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Association between hemodynamic activity and motor performance in six-month-old full-term and preterm infants: a functional near-infrared spectroscopy study

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Abstract. This study aimed to assess task-induced activation in motor cortex and its association with motor performance in full-term and preterm born infants at six months old. A cross-sectional study of 73 six-month-old infants was conducted (35 full-term and 38 preterm infants). Motor performance was assessed using the Bayley Scales of Infant Development third edition—Bayley-III. Brain hemodynamic activity during motor task was measured by functional near-infrared spectroscopy (fNIRS). Motor performance was similar in full-term and preterm infants. However, differences in hemodynamic response were identified. Full terms showed a more homogeneous unilateral and contralateral activated area, whereas in preterm-born the activation response was predominantly bilateral. The full-term group also exhibited a shorter latency for the hemodynamic response than the preterm group. Hemodynamic activity in the left sensorimotor region was positively associated with motor performance measured by Bayley-III. The results highlight the adequacy of fNIRS to assess differences in task-induced activation in sensorimotor cortex between groups. The association between motor performance and the hemodynamic activity require further investigation and suggest that fNIRS can become a suitable auxiliary tool to investigate aspects of neural basis on early development of motor abilities.

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1 Introduction

Premature infants are at high risk for neurodevelopmental impairment even in the absence of any identifiable event involving possible brain injury.¹ Motor development is one of the most affected areas by premature birth, potentially causing a substantial number of limitations in later life.² Advanced motor skills are determined by a brain and neuromuscular maturation,³ in addition to factors such as physical growth, caregiving practices, opportunities for practicing emerging skills, and favorable emotional, social, and environmental conditions.⁴

Since human neurodevelopment is a dynamic interplay between biology and environment, and it can be changed by interventions in one of these features, it is interesting to have accurate instruments to identify early disabilities in infants at risk for neurodevelopment delays, as in prematurely born infants.⁵ This has aroused interest in the understanding of how brain activity relates to the manifestation of a particular behavior or action, especially at early stages of neurodevelopment. Improving our understanding of these factors could be helpful in ameliorating our ability to identify and measure impairments in the course of early childhood development.

The motor and sensory areas appear particularly sensitive to events in late pregnancy since fetal development is rapid between 20 and 37 weeks of gestational age (GA),⁶ and many of the sensorimotor networks are initially established during the second half of gestation.⁷ Motor and sensory areas are one of the most common sites of perinatal brain damage probably due to their high sensibility aforementioned.⁶

In this context, functional near-infrared spectroscopy (fNIRS) appears to be a promising technique for child development studies offering greater safety and operability.⁸ The principles of fNIRS are based on the fact that neural activity is accompanied by changes in oxygenation and also in cerebral blood flow and blood volume.⁹ In fNIRS, changes in oxy-hemoglobin (HbO), deoxy-hemoglobin (HbR), and total hemoglobin concentrations are estimated by detecting near-infrared light (~700 to 900 nm) scattered from tissue, which allows one to evaluate quantitatively and qualitatively hemodynamic changes in microvasculature due to brain activation.

Considering the importance for improving early motor skills measures, especially in preterm infants, we compared, in a transversal study, six-month-old full-term and preterm infants performing a motor task registering their cortical hemodynamic

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responses using fNIRS and its association with motor performance results.

2 Materials and Methods

2.1 Study Design

This was a cross-sectional study performed between September 2013 and April 2015. Motor performance and cortical activity assessments were evaluated during a single session, at six months of age. For preterm infants, we considered their corrected age. All parents gave their written informed consent, and the study was approved by the Human Ethics Committee of the Federal University of Minas Gerais (UFMG), Brazil. The study was in accordance with the Helsinki Declaration.

2.2 Participants

Seventy-three infants participated in this study were allocated into two groups: full term and preterm. Both groups were born between 2013 and 2014 at the maternity unit of the UFMG University's Hospital. The full-term group included 35 infants born with GA > 37 weeks and with no known medical diagnoses or delays. The preterm group included 38 infants born at the same maternity hospital with GA < 34 weeks. They were recruited from the institution's follow-up program for high-risk children. Infants with severe sensory impairments (blindness, deafness), cerebral palsy, genetic syndromes or any malformation, congenital heart defects, Apgar score less than 7 at 5 min, intraventricular hemorrhage grade 3 or 4, and periventricular leukomalacia, were excluded. All children underwent a cranial ultrasound to exclude morphological brain abnormalities.

