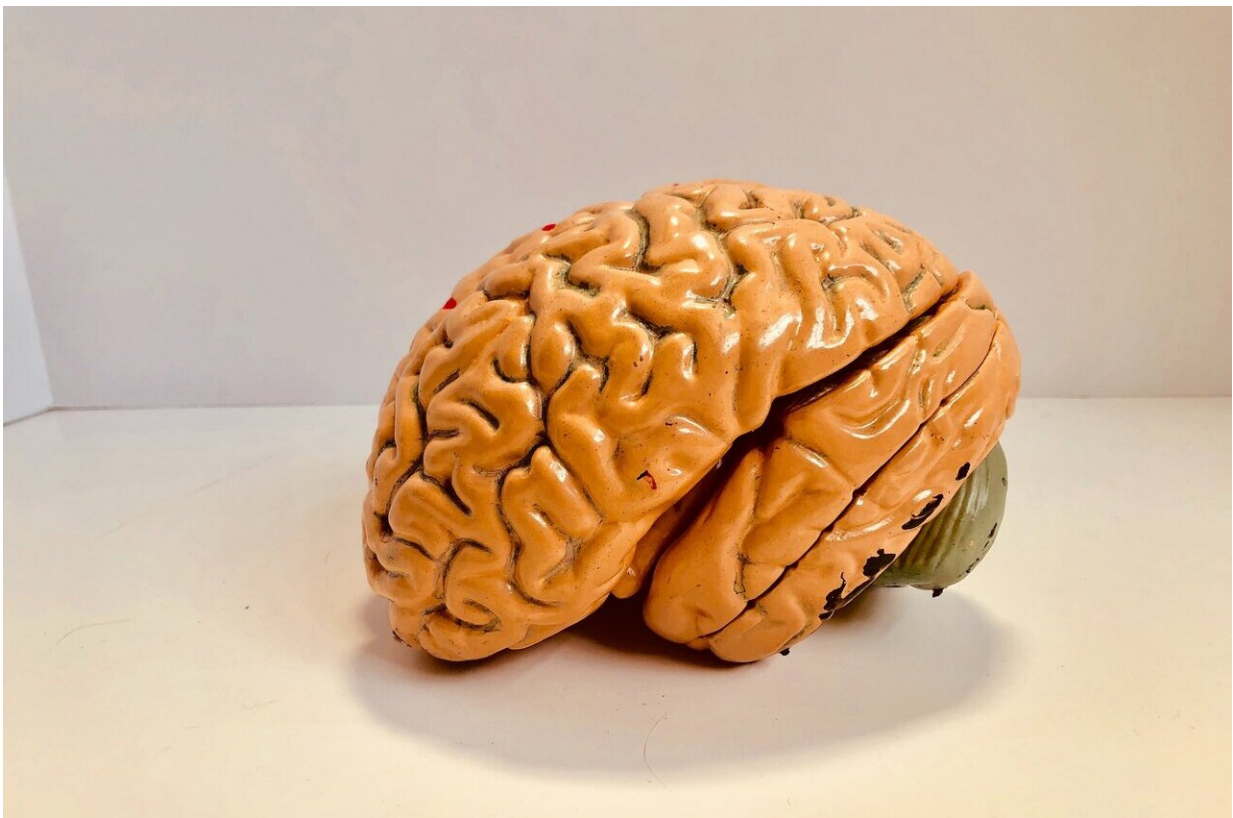


Diverse amyloid structures and dynamics revealed by high-speed atomic force microscopy

