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Brain Mapping in Sedated Infants and Young Children with Passive-Functional Magnetic Resonance Imaging

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Key Words

fMRI · Cortical mapping · Brain mapping · Passive stimulation

Abstract

Functional magnetic resonance imaging (fMRI) in pediatric patients presents a unique set of problems due to the need for patient compliance, the frequent need for sedation and an early developmental status. A new method for using fMRI in sedated infants and young children is presented using passive stimuli focused on visual, sensorimotor and language functions. All of these stimuli are presented such that no patient interaction is required. Eight sedated children undergoing diagnostic MRI scans of the brain participated in these passive fMRI procedures. Cortical regions were identified using standard techniques applied to the blood-oxygen-level-dependent signal which is the basis for fMRI. The results support the feasibility of brain mapping in sedated children with passive fMRI techniques.

Introduction

Recent developments in several imaging modalities have resulted in nonoperative methods for brain mapping. Functional magnetic resonance imaging (fMRI), magnetic source imaging and positron emission tomography have recently been utilized to define regional areas of cerebral function. Relative cost, superior spatial resolution and avoidance of either external or intravenous ionizing radiation are issues that favor fMRI as a superior method for functional imaging. The reliability of this technique has been confirmed through conventional methods of brain mapping [1–9]. Given this level of reliability, fMRI is currently being utilized as an adjunct for assessing surgical risk and tailoring intraoperative strategy in patients with lesions juxtaposed to functional domains.

Functional MRI mapping typically requires that a series of specified tasks be performed by the patient being imaged. These tasks are dictated based on the cortical representation area of interest. As an example, object naming is a method used to perform functional imaging of

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Table 1. Patient data

Patient	Age months	Pathology	Anesthesia (propofol) μg/kg/min	Neurologic findings
cc125	3	medulloblastoma	80	divergent gaze
cc114	4	pineoblastoma	150–225	none
cc108	7	optic nerve glioma	100	nystagmus
cc60	15	cerebral PNET	100	left hemiparesis
cc83	31	pilocytic astrocytoma	50	none
cc107	39	rhabdomyosarcoma	100	none
cc90	70	AML	100	none
cc81	96	ALL	50	none

PNET = Primitive neuroectodermal tumor; ALL = acute lymphoblastic leukemia; AML = acute myeloblastic leukemia.

cortices responsible for speech expression. Likewise, finger tapping is requested of the patient during imaging when one wishes to visualize contralateral primary sensorimotor cortex. Similarly, visual, auditory, sensory and language representation areas can be imaged through a dynamic interplay between the patient and the investigator. Brain mapping using fMRI is, therefore, limited by the subject's ability or willingness to cooperate. It thus follows that young children and infants have been considered poor candidates for fMRI mapping, not only because of the compliance requirement, but also due to their frequent need for sedation.

An ideal fMRI technique for pediatric patients would thus impose no demands on patient cooperation and permit the continued use of sedation during imaging. We have recently investigated the feasibility of using a novel and, hitherto, undescribed approach toward brain mapping in sedated young children and infants using fMRI with a completely passive stimulation technique during anesthesia.

Materials and Methods

Patients

All children less than 16 years of age who were scheduled to undergo diagnostic MRI scanning of the brain with anesthetic support were considered for investigation. Children with diffuse or bihemispheric disease processes were excluded in an effort to maintain an internal control for each patient. This study was approved for patient accrual by the Institutional Review Board at the Memorial Sloan-Kettering Cancer Center. Following informed consent from a parent or guardian, 8 patients underwent functional studies. The children ranged in age from 3 months to 8 years (mean 33 months) at the time of their fMRI. All children were being evaluated for either primary cerebral neoplasms or extent of disease staging for an extracerebral primary cancer. Only 1 patient had a significant neurologic deficit which was limited to a single hemisphere. Patient data are summarized in table 1.

