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Proc Natl Acad Sci U S A. 2003 September 16; 100(19): 10722–10727.

Published online 2003 September 5. doi: 10.1073/pnas.1932552100.

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Brain imaging in awake infants by near-infrared optical topography

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Edited by Britton Chance, University of Pennsylvania School of Medicine, Philadelphia, PA, and approved July 22, 2003

Received April 30, 2003.

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ABSTRACT

Studies of young infants are critical to understand perceptual, motor, and cognitive processing in humans. However, brain mechanisms involved are poorly understood, because the use of brain-imaging methods such as functional magnetic resonance imaging in awake infants is difficult. In the present study we show functional brain imaging of awake infants viewing visual stimuli by means of multichannel near-infrared spectroscopy, a technique that permits a measurement of cerebral hemoglobin oxygenation in response to brain activation through the intact skull without subject constraint. We found that event-related increases in oxyhemoglobin were evident in localized areas of the occipital cortex of infants aged 2–4 months in response to a brief

presentation of a checkerboard pattern reversal while they maintained fixation to attention-grabbing stimuli. The dynamic change in cerebral blood oxygenation was qualitatively similar to that observed in the adult brain. This result introduces near-infrared optical topography as a method for investigating the functional development of the brain in early infancy.

Studies examining the perceptual development of young infants have been dominated by behavioral reports using preferential looking and habituation/dishabituation methods. The results of these studies suggest that infants in the first few months of life display considerable perceptual competence (1–3). However, the specific brain mechanisms involved are poorly understood, because brain-imaging methods such as functional MRI (fMRI) (4, 5) or positron emission tomography in awake infants are quite difficult. Studies using fMRI in young infants have examined only at-risk infants who were sedated to ensure the acquisition of motion-free images (6–11). In contrast, near-infrared (NIR) spectroscopy (NIRS) has permitted noninvasive and safe measurement of activation of single sites of the cerebral cortex in adults (12–15) and infants (16). Recent advances in the multichannel NIRS technique, NIR optical topography (OT), have provided functional brain imaging with improved spatial resolution and higher temporal resolution in adults (17–22). OT has been also used to study spontaneous changes in oxygenation of the cortex of sleeping infants (23). Other researchers have proposed different techniques by using NIR lights to obtain functional brain imaging of passive motor response in preterm and term infants (24, 25). In the present study, we used OT to obtain functional brain images of awake infants when exposed to visual stimuli.

A standard method of functional imaging of the visual cortex by means of fMRI and NIRS has been to use either flashing lights or checkerboard patterns with a uniform dark field as a background condition (4–11, 13, 15, 16). However, infants typically show a strong habituation to the same stimuli, and coaxing infants to fixate on a checkerboard pattern for a long duration is practically impossible. Moreover, keeping an awake infant sufficiently still to perform reliable data acquisition during a long rest period is challenging. In the present study we devised elaborate stimuli to maintain the attention of infants and adopted an event-related paradigm that has been used to detect transient hemodynamic responses to brief stimulation in fMRI studies (26, 27). By means of OT with an event-related paradigm, we explored the functioning of the developing brain of young infants in relation to visual perception. Because our apparatus could not cover the whole brain, we focused on the occipital cortex and the frontal cortex. We hypothesized that an expected location of the primary visual area over the occipital cortex showed activation in response to visual stimuli. A prefrontal area of the frontal cortex, the cortical region that mediates higher functions in adults, was examined to test whether the region showed any responses due to the absence of selectivity in its response properties in early infancy.

METHODS

Subjects. We tested 20 infants ranging in age from 2 to 4 months. We obtained data from seven infant subjects. The other 13 infants were tested but not included in the sample because of head movements producing large motion artifacts in the signals ($n = 8$), crying ($n = 3$), insufficient attention to the stimuli ($n = 1$), and failure in probe placement due to obstruction by hair ($n = 1$). Informed consent was obtained from the parents of infants before the initiation of experiments. These experiments were approved by the Department of Physical and Health Education at the Graduate School of Education (University of Tokyo).

