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A rapid brain metabolic change in infants detected by fMRI

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To determine developmental changes of activity-related metabolism in human visual cortex, we performed functional magnetic resonance imaging (fMRI) from the neonatal period. A rapid metabolic changing pattern accompanying normal human brain maturation was revealed by fMRI with photic stimulation. Infants older than 8 weeks of age showed a stimulus-related signal decrease in the visual cortex, whereas younger neonates showed a signal increase. This inversion of response in infants suggests a change in oxygen consumption during neuronal activation, which is related to rapid synapse formation and accompanying increased metabolism. fMRI can detect dynamic metabolic changes during the brain maturation, and provides a new clue in the detection of abnormal brain development or CNS plasticity.

Key words: Brain activation; Critical period; fMRI; Infant; Visual cortex

Introduction

The anatomy, function, and metabolism of the human brain changes rapidly in early life.[1–4] Since the principal brain substances 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 (rCMRGlu) with positron emission tomography (PET).[4,5]

The development of functional magnetic resonance imaging (fMRI), which is a non-invasive imaging tool for detecting neuronal activity induced by the external stimuli, has enabled us to directly study human cerebral functional development. Blood oxygenation level dependent (BOLD) contrast and inflow effect from relatively large veins were thought to be the contrast mechanism of fMRI, especially in the clinically available 1.5 T MRI system.[6–9] Previous fMRI studies have demonstrated that functional signal change within the visual cortex in infants shows negative response to photic stimulation.[10] However, visual function of neonates is poorly understood. To determine developmental changes of activity-related metabolism in human visual cortex, we performed fMRI from the neonatal period.

Materials and Methods

We studied 15 infants (8 males and 7 females), corrected for gestational age at birth (Table 1), aged less than 1–54 weeks, whose perinatal risk factors warranted screening for possible brain damage. Seven infants had been born pre-term. Informed consent was obtained from the parents.

All infants were sedated with pentobarbital 3–5 mg/kg injected intravenously. The peripheral pulse rate and respiratory rate were monitored, and the infants were closely observed in the MRI unit. Other than the constant gradient noise of echo planar imaging and the photic stimulation, other sensory stimuli were minimized. Patients' eyes were closed during the study. MRI was performed with a 1.5 T MRI system (Signa Horizon, GE) using a standard birdcage head coil. With the use of sagittal T2-weighted spin echo images (repetition time (TR) of 3 s; echo time (TE) of 88 ms; matrix size 256 × 256, a field of view (FOV) of 240 mm) as an anatomical guide, five axial slices approximately parallel to the calcarine fissure were selected for the activation studies. For T2*-weighted fMRI, 102 consecutive gradient-echo echo planar image sequences were acquired with TR/TE of 3 s/50 ms, a flip angle of 90°, a FOV of 220 mm, a 128 × 128 image matrix, and a slice thickness of 5 mm (voxel size: 1.7 × 1.7 × 5 mm). An initial baseline phase of rest for 30 s was followed by a photic stimulation phase alternating with a rest phase, with a total of 10 phases per trial. Visual stimulation was performed with 8 Hz flickering light projected onto the sedated infant's eyelids. Eighty data sets were analyzed, with 22 sequences as prescan data points. The statistical significance of each voxel's response was calculated

Table 1. Summary of results

Patient	Gestational age (weeks)*	Age at fMRI (weeks)		SPM outcome in visual cortex	
		Corrected	Chronological	Max Z value**	Activated voxels
1	38	<1	2	4.52	99
2	40	2	2	4.59	206
3	40	2	2	4.61	224
4	42	3	1	4.19	263
5	30	3	13	4.56	423
6	29	5	16	5.99	425
7	40	8	8	-5.22	622
8	32	16	24	-3.68	69
9	38	16	18	-4.88	428
10	34	17	23	-4.39	225
11	35	18	23	-4.53	371
12	29	22	33	-4.59	514
13	36	28	32	-4.69	505
14	40	53	53	-4.26	238
15	40	54	54	-4.34	110

*Gestational age was calculated from the mother's last memoposal period. **Minus value means a negative response.

with statistical parametric mapping (SPM) (using software from the Welcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Inc., Sherborn MA, USA).[11,12] 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, 10 mm for the X, Y, 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 ($p < 0.05$).

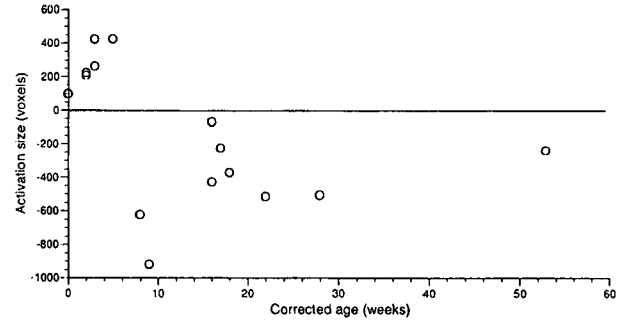

FIG. 1. Significantly activated voxels as a function of age for all 15 infants.

