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# Functional Magnetic Resonance Imaging Reveals Atypical Language Organization in Children Following Perinatal Left Middle Cerebral Artery Stroke

**L.M. Jacola**[1], **M.B Schapiro**[1], **V.J. Schmithorst**[2,3], **A.W.. Byars**[1], **R.H. Strawsburg**[1], **J.P. Szaflarski**[4], **E. Plante**[5], and **S.K. Holland**[2,3]

1 *Division of Neurology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, Ohio 45229-3039.*

2 *Department of Radiology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, Ohio 45229-3039.*

3 *Imaging Research Center, Cincinnati Children's Hospital Research Foundation, 3333 Burnet Avenue, Cincinnati, Ohio 45229-3039.*

4*Department of Neurology and Center for Imaging Research, University of Cincinnati Medical Center, Cincinnati, OH 45267-0525.*

5*Department of Speech and Hearing Sciences, University of Arizona, 1131 E. 2nd Street, Tuscon, Arizona 85721-0071*

## Abstract

We used verb generation and story listening tasks during fMRI to study language organization in children (7, 9- and 12-year old) with perinatal left MCA infarctions. Healthy, age-matched comparison children (n=39) showed activation in left Broca's area during the verb generation task; in contrast, stroke subjects showed activation either bilaterally or in the right hemisphere homologue during both tasks. In Wernicke's area, comparison subjects showed left lateralization (verb generation) and bilateral activation (L>R) (story listening). Stroke subjects instead showed bilateral or right lateralization (verb generation) and bilateral activation (R>L) (story listening). Language is distributed atypically in children with perinatal left hemisphere stroke.

### Keywords

fmri; language; stroke; reorganization; plasticity

## Introduction

Neural activation associated with both receptive and productive language processing in children is preferentially distributed, as in adults, primarily to the left inferior frontal gyrus (Broca's area), and posterior superior and middle temporal gyri and parts of inferior parietal cortex (Wernicke's area).[2,5] This pattern of left lateralization is well established by at least age 5 years. [1] In adult patients with aphasia-producing lesions, functional recovery is marked

Corresponding Author: Lisa M. Jacola., Division of Neurology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, Ohio 45229-3039. phone: (513) 636-9669 fax: 513-636-1888 email: lisa.jacola@cchmc.org.

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by increases in activation in either right hemisphere homologues of classical left hemisphere language cortex or in areas outside of the infarcted area ipsilateral to the stroke hemisphere.[11] The limited available studies in children suggest that early insult to the left hemisphere may induce a right hemisphere organizational pattern in children similar to adults,[3,4,6,7,9] but incongruities exist among studies (perhaps due to the specific processing demands of the language function(s) being assessed).

This study used fMRI to investigate patterns of language organization in children with perinatal infarction in left MCA distribution, the damage from which generally manifests in the gray matter.[10] We hypothesize that stroke patients will show preferential right hemisphere activation with fMRI in response to both receptive and productive language tasks.

## Materials and Methods

### Subjects

**Case 1—**The 7-year-old male (left-handed; mother left-handed), delivered vaginally at full term, developed right sided seizures on day one of life. On day 10, an MRI scan confirmed a left MCA infarction. He was treated with phenytoin, then carbamazepine until age 4 months without further seizures. Follow-up MRI at 10 months showed extensive encephalomalacia in the left MCA distribution (posterior inferior frontal lobe, superior temporal, and anterior parietal lobes). At age 7 years, there was mild clumsiness of the right hand and mild weakness in pragmatic language.

**Case 2—**The 9-year-old female (left-handed), delivered vaginally at full term, developed right sided seizures at 10 hours. Phenobarbital treatment continued without seizure recurrence until age 4 months. For developmental work-up at 5 years, an MRI scan showed a remote infarction in the left MCA distribution (perisylvian and posterior parietal regions). At 9 years, she showed poor fine motor control of her right hand; basic language was normal but there were variable deficits in naming and phonological processing.

