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# Toward Treating Alzheimer's Disease with Brain Waves

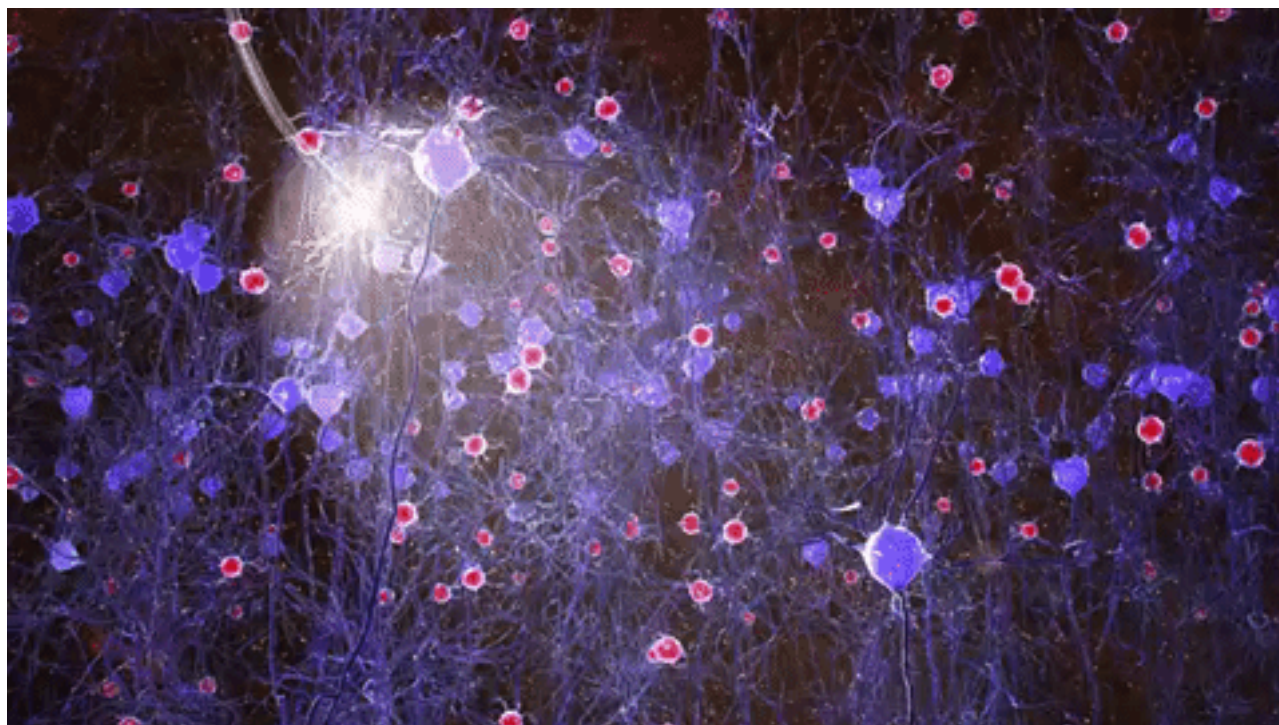
In a mouse model, researchers mitigated three Alzheimer's disease-associated symptoms by stimulating gamma waves with light.

By Ashley P. Taylor | December 7, 2016

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When brain cells fire rhythmically and in sync, they produce waves, which are categorized by their firing frequencies. Delta waves (1.5 Hz to 4 Hz), for example, are produced during deep sleep, theta waves (4 Hz

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disease pathology, according to a mouse study published today (December 7) in [Nature](#). And the restoration of these waves, researchers propose, may one day be an option for Alzheimer's disease treatment.

MIT's [Li-Huei Tsai](#), [Ed Boyden](#), and their colleagues have shown that stimulating neurons to produce gamma waves at a frequency of 40 Hz reduces the occurrence and severity of several Alzheimer's-associated symptoms in a mouse model of the disease. The researchers induced slow gamma waves using optogenetics, and by exposing the mice to flickering light—an approach they suggest could translate to human therapies.

"It's a pretty striking result that at one particular frequency with which they entrained the brain . . . they were able to reduce, in the mouse at least, all three hallmarks of Alzheimer's pathology," said [Rudolph Tanzi](#), who leads genetics and aging research at Massachusetts General Hospital and was not involved in the work.

Stimulation of gamma waves reduced levels of amyloid- $\beta$ , decreased phosphorylation of tau, and led the brain's immune cells—microglia—to perform their usual housekeeping role, clearing away cellular debris, including amyloid- $\beta$  (as opposed mounting an inflammatory response as microglia do in Alzheimer's disease, [Tanzi](#) explained).

The results are "important both for mechanistic study and also for potentially therapeutic developments," said [Yadong Huang](#) of the University of California, San Francisco, and the Gladstone Institute of Neurological Disease, who also was not involved in the work. The study suggests that "a slow-gamma deficit might be part of this [Alzheimer's disease] pathogenesis [and that] manipulating slow-gamma activity . . . could be a new way to suppress amyloid- $\beta$  production and increase amyloid- $\beta$  clearance," [Huang](#) added. Scientists have long hypothesized that decreasing amyloid- $\beta$  accumulation could help reverse—or even prevent—symptoms of Alzheimer's disease.

