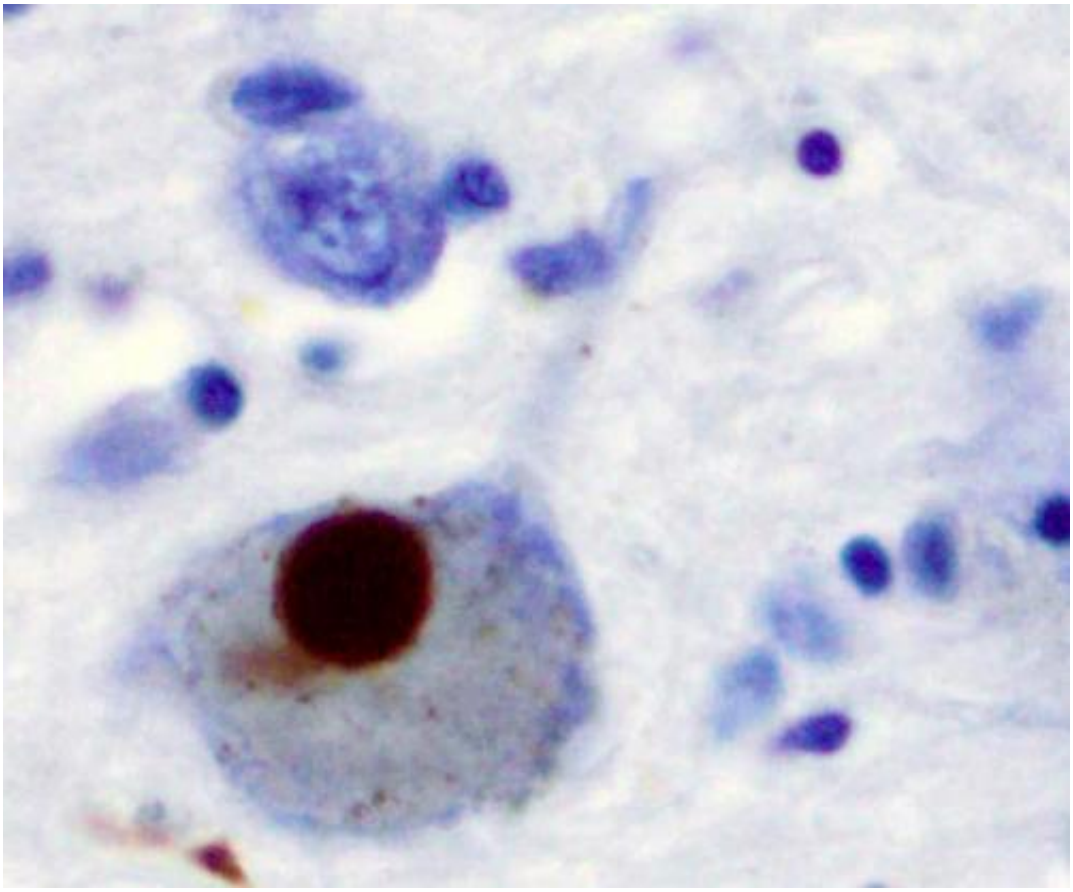
Medical Xpress

Does a prion hypothesis explain Parkinson's? The jury is still out

August 29 2019, by Delthia Ricks



Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

In recent years, neuroscientists have debated whether prion-like activity

damages the brain in people with Parkinson's, but scientists in Japan, after an exhaustive analysis, report no evidence of misfolded, transmissable proteins persisting at the core of the disease

