Functional and Structural Alterations in the Frontal Lobe in Acute Lymphoblastic Leukemia: A Combined fMRI and Voxel-Based Morphometry Study

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INTRODUCTION: Childhood Acute Lymphoblastic Leukemia (ALL) is the most common type of childhood cancer[1]. With increasingly effective treatments for ALL leading to improved survival, long-term effects of cancer and cancer therapy have become an important focus of investigation. Outcome studies have identified neurocognitive deficits in ALL[2-3]. Chemotherapy-induced neurotoxicity is suspected as the cause of the deficits[4-6] but the mechanisms and locations of such pathophysiology are not well understood. To assess brain cognitive function and cerebral morphology, we analyzed both fMRI and voxel-based morphology (VBM) from the brain scans of children with ALL who were treated with prophylactic CNS-directed chemotherapy without cranial radiation. Our study design included developmental cohorts who varied in time since diagnosis and completion of treatment, so that recovery and cerebral plasticity effects could be examined.

METHODS: Participants included 30 children with ALL and 10 age-matched normal controls (mean age 14.0 ± 2.3 yrs). ALL patients consisted of 3 cohorts: cohort I (12.8 ± 3.7 yrs, n=10) who had been receiving maintenance therapy for 1-3 yrs after diagnosis, cohort II (12.2 ± 3.2 yrs, n=10) and cohort III (12.3 ± 2.1 yrs, n=10) who had completed therapy for 3-5 yrs and >5 yrs, respectively. Participants underwent standardized neurocognitive tasks. All MRI data were acquired on 3.0 T (SIEMENS, Trio) with 8-channel head coil. For fMRI studies, EPI images (TR/TE/FA=3000 ms/30 ms/90°, 5 mm slice thickness, 25 axial slices, and 80×80 matrix size) were acquired during execution of N-Back, a number working memory task with 1-back and 2-back loads of information processing. Presentation was comprised of 3 runs of a 6-second instructional slide, and 30-second baseline, 30-second experimental, and 15-second rest conditions. fMRI data were processed with SPM5 software including following steps: realignment, co-registration of T_1-weighted images with fMRI images, spatial normalization, and smoothing).

For VBM analysis, high resolution T1-weighted images (3D-MPRAGE, TR/TE/FA= 2300 ms/2.98 ms/9°, isotropic 1-mm voxel) were acquired. To avoid bias from adult brain templates, customized pediatric brain probability maps were generated based on participants' age and gender[7] (Fig. 3). Original T_1 images were then segmented and spatially normalized into GM/WM/CSF with the generated probability maps using VBM5[8]. The normalized WM images were modulated with the Jacobian matrix and smoothed with an isotropic 8-mm FWHM Gaussian kernel. Differences in age, gender, and total intracranial volumes were included as covariates in the analysis.

One-way ANOVA was used for between-group comparisons. Conjunction analysis was used to detect common activation difference between the three ALL patient cohorts and the control group.

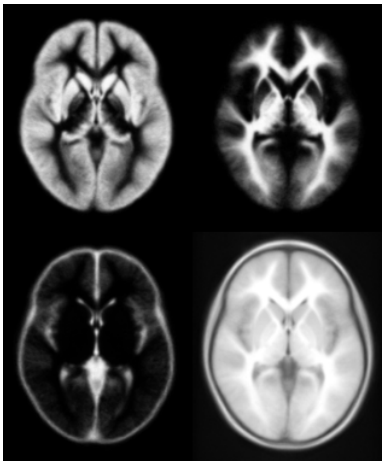

Fig. 3 Customized pediatric brain probability maps of GM/WM/CSF and the T1 template based on all participants' age and gender

