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Bedside optical imaging of occipital resting-state functional connectivity in neonates

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ABSTRACT

Resting-state networks derived from temporal correlations of spontaneous hemodynamic fluctuations have been extensively used to elucidate the functional organization of the brain in adults and infants. We have previously developed functional connectivity diffuse optical tomography methods in adults, and we now apply these techniques to study functional connectivity in newborn infants at the bedside. We present functional connectivity maps in the occipital cortices obtained from healthy term-born infants and premature infants, including one infant with an occipital stroke. Our results suggest that functional connectivity diffuse optical tomography has potential as a valuable clinical tool for the early detection of functional deficits and for providing prognostic information on future development.

Introduction

Survival rates for preterm infants have improved dramatically in recent decades due to advances in perinatal and neonatal care. However, this reduction in mortality has not translated into a reduction in neurodevelopmental morbidity (Fanaroff et al., 2003). More than one half of preterm infants will suffer from neurobehavioral (or functional) impairments in a broad range of motor, cognitive, and behavioral domains (Holsti et al., 2002; Taylor et al., 2004; Woodward et al., 2009), placing a significant burden on families and society (Gilbert, 2006; Korvenranta et al., 2010). Furthermore, there is often a delay in the recognition of functional deficits due to few early behavioral manifestations and a paucity of effective early screening methods (Anderson et al., n.d.; Hack et al., 2005). While recent neuroimaging research using magnetic resonance imaging (MRI) and cranial ultrasonography has provided an understanding of the structural alterations associated with adverse neurodevelopmental outcomes in preterm infants (El-Dib et al., 2010), prediction of later disability remains modest. An enhanced understanding of the nature and timing of alterations in cerebral development associated with preterm birth (and improved predictive power for later disability) is likely to be achieved using methods based on cerebral function rather than structure (Seghier and Huppi, 2010).

Novel imaging methods using functional connectivity MRI (fcMRI) have been employed to define the brain's functional network architecture (Biswal et al., 1995; Fair et al., 2007; Fox et al., 2005; Fox and Raichle, 2007). These techniques are based on the synchronous, spontaneous fluctuations of cerebral blood flow in different regions of the brain that are functionally, yet not necessarily anatomically connected. These resting-state approaches have the advantage of mapping many different networks simultaneously and (importantly for infants) of not requiring the subject to perform tasks. Recent fcMRI studies have begun to establish the patterns of longitudinal functional network development (Fair et al., 2007; Fransson et al., 2007, 2009; Lin et al., 2008; Smyser et al., 2010). However, MRI techniques pose significant logistical barriers for use in preterm infants, largely related to challenges in transportation to the MRI scanner. Access is most difficult for the smallest and sickest prematurely born infants; yet these infants are at greatest risk for adverse neurodevelopmental outcomes. In addition, as cerebral structure and function are evolving rapidly from 24 weeks postmenstrual age (PMA) to term equivalence, frequent serial scanning (e.g., daily or weekly), which is not practical with MRI, may reveal the development of disease or disability over the neonatal intensive care course. Thus, the development of a bedside method to define

Abbreviations: Fc, functional connectivity; DOT, diffuse optical tomography; HbO_2, oxyhemoglobin; HbR, deoxyhemoglobin; HbT, total hemoglobin.

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functional networks in the preterm infant would allow serial evaluation of functional cerebral development in all infants within the neonatal intensive care unit setting.

Optical neuroimaging methods could potentially fulfill this role. Using a non-invasive measurement of hemoglobin absorption spectra as used in pulse oximetry, optical systems map the concentrations of both oxy- (HbO_2) and deoxy- (Hb_R) hemoglobin. At its simplest, this technique can be used with distinct (or "sparse") source-detector pairs, each over a brain region of interest—an implementation usually called near infrared spectroscopy (NIRS). However, standard NIRS systems take only a few widely distributed measurements and are thus limited with regard to comprehensive brain mapping. Additionally, they can suffer from drawbacks. First, as every measurement is a mixture of hemodynamics occurring in multiple tissue layers, it can be difficult to discriminate the brain signal of interest (Gregg et al., 2010). Second, the large gaps between measurements result in low spatial resolution and a decreased ability to correctly localize activations (White and Culver, 2010a).

In order to overcome these limitations, diffuse optical tomography (DOT) systems have been developed (Bluestone et al., 2001; Hebden et al., 2004; Joseph et al., 2006; Wylie et al., 2009; Zeff et al., 2007). Improved source and detection instrumentation allows measurements that overlap both laterally and in depth. The entire set of measurements can be inverted to create a 3D reconstruction of hemodynamic changes (in much the same way as a CT scan is derived from multiple X-rays) (Arridge, 1999). DOT systems thus have improved spatial resolution and the ability to distinguish superficial noise from the brain signal of interest.

