Structural neuroimaging phenotype of dementia in adult survivors of childhood ALL

Wilburn E. Reddick[1], John O. Glass[1], Nan Zhang[2], Ronald C. Peterson[3], Larry E. Kun[1], Ching-Hon Pui[4], Melissa M. Hudson[4], Leslie L. Robison[5], Kevin R. Krull[5], and Gregory T. Armstrong[5]

[1]Radiological Sciences, St. Jude Children's Research Hospital, Memphis, TN, United States, [2]Biostatistics, St. Jude Children's Research Hospital, Memphis, TN, United States, [3]Neurology, The Mayo Clinic, Rochester, MN, United States, [4]Oncology, St. Jude Children's Research Hospital, Memphis, TN, United States, [5]Epidemiology & Cancer Control, St. Jude Children's Research Hospital, Memphis, TN, United States

PURPOSE: Survival rates for most childhood cancers have improved significantly over the last four decades resulting in a growing population of adult survivors of childhood cancer, with current estimates that one in every 640 young adults between the ages of 20 and 39 is a survivor of a pediatric malignancy [1]. As survivors age, global brain injury from early cranial radiation therapy (CRT) may reduce cognitive reserve, placing them at risk for early onset dementia or memory impairment [2,3]. Our objective was to determine whether neuroanatomical characteristics of dementia (e.g. reduced hippocampal volume, thinner parietal and frontal cortices, and loss of white matter integrity) were associated with memory impairment in this unique cohort of patients.

PATIENTS AND METHODS: Eighty-five subjects treated for childhood acute lymphoblastic leukemia with CRT before 16 years of age, and who were at least 25 years of age at the time of follow-up were evaluated on an IRB-approved prospective trial to evaluate prevalence of memory impairment and associated neuroanatomical characteristics. Patients were 27-51 years of age (mean 36.5±6.2 years) at the time of imaging.

Structural MR imaging was performed on a 3T whole-body system (Trio, Siemens Medical Systems, Iselin, NJ). 3D-T1-weighted, T2-weighted, and FLAIR-weighted imaging sets were acquired, registered to the ICBM average 152 T2 atlas aligned in Talairach space, resampled to a 1 mm isotropic resolution, intensity corrected [4], and segmented by tissue class [5,6]. White matter, gray matter and CSF volumes were assessed for frontal, parietal, occipital, and temporal lobes. Diffusion tensor imaging was acquired with twelve non-collinear, non-coplanar diffusion gradient directions and voxel-wise tensor calculations were performed with the DTI toolkit under SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) to generate maps of fractional anisotropy, radial, and axial diffusivity. After registering the parametric maps to the atlas space, average values for each parameter within the segmented white matter regions were assessed for each lobe. The T1-weighted MR imaging set was further processed with the FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/) to assess cortical thickness and hippocampal volumes.

Neurocognitive testing was conducted using the Wechsler Memory Scale IV, including four composite memory domains (Immediate, Delayed, Auditory and Visual Memory), the Brief Cognitive Status Exam, the Brief Cognitive Status Exam, and the Wechsler Abbreviated Scale of Intelligence. Impairment for each memory test was defined as an age-adjusted z-score lower than 1SD below the normal mean. Comparison of structural neuroimaging measures between impaired and unimpaired survivors for both immediate and delayed memory function were assessed using t-tests.

RESULTS: On MRI structural imaging assessment, impaired immediate memory was associated with smaller right (p=0.020) and left (p=0.008) temporal lobe white matter volumes (Figure 1A), and on diffusion tensor imaging, with increased radial diffusivity, an inverse measure of white matter integrity, in the right parietal (p=0.037) and temporal lobes (p=0.028) (Figure 1B). Smaller right hippocampal volumes in region CA2-3 (Figure 1C-D) were associated with impaired immediate (p=0.020) and delayed memory (p=0.019) while smaller volumes in region CA4-Dentate Gyrus was associated with impaired delayed memory (p=0.019). Impaired delayed memory was also associated with thinner bilateral parietal and frontal cortices (Figure 1E-F).

