# Regional changes of cortical thickness and cortical surface in children born prematurely and children born with intrauterine growth restriction at school age

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## Introduction

Premature birth and the early exposure to environmental sensory information influence the cascade of histogenetic events that occur during the development of human telencephalon[1-3]. The prenatal establishment of the genetically driven number and size of the elements that constitute the neuronal architecture of the telencephalon (e.g. number of axonal fibres and neurons)[4-6] is the basis for the lifelong neuronal reorganisation (e.g. synapse pruning, dendrite growth, axonal overgrowth, axonal retraction and myelinisation)[7]. Our hypothesis was driven by the experimental data[5, 6] and data from literature according to which the results of early alteration of histogenetic prenatal events can be seen in childhood too[8, 9]. Thus, we have tested the effect of the premature birth and birth weight on the regional size of cerebral cortex (cortical thickness and cortical surface) at school age.

## Material and Methods

MR images of the 40 prematurely born children (Gestational age (GA)=28.80±3.05 gestatational weeks (GW)) scanned at school age (6.62±0.48 years) were acquired using the MPRAGE 3D protocol of the 3T Siemens TrioTim System. We have calculated the sex-, gestational-age specific z scores (-0.47±1.3) of the birth weight (1105.25±440 g) for all the subjects included in our study. Furthermore, we divided the subjects in two groups. Intrauterine growth restricted subjects (N=13) and premature subjects with adequate growth (N=27). IUGR was defined as GW below 10th-percentile for GA and gender, and based on criteria of placental insufficiency according to intra-uterine growth assessment, prenatal ultrasound and Doppler measurement within the umbilical artery. High-resolution T1 weighted images ($1x1x1mm^3$) were processed using the CIVET[10], a fully automated pipeline developed at the Montreal Neurological Institute, ACE Lab[11]. The extraction of the surfaces and the expansion to the pial surface was fully automated[12] and was based on the previously classified images[13]. Surfaces were extracted by hemisphere, with 81920 triangles and 40962 vertices[14, 15]. The thickness of cortex, defined at the surfaces vertices, was evaluated between the white and grey extracted surfaces. The thickness was measured by taking the absolute distance between corresponding vertices on each surface after the surface registration[14, 16], and blurred with a 20mm kernel (fwhm) [17]. By first evaluating elemental areas at the vertices, the area of a triangle distributed equally (weight 1/3) to each of its three vertices, and then summing these measures over the vertices defining each region we have calculated the regional areas ($mm^2$) of the cortex (Figure 1.). The effect of the GA at birth and the z-scores on the cortical thickness was tested using the general linear model, T statistics, and the SurfStat toolbox[11]. To test the effect of the GA and z-scores on the regional size of the cortical surface (corrected for the total hemispheric surface) we used the general linear model (GLM) and the SPSSStatistics 17.0 toolbox. Significance level was set to a P-value of 0.05 after family-wise error (FWE) correction.

## Results

**Cortical surface;** *Left hemisphere* The GA had an positive effect on the percentage of the total left hemispheric cortical surface size occupied by the left frontal cortex (p=.018) and the left isthmus of gyrus cinguli (p=.013) while the group did not have an effect on the percentage of the total hemispheric surface occupied by the segmented regions (p>.2) after a FWE correction. *Right hemisphere* Using the GLM, after the removal of the GA, age at scan and gender, we found statistically significant effect of the group on the percentage of the total right hemispheric cortical surface occupied (positive for non IUGR and negative for IUGR subjects) by the right cingular gyrus (p=.021) and right insula (p=.014) while the GA, after removal of the effects by group, gender and age at scan, showed significant positive effects on the percentage of the total hemispheric surface occupied by the right cingular gyrus (p=.028) only. Furthermore, we found statistically significant positive effects of the GA and z-scores on the cortical thickness measured at 6 years of age (Fig. 2). Both GA and group had statistically significant effect on the total surface size of the left and right hemisphere (p>.005). **Cortical thickness** The effect of the GA and z-scores on the cortical thickness is shown in Fig2a and Fig2b.

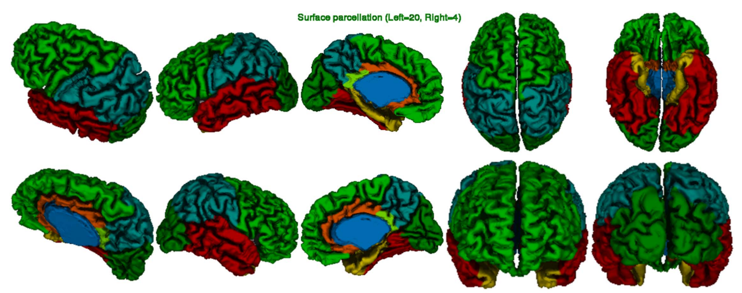


**Figure 1.** Example of the cortical surface extraction and segmentation in the cortical regions. Red (*temporal cortex),* Blue *(excluded area),* Orange *(gyrus cinguli),* Green *(frontal cortex),* Sea green (*parietal cortex),* Light green *(isthmus gyri cinguli),* Dark yellow *(parahippocampal cortex),* Yellow *(insular cortex).*