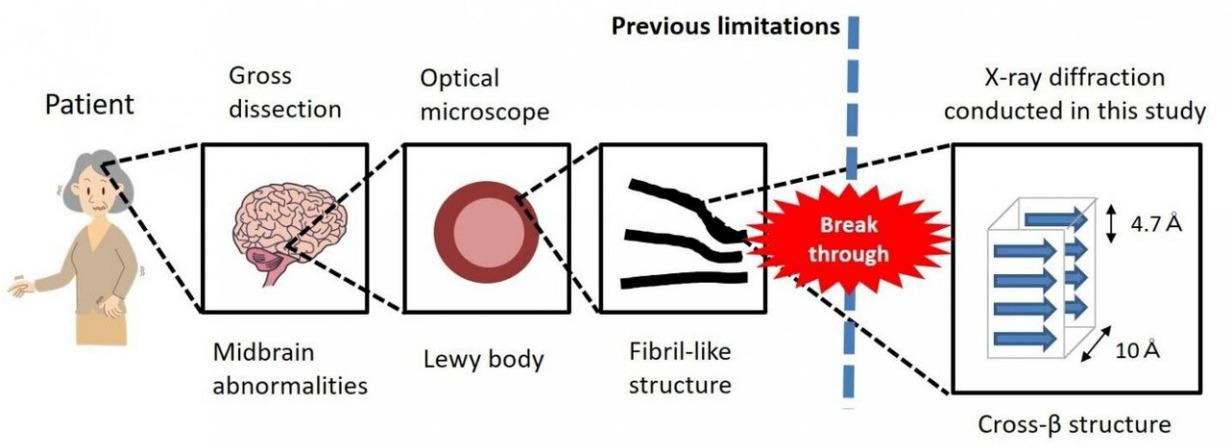
All proteins fold into complex forms that dictate function. Prions are misfolded, transmissable proteins that destroy nerve tissue and are the cause of several catastrophic but rare disorders, spongiform encephalopathies, that affect humans and animals. Creutzfeldt-Jakob, Gerstmann-Straussler-Scheinker syndrome and kuru are examples of human degenerative brain disorders caused by prions. Among animals, scrapie in sheep and bovine encephalopathy, known as mad cow disease, are prion disorders.

In healthy people, misfolded proteins are discarded by cells and broken down into their individual amino acid building blocks. Prions are lethal because they have characteristics of an infectious agent, spreading throughout healthy tissue, inducing misfolding in previously normal proteins.

In the case of Parkinson's, some scientists have suggested that prion-like mechanisms help drive the neurodegenerative processes associated with the disease. But Dr. Katsuya Araki, a researcher at Osaka University's Graduate School of Medicine, who led a large team of scientists from multiple research centers in Japan, has found no signs of prion-like activity following microbeam X-ray diffraction analyses of autopsied human brain tissue from patients with Parkinson's. The finding suggests no support for a prion hypothesis in Parkinson's disease.

The team examined a wide range of samples from patients with Parkinson's, a progressive, age-related disorder of the central nervous system. The condition is marked by tremors, muscular rigidity and slow gait. Parkinson's is further characterized by the degeneration of the brain's basal ganglia and depletion of the vital neurotransmitter

dopamine. Equally important among characteristics are the aggregates of alpha-synuclein, a protein that clumps in Parkinson's to form structures called Lewy bodies. These tissue-damaging structures are associated with brain-cell death.



Abnormal changes in the brains of patients with Parkinson's disease Credit: Osaka University

