A milestone for normal development of the infantile brain detected by functional MRI

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Article abstract—*Objective:* To investigate the relationship between cerebral cortical function and white matter myelination in the visual pathway in the evaluation of normal brain development. *Methods:* The authors performed quantitative analysis of white matter myelination detected with conventional T1-weighted spin echo (SE) MRI and brain functional MRI (fMRI) using echoplanar imaging with photic stimulation in 27 neurologically normal infants (age range, 0 to 22 weeks). *Results:* An age-dependent gradual increase in signal intensity was observed in optic radiation on the T1-weighted SE images, indicating progression of white matter myelination. A rapid age-dependent reverse in signal response was observed on fMRI. Infants older than 8 weeks showed a stimulus-induced signal decrease in the visual cortex, whereas infants younger than 7 weeks showed a signal increase. *Conclusions:* A rapid inversion of response revealed by fMRI with photic stimulation 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 brain maturation, which is a different developmental process from white matter myelination. The metabolic changes detected by fMRI provide a milestone for the evaluation of normal brain development.

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The anatomy, function, and metabolism of the human brain change rapidly in early life.[1-4] 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.[5,6] MRI has been widely used to evaluate normal and abnormal morphologic changes during brain development.[7-9] MRI can detect myelination of the CNS, which is a dynamic process starting during intrauterine life and continuing after birth that can be used as an index of brain maturation.[10] Normal myelination patterns on MRI in healthy full-term and preterm infants have been extensively described.[7,11-15] T1-weighted images are believed to be most useful in the monitoring of normal brain development in the first 6 to 8 months of life.[7-9]

Functional MRI (fMRI), which is a noninvasive imaging tool for detecting neuronal activity induced by external stimuli, has recently become available for clinical examination of brain function during development.[16-18] Blood oxygenation level dependent (BOLD) contrast and the inflow effect from relatively larger veins are thought to be the mechanisms of fMRI signal change, especially in the clinically available 1.5-T MRI system.[19-21] Assessment of visual function provides important information on the integrity of brain function in the neonatal period.[22,23] fMRI studies have shown an age-dependent change of the functional signal response within the visual cortex of a small number of infants.[16,18] It has been suggested that a negative signal response to photic stimulation early in normal development reflects rapid synapse formation in the visual cortex.[16,18] This finding may be used as a developmental milestone of 8 weeks of age.

In addition to the earlier studies in a small number of infants,[16,18] fMRI and anatomic MRI studies of a larger number of infants are needed for the quantitative comparison of fMRI and white matter myelination in normal developing infants. We investigated the relationship between fMRI and white matter myelination in the visual pathway in the same group to ascertain the usefulness of fMRI in the evaluation of normal development of the neonatal and early infantile brain.

Materials and methods. *Subjects.* From December 1996 to March 1998, we performed MRI and fMRI of the brain in 27 infants (13 boys and 14 girls), age 0 to 22 weeks, corrected for gestational age at birth, whose perinatal risk factors warranted screening for possible brain damage (table). The indication for the MRI protocol was

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Table Summary of patients and results of statistical parametric mapping (SPM)

Patient no.	Age at functional MRI (wk)		Sex	Indication for MRI	SPM outcome in visual cortex†	
	Corrected*	Chronologic			Activated voxels	Max *z* value
1	0	9	M	Prematurity	99	4.52
2	0	12	M	Asp (5)	424	5.4
3	1	2	M	Rule out hydrocephalus	609	4.64
4	1	14	M	RDS	185	5.08
5	2	2	F	Low birth weight	206	4.59
6	3	1	F	MAS	209	4.19
7	3	13	F	Prematurity	423	4.56
8	3	13	M	Prematurity	417	4.78
9	4	10	M	RDS	592	6.69
10	4	11	F	Asp (6)	185	5.78
11	5	5	M	Face hemangioma	300	4.44
12	6	17	F	Asp (7)/RDS	394	5.25
13	7	7	F	Asp (6)	571	4.64
14	7	8	F	Acidosis	286	4.14
15	7	16	F	Asp (6)/RDS	431	4.39
16	7	19	F	RDS	465	4.3
17	8	8	F	Rule out hydrocephalus	−689	−5.22
18	8	20	M	Prematurity	−919	−5.18
19	9	13	M	Prematurity	−306	−6.7
20	9	16	F	Prematurity	−227	−4.57
21	13	13	F	Hypothyroidism	−276	−3.75
22	13	18	M	Squint	−764	−6.16
23	17	23	M	Prematurity	−225	−4.39
24	17	26	F	Prematurity	−279	−5.06
25	18	23	F	RDS	−371	−4.53
26	18	31	M	RDS	−348	−5.07
27	22	33	M	Prematurity	−514	−4.59