Imaging

Our technique used for fMRI has previously been discussed in detail [10, 11]. A GE 1.5 Tesla echo speed scanner (General Electric) was employed to acquire 16 slices, 4.5 mm thick, oriented parallel to the AC/PC line and with an in-plane resolution of 1.5 × 1.5 mm (19 × 19 cm field of view and an array size of 128 × 128 pixels). Images were acquired using a typical T_2-weighted sequence (TR = 3,000 ms, TE = 60 ms, flip angle = 60° or 90°) which is sensitive to MR signal changes caused by endogenous alterations in the proportion of deoxyhemoglobin in the local vasculature accompanying changes in neuronal activity, referred to as the blood-oxygen-level-dependent (BOLD) signal [12–15]. An imaging run consisted of 66 image acquisitions (102 s) partitioned into four temporal epochs. Following the preconditioning acquisitions (images 1–3; 9 s), a baseline epoch was acquired during images 4–18 (45 s), a 1st stimulation epoch during images 20–34 (45 s), a 2nd stimulation epoch during images (35–49 (45 s) and a final baseline epoch during images 52–66 (45 s). Each study consisted of four runs. Images were reconstructed off-line (using GE code) and computationally aligned [16]. As a result of this computational alignment and reslicing, the top and bottom brain slices sometimes appear partially removed, so the reported data set includes the 14 'inner' slices. A voxel (volume element) by voxel statistical analysis was employed to compare signal averages during baseline and stimulation epochs using a multistage statistical process [13]. Rates of false-positive results were determined by phantom studies and found to range from $p \leq 0.01$ (red) to $p \leq 0.005$ (orange) to $p \leq 0.0002$ (yellow). T_1-weighted images were also acquired at the same slice locations to optimize structural image quality. T_1- and T_2-weighted images were registered based on ventricular and sulcal features for enhanced precision of the structural/functional relationships.

Anesthesia

All children were sedated using a standard institutional regimen for pediatric imaging which is coordinated by a staff anesthesiologist. A preanesthetic fasting period of at least 6 h is mandated. To maintain simplicity, a single anesthetic agent was utilized in all cases. Pro-

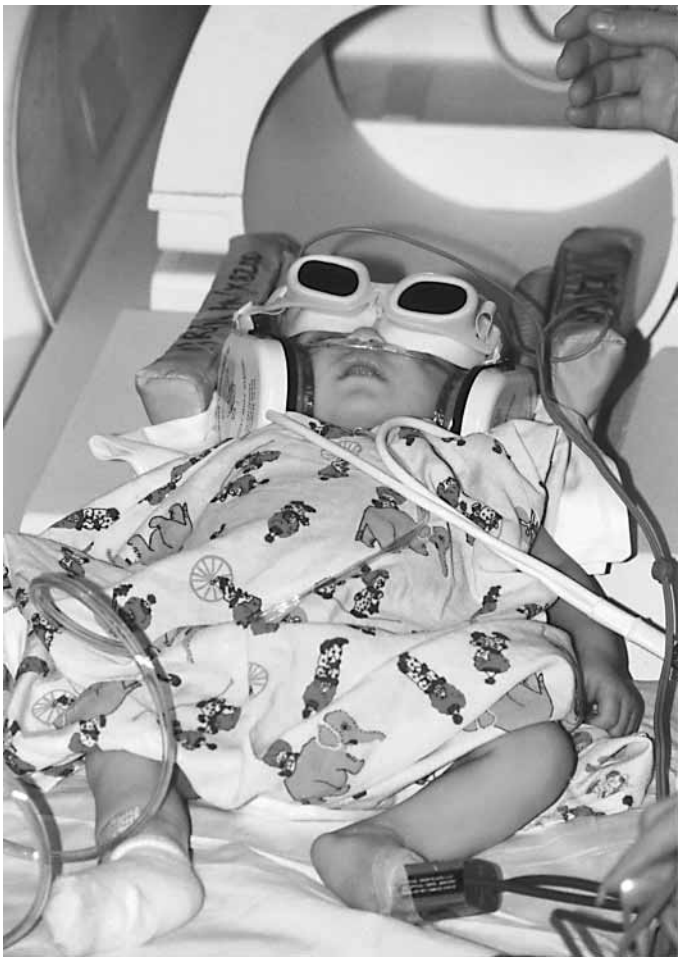

Fig. 1. A 4-month-old infant male (cc114) at the time of functional imaging. Passive stimulation devices including the LED goggles and headphones are in place. Supplemental oxygen delivered via a nasal cannula and pulse oximetry are integral to the anesthetic preparation and monitoring.

pofol, an alkylphenol, has a relatively rapid half-life and rapid rate of redistribution. Because of these particular pharmacokinetic properties, intravenously administered propofol has a rapid onset of action and is easily titrated. Although cerebral blood flow and cerebral metabolic rate can be affected in a dose-dependent fashion, propofol has little effect on the cerebral autoregulation. The end point for depth of anesthesia was titrated (50–225 μg/kg/min) based on patient response and balanced with hemodynamic and respiratory parameters. Supplemental oxygen via a nasal cannula (2–3 liters/min) was routinely administered. To insure safety, and to help govern the titration of anesthesia, monitoring techniques included pulse oximetry, temperature monitoring and noninvasive blood pressure recordings.

