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Functional brain imaging using fMRI and optical topography in infancy

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Abstract

We performed functional magnetic resonance imaging and optical topography over the visual cortex of subjects during sedation with pentobarbital, and 8-Hz flickering light was intermittently projected onto their eyelids. Two age groups were analyzed: infants <60 days old and those >60 days old (corrected for gestational age at birth). The stimulus-related signal change was positive in the lateral geniculate nucleus regardless of the infant's age, but it reversed in the primary visual cortex from positive in the infants less than 60 days old to negative in the infants more than 60 days old (Experiment 1). We also investigated spontaneous changes in the cerebral oxygenation state of neonates and infants aged 1 month during quiet sleeping by using a form of multi-channel near-infrared spectroscopy: non-invasive optical topography. Spatially synchronized oscillations of changes in the concentration of oxy-hemoglobin (oxy-Hb) and deoxy-Hb were observed throughout the occipital cortex in neonates but not in the infants aged 1 month. Time series analysis based on the theory of non-linear oscillations showed that the mean periods of the oscillation for each infant ranged from 11 to 18 s. The phase lag of oxy-Hb relative to deoxy-Hb was stable at about $3\pi/4$ in neonates but in the infant aged 1 month, time lag was unstable. These findings may be due to rapid synaptogenesis in early life.

Keywords: Functional magnetic resonance imaging; Near-infrared spectroscopy; Blood oxygenation level-dependent contrast; Synaptogenesis; Spontaneous oscillation

1. Introduction

The anatomy, function, and metabolism of the human brain change rapidly in early life. It is clinically important to assess the normal development of brain anatomy and function in order to detect abnormal brain development in the early infantile period. Since the principal brain substrates for energy production are glucose and oxygen, indirect assessment of local energy requirements for maintenance processes and functional activity in resting condition in infants has been obtained by the measurement of regional cerebral metabolic rates for glucose with positron emission tomography (PET). However, developmental changes of activity-related metabolism in infants is poorly understood. The development of functional magnetic resonance imaging (fMRI) and the optic topography, extending the methods of near-infrared spectroscopy (NIRS), which are sensitive to blood oxygenation has enabled us to directly study human cerebral function. We performed fMRI and optical topography over the visual cortex of the subjects during the neonatal period.

2. Experiment 1

2.1. Introduction

fMRI which is a non-invasive technique for detecting neuronal activity induced by external stimuli, has recently become available for clinical examination of function during development. Blood oxygenation level-dependent (BOLD) contrast and inflow effect from relatively larger veins are thought to be the mechanisms of fMRI signal change. The aim of the first experiment is to investigate developmental changes of activity-related metabolism in human visual cortex from the neonatal period.

2.2. Materials and methods

We performed MRI and fMRI of the brain in 27 infants, aged 0–22 weeks, corrected for gestational age at birth, whose perinatal risk factors warranted screening for possible brain damage. Infants with severe brain damage, such as periventricular leukomalacia, severe asphyxia, and neonatal convulsions were excluded. All 27 subjects had normal brain MRI, were prospectively followed up after the MR examination, and showed normal neurologic development until they were at least 1 year of age. All subjects were

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sedated with pentobarbital 3–5 mg/kg intraveneously (IV) per our institution's routine clinical MR examination protocol. The peripheral pulse rate and respiratory rate were monitored, and the infants were closely observed in the MRI unit. Their eyes were closed throughout the examination. A scanning session consisted of two rest periods and two stimulus periods, each 30 s long, with rest and stimulus alternating. An on–off cycle of 60 s was chosen to maximize the induced signal amplitude and to obtain a stable period, 8-Hz flickering light was projected onto the sedated infant's eyelids. The session was repeated twice. A time-course series of 42 volumes was acquired with a T2-weighted, gradient echo echo-planar sequences with a 1.5 T Signa Horizon MRI system (GE) equipped with a standard birdcage. Each volume consisted of 12 contiguous horizontal slices 6–7 mm thick, including the calcarine fissure. The time interval (TR) between two successive acquisitions of the same slice was 3000 ms, and hence, ten volumes were obtained in each rest and stimulus period. Echo time (TE) was 50 ms, and flip angle 90°. The field of view was 22 cm, and matrix size was 64×64, giving voxel dimensions of $3.4 \times 3.4 \times 6$–7 mm. Soon after the acquisition of all functional images was completed, structural T1-weighted images were collected in planes identical to the functional imaging slice (TR of 350 ms, TE of 15 ms, matrix size of 256×256, and voxel dimensions of $0.86 \times 0.86 \times 6$–7 mm).