We obtained fNIRS data from 51 infants (26 full-term and 25 preterm). The remaining 22 infants were tested but not included in the sample due to high motion artifacts caused by: (i) crying during the experiment ($n = 16$); (ii) large head movements ($n = 4$); and (iii) stimulus refusal ($n = 2$). All 73 infants' motor development was assessed before the fNIRS experiment.

2.3 Procedures

2.3.1 Characterization of the studied population

Information such as infant birth data, socioeconomic status (SES), and neonatal morbidities were collected from medical records. SES was assessed by the Brazilian Economic Classification Criterion (CCEB).¹⁰ The CCEB is an economic segmentation tool that uses household characteristics to classify population according to average monthly income. CCEB results were categorized into two groups considering monthly income values: "monthly income > \$455" and "monthly income < \$455."

2.3.2 Motor performance assessment

Motor performance was assessed using the motor scale of the Bayley Scales of Infant Development (BSID), composed by fine and gross motor subtests.¹¹ The BSID is the most commonly used instrument to assess early development, both in clinical practice and research settings. The last edition, Bayley-III, includes five distinct scales to assess cognitive, receptive/expressive communication, social-emotional, adaptive behavior, and fine/gross motor development.¹¹ The Bayley-III assesses developmental functioning through items administered

in a structured play format. The motor composite score was calculated by using test norms (mean = 100; SD = 15).¹¹

The same researcher conducted all motor development assessments. Infants who scored in the delayed range on the Bayley-III were included in the study and readily referred to pediatric follow-up at the institution where the study was developed.

2.3.3 Functional experimental protocol

We performed a motor functional activation experiment with a block paradigm. The motor stimulus consisted of a vibration produced by a microdirect current motor (coreless motor 9321, 6 × 10 mm, 6200 R/min or 103.3 Hz) that was held against the infant's right hand.

The motor stimulus was presented for 8 s of continuous stimulation followed by a 20 s rest period between trials [Fig. 1(a)]. In total, we performed eight trials of the task. Trials affected by motion artifacts were discarded. Each infant contributed with at least four blocks of motor data. The infants were seated on their parent's lap during the trial [Fig. 1(b)]. To reduce motion artifact during the experiment, they watched a colorful silent video throughout the data acquisition protocol.

2.3.4 Near-infrared spectroscopy acquisition and analysis

Hemodynamic activity in response to functional activation of motor areas was assessed by a commercial continuous-wave near-infrared spectroscopy (NIRS) equipment (NIRScout Tandem 1616, NIRx Medical Technologies, Glen Head). The system employs 32 sources (each source has 2 LED emitters at 760 and 850 nm) and 32 detectors. The optodes were bilaterally positioned in the frontal, parietal, temporal, and occipital areas, according to the international 10–20 system coordinates¹² [Fig. 1(c)]. In this study, we used 30 sources and 28 detectors, providing 84 different source–detector combinations (channels) with source–detector distances ranging from 1.9 to 3.5 cm. From the 84 channels, 38 of those were positioned in the frontal lobe and 16 channels were located in the parietal lobe. The temporal and occipital lobes contained 22 and 8 channels, respectively. More importantly, the probe had 10 channels per hemisphere positioned in the sensorimotor cortex.

For fNIRS data analysis, we used homemade scripts based on HomER 2 functions¹³ in MATLAB (Mathworks, Inc., Natick, Massachusetts). First, channels with low signal-to-noise ratio (SNR) were discarded from analysis. By analyzing the power spectrum, we empirically found that for infants' data and our commercial system, channels with SNR < 8 contain no significant hemodynamic information when compared to noise. Therefore, a threshold of 8 for SNR was employed in channel removal. With the remaining channels, motion artifacts were visually inspected and manually removed from the data. Detected light intensity for each channel was bandpass filtered between 0.003 and 0.5 Hz to eliminate DC trends and physiological interference (mostly heartbeat, breathing) and high-frequency artifacts. Then, time series of hemodynamic concentrations were computed for each channel by using the modified Beer–Lambert's law.¹⁴

For each subject, the hemodynamic response function (HRF) of each channel was independently obtained by averaging all trials from 5 s before the start of stimulation until 20 s after the beginning of the stimulation. For each channel, we compared the amplitude of the time points during the period of stimulation to the amplitude of the time points during the

