A pulse of hope in the fight against Alzheimer's

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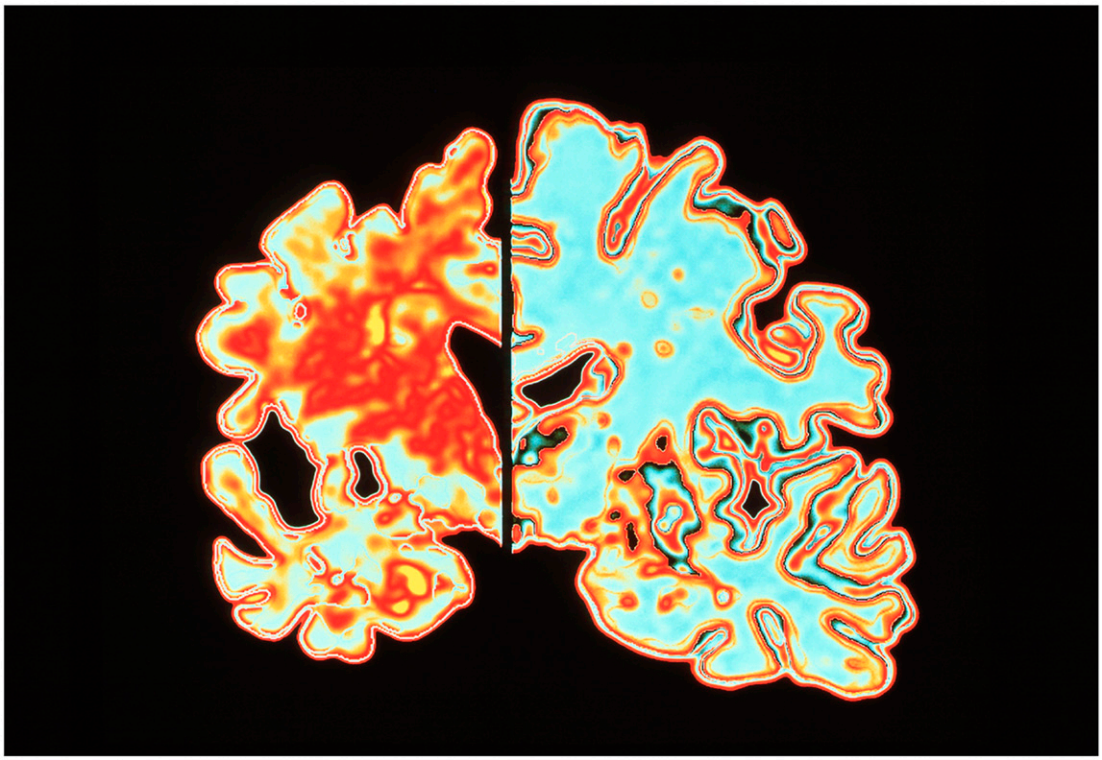
Flashes of strobe lights and the beat of stereo speakers filled the otherwise pitch-black, shoebox-sized cages. The mice inside may not have danced, but their brains caught the rhythm.

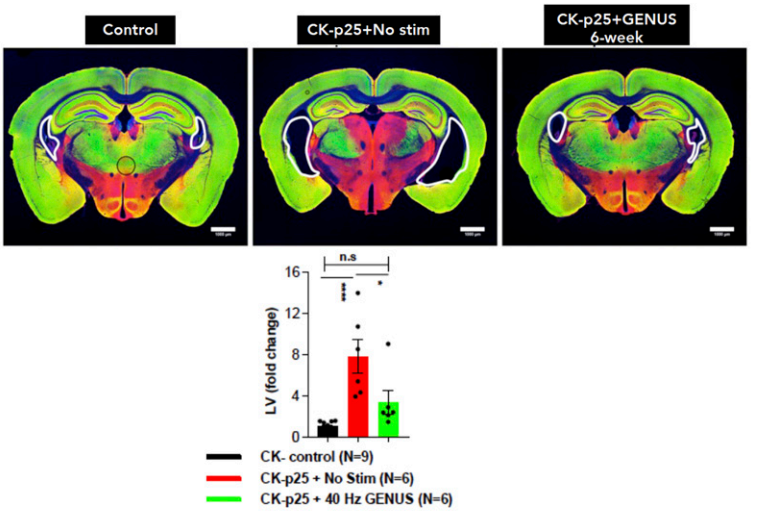
The pulses of light and sound, delivered at a frequency of 40 per second, or 40 hertz, jumpstarted the mice's neurons to fire electrical signals in time with the pulses—and subsequently reduced the number of amyloid plaques and tau protein tangles in their brains, two hallmarks of Alzheimer's disease. Hour-long sessions on seven days in the nightclub-esque boxes also improved the animals' working memory, sensory processing, and spatial navigation (1). "Every result seems to be too good to be true," says Li-Huei Tsai, director of The Picower Institute for Learning and Memory at the Massachusetts Institute of Technology in Cambridge, who led the experiment.

