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Structure of brain plaques in Huntington's disease described

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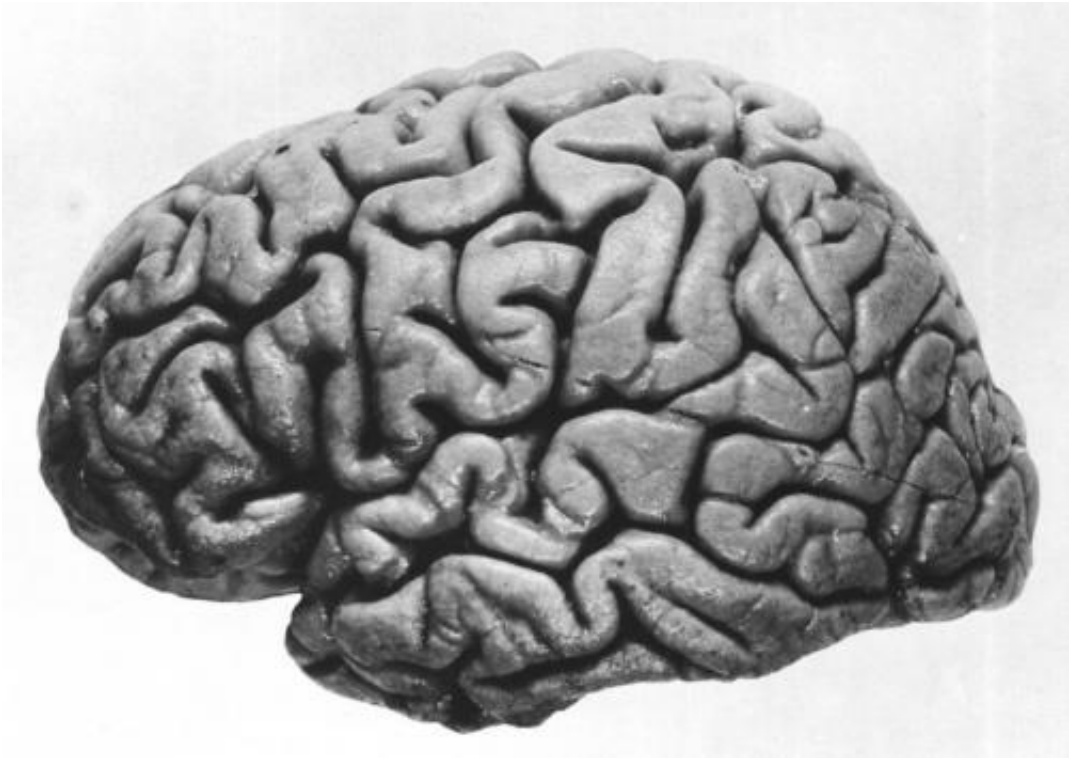

Left hemisphere of J. Piłsudski's brain, lateral view. Credit: public domain

Researchers at the University of Pittsburgh School of Medicine have shown that the core of the protein clumps found in the brains of people with Huntington's disease have a distinctive structure, a finding that could shed light on the molecular mechanisms underlying the neurodegenerative disorder. The findings were published this week in

the *Proceedings of the National Academy of Sciences*.

In Huntington's and several other progressive brain diseases, certain proteins aggregate to form plaques or deposits in the brain, said senior investigator Patrick C.A. van der Wel, Ph.D., assistant professor of structural biology, Pitt School of Medicine.

"Despite decades of research, the nature of the protein deposition has been unclear, which makes it difficult to design drugs that affect the process," he said. "Using advanced nuclear magnetic resonance spectroscopy, we were able to provide an unprecedented view of the internal structure of the protein clumps that form in the disease, which we hope will one day lead to new therapies."

The gene associated with Huntington's makes a protein that has a repetitive sequence called polyglutamine. In the 1990s, it was discovered that the patients have mutated proteins in which this sequence is too long, yet it has remained unclear how exactly this unusual mutation causes the protein to misbehave, clump together and cause the disease.

"This is exciting because it may suggest new ways to intervene with these disease-causing events," Dr. van der Wel said. "For the first time, we were able to really look at the protein structure in the core of the deposits formed by the mutant protein that causes Huntington's. This is an important breakthrough that provides crucial new insights into the process of how the protein undergoes misfolding and aggregation.

He added Huntington's is one of many neurodegenerative diseases in which unusual protein deposition occurs in the brain, suggesting similar biochemical mechanisms may be involved. Lessons learned in this disease could help foster understanding of how these types of diseases develop, and what role the protein aggregates play.

More information: Huntingtin exon 1 fibrils feature an interdigitated β-hairpin–based polyglutamine core, www.pnas.org/cgi/doi/10.1073/pnas.1521933113