A Scalable, Cost-Effective and Noninvasive Optogenetic Platform for Probing Synaptic Plasticity in Neurodegenerative Disease Research

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Neurodegenerative diseases (NDDs), like Alzheimer's and Parkinson's, are characterized by impairment of synaptic plasticity, the brain's capacity to rewire connections critical for cognition. Yet, standard tools to investigate plasticity—such as two-photon imaging and electrophysiology—are costly, invasive, and poorly suited for high-throughput screening. This study introduces a rapid, cost-effective, reproducible optogenetic platform to address these constraints. Transgenic Caenorhabditis elegans expressing channelrhodopsin-2 (ChR2) in mechanosensory neurons were used to probe frequency-dependent behavioral plasticity as a proxy for synaptic modulation via noninvasive stimulation. Worms were exposed to 473 nm light pulsed at 5, 20, or 50 Hz for 30 minutes in the presence of all-trans-retinal (ATR). Synaptic strength was assessed via chemotactic response to diacetyl. Control groups included N2 (-ChR2/-ATR), AML1 (ChR2/-ATR), and N2 (-ChR2/+ATR), isolating ChR2-specific effects. Twenty-Hz stimulation significantly enhanced chemotaxis indices, nearly doubling baseline responses ($p < 0.00001$), while 5 Hz and 50 Hz stimulation produced attenuated, overlapping results. One-way ANOVA with Tukey's HSD confirmed 20 Hz as the optimal tested frequency for behavioral potentiation ($p < 0.05$), demonstrating frequency-tuned modulation of connectivity in vivo. This system validates a scalable, low-cost assay for probing neural circuit plasticity and pinpointing optimal patterns for synaptic strengthening with spatiotemporally precise stimulation. Future identification of stimulation conditions that support synaptic resilience positions this readout platform as a robust front-end model to accelerate neuromodulation research including optimization of transcranial magnetic stimulation.

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