensional images of haemodynamics and oxygenation of the whole brain. In order to obtain such an image, it is necessary to detect light transmitted across the brain. Given the inherent 3D scattering of light as it enters biological tissue, reconstructing images is a non-trivial task. Unlike conventional NIRS, which just measures light attenuation, optical tomographic images are obtained by measuring the time of flight of pulses of photons as they cross the head. The distribution of photon flight times is unique for each source-detector pairing and provides information on the light absorbing and scattering characteristics of the tissue being interrogated (**FIGURE 2**). Measuring the time taken for light to cross the head requires a system which can deliver pulses of photons every few pico seconds (1/1,000,000,000,000s) and detect the photons at nanosecond resolution (1/1,000,000,000s). The initial 32-channel system, built at University College London over 10 years ago, was known as MONSTIR (Multichannel Opto-electronic Near-infrared System for Time-resolved Image Reconstruction) and consisted of two large racks and its own air-conditioning unit given the amount of heat it produced! Individualised rigid caps were made and it took 10 minutes to acquire a complete set of data. However, with this prototype system, the first 3D optical images from the preterm brain, and of intraventricular haemorrhage were obtained[14] (**FIGURE 3**). In 2013, the second-generation system was transported to the Evelyn Perinatal Imaging Centre. The new system, as well as being considerably smaller, is able to collect a full set of data in less than 30 seconds, and thus offers the possibility of obtaining fast haemodynamic information associated with functional brain activation[15] (**FIGURE 4**).

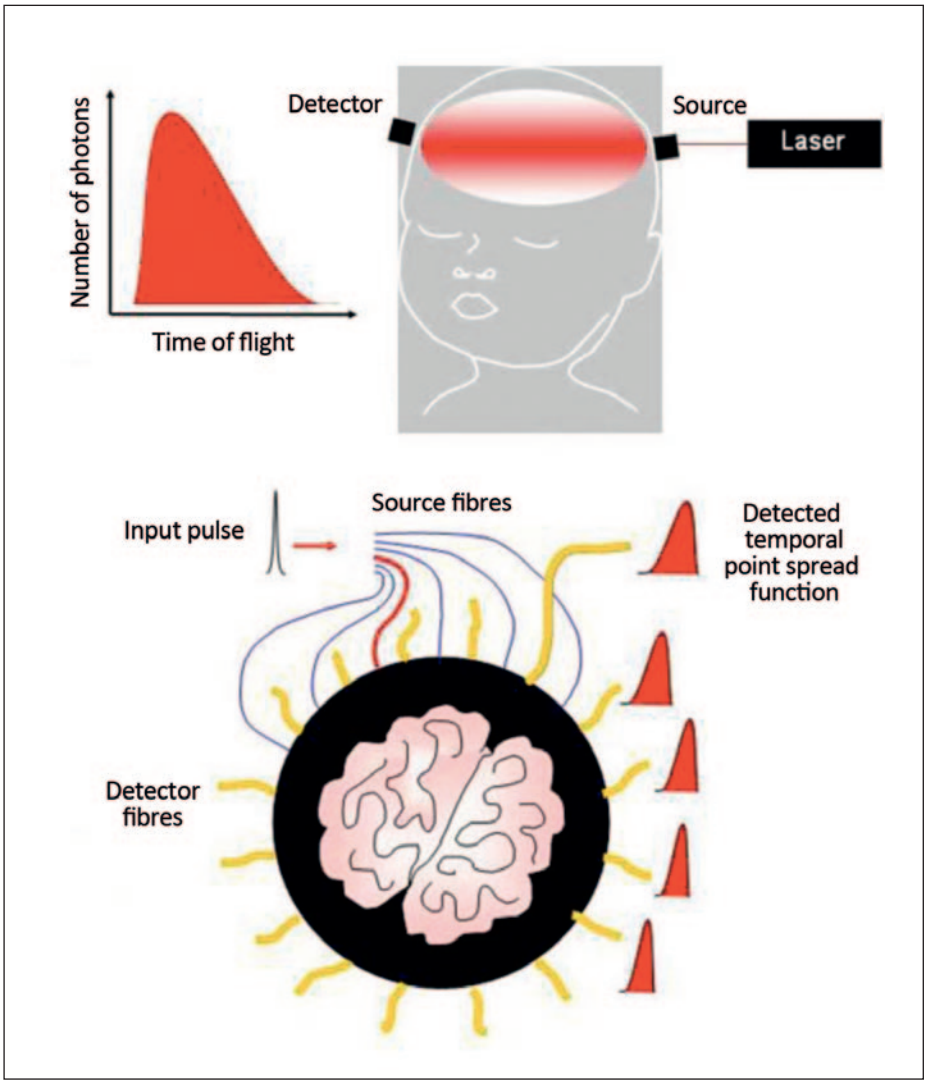


**FIGURE 2** The principles of optical tomography. Unique histograms of the time taken for photons to cross the brain are generated for each source-detector pair (top). These graphs contain information on the absorption and scattering of light as it passes through the brain and hence information on regional haemodynamics and oxygenation. Each of the 32 sources is activated sequentially and photons detected simultaneously from all of the detectors. Images are generated using a computer programme that models the dispersion of photons across the brain, compares model data with acquired data and changes the model iteratively until there is acceptable convergence between model and acquired data.

