Feasibility of cortical thickness measures in survivors of childhood acute lymphoblastic leukemia


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PURPOSE: Pediatric patients treated for Acute Lymphoblastic Leukemia (ALL) have a 5-year event free survival of nearly 93% [1]. However, neurotoxicity is still a relevant issue, and ALL survivors remain subject to increased cognitive impairments in attention and working memory secondary to disease and treatment [2]. While several studies have identified white matter damage during therapy [3], little attention has been focused on the cortical regions subserved by these fiber tracts and the potential impact of changes in cortex on neurocognitive performance. The goal of this study was to determine the feasibility of assessing cortical thickness development in survivors of childhood ALL treated without irradiation.

PATIENTS AND METHODS: Twelve survivors now at least five years from end of therapy were evaluated on an IRB-approved prospective trial to evaluate the long-term effects of ALL therapy. All survivors were treated without irradiation on a combination of chemotherapy agents including high dose methotrexate given as either 2.5 or 5.0 g/m² dose adapted therapy. Patients ranged in age from 10.4 – 24.1 years of age (median 13.2 yrs) at follow-up, which was 5.8 ± 0.7 years from completion of therapy. Patients completed both neurocognitive assessment as well as an MRI of the brain.

MR imaging was performed on a 1.5T whole-body system (Siemens Medical Systems, Iselin, NJ). 3D anatomical T1-weighted imaging was acquired with an MPRAGE sequence (TR/TE/TI = 1920/2.38/1100 ms) in order to assess cortical thickness. The FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/) was used to generate cortical thicknesses from 33 different anatomical regions from each hemisphere. The cortical thickness estimates were evaluated and compared against the corresponding age and gender matched model predictions for all cortical regions from our previous work with 140 normal subjects from the NIH MRI Study of Normal Brain Development [4]. Statistical comparisons between the predicted model and the measured cortical thicknesses were completed for each of the regions.

Neurocognitive assessments consisted of measures of attention (Conners’ Continuous Performance Test (CPT)), processing speed (Wechsler Intelligence Scale for Children–IV or Wechsler Adult Intelligence Scale-III), and working memory (N-Back). The neurocognitive measures were then statistically compared to all regions that showed significantly different or trending differences in cortical thickness compared to the predicted model.

RESULTS: FreeSurfer was able to process the patient examinations with minimal editing of the white matter / gray matter surfaces. Once an average cortical thickness was evaluated for each of the regions throughout the whole brain, independent samples t-tests demonstrated significantly thinner cortex or trends of thinner cortex in thirteen frontal and temporal regions labeled on Figure 1 on at least one if not both sides of the brain. The remaining regions were not significantly different from the model. Neurocognitive testing revealed significant correlations among attention (p<0.01) and working memory (p<0.05) with caudal anterior cingulate. Thinner cortex was associated with poorer performance. Also noted was a significant correlation between processing speed (p<0.05) and superior temporal and temporal pole cortical thickness with thinner cortex being associated with slower processing.

CONCLUSIONS: We were able to successfully extract average cortical thickness values from regions throughout the brains of 12 childhood cancer survivors using the FreeSurfer software to analyze MPRAGE images acquired at 1.5T demonstrating the feasibility of these measures. Even with this limited sample size, we demonstrated significantly thinner cortex in regions of the frontal and temporal lobes of survivors which were associated with decreased performance in specific neurocognitive domains of attention, working memory, and processing speed.

REFERENCES: