

MRI study of the cortical folding process in the premature newborn brain

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Introduction

In the adult brain, the cortical sulci morphology is highly variable among individuals [1], whereas the primary folds (called “sulcal roots”) are assumed to develop in a stable way during intra-uterine life [2]. So far, several hypotheses have been conducted on the factors that underlie this folding process, like the mechanical tension from white matter fibers [3], but quantitative measurements of the sulci formation are still lacking in support of such theories. As MRI is now used clinically for the non-invasive evaluation of the preterm newborn [4], we investigated the emergence of cortical folding through the application of post-processing tools dedicated to the immature brain.

Materials and Methods

MR acquisition 35 premature newborns (mean gestational age - GA: 30.9±2.1 weeks, range: 26.7w-35.9w) were studied by MRI on a 1.5T scanner (Philips Medical Systems). Coronal slices covering the whole brain were imaged by a fast spin echo sequence yielding a T2 contrast between cerebral tissues, with a spatial resolution of 0.7x0.7x1.5mm³ or 0.8x0.8x1.2mm³ (Figure 1a).

Data post-processing Cortical surface reconstruction The cortical surface was reconstructed through a sequence of image post-processing tools adapted from a sequence developed for the adult brain [5-6], as described previously for foetal images [7]. It included a bias correction and semi-automatic segmentations of the brain and of the interface between cortex and white matter, which used mathematical morphology and a manual optimization of the threshold parameters for each newborn. A smooth triangle based mesh of this detected surface was computed, and its curvature was estimated locally. Cortical sulci identification The sulci were highlighted through a curvature threshold and a detection of connected components, and labelled manually according to post-mortem atlases [8-9] and prenatal images [10]. Their area (A) was calculated as a marker of their maturation.

Evaluation of the preterm structural maturation Sulcation index For each newborn, we computed a sulcation index, defined as the ratio between the areas of external sulci (except the sylvian fissure) and the closed surface of the whole brain, and we assessed the age-related changes of this index over the newborn group. Inter-individual variability Then we compared the folding process in newborns with similar sulcation index, by realigning their images with an iterative normalization procedure based on the creation of template images with SPM2 software [11] (Figure 1b). Inter-hemispherical asymmetries Finally, we evaluated the differences in maturation between the right (r) and left (l) sulci by testing the nullity of asymmetry indices $(A(r)-A(l))/(A(r)+A(l))$ over the group using one-paired Student t tests.

Results

Cortical surface reconstruction From high quality images, cortical surfaces could be reconstructed semi-automatically for all newborns (Figure 2). In the older ones (>31w old), some manual corrections were required around the central sulcus and at the level of the sylvian fissure, because the increasing gyration and myelination implied partial volume effects and decreasing contrast in the image. Imaging more isotropic voxels (0.8x0.8x1.2mm³) enabled to prevent in part these corrections, while having no influence on the sulcus quantification. We optimized the reconstruction quality for the brain external surface, where most sulci are localized (Figure 3a), as the central grey nuclei and the ventricles complicated the segmentation of the internal surface, where the sulci appeared roughly connected (Figure 3b).

Cortical gyrification We observed an increasing sulcation index with gestational age (correlation coefficient: 0.9, p<0.001), but the onset of the folding process differed between individuals. Several sulci were identified in all newborns (Figure 3a-b): the sylvian fissure (SF), the callosal and cingulate sulci (CaS, CiS), the calcarine and parieto-occipital fissures (CF, POF) in the internal surface, and the central sulcus (CS) in the external surface. In the temporal lobe, we observed the appearance of the superior and inferior temporal sulci (STS/ITS) from 26.7/27.3w GA to 30.5/31w GA respectively, and of the collateral sulcus (CoS) from 27.9w GA to 30.6w GA. In the frontal lobe, the pre-central sulcus (preCS) seemed to form in two parts between the superior and inferior frontal sulci (SFS/IFS), between 27.3w GA and 32.4w GA; the uncinata sulcus (UnS) was present from 30.3-31w GA on. Finally, the post-central sulcus (postCS) development was concomitant to the parietal and parieto-occipital sulci (POS) folding, from 27.9/27.3w GA to 31/32.4w GA respectively.

