ELSEVIER

Magnetic Resonance Imaging 19 (2001) 1–5

MAGNETIC RESONANCE IMAGING

Neonatal auditory activation detected by functional magnetic resonance imaging

Adam W. Anderson, Ph.D.[a], Rene Marois, Ph.D[b], Eve R. Colson, M.D.[c], Bradley S. Peterson, M.D.[d], Charles C. Duncan, M.D.[c,e], Richard A. Ehrenkranz, M.D.[c,f], Karen C. Schneider, M.P.H.[c], John C. Gore, Ph.D.[a], Laura R. Ment, M.D.[c,g]

[a]*Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, CT, USA*
[b]*Department of Psychology, Vanderbilt University, Nashville, TN, USA*
[c]*Department of Pediatrics, Yale University School of Medicine, New Haven, CT, USA*
[d]*Child Study Center, Yale University School of Medicine, New Haven, CT, USA*
[e]*Department of Neurosurgery, Yale University School of Medicine, New Haven, CT, USA*
[f]*Department of Obstetrics & Gynecology, Yale University School of Medicine, New Haven, CT, USA*
[g]*Department of Neurology, Yale University School of Medicine, New Haven, CT, USA*

Received 3 November 2000; accepted 2 December 2000

Supported by NS 27116, NS 33332, and NS 35476 of the National Institute of Neurologic Disorders and Stroke, MH 01232 of the National Institute of Mental Health, and RR 06022 of the National Center of Research Resources

Abstract

The objective of this study was to detect auditory cortical activation in non-sedated neonates employing functional magnetic resonance imaging (fMRI). Using echo-planar functional brain imaging, subjects were presented with a frequency-modulated pure tone; the BOLD signal response was mapped in 5 mm-thick slices running parallel to the superior temporal gyrus. Twenty healthy neonates (13 term, 7 preterm) at term and 4 adult control subjects. Blood oxygen level-dependent (BOLD) signal in response to auditory stimulus was detected in all 4 adults and in 14 of the 20 neonates. FMRI studies of adult subjects demonstrated increased signal in the superior temporal regions during auditory stimulation. In contrast, signal decreases were detected during auditory stimulation in 9 of 14 newborns with BOLD response. fMRI can be used to detect brain activation with auditory stimulation in human infants.

Keywords: Functional magnetic resonance imaging; Auditory cortex; Neonate; Term

1. Introduction

Recent advances in functional magnetic resonance imaging (fMRI) have permitted the noninvasive study of cerebral function during a variety of tasks in adults and older children [1–3]. In addition, several recent studies have demonstrated cortical visual activation in older infants and children using fMRI [4–8]. Because the central processing of auditory information is critical to the synthesis of language systems in the developing brain [9,10], we tested the hypothesis that fMRI could be employed to detect cortical activation in response to a frequency-modulated pure tone stimulus in non-sedated newborn infants.

2. Subjects and methods

The protocol was reviewed and approved by the Human Investigation Committee at the Yale University School of Medicine. Parents of all study infants provided written permission for the protocol. All infants were monitored by electrocardiography and pulse oximetry (Invivo Research, Inc., Orlando, FL), and a neonatal research nurse and pediatrician remained with the infant throughout the MRI study. No sedation was necessary for the MRI studies.

The fMRI study was performed on twenty neonates.

* Corresponding author. Tel.: +1-203-785-5708.
E-mail address: laura.ment@yale.edu (L.R. Ment).

0730-725X/01/$ – see front matter
PII: S0730-725X(00)00231-9

Prior to beginning the neonatal studies, four healthy adults were scanned to assess the experimental protocol.

2.1. Subjects

Healthy term infants (N = 13) and preterm infants (N = 7) were recruited from the Well Baby Nurseries and the Newborn Intensive Care Unit of Yale New Haven Hospital. Subjects had birth weights appropriate for gestational age and had no known chromosomal or congenital anomalies. The preterm subjects all had normal cranial ultrasound examinations and normal otoacoustic emission hearing assessments. Term infants all had normal clinical assessments of hearing.

The mean birth weight of the 13 term infants (7 male, 6 female) was 3.4 kg (range 2.6–3.8 kg), the mean gestational age was 38.7 ± 1.0 weeks (range 36–40 wks). For the eleven term children studied at term, the studies were performed at mean postnatal age 7 days (range 1–14 days), when the infants were mean PMA 39.6 wks (range 37–42 wks). Three preterm infants were female and four were male. Their gestational ages and postmenstrual ages at the time of imaging are shown in the Table below. Two term infants were imaged at 47.5–52 wks PMA. Conventional MRI structural imaging was performed on all study infants; no abnormalities were noted for any infant.