Passive Stimulation

All stimuli were presented in a passive manner, thus eliminating the need for subject interaction. Repetitive photic stimulation through closed eyelids was accomplished with a full-field light-emitting diode (LED) display (frequency of 4 or 8 Hz, 45 s) mounted on the inner surface of goggles covering the eyes and eliminating ambient light (Grass Instruments, Model SIOVSB; fig. 1). Tactile stimuli was provided by rubbing the hand with a coarse, atraumatic device. The hand is selected based on the large cortical representation area and accessibility during scanning. In very small children, an extension device was used in an attempt to avoid manipulations within the bore of the magnet. Language-sensitive functions were measured by presenting a 45-second recording of the mother's or father's voice consisting of words or sentences familiar to the patient. The content of the recording was tailored by the parent based on their own child's working vocabulary. These recordings, obtained prior to imaging, were replayed to the patient through headphones (Gradient Muff Headset; Resonance Technology Inc.) designed to filter out background scanner noise (fig. 1).

Results

Eight fMRI studies were performed using the described technique. There were no complications using the aforementioned protocol. In addition to the time alotted for diagnostic imaging, 15–20 min were required to perform the functional imaging. Using the passive stimulation paradigm (photic, tactile and auditory stimulation), multiple and varied discreet regions of cortical activity were observed in all subjects. Typical results are illustrated in figures 2–5. Using the photic stimulation paradigm, activation occurred in the interhemispheric region of the occipital lobes (fig. 2). Areas of activation consistent with the anatomical region of the postcentral gyrus were obtained using the passive stimulation technique for tactile sensation (fig. 3). Auditory stimulation with familiar voice recordings consistently resulted in activation of multiple specific cortical and subcortical regions (fig. 4, 5).

Discussion

Conventional methods of cortical mapping rely upon electrophysiologic data through direct cortical stimulation, cortical evoked potential monitoring, or extraoperative mapping through the use of implanted grids and electrodes. These methods have contributed significantly toward improving surgical goals and potentially reducing morbidity in patients undergoing resective procedures for brain tumors and chronic epileptic foci [17–21]. Although considered the gold standard for identifying cortical areas of representation, electrophysiologic mapping is an invasive procedure with some inherent risk. Further, direct cortical mapping in very young children is hampered by a

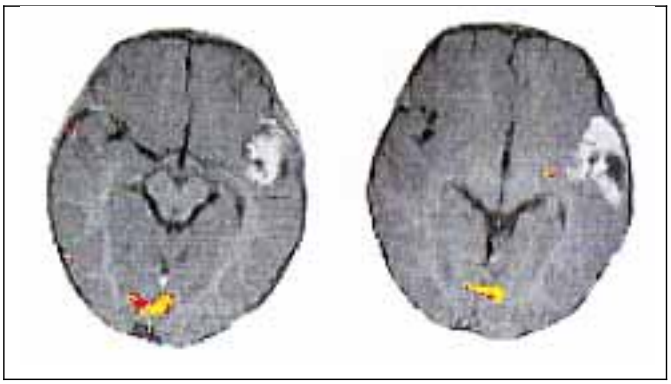

Fig. 2. Axial fMRI images in a 15-month-old child (cc60) during LED visual stimulation. Activation patterns are clearly seen in a region consistent with the primary visual cortex.

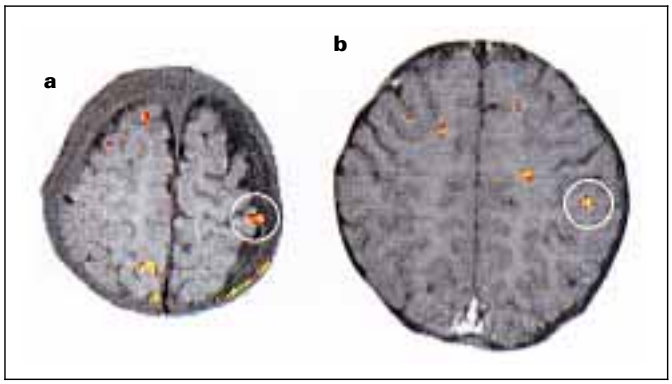

Fig. 3. Examples of passive sensory mapping in a (**a**) 7-month-old female (cc108) and (**b**) a 3-year-old (cc107) following stimulation of the right hand. The predominant activation areas (circles) are located in the postcentral gyrus.

lack of patient cooperation and poorly defined parameters for electrical stimulation [22].

fMRI is an accepted technique for extraoperative cortical mapping in adults. Activated cortical regions typically coincide with the expected anatomical domains specific for the function tested. Not only do these domains agree with expected anatomical correlates, but confirmation through electrophysiologic testing has been performed with excellent concordance [1, 3–8].

