Using Functional Magnetic Resonance Imaging to Detect Preserved Function in a Preterm Infant with Brain Injury

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We studied developmental plasticity using functional magnetic resonance imaging (fMRI) in a preterm infant with brain injury on structural MRI. fMRI showed preserved brain function and subsequent neurodevelopment was within the normal range. Multimodal neuroimaging including fMRI can improve understanding of neural plasticity after preterm birth and brain injury. *(J Pediatr 2017;189:213-7).*

Preterm birth has been associated with an increased risk for an adverse neurodevelopmental outcome.[1,2] Brain injury is common among prematurely born infants and often affects cerebral white and gray matter,[3-6] which in turn affects function[7,8] and leads to neurodevelopmental impairments. The consequences of altered brain development and its relation to prematurity, however, are highly variable, and currently available measures are poor (or at best moderate) prognostic indicators of neurodevelopmental impairments. Recent studies highlight the potential diagnostic value of magnetic resonance imaging (MRI) in preterm born infants.[9-11] We studied an extremely preterm infant, whose early birth, brain injury, and difficult course in the neonatal intensive care unit indicated a high risk of poor neurodevelopmental outcome. Multimodal neuroimaging was used to evaluate structure and function in the motor and auditory/language systems, domains commonly affected in preterm born infants.[12] Subsequent neurodevelopment was evaluated using standard clinical behavioral measures from term-equivalent age to 25 months corrected age (CA).

Methods

A male infant was born at 24 weeks of gestation through spontaneous vaginal delivery. His birth weight was 830 g, and his Apgar scores were 6, 5, 6, 7, and 7 at 1, 5, 10, 15, and 20 minutes, respectively. He required invasive and noninvasive respiratory support for 66 days. In the neonatal intensive care unit, he was treated for respiratory distress syndrome, apnea of prematurity, pulmonary interstitial emphysema, bronchopulmonary dysplasia, intraventricular hemorrhage (grade III right, grade IV left) with posthemorrhagic ventricular dilation, coagulase negative staphylococcal sepsis, group B streptococcal pneumonia, patent ductus arteriosus, necrotizing enterocolitis, retinopathy of prematurity, anemia, hypertension, and gastroesophageal reflux. At term-equivalent age, atypical auditory function was indicated by an auditory brainstem response screen for hearing in the right ear. The patient was part of a larger study investigating the effects of prematurity on early brain function and development. Ethical approval was obtained from the Western University Health Sciences Research Ethics Board, and informed consent given by a parent.

An MRI was acquired at 38 weeks postmenstrual age (PMA) and 3 and 9 months CA during natural sleep without the use of sedation. Parental questionnaires at 3, 6, and 9 months CA included the Vineland Adaptive Behavior Scales, second edition[13] and the Receptive-Expressive Emergent Language Scales, third edition.[14] In addition, the patient was evaluated at 41 weeks PMA, as well as at 4, 8, 13, and 25 months CA in the Developmental Follow-Up Clinic at Children's Hospital, London, Ontario, Canada, with assessments of motor development (Test of Infant Motor Performance Alberta Infant Motor Scale),[15,16] neurologic integrity (Infant Neurologic International Battery),[17] and overall development (Bayley Scales of Infant and Toddler Development, third edition).[18]

Structural brain images were acquired using a T2-weighted imaging sequence (at 38 weeks PMA: 1.5T 450W GE MRI system [General Electric Healthcare, Milwaukee, Wisconsin], TR/TE = 5495/8.12 ms, flip angle = 160°, 106 slices, 0.7 × 0.7 × 4 mm resolution; at 3 months: 3T Siemens Prisma MRI system [Erlangen, Germany], TR/TE = 10 810/156 ms, flip angle = 144°, 96 slices, 1 mm^3 resolution; at 9 months: 3T Siemens Prisma MRI system, TR/TE = 3200/412 ms, flip angle = 120°, 128 slices, 1 mm^3 resolution). T2-weighted structural MRI images at all time points were reviewed by a neuroradiologist and scored based on the classification system by Inder et al[19] and Woodward et al.[20,21] To characterize key white-matter tracts, 2 diffusion-weighted MRI sequences with opposite phase-encoding polarities (right-left and left-right) were acquired at

CA	Corrected age
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging
GLM	General linear model
MRI	Magnetic resonance imaging
PMA	Postmenstrual age
TE	Time echo
TR	Time repetition

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Supported by a Collaborative Health Research Projects Grant (201110CPG), the Natural Sciences and Engineering Research Council of Canada, and the Canadian Institutes of Health Research (418293DG-2012). The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2017.06.063

3 and 9 months CA (multiband echo planar imaging with acceleration factor 4, 138 images comprising 10 images with b = 0 s/mm^2 and 128 noncollinear diffusion weighting directions with b = 1500 s/mm^2, 2 mm^3 isotropic voxel resolution, matrix 96 × 96, TR/TE = 1980/71 ms).