Results

In all subjects, a stimulus-related signal change was observed in the anterolateral region of the calcarine fissure. Although the anatomical distribution of activated voxels was similar in all subjects, fMRI revealed distinctly different patterns of stimulus-related signal changes in neonates less than 5 weeks of age and older infants. Fig. 1 shows the size of activated voxels as a function of age for all subjects. Six neonates less than 5 weeks of corrected age showed a stimulus-related signal increase in the occipital cortex, as in a previous study of human adults (adult pattern, Fig. 2a). Eight infants older than 8 weeks of corrected age showed a stimulus-related signal decrease, which is opposite to that of the normal adult pattern (Fig. 2b). Two premature subjects older than 8 weeks of postnatal (chronological) age, but less than 5 weeks of corrected age, showed a positive response to photic stimulation (patients 5 and 6 on Table 1).

Discussion

This is the first report showing that activity-related metabolism in human cerebral cortex alters rapidly early in life. Developmental changes of cerebral blood flow and glucose metabolism have been reported.[4,5,13] Average global cerebral blood flow and cerebral oxygen utilization in normal children were approximately 1.8 times and 1.3 times as large, respectively, as those in normal young adults.[13] In the neonatal period (less than 4 weeks of age), the most prominent glucose consumption rate (cerebral metabolic rate of glucose; CMRGlu) was found in the primary sensorimotor area, and the remaining cerebral cortical regions showed relatively lower metabolic activity.[4,5] By approximately the second month of age, CMRGlu had increased in calcarine and temporal cortices.[4,5]

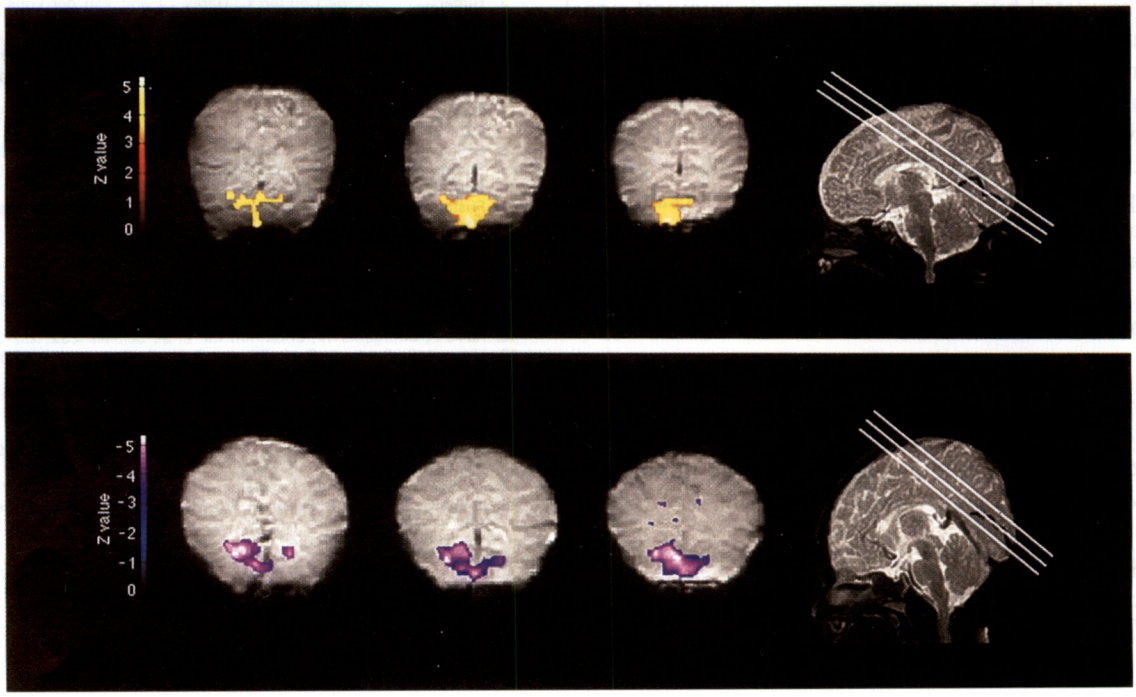

FIG. 2**a**. Functional MRI (left) and reference sagittal T2-weighted image (right) of patient 3, a neonate of 3 weeks corrected aged. The oblique white lines in sagittal image indicate the plane of echo planar images, located along the bank of the calcarine fissure (curved black line). A statistical parametric map of this subject was superimposed onto the subject's original 3 echo planar images parallel to the calcarine fissure. Red and yellow indicate areas with significant positive correlation with visual stimulation in the occipital cortex. **b**. Functional MRI and reference sagittal image of patient 7, an 8-week-old infant. Blue and purple indicate areas with significant negative correlation with visual stimulation in the primary visual cortex.