* Corrected for gestational age at birth, calculated from the mother's last menstrual period.
† Minus value indicates a negative response.

Asp = birth asphyxia (Apgar score at 5 minutes); RDS = respiratory distress syndrome; MAS = meconium aspiration syndrome.

screening for intracranial pathology in patients with suspicion of developmental delay due to prematurity or low birth weight and with a history of birth asphyxia and infantile respiratory distress. Infants with a history of severe birth asphyxia, neonatal seizure, sepsis, severe developmental delay, congenital brain anomaly, or periventricular leukomalacia were excluded. Standard pediatric neurologic examinations were performed by two pediatric neurologists (Y.K., K.K.) in all cases. 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. Each subject underwent MR examination once. Some of the patients were included in our previous report.[18] This study was approved by the Ethical Committee of the Fukui Medical University. In all infants, informed consent was obtained from their parents.

All subjects were sedated with pentobarbital 3 to 5 mg/kg 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. We confirmed that their eyes were closed via a mirror placed on the head coil during the study. Other than the constant gradient noise of echoplanar imaging and the photic stimulation, other sensory stimuli were minimized.

Quantitative assessment of myelination. All MRI was performed with a 1.5-T MRI system (Signa Horizon; GE Medical Systems, Milwaukee, WI) and a standard birdcage head coil. Sagittal T2-weighted fast spin echo (SE) (repetition time 3000 msec/echo time 88 msec, 256 × 256 matrix, 240-mm field of view) and axial T1-weighted SE (350/20, 256 × 192 matrix, 22-cm field of view, 8-mm section thickness, and 1-mm gap) MRI parallel to the orbitomeatus line were acquired from all subjects. During the first 6 months of age, T1-weighted images are the most useful for assessing normal white matter myelination.[7] Hence, on the T1-weighted axial images, signal intensities from regions of interest (ROI) at different anatomic locations were ana-

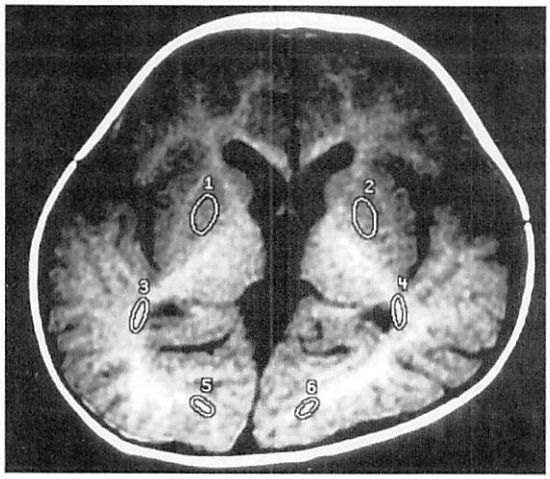

Figure 1. Examples of selected regions of interest for assessment of myelination on T1-weighted images (repetition time 350/echo time 20): bilateral putamen (1 and 2), proximal optic radiation (3 and 4), and distal optic radiation (5 and 6).