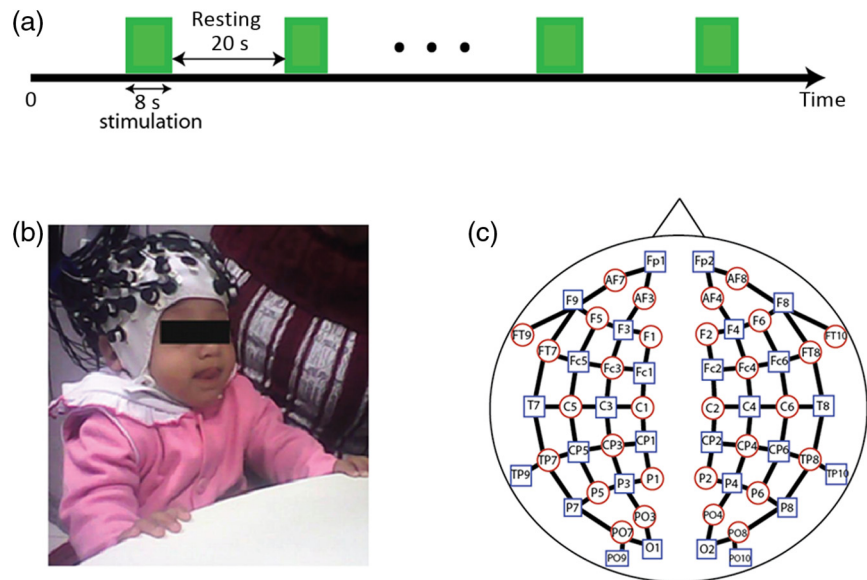


Fig. 1 (a) Functional experimental protocol consisting of 8 trials of 8 s of motor stimulation followed by 20 s of resting. (b) Photo of a six-month-old infant in its mother's lap during fNIRS acquisition. (c) Topographic (two-dimensional) figure showing the arrangement of all sources (red circles) and detectors (blue squares) according to the international 10–20 system coordinates. The source–detector combinations (channels) used in this study are represented by the black solid lines.

baseline (i.e., prior to stimulation). The activated channels were defined as the channels that showed a significant increase of amplitude in HbO during the stimulation and a significant decrease of amplitude in HbR during the stimulation, when compared to baseline. Here, significance was measured with the standard z -score between the two distributions of time points (baseline versus stimulation). This procedure compares the mean of the time points during the stimulation with the mean of the time points during baseline, considering the standard deviation of the sample during the baseline period. It is also worth noting that all analysis was performed independently for each channel, since we were also interested in analyzing spatial differences induced by the functional task across subjects.

Quantitative parameters were extracted from the HRF for posterior analysis for both HbO and HbR independently. To avoid misinterpretation of NIRS-based parameters due to noise fluctuations, we fit the HRF to a least squares moving average model with a period of five time points. Then, we quantified the magnitude of the activation as the amplitude of the HRF at 80% of its maximum and its latency as the time to reach 80% of its maximum amplitude. The integrated response during activation was estimated by calculating the area under the HRF, from the beginning of activation until the time it comes back to baseline.

2.4 Statistical Analyses

We compared the full-term and preterm groups regarding motor performance scores on Bayley-III, socioeconomic, and perinatal data employing chi-square tests (categorical/ordinal data) or independent samples t -tests (linear/scale data), after verifying for normality of data. Quantitative data of NIRS-based hemodynamic response (latency, magnitude of the activation, and the integrated response during activation) were expressed as the mean (M) and standard deviation (SD) for the group. Using Spearman's correlation, we estimated the association

between the HRF values of activated channels across the sensorimotor region and Bayley-III scores in the total sample. Statistical significance was established at 0.05.

3 Results

Table 1 presents a summary of descriptive statistics for infant birth data, SES, neonatal morbidities, and motor performance, assessed by Bayley-III. There were no significant differences regarding motor performance between full-term and preterm groups (full-terms: $M = 109.11$, $SD = 10.34$; preterm: $M = 106.04$, $SD = 14.85$; $p = 0.89$).

Concerning the hemodynamic response measured with fNIRS, we observed robust activation in at least one channel located in the contralateral sensorimotor cortex for all infants in both groups. Across all infants, we observed a highly localized, bilateral response in the sensorimotor cortex in both groups (Fig. 2). On average, the full-term group has more channels activated, both in the contralateral and ipsilateral sensorimotor cortex than the preterm groups. The HRF in the preterm-born appears to be more localized than the functional response in the full-terms.

