

Tracking the Neurodegeneration and Behavioral Changes in Mice Model of Prodromal Phase Alpha-Synucleinopathy

Yasin Bari¹, Hammad Khan², Krishna Jayant²

¹Indiana University School of Medicine; ²Purdue University, Department of Biomedical Engineering

Background:

The aggregation of misfolded alpha-synuclein (α Syn) has been shown to cause neurodegeneration in a mouse model and lead to behavioral changes. While others have examined end-stage (after neurodegeneration has set in) behavioral changes in mice after α Syn preformed fibrils (PFF) seeding, the precise timeline of circuit changes and associated behavioral deficits during the prodromal phase of synucleinopathic spread is poorly understood. We set out to measure and characterize the extent to which behavior is affected by primary motor cortex (M1) PFF seeding in mice.

Experimental Design:

We quantified the neuronal cell body density at M1 layers 2/3 and 5 using immunohistochemistry cell assays to determine if there were neurodegenerative effects under the PFF seeding strategy. Furthermore, using Bonsai, a visual reactive programming language, we tracked the behavior of the PFF seeded mice for exploratory motives, decreases in which can be used to show cognitive decline. To further ascertain the effect of α Syn on vulnerable excitatory pathways in the cortex, we performed prodromal injections of α Syn PFF into the M1 of ChAT^{Cre} mice along with projection tracing in the basal forebrain.

Results:

During the first 3 months following PFF seeding, the density of neuronal cell bodies in M1 layers 2/3 and 5 remains unchanged in PFF seeded mice compared to control mice. The exploratory index of PFF seeded mice was comparable to that of control mice. These results suggest insignificant neurodegeneration and behavioral change in the first 3 months following PFF seeding.

Conclusion:

Work done previously in this lab tracking the spread of PFF in M1 shows significant spread of α Syn for 3 months following prodromal injection. The results from this work show that there is little neurodegeneration or behavioral change in that timeframe despite the significant spread of α Syn. Future work hinges on further probing this phenomenon.