Neurophotonics

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Neurophotonics 1(1), 011009 (Jul–Sep 2014)

OUTLOOK

Diffuse correlation spectroscopy for measurement of cerebral blood flow: future prospects

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Abstract. Diffuse correlation spectroscopy (DCS) is an emerging optical modality used to measure cortical cerebral blood flow. This outlook presents a brief overview of the technology, summarizing the advantages and limitations of the method, and describing its recent applications to animal, adult, and infant cohorts. At last, the paper highlights future applications where DCS may play a pivotal role individualizing patient management and enhancing our understanding of neurovascular coupling, activation, and brain development. [DOI: 10.1117/1.NPh.1.1.011009]

Keywords: cerebral blood flow; biomedical optics; spectroscopy; medical imaging.

Paper 14045KSSR received Apr. 3, 2014; revised manuscript received May 4, 2014; accepted for publication May 7, 2014; published online Jun. 20, 2014.

1 Introduction

Cerebral blood perfusion is a biomarker of brain health and function. Functioning neurons need adenosine triphosphate (ATP), and ATP is produced almost entirely through oxidative metabolism. Therefore, if the oxygen supply is insufficient, then energy-dependent neuronal processes cease, and irreversible cellular damage ensues. Adequate cerebral blood flow (CBF) ensures the delivery of oxygen and needed substrates to tissue, and it also ensures removal of metabolic waste products. Thus, the quantification of CBF is useful for diagnosis and management of any brain injury or disease associated with ischemia or inadequate vascular autoregulation. Further, the quantification of CBF in healthy subjects, for example with respect to age or during functional activation, can elucidate connections between vascular physiology and neurophysiology, and these normative parameters, in turn, improve our ability to recognize and understand a diseased brain.

This paper is focused on a relatively new blood flow measurement modality that utilizes the intensity fluctuations of near-infrared (NIR) light to noninvasively quantify CBF at the bedside. This technology is called diffuse correlation spectroscopy (DCS). Initial research in animals and in humans has validated DCS indices of CBF and has demonstrated its potential as a preclinical and neuroscience research tool and as a clinical monitoring tool. Herein, we present a brief background about DCS instrumentation and the underlying theory, and we summarize its most prominent cerebral monitoring applications to date. Then, we discuss the advantages and limitations of current technology and indicate directions for improvement. Finally, we suggest clinical and neuroscience applications that could benefit significantly from this novel technology in the future.

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2 Diffuse Correlation Spectroscopy Background

As noted above, DCS is an emerging optical modality to monitor CBF. In recent years, excellent reviews about the theory, instrumentation, validation, and clinical applications of DCS have been published, and the interested reader will enjoy these papers.[1–5] DCS detects blood flow by quantifying temporal fluctuations of light fields emerging from the tissue surface. Typically, these light fields are generated by illuminating the brain surface with NIR laser light; some of the NIR light propagates through the scalp and skull and into the brain where it is scattered by moving red blood cells in tissue vasculature before emerging from the tissue surface. This "dynamic" scattering from moving cells [Fig. 1(a)] causes the detected intensity to temporally fluctuate [Fig. 1(b)], and the time scale of these fluctuations is quantified by the intensity temporal autocorrelation function of the collected light [see Fig. 1(c)].

In practice, the correlation diffusion equation,[6,7] or its integral analog,[8,9] is employed to fit the measured autocorrelation function to simple physical models and thereby extracts a cerebral blood flow index (CBF_i, cm^2/s). Numerous studies in humans and in animals (recently reviewed in[2]) have shown that the relative changes of CBF_i over time, that is, relative cerebral blood flow (rCBF), agree very well with relative changes in CBF measured by "gold standard" blood flow measurement techniques, such as arterial spin-labeled MRI (ASL-MRI) and fluorescent microspheres as shown in Fig. 2(a). Further, in neonatal piglets and humans, absolute CBF_i has been shown to correlate strongly with CBF measured by bolus tracking time-domain near-infrared spectroscopy (NIRS) and with CBF measured by phase-encoded velocity mapping magnetic resonance imaging (MRI) in the sagittal sinus [see Fig. 2(b)], respectively.[10–12] Additionally, the combination of NIRS-measured hemoglobin oxygen saturation (SO_2) and DCS-measured CBF_i has been utilized to derive quantitative information about cerebral oxygen metabolism ($CMRO_2$).[1,11,13]

