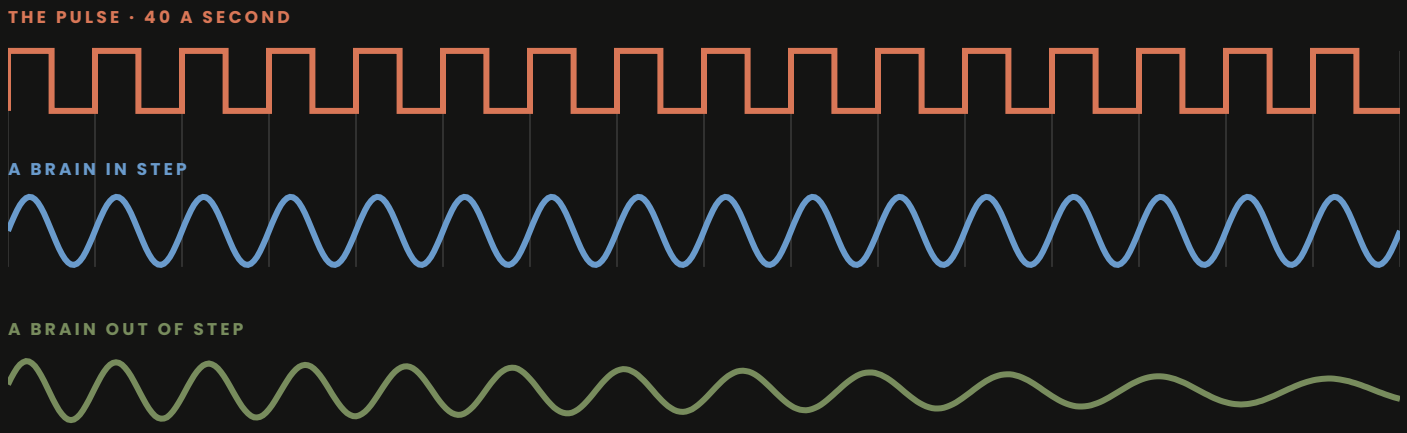
INFLECTION.

THE WEEKLY MAGAZINE OF INNOVATION

ISSUE 05 · FRIDAY, 20 NOVEMBER 2026 · DEEP DIVE — NEUROTECHNOLOGY



THE DEEP DIVE

The Case of the Missing *Dose*

The largest test yet of a drug-free Alzheimer's therapy, an hour a day of light and sound pulsing 40 times a second, missed its main goal this week. Inside the miss sits a stranger number: fewer than half of the patients it seemed to help met the bar for using it. The pulse is the cheap part. Getting it into a brain every day is the hard part.

- Why a 56 percent slowdown inside a failed trial is neither a breakthrough nor nothing
- Against the Grain: a hobby chip can make the flicker, so the dose is the product
- Signals: a magnetic film a few atoms thick · 900 million galaxies · half of a million-dollar proof

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THE DISPATCH

A result is only as good as its delivery.

> *Ask where the dose went.*

A gym membership is a proven way to get fit, and most of them fail for a reason that has nothing to do with exercise science. This week a medical trial ran into the same wall. A headset that flickers light and sound 40 times a second was tested for a year in 673 people with Alzheimer's disease. It missed its main goal. Four in ten participants did not finish.

The tempting readings are "it failed" and "it worked in mild patients." Both skip the more useful question. Among mild-stage patients the benefit looked largest in those who used the device as prescribed, and they were a minority. That pattern proves nothing on its own. It does tell an engineer where to look.

So this issue's lens is to ask where the dose went. It runs through the feature, drives the contrarian column on page six, and turns up again in our Signals, where a magnetic film, a sky survey and a mathematical proof each raise the same question: the thing was made, but did it arrive?

— THE EDITORS

Sources for every figure are listed on page 9. Company figures, expert opinion and our own arithmetic are labelled as such. Nothing here is medical advice. Previously: Issue 04, supercomputing · Issue 03, base editing · Issue 02, building in orbit · Issue 01, photonic computing.

