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Relation between clinical risk factors, early cortical changes, and neurodevelopmental outcome in preterm infants

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ABSTRACT

Cortical folding mainly takes place in the third trimester of pregnancy and may therefore be influenced by preterm birth. The aim of this study was to evaluate the development of specific cortical structures between early age (around 30 weeks postmenstrual age) and term-equivalent age (TEA, around 40 weeks postmenstrual age) in 71 extremely preterm infants, and to associate this to clinical characteristics and neurodevelopmental outcome at two years of age. First, analysis showed that the central sulcus (CS), lateral fissure (LF) and insula (INS) were present at early MRI in all infants, whereas the other sulci (post-central sulcus [PCS], superior temporal sulcus [STS], superior [SFS] and inferior [IFS] frontal sulcus) were only seen in part of the infants. Relative growth from early to TEA examination was largest in the SFS. A rightward asymmetry of the surface area was seen in development between both examinations except for the LF, which showed a leftward asymmetry at both time points. Second, lower birth weight z-score, multiple pregnancy and prolonged mechanical ventilation showed negative effects on cortical folding of the CS, LF, INS, STS and PCS, mainly on the first examination, suggesting that sulci developing the earliest were the most affected by clinical factors. Finally, in this cohort, a clear association between cortical folding and neurodevelopmental outcome at two years corrected age was found, particularly for receptive language.

Introduction

During the third trimester of pregnancy, large morphological changes occur in the human brain. Not only an impressive volumetric growth, but also the majority of cortical gyrification and sulcation takes place during this period of brain development, changing the human brain from its largely lissencephalic appearance at 24 weeks of gestation to a brain folded similarly to an adult brain at term age (Habas et al., 2012; Clouchoux et al., 2012; Battin et al., 1998; Chi et al., 1977). Many different mechanisms to explain cortical folding have been proposed, but no clear consensus has been reached so far. Two of the most popular theories are the tension-based theory, which states that tension along growing axons causes folding (Van Essen, 1997), and the differential growth hypothesis, which states that folding is driven by different growth rates between various regions and layers of the brain (Xu et al., 2010; Toro and Burnod, 2005). A recent study integrated both theories and proposed a morphogenetic model based on a growing outer surface and a stretch-driven growing inner core (Budday et al., 2014). This model showed good prediction of cortical folding between 27 and 32 weeks of gestation. A similar theory has been described looking at cortices of several mammalian species (Tallinen et al., 2014).

Over the last decades, magnetic resonance imaging (MRI) has been used to visualize these changes in vivo, and to describe the standard order in which sulci develop (Dubois et al., 2008b; Garel et al., 2001; van der Knaap et al., 1996). With foetal MR imaging normal

Abbreviations: BSITD-III, Bayley Scales of Infant and Toddler Development, third edition; BWZ, Birth weight z-score; CS, Central sulcus; cUS, Cranial ultrasound; IFS, Inferior frontal sulcus; INS, Insula; IVH, Intraventricular haemorrhage; LF, Lateral fissure; MRI, Magnetic resonance imaging; PCS, Postcentral sulcus; PHVD, Post-haemorrhagic ventricular dilatation; PMA, Postmenstrual age; SFS, Superior frontal sulcus; STS, Superior temporal sulcus; TE, Echo time; TEA, Term equivalent age; TR, Repetition time.

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development has been studied, although it still has its methodological challenges mainly related to motion of the infant and maternal womb/rib cage, as well as constraints in acquisition time. Studies using foetal MRI have shown the characteristic pattern of folding, with primary folds actively developing from 25 weeks onwards, and secondary folds starting to delineate after 30 weeks (Clouchoux et al., 2012; Garel et al., 2001; Habas et al., 2012). Studies of preterm infants imaged ex utero have also detailed the progression of folding (Dubois et al., 2008b). Some discrepancies between folding patterns measured at birth and those measured in utero at equivalent ages have been described (Lefevre et al., 2015).

Infants born extremely preterm spend the last trimester of gestation outside the womb, in a neonatal intensive care environment in which they are exposed to a multitude of potentially damaging factors. This may lead to disturbances in the normal folding process taking place during this critical period for brain development (Ajayi-Obe et al., 2000; Dubois et al., 2008b; Lefevre et al., 2015), which may be reflected in impaired neurodevelopmental outcome of especially the cognitive and behavioural domains that are frequently seen in this population (Kapellou et al., 2006; Rathbone et al., 2011). So far, studies evaluating cortical folding in preterm infants up to term equivalent age (TEA) have been mainly cross-sectional, and longitudinal relationships with neurodevelopmental outcome have remained scarce. Measurements were further applied to the entire brain or to large brain regions involved in several functional networks (Dubois et al., 2008b; Kapellou et al., 2006; Melbourne et al., 2014).

Thus, the aim of this study was to evaluate folding of specific sulci in a longitudinally scanned cohort of extremely preterm infants, and to correlate this with both clinical characteristics and neurodevelopmental outcome at two years of age.

