Contrast-enhanced diffuse optical tomography of brain perfusion in humans using ICG

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ABSTRACT

Continuous monitoring of brain perfusion at the bedside in neurointensive care is desirable. Currently used imaging modalities are not suited for frequent monitoring and often require the transport of the patient. Noninvasive near infrared spectroscopy (NIRS) in combination with an injection of a safe dye (indocyanine green, ICG) could serve as a quasi-continuous brain perfusion monitor. In this work, we evaluate prerequisites for the development of a brain perfusion monitor using continuous wave (cw) NIRS technique. We present results from a high-resolution diffuse optical tomography (HR-DOT) experiment in humans demonstrating the separation of signals from skin from the brain. This technique can help to monitor neurointensive care patients on a regular basis, detecting changes in cortical perfusion in time.

Keywords: near infrared spectroscopy, diffuse optical tomography, brain perfusion, humans, ICG

1. INTRODUCTION

In neurointensive care units, brain perfusion cannot be monitored easily. Existing imaging modalities such as X-ray computed tomography, magnet resonance imaging (MRI), or positron emission tomography are not always within a timely reach to the intensive care unit (ICU) and are not suited for constant monitoring of the brain. Furthermore, imaging facilities may be remote from the ICU and require undesirable intensive-care patient transport. Other established neurological monitoring techniques like intracranial pressure assessment, microdialysis and transcranial Doppler ultrasonography cannot monitor perfusion of the brain parenchyma. However, bedside monitoring of brain perfusion or perfusion based therapies is desirable to evaluate the patient's pathologic state and to guide treatment. Near infrared spectroscopy (NIRS) is portable, noninvasive and can be used at the bedside. In combination with a regular injection of a safe dye (ICG) it could serve as a quasi-continuous brain perfusion monitor.

The widely used topographical NIRS approach relies on data from neighboring source-detecto-pairs with an inter-optode distance of ~ 3 cm (Fig. 1a). Previous topographic NIRS studies of brain perfusion using indocyanine green (ICG) focused on the measurement of cerebral blood flow (CBF) and cerebral blood volume (CBV) [1, 2] or differences of bolus kinetics in affected and unaffected hemispheres in stroke patients [3, 4]. This approach has one major limitation: the signal of the contrast agent in superficial layers, like skin, dominates the measured absorption change signals from the brain. This lack of depth resolution interferes with the goal of monitoring cortical perfusion. Therefore, methods are needed which differentiate perfusion signals originating from the brain from extracerebral contributions.

Depth resolving NIRS methods such as time-domain (TD) and frequency-domain (FD) techniques overcome the drawbacks of topographical NIRS by relying on the measurement of phase and modulation of the transmitted light, or by measuring the distribution of photon time-of-flight. Experiments using these techniques have shown the passage of an ICG bolus in the brain [5-7]. Consistently, it was found that the ICG bolus was detected first in deeper layers (brain) and a few seconds later in the superficial layers (scalp/skin). A higher absorption was longer seen in superficial layers. Due to the high perfusion of brain tissue, the ICG is washed out faster in deeper layers. This specific bolus behavior (see Fig 1c for a schematic) allows the separation of intra- and extracerebral fractions of the signal. While FD and TD results are promising, we believe that the introduction into clinical use would benefit greatly from the application of cw DOT, which is more economic and technically much less demanding.

In this study, we used a cw HR-DOT system with a dense optical fiber set-up (inter-optode distance < 1cm) to measure absorption changes caused by an injected ICG bolus. DOT is based on acquiring NIRS signals from different inter-

optode distances (Fig 1b), which facilitates the measurement of overlapping photon paths [8, 9] and thereby provides an enhanced lateral and an additional depth resolution [10-12].