However, careful inspection of data showed that no infant in any group had significant activation in all the channels indicated in Fig. 2. Instead, the activation profile varied greatly in infants within the same group, as well as the total number of activated channels. In order to better understand the common activation pattern across all infants from the same group, we performed a frequency analysis considering only channels that showed activation in at least 50% of the subjects in that group. Unlike typical average responses shown in Fig. 2, the frequency analysis procedure allowed us to find the most common and repetitive response across all subjects in a group. The threshold of 50% was arbitrarily chosen so that the channels reflected robust activation in the majority of the subjects within the same group. Figures 3(a) and 3(b) shows the topographic map of the frequency analysis, with the channels color-coded by frequency

Table 1 Demographic data and group comparisons in six-month-old full-term and preterm-born infants.

Measures	Full term	Preterm	Test	<i>p</i>	
Perinatal characteristics					
Birth weight (g) ^a	3,261(±446)	1,123(±475)	30.81	<0.001	
GA (weeks) ^a	39(±1.05)	31(±1.83)	18.66	<0.001	
Male gender ^b	16 (61%)	8 (36%)	3.66	0.068	
SES ^b	>455 monthly	6 (24%)	9 (45%)	0.729	0.460
	<455 monthly	19 (76%)	11 (55%)		
Days in neonatal unit ^a	—	15.60(±12.11)	—	—	
Retinopathy of prematurity ^b	—	5 (23%)	—	—	
Intraventricular hemorrhage (grade I or II) ^b	—	16 (73%)	—	—	
Bronchopulmonary dysplasia ^b	—	3 (14%)	—	—	
Necrotizing enterocolitis ^b	—	1(4%)	—	—	
Motor development measurements at six months old					
Bayley-III motor composite score ^a	109.11 (10.34)	106.04 (14.85)	0.82	0.89	
Age at motor develop. assessment (days) ^b	205.23 (2.05)	195.96 (2.98)	2.57	0.13	
Head circumference (cm) ^a	43.87 (0.47)	43.56 (0.37)	-0.51	0.63	

^aContinuous data were expressed as mean (standard deviation) and compared using independent samples *t*-test.

^bCategorical data were expressed as *n* (%) and compared with chi-square test.

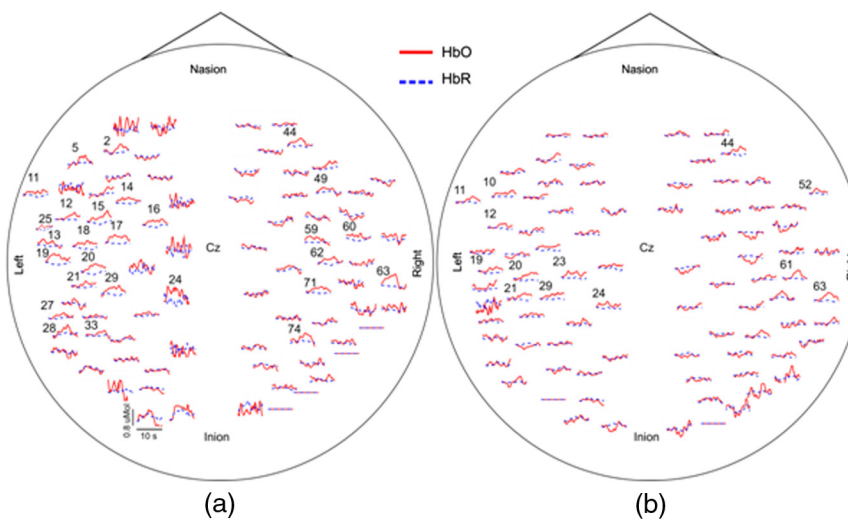


Fig. 2 Average HRF of all individual channels for all the infants in the (a) full-term and (b) preterm-born groups. The numbers next to some of the HRFs indicate the channels that show significant activation compared to baseline. They are mostly located in the sensorimotor cortex. Additional channels, located anterior and posterior to the sensorimotor cortex, also exhibited increase (decrease) in HbO (HbR) on average.

of activation in the group, for both the full-term and the preterm groups.

