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Abstract: During neural activity, increases in glucose and oxygen consumption and release of vasoactive neurotransmitters cause a local increase in cerebral blood fl ow (CBF) [1] and cerebral blood volume (CBV). Increases in oxygen consumption are signifi-cantly lower than increases in CBF and as a result we see a net increase in the amount of oxygen in the blood and tissue [2]. Typical measures of neural activity in adults with near-infrared spectroscopy (NIRS) show a local increase in oxy-hemoglobin concentration (HbO) and a decrease in deoxy-hemoglobin concentration (HbR), which corresponds to a local increase in BOLD signal measured with fMRI. In many neonatal functional studies inversions of these hemoglobin signals have been reported, across visual [3, 4], olfactory [5], sensory-motor [6] and auditory [7] cortices. In general, the inversion starts at a few weeks of age. The reason for such an inversion in the functional hemodynamic signals is not yet understood. We hypothesize that changes in hematocrit during the transition from fetal to adult hemoglobin and the consequent period of low hematocrit cause such an inversion. To test this hypothesis, we performed a longitudinal auditory functional study in premature infants.

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The Confounding Effect of Systemic Physiology on the Hemodynamic Response in Newborns

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1. Introduction

During neural activity, increases in glucose and oxygen consumption and release of vasoactive neurotransmitters cause a local increase in cerebral blood fl ow (CBF) [1] and cerebral blood volume (CBV). Increases in oxygen consumption are signifi-cantly lower than increases in CBF and as a result we see a net increase in the amount of oxygen in the blood and tissue [2]. Typical measures of neural activity in adults with near-infrared spectroscopy (NIRS) show a local increase in oxy-hemoglobin concentration (HbO) and a decrease in deoxy-hemoglobin concentration (HbR), which corresponds to a local increase in BOLD signal measured with fMRI. In many neonatal functional studies inversions of these hemoglobin signals have been reported, across visual [3, 4], olfactory [5], sensory-motor [6] and auditory [7] cortices. In general, the inversion starts at a few weeks of age.

The reason for such an inversion in the functional hemodynamic signals is not yet understood. We hypothesize that changes in hematocrit during the transition from fetal to

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adult hemoglobin and the consequent period of low hematocrit cause such an inversion. To test this hypothesis, we performed a longitudinal auditory functional study in premature infants.

2. Materials and Methods

We recruited six premature neonates from either the neonatal intensive care unit (NICU) or the Well Baby Nursery at the Massachusetts General Hospital (MGH) [26–33.4 weeks, mean 30 weeks gestational age (GA)]. All of the neonates had APGAR scores between 6 and 9 after 5 min. We conducted a total of 18 recording sessions, with an average of three sessions per infant (range: 2–5). The age of the infants at the time of each session ranged from 1 to 11 weeks of age, with a mean of 5.5 weeks [30–38 weeks, mean 35 weeks corrected gestational age (CGA)]. Our Institutional Review Board approved the study and parents provided informed consent.

All measurements were done at the infant's bedside. The protocol consisted of two parts: a measure of evoked hemodynamic changes in response to auditory stimuli (functional measurements) with a continuous-wave (CW-NIRS) system, and a measure of baseline hemoglobin concentration and oxygenation during rest (baseline measurements) with a frequency-domain system (FD-NIRS).

2.1 Functional Measurements

Auditory stimuli consisting of computer-generated repetitive syllables (e.g., "ma, ma, ma," or "bi, bi, bi") read by a female computer voice (AT&T Labs, Inc., Florham Park, NJ) were presented in periods of 6 s followed by 6- to 16-s periods of silence (event-related presentation). Depending on cooperativeness of the baby, a session consisted of four runs of 250 s and 15 stimulation periods each. A sound-level meter allowed us to adjust the volume of the sound to a level of 60–65 dB.

For the functional measurements, we used a commercial continuous-wave NIRS imaging system (CW4, TechEn Inc.) with 18 laser sources and 16 avalanche photo diode (APD) detectors [8]. Light from the sources is conducted to the functional probe and from there to the detectors by means of fiber-optic bundles. Each source fiber combines the light of a 690- and an 830-nm laser. For these measurements, we used three source and six detector positions. The custom-made probe was made of black latex-free rubber and cushioning foam, and sources and detectors were arranged in two rows with a minimum source–detector distance of approximately 2.5 cm. The functional probe was positioned over the left auditory cortex and fixed in position with sterile, self-adhesive elastic gauze. Data were acquired continuously during the functional runs and down-sampled to 10 Hz.

