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Extremely Preterm-Born Infants Demonstrate Different Facial Recognition Processes at 6-10 Months of Corrected Age

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Objectives To compare cortical hemodynamic responses to known and unknown facial stimuli between infants born extremely preterm and term-born infants, and to correlate the responses of the extremely preterm-born infants to regional cortical volumes at term-equivalent age.

Study design We compared 27 infants born extremely preterm (<28 gestational weeks) with 26 term-born infants. Corrected age and chronological age at testing were between 6 and 10 months, respectively. Both groups were exposed to a gray background, their mother's face, and an unknown face. Cerebral regional concentrations of oxygenated and deoxygenated hemoglobin were measured with near-infrared spectroscopy. In the preterm group, we also performed structural brain magnetic resonance imaging and correlated regional cortical volumes to hemodynamic responses.

Results The preterm-born infants demonstrated different cortical face recognition processes than the term-born infants. They had a significantly smaller hemodynamic response in the right frontotemporal areas while watching their mother's face (0.13 μmol/L vs 0.63 μmol/L; $P < .001$). We also found a negative correlation between the magnitude of the oxygenated hemoglobin increase in the right frontotemporal cortex and regional gray matter volume in the left fusiform gyrus and amygdala (voxels, 25; $r = 0.86$; $P < .005$).

Conclusion At 6-10 months corrected age, the preterm-born infants demonstrated a different pattern in the maturation of their cortical face recognition process compared with term-born infants. *(J Pediatr 2016;172:96-102)*.

The ability to recognize faces is an important element in human social interaction, for infants as well as children and adults. This talent is already present at birth, to a certain extent, when infants express a strong interest in facial-like figures and can differentiate between facial and non-facial images.[1] Our previous study using near-infrared spectroscopy (NIRS) revealed that at 6-9 months of age, infants who were born full term were able to differentiate between their mother's face and an unknown face.[2]

Extremely preterm infants born at less than 28 gestational weeks often suffer from different neurodevelopmental problems and neuropsychological disorders, including prosopagnosia, the inability to recognize faces.[3-6] Prosopagnosia can form part of a severe neurodevelopmental disorder or be an isolated event. This deficit leads to a social handicap because of difficulties making friends and participating in social activities at school. Prosopagnosia can cause both depression and anxiety, which both are common morbidities following preterm birth.[6]

In adults, functional magnetic resonance imaging (MRI) studies have shown that parts of the ventral stream, the fusiform face area, the superior temporal sulcus, and the anterior temporal lobe are the most important cortical areas for face processing.[7,8] These areas have been shown to develop slowly during childhood. Golarai et al[9] found that the volume of activations in the right fusiform gyrus in response to faces, was substantially larger in adults than in adolescents and was positively correlated with age. We have previously shown that extremely preterm-born infants have decreased volumes in their global and regional cortical gray matter at term-equivalent age (TEA) than full-term controls, suggesting reduced brain growth.[10] Gray matter decrements in the temporal lobe and the amygdala are of particular interest, because these cortical regions are part of the face-processing network and are dedicated to face perception and associated emotional information.[11] The relationship between decreased brain volumes in these structures and alterations in face recognition in extremely preterm infants remains largely unexplored.

We hypothesized that when extremely preterm-born infants viewed their mother's face at 6-10 months corrected age, this would yield a smaller

HbO_2	Oxygenated hemoglobin
HHb	Deoxygenated hemoglobin
IVH	Intraventricular hemorrhage
MRI	Magnetic resonance imaging
NIRS	Near-infrared spectroscopy
PVL	Periventricular leukomalacia
TEA	Term-equivalent age

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hemodynamic response in the right frontotemporal cortex compared with that seen in term-born infants at the same age. We also hypothesized that when the 2 groups of infants saw their mother's face and an unknown face, the hemodynamic response in the right frontotemporal cortex would be significantly different in term-born infants, but would not elicit the same hemodynamic differences in extremely preterm-born infants. Furthermore, we hypothesized that the regional cortical volumes of the areas involved in face processing in extremely preterm-born infants at TEA would correlate with how they performed in the face recognition task at corrected age 6-10 months. Our aim was to perform functional cortical hemodynamic measurements using NIRS when the extremely preterm-born infants looked at a familiar face and an unfamiliar face at corrected age 6-10 months. These results would then be compared with term-born infants at age 6-10 months and the functional results would be correlated to regional cortical volumes at TEA.

