Comparative seeding of Multiple System Atrophy brain regions

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Alpha-synuclein is normally an abundant and soluble protein in the central nervous system, however, its aggregation is a hallmark of several neurodegenerative disorders such as Multiple System Atrophy (MSA) and Lewy Body disease. The induction of aggregation and propagation of alpha-synuclein pathology can be studied experimentally using pathogenic seeds derived from human disease tissue or synthetic alpha-synuclein fibrils. It has been demonstrated that the source of these seeds influences the characteristics and distribution of the resulting pathology in disease models. We have previously shown using a transgenic mouse model expressing human alpha-synuclein that the pathology induced by MSA brain lysate differs in potency and distribution from that induced by recombinant alpha-synuclein fibrils. This finding suggests strain-like properties of alpha-synuclein seeds and has prompted further investigation into brain tissue-derived seeding to model disease-relevant processes. In the present study, we make a novel comparison of seeds derived from distinct brain regions within MSA cases. The cerebellum and pons are two regions critically affected in MSA, each exhibiting distinct cell-type–specific distributions of pathology. By comparing seeding activity between these regions, we aim to understand how region-specific pathology influences seed potency and the spread of induced pathology. These findings provide insights into the determinants of alpha-synuclein seeding behavior and the development of more precise models of alpha-synuclein pathology.

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