Mapping the Maze of Time: Unraveling Chronological Age-Induced Structural Transformations in the C57BL6 Mouse Brain

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A comprehensive investigation of temporal alterations in neuronal structures can further our understanding of natural age-associated changes in neuronal function. While efforts are underway to curate mesoscopic connectomic databases describing natural and pathologic structural alterations in humans, to our knowledge, no equivalent measures have been comprehensively pursued in mice. To better define age-related disease-independent changes in a murine model, we used a multimodal approach via Diffusion Tensor Imaging and a powerful analyzation software [DSI Studio] in young and old *ex vivo* C57BL6 mice brains (n=4/age group) segmented into 12 areas and 356 subregions. In addition to volumetric comparison, age-related changes in white matter integrity were assessed via two anisotropic measures, and the impact of such changes on neural networks were calculated via network analysis. Consistent with human findings, we observed volumetric decreases in cortical and hippocampal areas in aged mice compared to young controls. However, we observed age-related increases in brainstem nuclear volumes—findings not previously shown in humans. Next, to assess white matter axonal integrity, we quantified anisotropic measures where decreased fractional anisotropy and increased quantitative anisotropy suggest worsening integrity. Indeed, as seen in humans, we observed both decreases in fractional anisotropy and increases in quantitative anisotropy with increasing age in the hippocampus, cortex, and associated fiber tracks bilaterally. Furthermore, aging-associated decreases in all network measures revealed compromised neural communication patterns and deleterious changes in information processing efficiency within 61 brain regions and all 12 areas. These groundbreaking findings unveil that structural age-related neuronal changes in mice mirror those in humans while simultaneously illuminating the anisotropic and network-driven aspects of age-related cognitive and behavioral changes.