Gray Matter Perfusion and its Association with Neurocognitive Performance to Evaluate Late Effects of Cancer Treatment
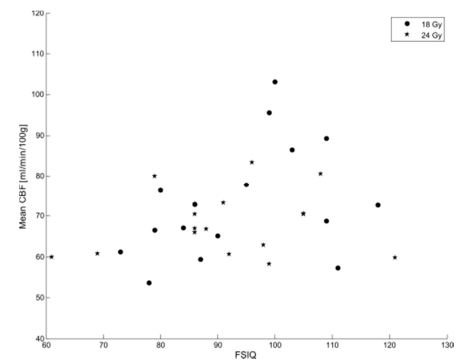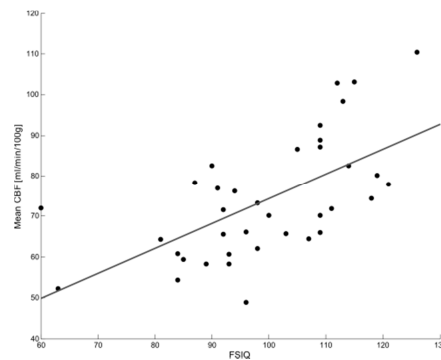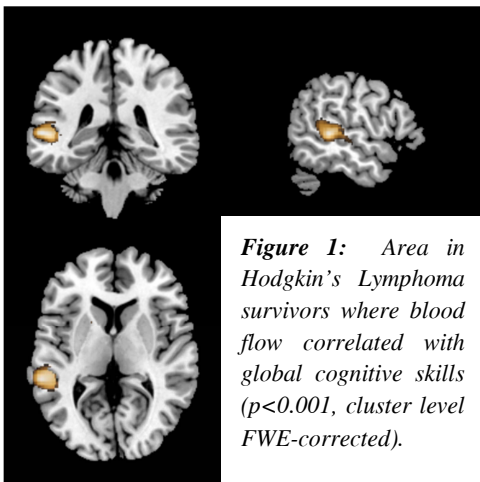
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Introduction: Cancer treatments have greatly improved over the last decades raising survival rates for Acute Lymphoblastic Leukemia (ALL) from 5-10% in the early 1960's to over 93% today [1]. Consequently, late effects of treatment with radiation and chemotherapy have become more apparent. Expanding our knowledge in this area is necessary to derive effective treatment options that simultaneously minimize late effects for future patients. Children treated with cranial radiation (CRT) for childhood leukemia are at significant risk of developing cognitive problems [2] as are long-term survivors of Hodgkin Lymphoma (HL) treated with thoracic radiation (TR) [3]. The purpose of our study was to explore the association between gray matter (GM) perfusion assessed by arterial spin labeling (ASL)-MRI and neurocognitive function in long-term adult survivors of ALL and HL.

Methods: ASL-MRI was measured in long-term adult survivors of ALL and HL who were treated about 20 years previously in IRB approved studies. Global cognitive skills were assessed using the Wechsler Abbreviated Scale of Intelligence [4]. ALL survivors were divided into two subgroups by CRT dose: 18Gy (F=9, M=8, age=25.6y ±3.9y, FSIQ=93.7±13.2) or 24Gy (F=10, M=7, age=26.9y±3.1y, FSIQ = 91.5±14.5). HL (F=18, M=20, age=41.5y±3.9y, FSIQ=99.5±14.7) survivors received TR but no CRT. ASL-MRI (Q2TIPS) measurement parameters were: TE/TR =23ms/2280ms, TI1/TI2=700ms/1400ms, FOV=210x210mm, matrix=64x64, slice thickness=5mm, 11 slices. Quantitative CBF measures were calculated [5] using MATLAB. SPM8 was used for the remaining image processing. The ASL images were coregistered and resliced according to the 3D high-resolution T1w MPRAGE acquired during the exam. GM was segmented from the T1w images and nonlinearly realigned to create a group GM template and was normalized to MNI space using DARTEL. The deformations from the nonlinear warping were applied to ASL images and smoothed with a 12mm Gaussian kernel. To account for natural physiological variation in CBF (e.g. age), exams were normalized according to their global GM CBF. Standard general linear model (GLM) analysis was used to test relationships between global cognitive skills (FSIQ) and blood flow. P-values <0.05 FWE-corrected at cluster level were considered significant.

Results: GLM analysis identified a significant (p<0.001) region in the left superior temporal gyrus (figure 1) where GM resting state blood flow was correlated with FSIQ performance in HL survivors (figure 2). In the ALL survivors, no correlation in the brain was found between CRT and blood flow or between FSIQ and CRT dose (Figure 3).

Figure 1: Area in Hodgkin's Lymphoma survivors where blood flow correlated with global cognitive skills (p<0.001, cluster level FWE-corrected).

Figure 2: Correlation of increased resting state CBF in the area depicted in figure 1 with improve cognitive performance in survivors of Hodgkin's Lymphoma.

Figure 3: No correlation of resting state CBF in the area depicted in figure 1 with cognitive performance in survivors of Acute Lymphoblastic Leukemia.

Discussion/Conclusion: The coupling of blood flow and brain function is routinely applied in functional MRI. A higher resting state CBF in the area of left superior temporal gyrus in long-term survivors of HL was found to be associated with improved cognitive performance (FSIQ). Resting state CBF was not correlated with cognitive performance in ALL survivors who receive CRT. Our data suggest either a decoupling of blood flow and cognitive performance due to CRT, or cardiovascular driven cognitive performance in survivors treated with TR. It cannot be determined if this pattern is the result of group differences between the ALL and HL survivors or other treatment related factors like age at treatment. The ALL survivors had CRT very early in their life. Although the HL survivors were more cognitively normal, they are known to have increased risk of cardiac complications due to anthracycline chemotherapy or thoracic radiation [6-7], which could disrupt a normal resting state CBF. Generally, it is not known if resting state CBF correlates with cognitive performance in normal healthy controls or if other areas of the brain could be found to correlate with other cognitive performance measures like working memory. Finding correlations of resting state CBF and performance measures offers a new method of examining treatment related effects.

References: [1] Pui C, et.at. NEJM. 2009;360:2730-41. [2] Nina K, et.al. J Natl Cancer Inst. 2010;102:881-893. [3] Krull K, et.al. JCO. 2012;30:3618-24[4] Wechsler D. Wechsler Abbreviated Scale of Intelligence. Psychological Corporation; 1999. [5] Wang J, et.al. MRM. 2002;48:242-54. [6] Kremer LC, et.al. Ann Oncol. 2002;13819-29, [7] Hull MC, et.al. Jama. 2003;209:2831-7