Elsevier Editorial System(tm) for NeuroImage

Manuscript Draft

Manuscript Number:

Title: THREE DIMENSIONAL OPTICAL IMAGING OF BLOOD VOLUME AND OXYGENATION IN THE NEONATAL BRAIN

Article Type: Regular Article

Section/Category: Methods & Modelling

Keywords:

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Corresponding Author's Institution: University College London

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Manuscript Region of Origin:

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Cover Letter

Department of Paediatrics & Child Health

26th October 2005

The Editor
Neuroimage
Elsevier Publishing

Dear Sir,

This is a letter to accompany our manuscript 'Three dimensional optical imaging of blood volume and oxygenation in the neonatal brain'. The manuscript is being submitted only to Neuroimage. It will not be submitted elsewhere whilst under consideration, has not been published elsewhere and should it be published in neuroimage will not be submitted elsewhere.

We certify that we are responsible for the reported research and that we have participated in the concept and design; analysis and interpretation of data; drafting or revising of the manuscript, and approve of the manuscript as submitted. We have no affiliation, financial agreement or any other involvement with any company, in connection with this research study.

Yours sincerely,

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THREE DIMENSIONAL OPTICAL IMAGING OF BLOOD VOLUME AND OXYGENATION IN THE NEONATAL BRAIN

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Abstract

Optical methods provide a means of monitoring cerebral oxygenation in newborn infants at risk of brain injury. A 32 channel optical imaging system has been developed with the aim of reconstructing three dimensional images of regional blood volume and oxygenation. Full image data sets were acquired from 14 out of 24 infants studied; successful images have been reconstructed in 8 of these infants. Regional variations in cerebral blood volume and tissue oxygen saturation are present in healthy preterm infants. In an infant with a large unilateral intraventricular haemorrhage a corresponding region of low oxygen saturation was detected. These results suggest that optical tomography may provide an appropriate technique for investigating regional cerebral haemodynamics and oxygenation at the cotside.

1. Introduction

Brain injury arising in the perinatal period leads to death or permanent and severe impairment in a significant number of children born prematurely (Marlow *et al* 2005). Alterations in cerebral perfusion and oxygenation have been described and implicated in the pathophysiology of haemorrhagic and hypoxic-ischaemic brain injury in these infants (Volpe 1997). Regional variations in cerebral oxygen are also known to exist, so that whilst global oxygenation may appear adequate, regional variations leave areas of the brain at risk of permanent neurological damage (Borch *et al* 1998). Non-invasive techniques have the potential to play an important role in the introduction of novel clinical strategies designed to minimize the incidence and severity of this form of brain damage. Currently there is no technique which can provide repeated quantitative regional information on cerebral oxygenation at the cotside. The ability to do so would represent a major advance in the brain orientated care of critically ill neonates.

The application of near-infrared spectroscopy (NIRS) to continuously monitor cerebral haemodynamics and oxygenation non-invasively was first reported by Jöbsis (1977). This technique exploits the optical properties of natural chromophores, including haemoglobin, which has oxygenated and deoxygenated forms with different characteristic absorption spectra in the visible and near-infrared wavelength range. By measuring at two or more wavelengths, NIRS has been used to obtain global quantitative measurements of cerebral blood flow, cerebral blood volume, and cerebral venous oxygen saturation (Edwards *et al* 1988, Yoxall *et al* 1995).

Near-infrared imaging represents a natural extension of current efforts to improve quantitation and localisation of cerebral haemodynamics and oxygenation, and two distinct approaches are being pursued (Gibson *et al* 2005a). The most straightforward of these is *optical topography*, which involves acquiring multiple reflectance measurements at small

source-detector separations over a large area of the head simultaneously or in rapid succession. By keeping the separations small, measured signals are relatively high and therefore may be acquired quickly, enabling brain activity with characteristic responses as fast as 100 ms or so to be studied. However, the small separations also imply an overwhelming sensitivity to changes occurring in the surface (cortical) tissues, and little information is revealed about deeper regions of the brain. Optical topography has been successfully used to assess functional activation of the infant cortex to a variety of sensory stimuli (Chance *et al* 1998, Hintz *et al* 2001, Kusaka *et al* 2004, Taga *et al* 2003).

The second and considerably more challenging approach to near-infrared imaging of the brain is known as *optical tomography*, where the objective is to generate a transverse slice or three-dimensional (3D) image. The sensitivity to deep tissues requires measurements at large source-detector separations, and consequently transmitted light must be integrated over periods of several seconds or longer per source to obtain adequate signal. Whilst this inhibits the display of fast haemodynamic phenomena associated with functional activation, unless averaged over repeated stimuli, this technique has the potential to obtain novel information on oxygenation in deeper areas of the brain vulnerable to damage.

To date, two systems have successfully demonstrated optical tomography of the newborn brain. The first, built by a group at Stanford, was used to reconstruct 2D images from a cohort of preterm infants (Hintz *et al* 1999). The second system, developed by our group at University College London (UCL) and described in the following section, has been employed to generate the first 3D images of the entire newborn infant brain (Hebden *et al* 2002; Hebden *et al* 2004; Gibson *et al* 2005b). In this paper we review the results obtained with the UCL system so far, throughout a four year period during which twenty four infants have been studied. We summarise results achieved for preterm infants with and without

evidence of cerebral injury, and discuss the difficulties encountered and our progress towards overcoming them.