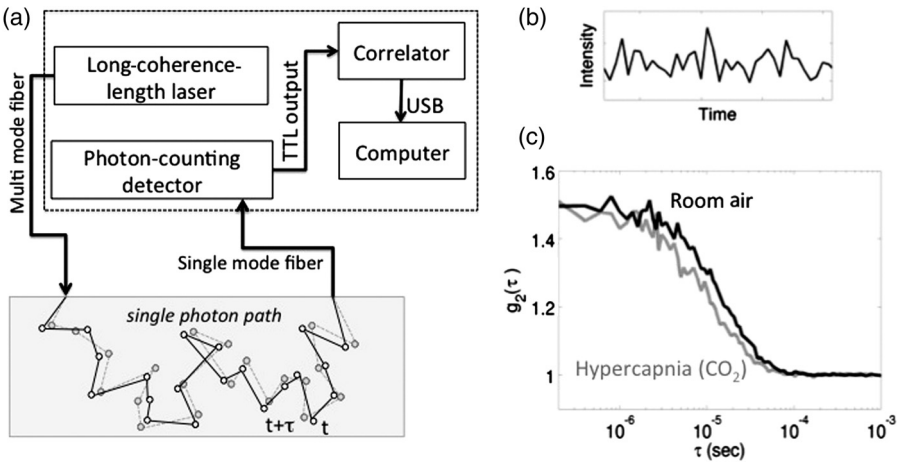

Fig. 1 (a) Schematic of typical DCS instrumentation that consists of a long-coherence length source coupled to a multimode fiber for light delivery to the tissue, photon-counting detector(s), and an autocorrelator board that computes the intensity of the autocorrelation function, $g_2(\tau)$, based on photon arrival times (b), (c) Sample $g_2(\tau)$ curves obtained over the frontal cortex in a subject under baseline conditions (black) and under hypercapnia (3% inspired carbon dioxide, gray). The increased decay rate of $g_2(\tau)$ during hypercapnia reflects the increase in CBF by vasodilation.

DCS instrumentation consists of three main components: a long-coherence-length (>5 m) laser operating in the NIR to deliver light to the tissue; single photon counting avalanche photodiode (APD) detectors that output an electronic pulse for every photon received; and a photon correlator that keeps track of the arrival times of all photons detected by the APDs and derives an intensity correlation function from the temporal separations of all pairs of photons (see Fig. 1). The correlator has traditionally been a piece of hardware, but with improved computation power and speed, software computation of temporal correlation functions will soon become increasingly prevalent. These components are readily housed in lightweight, portable enclosures that can be incorporated into a bedside clinical monitoring unit. To date, most DCS instruments have been home-built; however, recently several companies (Hemophotonics, ISS Inc., Flox Medical, Canon USA) have initiated commercialization of DCS systems.

2.1 *Advantages*

DCS offers several advantages over other methods that measure CBF. Unlike traditional clinical CBF measurement modalities, such as xenon-133 computed tomography (xenon-CT) and positron emission tomography, DCS does not expose the patient to ionizing radiation. Furthermore, unlike safer new methods such as ASL-MRI, DCS is relatively inexpensive, portable, and the DCS measurement can easily be carried out multiple times during a patient's hospital stay. Lastly, in contrast to transcranial Doppler ultrasound, which probes blood flow in major vessels, DCS can be used at any location on the patient's head to assess regional cortical microvascular flow.

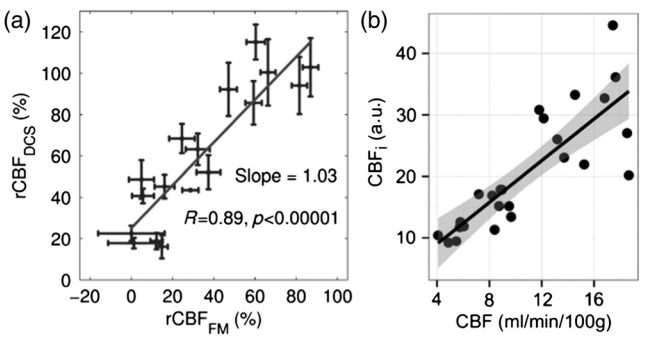

Fig. 2 Selected validation of DCS measured CBF_i against other CBF modalities. (a) Relative changes in CBF measured by DCS ($rCBF_{DCS}$) is highly correlated with relative CBF measured with fluorescent microspheres ($rCBF_{FM}$);[14] (b) Absolute CBF_i correlates well with absolute CBF measured with phase encoded velocity mapping MRI in neonates.[12]

While these advantages of DCS are important for patients of all ages, they are most significant for infants, a population for whom access to MRI is limited. Indeed, DCS holds the potential to fill a critical niche for the assessment of neonatal brain health, brain development, autoregulation, responses to physiological manipulation or therapeutic intervention, and functional responses to sensory and cognitive stimuli. Because measurements can be performed in a rapid, noninvasive, and low-risk fashion using a portable bedside instrument without anesthesia or sedation, DCS provides distinct advantages over other perfusion modalities used in infants, such as ASL-MRI, which requires transport from clinical units to the radiology department, sedated or sleeping patients to limit motion, and which suffers from noise when CBF is low (as is typically seen in infants).

DCS instrumentation is easy to assemble and requires only one wavelength that can be chosen based on laser availability and cost (e.g., by contrast, NIRS requires multiple wavelengths within the NIR tissue absorption window). In addition, unlike the NIRS technique, DCS measurements do not require reference phantoms for quantification. Finally, as noted above, when DCS is integrated with NIRS, the combined instrumentation derives a more robust picture of brain health, i.e., via measurement of tissue oxygenation, cerebral blood flow, and oxygen metabolism.

