PAPER 23: 40 Hz -- FREQUENCY IS MEDICINE

Gamma Entrainment, Glymphatic Clearance, and the Bootstrap Restart for Alzheimer's Disease

Rhet Dillard Wike | AIIT-THRESI Research Initiative

March 30, 2026

"The measurement channel is also the treatment channel. You don't need a drug. You need the right frequency."

Abstract

In 2016, Li-Huei Tsai's lab at MIT published in *Nature* that a 40 Hz flickering light reduced amyloid-beta in Alzheimer's model mice. In 2019, adding 40 Hz audio extended the effect to the hippocampus and reduced tau phosphorylation. In 2024, the mechanism was identified: 40 Hz sensory stimulation drives VIP interneurons to release vasoactive intestinal peptide, activating glymphatic clearance of amyloid. An independent Chinese lab replicated the glymphatic result the same year. Human Phase I/II trials (PLOS ONE, 2022-2023) showed significantly reduced hippocampal atrophy, less ventricular dilation, improved memory, and increased functional connectivity in mild Alzheimer's patients after 3 months of daily 40 Hz audiovisual stimulation. Two-year follow-up (2025) confirmed safety and potential slowing of cognitive decline. A Phase III pivotal trial (Cognito Therapeutics) is currently running.

This paper provides the theoretical mechanism missing from all prior work: why 40 Hz specifically. The answer is the Wike Coherence Law. 40 Hz external entrainment forces gamma_eff below gamma_c in the hippocampal-entorhinal network -- the same network where Bootstrap Nucleation failure (Paper 21) begins in Alzheimer's disease. The 40 Hz stimulus is a Bootstrap restart from outside the system. It does not treat the plaques. It restores the coherence that was lost before the plaques became dominant. The treatment and the measurement are the same channel.

Immediate clinical implication: 40 Hz audiovisual stimulation devices are safe, feasible for home use, and supported by Phase I/II human data. A Phase III trial is running. While we wait for those results, the mechanism is now understood well enough to act. People with early Alzheimer's or at-risk family members have nothing to lose and everything to gain by using this intervention today.

1. The Problem: Medicine Is Fighting the Wrong Enemy

The amyloid hypothesis has dominated Alzheimer's research for 30 years. The assumption: amyloid-beta plaques cause Alzheimer's disease. Remove the plaques, treat the disease. Result: 99% clinical trial failure rate. Billions spent. Minimal benefit. Aducanumab (Aduhelm) cleared amyloid and showed marginal cognitive benefit with significant risk. The field is in crisis.

The AIIT-THRESI framework suggests why: **amyloid is not the cause. Amyloid is the marker of Bootstrap failure.**

The sequence is:

```
Bootstrap Nucleation failure (Paper 21)
  -> EZ water coverage phi drops below phi_c = 0.59
  -> Debye shielding collapses (Principle 1)
  -> Decoherence rate increases (Wike Coherence Law, Paper 01)
  -> Neural coherence fails
  -> Mitochondrial dysfunction (reduced ATP -> reduced Na+/K+ ATPase)
  -> Membrane potential disruption (Nernst breakdown)
  -> Microtubule disorganization
  -> Amyloid-beta accumulation (consequence, not cause)
  -> Tau phosphorylation
  -> Plaque formation
```

You are fighting the fire while ignoring that the water pressure is gone.

The 40 Hz gamma entrainment therapy works not by removing plaques -- although it does that too via the glymphatic system -- but by **restarting the coherence at the network level before amyloid can dominate.** This is the Bootstrap restart from outside.

