PFF-Induced Lewy-Like Pathology Yields Deficits in Executive Function and Alterations in both Intrinsic Properties and Cortical Excitability in Mice

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Lewy body dementias are characterized by α-synuclein aggregation, leading to cognitive, motor, and psychiatric symptoms. Among these, executive dysfunction is especially debilitating, yet mechanisms linking α-synuclein pathology to these deficits remain unclear. The prefrontal cortex, a key hub for executive function and a region heavily affected by Lewy pathology, may play a central role. To investigate this, we used pharmacological, electrophysiological, and behavioral methods in a pre-formed fibril (PFF) mouse model of LBD at 6-week, 3-month, and 1-year time points. At each time point, we examined effects of pathological α-synuclein on layer V pyramidal neurons in the prelimbic medial prefrontal cortex (PL-mPFC). To distinguish neurons with and without α-syn inclusions, we used a novel auto-fluorescent aggregate binder, enabling real-time identification of Lewy-like inclusion-positive (LLI+) and inclusion-negative (LLI−) neurons during patch-clamp recordings. At 3- and 12-months post-injection, LLI+ neurons exhibited decreased rheobase and increased excitability, while LLI− neurons showed the opposite—elevated rheobase and reduced excitability—suggesting α-syn inclusions drive hyperexcitability in affected cells and potentially cause compensatory hypoactivity in surrounding neurons, contributing to PL-mPFC circuit dysfunction. To assess executive function, we used a pairwise visual discrimination task with reversal. At 6 weeks, both monomer- and PFF-injected mice performed similarly, indicating no early deficits. By 3 months, PFF-seeded mice showed impairments in both task acquisition and reversal accuracy, suggesting an aggregate burden–related decline in cognitive flexibility. Together, these findings provide new insights into how α-syn pathology disrupts prefrontal circuits and executive function in LBD, offering potential targets for therapeutic intervention.

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