THE FEATURE

Forty Flashes a Second

A decade ago, flickering light cleared Alzheimer's plaques from the brains of mice. This week the idea met its first large human trial. The headline is a miss. The fine print is a lesson in how treatments reach people.

BY THE INFLECTION DESK · RESEARCH DRAWN FROM COGNITO, IEEE SPECTRUM, BEING PATIENT, MIT AND NATURE NEUROSCIENCE · 9-MINUTE READ

On 16 November, at the Clinical Trials on Alzheimer's Disease conference in Boston, the neurologist Marwan Sabbagh presented the results of a study called HOPE. For twelve months, 673 people with mild-to-moderate Alzheimer's had put on a headset of opaque glasses and headphones for an hour a day at home. For half of them it flashed and beeped 40 times a second. For the other half it was a look-alike set to settings not expected to work. On the trial's main measure, a combined score of thinking and daily function, the two groups ended the year in the same place.

The idea: a metronome for the brain

Neurons fire in rhythms. One of them, the gamma rhythm, runs at roughly 40 cycles a second and is tied to attention and memory. It weakens early in Alzheimer's. In 2016 a team at MIT led by Li-Huei Tsai reported in *Nature* that an hour of LED light flickering at 40 hertz made neurons in a mouse's visual cortex fire in time with it, and that amyloid, the protein that clumps into Alzheimer's plaques, fell.

The appeal is easy to see. A flicker is not a molecule. It needs no infusion clinic, and it does not carry the brain swelling and bleeding seen with the antibody drugs now approved for the disease. Tsai and the MIT neuroengineer Ed Boyden co-founded Cognito Therapeutics in 2016 to turn the idea into a device, called Spectris.

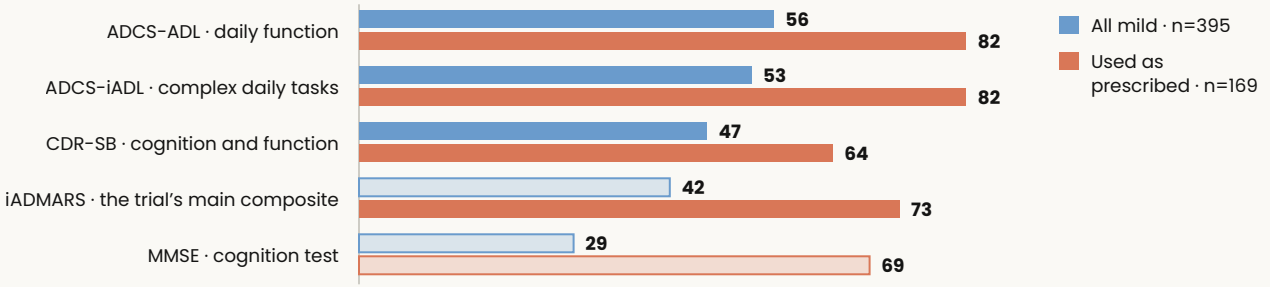
The problem: mice are not people

The mouse result was contested. In 2023 a group led by György Buzsáki at New York University reported in *Nature Neuroscience* that 40-hertz light did not engage the brain's own gamma rhythms in two mouse models, and that the mice avoided the flicker when they could. Tsai's reply was that a driven rhythm and a native one are probably different things, and that the therapy does not depend on their being the same.

Small human studies showed the stimulation was safe and could drive the rhythm. None was large or long enough to show whether it slows the disease. HOPE, run at 70 sites in the United States, was built to settle that. Cognito calls it the largest pivotal device trial devoted to Alzheimer's.

What the week put on the table

SLOWING OF DECLINE AGAINST SHAM, MILD SUBGROUP · PERCENT, AT 12 MONTHS



Source: Cognito results release, 16 Nov 2026. Hollow bars did not reach nominal significance (p > 0.05). No p-value here is adjusted for the number of comparisons. Company data, not yet peer reviewed.

A miss, stated plainly

The primary analysis covered 663 people: 333 on the active device, 330 on sham. The main endpoint was a 108-point composite of a cognition test (MMSE) and a daily-function scale (ADCS-ADL). It showed no difference at month 12, and neither did the secondary measures across the whole group. "We had hoped to see an effect across that overall population, and we did not," said Cognito's chief executive, Christian Howell.

