Review

Simultaneous quantitative assessment of cerebral physiology using respiratory-calibrated MRI and near-infrared spectroscopy in healthy adults

T. Alderliestena,⁎, J.B. De Visc, P.M.A. Lemmerson, F. van Bela, M.J.N.L. Bendersa, J. Hendrikseb, E.T. Petersenb

a Department of Neonatology, Wilhelmina Children's Hospital/University Medical Center Utrecht, Room KE.04.123.1, P.O. Box 85090, 3508 AB, Utrecht, The Netherlands
b Department of Radiology, University Medical Center Utrecht, Room E.01.132, P.O. Box 85500, 3508 GA, Utrecht, The Netherlands

Abstract

Background: Functional near-infrared spectroscopy (fNIRS) and functional MRI (fMRI) are non-invasive techniques used to relate activity in different brain regions to certain tasks. Respiratory calibration of the blood oxygen level dependent (BOLD) signal, and combined fNIRS–fMRI approaches have been used to quantify physiological subcomponents giving rise to the BOLD signal. A comparison of absolute oxygen metabolism parameters between MRI and NIRS, using spatially resolved (SRS) NIRS and respiratory calibrated MRI, could yield additional insight in the physiology underlying activation.

Materials and methods: Changes in the BOLD signal, cerebral blood flow (CBF), and oxygen saturation (SO2) were derived from a single MRI sequence during a respiratory challenge in healthy volunteers. These changes were compared to SO2 obtained by a single probe SRS NIRS setup. In addition, concentration changes in oxygenated (O2Hb), deoxygenated (HHb), and total haemoglobin (tHb), obtained by NIRS, were compared to the parameters obtained by MRI.

Results: NIRS SO2 correlated with end-tidal CO2 (0.83, p < 0.0001), the BOLD signal (0.82, p < 0.0001), CBF (0.85, p < 0.0001), and also MRI SO2 (0.82, p < 0.0001). The BOLD signal correlated with NIRS HHb (r = −0.76, p < 0.0001), O2Hb (0.41, p = 0.001), and tHb (r = 0.32, p = 0.01).

Conclusions: Good correlations show that changes in cerebral physiology, following a respiratory challenge, go hand in hand with changes in the BOLD signal, CBF, O2Hb, HHb, NIRS SO2, and MRI SO2. Out of all NIRS derived parameters, the SO2 showed the best correlation with the BOLD signal.

© 2013 Elsevier Inc. All rights reserved.

Keywords:
Near-Infrared Spectroscopy
fMRI
fNIRS
Respiratory-calibrated MRI
Adult
Brain
ASL

Contents

Introduction ................................................................. 0
Theory ................................................................... 0
MRI .................................................................. 0
Respiratory calibration of the BOLD signal 0
Total cerebral blood volume 0
Oxygen saturation 0
Near-infrared spectroscopy 0
Modified Lambert-Beer law 0
Spatially resolved spectroscopy 0
Total cerebral blood volume 0
Materials and methods ............................................................ 0
Computerized respiratory challenge 0
MRI 0
Near-infrared spectroscopy 0

Statement of Financial support: This research is supported by the Dutch Technology Foundation STW, applied science division of NOW, the Technology Program of the Ministry of Economic Affairs and ZonMW Electromagnetic Fields and Health program.

⁎ Corresponding author at: Department of Neonatology, University Medical Center Utrecht/Wilhelmina Children’s Hospital, P.O. Box 85090, 3508 AB, Utrecht, The Netherlands.
Fax: +31 88 7555320.
E-mail addresses: talderliesten-2@umcutrecht.nl (T. Alderliesten), jdevis-2@umcutrecht.nl (J.B. De Vis), plemmers@umcutrecht.nl (P.M.A. Lemmers), fvanbel@umcutrecht.nl (F. van Bel), mbenders@umcutrecht.nl (M.J.N.L. Benders), jhendrikse@umcutrecht.nl (J. Hendrikse), epetersen-5@umcutrecht.nl (E.T. Petersen).

1053-8119/5 – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.07.015

Please cite this article as: Alderliesten, T., et al., Simultaneous quantitative assessment of cerebral physiology using respiratory-calibrated MRI and near-infrared spectroscopy in healthy adults, NeuroImage (2013), http://dx.doi.org/10.1016/j.neuroimage.2013.07.015
Introduction

Functional neuroimaging techniques are primarily used in research settings to relate activity in certain brain areas to specific tasks or functions (Heinzel et al., 2012; Koch et al., 2010; Taga et al., 2011). Based on methodology, these techniques can be divided into two groups. Topographic-electroencephalography (EEG) (Michel and Murray, 2012) and magnetoencephalography (MEG) (Cohen, 1968) map electrical activity and changes in local magnetism brought about by changes in electrical activity to brain anatomy, respectively. On the other hand, techniques such as positron emission tomography (PET), functional near-infrared spectroscopy (fNIRS) and functional magnetic resonance imaging (fMRI), rely on visualizing hemodynamic changes related to neuronal activation. fNIRS (Ferrari and Quaresima, 2012) and fMRI (Price, 2012) are of special interest as they do not require the injection of a tracer substance. Both fNIRS and fMRI have their own advantages and disadvantages regarding costs, mobility, spatial and temporal resolution (Cui et al., 2011).

Localized changes in tissue oxidative metabolism, blood volume (CBV), and cerebral blood flow (CBF) (Fox and Raichle, 1986) are responsible for the contrast generated in blood oxygen-level dependent (BOLD) fMRI (Bandettini et al., 1992; Kwong, 1995; Kwong et al., 1992; Ogawa et al., 1990). Calibration of the resting-state BOLD signal can be done by either performing a hypercapnia (Davis et al., 1998; Hoge et al., 1999), or a hyperoxia experiment (Chiarelli et al., 2007b). This calibration allows for the quantification of specific physiological subcomponents of the BOLD response. More recently, combined approaches of hypercapnia and hyperoxia were introduced (Bulte et al., 2012; Gauthier and Hoge, 2013). These approaches enable a more accurate and quantitative assessment of local changes in the cerebral metabolic rate of oxygen (CMRO2).