However, the ability to obtain informative fMRI maps is dependent upon the subject's capacity to perform task-specific activities. This premise presents several difficulties in the pediatric population. First, young children and infants are poorly compliant with instructions to participate in specific activities. Second, since many young children require sedation for MR scanning, most will not have the capacity to follow instructions. Third, immature developmental status, especially in the infant population, restricts elaborate language-mapping paradigms currently being used in older children and adults. The preoperative use of fMRI in children has been briefly addressed in previous works [2, 8, 9, 23, 24]. All of these investigators recognized age limitations with functional imaging in children. In 1996, Atlas et al. [23] concluded that 'unfortunately, sedation does not seem to be a useful option ... because psychoactive agents would reduce cooperativeness with task performance. Clearly, clinical uses of BOLD fMRI will be limited to selected patients'. At the Hospital for Sick Children [9] in Toronto, 16 children underwent fMRI studies without sedation. The task-specific functions were rehearsed with the children prior to imaging. From their experience, this group recognized the difficulty in using fMRI in young children and concluded that 'children less than 6 years of age may be difficult to study with fMRI'. In commenting on brain mapping using position emission tomography, Duncan et al. [24] felt that the 'limitation in the pediatric population is the time needed to obtain the study, as well as the absolute cooperation of the child'. Some recent success in single modality

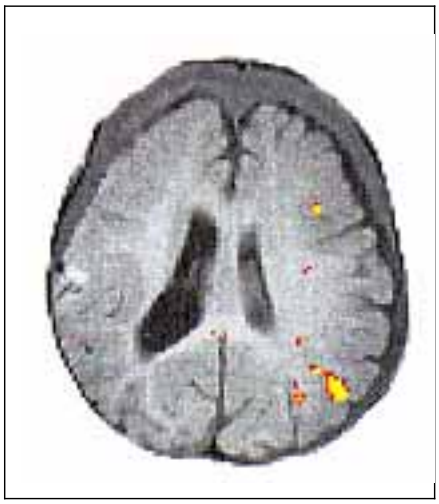

Fig. 4. A postoperative fMRI scan of a 7-month-old female (cc108) with an optic nerve glioma. Stimulation with the mother's recorded voice resulted in discreet regions of activation including the left temporoparietal junction and the depth of a sulcus in the posterior frontal lobe.