In addition to the direct advantages of the diffuse optical technology over the existing methods, DCS theoretical concepts can be adapted to improve other blood flow imaging techniques. For example, the elements and concepts from DCS have recently found use in more surface-sensitive CBF imaging methods, such as laser speckle contrast imaging (LSCI);[15–20] further, the combination of DCS theory, spatial frequency-domain imaging, and LSCI has led to quantitative measurements of the physical

properties of liquids[21] and depth resolved blood flow measurements.[22] Recent experiments have also increased the depth sensitivity of blood flow imaging using DCS concepts.[23]

2.2 *Limitations*

Numerous validation studies in both adults and children have shown that the relative changes in CBF_i over time (i.e., rCBF) measured by DCS agree quite well with rCBF measured by other modalities (see Fig. 2 and Ref. 2). However, the quantification of absolute CBF_i remains to be determined across a wide range of subjects and tissue types. To date, the correlations between CBF_i and absolute CBF (measured by other modalities) have only been observed in young piglets and in human neonates, i.e., population cohorts in whom the ratio of extracerebral thickness to the source-detector separation is approximately 0.25 or smaller. In older pediatric populations and in adults, the contribution of the thick scalp and skull layers to CBF_i cannot be neglected; in these cases, the absolute quantification of CBF_i will most likely require the use of multilayered modeling.[24] Moreover, because of the relevant scalp contribution in adults, it is desirable to account for probe pressure effects,[25] especially when the source-detector separation is less than 2.5 cm. In neonates and in small animals, these factors play a relatively small role, most likely because the ratio of extracerebral thickness to source-detector separation is small, and it is therefore more likely that the detected photons will travel through the cortex.

Another important parameter needed for quantification of CBF_i is the tissue reduced scattering coefficient, μ_s', i.e., the reciprocal of the photon random walk step length. Although CBF_i is influenced by both tissue absorption and scattering coefficients, μ_a and μ_s', respectively, uncertainties in μ_a lead to relatively small errors in CBF_i (<20%), whereas uncertainties in μ_s' can translate to substantial errors in CBF_i.[26] Thus, when quantifying an absolute CBF_i, it is desirable to combine DCS with a method to determine absolute μ_a and μ_s' for the tissue of interest, e.g., frequency- or time-domain NIRS. We note, however, that in neonates, Jain et al. observed a strong correlation between CBF_i and CBF in the sagittal sinus despite assuming a fixed μ_s' across the entire cohort [see Fig. 2(b)].[12] This agreement, at least in part, may have been a result of the homogeneity of the patient cohort, i.e., all were <1 week neonates with congenital heart defects. Clearly, in future studies it will be better to measure μ_s' in all subjects whenever possible. (Note: the effects of uncertainties in μ_a and μ_s' on CBF_i are diminished when monitoring relative changes in CBF_i over time, since these tissue parameters change little except in cases of extreme interval blood loss/gain, edema, etc).

As is the case with other optical modalities, the penetration depth of DCS, while larger than wide-field optical methods, such as LSCI, is limited compared to traditional clinical modalities, such as MRI and CT. Like NIRS, a common rule-of-thumb for DCS is that it samples a banana-shaped region underneath the optical probe that is roughly one-third to one-half of the source-detector separation;[1] thus, typical DCS experimental setups with source-detector separations of 2 to 3 cm are sensitive to superficial cortical regions. CBF in deep brain structures has not been quantified by DCS. To increase the penetration depth, larger source-detector separations are required. The use of larger source-detector separation configurations, however, is challenging since DCS optimally requires single-mode detection fibers for measurement of the intensity autocorrelation function. The throughput of single-mode fibers is relatively low and leads to a low signal-to-noise ratio (SNR), especially in adults where large source-detector separations (>2 cm) are needed to detect cerebral signals. This low SNR becomes even more problematic in the presence of hair and/or dark skin; it can increase acquisition times and reduce temporal resolution. To overcome the issue of low SNR, most groups employ multiple detector fibers bundled together in the same position, and then the autocorrelation curves from all detectors are averaged to derive a single curve. Unfortunately, this strategy is a relatively expensive option that requires many photon counting detectors. Alternative strategies to improve SNR include increased light collection through improved collection optics, such as those presented by Dietsche et al.,[27] or the use of few-mode (rather than single mode) detection fibers.[28] Additionally, improved SNR can be achieved by increasing the amount of light delivered to the tissue;[29] however, the ANSI standards for skin exposure must be considered, and a large diameter source fiber and/or diffuser should be used to keep light exposure levels within safe limits.

Finally, a significant limitation of DCS is its susceptibility to motion artifacts. Of course, most neuroimaging techniques are sensitive to motion artifacts, hence this issue is not unique to DCS. To understand this problem more deeply, recall that blood flow contrast in DCS primarily derives from intensity fluctuations due to moving particles in the sampled volume. Therefore, the motion of the probe when it is in contact with the patient can cause additional fluctuations due to static tissue (and other) structures that can add noise (random and systematic) to estimates of CBF_i. In practice, securing the optical probes as firmly as possible to the subject's head has reduced motion artifacts. Looking forward, DCS can employ the same analytical approaches used in functional NIRS to account and filter for motion (principle component analysis, wavelet analysis, spline interpolation, etc.[30,31]) and thereby eliminate artifacts via improvements in optical probes.[32] On the experimental side, Yucel et al. have had excellent recent success in reducing motion artifacts in NIRS data by gluing optodes to the tissue surface with collodion, a glue used with electroencephalogram (EEG) electrodes.[32] This approach may also be feasible for DCS, although it may be more practical for utilization in critically ill patients when the potential benefits from cerebral blood flow monitoring outweigh the annoyances of gluing fibers. Additionally, recent approaches with DCS in muscle studies during exercise have successfully employed a dynamometer to gate DCS acquisition and partially remove the effects of motion;[33,34] variants of this approach might be useful for the brain.

