Quantifying Typical Cortical Thickness Development in Children

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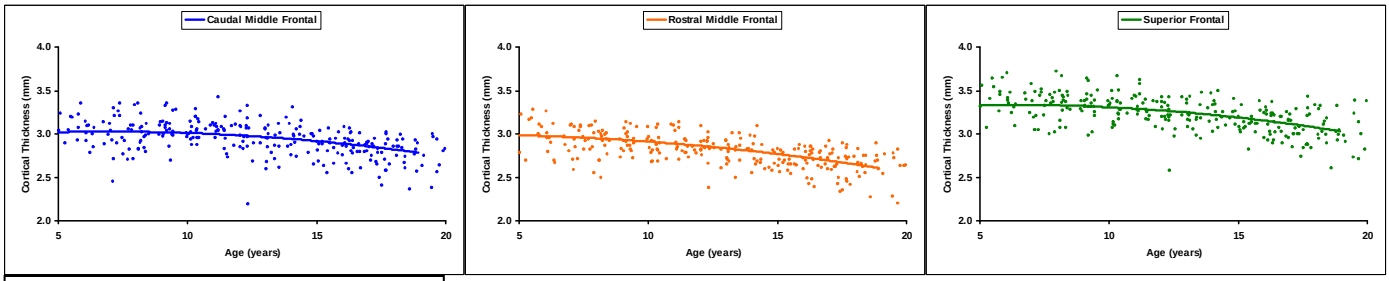
PURPOSE: Survivors of childhood cancer have significantly decreased volumes of white matter which are associated with deficits in neurocognitive function[1-4]. More recent studies have shown a direct relationship between white matter volumes and gray matter volumes[5]. Therefore, we have hypothesized that survivors of childhood cancer will exhibit significantly decreased cortical thicknesses compared to age and gender matched controls. While there are several studies reporting normal cortical thickness development in children[6-7], none have published actual models which could be used to quantify atypical development. Therefore, the first phase of our research was to develop models of typical cortical thickness development in children to serve as a benchmark for direct comparison with cancer survivors.

METHODS: 140 subjects (70 male, 70 female) from the NIH MRI Study of Normal Brain Development were selected based on age, gender, availability of 3D T1-weighted MR scans, and availability of 2 scans (approximately 2 years apart) (http://www.bic.mni.mcgill.ca/nihpd/info/). Five male and five female subjects were selected based on age at the time of the first MR for each year of age from 5-18 years. MR images consisted of sagittal T1-wieghted 3D RF-spoiled gradient echo images (TR/TE = 22-25/10-11 ms; slice thickness = 1-1.5 mm). Cortical reconstruction was performed with the FreeSurfer image analysis package (http://surfer.nmr.mgh.harvard.edu/). To generate models for each cortical region, we modeled the cortical thickness using a mixed-effects polynomial regression model which permitted the inclusion of repeated measurements per person, testing for cubic, quadratic and linear age effects using a step-down selection procedure. A random effect for each individual was included in the model to account for within-person dependence.

RESULTS: Cortical thicknesses throughout different regions of the brain averaged 2-5 mm. Each region analyzed showed a trend of steady decrease in thickness for the age range studied. While cortical regions throughout the entire brain were analyzed and modeled, we have chosen to demonstrate the results from the superior frontal and middle frontal (rostral and caudal) cortices. Only the results from the right hemisphere in female patients are shown but are very comparable for left hemisphere and males. These results demonstrate the variance in these measures and the type of models that can be produced. This data is ideally suited for either cross-sectional or longitudinal studies of pediatric patient populations with similar MR imaging to test for atypical cortical thickness development in specific anatomical regions.

Fig. 1. Plots of cortical thickness as a function of age for three structures within the right hemisphere of female subjects.



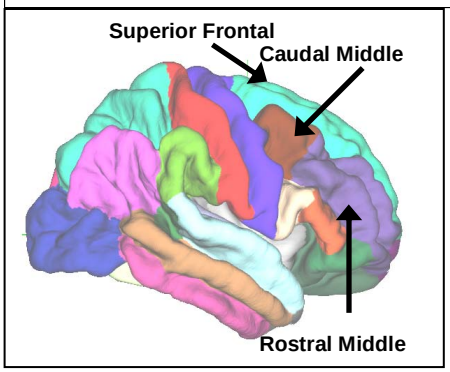


Table 1 Results of mixed-effects polynomial regression model where *Cortical thickness* = $\alpha_0 + \alpha_1(sex) + \alpha_2(age) + \alpha_3(age)^2 + \alpha_4(age)^3$. Sex = 0 (female) or 1 (male). Age is measured in years.

	α_0	α_1	α_2	α_3	α_4
Caudal Middle Frontal	2.938	0.006	0.024	-0.002	0
Rostral Middle Frontal	2.979	0.010	0.006	-0.001	0
Superior Frontal	3.261	0.014	0.021	-0.002	0

CONCLUSIONS: Children and young adults 5-18 years of age show steady rates of decrease in cortical thickness. The models that we have developed can now be used to compare with survivors of childhood cancer, as we further analyze the impact of treatment on the developing brain. In addition, these longitudinal cortical thickness development models will be made publicly available on our division website after publication. Other investigators can then use these models to test cortical thickness measures from specific anatomical regions in any pediatric population against the normal developmental trajectory.

REFERENCES

[1]Reddick WE, Cancer, 106:941-9, 2006. [2]Reddick WE, Neuroradiology, 49:889-904, 2007. [3]Reddick WE, NeuroOnc, 7:12-9, 2005.
[4]Liu AK, Int J Rad Onc, 68:992-8, 2007. [5]Zhang K, PNAS, 97:5621-6, 2000. [6]Sowell ER, J Neuroscience, 24:8223-31, 2004.
[7]Shaw P, J Neuroscience, 28:3586-94, 2008.