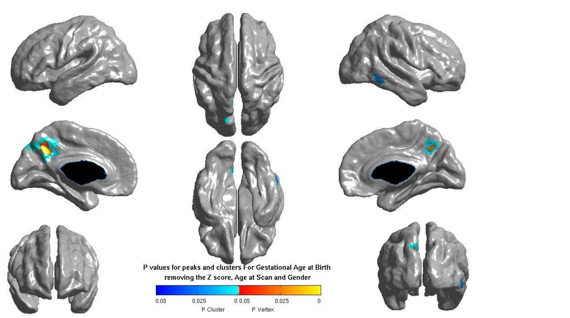


**Figure 2a** shows the effect of the GA on the regional thickness of cerebral cortex. Using the random field theory (RFT) for peaks and clusters we computed the figure above showing statistically significant P-values (>.05) for peaks and clusters. Statistically significant effects of the GA on the cortical thickness (removing the effects of z-scores, gender and age at scan) were found in bilateral areas of the precuneus and the right areas of the posterior part of the temporal gyrus. This suggests that the gestational age effect covers large regions (precuneus) as well as the local foci.

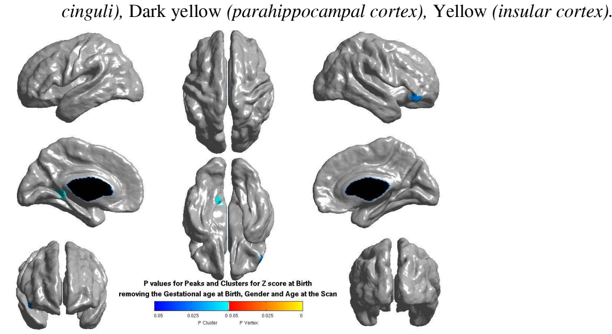


**Figure 2b** shows the effect of the z-score on the regional thickness of cerebral cortex. Using the random field theory (RFT) for peaks and clusters we computed the figure above showing statistically significant P-values (>.05) for peaks and clusters. Statistically significant effect of the z-scores on the cortical thickness (removing the effect of the gender, GA and age at scan) at childhood was found in right frontal operculum and posterior junction of the left fusiform and parahippocampal gyrus. This suggests that the z-score effect covers large regions, rather than local foci.

## Disscusion and Conclusion

Our results suggest that the birth weight deviation (z-score) and the gestational age at birth affected the cortical thickness measured in childhood within the different regions of cerebral cortex. Furthermore, while there is a similar effect of the birth weight and GA on the total size of the hemispheric cerebral surface the relative size of the regional cortical surfaces is differently affected by IUGR and GA. In conclusion, our results suggest that premature birth has more local effects (measured as a percentage of total hemispheric surface occupied by regions as well as the effect on thickness in the large regions and small foci) while IUGR is associated with effects on the more generalized parameters (size of the total surface).

**References**: *1. Kostovic, I. and M. Judas Neurosci Biobehav Rev, 2007, 2. Bourgeois, J.P. et al Proc Natl Acad Sci U S A, 1989. 3. Burkhalter, A. et al Cereb Cortex, 1993., 4. Kang, H.J., et al., Nature, 2012., 5. Antonow-Schlorke, I., et al., Proc Natl Acad Sci U S A, 2011., 6. Rakic, P., Philos Trans R Soc Lond B Biol Sci, 1991., 7. Judas, M., Fetal MRI, ed. P. D2011, Berlin Heidleberg: Springer, 8. Raznahan, A., et al., Proc Natl Acad Sci U S A, 2012., 9. Zubiaurre-Elorza, L., et al., PLoS One, 2012., 10. Ad-Dab'bagh, Y., et al Proceedings of the 12th Annual Meeting of the Organization for Human Brain Mapping, ed. M. Corbetta2006., 11. http://cbrain.mcgill.ca/., http://www.bic.mni.mcgill.ca/~alan/., http://www.math.mcgill.ca/keith/surfstat/. 12. Kim, J.S., et al., Neuroimage, 2005., 13. Tohka, J., et al. Neuroimage, 2004. 14. Lyttelton, O., et al., Neuroimage, 2007., 15. Lyttelton, O.C., et al., Neuroimage, 2009., 16. Robbins, S., in School of Computer Science2004, McGill University: Montreal, 17. Lerch, J.P. and A.C. Evans, Neuroimage, 2005.*