In contrast to fMRI, NIRS relies on the permeability of biological tissue to near-infrared light (~650–950 nm). Light in this wavelength range is attenuated by different compounds (chromophores), including deoxygenated (HHb) and oxygenated haemoglobin (O2Hb). Therefore, NIRS can be used to estimate changes in HHb and O2Hb concentration (Delpy et al., 1988; Sfareni et al., 1997; Wray et al., 1988). In NIRS, multiple transmitters and receivers (channels) are used to record signal changes arising from different brain regions. Subsequently, the point of origin of these signal changes can be mapped to brain anatomy by using spatial mapping tools (Ferrari and Quaresima, 2012). NIRS can also be used to assess the tissue oxygen saturation (SO2). This can be done by using spatially resolved spectroscopy (SRS), time resolved spectroscopy (TRS), or phase modulation spectroscopy (PMS) (Suzuki et al., 1999; Wolf et al., 2007).

Simultaneous fMRI-NIRS studies have been performed to identify the relation between BOLD signal changes and the hemodynamic response observed by NIRS (Cui et al., 2011; Gagnon et al., 2012; Huppert et al., 2006b; Mehagnoul-Schipper et al., 2002; Steinbrink et al., 2006). This has led to a better understanding of the different physiological parameters contributing to the BOLD response.

A detailed comparison of absolute oxygen metabolism parameters between MRI and NIRS has not yet been performed. The purpose of this study was to compare quantitative data obtained by respiratory calibrated MRI to quantitative data obtained by SRS NIRS.

Theory

MRI

Respiratory calibration of the BOLD signal

The changes in the BOLD signal detected in fMRI depend on localized changes in tissue oxygen content (Bandettini et al., 1992; Boxerman et al., 1995; Kwong et al., 1992). The tissue oxygen content influences HHb and O2Hb concentrations. As HHb is paramagnetic, the HHb concentration influences the transversal relaxation rate $R_2^\alpha$ (Ogawa et al., 1993). Therefore, changes in HHb concentration can be visualized on $T_2^\alpha$-weighted images.

Calibration of the BOLD signal is possible by estimating the theoretical maximal BOLD signal change (M) that would occur during a complete washout of HHb. During a hypercapnia experiment, the CBF is increased by CO2-induced vasodilatation. The increase in CBF causes a washout of HHb and thus a change in the BOLD signal. When this signal change, and the change in CBF are recorded, M can be estimated (Davis et al., 1998). Subsequently, M can be expressed in HHb concentration in relation to cerebral blood volume (CBV) (Hoge et al., 1999). Using both the Grubb power law relationship (Grubb et al., 1974) and Fick's mass conservation principle (Guyton, 1986), the full hypercapnia calibration model can be expressed in terms of BOLD, CMRO2 and CBF:

$$\Delta \text{BOLD} = M \left[ 1 - \left( \frac{\text{CMRO}_2}{\text{CMRO}_{2\alpha}} \right)^{\frac{1}{2}} \left( \frac{\text{CBF}}{\text{CBF}_0} \right)^{\alpha - 1} \right]$$

where $\text{BOLD}_0$, $\text{CMRO}_{2\alpha}$ and $\text{CBF}_0$ represent the values obtained at baseline. The corresponding variables without subscripts represent the values measured during hypercapnia. The $\beta$ is a constant that depends on magnetic field strength, typically set at 1.3 for 3.0 T field strengths (Chiarelli et al., 2007b). The $\alpha$ is the Grubb coefficient, which was set at 0.18 to represent the non-arterial blood volume (Chen and Pike, 2009, 2010). The calibration model can also be expressed in terms of BOLD, CBF and HHb concentrations (Gauthier and Hoge, 2013):

$$\Delta \text{BOLD} = M \left[ 1 - \left( \frac{\text{CBF}}{\text{CBF}_0} \right)^{\alpha} \left( \frac{[\text{HHb}]}{[\text{HHb}_0]} \right)^{\beta} \right].$$

Here $[\text{HHb}]_0$ represents the HHb concentration in the venous compartment. A dual echo pseudocontinuous arterial spin labelling (pCASL) sequence can be used to obtain changes in the BOLD signal and CBF simultaneously (Wong et al., 1997). After estimating $M$ (Eq. (1)), changes in the BOLD signal and CBF can be transformed to changes in [HHb] in the venous compartment by using Eq. (2).
Total cerebral blood volume

The measured changes in CBF can be directly related to changes in tCBV according to the Grubb power law by using the original value of \( \alpha_t = 0.38 \) for the Grubb exponent (Grubb et al., 1974):

\[
\frac{\text{CBV}}{\text{CBV}_0} = \left( \frac{\text{CBF}}{\text{CBF}_0} \right)^\alpha_t.
\]  
(3)

The change in tCBV (in ml/100 g) can be calculated when Eq. (3) is combined with an assumed baseline blood volume fraction of 0.05 (Roland et al., 1987).

