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Age-related pathology after adenoviral overexpression of the leucine-rich repeat kinase 2 in the mouse striatum

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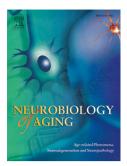
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ACCEPTED MANUSCRIPT

- 1 Age-related pathology after adenoviral overexpression of the leucine-rich repeat kinase
- 2 2 in the mouse striatum
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- 8 Abstract
- 9 Mutations in LRRK2 age-dependently cause Parkinson's disease and are associated with several inflammatory diseases. So far, the potential role of LRRK2 expression in glial cells as mediators of 10 11 neuroinflammation and the influence of aging have not been investigated in viral vector-based LRRK2 animal models. In this study we compared the effect of striatal injection of high-capacity 12 adenoviral vectors expressing either kinase-overactive LRRK2 with the familial G2019S mutation or 13 a kinase-inactive LRRK2 variant in young and old C57BL/6J mice. The intrinsic adenovirus tropism 14 guided preferential glial transduction and the vector design led to stable expression for at least 6 15 months. In histopathological analysis young mice expressing either LRRK2 variant presented with 16 17 transient vacuolization of striatal white fiber tracts accompanied by accumulation of microglial cells and astrogliosis, but inflammation resolved without permanent damage. Old mice had a stronger and 18 prolonged inflammatory reaction and experienced permanent damage in form of partial neuron loss 19 20 after 3 months exclusively in case of LRRK2_G2019S expression. The autophagic receptor p62 accumulated in cells with high levels of either LRRK2 variant, even more so in old mice. We 21 conclude that the aging mouse brain is more susceptible to LRRK2-associated pathology and in this 22 23 model glial LRRK2 expression significantly contributes to neuroinflammation, ultimately causing 24 neurodegeneration.
- 25 Keywords: LRRK2; Age; Glia; Neuroinflammation; Autophagy; Parkinson's disease; Adenoviral vector
- 26 Abbreviations²

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² Abbreviations: ALP, autophagy-lysosome pathway; CAG, CMV-IE enhanced chicken β-actin promoter with rabbit β-globin splice acceptor; CMV-IE, cytomegalovirus-immediate early; DAB, 3,3'-diaminobenzidine; dpi, days post-injection; HC-AdV, high-capacity adenoviral vector; IU, infectious units; (i)MOI, (infectious) multiplicity of infection; mpi, months post-injection; LFB, Luxol Fast Blue; LRRK2, leucine-rich repeat kinase 2; OD, optical density; PD, Parkinson's disease; SNpc, Substantia Nigra pars compacta; wpi, weeks post-injection

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