lyzed for white-to-gray matter contrast. We performed quantitative assessment of myelination by measuring pixel intensities over small, oval ROI. ROI were placed over the proximal and distal optic radiation and putamen bilaterally. The optic radiation was identified with established landmarks: it originates from the lateral geniculate nucleus capping the lateral recess of the ambient cistern,[24] runs just lateral to the posterior horn of the lateral ventricle, and reaches the calcarine sulcus. In the slice, which included the ambient cistern, single ROI was placed on the proximal optic radiation lateral to the posterior horn of the lateral ventricle. Similarly, a ROI was placed on the distal optic radiation just beneath the calcarine sulcus. The shape of ROI was adjusted so that it fit the elongated structure of the optic radiation while keeping the size of at least 10 pixels. Hence we placed 6 ROI for each subject. The boundaries and locations of these ROI were typically as demonstrated in figure 1. The white-to-gray matter contrast was calculated bilaterally, as a percentage, by use of the following formula, which is based on one used in a previous study[25]:

$$\text{Percent contrast} = 100 \times (\text{Siw} - \text{Sig})/\text{Sig}$$

where Siw and Sig are signal intensity for white matter (from the proximal optic radiation or the distal optic radiation) and gray matter (from putamen). The percent white-to-gray matter contrasts from each location (proximal and distal optic radiation, bilaterally) were averaged for each location and plotted against age.

Functional MRI. With the use of sagittal T2-weighted SE images as an anatomic guide, five oblique slices approximately parallel to the calcarine fissure were selected. With the technical limitation of echoplanar images on slice number, we maximized the coverage of the calcarine sulcus by selecting oblique direction, and hence the coverage was different from that of the anatomic MRI. For T2*-weighted fMRI, 102 consecutive gradient-echo echoplanar image sequences (repetition time 3000 msec/echo time 50 msec, 90-degree flip angle, 128 × 128 matrix, 22-cm field of view, 5-mm section thickness, and 1-mm gap) were acquired. An initial baseline phase of rest for 30 seconds was followed by a photic stimulation phase alternating with a rest phase, for a total of 10 phases per trial. Visual stimulation was performed with an 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 the response from each voxel was calculated with statistical parametric mapping (SPM96) (using software from the Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Inc., Sherborn, MA).[26,27] The images from each subject were realigned, with the first image used 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 was performed. Finally, voxel-wise statistical analysis was performed by means of 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 according to 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 of significance ($p < 0.05$).

Results. *Quantitative assessment of myelination.* On the T1-weighted images, the signal intensity in the optic radiation increased gradually with increasing age (0 to 22 weeks of corrected age). There was a gradual increase in the percent contrast of white-to-gray matter in the proximal optic radiation, and a slight delay in the increase in the distal optic radiation. A positive linear correlation between percent contrast of white-to-gray matter and age was observed in both locations (both $p < 0.001$, $df = 27$) (figure 2).

Signal change in fMRI. From fMRI, a stimulus-induced signal change was observed in the anterolateral region of the calcarine fissure in all subjects. Although the anatomic distribution of activated voxels was similar in all subjects, fMRI revealed distinctly different patterns of stimulus-induced signal changes in infants younger than 7 weeks and older infants. Figure 3 shows the size of activated voxels as a function of age for all subjects. Ten infants younger than 7 weeks of corrected age showed a stimulus-induced signal increase in the occipital cortex (figure 4, A and B, and figure 5, A and B), which is the pattern shown by normal human adults.[20] Eight infants older than 8 weeks of corrected age showed a stimulus-induced signal decrease (figure 4, C and D, and figure 5, C and D). The rapid changes in patterns of stimulus-induced signals on T2*-weighted fMRI in the occipital cortex of infants occurred earlier than the reverse in signal intensity on the T1-weighted SE images in optic radiation, which suggests progression of myelination with advancing age.