2. Methods

2.1 Instrumentation

The UCL imaging system is a 32-channel time-resolved device known as MONSTIR (Multi-channel Opto-electronic Near-infrared System for Time-resolved Image Reconstruction). It measures the flight times of photons transmitted between pairs of points on the surface using very short (a few picoseconds) pulses of laser light at two wavelengths (780nm and 815nm) and 32 parallel time-resolved detectors. Light collected by fibre bundles is delivered to microchannel plate photomultiplier tubes via 32 variable optical attenuators (VOAs), which ensure that the detected light does not saturate or damage the detectors as the point of illumination is moved between positions on the head. Histograms of photon flight times are built up, known as temporal point spread functions (TPSFs). Each TPSF corresponds to a distinct line-of-sight across the head, and the shape and amplitude of the TPSF depend on the optical properties within the brain. Up to thirty-two co-axial optical fibre bundles are placed around the infant head, enabling MONSTIR to illuminate the head at each position sequentially while detecting transmitted light at each location simultaneously, resulting in a maximum of 1024 separate TPSFs. A more detailed description of the instrument is given by Schmidt *et al* (2000).

2.2 Image reconstruction

Three-dimensional optical tomography is based on the general principle that a finite set of measurements of transmitted light between pairs of points on the surface of an object is sufficient to reconstruct a 3D volume representing the distribution of internal scatterers and absorbers. Our approach has been to determine the parameters which describe an appropriate

model of photon transport within the volume of interest by comparing the predictions of the model with acquired data (Arridge 1999). The model is adjusted iteratively until acceptable correspondence is achieved. This method is the basis of the reconstruction package known as TOAST (Temporal Optical Absorption and Scattering Tomography) which has been developed at UCL by Arridge and Schweiger (Arridge *et al* 2000; Schweiger *et al* 2005). TOAST employs a finite element method (FEM) forward model, and uses an iterative model-fitting routine wherein the FEM model parameters are repeatedly updated to optimize the match of the model to the data. To reduce computation time, TOAST simulates specific characteristics of the TPSF for given source-detector locations, known as datatypes, such as the intensity, the mean flight time and the variance about the mean (Arridge 1999). In this work, the mean photon flight time was used to reconstruct images.

TOAST generates images of absorption and scattering at each of the two wavelengths. From the absorption images, we derive 3D images of regional cerebral blood volume (rCBV) and regional tissue oxygen saturation ($rStO_2$) (Hillman 2002).

2.3 Fibre holding helmet

Coupling multiple optical fibre bundles onto the head of an infant in the neonatal intensive care unit environment represents a significant technical challenge. An interface is required which sits comfortably on the infant head, excludes ambient light, and prevents light travelling around the head from the source to a detector. The initial solution to the problem was to construct a custom-made helmet for each infant, consisting of an outer shell constructed from thermoplastic, lined with soft NIR-absorbing foam *(figure 1)*. More recently, initial designs of an adjustable helmet have been evaluated, which will eventually enable studies to be performed on infants at a range of gestational ages without the need to construct individual helmets.

2.4 Difference imaging

Reliable reconstruction of the *absolute* optical properties requires accurate knowledge of the head shape and the positions of the optodes. This presents a challenging problem when obtaining data from the neonatal head. Our custom built helmets are naturally deformable to ensure the comfort and safety of the infant. Although the positions of the bundles on the helmet are recorded using a 3D digitising arm immediately before or after the clinical measurement, these are not always sufficiently accurate for absolute imaging given the natural displacement during the scan.

This problem can be largely overcome by reconstructing images using *differences* in data resulting from a change in optical properties, analogous to inducing changes in attenuation to quantify haemodynamic variables using NIRS. Difference imaging is achieved either by scanning the infant before and after a change in the cerebral blood volume and/or oxygenation, or by comparing acquired infant data with data obtained from a homogenous "reference" phantom inserted into the helmet immediately following an infant scan.

For initial studies on infants the homogenous reference phantom consisted of a white rubber balloon filled with a scattering fluid. The fluid was made from a mixture of 10% Intralipid^{TM}, water-soluble NIR dye, and distilled water, with overall optical properties similar to neonatal brain tissue. The balloon is attached via plastic tubing to a reservoir containing the scattering fluid, with valves and a 60 ml syringe in the circuit to facilitate filling and emptying of the balloon. Validation of this technique has been performed using appropriate phantom experiments (Yusof *et al* 2003). The disadvantage of this approach is the tendency of the near-spherical balloon not to deform sufficiently to the shape of the helmet when placed within it. As a result, some optical fibre bundles in the helmet sometimes do not make sufficient contact with the surface of the balloon. Recently we have developed an alternative reference phantom based on a thin head-shaped latex shell. The shell is made by

coating the head of a child's doll with a thin layer of liquid latex, and peeling it off when set. A series of shells of different sizes has been generated using an assortment of dolls. A shell is chosen which best matches the size and shape of the infant being studied, and is filled with scattering fluid after being placed in the helmet. The helmet is carefully rotated by 90 degrees for the reference measurement, so that fluid does not escape from the open "neck" of the shell. The weight of the fluid tends to make the shell conform more closely to the helmet shape, proving good contact with all the fibre bundles.

2.5 Clinical Measurements

Scans are performed at the cotside in low ambient light, but not complete darkness. As soon as the infant is lying comfortably in the helmet, a "pre-scan" is performed to find the optimum positions of the detector VOAs for each source position. This is an automated process which involves briefly illuminating each source and finding the VOA positions for every detector which maximises the detected signal without exceeding the maximum allowable count rate. This process currently requires a period of at least 20 minutes. Following completion of the pre-scan, data is acquired by illuminating at each source position sequentially for 10 seconds and detecting light transmitted through the head at all positions simultaneously. It takes approximately 12 minutes to obtain a complete dataset. Depending on the comfort and stability of the infant, two or three scans are performed over a period not usually exceeding one and a half hours.

2.6 Infants studied

To date 24 infants have been studied. The majority of infants recruited were preterm, with a corrected median (range) postmenstrual age of 36 (31-46) weeks. Infants were studied in the period following a feed as this is when they were most likely to be settled. Most of the

infants had a degree of gastroesophageal reflux; to address this, the cot was raised at an angle, although this meant that some infants tended to slip out of the helmets particularly if they moved their head. Ethical permission for the study was obtained from the local ethics committee, and informed consent was obtained from one or both parents of each infant prior to the study.