Oxygen saturation

Eq. (3) can be used to relate CBF to tCBV and non-arterial CBF (vCBV) by using an \( \alpha_t \) of 0.38 (Grubb et al., 1974) and an \( \alpha_v \) of 0.18 (Chen and Pike, 2010), respectively. In turn, tCBV and vCBV are directly proportional to tHb and total haemoglobin in the non-arterial compartment (tHb), respectively. Changes in blood volume fractions over time can be assessed when baseline arterial (0.2) and non-arterial (0.8) blood volume fractions (Weber et al., 2008) are combined with the estimated values of tCBV and vCBV (Eq. (3)). Assuming that the HHb concentration in the arterial compartment is negligible, total HHb is represented by [HHb]. In Eq. (2), HHb can be related to tHb by using a baseline oxygen extraction fraction (OEF), which was set at 0.4 (Marchal et al., 1992). Calculation of the SO2 is then possible by determining the ratio of O2Hb (1 − HHb) vs. tHb:

\[
\text{SO}_2(\%) = \frac{(1 - \text{vCBV}) + \text{vCBV} 
\times (1 - \text{HHb})}{\text{tHb}}
\]  
(4)

where the term (1 − vCBV) represents the arterial blood volume and vCBV represents the non-arterial blood volume.

Near-infrared spectroscopy

Modified Lambert-Beer law

In NIRS it is assumed that the contribution to total attenuation caused by oxygen independent light losses (static tissue) remains constant over time. Therefore, a change in attenuation, from one point in time to another, is caused by a change in concentration of oxygen dependent chromophores. These concentration changes can be expressed in terms of optical densities (ODs) according to the modified Lambert-Beer law (Delpy et al., 1988):

\[
\Delta c = \frac{\Delta \text{OD}_\lambda}{\varepsilon_\lambda \times L \times B}
\]  
(5)

where \( \Delta c \) represents the change in chromophore concentration, \( \Delta \text{OD}_\lambda \) is change in optical density at a certain wavelength, and \( \varepsilon_\lambda \) is the molecular extinction coefficient of a chromophore at a certain wavelength. The L represents the distance between the light source and the detector, and B is the differential path length factor (DPF). The DPF accounts for the fact that photons travel a longer distance (than L) through tissue due to scatter. As \( \varepsilon_\lambda \), L, and B are known, measured changes in ODs can be converted into concentration changes when one wavelength per observed chromophore is used (Delpy et al., 1988).

Spatially resolved spectroscopy

Scatter of photons becomes homogeneous at sufficiently large distances (>3.0 cm) from a light source (Patterson et al., 1989). Therefore, the contribution to attenuation caused by scatter is equal at multiple (light source vs. detector) distances. Multiple distances can be created by using a single source with multiple detectors, or vice versa. With data from multiple distances it is possible to calculate the relative attenuation coefficients of O2Hb and HHb (Suzuki et al., 1999). When O2Hb is expressed as a ratio of tHb (O2Hb + HHb) the tissue SO2 can be calculated:

\[
\text{SO}_2(\%) = \frac{O_2\text{Hb}}{O_2\text{Hb} + \text{HHb}}
\]  
(6)

The SO2 is an absolute value that represents the weighted average of O2Hb as a ratio of tHb (O2Hb + HHb) in arterial, capillary and venous vessels.

Total cerebral blood volume

Total cerebral haemoglobin is directly proportional to tCBV. Therefore, changes in tHb can be converted to changes in tCBV (Wyatt et al., 1991):

\[
\Delta \text{CBV} = \frac{\Delta t\text{Hb}}{\text{MWHb}} \times \text{MW}_{\text{blood}} \times \text{Dbt} + D_{\text{atm}} + R
\]  
(7)

where \( \Delta \text{CBV} \) is the change in tCBV (ml per 100 g brain tissue), MW_{\text{blood}} is the molecular weight of haemoglobin (64,500 g/mol), [Hb]_{\text{blood}} is the haemoglobin concentration in the blood (in g/dl), Dbt is the density of brain tissue set at 1.05 g per ml (Nelson et al., 1971), and R is the large to small vessel haematocrit ratio set at 0.69 (Lammertsma et al., 1984).

Materials and methods

The experimental protocol was approved by the Institutional Review Board. Informed consent was obtained in 7 (3 female, 4 male) healthy, non-smoking volunteers. Volunteers were instructed not to drink any caffeine containing substances, and not to perform heavy exercise before the experiment (Chen and Parrish, 2009). MR imaging and NIRS were performed simultaneously during a respiratory challenge.

Computerized respiratory challenge

A computerized end-tidal gas targeting system (RespirAct™, Thornhill Research Inc., Toronto, Canada) was used to supply varying gas concentrations to the subject’s mask via a single tube system (Sillesare et al., 2007). To ensure an airtight seal, transparent medical dressings (Tegaderm; 3M, St Paul, MN) were used to fixate the mask over the subject’s nose and mouth.

Before each experiment, the RespirAct™ was calibrated using a calibration gas (9.01/90.99% CO2/N2). Subsequently, gas concentrations of the four connected gases (gas A: 21% O2/79% N2, gas B: 100% O2, gas C: 10% O2/90% N2, and gas D: 20% CO2, 10% O2/70% N2) were validated. Tidal CO2 and O2 partial pressures were continuously sampled and recorded by the RespirAct™. This enabled the automatic identification of respiratory rate, end-tidal CO2 (P_{ETCO2}), and end-tidal O2 (P_{ETO2}). Baseline parameters (i.e. P_{ETCO2}, P_{ETO2}, respiratory rate, and gas breathing volume) of each individual were recorded before the experiment. These parameters were used to tailor the settings of the RespirAct™. Thereafter, the P_{ETCO2} was targeted at 50 mm Hg for 2 min to let the subjects get accustomed to hypercapnic breathing.

The actual respiratory paradigm started with a 180 s baseline period (Fig. 1). The paradigm contained two hypercapnic segments where P_{ETCO2} was gradually ramped up from the individual’s baseline to 50 mm Hg in 75 s, and then maintained at 50 mm Hg for 105 s. The hypercapnic segments were separated by a 330 s baseline period.
The paradigm ended with a 240 s baseline. The total duration of the respiratory challenge was 18 min 30 s.