Considerable rises in CMRGlu were observed in the calcarine cortex by approximately 3 months postnatally.[4,5] These findings support the concept that a rise in the metabolic rate of a particular structure marks the time of its contribution to behavior. Actually, by the third month of age, normal infants can follow the motion of a mother's hand.[14]

We observed different fMRI responses to photic stimulation in the occipital cortex: a signal increase in neonates younger than 5 weeks of age and a signal decrease in older infants. The mechanism of the positive signal change has generally been interpreted as a reflection of an increase in blood oxygenation due to an excessive increase in cerebral blood flow with an oxygen supply in excess of metabolic demands.[6,7] The blood oxygen level dependent (BOLD) technique[6,7] would show a negative effect if an increase in oxygen consumption of the neurons with increased activity is not compensated by the flow of blood. During development, the brain produces a vast excess of neurons, synapses, and dendritic spines.[3,15–18] The overproduction of neurons and synapses is advantageous in the adaptation and plasticity of the brain. Huttenlocher *et al.*[3] determined age-related changes in synaptic density in the human primary visual cortex. They defined a period of rapid synapse production that starts postnatally at the age of 2 months and a subsequent period of synapse elimination that extends past the age of 3 years. LeVay *et al.*[19] and Wiesel[20] have demonstrated that monocular deprivation performed during the early stages of postnatal development dramatically affects the functional organization of the visual cortex. They termed this the 'critical period' during which synaptic connections in the primary visual cortex are modified by visual experience. The experience in human infants with cataract removal indicates that visual acuity may be impaired after 2 months of age, even if cataract removal is successful.[21,22] A negative response to visual stimuli in the occipital cortex was observed in the period between postnatal ages 2 and 13 months, which corresponds well with the period of rapid formation of synapses and rapid increase of CMRGlu in human visual cortex.[3–5] It is therefore very likely that in fMRI the reverse signal response in neonates and infants represents the excessive production of synapses, which results in a rapid increase of oxygen and glucose demand. As shown in premature infants, patients 5 and 6, the inversion of the signal response depends on the age corrected for gestational age at birth, not on chronological age. This finding suggests that a rapid increase in metabolic and synaptic activity in the occipital cortex may not depend on the length of light exposure. This is consistent with a previous study in rhesus monkeys.[15] The ascending phase of synapse overproduction may

be regulated by a common genetic or humoral signal that is relatively independent of the age of onset and duration of visual stimulation.[15] The effect of sedation by pentobarbital, as used in this study, on the MRI signal would be minimal because adults sedated with pentobarbital showed an increased signal in response to visual stimulation,[23] and because our protocol for sedation with pentobarbital was identical in all subjects.

Conclusion

By establishing changes in fMRI during normal development, it will be possible to use fMRI for the detection of visual and other functional impairments in the early infantile period and for the noninvasive study of plasticity of the human CNS.

References

1. Chi JG, Dooling EC and Gilles FH. *Ann Neurol* **1**, 86–93 (1977).
2. Herschkowitz N. *Biol Neonate* **54**, 1–19 (1988).
3. Huttenlocher PR, de Courten C, Garey LJ and Van der Loos H. *Neurosci Lett* **33**, 247–252 (1982).
4. Chugani HT and Phelps ME. *Science* **231**, 840–843 (1986).
5. Chugani HT, Phelps ME and Mazziotta JC. *Ann Neurol* **22**, 487–497 (1987).
6. Ogawa S, Tank DW, Menon R *et al. Proc Natl Acad Sci USA* **89**, 5951–5955 (1992).
7. Kwong KK, Belliveau JW, Chesler DA *et al. Proc Natl Acad Sci USA* **89**, 5675–5679 (1992).
8. Belliveau JW, Kennedy DN, McKinstry RC *et al. Science* **254**, 716–719 (1991).
9. Sereno MI, Dale AM, Reppas JB *et al. Science* **268**, 889–893 (1995).
10. Born P, Rostrup E, Leth H *et al. Lancet* **347**, 543 (1996).
11. Friston KJ, Worsley KJ, Frackowiak RSJ *et al. Hum Brain Mapp* **1**, 210–220 (1994).
12. Friston KJ *et al. NeuroImage* **2**, 45–53 (1995).
13. Kennedy C and Sokoloff L. *J Clin Invest* **36**, 1130–1137 (1957).
14. Bronson G. *Child Dev* **45**, 873–890 (1974).
15. Bourgeois JP, Jastreboff PJ and Rakic P. *Proc Natl Acad Sci USA* **86**, 4297–4301 (1989).
16. Rakic P, Bourgeois JP, Eckenhoff MF *et al. Science* **232**, 232–235 (1986).
17. Lidow MS, Goldman Rakic PS and Rakic P. *Proc Natl Acad Sci USA* **88**, 10218–1021 (1991).
18. Lidow MS and Rakic P. *J Comp Neurol* **360**, 393–402 (1995).
19. LeVay S, Wiesel TN and Hubel DH. *J Comp Neurol* **191**, 1–51 (1980).
20. Wiesel TN. *Nature* **299**, 583–591 (1982).
21. Beller R, Hoyt CS, Marg E and Odom JV. *Am J Ophthalmol* **91**, 559–565 (1981).
22. Jacobson SG, Mohindra I and Held R. *Br J Ophthalmol* **65**, 727–735 (1981).
23. Loenneker T, Joeri P, Huisman TAGM *et al. Proceedings of the ISMRM* **3**, 1897 (1996).

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