The synchronous rhythmic firing of neurons is critical for a healthy, functioning brain (2)—one that can accurately recall old memories and efficiently process new information. Large groups of neurons oscillating on and off together generate brain waves. Although it's not yet clear why, this synchrony seems to strengthen coordination across brain regions and between different types of brain cells.

"Brain rhythms are known to participate in all forms of cognition. And changes of brain rhythms appear to be implicated in all forms of neurological disease,"



Pulses of light and sound delivered to mouse brains at a frequency of 40 hertz appeared to reduce the number of amyloid plaques and tau protein tangles, hallmarks of the Alzheimer's brain—seen here in a coronal slice from a patient with Alzheimer's disease (*Left*), compared with normal brain (*Right*). Image credit: Science Source/Alfred Pasieka.



Researchers have shown that inducing gamma oscillations with visual stimulation (gamma entrainment using sensory stimuli [GENUS]) can prevent neuronal loss in a CK-p25 mouse model of neurodegeneration. Reprinted from ref. 14. Copyright (2019), with permission from Elsevier.

says Nancy Kopell, a math professor and director of the Cognitive Rhythms Collaborative at Boston University in MA. Growing evidence indicates that neurons in many animals, including humans, can strongly synchronize in the gamma range of frequencies—between 30 and 80 hertz, and peaking around 40 hertz. As far back as a 1955 study of meditating yogis (3), researchers have associated gamma waves with peak concentration and high levels of cognitive functioning. Studies in the last decade that manipulated brain rhythms in lab animals and humans have confirmed the impact of those rhythms on cognition and disease. Researchers have also found that fewer neurons fire together at this rate in patients with Alzheimer's disease or other neurological conditions (4), suggesting that gamma rhythms may play a role in the cognitive impairments associated with such disorders.

Now Tsai and other researchers are investigating how to enhance gamma oscillations in hopes of preventing, slowing, or even reversing damage caused by neurodegenerative conditions—without the need for drugs, surgeries, or invasive devices.

Flashes of Insight

Networks of cells in the brain's cortex, the outermost layer of the brain, have a propensity to oscillate in unison in the presence of the right stimulus, explains Wolf Singer, a neurophysiologist and emeritus director of the Max Planck Institute for Brain Research in Frankfurt, Germany. Electrochemical connections synchronize the networks.

Coordinated interactions between excitatory and inhibitory neurons sum to create brain waves. But it's the inhibitory neurons, whose task it is to ensure that our brain functions smoothly and accident free, that lead the charge in synchronous firing. "They act as conductors of the orchestra," says Jorge Palop, a neurologist at the University of California, San Francisco. His research has linked impairments in these neurons with weakened gamma waves and Alzheimer's-like dysfunction in mice (5).

Researchers are exploring several potential mechanisms for just how this synchronous firing translates into brain changes. "This very synchronous bursting pattern predictably loads inhibitory neurons with calcium," Singer says. That calcium triggers a series of biochemical reactions including the release of nitrous oxide, which is known to dilate blood vessels and increase blood flow. Singer coauthored a November study showing that gamma oscillations in cats can also alter the strength of connections between neurons (6).

And in mice, Tsai and her team have shown that inputs of gamma waves boost the activity of immune cells in the brain called microglia that clear amyloid plaques and tau tangles. Oscillating light and sound waves also increased blood flow, improved the survival and health of the animals' neurons, and bolstered their connectivity across brain regions. "All of these effects converge to reduce cognitive impairment and pathology," Tsai says.

An Urgent Need

Tsai still remembers the moment when, as a young child, she realized something was wrong with her grandmother: "She forgot how to get home." The experience continues to inspire her work. Nearly six million people are currently living with Alzheimer's disease in the United States (7). One in every three seniors dies with Alzheimer's or another form of dementia.

Yet pharmaceutical companies hunting for better treatments continue to come up short. Tsai's group hopes to change that by understanding how sensory stimulation strengthens healthy brain waves and staves off the abnormal firing patterns associated with disease. In 2009, Tsai and colleagues enhanced gamma oscillations in mice using a technique called optogenetics, in which brain cells are engineered to fire in response to a flash of light delivered through an optical fiber implanted in the brain (8). In search of a less invasive approach, the team began investigating whether sensory stimulation could have the same effect by acting as a kind of metronome for brain waves.

In 2016, they discovered that exposure to 40-hertz flickers of light could drive 40-hertz gamma power and reduce amyloid plaques in the visual cortex of the mouse brain (9). But it was only when combining the light and sound in their latest study that the gamma entrainment, or brainwaves aligned to the frequency of a given beat, propagated across the entire brain, making it feasible as a therapy.

Barry McDermott, a researcher with the Translational Medical Device Laboratory at the National University of Ireland Galway, remains cautious about the clinical promise of 40-hertz therapies. Like pharmaceutical studies, gamma wave research builds on studies in rodents. And rodents don't actually get Alzheimer's. They're merely engineered to showcase some of the physical and behavioral hallmarks of the disease, including amyloid plaques. "Still, we absolutely need some innovation," says McDermott alluding to Tsai's work, "and that's what they are doing for sure."