**MRI**

MR imaging was performed using a 3.0 T Phillips scanner (Phillips Achieva, Phillips, Best, The Netherlands) with a 8-channel head coil. The MR imaging protocol contained a T1-weighted magnetization prepared rapid acquisition echo (MP-RAGE), a T2-weighted fluid attenuation inversion recovery (T2-FLAIR), a 2D phase contrast magnetic resonance angiography (PC-MRA), and a respiratory-calibrated dual echo pCASL sequence (Bulte et al., 2012). All sequences, except for the dual echo pCASL sequence, were performed during regular breathing.

A multislice dual-echo gradient-echo pCASL sequence was used with an echo-planar imaging (EPI) readout. Scan parameters were: EPI factor = 35, matrix = 80 × 80, FOV = 240 × 240 mm, TR/TE1/TE2: 4000/13.79/36.25 ms, and a 90° EPI readout flip angle. Eleven axial slices were prescribed, with a 7 mm slice thickness and a 1 mm slice gap (3 × 3 × 7 mm³ voxel). A labelling duration of 1650 ms was used with a post label delay of 1550 ms. To ensure optimal label efficiency, the labelling slab was positioned perpendicular to the internal carotid and vertebral arteries using a sagittal PC-MRA image as a reference. A total of 135 dynamics, equivalent to 18:15 (mm:ss) scan time, were performed. The sequence was started 15 s after the start of the respiratory paradigm. The MPRAGE and T2-FLAIR sequences were used for anatomical reference.

**Near-infrared spectroscopy**

An Oxymon Mk III continuous wave NIRS system (Artinis Medical Systems, Zetten, The Netherlands) was used to determine SO₂ (in %), and also absolute changes in O₂Hb, HHb and tHb (O₂Hb + HHb) concentration (in μM). This system uses three laser sources, each combining two wavelengths (i.e. 764 nm, and 857 nm), and a single receiver. The average inter-optode distance was 40 mm, with a source separation of 4 mm (δρ).

A fibre optic MR compatible probe with 10 m fibres was positioned on the right side of the subject’s forehead. The probe was carefully positioned to avoid contact with hair, and to avoid the measurement of cerebral venous sinuses. The probe position approximately corresponded to the Fp2 and F8 positions according to the international 10–20 EEG system (Fig. 2). The probe position was marked with a vitamin E capsule that was visible on MRI. The NIRS device was calibrated before each experiment to assure equal signal quality between experiments. The DPF was varied according to age (Duncan et al., 1996). NIRS data was obtained continuously during all MRI sequences.

**Data analysis**

All MR data was analysed using IDL 6.1 for Windows (ITT Visual Information Solutions, Boulder, CO, U.S.A.). The paired labelled and non-labelled ASL images were surround subtracted to produce ASL subtraction (ΔM) images (Liu and Wong, 2005; Wong et al., 1997). Perfusion was quantified on the ΔM images using the following assumptions: a longitudinal relaxation time of tissue of 1.5 s, a longitudinal relaxation time of blood of 1.6 s, and an average water partition coefficient between blood and grey-white matter (λ) of 0.91. The average labelling efficiency was set at 0.90. The fully relaxed magnetization of arterial blood (Mob) was estimated from the data. BOLD signal changes were simultaneously acquired from the second TE. Drift of the BOLD signal was removed by a quadratic fit to the baseline points.

Fig. 2. Four MR slices obtained with the pCASL sequence in a representative subject. Top row: raw EPI data during baseline, middle row: CBF (in ml/100 g/min) map at baseline and bottom row: CBF map at hypercapnia. Representative ROIs and a schematic representation of the NIRS optodes (second and third image from the left) are shown on the raw EPI images.

Please cite this article as: Alderliesten, T., et al., Simultaneous quantitative assessment of cerebral physiology using respiratory-calibrated MRI and near-infrared spectroscopy in..., NeuroImage (2013), http://dx.doi.org/10.1016/j.neuroimage.2013.07.015
Changes in CBF (ΔCBF) and the BOLD signal (ΔBOLD), from baseline to hypercapnia, were used to estimate $M$ (Eq. (1)). To increase the signal to noise ratio (SNR), and to ensure more reliable estimation of $M$, data from both hypercapnic episodes were used (Chiarelli et al., 2007a). After the estimation of $M$, the HHb concentration could be calculated (Eq. (2)). A temporal SO2 was generated (Eq. (4)) by combining a baseline OEF (0.4) with vCBV and tCBV estimates (Eq. (3)). Table 1 lists the standard physiological parameters that were used to calculate MR and NIRS derived parameters. An error analysis was performed to calculate the minimum and maximum possible values of these derived parameters. To do so, standard physiological parameters were allowed to vary in a pre-specified physiological range based on the literature (Table 1).

For comparison with NIRS data, regions of interest (ROIs) were manually drawn by one observer (MRmicro version 1.4, www.mricro.com). The vitamin E capsule was identified on the MR images and subsequently used as a reference for drawing the ROIs. In order to obtain sufficient SNR, data from four ROIs placed on the 4 slices surrounding the NIRS optode were averaged (Fig. 2). For NIRS, the absolute concentration changes in $O_2$Hb and HHb recorded from the three different inter-optode distances (channels) were averaged.

At the time of the first pCASL dynamic, an event was inserted simultaneously on the NIRS device and the RespirAct™ to temporally align NIRS, RespirAct™, and MRI data.

Absolute values and normalised values (normalised to an assumed change of 10 mm Hg $P_{T_{CO2}}$) were calculated in order to facilitate comparison between subjects. Values of all subjects were grouped and are displayed as a group mean with error bars.