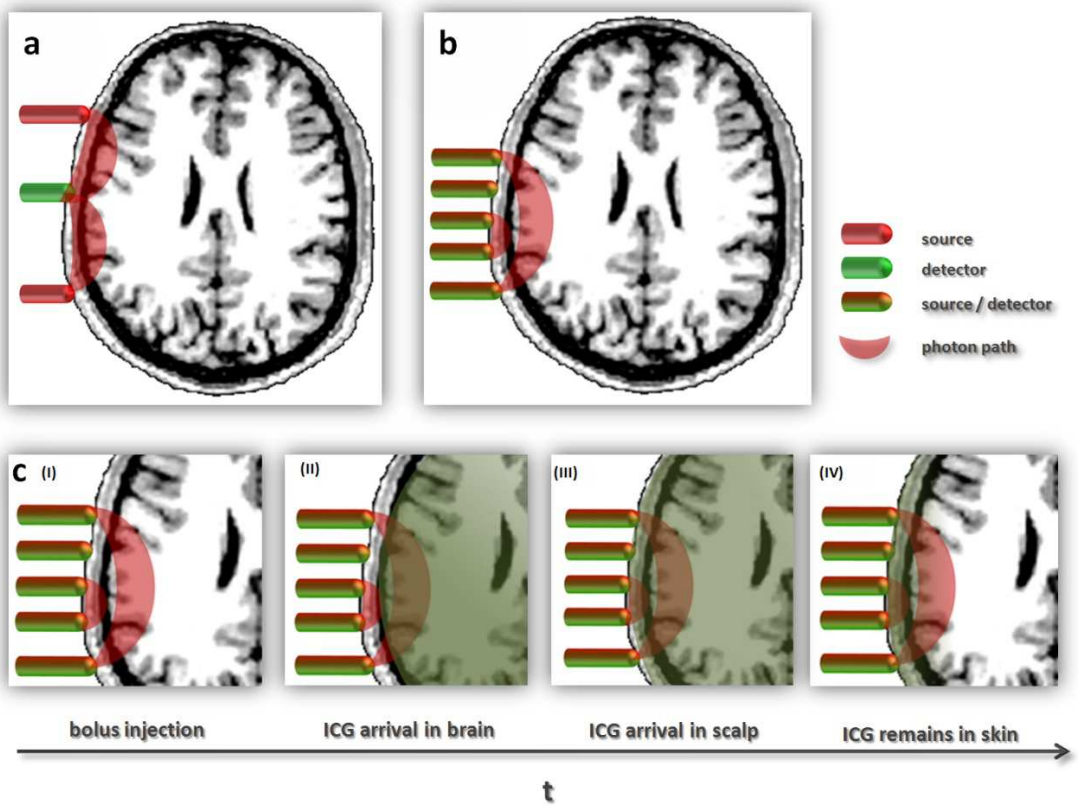

Fig. 1 (a) Schematic of a topographical NIRS measurement. Inter-optode distances of 3-4 cm allow measurement of concentration changes of different chromophores in the cortex but the signal is contaminated with signals from the scalp and skin. A separation of different layers is hardly possible. (b) Tomographical NIRS approach uses different inter-optode distances and a dense grid of co-located optical fibers (inter-optode distance <1 cm). Overlapping photon paths from different source-detector combinations allow a reconstruction of absorption changes in different tissue depths. (c) Schematic of the bolus behavior in the human head. (I) Few seconds after injection of the bolus (II) ICG arrives first in the brain due to a better perfusion and (III) some seconds later in the scalp. (IV) ICG is washed out of the brain and remains in the skin.

In this work we present results from an *in vivo* experiment of absorption change measurements due to an ICG injection using a cw HR-DOT system in humans. We visualize the expected bolus kinetics in the several compartments of the head and demonstrate the separation of intra-and extracerebral tissue in a three-dimensional view. In addition we investigate prerequisites for using an even less complex and more compact imaging system by mimicking the use of less optical data channels. We find that the use of co-located optical fibers is not mandatory for achieving a good separation of layers. These results are encouraging for a further development of a low-cost and portable bedside brain perfusion monitor.

2. METHODS

We investigated three healthy, voluntary subjects (2 male, mean age 38 years). All subjects were authors of this work. We diluted 50 mg indocyanine green (ICG-PULSION, PULSION Medical Systems, Germany) in 30 ml *aqua ad injectabilia*. Different amount of ICG was injected into the cubital vein of the right arm of each subject. Subject 1 received two boli (9 mg ICG as the first bolus, 16 mg as the second bolus) with a 10 min delay. Subject 2 and 3 were administered one bolus of 12.5 mg ICG each.

ICG is a non-toxic fluorescent dye [13, 14] that binds tightly to serum proteins and has been frequently used in clinical routine. ICG absorbs light in the near infrared spectrum with an absorption and emission maximum at 805 nm in plasma solution [15]. In experimental stroke models, it was shown that a disturbance of the blood-brain-barrier (BBB) together with an ICG injection and the exposure to near-infrared light does not lead to photo toxicity [16]. This is important since stroke patients often suffer from a disruption of the BBB.