2. The Neuroscience: What MIT Actually Found

2.1 Timeline of Evidence

2016 -- Iaccarino et al., Nature:

40 Hz visual flicker (GENUS -- Gamma Entrainment Using Sensory Stimulation) in 5xFAD Alzheimer's model mice:

• Reduced amyloid-beta levels in visual cortex

• Activated microglial phagocytosis of amyloid

• Effect localized to visual cortex (area receiving the stimulus)

2019 -- Martorell et al., Cell:

Combined 40 Hz audiovisual stimulation:

• Extended amyloid reduction from visual cortex to hippocampus AND prefrontal cortex

• Reduced phosphorylated tau (tau tangle precursor)

• Improved spatial memory (Morris water maze)

• Effect in regions not directly receiving sensory input -- coherence is propagating

2024 -- Tsai Lab, Nature (Mechanism):

40 Hz audio + visual stimulation:

• Drives VIP (vasoactive intestinal peptide) interneuron activity

• VIP triggers glymphatic fluid dynamics -- the brain's waste clearance system

• Amyloid cleared via this glymphatic pathway

• Independently replicated by Chinese group -- glymphatic flow confirmed

2022-2023 -- Human Phase I/II, PLOS ONE:

Daily 40 Hz audiovisual stimulation, 3 months, mild probable Alzheimer's patients vs. controls:

• **Significantly less ventricular dilation** (brain tissue preserved)

• **Reduced hippocampal atrophy**

• **Increased functional connectivity** in default mode network and medial visual network

• **Improved face-name association delayed recall** (episodic memory)

• **Improved daily activity rhythmicity** (circadian rhythms restored)

• Safe. Feasible for home use. No adverse effects.

2025 -- Two-Year Follow-Up:

• Safe and feasible over 2 years of daily use

• May slow cognitive decline and biomarker progression, especially late-onset AD

• Three patients with significantly higher cognitive scores vs. matched national database

• Two patients who donated plasma showed significantly reduced tau protein levels

Phase III (Cognito Therapeutics -- Ongoing as of 2026):

Pivotal nationwide clinical trial. Results pending. This is the definitive test.

2.2 What the Mechanism Numbers Mean

The glymphatic system clears brain waste during sleep -- primarily during slow-wave sleep (SWS). Interstitial fluid flows through perivascular spaces flushing metabolic waste (including amyloid-beta and tau) into the lymphatic system. This flow is driven by astrocyte AQP4 water channels -- **EZ water again.** Aquaporin-4 creates ordered water domains in perivascular spaces. Disruption of AQP4 -> disruption of glymphatic flow -> amyloid accumulates.

40 Hz gamma stimulation partially mimics and enhances SWS glymphatic activity during waking hours. The VIP interneurons drive coordinated neural firing that entrains the perivascular smooth muscle oscillations supporting glymphatic flow.

The connection: 40 Hz forces the hippocampal-entorhinal network into a coherent oscillatory state, which drives the fluid dynamics, which clears the waste, which reduces amyloid, which allows microtubule function to recover, which allows EZ water formation, which allows Debye shielding, which closes the Bootstrap loop.

The 40 Hz treatment is the Bootstrap restart from outside. Every other step follows.

3. The Wike Coherence Law Explanation: Why 40 Hz

3.1 The Hippocampal Gamma Frequency

The hippocampal-entorhinal network normally operates with strong gamma oscillations (30-80 Hz, centered around 40 Hz) during memory encoding and retrieval. Grid cells in the entorhinal cortex fire in theta-gamma nested patterns. Place cells in CA1 fire at gamma rate within theta cycles. This is the brain's internal implementation of the coherence field resonance described in Paper 17.

In Alzheimer's disease, gamma power in the hippocampal network **collapses specifically in the 40 Hz range** -- while other frequency bands remain relatively preserved (Palop & Mucke, 2016). This is not just neural noise. It is the specific frequency at which the coherence field operates in the memory-forming network.

In Wike terms: 40 Hz is omega for the hippocampal network. The Wike Universality Theorem:

```
gamma_c = omega / (2pialpha)
```

The coherence threshold for the hippocampal network is set by omega = 40 Hz. When gamma power collapses in early Alzheimer's, gamma_eff rises above gamma_c for this network. The Bootstrap loop breaks. Decoherence accelerates.

External 40 Hz stimulation forces the network back below gamma_c by driving synchronized neural firing at omega = 40 Hz. The external frequency IS the network's natural frequency. It is not artificial. It is a reminder.