[Huang](#) and colleagues previously [reported](#) that, during sharp-wave ripples in the hippocampus, patterns of brain activity thought to occur during memory replay and consolidation, gamma waves were disrupted in a mouse model of Alzheimer's disease. Gamma waves [are also disrupted](#) in the brains of people with Alzheimer's disease. But exactly how gamma waves contribute to this neurodegenerative pathology remains unclear.

To learn more, [Tsai](#) and [Boyden](#) first examined gamma waves in the hippocampi of Alzheimer's disease-model mice. Compared with those of control animals, the hippocampi of the model mice had fewer gamma waves during sharp-wave ripples, but gamma waves during theta waves were unaffected.

Next, the researchers optogenetically stimulated hippocampal neurons to produce gamma waves in Alzheimer's disease-model mice that had transgenically received both a light-responsive ion channel and a fluorescent label in their hippocampal neurons. Compared with control animals (model mice that were stimulated at stochastic frequencies or mice stimulated at 40 Hz that received the fluorescent label but not the ion channel), the gamma-stimulated mice had lower hippocampal levels of amyloid- $\beta$ . Further experiments revealed that the mice that underwent gamma stimulation had reduced amyloid- $\beta$  production. Additionally, gamma stimulation led microglia to shift toward their housekeeping function and engulf amyloid- $\beta$ . The resulting amyloid- $\beta$  reductions in gamma-stimulated animals were likely due both to lower production of the protein and to microglia clearing more of it away, the authors wrote.

"Optogenetics is very precise and therefore a good way to study how cell types and oscillations can be used in potential therapeutic prototyping," [Boyden](#) said during a press briefing this week (December 6). However the procedure, as performed on mice, involves drilling a hole in the skull and injecting a transgene-delivering virus into the brain. "When it came time to think about how we could translate this to humans, we started thinking about non-invasive strategies to achieve this result," said [Boyden](#).

Their solution? Flickers of visible light—"like a strobe light, but faster," coauthor [Annabelle Singer](#) of Georgia Tech and Emory University said during the press conference—to stimulate not the hippocampus but the visual cortex.

After an hour of stimulation by an LED light flickering at 40 Hz to induce gamma waves, Alzheimer's disease-model mice had lower levels of amyloid- $\beta$  than control model mice that were kept in the dark. The



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reduction. Finally, in a mouse model of tauopathy, mice subjected to the flickering-light treatment had lower levels of tau phosphorylation associated with formation of neurotoxic tangles.

It remains to be seen, however, whether gamma stimulation can prevent memory loss or rescue learning and memory deficits, Huang noted.

Going forward, Tsai and colleagues hope to develop a technology based on this flickering-light treatment to treat Alzheimer's disease patients.

Tanzi has already developed goggles that flash light at other frequencies in order to stimulate other kinds of brain waves—such as the theta waves that can occur during meditation. "We invented this so that people could relax. The glasses are used recreationally," Tanzi said. "In the future, you could think about how this type of thing could be used to flicker at gamma to get these beneficial effects that they saw in the current study."

Tsai and some of her coauthors have started a company, Cognito Therapeutics, to develop treatments for Alzheimer's disease, including technologies based on gamma stimulation via flickering light.

"While this is promising, we have many steps to go to translate these discoveries from mice into a therapy for humans using this noninvasive technique," Singer said during the press conference. "We need to do clinical studies in humans, and we're currently working hard to do that."

H. Iaccarino et al., "Gamma frequency entrainment attenuates amyloid load and modifies microglia," Nature, doi:10.1038/nature20587.

### Tags

optogenetics, neurodegeneration, mouse study, mouse research, animal research, amyloid plaques, amyloid beta plaques and Alzheimer's disease

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This technique appears to sidestep the beta amyloid or tau discussion because it appeared to reduce levels of both and speeds up the brain's clearing function. While promising, it does not speak to the potential impact on memory loss, which is the most devastating impact of Alzheimer's.

Memory loss, whether it is a person's inability to remember what happened five minutes, let alone five days ago or the inability to recognize one's spouse or children, tears apart the fabric of everyday life and relationships with friends and family. Thus, preventing memory loss or halting its

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I own a business in Washington DC that provides caregivers for persons with Alzheimer's and memory loss.

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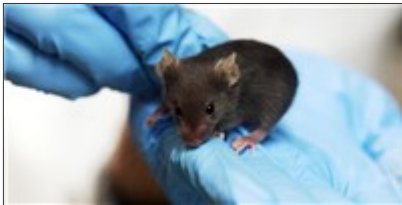
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January 14, 2017

While this finding doesn't speak to the memory loss element, other finding support the idea that reduction in beta amyloid comes with direct (and positive) impact on memory retrieval and formation. This is mentioned in the NPR RadioLab episode "Bringing Gamma Back". All of this is what lead us to start designing flickerthing, and we are crowdfunding at <http://indiegogo.com/at/flickerthing>.

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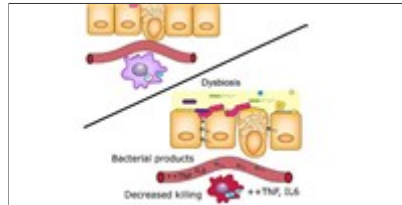
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