To be fully convinced of the approach, McDermott adds, future research should show clear cognitive improvement in severe Alzheimer's patients "as quickly as the lesions in the mouse model cleared up." Scott Small, director of the Alzheimer's Disease Research Center at Columbia University in New York, agrees. "To know if that really helps Alzheimer's patients will require testing in humans," Small says, "and, ultimately, to really know if it works in humans, we have to see some improvement in cognition."

Because the root cause of Alzheimer's remains unclear, reducing amyloid plaques and tau tangles may not necessarily decrease Alzheimer's symptoms. So clearing those plaques could be "more like clearing the smoke but not the fire," adds Small. "This has the potential to be really transformative. It would be phenomenal if it is effective in patients."

Replication of Tsai's research is also key to legitimizing the approach, notes David Sulzer, a neurobiologist at Columbia University Irving Medical Center. "I would like to see if other labs find the same sorts of changes," he says.

Coming to Your Senses

Emiliano Santarnecchi, a neurologist at Harvard Medical School in Boston, MA, had been experimenting with gamma entrainment in healthy humans—to boost memory and intelligence (10)—when he first learned about Tsai's work. "It was serendipitous," he says. "We were using exactly the same frequency."

Tsai's work inspired him to apply his technique to unhealthy brains in an effort to induce gamma oscillations and reduce amyloid plaques and tau tangles. Using a technique called transcranial alternating current stimulation—essentially a swim cap fitted with up to a dozen electrodes—Santarnecchi's team now zaps specific brain regions where magnetic resonance imaging (MRI) and positron emission tomography (PET) scans have spotted diseased tissue. He is even exploring the potential of using brain stimulation devices to counteract the brain damage induced by microgravity and cosmic radiation during space flight.

At first he was skeptical of Tsai's sensory stimulation strategy. "In Alzheimer's, you don't usually accumulate amyloid or tau proteins in the visual cortex or in the sensory cortex in general," he says. These pathologies are more likely found in areas such as the frontal and temporal lobes. But after seeing Tsai's results of widespread effects throughout the mouse brain in response to coupled light and sound, Santarnecchi is now pursuing multisensory stimulation too. His team has embedded a flickering light in an hour-long documentary video shown to Alzheimer's patients, along with auditory stimulation in its soundtrack. "After two or three minutes, you barely notice it," says Santarnecchi.

So far, both his electrode and sensory approaches are showing encouraging results, including increased gamma expression and improvements in sleep, speech, and activities of daily living. Follow-up with a subset of the patients confirmed the changes three months later. Although the team has not yet done further follow-up assessments to determine just how long the effects last, Santarnecchi says the long-term goal is to "stop the cascade effect that leads to the accumulation of protein." That means not just reactivating neurons that survive in the early stages of Alzheimer's, but preserving them before the disease begins to ravage the brain. Indeed, Tsai has identified reduced gamma power even in presymptomatic stages of the disease in mice. "This could translate into something you do every week as prevention, as soon as you're older than 45," says Santarnecchi.

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> —Li-Huei Tsai

Last summer, Tsai's team launched a pair of yearlong clinical trials in people with Alzheimer's disease (11, 12). The patients receive gamma frequency light and sound stimulation, akin to what the team's mice experienced in their darkened cages. Although the team has not yet released any results, Tsai notes that daily hour-long light and sound sessions so far appear to improve the 40-hertz brain waves in patients, with no side effects. Behavioral and cognitive outcomes, including electroencephalogram (EEG) and MRI measurements of connectivity in the brain, should be available later this year. If early results are promising, Tsai suggests that sensory stimulation could prove beneficial in treating other neurological conditions as well.

The use of high-frequency light and sound may not be without risk, however. Flickering lights would likely be contraindicated for patients with photosensitive epilepsy, for example. Tsai and other researchers are exploring other types of sensory stimulation to impose 40-hertz gamma waves on brains.

Amy Clements-Cortes, a music therapist and psychotherapist at the University of Toronto in Ontario, Canada, is using a chair fitted with speakers that produce 40-hertz sound. "When you sit on it, it's like a subwoofer," she says. "You feel vibrations through all parts of the body." In a study of 18 dementia patients, she and her colleagues found that patients who used the chair for 30 minutes twice a week for six weeks had improved cognition, alertness, and awareness of their surroundings with no side effects (13). Patients' scores trended higher with each treatment. However, the study did not include any quantitative measurements, such as brain scans, nor did it follow patients to see whether the improvements were maintained over time. Clements-Cortes says her team hopes to pursue a larger and longer study to confirm their initial findings.

Meanwhile, Tsai and her colleagues are considering how they might tap additional senses. They intend, for example, to investigate a device that can emit odor pulses at 40 hertz. "Virtually all sensory inputs could make sense," adds Sulzer. "It's possible that you could work up the right rhythm with pin pricks or sandpaper."

Tsai's team is also considering multisensory stimulation for other neurological diseases in which researchers have observed gamma deficiencies: Parkinson's disease, other dementias, even traumatic brain injury and stroke. "I have a protocol to test this in schizophrenia and autism," says Tsai. "I think we are up to something potentially big."

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