The time series of raw BOLD signals of the regions of interest (ROIs) on the lateral geniculate nucleus (LGN) and primary visual cortex (V1) obtained from the coregistered T2-weighted echo planar images were analyzed with in-house software written by Matlab. The images from each subject were realigned using the first image as a reference. After realignment, spatial smoothing to a full width at half maximum of 5, 5, and 10 mm for the *X*-, *Y*-, and *Z*-axis, respectively, was performed. Finally, voxel-wise statistical analysis was performed using the general linear model (with temporal smoothing and autocorrelation over time) and statistical inference based on the spatial extent and maxima of thresholded activation foci using the theory of Gaussian fields. Significance was defined as $P < 0.05$. The threshold of SPM(Z) was set at 2.8 with correction for multiple comparisons to keep the false-positive rate at the defined level ($P < 0.05$).

2.3. Results

In the V1, the percentage of signal change was positive in infants younger than 60 days, but negative in infants older than 60 days. The signal response abruptly reversed from positive to negative at 60 days, whereas marked overlap was noted if chronological age was adopted. On the other hand, age-related stimulus-related signal change in LGN was positive regardless of the infants' age.

2.4. Discussion

Present study have shown that the V1 response to the photic stimulation depends on the age corrected for gestational period. The signal response abruptly reversed from positive to negative at 8 weeks old, whereas marked overlap was noted if chronological age was adopted. This is due to the fact that subjects with perinatal risks which warranted the screening for MRI examination tended to be prematurely delivered, and hence chronological age usually surpasses the corrected age. This overlap suggests that the abrupt reversal of signal response reflects developmental processes which are not dependent on the period of visual exposure.

Considering that the underlying mechanism of fMRI is the BOLD contrast arising from the paramagnetic property of deoxy-hemoglobin (deoxy-Hb), the stimulus-related decrease in the BOLD signal in the V1 of older infants is probably due to increased deoxy-Hb. The reversal of the stimulus-related MRI signal change may be explained by the dynamic morphological and metabolic changes of the V1 in early life. The V1 shows an exponential increase of synaptogenesis in the pre- and postnatal developmental periods both in non-human primates and in humans. Measurement of regional cerebral metabolic rate of glucose (rCMRG) using PET scan showed that rCMRG correlate with postconceptional age up to 6 months. By 3–5 months of age, rCMRG has increased in the occipital cortex, as well as the frontal, parietal, temporal, and cerebellar cortical regions. As the rCMRG reflects synaptic activity, an increase of rCMRG in the visual cortexis compatible with the rapid synaptogenesis starts from the second month of age.

Dynamic metabolic changes in the V1 in early life may explain the age-related reversal of the MRI signal. Because of rapid synapse formation, stimulus-related synaptic activity requires a larger amount of oxygen extraction than can be compensated by the rise in oxygen delivery from increased regional cerebral blood flow (rCBF) and cerebral blood volume (CBV). The resulting increase in deoxy-Hb concentration may cause reversal of the MRI signal.

Our findings showed that the time course of the stimulus-related BOLD signal change in the V1 and LGN are different. As these structures are on the same visual pathway, it is conceivable that the neuronal activation of both increases during the stimulus. Hence, the difference in the time course can be attributed to a difference in the developmental course of these structures. It is known that synaptogenesis in the LGN peaks before birth, and in the V1 accelerates in the second month after birth. Hence, the inversion of the stimulus-related signal change in the V1 may be due to an increased demand for oxygen owing to rapid synaptogenesis.