CONCLUSIONS: Survivors with memory impairment demonstrated a structural neuroimaging phenotype characterized by elevated diffusivity in the temporal-parietal memory network, atypical cortical thinning of the medial orbito-frontal and parietal regions, and smaller hippocampal volumes in regions CA2-3 and CA4-Dentate Gyrus. These characteristics are most consistent with early aging and increased risk for memory impairment in these childhood cancer survivors.

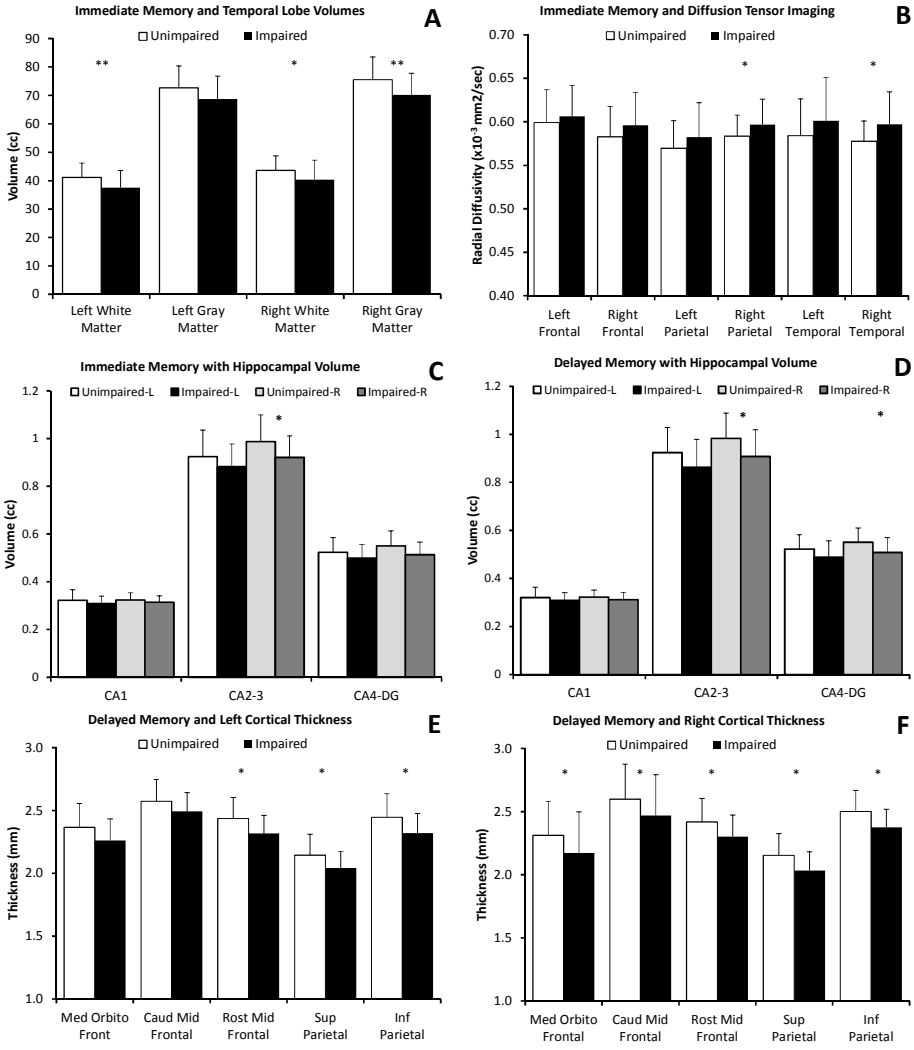

Figure 1. Neuroimaging phenotype for survivors with impaired memory (* $P<.05$; ** $P<.01$).

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