As DOT combines the portability and cap-based scanning of EEG with spatial resolution high enough to create detailed cortical maps (White and Culver, 2010a, 2010b), it has the potential to be a powerful bedside clinical neuroimaging tool. Recently, functional connectivity methods have been extended to high density DOT (fcDOT) in adults (White et al., 2009) and have been subsequently developed with sparse NIRS topography in adults (Lu et al., 2010) and infants (Homae et al., 2010). In this paper, we apply fcDOT to bedside imaging of neonates within the first month of life, further developing pilot studies in infants that have demonstrated the feasibility of high-density imaging arrays in the neonatal environment (Liao et al., 2010). We show fcDOT images in both term and premature infants. Additionally, we show how these maps can be disrupted through brain injury. As these proof-of-concept results are extended, we expect that fcDOT can become an important diagnostic and prognostic tool for neonatologists.

Materials and methods

Subjects

Subjects were recruited from the nurseries of Barnes-Jewish and St. Louis Children's Hospitals. Informed consent was acquired from the infants' parents. The study was approved by the Human Research Protection Office of Washington University in St. Louis. We scanned three term-born and five premature infants. One preterm infant had a unilateral occipital stroke. Another preterm infant had significant morbidities including extreme prematurity (born at 23 5/7 weeks of gestation), chronic lung disease, high stage retinopathy of prematurity, and bowel perforation. This infant had evidence of evolving grade III intraventricular hemorrhage (IVH) on serial cranial ultrasounds, but the term-equivalent MRI of the head showed only minimal anatomical abnormalities. All other preterm infants had relatively less complicated hospital courses. The term-born infants were scanned within the first three days of life. Each premature infant was scanned once, at a time point based on availability during his/or hospitalized course (see Table 1 for specifics). Relevant demographic and clinical information about the patients is included in Table 1. All infants were scanned in their bassinets or incubators while quietly resting or sleeping (although sleep state was not actively monitored) (Liao et al., 2010).

Table 1
Subject demographic and clinical information.

Subject code	Gestational age at delivery	Gestational age at DOT scan	Relevant clinical remarks
Term1	38 6/7	39 1/7	Healthy term infant
Term2	41 1/7	41 3/7	Healthy term infant
Term3	39 0/7	39 2/7	Healthy term infant
Preterm1	30 6/7	33 3/7	IUGR*, no known CNS injury
Preterm2	28 2/7	30 1/7	IUGR*, BPD†, grade I IVH**
Preterm3	24 6/7	32 5/7	BPD†, no known CNS injury
Preterm4	23 5/7	39 2/7	BPD†, intestinal perforation, ROP‡, grade III IVH**
Preterm5	30	40	BPD†, left occipital hemorrhage

IUGR* = intrauterine growth retardation; BPD† = bronchopulmonary dysplasia; IVH** = intraventricular hemorrhage; ROP‡ = retinopathy of prematurity.

DOT data collection

For this study, we used a custom-built high-density DOT system (Zeff et al., 2007) with an optode array consisting of 18 sources and 16 detectors (Fig. 1A) for 106 total measurements. Each source position consisted of two near infrared wavelengths (750 nm and 850 nm) of light emitting diodes (LEDs). The system operates in continuous-wave mode with a frame rate of 10.78 Hz. The imaging cap consisted of flexible optical fiber bundles embedded in a silicone array. This soft pad was held against the head using neoprene straps and Velcro. The array was placed just superior to the inion, in order to be superficial to the occipital (visual) cortex (Fig. 1B). All scans were taken within 2 h after feeding in an isolated, dimly lit room either in the nursery at Barnes-Jewish Hospital or in the Neonatal Intensive Care Unit (NICU) at St. Louis Children's Hospital. The total duration of the resting-state data acquisition ranged from 10 to 20 minutes depending on the cooperativeness of the infant.

Data pre-processing

Resting state data were acquired using the DOT system with good signal-to-noise well above the noise floor (Fig. 1C). The data were cleaned of both motion artifacts and superficial hemodynamic signals. Motion artifacts are visible as sharp changes in intensity across many channels in the raw intensity measurements. Using this visual identifier of motion, time periods with no visible artifacts were chosen for further analysis (yielding data of lengths between two and eleven minutes). The source-detector data was converted to log-ratio data consistent with the tomographic data inversion routine (Rytov approximation) and was filtered to the frequency band of 0.009 to 0.08 Hz following fcMRI and fcDOT algorithms (Fox et al., 2005; White et al., 2009).

Physiological noise was reduced using a superficial signal regression procedure (Gregg et al., 2010). The source-detector measurements with the shortest separations (called first-nearest neighbors) are separated by 1 cm and are primarily sensitive to the scalp and skull. Second-nearest neighbors (2.2 cm separation) have significantly greater sensitivity to the brain. To remove systemic and superficial hemodynamics we linearly-regressed out an average of the first-nearest neighbor measurements from all of the individual measurements (Gregg et al., 2010; Saager and Berger, 2005, 2008; Zeff et al., 2007). In order to reject measurements with motion artifacts or poor optode coupling to the head, source-detector channels with high standard deviation (>7.5%) are excluded from further analysis. An average first-nearest neighbor measurement had a standard deviation of 1.6%, and an average second-nearest neighbor, 3.0%. So, the adopted standard deviation threshold can exclude abnormally large variations while preserving normal physiology. Within a range, the reconstruction is relatively insensitive to the exact threshold chosen. Across all sessions, this