3. Experiment 2

3.1. Introduction

NIRS is an optical method that allows non-invasive measurement of changes in cerebral blood and oxygenation through the transmission of near-infrared light through the

intact cranium. NIRS is attracting progressively more attention as a means to study brain functioning, since it is portable and allows repeated and long-time measurements of the same subjects, as an alternative to other methods of brain imaging such as fMRI or PET. NIRS is particularly suitable for the study of infants, since other methods cannot routinely be used without sedation. Extending the NIRS method, the use of optical topography to measure spatio-temporal changes in the concentration of oxy- and deoxy-Hb in relation to human brain functions has been proposed. We have used optical topography to study spatio-temporal changes in oxy- and deoxy-Hb over the occipital cortex of neonates during quiet sleeping.

3.2. Materials and methods

Eight neonates born at 32–39 weeks and eight infants, aged 4–7 weeks after birth were studied. Informed parental consent was obtained before each study. Measurement of neonates were made at comparable postconceptional term ages (38–43 weeks).

We used optical topography system (Hitachi Medical Corp.) to detect changes in the oxy- and deoxy-Hb of the occipital cortex at 24 measurement positions located midway between eight incident and eight detection positions with two wavelengths (780 and 830 nm). The intensity of light at each incident position was 0.15 mW. The 16 optical-fiber probes used at the incident and detection points were mounted on a flexible shell in a 4×4 array with an inter-probe distance of 15 mm. The measurement positions were set at the midpoints between the incident and detection points. We attached the probe shell to the surface of a bed and let the infants lie on the bed so that the occipital region of the head touched the probes in the spine position. We evaluated the relative changes in oxy- and deoxy-Hb from an arbitrary zero baseline at the start of the measurement period.

We performed measurements when the infants were sleeping in a dimly lit room. Data were collected only when the infants were in a state of quiet sleeping.

3.3. Results

Spontaneous oscillations of the hemoglobin oxygenation state were observed in all the infants. Time series analysis based on the theory of non-linear oscillators showed that the mean periods of the oscillation for each infant ranged from 11 to 18 s.

Spatially synchronized oscillations of changes in the concentration of oxy- and deoxy-Hb were observed throughout the occipital cortex in the neonates but not in the infants aged 1 month after birth. It was observed that the phase lag of oxy-Hb relative to deoxy-Hb was stable at about $3\pi/4$ in neonates but in the infants aged 1 month, the phase lag was not stable. This phase difference may result from interplay between the vasomotion and the oxygen consumption in relation to brain activity.

3.4. Discussion

Our finding was that the phase advancement of oxy-Hb relative to deoxy-Hb was maintained at around $5\pi/4$. This was revealed by an analysis based on the theory of non-linear oscillations. Changes in oxy- and deoxy-Hb always oscillated with a fixed phase relationship among them. In contrast, an NIRS study of adults showed that significant fluctuations in hemoglobin oxygenation occur during resting periods and that the patterns of changes in oxy- and deoxy-Hb were variable within a 20-min recording. The effect of vaomotion is probably important to consider in understanding the origin of the spontaneous oscillations of the hemoglobin oxygenation state, the CBV, and the CBF velocity (CBFV). However, the coupling mechanism between vasomotion and activity-dependent changes in the metabolism of the cerebral tissue is not clear. The BOLD contrast in fMRI has been thought to reflect the fact that functional brain activation produces a localized increase in the CBF that is larger than the increase in oxygen consumption and that the deoxy-Hb decreases due to washout by the blood flow. We speculate that a similar mechanism underlies the increase in deoxy-Hb and the delayed increase in oxy-Hb with the phase lag of $3\pi/4$ that we found in this study.

Our study also showed the large differences in the oscillations of change in the concentrations of hemoglobin in both neonates and young infants. Spatially synchronized oscillations were observed throughout the occipital cortex in neonates but not observed in infants aged 1 month. Moreover, time lag between the change of deoxy-Hb and oxy-Hb were almost regular in neonates, but not in young infants.

These findings may be explained by the dynamic morphological and metabolic changes of the visual cortex in early life.

Further reading

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