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# Assessing Atrophy and Neurocognitive Decline in Hippocampal Subfields After Fractionated Brain Radiation Therapy

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**Abstract**
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## Abstract

Purpose: Radiation therapy (RT) is indispensable in the management of primary brain tumors, however many patients will inevitably experience some degree of neurocognitive decline. This relationship has been best established in a large body of research examining the hippocampus and changes in memory after treatment. We have previously described that dose-dependent atrophy can be seen in the hippocampus, yet just as the brain is a complex and interconnected organ the hippocampus itself has many subfields which subserve different components of memory. Here we examine changes in hippocampal subfield volume after RT, in relation to dose and time from treatment, as well as the association between these changes and decline in verbal and visuospatial memory.

Methodology: Data were analyzed from a prospective longitudinal clinical trial. Patients (n=85) with primary brain tumors receiving fractionated RT completed high-resolution volumetric brain MRI and neurocognitive evaluation at baseline and 3-, 6-, and 12-month intervals. Image processing using robust, validated automated parcellation segmented the bilateral hippocampi and their subfields. Neurocognitive testing was performed by certified neuropsychologists and included the Brief Visuospatial Memory Test (BVMT) and Hopkins Verbal Learning Test (HVLT). Multivariable linear mixed-effects models assessed longitudinal changes in hippocampal and nuclei volumes as well as associations between dose, volume, and decline in verbal and visuospatial memory.

Results: Atrophy was noticed in the left hippocampus at 6 months ($P = 0.032$). The left hippocampus showed dose-dependent atrophy at 12 months ($P = 0.025$), and in the right hippocampus at 3 months ($P = 0.018$), 6 months ($P = 0.016$) and 12 months ($P = 0.0087$). Poor HVLT total and delayed recall was associated with decreased volume in the left hippocampal tail ($P = 0.0098$, $P = 0.0090$, respectively) and left hippocampus–amygdaloid transitional area ($P = 0.013$, $P = 0.026$, respectively). Poor BVMT total recall was associated with atrophy of the right body of the subiculum ($P = 0.024$), right head of the presubiculum ($P = 0.045$), right body of the molecular layer ($P = 0.031$), and right parasubiculum ($P = 0.024$). Atrophy of the left hippocampal tail ($P = 0.0044$) was associated with poor BVMT delayed recall.

Conclusions: Significant overall atrophy was only noted in the left hippocampus at 6 months; however, dose-dependent atrophy was found in the bilateral hippocampi. Decrease in verbal and visuospatial memory was generally associated with left-sided hippocampal subfield atrophy, while decrease in visuospatial memory was associated with right-sided hippocampal subfield atrophy.