The first two studies successfully established the feasibility of transferring MONSTIR from the laboratory to the neonatal unit. However, reference measurements were not made and image reconstruction was not attempted. The first successful images were reconstructed of the brain of a 30-week preterm infant with a large unilateral intraventricular haemorrhage (IVH) (Hebden *et al* 2002). This was followed by images obtained on an infant requiring mechanical ventilation (Hebden *et al* 2004). By making appropriate changes to the ventilator settings, difference images could be generated without requiring measurements on a reference phantom. A unique series of dynamic images revealed changes in cerebral blood volume and oxygenation.

In this paper we present results from 14 infants from whom full image data sets were acquired. Their median (range) postmenstrual age was 31 (26-39) weeks, and their median (range) birthweight was 1256 (800-3586)g. Their median (range) age at study was 33 (3-92) days, giving them a median (range) corrected age of 35 (32-46) weeks. Clinical details of these infants are shown in table 1.

An FEM mesh of each infant's head was generated by warping a generic infant head surface mesh to the measured coordinates of the sources and detectors, and then using the new surface to construct a volume mesh (Gibson *et al* 2003b). TOAST performed 20 iterations using the data recorded at each wavelength. Three-dimensional images were reconstructed using differences between the mean flight times measured from the head and the corresponding values for the reference phantom. The use of a single datatype prevents

adequate separation between the absorbing and scattering properties, and therefore we generally present the absorption images only. In most cases, the scatter images exhibit very similar features to the absorption images due to parameter "cross-talk". Using the absorption images, images of rCBV and $rStO_2$ were then reconstructed.

3. Results and Discussion

3.1 Summary of all babies studied

The results from the 24 infants imaged to date can be divided into three groups: those from whom images could not be successfully reconstructed; reconstructed images of the healthy brain; and reconstructed images of pathology.

Eight of the 24 studies performed so far have yielded data sufficient to generate images. Two of the 16 failed attempts were preliminary tests of the clinical acceptability of the system and image reconstruction was not attempted. Eight more involved evaluations of designs for an adjustable helmet. To date, only custom-built helmets have provided acceptable data, largely because of the inability of different designs of the adjustable helmet to conform to the wide range of headshapes found in premature babies. If these technical trials are excluded, 8 of the remaining 14 clinical studies (57% success rate) were successfully reconstructed. The reasons for the failure to acquire adequate data from the remaining six infants include: restlessness or instability of the infant (2), insufficient light across the head (1), and poor contact between the infant head and the helmet fibre bundles, due to poor helmet design (3). Unlike many optical studies, movement was rarely a significant source of error due to the sequential measurement of data. If a baby did move, this tended to only affect data acquired using a single source, which was identified and excluded from the data set used for image reconstruction.

Five of the eight successfully reconstructed images were of anatomically normal infants; the remaining three were from babies with some form of pathology: one of the infants had unilateral IVH on cranial ultrasound, with evidence of the haemorrhage persisting at the time of study and another infant had evidence of a haemorrhagic parenchymal infarct (HPI) associated with the IVH. One term infant had suffered acute hypoxic-ischaemic brain injury at birth and required muscle paralysis, sedation and ventilatory support.

3.2 Images of the normal brain

Figure 2 shows transverse, coronal and sagittal views across the 3D images of each infant head, representing the distribution of absorption at 780nm and 815nm respectively. The sagittal views correspond to the midplane, and the coronal and transverse views are centred on the expected locations of the cerebral ventricles. By making the assumption that the oxygenated and deoxygenated forms of haemoglobin are the only wavelength-dependent chromophores, and by assuming a value for the background absorption, absorption images at both wavelengths can be combined to generate 3D images of rCBV and $rStO_2$ (figure 3).

These results represent the first 3D images of cerebral blood volume and oxygenation from the newborn infant using any technology. There is no 'gold standard' imaging system able to provide absolute quantitative information of these parameters, so validating the images can be difficult.

In the five infants with normal cranial ultrasound scans, the images of absorption appear symmetrical. There appears to be increased absorption in the outer regions compared to the central areas. The images of rCBV are consistent with the absorption images. The images of $rStO_2$ are also symmetrical: $rStO_2$ ranges from 35% at the base of the brain to 85% in the region of the cerebral cortex. This regional heterogeneity is consistent with studies of

regional cerebral perfusion using SPECT, demonstrating the vulnerability of the periventricular white matter to hypoxic-ischaemic injury (Borch *et al* 1998).

The coronal sections of the optical tomography images we have obtained of the neonatal brain exhibit a horizontal band of reduced absorption across the image. This feature is probably due to the direct (i.e. unscattered) migration of light through the CSF within the Sylvian fissures on either side and within the central ventricular system. The path of light across the brain via these CSF-filled regions is illustrated in figure 4. The current inability of TOAST to model non-scattering regions contributes towards this feature. Until more sophisticated reconstruction techniques can be employed (*e.g.* Riley *et al* 2000), this and other possible object-dependent artefacts must be taken into account when attempting to interpret optical tomography images of the newborn infant brain.

3.3 Images of infants with intraventricular haemorrhage

In the two infants with evidence of unilateral haemorrhagic lesions there is asymmetry in the images with increased absorption on the side of the haemorrhage. The images from one of these infants have been published as the first 3D optical tomography images of the whole head (Hebden *et al* 2002). The absorption coefficient in the region of the haemorrhage was 2-3 times greater than the overall absorption in the other areas of the brain. This reflects an increase in regional haemoglobin concentration on the side of the haemorrhage (r[Hb_{tot}]).