Inter-individual variability Thus some inter-individual variability was observed in the folding process of newborns of equivalent age. Besides, the sulci morphology and localization in the external surface also differed between newborns with similar sulcation index (Figure 3c-e), particularly in the frontal and parietal lobes at the level of the pre- and post-central sulci, as shown by the sulci superposition resulting from images realignment.

Inter-hemispherical asymmetries Finally, the area of the superior temporal sulcus was significantly larger in the right hemisphere ($t=-3.49$, p<0.001).

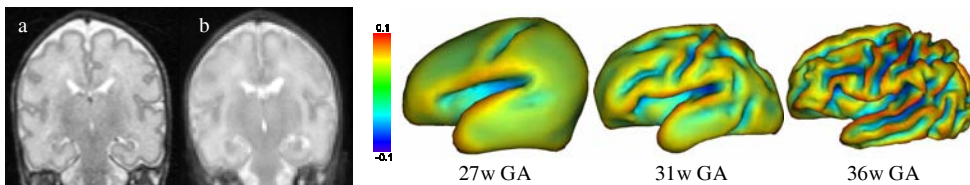


Figure 1: Image of a 31w-old newborn (a), and template from 6 newborns with similar sulcation index (b).

Figure 2: 3D reconstruction of the interface between cortex and white matter for 3 newborns of different gestational age (the colours outline the surface curvature).

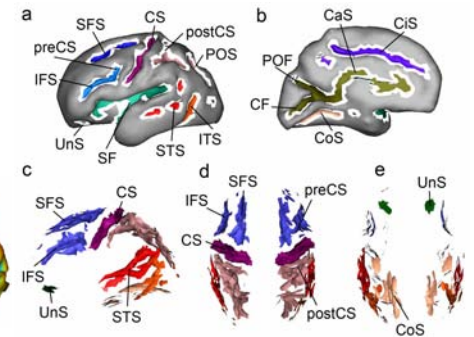


Figure 3: Cortical sulcus identification in the brain of a 31w-old newborn (a, b: external and internal surfaces), and superposition in Talairach space of the sulci from 6 newborns with similar sulcation index (c, d, e: sagittal, axial superior and inferior views).

Discussion and Conclusion

With brain MR images from premature newborns and dedicated post-processing tools, we were able to precisely reconstruct cortical surfaces in vivo over a developmental period that is critical for the folding process. In comparison with previous post-mortem [8-9] and prenatal [10] studies, we observed equivalent sulci appearance over the brain in premature infants, but with slightly later appearance. The inter-individual variability with age may be influenced by the accuracy of the gestational age estimation, and by varying post-natal age and environmental stimulation. Nevertheless, such approach enables to overcome the post-mortem limitations (potential brain pathology, deformation of the tissues after birth), it can be included in a longitudinal follow up, and further correlated to the emergence of neurological functions. Thus it may provide important insights on the formation of sulci and gyri, and define developmental asymmetries that are early indicators of the functional specialisation of cortical areas [8].

References [1] Ono *et al*, Atlas of the cerebral sulci 1990, Georg Thiem Verlag. [2] Regis *et al*, Neurol Med Chir 2005, 45(1):1-17. [3] Van Essen, Nature 1997, 385:313-318. [4] Huppi and Inder, Semin Neonatol 2001, 6:195-210. [5] Mangin *et al*, NeuroImage 2004 23:S129-138. [6] Riviere *et al*, NeuroImage 2000, 11:S912, <http://anatomist.info/>. [7] Cachia *et al*, IEEE Trans Med Imaging 2003, 22:754-765. [8] Chi *et al*, Ann Neurol 1977, 1:86-93. [9] Feess-Higgins and Laroche, Development of the human foetal brain: an anatomical atlas 1987, Inserm-CNRS, Masson. [10] Garel *et al*, AJNR 2001, 22:184-189. [11] <http://www.fil.ion.ucl.ac.uk/spm/>.