### Results

The subjects had a mean age of 28 years (range 25–33). Data of both hypercapnic episodes were used in all 7 subjects. Fig. 2 displays ASL images of a representative subject. Fig. 3 displays the group average of the actual measured data during the respiratory challenge both for MRI and NIRS. Fig. 4 presents the $\Delta SO_2$ and $\Delta$CBV estimates. Table 2 lists the absolute values (per subject) of all measured parameters obtained during normocapnia (NC) and hypercapnia (HC), as well as the absolute difference (NC−HC) and the values standardized to an increase in $P_{T_{CO2}}$ of 10 mm Hg (CP10). Table 3 presents all calculated values for the individual subjects. Mean increase in SO2, normalised per 10 mm Hg CO2 change, was 3.8% (p < 0.001) for NIRS and 11.3% for MRI (p < 0.001). Mean change in CBF and BOLD signal were 12.2 ml/100 g/min (p < 0.001) and 3.2% (p < 0.001) per 10 mm Hg CO2, respectively. Temporally, the onset of the increase in tCBV coincided between both methods. The return to baseline was delayed in NIRS, as compared to MRI. The mean change in tCBV was higher in MRI (0.36 ml/100 g vs. 0.12 ml/100 g).

The BOLD signal correlated with changes in HHb (r = −0.76, p < 0.0001), $O_2$Hb (r = 0.41, p = 0.001), and HHb (r = 0.32, p = 0.01) concentrations. NIRS SO2 correlated with the BOLD signal (r = 0.82, p < 0.0001), CBF (r = 0.85, p < 0.001), and MRI SO2 (r = 0.82, p < 0.0001), $P_{T_{CO2}}$ correlated with NIRS SO2 (r = 0.83, p < 0.0001), BOLD (r = 0.97, p < 0.0001), and CBF (r = 0.85, p < 0.0001).

Table 4 presents the results of the error analysis. By varying the standard physiological parameters, the MRI-based $\Delta SO_2$ ranged from 5.9 to 14.6% per 10 mm Hg CO2. The minimum and maximum values of $\Delta$CBV obtained by MRI were 0.16 and 1.30 ml per 100 g, respectively. The possible range of $\Delta$CBV obtained by NIRS was 0.07 to 0.20 ml per 100 g.

![Fig. 3. Group average with error bars of induced changes in $P_{T_{CO2}}$, data obtained with MRI, and data obtained with NIRS.](image-url)
NC-HC = Change from normocapnia to hypercapnia. 
NC = Normocapnia, HC = Hypercapnia.

During a respiratory challenge, the CO₂ concentration in the breathing air can be increased. A higher CO₂ concentration increases CBF across all brain regions while CMRO₂ remains relatively stable (Chen and Pike, 2010; Tachtsidis et al., 2006). In contrast, during functional activation there is a relative overshoot of CBF, as compared to the subject’s individual baseline.

In addition, more conventional signal changes were compared between the two modalities (e.g. ΔBOLD vs. ΔHHb).

A higher CO₂ concentration increases CBF across all brain regions while CMRO₂ remains relatively stable (Chen and Pike, 2010; Tachtsidis et al., 2006). In contrast, during functional activation there is a relative overshoot of CBF, as compared to the increase in CMRO₂. Moreover, the changes in cerebral physiology following functional activation are spatially restricted to the regions of activation. Despite these differences, the two approaches have in common an increase in CBF, as compared to CMRO₂. This makes the manner of generating a BOLD signal change rather comparable between the two.

In fNIRS experiments, spatial mapping tools are essential to pinpoint the origin of the changes in cerebral physiology (Ferrari and Quaresima, 2012; Sassaroli et al., 2006). In this study, a respiratory challenge with hypercapnia was used to eliminate the need for spatial mapping tools. In addition, only a single SRS NIRS probe was used.

Good spatial and temporal agreements have been found in qualitative comparisons between fMRI and fNIRS (Cui et al., 2011; Gagnon et al., 2012; Huppert et al., 2006a; Kleinschmidt et al., 1996; Mehagnoul-Schipper et al., 2002; Okamoto et al., 2004; Sasai et al., 2012; Strangman et al., 2002; Toronov et al., 2001; Yamamoto and Kato, 2002).

Out of the three haemoglobin species that were measured (i.e. HHb, O₂Hb, THb), HHb had the best correlation with the BOLD signal. This has also been found by several others (Boas et al., 2003; Kleinschmidt et al., 1996; Toronov et al., 2001; Yamamoto and Kato, 2002). Conversely, the BOLD signal has been shown to have the best correlation with O₂Hb (Strangman et al., 2002) while others (Okamoto et al., 2004) found no distinct difference between the haemoglobin species. Interestingly, we initially observed a small change in O₂Hb and THb concentrations at the onset of the rise in PETCO₂. This change was followed by an accelerated and more prolonged rise in O₂Hb and THb concentrations.

The average amplitude of the ΔtCBV estimated by NIRS was half that of ΔtCBV estimated by MRI. The onset of the rise in tCBV was comparable between the two modalities. However, the return to baseline of NIRS tCBV was delayed.

The baseline and the temporal alignment of the SO₂ were found to be comparable between NIRS and MRI. Nevertheless, the average amplitude of the ΔSO₂ estimated by MRI was almost 3 times higher. An excellent correlation was found between NIRS SO₂ and CBF measured by MRI. In fact, out of all parameters measured by NIRS (i.e. SO₂, HHb, O₂Hb, THb), the SO₂ was found to correlate the best both with the BOLD signal and CBF. Therefore, the use of NIRS SO₂ as a biomarker for changes in cerebral hemodynamics seems justified. It should be realised that this SO₂ is calculated from a combination of arteries, veins, and capillaries. As a consequence, changes both in the oxygen supply (i.e. arterial saturation, and CBF), and the oxygen demand (i.e. CMRO₂) can result in an altered SO₂.

Before final interpretation of the results can be done, several aspects regarding the used techniques and the applied models need to be discussed.