The regional tissue saturation image from the first infant studied is dominated by an area of low saturation in the front part of the brain. This is likely to be artefactual and makes interpretation of this image difficult. However, the corresponding image from the other infant is more encouraging (figure 5). The fractional oxygenation image has a distinct area of desaturated haemoglobin on the side of the haemorrhage, although more lateral and superficial than the anatomical location of the haemorrhage. The percentage saturation over

this area is 10%, compared with 62% on the contralateral side. This area of deoxygenated tissue on the side of the haemorrhage is consistent with a resolving blood clot. An ischaemic penumbra surrounding haemorrhagic lesions has been described both in adults and infants (Powers *et al* 1987, Volpe *et al* 1983). Although the current limitations in image reconstruction make it difficult to comment on this observation with regard to the images presented here, optical tomography is the ideal tool to explore this concept further.

3.4 Development of fibre-holding helmets

We believe a limiting factor in the image acquisition and quality is the fibre-holding helmet. We have only been able to reconstruct images from data acquired using custom-built helmets. This is time-consuming and cannot be used if imaging is required urgently. A considerable amount of work has been undertaken to develop an adjustable helmet and although to date we have been unable to reconstruct images we anticipate that this helmet will ultimately provide a practical solution to carry out studies on a range of infants of different gestational ages at a much shorter notice.

3.5 Technical developments

We have shown that it is possible to reconstruct images from clinical data which agree with the known anatomy and physiology. However, the spatial resolution is relatively poor and reconstruction artefacts still occur. We believe the limiting factor in the image reconstruction is currently our lack of accurate knowledge of the shape of the head and the positions of the optodes upon it. Reconstructing images of the difference in optical properties between two states reduces the effect of these uncertainties, but errors remain. We are attempting to reduce these errors by improving both the experimental design and the image reconstruction procedure. A robust adjustable helmet will hold the connectors in fixed

positions which can be measured more accurately than we can at present. We are developing photogrammetric techniques which will allow the headshape and the optode positions to be calculated accurately from multiple photographs. Ultimately, simultaneous optical/MRI imaging will allow the internal and external anatomy to be identified from MRI, allowing the optical data to be used for accurate reconstruction of the blood volume and oxygenation from a region of interest.

We currently model light transport in the head using the diffusion equation (Arridge 1999). For this equation to hold, the scatter coefficient must be much more than the absorption coefficient and scatter must be isotropic. Neither of these requirements are met throughout the head: the CSF has very low scatter, a region of haemorrhage has very high absorption and the white matter in particular is anisotropic. The CSF in particular, is thought to distort light propagation significantly, particularly in preterm infants with post haemorrhagic ventricular dilatation, or isolated ventriculomegaly following white matter injury. Theoretical developments are underway to extend the modelling to include non-diffusive regions (Riley *et al* 2000; Arridge 1999 and Gibson *et al* 2005a).

Finally, a full image currently takes 12 minutes to acquire, approximately half of which is taken up by downloading the data to a computer. We are currently updating the electronics in MONSTIR (Becker *et al* 2005). The new system will not require additional download time, and will allow images to be acquired in as little as 5 minutes, or even less at the expense of decreased signal-to-noise ratio. This will open up the use of MONSTIR to more rapid changes such as functional activity and clearance of contrast agents.

4. Acknowledgements

Support for this work has been generously provided by the Wellcome Trust and the EPSRC.

5. References

Arridge, SR (1999). Optical tomography in medical imaging. Inverse Problems **15**, R41-R93.

Arridge, SR, Hebden, JC, Schweiger, M, Schmidt, FEW, Fry, ME, Hillman, EMC, Dehghani, H, Delpy, DT (2000). A method for 3D time-resolved optical tomography. Int. J. Imag. Sys. Tech. **11,** 2-11.

Becker, W, Bergmann, A, Gibson, AP, Everdell, N, Jennions, D, Schweiger, M, Arridge, SR, Hebden, JC (2005). Multi-dimensional time-correlated single photon counting applied to diffuse optical tomography. *Proc. SPIE* **5693,** p34-42.

Borch, K, Greisen, G (1998). Blood flow distribution in the normal human preterm brain. Pediatric Research **43**, 28-33.

Chance, B, Anday, E, Nioka, S, Zhou, S, Hong, L, Worden, K, Li, C, Murray, T, Ovetsky, Y, Pidikiti, D, Thomas, R (1998). A novel method for fast imaging of brain function, non-invasively, with light. *Opt. Express* **2**, 411-423.

Edwards, AD, Wyatt, JS, Richardson, EC, Delpy, DT, Cope, M, Reynolds, EOR (1988). Cotside measurement of cerebral blood flow in ill newborn infants by near-infrared spectroscopy. *Lancet* **8614**: 701-702.

Gibson, AP, Yusof, RM, Dehghani, H, Riley, J, Everdell, NL, Richards, R, Hebden, JC, Schweiger, M, Arridge, SR, Delpy, DT (2003a). Optical tomography of a realistic neonatal head phantom. Applied Optics **42**, 3109-3116.

Gibson, AP, Riley, J, Schweiger, M, Hebden, JC, Arridge, SR, Delpy, DT (2003b). A method for generating patient-specific finite element meshes for head modelling. Physics in Medicine and Biology **48**, 481-495.

Gibson, AP, Hebden, JC, Arridge, SR (2005a). Recent advances in diffuse optical imaging. Physics in Medicine and Biology **50**, R1-R43.

Gibson, AP, Austin, T, Everdell, NL, Schweiger, M, Arridge, SR, Meek, JH, Wyatt, JS, Delpy, DT, Hebden, JC (2005b). Three-dimensional whole-head optical tomography of passive motor evoked responses in the neonate. Neuroimage (in press).

Hebden, JC, Gibson, A, Yusof, RM, Everdell, N, Hillman, EMC, Delpy, DT, Arridge, SR, Austin, T, Meek, JH, Wyatt, JS (2002). Three-dimensional optical tomography of the premature infant brain. Physics in Medicine and Biology **47**, 4155-4166.

