ABSTRACT TITLE: TIMECOURSE ASSESMENT OF PATHOLOGY FOLLOWING BILATERAL INOCULATION OF ALPHA-SYNUCLEIN PREFORMED FIBRILS IN C57BL/6 MICE

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Objectives:

We sought to improve on previously published Parkinson's disease models based on alpha-synuclein, by studying the pathology that develops over time post-inoculation uni- or bilaterally of *in vitro* generated mouse alpha-synuclein preformed fibrils into wild type mice.

Methods:

C57BL/6J mice were inoculated with PFF either uni- or bilaterally following striatal stereotaxic cannulation. Behavior and immunohistochemistry were assessed 30, 60, 90 and 180 days post-inoculation (DPI).

Results:

No significant motor deficits were observed following uni- or bilateral PFF striatal inoculation. PFF-injected mice displayed strong Lewy-body-like pathology with hyperphosphorylated alpha-synuclein aggregates spreading from the striatum to the substantia nigra (SN), amygdala and layer IV of the neocortex. Stronger pathology was seen in striatum of bilaterally inoculated mice at 30DPI and dropping by 50% at 60DPI onwards. In the SN, the drop occurred at later DPI reflecting loss of neurons in this region. In contrast, multimeric alpha-synuclein increased from 30 to 90DPI while not altered in the unilateral model 90DPI. Formed pathological aggregates seeding potency was confirmed *ex vivo* in primary neurons, being more prominent for the 30DPI group. Substantial neuronal loss observed in the SN of bilaterally injected mice at 60DPI, 30 days earlier than the unilateral model and in the striatum between 90 and 180DPI.

Conclusions:

Inoculating PFF bilaterally into the striatum of wild type mice led to a substantial enhancement of pathology that was apparent as a much as 30 DPI with no impact in motor behavior readouts. Further investigations are required to characterize this model for testing disease-modifying therapies for Parkinson's disease.