**Case 3—**With a previously unremarkable history, the 12-year-old female (right-handed) presented at age 5 years with brief staring episodes. An MRI scan showed mild left lateral ventricular enlargement, a small left caudate, and a subtle decrease in left frontal white matter volume indicative of prenatal or early postnatal insult. Her complex partial seizures were treated with valproic acid, carbamazepine, and lamotrigine; she had good seizure control for 3 years prior to fMRI. Neurological examination at 8 ½ years showed posturing of upper extremities on stressed gait (right greater than left). She had low normal scores in receptive and expressive language; fluency and articulation were normal.

**Comparison Subjects—**Comparison groups consisted of all 7, 9, and 12 year old right-handed (self report) children scanned as part of an ongoing fMRI study of normal language development.[5]

The research protocol was approved by the CCHMC Institutional Review Board. Informed consent was obtained from the parents of all subjects.

### MRI Procedures

The details of the verb generation task, MR data acquisition, and data analysis were previously reported.[5] Imaging was carried out on a 3T Bruker Biospec MRI scanner. Twenty-four contiguous axial slices, 5 mm thick, were collected at each time point using a single-shot T2*-weighted, gradient echo-planar imaging (EPI) pulse sequence (TR = 3000 ms, TE = 38 ms,

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acquisition matrix = 64 × 64 pixels, FOV = 25.6 × 25.6 cm). One hundred and ten repetitions were employed for an imaging time of 5 mins, 30-s per task.

In the verb generation task, 30-s blocks of covert verb generation were interleaved with 30-s blocks of a bilateral finger tapping task prompted by a target tone. The finger-tapping control task was designed to control for the auditory prompt signaling a subject to the auditory presentation of a noun, as a method of distraction from continuing to generate verbs, as a measure of compliance, and to provide activation of the motor strip. [5]

In the story processing task, 30-s blocks consisting of a 5-sentence story presentation were interleaved with 30-s blocks of a randomly ordered series of pure tones. The stories contained both conjoined sentences and center-embedded sentences. The subject was instructed to listen to the stories so that he or she could answer questions about them after the scans. All stroke patients performed well on this quiz (7 year old 90%, 9 year old 80%, 12 year old 100%).

All data reconstruction and post-processing was performed using Cincinnati Children's Hospital Image Processing Software (CCHIPS)[8]. The 3D anatomical images as well as the reconstructed, co-registered EPI datasets were transformed into Talairach space. Individual subject data for each task were analyzed using the general linear model to identify voxel with a time course similar to the time course of stimulus presentation; results of this analysis were transformed into z-score maps. Composite z-score maps were generated separately for the 7-, 9-, and 12-year-old comparison subjects for each task, and a random-effects analysis was performed to determine regions of significant group activation. A post-processing Gaussian filter was used (width 4 mm for stroke subjects, 2 mm for group composites).

All images displayed in Figures 2 and 3 are thresholded at $z = 2.5$. This nominal score value combined with a cluster size of 20, resulted in a corrected p-value of <.001, as determined via Monte Carlo simulation. Regions of interest (ROIs) were defined functionally, based on a global composite map from 239 normal subjects performing the verb generation task. An ROI was created for both frontal and posterior regions corresponding to classically recognized language areas (i.e. Broca's and Wernicke's). ROIs were generated from the left hemisphere, and right hemisphere homologues were defined by mirroring the regions. These ROIs were used in the calculation of lateralization indices for both the stroke patients and normal data.

Only voxels with z scores greater or equal to 1.96 were used in the calculation of lateralization indices (LI's). Pixels were counted and a LI was defined as the difference in the number of activated voxels, summed independently for the left and right regions of interest, divided by the summed total of active voxels in the left and right regions of interest.

## Results

### Verb Generation

As ROIs do not distinguish specific gyri, maps were interpreted both visually and with ROI analysis. As seen in Figure 2, in comparison subjects significant activation occurred in the left inferior gyri, extending dorsolaterally into middle frontal gyri, and the left superior and middle temporal gyri, including Broca's and Wernicke's areas. Smaller areas of activation also were present in the right inferior frontal gyrus in the 9 and 12 year old comparison subjects and in the left superior frontal gyrus in the 7 year old comparison subjects. Left anterior cingulate activation also occurred.