Hebden, JC, Gibson, AP, Austin, T, Yusof, RM, Everdell, NL, Delpy, DT, Arridge, SR, Meek, JH, Wyatt, JS (2004). Imaging changes in blood volume and oxygenation in the newborn infant using three-dimensional optical tomography. Physics in Medicine and Biology **49**, 1117-1130.

Hillman, EMC (2002). Experimental and theoretical investigations of near-infrared tomographic imaging methods and clinical applications. PhD Thesis University of London. *www.medphys.ucl.ac.uk/research/borg/theses.htm*.

Hintz, SR, Cheong, W-F, van Houten, JP, Stevenson, DK, Benaron, DA (1999). Bedside imaging of intracranial haemorrhage in the neonate using light: comparison with ultrasound, computed tomography and magnetic resonance imaging. Pediatric Research **45**, 54-59.

Hintz, SR, Benaron, DA, Siegal, AM, Zourabian, A, Stevenson, DK, Boas, DA (2001). Bedside functional imaging of the premature infant brain during passive motor activation. Journal of Perinatal Medicine **29**, 335-343.

Jobsis, FF (1977). Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science **198**, 1264-1267.

Kusaka, T, Kawada, K, Okubo, K, Nagano, K, Namba, M, Okada, H, Imai, T, Isobe, K, Itoh, S (2004). Noninvasive optical imaging in the visual cortex in young infants. Human Brain Mapping **22**, 122-132.

Marlow, N, Wolke, D, Bracewell, MA, Samara, M (2005). EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. New England Journal of Medicine **352**, 9-19.

Powers, WJ, Press, GA, Grubb, RL, Gado, M, Raichle, ME (1987). The effect of hemodynamically significant carotid artery disease on the hemodynamic status of the cerebral circulation. Annals of Internal Medicine **106**, 27-34.

Riley, J, Dehghani, H, Schweiger, M, Arridge, SR, Ripoll, J, Nieto-Vesperinas, M (2000), 3D optical tomography in the presence of void regions. Optics Express **7** 462-467.

Schmidt, FEW, Fry, ME, Hillman, EMC, Hebden, JC, Delpy, DT (2000). A 32 channel time-resolved instrument for medical optical tomography. Review of Scientific Instruments **71**, 256-265.

Schweiger, M, Arridge, SR, Nissila, I (2005). Gauss–Newton method for image reconstruction in diffuse optical tomography. Physics in Medicine and Biology **50,** 2365-2386.

Taga, G, Asakawa, K, Maki, A, Konishi, Y, Koizumi, H (2003). Brain imaging in awake infants by near-infrared optical topography. Proc. Nat. Acad. Sci. **100**, 10722-10727.

Volpe, JJ, Herscovitch, P, Perlman, JM, Raichie, ME (1983). Positron emission tomography in the newborn: extensive impairment of regional cerebral blood flow with intraventricular haemorrhage and haemorrhagic intracerebral involvement. Pediatrics **72**, 589-601.

Volpe, JJ (1997). Brain injury in the premature infant. Clinics in Perinatology **24**, 567-587.

Volpe, JJ (2001). Neurobiology of periventricular leucomalacia in the premature infant. Pediatric Research **50**, 553-562.

Yoxall, CW, Weindling, AM, Dawani, NH, Peart I (1995). Measurement of cerebral venous oxyhaemoglobin saturation in children by near-infrared spectroscopy and partial jugular venous occlusion. Pediatric Research **1995**, 319-323.

Yusof, RM, Hebden, JC, Gibson, AP, Everdell, NL, Austin, T, Meek, JH, Arridge, SR, Wyatt, JS, Delpy, DT (2003). Validation of the use of homogeneous reference phantoms for optical tomography of the neonatal brain. SPIE Proc **4955**, 6-11.

Figures

Figure 1. Making a customised helmet: a) measuring and photographing the infant head; b) a 3D cardboard representation of the head constructed using photographs printed to scale; c) a helmet constructed from a thermoplastic shell lined with soft NIR-absorbing foam; d) an infant lies in the cot resting on the base of the helmet with the removable top half of the helmet placed gently over the infants forehead.

Figure 2. Transverse, coronal, and sagittal images of absorption coefficient (mm^{-1}) at 780 and 815nm, successfully reconstructed from 5 healthy infants.

Figure 3. Sagittal, coronal, and transverse slices from infant 10 showing (a) regional blood volume and (b) regional oxygen saturation across the brain.

Figure 4. a) A path which light can take across the brain, via the CSF-filled Sylvian fissures and the central ventricular system, with minimal scatter. b) A coronal slice across an optical image which exhibits a characteristic band of low absorption, probably due to light taking this path of minimal scatter.

Figure 5 A coronal section from infant 11 showing (a) regional blood volume, (b) regional oxygen saturation and (c) corresponding cranial ultrasound scan. There is an increase in regional haemoglobin concentration and 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.