The mild signal

The trial had been split in advance into mild and moderate patients. In the 395 with mild disease, decline on daily function was 56 percent slower than on sham, and on CDR-SB, a clinician's rating of memory, judgment and function, 47 percent slower. Cognito translates that into about five and a half months of decline delayed over the year, an estimate it calls exploratory. The 268 moderate patients showed no benefit, and on the cognition test alone even the mild group's 29 percent gap was not significant.

> *"It's simply negative."*
>
> PAUL AISEN · UNIVERSITY OF SOUTHERN CALIFORNIA, TO IEEE SPECTRUM

The adherence clue

Now look at the clay bars. Among mild patients who met the trial's bar for proper use (six months of treatment, at least 50 minutes a day on five days in seven), every effect was larger: 82 percent on daily function, 64 on CDR-SB. Only 169 of the 395 cleared that bar. And across the whole trial just 403 people, about 60 percent, completed the year.

The price in side effects

Low. Device-related effects were reported by 18.3 percent on Spectris and 15.5 percent on sham, mostly headache (5.7 against 3.9 percent) and ringing in the ears (3.3 against 1.2). Seizures, tracked as an event of special interest, occurred in 0.9 percent against 0.3.

How the room heard it

Split. "There seems to be a pervasive signal in the mild group," said Michelle Papka, a neuropsychologist who worked on the study and advises Cognito. "The results are, overall, not very encouraging," said Andrea Bozoki, who heads memory disorders at the University of North Carolina.

FROM LAB TO MARKET

What it means, and what it does not

Proven: the device is tolerable, and across mild-to-moderate Alzheimer's it did not beat a sham. **Not yet shown:** that it works in mild disease. The subgroup was planned in advance, but its p-values are unadjusted and the main result was negative. Suzanne Schindler of Washington University told Being Patient that a confirmatory trial in mild patients "would seem reasonable."

Cognito is not waiting for one. Howell told IEEE Spectrum the company is on track to ask the US Food and Drug Administration for authorization in mild Alzheimer's by mid-2027, through the De Novo route for new kinds of low-to-moderate-risk devices. His argument is that regulators weigh a device's benefit against its risk, and this one's risk is small.

For scale, the antibody drug lecanemab slowed decline on CDR-SB by 27 percent over 18 months, with brain swelling on scans in 12.6 percent of patients against 1.7 on placebo. Those numbers are not comparable with HOPE's. One is a primary endpoint that was met. The other is a subgroup of a trial that missed.

The market has not waited either. A 40-hertz lamp from OptoCeutics sells for $2,999 as a wellness product, and a Vielight headset for $1,799. Neither is authorized to treat anything.

For the CTO. Any product whose effect depends on daily use has two efficacies: what it does when used, and how often it gets used. HOPE measured their product. If you ship software, wearables or anything else people must return to, your headline metric has the same hidden factor.

Timeline: FDA filing planned by mid-2027, per the company · open-label extension continuing · peer-reviewed publication not yet announced.

FIELD NOTES · HOW A FLICKER IS MEANT TO TREAT A BRAIN

1. **Pulse.** Glasses flash and headphones click 40 times a second, as bright and loud as the wearer can tolerate.
2. **Entrain.** Sensory neurons fire in step with the pulse, like a crowd clapping along to a drummer. Sound is added to carry the rhythm toward the hippocampus, a memory hub.
3. **Clear.** In mice, the driven rhythm was followed by lower amyloid, protected synapses and faster flushing of waste fluid. Whether that chain holds in people is the open question.

Try it. Test five outcomes, each with a 5 percent chance of a false alarm. If they were independent, the chance that at least one lights up by luck is $1 - 0.95^5$, about 23 percent. That is why unadjusted subgroup wins are treated as hints.

GLOSSARY

Gamma rhythm. Fast, coordinated brain waves of roughly 30 to 100 cycles a second.

Entrainment. An outside rhythm pulling an oscillator into step with it.