Recordings. We used an NIR OT instrument (Hitachi Medical) (17–19). This instrument generated two wavelengths NIR (780 and 830 nm) and measured time courses of the levels of oxyhemoglobin ([oxy-Hb]) and deoxyhemoglobin ([deoxy-Hb]) at multiple channels with 0.1-s time resolution. The NIR light generated by 20 laser diodes (10 per wavelength) was modulated at different frequencies to prevent crosstalk between the channels and the wavelengths. The light from the instrument to the brain tissue and back to the instrument was guided by optical fiber bundles (1 mm in diameter). The received light was detected by eight avalanche photodiodes and separated into individual light sources with each wavelength by 48 lock-in amplifiers. We placed a pair of 3×3 arrays with five incident and four detection fibers, which were mounted on a flexible cap, over the occipital and frontal areas of each subject's head as shown in Fig. 1a. Each pair of adjacent incident and detection fibers defined a single measurement channel (illustrated in Fig. 1b), which allowed the measurement of [oxy-Hb] and [deoxy-Hb] changes at 12 channels for each of the occipital and frontal areas. The distance between incident and detection fibers was set at 2 cm, and therefore a 4×4 -cm region for each cortex was covered. We evaluated relative changes in [oxy-Hb] and [deoxy-Hb] from an arbitrary zero baseline at the start of the measurement period on the basis of Lambert–Beer law (28). Because the exact optical path length of the light traveling through the brain tissue was not known, the unit of these values was molar concentration multiplied by length (mM·mm). Other studies have measured and/or estimated a differential path-length factor, which accounted for the longer optical path length than the geometrical spacing between incident and detection fibers due to the effects of scattering of light by the tissue (29, 30). Assuming that the value of differential path-length factor is 5 for infants, the optical path length with respect to a 20-mm interprobe distance can be estimated as 100 mm. In this case, 0.1 mM·mm change corresponds 1.0 μ M change in the absolute concentration. In the present study, we did not aim at quantifying the absolute changes in Hb oxygenation, but rather we aimed at the analysis of temporal characteristics of relative changes. The intensity of illumination at each incident position was 1.5 mW. Systematic evaluation of thermal effects in human skin during NIRS has shown that the range of laser power used in OT does not have a potential risk of heating (31).

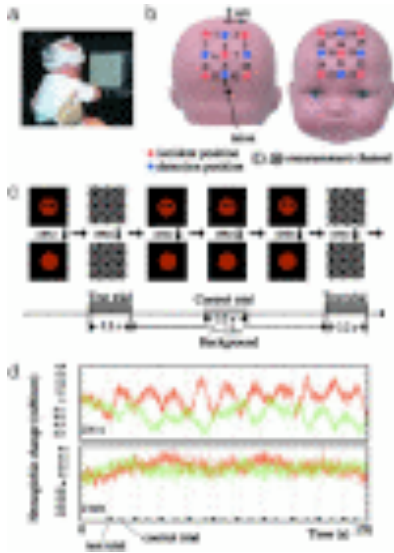


Fig. 1.

(a) Experimental setup. Each subject was seated on a parent's lap facing a computer display. The probes of the OT were attached to the occipital and frontal cortex. (b) Arrangement of measurement channels over the occipital and frontal cortex of infants ([more ...](#))

Procedure. Infants to whom the probes of the optical topograph were attached were allowed to assume the most comfortable posture on their parent's lap and viewed visual stimuli on a 19-inch LCD display at ≈ 30 cm distance as shown in [Fig. 1a](#). While infants were oriented toward the display, they were presented with a red face-like pattern with eyes blinking, which was chosen for the background as opposed to a uniform dark field, to control the level of attention and thus to minimize the motion artifact. The face-like pattern consisted of a red circle (15° of visual angle) with two small circular blobs that resembled eyes (4°) and was colored red against a black background with a luminance of 55 cd/m^2 as shown in [Fig. 1c](#). The rate of blinking was set at 2 Hz. To attract the infants' attention more strongly and reduce the habituation of infants to the same stimuli, beep sounds (60-dB) were produced synchronously with the timing of blinking (2 Hz), and the pitch of beep was changed randomly in the beginning of each trial. The sounds were presented with a speaker behind the display.

