Investigations and research

Functional MRI of the sensorimotor system in newborns

H. Boecker
L. Scheef
A. Heep

Department of Radiology, University Hospital Bonn, Bonn, Germany.
Department Neonatology, University Hospital Bonn, Bonn, Germany.

Preterm birth before 32 weeks gestational age (GA) is associated with a high incidence of periventricular white matter injury (PWMI). Early prediction of motor deficits associated with PWMI has a fundamental clinical impact on the management of extremely preterm children. Reliable early predictive measures are warranted to allow for prompt and lesion-oriented rehabilitative treatment approaches. Unfortunately, neurological examination in the first months of life is poorly predictive for later cerebral palsy [1-3].

At present, the most predictive measures regarding long-term neurodevelopmental deficits [4-6] and cerebral palsy [6-8] in preterm and term infants are provided by structural imaging techniques. PWMI can be identified during the early postnatal period by means of ultrasound imaging [9] but magnetic resonance imaging (MRI) provides a better differentiation of brain tissue and pathology [10-13]. It is therefore highly sensitive to detecting white matter and gray matter lesions [5].

It has been shown that T1-hyperintensities or cysts located in the corona radiata above the posterior limb of the internal capsule are important predictors for motor prognosis of preterm infants with PWMI [14]. Compared to ultrasound imaging, a general advantage of MRI is that subventricular lesions can be recognized as well.

Since structural MRI allows only indirect inference upon functional states, we were interested in using functional magnetic resonance imaging (fMRI) as a non-invasive in vivo imaging tool for studying the sensorimotor system in the neonatal brain. This is initially described in passive sensorimotor stimulation tasks by Erberich and co-workers [15, 16]. Starting from initial block-design work and extending the initial approach by Erberich and co-workers, this review article describes the workflow of our interdisciplinary work at the University of Bonn.

Our review article is aimed at establishing reliable and safe neonatal fMRI procedures and to correlate the in vivo data with subsequent clinical outcome parameters. The main section of the review is focused on our published data [17, 18] of blood oxygenation level dependent (BOLD) responses. The responses are associated with unilateral passive forearm extension/flexion in a group of preterm infants with a median GA of 26.5 weeks (fMRI at term-equivalent age). The last part of the review deals with safety issues and technical developments.

Methods

Continuous passive sensorimotor stimulation - blocked design

Eight preterm infants with a median gestational age of 26.5 weeks (range 24-30 weeks) were included in the study, which was approved by the ethical committee of the Medical Faculty of the University of Bonn. One patient had to be excluded from the analysis because of incomplete MRI acquisition and two patients due to major movement artifacts.

The fMRI was performed at term-equivalent (median 39 weeks post conceptional age (PCA); 38 3/7 - 39 6/7 weeks range). Stable respiratory and circulatory function by continuous monitoring during at least one week before fMRI was a prerequisite for inclusion in the study. Chloral hydrate (50 mg/kg) was administered via a gastric tube for sedation 30 minutes before MRI. During MRI, vital signs (body temperature, heart rate and oxygen saturation) were continuously monitored. Acoustic protection was performed with earplugs, mini muff acoustic shells, and headphones.

The MRI was performed on a 3.0T Achieva system (Philips Healthcare, Best, the Netherlands) using an 8-channel adult SENSE head coil. The clinical protocol consisted of a standard T1-weighted SpinEchO sequence (TR/TE/flip: 580 ms/13 ms/90°, 22 slices,
A T2-weighted TSE-sequence (TR/TE/flip: 4200 ms/80 ms/90°, 22 slices, reconstruction resolution: 0.6 x 0.8 x 4.0 mm³) and a diffusion weighted sequence (TR/TE/flip: 2858 ms/40 ms/90°, 22 slices, reconstruction resolution: 2.0 x 2.0 x 5.0 mm³; b value: 1000 s/mm²) were obtained for anatomical overlay of the fMRI data (TE/TR/flip: 35 ms/2.60 ms/90°, spatial resolution: 1.88 x 1.88 x 3.50 mm³). Passive sensorimotor stimulation was induced by a physician in the scanning room via manual traction of one forearm at a frequency of ~1 Hz.