Sham control. A look-alike device set not to treat; the placebo of the device world.

Per-protocol analysis. Counting only people who followed the rules. Informative, and easily biased.

THE CONTRARIAN

The Dose Is the *Product*

Everyone is arguing about whether the flicker works. The stranger bet is that the flicker was never the hard part.

The unfashionable read

The debate after HOPE has two camps: the trial failed, or the trial worked in mild disease. Both treat the stimulus as the invention. It is not much of one. IEEE Spectrum describes a retired engineer in the trial who built his own 40-hertz glasses from sunglasses, a strip of LEDs and a 555 timer, a chip hobbyists use to blink Christmas lights.

What nobody has built is the delivery. Spectris asks a person with a failing memory to sit behind opaque goggles for an hour, every day, for a year. Mariana Figueiro of Mount Sinai, who has tested light therapies in care homes, called compliance "a big issue." Read that way, HOPE tested a seat as much as a signal. Rivals are already working on the seat: a lamp whose flicker the eye blends into steady white, and see-through OLED glasses from South Korea that strobe while the wearer gets on with the day.

What follows (our proposal)

Here is an idea to test, not a finding. The dose in HOPE's public results is counted in minutes of device use. Count it in minutes of brain response instead. A dry electrode or two in the headband can pick up the 40-hertz echo the stimulus should evoke. Log "entrained minutes" as the dose, adjust brightness to hold it, and give the next trial a run-in period, as sleep-apnea device trials do, so only proven users are randomized. Whoever owns a verified dose owns the evidence, and the lamp becomes a commodity.

WHY THE CONSENSUS DISAGREES

01 **A subgroup of a failed trial is a hint.** The mild-patient p-values are unadjusted. Robert Alexander of the Alzheimer's Prevention Initiative told Being Patient the data "isn't very convincing."

02 **People who comply are different people.** The statistician Daniel Gillen notes HOPE was not designed for an unbiased comparison among compliers. Those who manage an hour a day may simply be declining more slowly. Cognito's own release says the adherence analysis does not establish cause.

03 **The mechanism is unsettled.** Buzsáki's group could not reproduce entrainment of native gamma in mice. And Andrea Bozoki of the University of North Carolina points out that the mild-group gains were in daily function, with the pure cognition test not significant, which is not what a memory-rhythm story predicts.

04 **Dropout may be the answer, not the noise.** "Why so many drop-outs," Bozoki asked, in a trial with almost no side effects? If patients cannot or will not do this, better metering fixes nothing. The results are also a company release, not yet peer reviewed.

MATERIALS

3 layers

A magnetic film survives being made a few atoms thick

Multiferroics are materials whose electric and magnetic states are linked, so a tiny voltage can write a bit that is then read magnetically. They have a flaw: thinned to chip dimensions, they go inert, a failure known as the dead layer. A team led by Lucas Caretta at Brown University reports in *Nature Materials* that bismuth ferrite stays ferroelectric and magnetic "down to a few angstroms" when grown as a three-layer stack: a dysprosium scandate base that squeezes its crystal lattice, the film, and a metal layer that cancels stray electric fields. The stack also showed signs of altermagnetism, a recently confirmed third kind of magnetism. This is a materials result. No device, speed or power figure was reported.

SOURCE · Brown University via ScienceDaily, 12 Nov 2026 · sciencedaily.com/releases/2026/11/261111005853.htm · Nature Materials, doi:10.1038/s41563-026-02786-1

SPACE

900 million

Euclid hands astronomers the raw material for a 3D map of the universe

On 12 November the European Space Agency released DR1-Foundation, the first large batch of data from its Euclid space telescope: about 13 months of observing, more than a billion catalogued objects, over 900 million of them classed as galaxies, plus spectra for more than 160 million sources and roughly 15,000 candidate gravitational lenses. It covers about 1,900 square degrees, some 14 percent of the planned survey, in about 1.7 petabytes. The release is images and catalogues. The measurements that test theories of dark energy, including the subtle distortion of galaxy shapes called weak lensing, come with the full release due in mid-2027. The lens candidates still need confirming.