Four sessions at 38 weeks PMA and 2 sessions at 3 and 9 months CA, respectively, of functional MRI (fMRI) were acquired, each lasting 7 minutes with 15 seconds of auditory stimulation alternating with 11 seconds of silence (at 38 weeks PMA: TR/TE = 1920/60 ms, flip angle = 70°, 22 slices, 3 mm^3 resolution; at and 9 months: TR/TE = 780/40 ms and 686/30 ms, respectively, multiband factor 4, flip angle = 54°, 36 slices, 3 mm^3 resolution). Auditory stimuli consisted of sung lullabies as previous studies reported robust brain responses to naturalistic, language-related sounds even in sleeping infants.[22,23] Sounds were presented through customized ear defenders, using earplugs and minimuffs (Scanmedics, Chatswood, NSW, Australia; http://scanmedics.com/mini-muffs/) for additional ear protection.

Structural and fMRI data preprocessing were performed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom) with the automatic analysis pipeline.[24] The fMRI data were analyzed using a general linear model (GLM) containing the block stimulation paradigm, convolved with neonate-specific (at 38 weeks PMA) or adult (at 3 and 9 months CA) hemodynamic response functions, a lag-3 second order Volterra expansion of the 6 realignment variables, and "spike" regressors to model sudden intensity (>3 SDs) and motion (>2 mm) outliers. The GLM included a high-pass filter (length 120s) for sound-evoked activation analysis and a bandpass filter from 0.01 to 0.1 Hz for the functional connectivity analysis. "Sound > silence" contrasts identified voxels with increased activity to auditory stimulation. To assess functional connectivity, the activation time course of a seed region (left motor and left auditory cortex, respectively) was included as an additional regressor in the GLM to identify voxels with similar activation patterns. Although networks were derived from fMRI with a stimulus rather than in resting state it has been shown to give similar overall networks[25] and to preserve individual differences in connectivity.[26] Diffusion image processing was performed using FSL software (Analysis Group, FMRIB, Oxford, United Kingdom)[27] by means of the *TOPUP* toolbox to combine the 2-phase encoding data into 1 corrected image. *EDDY* was applied to correct for eddy current-induced distortions and subject movement. Nonbrain tissue was removed with the brain extraction tool,[28] and fractional anisotropy (FA), mean diffusivity, axial diffusivity, and radial diffusivity maps generated by using *DTIFIT* (Functional Magnetic Resonance Imaging of the Brain diffusion toolbox). Seed and waypoint mask of interest were generated on color coded FA maps, and white matter pathways of interest were obtained with a probabilistic tracking algorithm.

Results

T2-weighted structural MRI images showed pronounced ventriculomegaly, increased extracerebral space, and moderate white matter abnormality with a score of 12 (moderate score range 10-12). White matter abnormalities noted were thinning of the corpus callosum, ventricular dilatation, and reduced white matter volumes, although there was no loss in the volume of periventricular white matter (**Figure**, A). Gray matter was unremarkable with a score of 5 (normal score range 3-5). Tractography from the diffusion-weighted imaging revealed overall and tract-specific increments of FA and decreases for diffusivity indices (mean, axial and radial diffusivity) between 3 and 9 months CA (**Table I**; available at www.jpeds.com). Compared with reported development of diffusion indices during the first year of life in term-born infants, similar or potentially slightly reduced rates of change were noted between the 2 time points (ie, 2%-13% FA increase from 3 to 9 months CA compared with 9%-44% change between birth and 1 year reported in term-born peers).[29] The cortico-spinal tract, connecting the posterior limb of the internal capsule with the motor cortex in the precentral gyrus (**Figure**, B), appeared typical at 3 and 9 months CA. In contrast, the auditory interhemispheric pathway was atypical, as it did not connect through the corpus callosum, but instead followed an unusual path through the brainstem at 3 months CA, and through the thalamus at 9 months CA (**Figure**, B).

In contrast to the structural injury, the fMRI analysis found strong interhemispheric connectivity in both the auditory and motor cortical networks at all time points (**Figure**, C). This is in accordance with earlier studies showing that localized interhemispheric connections between homotopic counterparts is established around term equivalent age in term- and preterm-born infants.[30,31] The focus of the current case report is motor and auditory/language development, thus, other networks were not further explored. In addition, fMRI data revealed bilateral activity evoked by sound in the auditory network at 38 weeks PMA and 3 months CA (**Figure**, D). No cortical correspondence of the unilateral failure in auditory brainstem response was observed.