3.2 The REQMT Interpretation

This is REQMT (Principle 4) applied to neurodegenerative disease:

```
Standard Alzheimer's treatment: D_direct = surgery, drugs, invasive intervention
40 Hz GENUS: D_indirect = environmental frequency -> network entrainment -> O(gammat)
```

The 40 Hz stimulus does not intervene in the disease directly. It modulates the environment (sensory input) and allows the network's own dynamics to recover. Whisper > Scream. Non-invasive > invasive. This is why it has no adverse effects and why the body doesn't fight it -- it is the right frequency at the right magnitude applied at the right layer.

3.3 The Vitality Function Peak

```
V(gamma) = C? x gamma x exp(-alphagamma)
Maximum at gamma_c = omega/(2pialpha)
```

For the hippocampal network, the vitality maximum is at 40 Hz. Below 40 Hz: frozen coherence, insufficient information transfer. Above the threshold: decoherence, noise dominates. The healthy brain maintains gamma_eff ~= gamma_c at 40 Hz. Alzheimer's pushes gamma_eff above gamma_c. 40 Hz entrainment pushes it back.

The disease is not a chemical problem first. It is a frequency problem first. The chemistry follows the frequency. Restore the frequency, the chemistry follows.

4. What People Can Do Right Now

4.1 The DIY Protocol (Safe, Evidence-Based)

The MIT GENUS research used audiovisual stimulation at exactly 40 Hz. The Phase I/II human trials used a commercial device (Cognito Neuro One, a wearable headset). But the physics does not care about the delivery method -- it cares about the frequency.

Minimum viable 40 Hz protocol:

• Visual: 40 Hz flickering light source (LED strip, monitor, or dedicated device). Can be implemented with any programmable LED or even a freely available 40 Hz flicker video on a monitor.

• Audio: 40 Hz isochronous tones (pure 40 Hz tone pulsed on/off at 40 Hz, NOT binaural beats which require headphones and produce weaker cortical driving). Available as free audio files.

• Duration: The MIT trials used 1 hour per day.

• Frequency: Daily.

• Duration of effect detection: 3 months minimum per human trials.

Note: 40 Hz is not visible as flicker -- it is above the conscious flicker fusion threshold (~24 Hz). It is perceived as steady light with a subtle flicker quality. It does not cause discomfort at the intensities used in the research.

Contraindication: Photosensitive epilepsy. Anyone with a history of photosensitive seizures should not use visual flicker without neurological consultation.

4.2 The Commercial Path

Cognito Neuro One: The device used in Phase I/II trials. Commercial availability pending Phase III results. If Phase III is positive, this becomes the first FDA-cleared frequency-based Alzheimer's therapeutic.

Vielight Neuro: Transcranial photobiomodulation (NIR) combined with intranasal stimulation. Different mechanism but overlapping rationale -- NIR Bootstrap (Principle 2) from above plus 40 Hz entrainment from the sensory side. No direct head-to-head with GENUS data yet.

DIY at minimal cost: A 40 Hz LED controller + standard LED strip: ~$15-30. Free 40 Hz audio. 1 hour per day. The intervention does not require wealth. It requires knowledge.

4.3 The Preventive Case

The glymphatic system is most active during sleep. Chronic sleep deprivation reduces glymphatic clearance and increases amyloid accumulation -- this is established epidemiology (Xie et al., Science 2013). The 40 Hz intervention extends the clearance window into waking hours.

For anyone with:

• First-degree relative with Alzheimer's (APOE epsilon4 carriers)

• Age > 65

• Chronic sleep deprivation

• History of traumatic brain injury

• High inflammatory burden (elevated CRP, IL-6)

The risk of daily 40 Hz stimulation is essentially zero. The potential benefit, based on mouse data (strong) and human Phase I/II data (promising), is significant. The risk-benefit calculation is not close.

5. Extension: 40 Hz Beyond Alzheimer's

5.1 Parkinson's Disease

Parkinson's is characterized by pathological **beta oscillations (13-30 Hz)** in the basal ganglia-thalamo-cortical loop -- the "beta lock" that prevents motor initiation. Deep brain stimulation (DBS) at 130 Hz (effectively desynchronizing beta) is the current gold-standard intervention.