3 Diffuse Correlation Spectroscopy Applications

3.1 *Animals*

Animal models have provided a rich environment for the validation of DCS. Early studies focused on measurement and validation of relative changes in CBF with time (rCBF): Zhou et al. used a closed head injury neonatal piglet model to demonstrate excellent one-to-one agreement of DCS changes in CBF against the changes in CBF measured with fluorescent microspheres [see Fig. 2(a)];[14] Carp et al. validated rCBF measured by DCS in a rodent model against ASL-MRI.[35] Recent work has also shown agreement between absolute CBF_i

with absolute CBF measured with bolus tracking time-domain NIRS using indocyanine green dye in piglets. Diop et al. calibrated DCS CBF_i to physiologic units (ml/min/100 g) in piglets,[10] while Verdecchia et al. performed a similar experiment to calibrate CBF_i for individual piglets during various physiological manipulations.[13]

In addition to these validation studies, the quantitative and noninvasive aspects of DCS CBF measurements are very attractive for a variety of animal studies. In rodents, DCS offers the possibility of deep tissue CBF quantification without the need for thinning or removal of the skull, thus leaving the brain unperturbed (i.e., as opposed to more traditional methods of CBF measurement in animals such as laser Doppler flowmetry and laser speckle contrast imaging). DCS has been used in animal models to study baseline and activated hemodynamics as well as related metabolic changes.[36] DCS has also been used to study diseases such as ischemic stroke,[37,38] phenomena such as cortical spreading depressions,[39] and CBF responses to different anesthetics and carbon dioxide.[40] Additionally, DCS has been used to extract depth-resolved spatial maps of blood flow.[37,39] In sum, these studies have demonstrated the potential of DCS in preclinical and neuroscience animal studies. Arguably, it appears to be a more robust and quantitative measure of CBF than laser Doppler (which has limited depth penetration and poor repeatability), and its validation has opened the possibility for future longitudinal studies due to the noninvasive nature of the technique.

3.2 *Adults*

Although DCS has been largely restricted to measures of rCBF in adults due to difficulties in absolute baseline quantification (see Sec. 2.2), the above-mentioned advantages (see Sec. 2.1) have resulted in numerous preliminary studies demonstrating the clinical potential of DCS. DCS has been successfully applied to monitor rCBF during clinical interventions, such as postural manipulation or blood pressure regulation in patients with ischemic stroke,[41] traumatic brain injury, and subarachnoid hemorrhage.[42,43] These works have demonstrated the need (and potential) for individualized monitoring of cerebral hemodynamics during therapeutic interventions. In essence, we are discovering that the standard treatment protocols designed to optimize cerebral perfusion in damaged tissue do not always yield the desired result; this limitation of the standard protocols is understandable in light of the often highly heterogeneous nature of these brain injuries, and it points to the need for more individualized management (see Fig. 3). In addition, DCS has been used to detect acute spinal cord ischemia in sheep models,[44] to assess CBF changes due to vocal stuttering,[45] and to elucidate the effects of normal aging on posture manipulations.[46] Per new therapeutics, DCS has been used to characterize the cerebral hemodynamic responses due to transcranial magnetic stimulation (TMS) in an effort to elucidate the mechanisms of TMS.[47] Finally, per functional activation studies, DCS has shown spatiotemporal sensitivity to finger tapping[48] and visual stimulation,[49,50] thereby demonstrating its utility for basic neuroscience/physiological studies in patients in a natural environment.

By directly addressing some of the limitations noted above (Sec. 2.2), it should be possible to expand the use of DCS for clinical monitoring in adults. Improvements to increase SNR and temporal resolution will help the development of functional experiments in adults. Lower costs for sources and detectors should permit whole brain functional imaging experiments that will start to investigate multiregion evoked CBF and $CMRO_2$ changes as well as global resting state CBF and $CMRO_2$ for exploration of regional functional activity and functional connectivity in the adult brain.

3.3 *Infants*

Infants and young children are ideal populations to study with DCS, because they have thinner extracerebral layers than adults. Thus, in this population the community has observed higher SNR, excellent reproducibility of CBF_i (i.e., within 10% to 15%[11]), and greater sensitivity to cortical tissue as compared to adults. Further, infants often have less hair than adults, a mundane but important factor that improves SNR.

