

Sound Deprivation Exacerbates Region-Specific Amyloid Pathology and Cognitive Impairment in a Mouse Model of Alzheimer's Disease

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Hearing loss is a major modifiable risk factor for Alzheimer's disease (AD), but the underlying mechanisms linking auditory dysfunction to AD pathology remain poorly understood. Here, we investigated whether sound deprivation impacts amyloid-beta (A β) accumulation and cognitive decline using the 5xFAD mouse model of AD. Conductive hearing loss was induced by bilateral earplug insertion from 2 to 4 months of age in wild-type (WT) and 5xFAD mice of both sexes. Auditory function was assessed by an auditory brainstem response (ABR) test after earplug removal. ABR thresholds were elevated in both male and female 5xFAD mice, indicating a strong vulnerability to auditory deprivation of 5xFAD. While WT mice exhibited no detectable changes in A β pathology following sound deprivation, as expected, 5xFAD mice showed significantly increased A β accumulation in subcortical auditory brainstem regions, including the inferior colliculus and trapezoid body. To determine the reversibility of these effects, mice underwent a 2-month recovery period post-earplug removal. Although hearing thresholds fully recovered in 5xFAD mice, amplitude still decreased. Moreover, A β accumulation in auditory brainstem regions continued to progress. Behavioral testing further revealed impaired recognition memory, specifically in sound-deprived female 5xFAD mice, despite no changes in hippocampal A β pathology. These findings suggest that auditory brainstem pathology may contribute to cognitive deficits independently of the hippocampus, with sex-specific vulnerability. Overall, our results demonstrate that reduced auditory input accelerates AD-like pathology, specifically within the auditory pathway, and contributes to cognitive impairment, highlighting a potential mechanistic link between hearing loss and AD progression.

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