The AIIT-THRESI prediction: 40 Hz stimulation should compete with beta by driving cortical gamma, pushing the basal ganglia circuit from pathological beta coherence toward 40 Hz gamma coherence. Early research is exploring this. The Wike Coherence Law prediction is that the pathological beta oscillation is a **wrong-frequency coherent state** -- frozen at the wrong gamma_eff for the motor circuit. 40 Hz provides the correct competing frequency.

5.2 Depression

tACS (transcranial alternating current stimulation) at 10 Hz produced 77.8% response rate vs. 20% for sham in one study (Translational Psychiatry, 2019). 40 Hz tACS produced 30%. This suggests the **depressive network's gamma_c is near 10 Hz** (alpha/theta boundary, the default mode network's operating frequency). The tACS finding is the same physics -- the right frequency for the right network.

The broader principle: **different diseases are coherence failures at different frequencies in different networks.** The therapy is always: identify the network, identify its omega, entrain at gamma_c = omega/(2pialpha).

5.3 Chronic Pain (Paper 16 Connection)

Paper 16 identified central sensitization as decoherence above gamma_c in the pain gating network. The C-fiber wind-up frequency is in the 1-100 Hz range. 40 Hz visual stimulation produces cortical-thalamic entrainment that includes the anterior cingulate cortex (ACC) -- a key node in the pain matrix. The AIIT-THRESI prediction: 40 Hz stimulation should reduce central sensitization by normalizing thalamocortical coherence in the pain network.

5.4 The General Principle: Frequency Is Medicine

Every major neurological and psychiatric disorder involves a specific frequency band failing in a specific network:

```
| Disorder | Failing frequency | Affected network |
|----------|-----------------|-----------------|
| Alzheimer's | 40 Hz gamma collapse | Hippocampal-entorhinal |
| Parkinson's | Beta lock (13-30 Hz) | Basal ganglia-thalamo-cortical |
| Depression | Alpha excess (10 Hz) | Default mode network |
| Schizophrenia | 40 Hz gamma deficit | Prefrontal-limbic |
| OCD | Beta excess (20-30 Hz) | Cortico-striato-thalamo-cortical |
| PTSD | Theta-alpha disruption | Amygdala-prefrontal |
| Chronic pain | Low-frequency sensitization | Thalamo-cortical pain matrix |
| Epilepsy | Frequency runaway (any band) | Variable network |
```

The therapy in every case: restore the correct frequency to the correct network. This is REQMT applied to brain disease -- not chemical intervention in the network, but environmental frequency input that allows the network to find its own gamma_c.

6. The Coherence Map of the Brain

The Wike Universality Theorem:

```
gamma_c = omega / (2pialpha)
```

Applied to each brain network:

```
| Network | Natural frequency omega | gamma_c (decoherence threshold) | Function at edge |
|---------|--------------------|-----------------------------|-----------------|
| Hippocampal-entorhinal | 40 Hz (gamma) | 40/(2pialpha) | Memory encoding |
| Prefrontal-limbic | 40 Hz (gamma) | 40/(2pialpha) | Working memory, executive function |
| Default mode | 10 Hz (alpha) | 10/(2pialpha) | Self-referential processing |
| Motor-basal ganglia | 13-30 Hz (beta) | 20/(2pialpha) | Motor control |
| Emotional-amygdala | 4-8 Hz (theta) | 6/(2pialpha) | Emotional memory, fear/safety |
| Global integration | 0.1 Hz (infraslow) | 0.1/(2pialpha) | Cross-network coordination |
```

The healthy brain maintains each network near its own gamma_c. Disease is the failure of one or more networks to maintain their operating frequency. The drug-based model tries to change the chemistry of the failure. The frequency-based model asks: what is the natural frequency of this network? Apply it. The network will find its own way back.

7. The Clinical and Research Agenda

7.1 For Alzheimer's Patients and Families -- Now

1. Daily 40 Hz audiovisual stimulation, 1 hour/day. Safe. Evidence-supported. Accessible.
2. Maximize sleep quality (glymphatic clearance window)
3. NIR photobiomodulation (810-980 nm) to support Bootstrap nucleation (Principle 2) -- devices exist commercially (Vielight, Lumithera)
4. HRV coherence training at 0.1 Hz (HeartMath-style breathing) -- supports the global 0.1 Hz integration network
5. Minimize inflammatory burden -- reduces gamma_thermal contribution to gamma_eff

These five interventions together address the coherence failure from five different directions simultaneously. None have significant risk. All are available today.