It is possible to note that the HRF of the full-term born group in the contralateral sensorimotor cortex is quite reproducible

across infants in the group [Fig. 3(a)]. Eight different channels in this region responded to the stimulation in at least 50% of the subjects. Although full-term born infants showed activation in different channels around the ipsilateral sensorimotor cortex, the

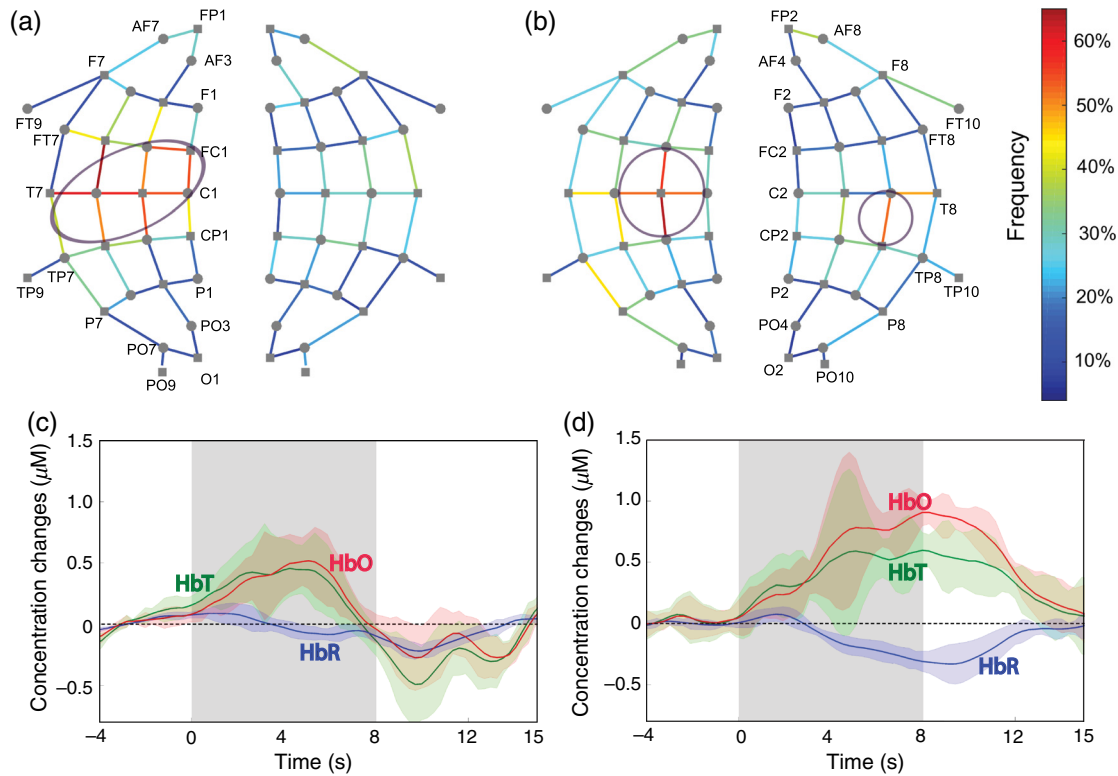


Fig. 3 Topographic map based on frequency of activation of each channel for infants in the (a) full-term and (b) preterm-born groups. The black circles in the maps identify the most frequent channels in the somatosensory cortex. No other channel in a different location reached our threshold. The average HRF across the channels that showed reproducibility (i.e., response in more than 50% of infants) in the contralateral sensorimotor cortex is plotted in (c) for the full-term born group and in (d) for the preterm-born. In the graphs, the gray area represents the stimulation period, and the dashed black line indicates the baseline level. The shadows indicate the standard error across all channels and all subjects.

ipsilateral response is quite heterogeneous; no individual channel in the ipsilateral sensorimotor cortex was activated in more than 8 (31%) full-term born infants.

On the other hand, the preterm group presented a more heterogeneous activation pattern across all its subjects in the contralateral sensorimotor cortex [Fig. 3(b)]. Only four channels are frequently used in the majority of infants in the preterm group. However, in the ipsilateral sensorimotor cortex of the preterm group, the response was more reproducible, with two channels being constantly used by the infants.

Considering only the most reproducible channels in the contralateral sensorimotor cortex for each group, we observed an average (standard error) HbO increase of $0.51(0.03) \mu\text{M}$ from baseline in full-term born, whereas the average HbR decrease for the same group was $-0.22(0.03) \mu\text{M}$. Similarly, the average HbO increase from baseline across all preterm subjects was $0.71(0.04) \mu\text{M}$ in the contralateral sensorimotor cortex, whereas the HbR decrease in the same region was $-0.33(0.02) \mu\text{M}$. We did not observe any significant differences between the two groups regarding the activation's amplitude ($p = 0.9$ and $p = 0.4$ for HbO and HbR, respectively).