No activity was observed with fMRI at 9 months CA, which might be due to increased patient movement in the scanner with resultant lower signal-to-noise. Although identification of brain activity in response to a stimulus may be inferred to indicate normal brain function and can be related to other measures, caution must be used in interpreting absence of brain activation.

Neurodevelopment in the domains of motor, cognitive, language, and social behavior was within the normal range from 38 weeks PMA to 25 months CA (**Table II**). Mild abnormalities in muscle tone were reported at 4 and 8 months CA. At 9 and 13 months CA, motor development was at the 25th-27th percentiles. At 25 months CA, the patient was able to walk and run and used both hands equally. He had play behavior and social interactions that were within the normal range. He knew approximately 100 words, produced 3 word sentences, and followed simple instructions. His scores on the Cognitive, Language, and Motor subscales of the Bayley Scales of Infant and Toddler Development, third edition were within the average range.

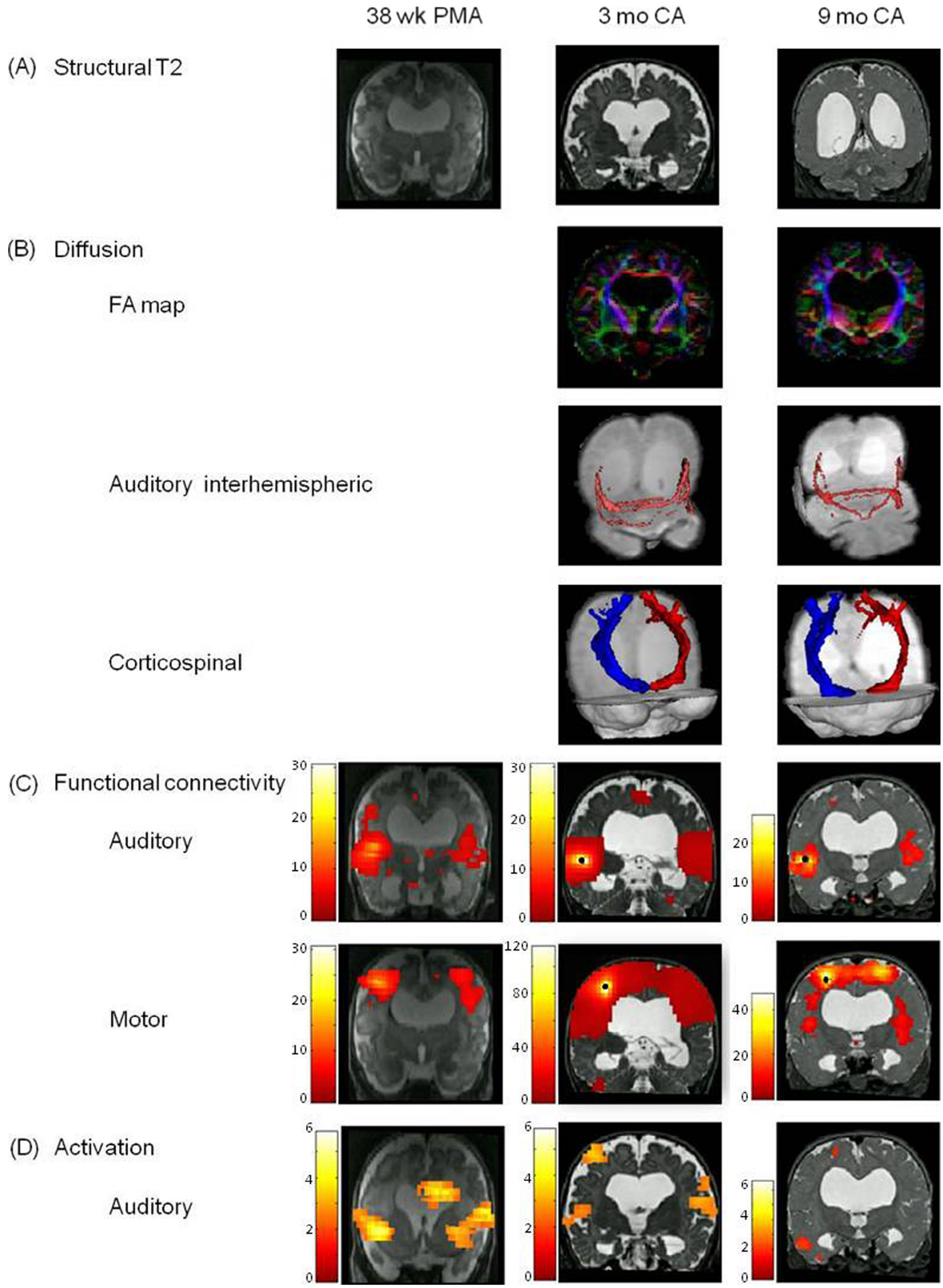

Figure. Coronal brain images of **A,** structural, **B,** diffusion, **C,** functional connectivity (*black dots indicate seed regions; P < .05 family-wise corrected*), and **D,** task-based activation (*P* < .05 uncorrected) at different acquisition time points. Images presented in neurologic convention.

Table II. Neurodevelopmental outcomes

	TIMP raw score (percentile)	Vineland-2 standard score (percentile)	REEL-3 standard score (percentile)	AIMS raw score (percentile)	INFANIB raw score	Bayley III standard score (raw score)
41 wk GA	70 (50-70)					
3 mo CA		AB 105 (63) Motor 112 (79)	106 (65)			
4 mo CA				14 (25-50)	76	
6 mo CA		AB 106 (66) Motor 100 (50)	113 (81)			
8 mo CA				29 (>10)	78	
9 mo CA		AB 108 (70) Motor 91 (27)	106 (65)			
13 mo CA				52 (25)	96	
25 mo CA						Cognitive 91 (58) Language 90 (Receptive 23) (Expressive 28) Motor 97 (Fine 39) (Gross 55)

AIMS, Alberta Infant Motor Scale; *Bayley III*, Bayley Scales of Infant and Toddler Development, third edition; *GA*, gestational age; *INFANIB*, Infant Neurologic International Battery; *REEL-3*, Receptive-Expressive Emergent Language Scales Test, third edition; *TIMP*, Test of Infant Motor Performance; *Vineland-2*, Vineland Adaptive Behavior Scales, second edition.
Data are presented as the standard or raw score and (percentile ranks), if available.

Discussion