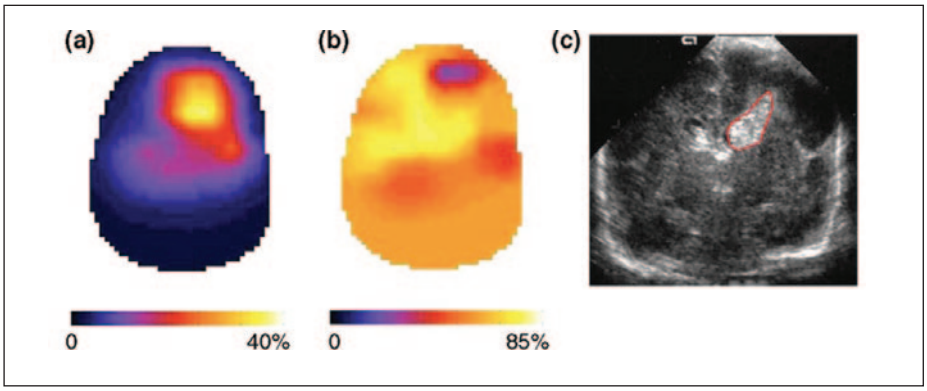


**FIGURE 3** Optical tomographic images. A coronal section showing (a) regional blood volume, (b) regional oxygen saturation, and (c) the corresponding cranial ultrasound scan. There is an increase in regional haemoglobin concentration and a decrease in regional oxygen saturation in the area corresponding to the intraventricular haemorrhage and haemorrhagic parenchymal infarct. The lesion is outlined in the ultrasound scan. *Adapted from Austin et al*[14] *with permission from Elsevier.*

## Conclusions

Whether it is a single channel NIRS monitor, or 32-channel optical imaging scanner, the same basic principle of light transmission across the brain has enabled new insights in the brain to be obtained from sick and preterm babies safely at the cotside. The unique partnership between physicists, computer scientists, engineers and clinicians at neoLAB are enabling the next generation of systems to be developed. The light is shining brightly on the newborn brain.


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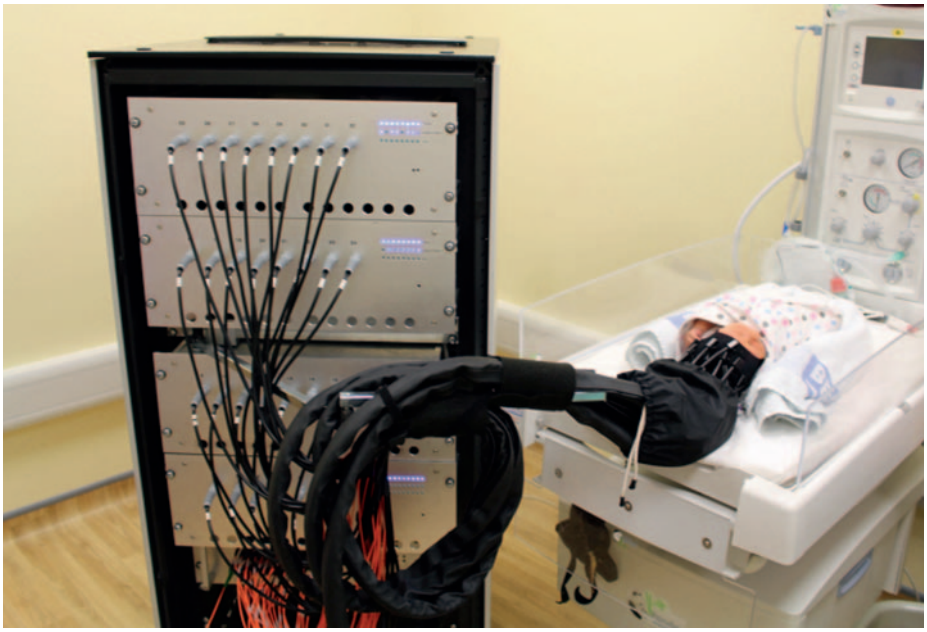

**FIGURE 4** Scanning a newborn infant with the Multichannel Opto-electronic Near-infrared System for Time-resolved Image Reconstruction (MONSTIR) II at the Evelyn Perinatal Imaging Centre in the Rosie Hospital, Cambridge.

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