**Calibration of the BOLD signal**

The Davis model (Davis et al., 1998) was the first model to use hypercapnia for the calibration of the BOLD signal. This model relies on three main assumptions. Firstly, that only extravascular BOLD effects contribute to the BOLD signal changes. Secondly, that signal changes are brought about by changes in venous oxygenation, and venous CBV (Boxerman et al., 1995). Finally, that CBF will rise while CMRO₂ remains stable (Chen and Pike, 2010; Tachtsidis et al., 2006). It has been shown that more refined models (Gauthier et al., 2011; Griffeth and Buxton, 2011) can increase accuracy. Moreover, recent

**Table 2**

<table>
<thead>
<tr>
<th>Subject</th>
<th>( P_{\text{\text{HCO}_3}} ) [mm Hg]</th>
<th>CBF [ml/100 g/min]</th>
<th>( \Delta \text{BOLD}/\text{BOLD}_0 ) [%]</th>
<th>NIRS SO₂ [%]</th>
<th>NIRS HHb [μmol]</th>
<th>NIRS O₂Hb [μmol]</th>
<th>NIRS THb [μmol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (F, 30)</td>
<td>35.8/45.7</td>
<td>50.4/51.7/1.3</td>
<td>3.5/3.5</td>
<td>69.3/73.6/4.3</td>
<td>-0.71/−0.75</td>
<td>3.57/3.64</td>
<td>2.86/2.89</td>
</tr>
<tr>
<td>2 (F, 33)</td>
<td>36.7/47.6</td>
<td>40.4/43.2/2.2</td>
<td>6.0/5.7</td>
<td>63.5/67.5/3.7</td>
<td>0.12/−1.12</td>
<td>5.2/4.82</td>
<td>4.00/3.70</td>
</tr>
<tr>
<td>3 (M, 27)</td>
<td>46.9/51.8</td>
<td>49.7/55.7/1.2</td>
<td>0.0/2.0</td>
<td>69.1/71.4/4.9</td>
<td>0.24/−0.51</td>
<td>1.1/2.2</td>
<td>0.88/1.96</td>
</tr>
<tr>
<td>4 (M, 28)</td>
<td>37.6/47.4</td>
<td>41.9/46.8/4.9</td>
<td>1.9/2.1</td>
<td>65.2/68.9/4.7</td>
<td>0.09/−0.07</td>
<td>2.98/3.02</td>
<td>2.89/2.95</td>
</tr>
<tr>
<td>5 (M, 26)</td>
<td>43.0/48.3</td>
<td>42.9/54.0/2.1</td>
<td>2.1/4.2</td>
<td>76.9/78.3/5.5</td>
<td>0.36/−0.69</td>
<td>1.1/2.03</td>
<td>0.73/1.34</td>
</tr>
<tr>
<td>6 (M, 25)</td>
<td>40.4/47.5</td>
<td>30.8/35.4/6.6</td>
<td>1.4/1.9</td>
<td>68.9/70.1/1.7</td>
<td>0.41/−0.57</td>
<td>0.31/0.34</td>
<td>0.71/0.92</td>
</tr>
<tr>
<td>7 (F, 26)</td>
<td>36.5/46.2</td>
<td>54.2/90.1/36.9</td>
<td>2.7/2.8</td>
<td>64.6/68.6/4.1</td>
<td>0.18/−0.17</td>
<td>3.29/3.38</td>
<td>3.11/3.22</td>
</tr>
<tr>
<td>Total: Mean (SD)</td>
<td>39.6 (4.1)/47.8</td>
<td>44.4 (7.8)/53.9</td>
<td>2.7 (1.7)/3.2</td>
<td>68.2 (4.5)/71.4</td>
<td>-0.34 (0.51)/−0.39</td>
<td>2.51 (1.71)/2.82</td>
<td>2.17 (1.36)/2.43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th>( C_{\text{\text{HCO}_3}} ) [μmol]</th>
<th>( C_{\text{\text{HCO}_3}} ) [μmol]</th>
<th>( C_{\text{\text{HCO}_3}} ) [μmol]</th>
<th>( C_{\text{\text{HCO}_3}} ) [μmol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (F, 30)</td>
<td>0.17</td>
<td>3.29/3.38</td>
<td>3.11/3.22</td>
<td>2.51/2.82</td>
</tr>
<tr>
<td>2 (F, 33)</td>
<td>0.69</td>
<td>1.11/2.47</td>
<td>0.73/1.96</td>
<td>0.88/1.96</td>
</tr>
<tr>
<td>3 (M, 27)</td>
<td>0.07</td>
<td>2.98/3.02</td>
<td>0.73/1.96</td>
<td>0.88/1.96</td>
</tr>
<tr>
<td>4 (M, 28)</td>
<td>1.12</td>
<td>2.98/3.02</td>
<td>0.73/1.96</td>
<td>0.88/1.96</td>
</tr>
<tr>
<td>5 (M, 26)</td>
<td>1.11</td>
<td>2.98/3.02</td>
<td>0.73/1.96</td>
<td>0.88/1.96</td>
</tr>
<tr>
<td>6 (M, 25)</td>
<td>1.11</td>
<td>2.98/3.02</td>
<td>0.73/1.96</td>
<td>0.88/1.96</td>
</tr>
<tr>
<td>7 (F, 26)</td>
<td>1.11</td>
<td>2.98/3.02</td>
<td>0.73/1.96</td>
<td>0.88/1.96</td>
</tr>
<tr>
<td>Total: Mean (SD)</td>
<td>1.11</td>
<td>2.98/3.02</td>
<td>0.73/1.96</td>
<td>0.88/1.96</td>
</tr>
</tbody>
</table>

NC = Normocapnia, HC = Hypercapnia.
NC-NC = Change from normocapnia to hypercapnia.
CP10 = change per 10 mm Hg \( P_{\text{\text{HCO}_3}} \) increase.