2.2 Baseline Measurements

The baseline hemoglobin measurements were performed a few minutes after the functional measurements, with a customized near-infrared frequency-domain oxime-ter (ISS Inc., Champaign, IL, USA), as in [9, 10]. The system includes 16 laser sources emitting at eight wavelengths with two redundant pairs (659, 2 × 685, 755, 778, 798 and 2 × 825 nm) and two photomultiplier tube (PMT) detectors. The sources are modulated at 110 MHz, and the detectors at 110.005 MHz, to achieve heterodyne detection. Separation of the sources is achieved by rapid (10 ms) multiplexing. Two groups of eight lasers (~1 mW power each) are combined into two source fiber bundles, and each detector is coupled to a fiber bundle. The fiber bundles are arranged in a row on a black rubber probe with source–detector distances of 1, 1.5, 2, and 2.5 cm. Multiple distances are necessary to quantify tissue optical properties and to derive hemoglobin concentration and saturation with this system. The probe was

hand-held above the left-temporal position for 8 s and the measure was repeated 3–5 times as in [9].

2.3 Data Analysis

CW-NIRS data were analyzed with a new version of Homer (Homer 2) which, instead of working with a graphical user interface [11], is fully script-based and allows for comfortable batch processing of all measurements with the same parameters for an unbiased analysis. First the data are converted from light intensity to changes in optical density (ΔOD). Segments of data showing rapid changes in optical density larger than a preset threshold of 1.5% are discarded as motion artifacts. Remaining evident motion artifacts are manually removed. If the motion artifacts occur during a stimulus period, that stimulus is removed from the average. Channels with low SNR or with Fourier spectra that do not show an arterial pulsation peak are removed. The 10 Hz ΔOD data are then band-pass-filtered between 0.02 and 0.5 Hz to remove slow drift and arterial and respiratory oscillations. To remove 0.1 Hz Mayer oscillations and remaining noise common to all channels, we performed principal component analysis (PCA) and removed principal components that described up to 75% of temporal covariance. Finally, the optical densities are converted to oxy and deoxy-hemoglobin concentration (HbO, HbR) changes using the modified Beer–Lambert law and all stimulation sequences in a subject are block-averaged. To quantify the amplitude of HbO and HbR changes, we calculated the difference between the mean concentration of the last second of stimulation and the last second before stimulation. For every subject, the channel with the largest HbO absolute change is selected and reported and further analyzed.

Frequency domain multi-distance and multi-wavelength data are used to quantify baseline hemoglobin concentration and tissue oxygenation. To achieve standardized analysis of the FD-NIRS data, an automated routine developed in [10] was used. This script includes data quality assessment and rejection based on previously established statistical criteria. In particular, measurements were discarded if $R^2 < 0.9$ for the fit of the raw optical data (amplitude and phase) to the light transportation model, if $p > 0.05$ for the fit of the absorption coefficients with the hemoglobin spectra, and for a linear fit of the reduced scattering coefficient versus wavelength.

3. Results

3.1 Baseline Measurements

In agreement with previous results [9, 10], we found that, at ~ 4–6 weeks of age, total hemoglobin concentration (HbT) and HbO have a minimum corresponding to the minimum of hematocrit due to conversion of fetal to adult hemoglobin (see Fig. 16.1a, c). In contrast, HbR concentrations during the first 6 weeks of life remain constant (see Fig. 16.1b) probably because of two counterbalancing factors: decrease of hemoglobin in the blood because of faster depletion of fetal hemoglobin than formation of adult hemoglobin and increase of oxygen extraction fraction with adult relative to fetal hemoglobin. After this initial period HbR increases as HbO and HbT. Consequently, tissue oxygenation (StO_2) decreases during the first 6 weeks of life and then becomes constant (see Fig. 16.1d). As in our previous studies, we did not observe any correlation between any hemoglobin parameter and corrected gestational age.

3.2 Functional Measurements

We observed the expected increase in ΔHbO with stimulation in only 7 out of 18 cases. The remaining 11 measurements showed a decrease in ΔHbO with stimulation. In all but one case ΔHbT followed ΔHbO and in all but four cases ΔHbR was inversely proportional to Δ

HbO. The inverted hemoglobin responses are not correlated with age or corrected gestational age (see Fig. 16.2b, c), but all occur between ages 3 and 8 weeks, when hematocrit and hemoglobin are low. Though for most of these babies we did not have a direct measure of hematocrit on the day of the measurement, we do have the measure of baseline cerebral hemoglobin and we can correlate it with the functional hemoglobin changes. If we divide the ΔHbO responses into two groups, positive and negative, we found a strong correlation between the sign of the functional changes and the baseline total hemoglobin concentration (p-value =0.002 for HbT (two-sample, two-tailed, unequal variance T-test), p-value = 0.01 for HbO and HbR). The R^2 of the scatter plot of ΔHbO versus baseline HbT is 0.5. More importantly we found that, for baseline HbT lower than 38 μM all ΔHbO were negative, while for baseline HbT larger than 38 μM, all but one ΔHbO were positive (see Fig. 16.2a). Results were similar when considering baseline HbO or HbR. Results for ΔHbT were consistent with the results for ΔHbO, while results for ΔHbR were less statistically significant (p-value = 0.026 between ΔHbR and baseline HbR, larger than 0.05 for the HbO and HbT) probably due to the smaller changes in ΔHbR with respect to ΔHbO, and to consequent larger relative noise.