Tables

Table 1 Clinical details of infants from whom full image data sets were acquired

Figure

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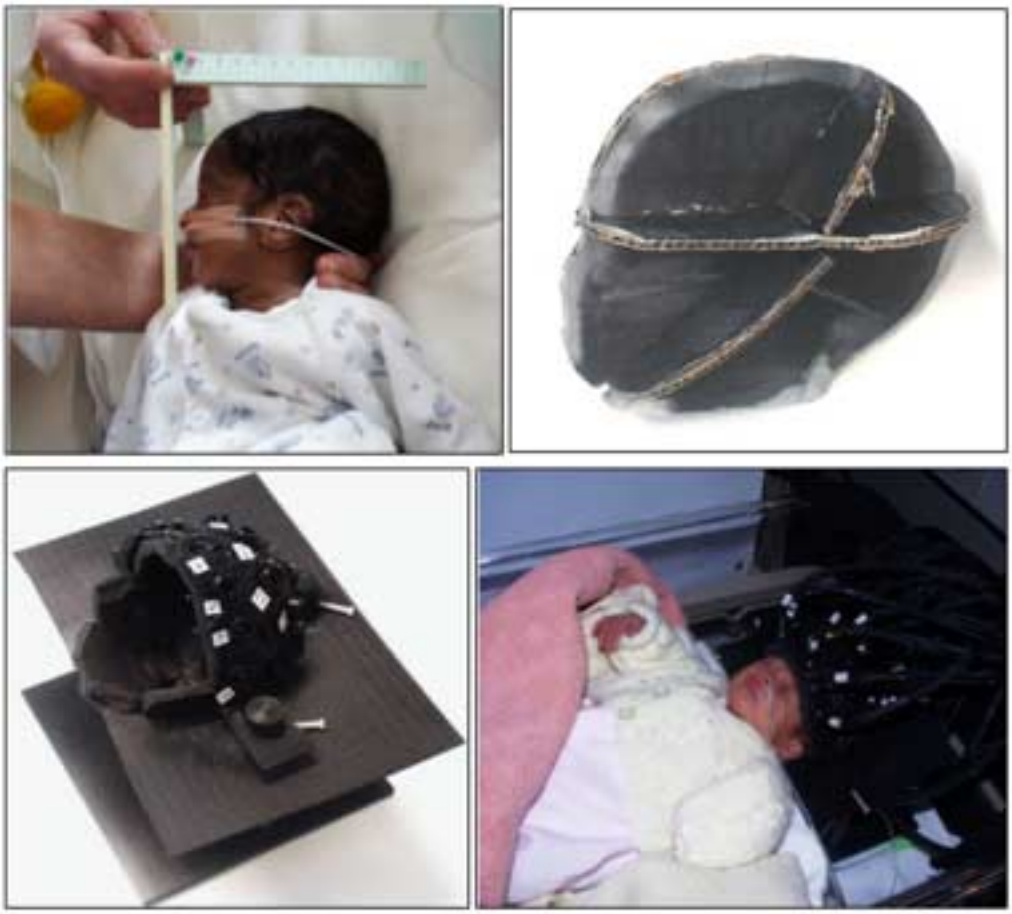

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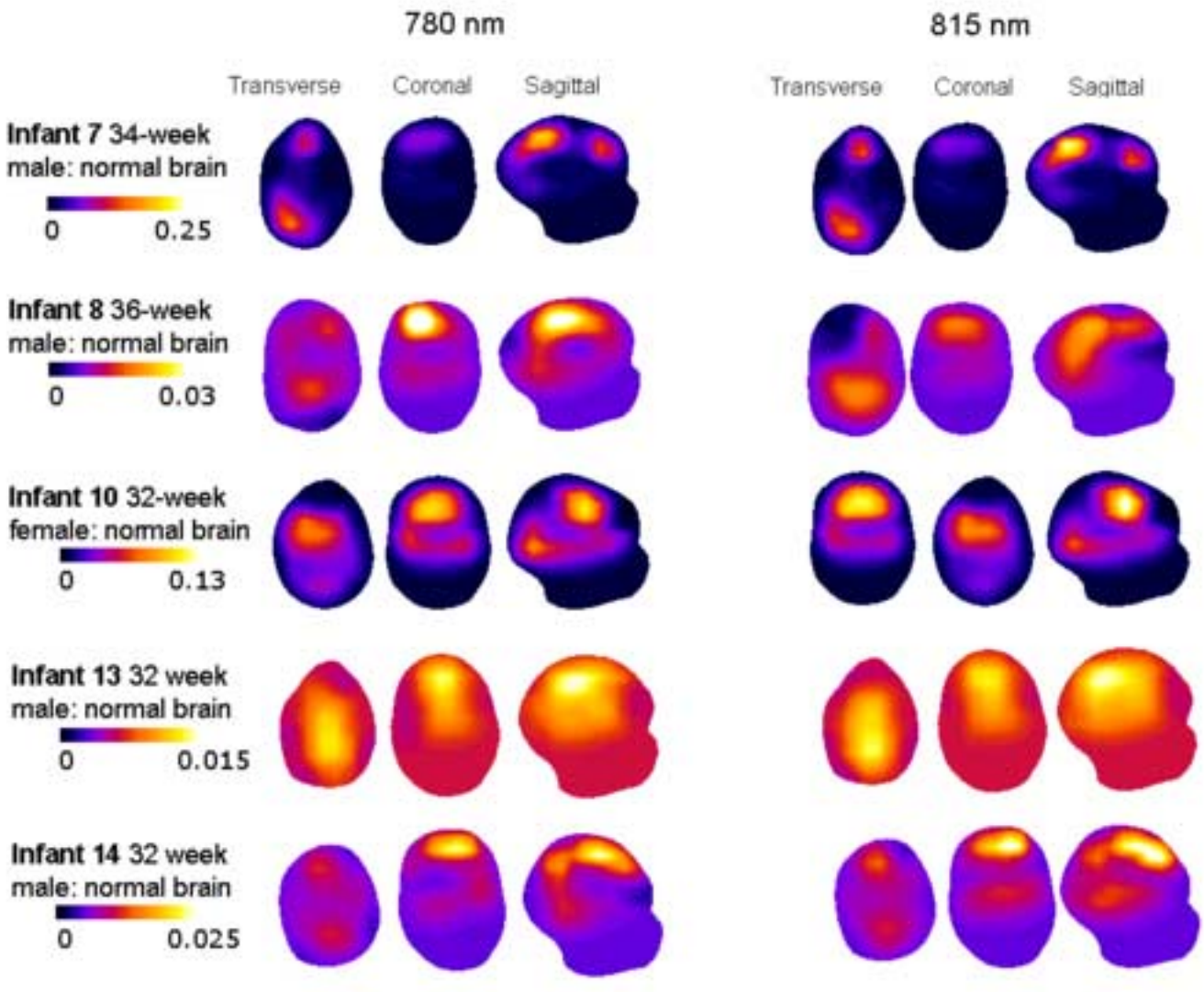