SOURCE · ESA, 12 Nov 2026 · esa.int/articles/about-us/directorates/science/euclid/euclid-lays-the-foundation-for-its-best-ever-3d-map-of-the-universe · figures via Nature World News, 13 Nov 2026

AI & MATHEMATICS

$1M

A machine-written proof of half a Millennium Prize problem is vouched for

Yang-Mills theory underpins the Standard Model of particle physics, yet nobody had shown that its quantum version can be built from valid mathematical steps. That question is one half of a problem carrying a million-dollar prize. On 10 November a five-person committee led by the physicist David Gross, appointed by OpenAI, posted an explanation of the company's AI-generated proof and affirmed that it had been formally verified in Lean, a language that checks proofs line by line. Scientific American reported it the next day. The harder half, the "mass gap," is untouched. Critics object that the company picked its own referees, and outside experts have yet to confirm that the statement checked in Lean matches the prize problem.

SOURCE · Scientific American, J. Howlett, 11 Nov 2026 · scientificamerican.com/article/openais-shepherds-affirm-blockbuster-physics-result/

40 Hz

Pulses of light and sound per second from the Spectris headset, for an hour a day over twelve months.

673

People enrolled in the HOPE trial at 70 US sites. On its main measure, the device did not beat a sham.

47%

Slower decline on the CDR-SB rating among 395 mild-stage patients. Nominal p = 0.004, unadjusted, in a trial that missed.

169 of 395

Mild-stage patients who met the trial's bar for using the device as prescribed: about 43 percent (our arithmetic).

60%

Share of enrolled participants who completed the year: 403 people, as reported by Being Patient.

12.6%

Patients with brain swelling on scans in the phase 3 trial of the antibody drug lecanemab, against 1.7 percent on placebo. A flicker carries no such risk.

$2,999

Price of a consumer 40-hertz lamp sold as a wellness product. No light-and-sound device is authorized to treat Alzheimer's.

Made is not the same as delivered

Four stories this week share a gap between a thing existing and a thing arriving. A 40-hertz pulse is trivial to make and, on this week's evidence, hard to get into a brain every day for a year. Brown's film keeps its magnetism at a few atoms thick, and now has to be built into a device. Euclid has released 900 million galaxies and none of the cosmology yet. A proof has been checked by a machine, and human mathematicians still have to agree on what exactly was checked.

The warning label is the same for all four. HOPE's mild-patient signal is an unadjusted subgroup in a company release. The film has no power or speed figure. The lens candidates are candidates. The proof's referees were chosen by its author. Each is real progress with the last step missing, and the last step is where most ideas are lost.

What to watch: whether Cognito files with the FDA by mid-2027 as planned, and whether it runs a confirmatory trial in mild patients; the full HOPE paper; and whether a second sensory approach holds up. In September an MIT team reported that 50-millisecond bursts of pink noise, timed to sleeping brain waves, strengthened the flow of the fluid that clears waste from the brain, in 14 healthy adults.