4 Conclusions

Our results show that the inversion in the functional hemodynamic responses in infants correlates with the total hemoglobin concentration. We used auditory stimuli which is known to cause neuronal activity in premature babies 30 weeks GA and older. While neural activity increases with age because of an increase in synapto-genesis and increasing synaptic density, an inversion of the hemodynamic responses is difficult to explain solely based on neural activity differences in the period 3–8 weeks of age. Our results suggest that while neural activity and metabolic demand increase with age, the available hemoglobin supply during the low hematocrit period is not sufficient to overcome oxygen demand during functional activation. We are developing a mathematical model to describe these results.

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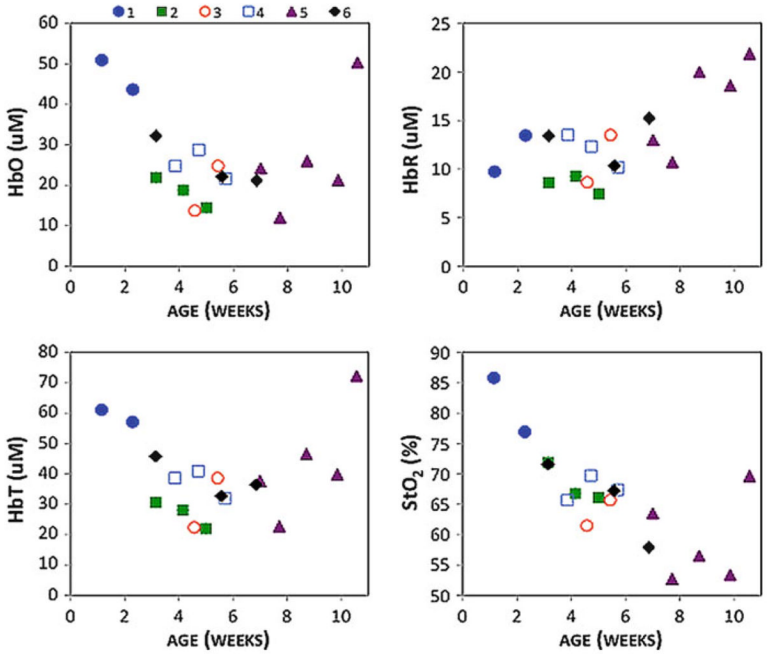

Fig. 16.1.

(a) Scatter plot of baseline oxy-hemoglobin (HbO) versus age, **(b)** deoxy-hemoglobin versus age, **(c)** total hemoglobin versus age, and **(d)** tissue oxygen saturation versus age. Different babies are indicated by different symbols

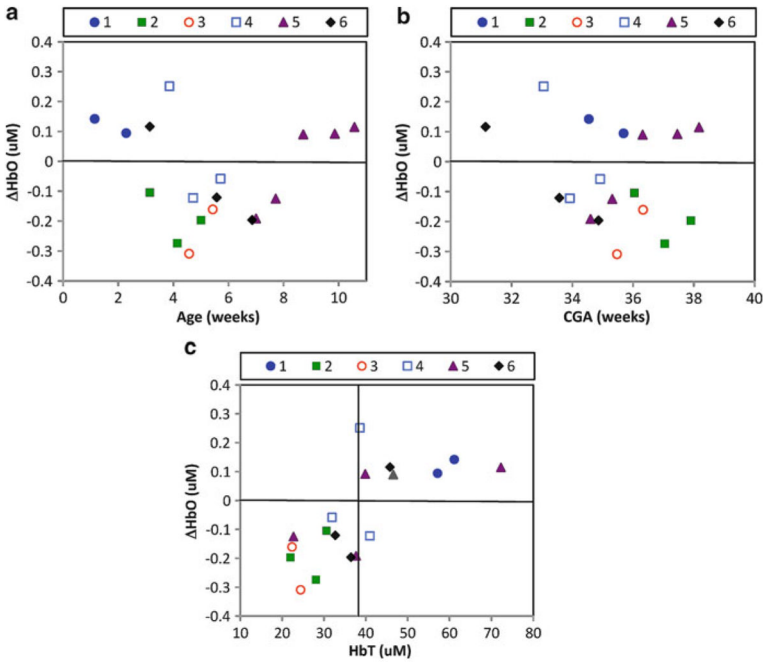

Fig. 16.2.

(a) Scatter plot of functional oxy-hemoglobin changes (ΔHbO) versus baseline total hemoglobin concentration (HbT), **(b)** ΔHbO versus age, and **(c)** ΔHbO versus corrected gestational age. Different babies are indicated by different symbols. A line through the zero *y*-axis is shown in all graphs. Also in **(a)** a *dashed line* at 38 μM *x*-axis divides the data in two groups: negative and positive ΔHbO changes