The four adult (male) subjects had mean age 34 (range 23–49).

2.2. Stimulus

The auditory stimulus consisted of a 60–80 dB tone centered at 1.3 kHz and frequency modulated over a range of ±1 kHz at a rate of 8 Hz. The stimulus duration was 35 s. The amplitude of the tone increased gradually from zero to its maximum value over the first 4 s, and decreased gradually to zero again during the last 4 s. The amplitude and sound frequencies were selected to correspond to infants' optimal frequency sensitivity range [11] and at the same time be largely distinct from the noise frequency generated by the scanner hardware. The amplitude ramps were introduced to reduce startle at stimulus onset and termination. Despite the presence of the ramps, some of the experiments were terminated by infants awakening at the onset of sound presentation, attesting to the saliency of the auditory stimuli to the infants.

2.3. Imaging protocol

Infants were swaddled, outfitted with earphones, and placed in the extremity (knee) coil of a 1.5 Telsa MR scanner ("Signa LX," GE Medical Systems, Milwaukee, WI). The infants' heads were lightly packed using foam padding and towels. Adults were imaged using a standard head coil. The auditory stimulus was generated by a personal computer and delivered to the subjects via pneumatic earphones. The infants were protected from the loud noise generated by the imaging hardware by incorporating the earphones into standard neonatal ear shields ("Minimuffs," Natus Medical Inc., San Carlos, CA). The amplitude of the auditory stimulus was controlled by a stereo amplifier (Resonance Technology, Northridge, CA), and was set to the same level for all study subjects.

Subjects were presented with the frequency-modulated stimulus for 35 s epochs interleaved with longer rest periods of 60 s (10 infants and 4 adults) or 40 s (3 infants and an adult repeat study) to ensure that the BOLD signal returned to baseline between experimental conditions. The BOLD signal response was mapped in echo planar images of five to seven 5 mm-thick slices running parallel to the superior temporal gyrus (FOV = 20 cm, 64 × 64 image matrix, 0 slice gap, TR = 5 s, TE = 60 ms). Each run alternated between baseline and stimulation epochs for 12 minutes. Runs were repeated two or three times, depending on subject tolerance. The relatively long TR and small number of slices were chosen in part to keep the repetition rate of the scanner noise low, and hence avoid disturbing the infants and masking the stimulus.

2.4. Data analysis

SPM99b was used to estimate subject motion and to correct the image data for the effects of motion in the *x*, *y*, and *z*-directions [12]. Images that represented more than 2 mm translation or more than 3 degrees rotation (in any plane) were discarded. Studies with fewer than 50 acceptable images in both baseline and stimulus conditions were discarded. In addition, studies that demonstrated variability in head displacement (standard deviation >1 mm) or rotation angles (standard deviation >1 degree) were dropped from further analysis.

The image data were first smoothed using a Gaussian kernel (6 mm full width at half-maximum). Signal intensity during stimulation was then compared to the baseline control condition. Statistical parametric maps (SPM's) of the *t*-statistic and fractional signal change were computed to identify regionally specific responses to the auditory stimulus. Region of interest (ROI) measurements were made by centering a 4 × 4 pixel region on the activation maximum (indicated by a *t* statistic map) in the SPM. Within this area, pixels that correspond to t values greater than 1 were averaged to find a mean fractional signal change.

3. Results

BOLD signals in response to auditory stimulus were detected in all 4 adults and all 14 infants passing the inclusion criteria for motion. Although some infants awoke during the scan sessions, no adverse events were experienced by the subjects and no significant changes from baseline in

Table 1
Neonatal and fMRI data for the infants with BOLD response to auditory stimulation

Subject Number	Gestational Age (wks)	Age at Study (days)	PMA at Study (wks)	% BOLD Signal Change
1	38	13	40	−0.51
2	39	3	39.5	−0.34
3	40	1	40	−0.09
4	25	77	36	+0.32
5	40	9	41	−0.50
6	36	10	37.5	−0.68
7	39	11	41.5	−0.25
8	40	6	41	+0.23
9	32	11	33.5	−0.33
10	40	2	40	−0.21
11	40	53	47.5	+0.11
12	28	35	33	+0.70
13	28	42	34	+0.21
14	32	23	35	−0.09

either the oxygen saturation or heart rate recordings were noted during scanning sessions.