We measured absorption changes with the DYNOT tomography imager (NIRx Medizintechnik GmbH, Berlin, Germany), which applies light of two wavelengths (λ=760 nm & λ= 830 nm) to the subject's head. Thirty co-located optical fibers (serving as source and detector) were placed over C4 in a 5 x 6 optical fiber grid covering ~12 cm^2 of the right hemisphere (inter-optode separation: 7.5 mm) (Fig 2 a, b) thereby achieving 900 overlapping optical data channels. To fixate the optical fibers on the head surface and to ensure stable optical contact, we used an open scaffolding structure and individually spring-loaded fibers. This design allows easy access of the fiber tips for parting of the hair before placing an optode.

We obtained images of hemodynamic changes using the normalized difference method [17]. Differences between predicted and measured surface data are related to changes of interior optical properties (e.g. absorption) of the investigated medium compared to a reference medium (perturbation approach). Instead of recovering absolute values, which causes difficulties when an arbitrary target medium is imaged with diffuse light, the algorithm reconstructs relative changes of interior optical properties and therefore only considers relative variations in the detector readings. One main limitation of perturbation methods is that they can produce incorrect solutions if the reference medium which is used to produce the initial guess differs considerably from the real background optical properties. Reconstructing relative changes rather than absolute values greatly relieves the demands on the accuracy of the initial guess [17, 18] . By using the perturbation approach, the image reconstruction is reduced to an inversion problem of the weight (sensitivity) matrix W, which is calculated by performing a truncated singular value decomposition using all singular values that explain 98% of the data.

The weight matrix W was determined using BrainModeler (NIRx Medical Technology, LLC, NY) which provides a library of subvolumes from a MRI-scan based finite element (FE) mesh with precalculated inverse parameters for all possible source and detector combinations on the subvolume's boundary (see, Fig 2 c). Each of these subvolumes contains precalculated forward solutions of the photon diffusion equation and reference detector values. These forward solutions are computed based on the simplified assumption of homogenous interior optical properties (μ_a= 0.06 cm^{-1}, μ_s= 10 cm^{-1}). We used the same FE mesh for image reconstruction for all three subjects. This mesh contains 3332 nodes with a resolution of ~4 mm and has the dimension of 72x68x52 mm (height x width x depth).

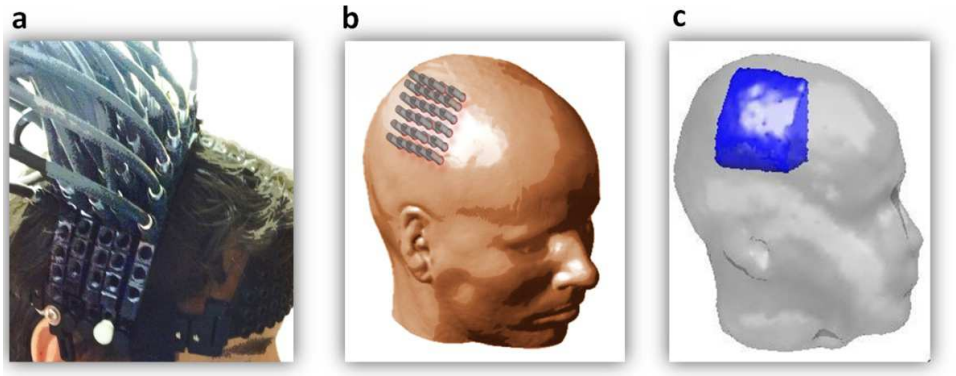

Fig. 2. Imaging setup. (a) Absorption changes were measured with a DOT imaging system (DYNOT, NIRx Medizintechnik GmbH, Berlin, Germany) (b) A 5x6 fiber grid with 30 co-located sources and detectors was placed pericentrally over the right hemisphere. (c) Location of the finite element mesh that was used for image reconstruction of relative absorption changes.