Methods

Study Group

We enrolled 71 infants to the study, divided among 2 cohorts. The preterm-born cohort comprised 33 infants (19 males and 14 females), and the term-born cohort comprised 38 infants (21 males and 17 females). Infants were included in the preterm-born group if they were born below gestational week $28^{0/7}$ and had no periventricular leukomalacia (PVL) or other major brain abnormalities. The only other formal exclusion criterion was a diagnosis of retinopathy of prematurity. However, we excluded 6 preterm-born infants and 12 term-born infants from the study group owing to motion artifacts or the inability to complete the whole trial, resulting in a final cohort of 27 preterm-born infants and 26 term-born infants. The preterm-born group had a mean gestational age of $25^{6/7}$ weeks (range, $23^{6/7}$-$27^{3/7}$ weeks), a mean birth weight of 857 g (range, 614-1141 g), and the mean time spent on a ventilator and continuous positive airway pressure were 10 days and 34 days, respectively. They were examined at a corrected age between 6-10 months and their mean weight at examination was 8 kg (range 5.9 kg-10.5 kg). The term-born group consisted of data on 19 infants from our previous study,[2] together with an additional 11 infants. Their mean gestational age was $39^{3/7}$ weeks (range $35^{6/7}$ to $42^{3/7}$), mean birth weight 3.424 g (range 1.700 g-4.585 g), and mean weight at examination was 8 kg (range 6.2 kg-10.5 kg). In addition, all the extremely preterm infants born in the Stockholm area during the investigation period were included in a study that performed brain MRI at TEA. This meant that we had scans for the preterm-born infants in our study and 10 of the scans were of a high enough quality to be included in our analysis. We did not include infants with any grade of PVL or intraventricular hemorrhage (IVH) grade III and IV on neonatal ultrasound, focal brain lesions such as cysts and malformations, persistent ventricular dilatation on MRI examination at TEA, or qualitatively defined moderate or severe white matter abnormalities.[12]

The local Ethical Committee approved the study, and parents provided written, informed consent for all infants included.

NIRS Technique

A double-channel NIRS device (NIRO 300 or NIRO 200; Hamamatsu Photonics, Hamamatsu, Japan) was used to monitor the concentration changes of oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (HHb). The basic principles of the NIRS technique have been described in detail previously.[13] In brief, the NIRS device was equipped with 2 channels, each consisting of a light transmitter and a receiver. It produced light with a wavelength of 700-1000 nm, and the sampling frequency was 2 Hz. Data were transferred via an RS-232 interface to an offline computer for statistical analysis.

NIRS optodes were lodged in a semirigid black rubber holder and placed over the infant's right hemisphere, with a distance of 4 or 5 cm between the transmitter and the receiver. We placed NIRS optodes according to the 10-20 international electroencephalography system, as outlined in our previous studies.[2,14] One NIRS channel was positioned over the right frontotemporal region, with the emitter just posterior to F4 and the receiving optode slightly anterior to T4. The other channel was located over the right occipital region, with the emitter slightly posterior and below P4 and the receiver over O2.

MRI Data Acquisition

All preterm-born infants were scanned at TEA on a Philips Intera 1.5-T magnetic resonance imager (Philips International, Amsterdam, The Netherlands). The conventional MRI protocol consisted of a sagittal T1-weighted turbo spin echo sequence, an axial inversion recovery sequence, and an axial T2-weighted sequence. The 3-dimensional T1-weighted gradient echo images were acquired with an echo time of 4.6 minutes, a repetition time of 40 minutes, a flip angle of 30 degrees, a voxel size of $0.7 \times 0.7 \times 0.1$ mm, and a 180-mm field of view. Details of the sequence parameters have been published previously.[15] T1-weighted images were assessed for quality assurance, as described previously.[10]

Procedure

Pictures of the mothers and the unknown women were taken using a digital camera (μ-700; Olympus, Tokyo, Japan or FX-100; Panasonic, Osaka, Japan). The facial images were shot on a neutral gray background and the women were asked to assume a neutral, slightly happy facial expression. We used a 22″ screen (LG, Seoul, Korea) for picture presentation in this trial. The pictures of the mothers of the term-born infants who were also included in our previous study were presented on a laptop with a 15″ screen (Fujitsu-Siemens, Munich, Germany). The trials were filmed using a digital video camera (Canon, Tokyo, Japan).