In contrast, stroke patients showed inferior frontal gyrus activation either bilaterally (7 year-old) or predominately in the right hemisphere homologue (9 and 12 year-olds). Activation of middle frontal gyrus was restricted to the right hemisphere in the 7 and 9 year-olds and bilateral (right greater than left) in the 12 year-old. Activation of the superior and middle temporal gyri was bilateral (7 and 12 year-olds) or predominately right sided (9 year-old). Anterior cingulate activation was more variable than in comparison subjects. Superior frontal gyrus activation was observed in the 9 and 12 year olds.

An inferior frontal LI showed left lateralization in the comparison group (0.23 ± 0.17, 0.28 ± 0.16, and 0.24 ± 0.09 in the 7, 9, and 12 year-olds respectively) compared to more rightward shift of activation in stroke patients (−0.17, −0.16, −0.36).

### Story Listening

As shown in Figure 3, in comparison subjects significant activation occurred in superior and middle temporal gyri bilaterally (leftward bias). Activation in left inferior frontal gyrus occurred in 7 and 9 year old comparison subjects. Midline superior frontal gyrus activation was noted in 7 and 9 year old comparison subjects.

Stroke patients showed a different pattern. Similar to controls, there was bilateral activation of superior and middle temporal gyri. In the 9 and 12 year olds there was right-sided inferior and middle frontal gyrus activation, while the 7 year old showed left-sided activation in this region. Midline activation of superior frontal gyrus was seen in all stroke patients.

A superior and middle temporal region LI showed left or bilateral lateralization in the comparison group (0.16 ± 0.24, 0.18 ± 0.21, and 0.07 ± 0.15 in the 7, 9, and 12 year-olds respectively) but more right sided activation in the stroke patients (−0.20, −0.23, −0.09).

## Discussion

Consistent with our initial hypothesis, these results provide preliminary evidence supporting atypical language organization in children with perinatal left MCA stroke. This reorganization, demonstrated in both productive and receptive language tasks in our perinatal left MCA stroke patients stands in contrast to the results obtained from patients with left periventricular white matter lesions of prenatal onset. [4,9] Taken together, these results suggest that lesion location (cortical/subcortical v. periventricular) could potentially exert a substantial influence on task-related hemispheric differences in organizational potential. When language tasks produced activation in the right hemisphere in our stroke patients, these areas were homologues of the traditional left hemisphere language areas. As the amount of right hemisphere activation varied among patients, these findings suggest that language processing is redistributed to different degrees among homologous brain regions in children who have suffered stroke involving left hemisphere language areas. Thus, in children, either hemisphere can be activated by language tasks and provide support for language development, though both hemispheres may be needed for normal language development. Similarly, in adults both hemispheres appear to be involved in recovery of language in patients with left hemisphere stroke.

Despite the derangement of blood flow that occurs in stroke and other neurological diseases, fMRI has been useful in studies of these conditions. e.g.[3,4, 9, 12] While it is true that baseline blood flow is likely to be lower in the injured hemisphere, blood flow in the contralateral hemisphere should not be compromised. Our findings describe contralateral reorganization of fMRI activation to analogous regions in the right hemisphere.

Our results must be taken as only preliminary. Limitations include small subject number, lack of in-scanner compliance measures, and lack of control for infarction size, seizures, and anticonvulsant treatment. Our findings must be interpreted along with diffusion tensor imaging studies have shown that besides cortical damage, middle cerebral artery stroke usually also involves white matter tracts leading to disruption in intra- and interhemispheric connectivity and, therefore, it may also affect cortical reorganization or compensation. [13] Despite these limitations, these results begin to delineate the networks involved in language development after stroke, whether language is assumed by right hemisphere homologues or unaffected regions in the left hemisphere. Such work may contribute to a better understanding of neuroplasticity in cortical reorganization following stroke.