All data were low-pass filtered to reduce high-frequency noise before further processing (f_{cutoff} = 0.3 Hz). We reconstructed the time courses of relative absorption changes for every node of the finite element mesh which resulted in an array of 3332 time courses. For visualizing the bolus kinetics in different compartments of the volume, we determined the time (in s after bolus injection) of the ICG arrival for each node (defined as the time point when 50% of the maximum value was reached). In combination with the spatial coordinates of each node we finally converted the result in

a 3D volume. Results were comparable in all three subjects. Interestingly, no quantitative differences were observed due to different amount of injected ICG. Therefore we will report detailed results for one subject only.

3. RESULTS

The first column of Fig. 3 shows the reconstructed results obtained on a single subject, considering all 900 data channels. The first row illustrates the FE mesh with the defined position of the 30 co-located sources and detectors on the boundary. The second and third row depict the time of arrival of the bolus in each voxel, seen from different angles. We clearly observe an early increase in absorption in deeper layers (~ 12mm depth) and a later increase in superficial layers. This is confirmed when defining two separate regions of interest (ROI, indicated) for skin and brain and averaging all time courses within each of these (last row). As expected, the absorption dynamic in the brain region shows an early increase, followed by rapid decay. In contrast, we find a delayed increase and a slower decline in superficial voxels.

The center column of Fig. 3 shows reconstructed results from the same experiment; however, here we only considered data from those 225 optical channels that one would obtain using a dense grid of 30 optodes, of which 15 are sources and 15 are detectors (i.e., no collocated positions). Even though the spatial resolution decreases to some extent, this setup would be sufficient to separate both layers and reconstruct the different bolus kinetics in the two ROI.

The right column presents the reconstructed result volume with data from 9 optical data channels. This corresponds to a topographical NIRS setup which contains only neighboring optodes and does not afford any overlapping measurement channels. The so reduced setup is not capable of distinguishing between different layers, and the spatial resolution is greatly diminuished. The location of regions with specific arrival times is greatly distorted in comparison to the cases shown in the left and center columns. The time varying absorption from ROI in the skin and brain layer show no clear separation in flooding or washout dynamics.

4. DISCUSSION

An optical monitoring of cerebral perfusion at the bedside is highly desirable and some groups working in that field [3, 4, 6, 16, 19-25]. A tool that enables the regular monitoring at short intervals at the bedside using a safe dye would be helpful, also because many patients cannot easily be transported.

In this work we demonstrated the potential of cw HR-DOT as a cerebral perfusion monitoring. We showed the sufficient separation of brain and scalp signals and observed the expected bolus behavior in different compartments. By using three-dimensional tomography instead of the planar topographic approach, cw NIRS can overcome the drawbacks and could serve as an economic and noninvasive monitor. Cw NIRS is much less demanding than time-domain and frequency-domain devices. Volumetric images of absorption changes could be calculated in time while running the measurement.

The used wavelengths (λ=760 nm & λ= 830 nm) are close to the maximal absorption spectrum of ICG in plasma. There are three chromophores that mainly contribute to the measured signal: oxygenated hemoglobin (HbO), deoxygenated hemoglobin (HbR) and ICG. The impact of changes in HbO and HbR concentration (which can be seen in fluctuations of the baseline) is relatively small and stable over time compared to the high amplitude changes in light attenuation caused by the ICG. For example, referring the measurement with λ=760 nm we found in subject 1 in the intracerebral ROI an almost 10-fold increased amplitude of the ICG response ($1.1*10^{-5}$ mol/l) compared to the standard deviation of a 45s pre-bolus baseline ($1.2*10^{-6}$ mol/l). For λ=830 nm in the same measurement we found a more than 20-fold increase.

Nevertheless, hemodynamics can be observed in the signal; especially within the 830 nm time courses, to which HbO is the predominantly contributing hemoglobin species, we see oscillations that are part of systemic signals [26]. For further studies, we consider the implementation of a third wavelength, allowing for a better separation of the signals. However, the typical bolus kinetics with different bolus arrival times within the different compartments and the fast decline of the signal within cerebral tissue and can clearly be seen using a single wavelength. The distinct border of the early arrived bolus at 12 mm tissue depth indicates the cerebral boundary.

Although mostly clustered, we observer some heterogeneities in the location of the voxels showing the earliest bolus arrival.. We attribute this behavior to the presence and irregular distribution of larger vascular structures in brain and skin. For further investigations of the effect of blood vessels on our signal, we consider the use of other imaging modalities, which may be used to correlate our optical perfusion data with anatomical images. Furthermore, we will

investigate the distribution of intrinsic hemodynamic features such as the cardiac pulse and low frequency oscillations within theoptical images. Changes of the pattern of these hemodynamic features within the investigated volume may allow conclusions about changes in brain perfusion. This may potentially avoid the need for an exogenic contrast agent and to develop a truly continuous monitor.