While the subject viewed the background pattern, we presented the test stimulus consisting of a black-and-white checkerboard (0.5 cycles per degree) with a 4-Hz pattern reversal that was displayed for 3.2 s. The interstimulus interval was chosen randomly between 7 and 15 s. The test pattern had a higher luminance contrast (225 cd/m^2) and a larger visual field ($36^\circ \times 36^\circ$) in comparison with the face-like pattern. Given the monotonic increase in the fMRI blood oxygenation level-dependent signal with the luminance contrast ([32](#)) and the retinotopic organization ([33](#)) in the adult visual cortex, the brief presentation of the test pattern was expected to produce an event-related hemodynamic response in the visual cortex but not in the frontal cortex. During

presenting the test pattern, beep sounds were generated synchronously with the timing of pattern reversal (4 Hz) and the pitch frequency of the beep sounds was changed according to an ascending scale. This change in a pattern of sounds was provided to reinforce the infants' attention to the visual stimuli.

Between the test trials we inserted a control trial to examine whether the changes in the sound stimuli alone evoke any response. In this trial, the face-like pattern remained visible in the same way as the background periods, but the rate of the blinking and the accompanied beep sounds were changed in the same way as the test trial. The duration of the control trial was 3.2 s. The responses to adjacent test and control trials may overlap, because the hemodynamic response needs more than 10 s to return to baseline ([32](#), [34](#), [35](#)). Because there was only a change in the auditory stimulus, we hypothesized that the cortical areas, particularly in the occipital cortex, would be unlikely to respond to the control stimuli. The control trials were rather important to prolong the infants' fixation time enough for the measurement of the time evolution of event-related responses to the test stimuli.

Ten epochs of test and control trials were examined with each of the infant subjects. The behavior of the infants was video-recorded to identify epochs when they were attending to the stimuli without moving their head.

Data Analysis. By using video recordings of an infant's gaze direction, we removed the data blocks in which the infant did not look at the visual stimuli. We further removed the data blocks that included movement artifacts, which were detected by the analysis of sharp changes in the time series of [oxy-Hb] and [deoxy-Hb]. Finally, we obtained continuous time series of [oxy-Hb] and [deoxy-Hb], which contained at least four good epochs from each of the seven infants who kept their head still for ≈ 1 min. The raw data of [oxy-Hb] and [deoxy-Hb] from individual channels were digitally high-pass-filtered at 0.02 Hz to remove the long-time drift of baseline, which can arise from physiological effects such as changes in respiratory or cardiac activities and body movements or from measurement instability such as unstable contacts between the optical probe and the head and the unstable power of NIR light. The processed time series were split into epochs of 15 s by using the onset of each test or control trial. By averaging the time series over epochs, we obtained the hemodynamic response at each channel with 0.1-s time resolution. We further executed the two-dimensional spline interpolation on the basis of the spatial arrangement of channels and obtained spatiotemporal hemodynamic response as a series of images.

To identify activated channels at which the time course showed a repeatable response to each stimulus, we used a statistical technique of analysis of variance (ANOVA), which had been used in an fMRI study ([36](#)). The ANOVA technique did not make any

assumption of the exact shape or timing of the time course and was suitable for detecting an unknown pattern of changes in [oxy-Hb] and [deoxy-Hb] in response to the stimuli in infants. The method of detection of activation was based on the feature that activated channels displayed reproducible time-course patterns as the subjects underwent the same stimulation in repeated epochs. If x_{ij} referred to the signal measured at the i th time point after the stimulus ($i = 1, \dots, m$) and of the j th trial of an experiment ($j = 1, \dots, n$), the averaged time course, \bar{x}_i , can be obtained by averaging x_{ij} at the i th time point. The null hypothesis was that there was no significant difference in the means \bar{x}_i . This hypothesis can be tested by calculating the F score, which was the ratio of the variance of the averaged data set between time points to the variance of the unaveraged data set at the same time point. The F score was calculated for each of [oxy-Hb] and [deoxy-Hb] on a channel-by-channel basis, and the channels that showed significant changes were statistically identified based on F distribution with $m - 1$ and $m(n - 1)$ degrees of freedom. Because the ANOVA method *per se* did not specify whether the signal change was an increase or a decrease, we further compared the mean values of [oxy-Hb] and [deoxy-Hb] 0–5 and 5–10 s after the onset of each test or sound stimuli.