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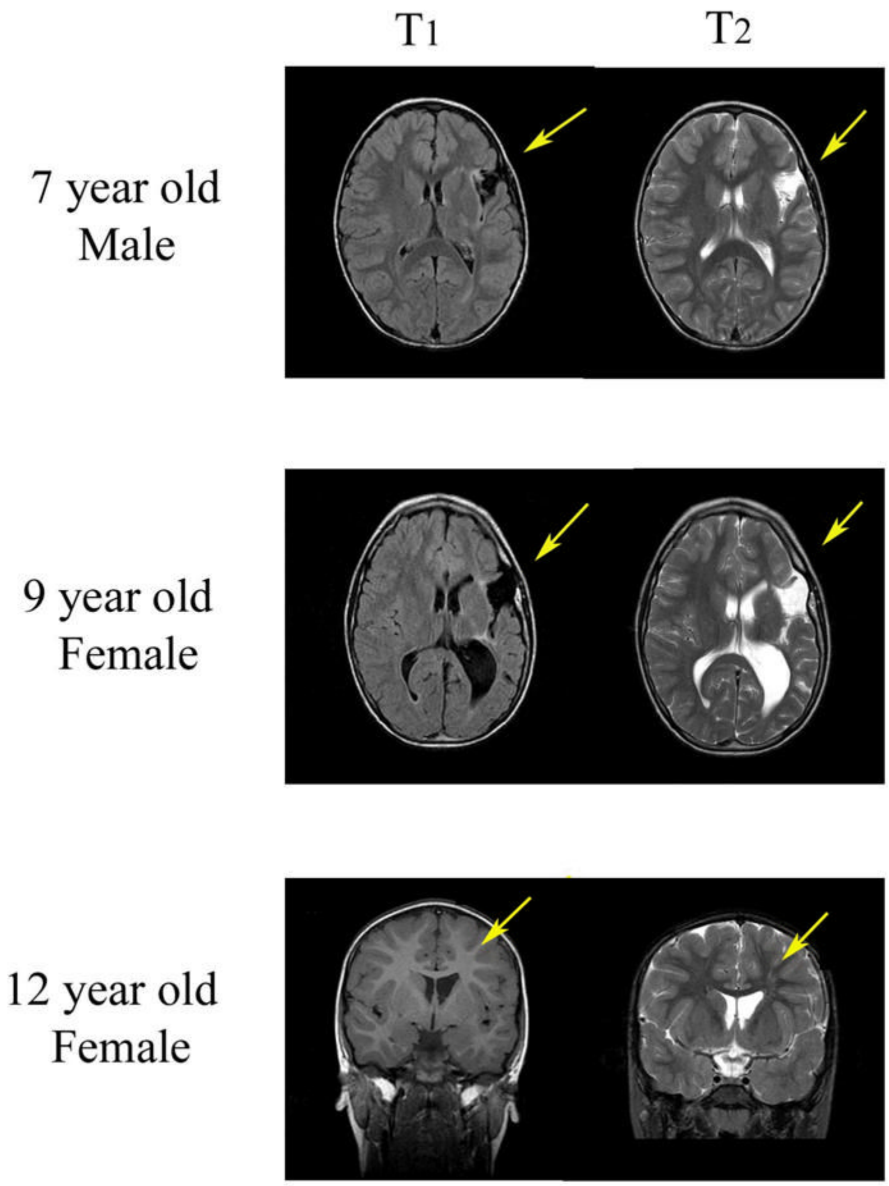


**Figure 1.**

Structural MRI images depicting lesion area for each patient. Lesions are shown on $T_1$ and $T_2$ weighted images, respectively. Seven and nine year old patients show clear left MCA infarction, while the 12 year old show mild left lateral ventricular enlargement, a small left caudate, and a subtle decrease in left frontal white matter volume indicative of prenatal or early postnatal insult.