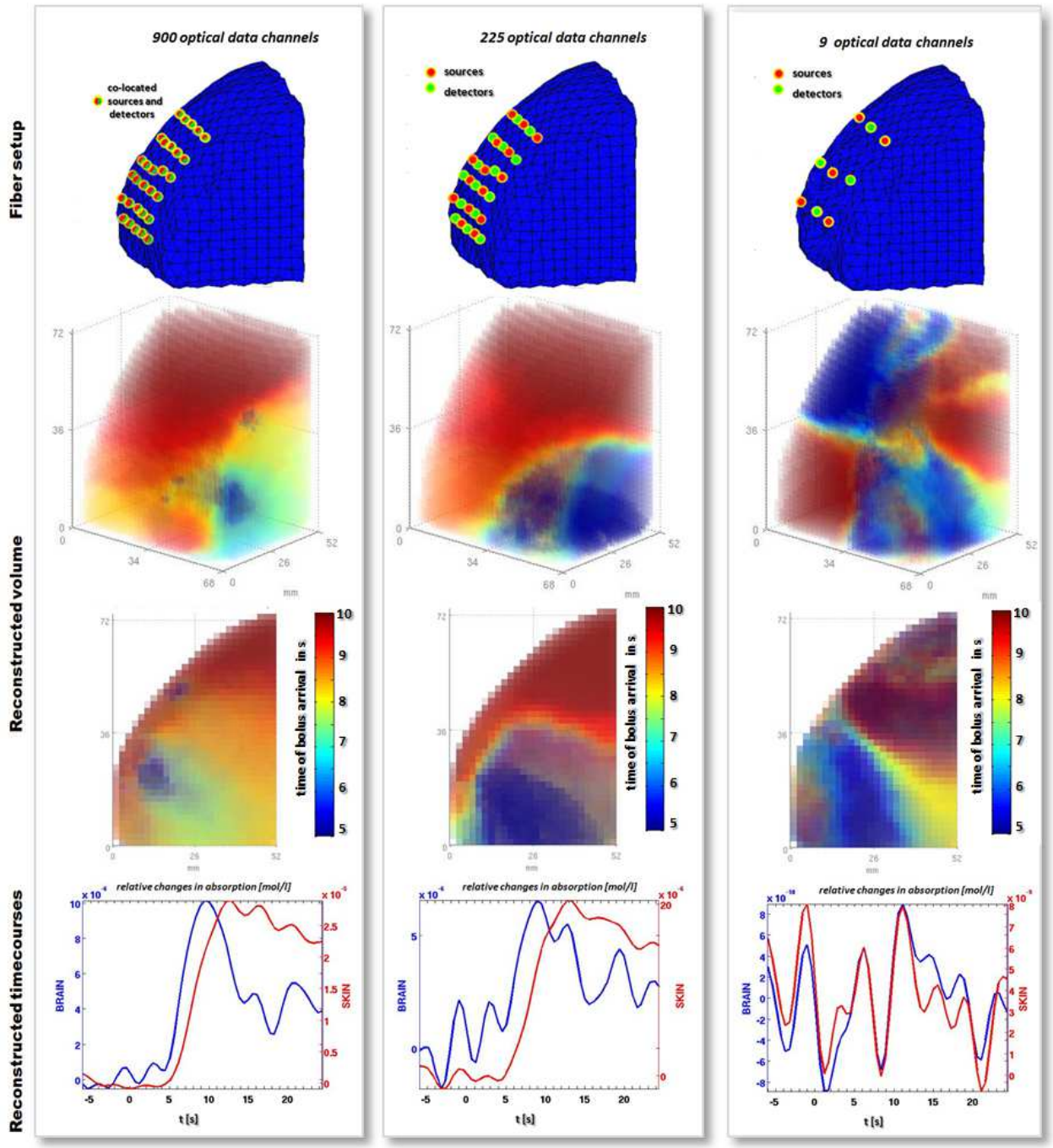

Fig. 3 Results for one subject. The first row shows the fiber location on the FE-mesh, the second and third rows present the reconstructed volume with the voxels color-coded with the time of arrival of ICG (defined as the time in s after injection when 50% of the maximum value was reached).The bottom row shows the reconstructed time courses of brain and skin region. Left column: Results using data from all 900 optical data channels (including zero-distance measurements).. Center column: Results considering a subset of data corresponding to a fiber-setup using separate sources and detectors.. Right column: Results considering only fibers at topographic distances

