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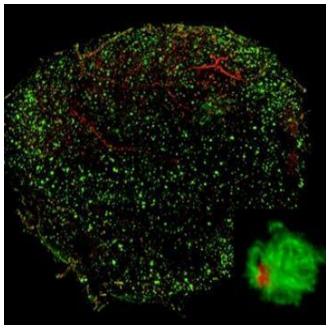
See-through Brains Ready for Study



A new technique for creating transparent tissue has enabled Japanese researchers to visualise brain anatomy in 3D, giving them new insights into Alzheimer's disease plaques. "While Superman's x-ray vision is only the stuff of comics, our method, called Sca/eS, is a real and practical way to see through brain and body tissue," says lead scientist Atsushi Miyawaki, of the RIKEN Brain Science Institute in Japan. The results are published in *Nature Neuroscience*.

In recent years, generating see-through tissue — a process called optical clearing — has become a goal for many researchers in life sciences because of its potential to reveal complex structural details of our bodies, organs, and cells — both healthy and diseased — when combined with advanced microscopy imaging techniques. Previous methods were limited because the transparency process itself can damage the structures under study.

The new technique developed by Miyawaki's team creates transparent brain samples that can be stored in Sca/eS solution for more than a year without damage. Internal structures maintain their original shape and brains are firm enough to permit the micron-thick slicing necessary for more detailed analyses.

"The key ingredient of our new formula is sorbitol, a common sugar alcohol," explains Miyawaki. "By combining sorbitol in the right proportion with urea, we could create transparent brains with minimal tissue damage, that can handle both fluorescent and immunohistochemical labelling techniques, and is even effective in older animals."

The team has devised several variations of the technique that can be used together. One of these variations allowed them to generate multicolour high-resolution 3D images of amyloid beta plaques in older mice from a genetic mouse model of Alzheimer's disease developed at the RIKEN BSI by Takaomi Saido team.

After showing how Sca/eS treatment can preserve tissue, the researchers put the technique to practical use by visualising in 3D the mysterious "diffuse" plaques seen in the postmortem brains of Alzheimer's disease patients that are typically undetectable using 2D imaging. Contrary to current assumptions, the diffuse plaques proved not to be isolated, but showed extensive association with microglia (mobile cells that surround and protect neurons).

The researchers also examined the 3D positions of active microglial cells and amyloid beta plaques. While some scientists suggest that active microglial cells are located near plaques, a detailed 3D reconstruction and analysis using Sca/eS clearing showed that association with active microglial cells occurs early in plaque development, but not in later stages of the disease after the plaques have accumulated.

"Clearing tissue with Sca/eS followed by 3D microscopy has clear advantages over 2D stereology or immunohistochemistry," Miyawaki points out. "Our technique will be useful not only for visualising plaques in Alzheimer's disease, but also for examining normal neural circuits and pinpointing structural changes that characterise other brain diseases."

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