Discussion. In the current study of normal early development, optic radiation showed a gradual increase in white-to-gray matter contrast on conventional T1-weighted SE images, whereas primary visual cortex revealed a rapid reverse in signal response with photic stimulation on fMRI. Previous qualitative study has charted the normal MRI milestones for myelination of brain.[7] According to those results, high signal

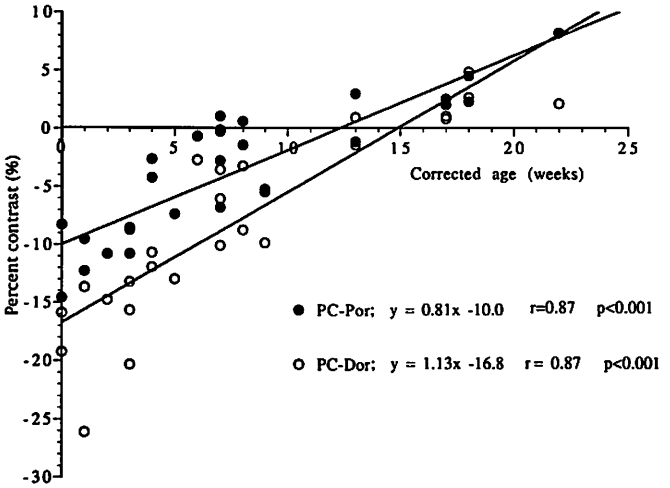

Figure 2. Percent contrast of white-to-gray matter, plotted against age, in the proximal optic radiation versus the putamen (PC-Por) and the distal optic radiation versus the putamen (PC-Dor). The value 0 on the ordinate reflects the point at which white and gray matter are isointense. With a value greater than 0, white matter is hyperintense to gray, and with a value less than 0, white matter is hypointense to gray. The general increase in percent contrast of white-to-gray matter with an increase in age in the optic radiation in T1-weighted images reflects progression of myelination with advancing age. The percent contrast of white-to-gray matter is higher for proximal optic radiation than for distal optic radiation in the occipital lobe, causing myelination to appear slightly more advanced on the proximal site.

intensity should appear in the central occipital white matter by 3 to 5 months of age on T1-weighted images and by 9 to 14 months of age on T2-weighted images. Changes in signal intensity on T1-weighted images correlate with an increase in cholesterol and glycolipids that accompanies the formation of myelin from oligodendrocytes. Considering that myelin formation of the optic radiation is completed by 28 weeks of age,[28] the qualitative signal change in T1-weighted MRI may reflect the maturation of the white matter. Our quantitative analysis of the signal change in T1-weighted SE images showed a gradual increase in percent contrast of white-to-gray matter in optic radiation from 0 to 22 weeks; hence, the process reflected in this signal change is gradual and ranges widely over several months. Conversely, an abrupt reversal of the signal response by fMRI was observed between 7 and 8 weeks of corrected age. The reversal of BOLD signal may represent a different aspect of brain maturation from myelination.

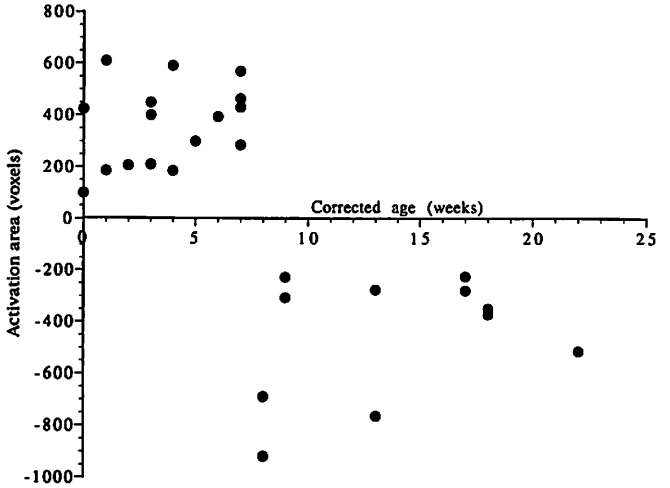

Figure 3. Significantly activated voxels as a function of age for all 27 infants.

During development, the brain produces a vast excess of neurons, synapses, and dendritic spines as part of the maturational process.[2,29-31] The overproduction of neurons and synapses is advantageous in adaptation and plasticity of the brain. An age-related change in synaptic density has been determined in the human primary visual cortex.[2] In this study, a period of rapid synapse production was defined that starts postnatally at age 2 months and ends at about postnatal age 8 months; a subsequent longer period of synapse elimination extends past age 3 years. More recently, a study showed that a remarkable diversity of neurotransmitter receptors develops concurrently in disparate areas of the primate cerebral cortex.[31] The density of dopaminergic, adrenergic, serotonergic, cholinergic, and GABAergic receptors (GABA, gamma-aminobutyric acid) in rhesus monkey reached a maximum between 2 and 4 months of age and then declined gradually to adult levels in all layers of sensory, motor, and association regions.