Additionally, this work showed that, even though a dense grid of optical fibers is needed to obtain a depth resolution, no co-located optical fibers are mandatory to separate scalp from skin. This is encouraging for further development and testing of a compact tomography device. As an outlook, Fig. 4 depicts the DYNOT tomography imager which was used for this study in comparison to the compact and easily transportable NIRScoutX 3232 (both NIRx Medizintechnik GmbH, Berlin, Germany) which will be tested for application of contrast enhanced DOT in the close future.

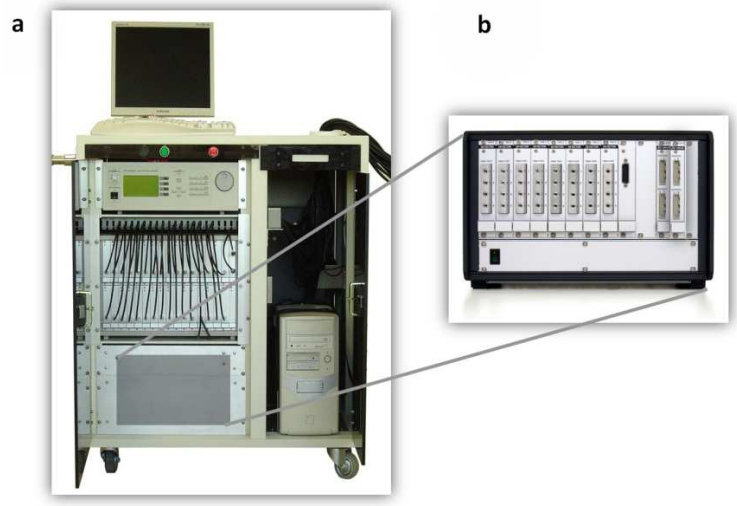

Fig. 4 Comparison of optical tomography imaging systems (both: 32 sources x 32 detectors, 2 Wavelengths). (a) DYNOT-232 (WxHxD: 1016 mm x 1003mm x 137mm, 200kg) (b) NIRScoutX-3232 (WxHxD: 364mm x 203mm x 330mm, 10kg)

REFERENCES

[1] P. Hopton, T. S. Walsh, and A. Lee, “Measurement of cerebral blood volume using near-infrared spectroscopy and indocyanine green elimination,” J Appl Physiol, 87(5), 1981-7 (1999).

[2] E. Keller, A. Nadler, H. Alkadhi *et al.*, “Noninvasive measurement of regional cerebral blood flow and regional cerebral blood volume by near-infrared spectroscopy and indocyanine green dye dilution,” Neuroimage, 20(2), 828-39 (2003).

[3] C. Terborg, S. Bramer, S. Harscher *et al.*, “Bedside assessment of cerebral perfusion reductions in patients with acute ischaemic stroke by near-infrared spectroscopy and indocyanine green,” J Neurol Neurosurg Psychiatry, 75(1), 38-42 (2004).

[4] C. Terborg, K. Groschel, A. Petrovitch *et al.*, “Noninvasive assessment of cerebral perfusion and oxygenation in acute ischemic stroke by near-infrared spectroscopy,” Eur Neurol, 62(6), 338-43 (2009).

[5] M. Kohl-Bareis, H. Obrig, J. Steinbrink *et al.*, “Noninvasive monitoring of cerebral blood flow by a dye bolus method: separation of brain from skin and skull signals,” J Biomed Opt, 7(3), 464-70 (2002).

[6] A. Liebert, H. Wabnitz, H. Obrig *et al.*, “Non-invasive detection of fluorescence from exogenous chromophores in the adult human brain,” Neuroimage, 31(2), 600-8 (2006).

[7] A. Liebert, H. Wabnitz, J. Steinbrink *et al.*, “Time-resolved multidistance near-infrared spectroscopy of the adult head: intracerebral and extracerebral absorption changes from moments of distribution of times of flight of photons,” Appl Opt, 43(15), 3037-47 (2004).