Please cite this article as: Alderliesten, T., et al., Simultaneous quantitative assessment of cerebral physiology using respiratory-calibrated MRI and near-infrared spectroscopy in..., NeuroImage (2013), http://dx.doi.org/10.1016/j.neuroimage.2013.07.015
work suggests that CMRO₂ decreases during hypercapnia (Xu et al., 2011). Although, the Davis model might be an oversimplification of physiology, it has been shown to be a reasonable approximation of more complex models (Griffeth and Buxton, 2011). The Davis model has also been reported to be relatively insensitive to fluctuations in common physiological parameters (Bulte et al., 2012). Recently, the use of calibrated BOLD methods in fMRI has been discussed in great detail (Blockley et al., 2012).

**Estimation of the M parameter and region of interest**

The outcome of neurovascular coupling studies can be predicted based on the value of the calibration parameter M (Chiarelli et al., 2007a). Accuracy of the estimation of M can be improved by using multiple hypercapnia segments, increasing the ΔCBF change, or by combining hypercapnia with hypoxia in one experiment (Bulte et al., 2012; Gauthier and Hoge, 2013). We found a mean value of M of 10.9%, which is in the upper range of earlier reported values (Bulte et al., 2012; Gauthier et al., 2011; Leontiev and Buxton, 2007; Lin et al., 2008). Remarkably, the M values of subjects 1, 2, and 4 were high (i.e. 15.5%, 22.8%, and 11.7%). These three subjects also showed the lowest increase in CBF in response to hypercapnia (i.e. 1.3, 2.2, and 4.9 ml/100 g/min per 10 mm Hg P_{ETCO₂} increase).

As a consequence of low perfusion in white matter, ASL has a low sensitivity for detecting perfusion changes within the white matter. A partial-volume effect of white matter or CSF in the ROI could have resulted in an underestimation of CBF. An underestimation would subsequently lead to an overestimation of M (Eq. (1)). Another factor could be a relatively large contribution of veins in the ROI. Reviewing data on the ROI selection, and pCASL data quality did not reveal any different distinctions between subjects. As such, these two factors can probably not explain the marked difference between the subjects. Nevertheless, we cannot exclude these factors from biasing the overall estimation of M. Due to the global effect of hypercapnia during the respiratory challenge, we do not expect that averaging of 4 ROIs (slices) per subject was a major source of bias.

**Spatial resolution, extra-cerebral contamination, and optical fibres**

The spatial resolution of NIRS is in the order of 1–3 cm (Boas et al., 2004), while the spatial resolution of (functional) MRI scanners nowadays is around 1–2 mm. This difference in spatial resolution is mostly a concern when functional data is compared between the two modalities.

However, an aspect that should not be overlooked is the difference in vascular sensitivity between the two. As stated before, the BOLD signal arises both from extra- and intra-vascular compartments. Furthermore, it originates largely from tissue surrounding larger venous structures (Boxerman et al., 1995; Detre and Wang, 2002; Hoogenraad et al., 2001). In contrast, NIRS is susceptible to all vascular compartments (i.e. arterial, capillary, and venous), with a decreased sensitivity to vessels with a diameter above 1 mm (Liu et al., 1995). The difference in vascular sensitivity is likely to contribute to the observed differences between the two modalities, both in amplitude and temporal alignment. In addition, the NIRS signal is obtained from all tissue layers underneath the probe. This makes NIRS prone to contamination by signals originating from extra-cerebral tissue, e.g. the pial vessels. It has been shown that Hb and O₂Hb are less affected by pial vein contribution than Hb (Gagnon et al., 2012). Surprisingly, we found the best correlation between Hb and the BOLD signal.

Another possible source of bias is the penetration depth of near-infrared light, which is approximately ½ the inter-optode distance (Boas et al., 2004). With an inter-optode distance of 40 mm, considering the thickness of the scalp and skull, the sensitivity of NIRS is limited to the most superficial regions of the brain. Variations in skull thickness, scalp thickness, and inter-optode distance could thereby influence the amount of cerebral tissue that is measured, as compared to that of extra-cerebral tissue (Boas et al., 2004; Cui et al., 2011). Interestingly, stronger correlations were found between the BOLD signal and the haemoglobin species when only data of the largest inter-optode distance was used, as compared to the average of the three inter-optode distances that is reported here (data not shown).

It has been suggested that optical fibres longer than 10 m give a lower SNR due to higher signal attenuation (Duan et al., 2012). During calibration of the NIRS device, we found no difference in SNR between 3 m and 10 m fibres.

**Table 3**

Estimated parameters.

<table>
<thead>
<tr>
<th>Subject</th>
<th>M [%]</th>
<th>MRI ΔO₂sat [%]</th>
<th>NIRS ΔO₂sat [%]</th>
<th>MRI ΔCBV [ml/100 g]</th>
<th>NIRS ΔCBV [ml/100 g]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC-HC</td>
<td>1</td>
<td>15.5</td>
<td>63.6/74.5/7.0</td>
<td>0.19/0.24</td>
<td>0.15/0.15</td>
</tr>
<tr>
<td>NC/HC/CP10</td>
<td>2</td>
<td>22.8</td>
<td>63.5/75.6/7.5</td>
<td>0.27/0.23</td>
<td>0.19/0.18</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>4.5</td>
<td>69.4/74.6/10.7</td>
<td>0.20/0.40</td>
<td>0.03/0.08</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>11.7</td>
<td>68.0/73.5/5.4</td>
<td>0.32/0.33</td>
<td>0.14/0.14</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>6.0</td>
<td>68.5/79.3/8.5</td>
<td>0.57/1.09</td>
<td>0.04/0.07</td>
</tr>
<tr>
<td>6</td>
<td>5.2</td>
<td>5.8</td>
<td>68.2/75.9/10.8</td>
<td>0.32/0.47</td>
<td>0.03/0.03</td>
</tr>
<tr>
<td>7</td>
<td>3.0</td>
<td>0</td>
<td>69.0/85.4/16.9</td>
<td>1.12/1.17</td>
<td>0.16/0.16</td>
</tr>
<tr>
<td>mean (SD)</td>
<td>7.0</td>
<td>(4.2)/11.3/5.5</td>
<td>71.4/8.3/3.8/0.56/0.12/0.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4**

