Resting State Functional Connectivity of the Hippocampus in Patients Receiving Radiation Therapy for Extra-Axial Tumors

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Target Audience: Neuroradiologists, Neuroscientists, Radiation Oncologists, Neuro-oncologists.

Introduction/Purpose: Radiation therapy to the brain can result in brain toxicity and radiation-induced cognitive decline with the hippocampus playing an important role.[1, 2] Resting state functional MRI offers an opportunity to study the effects of radiation therapy on the brain, however there has been little research so far into this area.[3, 4] We aim to evaluate differences in the functional connectivity of the hippocampus in the pre- and post-radiation therapy brain by evaluating resting state functional MRIs performed in patients with extra-axial tumors.

Methods: BOLD sensitized 2D EPI (TR/TE = 2000/30 ms; FA = 75°; FOV = 240x240x150 mm; voxel size = 3x3x4 mm) was used to acquire functional MRI without an explicit task (resting state functional MRI) prospectively on Radiation Oncology clinic patients undergoing brain MRI on a 3 T scanner (GE Healthcare Systems). The above resting state fMRI (rs-fMRI) from 12 pre-radiation therapy and 27 post-radiation therapy MRIs in 33 patients (6 with pre and post imaging, 6 with pre imaging only, 21 with post imaging only) with extra-axial tumors treated with focal radiation therapy (stereotactic radiosurgery) were analyzed in this study. Acquired data were processed through a standardized processing pipeline using custom built software from GE Global Research for motion correction, registration to anatomical images, registration to MNI atlas, physiological nuisance removal (using CompCor)[5], spatial Gaussian smoothing (FWHM of 6 mm), and temporal band pass filtering to restrict signal bandwidth to 0.01 to 0.1 Hz. Seed regions for left and right hippocampal area associated with the default mode network were drawn as a spherical region of 6 mm radius. Pearson correlation coefficient of the mean time course of the seed region to every voxel's time course was computed to create left and right hippocampal functional connectivity maps. Fisher's transform was used to transform the connectivity values to z-scores. Pre-radiation functional networks were compared to post-radiation networks using voxel wise t-tests with cluster size constraints to account for multiple comparisons.

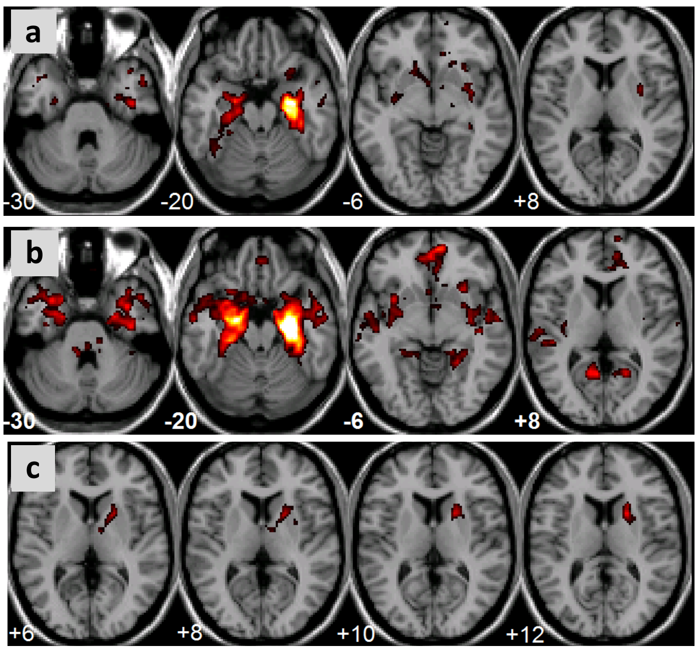

Figure 1: Right hippocampal connectivity pre-RT (panel a), post-RT (panel b), and regions showing decreased functional connectivity after RT (panel c). ***Note: Higher z-scores in the post-RT networks in panel b are related to higher statistical power (larger n).***

Results: Both right and left hippocampal functional connectivity networks showed connectivity to the contralateral hippocampus and a few default mode network regions such as medial temporal lobe and the anterior cingulate cortex (Figure 1). A statistically significant decrease in functional connectivity ($p<0.009$ after cluster-size correction) to the right putamen was encountered in the post-radiation right hippocampus networks as compared to the pre-radiation networks.

Discussion: The assessment of functional connectivity in the brain following radiation therapy with resting state functional MRI may allow potential insight into the effects and complications of radiation therapy. The irradiated brain may also offer the ability to study the effects of selective lesioning by radiation therapy if combined with volumetric dosimetry data. In this study we focused on extra-axial tumors treated with focal radiation therapy in order to help negate the effects of infiltrative tumor involvement and tumor location on functional connectivity; these patients generally received lower radiation dose to the brain than patients with intra-axial tumors, which may make our findings more subtle. We encountered evidence of altered functional connectivity between the pre- and post-radiation therapy brain in this study. Specifically, we encountered decreased functional connectivity in the right hippocampal network at the putamen in the post-radiation networks as compared to the pre-radiation networks. Since both the hippocampus and the putamen are functionally complex and heterogeneous, investigation of the relationship of this connectivity decrease to cognitive function decline is warranted. Interestingly, the left hippocampal network did not show any statistically significant difference post radiation. This right lateralized change in functional connectivity may be related to radiation received at this location due to right side predominance of tumors in our cohort. However lateralized connectivity changes of the right hippocampus has been previously reported in the setting of Alzheimer's disease.[6] Further analysis with volumetric dosimetry data to determine the radiation dose received in the right and left hippocampus is being undertaken to explore the lateralization of the hippocampal networks with subgroup analysis.

Conclusion: We provide evidence of altered hippocampal functional connectivity in the post-radiation therapy brain as compared to the pre-radiation therapy brain in a cohort of patients with extra-axial tumors. Further investigation into the functional connectivity of the post-radiation therapy brain is warranted including correlation with volumetric dosimetry data and neurocognitive function. This may provide insight into the effects of radiation therapy on brain function and ultimately may affect ultimately improve radiation therapy planning.

References:

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