Materials and methods

Clinical data

Between June 2008 and March 2013, preterm infants with a gestational age at birth between 24 and 28 weeks, admitted to the level three neonatal intensive care unit of the Wilhelmina Children's Hospital/University Medical Center Utrecht, were consecutively included in a prospective neuroimaging study. Permission from the medical ethics review committee was obtained for this study. Infants were scanned twice: once – if clinically stable – around 30 weeks postmenstrual age (28.7–32.7 weeks) and again around TEA (40.0–42.7 weeks). Serial imaging data were acquired in 137 of the 265 infants born during the inclusion period. Most of the infants that were not scanned serially either died ($n = 32$), were too unstable to be transported to the MRI scanner ($n = 62$), or their parents did not give permission for the MRI ($n = 17$). Forty-three of the 137 serially scanned infants were not yet two years of corrected age at the time of this report, and their outcome data were therefore not yet available. Of the remaining 94 infants, severe motion artefacts on either of the scans was reason for exclusion in 10 infants and in an additional 13 infants, segmentation errors were too severe to correctly process the data, leading to a final cohort of 71 infants to be included in this study. Supplementary Fig. 1 shows a flowchart with the final inclusion of all infants. Perinatal data were obtained by chart review. Birth weight z-scores (BWZ) were computed according to the Dutch Perinatal registry reference data (Visser et al., 2009). Corrected weight at scan was defined based on the z-score of the absolute weight at scan, thus correcting for the intrinsic differences between boys and girls. Socioeconomic status was determined based on maternal educational level (Divisie Sociale en ruimtelijke statistieken, 2014). Prolonged mechanical ventilation was defined as total duration of mechanical ventilation before the first scan of >7 days and this parameter was used as a measurement of severity of illness. Serial cranial ultrasound (cUS) was obtained and reported as part of standard clinical care. Intraventricular haemorrhage (IVH) grading on cUS was scored according to Papile and post-haemorrhagic ventricular dilatation (PHVD) was defined as a ventricular index 4 mm > 97th percentile (Papile et al., 1978; Levene, 1981).

MRI acquisition

MR imaging was performed on a 3.0 Tesla MR system (Achieva, Philips Medical Systems, Best, The Netherlands). At the early MRI, infants were scanned in an MRI compatible incubator (Dräger MR Incubator, Lübeck, Germany and later Nomag® IC 3.0, Lammers Medical Technology GmbH, Lübeck, Germany, with a dedicated neonatal head coil), while at TEA an 8-channel SENSE (sensitivity encoding) head coil was used. The protocol included T2-weighted imaging with a turbo spin echo sequence in the coronal plane (at early MRI: repetition time [TR] 10,085 ms; echo time [TE]120 ms; slice thickness 2 mm, in-plane spatial resolution 0.35 × 0.35 mm; at TEA: TR 4847 ms; TE 150 ms; slice thickness 1.2 mm, in-plane spatial resolution 0.35 × 0.35 mm). After evaluation by a paediatric radiologist, all scans were re-assessed by two neonatologists (LdV and MB) with over 10 years of experience in neonatal neuro-imaging. The presence of IVH, periventricular haemorrhagic infarction, PHVD, cystic periventricular leukomalacia, punctate white matter lesions, central or cortical grey matter infarctions and punctate or larger lesions in the cerebellum were noted.

MR image post-processing

In order to assess the folding stage and measure changes in cortical sulci, a dedicated approach was implemented by taking benefit of the complementarity of three previously validated methods that enable 1) reliable brain tissue segmentation of preterm images (Moeskops et al., 2015), 2) relevant 3D reconstructions of inner cortical surfaces in infants (Leroy et al., 2011), and 3) sulci identification in the adult brain (Fischer et al., 2012). First, T2-weighted images were segmented with a recently developed automatic segmentation method, defining masks of the cortical grey matter, unmyelinated white matter and cerebrospinal fluid in the extracerebral space (Moeskops et al., 2015). In short, this method uses supervised voxel classification on T2-weighted images in three subsequent stages. In the first stage, voxels that can be easily assigned to one of the three tissue types are labelled. In the second stage, dedicated analysis of the remaining voxels is performed. The third stage is used to resolve possible inconsistencies resulting from the first two tissue-specific segmentation stages by performing multi-class classification (Moeskops et al., 2015). Before the segmentation, a brain mask was automatically generated based on the T2-weighted image using the Brain Extraction Tool (BET) from the FMRIB Software Library (FSL) (Smith, 2002). For both early and TEA segmentations, the same set of features was used.

This method has been evaluated on images of preterm infants acquired at both early and term equivalent age, and has been validated by comparison with several manually segmented scans, as described in detail in Moeskops et al. (2015). The probabilistic segmentations resulting from the second stage were used to subsequently reconstruct inner cortical surfaces of both hemispheres, by adapting the anatomical pipelines of the BrainvVISA® software (Baby and Morphologist pipelines) (Leroy et al., 2011; Mangin et al., 2004). Probability maps for the tissues of interest (cortical grey matter, unmyelinated white matter and cerebrospinal fluid) (Moeskops et al., 2015) were combined within a single feature map to maximize the contrast between grey and white matter. This optimized feature field was used in the stage of homotopic deformation of coupled surfaces (Leroy et al., 2011), which computes a mask of white matter with homotopic properties and reconstructs 3D meshes of inner cortical surfaces. While this method is already robust to partial volume effects and loss of tissue contrast due to maturation up to six months after birth (Leroy et al., 2011), we further increased its performance by using probability maps as an extra feature. Where