Concerning the dynamics of the hemodynamic response, the HbO changes in the contralateral sensorimotor cortex had a mean (standard error) latency of $5.1(0.7)$ s in the full-term born group, which is significantly faster than the response found in the preterm group, $8.2(0.9)$ s ($p = 0.03$). The time for HbR to reach its minimum did not vary between the groups

(9.4 ± 0.8 s and 9.8 ± 1.1 s for full-term and preterm-born groups, respectively). In addition, the integrated HbR response (measured as the area under the curve) varied significantly between groups ($p = 0.03$). The full-term born had a mean HbR decrease of $4.2 \pm 1.9 \mu\text{M}\cdot\text{s}$ following motor stimulation in the contralateral hemisphere, whereas the preterm infants had a larger HbR decrease from baseline, $8.3 \pm 2.5 \mu\text{M}\cdot\text{s}$. We did not observe any significant difference between the groups in the integrated HbO response.

Correlation analysis was calculated between the HRF values of the reproducible activated channels in sensorimotor region [as detailed in Figs. 3(a) and 3(b)] and Bayley-III motor scores in the total sample. We identified that the HRF in the channels FC3–C3, C5–F7, and C3–CP3 was positively associated with motor performance measured by the Bayley-III (FC3–C3: Spearman's $\rho = 0.315$, $p = 0.020$; C5–F7: Spearman's $\rho = 0.320$, $p = 0.022$, and C3–CP3: Spearman's $\rho = 0.308$, $p = 0.028$).

4 Discussion

Using an event-related design, we were able to characterize the hemodynamic response to motor stimulation in six-month-old full-term and preterm born infants with similar motor performance. From the average approach, we observed that both groups exhibited a bilateral activation response to unilateral right-hand stimulation. These results are in agreement with previous studies using different patterns of somatosensory

stimulations in neonates (even in preterm-born at term equivalent age).¹⁵⁻¹⁸ However, in our study, despite both groups responding with a bilateral activation pattern, the full-term group demonstrated a more prominent unilateral contralateral response, whereas preterm infants demonstrated a more homogeneous bilateral response. In the preterm group, we observed a more reproducible ipsilateral response around C6–Cp6 and a less reproducible contralateral activated area when compared to the term group. These differences observed in full-term and preterm born lateralization of evoked sensorimotor cortex responses suggest that a considerable degree of functional lateralization may already be developed in the first months of postnatal life. This early development could explain the fact that the full-term born infants had a more homogeneous contralateral activation and only about 30% of its subjects showed bilateral activation, whereas in the preterm group, the bilateral response was more homogeneous, occurring in most subjects. Our results are consistent with the assumption that the hemispheric lateralization increases with age or development. Recent studies^{16,19} have identified an emerging trend of contralateral lateralization of the somatosensory systems with increased age/development and suggest that a refinement of the sensorimotor pathways, or lateralization, plays an important role during the postnatal period.

Despite consistent involvement of the sensorimotor cortex, studies produced thus far have reported conflicting results.¹⁹ However, recent studies in age-related HRF-modeling of event-related fMRI have improved the specificity of neonatal fMRI,^{19,20} demonstrating predominantly lateralized activation in the sensorimotor cortex at early ages (38 to 42 postconceptual weeks).¹⁹

The more homogeneous bilateral activation, observed in the majority of the infants from the preterm group, may also indicate a cortical maturity status, suggesting that the preterm cortex is less specialized than in term-born infants. Changes in location can be viewed as a direct consequence of specialization.²¹ One possible mechanism that converges to the specialization of the neural pathways is the selective pruning of inadequate synaptic connections and also the inhibition of alternative routes.^{22,23}

Another possible explanation for the robust bilateral activation observed more in preterm than in full-term born infants is to consider that “the brain’s resource constraints” may affect the level of cortical information processing.²⁴ The resource constraints are a simple and inescapable consequence of the fact that the brain, like all biological systems, is subject to hard limited bioenergetic and structural resources. Therefore, preterm and full-term individuals in different rates, during the development, may have a reduced availability of resources in these regions, and additional areas will be permanently recruited.²⁴

About the location of the cortical hemodynamic response, it is important to note that we designed the optical probe to cover the whole head. With this geometry, we were able to identify the hemodynamic response to somatosensory stimulation in six-month-old infants mainly localized on the sensorimotor area, despite the differences observed concerning lateralization response of each group. This activation pattern not only reinforces the adequacy of the stimulus but also rejects the occurrence of activation in unexpected cortical regions. Therefore, our optical design provided the intrinsic advantage of investigating the activation response in a broader cortical area. This kind of investigation is crucial since little is known about changes in the physiology of the neural pathways that underlies the preterm brain.