The sensorimotor stimulation blocks, each of 20s duration, were repeated five times per stimulation side, alternating with an equal amount of rest (no movement) blocks. The data was analyzed with the SPM5 software (Wellcome Department of Imaging Neuroscience, London, United Kingdom) based on Matlab 7.1 (The Mathworks Inc, Natick, MA) and included spatial realignment, co registration to the individual T1-weighted MRI and spatial smoothing (6-mm isotropic Gaussian kernel). Whole-brain voxel-based statistical analyses were performed between the movement and rest conditions on a single-subject basis.

Results

The fMRI was well tolerated by all infants and no adverse effects of the sedation were observed under continuous monitoring for vital signs. The manipulation of the hand did not induce disruption of sleep under sedation. SPM5 analyses revealed that passive unilateral sensorimotor stimulation was associated with a consistent bilateral activation pattern involving the sensorimotor cortex in 9/10 trials [17].

An exemplary case showing bilateral sensorimotor cortex activation is given in Figure 1.

As predicted, based on previous studies [14, 15], the prevailing BOLD response was a negative BOLD signal (N= 7/10 datasets), as clearly shown in Figure 2.

Discussion

Our experience shows that fMRI of the sensorimotor system can be performed as part of a clinical MRI protocol in extremely preterm high-risk infants. The published ten data sets acquired in preterm infants at term-equivalent age [17] indicate a bilateral negative BOLD response in primary sensorimotor cortices as predominant activation pattern. This bilateral activation pattern is compatible with a bilaterally distributed system at this developmental stage.

The negative BOLD activation pattern is compatible with previous fMRI findings in infants born at term [15, 16] and it is thus likely (but as yet unproven) that negative BOLD responses constitute the prototypical hemodynamic response at this stage of brain maturation. However, these findings warrant confirmation in a larger cohort.

Studies relating fMRI patterns in relation to maturation status are important prerequisites for clinical fMRI applications aimed at detecting functional compromises related to brain development.
pathology. It has to be pointed out, however, that despite the inversion of the BOLD signal in infants, the spatial localization in primary sensor-motor cortex was robustly determined. Therefore, the presented approach, namely studies of cortical responses to passive sensorimotor stimulation, may prove helpful in determining functional impairments at an extremely early age of life.

At present, however, the small number of studied infants does not yet allow making any inference as to later motor status. Neurological examination and neurodevelopmental testing at the age of four to six months did not show a constant pathological pattern, except one child demonstrating a differing positive and unilateral BOLD response. This patient had abnormalities on neurological examination at term-equivalent age (muscular hypertonia, poor movement repertoire) and impaired motor skills in Griffith’s mental development scales at four month corrected age; possibly reflecting delayed developmental organization of the sensorimotor system.

This investigation is currently being extended with the focus on the long-term neurodevelopmental follow-up investigations to validate the significance of these findings.

It is important to point out that there are several relevant safety issues that have be carefully controlled in sedated neonates. Continuous monitoring of vital signs (body temperature, heart rate, and oxygen saturation) is required during the entire MRI procedure. Beyond strict compliance to SAR restriction, acoustic noise is another major safety issue and warrants adequate protection (ear prongs, mini muff acoustic shells, head phones) and electrophysiological monitoring with brainstem evoked response audiometry pre- and post-MRI. Experience shows the fMRI procedure is well tolerated when these issues are carefully respected.

**Future outlook**

Optimized head coils for neonatal MRI are warranted to gain higher signal-to-noise contrast. For studies of the sensorimotor system, MRI-compatible devices are warranted that allow standardized and reproducible passive sensorimotor stimulation in event-related acquisitions. A mechanical, MR-compatible device (Figure 3) has been developed for passive unilateral hand extension/flexion movements in which each wrist can be stimulated independently with fully controlled speed and velocity of individual movements [19].

**Acknowledgment**

We wish to thank Senior Clinical Scientist Dipl. Phys. Jürgen Gieseke from Philips Healthcare for technical advice and support.

---

**References**


Fourteen years of Medicamundi archives are now available online. They can be accessed via: www.philips.com/medicamundi