3.1. Adult control subjects

A total of 9 runs were acquired during the studies on the 4 adult control subjects. BOLD signal in response to auditory stimulation was detected in all 4 subjects. Positive signal change was noted in both the medial and lateral temporal regions bilaterally (mean change ± standard deviation, 0.53 ± 0.35%).

3.2. Motion assessment for the neonates

A total of 48 runs were acquired in the 20 neonatal examinations. Studies for 6 of the 20 (30%) infants (4/13 term infants and 2/7 preterm subjects) were considered unreliable because of either translational or rotational motion or inadequate number of images. Neonatal and fMRI data for the 14 infants with acceptable data sets are shown in the Table.

3.3. Activation in the neonates

BOLD signal decreases during auditory stimulation were detected in 9 of 14 (64%) newborns with acceptable data. Positive increases in BOLD signal were noted in the other five infants. The mean percent change was −0.35 ± 0.21% for those infants with negative BOLD signal and 0.32% ± 0.23% for the 5 infants with positive BOLD signal. Similar to the adults, BOLD response was detected in the superior temporal regions bilaterally, as shown in the Fig.

4. Discussion

We employed fMRI to study the response of non-sedated term infants to a frequency-modulated tone and detected fMRI signal in the auditory cortex bilaterally in the 14 infants with acceptable head motion. In most (9) of these infants, the fMRI signal decreased during stimulation (negative activation). By contrast, all adult controls demonstrated increased signal during stimulation (positive activation). Decreased signal has also been observed in the occipital cortex of human infants following visual stimulation [4–6]. In particular, Born noted negative BOLD response in 2 of 3 infants of 41 wks PMA [4]. Taken together with these visual studies, the present auditory experiment suggests that (1) decreased signal is a common response to sensory stimulation in the human infant cortex, and (2) the coupling between neural activity and the vascular response is significantly different in human infant and adult brain. Although Yamada reported positive BOLD signal change in response to visual stimulation in 6 of 6 infants less than 5 weeks of age who were sedated with pentobarbital [13], the role of sedating agents in the stimulus response of infants is not yet certain [4,14]. None of the infants in our study received sedating medication. Further, the number of infant studies which we were forced to discard due to motion, 30%, is consistent with studies employing sedation, including chloral hydrate, pentobarbital and general anesthesia [4–8].

The polarity of the BOLD signal depends on the amounts of oxygenated and deoxygenated hemoglobin present in tissue volumes. In adults and older children, the increase in fMRI signal during cortical activation is thought to arise from the disproportionate increases in cerebral blood flow and oxygenation relative to oxygen consumption [15]. In infants, it has been suggested that the negative signal change may be due to the inability of the cerebral vasculature to meet increased oxygen demand by increasing local blood flow, leading to a decrease in the ratio of oxy- to deoxyhemoglobin [16].

While we found little relationship between the infants' PMA and the sign of auditory activation within the age range studied, the response of the visual cortex appears to reverse during infancy. Infants older than about 50 weeks PMA predominantly show negative activation in the visual