To date, neonatal studies with DCS have branched in many directions. In contrast to adults, where the majority of clinical research has focused on changes over time caused by relatively brief interventions (i.e., interventions of order 1 h), neonatal experimental results encompass both episodic monitoring as well as periodic quantification of absolute CBF_i. Episodic monitoring has been used to quantify the response to hypercapnia,[51] postural manipulation,[52] drug delivery,[53] surgical intervention,[54] therapeutics,[53,55] and functional activation.[56] These studies have provided previously unknown and very valuable information about CBF and $CMRO_2$ responses to intervention. For example,

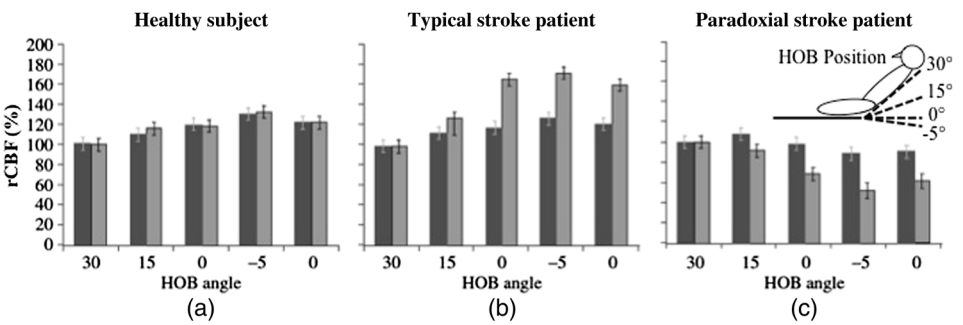

Fig. 3 Relative changes in cerebral blood flow measured with DCS during postural manipulation of head-of-bed (HOB) position from 30 to −5° (inset) for (a) a typical healthy subject, (b) a stroke patient who demonstrated the typical response of impaired autoregulation in the injured hemisphere when HOB is lowered, and (c) a stroke patient who demonstrated a paradoxical response in the injured hemisphere during the lowering of HOB, seen in approximately 20% of stroke patients. (a) Left hemisphere in dark gray, right in light gray, (b,c) contralesional in dark gray, ipsalesional in light gray. Figure courtesy of Mesquita et al.[3]

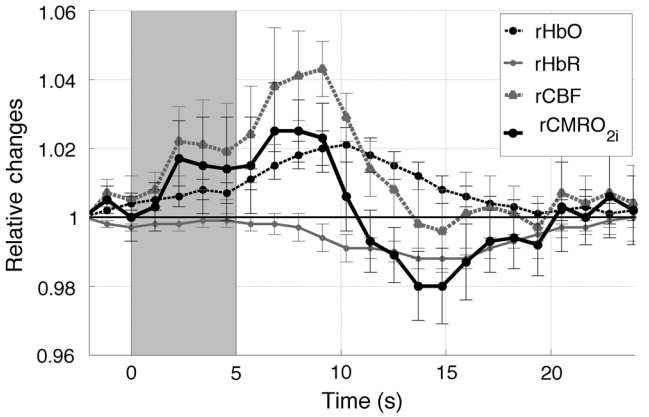

Fig. 4 Fractional changes of oxy- and deoxy-hemoglobin concentrations (rHbO and rHbR, respectively), as well as cerebral blood flow (rCBF) and cerebral oxygen metabolism ($rCMRO_{2i}$) measured with NIRS and DCS overthe left somatosensory cortex in preterm infants during 5 seconds of gentle stimulation of the hand, indicated by the gray shaded region.[56]

Buckley et al. observed significant and substantial dose-dependent increases in CBF following bolus administration of sodium bicarbonate to correct metabolic acidosis.[53] Recognizing these dose-dependent effects may be especially important in treating patient populations where the risks of rapid fluctuations in CBF may lead to subsequent brain injury and thus limit the benefits of correcting the underlying acidemia. Dehaes et al. have observed substantial decreases in CBF_i and $CMRO_{2i}$ in hypoxic ischemic injured neonates under therapeutic hypothermia.[55] The ability to measure $CMRO_2$ during therapeutic hypothermia and assess its dynamic may help to individually optimize and guide this therapy.

Further, Roche-Labarbe et al. recently demonstrated the feasibility of DCS functional studies in infants.[56] By combining NIRS with DCS, both CBF and $CMRO_2$ changes are measured (see Fig. 4). Understanding metabolic and vascular functional measures, as well as their coupling relationships, holds tremendous potential for assessment of perceptual and cognitive development and for deriving early indications of neuropsychological and behavioral deficits in at-risk populations.

Following numerous validation studies,[2] the periodic measures of CBF_i have been used to investigate changes in cerebral hemodynamics over the first month of development in term and preterm infants,[11,57] as well as regional and hemispheric differences in cortical flow.[58] These works elucidate the normal evolution of SO_2, CBF, and $CMRO_2$ in the developing neonate, which is critical to understanding brain in disease states. Furthermore, the works by Roche-Labarbe et al.[57] and Dehaes et al.,[55] in particular, highlight the relative insensitivity of SO_2 alone, i.e., the standard parameter provided by commercially available stand-alone NIRS devices, as a measure of brain health. These works demonstrate the obvious advantage that DCS adds in providing a more complete picture of neonatal development through quantification of CBF and $CMRO_2$.