We obtained statistical parametric mappings based on F scores of signal changes in [oxy-Hb] or [deoxy-Hb]. The two-dimensional F -statistical parametric map was interpolated by using the bicubic spline. We finally produced topographic mappings of activated areas over the occipital and frontal cortex for each of the subjects.

RESULTS

[Fig. 1d](#) displays the measured signal changes at specific channels in the occipital cortex and the frontal cortex of a 2-month-old subject. In response to the checkerboard pattern reversal with high luminance contrast, a distinctive increase in [oxy-Hb] and a decrease in [deoxy-Hb] were observed in the occipital cortex, whereas no clear response was observed in the frontal cortex.

[Fig. 2](#) shows spatiotemporal hemodynamics over the occipital and frontal cortex of a 4-month-old infant in response to the test visual stimulation. A series of images clearly demonstrates the delayed and localized response to the test visual stimulation and the slow decay of the response over the occipital cortex.



Fig. 2.

Time evolution of images of hemodynamic response to the test visual stimulation. Epoch-averaged images of [oxy-Hb] over the occipital and frontal cortex of a 4-month-old infant (S6) are illustrated at 2-s intervals. The time of initiation of test trial ([more ...](#))

The time series were analyzed with the ANOVA method described above on a channel-by-channel basis. The data obtained from the seven subjects revealed that the response to the test stimuli was robustly detected as a localized increase in [oxy-Hb] in the occipital cortex. [Table 1](#) reports those channels that exceeded criterion ($P < 0.01$), statistical scores, and magnitudes of changes in [oxy-Hb] and [deoxy-Hb] for each of the subjects. [Fig. 3a](#) illustrates the localization of the activated channels, which were consistently observed among the subjects. Six of the seven infants (subjects 1, 2, and 4–7) showed significant changes in [oxy-Hb] at CH11 over the occipital cortex that were consistent with the expected location of the visual cortex. Moreover, the maximum F score was found at CH11 of 24 channels in five infants (subjects 1, 2, and 5–7). All the significant changes in [oxy-Hb] at CH11 were event-related increases in signal, which were detected by calculating the difference between the mean values of [oxy-Hb] 0–5 and 5–10 s after the onset of the test stimulus. CH24 was the only channel that exceeded the criterion for [oxy-Hb] over the frontal cortex. However, this was observed in only two infants (subjects 1 and 4), and the magnitude of signal change was very small.

Table 1.

Individual changes in [oxy-Hb] and [deoxy-Hb] for the test and control trials

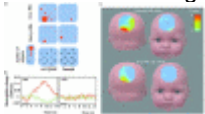


Fig. 3.

(a) Locations of significant changes in [oxy-Hb] and [deoxy-Hb] that were consistently observed among the subjects. The relative size of each red circle represents the number of the subjects who showed significant changes ($P < 0.01$) at the corresponding ([more ...](#))

With regard to [deoxy-Hb] for the test trials, there were no consistent locations of significant changes among the infant subjects. However, it should be noted that a significant decrease ($P < 0.001$) in [deoxy-Hb] was observed at CH11 in three infants (subjects 1, 2, and 6), who showed the high F score ($P < 0.0001$) for the increase in [oxy-Hb] at CH11.

We performed the same statistical analysis for the control trials and found that some of the channels that showed a significant increase for the test trial exceeded the criterion for the control trial. However, most of them showed a decrease, which was in contrast to the test trial. It is likely that the decrease in [oxy-Hb] in the control trial was caused by the short interval between the test and control trials, which was less than the time for the hemodynamic response of the test trial to fully return to baseline (35). Significant changes in [deoxy-Hb] for the test trials were not observed consistently among the subjects.

