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Imaging study reveals rapid formation of Alzheimer's-associated plaques

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The amyloid plaques found in the brains of Alzheimer's disease patients may form much more rapidly than previously expected. Using an advanced microscopic imaging technique to examine brain tissue in mouse models of the devastating neurological disorder, researchers from the MassGeneral Institute for Neurodegenerative Disease (MGH-MIND), working with colleagues from Washington University School of Medicine, find that plaques can develop in as little as a day and that Alzheimer's-associated neuronal changes appear soon afterwards. Their report will appear in the Feb. 7 issue of *Nature*.

"While we've known for a long time what amyloid plaques and other changes seen in the brains of Alzheimer's patients look like, we didn't know in what order and at what speed those changes occur," says Bradley Hyman, MD, PhD, director of the Alzheimer's Unit at MGH-MIND and senior author of the Nature paper. "Understanding the rules that govern plaque formation may lead us to ideas about how to intervene in the process."

To investigate the timing of these brain changes, the researchers used a novel technique for microscopically imaging the brains of living animals. Using several strains of transgenic mice destined to develop amyloid plaques, they imaged initially plaque-free areas of the brain on a regular basis – first weekly and, in subsequent experiments, daily. Although plaques formed rarely, they could appear as little as 24 hours after a previous plaque-free image was taken. The new plaques were similar in appearance to those seen in the brains of Alzheimer's patients and in the

mouse models, and subsequent imaging showed little change in the size of plaques once they had formed.

Earlier investigations have shown that levels of microglia – neuronal support cells that react to inflammation and other damage – rise in the vicinity of amyloid plaques. Imaging an Alzheimer's mouse model that expresses a fluorescent marker in microglia showed that the cells were attracted to new plaques within a day of formation. Although there was no evidence that microglia were actively removing the plaques, the investigators hypothesize that they may help restrict further plaque growth. Examining neurons adjacent to plaques showed that the kind of changes associated with Alzheimer's – distortions in the projections through which neuronal signals pass – appear rapidly and approach maximum effect within five days.

"These results confirm the suspicion we've had that plaques are a primary event in the glial and neuronal changes that underlie Alzheimer's dementia," Hyman says. "We hope that what we've learned about the time frame and sequence of events will help us find ways to keep plaques from forming." Hyman is the John Penny Professor of Neurology at Harvard Medical School.

Source: Massachusetts General Hospital