In vivo fetal cortical development

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Introduction

A number of recent studies have characterized total and regional brain volume in the living fetus [Limperopoulos 10; Gholipour 10a; Grossman 06]. However, very few studies have delineated *in vivo* fetal cerebral cortical development. Batchelor et al., (2002) described the folding process in 10 *ex vivo* fetuses between 19-40 weeks of gestation. More recently, Dubois and colleagues (2008) provided one of the first descriptions of cerebral gyrification from 26-35 weeks gestational postnatal age (GA); however, this work was conducted on ex-utero premature infants. Awate et al. (2009) described cortical development in newborns between 1 and 2 weeks postnatal age, using a combination of shape indexes computed on the cortical surface. In the only previous study of cortical folding in the living fetus, Hu et al. [Hu 09] described fetal cortical development in vivo, but did not extract fetal cortical surfaces, precluding therefore explicit delineation of the cortical folding pattern. In the present study, we investigate cerebral cortical folding in the healthy *in-utero* brain between 25-35 weeks gestational age (GA). Fetal gyrification was assessed by applying a robust surface feature extraction algorithm, allowing labeling of the sulcal fundi directly on the reconstructed cortical surface.

Methods

We studied 12 healthy fetuses from 25.2 to 35.0 weeks GA. All fetuses were studied without maternal sedation using MRI scans performed on a 1.5-T scanner. Multiplanar single-shot turbo spin echo imaging was performed (2-mm slice thickness, no interslice gap) in axial, coronal and sagittal planes and provided multiple in-plane high-resolution volumes along the three principal axes. Fetal volumes were corrected for intensity and high-resolution volumes were reconstructed from the acquisitions in the three orthogonal plans [Gholipour 10b]. White matter delineation was then performed based on an atlas-based tissue segmentation method, using a manually segmented age-dependant fetal atlas as a reference [Guizard 08]. These segmentations were then manually corrected, in order to have an accurate delineation of the inner cortical surface. The cortical surface mesh was obtained using CLASP [McDonald 00]. The sulcal pattern was then extracted from each subject using a robust method aiming at extracting the global sulcal pattern, relying on a 3D vertex labeling and skeletonization performed directly over the mesh [Kudelski 10, Clouchoux 10]. This method relied on a two-step algorithm. First, each vertex of the mesh was labeled, according to the sign of local Gaussian and mean curvature, allowing the definition of regions of interest (ROI) corresponding to sulcal regions. The second step reduced each ROI to skeletons, by an iterative thinning process, guarantying the connectivity of the extracted sulcal lines. The global folding process was then described using local geometrical features.

Results

The 3-dimensional cortical surface representations enabled us to delineate sulcal organization between 25-35 weeks GA. Figure 1 shows the global folding evolution within this time frame, along with the sulcal depth [Boucher 09]. Figure 2 shows the evolution of the gyrification on 4 age-dependant cortical templates (A:25.2-27.3 weeks GA, B:28-29.3 weeks GA, C:30.4-32 weeks GA, D:33.1-35 weeks GA). The first folding occurs at the insula (25 weeks GA), although the operculation process is delayed until around 28 weeks GA. The central sulcus (CS) appears from 27 weeks GA. Between 25 and 27 weeks, the superior temporal sulcus (STS), calcarine fissure, parieto-occipital fissure (POF) and the calloso-marginal fissure (CMF) begin to appear, and are well formed by 28 to 29 weeks GA. The collateral sulcus is formed at 28 weeks. The frontal sulci are clearly visible from 27 weeks. In the parietal lobe, the intra-parietal fissure (IPF) appears very early, from 27 weeks GA. After this folding, the post-central sulcus appears, making the sulcal pattern in the parietal lobe more convoluted. The inferior and superior sulci folding in the frontal lobe appears around the 28th week of gestation, while the pre-central sulcus is present from the 29th week. Secondary sulci also appear before birth, including the orbital and olfactory sulci which become visible at the 30th week GA. After 31 weeks, the folding pattern of previously formed sulci becomes more complex, such as the folds in the cingulate gyrus, especially the frontal part of the calloso-marginal fissure.

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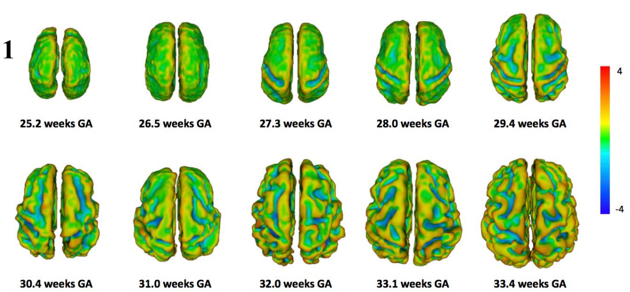

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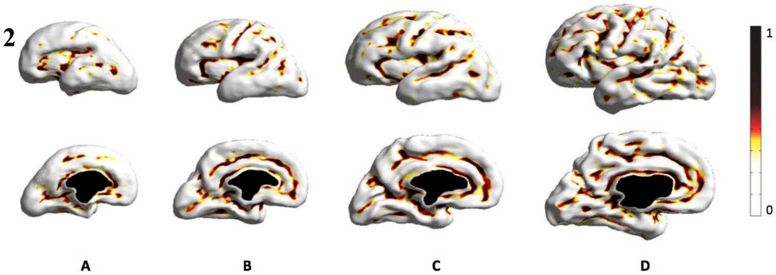

Conclusion

We provide for the first time *in vivo* description of gyral development in the human fetal brain during the critical period of rapid cortical development from 25 to 35 weeks of gestation. We propose a novel robust methodology for capturing the evolution of sulcal development during the second and third trimester that will enable the quantification of cortical development in the living fetus. Our data corroborate the exuberant gyrification process occurring after 28 weeks gestation, and suggest a non-linear evolution of the sulcal pattern. Future work will focus on extending the study to a larger database and the extraction of a formal model of the gyrification process in the *in vivo* fetus.

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