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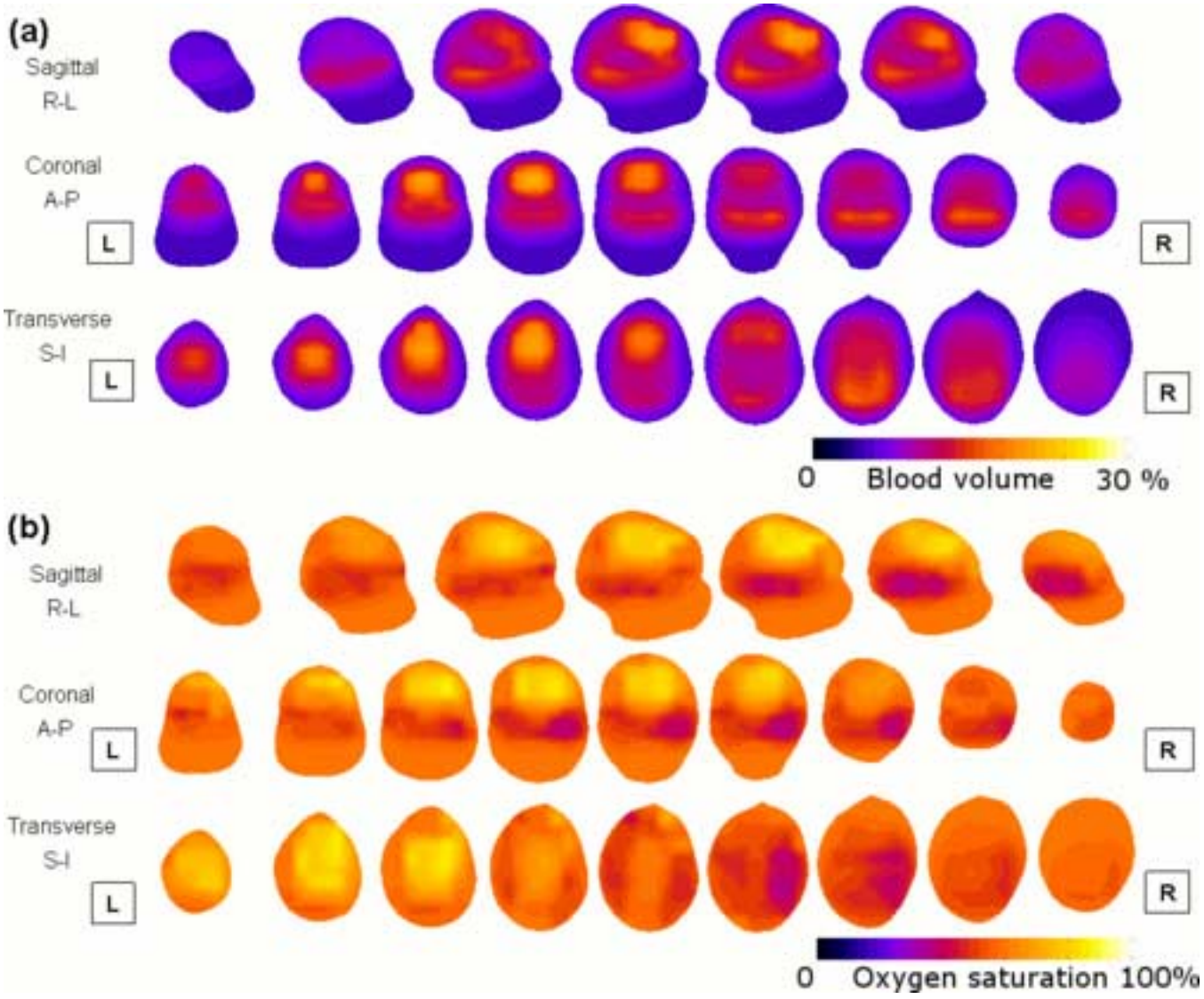

Figure

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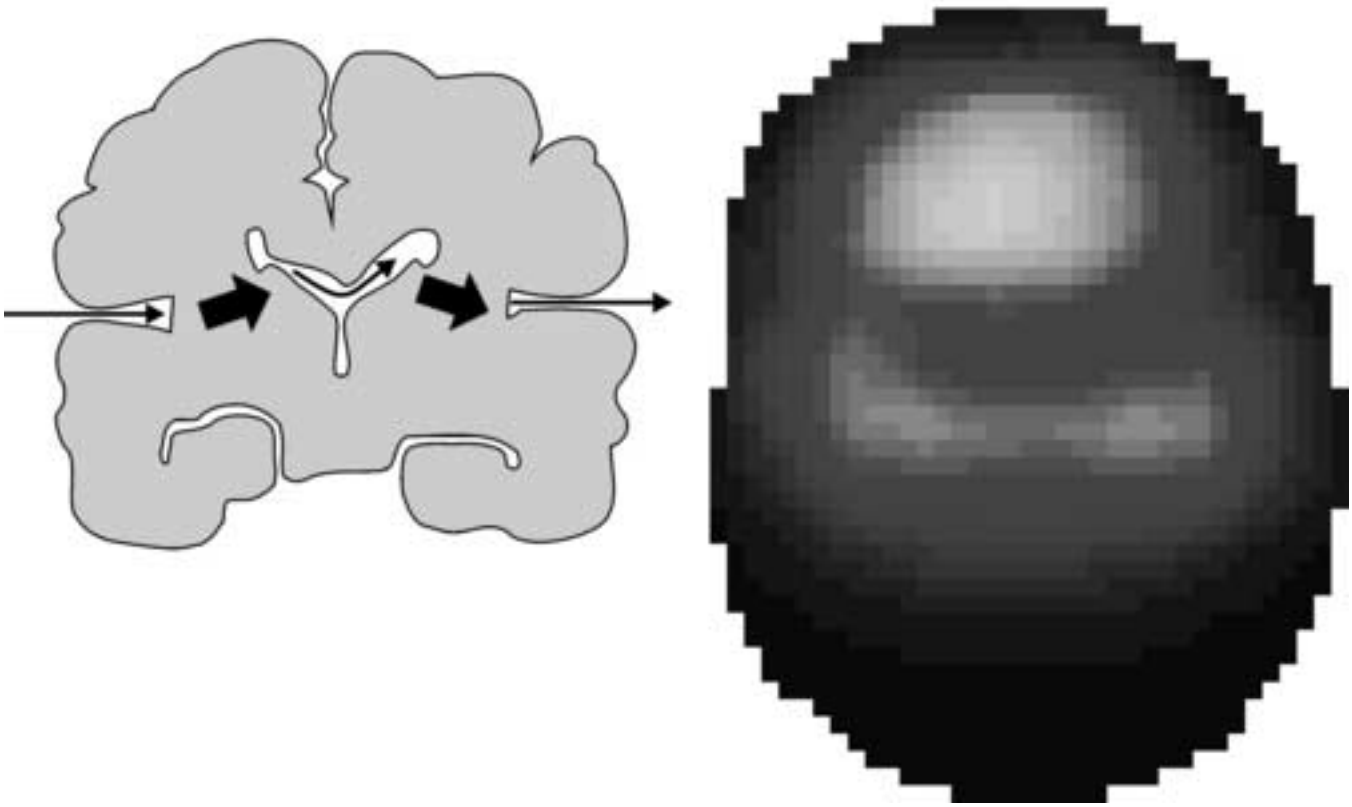

