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# Somatosensory cortical activation identified by functional MRI in preterm and term infants

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A B S T R A C T

Functional MRI (fMRI) has not previously been used systematically to investigate brain function in preterm infants. We here describe statistically robust and reproducible fMRI results in this challenging subject group using a programmable somatosensory stimulus synchronized with MR image acquisition which induced well-localized positive blood oxygen level dependent (BOLD) responses contralateral to the side of the stimulation in: 11 preterm infants (median post menstrual age 33 weeks and 4 days, range 29 + 1 to 35 + 3); 6 control infants born at term gestational age; and 18 infants born preterm (median gestational age at birth 30 weeks and 5 days, range 25 + 4 to 36 + 0) but studied at term corrected gestational age. Bilateral signals were identified in 8 of the ex-preterm infants at term age. Anatomical confirmation of appropriate activations was provided with diffusion tensor imaging (DTI) based tractography which identified connecting pathways from the regions of activation through the ipsilateral corticospinal tracts and posterior limb of the internal capsule. These results demonstrate that it is possible to reliably identify positive BOLD signals in the infant brain and that fMRI techniques can also be applied in the study of preterm infants.


## Introduction

Preterm birth now accounts for up to 13% of all births in the United States (Goldenberg et al., 2008), and is associated with a significantly increased risk of cerebral palsy and cognitive impairment in survivors (Larroque et al., 2008). New and reproducible ways of understanding the mechanisms that underlie these difficulties are vital to aid the development and implementation of therapeutic interventions for this population.

Functional magnetic resonance imaging (fMRI) allows the non-invasive investigation of neural activity by the interpretation of dynamic changes in the blood oxygen level dependent (BOLD) signal (Ogawa et al., 1992; Kwong et al., 1992). There is a body of research investigating functional activation in ex-preterm infants through childhood (for a review see Ment and Constable, 2007), but technical problems and inconsistent results have meant that there are few fMRI studies during the neonatal period and no systematic data have been reported on infants before term, when they seem most at risk of developing intracerebral abnormalities. Furthermore, studies in young children have reported considerable variability with the identification of both positive and negative BOLD signal responses within the same study population. It is unclear if this heterogeneity is due to technical issues with the stimulus paradigms or analysis techniques (in particular the form of the hemodynamic response function (HRF) convolved in the general linear model), or due to genuine physiological differences in the developing brain.

We hypothesized that well-localized positive BOLD signal cortical activation could be identified with fMRI in the preterm infant brain using an appropriate synchronized tactile and proprioceptive stimulus. The aim of this study was to therefore characterize the identified BOLD response to somatosensory stimulation in preterm infants, and to compare it with those detected at term corrected age and in term-born control infants. The somatosensory cortex was chosen as the ideal substrate for a stimulus-based fMRI experiment in the preterm brain because the central sulcus can be identified by MRI from 26 to 28 weeks of corrected gestational age (Van der Knaap et al., 1996; Battin et al., 1998), and electrophysiological techniques have demonstrated that brain activity can be identified in response to peripheral somatosensory stimuli in both preterm and term neonates (Karniski, 1992; Karniski et al., 1992; Lauronen et al., 2006; Pike and Marlow, 2000; Vanhatalo and Lauronen, 2006).

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We developed a fully synchronized stimulation device which can provide well controlled proprioceptive and tactile stimuli to the infant's hand during the image acquisition, and used an analytical technique which provided flexible characterization of the HRF. We also confirmed the anatomical plausibility of the activated cortical regions by performing probabilistic tractography on diffusion tensor imaging (DTI data) to delineate the structural connectivity of the areas of functional activity.

## Methods and materials

The study was approved by the Hammersmith Hospitals Research Ethics Committee and written parental consent was obtained prior to all sessions of experimental stimulation and MR image acquisition.

### *Subjects*

All of the subjects were recruited from the Neonatal Intensive Care Unit or postnatal wards of Hammersmith Hospital, London, UK during a period of 6 months between 2008 and 2009. The study group consisted of: 13 preterm infants; 19 ex-preterm infants who were scanned at term corrected gestational age (CGA); and 8 healthy control infants who were born at term gestational age (see Table 1). Clinical details including antenatal, birth and postnatal care were recorded for each patient, and a neurological assessment was carried out. Infants with extensive intraventricular hemorrhage diagnosed on cranial ultrasound examination (grade 3 with ventricular dilatation, or grade 4 with parenchymal involvement), other focal intracerebral parenchymal lesions, hydrocephalus, congenital brain malformations or metabolic disorders were excluded from the study group.