[8] R. L. Barbour, H. L. Graber, Y. Pei *et al.*, “Optical tomographic imaging of dynamic features of dense-scattering media,” J Opt Soc Am A Opt Image Sci Vis, 18(12), 3018-36 (2001).

[9] A. Bluestone, G. Abdoulaev, C. Schmitz *et al.*, “Three-dimensional optical tomography of hemodynamics in the human head,” Opt Express, 9(6), 272-86 (2001).

[10]D. A. Boas, K. Chen, D. Grebert *et al.*, "Improving the diffuse optical imaging spatial resolution of the cerebral hemodynamic response to brain activation in humans," Opt Lett, 29(13), 1506-8 (2004).
[11]C. Habermehl, S. Holtze, J. Steinbrink *et al.*, "Somatosensory activation of two fingers can be discriminated with ultrahigh-density diffuse optical tomography.," Neuroimage, (in press).
[12]B. R. White, and J. P. Culver, "Quantitative evaluation of high-density diffuse optical tomography: in vivo resolution and mapping performance," J Biomed Opt, 15(2), 026006 (2010).
[13]T. Desmettre, J. M. Devoisselle, and S. Mordon, "Fluorescence properties and metabolic features of indocyanine green (ICG) as related to angiography," Surv Ophthalmol, 45(1), 15-27 (2000).
[14]B. Ebert, B. Riefke, U. Sukowski *et al.*, "Cyanine dyes as contrast agents for near-infrared imaging in vivo: acute tolerance, pharmacokinetics, and fluorescence imaging," J Biomed Opt, 16(6), 066003.
[15]M. L. Landsman, G. Kwant, G. A. Mook *et al.*, "Light-absorbing properties, stability, and spectral stabilization of indocyanine green," J Appl Physiol, 40(4), 575-83 (1976).
[16]E. Keller, H. Ishihara, A. Nadler *et al.*, "Evaluation of brain toxicity following near infrared light exposure after indocyanine green dye injection," J Neurosci Methods, 117(1), 23-31 (2002).
[17]Y. Pei, H. Graber, and R. Barbour, "Normalized-constraint algorithm for minimizing inter-parameter crosstalk in DC optical tomography," Opt Express, 9(2), 97-109 (2001).
[18]Y. Pei, H. L. Graber, and R. L. Barbour, "Influence of Systematic Errors in Reference States on Image Quality and on Stability of Derived Information for dc Optical Imaging," Appl Opt, 40(31), 5755-69 (2001).
[19]B. L. Edlow, M. N. Kim, T. Durduran *et al.*, "The effects of healthy aging on cerebral hemodynamic responses to posture change," Physiol Meas, 31(4), 477-95 (2010).
[20]D. A. Goff, E. M. Buckley, T. Durduran *et al.*, "Noninvasive cerebral perfusion imaging in high-risk neonates," Semin Perinatol, 34(1), 46-56 (2010).
[21]D. Highton, C. Elwell, and M. Smith, "Noninvasive cerebral oximetry: is there light at the end of the tunnel?," Curr Opin Anaesthesiol, 23(5), 576-81 (2010).
[22]E. Keller, J. Froehlich, C. Muroi *et al.*, "Neuromonitoring in intensive care: a new brain tissue probe for combined monitoring of intracranial pressure (ICP) cerebral blood flow (CBF) and oxygenation," Acta Neurochir Suppl, 110(Pt 2), 217-20 (2011).
[23]R. C. Mesquita, T. Durduran, G. Yu *et al.*, "Direct measurement of tissue blood flow and metabolism with diffuse optics," Philos Transact A Math Phys Eng Sci, 369(1955), 4390-406 (2011).
[24]R. Mudra, A. Nadler, E. Keller *et al.*, "Analysis of near-infrared spectroscopy and indocyanine green dye dilution with Monte Carlo simulation of light propagation in the adult brain," J Biomed Opt, 11(4), 044009 (2006).
[25]J. Steinbrink, A. Liebert, H. Wabnitz *et al.*, "Towards noninvasive molecular fluorescence imaging of the human brain," Neurodegener Dis, 5(5), 296-303 (2008).
[26]H. Obrig, M. Neufang, R. Wenzel *et al.*, "Spontaneous low frequency oscillations of cerebral hemodynamics and metabolism in human adults," Neuroimage, 12(6), 623-39 (2000).

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