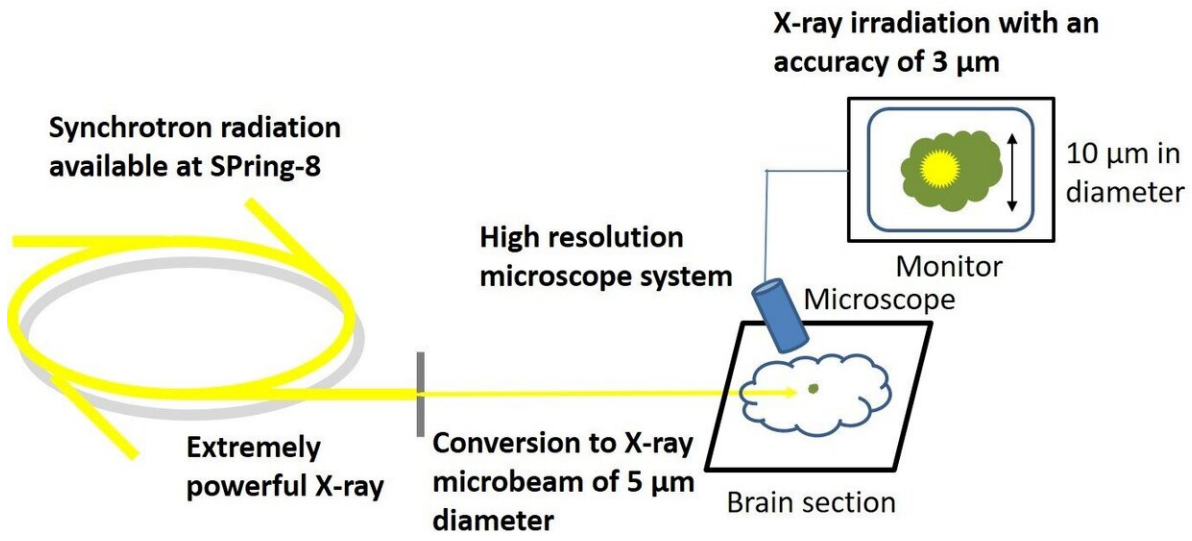
"Recently, it has been reported that aggregates of alpha-synuclein and cross-beta structures are capable of propagating within the brain in a prion-like manner," Araki and colleagues wrote in a recent issue of *PNAS* . "However, there is still no evidence that such propagation occurs in the patient's brain."

While alpha-synuclein is abundant in the healthy brain and present elsewhere in the body, it is thought to misfold in Parkinson's disease, according to in vitro and animal studies. These findings have led some neurobiologists to suggest prion-like mechanisms. Animal studies dating back years have added credence to the possibility that alpha-synuclein

may have prion-like activity, but there has never been definitive proof.

In 2012, Virginia Lee, a neurobiologist at the University of Pennsylvania, injected malformed synthetic alpha-synuclein into the brains of normal mice and observed not only the emergence of key characteristics of Parkinson's, but worsening of symptoms over time. Lee concluded the disease was spread from nerve cell to nerve cell by misfolded alpha-synuclein.

Araki and a team from a half-dozen institutions throughout Japan pursued another route. By using microbeam X-ray diffraction to study samples, scientists had a technological means to reveal links between structure and pathology, but the technique produced no evidence that alpha-synuclein had spread cell to cell.



Measurement system used in this study. Credit: Osaka University

A deeper understanding of various types of protein misfolding is beginning to emerge as a result of microbeam X-ray diffraction research, which is becoming a method of choice in the study of several disease pathologies. The technique has revealed that protein misfolding without prion-like behavior is associated with several other disorders, including cataracts, type II diabetes and Alzheimer's disease.

As a result of the new research, scientists in Japan concluded that Parkinson's shares features common to Alzheimer's, which is marked by gummy plaques made up of amyloid protein. "Our finding supports the concept that Parkinson's disease is a type of amyloidosis, a disease featuring the accumulation of amyloid fibrils of alpha-synuclein," Araki and colleagues wrote.

Numerous studies in recent years have pursued a variety of scientific questions on possible deleterious mechanisms underlying Parkinson's disease, including the prion hypothesis, which emerged more than a decade ago. Aside from the prion pursuit, other scientists have explored whether alterations in the gut microbiome are influencing the disease in the brain.

Parkinson's is a growing global health concern that impacts an inexorably aging population worldwide. Japan's population is aging faster than any other on Earth, a factor that is accelerating research on several neurodegenerative disorders in that country.

More than 10 million people worldwide are coping with Parkinson's disease, according to data from the World Health Organization.

More information: Katsuya Araki et al. Parkinson's disease is a type of amyloidosis featuring accumulation of amyloid fibrils of α-synuclein, *Proceedings of the National Academy of Sciences* (2019). DOI: 10.1073/pnas.1906124116

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