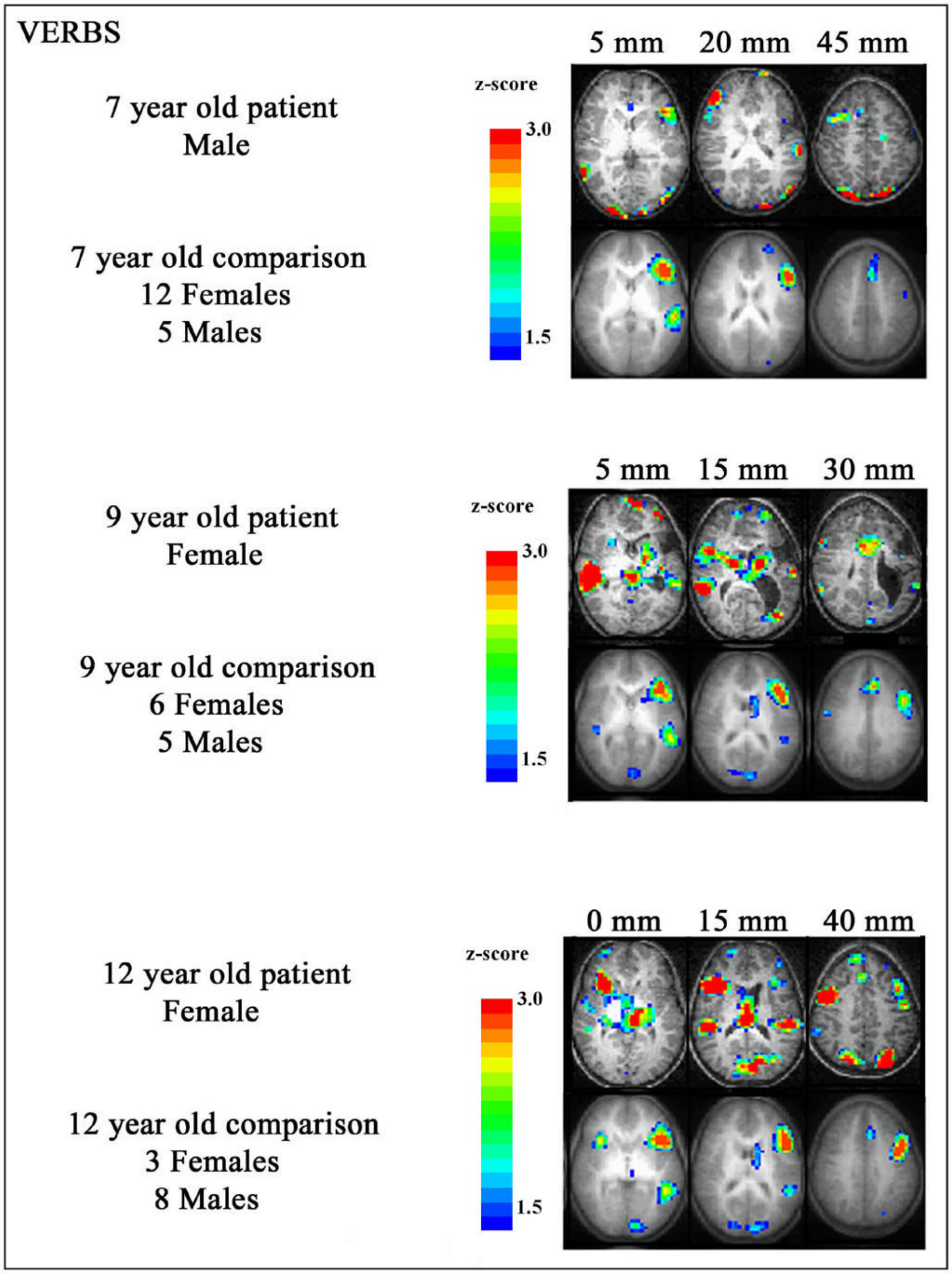


**Figure 2.**
Z-score activation maps computed for individual stroke patients and age-matched comparison groups during the verb generation task. Maps are thresholded at z = 2.5 – 5.0. Numbers above representative slices refer to the location of the slice in millimeters (mm) above the AC-PC line.