Oral sedation (chloral hydrate 30 mg/kg) was administered before scanning to 15 of the 19 ex-preterm infants, but to none of the premature infants and only one of the term control infants. Two of the preterm infants were receiving respiratory support with nasal continuous positive airway pressure (nCPAP) at the time of scanning, while a further 4 required low flow supplementary oxygen (range 50–100 cc) via nasal cannulae. One ex-preterm infant required supplementary oxygen at the time of scanning.

### *Imaging*

MR imaging was performed on a Philips 3-T system (Best, Netherlands) with an eight channel phased array head coil, located on the neonatal intensive care unit.

All infants were assessed to be clinically safe for scanning by an experienced pediatrician prior to the scan. The infants' temperatures, arterial oxygen saturations and heart rates were monitored throughout the scan. Ear protection was used in all infants in the form of dental putty and adhesive ear muffs, and the head was immobilized using a polystyrene bead filled pillow from which the air was evacuated.

Three-dimensional dual echo-weighted (proton density and T2-weighted), and 3D MPRAGE T1-weighted images were acquired for all infants to provide clinical information and to act as a high resolution image with which the functional data could be registered. All structural images were also reviewed and fully reported by a neonatal neuroradiologist, and any resultant clinical implications were fully discussed with parents and relevant members of the clinical team.

Functional MR data were acquired with an echo-planar imaging (EPI) sequence lasting a total of 6 min and 30 s with the following parameters; TR 1500 ms, TE 45 ms, flip angle 90°, 22 slices, voxel size 2.5 $mm^2$, slice thickness 3.25 mm, and total 256 volumes.

DTI data were also acquired from 9 infants (2 preterm, 2 term control and 5 ex-preterm) during the same image acquisition session as the fMRI data. Data were acquired with a single shot EPI sequence in 32 non-collinear directions with a b-value of 750 $s/mm^2$ and the following parameters; TR 9000 ms, TE 49 ms, voxel size 1.75 $mm^2$, slice thickness 2 mm, matrix $128 \times 128$, field of view (224 mm).

### *Somatosensory stimulation*

The somatosensory stimulus was elicited by a programmable hand interface, consisting of a tailor-made inflatable balloon composed of 2 layers of latex around a nylon mesh, a control box and customizable software (see Fig. 1). The control box consisted of a pressure regulator valve controlled by software on a standard PC, both of which were connected to the MRI scanner via a Data Acquisition Card. Synchronized stimulation was achieved via detection of the MRI scanner transistor to transistor logic (TTL) pulse with each TR.

The balloon was sized and placed in the right hand of each subject, and then intermittently inflated/deflated with pressurized air via a 7 m plastic pipe connected to the control box outside the examination room. Inflation resulted in passive extension of the fingers, while deflation allowed flexion. Using the software interface on the PC, the investigators were able to adjust the amplitude of balloon inflation appropriately for hand size (balloon volume range 1.2 $cm^3$–3.1 $cm^3$).

It was confirmed that the device was MR safe and compatible (for review see Gassert et al., 2008) and produced characteristic patterns of cortical activation in fMRI images collected from 3 healthy adult volunteers before it was used with newborn infants.

### *Experimental design*

An “on–off” block stimulation paradigm was programmed on the PC interface, with alternating periods lasting 24 s each (16 TRs) as

**Table 1**
The study population group, with corresponding clinical and birth details.

| Patient group | *n* | Median age at birth (range) at birth in weeks + days of gestation | Median (range) age at scan in weeks + days post menstrual age | Birth weight (range) in grams | Birth head circumference in centimeters (range) | Sedation given during scan (number) | Median (range) number of hours of mechanical ventilation | Number of infants with blood culture positive sepsis in the neonatal period (number) | Number of infants with intraventricular hemorrhage (number) |
|---|---|---|---|---|---|---|---|---|---|
| Preterm | 13 | 29 + 4<br>(25 + 4–34 + 0) | 31 + 1<br>(27 + 1–35 + 3) | 1037<br>(795–2374) | 26.5<br>(22–33) | 0 | 0.5<br>(0–120) | 1 | Grade 1: 0<br>Grade 2: 0<br>Grade 3: 0<br>Grade 4: 0 |
| Term control | 8 | 40 + 3<br>(36 + 3–41 + 6) | 40 + 4<br>(36 + 5–43 + 0) | 3571<br>(2176–4242) | 34.5<br>(32–38.9) | 1 | 0<br>(0–0) | 0 | Grade 1: 0<br>Grade 2: 0<br>Grade 3: 0<br>Grade 4: 0 |
| Ex-preterm at term corrected gestational age | 19 | 30 + 5<br>(25 + 4–36 + 0) | 42 + 0<br>(39 + 0–44 + 6) | 1050<br>(795–2430) | 27.5<br>(22–33) | 15 | 0.5<br>(0–126) | 1 | Grade 1: 3<br>Grade 2: 0<br>Grade 3: 0<br>Grade 4: 0 |