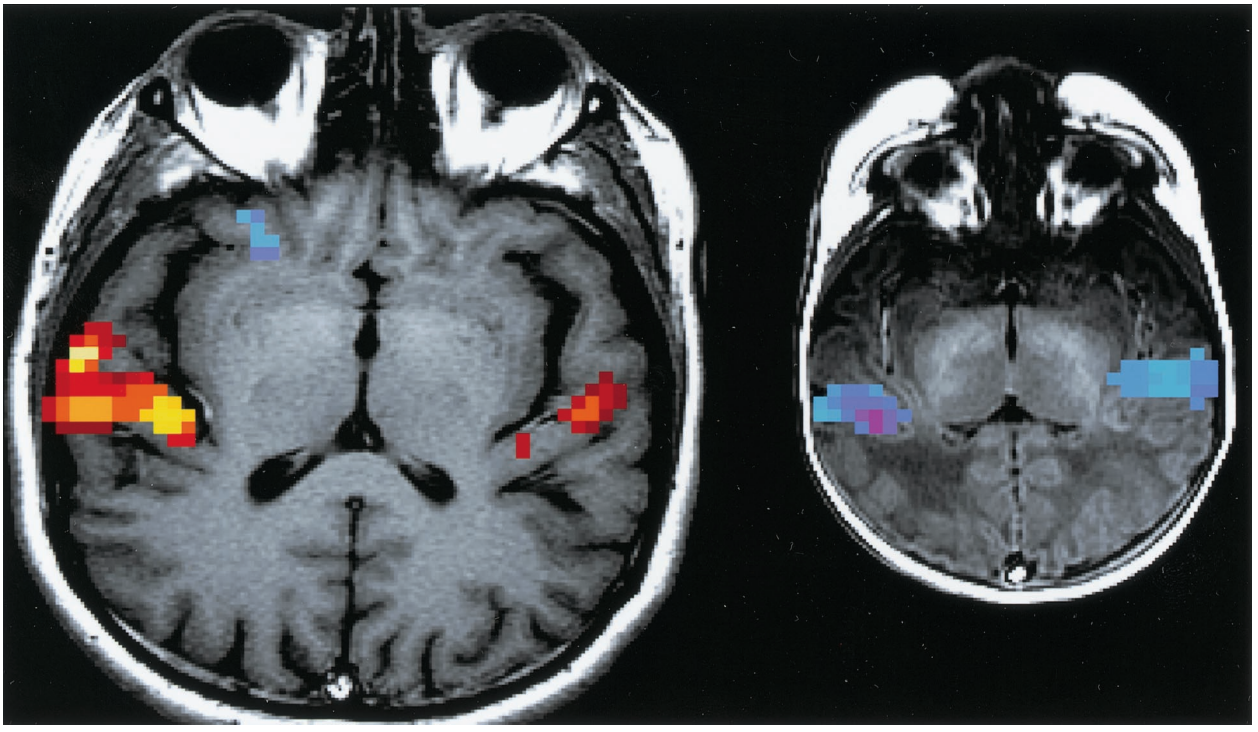

Fig. 1. BOLD signal response to auditory stimulation in single adult (*left*) and newborn (*right*) subjects. The parametric statistical maps are overlaid on T_1-weighted anatomical images and show regions of signal increase relative to baseline as red and regions of signal decrease relative to baseline as blue. All four adult subjects showed signal increases with auditory stimulation. In contrast, six of eight newborns showed signal decreases and two showed signal increases in response to the same stimulus.

cortex, while infants between 40 and 50 weeks demonstrate mostly positive activation [4,8]. Furthermore, infants 40 weeks or younger showed no measurable response [4]. By contrast, the present study demonstrated reliable negative auditory activation in infants ranging from 36 to 41 weeks PMA. These results suggest that the neural and/or vascular components of the auditory cortex respond to sensory stimulation at an earlier age than does the visual system. Indeed, the cortical auditory system of the human neonate is highly functional at birth [11,17] while the cortical visual system undergoes a more protracted development [18,19]. Several studies have also suggested that the human fetus can hear at 27 weeks' gestation [20,21], and a recent fMRI study has even shown auditory activation in fetal human brain [22]. The possibility that the auditory cortex functionally matures at a faster rate than the visual cortex also receives support from metabolic studies of the developing brain in both human and non-human primate infants [23,24]. However, given that the various (auditory and visual) infant fMRI studies used subjects of different age groups, health status and arousal states (e.g. awake, sleeping, and sedated), any comparisons must be treated with caution. Clearly, strong evidence in favor of differential auditory and visual cortical maturation will await simultaneous auditory and visual stimulation performed on non-sedated infants.

The developmental period covered by the present fMRI study corresponds to a critical stage of the development of the human auditory cortex. The primary auditory cortex undergoes intensive synaptogenesis between 27 weeks PMA and three months post-term [25]. This critical period has been shown to parallel that of dendritic development and myelination in the central auditory cortex [25,26], and positron emission tomography studies have demonstrated increased glucose use in the temporal regions of infants of similar postmenstrual ages [24,27]. Furthermore, the central processing of auditory information is critical to the synthesis of language systems in the developing brain [9,10]. The present study demonstrates the feasibility of using fMRI for studying the functional development of the auditory cortex at a time that is critical for the refinement of hearing and the acquisition of language by the human infant.

Acknowledgements

The authors thank Drs. Giovanna Spinella, Jeffrey Gruen and Robert Fulbright for scientific advice and Marjorene Ainley, B.A., Patricia Gettner, RN, Monica Konstantino, R.N., Hedy Sarofin, R.T.R/M.F., Terry Hickey, R.T.R./M.F., and Joanne Poulsen, R.N. for secretarial, nursing and technical assistance.