Across all subjects, we also observed a faster HbO response in the contralateral sensorimotor cortex in the full-term born group. Recent studies have shown a maturational trend on parameters of the hemodynamic response in terms of decreasing time-to-peak and an increasing positive peak amplitude associated with increasing age.^{25,26} The physiological reasons underlying these dynamic differences are probably multifactorial and involve both the development of the neural network, as many stages of the neurovascular coupling culminate in the hemodynamic changes measured by fNIRS or BOLD signals.^{25,27} Considering the development of neural networks, preterm birth should affect the development and maturation of cortical pathways, including cortico-cortical and thalamo-cortical connections.⁷ Infants born preterm, even in the absence of focal brain lesions, have reduced regional brain volumes, reduced development of both white and gray matter,²⁸ reduced cortical surface area and gyrification,^{28,29} and reduced cortico-motor excitability,³⁰ which can result in slower neural conduction rates in the preterm infant brain, lengthening the mean time-to-peak response in this group.

We also observed that the increase in the average hemodynamic response in the left sensorimotor region [Figs. 3(c) and 3(d)] was correlated with higher Bayley-III motor scores. We propose that the activation response in sensorial and motor areas develops in close association with the emergence of related motor skills within the same individual. Therefore, we show that infants with the same performance in Bayley-III could have different activation during motor stimulation in the sensorial and motor regions of the cortex. Thus, fNIRS presented new and different information of which it is not clear as to the meaning of these different activation responses in long-term or in clinical context. Moreover, previous studies have shown the association between neurodevelopmental outcomes and brain status.^{31,32} Using diffusion tensor imaging, Yeo et al.³³ showed that the maturation status of motor pathways appears to be related to different periods of fine and gross motor development. Conventional MRI data, volumetric measurements, brain metrics, and surface-based studies of cerebral cortex have shown moderate to high predictive value for neurodevelopment, such as motor performance, cerebral palsy, and sensory impairments (see Ref. 34 for a review). Therefore, an understanding correlation of neurobiology and behavior in preterm infants requires further efforts to clarify the individual and combined contributions of multiple risk factors, inherent to premature birth to neurodevelopmental outcomes. Assessments of brain status and neuropsychological skills are likely to play a critical role in decoding these mechanisms.³⁴

Even in infants with similar mean motor scores (using Bayley-III Scale), we observed differences in brain activation between groups. We questioned whether this is due to a fragility of the scale for specific populations or whether these differences in hemodynamics may suggest a compensatory mechanism to maintain function. Bayley-III has been previously criticized for the possibility of developmental status overestimates and presents a poor predictor of later functioning.³⁵

It was not our intention to establish a causal relationship between motor development and cortical activity during motor stimulation because we understand that the relation between neurobiology and behavior should be much more complex than the direct correlation between brain activity and behavioral response.³⁶ The modest values of association between the two instruments (fNIRS and Bayley-III) in this study reinforce this

view. Furthermore, our limited sample size did not allow us to stratify the preterm group neither by GA nor by motor development outcome (i.e., normal or delayed in motor domain). This may be seen as a limitation, but we reinforce that we exclude many risk factors for motor changes that are often associated with prematurity and their complications.

In conclusion, our results suggest that full-term born infants at six months of age have different task-induced activation response in motor cortex compared with preterm infants with similar motor performance at Bayley-III Scale, both in relation to the activated area and to the magnitude and dynamic aspects of the activation response. The brain hemodynamic response measured by NIRS appears to be related, at least to some degree, to the motor performance exhibited by these infants. The results support the need for additional efforts to better understand the mechanisms involved on early development of motor abilities in premature infants and suggest that fNIRS can become a suitable auxiliary tool to investigate aspects of neural basis on early development of motor abilities.

Disclosures

The authors have no conflicts of interest to declare.

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