Figure

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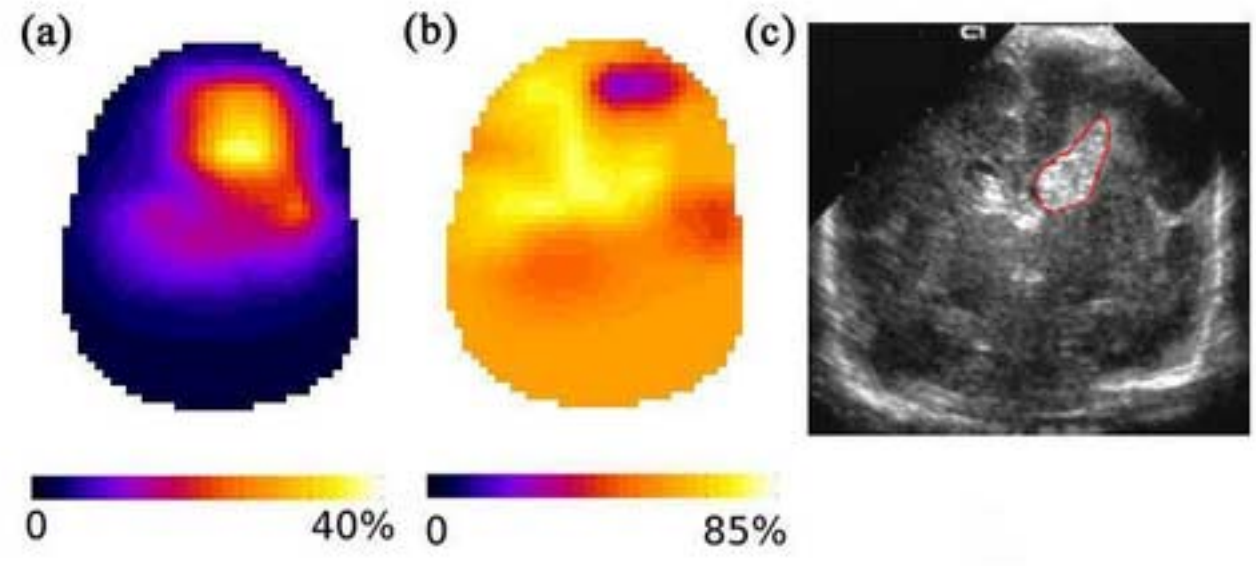

Table 1 Clinical details of infants from whom full image data sets were acquired

Study	Postmenstrual age (weeks)	Age at study (days)	Corrected age (weeks)	Clinical problem	Comments
1	30+0	12	31+5	Preterm Bilateral IVH L>R	IMAGE RECONSTRUCTED (Hebden *et al* 2002)
2	39+0	46	45+4	Healthy term infant	insufficient light across the head
3	37+0	3	37+3	Severe birth asphyxia	VOLUME AND OXYGENATION DIFFERENCE IMAGING (Hebden *et al* 2004)
4	25+5	42	31+5	R HPI	on CPAP: did not tolerate helmet
5	32+6	27	36+5	Preterm	abandoned because of movement
6	28+5	38	34+1	Preterm Bilateral IVH	poor optode contact
7	28+5	40	34+3	Preterm	IMAGE RECONSTRUCTED
8	32+1	28	36+1	Preterm twin, low Hb	IMAGE RECONSTRUCTED
9	32+1	28	36+1	Preterm twin	poor optode contact
10	29+0	39	34+4	Preterm twin 2	IMAGE RECONSTRUCTED
11	29+0	39	34+4	Preterm twin 1, L IVH	IMAGE RECONSTRUCTED
12	26+1	92	39+2	Preterm	poor optode contact
13	32+1	25	35+5	Preterm	IMAGE RECONSTRUCTED
14	32+1	25	35+5	Preterm	IMAGE RECONSTRUCTED

IVH: intraventricular haemorrhage; HPI: haemorrhagic parenchymal infarct; CPAP: continuous positive airway pressure

*** Reviewer Suggestions**

THREE DIMENSIONAL OPTICAL IMAGING OF BLOOD VOLUME AND OXYGENATION IN THE NEONATAL BRAIN

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