Cortical development in children between 6 and 11 years

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Introduction:
There is evidence that various cognitive and psychiatric disorders might stem from abnormal cerebral development during childhood [1, 2]. Therefore understanding normal cortical development is of great importance to study these abnormalities. For that purpose, we used high resolution T1 weighted MRI images from a population of 129 normally developing children to investigate cerebral gray matter (GM) development between ages 6 and 11 years. Longitudinal studies of cortical development that spanned an age range of 4 – 21 years have been reported in subjects scanned in 2-year intervals [1, 2]. Cortical development between the ages of 5 and 11 years also was investigated by Sowell et al, in which the data were collected longitudinally from a population of 45 children within 2-year intervals [3]. In all of those studies they used a technique that required exhaustive manual processing that involved tracing 30-40 sulcal and gyral landmarks on each brain image. Besides, the authors either used a metric that was difficult to interpret in terms of changes in GM morphology or sacrificed the sensitivity and spatial specificity. They defined a 15 mm diameter sphere at each cortical surface point and either a *GM density* was calculated from the ratio of GM pixels to total pixels in the sphere [1, 2] or *average thickness* was calculated within the 15mm sphere [3]. In the present study we used FreeSurfer software suite, a fully-automated brain image analysis program for cortical thickness analysis [4], which has been validated previously by numerous studies. Unlike the longitudinal studies with 2-year intervals, our cohort covers uniform, constricted age range with a much larger population. In the analysis, we first studied the changes in cortical thickness across the whole age range. Then, the same analyses were carried out in shorter age ranges, spanning only 2 years on an overlapping, sliding window. The results demonstrated that different areas of the brain underwent maturational changes during different developmental periods. The findings extend the published literature, by revealing the development of cortical thickness in a much finer spatial and temporal detail than has been previously reported.

Methods:
Subjects between the ages of 74 and 134 months (~6 – 11 years) were recruited for this study. In order to represent the normal population, 10% of the children were left-handed and 10% were prematurely born (only those born between 29 to 34 weeks' gestational age with a relatively uncomplicated neonatal course). The study was approved by the IRB of the university and written consents were obtained from the parents. T1 weighted scans were acquired in a 3T Philips Achieva system using an MPRAGE pulse sequence (FOV=240×240mm^2, 1mm^3 isotropic voxel dimensions, 150 slices, TR=11ms, TE=3.3ms, inversion pulse delay =1100ms, flip angle=18^0, no averages and no SENSE acceleration). Structural MRI scans were reviewed by a radiologist and subjects with an evidence of intraventricular hemorrhage, periventricular leukomalacia, and/or low-pressure ventriculomegaly were excluded from analysis. Cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis software (http://surfer.nmr.mgh.harvard.edu/) which computes accurate registration of brain images onto a stereotactic image and calculates maps of cortical thickness at submillimeter precision for each subject [4]. The age related changes in cortical thickness maps were analyzed at each and every node on the cortical surface using a linear regression model. Child's age in months was entered as a continuous variable and gender was entered as a categorical variable. Using this model, we analyzed age related changes in cortical thickness as well as gender based differences in cortical development. In the first analysis, all 129 subjects were entered and a linear change in thickness across the whole age range was determined. Then, the same analysis was repeated for the following age ranges: 73-97 months (74 subjects), 86-110 months (71 subjects), and 99-134 months (54 subjects).

Results and Conclusion:
Several areas showed significant thinning with age (Fig.1, blue overlays). All statistical tests were thresholded at p <0.05, corrected for multiple comparisons using False Discovery Rate (FDR). The results show significant decrease in cortical thickness with brain maturation. This cortical thinning was expressed in different anatomical locations within each time frame. Overall, significant thinning was seen bilaterally in occipital and somatosensory areas as well as temporal and frontal regions. Similar findings were also reported by others [1, 2, 3]. The causes for the loss in cortical thickness are not clearly known. Gogtay suggested that this could be driven partially by the synaptic pruning together with trophic glial and vascular changes and possible cell shrinkage. It is interesting to note that earlier changes appeared in the visual cortex and posterior temporal lobe, followed by the somatosensory cortex. Later changes appeared mostly in the temporal lobes and the frontal lobe. Even though there were a few small areas that showed gender related differences in cortical development, they were not significant at p<0.05 (FDR corrected). Thus we conclude that cortical development within this age range is not significantly gender dependent.

References: [1] *Gogtay et al PNAS 2004 101:8174-79*; [2] *Giedd et al JAACP 2009, 48:465-70*; [3] *Sowell et al J. Neuroscience, 2004, 24:8223-31*; [4] *Fischl and Dale, 2000. PNAS 97:11050-55*
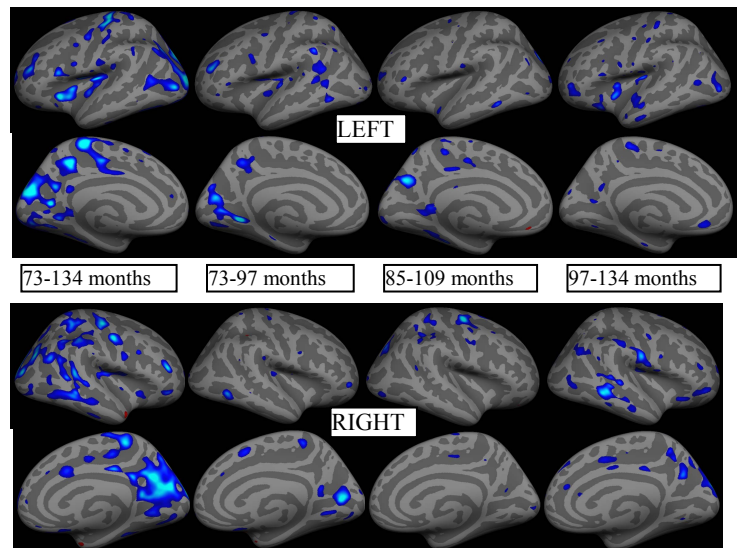
Fig.1. Inflated brain surface with statistically significant changes in cortical thickness with age shown with blue overlay. Upper row is the lateral and medial surfaces of the left hemisphere and lower row is the right hemisphere. Each column shows cortical development during the specified age range.

73-134 months | 73-97 months | 85-109 months | 97-134 months