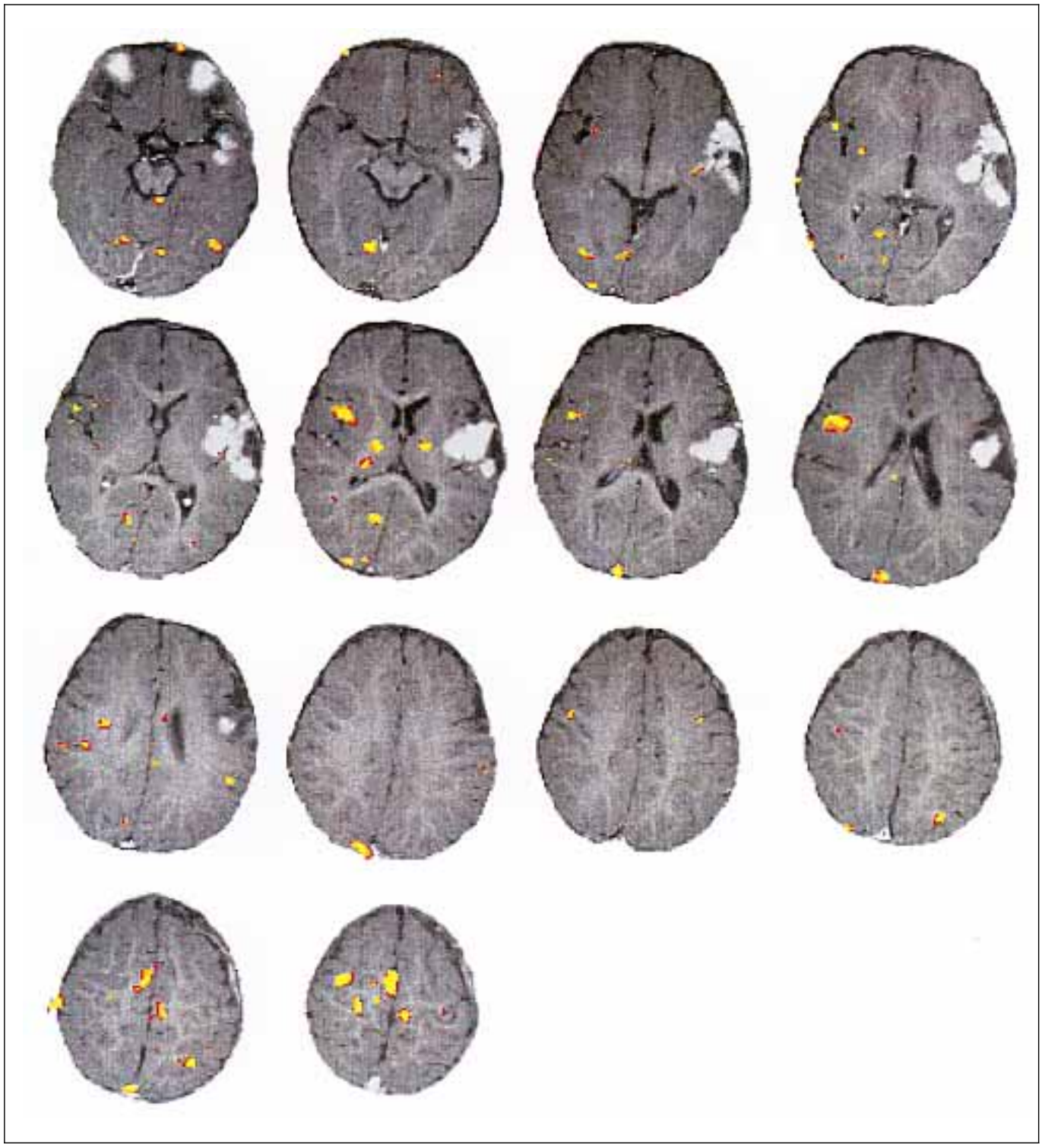

Fig. 5. Complete series of fMRI axial images in a 15-month-old girl (cc60) while listening to her mother's recorded voice shows a distribution of multiple foci of activity.

imaging in infants has been reported while using chloral hydrate sedation [25].

In an effort to overcome the aforementioned difficulties and to expand the range of modalities being tested, we have developed a novel method for utilizing fMRI in sedated infants and young children through passive stimulation paradigms. In the current study, children sedated with intravenous propofol were stimulated with a battery of passive stimuli, including photic (flashing LEDs), tactile (hand brushing) and auditory (parent's recorded voice) provocations. All paradigms were effective in mapping cortical activity.

Although our described technique has produced reproducible and encouraging results, several features of the method warrant further discussion. First, does the dose of propofol alter the fMRI signal? Previous work using positron emission tomography has shown that the cerebral metabolic rate is clearly influenced by propofol anesthesia in a dose-dependent fashion [26]. Since the BOLD signal is a function of regional cerebral blood flow as well as oxygen utilization, one cannot simply extrapolate that attenuated glucose utilization would result in a diminished fMRI signal. It remains unknown whether the propofol doses utilized in this study (50–225 μg/kg/min) had any impact on the fMRI signal since the individuals were not imaged without sedation. However, given that some fMRI results (fig. 2) are clearly in agreement with established functional topography as well as fMRI results in nonsedated individuals, this would suggest that the effects of propofol anesthesia in the range we utilized are not detrimental. The propofol dose in the current study was dictated only by the need to sedate the patient for a diagnostic study. More work is admittedly needed to determine the specific effects of propofol on the sensitivity of the fMRI signal. Nevertheless, it is concluded that the use of propofol anesthesia is not prohibitive in fMRI mapping, although we cannot offer specific guidelines with respect to the optimal dose.

The strict reliance on passive stimulation is an additional source of concern with respect to the effect on the fMRI signal and the inherent limitations of the testing paradigm. Our passive stimulation paradigm is limited to activation that does not require a patient resposne. We are confident that the passive stimulation is very reliable in producing fMRI signals, based on this current work and previous works by others. Similar passive visual stimulation has been employed to document the validity of the fMRI signal in a awake adult subjects [11]. As is shown in figure 2, the results of this study are consistent with these previous findings. Further, work that has focused on the somatosensory cortex has shown strong correlations between an active and passive mode of stimulation [27]. In this current study, we document the reliability of the passive signal in the sedated patient. However, since complex functional activity is not possible due to the noninteractive state of the patient, the technique is currently limited. We are optimistic that future innovations and refinements may overcome some of these limitations.

In summary, our results indicate that a child's age, a passive stimulation paradigm, or propofol anesthesia is not prohibitive of performing functional MRI. The development of this passive fMRI paradigm for infants and young children is believed to extend the advantages of noninvasive brain mapping to the very young pediatric neurosurgical patient.

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