The infant's extremely premature birth, low Apgar score, difficult clinical course, and substantial brain injury put him at high risk for poor developmental outcome.[32,33] However, brain injury does not automatically imply functional impairment. Our patient presented with ventriculomegaly, increased extracerebral space, white matter abnormality, and disrupted white matter tracts for auditory interhemispheric connectivity. However, functional connectivity between auditory and motor networks was typical and stimulus-evoked brain responses were found in the auditory-language network. These functional responses suggest preservation of function through plasticity, which was confirmed in the attainment of neurodevelopmental milestones within the normal range. The assessment of brain function in addition to the evaluation of structural anomalies in our case, thus, provided a measure of the effect of injury on the establishment of brain function and plasticity. Particularly for infants at risk for adverse neurodevelopment, fMRI might provide a valuable addition to clinical assessment for early prognosis. Future evaluation of the sensitivity of different MRI modalities to certain types of brain injury in preterm born infants has the potential to allow detailed assessments of the degree of preservation or disruption of brain function within neurocognitive networks. ■

We thank the families and infants who participated in our study, the MRI technicians and the neuroradiologist, Dr Keng Yeow Tay, at Children's Hospital (London Health Sciences Centre) and the Robarts Research Institute at Western University, London, Ontario, Canada.

Submitted for publication Jan 5, 2017; last revision received May 15, 2017; accepted Jun 26, 2017

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Table I. Overall and interhemispheric white matter indices for patient at 3 and 9 months CA and percent change

			3 mo CA	9 mo CA	% change
Overall white matter	FA		.1232	.1386	↑13%
	MD		.0013	.0011	↓15%
	AD		.0015	.0013	↓13%
	RD		.0012	.0011	↓ 8%
Auditory interhemispheric connectivity	FA		.3324	.3444	↑ 4%
	MD		.0011	.0010	↓ 9%
	AD		.0015	.0014	↓ 7%
	RD		.0009	.0008	↓11%
Cortico-spinal tract	FA	L	.3514	.3601	↑ 2%
		R	.3460	.3611	↓ 4%
	MD	L	.0010	.0010	↓ 0%
		R	.0010	.0010	↓ 0%
	AD	L	.0015	.0014	↑ 7%
		R	.0015	.0013	↓13%
	RD	L	.0008	.0008	↓ 0%
		R	.0008	.0008	↓ 0%

AD, axial diffusivity; *L*, left; *MD*, mean diffusivity; *R*, right; *RD*, radial diffusivity.
FA was expected to increase (denoted by ↑) while the other metrics were expected to decrease (denoted by ↓).