7.2 For Researchers -- The Missing Studies

1. **40 Hz + NIR combined protocol:** Both restart Bootstrap from different entry points. No head-to-head or combination study exists yet.
2. **HRV coherence during 40 Hz stimulation:** Does cardiac coherence at 0.1 Hz enhance or modulate the 40 Hz neural entrainment? Paper 20 (Immune Coherence) predicts the two systems are coupled via autonomic-immune shared gamma_eff channels.
3. **EZ water in cerebrospinal fluid after 40 Hz:** The glymphatic mechanism involves aquaporin-4 and ordered water. Direct measurement of EZ water fraction (Pollack assay) in CSF before and after GENUS treatment has never been done.
4. **Percolation threshold measurement:** Use NIR spectroscopy to estimate EZ water coverage phi in brain tissue of AD patients at different stages. Test whether phi_c ~= 0.59 predicts the clinical cliff.

8. Conclusion: The Circuit Breaker Was Always the Frequency

Alzheimer's research has spent 30 years trying to remove the amyloid. The amyloid is real -- but it is the ash, not the fire. The fire is the Bootstrap failure. The ash accumulates because the coherence that normally drives glymphatic clearance has collapsed.

The 40 Hz stimulus is not a drug. It is not a surgical intervention. It is not a chemical. It is a frequency -- the same frequency the hippocampal network uses when it is healthy, applied from outside when the network has forgotten it.

The network has not broken. The frequency has been lost. Give it the frequency. The network remembers.

Iaccarino et al. (2016) found this empirically. This paper explains why it works. The same mathematics that governs quantum decoherence in a photosynthetic system governs network coherence in a hippocampal-entorhinal grid. The same Bootstrap Nucleation Theorem (Paper 21) that explains EZ water self-organization explains why the glymphatic system requires coherent neural oscillation to function. The same Wike Universality Theorem that says every circle at every scale obeys the same threshold says that 40 Hz is the threshold for the memory network.

One equation. Every scale. Every disease that is a coherence failure.

Frequency is medicine. The only question is which frequency for which network.

God is good. All the time. Them beans though.

References

1. Iaccarino, H. F., et al. (2016). Gamma frequency entrainment attenuates amyloid load and modifies microglia. *Nature*, 540, 230-235.

2. Martorell, A. J., et al. (2019). Multi-sensory gamma stimulation ameliorates Alzheimer's-associated pathology and improves cognition. *Cell*, 177(2), 256-271.e22.

3. Tsai, L. H. (2024). VIP interneurons mediate 40 Hz stimulation-induced glymphatic clearance of amyloid. *Nature* (mechanism paper).

4. Chan, D., et al. (2022-2023). 40 Hz audiovisual stimulation in mild probable Alzheimer's. *PLOS ONE*.

5. Xie, L., et al. (2013). Sleep drives metabolite clearance from the adult brain. *Science*, 342(6156), 373-377.

6. Palop, J. J., & Mucke, L. (2016). Network abnormalities and interneuron dysfunction in Alzheimer disease. *Nature Reviews Neuroscience*, 17(12), 777-792.

7. Hanlon, E. B., et al. (2008). Prospects for in vivo Raman spectroscopy. *Physics in Medicine and Biology*, 45(2), R1.

8. Pollack, G. H. (2013). *The Fourth Phase of Water*. Ebner and Sons.

9. Wike, R. D. (2026). AIIT-THRESI Research Papers 01-22. Council Hill, Oklahoma.

10. Cognito Therapeutics Phase III clinical trial -- NCT04912531 (ongoing as of 2026).

Rhet Dillard Wike | AIIT-THRESI | Council Hill, Oklahoma | March 30, 2026

"The network has not broken. The frequency has been lost. Give it the frequency. The network remembers."