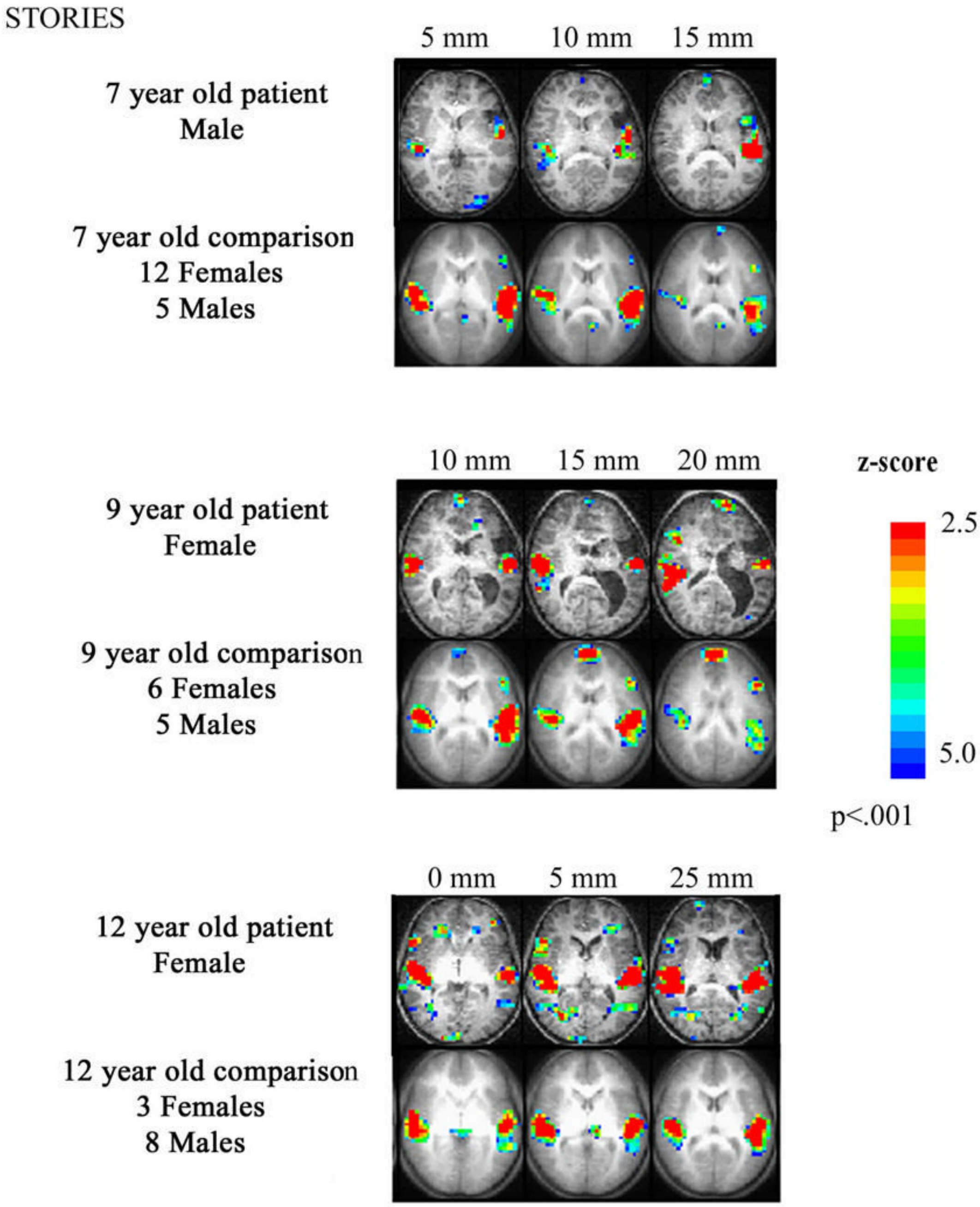


**Figure 3.**
Z-score activation maps computed for individual stroke patients and age-matched comparison groups during the story listening task. Maps are thresholded at z = 2.5 – 5.0. Numbers above representative slices refer to the location of the slice in millimeters (mm) above the AC-PC line.