RESULTS & DISCUSSION: The cumulative dosage of the chemotherapy agents did not differ among the three cohorts; all but one participant had normal levels of hemoglobin. Compared to controls, the 3 ALL cohorts had significantly lower in-magnet working memory scores. fMRI analysis revealed stronger activation in the medial frontal cortex commonly to the 3 ALL cohorts compared to controls during the working memory task. This may represent the fact that the ALL cohorts had to work harder on the same task, and yet did not perform as well. VBM analysis uncovered a significant decrease in bilateral white matter (WM) volume of the medial frontal lobe of the ALL cohorts compared to controls (Fig. 4). This morphologic finding is consistent with previous findings[4, 6] and suggests both a more acute and perhaps more enduring treatment effect of prophylactic CNS–directed chemotherapy. The maturation and growth of regional WM, especially in the frontal lobe, plays a vital part in cognitive development. WM volume loss (or developmental delay in its growth) in the frontal lobe has been linked to deficits in attention, working memory, academic achievement and intelligence[4-6] and may be linked with cortical overactivation as a compensatory processing mechanism. Our data provides important insight, identifying an affected brain region common to ALL cohorts at various time intervals since treatment with converging methods of analysis. Both cognitive and educational interventions may help counter these anatomical, functional, and neurocognitive effects. Longitudinal studies and larger sample sizes are needed to further explicate and confirm longer-term sequela.

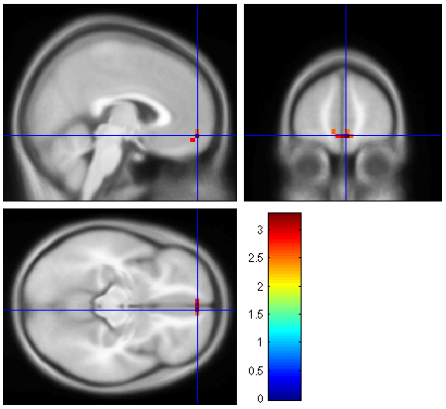

Fig. 1 fMRI analysis for 1-back test shows an overactivation in the medial frontal cortex in all ALL cohorts compared to controls. A color bar indicates T-score. Conjunction analysis, $p < 0.01$ uncorrected

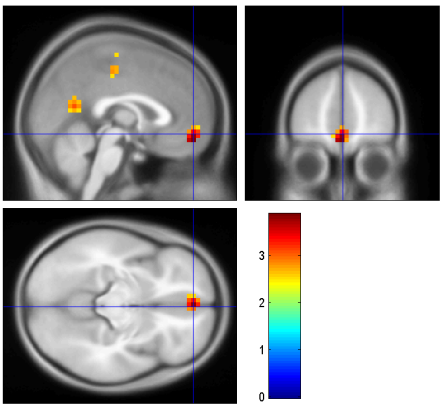

Fig. 2 fMRI analysis for 2-back test revealed strong overactivation in the medial frontal cortex in all ALL cohorts compared to controls.
Conjunction analysis at $p < 0.01$ uncorrected

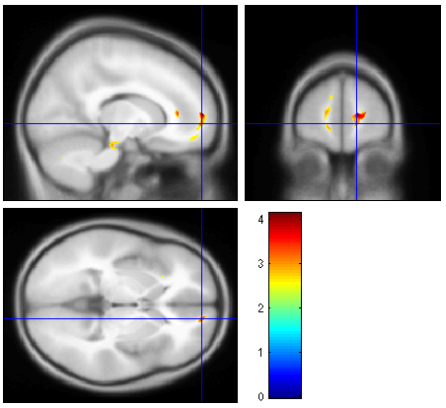

Fig. 4 VBM analysis shows decrease in medial frontal white matter volume in ALL patients compared to controls. Conjunction analysis at $p < 0.005$ uncorrected

REFERENCES: [1]American Cancer Society, 2006; [2]Farzin-Gohar *et al*., 2010; [3]Brown *et al.,* CAN, 1992; [4]Carey *et al*., AJNR, 2008; [5]Lesnik *et al*., Arch Neurol,1998; [6]Reddick *et al*., Cancer, 2006; [7]Wilke *et al*., NeuroImage, 2008; [8]VBM5, http://dbm.neuro.uni-jena.de/vbm.

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