SOURCES & FURTHER READING

1. **Cognito**, "Spectris Showed Consistent Slowing of Cognitive and Functional Decline in Early Symptomatic Alzheimer's Disease in HOPE Pivotal Study," 16 Nov 2026 (via BioSpace) — https://www.biospace.com/press-releases/cognitos-non-invasive-at-home-therapy-spectris-showed-consistent-slowing-of-cognitive-and-functional-decline-in-early-symptomatic-alzheimers-disease-in-hope-pivotal-study
2. **IEEE Spectrum** (E. Dolgin), "Can Flashing Lights Slow Alzheimer's? Only if You Start Early," 17 Nov 2026 — https://spectrum.ieee.org/40-hz-therapy-alzheimers
3. **Being Patient** (S. Spichak), "CTAD: Audiovisual Stimulation Headset for Alzheimer's Misses Mark in Phase 3 Trial," 17 Nov 2026 — https://beingpatient.com/alzheimers-stimulation-headset-fails-phase-3-trial/
4. **MIT Picower Institute**, "Mild Alzheimer's patients benefit from 40Hz sensory stimulation in national clinical trial," 16 Nov 2026 — https://picower.mit.edu/news/mild-alzheimers-patients-benefit-40hz-sensory-stimulation-national-clinical-trial
5. **Medical Daily** (C. Mercer), "At-Home 40 Hz Light and Sound Alzheimer's Device Missed Its Main Goal in 673-Person Pivotal Trial," 17 Nov 2026 — https://www.medicaldaily.com/spectris-40hz-alzheimers-trial-missed-primary-goal-481325
6. **Alzheimer's Drug Discovery Foundation**, "Cognito Reports Pivotal Phase 3 Results for Spectris AD," 16 Nov 2026 — https://www.biospace.com/press-releases/cognito-reports-pivotal-phase-3-results-for-spectris-ad-a-non-invasive-at-home-approach-for-alzheimers-treatment-backed-by-addf-investment
7. **ClinicalTrials.gov**, HOPE study record, NCT05637801 — https://www.clinicaltrials.gov/study/NCT05637801
8. **H. Iaccarino et al.**, "Gamma frequency entrainment attenuates amyloid load and modifies microglia," Nature, 2016 — https://www.nature.com/articles/nature20587
9. **M. Soula et al.**, "Forty-hertz light stimulation does not entrain native gamma oscillations in Alzheimer's disease model mice," Nature Neuroscience 26, 570–578, 2023 — https://www.nature.com/articles/s41593-023-01270-2
10. **Alzforum**, "Does Flashing Light Really Lower Cortical Amyloid?" (Tsai's reply) — https://alzforum.org/node/2701666
11. **Alzheimer Europe**, "Eisai presents full results from the Clarity AD Phase III trial of lecanemab," 30 Nov 2022 — https://www.alzheimer-europe.org/news/eisai-presents-full-results-clarity-ad-phase-iii-trial-lecanemab
12. **MIT News** (A. Trafton), "A burst of 'pink noise' may lead to more restorative sleep," 9 Sep 2026 — https://news.mit.edu/2026/pink-noise-burst-may-mean-more-restorative-sleep-0909
13. **Brown University** via ScienceDaily, "A breakthrough in magnetism could make AI chips use dramatically less energy," 12 Nov 2026 — https://www.sciencedaily.com/releases/2026/11/261111005853.htm
14. **G. Fratian et al.**, "Altermagnetic signatures and topological textures in ultrathin multiferroic BiFeO3," Nature Materials, 2026 — https://doi.org/10.1038/s41563-026-02786-1
15. **ESA**, "Euclid lays the foundation for its best-ever 3D map of the Universe," 12 Nov 2026 — https://www.esa.int/articles/about-us/directorates/science/euclid/euclid-lays-the-foundation-for-its-best-ever-3d-map-of-the-universe
16. **Nature World News**, "Euclid Releases Data Covering More Than 900 Million Galaxies," 13 Nov 2026 — https://www.natureworldnews.com/articles/73846/20261113/euclid-releases-data-covering-more-900-million-galaxies.htm
17. **Scientific American** (J. Howlett), "Scientists confirm OpenAI's blockbuster quantum physics result," 11 Nov 2026 — https://www.scientificamerican.com/article/openais-shepherds-affirm-blockbuster-physics-result/
18. **CASRAI**, "OpenAI Yang-Mills proof: committee verification" (what remains unresolved) — https://casrai.org/news/ai-rivals-physics-mathematical-challenge-2026

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THE LENS · A QUESTION FOR YOUR WEEK

What have you built that works when it is used, and how sure are you that it is being used?

NEXT ISSUE · FRIDAY, 27 NOVEMBER 2026

A fresh deep dive from a different domain, three new Signals, and a contrarian column that argues with the consensus.



TOP: A YEAR OF DAILY SESSIONS, PRESCRIBED. BOTTOM: A YEAR AS IT MIGHT BE LIVED. AN ILLUSTRATION, NOT DATA.

RESEARCHED, WRITTEN & DESIGNED WITH CLAUDE. TYPESET IN POPPINS & LORA ON THE ANTHROPIC PALETTE.
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