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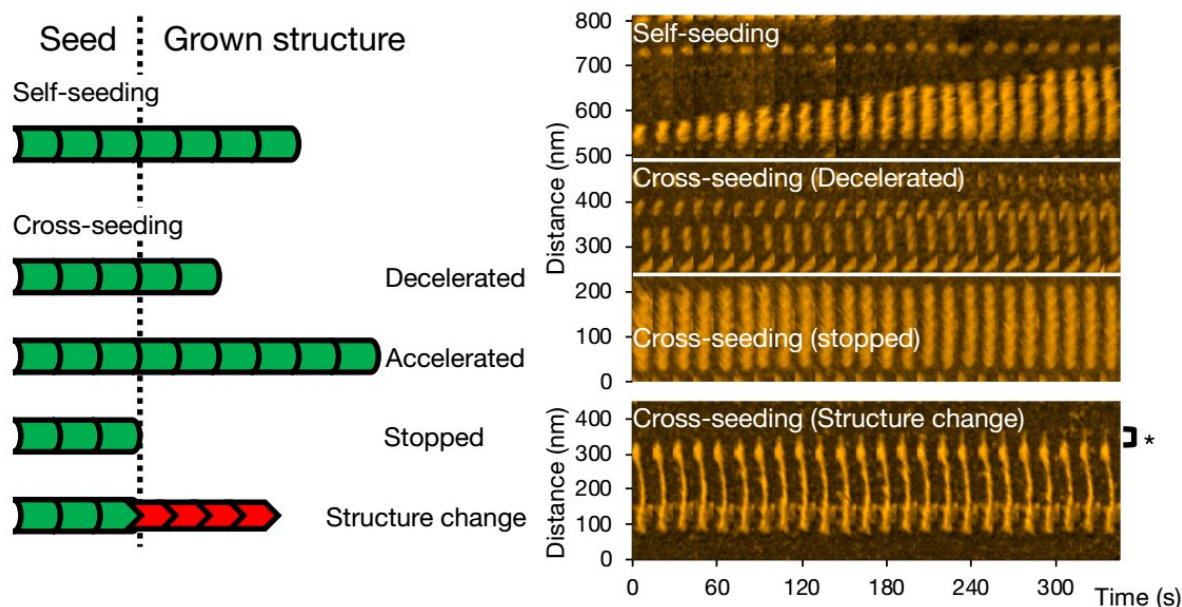
In the human body, proteins sometimes occur in fibrillar aggregates called amyloids. Although certain amyloids are known to have a

biological function, amyloid formation is often associated with pathologies, including Alzheimer's and Parkinson's diseases. Understanding how exactly amyloid fibrils form is crucial for gaining insights into the development of such diseases and for advancing with treatment approaches.

Now, Takahiro Watanabe-Nakayama from Kanazawa University, Kenjiro Ono from Showa University, and colleagues have investigated the formation process of particular amyloid fibrils using a technique enabling visualization of growth over time. The scientists specifically looked at the effect of cross-seeding ('mixing') different proteins forming aggregates, and found variations in elongation rates and the structures of the fibrils.

The researchers studied alpha-synuclein, a protein abundant in the human brain. They looked at what happened when letting wild-type alpha-synuclein molecules—the natural, most abundant variant—form aggregates, and also how aggregation is different when introducing (cross-seeding) mutant variants associated with Parkinson's disease. In addition, the scientists examined the influence of the pH level of the microenvironment in which [fibril](#) growth takes place.

By means of high-speed atomic-force microscopy (HS-AFM), Watanabe-Nakayama, Ono and colleagues could record fibril aggregation at nanometer resolution and high video rate for various cases. First, the scientists looked at the growth of single variant types (self-seeding). They found that mutants produced more aggregates, or that they aggregated faster at neutral pH than the wild-type variants. Another observation was that elongation was faster at lower pH (5.8, i.e. acidic) than at higher pH (7.4, i.e. basic).



High-speed atomic force microscopy enables visualizing and analyzing fibril formation of variants of a single protein. Credit: Kanazawa University

For cross-seeding, different scenarios can occur. Fibril growth can be accelerated or slowed down, or even stopped. The morphology of the original seed can be preserved, but it also happens that the structure of the resulting fibril is different—typical structural forms are 'straight' or 'spiral'. The researchers checked that fibril structure and dynamics as observed with HS-AFM correspond to the processes in solution by means of fluorescence experiments; similar conclusions were obtained.

The findings of Watanabe-Nakayama, Ono and colleagues are relevant for better understanding [amyloid](#)-related diseases. Quoting the researchers: "Cross-seeding combined with variations in elongation rates has the effect of increasing the structural diversity of the resulting assemblies. This diversity may be reflected in distinct neurotoxic effects

for various [protein] assemblies."

More information: Takahiro Watanabe-Nakayama et al, Self- and Cross-Seeding on α -Synuclein Fibril Growth Kinetics and Structure Observed by High-Speed Atomic Force Microscopy, *ACS Nano* (2020).
[DOI: 10.1021/acsnano.0c03074](https://doi.org/10.1021/acsnano.0c03074)

Provided by Kanazawa University

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