References

[1] Casey BJ, Cohen JD, Jezzard P, et al. Activation of prefrontal cortex in children during a non-spatial working memory task with functional MRI. Neuroimage 1995;2:221–9.

[2] Nelson CA, Monk CS, Lin J, Carver LJ, Thomas KM, Truwit CL. Functional neuroanatomy of spatial working memory in children. Develop Psychol 2000;36:109–16.
[3] Peterson BS, Skudlarksi P, Gatenby JC, Zhang H, Anderson A, Gore JC. An fMRI study of Stroop word-color interference: Evidence for cingulate subregions subserving multiple distributed attentional systems. Biol Psych 1999;45:1237–58.
[4] Born P, Leth H, Miranda MJ, et al. Visual activation in infants and young children studied by functional magnetic resonance imaging. Pediatr Res 1998;44:578–83.
[5] Born AP, Miranda MJ, Rostrup E, et al. Functional magnetic resonance imaging of the normal and abnormal visual system in early life. Neuropediatrics 2000;31:24–32.
[6] Martin E, Joeri P, Loenneker T, et al. Visual processing in infants and children studied using functional MRI. Pediatr Res 1999;46:135–40.
[7] Soudweidane MM, Kim KHS, McDowall R, et al. Brain mapping in sedated infants and young children with passive-functional magnetic resonance imaging. Pediatr Neurosurg 1999;30:86–92.
[8] Yamada H, Sadato N, Konishi Y, et al. A rapid brain metabolic change in infants detected by fMRI. NeuroReport 1997;8:3775–8.
[9] Paradise J, Dollaghan C, Campbell T, et al. Language, speech sound production, and cognition in three-year-old children in relation to otitis media in their first three years of life. Pediatrics 2000;105:1119–30.
[10] Sininger Y, Doyle K, Moore J. The case for early identification of hearing loss in children. Auditory system development, experimental auditory deprivation, and development of speech perception and hearing. Pediatr Clin North Am 1999;46:1–14.
[11] Ruben RJ. The ontogeny of human hearing. Acta Otolaryngol (Stockh) 1992;112:192–6.
[12] Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. Magn Reson Med 1996;35: 346–55.
[13] Yamada H, Sadato MD, Konishi Y, et al. A milestone for normal development of the infantile brain detected by functional MRI. Neurology 2000;55:218–23.
[14] Lindauer U, Villringer A, Dirnagl U. Characterization of CBF response to somatosensory stimulation: model and influence of anesthetics. Am J Physiol 1993;264:1223–8.
[15] Belliveau JW, Kennedy Jr DN, McKinstry RC, et al. Functional mapping of the human visual cortex by magnetic resonance imaging. Science 1991;254:716–9.
[16] Meek JH, Firbank M, Elwell CE, Atkinson J, Braddick O, Wyatt JS. Regional hemodynamic responses to visual stimulation in awake infants. Pediatr Res 1998;43:840–3.
[17] Aslin RN, Pisoni DB, Juczyk PW. Auditory development and speech perception in infancy. In: Mustard TH, ed. Handbook of child psychology. Vol. 2. New York: John Wiley & Son, 1983:573–687.
[18] Granrud E. Visual perception and cognition in infancy. Hillsdale, NJ: Lawrence Erlbaum Associates, 1993.
[19] Johnson MH. Cortical maturation and the development of visual attention in early infancy. J Cogn Neurosci 1990;2:81–95.
[20] Johansson B, Wedenberg E, Westin B. Measurement of tone response by human fetus. Acta Otolaryngol (Stockh) 1964;57:188.
[21] Starr A, Amlie RN, Marondel WH. Development of auditory function in newborn infants revealed by auditory brain stem potentials. Pediatrics 1977;60:831.
[22] Hykin J, Moore R, Duncan K, et al. Fetal brain activity demonstrated by functional magnetic resonance imaging. Lancet 1999;354:645–6.
[23] Kennedy C, Sakurada O, Shinohara M, Miyaoka M. Local cerebral glucose utilization in the newborn macaque monkey. Ann Neurol 1982;12:333–40.
[24] Chugani HT, Phelps ME. Imaging human brain development with positron emission tomography. J Nucl Med 1990;32:23–5.
[25] Huttenlocher P, Dabholkar A. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 1997;387:167–78.
[26] Barkovich A. Normal development of the neonatal and infant brain. In: Barkovich A, ed. Pediatric Neuroimaging. New York: Raven Press, 1990:5–34.
[27] Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. Ann Neurol 1987; 22:487–97.