Error analysis.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MRI ΔO₂sat [ %]</th>
<th>MRI ΔCBV [ml/100 g]</th>
<th>NIRS ΔCBV [ml/100 g]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum within search range</td>
<td>α = 0.18</td>
<td>5.9</td>
<td>α = 0.28</td>
</tr>
<tr>
<td></td>
<td>α = 0.28</td>
<td></td>
<td>V₀ = 0.02</td>
</tr>
<tr>
<td></td>
<td>α = 0.3</td>
<td></td>
<td>OEF = 0.25</td>
</tr>
<tr>
<td></td>
<td>OEF = 0.25</td>
<td></td>
<td>11.3</td>
</tr>
<tr>
<td>Reported</td>
<td>α = 0.18</td>
<td></td>
<td>V₀ = 0.05</td>
</tr>
<tr>
<td></td>
<td>α = 0.38</td>
<td></td>
<td>R = 0.69</td>
</tr>
<tr>
<td></td>
<td>α = 0.2</td>
<td></td>
<td>OEF = 0.4</td>
</tr>
<tr>
<td></td>
<td>OEF = 0.4</td>
<td></td>
<td>Maximum within search range</td>
</tr>
<tr>
<td></td>
<td>α = 0.38</td>
<td></td>
<td>V₀ = 0.07</td>
</tr>
<tr>
<td></td>
<td>α = 0.1</td>
<td></td>
<td>OEF = 0.45</td>
</tr>
</tbody>
</table>

CP10 = change per 10 mm Hg P_{ETCO₂} increase.

Please cite this article as: Alderliesten, T., et al., Simultaneous quantitative assessment of cerebral physiology using respiratory-calibrated MRI and near-infrared spectroscopy in..., NeuroImage (2013), http://dx.doi.org/10.1016/j.neuroimage.2013.07.015
Baseline assumptions on standard physiology

The importance of the baseline assumptions is stressed by the results of the error analysis (Table 4). By varying these baseline assumptions, MRI SO₂ could be closely matched to NIRS SO₂. This was also seen for the two tCBV estimates. However, instead of finding the optimal agreement between the two methods, we chose to use values on standard physiology that have been reported in similar literature on calibrated BOLD (Bulte et al., 2012; Griffeth and Buxton, 2011).

Cross talk between HHb and O₂Hb in NIRS

Cross talk of O₂Hb into HHb can occur when a change in O₂Hb concentration is large, as compared to a change in HHb concentration (Strangman et al., 2002, 2003). There are four possible sources of error when NIRS is used to determine changes in HHb and O₂Hb concentrations (Boas et al., 2001; Strangman et al., 2003). Firstly, the absolute magnitudes and relative differences in pathlength factors as a function of wavelength. Secondly, the location of the change in absorption with respect to the position of the optical probe. Thirdly, possible differences in spatial distribution of the haemoglobin species (e.g. HHb). Finally, the possibility of measuring multiple regions of activation at once.

In the current study, cross talk was minimized by three elements of the study design: (i) wavelengths of 764 nm and 857 nm were selected (Strangman et al., 2003), (ii) the DPF was set at approximately 6 (Strangman et al., 2002) in all 7 subjects by varying the DPF according to age (Duncan et al., 1996), and (iii) a respiratory challenge was used to induce global changes in cerebral physiology, as opposed to focal changes during functional activation.

All things considered, a partial-volume effect of white matter or CSF in the ROI selection, the differences in vasculature sensitivity between the two modalities, the measurement of extra-cerebral tissue by NIRS, and the baseline assumptions could bias the results. These potential sources of bias might explain the differences in SO₂ and tCBV that were found between MRI and NIRS.

Implications and directions for future research

Two approaches can be used to quantify cerebral SO₂ by MRI. The calibration of the BOLD signal is one approach (Bulte et al., 2012; Davis et al., 1998; Gauthier and Hoge, 2013). A different approach is to directly estimate SO₂ by measuring the T₂ of pure blood (Alderliesten et al., 2012; Bolar et al., 2011; Lu et al., 2012; Petersen et al., 2012). The advantages of measuring the T₂ of pure blood are that a respiratory challenge is not required, and that fewer assumptions, MRI SO₂ could be closely matched to NIRS SO₂. This was also determined by NIRS (i.e. HHb, O₂Hb, tHb, and SO₂), it was found that the SO₂ had the best correlation both with CBF and the BOLD signal. These results are of importance, as absolute values play a key role in the quantitative interpretation of fNIRS and fMRI. Moreover, this initial framework for MRI SO₂ evaluation might be used for validating NIRS in neonates.

Acknowledgments

We are grateful to acknowledge Willy Colier (Artinis Medical Systems, The Netherlands) for supplying us with the NIRS equipment. We also thank Julia Gunkel and Wim Baerts for their help in revising the manuscript.

Conflict of interest

None.

References


Patterson, M.S., Chance, B., Wilson, B.C., 1989. Time resolved reflectance and transmit-}

Please cite this article as: Alderliesten, T., et al., Simultaneous quantitative assessment of cerebral physiology using respiratory-calibrated MRI and near-infrared spectroscopy in..., Neuroimage (2013), http://dx.doi.org/10.1016/j.neuroimage.2013.07.015