Because the principal brain substances for energy production are glucose and oxygen, the local energy requirement for this process in developing brain is indirectly assessed by measuring regional cerebral metabolic rate of glucose utilization (rCMRGlu) with PET.[3,31,32] Previous PET studies showed that the most prominent rCMRGlu was in the primary sensorimotor area, and remaining cerebral cortical regions showed relatively lower metabolic activity in the neonatal period (<4 weeks of age).[3,32] By approximately the second month of age, rCMRGlu had increased in the calcarine and temporal cortices. Considerable rises in CMRGlu were observed in the calcarine cortex by approximately 3 months postnatally. This is consistent with rapid synapse production starting at age of 2 months, as synaptic activities are thought to account for a large fraction of CMRGlu.[29] Note should be made that previous PET studies[3,32] described development-related change in glucose metabolism at rest, not the task-related neuronal activities.

We observed reversal of fMRI responses to photic stimulation in the occipital cortex at the age of 7 to 8 weeks. In adults, energy-dependent changes in neuronal function and blood flow are supposed to be coupled.[29] Photic stimulation is a well-known task that activates the visual cortex, causing increase in regional cerebral blood flow (rCBF) there. In the T2*-weighted gradient echo sequence, MR signal intensity change is proportional to changes in the total

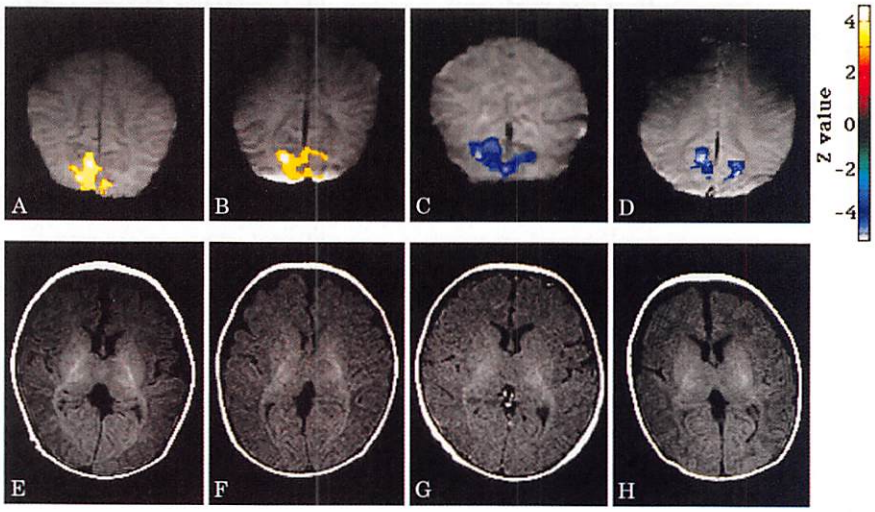

Figure 4. Functional MRI (fMRI) (A–D) and conventional MRI (E–H) of four subjects. For fMRI analysis, the subject's statistical parametric map was superimposed onto the individual's original echoplanar image parallel to the calcarine fissure. (A, B) fMRI of Patients 13 and 14, infants of 7 weeks corrected age. Red and yellow indicate areas with a significant positive correlation with visual stimulation in the occipital cortex. (C, D) fMRI of Patients 17 and 18, 8-week-old infants. Green and blue indicate areas with a significant negative correlation with visual stimulation in the occipital cortex. (E–H) T1-weighted spin echo MRI (repetition time 350/echo time 20) of Patient 13 (E), Patient 14 (F), Patient 17 (G), and Patient 18 (H). The images show no apparent differences in signal intensity in optic radiation in the occipital lobe.