We investigated the form of the hemodynamic response at CH11 over the occipital cortex and CH24 over the frontal cortex for the test trials. Fig. 3b shows the time courses of [oxy-Hb] and [deoxy-Hb] averaged over subjects ($n = 7$). The event-related increase in [oxy-Hb] and slight decrease in [deoxy-Hb] were evident at CH11 of the occipital cortex. The observed positive signal change of [oxy-Hb] reached its maximum between 8 and 10 s after the onset of the stimulus, and the peak of the negative signal change of [deoxy-Hb] was slightly delayed. On the other hand, the averaged time series at CH24 did not show clear changes.

Fig. 3c illustrates topographic maps on the basis of the changes in [oxy-Hb] for two infants (subjects 1 and 6). These images typify the functional mapping of the visual cortex that was obtained for each of the subjects.

DISCUSSION

Our results demonstrate that a localized area of the occipital cortex of awake infants aged 2–4 months responded to brief changes in the luminance contrast of visual stimulation and produced event-related changes in cerebral blood oxygenation, which was robustly detected as a focal increase in [oxy-Hb].

We observed the increase in [oxy-Hb] and the accompanied decrease in [deoxy-Hb] over the occipital cortex in response to the visual stimulation in infants as young as 2 months of age. This pattern of hemodynamic response is qualitatively similar to the one that has been observed in adults (15, 21, 34). Our finding suggests that the changes in cerebral blood flow in response to visual stimulation are similar in infants and adults.

A number of studies with fMRI have demonstrated that sedated and sleeping infants responded to visual stimulation with a decrease in blood oxygenation level-dependent (BOLD) signal, whereas an identical stimulus in adults caused an increase in the BOLD signal (6–11). In contrast with these data, we did not find such a drastic difference in the pattern of hemodynamic responses between infants and adults. Our study thus suggests that the sedation or state of consciousness and attention may profoundly affect the

hemodynamic responses to the visual stimulation. The technique of NIRS allows unique opportunities for brain imaging of awake infants under natural conditions.

Our study clearly demonstrated the feasibility of the event-related paradigm in NIR OT measurement for awake infants. The block designs with long periods of stimulation and rest have potential risks for faulty positive/negative changes in signals due to either the low-frequency fluctuations of baseline (23) or motion artifacts. These problems were overcome by detecting a time-locked and spatially localized increase in [oxy-Hb] in response to brief sensory stimulation. However, we still observed variability of the response of [deoxy-Hb] among subjects. In contrast with our data, a previous study using a single-site NIRS showed the [deoxy-Hb] increase during the visual stimulation in awake infants (16). The difference in the result may reflect several factors such as the lower signal-to-noise ratio of the measurement of [deoxy-Hb] in comparison with the one of [oxy-Hb] and the different path lengths of the NIR light depending on the anatomical variations of the subjects and the distance between incident and detection fibers.

There are some limitations to the present study. In the OT measurement, the exact positions of probes with respect to the underlying brain were not available. It was difficult to determine the placement of the probes for awake infants by using only external landmarks such as inion. Although we hypothesized that the primary visual area was located ≈ 2 cm above the inion, the most active channel was located very close to the inion. Overcoming this limitation is one of the important issues for improving the technique. Another issue is that we had to exclude many infants from the analysis because they made a lot of jerky movements of their head and body, which caused such large noises that we were unable to obtain reliable signals. It is important to devise good optical probes that are robust to motion artifacts. It is also open to future studies to clarify the complex relationship among the cerebral metabolic rate of oxygen, the cerebral blood flow, and the cerebral blood volume.

We demonstrated that NIR OT had great advantages in brain imaging of young infants not only for safety and portability but also for sensitivity to detect dynamic changes in the cerebral blood oxygenation in relation to the focal activation of the cerebral cortex. Although our study was focused on the functioning of the primary sensory area of the cortex, the technique of NIR OT with an event-related paradigm should provide windows into the functioning of the brain underlying perceptual, motor, and cognitive development in early infancy.

ACKNOWLEDGMENTS

We thank Professor R. Turner for critical comments on an earlier draft of the manuscript and M. Fujiwara for developing probes of OT for measurement with infants.

NOTES

This paper was submitted directly (Track II) to the PNAS office.

Abbreviations: fMRI, functional MRI; NIR, near infrared; NIRS, NIR spectroscopy; OT, optical topography.

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