4 Future Applications

From a clinical perspective, because DCS is a safe, inexpensive, noninvasive, and portable modality, it can be used as a bedside monitor of cerebral perfusion in both the intensive care unit (ICU) and the operating room (OR). Commercially available continuous-wave NIRS devices that estimate regional cerebral oxygenation (rSO_2) are already in widespread use in ICUs and ORs. DCS provides valuable complementary information to NIRS per microvascular CBF and, therefore, regional oxygen delivery. The combination of NIRS with DCS also enables the quantification of regional $CMRO_2$, a parameter that many believe is a direct measure of neuronal health;[59] this information provides the clinician with a more complete assessment of cerebral health and physiology than either SO_2 or CBF alone.

As an example of how the combination of NIRS and DCS can be used, we note that SO_2 can increase either with increased neuronal activity (i.e., when supply exceeds neuronal demand) or with decreased neuronal activity (i.e., when neuronal oxygen consumption is decreased). Therefore, when increases in SO_2 are noted by NIRS, it is vital to determine if the changes are associated with increased delivery or decreased oxygen consumption; DCS measures of CBF combined with NIRS can help assess increases/decreases in neuronal activity. In addition, if decreases in SO_2 are observed, simultaneous quantification of CBF can help clinicians ascertain whether these decreases are due to the failure of oxygen delivery (as when CBF decreases due to decreased cardiac output) or due to increased oxygen consumption. Looking forward, the potential for DCS combined with NIRS to enable ICU and OR management of subjects based on optimizing regional cerebral $CMRO_2$ should be explored as an alternative to strategies based on a secondary systemic and/or cerebral parameters, such as SO_2.

Per therapy development, DCS can be used in both animal and human studies, especially for therapies (e.g., drugs, etc.) aimed at altering cerebral microvascular perfusion. This approach would see first testing in animal studies, which, in turn, would then set the stage for DCS monitoring in human trials.

Beyond the immediate potential for DCS in the clinic, DCS and other diffuse optical tools should be expected to help scientists increase our understanding of neurovascular coupling and early brain development. The ability to monitor neurovascular responses in more natural environments, outside the noisy MRI scanner, will enable the use of more complex stimulation paradigms. In addition, monitoring CBF with DCS or the entire suite of $CMRO_2$, SO_2, and CBF (when combined with NIRS) will enable us to better understand the nature of the neurovascular response. The ability to quantify $CMRO_2$ during functional changes, for example, will permit better interpretation of functional response, since oxygen metabolism changes will be less influenced by systemic physiology.

Acknowledgments

We thank David Boas, Turgut Durduran, Stefan Carp, Rickson Mesquita, Wesley Baker, Ivy Lin, Nadege Roche-Labarbe, Mathieu Dehaes, Linda van Marter, Harsha Radakrishnan, Malavika Chandra, Meeri Kim, John Detre, Joel Greenberg, and Daniel Licht for valuable discussions. We also gratefully acknowledge support from the National Institutes of Health through Grant Nos. R01-NS060653, P41-EB015893, P41-RR14075, R01-HD042908, and R01-EB001954.

References

1. T. Durduran et al., "Diffuse optics for tissue monitoring and tomography," *Rep. Prog. Phys.* **73**(7), 1–43 (2010).
2. T. Durduran and A. G. Yodh, "Diffuse correlation spectroscopy for noninvasive, micro-vascular cerebral blood flow measurement," *Neuroimage* **85**(Part 1), 51–63 (2014).