deoxyhemoglobin concentration in the voxel, which is affected by changes in cerebral blood volume (CBV) and hematocrit as well as by changes in percent saturation of oxygen.[33] Oxygen delivery, CBF, and CBV increase with neuronal activation.[20] In adults, CBF (and oxygen delivery) changes exceed CBV change two- to fourfold and oxygen extraction increases only slightly[34]; hence, total deoxyhemoglobin decreases, and reduced intravoxel dephasing and increased MR signal occurs.[19,20] Therefore, an increase in MR signal is a reflection of an increase in blood oxygenation due to an excessive increase in CBF with an oxygen supply in excess of metabolic demands. As infants younger than 8 weeks showed a signal increase, we presume that photic stimulation caused increase in rCBF of the visual cortex of infants irrespective of age. Conversely, infants older than 8 weeks have excessive synapses, which may require larger metabolic demand during neural activation, which in turn necessitates a larger amount of oxygen. Greater oxygen extraction during photic stimulation may not be compensated by increased oxygen delivery due to an increase in rCBF and rCBV, causing increase in deoxyhemoglobin concentration during photic stimulation, hence a decrease in MR signal. The reversal of BOLD signal during photic stimulation at 7 to 8 weeks may represent rapid synapse formation in the visual cortex disproportionate to the oxygen delivery.

Effect of sedation on the reversal of BOLD signal would be minimal, because our protocol for sedation

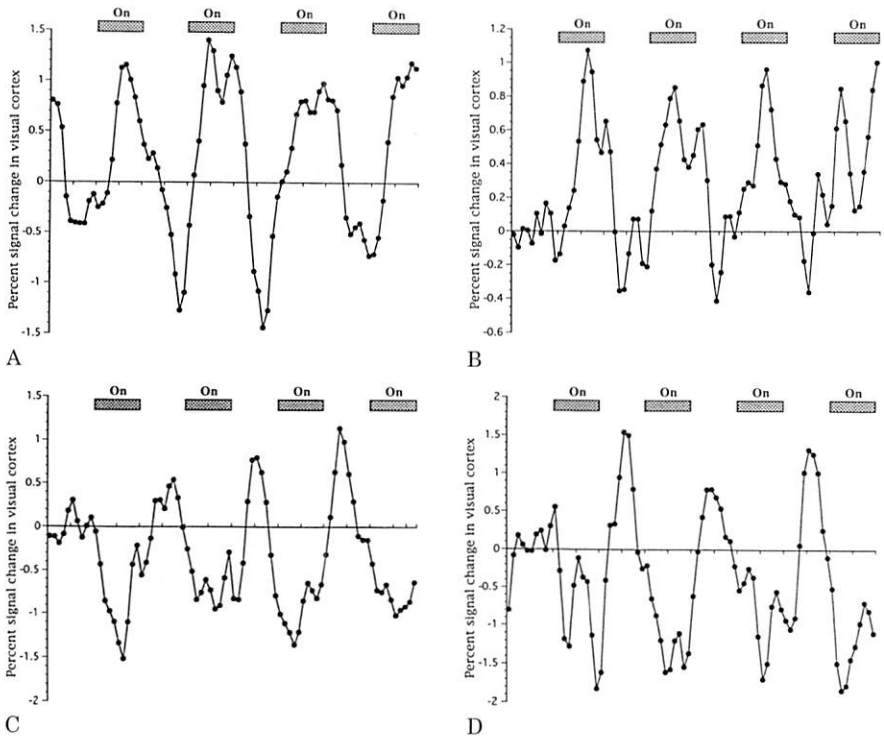

Figure 5. Percent signal time intensity curve in the primary visual cortex of Patient 13 (A), Patient 14 (B), Patient 17 (C), and Patient 18 (D). Infants of 7 weeks corrected age showed a stimulus-induced signal increase in the primary visual cortex (A, B), whereas infants of 8 weeks corrected age showed a stimulus-induced signal decrease (C, D).

with pentobarbital was identical in all infants, although the possibility of a sudden change in the developing brain's sensitivity to pentobarbital cannot be ruled out. Further studies without sedation are needed to resolve this issue.

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