Mitigating Stress-Driven Potentiation of Amyloid Pathology via 40Hz Sensory Flicker Stimulation

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Psychological stress increases the risk of neurodegenerative disease by twofold or more, partly through maladaptive changes in brain immune function. Our previous work showed that noninvasive, periodic light and sound stimulation presented at specific frequencies (flicker) can modulate neuroimmune signaling in regions affected by stress and neurodegenerative pathology. Specifically, 40 Hz stimulation improved microglial function in the presence of amyloid pathology in unstressed 5xFAD mice. However, the combined impact of chronic stress and amyloid pathology remains unexplored, and it is unclear whether flicker can mitigate stress-related pathology in the context of neurodegeneration. To address this gap, we exposed male and female 5xFAD mice to mild chronic unpredictable stress to model the “multi-hit” interaction of stress and amyloid burden. A subset of animals was also exposed to audiovisual flicker at frequencies previously shown to alleviate stress- or amyloid-related effects. High-resolution confocal imaging (40×) and 3D machine-learning analyses in Imaris quantified total (>6 μm³) and large (>10 μm³) amyloid plaques and microglia in the hippocampus. We further examined microglia–plaque interactions to assess functional modulation by flicker. Flicker at 40 Hz (gamma frequency) mitigated stress-induced increases in aggressive amyloid deposition in stressed 5xFAD males and enhanced microglial engagement with plaques. These findings suggest that 40 Hz flicker beneficially modulates microglial function under combined stress and amyloid conditions. Collectively, our results identify stress as a potentiator of neurodegenerative vulnerability and highlight 40 Hz flicker as a promising noninvasive strategy to counteract these effects, particularly in males.