3. R. C. Mesquita et al., "Direct measurement of tissue blood flow and metabolism with diffuse optics," *Philos. Transact. Series A. Math. Phys. Eng. Sci.* **369**(1955) 4390–4406 (2011).
4. G. Yu, "Diffuse correlation spectroscopy (DCS): a diagnostic tool for assessing tissue blood flow in vascular-related diseases and therapies," *Curr. Med. Imag. Rev.* **8**(3), 194–210 (2012).
5. G. Yu, "Near-infrared diffuse correlation spectroscopy (DCS) for assessment of tissue blood flow," Chapter 10 in *Handbook of Biomedical Optics*, D. A. Boas, C. Pitris, and N. Ramanujam, Eds., pp. 195–216, Taylor and Francis Books, Inc., Boca Raton, Florida (2011).
6. D. A. Boas, L. E. Campbell, and A. G. Yodh, "Scattering and imaging with diffusing temporal field correlations," *Phys. Rev. Lett.* **75**(9), 1855–1858 (1995).
7. D. A. Boas and A. G. Yodh, "Spatially varying dynamical properties of turbid media probed with diffusing temporal light correlation," *J. Opt. Soc. Am. A.* **14**(1), 192–215 (1997).
8. G. Maret and P. E. Wolf, "Multiple light scattering from disordered media. The effect of Brownian motion of scatterers," *Z. Physik B* **65**(4), 409–413 (1987).
9. D. J. Pine et al., "Diffusing wave spectroscopy," *Phys. Rev. Lett.* **60**(12), 1134–1137 (1988).
10. M. Diop et al., "Calibration of diffuse correlation spectroscopy with a time-resolved near-infrared technique to yield absolute cerebral blood flow measurements," *Biomed. Opt. Exp.* **2**(7), 2068–2081 (2011).
11. N. Roche-Labarbe et al., "Noninvasive optical measures of CBV, StO2, CBF index, and rCMRO2 in human premature neonates' brains in the first six weeks of life," *Hum. Brain Mapp.* **31**(3), 341–352 (2010).
12. V. Jain et al., "Cerebral oxygen metabolism in neonates with congenital heart disease quantified by MRI and optics," *J. Cereb. Blood Flow Metab.* **34**(3), 380–388 (2014).
13. K. Verdecchia et al., "Quantifying the cerebral metabolic rate of oxygen by combining diffuse correlation spectroscopy and time-resolved near-infrared spectroscopy," *J. Biomed. Opt.* **18**(2), 027007 (2013).
14. C. Zhou et al., "Diffuse optical monitoring of hemodynamics in piglet brain with head trauma injury," *J. Biomed. Opt.* **14**(3), 034015 (2009).
15. T. Durduran et al., "Spatiotemporal quantification of cerebral blood flow during functional activation in rat somatosensory cortex using laser-speckle flowmetry," *J. Cereb. Blood Flow Metab.* **24**(5), 518–525 (2004).
16. A. F. Fercher and J. D. Briers, "Flow visualization by means of single-exposure speckle photography," *Opt. Commun.* **37**(5), 326–330 (1981).
17. A. B. Parthasarathy, "Laser speckle contrast imaging of cerebral blood flow in humans during neurosurgery: a pilot clinical study," *J. Biomed. Opt.* **15**(6), 066030 (2010).
18. S. M. Kazmi et al., "Chronic imaging of cortical blood flow using multi-exposure speckle imaging," *J. Cereb. Blood Flow Metab.* **33**(6), 798–808 (2013).
19. D. A. Boas and A. K. Dunn, "Laser speckle contrast imaging in biomedical optics," *J. Biomed. Opt.* **15**(1), 011109 (2010).
20. A. K. Dunn, "Dynamic imaging of cerebral blood flow using laser speckle," *J. Cereb. Blood Flow Metab.* **21**(3), 195–201 (2001).
21. T. B. Rice et al., "Quantitative determination of dynamical properties using coherent spatial frequency domain imaging," *J. Opt. Soc. Am. A.* **28**(10), 2108–2114 (2011).
22. A. Mazhar et al., "Laser speckle imaging in the spatial frequency domain," *Biomed. Opt. Exp.* **2**(6), 1553–1563 (2011).
23. R. Bi, J. Dong, and K. Lee, "Deep tissue flowmetry based on diffuse speckle contrast analysis," *Opt. Lett.* **38**(9), 1401–1403 (2013).
24. L. Gagnon, "Investigation of diffuse correlation spectroscopy in multi-layered media including the human head," *Opt. Exp.* **16**(20), 15514–15530 (2008).
25. R. Mesquita et al., "Influence of probe pressure on the diffuse correlation spectroscopy blood flow signal: extra-cerebral contributions," *Biomed. Opt. Exp.* **4**(7), 978–994 (2013).
26. D. Irwin et al., "Influences of tissue absorption and scattering on diffuse correlation spectroscopy blood flow measurements," *Biomed. Opt. Exp.* **2**(7), 1969–1985 (2011).
27. G. Dietsche et al., "Fiber-based multispeckle detection for time-resolved diffusing-wave spectroscopy: characterization and application to blood flow detection in deep tissue," *Appl. Opt.* **46**(35), 8506–8514 (2007).
28. L. He et al., "Using optical fibers with different modes to improve the signal-to-noise ratio of diffuse correlation spectroscopy flow-oximeter measurements," *J. Biomed. Opt.* **18**(3), 037001 (2013).
29. P. Lin et al., "Non-invasive optical measurement of cerebral metabolism and hemodynamics in infants," *J. Visual. Exp.* **14**(73), e4379 (2013).
30. M. A. Yucel et al., "Targeted principle component analysis: a new motion artifact correction approach for near-infrared spectroscopy," *J. Innovative Opt. Health Sci.* **7**(2), 1350066 (2014).
31. R. J. Cooper et al., "A systematic comparison of motion artifact correction techniques for functional near-infrared spectroscopy," *Front. Neurosci.* **6**(147) (2012).
32. M. A. Yucel et al., "Reducing motion artifacts for long-term clinical NIRS monitoring using collodion-fixed prism-based optical fibers," *Neuroimage* **85**(Pt 1), 192–201 (2014).
33. Y. Shang et al., "Effects of muscle fiber motion on diffuse correlation spectroscopy blood flow measurements during exercise," *Biomed. Opt. Exp.* **1**(2), 500–511 (2010).
34. K. Gurley, Y. Shang, and G. Yu, "Noninvasive optical quantification of absolute blood flow, blood oxygenation, and oxygen consumption rate in exercising skeletal muscle," *J. Biomed. Opt.* **17**(7), 075010 (2012).
35. S. Carp et al., "Validation of diffuse correlation spectroscopy measurements of rodent cerebral blood flow with simultaneous arterial spin labeling MRI; towards MRI-optical continuous cerebral metabolic monitoring," *Biomed. Opt. Exp.* **1**(2), 553–565 (2010).
36. C. Cheung et al., "In vivo cerebrovascular measurement combining diffuse near-infrared absorption and correlation spectroscopies," *Phys. Med. Biol.* **46**(8), 2053–2065 (2001).
37. J. P. Culver et al., "Diffuse optical tomography of cerebral blood flow, oxygenation, and metabolism in rat during focal ischemia," *J. Cereb. Blood Flow Metab.* **23**(8), 911–924 (2003).
38. Y. Shang et al., "Diffuse optical monitoring of repeated cerebral ischemia in mice," *Opt. Exp.* **19**(21), 20301–20315 (2011).
39. C. Zhou et al., "Diffuse optical correlation tomography of cerebral blood flow during cortical spreading depression in rat brain," *Opt. Exp.* **14**(3), 1125–1144 (2006).
40. M. A. Franceschini et al., "The effect of different anesthetics on neurovascular coupling," *Neuroimage* **51**, 1367–1377 (2010).
41. T. Durduran et al., "Transcranial optical monitoring of cerebrovascular hemodynamics in acute stroke patients," *Opt. Exp.* **17**(5), 3884–3902 (2009).
42. M. N. Kim et al., "Noninvasive measurement of cerebral blood flow and blood oxygenation using near-infrared and diffuse correlation spectroscopies in critically brain-injured adults," *Neurocrit. Care* **12**(2), 173–180 (2010).
43. M. N. Kim et al., "Continuous optical monitoring of cerebral hemodynamics during head-of-bed manipulation in brain-injured adults," *Neurocrit. Care* (2013).
44. R. C. Mesquita et al., "Optical monitoring and detection of spinal cord ischemia," *PLoS One* **8**(12), e83370 (2013).
45. G. M. Tellis, R. C. Mesquita, and A. G. Yodh, "Use of diffuse correlation spectroscopy to measure brain blood flow differences during speaking and nonspeaking tasks for fluent speakers and persons who stutter," *SIG 4 Perspect. Fluency Fluency Disord.* **21**, 96–106 (2011).
46. B. L. Edlow et al., "The effects of healthy aging on cerebral hemodynamic responses to posture change," *Physiol. Meas.* **31**(4), 477–495 (2010).
47. R. C. Mesquita et al., "Blood flow and oxygenation changes due to low-frequency repetitive transcranial magnetic stimulation of the cerebral cortex," *J. Biomed. Opt.* **18**(6), 067006 (2013).
48. T. Durduran et al., "Diffuse optical measurement of blood flow, blood oxygenation, and metabolism in a human brain during sensorimotor cortex activation," *Opt. Lett.* **29**(15), 1766–1768 (2004).
49. F. Jaillon et al., "Activity of the human visual cortex measured non-invasively by diffusing-wave spectroscopy," *Opt. Exp.* **15**, 6643–6650 (2007).
50. J. Li et al., "Transient functional blood flow change in the human brain measured noninvasively by diffusing-wave spectroscopy," *Opt. Lett.* **33**(19), 2233–2235 (2008).
51. T. Durduran et al., "Optical measurement of cerebral hemodynamics and oxygen metabolism in neonates with congenital heart defects," *J. Biomed. Opt.* **15**(3), 037004 (2010).
52. E. M. Buckley et al., "Cerebral hemodynamics in preterm infants during positional intervention measured with diffuse correlation spectroscopy and transcranial Doppler ultrasound," *Opt. Exp.* **17**(15), 12571–12581 (2009).

53. E. M. Buckley et al., "Sodium bicarbonate causes dose-dependent increases in cerebral blood flow in infants and children with single ventricle physiology," *Pediatr. Res.* **73**(5), 668–673 (2013).
54. E. M. Buckley et al., "Early postoperative changes in cerebral oxygen metabolism following neonatal cardiac surgery: effects of surgical duration," *J. Thorac. Cardiovasc. Surg.* **145**(1), 196–203 (2013).
55. M. Dehaes et al., "Cerebral oxygen metabolism in neonatal hypoxic ischemic encephalopathy during and after therapeutic hypothermia," *J. Cereb. Blood Flow Metab.* **34**(1), 87–94 (2014).
56. N. Roche-Labarbe et al., "Somatosensory evoked changes in cerebral oxygen consumption measured non-invasively in premature neonates," *Neuroimage* **85**(Pt 1), 279–286 (2014).
57. N. Roche-Labarbe et al., "Near-infrared spectroscopy assessment of cerebral oxygen metabolism in the developing premature brain," *J. Cereb. Blood Flow Metab.* **32**(3), 481–488 (2012).
58. P.-Y. Lin et al., "Regional and hemispheric asymmetries of cerebral hemodynamic and oxygen metabolism in newborns," *Cereb. Cortex* **23**(2), 339–348 (2013).
59. D. A. Boas and M. A. Franceschini, "Haemoglobin oxygen saturation as a biomarker: the problem and a solution," *Philos. Transact. A, Math. Phys. Eng. Sci.* **369**(1995), 4407–4424 (2011).

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